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UNIVERSITY OF BRISTOL

Using routine healthcare data to investigate the utility of cardiac screening prior to kidney transplantation

Ailish Mairi Seana Airlie Nimmo

BSc (Hons) MBChB (Hons) MRCP (UK)

A dissertation submitted to the University of Bristol in accordance with the requirements for award of the degree of Doctor of Medicine in the Faculty of Translational Health Sciences

Bristol Medical School

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Abstract

Introduction
Kidney transplantation is the optimal treatment for most people with end stage kidney disease (ESKD). Before transplantation, patients are thoroughly assessed, which frequently includes investigating for asymptomatic coronary artery disease (CAD) due to the increased risk of major adverse cardiac events (MACE) in the peri-transplant period. However, there is no evidence that screening improves outcomes.

Methods
This thesis investigates:

1. **Whether routinely collected healthcare data accurately record ischaemic heart disease diagnoses in patients with ESKD.**
2. **The incidence, associations, and impact of post-transplant MACE on kidney transplant recipients.**
3. **Factors associated with screening for CAD disease and whether screening associates with post-transplant MACE.**
4. **Current CAD screening practice in the UK.**

Data from the Access to Transplant and Transplant Outcome Measures study and Hospital Episode Statistics (HES) were used to examine these aims.

Results
Ischaemic heart disease was recorded with a sensitivity and specificity of 82.6% and 93.4% within HES. The incidence of post-transplant MACE was 1.5%, 2.6% and 9.6% at 90-days, 1- and 5-years respectively, and associated with increased age, Asian ethnicity, ischaemic heart disease, diabetes, peripheral vascular disease, and smoking. Non-fatal MACE within 6 months of transplantation associated with reduced patient survival over median 6.7 years follow up. Screening practice varied by centre, ranging from 5-100% of recipients. There was no association between screening and MACE post-transplant. Of 23 transplant centres, 10 had recently updated their screening protocol and 22 reported willingness to participate in a randomised control trial to investigate utility of screening.

Conclusions
HES data has reasonable potential for recording study outcomes. Peri-transplant MACE associates with post-transplant mortality. Identifying ways to minimise this risk is vital, but routine screening for CAD did not reduce MACE in the studied cohort. There is appetite for a randomised control trial amongst nephrologists to give definitive evidence of benefits and harms of screening.

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Author’s Declaration

I declare that the work in this dissertation was carried out in accordance with the requirements of the University's *Regulations and Code of Practice for Research Degree Programmes* and that it has not been submitted for any other academic award. Except where indicated by specific reference in the text, the work is the candidate's own work. Work done in collaboration with, or with the assistance of, others, is indicated as such. Any views expressed in the dissertation are those of the author.

SIGNED:  DATE: 9/2/2022

Published Material

Work from this thesis has been published as:

- **Nimmo A**, Steenkamp R, Ravanan R, Taylor D. Do routine hospital data accurately record comorbidity in advanced kidney disease populations? A record linkage cohort study. *BMC Nephrol* 22, 95 (2021). PMID: 33731041
- **Nimmo A**, Forsyth J, Oniscu G, Robb M, Watson C, Fotheringham J, Roderick P, Ravanan R, Taylor D. A propensity score-matched analysis indicates screening for asymptomatic coronary artery disease does not predict cardiac events in kidney transplant recipients. Kidney International 2021; 99(2): 431-442. PMID: 33171171
- **Nimmo A**, Ravanan R, Taylor D. The authors reply. Kidney International 2021; 99(3): 772-773. PMID: 33637207
- **Nimmo A**, Graham-Brown M, Griffin S, Sharif A, Ravanan R, Taylor D. Pre-kidney transplant screening for coronary artery disease: current practice in the UK. Transplant International. 2022; 35:4.

The following paper was accepted by Transplant International in May 2022:

- **Nimmo A**, Latimer N, Oniscu G, Ravanan R, Taylor D, Fotheringham J. Propensity score and instrumental variable techniques in observational transplantation studies: an overview and worked example relating to pre-transplant cardiac screening.

For each of the publications, Ailish Nimmo designed the study question and methodology, performed the statistical analyses, and wrote the manuscripts under the supervision of Rommel Ravanan and Dominic Taylor.

SIGNED (First author): DATE: 9/2/2022

SIGNED (Final author):  DATE: 9/2/2022

COVID-19 Statement

From April-May 2020 I returned to full time clinical work at Southmead Hospital. I was able to resume my research activities in June 2020, though was not able to access the data stored at NHS Blood and Transplant due to social distancing rules until July 2020 and therefore was not able to perform analyses over this time, instead focusing on writing up elements of completed work. Aside from this, I was fortunate that my planned research activities were not overly disrupted by COVID-19 restrictions, and I was able to complete analyses largely as planned.

Acknowledgements

Over the two and a half years I have spent working on this thesis, I have received a huge amount of support and encouragement from my supervisors Dr Rommel Ravanan and Dr Dominic Taylor. I have learnt a lot from them academically, but they have also shown me how to balance clinical work and research, that it is possible to stick by what you believe is important, and how to keep perspective when things were difficult. They have been patient and kind and provided me with many opportunities both within and beyond the work in this thesis. I hope we will stay in touch though I'm sure they will appreciate fewer emails! I would also like to thank Professor Simon Satchell for giving me this opportunity even though it is not in his usual remit.

I am grateful to the ATTOM investigators whose work produced the data analysed in this thesis, and the National Institute for Health Research who funded the ATTOM programme. I am appreciative of the guidance I received from members of the Kidney Research Transplantation Clinical Study Group, in particular Dr Sian Griffin, Dr Matthew Graham-Brown and Dr Adnan Sharif who encouraged me to think how to progress the work discussed in this thesis.

I received additional statistical support from Dr Retha Steenkamp (Statistician, UK Renal Registry) and Dr James Fotheringham (Nephrologist, University of Sheffield) for analysis of HES data and instrumental variable analyses respectively. Dr Matthew Robb (Statistician, NHS Blood and Transplant) also provided invaluable support with ATTOM study data.

I have been fortunate to continue clinical work whilst completing this thesis. Caring for people with kidney disease has helped put this work into context and I am grateful to the patients who took part in the ATTOM study.

Finally, I would like to thank my friends and family who definitely have experienced the highs and lows of the past two years with me – Wendy for suggesting the opportunity in the first place and always having the right balance of guidance and autonomy, Cat for persevering with the daily updates, Helen for Friday research lunches, Katie, Rory and Tunnock for being the best bubble buddies I could have asked for, and my mum and dad who have always given me support and provided perspective to everything in life.

Abbreviations and Glossary

The following abbreviations are used in the main text and tables of this thesis. Any abbreviations used only in tables are also defined in the table legends.

Abbreviation	
ACE	Angiotensin Converting Enzyme
ACR	Albumin: Creatinine Ratio
ACS	Acute Coronary Syndrome
AKI	Acute Kidney Injury
AMI	Acute Myocardial Infarction
APC	Admitted Patient Care (within HES data)
ATE	Average Treatment Effect
ATT	Average Treatment Effect on the Treated
ATTOM	Access to Transplant and Transplant Outcome Measures (study)
CABG	Coronary Artery Bypass Graft
CAD	Coronary Artery Disease
CARSK	Canadian-Australasian Randomised Trial of Screening Kidney Transplants for CAD
CeVD	Cerebrovascular Disease
CI	Confidence Interval
CKD	Chronic Kidney Disease
CKD-EPI	Chronic Kidney Disease-Epidemiological Collaboration (eGFR equation)
CSG	Clinical Study Group
CTCA	CT Coronary Angiogram
CVD	Cardiovascular Disease
DBD	Donor after Brain Death
DCD	Donor after Cardiac Death
DSE	Dobutamine Stress Echocardiogram
ECD	Extended Criteria Donor
ECG	Electrocardiogram
ED	Emergency Department (within HES data)
ERA	European Renal Association
ES	Effect Size
ESKD	End Stage Kidney Disease

Abbreviations and Glossary

ETT	Exercise Tolerance Test
eGFR	estimated Glomerular Filtration Rate
GN	Glomerulonephritis
HD	Haemodialysis
HES	Hospital Episode Statistics
HLA	Human Leucocyte Antigen
HR	Hazard Ratio
IMD	Index of Multiple Deprivation
IHD	Ischaemic Heart Disease
LAD	Left Anterior Descending (coronary artery)
LATE	Local Average Treatment Effect
LD	Living (kidney) Donor
LDL	Low Density Lipoprotein
LVH	Left Ventricular Hypertrophy
ICD-10	International Classification of Diseases 10th Revision
IQR	Interquartile Range
IV	Instrumental Variable
KDIGO	Kidney Disease Improving Global Outcomes
KRT	Kidney Replacement Therapy
LKD	Living Kidney Donor
MACE	Major Adverse Cardiac Event
MDRD	Modification of Diet in Renal Disease (eGFR equation)
METS	Metabolic Equivalents
MINAP	Myocardial Ischaemia National Audit Project
MPS	Myocardial Perfusion Scan
mmHg	Millimetres of Mercury (blood pressure measurement)
NIHR	National Institute for Health Research
NHS	(UK) National Health Service
NHSBT	NHS Blood and Transplant
NICE	National Institute for Health and Clinical Excellence
NPV	Negative Predictive Value
NSTEMI	Non-ST Elevation Myocardial Infarction
OP	Outpatient (within HES data)
OPCS-4	Office of Population, Censuses and Surveys Classification of Surgical Operations and Interventions 4th revision
OR	Odds Ratio
PCI	Percutaneous Coronary Intervention

PD	Peritoneal Dialysis
PKD	Polycystic Kidney Disease
pmp	Per Million Population
PN	Pyelonephritis
PPV	Positive Predictive Value
PRD	Primary Renal Diagnosis
PVD	Peripheral Vascular Disease
RCT	Randomised Control Trial
SD	Standard Deviation
SMD	Standardised Mean Difference
SPK	Simultaneous Pancreas-Kidney (Transplant)
STEMI	ST Elevation Myocardial Infarction
UKRR	UK Renal Registry

The following glossary defines statistical terms used within the main text of the thesis.

Term	Definition
Confounder	A variable that associates with both the exposure and the outcome of interest, that if not controlled for can lead to spurious associations between the exposure and outcome being observed.
Confounding by indication	Confounding that occurs because the clinical indication for selecting a certain treatment, e.g. how severe a person's illness is, also affects the outcome.
Immortal time bias	When the association between an exposure and outcome is distorted due to follow up including a period during which participants in the treatment group cannot experience the outcome and therefore essentially become immortal.
Survivor bias	A form of selection bias that would occur if only surviving/existing observations are considered, excluding those that had ceased to exist.
Propensity score	A value between 0 and 1 that summaries the likelihood of an individual receiving a treatment based on their compliment of measured covariates.
Propensity score matching	Process through which individuals in treated and untreated groups are matched to each other based on their propensity score.
Nearest neighbour matching	Matching process which identifies pairs based on them having the closest propensity scores.
Optimal matching	Matching process which aims to minimise the difference in propensity scores between pairs across the whole population.
Propensity score weighting	Technique which weights individuals based on their propensity score to create a pseudo-population with balanced measured covariates in treated and untreated groups.
Instrumental variable	A variable causally associated with the exposure, that only affects outcome through its association with that exposure, and has no common confounders with the outcome. Allows individuals to be examined based on the instrument to minimise the risk of unmeasured confounding.

Foreword

Chronic kidney disease is the reduced ability of the kidneys to remove waste products from the body. It affects 1.8 million people in the UK, and £1 of every £77 spent by the National Health Service is for the treatment of kidney disease and its associated complications. [1] At the severe end of the spectrum, people develop kidney failure and need dialysis or a kidney transplant. Kidney transplantation is associated with improved survival compared to dialysis, largely through a reduction in cardiovascular risk, [2] in addition to offering improved quality of life [3] and cost effectiveness. [4] It is therefore the recommended treatment for most people with kidney failure. [5]

Although kidney transplantation is associated with a long-term reduction in cardiovascular risk, there is an increased risk of cardiovascular events for 3 months after the transplant operation. [2] To select patients for transplant who have an acceptable peri-operative cardiovascular risk, and to try and reduce the chance of peri-transplant cardiac events, it is common practice to perform screening investigations for asymptomatic coronary artery disease prior to transplant listing. If there are concerns about coronary artery disease, revascularisation may be recommended, or patients may be determined to be too high risk to proceed with transplantation.

Although screening for coronary artery disease is recommended within clinical practice guidelines, [6] there are outstanding questions with respect to the occurrence of post-transplant cardiac events and the utility of these screening tests. This thesis aims to investigate the following:

- The rate of major adverse cardiac events following kidney transplantation in England **(Chapter 4)**.
- The association between early post-transplant cardiac events and longer-term patient and graft survival **(Chapter 4)**.
- Whether undergoing pre-transplant cardiac screening tests associates with post-transplant major adverse cardiac events **(Chapter 5)**.
- What the current pre-transplant cardiac screening practice is in the UK **(Chapter 6)**.

A clinical trial to address the utility of cardiac screening would be challenging, therefore observational research methods are used within Chapter 5. To prepare the reader for the novel work in Chapters 4-6, **Chapters 1 and 2** provide background information on CKD, cardiovascular disease, and the context for investigation for asymptomatic coronary artery disease prior to transplantation. **Chapter 3** examines the quality of the data used to examine major adverse cardiac events in subsequent chapters. The final chapter (**Chapter 7)** discusses the thesis findings.

Chapter 1: Introduction to chronic kidney disease and cardiovascular disease

This chapter describes the structure and function of the kidneys in health and the implications of loss of kidney function and resultant chronic kidney disease (CKD). The epidemiology of CKD, treatment options, and modes of kidney replacement therapy (KRT) are discussed. The risk of cardiovascular disease in patients with CKD is highlighted, and the epidemiology and management of cardiovascular disease is summarised to provide context for the thesis aims.

1.1 Structure and function of the kidneys in health

Understanding the role of the kidneys in health is key to understanding the implications of kidney dysfunction.

1.1.1 Anatomical structure of the kidneys

The kidneys are solid abdominal organs which sit in the retroperitoneal space, one on either side of the midline, measuring around 11cm in cranio-caudal length.

Each kidney contains 1-1.5 million functional units called nephrons (Figure 1.1A). Each nephron is comprised of a filter, called the glomerulus, and a renal tubule. The glomerulus is made of a network of semi-permeable capillaries which filter water and solutes (filtrate) into the urinary space. From the urinary space, filtrate passes through the renal tubule (where its composition is modified to maintain fluid and electrolyte homeostasis) until it reaches the final part of the nephron called the collecting duct. The collecting duct drains into a renal calyx, at which point the filtrate is referred to as urine. Each kidney contains several renal calyces which converge into the renal pelvis, draining urine down the ureter to the bladder.

In most people, the kidney receives its blood supply from a single renal artery, which is a direct branch of the abdominal aorta. Within the kidney, the renal artery branches into successively smaller arteries and arterioles, down to the semi-permeable capillaries of the glomerulus. The afferent arteriole supplies blood to the glomerulus where filtration occurs; from here blood flows into an efferent arteriole and into the peritubular capillaries which surround the renal tubules (Figure 1.1A). The capillaries then drain into sequentially larger veins and ultimately into the

inferior vena cava via the renal vein (Figure 1.1B). The kidneys receive 20% of the cardiac output, filtering around 1L of blood every minute.

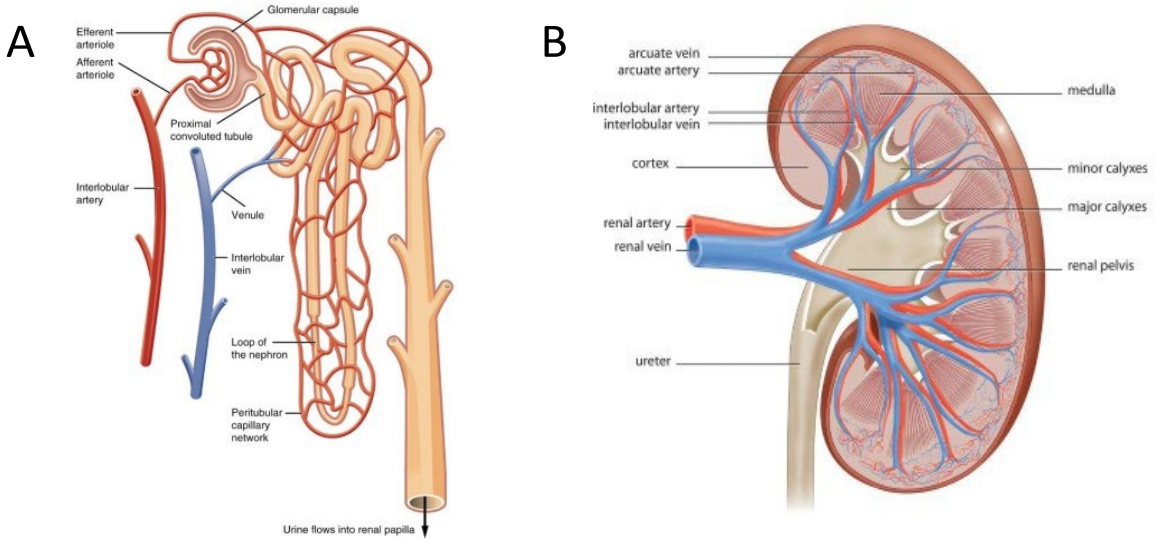


Figure 1.1. A: Structure of the nephron beginning with the glomerulus and ending with the collecting duct. B: Macroscopic structure of the kidney demonstrating the blood supply and urine drainage system. From 'Anatomy of the Kidney'. [7]

1.1.2 Physiological functions

The functions of the kidneys are wide-ranging and include: [8]

- Excretion of metabolic waste products such as urea, creatinine, and uric acid
- Water and electrolyte homeostasis
- Endocrine functions including activation of vitamin D (critical in bone-mineral metabolism), the production of erythropoietin (which promotes red blood cell production in the bone marrow) and in the regulation of blood pressure through the renin-angiotensin-aldosterone system

1.1.2.1 Water and electrolyte homeostasis and excretion of waste products

The filtrate produced at the glomerulus passes into the renal tubule. As it passes through the tubule, the constituents of the filtrate are altered: ion or electrolyte channels and transporters in each section of the tubule absorb or secrete water or electrolytes from the peritubular capillaries.

Through this process, the constituents of extracellular fluid are maintained to provide optimal conditions for cellular functioning.

1.1.2.2 Endocrine functions

The kidneys activate vitamin D (cholecalciferol) which exists in an inactivate form from dietary intake or synthesis in the skin. The first activation step occurs in the liver, where it is converted into 25-hydroxy-cholecalciferol, before being converted into 1-25-hydroxycholecalciferol by 1-alpha-hydroxylase in the kidney. Once activated as 1-25-hydroxycholecalciferol, vitamin D promotes absorption of calcium from the gut and calcium reabsorption from the renal tubule. This process is vital for maintaining calcium homeostasis and bone health.

Peritubular fibroblasts in the kidneys also produce erythropoietin in response to tissue hypoxia. Erythropoietin stimulates the bone marrow to increase red blood cell production and thus increase oxygen delivery.

Finally, the kidneys have a role in regulating blood pressure. The juxtaglomerular apparatus, situated beside the glomerulus, secretes the hormone renin in response to decreased renal perfusion pressure or reduced sodium delivery. Following a series of cleavage and activation reactions, angiotensin II is produced. Angiotensin II directly affects blood pressure through arteriolar vasoconstriction, salt and water retention, and activation of the sympathetic nervous system, and indirectly through the stimulation of aldosterone secretion from the adrenal gland. These processes maintain blood pressure. [9]

1.2 Chronic kidney disease: definition and classification

The different functions of the kidneys cannot be encompassed in a single measure. Usually, the measurement of kidney function is used to refer to 'excretory' kidney function, as the loss of this is the most immediately life-threatening. The other physiological functions of the kidneys can also be measured however through a combination of blood and urine tests.

1.2.1 Excretory kidney function

Excretory kidney function refers to the ability of the kidneys to eliminate waste products, principally the nitrogenous by-products of protein metabolism. It is measured by calculating the

volume of blood that is filtered by the glomeruli every minute, which is termed the glomerular filtration rate (GFR).

To accurately calculate GFR, there needs to be a way of measuring a substance in the blood or urine that is freely filtered at the glomerulus and is not reabsorbed or secreted in the renal tubule. This would allow the rate of excretion of this product in urine, and thus the GFR, to be calculated. The most accurate way of measuring GFR is through the administration of an exogenous filtration marker such as inulin, but this process is invasive and time-consuming and is not feasible to perform routinely. There are no endogenous substances that fit the required GFR criteria perfectly, and so in clinical practice GFR is estimated (termed 'eGFR') by measuring substances that are close to meeting these criteria, such as creatinine or cystatin C. When serum creatinine or cystatin C levels are high, this reflects reduced glomerular filtration and excretion and thus corresponds with a lower eGFR.

Creatinine is produced from the breakdown of creatine in muscle. It has potential to be a good marker of kidney function as it is freely filtered at the glomerulus, however some creatinine is secreted into the renal tubule, and creatinine production varies with muscle mass and protein intake. A person with greater muscle mass would therefore have a higher creatinine but potentially equal GFR to someone with a lower muscle mass and lower serum creatinine. The equations which calculate eGFR from serum creatinine use a person's age and sex as markers of muscle mass and aim to standardise measurements. Ethnicity has historically been included in eGFR equations as a proxy for muscle mass but was recommended to be removed in the National Institute for Health and Care Excellence (NICE) 2021 guidelines as ethnicity does not account for the genetic diversity within racial groups and could lead to inaccurate kidney function estimation particularly in individuals of Black ethnicity. [10 11]

To calculate eGFR using serum creatinine, the Modification of Diet in Renal Disease (MDRD) and Chronic Kidney Disease- Epidemiology Collaboration (CKD-EPI) formulae are commonly used. [12 13] The MDRD equation was derived from a population with kidney disease, whilst CKD-EPI was derived from the general population. The CKD-EPI formula is more accurate than the MDRD equation and is recommended by both 'Kidney Disease – Improving Global Outcomes' (KDIGO) and NICE clinical guidelines. [14 15] Both MDRD and CKD-EPI formulae adjust for body surface area and so report eGFR in ml/min/1.73m^2, where 1.73m^2 approximates to mean body surface area.

Cystatin C is a protein produced by all nucleated cells in the body and is less subject to variation by muscle mass than creatinine. [16] Additional advantages include its superiority at quantifying risk of cardiovascular disease. [17] However, it is a newer test and there are still uncertainties over the best way of using cystatin c to estimate GFR. For this reason, in clinical practice, serum creatinine is the first-line biomarker for measuring eGFR, though cystatin C is recommended in some situations to confirm the presence of chronic kidney disease (Section 1.2.5).

1.2.2 Proteinuria

The presence of protein in the urine is an important marker of kidney damage. In health, less than 200mg of total protein, or 30mg of a specific protein called albumin, should be filtered across the glomerular basement membranes and excreted in the urine each day.

Increased excretion of protein ('proteinuria') can occur in diseases of the glomerulus, tubules, or in cases of 'overflow' where there is an increased protein load reaching the glomerulus. In the early stages of kidney disease, the overall urine protein excretion may be normal but there can be increased urine albumin excretion. Even low levels of albuminuria ('microalbuminuria'), between 30-300mg/day, are strongly predictive of CKD progression and independently associate with cardiovascular disease. [18]

Urinary albumin excretion is measured using the urine albumin creatinine ratio (ACR), which standardises results by relating urine albumin concentration to overall urine concentration (by creatinine concentration). This measure is used in the classification of CKD (Section 1.2.5).

1.2.3 Endocrine functions

If the number of functional nephrons in the kidney falls, or there is fibrosis of the supporting parenchymal tissue, the kidney becomes less able to perform its endocrine functions (Section 1.1.2.2). This can result in anaemia (requiring erythropoietin administration), impaired vitamin D metabolism and bone mineral disturbance (requiring administration of activated vitamin D) and hypertension. There are clinical recommendations for the monitoring and correction of these parameters, but unlike eGFR and proteinuria these functions are not part of the classification of CKD (Section 1.2.5).

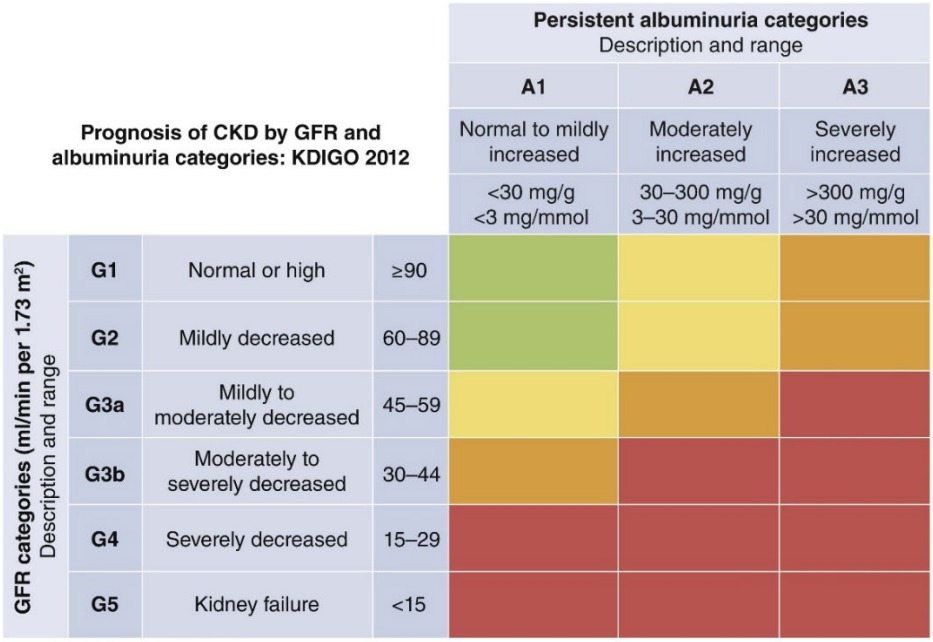
1.2.4 Definition of chronic kidney disease

The KDIGO guidelines define CKD as an "abnormality in the structure or function of the kidneys, present for at least 3 months, with implications for health". [14] Whilst an abnormality of kidney function usually refers to excretory kidney function (Section 1.2.1), other markers of kidney damage include the presence of proteinuria, urine sediment abnormalities, electrolyte abnormalities and abnormal kidney histology.

1.2.5 Classification of chronic kidney disease

Both KDIGO (international) and NICE (national) guidelines recommend that CKD is described using a risk-stratified system. This considers the level of excretory kidney function and level of proteinuria (measured by ACR) as these are most predictive of progressive decline in kidney function and cardiovascular risk. [11] [14] Excretory function is measured on a scale from G1 (best function) to G5 (worst function), and albuminuria on a scale of A1 (least albuminuria) to A3 (most albuminuria) (Figure 1.2).

For individuals with only modestly reduced excretory kidney function (eGFR 45-60ml/min/1.73m^2) using a creatinine measurement, KDIGO recommends that eGFR is also estimated using cystatin C. [14] If the eGFR calculated using cystatin C is over 60ml/min/1.73m^2 and there are no urine dipstick abnormalities, the diagnosis of CKD should not be made. As discussed in Section 1.2.1, cystatin C is not yet widely used in clinical practice due to the widespread establishment of creatinine-based equations. In this thesis, eGFR will refer to creatinine-based measurements.



Prognosis of CKD by GFR and albuminuria categories: KDIGO 2012				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30 mg/mmol
GFR categories (ml/min per 1.73 m²) Description and range	G1	Normal or high	≥90			
	G2	Mildly decreased	60–89			
	G3a	Mildly to moderately decreased	45–59			
	G3b	Moderately to severely decreased	30–44			
	G4	Severely decreased	15–29			
	G5	Kidney failure	<15			

Green, low risk (if no other markers of kidney disease, no CKD); yellow, moderately increased risk; orange, high risk; red, very high risk.

Figure 1.2. Classification of CKD and associated risk of CKD progression, end stage kidney disease and all-cause and cardiovascular mortality as per KDIGO guidelines. [14]

1.2.6 Definition of end stage kidney disease

At advanced stages of CKD, kidney replacement therapy (KRT) may need to be considered. The point at which KRT is initiated is generally considered the point of 'kidney failure'. In the UK, the mean eGFR at KRT initiation is 7-10ml/min/1.73m^2, so is lower than the upper eGFR limit of the CKD G5 category. [19] There is no universal consensus on the definition of kidney failure, though for clinical trials the KDIGO guidelines recommend it is defined as a composite of initiation of dialysis, kidney transplantation or death from kidney failure, and can include a sustained low eGFR or sustained decline in eGFR. [20] Kidney failure is commonly referred to as End Stage Kidney Disease (ESKD), but other terms include Established Kidney Failure (EKF), Established Renal Failure (ERF) and End Stage Renal Disease (ESRD). These terms are synonymous; in this thesis it will be referred to as ESKD.

1.3 Aetiology of CKD

A large range of primary kidney disorders or systemic diseases can cause CKD and are grouped into primary renal disease (PRD) categories. The European Renal Association (ERA) registry have

defined eight PRD categories which are widely adopted in registry reporting and research studies. [21] These are shown in Table 1.1, alongside the proportion of the prevalent UK KRT population with each diagnosis.

Primary renal disease	Proportion of prevalent UK KRT population (%) [19]
Glomerulonephritis (GN)	19.5
Diabetes	18.3
Other	18.2
Uncertain	14.9
Polycystic kidney disease (PKD)	10.4
Pyelonephritis (PN)	9.6
Hypertension	6.3
Renovascular disease	2.8

Table 1.1. Primary renal disease categories, and proportion of prevalent KRT patients in the UK in each category.

A kidney biopsy is the gold standard way of making a definitive diagnosis of the cause of CKD. As kidney biopsies are not risk-free procedures, they are usually only performed according to clinical need. Many people with CKD are therefore coded as having a PRD that reflects the most likely diagnosis without histological confirmation. Confirmation of PRD is useful as PRD is associated with comorbidity and survival, [22] can help family members in the case of inherited diseases, [23] and can assist counselling patients with respect to risk of post-transplant disease recurrence. [24]

1.4 Progression of CKD

The rate of decline in excretory kidney function ('CKD progression') is variable and the processes contributing to progression can be described in a 'multi-hit' model with interactions of multiple factors often unrelated to the underlying PRD. Faster progression is associated with uncontrolled hypertension (as a cause or consequence of CKD), higher levels of proteinuria, male sex, obesity, cardiovascular disease, smoking and African-American ethnicity. [25] [26] Management of modifiable risk factors forms the mainstay of CKD management including lowering blood pressure, reducing proteinuria, and treating dyslipidaemia, in addition to avoiding obesity, smoking and reducing dietary salt intake. [26] For people with certain PRDs there may be specific disease-modifying treatments, such as immunosuppression for glomerulonephritis. Usually, the above 'injuries' affect both kidneys equally such that the function of both kidneys decline in tandem with each

other. In some disease processes, such as renal artery disease, the function of one kidney may decline faster than the other.

Acute kidney injury (AKI), defined as a rapid decline in kidney function from the baseline level within 7 days, is also a risk factor for progressive CKD, ESKD and death. [27] People with comorbidities such as diabetes and heart failure are more susceptible to AKI [28] and AKI is associated with development of cardiovascular disease, [27] meaning a complex positive-feedback loop can occur in affected individuals.

At a set rate of decline in kidney function, the likelihood of reaching ESKD is also dependent on a person's age and whether ESKD will be reached before the end of their life – that is, death is a competing risk for the development of ESKD. An older person will be more likely to die of causes other than their kidney disease at a set rate of decline than a younger person, who will be more likely to reach ESKD during their lifetime. This makes estimating the likelihood of an individual reaching ESKD difficult, but new tools such as the kidney failure risk equation take the competing risk of death into account and can be helpful in clinical practice. [29]

The path to ESKD therefore varies between individuals, and depends on the number, severity, and duration of 'hits' to the kidney, PRD and the availability and use of disease-modifying treatments. Individuals with multiple risk factors are at risk of rapid CKD progression, but if risk factors can be managed it may be possible to slow the progression of CKD.

1.5 Epidemiology of CKD

Patients with CKD often don't develop symptoms until CKD has reached advanced stages (G4-G5), and even at this point symptoms tend to be non-specific such as fatigue and loss of appetite. Whilst people with risk factors for developing CKD, such as diabetes and hypertension, are recommended to undergo blood tests to investigate for the presence of CKD, [30] it is likely that there are many asymptomatic individuals with undiagnosed CKD as they have not had blood or urine tests performed. It is therefore difficult to establish the true incidence and prevalence of CKD.

Most studies estimating the prevalence of CKD across the world use eGFR as the surrogate to diagnose CKD. There is wide variation in the estimated prevalence of CKD between countries, though the global prevalence is estimated to be around 9%. [31] International variation may reflect

differences in the way GFR is estimated, but also differences in levels of obesity, smoking, genetic factors, health policy, and access to healthcare. [32]

In the UK, the prevalence of CKD in adults over the age of 18 has been estimated as 5.4%, [33] although this increases dramatically with age. [34] Up to 45% of people with CKD in the UK may be undiagnosed – either as they have never been tested or have been tested but not had a CKD code documented in their health records - and so the accuracy of these estimates is uncertain. [35] Additionally, up to 40% of individuals with a diagnosis of CKD in their health records are unaware of this diagnosis; unawareness is associated with older age, female sex, lower education level and lower (less severe) stage of CKD. [36]

Despite the high prevalence of CKD, the proportion who progress to the point of needing KRT is low. In 2019, the incidence of KRT in the UK was 151 per million population (pmp). [37] The median age at KRT initiation was 64 years (younger for South Asian and Black individuals), and there was a male preponderance despite female sex being associated more strongly with all-stage CKD. The prevalence of KRT was 1293 pmp, reflecting a rise of around 2% a year. [37] These data do not include individuals who are not known to have ESKD or who do not receive KRT.

1.6 Patient pathways in CKD

Management of CKD aims to slow or prevent progressive loss of kidney function. Whilst some individuals develop progressive CKD, most do not reach ESKD. [29] For those individuals who are anticipated to progress to ESKD, management options including KRT are discussed (Figure 1.3).

KRT comprises haemodialysis, peritoneal dialysis and kidney transplantation. Some people may be eligible for dual organ transplantation e.g. simultaneous pancreas and kidney (SPK) transplantation for people with type 1 diabetes.

The timing of KRT initiation depends on factors such as hyperkalaemia, volume overload, or symptomatic uraemia, and the point at which this is reached varies. [38] The mean eGFR at dialysis start in the UK in 2019 was 7.3ml/min/m^2, and 10.0ml/min/1.73m^2 for individuals receiving a pre-emptive kidney transplant. [37] The eGFR at pre-emptive transplantation is higher as the operation is planned to take place before the patient requires dialysis, the exact time of which can be difficult to predict. Observational data suggests that pre-emptive transplantation offers improved outcomes compared to dialysis, therefore transplantation is the recommended initial mode of KRT where possible. [39]

Many patients with progressive CKD, and all patients who receive KRT, are cared for by nephrology services. In the UK, there are 71 renal centres which look after people with CKD who are on KRT, of which 23 are also transplanting centres. If a patient's local renal centre does not perform kidney transplantation, they travel to their nearest transplant centre for the operation. Post-transplant outpatient follow up may be provided by the patient's local renal centre, or patients may have a period of outpatient follow up at the transplanting centre before transfer back to their local unit.

Maximal medical care without KRT is termed 'conservative care'. This should not be thought of as 'withdrawing' care; instead, it prioritises treatments to improve symptoms such as management of anaemia, acidosis, and fluid overload. [40] The benefit in quality and quantity of life provided by KRT falls with advancing age and rising comorbidity because of higher mortality on KRT, [41] and studies to understand who benefits from dialysis are ongoing. [42] The patients examined in this thesis were under 75 years of age and planned for KRT as opposed to conservative care, so this treatment option is not covered in detail.

The pathways through CKD and options for management of ESKD are demonstrated in Figure 1.3.

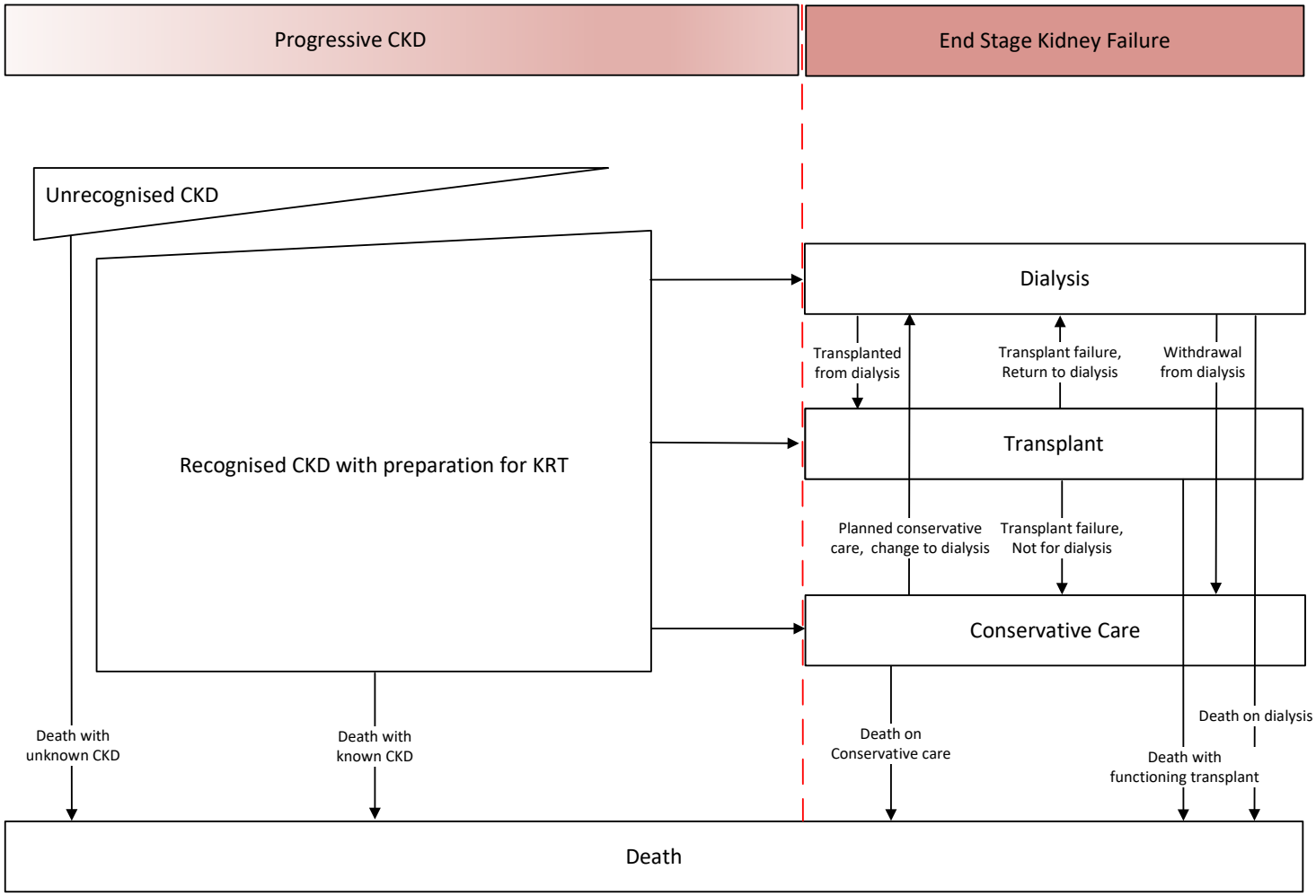


Figure 1.3. Pathways through chronic kidney disease. Adapted from thesis by Taylor. [43]

1.6.1 Haemodialysis

Haemodialysis (HD) involves exposing the blood of a patient with ESKD to an electrolyte solution ('dialysate') across a semi-permeable membrane, via a pump-driven machine. Blood and dialysate run in opposite directions, separated by the dialysis membrane, through which water and waste products pass by diffusion and convection. To achieve adequate removal of waste products and prevent the blood clotting, HD requires access to a large-calibre blood vessel which is preferentially achieved by the formation of an arterio-venous fistula, a connection between an artery and vein usually in the upper arm.

Just under 40% of prevalent KRT patients in the UK received HD in 2019. [37] Typically, HD involves 3 treatments per week each lasting around 4 hours. It is usually performed in a dialysis unit with trained nurses performing the treatment. Some patients learn to perform HD themselves and dialyse in their own home. Those who dialyse at home often undergo treatment more frequently and for longer hours e.g. overnight, which is likely to lead to improved clinical outcomes and better quality of life. [44]

1.6.2 Peritoneal dialysis

Peritoneal dialysis (PD) uses the peritoneum as the semi-permeable membrane across which water and waste products travel and is generally performed in the patient's own home. A tube called a Tenckhoff catheter is inserted into the abdomen, with one end sitting externally and the other within the pelvis, allowing dialysate to be instilled into the abdominal peritoneal cavity. Once the dialysate has been instilled, the catheter is closed to allow equilibration between serum and dialysate, and when re-opened the dialysate is drained from the peritoneal cavity. This is repeated several times a day.

PD was the mode of KRT in 5% of the prevalent UK KRT population in 2019. [37] Generally people on PD are younger and healthier than those treated with HD, and differences in clinical outcomes between modalities reflects differences in age, PRD and comorbidity. [45] When comparing only patients eligible for both modalities however there is no survival difference [46] and so unless there is a contraindication to PD the choice is patient-led.

1.6.3 Kidney transplantation

Kidney transplantation is the most prevalent mode of KRT in the UK, comprising 57% of KRT patients in 2019. [37] For most people, transplantation is the optimal recommended treatment for ESKD. Compared to dialysis, it is associated with increased survival, [2] better quality of life [3] and lower cost. [4]

Donor kidneys may be received from deceased donors, who have consented to donate their organs after death, or from living donors. There are several terms that are used to describe kidney transplants based on the type of donor, recipient, their immunological matching, and the surgical procedure. These are summarised in Table 1.2.

Donor type	Definition
DD: Deceased donors	
DBD: Donor after brainstem death	Donors with brainstem death but who have a cardiac output at organ retrieval.
DCD: Donor after cardiac death	Donors with no cardiac output at organ retrieval; retrieval occurs as soon as possible after loss of cardiac output. DCD kidneys are more prone to ischaemia reperfusion injury and delayed graft function than DBD kidneys but have comparable long term outcomes. [47]
ECD: Extended criteria donor	Donors aged over 60, or over 50 with at least 2 out of 3 of: terminal creatinine over 133µmol/L, history of hypertension or death from cerebrovascular accident. These characteristics can predict poorer transplant outcomes but still offer improved survival compared to remaining on dialysis.
LD: Living donors	Living donors are people who chose to donate one of their kidneys in a planned operation.
Directed donor	LDs who donate their kidney to a person known to them e.g. a friend or relative.
Altruistic (non-directed) donor	LD who donates to a recipient unknown to them.
Recipient factors	**Definition**
Pre-emptive transplantation	Recipient receives a transplant before starting dialysis (or receives a further kidney transplant before failure of a prior transplant).
Immunological factors	**Definition**
HLAi: HLA incompatible	If a LD and recipient are incompatible based on human leukocyte antigen (HLA) type, the transplant may proceed with enhanced immunosuppression to reduce the risk of rejection.
ABOi: ABO incompatible	If a LD and recipient are incompatible based on blood group, the transplant may proceed with enhanced immunosuppression to reduce the risk of rejection.
Paired exchange	If a LD is incompatible or poorly matched with their recipient, compatible pairs may be matched.
Procedure type	**Definition**
SPK: simultaneous pancreas and kidney transplant	For selected patients with diabetes and ESKD, SPK transplantation may be considered to also manage diabetes. Other dual organ transplants e.g. liver and kidney can also be performed.

Table 1.2. Glossary of terms used in kidney transplantation.

In the UK, deceased donor kidneys comprised 70% of kidney-alone transplants in 2019/2020 with the remaining 30% being from living donors. [48] Living donor kidney transplantation offers superior outcomes to deceased donor transplantation: the time of the operation can be planned and potentially performed pre-emptively, it allows time for desensitisation therapies to be given for immunological incompatible transplants, and kidneys are generally of better quality. Living donor transplantation is therefore associated with better graft and patient survival. [49]

Kidney transplant outcomes are better if transplantation is performed pre-emptively due to an associated reduction in cardiovascular risk, based on observational data. [39] As patients who receive a pre-emptive transplant are more likely to be of White ethnicity and of higher educational status than those who are transplanted after starting dialysis, caution is needed when extrapolating these results as selection bias may exist. [50] Both deceased and living kidney donations can occur pre-emptively; in 2019/20 21% of kidney transplants were pre-emptive. [48(p20)]

1.6.3.1 Immunological matching and the kidney sharing scheme

When a deceased or living donor kidney is offered to a recipient, the level of immunological 'match' is considered. Each person has markers on the surface of their white blood cells that identify them as 'self', called Human Leukocyte Antigens (HLA). If the HLA expressed on donor and recipient cells are the same, this reduces the risk of rejection and increases the lifespan of the organ. [51] In transplant matching, there are 3 HLA types that are most important with respect to rejection. These are HLA-A, HLA-B and HLA-DR, with 2 of each HLA antigens expressed on the cell surface (one inherited from each parent). This means the number of HLA mismatches in a donor-recipient pair ranges from 0 to 6. Having identical HLA antigens is not essential as differences does not mean rejection will occur. It is however essential to ensure the recipient does not have pre-formed sensitisation towards donor HLA that would recognise the kidney as 'foreign'. Sensitisation can develop after blood transfusions, pregnancies and with previous transplants. If the sensitisation is directed against the mismatched HLA antigens on the donated kidney i.e., donor specific sensitisation, this can lead to rapid rejection of the graft and graft failure. A crossmatch is therefore performed prior to transplantation to test for donor specific sensitisation – specifically the presence of donor specific anti-HLA antibodies. The extent of HLA sensitisation can be quantified; highly sensitised patients are those who are sensitised to 85% or more of the potential organ donor pool. [52]

If a recipient has a potential living donor, but they are incompatible due to blood group (ABO incompatible) or antibody status (HLA incompatible), they can enter the UK Living Kidney Sharing Scheme to try and find another pair which together could result in a match ('paired exchange'). As ABO and HLA compatible transplants are associated with better outcomes than incompatible transplants, [51] incompatible donor and recipient pairs are encouraged to join this scheme.

1.6.3.2 Deceased donor offering scheme

Due to the high demand for kidney transplants and limited number of deceased donors, a deceased donor kidney transplant waiting list exists to improve equity of access to transplantation and maximise the net benefit from available organs.

The data used in this thesis were collected between 2011-2013, at which time the allocation of deceased donor kidneys was done under the 2006 kidney allocation scheme. Kidneys were allocated based on a points system, with points of varying weights being awarded to potential recipients based on: [53]

- Level of immunological matching between donor and recipient (Section 1.6.3.1)
- Recipient age
- Time on the waiting list (1 point for each day from when the patient joined the waiting list)
- Donor-recipient age difference
- Geographical distance between donor organ and recipient centre
- Blood group

Kidneys from DBD donors were allocated nationally to the highest scoring patient in the UK. For kidneys from DCD donors, one kidney was allocated nationally and one regionally (to the transplant centre nearest to the donor) to allow transplantation to occur more quickly after organ retrieval, minimising the risk of ischaemic injury to kidneys that have already had a period of absent blood supply prior to retrieval (Table 1.2).

Due to the increased use of DCD kidneys and inadequacies in the age matching of donors and recipients, a new offering scheme was introduced in 2019. This scheme offers both DBD and DCD kidneys nationally, aims to improve longevity matching using donor recipient risk indices, prioritises highly sensitised patients, and counts waiting time from the earliest of either date of activation on the waiting list or start of KRT (as opposed to only counting time from date of joining the waiting list). [53]

1.6.3.3 Kidney transplant workup and listing

Patients being considered for kidney transplantation are thoroughly assessed to ensure they are likely to benefit from this treatment and to ensure there is equitable use of the finite organ donor pool. Guidance recommends potential recipients should have a life expectancy of at least 5 years with a transplant. [54] Pre-transplant assessment examines whether patients are fit to undergo major surgery, are concordant with medications given immunosuppression is needed to reduce the risk of transplant rejection, and do not have contraindications to immunosuppression such as recent malignancy or active infection. [5] Additional appointments or investigations may be required to verify these points e.g. psychology assessment to discuss periods of non-concordance, or cardiology review to establish cardiac fitness. Cardiac workup is discussed in detail in Chapter 2.

After workup is complete, patients are discussed at a multidisciplinary meeting at the transplant centre which will perform their operation. [55] This typically involves transplant nephrologists, surgeons, anaesthetists, and transplant co-ordinators and aims to ensure all necessary pre-transplant investigations have been performed, the patient is suitable for transplantation, and any special considerations for monitoring on the waitlist or in the early post-transplant period are clarified. The multidisciplinary team may ask for further investigation if there are uncertainties about suitability for transplant listing. Once a patient is deemed suitable for transplantation, they can be activated on the kidney transplant waiting list. The earliest patients should be activated on the waiting list is 6 months before they are expected to require KRT (Figure 1.4). [54] Some patients who have a planned living donor will not be activated on the deceased donor list, and instead await the time of their planned transplant surgery.

Once a patient is active on the waiting list, they may receive a deceased donor offer at any time. The average waiting time for a deceased donor organ in 2017/18 was 675 days. [52] Sometimes patients need to be temporarily suspended from the waiting list (Figure 1.4). This could be because of practical reasons, e.g. if the patient is on holiday or when transplant programmes were temporarily closed during the COVID-19 pandemic, or may relate to the development of transient health problems making transplantation unsafe. Around a third of patients who are waitlisted are suspended at least once. [52] Suspensions are associated with an increase in mortality both whilst on the waitlist and post-transplantation. [56] Patients who are suspended can be re-activated, but if a patient is thought to no longer be fit for transplantation, they are removed from the waitlist (Figure 1.4).

1. Waitlisting
A: Before being activated on the waitlist patients may need investigations such as cardiac screening tests to ensure fitness for transplantation. These may take several months to complete.

B: Pre-emptive waitlisting
Patients can be activated on the transplant waitlist 6 months before anticipated start date on dialysis.

C: Waitlisting after dialysis start
Patients can be activated on the transplant waitlist once on dialysis. In the 2019 kidney offering scheme, once activated patients accrue points from their start date on dialysis.

2. Suspensions
D: Patients may be suspended from the waitlist for personal, medical or service reasons during which time they cannot receive a transplant offer.

3. Removal from the waitlist
E: Patients may be removed from the waitlist if transplantation is no longer appropriate, which may be due to medical reasons e.g. no longer fit to receive a transplant, or due to patient preference.

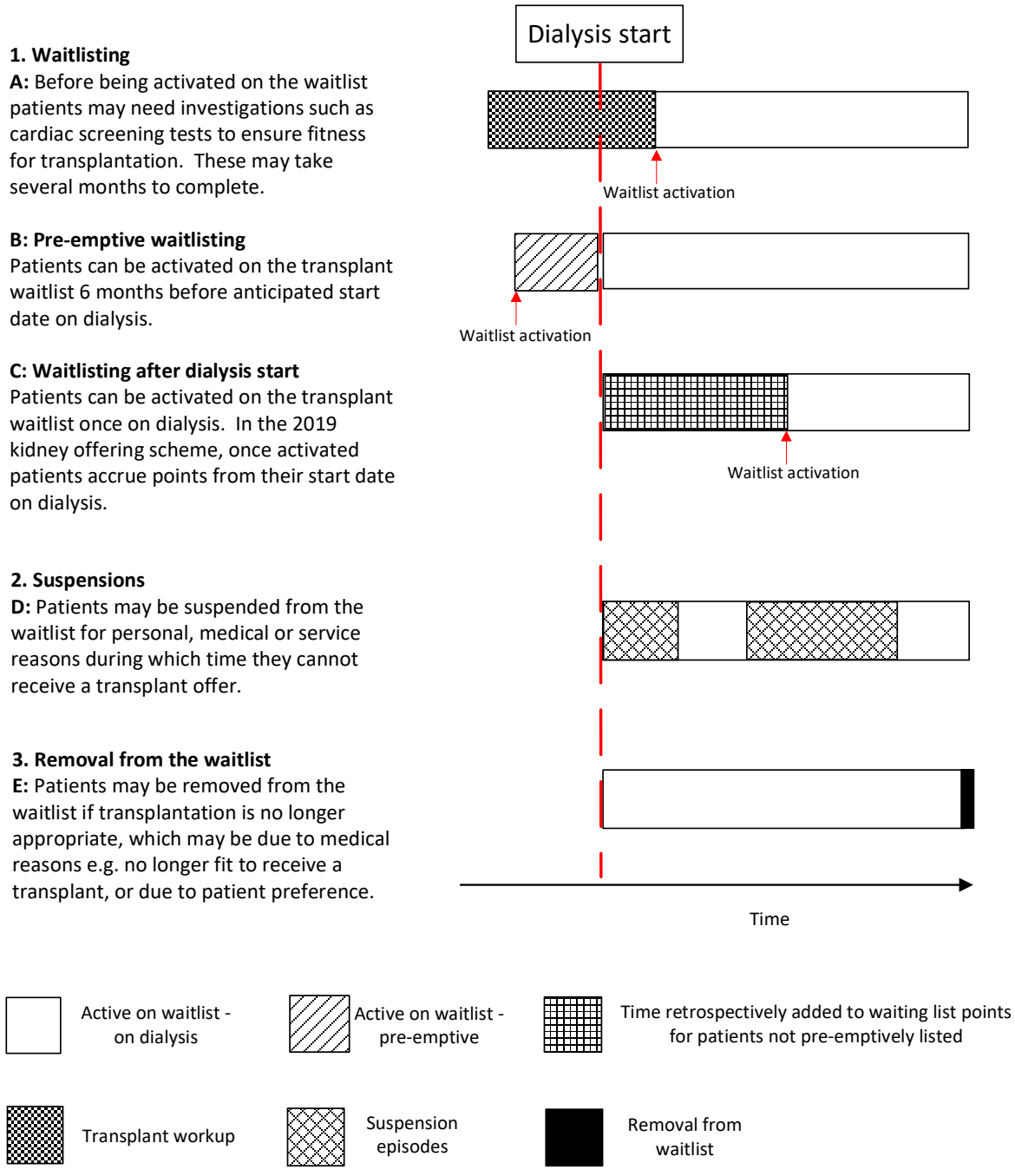


Figure 1.4. Diagram illustrating time spent on the kidney transplant waitlist.

1.7 Cardiovascular disease

Cardiovascular disease (CVD) encompasses diseases that affect the heart or blood vessels, including coronary artery disease (CAD), cerebrovascular disease (stroke and transient ischaemic attacks), peripheral vascular disease, and aortic disease. CVD is the leading cause of death in

patients with CKD, with a risk 2-16 times that of the general population. [57] Patients with CKD are more likely to develop CVD than they are to reach ESKD. [58]

This thesis focuses on CAD in patients with ESKD and so this section will specifically cover the aetiology and management of CAD, though it should be noted that cardiac disease can also manifest as disturbances of heart rhythm (arrhythmia), heart failure, or sudden cardiac death (unexpected deaths from a cardiac cause within an hour of symptom onset, or within 24 hours of last proof of life).

The pathophysiology, presentation, and treatment of CAD in the general population will first be covered, followed by the key differences in patients with CKD.

1.7.1 Anatomy of the heart

The heart is situated within the chest cavity and is made of 4 chambers which pump blood through pulmonary and systemic circulations. The heart muscle (myocardium) is supplied with blood from the right and left main coronary arteries, arising from the right and left aortic sinuses in the aorta. When the heart is relaxed (diastole), blood backflows into the aortic valve pockets and enters the coronary arteries.

The left main coronary artery (left main stem) has two branches: the left anterior descending artery (LAD) and the left circumflex artery (Figure 1.5). The LAD is the largest coronary artery, supplying 40% of the ventricular myocardium. Occlusion of this vessel can result in a major reduction in cardiac function. [59]

The right coronary artery branches to form the right marginal artery, and in 80% of people also forms the posterior interventricular artery. This system supplies the right atrium and ventricle, and the sinoatrial and atrioventricular nodes which control the electrical activity through the heart.

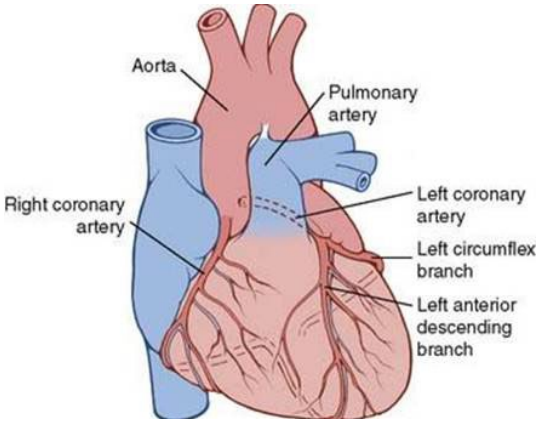


Figure 1.5. Blood supply to the heart. From Guyton and Hall Textbook of Medical Physiology. [60]

1.7.2 Pathophysiology and presentation of CAD in the general population

The cardinal feature of CAD is atherosclerotic plaques. These are characterised by thickening of the intima of vessel walls with lipid-laden macrophages and extracellular matrix, creating a 'fatty streak'. As the disease progresses, smooth muscle cells accumulate and a core of extracellular lipid develops, turning the fatty streak into an atherosclerotic plaque, which may be covered by normal intima or subsequently, a fibrous cap.

Atherosclerotic plaques cause clinical disease through limitation of blood supply. This typically presents with chest pain that initially occurs when increased myocardial oxygen supply is required e.g. during exercise. If there is plaque progression or plaque rupture, patients can experience symptoms at rest.

The clinical consequences of atherosclerosis in coronary arteries comprises stable angina (predictable chest pain precipitated by activity which resolves at rest), unstable angina (chest pain on minimal exertion or at rest without evidence of myocardial injury), and acute myocardial infarction (AMI, chest pain relating to myocardial ischaemia with evidence of myocardial injury). Together, unstable angina and AMI are termed acute coronary syndromes (ACS). AMI occurs when reduced blood supply to the heart causes muscle injury and necrosis, signified by the finding of troponin - a myocardial protein - in the blood above the 99th percentile of the upper reference limit. The diagnosis of AMI relies on a rise in troponin and at least one of: consistent symptoms, new ischaemic electrocardiogram (ECG) changes, imaging showing loss of viable myocardium, or coronary thrombus. [61] ST elevation on an ECG typically reflects complete

coronary artery occlusion due to plaque rupture, but other ECG features such as ST depression or T wave inversion can also indicate AMI. Unstable angina is distinguished from AMI by the absence of a troponin rise.

For the purposes of treatment, AMIs are broadly classified into ST elevation myocardial infarctions (STEMI; ST elevation in 2 contiguous ECG leads) and non-ST elevation myocardial infarctions (NSTEMI; ECG changes consistent with ischaemia but without ST elevation). A STEMI has a clearly defined urgent treatment pathway, usually involving angioplasty with stent insertion within 120 minutes of diagnosis. [62] NSTEMIs occur when there is a partial blockage to a coronary artery. NSTEMIs are more common, typically affect older patients with more comorbid medical conditions, [63] and have a worse prognosis than STEMIs. [64]

The classification of AMI has been further developed over the last 10 years, with additional subclassifications being based on the pathophysiological cause of ischaemia: [61]

- Type 1: occurs secondary to plaque rupture or erosion with thrombus formation.
- Type 2: occurs in situations with oxygen supply and demand mismatch, with or without superadded atherosclerosis, vasospasm, or coronary dissection (Figure 1.6).
- Type 3: occurs when there is high clinical suspicion for an ischaemic event but no biomarker evidence e.g. where a patient dies before blood tests are taken.
- Type 4: occurs in the context of percutaneous coronary intervention (PCI).
- Type 5: occurs in the context of coronary artery bypass grafting (CABG).

Distinguishing type 1 and type 2 AMI is challenging and requires a coronary angiogram to make a definitive diagnosis by identifying if occlusive thrombus is present. The management of type 1 AMI is well defined, typically involving coronary intervention (PCI or CABG), whilst the management of type 2 AMI is heterogenous with no validated treatment pathway, and outcomes remain poor for this group. [65] In people on haemodialysis, the rate of type 1 AMI is around 2.5 greater than that of type 2 AMI. [66]

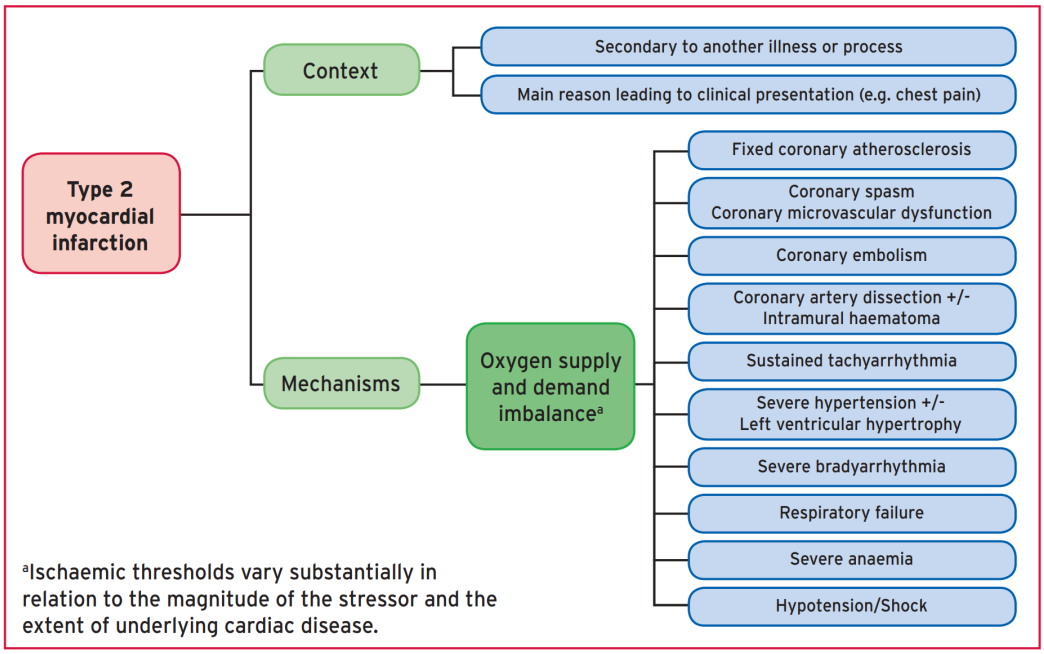


Figure 1.6. Aetiology of type 2 myocardial infarction, which is more frequently observed in individuals with CKD than the general population. From Thygesen et al. [61]

1.7.3 Risk factors for cardiovascular disease and risk prediction models

In the general population, risk factors for cardiovascular disease include modifiable lifestyle factors, modifiable physiological characteristics and non-modifiable patient characteristics (Table 1.3). [67]

Lifestyle factors	Physiological characteristics	Patient characteristics
Smoking	Hypertension	Increasing age
Excess alcohol	High LDL cholesterol	Male sex
Physical inactivity	Low HDL cholesterol	Family history of CAD
Diet high in saturated fat	Obesity	South Asian ethnicity
	Hyperglycaemia/diabetes	Social deprivation

Table 1.3. Risk factors for cardiovascular disease in the general population.

Based on these causal factors, risk prediction tools can be used to estimate a person's cardiovascular risk and inform the use of primary preventative therapy, that is, treatment to reduce the risk of developing cardiovascular disease in the first place. [68] Risk is calculated based on the presence of combinations of causal factors as these together can result in a higher risk

than a single, particularly elevated, risk factor. [69] NICE guidance recommends the QRISK2 risk calculator be used to calculate cardiovascular risk every 5 years in people over the age of 40, and those with a 10 year risk of cardiovascular disease of greater than 10% should be offered statin therapy to reduce this risk. [70]

1.7.4 Management of CAD in the general population

The management of CAD can be divided into treatments recommended for primary prevention, treatments for stable CAD (stable angina), and treatment for patients for ACS. Progression through each of these stages requires the addition of extra therapy.

As per NICE guidance, primary prevention of CAD comprises: [70]

- Lifestyle modifications, such as reducing saturated fat and salt intake, increasing physical activity, and smoking cessation
- Anti-hypertensive treatment for patients who have a blood pressure over 140/90mmHg
- Lipid-lowering therapy with a statin

For patients with established CAD but stable symptoms, management should include that given for primary prevention, with the addition of: [71]

- Aspirin, if the patient is not thought to be at increased risk of bleeding complications
- Angiotensin-converting enzyme (ACE) inhibitors for patients with stable angina and diabetes, or patients with other conditions that would recommend ACE inhibition
- Beta blockers, to be used as an anti-anginal agent
- Coronary revascularisation with PCI or CABG (depending on the burden and complexity of CAD) [72] only if symptoms cannot be adequately controlled with the above optimal medical therapy

For patients who develop ACS, treatment is as above but also includes: [73]

- Coronary revascularisation (within 2 hours from diagnosis for patients with a STEMI or within 72 hours for patients who are clinically stable with NSTEMI)
- Dual antiplatelet therapy (aspirin plus a second agent) for up to 12 months
- Aldosterone antagonists for patients with a reduced left ventricular ejection fraction
- Cardiac rehabilitation

1.7.5 Epidemiology and pathophysiology of cardiovascular disease in CKD

As discussed at the beginning of Section 1.7, patients with CKD are at a heightened risk of CVD than the general population. The increased risk of CVD begins at mildly depressed levels of kidney function (eGFR<60ml/min/1.73m^2) and increases in amplitude as CKD progresses. The highest risk occurs in people with ESKD (Figure 1.7). [74] For a given eGFR, albuminuria further increases CVD risk. [18] For patients with CKD not on KRT, the risk of developing CVD is greater than that of reaching ESKD. [58] Around 50% of patients with CKD stages 4 or 5 have known CVD. [75]

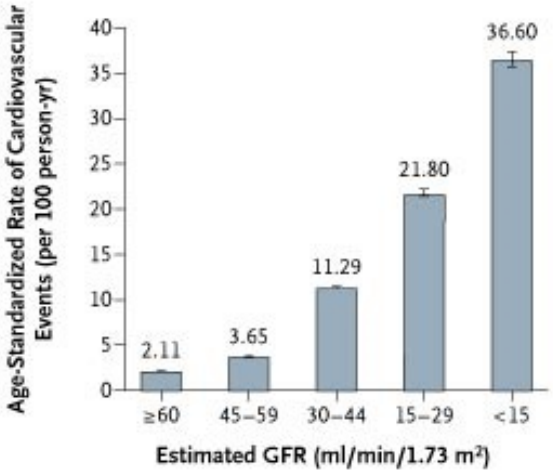


Figure 1.7. Age-standardised cardiovascular event rate according to eGFR. From Go et al. [57]

The accelerated development of CVD in CKD relates to a combination of shared risk factors such as diabetes, smoking and hypertension, [76] but also CKD-specific mechanisms. These include chronic inflammation and oxidative stress, uraemia, endothelial dysfunction, and calcium-phosphate dysregulation relating to alterations in vitamin D metabolism (Section 1.2.3) which result in the accelerated formation of atherosclerotic plaques. [77] [78] Further, in patients with ESKD, dialysis acts as a disease modifier in the development of CVD by stimulating systemic circulatory stress responses relating to haemodynamic and electrolyte shifts (Figure 1.8). [79] The pathways

that lead to CVD in patients with CKD are therefore complex, with the increased risk of CVD persisting after adjustment for traditional risk factors.

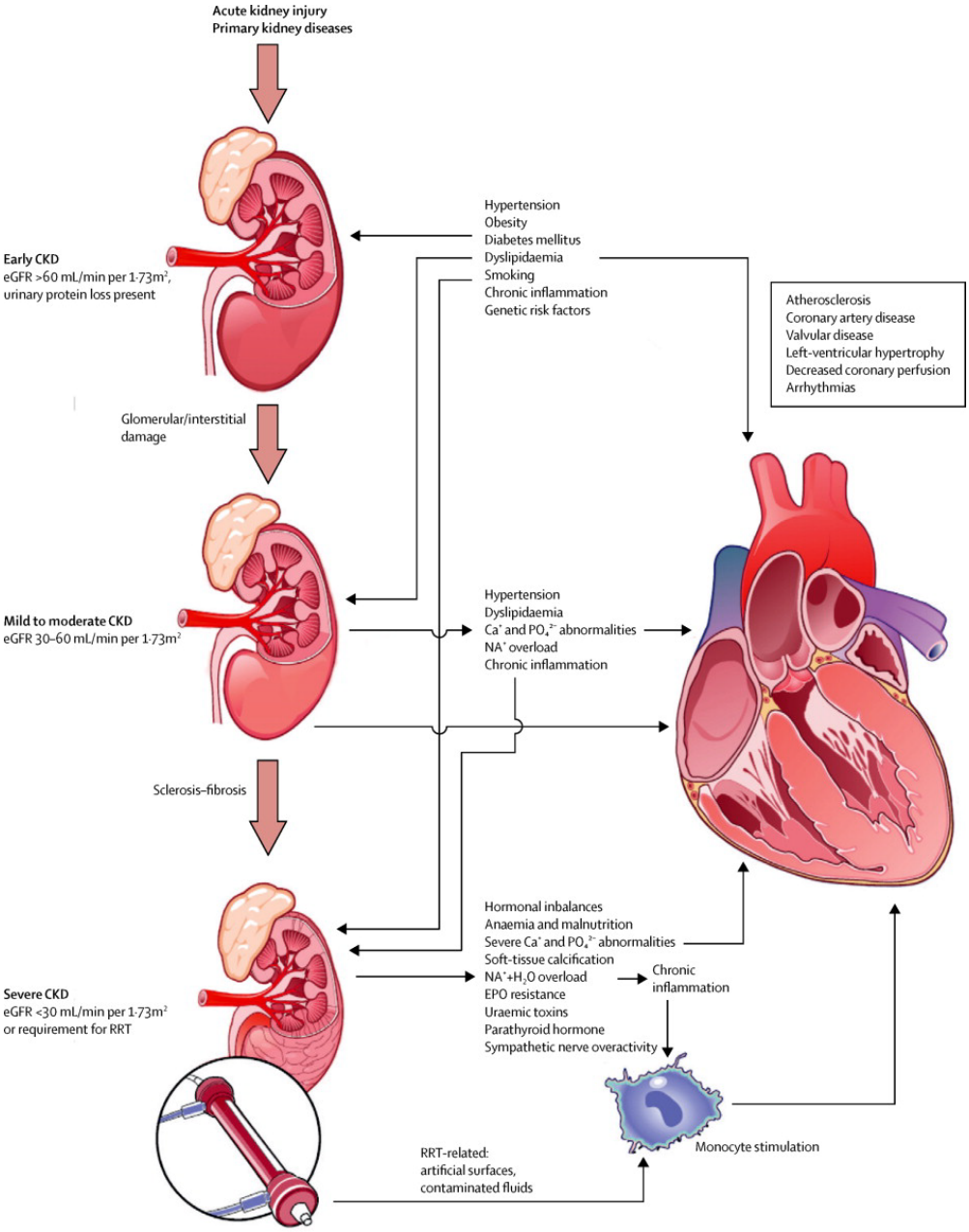
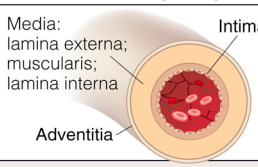
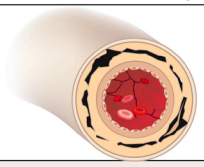
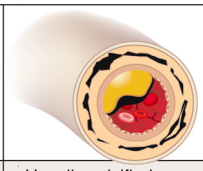
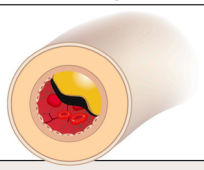


Figure 1.8. Mechanisms by which CKD and dialysis modify disease processes and contribute to end-organ damage. From Gansevoort et al. [79]

In addition to a higher prevalence of CAD compared to general populations, the pattern of CAD also differs in patients with CKD. Patients with CKD are more likely to have multi-vessel CAD, [80] with a greater proportion having triple vessel or left main stem disease than people with normal kidney function. [81] Patients with CKD also have a higher plaque burden and greater degree of

luminal narrowing. [82] Further, whilst calcification of the atherosclerotic plaque and vessel wall intima is a common finding, patients with CKD are more likely to also have calcification of the tunica media of blood vessel walls ('arteriosclerosis'; Figure 1.9). [83] Arteriosclerosis is associated with increased vascular stiffness and reduced compliance, resulting in left ventricular hypertrophy (LVH) and reduced cardiac perfusion during diastole. [84] Arteriosclerosis is difficult to detect on imaging [84] and there is no known therapy to reverse it, though the rate of progression slows after kidney transplantation. [85]

	Normal coronary artery	Chronic kidney disease–related CAD		Non–chronic kidney disease CAD
				
Intima / plaque	No calcification. No plaque. Contains normal endothelial cells.	Coronary artery without atherosclerotic plaque	Heavily calcified atherosclerotic plaque	Calcified atherosclerotic plaque
Media	No calcification. Smooth muscles organized.	Calcification present*	Calcification present	Typically no medial calcification
Effect on CAC score	No CAC on computed tomography.	Both intimal and medial calcification coexist in patients with CKD. This results in significantly higher CAC readings among patients with CKD, especially when atherosclerotic plaque is present, as compared to controls.		In patients without CKD, CAC score correlates with presence of athero-sclerotic plaque as the plaque is uniquely calcified, in comparison to the normal, noncalcified vessel wall.

*Calcification represented in black.

Figure 1.9. Coronary artery disease in people with and without CKD. From Mathew et al. [86]

Arteriosclerosis and LVH place patients at an increased risk of other cardiac diseases including arrhythmias, heart failure and sudden cardiac death. [87] These non-atherosclerotic diseases independently associate with all-cause and cardiovascular mortality beyond classical atherosclerotic processes (Figure 1.10) in patients with CKD, and sudden cardiac death is responsible for nearly 80% of cardiovascular mortality in patients on dialysis. [88] The relative contribution of non-atherosclerotic diseases to overall cardiovascular risk increases as CKD progresses. [89] The increased cardiovascular risk in patients with CKD is therefore not solely explained by a higher prevalence and severity of atheromatous CAD, but also these novel arteriosclerotic pathogenic processes.

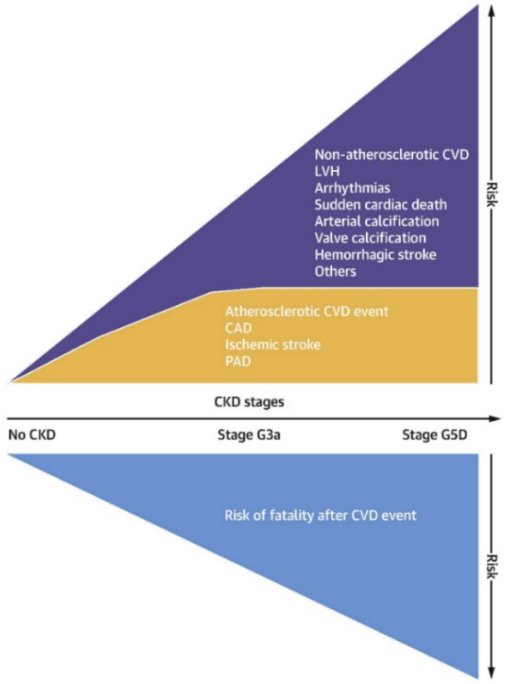


Figure 1.10. Cardiovascular risk with CKD progression. Cardiovascular risk is shown in the upper triangle, with contributions of atherosclerotic events (yellow) and nonatherosclerotic events (purple), and risk of death after CVD event (blue). From Sarnak et al. [89]

1.7.6 Presentation of CAD in patients with CKD

The presentation of CAD in patients with CKD also differs to the general population:

- Patients with CKD are more likely to have an AMI as their initial presentation of CAD as opposed to exertional angina. [90]
- Patients with CKD are more likely to present with atypical symptoms such as shortness of breath; only 44% of patients on dialysis experiencing AMI have chest pain compared to 68% of patients not on dialysis. [91] [92]
- Patients presenting with an NSTEMI as opposed to STEMI, and type 2 AMI as opposed to type 1 AMI, are more likely to have CKD. [93] This may be because supply and demand mismatch is common in patients with CKD, for example in the context of anaemia, hypotension, arrhythmia and LVH. [94] However type 1 AMI still occurs more frequently than type 2 AMI in patients with advanced CKD who are on haemodialysis. [66]
- Troponin levels are frequently elevated in the absence of ACS in people with CKD. [95] 97% of patients on HD have a troponin above the 99th centile [96] and there is no adapted

reference range for troponin in CKD. [97] Even if serial troponin measurements are stable, raised troponin remains associated with cardiovascular events and death. [98]

- The presence of LVH with strain may mask diagnostic ST segment changes on the ECG. [75]
- Likely relating to the above factors, patients on dialysis are less likely to be diagnosed with AMI on hospital admission, but are twice as likely to experience cardiac arrest and in-hospital death than general populations. [91]

Despite the increased risk of CVD in patients with CKD, these factors can make timely and accurate diagnoses of CAD-associated syndromes challenging. This may contribute to the increased morbidity and mortality of patients with CAD and CKD compared to patients with normal kidney function. [75]

1.7.7 Management of CAD in patients with CKD

The management of CAD in patients with CKD is challenged by the under-representation of these patients within clinical trials. Nearly half of contemporary trials into management of CVD excluded people with CKD. [99] Further, the lower contribution of atherosclerosis and greater contribution of arteriosclerosis to the development of CVD may reduce the success of treatments that are used in the general population (Figure 1.11).

1.7.7.1 Medical therapy

Given the high risk of CVD in CKD populations, primary prevention seems intuitively correct in this population and cardiovascular endpoints are frequently used as secondary outcomes in studies examining CKD progression. Differences to primary prevention strategies in selected patients with CKD include:

- Statins. Statins are well established in the primary prevention of CVD in non-CKD populations. [100] In patients with CKD not on dialysis, the Study of Heart and Renal Protection (SHARP) trial showed that lowering low density lipoprotein (LDL) cholesterol with simvastatin/ezetimibe reduced cardiovascular events but not mortality, [101] but no such benefit was found in patients on dialysis in two further statin trials (the 4D and AUROA studies). [102] [103] In kidney transplant recipients, fluvastatin has been shown to reduce non-fatal AMI and cardiac deaths compared with control. [104] A meta-analysis showed that as kidney function declines, the relative risk reduction for coronary events and strokes conferred by statins falls. [105] Whilst lowering LDL cholesterol is beneficial in

people with CKD not on dialysis and with a transplant, the same benefit is not seen if starting treatment in a person on dialysis. Despite the evidence for statins in patients with CKD not on dialysis, over 50% of patients with CKD in the UK are not prescribed a statin, with prescription rates varying based on comorbidities rather than stage of CKD. [106]

- Blood pressure. Blood pressure control is important for reducing progression of CKD and is a modifiable risk factor for cardiovascular disease. The Systolic Blood Pressure Intervention (SPRINT) trial showed that in patients with increased cardiovascular risk, of whom 30% had CKD not on dialysis, lowering systolic blood pressure to below 120mmHg compared to 140mmHg provided a mortality benefit but at the expense of more adverse side effects. [107] The KDIGO 2021 Clinical Practice Guideline for Management of Blood Pressure in CKD recommends a target blood pressure of below 120mmHg in patients with CKD not on KRT. [108] However it is less clear what the target blood pressure should be in patients on KRT due to the lack of clear association between hypertension and adverse cardiac outcomes.
- Sodium-glucose cotransporter 2 inhibitors have been studied in patients with an eGFR over 25ml/min/1.73m^2 and in addition to slowing the progression of CKD, they also reduce death from cardiovascular causes and hospitalisation with heart failure. [109] Results from studies examining patients with lower levels of kidney function are awaited.
- Nonsteroidal mineralocorticoid receptor antagonists reduce kidney inflammation and fibrosis. [110] These have been examined in a trial of patients with proteinuria and CKD down to an eGFR of 25ml/min/1.73m^2. The primary endpoint focused on kidney outcomes but significant reductions in the composite secondary outcome of death from cardiovascular disease, non-fatal AMI or stroke, and hospitalisation for heart failure was observed in the treatment group. [111]

For patients with CKD and AMI, optimal medical treatment with dual antiplatelets, ACE inhibitors, beta blockers and statins should be used, though these are less frequently prescribed than in patients without CKD. [112] [113]

1.7.7.2 Revascularisation

Observational studies suggest patients with CKD are less likely to undergo reperfusion therapy for AMI than patients with normal kidney function. [114] [115] A meta-analysis of patients with CKD and AMI showed that they still benefit from revascularisation, including patients on dialysis, [116] but

there is a higher rate of complications around these procedures including death, [75] bleeding [117] and AKI. [118] Whilst CABG has a higher early risk of mortality than PCI, it is associated with a lower long term risk of death (Figure 1.11). [119]

The benefit of revascularisation for CAD outwith AMI is less clear in patients with CKD. Until recently, data for management of stable CAD in patients with CKD largely came from post-hoc analyses of studies in general populations, who frequently had anatomically low risk disease, [120] with results suggesting no benefit to revascularisation over optimal medical therapy. The International Study of Comparative Health Effectiveness with Medical and Invasive Approaches-CKD (ISCHEMIA-CKD) study is covered in detail in Chapter 2 (Section 2.6.4.2). This study was much larger than previously published reports, examining 777 patients with an eGFR below 30ml/min/1.73m^2, stable symptoms and evidence of moderate to severe myocardial ischaemia on cardiac stress testing. They found no difference in cardiovascular events between those offered coronary intervention and those offered optimal medical therapy. [121]

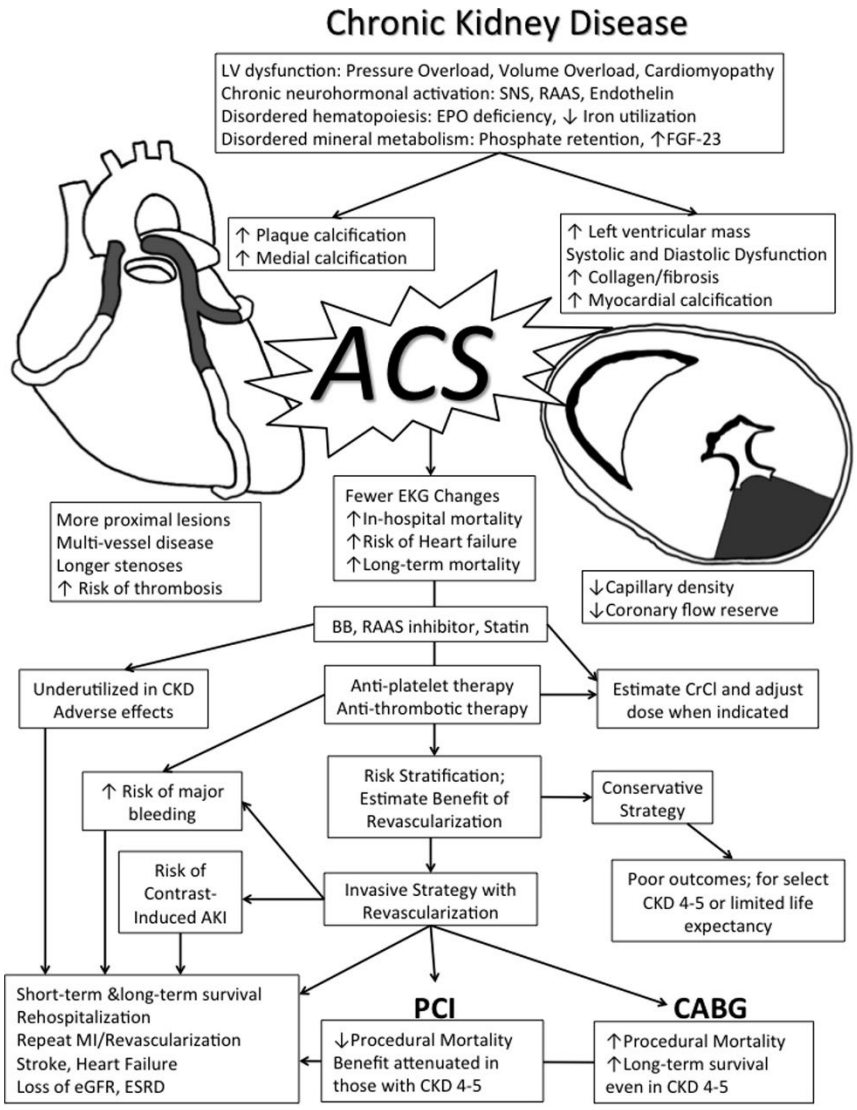


Figure 1.11. Aetiology, presentation, management, and outcomes of ACS in patients with CKD. From Roberts et al. [122]

1.7.8 Cardiovascular disease in kidney transplant recipients

Given that patients with CKD do not respond to the same treatments to reduce cardiovascular risk as people with normal kidney function (Section 1.7.4), alternative options need to be considered. For patients with ESKD, the best treatment to reduce the medium- to long-term cardiovascular risk is kidney transplantation.

The benefit with kidney transplantation has been shown in multiple studies. Two cardinal papers are those by Wolfe et al. (1999) and Meier-Kriesche et al. (2004). [2] [123] Both examined large cohorts of patients listed for kidney transplantation, and demonstrated increased cardiovascular

event rates for around 3 months post-transplant, followed by a rapid reduction in cardiac event rate and death falling below that of patients remaining on the waitlist. Wolfe et al. found equal survival was reached by 8 months post-transplant (Figure 1.12), and the long-term mortality for transplant recipients was 68% lower than in those who remained on the waiting list. [2]

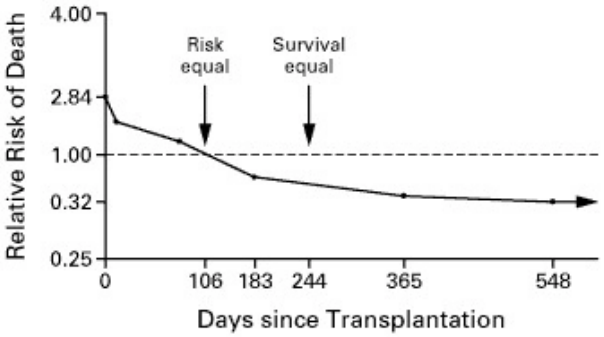


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Figure 1.12. Relative risk of death in transplant recipients relative to remaining on the waitlist, showing an increased risk of death in the first 3 months, equal survival by 8 months and improved survival thereafter. From Wolfe et al. [2]

The short term period of increased cardiovascular risk post-transplant relates to perioperative surgical and anaesthetic stress. [124] One aim of transplant workup is to identify patients likely to achieve an improvement in quality and quantity of life with a transplant and an acceptably low risk of premature death (Section 1.6.3.3), noting that early post-transplant deaths most frequently relate to cardiovascular events. [125] To achieve this aim, current practice is to consider screening for asymptomatic CAD prior to transplant listing. [126] This is covered in detail in Chapter 2.

Although long term cardiovascular outcomes are significantly better in kidney transplant recipients compared to patients on dialysis, cardiovascular risk remains elevated compared to the general population (Figure 1.13). [127] Heart disease accounts for 15% of deaths with a functioning graft, and is the fourth most common cause of death in transplant recipients after malignancy, infection and 'other' causes. [37(p23)] Transplant-specific risk factors, such as acute rejection, chronic allograft dysfunction, immunosuppression side effects and post-transplant diabetes (Figure 1.14) can accentuate traditional risk factors. [128] It is therefore still essential to implement strategies to improve cardiovascular outcomes post-transplant.

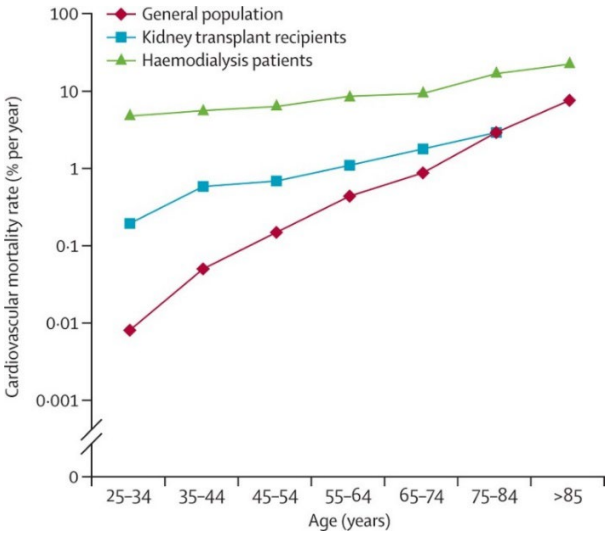


Figure 1.13. Cardiovascular mortality rate in KRT patients and the general population. From Jardine et al, [127] utilising data from Foley et al. [129] Cardiovascular mortality for kidney transplant and haemodialysis patients are taken from the United States Renal Data System, and for the general population from the US National Center for Health Statistics.

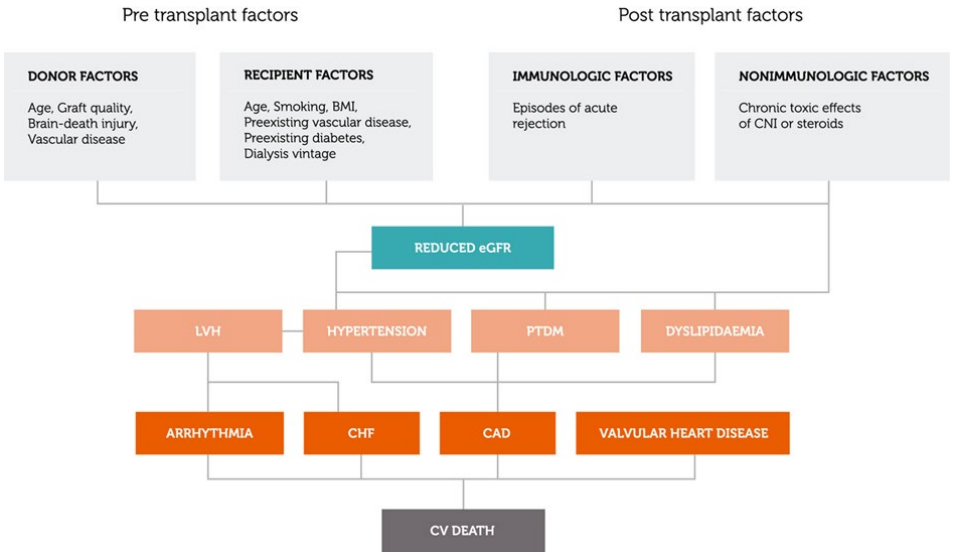


Figure 1.14. Reasons for increased cardiovascular risk in kidney transplant recipients. From Stoumpos et al. [128]

1.7.9 Cardiovascular risk estimation in patients with CKD

Cardiovascular risk calculators for general populations such as QRISK are poorly discriminative for people with CKD. They generally underestimate risk and fail to accurately identify those who experience cardiovascular events. The underestimation is not uniform so modification of equations does not create a sufficient risk prediction model. [130] Further, whilst algorithms may need adapted for early stages of CKD, entirely new models may be needed for people with ESKD due to its modification on the effect of traditional risk factors, potential for novel risk factors, and increased risk of sudden death. [131] Risk calculators for CKD populations not on dialysis have been created using data from the international Chronic Kidney Disease Prognosis Consortium [132] and in kidney transplant recipients using data from clinical trials [133] and are freely available for use.

1.8 Conclusion

This chapter describes the function of the kidneys in health, the development of CKD and treatments for ESKD including kidney transplantation. The management of cardiovascular disease in the general population and in patients with CKD is summarised.

We have established that kidney transplantation offers superior outcomes compared to dialysis, and that there is a thorough assessment before listing patients for transplantation to ensure recipient suitability and equitable use of the donor organ pool. One objective of transplant workup is to assess the cardiac risk of asymptomatic patients prior to transplant listing. Chapter 2 will outline the rationale of pre-transplant screening for asymptomatic CAD, evaluate the current evidence base, and identify the outstanding research questions that this thesis aims to address.

Chapter 2: Background to cardiac screening before kidney transplantation

2.1 Introduction

As discussed in Chapter 1, kidney transplantation is the best strategy for reducing medium- to long-term cardiovascular risk in patients with ESKD, but a short-term period of increased risk occurs around the time of the transplant operation (Figure 1.12). As peri-transplant cardiovascular events could result in premature death or graft loss, it is intuitively correct to stratify patients based on their risk of sustaining a cardiac event before listing them for a kidney transplant. However, this is challenging given the increased cardiovascular risk associated with ESKD, and fact that clinically significant CAD is frequently asymptomatic in this group of patients.

In clinical practice, it is generally accepted that potential kidney transplant candidates are screened for asymptomatic CAD prior to transplant listing to assist with cardiovascular risk stratification. [55] By identifying patients with significant CAD, screening could help select transplant candidates who have an acceptably low risk of peri-transplant cardiac events, minimising the risk of early post-transplant death and graft loss and ensuring equitable use of the deceased donor organ pool. Further, it could identify patients who benefit from interventions to reduce their cardiac risk before the transplant operation.

This chapter outlines the rationale and principles behind screening programmes and describes the evidence base when applying these principles to screening for CAD before kidney transplant listing. This leads on to a discussion of the outstanding research questions in this area, which are investigated in Chapters 3 to 6. It should be noted that the data in this chapter refers only to screening patients for asymptomatic CAD; patients with cardiac symptoms should be investigated and treated as outlined in Chapter 1.

2.2 Principles of screening and the concept of 'pre-disease'

Before examining whether screening for asymptomatic CAD in potential kidney transplant candidates is effective, it is first important to understand the general principles of screening.

Broadly, there are two public health approaches to preventing disease: [134]

- Population-based strategies: adopted when the risk factor for a condition occurs homogeneously across a population, meaning a preventative strategy can be applied to all individuals e.g. wearing a seatbelt to reduce the risk of death in a car accident.
- Risk-targeted strategies: adopted when certain individuals are more susceptible to disease, allowing preventative measures to be targeted to those at the greatest risk. High-risk strategies include screening programmes, as described in this chapter.

In screening programmes, individuals at high-risk of disease are offered investigation to identify early health problems that have not yet caused overt signs or symptoms – a period referred to as 'pre-disease'. If a person is found to have pre-disease, they are offered treatment to prevent its progression to overt disease. [135] Often the distinction between pre-disease and overt disease is arbitrary, as the disease process reflects a continuous spectrum from the early stages before it is clinically apparent (pre-disease) to the point where it starts to disrupt health (disease) and further progression in severity thereafter. [136] Ultimately, by identifying pre-disease and instigating treatment early, screening programmes aim to improve patient survival.

The principles of screening were first outlined by the World Health Organisation in 1968, [135] the key features of which are shown in Box 1.

Box 1. Principles of screening as determined by Wilson and Junger. [135]
1. The condition being screened for should be an important health problem. 2. The population being targeted should be clearly defined and access to the programme should be equitable. 3. There should be a suitable test to identify the disease. 4. The test should be acceptable to the population being targeted. 5. There should be a latent or early symptomatic stage of the disease. 6. The natural history of the condition, including progression from latent to clinical disease, should be understood. 7. There should be an accepted treatment for patients who are identified as having disease. 8. The programme should include education, testing and management. 9. Autonomy, confidentiality, and informed choice should be maintained. 10. The benefits should outweigh the risks, including patient experiences and health economics.

Whilst all these principles must be considered when designing a screening programme, for the purpose of this chapter the following four points will be discussed in more detail: [136]

1. Disease significance: the condition must be an important health problem.
2. Discriminating ability: pre-disease must be likely to develop into clinically significant disease in that person's lifespan, and the level of risk related to having pre-disease must be greater than that conferred by other risk factors.
3. Effective intervention: there must be an intervention that improves outcomes if it is given before the person becomes symptomatic.
4. Risks and benefits: the benefit of the screening process and intervention must outweigh the risks.

Screening for CAD in potential kidney transplant candidates is discussed with reference to these principles in Section 2.6.

2.3 Definitions of cardiac disease

Before discussing the aims and pathways of screening for asymptomatic CAD in kidney transplant candidates, the terms used in this, and subsequent, chapters of the thesis are first defined.

2.3.1 Asymptomatic coronary artery disease

In-keeping with published literature, asymptomatic patients refer to those who have no symptoms of CAD when completing an activity of 4 metabolic equivalents (METS), [137] roughly equal to climbing a flight of stairs. [138] The definition of coronary artery disease varies in the literature, with studies using different degrees of stenosis to reflect 'significant' disease. In this chapter, CAD will refer to a stenosis of at least 50% in a coronary artery as detected on coronary angiography, unless otherwise stated. CAD can affect a single vessel or multiple vessels. Triple vessel disease refers to the presence of a significant stenosis in all 3 major coronary arteries: the left anterior descending, left circumflex and right coronary artery.

2.3.2 Major adverse cardiac events

In studies examining cardiac outcomes, cardiac events are frequently grouped together to create a composite outcome variable termed 'Major Adverse Cardiac Events', or MACE. There is no consensus on which diagnoses constitute MACE, which differs between studies. Typically, a combination of unstable angina, AMI, coronary revascularisation, heart failure and cardiovascular death are included.

2.4 Aims of pre-transplant screening for asymptomatic CAD

The prevalence of CAD in asymptomatic patients being worked up for kidney transplantation is high: 37-53% of potential recipients have a significant stenosis in at least one coronary artery. [139] [140] [141] Further, many of these patients have high-risk lesions that are associated with the greatest mortality rates, [142] [143] with 17% having triple vessel and 5% having left main stem disease. [144] The absence of symptoms related to these lesions may relate to patients with ESKD not reaching the exercise threshold needed to induce symptoms of myocardial ischaemia, for example due to anaemia, fatigue or comorbid medical conditions, or not developing typical symptoms due to uraemic or diabetic neuropathy. [145]

In addition to the high prevalence of asymptomatic CAD, MACE occurs in 3-7% of kidney transplant recipients within the first post-transplant year, [146] [147] with the greatest incidence in the

first 3 months post-transplantation. [2] [123] Screening for asymptomatic CAD in potential transplant candidates therefore seems intuitively helpful as a risk assessment strategy.

For screening to be effective, it should identify patients with early coronary artery lesions that have not yet caused symptoms or resting myocardial damage, as represented by the yellow region of Figure 2.1, where patients with coronary lesions are identified through finding cardiac perfusion abnormalities or cardiac dysfunction on a screening test before the development of symptoms.

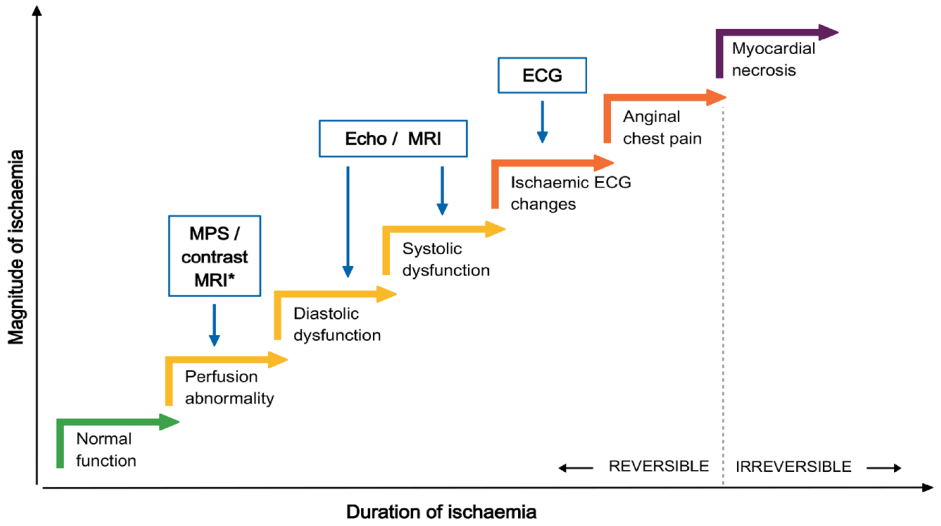


Figure 2.1. Sequence of pathophysiological events due to disrupted coronary artery blood flow. Screening aims to prevent or delay the development of cardiac events/ischaemic heart disease. Investigations (blue boxes) can identify manifestations of disrupted coronary flow at preclinical/pre-disease (yellow) and clinical/overt disease (orange/purple) zones. From Poli et al. [148]

By identifying kidney transplant patients with asymptomatic CAD, screening aims to: [137]

1. Identify <u>individual</u> patients at increased risk of cardiac events. This can allow:
    a. Counselling of patients on their risk of peri-transplant MACE.
    b. Informed decision making on donor type and timing of transplantation, aiming to reduce MACE risk by selecting the best possible transplant at the best possible time for the patient.

   c. Consideration of interventions to reduce MACE risk and its associated morbidity and mortality, such as coronary revascularisation or optimisation of medical therapy.
2. Risk-stratify the population in the potential recipient pool. This aims to select patients for transplantation who have an 'acceptable' MACE risk and exclude patients deemed too 'high' risk, thereby reducing early post-transplant death or graft loss, and ensuring maximum utility of the limited organ pool. It should however be noted that there is no consensus on what an acceptable risk is.

As optimising patient and graft outcomes and ensuring equity and utility of available organs are key aims of kidney transplant programs, [149] screening for asymptomatic CAD has been widely adopted. [150] The next section discusses CAD screening pathways, before applying the principles of screening to this scenario.

2.5 Screening pathways prior to kidney transplantation

2.5.1 Screening prior to kidney transplant listing

The assessment of peri-transplant cardiac risk is made as a patient with, or approaching, ESKD starts the workup process for transplant listing. Practice varies between transplant centres, with US studies suggesting the proportion of transplant recipients being screened by centre ranges from 11-96%, [151] with overall 46% of patients undergoing screening. [152] A 2001 US survey also highlighted this variation in practice, with 8% of centres screening all patients, and 18% screening none. [153] Whilst it is not known what proportion of patients are screened by centre in the UK, guidelines recommend using a risk stratified algorithm where a patient undergoes screening if they meet pre-determined criteria such as being over a certain age or having diabetes. [6] [139]

Screening tests can be broadly divided into non-invasive and invasive investigations, with the choice varying depending on test availability and local expertise. [154] A description of frequently performed screening tests are shown in Table 2.1. Most centres perform a non-invasive test in the first instance, such as an exercise tolerance test, dobutamine stress echocardiogram, myocardial perfusion scan or CT coronary angiogram, [55] though some go directly to an invasive coronary angiogram. [141]

Non-invasive screening tests	Description
Exercise tolerance test (ETT)	The patient is attached to an ECG monitor and exercises on a treadmill or bicycle at progressively increasing workloads as per a standardised protocol. The ECG is examined for changes suggestive of myocardial ischaemia. To be diagnostic, a heart rate of 85% of maximum predicted should be achieved. [155]
Dobutamine stress echocardiogram (DSE)	Stress echocardiograms can be performed following exercise, but more commonly medication is used to increase myocardial oxygen demand. This is most frequently dobutamine, but adenosine or dipyridamole can also be used. Following drug administration, trans-thoracic echocardiography is performed and compared to resting images to identify global cardiac dysfunction or regional wall motion abnormalities suggestive of ischaemia. [156]
Myocardial perfusion scan (MPS)	This is a nuclear medicine test which can be performed in the context of exercise or using medication to increase myocardial oxygen demand. A radioactive tracer is injected into the patient which emits gamma rays detected by a gamma-camera. The amount of tracer delivered to the myocardium is proportional to the blood supply, allowing perfusion defects to be identified. [157]
CT coronary angiogram (CTCA)	A CT coronary angiogram is a CT scan that uses intravenous contrast to examine the patency of the coronary arteries. The quality of the scan images is improved if the heart rate is slowed to 70 beats per minute or less, so patients may receive treatment with a beta blocker before the scan is performed.
Invasive screening tests	**Description**
Invasive coronary angiogram	In a coronary angiogram, a catheter is inserted into the radial or femoral artery and passed up to the heart and coronary arteries. Contrast is injected through the catheter and X-ray images are taken that show any areas of coronary artery stenosis. The procedure is usually performed under local anaesthetic.

Table 2.1. Description of non-invasive and invasive screening tests.

If the screening test suggests that patient has low risk of myocardial ischaemia, and other elements of transplant workup are satisfactory, clinical guidelines and clinician consensus recommend the patient be discussed at a multi-disciplinary listing meeting to ensure there is agreement amongst the team that they are suitable for activation on the transplant waiting list. [5] [55]

If a non-invasive screening test indicates a higher risk of myocardial ischaemia, clinical guidelines recommend the patient is referred to a cardiologist for evaluation, frequently with consideration for a coronary angiogram. [137] If CAD is confirmed, a decision is made on whether the lesion is amenable to revascularisation and, if so, whether this needs to be performed prior to transplant listing. If extensive CAD is present, the patient may be considered too high risk for transplantation.

An example CAD screening pathway is demonstrated in Figure 2.2.

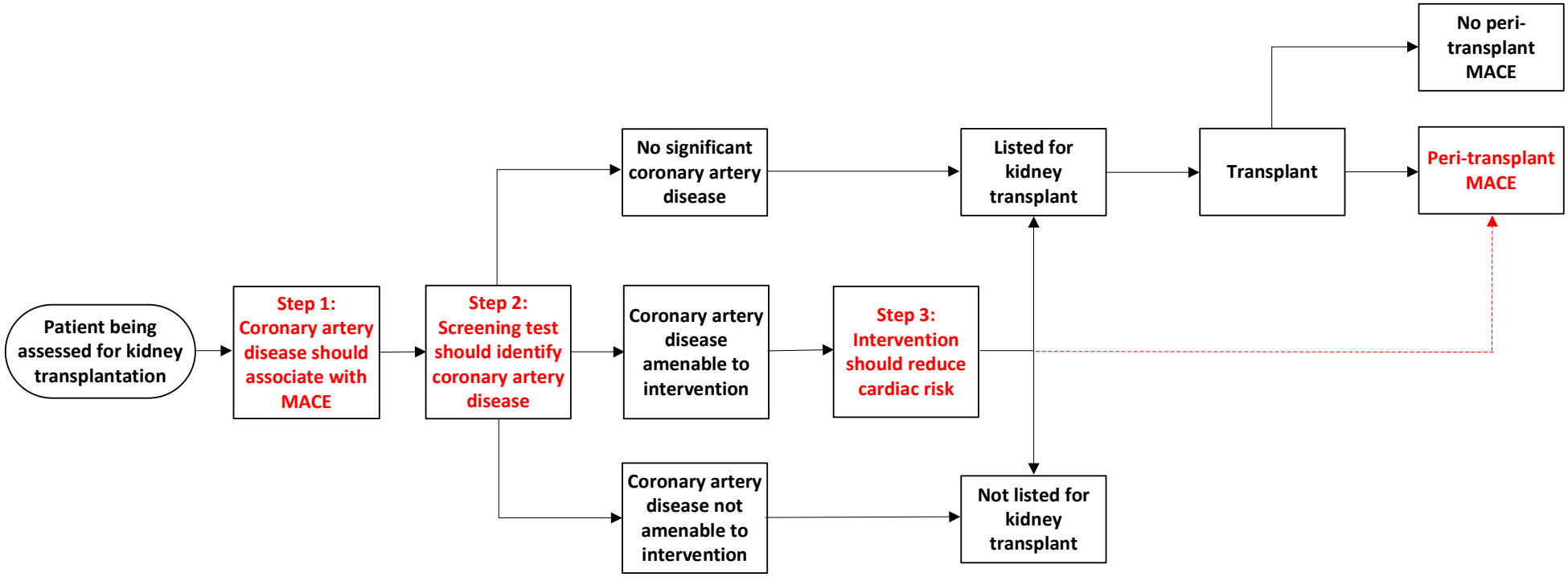


Figure 2.2. Patient pathway through CAD screening. The requirements of the screening test to reduce cardiac risk and the outcome measure of peri-transplant MACE are highlighted in red.

2.5.2 Repeated screening whilst on the waitlist

As the timing of transplantation is usually unknown (except in the case of a living kidney donor transplant), some guidelines advocate repeating screening investigations every 1-2 years whilst patients are on the waitlist to ensure they remain eligible for transplantation. [137]

The Canadian-Australasian Randomised Trial of Screening Kidney Transplants for CAD (CARSK study) is currently recruiting patients to investigate if repeated screening on the waitlist reduces MACE, with results expected in 2025. [158] This thesis examines the utility of screening to join the waitlist as opposed to repeated screening whilst on the waitlist. The data described in this chapter therefore relate to the former situation only.

2.6 Identifying asymptomatic CAD in kidney transplant candidates with reference to the principles of screening

Now the aims and pathways of screening for CAD have been described, this clinical scenario will be critically appraised with reference to four key screening principles:

1. The importance of post-transplant MACE (the disease being prevented) (Section 2.6.1)
2. The discriminating ability of asymptomatic CAD (Section 2.6.2)
3. Whether there are effective interventions to improve outcomes (Section 2.6.3 and Section 2.6.4)
4. The risk benefit balance (Section 2.6.5).

2.6.1 Disease significance

International data show the cumulative incidence of MACE in kidney transplant recipients is around 3% at 1 year and 7.5% at 5 years post-transplant, [146] with cardiovascular disease being the most common cause of death in the early post-transplant period. [125] Cardiac events, particularly in the early post-transplant period, are therefore an important health problem for kidney transplant recipients. As a comparison, colorectal cancer is the second highest cause of cancer death in the UK, and around 1% of those undergoing bowel screening require treatment for colorectal neoplasia. [159]

2.6.2 Discriminating ability

Discriminating ability refers to the likelihood of patients with asymptomatic CAD (the 'pre-disease'; Section 2.2) developing post-transplant MACE, and the strength of that association relative to other risk factors.

The multinational Patient Outcomes in Renal Transplantation (PORT) study examined 25,000 patients being assessed for kidney transplantation. It found known pre-transplant cardiovascular comorbidity to be the strongest risk factor for MACE in the first year post-transplant, with a risk 4 times that of patients without cardiovascular disease. [146]

Patients with asymptomatic CAD identified via screening are also at an increased risk of MACE compared to patients without CAD. De Lima et al. examined 535 kidney transplant recipients, 85% of whom were asymptomatic. Overall, 300 patients underwent coronary angiography prior to transplantation based on a risk-stratification algorithm. Patients with CAD had twice the risk of developing post-transplant MACE than patients without CAD, and a five times greater risk of MACE than low-risk patients not deemed to require angiography over median follow up of 3.3 years. [160] Similarly, Welsh et al. found angiographically confirmed CAD was predictive of MACE in 280 potential kidney transplant candidates with diabetes, with a risk twice that of patients without CAD. [161] Felix et al. also described a risk of MACE that was four times greater in kidney transplant recipients with underlying CAD. [162] A meta-analysis of studies examining potential kidney transplant recipients found that for every 100 patients with an abnormal coronary angiogram, an additional 22 patients experience cardiovascular death and 20 patients experience MACE compared to those with a normal angiogram. [163]

These observational studies suggest asymptomatic CAD is a key risk factor for post-transplant MACE and will progress to clinically significant disease in a relatively high proportion of patients. The discriminating ability of asymptomatic CAD is therefore likely to be met.

2.6.3 Effective tests and interventions: general populations

As there are limited data on interventions to manage asymptomatic CAD in potential kidney transplant recipients, the evidence base on interventions in the general population will be reviewed first before moving onto studies which examine patients with CKD in Section 2.6.4.

2.6.3.1 Non-invasive screening tests

The sensitivity and specificity of non-invasive screening tests at identifying angiographically confirmed coronary artery lesions in general populations are shown in Table 2.2. Higher sensitivities and specificities are found in general populations than in patients with ESKD. In the general population, abnormalities in each of these testing modalities are predictive of future MACE. [164] [165] [166]

	General population		Kidney transplant candidates	
	Sensitivity	**Specificity**	**Sensitivity**	**Specificity**
Exercise tolerance test	68% [167]	77% [167]	35% [168]	64% [168]
Stress echocardiogram	80% [169]	86% [169]	76% [170]	88% [170]
Myocardial perfusion scan	91% [171]	80% [171]	67% [170]	77% [170]
CT coronary angiogram	92% [172]	95% [172]	93% [173]	63% [173]

Table 2.2. Sensitivity and specificity of non-invasive screening tests in detecting angiographically-confirmed CAD in general populations and in kidney transplant candidates.

Two large randomised control trials (RCTs) have examined whether performing non-invasive screening tests in asymptomatic patients (not selected for the presence of CKD) can reduce the risk of MACE. The Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography (DECREASE) II study published in 2006 randomised patients undergoing vascular surgery with risk factors for CAD to receive a stress echocardiogram or no testing prior to surgery. There was no difference in the rate of cardiac death or non-fatal AMI between groups [174] but the integrity of the DECREASE trials has been questioned [175] and results should be interpreted with caution.

The Detection of Ischaemia in Asymptomatic Diabetes (DIAD) trial examined asymptomatic patients with type 2 diabetes: a cohort with increased cardiac risk akin to the CKD population. Patients were randomised to receive a myocardial perfusion scan (MPS) or normal care and followed up for a median of 4.8 years. The trial did not mandate further management in patients with an abnormal MPS, instead allowing decisions to made by their responsible clinician – a practice which closely reflects the transplant screening process. Of the 522 patients randomised to screening, abnormalities were identified in 133 patients and 31 underwent revascularisation.

Whilst having a moderate or large MPS defect was associated with higher MACE rates than those with a normal or small defect, the positive predictive value was low at just 12% and there was no significant difference in the primary outcome of cardiac death or non-fatal AMI between groups. [176] This study therefore concluded that the utility of screening asymptomatic high-risk patients (not undergoing surgery) is questionable.

2.6.3.2 Intervention: coronary revascularisation outwith surgery

Once asymptomatic CAD has been identified, the principles of screening require there to be an effective intervention to improve outcomes - in this case, coronary revascularisation. However, a systematic review and meta-analysis of 5 RCTs examining 4064 patients with reversible ischaemia on stress tests showed no difference in MACE rates between groups undergoing coronary intervention and those receiving optimal medical therapy over a median follow up of 5 years. [177]

The results of this meta-analysis are consistent with the International Study of Comparative Health Effectiveness of Medical and Invasive Approaches (ISCHEMIA) trial, published in 2020. [178] This study randomised 5179 patients with an eGFR>30ml/min/1.73m^2 and moderate or severe ischaemia on a stress test to receive coronary angiography (with or without revascularisation depending on angiography findings) or optimal medical therapy alone. They found no difference in their primary outcome - a composite of unstable angina, heart failure, AMI, resuscitated cardiac arrest or cardiovascular death – between groups over 3.2 years, and noted an increase in AMI rate around the time of angiography in patients randomised to the invasive strategy.

These studies show that in general populations, there is no strong evidence that revascularisation improves outcomes in patients with stable CAD not undergoing surgery.

2.6.3.3 Intervention: coronary revascularisation in the context of surgery

Whilst revascularisation shows no benefit to patients not undergoing surgery, it is feasible that surgical stress increases the risk of ischaemia such that prior intervention could be advantageous in a surgical setting. Surgery and anaesthesia can result in cardiac oxygen supply and demand mismatch, leading to ischaemia when there are obstructive coronary lesions, or precipitate rupture of non-obstructive coronary plaques. [179] Several RCTs have therefore been performed to

investigate whether coronary artery revascularisation in preparation for surgery reduces MACE in the peri-operative setting.

The Coronary Artery Revascularisation Prophylaxis (CARP) study is the most relevant, which recruited 510 patients at high cardiac risk based on clinical risk factors or having an abnormal stress test, who were undergoing major vascular surgery. All patients underwent pre-operative coronary angiography and those with at least a 70% stenosis in a coronary artery were randomised to undergo revascularisation or not. [180] There was no difference in peri-operative cardiac events or mortality between groups, although a post-hoc analysis showed the small group of individuals with unprotected left main stem disease benefitted from revascularisation. [181] This study excluded patients with a serum creatinine over 300µmol/L (equating to CKD stage G4/5) and therefore cannot be directly extrapolated to the ESKD population. [182]

Similarly, the DECREASE V study examined patients with ischaemia on stress testing due to undergo vascular surgery, randomising them to coronary revascularisation or optimal medical therapy. [183] No difference was found in all-cause mortality or AMI at 30 days or 1 year. They reported 20% of patients had 'renal failure' (this term was previously used synonymously with CKD, the severity of which was unspecified), but again concerns over the scientific conduct of this study mean results should be interpreted with caution. [184]

In patients without CKD, these studies suggest no benefit to intervening on CAD prior to major surgery in high-risk patients.

2.6.4 Effective tests and interventions: patients with ESKD

2.6.4.1 Non-invasive screening tests

Whilst non-invasive screening tests have reasonable sensitivities and specificities at detecting angiographically-confirmed CAD in general populations, lower accuracies are seen in kidney transplant candidates (Table 2.2). This may relate to the unique challenges in performing and interpreting these tests in patients with ESKD:

- Exercise tolerance tests. Low exercise capacity and resultant inability to achieve a diagnostic workload in patients with ESKD, alongside a high prevalence of baseline ECG

abnormalities mean diagnostic results are achieved in under 40% of transplant candidates undergoing exercise tolerance tests. [185] [186]

- Dobutamine stress echocardiogram (DSE) and myocardial perfusion scans (MPS). The lower sensitivity and specificity of DSE and MPS for detecting CAD in kidney transplant recipients may relate to the high prevalence of hypertension, LVH, and cardiomyopathy in these patients, meaning small perfusion defects are more easily missed.
- CT coronary angiogram. This investigation involves the administration of intravenous contrast, with contrast nephropathy occurring in around 12% of patients not yet on dialysis. [89] Although it has a high sensitivity for detecting coronary artery stenosis (Table 2.2), it has a lower specificity which may relate to medial vascular calcification in patients with ESKD blurring the image of the coronary lumen and making the identification of occlusive atherosclerotic disease challenging. [173]

The sensitivity and specificity of the non-invasive screening tests described above are therefore moderate in patients with ESKD, with other less-frequently adopted tests showing similar results (Figure 2.3). As such, they can only confidently predict underlying CAD when the pre-test probability is low. [187] If the pre-test probability is high (as it is in many patients with ESKD), the modest sensitivity of tests mean they have low negative predictive values. This means non-invasive screening tests could fail to identify a large proportion of patients with clinically significant CAD, resulting in patients with normal screening tests remaining at high risk of developing MACE.

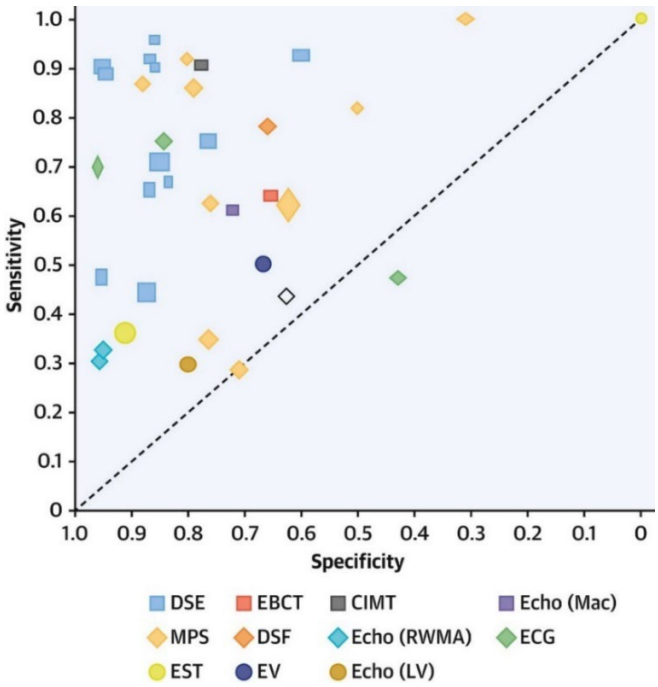


Figure 2.3. Sensitivity and specificity of non-invasive stress tests as compared to coronary angiography in kidney transplant candidates. From Sarnak et al. [89]
Abbreviations: CIMT carotid intimal medial thickness; DSE dobutamine stress echocardiography; DSF digital subtraction fluorography; EBCT electron beam computer tomography; ECG electrocardiogram; LV left ventricular dysfunction; MAC mitral annular calcification; RWMA resting wall motion abnormality; EST exercise stress electrocardiography; EV exercise ventriculography; MPS myocardial perfusion scintigraphy.

It should be noted that whilst screening tests have limited sensitivities and specificities in detecting CAD, and therefore may not help identify patients who could benefit from revascularisation, they could still assist with prognostication and risk stratification of patients before transplantation. In a meta-analysis of 52 studies comparing DSE or MPS to invasive coronary angiography in kidney transplant candidates, reversible ischaemia on non-invasive tests associated with MACE with a similar accuracy as coronary angiography. [163] This means there may be a role for screening tests in risk-stratifying patients, even if their ability to detect pre-disease is limited.

Non-invasive tests therefore have a low negative predictive value for detecting clinically significant CAD in patients with ESKD, but as test abnormalities are positively associated with MACE, they may still have a role in risk stratification of patients.

2.6.4.2 Intervention: coronary revascularisation outwith surgery

Even if non-invasive tests accurately identified CAD in patients with ESKD, it then needs to be determined if revascularisation reduces MACE in this population.

Until the 2020 publication of the ISCHEMIA-CKD trial, there were limited studies examining whether revascularisation improved outcomes in patients with stable CAD and CKD. A post-hoc analysis of the Clinical Outcomes Utilising Revascularisation and Aggressive Drug Evaluation (COURAGE) trial examined 320 patients with stable CAD and an eGFR below 60ml/min/1.73m^2 and found no difference in rate of AMI and death between those who underwent revascularisation and those who received optimal medical therapy alone. However only 5% of patients had an eGFR below 30ml/min/1.73m^2 and none were receiving KRT, so results are not directly applicable to the transplant population.[120] A meta-analysis of COURAGE alongside data from two further studies which included patients with CKD also showed no benefit of revascularisation compared to optimal medical therapy in patients with mildly depressed levels of kidney function. [188]

The ISCHEMIA-CKD study specifically examined patients with an eGFR below 30ml/min/1.73m^2, [121] recruiting 777 patients with moderate to severe ischaemia on an exercise or pharmacological stress test. Over half of patients had diabetes, over half were on dialysis, and 13% were listed for a kidney transplant. Patients were randomised to an invasive (angiography plus or minus revascularisation with optimal medical therapy) or conservative strategy (optimal medical therapy alone). No difference was found in primary outcome: a composite of all-cause death or non-fatal AMI (HR 1.01, 95% CI 0.79-1.29) or secondary outcome: all-cause death, non-fatal AMI, hospitalization with a cardiac event or resuscitated cardiac arrest (HR 1.02, 95% CI 0.79-1.29). Comparable results were seen in subgroup analyses of patients with diabetes and those on dialysis. Importantly, patients in the invasive group had an increased risk of stroke (HR 3.76, 95% CI 1.52-9.32), and increased incidence of the composite outcome of death or initiation of dialysis

(HR 1.48, 95% CI 1.04-2.11) that was largely driven by earlier dialysis initiation in the subset of pre-emptive patients assigned to this strategy. [121]

A post-hoc analysis of the 194 patients listed for kidney transplantation in ISCHAEMIA-CKD (who were younger and less comorbid than the overall cohort) found nearly a third of patients had a MACE event over 2.4 years of follow up, but similarly there was no difference in outcomes between invasive and conservative approaches. [189] It should be noted however that half of kidney transplant candidates assigned to the invasive approach were not revascularised, most frequently due to no obstructive lesions being found on angiography, and 20% of patients in the conservative group underwent off-protocol angiography, which may limit the power of this subgroup analysis. [189] One proposed explanation for the high frequency of off-protocol angiography was clinician anxiety around transplanting patients without coronary intervention.

Whilst ISCHEMIA-CKD has advantages over other trials due to its specific focus on patients with CKD, large sample size and randomised study design, limitations should be acknowledged:

- Only 50% of patients in the invasive treatment group underwent revascularisation – a lower proportion than in the main ISCHAEMIA trial (approximately 80%) [178] and what may be expected in real-world medicine.
- Of the patients randomised to the invasive strategy who did not undergo revascularisation, 75% had non-obstructive CAD, suggesting that stress tests did not adequately detect clinically significant coronary lesions (in-keeping with the evidence outlined in Section 2.6.4.1).
- Patients were excluded if they had known unprotected left main stem disease (stenosis over 50%), a left ventricular ejection fraction below 35%, heart failure with a New York Heart Association class III-IV, ACS within 2 months, revascularisation within 12 months or an unacceptable level of angina. Heart failure is common in patients on dialysis [190] and concern over asymptomatic left main stem disease may result in anxiety about directly extrapolating these results to potential transplant candidates.
- Patients in the invasive arm had a marginally longer median dialysis duration (3 years, IQR 1-6) then those in the conservative arm (2 years, IQR 1-4). Time on dialysis correlates with mortality, and patients with a longer duration of ESKD are at higher risk of non-

atherosclerotic coronary disease [89] which is not treated by revascularisation and therefore could mask a potential treatment benefit.

- The patients in this study did not undergo surgery, so it is not known if outcomes would differ in this context.

This trial on its own is therefore insufficient to change pre-transplant CAD screening practice.

2.6.4.3 Intervention: coronary revascularisation in the context of major surgery

The only randomised control trial examining the effect of revascularisation on peri-transplant MACE was performed in 1992. This study included 26 transplant candidates with insulin-dependent diabetes who had stable symptoms, a stenosis of over 75% in one or more coronary artery and an ejection fraction over 35%. The study was stopped early after a median follow up of 8 months due to a higher rate of peri-transplant MACE in the non-revascularised group. However, medical management differed to current practice with low use of beta blockers, statins and aspirin, and high use of short-acting calcium channel blockers. This, along with the very small study population, mean the current applicability of this study is questionable. [191]

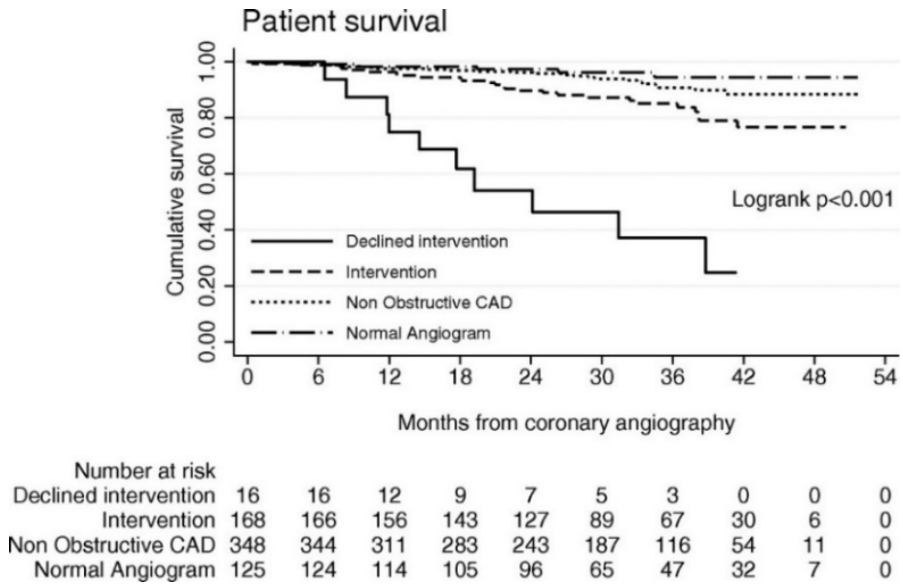
The remaining data on the association between pre-kidney transplant revascularisation and MACE comes from observational studies. These studies have inherent issues with confounding as patients who meet criteria for revascularisation have, by definition, underlying CAD, and therefore are at higher risk of MACE than those without CAD, and frequently are from single-centre reports. Such studies do however provide data on the proportion of patients undergoing revascularisation and allow crude survival rates to be compared between groups. A summary of selected studies is shown in Table 2.3, which compares the outcomes of patients found to have CAD undergoing revascularisation versus medical therapy.

Three UK transplant centres have published their screening experiences. Kumar et al. reported on the experience at Hammersmith transplant centre in 2011. Coronary angiography was recommended to all potential kidney transplant recipients over the age of 50, or with diabetes, cardiac symptoms, or ischaemic ECG changes. [141] Based on these criteria, 50% of transplant candidates underwent an angiogram, of whom 28% (14% of the whole cohort) were offered revascularisation. Of those undergoing angiography, 87% were deemed fit for transplantation. For the patients not listed, the reason for transplant preclusion was recorded as inability to

revascularise CAD in only 3.5% of unlisted patients, whilst 9.5% were due to a left ventricular ejection fraction below 30%, and 19.0% were due to patients declining revascularisation, with the remaining reasons being non-cardiac in nature.

Following angiography, all patients had high survival rates apart from the small group (n=16) who declined revascularisation and were therefore not waitlisted or transplanted (Figure 2.4). As the patients undergoing angiography were by default 'higher risk', the high survival rate may provide support for this proactive approach. However, the following points should also be noted:

- The patients who declined intervention were not listed for transplantation, and so would be expected to have poorer survival than the groups containing patients who received a transplant. Further, declining revascularisation may be a marker for poorer underlying health.
- 30% of patients had cardiac symptoms (thus not satisfying the criteria for asymptomatic screening) and it is not known whether the outcomes in this subgroup differed.
- This centre had easy access to coronary angiography and allowed rapid waitlisting after intervention (within 4-6 months if patients received clopidogrel, and within 5 weeks if a bare metal stent was used). This rapidity of intervention is not likely to be replicable across other UK centres.
- The patient and graft survival of transplant recipients from this centre are comparable to others with less aggressive screening strategies. [48]
- They note an increase in rate of coronary events post-revascularisation, but do not provide further information on this.



Number at risk										
Declined intervention	16	16	12	9	7	5	3	0	0	0
Intervention	168	166	156	143	127	89	67	30	6	0
Non Obstructive CAD	348	344	311	283	243	187	116	54	11	0
Normal Angiogram	125	124	114	105	96	65	47	32	7	0

Figure 2.4. Patient survival by subgroup based on angiogram findings. From Kumar et al. [141]

Other studies have been less supportive of such an invasive approach to screening. Glasgow transplant centre reported their experience in 2008. [186] They performed coronary angiography in kidney transplant candidates subjectively deemed to be at high cardiac risk. This resulted in a third of transplant candidates undergoing angiography, but only 17.2% of these (5.6% of the total cohort) required revascularisation. There was no difference in survival between patients who did not undergo angiography, patients who underwent angiography without intervention, and patients who underwent angiography with revascularisation (Figure 2.5). Whilst this study suggests no benefit of angiography and revascularisation, the results of their non-invasive screening tests (walking duration on an exercise tolerance test) did associate with survival, and so they suggest screening could still be used to risk-stratify patients and select those who could benefit from transplantation.

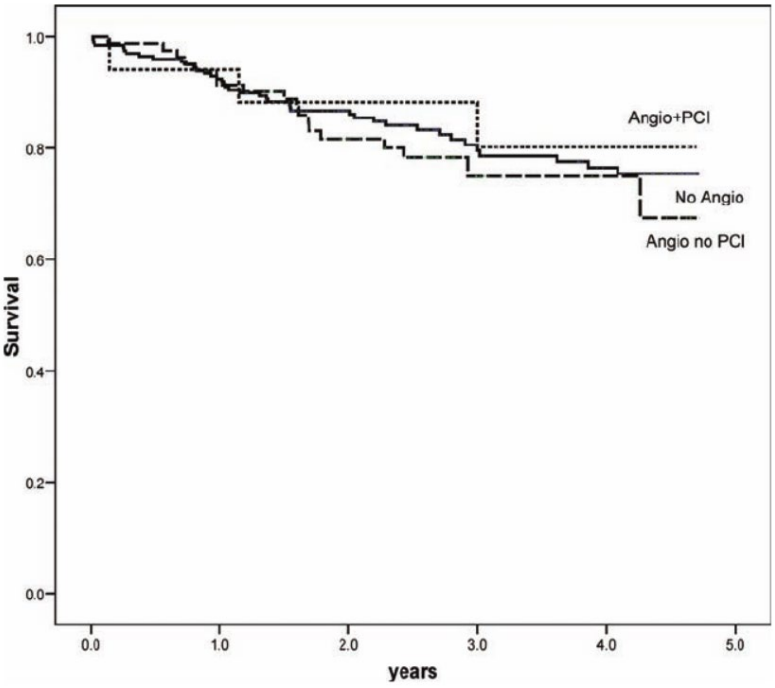


Figure 2.5. Kaplan–Meier curves comparing patients who had no angiography (solid line), angiography and no intervention (thick dashed line), and angiography and intervention (fine dashed line), with no difference in survival between groups. From Patel et al. [186]

Similarly low rates of coronary intervention after angiography were reported by Manchester transplant centre in 2020. [192] They performed non-invasive screening tests based on a risk-stratified protocol that saw 72% of potential transplant candidates being tested. Of those patients undergoing screening tests, 23% had an abnormality and 50% of these proceeded to angiography. However only 11% of patients undergoing angiography underwent revascularisation (2% of all waitlisted patients) and only 5 patients (0.5% of the total cohort) had multivessel CAD that precluded transplant listing. All patients requiring revascularisation had a history of diabetes or prior CVD, thus screening did not alter management in patients without these comorbidities and only influenced management in 5% of patients with diabetes or CVD. No difference in survival between patients who had normal and abnormal screening investigations were noted in this study.

An estimated example of the potential outcomes from screening based on the studies by Kumar et al, [141] Patel et al. [186] and Kanigicherla et al. [192] is shown in Figure 2.6.

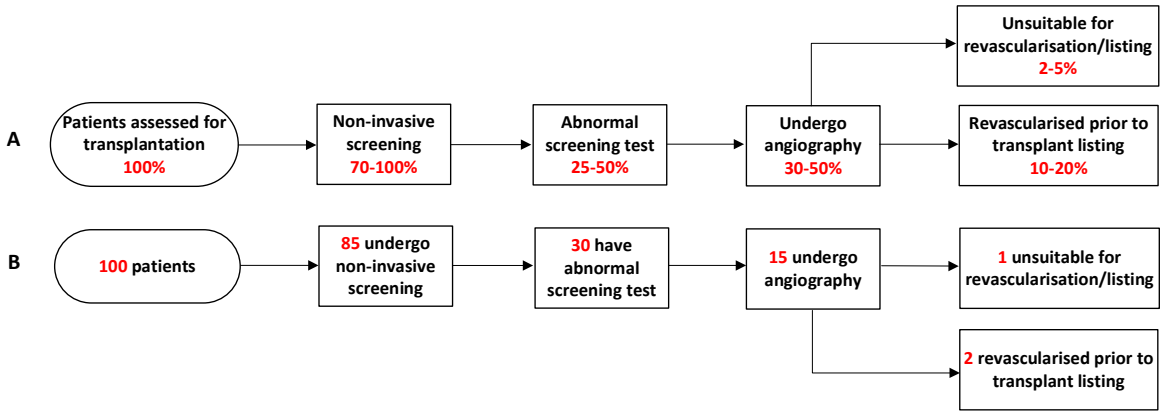


Figure 2.6. A: Estimated proportion of patients at each stage of the screening process based on UK observational data. B: Example of screening outcomes using a random sample of 100 transplant candidates based on the proportions estimated in (A).

Contrary to these studies, which suggest minimal gain to revascularisation, other observational studies have suggested some benefit. A US study examining 1460 transplant recipients found no difference in survival at 5 years post-transplant in those who had non-obstructive CAD on angiography and those who were revascularised (HR 1.24, 95% CI 0.51-3.01), but patients with medically managed obstructive CAD had higher mortality than those who were revascularised (HR 3.79, 95% CI 1.32-10.90). [193] A further US study examining 3698 potential transplant candidates found revascularisation improved survival but only in patients with triple vessel disease. [194] Finally, de Lima et al. reported on the outcomes of the 136 patients who had CAD on pre-transplant angiography and subsequently underwent transplantation, and whilst they found no difference in all-cause mortality between the 49 patients receiving revascularisation and 87 patients who received medical therapy, there was a trend towards reduced cardiac-event free survival in the medically managed group (HR 0.41, 95% CI 0.15-1.08) (Table 2.3). [160]

These data suggest there could be a benefit with revascularisation in selected patients prior to kidney transplantation, but ultimately are inconclusive.

Study	Herzog et al. [189]	Manske et al. [191]	Patel et al. [186]	Kumar et al. [141]	Kahn et al. [193]	De Lima et al. [160]
Sample size	194	26	34	532	212	136
Date published	2021	1992	2008	2011	2011	2016
Location	USA	USA	UK (single centre)	UK (single centre)	USA	Brazil
Design	RCT	RCT	Observational	Observational	Observational	Observational
Population	Kidney transplant candidates	Kidney transplant recipients	Kidney transplant candidates	Kidney transplant candidates	Kidney transplant recipients	Kidney transplant recipients
Inclusion criteria	Moderate-severe ischaemia on stress test	Coronary artery stenosis deemed haemodynamically significant on angiography	≥75% coronary artery stenosis on angiography	Coronary artery atheroma on angiography	≥70% coronary artery stenosis on angiography	≥70% coronary artery stenosis on angiography
Comparison	Invasive vs. conservative	Revascularisation vs. medical	Revascularisation vs. medical	Revascularisation vs. medical	Revascularisation vs. medical	Revascularisation vs. medical
Endpoint	AMI, all-cause death	Unstable angina, AMI, cardiac death	All-cause death	All-cause death	All-cause death	Coronary event-free survival
Follow up	3 years	8.4 months	2.6 years	30 months	2.9 years	3.3 years
Endpoint timings	Both pre- and post-transplant	Post-transplant	Both pre- and post-transplant	Both pre- and post-transplant	Post-transplant	Post-transplant
Findings	No difference in primary outcome (HR 0.91; 95% CI 0.54-1.54).	10/13 medical and 2/13 revascularised patients experienced an endpoint (p<0.01).	2/13 revascularised and 11/21 medically treated patients died, but transplant listing differed between groups.	Lower risk of death if lower risk angiographic findings vs. revascularisation (p=0.005)	Medical management associated higher mortality vs. revascularisation (HR 4.54; 95% CI 1.78–11.59).	Revascularisation associated with a non-significant reduction in post-transplant MACE (p=0.06).

Table 2.3. Table summarising selected studies examining outcomes in patients with CAD undergoing coronary angiography (+/- revascularisation) versus optimal medical therapy prior to kidney transplantation. The sample sizes reflect the number of kidney transplant candidates with CAD who received the treatment or control in each study rather than the number of patients in each overall study cohort. There is risk of negative confounding in these observational studies, as patients undergoing revascularisation may have more severe disease than those not proceeding to revascularisation.

2.6.5 Risks and benefits

Whilst the studies discussed above are aimed at identifying the benefits related to screening, there are also several risks, many of which are unquantified. These include:

- Exposure to ionising radiation. A coronary angiogram has a radiation dose around 100 times that of a chest X-ray. [195] The International Commission on Radiological Protection states the benefits of radiation exposure should outweigh the risks, [196] with the risk of malignancy with radiation exposure in particular being noted in younger patients and women. [195]
- Contrast nephropathy. CT and invasive coronary angiography require the administration of intravenous or intra-arterial contrast and come with an associated risk of contrast nephropathy. This may not be of clinical significance to patients already on dialysis but is relevant for pre-dialysis patients who could experience a potentially irreversible reduction in kidney function following the procedure. [89] The ISCHEMIA-CKD study reported an increase in the composite outcome of death or initiation of dialysis in patients who underwent coronary angiography. [121] It is good practice to minimise contrast load and the associated risk of contrast nephropathy by using low or iso-osmolar contrast agents when imaging is required. [197]
- Delays to activation on the transplant waitlist. A single-centre study at Manchester transplant centre showed that patients who required a screening test took longer to be activated on the waitlist from point of initial assessment, and those with an abnormal screening test took longer to be listed than those with a normal screening test (5.5 months for patients not requiring a screening test, 6.9 months for those with a normal screening test and 9.9 months for those with an abnormal screening test). [192] This may relate to waiting time for tests to be performed, and cardiology review if tests are abnormal. If patients require coronary angiography or intervention, delays may be more significant. The 2014 American College of Cardiology/American Heart Association guidelines recommend avoiding elective non-cardiac surgery for 1 year after implantation of a drug-eluting stent, and 30 days after a bare metal stent if dual antiplatelet medication needs to be stopped perioperatively. [198] Generally dual antiplatelet therapy is a contraindication to transplantation due to risks of bleeding intra-operatively or with

post-transplant kidney biopsies. [199] Screening tests and particularly revascularisation may therefore delay listing and could prevent pre-emptive transplantation.

- Morbidity and mortality relating to revascularisation procedures. Complications relating to revascularisation procedures include post-intervention coronary events [141] and increased risk of stroke. [121] Patients with ESKD have increased mortality with revascularisation procedures compared to the general population (2 year mortality of 12% vs. 0.6% following drug-eluting stent insertion, and in-hospital mortality of 5.4% vs. 1.8% following a CABG) so appropriate counselling of patients is needed. [200]
- Potential psychological burden to patients, with extra hospital visits and delays to listing.
- Inappropriately precluding transplantation for populations who may still benefit. Patients with severe CAD (2 vessel stenoses of over 50%) can still benefit from transplantation compared to remaining on the waitlist. [201] Caution needs to be taken to not exclude patients from transplantation who could benefit.

2.7 Clinical guidelines

Despite the limited evidence behind screening for asymptomatic CAD, screening is embedded within clinical practice. [6] [137] The lack of conclusive evidence however has resulted in inconsistencies between clinical guidelines. Whilst all guidelines recommend screening high risk patients based on the presence of risk factors with an initial non-invasive test (Table 2.4), there is no consensus on what combination of risk factors should trigger screening, which screening investigation should be used, and what further management should be undertaken in the event of a positive stress test. One study reported that by applying available guidelines to their population of transplant candidates, the proportion of patients requiring screening ranged from 20% to 100%. [150]

The most recent international guidelines are from KDIGO and were published in 2020. [6] This document differs from its more historic counterparts in that it does not recommend revascularisation exclusively to reduce perioperative cardiac events, nor excluding potential candidates with asymptomatic CAD from transplantation unless they have advanced triple vessel disease. They emphasise the importance of symptomatic individuals being reviewed by a cardiologist, ideally with a specialist interest in CKD given these patients are frequently excluded

from cardiac clinical trials. [6] This suggests a move away from routinely offering revascularisation, driven by the results from the ISCHEMIA-CKD study. [121]

Guideline	Publication year	Recommendation	Level of evidence
Kidney Disease: Improving Global Outcomes (KDIGO) [6]	2020	Evaluate all candidates for the presence and severity of cardiac disease with history, physical examination, and ECG.	Not Graded
		Patients with signs or symptoms of active cardiac disease e.g. angina, arrhythmia, heart failure, symptomatic valvular heart disease should undergo assessment by a cardiologist and managed according to current local cardiac guidelines prior to further consideration for a kidney transplant.	Not Graded
		We suggest that asymptomatic candidates at high risk for CAD e.g. diabetes, previous CAD or with poor functional capacity undergo non-invasive CAD screening.	2C
		We recommend that asymptomatic candidates with known CAD not be revascularised exclusively to reduce perioperative cardiac events.	1B
		We suggest that patients with asymptomatic, advanced triple vessel coronary disease be excluded from kidney transplantation unless they have an estimated survival which is acceptable according to national standards.	2D
European Renal Best Practice (ERBP) [202]	2015	We recommend that basic clinical data, physical examination, resting ECG and chest X-ray are sufficient standard work-up in asymptomatic low-risk transplant candidates.	1C
		We recommend performing a standard exercise tolerance test and cardiac ultrasound in asymptomatic high-risk patients (older age, diabetes, history of cardiovascular disease). In patients with a negative test, further cardiac screening is not indicated.	1C
		We recommend performing further cardiac investigation for occult coronary artery disease with non-invasive stress imaging in kidney transplant candidates with high risk and a positive or inconclusive exercise tolerance test.	1C

Guideline	Publication year	Recommendation	Level of evidence
		We recommend performing coronary angiography in kidney transplant candidates with a positive test for cardiac ischaemia. Further management should be according to the current cardiovascular guidelines.	1D
Caring for Australasians with Renal Impairment (CARI) [203]	2013	We recommend that all candidates for kidney transplant are screened for cardiovascular risk factors. Indicators of high risk include older age, diabetes mellitus, abnormal echocardiogram, previous ischaemic heart disease or congestive heart failure, increased duration of dialysis, smoker. We suggest that kidney transplant candidates with a low clinical risk of cardiovascular disease do not require stress testing for coronary artery disease. We suggest that kidney transplant candidates with a moderate or high clinical risk of cardiovascular disease undergo cardiac stress testing prior to transplantation. The following should be noted: • Exercise ECG has a poor predictive value in patients on dialysis. • Cardiac stress tests are predictive of significant coronary artery disease and major cardiac events in patients with higher clinical risk. Where possible we recommend testing be performed without concurrent b-blocker. • As the prognostic accuracy of cardiac stress testing is of limited duration, it is suggested that testing be repeated in high-risk patients. The interval at which testing should take place has not been well defined; however, the predictive value of a positive test diminishes after 24 months. We recommend that coronary angiography be considered for kidney transplant candidates with abnormalities on screening procedures.	1B 2B 2B 2B 1B 2C 1B

Guideline	Publication year	Recommendation	Level of evidence
		We suggest that the benefit of revascularisation prior to transplantation be reviewed on an individual basis.	2C
American Heart Association/American College of Cardiology Federation (AHA/ACCF) [137]	2012	Non-invasive stress testing may be considered in kidney transplantation candidates with no active cardiac conditions in the presence of multiple CAD risk factors regardless of functional status. Relevant risk factors include diabetes, prior cardiovascular disease, >1 y on dialysis, LV hypertrophy, age >60 y, smoking, hypertension, and dyslipidaemia; the specific number of risk factors that should be used to prompt testing remains to be determined. The committee considers ≥3 to be reasonable.	2B Not graded
Renal Association/British Transplant Society (BTS) [5]	2011	We suggest that there is no compelling evidence that pre-transplantation screening tests for CAD in asymptomatic patients with established renal failure is effective in preventing future cardiac events or reducing mortality after transplantation. Until better evidence emerges, screening tests may be best used to identify high-risk patients for exclusion from the transplant waiting list.	2C
Report of the Lisbon Conference on the Care of the Kidney Transplant Recipient [204]	2007	Assessment should include a history and physical examination to detect symptomatic disease, and an ECG. Evaluation of asymptomatic patients at highest risk for CVD events may include non-invasive and/or invasive testing depending on local expertise and availability. However, there are no data establishing that screening of asymptomatic patients prevents CVD events. Highest-risk patients are those with the following conditions: • Diabetes • Prior CVD • Multiple CVD risk factors e.g. more than 1 year on dialysis, left ventricular hypertrophy, age >60 years, smoking, hypertension, and dyslipidaemias	Not graded

Guideline	Publication year	Recommendation	Level of evidence
American Society Transplantation (AST) [153]	2002	Assess CAD risk factors: a prior history of CAD, men ≥45 or women ≥55 years, CAD in a first degree relative, current cigarette smoking, diabetes, hypertension, fasting total cholesterol, high density lipoprotein cholesterol and left ventricular hypertrophy. Risk factor modification should be aggressively pursued. Patients at high risk e.g. renal disease from diabetes, prior history of IHD, or ≥2 risk factors, should have a cardiac stress test. Patients with a positive cardiac stress test should undergo coronary angiography for possible revascularisation prior to transplantation. Patients with critical coronary lesions should undergo revascularisation prior to transplantation.	A A B B B

Table 2.4. Guideline recommendations on pre-transplant screening for CAD.

2.8 Conclusion

Although screening for asymptomatic CAD before kidney transplantation forms standard practice, there is an absence of contemporary studies that definitively evaluate the utility of screening for asymptomatic CAD before transplantation. It is currently not clear whether current practice results in net patient benefit or harm: normal screening tests may provide false reassurance of a patients' cardiovascular risk, and abnormal results may lead to interventions that do not improve outcome and come with potential risks. Further, whilst screening may identify high risk candidates who are not suitable to be listed, it is not known whether all patients who could benefit from transplantation are being selected.

2.9 Thesis aims and objectives

The aim of this thesis is to examine the incidence and impact of MACE following kidney transplantation, the current screening practice for asymptomatic CAD, and the impact of screening on MACE in England. These will be addressed using observational research methods with linked routine healthcare and clinical study datasets to allow a real-world assessment of MACE in kidney transplant recipients. The routine healthcare dataset captures cardiac events, whilst the clinical study dataset contains detailed information on which screening investigations patients underwent prior to transplant listing.

The aims of this thesis will be addressed by the following research questions:

1. **Chapter 3**: How accurate is the comorbidity information held in a routinely collected healthcare dataset, using data collected by research nurses as a reference?
2. **Chapter 4**: What is the incidence of MACE in kidney transplant recipients and waitlisted patients in England, what demographic and clinical factors are associated with these events, and what is the impact of early post-transplant MACE on patient, graft, and transplant survival?
3. **Chapter 5**: Is pre-transplant screening for CAD associated with peri-transplant MACE?
4. **Chapter 6**: What is the current CAD screening practice in 2021, and what are nephrologists' attitudes towards screening?

Chapter 3: The ATTOM study, linked HES dataset and accuracy of HES comorbidity recording

3.1 Introduction

This chapter introduces the datasets that are used to examine Major Adverse Cardiac Events (MACE) in kidney transplant candidates and recipients in Chapters 4 and 5. In total, data from four sources were linked to facilitate these analyses. These are:

- **The Access to Transplant and Transplant Outcome Measures (ATTOM) study**
- **Hospital Episode Statistics (HES)**
- **UK Renal Registry (UKRR)**
- **NHS Blood and Transplant (NHSBT)**

This chapter has two parts:

1. Part 1 (Sections 3.2 to Section 3.5): the aims, derivation, and output from the ATTOM study are explained, followed by an overview on the utility and structure of the HES dataset. The additional data obtained from the UKRR and NHSBT, and the process by which these datasets were linked to allow longitudinal follow up of ATTOM patients are then outlined.
2. Part 2 (Sections 3.6 to Section 3.9): the completeness and quality of comorbidity information held within HES are analysed to aid the interpretation of the data presented in Chapters 4 and 5.

The results in second part of this chapter (Sections 3.6 to Section 3.9) have been published as:

Nimmo A, Steenkamp R, Ravanan R, Taylor D. Do routine hospital data accurately record comorbidity in advanced kidney disease populations? A record linkage cohort study. *BMC Nephrol* 22**,** 95 (2021).

This paper is included in Appendix F.

3.2 The ATTOM study

The ATTOM study was a National Institute for Health Research (NIHR) Programme Grants for Applied Research funded prospective national cohort study, approved by the NHS Health and Social Care Research Ethics Committee (Ref:11/EE/0120). It recruited patients aged 18-75 years with ESKD between November 2011 and March 2013 from all 72 renal units in the United Kingdom (two have since merged, giving a total of 71) with the aim of examining factors associated with kidney transplantation. [205]

When patients were recruited to ATTOM, they were enrolled into one of 3 cohorts based on the treatment they received:

1. Incident dialysis cohort: if they had commenced haemodialysis or peritoneal dialysis within the preceding 90 days.
2. Incident transplant cohort: if they had received a transplant (kidney-alone or multi-organ) within the preceding 90 days.
3. Waitlisted cohort: if they were active on the transplant waitlist. These patients were identified from the waitlist by NHSBT (Section 3.4.2) and matched 1:1 to the incident transplant cohort based on age, time on the transplant waitlist, the type of organ they were listed to receive (kidney alone or simultaneous pancreas and kidney), the presence of diabetes, transplant centre, and whether they were pre-emptively listed (Table 3.1). Patients who were suspended for more than 30 out of their first 90 days on the waitlist were not included; this aimed to avoid bias from centres activating patients then immediately suspending them whilst they completed their assessment of fitness for transplantation, during which time they would gain waitlist points (Chapter 1 Section 1.6.3.2). [206]

Table 3.1. Process of identifying waitlisted patients as matched controls to the transplant cohort

1.1 For each transplant patient recruited into the ATTOM study a waitlisted control must be identified and recruited. The controls will be matched using all criteria shown below. If no controls are identified, criteria will be relaxed until a match is found. This is detailed in 1.3.

1.2 Agreed matching criteria:

- Transplant centre: same centre
- Age: within +/- 5 years
- Time on the list:
  - i. Within +/- 100 days if time ≤ 1000 days
  - ii. Within +/- 10% if time > 1000 days
  - iii. <365 days accrued time if unlisted living donor transplant
- Type of transplant: kidney only or simultaneous pancreas and kidney transplant
- Diabetic: yes/no (based on primary renal disease)
- Pre-emptive: yes/no (based on status at listing)

1.3 If no match is found based on the criteria above, rules will be relaxed to find a match that is as close to the pure criteria as possible. The rules will be relaxed in the following ways:

1. If age-matched, relax waiting time rules to within -/+ 1000 days and select the control with the closest waiting time to the case.
2. If age-matching unsuccessful, relax age matching to within -/+ 10 years and select the control with the closest age to the case. In the event of a tie, select the control with the closest waiting time to the case.
3. If no match is found after steps (1) and (2) then:
   If case is diabetic: remove diabetic matching and revert back to the pure match age and waiting time rules.
   If case was pre-emptive and waited >1800 days, remove pre-emptive matching rule and revert back to the pure match age and waiting time rules.
   If case is an outlying long waiter (> 3000 days) then select the control with the closest waiting time to the case (but only if they have waited at least 1800 days).

If a patient changed treatment status during ATTOM recruitment e.g. a waitlisted patient received a transplant or a dialysis patient became waitlisted, they could be recruited again creating a separate record in the dataset. One patient could therefore contribute data to more than one ATTOM cohort.

3.2.1 Data collection

Dedicated research nurses collected data on patient demographics, socioeconomic indicators and clinical information including PRD and comorbidity within 90 days of ATTOM recruitment from a structured review of the case notes. The presence or absence of 15 comorbidities was collected for each patient. For patients in the incident transplant and waitlisted cohorts, data on which (if

any) asymptomatic CAD screening tests patients underwent prior to transplant listing were collected. Data on the results of screening tests were not captured.

The research nurses involved in the ATTOM study underwent data collection training and received documentation with clear definitions against which to gather information (included in Appendix A). Independent data validation was performed by a senior nurse in a randomly-selected 5% of cases, with a concordance of over 98% for all collected variables. [205]

The patients recruited to ATTOM also completed a questionnaire at recruitment, to collect data on demographics including ethnicity and individual-level markers of socioeconomic status (Appendix A). These questionnaires were completed independently by the patient unless assistance was required due to a physical disability. Translation into other languages was provided if required. If a patient was recruited to more than one ATTOM cohort, their case notes were re-reviewed and any clinical information updated by the research nurses, but the patient questionnaire was not repeated.

3.2.2 Comparison of the ATTOM cohort to the incident KRT population

It is difficult to accurately quantify the proportion of incident dialysis patients recruited to ATTOM because the start and end dates of recruitment from each renal centre differed. A comparison of the incident dialysis patients recruited to ATTOM in 2012 (when recruitment was in process for the whole calendar year) to UKRR data for the same year (Section 3.4.1) showed that ATTOM recruited over 50% of that year's incident dialysis patients aged under 75 years. The incident transplant cohort contained 74% of patients who received a kidney transplant over the whole study period, and the waitlisted cohort contained 91% of the patients who were approached for inclusion.

An analysis comparing the incident dialysis patients recruited to ATTOM in 2012 to the non-recruited incident KRT patients from the UKRR that year showed ATTOM recruits were younger and more likely to be male than the UK incident dialysis population (Appendix B). Patients recruited to ATTOM were more likely to be of White ethnicity, which may be accounted for by the lower level of missing ethnicity data in ATTOM compared to UKRR data. They were also less likely to have diabetic nephropathy as their PRD, which may relate to better real-time recording of PRD by the ATTOM research nurses then centre returns to the UKRR. Finally, the proportion of patients receiving peritoneal dialysis in the ATTOM cohort was lower than that in the UKRR

report, which is likely to relate to greater ease of recruiting patients on haemodialysis who attended hospital three times a week for treatment.

3.2.3 Comorbidity indices

The comorbidity data collected by ATTOM research nurses are used in analyses in Chapters 3-5 of this thesis. In Chapters 4 and 5, comorbidities are examined individually (for example, the presence or absence of diabetes or ischaemic heart disease are included in statistical models). In this chapter, where the quality of HES data is compared to ATTOM, a composite measure of comorbidity is also assessed using the renal modified Charlson comorbidity index.

The renal modified Charlson comorbidity index was developed by Hemmelgarn et al. in 2003. [207] It was adapted from the original Charlson index [208] to provide a more accurate prediction of mortality in patients with ESKD. Comorbidities are assigned a weight depending on how strongly they associate with death. The weightings used in Hemmelgarn's index and the corresponding variables and weightings from the ATTOM dataset are shown in Table 3.2. Minor alterations to comorbidity definitions were allowed, given subtle differences in the way comorbidities were recorded. Peptic ulcer disease and rheumatological conditions were not captured within ATTOM so these comorbidities were excluded from the scoring algorithm, but other weightings were unchanged. From here, the renal modified Charlson score is simply referred to as the Charlson score, which has been calculated according to the modified weighting system shown in Table 3.2.

Comorbidity variables from Hemmelgarn et al.	Weight	Corresponding variable from ATTOM dataset	Weight
Myocardial infarction	**2**	Unstable angina, myocardial infarction or coronary intervention	**2**
Congestive heart failure	**2**	Heart failure	**2**
Peripheral vascular disease (includes Aortic aneurysm >6cm)	**1**	Peripheral vascular disease or aortic aneurysm repair	**1**
Cerebrovascular disease	**2**	Cerebrovascular disease	**2**
Dementia	**1**	Dementia	**1**
Chronic lung disease	**1**	Respiratory disease	**1**
Rheumatological /Connective tissue disease	**1**	Excluded	**-**
Peptic ulcer disease	**1**	Excluded	**-**
Diabetes without complications	**2**	Diabetes without diabetes as primary renal disease	**2**
Diabetes with complications	**1**	Diabetes as primary renal disease	**1**
Leukaemia	**2**	Leukaemia	**2**
Lymphoma (includes myeloma)	**5**	Lymphoma or myeloma	**5**
Moderate/severe liver disease	**2**	Liver cirrhosis	**2**
Metastatic cancer	**10**	Metastatic cancer	**10**
Maximum score	**33**	**Maximum score**	**31**

Table 3.2. Comorbidities and weights included in the renal modified Charlson score.

3.3 Hospital Episode Statistics dataset

HES is a routinely collected dataset that has been gathering information on secondary care attendances in England since 1989. It primarily exists for administrative purposes, to calculate reimbursement to secondary care providers in England through a process called Payment by Results, where each patient's hospital attendance is costed based on the medical complexity and amount of resource used. HES originally collected information solely on hospital inpatient stays (admitted patient care; APC) but has since expanded to include data on outpatient (OP) visits since 2003, accident and emergency (ED) attendances since 2007, and critical care stays since 2008. [209]

HES captures data on patients who receive NHS-funded treatment or privately funded treatment provided by an NHS provider at hospitals in England. People who have not attended hospital, received care in another country or privately, or had a hospital admission erroneously not recorded will not have a HES record. Additionally, linkage errors when combining datasets (false matches or missed matches), coding errors, or patients opting out of their records being shared

outside of NHS Digital ('type 2 opt out') can lead to errors in data or missing data. Generally, cross-border treatment is rare: for example, under 0.4% of HES episodes in 2014/2015 were from patients that live in Wales, [210] though the location of renal units in the UK mean patients with kidney disease may be more likely to cross borders for treatment e.g. patients in North Wales undergo kidney transplantation in Liverpool as opposed to Cardiff.

HES data are collected by care providers at each hospital and are submitted monthly to NHS Digital. Data in HES are processed, cleaned, and published annually. Data are collated based on the financial year; hospital admissions which span two financial years are only counted in the year in which the patient was discharged.

3.3.1 Structure of HES admitted patient care

HES data is gathered based on the attendance type (APC, OP or ED). APC data encompass all attendances which use a hospital bed, and therefore includes both day case admissions and overnight stays. APC divides inpatient stays into domains called 'episodes' and 'spells'. To explain these, an understanding of the patient journey through hospital is required.

A patient can be admitted to hospital as an emergency, as a planned admission, or as a transfer from another hospital. They are admitted under the care of one specialty but as their clinical picture evolves, their care may be assumed by another specialty. The time a patient is cared for by a single specialty is referred to as an episode. The time as an inpatient in one provider institution (usually one hospital) is referred to as a spell and can contain several episodes. A spell ends when a patient is discharged, transferred to another institution, or dies. If the journey includes episodes in different hospitals, the overall admission is called a 'continuous inpatient spell' and comprises the combined episodes and spells. A pathway depicting an inpatient journey is shown in Figure 3.1.

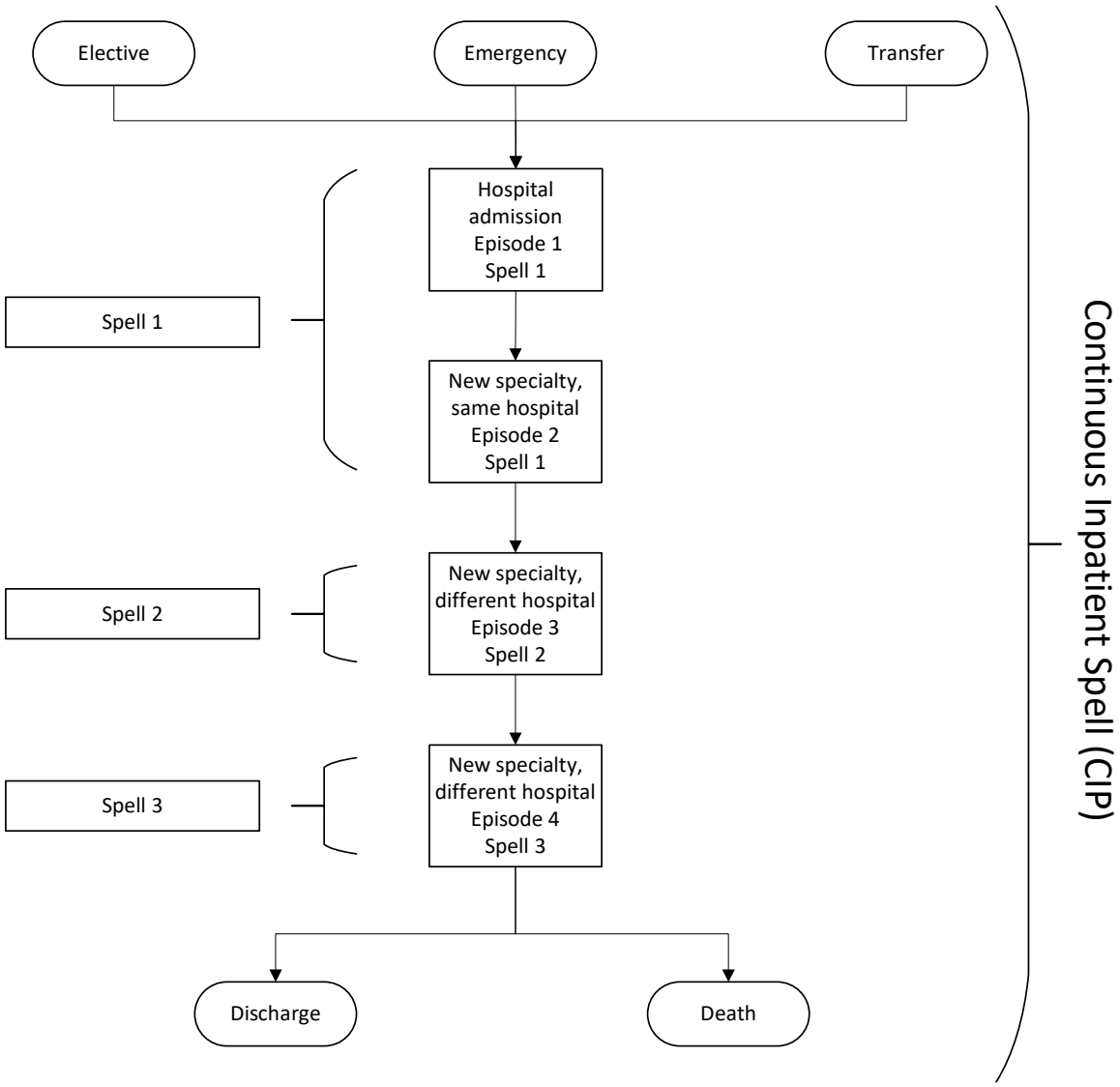


Figure 3.1. Structure of APC data in HES comprising episodes, spells, and continuous inpatient spells.

3.3.2 Content and coding of HES data

HES collects information on patient demographics, healthcare providers, administrative data (including admission and discharge dates, waiting times, admission, and discharge routes) and clinical data (diagnoses and procedures) that are inputted by professional clinical coders. Each row in the dataset reflects one episode (APC), appointment (OP) or attendance (ED).

The methods used to code diagnoses and procedures differ between HES datasets. APC and OP data use the International Classification of Diseases 10th Revision (ICD-10) and Office of

Population, Censuses and Surveys Classification of Surgical Operations and Interventions 4th revision (OPCS-4) to record diagnosis and procedures respectively. [211] [212] Bespoke classification systems are used in the ED dataset which allow recording of the overarching condition in addition to the anatomical area which it affected. The completeness of diagnosis data also differs between the HES datasets; in OP data diagnosis codes are poorly recorded with 95% of primary diagnoses recorded as 'unspecified cause of morbidity' in 2015/16. [213]

For each APC episode, HES allows recording of up to 20 ICD-10 diagnosis codes and 24 OPCS-4 procedure codes. The first diagnosis is the 'primary diagnosis' which reflects the main condition being treated in that episode. Each episode must have a primary diagnosis, although it can be recorded as unknown. Subsequent diagnoses reflect secondary diagnoses or comorbidities documented during that episode. The first procedure code reflects the most resource-intensive procedure performed. [209] If no procedure or intervention was performed this variable is left blank.

3.3.3 HES data in research settings

Although HES exists primarily for administrative purposes, it has potential applications in research settings and is increasingly being used in research studies to identify study participants and record outcomes. [209] [214] For example, data in research studies are frequently extracted from clinical notes by specially trained staff (as occurred in the ATTOM study). Whilst this allows collection of high-quality, consistent information with minimal missing data, it is resource intensive. HES collects data at the point of care delivery, is cheaper than direct data collection and is of minimal burden to study participants and researchers. Further, the use of routinely collected data allows long-term follow up of large populations across geographical areas that can be efficiently captured with reduced attrition, no recall bias, and the ability to adjust for residual confounding relating to the accrual of comorbidity over time. [215] [216] [217(p)]

HES data has also been used by disease registries to help supplement missing data. The UKRR (Section 3.4.1) uses clinician reporting to capture demographic and clinical information of patients on KRT but struggles with low data-completeness: comorbidity is only captured in half of patients. [218] HES can be used to supplement registry data, and the UKRR established HES linkage to improve its comorbidity recording in 2018. [219]

If HES data is of sufficient quality, it forms an attractive resource for use within clinical research. Whilst the accuracy of HES in recording individual medical conditions has been compared to

various disease registries, [220] [221] [222] its accuracy in people with CKD is less well documented. Patients with CKD have clustering of comorbidities [223] and higher hospitalisation rates [224] which may lead to differences in the data quality compared to the general population, and requires further exploration.

3.3.4 HES diagnosis data and the ATTOM cohort

HES allows longitudinal collection of data and provides near-universal coverage for patients treated in England. As such, linkage of HES and ATTOM datasets allows the quality of HES diagnosis data to be compared to that captured by the ATTOM research nurses. If HES data is of sufficient quality, it could be used to identify new medical conditions that develop post-ATTOM recruitment, including the occurrence of cardiac events. It therefore allows the impact of CAD screening on MACE in kidney transplant recipients to be evaluated – the key aim of this thesis.

On recruitment to ATTOM, patients consented for their identifiable data to be shared with the UKRR, Scottish Renal Registry and NHSBT. This consent was not considered sufficient to transfer identifiable information to NHS Digital for linkage to HES data. Approval for data transfer was obtained through the NHS Health Research Authority Confidentiality Advisory Group under Section 251 (4) of the NHS Act 2006, which allows processing of patient identifiable information without consent (Ref: 16/CAG/0102). This was deemed appropriate given that up to 25% of patients were anticipated to be deceased at the time of data transfer. An additional message was displayed on Renal PatientView [225] to allow ATTOM recruits to opt-out if they wished; no objections were received.

HES and ATTOM data were subsequently linked using unique patient identifiers under Data Sharing Agreement Number DARS-NIC-14342-Q8W0X (Appendix B). Data were stored in line with the United Kingdom Data Protection Act 1998 requirements at NHSBT.

3.4 Other datasets for linkage

3.4.1 UK Renal Registry

The UKRR collects data on all incident and prevalent KRT patients in the UK. Data are electronically reported to the UKRR directly from each renal unit in England, Wales, and Northern Ireland, or via the Scottish Renal Registry for patients residing in Scotland. It allows the care of

patients with ESKD to be audited against quality standards and provides information on the incidence and prevalence of KRT in the UK. Date and cause of death are reported to the UKRR, coded by clinicians at the patient's renal centre. For kidney transplant recipients, serum creatinine is also extracted on an annual basis. [37] In Chapters 4 and 5, these data from the UKRR are included within analyses.

3.4.2 NHS Blood and Transplant

NHSBT provides transplantation services to the UK, managing the donation, storage and transplantation of blood and solid organs. They are responsible for the allocation of kidneys via the deceased donor kidney offering scheme and run the living donor kidney sharing scheme. As such, NHSBT holds information on all patients on the kidney transplant waiting list, including dates of waitlist activation, suspension and removal, transplantation and graft failure, recipient immunological data and detailed donor information. Further, transplant centres return information on rejection episodes, serum creatinine, graft failure and cause of death to NHSBT. [226] In Chapters 4 and 5, date of waitlisting, suspension episodes, removal from the waitlist, date of transplantation and date of graft failure are analysed using data from NHSBT.

3.5 Benefits of dataset linkage

Examining the association between CAD screening tests and outcomes is challenging: the components of transplant workup that a patient undergoes varies between centres and are not reported to any national body; further, following up a national cohort of patients for cardiac events would be labour intensive if performed by trained research personnel. For these reasons, most studies reporting results of screening tests and post-transplant cardiac events come from single centre reports. [141] [186] [192] The use of the 4 combined datasets described in Sections 3.2 through to 3.4 therefore provides a novel opportunity to examine the incidence, associations and impact of post-transplant MACE on patient and graft outcomes (Chapter 4) and the association between screening and MACE (Chapter 5) in England.

A flow diagram showing the patients in the ATTOM study, their linkage with HES, UKRR and NHSBT data, and which patients are analysed in each chapter of this thesis are shown in Figure 3.2. Future chapters will also refer to this flowchart. As HES data were only available from

hospitals in England, ATTOM participants from elsewhere in the UK were excluded from all analyses in this thesis.

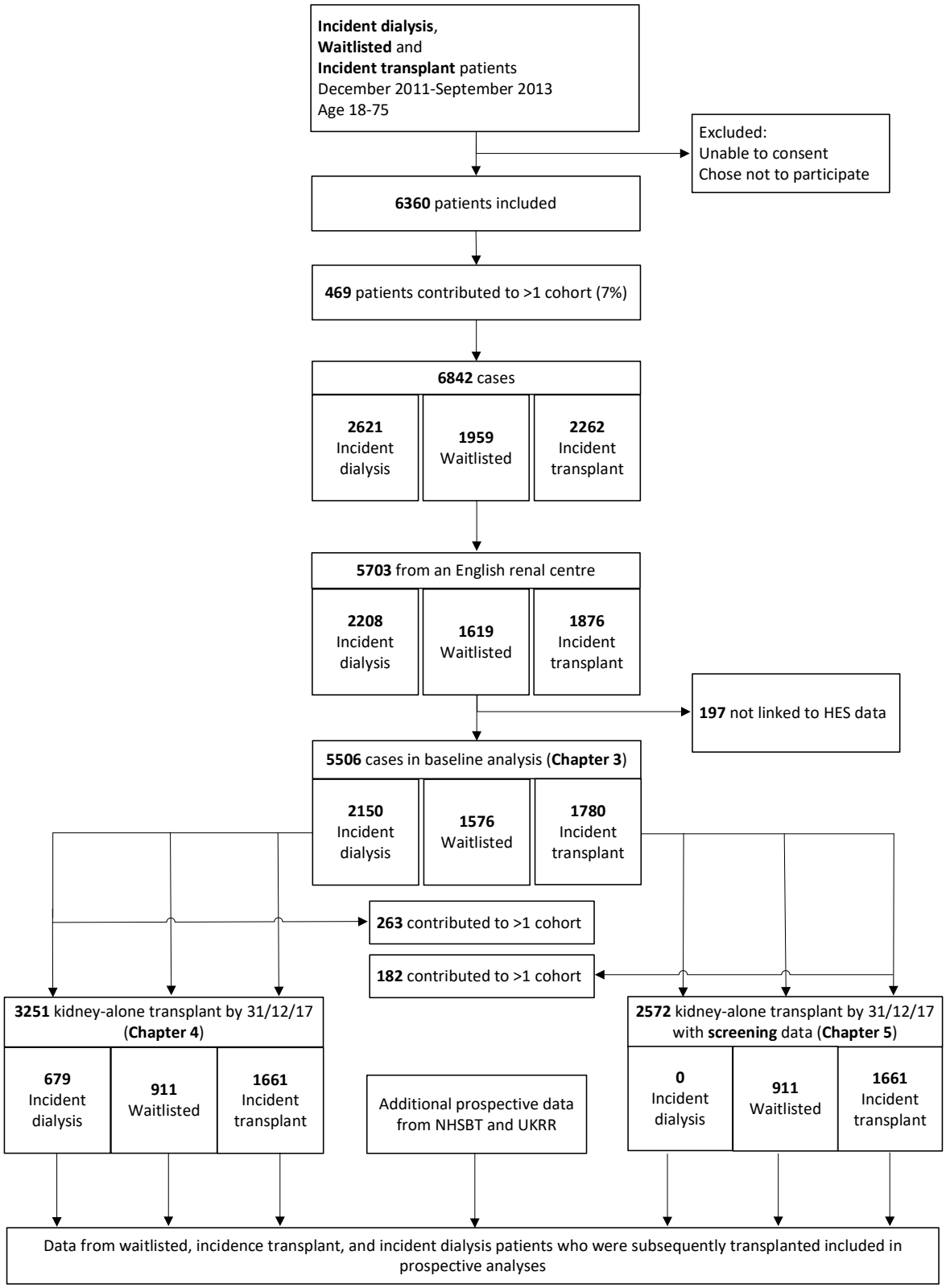


Figure 3.2. Flowchart of patients in the ATTOM study included in each thesis chapter, and the contribution of data from each of the linked datasets.

3.6 Aims

Having outlined the content and purpose of the linked datasets used within this thesis, the aims of this chapter are now to:

1. Examine the rate of data linkage between ATTOM and HES datasets
2. Identify factors associated with dataset linkage
3. Investigate the accuracy of HES comorbidity data with reference to that collected by the trained ATTOM research nurses

Examining these questions will inform the reliability of HES to capture information on comorbidities within epidemiological and clinical research in the KRT population and allow appropriate interpretation of the results in the subsequent chapters of this thesis.

3.7 Methods

3.7.1 Data cleaning and preparation

HES data were available from 1st January 2006 to 31st December 2017, were obtained from NHS Digital, and stored at NHSBT. The relevant data from the UKRR and NHSBT datasets (Section 3.4) were first merged with the ATTOM dataset, and HES data was then linked to the enhanced ATTOM database using unique patient identifiers (Section 3.3.4).

3.7.2 Data completeness and healthcare utilisation

To determine the completeness of HES data, the dataset linkage rate (to determine how many patients' records were linked) and number of HES entries per patient (to allow an assessment of the depth/granularity of HES data) were examined.

3.7.2.1 Dataset linkage

Univariable and multivariable logistic regression analysis was used to examine factors associated with successful linkage of ATTOM and HES records. Covariates defined *a priori* comprised age, sex, ethnicity, Index of Multiple Deprivation (IMD; an area-level marker of socioeconomic status ranging from 1: most deprived to 5: least deprived), ATTOM cohort, PRD and Charlson index. These variables were selected based on previous literature suggesting potential associations with

data linkage. [227] [228] [229] Centre was not included in the multivariable model as the centre at which a patient is registered does not necessarily represent the hospital which they attend or are admitted to.

Standardised differences were used to compare characteristics between patients with linked and non-linked datasets; values of 0.2, 0.5 and 0.8 reflected small, medium, and large standardised differences respectively. [230] The multivariable model included complete cases only, present in 5509 (97%) of cases. Robust standard errors to account for potential intragroup correlations within centres were used.

3.7.2.2 Healthcare utilisation

As diagnosis recording is most detailed within HES APC, [209] [213] only these episodes were used to extract comorbidity information. The number of patients with an APC episode prior to ATTOM recruitment was calculated and number of admissions determined. Comorbidities among individuals with and without an APC episode were compared.

3.7.3 Comorbidity recording

The comorbidities recorded by the ATTOM study nurses and their corresponding ICD-10 and OPCS-4 codes are included in Appendix B. Codes were identified from a systematic search of data dictionaries alongside consultation of established algorithms. [231] Comorbidities were extracted from all diagnosis and operation positions from APC episodes between January 2006 and date of ATTOM recruitment. If a condition was recorded once, it was considered to persist on subsequent attendances in-keeping with established methodology. [232] The prevalence of comorbidities were calculated using the denominator of all individuals with dataset linkage and complete ATTOM comorbidity records.

To maximise their statistical power, studies need to identify conditions with an adequate sensitivity (proportion of true 'cases' identified), specificity (proportion of true 'controls' identified) and positive predictive value (PPV; proportion of identified cases that truly have the condition). A higher PPV leads to greater statistical power through low misclassification of positive cases which could 'dilute' any observed effect. False negatives have less impact on power for conditions with a relatively low prevalence as they join the larger control population. If the condition of interest is rare, specificity and negative predictive value (NPV) are generally high.

Comorbidity recorded in ATTOM was taken to represent 'gold standard'. The sensitivity, specificity, PPV and NPV of comorbidities derived from HES were calculated. Cohen's kappa statistic was used to compare the agreement of recording between sources. Accepted values were taken to indicate poor (<0.2), fair (0.21-0.40), moderate (0.41-0.6), substantial (0.61-0.8) and strong (>0.8) agreement. [230 233] The ICD-10 and OPCS-4 codes of comorbidities with a PPV below 50% were scrutinised to identify diagnoses giving false positive results. To examine whether disease prevalence associates with recording accuracy, pooled sensitivities and PPVs were calculated using a subgroup meta-analysis.

Operations preferentially generate cost codes for hospital episodes, and the diagnosis being treated by an operation could be more 'secure' (or 'truly' present) if requiring an intervention. A subgroup meta-analysis was therefore performed to compare the sensitivity and PPV of conditions identified using ICD-10 criteria alone to those also derived from OPCS-4 codes. A random-effects model was used due to heterogeneity in the prevalence of comorbidities and variation in the sensitivity and PPV of comorbidities derived from hospital data reported previously. [221 222]

The Charlson score was calculated using comorbidities derived from ATTOM and HES data (Section 3.2.3). The sensitivity, specificity, PPV and NPV of the Charlson score derived from HES data were calculated.

3.7.4 Statistical Analyses

Descriptive statistics were used to report baseline characteristics with non-parametric continuous variables expressed as median [interquartile range, IQR] and categorical variables as frequency (percentage). The Chi-square test and Mann-Whitney U test were used to compare categorical and non-parametric continuous variables respectively. Results of regression analyses were presented as odds ratios with 95% confidence intervals. Statistical significance was defined *a priori* as a $p<0.05$. Analyses were performed using Stata 15 (Statacorp, College Station, TX).

3.8 Results

3.8.1 Study population

In total, 5703 patients were recruited to ATTOM from an English renal centre. ATTOM and HES records were linked for 5506 (97%) patients. Of the 197 patients whose records did not link, 49 had non-English postcodes and likely received treatment elsewhere in the UK, leaving 148 (2.6%) unmatched (Figure 3.3).

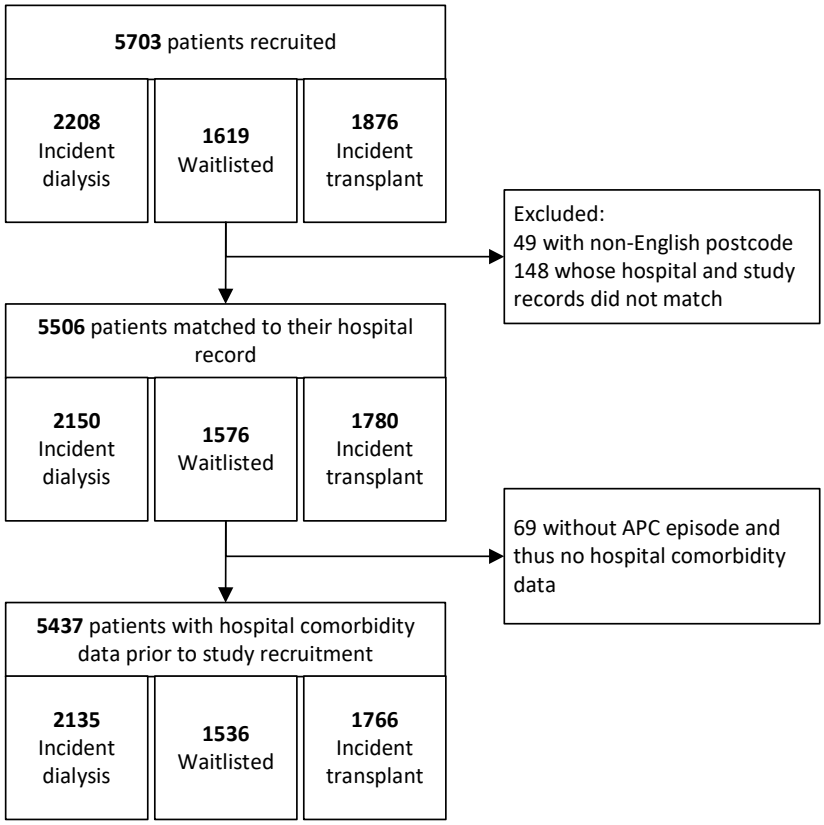


Figure 3.3. Flow chart of patients included in Chapter 3 analyses. There were 69 patients without an APC episode prior to ATTOM recruitment, 67 of whom had an APC episode post-ATTOM recruitment.

Of those patients with linked datasets, the median age was 53 years [IQR 43-63], 62% were male and 76% were of White ethnicity. Overall, 20% had a PRD classified as 'other', with a further 19% each having diabetes and glomerulonephritis (Table 3.3).

Variable	Linked dataset N= 5506	Non-linked dataset N= 148	P	Standard diff.
Age (n=5654)	53 [43 - 63]	51 [41 - 61]	0.09	0.15
Male sex (n=5654)	3422 (62)	84 (57)	0.18	0.11
Ethnicity (n=5632)				
White	4192 (76)	100 (69)		
Black	497 (9)	35 (24)	<0.001	0.47
Asian	750 (14)	10 (7)		
Mixed	48 (1)	0 (0)		
IMD (n=5654)				
1 – Most deprived	1420 (26)	31 (21)		
2	1169 (21)	29 (20)		
3	1052 (19)	35 (24)	0.51	0.11
4	983 (18)	27 (18)		
5 – Least deprived	882 (16)	26 (17)		
ATTOM cohort (n=5654)				
Dialysis	2150 (39)	49 (33)		
Transplant	1780 (32)	59 (40)	0.14	0.16
Wait listed	1576 (28)	40 (27)		
PRD (n=5590)				
Polycystic kidney disease	676 (12)	22 (16)		
Diabetes	1026 (19)	14 (10)		
Glomerulonephritis	1057 (19)	36 (24)		
Pyelonephritis	460 (8)	15 (10)	0.005	0.38
Hypertension	340 (6)	9 (6)		
Renovascular disease	97 (2)	7 (5)		
Other	1090 (20)	33 (22)		
Uncertain	697 (13)	11 (8)		
Charlson score (n=5571)				
0	3031 (56)	100 (68)		
1-2	1518 (28)	37 (25)	0.007	0.33
3-4	583 (11)	7 (5)		
5+	292 (5)	3 (2)		

Table 3.3. ATTOM and HES linkage by patient characteristic. Data expressed as number (%) or median [IQR]. Standardised differences of 0.2, 0.5 and 0.8 reflect small, medium, and large standardised differences. P values from the Chi square or Mann-Whitey U test.

3.8.2 Dataset linkage

By univariable analysis, there was a reduced likelihood of datasets being linked for patients of Black ethnicity (OR 0.34, 95% CI 0.23-0.50) and a lower Charlson score (Charlson score 0 vs. ≥5 OR 0.31, 95% CI 0.10-0.98) (Table 3.4). Patients with diabetic nephropathy were more likely to have linked datasets compared to those with polycystic kidney disease (OR 2.39, 95% CI 1.21-4.69) (Table 3.4). Significant variation was also observed between renal centres (Figure 3.4 and

Appendix B), though these vary in size. There was no association between dataset linkage and age, sex and ATTOM cohort which each had a standardised difference of under 0.2.

By multivariable analysis, after adjustment for age, sex, ATTOM cohort, PRD and Charlson score, Black ethnicity remained associated with reduced likelihood of dataset linkage (OR 0.25, 95% CI 0.15-0.41) (Table 3.4). Variation was seen with socioeconomic status, but this was not linear.

Variable	Univariable model Unadjusted OR (95% CI)	P	Multivariable model Adjusted OR (95% CI)	P
Age (years) (n=5654)	1.01 (0.99 – 1.02)	0.06	1.01 (0.99 – 1.02)	0.43
Sex (n=5654)				
Female	1.00	-	1.00	-
Male	1.25 (0.90 – 1.74)	0.18	1.18 (0.87 – 1.61)	0.28
Ethnicity (n=5632)				
White	1.00	-	1.00	-
Black	0.34 (0.23 – 0.50)	**<0.001**	0.25 (0.15 – 0.41)	**<0.001**
Asian	1.79 (0.93 – 3.44)	0.09	1.40 (0.73 – 2.67)	0.31
IMD (n=5654)				
1 – Most deprived	1.00	-	1.00	-
2	0.88 (0.53 – 1.47)	0.63	0.93 (0.54 – 1.60)	0.80
3	0.66 (0.40 – 1.07)	0.09	0.55 (0.38 – 0.79)	**0.001**
4	0.79 (0.47 – 1.34)	0.39	0.64 (0.33 – 1.25)	0.19
5 – Least deprived	0.74 (0.44 – 1.26)	0.27	0.61 (0.40 – 0.93)	**0.02**
ATTOM cohort (n=5654)				
Dialysis	1.00	-	1.00	-
Transplant	0.69 (0.47 – 1.01)	0.06	0.90 (0.58 – 1.41)	0.65
Wait listed	0.90 (0.59 – 1.37)	0.62	1.25 (0.74 – 2.11)	0.41
PRD (n=5590)				
Polycystic kidney disease	1.00	-	1.00	-
Diabetes	2.39 (1.21 – 4.69)	**0.01**	1.80 (0.78 – 4.15)	0.17
Glomerulonephritis	0.96 (0.56 – 1.64)	0.87	1.08 (0.58 – 2.04)	0.81
Pyelonephritis	1.00 (0.51 – 1.95)	0.99	1.00 (0.44 – 2.30)	1.00
Hypertension	1.23 (0.56 – 2.70)	0.61	1.76 (0.80 – 3.86)	0.16
Renovascular disease	0.45 (0.19 – 1.08)	0.08	0.36 (0.11 – 1.18)	0.09
Other	1.07 (0.62 – 1.86)	0.80	1.17 (0.59 – 2.33)	0.66
Uncertain	2.06 (0.99 – 4.29)	0.05	2.27 (0.99 – 5.22)	0.06
Charlson index (n=5571)				
5+	1.00	-	1.00	-
3-4	0.86 (0.22 – 3.33)	0.82	0.91 (0.23 – 3.59)	0.89
1-2	0.42 (0.13 – 1.38)	0.15	0.51 (0.15 – 1.69)	0.27
0	0.31 (0.10 – 0.98)	**0.04**	0.46 (0.14 – 1.45)	0.18

Table 3.4. Univariable and multivariable logistic regression of factors associated with dataset linkage, expressed as odds ratio (OR) with 95% confidence intervals. No OR is

expressed for Mixed ethnicity as datasets linked for all patients. The multivariable analysis adjusted for all variables with robust standard errors for centre. Complete cases only are included (n=5509, 97%).

Of the 52 renal centres, 30 contained patients whose datasets did not link. A funnel plot identified 5 centres as outliers (Figure 3.4). It is important to note the renal centre at which patients are registered does not necessarily represent the hospital which they attend. This is particularly relevant for kidney transplant recipients whose local renal centre is not a transplanting centre; the timing of transfer back to their local centre varies depending on local practice.

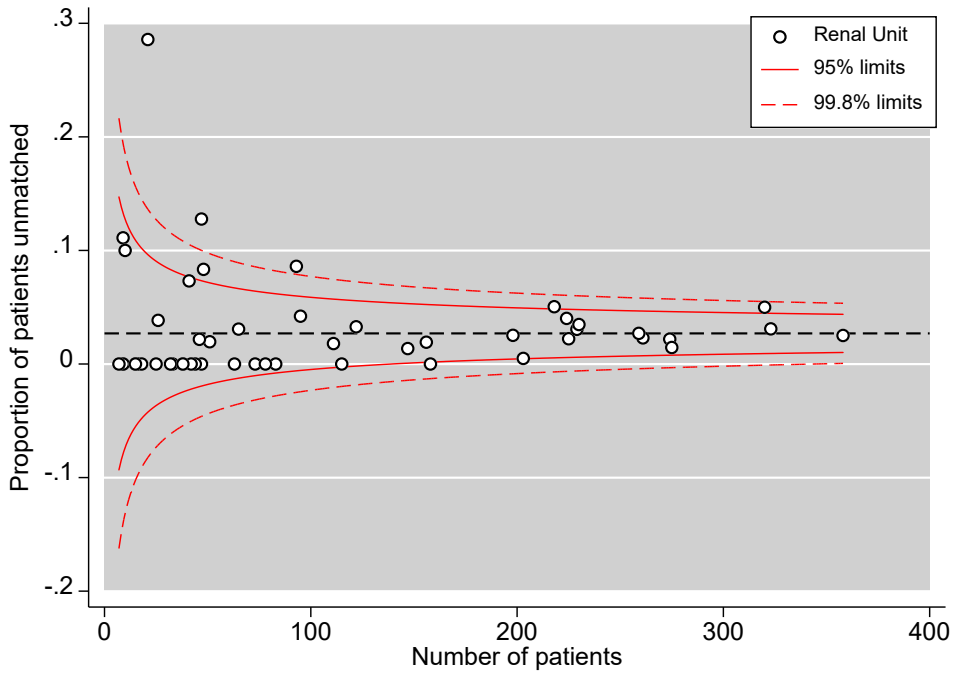


Figure 3.4. Funnel plot demonstrating proportion of patients with linked ATTOM and HES data by renal centre with 95% and 99.8% limits. The dotted black line shows the mean value across all centres.

3.8.3 Healthcare utilisation

The median time covered by HES data prior to ATTOM recruitment was 6.7 years [IQR 6.4-7.0]. Of the 5506 patients whose datasets linked, 5437 (99%) had an APC episode prior to ATTOM recruitment. The median number of APC episodes was 9 [IQR 5-16] and median time from last

admission to ATTOM recruitment was 58 days [IQR 19-258]. Of those patients with an admission, 89% had an admission within 1 year of ATTOM recruitment and 95% within 2 years.

There were 69 patients whose datasets linked but who had no APC encounter prior to ATTOM recruitment. These patients were more likely to be male (74% vs. 62%, p=0.04), in the waitlisted cohort (58% vs. 28%, p<0.001), have polycystic kidney disease (35% vs. 12%, p<0.001) and a lower comorbidity burden (Charlson score of 0: 83% vs. 56%, p<0.001).

The most prevalent comorbidity in patients without prior APC encounters based on ATTOM data was diabetes (n=7, 10%). As the number of patients in this group was small and they had a low prevalence of comorbidity, they represent a minority of people with each condition. Patients with blood borne viruses were most likely to not have had a prior hospital admission, but this occurred in just 2.6% of people with this diagnosis.

Of these 69 patients, 67 had an APC record after ATTOM recruitment. The median time between recruitment and first admission was 917 days [IQR 333-1582]. Due to this length of time, these patients were included in subsequent analyses and counted as having no comorbidity in HES records.

3.8.4 Comorbidity recording

There was variation in the sensitivity, specificity, PPV and NPVs of comorbidities (Table 3.5). Diabetes, ischaemic heart disease and malignancy were most prevalent (Figure 3.5) and recorded with a high sensitivity and PPV of 97.7% and 90.4% for diabetes, 82.6% and 82.9% for ischaemic heart disease and 62.8% and 71.9% for malignancy (Figure 3.6 and Figure 3.7). Alongside heart valve replacement, these conditions had a kappa statistic over 0.6 indicating adequate agreement.

Comorbidity	Sensitivity (95% CI)	Specificity (95% CI)	PPV (%) (95% CI)	NPV (%) (95% CI)	Kappa
Diabetes (n=5461)	97.7 (96.8 – 98.4)	96.1 (95.4 – 96.7)	90.4 (88.9 – 91.8)	99.1 (98.7 – 99.4)	0.91
Ischaemic heart disease (n=5450)	82.6 (79.6 – 85.4)	93.4 (92.7 – 94.1)	82.9 (77.3 – 87.6)	90.2 (89.4 – 91.0)	0.68
Malignancy (n=5453)	62.8 (58.3 – 67.2)	97.7 (97.2 – 98.1)	71.9 (67.3 – 76.2)	96.5 (96.0 – 97.0)	0.64
Chronic lung disease (n=5450)	86.0 (82.3 – 89.2)	90.4 (89.5 – 91.2)	41.9 (38.6 – 45.4)	98.8 (98.4 – 99.1)	0.52
Cerebrovascular disease (n=5448)	56.6 (51.2 – 61.9)	96.7 (96.2 – 97.2)	53.6 (48.3 – 58.9)	97.1 (96.6 – 97.5)	0.52
Mental illness (n=5451)	55.1 (49.7 – 60.5)	94.0 (93.3 – 94.7)	38.1 (33.8 – 42.6)	96.9 (96.4 – 97.5)	0.41
Peripheral vascular disease (n=5452)	67.2 (61.5 – 72.6)	95.8 (95.2 – 96.3)	47.7 (42.8 – 52.6)	98.1 (97.7 – 98.5)	0.53
Heart failure (n=5450)	68.4 (61.3 – 75.0)	91.4 (90.6 – 92.1)	22.3 (18.9 – 25.9)	98.8 (98.4 – 99.1)	0.30
Blood borne viruses (n=5450)	15.5 (10.2 – 22.2)	100 (99.9 – 100)	96.0 (79.6 – 99.9)	97.6 (97.1 – 98.0)	0.26
Liver disease (n=5452)	44.2 (34.0 – 54.8)	98.0 (97.6 – 98.4)	28.4 (21.3 – 36.4)	99.0 (98.7 – 99.3)	0.33
Heart valve replacement (n=5448)	92.6 (82.1 – 97.9)	99.5 (99.3 – 99.7)	65.8 (54.0 – 76.3)	99.9 (99.8 – 100)	0.77
Permanent pacemaker (n=5449)	84.9 (72.4 – 93.3)	98.6 (98.3 – 98.9)	37.5 (28.8 – 46.8)	99.8 (99.7 – 99.9)	0.51
Abdominal aortic aneurysm (n=5447)	29.5 (16.8 – 45.2)	99.9 (99.7 – 99.9)	61.9 (38.4 – 81.9)	99.4 (99.2 – 99.6)	0.40
Dementia (n=5453)	44.4 (13.7 – 78.8)	99.9 (99.7 – 99.9)	36.4 (10.9 – 69.2)	99.9 (99.8 – 100)	0.40

Table 3.5. Sensitivity, specificity, positive and negative predictive values (as percentages), and Kappa statistic of HES comorbidity as compared to ATTOM comorbidity. Conditions are ordered by prevalence.

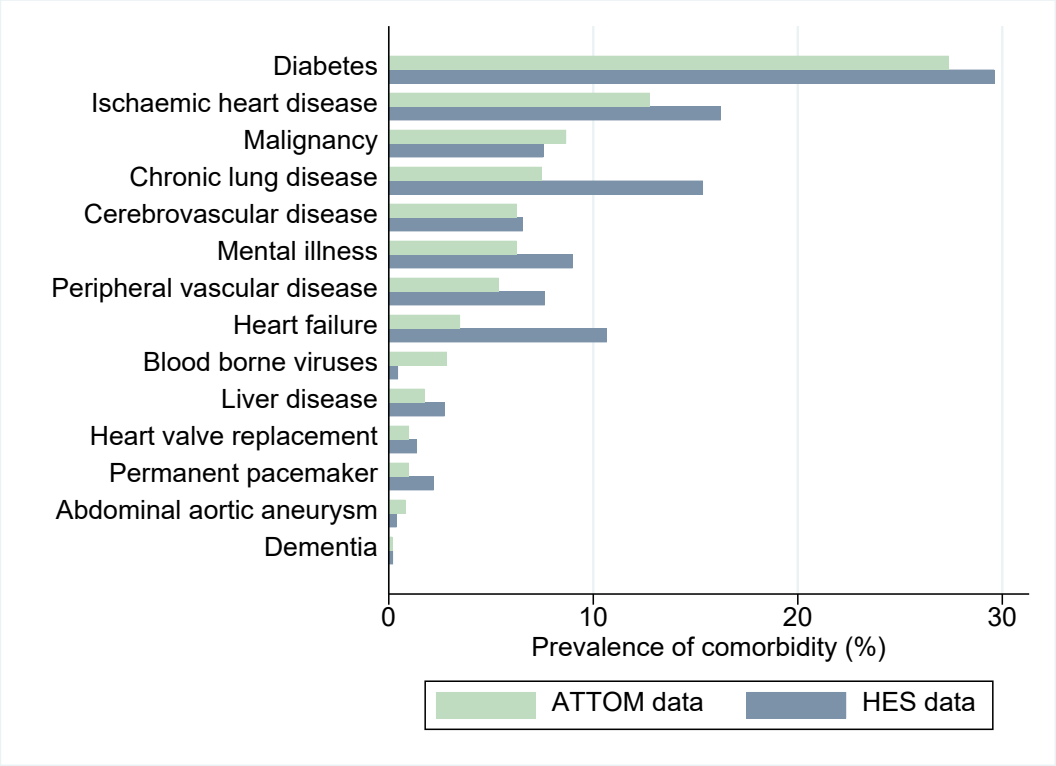


Figure 3.5. Prevalence of comorbidities derived from ATTOM and HES datasets.

Heart failure, chronic lung disease, mental illness, and peripheral vascular disease each had greater sensitivities relative to their PPV, reflecting a greater proportion of false positive cases in hospital data. False positive cases of chronic lung disease reflected recordings of asthma or COPD in 85% of cases, and false positive cases of mental illness were recorded as depression in 46% and harmful or dependent use of alcohol in 32% of cases (Table 3.6). Peripheral vascular disease was identified using both ICD-10 and OPCS-4 codes and had a sensitivity of 67.2% and PPV of 47.7%. Examining the ICD-10 code alone gave a similar sensitivity (51.2%, 95% CI 45.3-57.1) and PPV (51.5%, 95% CI 45.6-57.4).

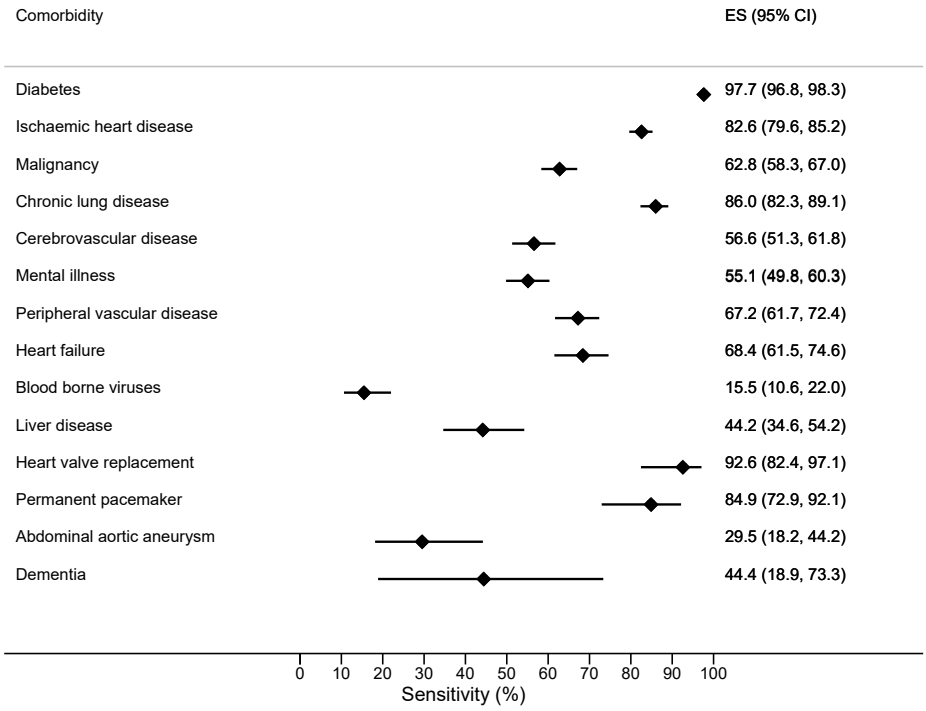


Figure 3.6. Plot displaying sensitivity (%) with 95% confidence intervals for comorbidities (ordered by prevalence) derived from HES. ES: effect size, represents sensitivity (%).

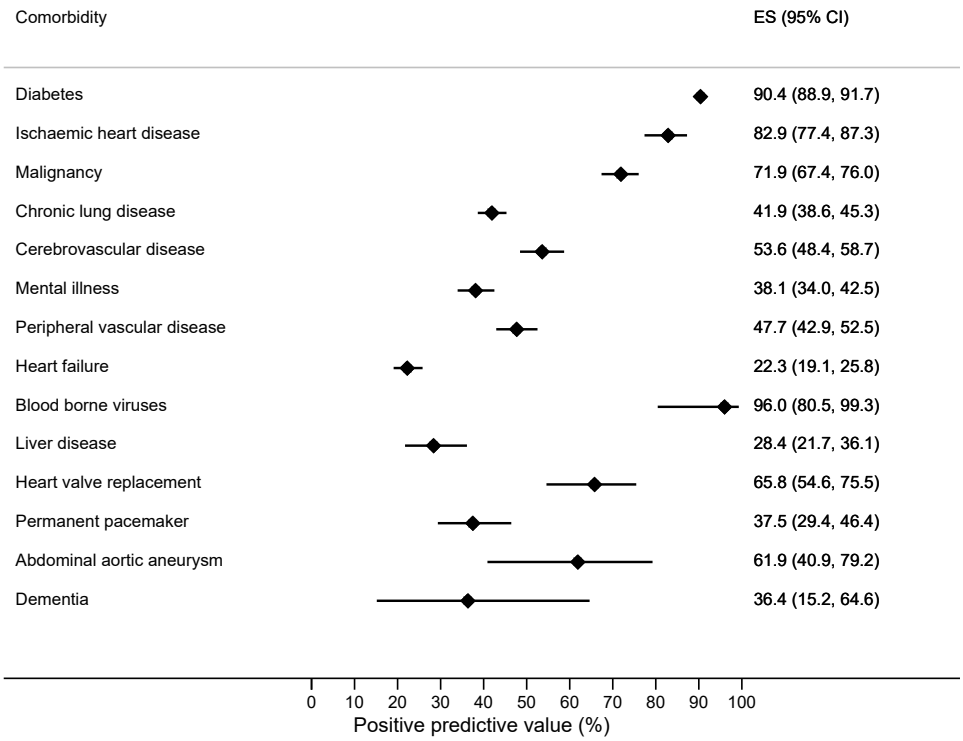


Figure 3.7. Plot displaying positive predictive values (%) with 95% confidence intervals for comorbidities derived from HES. ES: effect size, represents positive predictive value (%).

Blood borne viruses and abdominal aortic aneurysm had the lowest sensitivities but proportionately greater PPVs reflecting a higher rate of false negative cases. Liver disease and dementia both had poor sensitivities and PPVs under 50%. False positive liver disease cases were due to coding of liver transplant, fatty change of the liver and liver failure otherwise unspecified (Table 3.6).

Comorbidity	PPV (%) (95% CI)	ICD-10 or OPCS-4 code	Corresponding diagnoses	False positive cases (%)
Chronic lung disease	41.9 (38.6 – 45.4)	J45.9 J44.9	Asthma unspecified COPD unspecified	63 22
Mental illness	38.1 (33.8 – 42.6)	F32.9 F10.1 F10.2	Depression unspecified Harmful use of alcohol Alcohol dependence	46 18 14
Peripheral vascular disease	47.7 (42.8 – 52.6)	X11.8 L27.1 X10.4 X11.1	Amputation toe, other Endovascular stent graft for infrarenal AAA Amputation through metatarsal bones Amputation great toe	13 9 8 8
Heart failure	22.3 (18.9 – 25.9)	I50.1 I50.0	Congestive heart failure Left ventricular failure	47 39
Liver disease	28.4 (21.3 – 36.4)	Z94.4 K76.0 K72.9	Liver transplant Fatty change of liver Hepatic failure	30 20 19
Permanent pacemaker	37.5 (28.8 – 46.8)	K61.1 Z95.0	Implantation of cardiac pacemaker system Presence of electronic cardiac device	62 24
Dementia	36.4 (10.9 – 69.2)	F03 F01.9	Dementia unspecified Vascular dementia	75 25

Table 3.6. ICD-10 and OPCS-4 codes for conditions with a positive predictive value of under 50%, which were recorded as a positive case within HES data but a negative case within ATTOM data.

To examine whether disease prevalence was associated with the accuracy of comorbidity recording, pooled sensitivities and PPVs were calculated. The three most prevalent comorbidities comprising diabetes, ischaemic heart disease and malignancy had a greater pooled PPV than all other conditions combined at 81.8% (95% CI 70.1-93.6) versus 48.1% (95% CI 37.1-59.0) ($p<0.001$) but the association between recording accuracy and disease prevalence was not linear.

There was no variation in sensitivity or PPV based on whether a diagnosis was made using an ICD-10 code alone or a combination of ICD-10 and OPCS-4 codes. The pooled sensitivity of conditions identified from ICD-10 and OPCS-4 criteria was 69.6% (95% CI 56.4-82.8), and from ICD-10 codes alone 59.8% (95% CI 39.7-80.0) (p=0.43). The pooled PPV of ICD-10 and OPCS-4 diagnoses was 58.1% (95% CI 43.3-73.0) and for ICD-10 diagnoses alone was 53.5% (95% CI 29.5-77.5) (p=0.74).

The sensitivity and PPV of Charlson scores derived from hospital data are shown in Table 3.7. These declined with rising Charlson score. The sensitivity and PPV of a Charlson score of 0 were 88.2% and 82.9% respectively, and for a Charlson score of 1-2 were 83.9% and 66.6%.

Charlson comorbidity index	Sensitivity (95% CI)	Specificity (95% CI)	PPV (%) (95% CI)	NPV (%) (95% CI)	Kappa
0 (n=3031)	88.2 (86.8 - 89.5)	87.2 (86.1 - 88.4)	82.9 (81.3 - 84.4)	91.3 (90.3 - 92.3)	0.74
1-2 (n=1518)	83.9 (82.3 - 85.4)	70.9 (69.3 - 72.5)	66.6 (64.8 - 68.3)	86.5 (85.1 - 87.7)	0.53
3-4 (n=583)	73.1 (69.6 - 76.5)	84.7 (83.6 - 85.7)	39.3 (36.6 - 42.1)	95.9 (95.2 - 96.4)	0.42
≥5 (n=292)	67.9 (61.9 - 73.5)	93.0 (92.2 - 93.6)	32.8 (28.9 - 36.9)	98.3 (97.9 - 98.6)	0.40

Table 3.7. Sensitivity, specificity, positive and negative predictive values and Kappa statistic of HES data Charlson score as compared to ATTOM data.

3.9 Discussion

This chapter describes the datasets used within this thesis and examines the accuracy of comorbidity recording within HES compared to data collected by trained research nurses in the ATTOM study. This data validation exercise shows the record linkage rate and proportion of patients with comorbidity data before starting KRT are high, but there is variation in the sensitivity and positive predictive values of conditions derived from HES. This suggests HES is adequate for capturing comorbidities including diabetes, ischaemic heart disease and malignancy, but caution should be used if using this resource to identify a full spectrum of conditions.

There are several possible explanations for the variation in recording accuracy. First, accuracy may be influenced by the likelihood of a condition being directly implicated in hospital admission. Acute coronary syndromes and the management of malignancy are likely to require

hospitalisation and were accurately recorded, whilst conditions predominantly monitored as an outpatient such as blood borne viruses and aortic aneurysms had lower sensitivities. Whilst the working diagnosis will influence the likelihood of hospital admission, this will also vary with clinician, social and geographical factors. It was not possible to examine variation in recording accuracy between hospitals due to patients having admissions across multiple sites and the small number of patients attending certain hospitals, but inter-centre variation may exist.

Second, variations in diagnostic criteria may lead to discrepancies in recording. For example, echocardiogram abnormalities are common in people on dialysis in the context of volume overload but there may not be structural or functional cardiac dysfunction when the patient is at their dry weight. [234] Extracellular fluid overload could be misinterpreted as heart failure and recorded as such in clinical notes, but stricter diagnostic criteria were used in the ATTOM study proforma. Variation may also reflect how 'presumed' diagnoses are recorded e.g. malignancy without histological confirmation.

Third, the granularity of ICD-10 and OPCS-4 coding systems should be considered. Amputations are coded as a procedure within HES but the reason for amputation is not documented. Here it was assumed lower limb amputations relate to peripheral vascular disease, though some may have traumatic, infective, or malignant aetiologies. Examining ICD-10 diagnosis codes for peripheral vascular disease alone did not substantially improve the PPV. Previous studies have suggested that severe disease is more likely to be correctly recorded, [235] so it might have been expected that individuals with peripheral vascular disease requiring amputation to also have ICD-10 coding.

Previous studies have assessed the accuracy of hospital coding with reference to primary care and disease registry data, and recommended ways to maximise data quality. Herrett et al. examined the recording of acute myocardial infarction within HES, reporting a PPV of 91.5% with reference to a myocardial infarction registry. [220] However, a third of cases were missed and they suggest linked datasets from more than one source can reduce biased estimates. [220 236] Careful selection of ICD-10 codes is also important: a meta-analysis examining stroke recording found a wide variation in PPV, with the most accurate studies using stroke-specific as opposed to general cerebrovascular disease codes. [221] Finally, the PPV can be increased if diagnoses are counted only if they correlate to the treating specialty, are in the primary diagnosis position, or documented more than once. [237] These techniques will however reduce sensitivity, so a balance must be found.

Lessons on improving routine healthcare data quality can also be taken from countries which achieve higher data quality. [238] Denmark has a similar healthcare system to the UK and has excellent routine healthcare data which is easily accessible for research purposes. Consultants prospectively enter medical diagnoses into clinical databases that record the quality of healthcare delivered, and as these are used to assess treatment effectiveness and in research there are constant efforts to ensure the data is valid. [239] Coding accuracy in the UK does appear to be improving, [240] especially since the introduction of Payment by Results in 2004 which is presumed to have been driven by providers wishing to ensure payment meets costs incurred. One systematic review reported an improvement in the median accuracy of primary diagnosis from 74% to 96% when comparing datasets with case notes since 2002, and suggests that accuracy is now sufficiently high that data are robust enough for use in research studies. [240] It is likely however that data quality will fluctuate over time (even if there is a trend towards improvement) and between healthcare providers.

One study has previously examined the accuracy of HES comorbidity data in patients on KRT, using UKRR comorbidity returns as their reference. [241] Overall 'good' concordance was found between sources, but the information was not as granular as is presented here and 50% of patients had missing UKRR comorbidity information. HES comorbidity was however predictive of mortality and partially explained variation in outcomes between centres. [241] It is therefore possible that hospital data could minimise bias arising from comorbidity accrual in longitudinal observational studies. [242]

Using routine healthcare data for research purposes comes with economic and practical advantages: it is of low burden to participants and researchers, allows longitudinal follow up of patients, and captures a large study population with high data completeness (96% in this population) adding to the applicability of research findings. Datasets used for hospital reimbursement also provide a 'real-world' view of hospitals care and insight into the financial impact of treatment.

Challenges however do exist. First, not all patients are represented within HES and 2.6% of datasets in this chapter were not linked. This could be explained by patients opting-out of record sharing between NHS Digital and third parties which results in the loss of 2% of hospital episodes. [209] However, demographic factors were associated with linkage rates, with patients of Black ethnicity being less likely to have linked datasets. This has been noted in previous studies which hypothesise that this relates to errors in name structure or spelling with subsequent erroneous

hospital numbers used for record linking [227 243 244] and could result in bias and inequity of representation in research.

Second, HES does not capture treatment in primary care, in the private sector or outside of England. The development of comorbidity is often associated with hospitalisation and nearly 90% of individuals had an admission within a year of KRT start, so for this population it seems unlikely for significant uncaptured community comorbidity accrual to have occurred. Variation in admission thresholds between hospitals or over time however will impact the quantity of available information. It is also not known if the absence of hospital data reflects no hospital contact or a loss to follow up. Similarly, hospital data cannot code conditions as absent, so lack of documentation does not definitively confirm absence of disease.

Third, the data inputted into HES are extracted from patient notes often completed by junior members of the medical team, with trained medical coders selecting the best aligned ICD-10 and OPCS-4 codes. The quality of the data depends on the documented information, [245] experience of the coder and whether any systematic errors occur during the data collection process. Further, there may be changes in criteria for making a diagnosis over time or incentives to report certain treatments, which may result in variation in coding accuracy or completeness.

Fourth, whilst cheaper than employing staff to gather patient information, the time and cost in gaining access to hospital data may be a barrier to its use. A new application for HES data costs £1030 and linking a bespoke dataset costs £2060. [246] The time to receive data varies depending on the information required, but for this project took 2 years.

Finally, the granularity of routinely collected data may be inadequate for certain studies. For example, at the time of this data analysis the coding for AMI did not allow distinction between the different classes of AMI (Type 1-5; Chapter 1 Section 1.7.2). In 2017 an ICD-10 code for type 2 AMI was introduced. [247] However this code is still poorly utilised, and studies have had to use alternative strategies to distinguish type 1 and type 2 AMI, for example by removing patients where secondary diagnoses were present which were deemed to have potential to contribute to a type 2 event through cardiac oxygen supply and demand mismatch. [248] Type 2 AMI is more common in patients with CKD than in those with normal kidney function, [94] and recognising this diagnosis is essential when considering the utility of CAD screening (as screening may not be expected to prevent type 2 events). The granularity of codes may represent a limitation to the future analyses in this thesis. Further, it is not possible to determine disease severity through this

method of diagnosis recording. The diagnosis coding decisions adopted in this thesis are pragmatic, and work with clinical coders is needed to ensure accurate use of coding systems. [249]

The data presented here has several strengths. The ATTOM cohort is broadly representative of the UK KRT population [205] and the accuracy of HES data is reported with greater granularity and a lower rate of missing reference data than previous studies. [250] The reference data collected by trained research nurses is likely to be accurate and reflects standard practice in most clinical research studies.

There are limitations to these analyses. ATTOM comorbidity was used as gold standard, and although data validation suggested a high concordance between staff this source may still contain errors. Current HES data quality may also differ from the 2006-2013 dataset used here. A rise in the number of completed coding fields in HES over time could yield greater data accuracy, but the possibility of over-diagnosis should be considered. [240] [250]

3.10 Conclusion

The HES dataset captured comorbidity information in 96% of patients before the start of KRT, but there is variation in data accuracy as compared to study data collected by ATTOM research nurses. HES data were accurate for the most prevalent conditions, and notably ischaemic heart disease, but it may be less suitable for recording a full complement of comorbidities. Understanding patterns of comorbidity among people with advanced kidney disease is crucial in informing policy and service planning. The quality of ischaemic heart disease data is such that it could be used to examine the occurrence of cardiac events in patients with ESKD, hence it is used for this purpose in Chapters 4 and 5.

Chapter 4: Incidence and impact of major adverse cardiac events on transplant recipients and waitlisted patients

4.1 Introduction

As discussed in Chapters 1 and 2, kidney transplantation is the optimal treatment for patients with ESKD deemed fit to receive it. Transplantation is associated with an increased survival compared to being on dialysis due to a reduction in medium- to long-term cardiovascular risk. [123] However a short-term period of elevated cardiovascular risk is seen early post-transplant relating to an increased incidence of acute coronary syndromes, stroke, and cardiovascular death. [2 123 124 125 251 252]

Before examining whether pre-transplant screening for asymptomatic CAD is effective at reducing post-transplant MACE (Chapter 5), this chapter aims to determine the incidence, associations, and impact of MACE on kidney transplant recipients in the current English dataset. This is important because:

- Quantifying the incidence of MACE ensures the current 'comparator' rate is known if any change to screening practice were to occur.
- Determining the demographic and clinical factors associated with MACE can assist with identifying which patients are at the highest risk of cardiac events, aiding risk stratification and informing existing screening processes.
- Understanding the impact of MACE on patient and graft outcomes allows informed discussions with patients about the potential consequences of cardiac events.

To interpret cardiac risk in the context of transplantation, a comparison to a patient's risk if <u>not</u> transplanted must also be considered. As patients with ESKD are at an increased risk of cardiovascular disease compared to the general population, and transplant recipients are younger and less comorbid than the dialysis population (Chapter 1), the best comparator group are patients active on the kidney transplant waitlist. Cardiovascular disease is the leading cause of death on the kidney transplant waitlist, [253] but ischaemic cardiac events could also result in waitlist suspensions thereby delaying transplantation, or render patients unsuitable for

transplantation. The incidence and impact of MACE on waitlisted patients must therefore also be quantified.

4.2 Aims

The aims of this chapter are to:

1. Determine the incidence of MACE in kidney transplant recipients and waitlisted patients in England.
2. Define the demographic and clinical associations with MACE in kidney transplant recipients and waitlisted patients.
3. Examine the association between MACE and:
    a) Death and graft failure in transplant recipients
    b) Suspension episodes in waitlisted patients

Due to number and complexity of analyses, general methods are presented first, followed by specific methods, results, and discussion for analyses corresponding to each of the three aims.

4.3 General methods and results

4.3.1 Study population

Patients from the ATTOM study who either received a kidney-alone transplant or were active on the kidney transplant waitlist are included within this chapter, as demonstrated in Chapter 3 Figure 3.2.

Transplant recipients comprise all patients recruited to ATTOM who received a kidney-alone transplant by 31st December 2017 (the end of available HES data) irrespective of their original ATTOM cohort (incident transplant, waitlisted or incident dialysis). Patients who were transplanted but were recruited to more than one ATTOM cohort could only contribute 1 record to transplant recipient analyses.

Waitlisted patients comprise those from the ATTOM waitlisted cohort, and patients in the ATTOM incident dialysis cohort who were waitlisted following dialysis initiation. Data on waitlisting were only available for 2 years following dialysis initiation; patients waitlisted after 2 or more years on dialysis were therefore not included. Patients in the ATTOM incident transplant cohort were excluded to avoid introducing survivor bias, a form of selection bias that would occur given all

these patients survived the waitlisting period and went on to receive a transplant. To ensure an incident waitlisted population was examined, patients were excluded if they were activated on the transplant waitlist before 1st January 2011. This date was chosen as it was within 1 year of the start of ATTOM recruitment.

Waitlisted patients who were subsequently transplanted could contribute records to both the transplant recipient and waitlisted patient analyses in this chapter. There were 1012 patients who contributed to both waitlisted and transplanted groups. These patients were included in the waitlisted cohort until the day before transplantation, and in the transplant cohort from the day of transplantation to the date of study end or death (whichever occurred first).

The characteristics of transplant recipients and waitlisted patients were compared using descriptive statistics, using the Chi-square test for categorical variables and Mann Whitney U test for non-parametric continuous variables.

4.3.2 Definition of MACE

MACE was defined as the occurrence of unstable angina, acute myocardial infarction (comprising STEMI and NSTEMI), coronary artery bypass graft (CABG), coronary angioplasty or cardiac death (Chapter 2). [254]

Non-fatal MACE events were identified from HES APC data; only events requiring an overnight hospital stay were included. The ICD-10 codes for STEMI and NSTEMI were selected to be those used by the Myocardial Ischaemia National Audit Project (MINAP), a national initiative that audits the care of patients presenting to hospitals in England and Wales with acute coronary syndromes. [255] The additional ICD-10 and OPCS-4 codes used to identify unstable angina and revascularisation procedures were the same as those used in Chapter 3 to identify ischaemic heart disease diagnoses, as shown in Appendix B. Unstable angina and NSTEMI codes were only recorded as MACE if they were in the primary diagnosis position in HES, whilst STEMI codes were counted if they were present in any diagnosis position. This is in keeping with MINAP guidance, which selects codes in this manner in an attempt to improve capture of type 1 as opposed to type 2 AMI. [249]

Cardiac deaths comprised those caused by myocardial ischaemia and infarction, sudden death of unknown cause, cardiac failure or pulmonary oedema/fluid overload as per the ERA coding

system. [219] Date and cause of death were obtained from the UKRR and NHSBT (Table 4.1); these data were merged with the ATTOM dataset prior to HES linkage as per the HES data sharing agreement (Appendix B).

The definition of MACE was intentionally kept narrow to only include diagnoses consistent with ischaemic heart disease. The reasons for this are twofold: first, Chapter 5 focusses on screening for asymptomatic coronary artery disease prior to transplantation, where the outcome of interest is ischaemic cardiac events as opposed to other cardiovascular diseases such as stroke. Second, coding of ischaemic heart disease in HES has a greater sensitivity and specificity than coding for other cardiovascular diagnoses (Chapter 3) giving greater confidence in the accuracy of results.

A detailed summary of the sources of data used in Chapters 4 and 5 are demonstrated in Table 4.1. The last date of available data from HES was 31st December 2017, whilst data on graft and patient survival from the UKRR and NHSBT were available until 1st January 2020 (Figure 4.1). To make full use of the available data, there are different end dates for the analyses in Sections 4.4 to Section 4.7.

Data	Definition	ATTOM	HES	UKRR	NHSBT
Transplant recipients (Chapters 4 and 5)					
Date of transplantation	Date of transplantation and any subsequent transplant in the event of re-transplantation after graft failure	•			•
Transplant type	Organ received and donor type (living donor, DBD or DCD)	•			•
Comorbidities	Comorbidities present at transplantation	•	•		
MACE	Hospitalisation with unstable angina, AMI or revascularisation procedure, or death from a cardiac cause after transplantation		•	•	•
1- and 5-year creatinine	Creatinine and 1- and 5-years post-transplant for patients with a functioning graft at these time points			•	•
Date of graft failure	Date of graft failure with return to dialysis or re-transplantation (of note, it is not possible to capture patients choosing conservative management of ESKD on graft failure)				•
Date of death	Date of death			•	•
Cause of death	Cause of death as per ERA coding system (where applicable)			•	•
Waitlisted patients (Chapter 4)					
Date of waitlisting	Date of activation of transplant waitlist	•			•
Waitlist suspensions	Start date and duration of each suspension episode (where applicable)				•
Waitlist removal	Date of removal from waitlist				•
Comorbidities	Comorbidities present at date of waitlisting	•	•		
MACE	Hospitalisation with unstable angina, AMI or revascularisation procedure, or death from a cardiac cause whilst on the waitlist		•	•	•
Date of transplantation	Date of transplantation	•			•
Date of death	Date of death			•	•
Cause of death	Cause of death as per ERA coding system (where applicable)			•	•

Table 4.1. Origin of data used in analyses in Chapters 4 and 5.

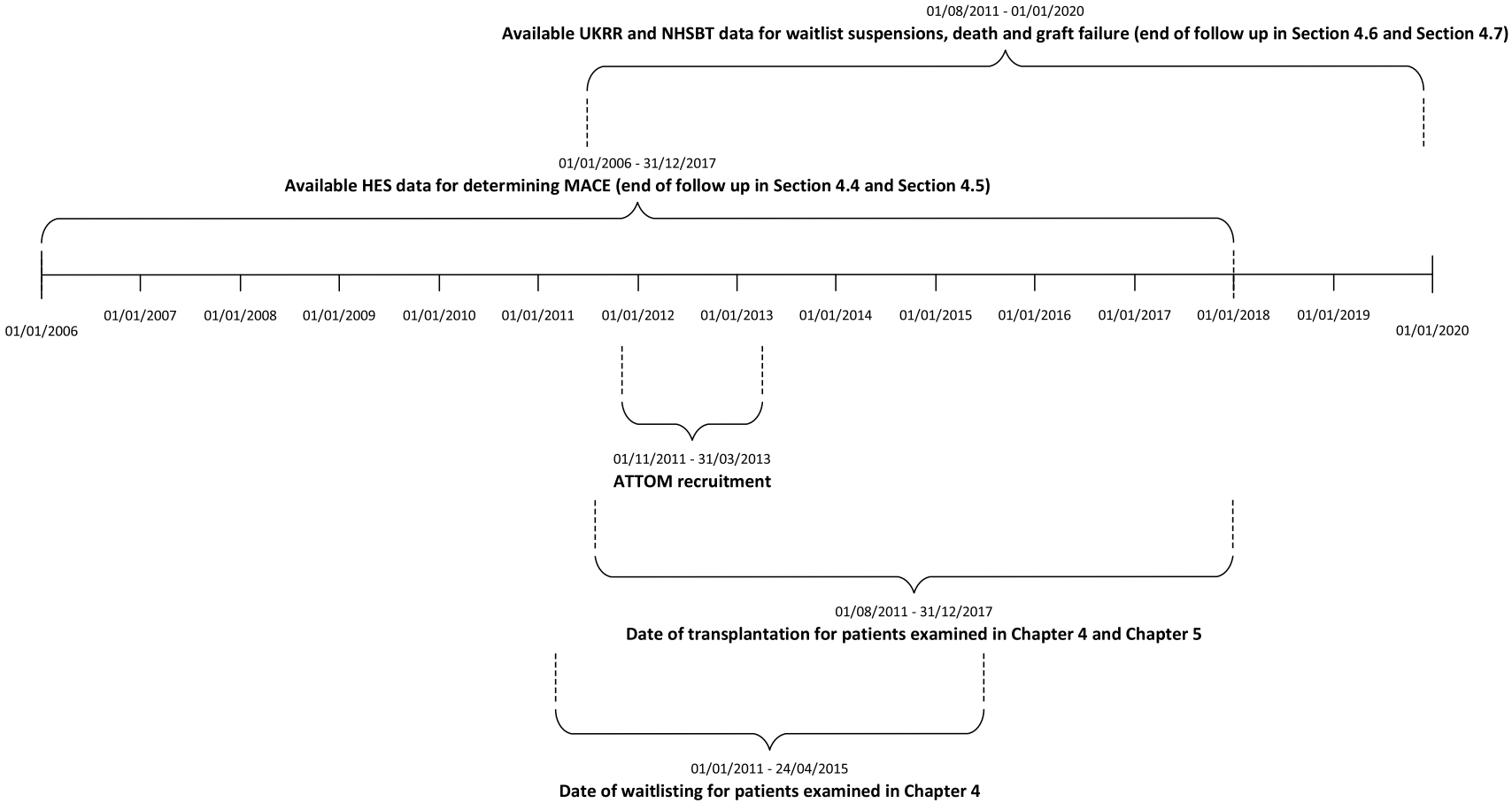


Figure 4.1. Timeline showing dates of transplantation and waitlisting, and dates of available HES, UKRR and NHSBT data resulting in the differing end points used in analyses within this chapter.

4.3.3 Description of study population

In total, 3251 patients received a kidney-alone transplant by 31st December 2017 (Figure 4.2). Median follow up time was 4.74 years [IQR 3.2-5.4].

There were 1432 patients waitlisted for a kidney-alone transplant after 1st January 2011 (Figure 4.2). Median follow up time was 2.35 years [IQR 1.10-4.12].

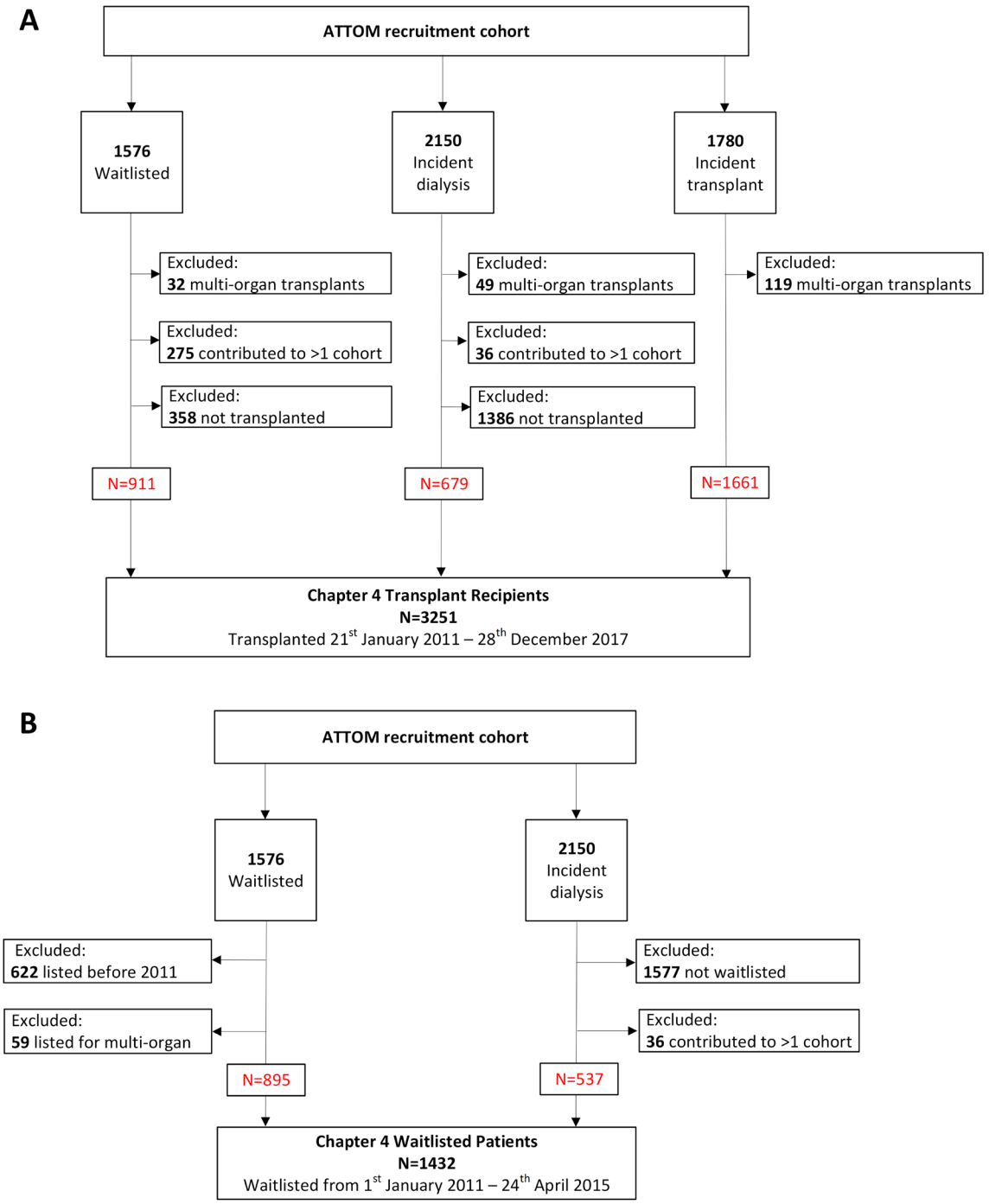


Figure 4.2. Flow chart depicting the origin of patients included within this chapter, in (A) transplant recipients and (B) waitlisted patients.

Characteristics of transplant recipients and waitlisted patients are shown in Table 4.2. Transplant recipients were less likely to have their PRD listed as diabetic nephropathy or 'uncertain' than those waitlisted and were less likely to have diabetes or peripheral vascular disease. Transplant

recipients had a longer follow up time, likely relating to waitlisted patients being censored at transplantation.

Of the 1432 waitlisted patients, 1012 (71%) were transplanted over follow up. The median time to transplant from waitlisting was 1.7 years [IQR 0.8-2.9]. These 1012 patients have contributed to the analyses of transplant recipients in addition to the analyses of waitlisted patients.

	Transplant recipients N=3251	**Waitlisted patients N=1432**	**P value**
Age (years) (n=4146)	50 [40-60]	50 [40-60]	0.70
Male sex (n=4146)	2013 (62)	888 (62)	0.95
Ethnicity (n=4134)			
White	2448 (75)	1027 (72)	
Asian	474 (15)	237 (17)	0.06
Black	290 (9)	151 (11)	
Mixed	31 (1)	11 (1)	
PRD (n=4102)			
GN	768 (24)	324 (23)	
Other	697 (22)	302 (22)	
PKD	512 (16)	196 (14)	
Uncertain	393 (12)	210 (15)	**0.003**
PN	312 (10)	104 (7)	
Diabetes	292 (9)	165 (12)	
Hypertension	215 (7)	87 (6)	
Renovascular	36 (1)	15 (1)	
History of Diabetes (n=4146)	465 (14)	272 (19)	**<0.001**
History of IHD (n=4146)	251 (8)	127 (9)	0.18
History of PVD (n=4146)	72 (2)	48 (3)	**0.02**
History of CeVD (n=4146)	134 (4)	72 (5)	0.16
Ever smoker (n=4036)	1076 (34)	513 (37)	0.06
IMD (n=4146)			
1 – Most deprived	793 (24)	397 (28)	
2	667 (21)	301 (21)	
3	622 (19)	259 (18)	0.12
4	623 (19)	258 (18)	
5 – Least deprived	546 (17)	217 (15)	
Median follow up time (years)	4.74 [3.2 – 5.4]	2.35 [1.10 – 4.12]	**<0.001**
MACE over follow up	251	161	**-**

Table 4.2. Baseline demographics of transplant recipients and waitlisted patients. Numbers presented are median [IQR] or number (%). Analyses are performed using the Chi-square test (categorical variables) or Mann Whitney U test (continuous variables).

4.4 Incidence of MACE

4.4.1 Methods

The incidence of MACE for transplant recipients and waitlisted patients was calculated and expressed as events per 1000 patient years [95% confidence interval] at 90 days, 1, 2, 3, and 5-years from transplantation or waitlisting respectively. The incidence of individual MACE components (STEMI, NSTEMI or unstable angina; revascularisation procedures; cardiac death) were calculated in addition to the composite outcome.

In all analyses, patients were censored for non-cardiac death. Waitlisted patients were additionally censored at transplantation and transplant recipients were censored at re-transplantation due to the increased risk of MACE in the peri-transplant period. Transplant recipients were not censored for graft failure to capture a 'real world' incidence of post-transplant MACE, with transplantation being the risk exposure event. Further, the reasons for graft failure are wide-ranging and may not be related to recipient cardiovascular events, [256] [257] though there is an increased risk of MACE after graft failure. [258] [259]

Time to MACE was calculated from day of transplantation or waitlisting to date of hospitalisation with unstable angina, STEMI or NSEMI, date of angioplasty or coronary artery bypass graft, or date of cardiac death. End of follow up was 31st December 2017.

4.4.2 Results

In transplant recipients, the incidence of MACE was greatest in the first 90 days post-transplantation, with 59.6 (95% CI 44.8-79.3) events occurring per 1000 patient years (Table 4.3). The incidence rate at 1 year was over 50% lower at 25.7 (95% CI 20.6-32.0) events per 1000 patient years and plateaued at 19-20 events per 1000 patient years by 2 years post-transplantation. Similar reductions in incidence rate were seen across the individual MACE components. The greatest event rate was for coronary revascularisation procedures, and the lowest was for cardiac deaths.

Of the 251 transplant recipients with a MACE event over follow up, 23 patients had an event during the index admission for kidney transplantation (9.2%). This represents 29% (n=23/80) of

MACE that occurred within the first post-transplant year and 0.7% of all kidney transplant admissions.

	Incidence rate per 1000 patient years (95% CI)				
	90 days	**1 year**	**2 years**	**3 years**	**5 years**
Unstable angina and myocardial infarction	35.4 (24.4-51.3)	11.8 (8.6-16.3)	8.2 (6.2-10.8)	8.0 (6.3-10.1)	7.7 (6.3-9.4)
Coronary angiography and CABG	40.5 (28.6-57.2)	19.5 (15.2-25.1)	16.1 (13.2-19.6)	15.3 (12.9-18.1)	15.6 (13.6-17.9)
Cardiac death	8.8 (4.2-18.5)	3.2 (1.7-5.8)	2.3 (1.3-3.8)	2.3 (1.5-3.5)	3.2 (2.3-4.3)
Overall MACE	59.6 (44.8-79.3)	25.7 (20.6-32.0)	20.1 (16.8-24.0)	19.6 (16.9-22.8)	19.2 (16.9-21.7)
Cumulative incidence	1.5%	2.6%	4.1%	5.9%	9.6%

Table 4.3. Incidence rate of MACE per 1000 patient years in transplant recipients (n=3251).

	Incidence rate per 1000 patient years (95% CI)				
	90 days	**1 year**	**2 years**	**3 years**	**5 years**
Unstable angina and myocardial infarction	17.9 (8.0-39.8)	12.0 (7.2-19.9)	10.5 (7.0-15.8)	12.3 (8.8-17.1)	11.5 (8.4-15.6)
Coronary angiography and CABG	38.9 (22.6-66.9)	26.3 (19.1-36.3)	33.1 (26.2-41.7)	36.8 (30.3-44.7)	37.2 (31.1-44.3)
Cardiac death	3.0 (0.4-21.1)	2.4 (0.8-7.4)	2.7 (1.2-6.0)	4.8 (2.9-8.2)	7.9 (5.5-11.4)
Overall MACE	41.8 (24.8-70.6)	33.0 (24.3-44.9)	36.8 (29.5-45.9)	42.3 (35.3-50.7)	43.8 (37.4-51.2)
Cumulative incidence	1.0%	3.3%	7.4%	12.8%	21.9%

Table 4.4. Incidence rate of MACE per 1000 patient years in waitlisted patients (n=1432).

Of the 1432 waitlisted patients, MACE occurred in 161 patients with a median time to MACE from waitlisting of 2.2 years [IQR 1.0-3.1].

In waitlisted patients (Table 4.4), the incidence rate of MACE in the first 90 days post-waitlisting was 41.8 (95% CI 24.8-70.6) events per 1000 patient years - lower than the equivalent rate post-transplantation. The incidence rate at 1 year was slightly higher than transplant recipients at 33.0 (95% CI 24.3-44.9) events per 1000 patient years and increased further to 36.8 events per 1000 patient years by 2 years post-listing. At all timepoints, the greatest event rate was for coronary revascularisation, and the lowest was for cardiac deaths.

Of the 843 (59%) patients still active on the transplant waitlist at the median waiting time to deceased donor transplantation in the UK (675 days in 2017/2018 [52]), 6.1% had developed a MACE event.

The timings of MACE are demonstrated pictorially in recurrent event plots following transplantation (Figure 4.3) and waitlisting (Figure 4.4).

Figure 4.3. Recurrent event plot demonstrating timing of non-fatal MACE and cardiac deaths (red triangle) in a sample of 1000 transplant recipients. Early events within the hashed box are those which screening aims to reduce.

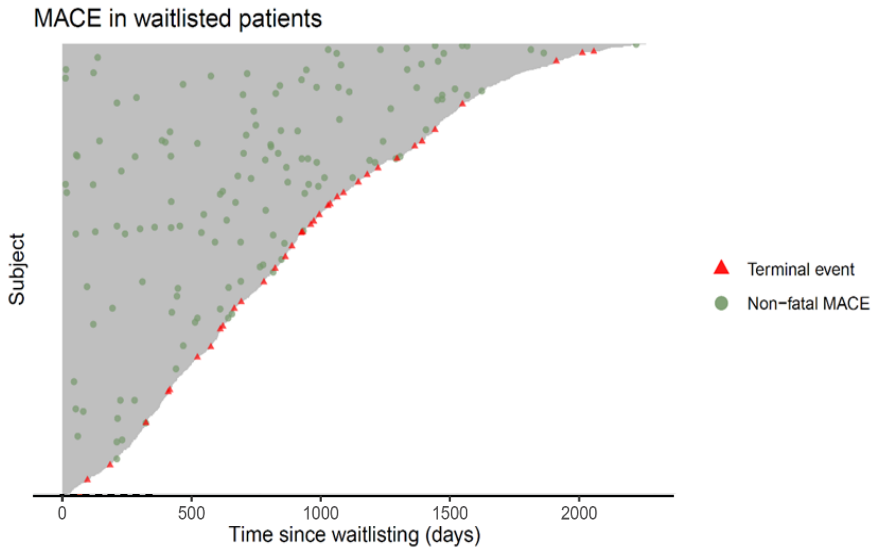


Figure 4.4. Recurrent event plot demonstrating the timing of non-fatal MACE and cardiac deaths (red triangle) in a sample of 1000 waitlisted patients. The density of events is roughly evenly distributed.

A Kaplan-Meier curve examining time to MACE in transplant recipients and waitlisted patients (Figure 4.5) highlights the increased incidence of MACE in transplant recipients compared to waitlisted patients in the early post-transplant period. After approximately 9 months a greater incidence of MACE was observed in the waitlisted patients.

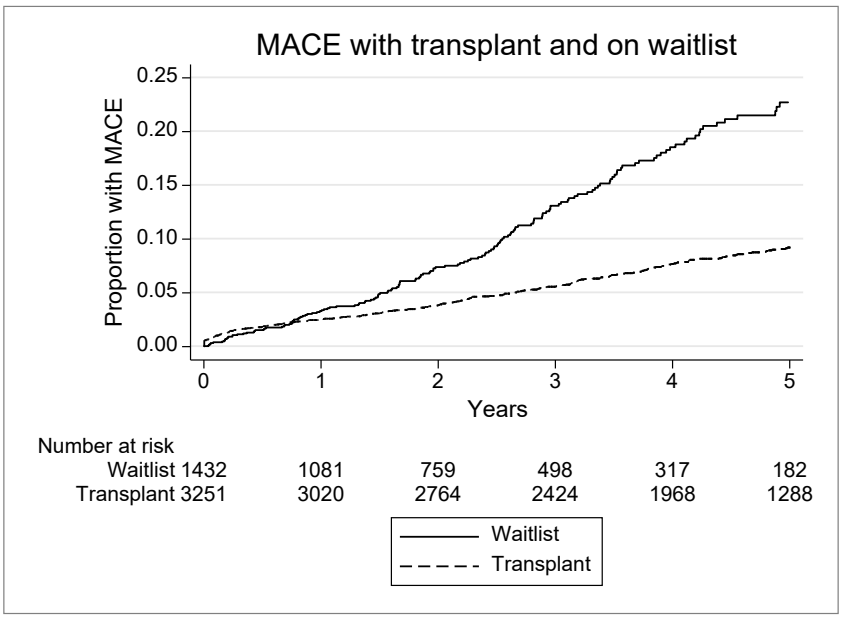


Figure 4.5. Kaplan-Meier curve demonstrating time to MACE in kidney transplant recipients and waitlisted patients, showing the increased incidence of MACE in the early post-transplant period.

4.4.3 Discussion

The incidence of MACE following kidney transplantation has been described previously in US studies but has not been quantified in a UK cohort. [146 260 261 262] This chapter reports a cumulative incidence of MACE at 3 months, 1-, 3- and 5 years post-transplant of 1.5%, 2.6%, 5.9% and 9.6% respectively. The highest rate of events was observed in the first 90 days after kidney transplantation, with a progressive fall thereafter and a stable MACE rate being reached from the second post-transplant year onwards.

This rate is considerably lower than that reported in North American studies. One US study of 35,000 transplant recipients from 1995-2000 reported a cumulative incidence of post-transplant AMI of 5.6% at 1 year and 11.5% at 3 years. [260] A more recent study of 147,000 patients transplanted between 2004-2013 used a broader definition of MACE, also including stroke, heart

failure and all-cause mortality, and described an incidence of 6.5% during the index admission alone, with three quarters of events being heart failure episodes. [147] The multi-national PORT study, which included patients from North America, Europe and the Pacific Rim, had a similar definition of MACE as to here and a comparable incidence of 3.1% and 5.2% at 1- and 3-years post-transplant respectively. [146]

The variation in incidence of MACE between studies likely relates to differences in the definitions used, data sources interrogated, and geographical location. For example, the US studies above extracted events from medical insurance records, with which there could be a possibility of over-diagnosis or treatment. [263] Even within one population and one MACE definition, the data source used could still alter incidence rates substantially, as demonstrated by the differing identification of AMI cases from HES, MINAP and primary care data within the UK [220] and in the comparison of ischaemic heart disease diagnoses between ATTOM and HES outlined in Chapter 3.

In addition to understanding how the rate of post-transplant MACE in the UK compares to other countries, it is also important to consider how the peri-transplant MACE risk compares to that of other surgical operations. In the current analysis, MACE occurred during the index admission of 0.7% of kidney transplant operations. A systematic review of peri-operative MACE in dialysis patients, defined as events within 30 days of surgery or during the index admission, reported an incidence of 2.0% in patients undergoing major abdominal surgery, 6.7% in patients undergoing orthopaedic surgery, and 7.7% in patients undergoing vascular surgery. [264] These rates were calculated from all dialysis patients – an unknown proportion of whom were listed for kidney transplantation – and so likely to reflect an older and more comorbid cohort than the population examined here. [265] Nonetheless, the MACE risk associated with transplantation is close to that of other major elective or emergency surgeries, so it would appear logical to apply similar patient selection principles to both settings.

Whilst in kidney transplant recipients the MACE rate fell over time, the MACE rate remained relatively static in patients on the kidney transplant waitlist (Table 4.4), though a progressive rise in the rate of cardiac death was observed with proportionately fewer unstable angina and AMI events. This may be surprising given that dialysis duration is associated with an increased risk of cardiovascular events, at least in kidney transplant recipients. [39 50] Whilst dialysis vintage is associated with mortality in patients who are not transplanted, [266 267] the same association with AMI may not be seen, [268] possibly due to the lesser contribution of atherosclerosis to cardiac risk in the ESKD population. [89]

The cumulative incidence of MACE in waitlisted patients was slightly lower than that described in North America, with annual incidence rates of 8.7-16.7% being reported in the USA, [252] and 4.5% for non-diabetics and 12.7% for diabetics in Canada. [269] When comparing the MACE rate in kidney transplant recipients and waitlisted patients however, a similar pattern to previous studies was observed. [2 123] Kidney transplant recipients had higher risk of MACE than waitlisted patients for around 9 months, following which the risk fell, similar to that reported by Wolfe et al. in 1999. [2]

4.5 Associations with MACE

4.5.1 Methods

The associations between patient demographic and clinical characteristics and MACE were examined in transplant recipients and waitlisted patients. Covariates included in the final model comprised age, sex, ethnicity, socioeconomic status (as per the index of multiple deprivation, IMD), PRD, history of diabetes, ischaemic heart disease, peripheral vascular disease or stroke, smoking history and KRT at the time of transplantation/waitlisting versus being pre-emptively transplanted/waitlisted. PRD was classified as diabetic nephropathy versus all other PRDs to reduce the number of covariates in the resulting model. Pre-emptive transplantation/waitlisting was used as an approximate marker for ESKD duration as KRT duration was not available. Obesity was originally examined but was not included in the final model due to a high proportion of missing data (6% in transplant recipients and 11% in waitlisted patients). Donor type was also examined in transplant recipients but given the interest was in determining patient characteristics associated with MACE, and fact donor type cannot be determined at the point of transplant listing when attempting to risk stratify patients, it was also not included in the final model. Similarly, other organ and post-transplant variables were not examined in transplant recipients as the aim was to identify pre-transplant factors that could identify patients at risk of MACE to guide the analysis of screening in Chapter 5, which is performed based on recipient characteristics alone. The multivariable model included complete cases only, present in 3135 (96.4%) and 1361 (95.0%) of transplant recipients and waitlisted patients respectively.

Univariable followed by multivariable Cox regression models were performed to examine the association between the above variables and time to MACE. The proportionality assumption of the Cox models were tested using Schoenfeld residuals and was satisfied in all analyses. Statistical tests were two-tailed with significance defined *a priori* as $p<0.05$.

4.5.2 Results

In transplant recipients, patient characteristics associated with MACE by multivariable analysis included increased age, Asian ethnicity, history of diabetes, ischaemic heart disease, peripheral vascular disease, smoking, and receiving KRT at the time of transplantation (Table 4.5). Donor type was not included in the final model; when examined there was no association between donor type and MACE on fully adjusted analyses. Similarly, obesity was not included in the final model but no association between obesity and MACE were seen.

	Transplant recipients (n=3251)				Waitlisted patients (n=1432)			
	Unadjusted HR (95% CI)	**P**	**Adjusted HR (95% CI)**	**P**	**Unadjusted HR (95% CI)**	**P**	**Adjusted HR (95% CI)**	**P**
Age (years)	1.04 (1.03 – 1.06)	**<0.001**	1.03 (1.02 – 1.05)	**<0.001**	1.04 (1.03 – 1.05)	**<0.001**	1.02 (1.01 – 1.04)	**0.001**
Male sex (Ref: Female)	1.53 (1.16 – 2.01)	**0.002**	1.31 (0.99 – 1.73)	0.06	1.37 (0.99 – 1.90)	0.06	1.03 (0.73 – 1.46)	0.86
Ethnicity (Ref: White)								
Asian	1.62 (1.19 – 2.21)	**0.002**	1.52 (1.09 – 2.13)	**0.02**	1.03 (0.69 – 1.54)	0.87	0.94 (0.61 – 1.45)	0.78
Black	1.11 (0.71 – 1.74)	0.65	0.99 (0.60 – 1.61)	0.96	0.72 (0.42 – 1.21)	0.21	0.70 (0.40 – 1.23)	0.22
Mixed	-	-	-	-	2.22 (0.55 – 9.02)	0.26	3.03 (0.73 – 12.51)	0.13
IMD (Ref: 1)								
2	1.03 (0.70 – 1.50)	0.89	0.91 (0.62 – 1.34)	0.62	1.78 (1.16 – 2.75)	**0.008**	1.61 (1.03 – 2.51)	**0.04**
3	1.14 (0.78 – 1.65)	0.50	0.99 (0.67 – 1.47)	0.97	1.40 (0.86 – 2.27)	0.18	1.17 (0.70 – 1.95)	0.56
4	0.96 (0.65 – 1.41)	0.82	0.90 (0.60 – 1.35)	0.61	1.06 (0.63 – 1.80)	0.63	0.91 (0.52 – 1.60)	0.75
5	1.03 (0.69 – 1.53)	0.89	0.89 (0.59 – 1.35)	0.59	1.47 (0.89 – 2.42)	0.14	1.30 (0.76 – 2.22)	0.34
Diabetic nephropathy (Ref: Other PRDs)	2.68 (1.96 – 3.66)	**<0.001**	0.86 (0.53 – 1.39)	0.54	2.22 (1.52 – 3.24)	**<0.001**	0.89 (0.51 – 1.54)	0.67
Diabetes (Ref: Absent)	2.83 (2.16 – 3.71)	**<0.001**	1.90 (1.25 – 2.89)	**0.003**	2.57 (1.86 – 3.54)	**<0.001**	1.83 (1.14 – 2.93)	**0.01**
IHD (Ref: Absent)	4.28 (3.21 – 5.73)	**<0.001**	2.48 (1.82 – 3.39)	**<0.001**	3.89 (2.73 – 5.55)	**<0.001**	2.38 (1.59 – 3.57)	**<0.001**
PVD (Ref: Absent)	3.88 (2.40 – 6.26)	**<0.001**	1.96 (1.18- 3.26)	**0.009**	3.80 (2.32 – 6.20)	**<0.001**	2.02 (1.15 – 3.55)	**0.01**
CeVD (Ref: Absent)	2.13 (1.33 – 3.40)	**0.002**	1.22 (0.74 – 2.01)	0.43	1.76 (1.03 – 2.99)	**0.04**	1.40 (0.80 – 2.47)	0.24
Ever smoker (Ref: never)	1.39 (1.08 – 1.79)	**0.01**	1.32 (1.01 – 1.71)	**0.04**	1.13 (0.82 – 1.56)	0.44	0.92 (0.65 – 1.29)	0.63
Pre-emptive (Ref: KRT)	0.46 (0.31 – 0.70)	**<0.001**	0.59 (0.39 – 0.89)	**0.02**	0.64 (0.37 – 1.09)	0.10	0.75 (0.43 – 1.31)	0.31

Table 4.5. Associations between patient characteristics and MACE in transplant recipients and waitlisted patients.

Abbreviations: IHD ischaemic heart disease, IMD index of multiple deprivation, PVD peripheral vascular disease, CeVD cerebrovascular disease

Patients with MACE events during their index transplant admission were more likely to have diabetic nephropathy than a non-diabetic PRD but did not differ by other patient characteristics compared to those with MACE at later timepoints (Table 4.6).

	MACE in index admission N=23	**MACE after index admission but <1 year N=57**	**MACE ≥ 1-year post-transplant N=171**	**P**
Age (years)	59 [54-64]	56 [50-64]	57 [49-63]	0.51
Male sex	17 (74)	42 (74)	120 (70)	0.84
Ethnicity				0.15
White	15 (66)	35 (61)	128 (75)	
Asian	4 (17)	17 (30)	31 (18)	
Black	4 (17)	5 (9)	12 (7)	
IMD				0.59
1	6 (26)	12 (21)	39 (23)	
2	8 (35)	13 (23)	30 (18)	
3	4 (17)	9 (16)	40 (23)	
4	2 (9)	12 (21)	32 (19)	
5	3 (13)	11 (19)	30 (18)	
Diabetes as PRD	10 (44)	13 (23)	26 (15)	**0.005**
Diabetes	10 (44)	16 (28)	50 (29)	0.35
IHD	7 (30)	17 (30)	36 (21)	0.30
PVD	2 (9)	6 (11)	10 (6)	0.48
CeVD	2 (9)	4 (7)	13 (8)	0.97
Ever Smoker	8 (35)	24 (44)	69 (41)	0.77
Obesity	5 (23)	11 (21)	43 (27)	0.64
Pre-emptive listing	3 (13)	6 (11)	16 (9)	0.85

Table 4.6. Characteristics of transplant recipients with MACE in their index admission, within the first post-transplant year, and over 1-year post-transplant. Values expressed are number (%) or median [IQR]. Analyses are made using the Chi-square test (categorical variables) or Kruskal-Wallis test (continuous variables).
Abbreviations: IHD ischaemic heart disease, IMD index of multiple deprivation, PVD peripheral vascular disease, CeVD cerebrovascular disease.

In waitlisted patients, factors associated with MACE by multivariable analysis included increased age and having a history of diabetes, ischaemic heart disease or peripheral vascular disease (Table 4.5). An association with one index of multiple deprivation (IMD quintile 2) was seen. There was no association between waitlist MACE and ethnicity, smoking history or whether they joined the

waitlist before they commenced dialysis. Again, obesity was not included in the final model but no association between obesity and MACE were seen on unadjusted or adjusted analyses.

4.5.3 Discussion

Identifying patient-level risk factors for post-transplant MACE aids risk-stratification prior to transplantation. In this dataset, increased age, Asian ethnicity, cardiovascular comorbidities, smoking, and waitlisting after starting dialysis associated with an increased risk of post-transplant MACE, in keeping with previous studies. [146] [270] Recognising these risk factors could aid counselling of patients prior to transplantation and identify those at increased risk of events who may benefit from closer peri-transplant monitoring. Patients with a MACE event during the index transplant admission were similar to those with MACE at later timepoints, with the exception of a higher prevalence of diabetic nephropathy.

The associations with MACE investigated in this chapter have focussed on patient characteristics that are known pre-transplantation, whilst the patient is being worked up for transplant listing. Whilst additional transplant-specific risk factors can influence a patient's cardiac risk such as acute rejection, [271] delayed graft function [260] and development of post-transplant diabetes, [146] these variables are not known pre-transplantation and so cannot assist with pre-transplant risk stratification.

Studying the transplant population specifically is important as conventional cardiovascular risk factors in patients with ESKD can associate with outcomes in the opposite direction to that observed in the general population: an observation called 'reverse epidemiology'. For example, obesity, hypercholesterolaemia and hypertension are frequently noted to be associated with improved survival in patients on dialysis. [272] This phenomenon may relate to competing risks over varying time periods e.g. the early mortality risk associated with under-nutrition outweighs longer term risks associated with obesity. It is therefore important not to rely on risk calculation tools developed for general populations (Chapter 1 Section 1.7.9) when identifying patients most likely to develop peri-transplant MACE.

Similar associations with MACE were observed in waitlisted patients as transplant recipients, with increased age, diabetes, ischaemic heart disease and peripheral vascular disease being associated with MACE. No association was seen with sex, ethnicity, or pre-emptive listing, though the

smaller population size may have prevented all risk factors being identified. As will be discussed in Section 4.8.2, recognising patients at risk of MACE whilst on the waitlist could aid decision making on organ offers, weighing up the risks and benefits on staying on the waiting list pending another offer versus proceeding with transplantation and avoiding potential accrual of waitlist cardiovascular comorbidity.

4.6 Association between early post-transplant MACE and patient and graft survival

4.6.1 Methods including description of landmark analysis

Examining the association between early post-transplant MACE and patient and graft survival is at risk of immortal time bias. Immortal time bias occurs when a patient's treatment or the exposure event occurs after the start of follow up. To experience the exposure event, patients need to survive until this point. The time between start of follow up and the exposure is therefore considered 'immortal' because individuals who die in this period cannot, by definition, experience the exposure of interest and so automatically join the control group.

Immortal time bias was first described in studies of heart transplantation as it was noted that the 'sickest' patients were more likely to die before receiving a transplant and comparatively 'healthier' patients were more likely to receive a transplant, thus giving an additional survival advantage to the transplanted group. [273] The waiting time before transplantation is 'immortal' as to receive a transplant, patients must survive until the time of the operation. Bias occurs when immortal time is misclassified as time when treatment was received (misclassified immortal time or misclassification bias) or is excluded from the analysis (excluded immortal time or selection bias) (Figure 4.6). Using this example:

- Misclassification bias occurs if transplant status is assumed to be known at the time of waitlisting, and patients who received a transplant are analysed in the transplanted group from study outset. If this is done, all follow up is counted in the 'transplanted' group even though time before transplantation is included.

- Selection bias occurs if transplanted patients are examined from the time of transplantation only, excluding waiting time from analyses. Patients in the transplanted group become immortal, as if they died before being transplanted, they are not included.

If immortal time bias is not acknowledged, the treated group will generally have observed outcomes that are superior to the actual experienced outcome. [274]

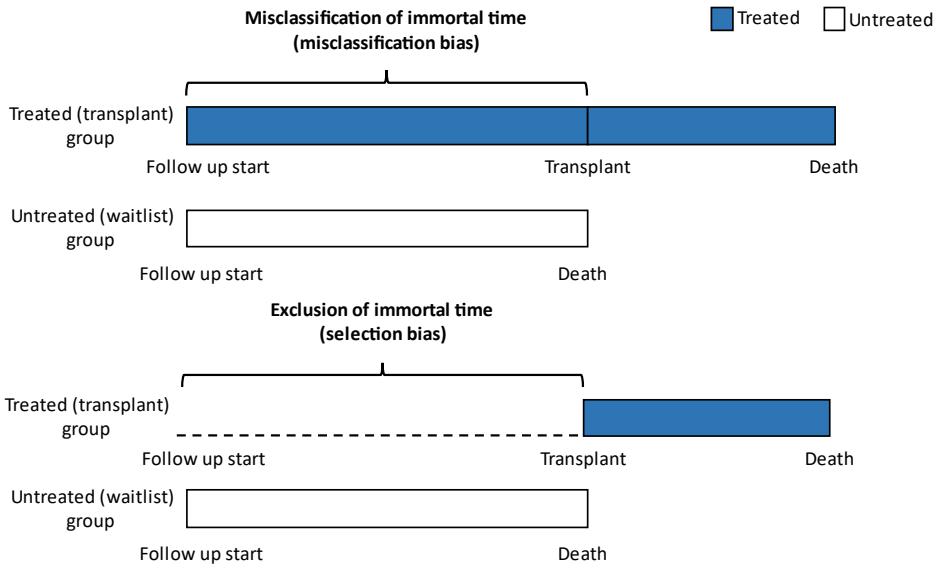


Figure 4.6. Immortal time bias relating to misclassification of immortal time (top picture) or exclusion of immortal time (bottom picture). Adapted from Levesque et al. [275]

Landmark analyses can be used to avoid immortal time bias. The 'landmark' is a clinically relevant timepoint used to divide patients into exposed and unexposed groups. Patients who are no longer at risk of the outcome at the landmark point, i.e. those who died or were censored prior to this time, are excluded from the analysis. The exposed and unexposed groups can then be compared using standard regression models with modification of follow up time to begin at the

landmark point. The benefit of this approach is that it eliminates immortal time bias, though limitations include:

1. A reduction in sample size and statistical efficiency due to the exclusion of patients no longer able to experience the outcome at the landmark time.
2. Reduced statistical precision i.e. analyses typically have wide confidence intervals.
3. Less generalizable results, as the examined population may differ from those who are excluded due to censoring prior to the landmark.
4. An inability to infer causality from results. [274 276]

Examining the association between early post-transplant MACE and patient and graft outcomes is at risk of immortal time bias as it is not known at transplantation when and in whom MACE will occur. As such, a landmark analysis was used to examine this association. As Chapter 5 examines the association between pre-transplant screening and MACE, a landmark of 6 months was chosen as there is a reasonable expectation that beyond 6 months the survival benefit from transplantation starts to accrue and events in the early post-transplant period are those which screening aims to minimise. [2] A sensitivity analysis using a landmark of 1 year is included in Appendix C.

The association between early post-transplant MACE and the following 3 outcomes were examined:

1. Patient survival (with or without a functioning graft)
2. Graft survival (censored for death)
3. Transplant survival (a composite of graft and patient survival)

Patients who died or experienced graft failure within 6 months of transplantation or had under 6 months of follow up were excluded from the landmark analysis. Kaplan-Meier curves and univariable followed by multivariable Cox proportional hazard models were then performed to examine the association between MACE in the first 6 months post-transplant and the above 3 outcomes. The proportionality assumption of the Cox models were tested using Schoenfeld residuals and met in all analyses. Statistical significance was defined *a priori* as $p<0.05$.

Variables included in the multivariable model were those hypothesized to associate with MACE and patient and graft outcome in which there was sufficient data completeness. These comprised age, sex, ethnicity, socioeconomic status (as per IMD), PRD, baseline comorbidity (as per Charlson

score), and donor type (living donor, DBD or DCD). The Charlson score was used instead of individual comorbidities, and PRD was divided into diabetes and non-diabetic diseases to preserve statistical power by reducing the number of covariates in multivariable models. The multivariable model included complete cases only, present in 95% of cases.

Patients were followed from 6 months post-transplantation until 1st January 2020 (Figure 4.1).

4.6.2 Results

Of the 3251 transplanted patients, 41 died (9 after a MACE event) and 104 experienced graft failure (24 of whom had a MACE event – 3 pre-graft failure and 21 post-graft failure) within 6 months of transplantation. A further 45 patients had under 6 months of follow up before the end of available HES data (1 of whom had a MACE event). These 190 patients (45% of those with MACE in the first 6 months post-transplant) were excluded from the landmark analysis. This section examines the remaining 3061 patients who were alive with a functioning graft at 6 months, at which point 41 (1.3%) had a MACE event.

Patients who had a cardiac death within 6 months of transplantation are excluded from these analyses. MACE therefore only refers to patients who experienced non-fatal events (unstable angina, AMI, or coronary revascularisation procedures) within Sections 4.6.2.1 to 4.6.2.3.

4.6.2.1 Patient survival

Over follow up, 318 patients died (10.4%). By univariable and multivariable analysis, MACE in the first 6 months of transplantation associated with an increased risk of death (adjusted HR 2.21, 95% CI 1.20-4.09) (Table 4.7, Figure 4.7). Additional factors associated with increased risk of death in the multivariable model included older age and higher comorbidity. Higher socioeconomic status (IMD 4 and 5) compared to lower socioeconomic status (IMD 1) were associated with reduced risk of death.

	Unadjusted HR (95% CI)	P	Adjusted HR (95% CI)	P
MACE within 6 months (Ref: no MACE)	3.56 (2.00 – 6.34)	**<0.001**	2.21 (1.20 – 4.09)	**0.01**
Age (years)	1.06 (1.05 – 1.07)	**<0.001**	1.06 (1.05 – 1.07)	**<0.001**
Male sex (Ref: Female)	1.05 (0.83 – 1.31)	0.69	0.95 (0.75 – 1.20)	0.67
Ethnicity (Ref: White)				
Asian	0.77 (0.55 – 1.09)	0.15	0.72 (0.51 – 1.06)	0.10
Black	1.04 (0.70 – 1.54)	0.86	0.92 (0.60 – 1.41)	0.70
IMD (Ref: 1)				
2	0.95 (0.69 – 1.31)	0.77	0.91 (0.65 – 1.28)	0.59
3	0.88 (0.63 – 1.23)	0.44	0.78 (0.55 – 1.12)	0.18
4	0.90 (0.65 – 1.25)	0.54	0.72 (0.51 – 1.03)	**0.07**
5	0.77 (0.53 – 1.10)	0.14	0.58 (0.39 – 0.84)	**0.004**
PRD (Ref: Non-diabetic) Diabetes	2.25 (1.68 – 3.02)	**<0.001**	1.08 (0.76 – 1.54)	0.66
Charlson score (Ref:0)				
1-2	2.28 (1.80 – 2.90)	<0.001	1.76 (1.33 – 2.34)	**<0.001**
3-4	4.30 (2.88 – 6.41)	<0.001	2.78 (1.78 – 4.35)	**<0.001**
≥5	4.38 (2.16 – 8.90)	<0.001	3.51 (1.72 – 7.19)	**0.001**
Donor type (Ref: LD)				
DBD	1.29 (0.96 – 1.74)	**0.09**	0.99 (0.73 – 1.33)	0.92
DCD	1.89 (1.43 – 2.51)	**<0.001**	1.19 (1.72 – 7.19)	0.24

Table 4.7. Associations with death post-transplant. Mixed ethnicity is not shown as no patients experienced events in this group.
Abbreviations: LD living donor, DBD donor after brainstem death, DCD donor after cardiac death.

The sensitivity analysis performed using the landmark time of 1 year is included in Appendix C. An association between MACE within the first post-transplant year and longer-term patient survival was noted by univariable analysis, but this association was not seen in the multivariable model.

4.6.2.2 Graft survival

Over follow up, 299 out of 3061 patients experienced graft failure (9.8%). There was no association between MACE in the first 6 months post-transplant and graft failure by univariable (HR 1.18, 95% CI 0.44-3.18) or multivariable (HR 1.41, 95% CI 0.52-3.82) analysis (Table 4.8, Figure 4.7). Factors associated with graft failure in the multivariable model included Black compared to White ethnicity, higher comorbidity (Charlson score 1-2 vs. Charlson score 0) and receiving a

kidney from a DCD donor as opposed to a living donor. Increased age was associated with a lower risk of graft failure.

	Unadjusted HR (95% CI)	P	Adjusted HR (95% CI)	P
MACE within 6 months (Ref: no MACE)	1.18 (0.44 – 3.18)	0.74	1.41 (0.52 – 3.82)	0.50
Age (years)	0.99 (0.98 – 0.99)	0.009	0.98 (0.97 – 0.99)	**<0.001**
Male sex (Ref: Female)	1.09 (0.86 – 1.38)	0.47	1.07 (0.83 – 1.37)	0.60
Ethnicity (Ref: White)				
Asian	0.86 (0.61- 1.23)	0.41	0.71 (0.48 – 1.05)	0.08
Black	1.69 (1.20 – 2.39)	0.003	1.64 (1.13 – 2.37)	**0.009**
Mixed	2.01 (0.83 – 4.88)	0.12	2.24 (0.92 – 5.47)	0.08
IMD (Ref: 1)				
2	0.82 (0.69 – 1.15)	0.25	0.91 (0.64 – 1.30)	0.61
3	0.98 (0.71 – 1.36)	0.91	1.14 (0.80 – 1.62)	0.48
4	0.70 (0.49 – 0.99)	0.04	0.92 (0.63 – 1.34)	0.66
5	0.66 (0.45 – 0.96)	0.03	0.86 (0.57 – 1.28)	0.45
PRD (Ref: Non-diabetic) Diabetes	1.12 (0.76 – 1.65)	0.57	0.80 (0.49 – 1.30)	0.36
Charlson score (Ref:0)				
1-2	1.41 (1.08 – 1.82)	**0.01**	1.54 (1.13 – 2.11)	**0.007**
3-4	1.66 (0.95 – 2.91)	**0.08**	1.68 (0.86 – 3.29)	0.13
≥5	1.40 (0.45 – 4.38)	**0.56**	1.78 (0.57 – 5.61)	0.34
Donor type (Ref: LD)				
DBD	1.25 (0.93 – 1.68)	**0.13**	1.28 (0.94 – 1.73)	0.11
DCD	1.31 (0.98 – 1.77)	**0.07**	1.42 (1.04 – 1.96)	**0.03**

Table 4.8. Associations with graft failure.

Abbreviations: LD living donor, DBD donor after brainstem death, DCD donor after cardiac death.

A sensitivity analysis performed using a 1-year landmark (Appendix C) showed similar results to the 6-month landmark. There was no association between MACE and graft failure on univariable or multivariable analysis.

4.6.2.3 Transplant survival

Over follow up, 549 out of 3061 patients died or lost their graft (17.9%). MACE in the first 6 months post-transplant was associated with transplant loss by univariable and multivariable

analysis (adjusted HR 1.99, 95% CI 1.16-3.41) (Table 4.9, Figure 4.7). Other factors associated with transplant loss in the multivariable model included older age, higher comorbidity and receiving a kidney from a DCD donor as opposed to a living donor. Asian ethnicity compared to White ethnicity and higher socioeconomic status were associated with a reduced risk of transplant loss.

	Unadjusted HR (95% CI)	**P**	**Adjusted HR (95% CI)**	**P**
MACE within 6 months (Ref: no MACE)	2.49 (1.49 – 4.16)	**<0.001**	1.99 (1.16 – 3.41)	**0.01**
Age (years)	1.02 (1.01-1.03)	**<0.001**	1.01 (1.01 – 1.02)	**<0.001**
Male sex (Ref: Female)	1.06 (0.89 – 1.26)	0.54	0.99 (0.83 – 1.19)	0.95
Ethnicity (Ref: White)				
Asian	0.85 (0.66 – 1.10)	0.23	0.73 (0.55 – 0.97)	**0.03**
Black	1.32 (1.00 – 1.74)	0.05	1.20 (0.89 – 1.62)	0.23
Mixed	1.07 (0.44 – 2.58)	0.88	1.38 (0.57 – 3.34)	0.48
IMD (Ref: 1)				
2	0.91 (0.71- 1.16)	0.43	0.93 (0.72 – 1.20)	0.55
3	0.93 (0.72 – 1.18)	0.54	0.94 (0.72 – 1.23)	0.67
4	0.77 (0.59 – 0.99)	**0.04**	0.79 (0.60 – 1.04)	0.09
5	1.69 (0.52 – 0.91)	**0.008**	0.68 (0.51 – 0.91)	**0.01**
PRD (Ref: Non-diabetic) Diabetes	1.65 (1.28 – 2.11)	**<0.001**	0.96 (0.71 – 1.31)	0.82
Charlson score (Ref:0)				
1-2	1.76 (1.46 – 2.12)	**<0.001**	1.61 (1.29 – 2.02)	**<0.001**
3-4	2.80 (1.99 – 3.95)	**<0.001**	2.22 (1.49 – 3.29)	**<0.001**
≥5	2.56 (1.32- 4.96)	**0.005**	2.59 (1.33 – 5.05)	**<0.001**
Donor type (Ref: LD)				
DBD	1.31 (1.05 – 1.64)	**0.02**	1.15 (0.92 – 1.45)	0.22
DCD	1.58 (1.27 – 1.97)	**<0.001**	1.30 (1.04 – 1.63)	**0.02**

Table 4.9. Associations between post-transplant MACE and death or graft failure ('transplant loss'). Abbreviations: LD living donor, DBD donor after brainstem death, DCD donor after cardiac death.

In the sensitivity analysis using a 1-year landmark, an association between MACE within the first year and transplant survival was noted by univariable analysis, but this was lost in the multivariable model.

The power to detect significant differences in the 6-month landmark analyses using a significance level of $p<0.05$ were 91% for mortality, 5% for graft failure and 83% for transplant survival.

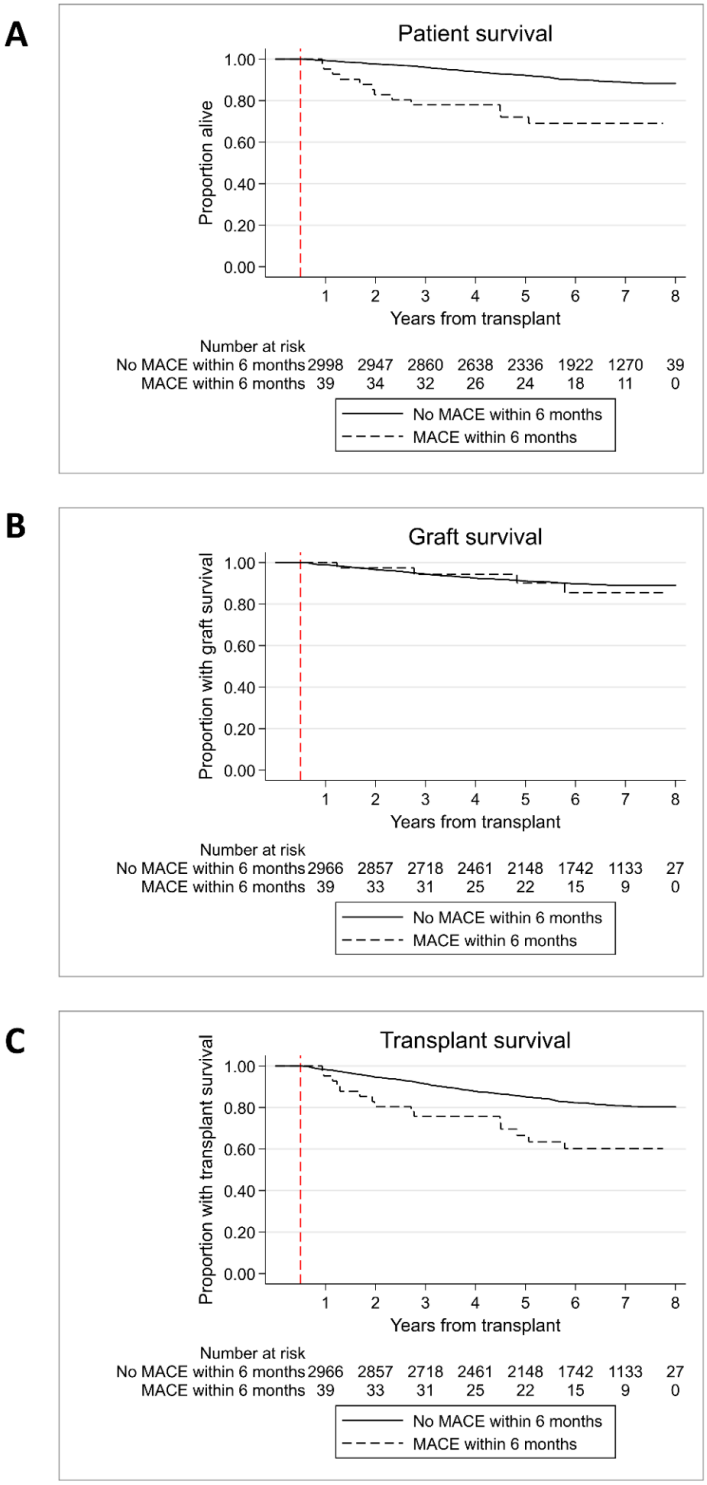


Figure 4.7. Kaplan-Meier curves examining (A) patient survival, (B) graft survival and (C) transplant survival following the landmark point of 6 months post-transplant (red dashed line).

4.7 Association between MACE and waitlist suspensions

4.7.1 Methods

Outcome data for waitlisted patients were available until 1st January 2020 from the UKRR and NHSBT (Figure 4.1). The proportion of patients who were suspended within 30 days of non-fatal MACE were identified and the duration of these episodes calculated.

4.7.2 Results

Of the 1432 waitlisted patients, 1055 (74%) were transplanted, 175 (12%) remained active on the waitlist, 75 (5%) had been removed from the list and 127 (9%) had died whilst on the waitlist by 1st January 2020. Of the 75 patients removed from the waitlist, 25 (33%) subsequently died.

Patients with waitlist MACE (n=161) had longer follow up (median 3.9 [2.8 - 5.0] years) than those who did not (n=1271) (2.2 [1.0 - 3.8] years, Mann Whitney U Test $p<0.001$). The median time to MACE in the 161 patients was 2.2 years [1.0 – 3.1].

Data on suspension episodes were only available for the 895 patients from the original ATTOM waitlisted cohort, of whom 91 had a MACE event whilst on the waitlist. Episodes of suspension occurred in 589 out of the 895 waitlisted patients (66%) over follow up. Patients who had a MACE event at any point pre-transplant spent 36% of their total follow up time suspended for any reason.

Of the 91 patients with waitlist MACE, 80 had unstable angina, AMI, or a revascularisation procedure, and 11 died with a cardiac cause. Of 80 patients with non-fatal MACE, 48 (60%) were suspended from the waitlist within 30 days of the event. The median suspension time was 312 days [IQR 171.5- 956], range 26-3003 days.

4.8 Discussion

4.8.1 Impact of early post-transplant MACE on kidney transplant recipients

The association between early non-fatal post-transplant MACE and patient and graft outcomes has not previously been definitively characterised in published literature and is challenged by immortal time bias. Of the patients experiencing MACE in the first 6 months post-transplantation, 45% died or lost their graft within this time frame. In those patients who were alive with a functioning graft at 6 months, early post-transplant MACE associated with an increased long-term risk of death and transplant loss, even after adjustment for potential confounders including age, deprivation, and baseline comorbidity. The sensitivity analysis performed using the 1-year timepoint did not show such association between MACE and survival by multivariable analysis, suggesting that cardiac events that occur early after kidney transplantation may have a greater impact on patient survival than later events. This highlights the detrimental effect of early post-transplant MACE on patient outcomes and rationalises the need to identify patients at increased risk of MACE and consider strategies to reduce early cardiac events.

Whilst early post-transplant MACE associated with reduced long-term patient survival, no such association was seen with graft failure, though the power to detect significant differences in this analysis was low (5% power to detect a significant difference with $p<0.05$, compared with 91% for mortality and 83% for transplant survival). Improving long term graft survival remains a challenge in kidney transplantation, [277] and it could be hypothesized that cardiac events or revascularisation procedures could adversely affect kidney function through reduced renal perfusion or contrast-associated nephropathy, although recent evidence suggests the impact of this may be less than previously thought. [278]

Factors associated with graft failure in this analysis included younger age, being of Black ethnicity, higher baseline comorbidity (those this was not linear) and receiving a kidney from a donor after cardiac death. Some of these associations may relate to residual confounding, such as poorer HLA matching in those of Black ethnicity, [279] the potential for higher medication non-adherence in younger adults with resultant increase in acute rejection episodes, [280] or difficulties distinguishing the severity of illness using the Charlson score in a group where selection bias relating to a healthier population selected for transplantation is likely.

4.8.2 Impact of MACE on waitlisted patients

When considering the timing of transplantation, it is also necessary to consider the impact that MACE on the waitlist has on kidney transplant candidates. Prior to the change in the UK organ allocation scheme in 2019, the average waiting time on the deceased donor list was 675 days. [52] Here, 6.1% of patients on the kidney transplant waitlist at this time had experienced waitlist MACE. Whilst only 60% of patients with a HES-recorded diagnosis of unstable angina, AMI, or coronary revascularisation procedure were suspended within 30 days of the event, the length of these suspensions was substantial with a median duration of approximately 10 months. There are around 3500 patients on the kidney transplant waitlist in the UK, [48] and so the absolute number of patients experiencing waitlist MACE are high.

This duration of suspension is unsurprising. Patients undergoing surgery within one month of myocardial infarction are at an increased risk of bleeding, [198 281] post-operative AMI, and early mortality. [282] Suspensions are therefore necessary to minimise these risks and ensure fitness for surgery, which is usually not recommended for 30 days after bare metal stent insertion or 1 year if a drug-eluting stent has been used. [198] This may prevent pre-emptive transplantation and could increase pre-transplant dialysis time for patients on the waitlist. Whilst the association between waitlist MACE and time to transplant has not been examined due to the small sample size and varying times to MACE and transplantation, patients who had a MACE event spent over one third of their follow up time suspended from the waitlist – though it cannot be determined whether this suspension duration is exclusively explained by the occurrence of MACE. Whilst the relative contribution of MACE occurring secondary to a longer time on the waitlist, or MACE delaying transplantation resulting in longer time on the waitlist, cannot be determined, suspensions from the waitlist associate with mortality both on the waitlist and with a transplant [56] and so keeping patients well without the need for these episodes is key.

Understanding the impact of waitlist MACE on patient outcomes could aid decision making on whether to accept organ offers. In a US study examining 280,000 patients on the kidney transplant waitlist, 30% of patients who had an offer declined either died or were removed from the waitlist prior to receiving a transplant. [283] Only 7% of declines were due to recipient factors and all donor kidneys were transplanted, suggesting the offers were deemed acceptable for certain patients. Further, 56% of patients transplanted in the US after declining an organ

ultimately accept a similar or poorer quality organ. [284] Whilst the kidney offering scheme, waiting times and organ acceptance thresholds between the USA and UK differ, [285] these studies highlight the need to balance organ quality with waiting time and cardiovascular risk for the patient in question. Registry data in the UK show that after 3 years on the waitlist, 5% of patients have been removed and 4% have died. [48] There is therefore likely to be a group of patients who have a window of opportunity for transplantation, in whom timing needs to be carefully considered.

4.8.3 Strengths and limitations

Strengths of the analyses performed in this chapter include the large, national cohort including all transplant centres in England with likely high external validity of results, and the use of routine healthcare data to address a clinical question that has not previously been able to be examined in this population.

There are limitations to the analyses performed in Section 4.6 to Section 4.7. These in part reflect the inherent difficulty in examining the impact of MACE on patient outcomes, which itself makes the question of screening utility difficult to answer (Chapter 5). These include:

- The limitations of landmark analysis. Whilst this technique removes the risk of immortal time bias, it results in loss of statistical power as patients experiencing the study outcome prior to the landmark point are excluded from analyses. Around one fifth of patients who lost their graft or died in the 6 months post-transplant had a MACE event, comprising 45% of patients with early events. The landmark analysis therefore does not demonstrate the impact of MACE on very early graft failure and death. Whilst the selected timepoint of 6 months reduces the number of patients excluded from the analysis (190 at 6 months versus 289 at 1 year), it does mean a relatively small number of patients had a MACE event at the selected timepoint. Alternative techniques including Cox models with time-varying covariates could be considered, but have their own limitations. [274]
- Transplant-specific factors may associate with patient and graft outcome such as extended criteria donors, number of HLA mismatches, delayed graft function and acute rejection episodes [286] [287] but these data were not available to be included in analyses, nor was there sufficient data to include duration of pre-transplant KRT in the models. [39] [288]

- The outcomes examined in the landmark analysis are limited to mortality and graft survival and do not quantify other important factors such as quality of life and medication burden.
- The sensitivity and specificity of HES in recording ischaemic heart disease compared to ATTOM records is described in Chapter 3, with values of 82.6% and 93.4% respectively. When examining waitlisted patients however, only 60% of those with a MACE event were suspended within 1 month of the event. It would be expected that patients with a 'true' AMI or revascularisation procedure would require dual anti-platelet therapy (Chapter 1), which would increase the risk of bleeding associated with transplant surgery. In clinical practice, patients would often be suspended from the waiting list in this context. It is possible that some HES-captured events therefore did not correspond to atheromatous disease and may have represented type 2 AMI in the context of precipitating factors such as anaemia or hypotension, or symptoms relating to fluid overload. A coronary angiogram (recorded as a MACE event) may have been performed without identifying occlusive disease or could represent a repeated cardiac screening investigation in some waitlisted patients. It is also possible that MACE may be unrecorded if NSTEMI or unstable angina codes were not in the primary diagnosis position e.g. if they occurred during the index transplant admission, where transplantation itself would likely be deemed the primary diagnosis.
- The reasons for waitlist suspensions are not known, and it cannot be confirmed whether suspensions related to MACE. Suspensions occur for wide-ranging reasons including changes in personal circumstances, holidays, patient preference, or the availability of a living donor, and may not have directly related to a cardiac event contraindicating transplantation.
- Finally, comparisons of transplanted and waitlisted patients assume that, aside from their transplant status, these patients are identical with respect to demographic and clinical backgrounds. All transplant recipients survived to the point of receiving the transplant and therefore may represent a 'healthier' subpopulation, meaning analyses are still at risk of selection bias (Section 4.6.1). The waitlisted patients examined in this chapter only included patients who were activated on the deceased donor list, whilst some transplant recipients may have received a living donor transplant without activation on the deceased donor list, meaning there is potential for differences between these populations.

4.9 Conclusion

This chapter has described:

1. The incidence of MACE in an English cohort of kidney transplant and waitlisted patients
2. The associations between pre-transplant patient characteristics and MACE, and
3. The associations between MACE and longer-term patient and graft outcomes in kidney transplant recipients.

The incidence of MACE in an English cohort of transplant recipients is described for the first time, demonstrating a rate that is substantially lower than that in US studies. A high proportion of early post-transplant MACE occurs in patients with early mortality or graft failure, and even in patients who survive, MACE within 6 months of transplantation is associated with an increased risk of death and transplant loss in the longer term. The risk of remaining on the waitlist are highlighted, with a higher incidence of MACE in waitlisted patients after 9 months, and substantial suspension times occurring in those who experience MACE.

These results highlight the potential harm associated with post-transplant MACE and show that efforts to predict and prevent these events in the immediate peri-operative period are logical to improve not only early, but also medium to long term outcomes after transplantation. These results provide the necessary background information for the analysis of utility of screening for asymptomatic coronary artery disease, covered in Chapter 5.

Chapter 5: Screening for asymptomatic coronary artery disease prior to kidney transplantation

5.1 Preface

Chapter 4 highlighted the negative impact that early post-transplant MACE can have on kidney transplant recipients. This chapter investigates the utility of screening for asymptomatic CAD prior to kidney transplantation. The rationale and process of screening is covered in Chapter 2, one of the aims of which is to minimise the risk of peri- and early post-transplant MACE.

Results and discussions relating to work in this chapter have been published as:

1. Nimmo A, Forsyth J, Oniscu G, Robb M, Watson C, Fotheringham J, Roderick P, Ravanan R, Taylor D. A propensity score-matched analysis indicates screening for asymptomatic coronary artery disease does not predict cardiac events in kidney transplant recipients. Kidney International 2021; 99(2): 431-442.
2. Nimmo A, Ravanan R, Taylor D. The authors reply. Kidney International 2021; 99(3): 772-773.

The following paper was accepted by Transplant International in May 2022:

- Nimmo A, Latimer N, Oniscu G, Ravanan R, Taylor D, Fotheringham J. Propensity score and instrumental variable techniques in observational transplantation studies: an overview and worked example relating to pre-transplant cardiac screening.

The published papers can be found in Appendix F.

Additional material for the supplementary analyses in this chapter are in Appendix D.

All analyses were performed by Ailish Nimmo. James Fotheringham (Consultant nephrologist/NIHR Clinician Scientist, University of Sheffield) advised on the methodology of instrumental variable analyses.

5.2 Aims

This chapter analyses data from the combined ATTOM and HES dataset described in Chapter 3 and shown in Figure 3.2. The aims are to:

1. Describe the pattern of screening investigations performed prior to kidney transplantation in England
2. Identify patient factors associated with undergoing screening investigations prior to transplantation
3. Determine whether screening for asymptomatic coronary artery disease is associated with post-transplant MACE using three causal inference techniques:
    a. Propensity score matching
    b. Propensity score weighting
    c. Instrumental variable analysis

5.3 Methods

5.3.1 Patient population

Information on screening investigations performed prior to transplant waitlisting were collected for incident transplant and waitlisted patients at recruitment to the ATTOM study. Patients from both these ATTOM cohorts who were transplanted before 31st December 2017 are included in the analyses in this chapter (Figure 3.2). As screening investigations and MACE risk differ for patients undergoing multi-organ transplantation, only patients receiving a kidney-alone transplant were included.

5.3.2 Major adverse cardiac events

MACE was defined as in Chapter 4. Non-fatal MACE events were identified from HES data using ICD-10 and OPCS-4 codes, whilst death data was taken from UKRR and NHSBT reporting. Events from transplantation until 31st December 2017 were identified, with patients censored for non-cardiac death. The incidence of MACE was calculated from Kaplan-Meier analyses.

5.3.3 Patterns of CAD screening

A screening investigation was defined as any form of stress test (exercise tolerance test (ETT), dobutamine stress echocardiogram (DSE) or myocardial perfusion scan (MPS)) or coronary angiogram (either CT or invasive) that was performed in an asymptomatic patient with the intention of assessing suitability for transplant waitlisting. Patients who underwent an echocardiogram alone were not included in the screening group as this is not a dynamic test for CAD and may instead be used to identify valvular heart disease or heart failure. A low ejection fraction identified on echocardiogram may be a contraindication to transplantation, but as revascularisation can improve left ventricular function [289] patients with clinically significant findings on echocardiogram are likely to undergo further investigation, which would have placed them in the 'screened' group.

The patterns of screening investigations pre-transplantation were described. The proportion of patients undergoing coronary angiography following a non-invasive screening test (ETT, DSE, MPS or CT coronary angiogram) were identified from ATTOM data. In patients undergoing a coronary angiogram as a screening investigation from ATTOM data, the proportion who underwent revascularisation (coronary angioplasty with or without stent insertion, or coronary artery bypass grafting) prior to kidney transplantation was determined from interrogation of HES data.

5.3.4 Factors associated with CAD screening

Univariable followed by multivariable logistic regression analyses were performed to identify factors associated with screening. The covariables included in the model were defined *a priori* to include age, sex, ethnicity, PRD, cardiovascular comorbidities, smoking history, prior KRT modality and socioeconomic status (as per the index of multiple deprivation, IMD). Obesity was not included due to a relatively high proportion of missing data (n=156, 6%).

5.3.5 Statistical techniques including description of propensity score and instrumental variable analyses

In observational studies, the exposure or intervention, in this case - screening, is not randomly assigned. Differences in case-mix between exposed and unexposed groups can therefore lead to confounding bias, making it impossible to infer causality. [290] As the characteristics of patients in

the 'screened' and 'unscreened' groups are different, these groups have different baseline levels of cardiac risk and a direct comparison between groups could produce biased results. Whilst multivariable models aim to adjust for the differences in characteristics between groups, they may be overfitted if the number of covariates is large relative to the number of outcome events. [291] Further, only known confounders can be adjusted for and unmeasured confounding can persist.

To improve the validity of causal inference and reduce the risk of confounding, three types of statistical analysis are performed in this chapter to analyse the association between pre-transplant screening and MACE. These are:

1. Propensity score techniques, including:
    a. Propensity score matching
    b. Propensity score weighting
2. Instrumental variable analyses

These methods go some way to addressing clinical questions from observational data that are not immediately suited to a randomised study design, but still do not confidently allow causal conclusions to be made and therefore do not replace the need for a randomised control trial.

5.3.5.1 Propensity score matching

The propensity score refers to the predicted probability of a person receiving treatment based on their known characteristics which confound the association between treatment and outcome, also known as measured confounders. [292] The score ranges from 0 (no probability) to 1 (absolute probability) that a person receives the treatment and can be thought of as a single numerical value that summarises measured confounders. As conventional multivariable models require around 10 events per covariate to produce a stable estimate, combining covariates into a single propensity score is useful when the population is small, event rate is low, or number of covariates is large. [293] [294]

To determine the propensity score for screening, a logistic regression model containing measured confounders as independent variables was performed. Measured confounders were those associated with both the treatment (screening) and the outcome (MACE); variables only related to screening were not included as this can increase the variance of the estimated exposure effect

without reducing bias. [295] Confounders were chosen based on hypothesised pathways between screening and MACE with the use of a direct acyclic graph. [296] The variables deemed to potentially relate to screening and MACE, other than transplant centre, comprised age, sex, ethnicity, socioeconomic status, smoking status and history of ischaemic heart disease, diabetes, cerebrovascular disease, and peripheral vascular disease. Analyses included complete cases only, present in 2477 (96.3%) of cases.

Once the propensity score was generated, two groups with a similar distribution of measured confounders were created to allow direct comparisons to be made. Screened and unscreened patients were 'paired' based on their propensity score. As the prevalence of screening was around 50%, patients were matched on a 1:1 basis based on them having the closest propensity scores (nearest-neighbour matching). A caliper was used to avoid the inclusion of poorly matched pairs; the maximum acceptable difference in propensity scores was 0.2 times the log odds of the standard deviation of the propensity score. [297] This means difficult to match patients were not matched, reducing the sample size (Figure 5.1A and B). The characteristics of matched and unmatched patients were compared using univariable analyses.

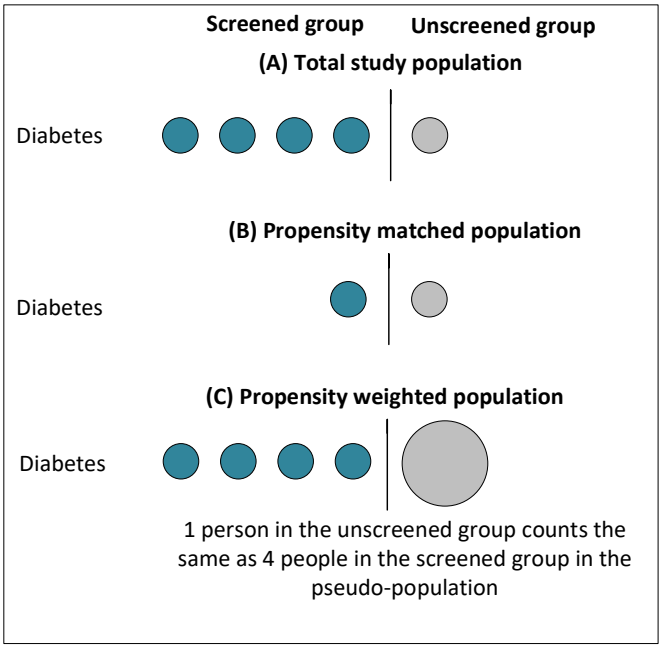


Figure 5.1. Included subjects using propensity score matching and weighting techniques.

Propensity score matching should create two groups of patients with an equal distribution of measured covariates. The balance of covariates between screened and unscreened groups were examined using standardised differences, calculated by dividing the difference in proportion (for binary variables) or sample mean (for continuous variables) by the pooled standard deviation. A value of under 0.2 was taken as acceptable 'balance', although there is no clear consensus on what an acceptable standardised difference is. [298] Once it was confirmed the groups were balanced, they were compared using standard univariable and multivariable regression techniques. The multivariable propensity score matched technique (also known as 'doubly robust') also includes the variables used to generate the propensity score. A multivariable model compensates for imperfect covariate balance and minimises the risk of a biased estimator, [299] but loses the advantage of having only 1 covariate in the final model.

Univariable 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. The proportionality assumption of 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 further Cox regression model including transplant centre was used to examine if MACE at 5 years was independently associated with transplant centre.

As differences in transplant-specific cardiovascular risk factors could influence post-transplant MACE, creatinine at 1- and 5-years post-transplant, HES-documented graft rejection, HES-documented post-transplant diabetes, and donor type (living or deceased) were also compared between the propensity matched groups.

5.3.5.2 Propensity score weighting

The propensity score can also be used with a weighting technique, which creates a pseudo-population informed by all patients which balances the distribution of observed variables in screened and unscreened groups (Figure 5.1C). [300] This technique therefore includes patients who are 'dropped' during propensity score matching and may result in better covariate balance. [301]

In these analyses, each patient is assigned a 'weight' depending on their measured covariates and the treatment they receive. Patients who are screened (the treated group) have a weight of 1/PS, whilst patients who are not screened (the untreated group) have a weight of 1/(1-PS). This means patients allocated to an 'unexpected' treatment group are upweighted relative to those allocated to the 'expected' treatment group (Figure 5.1C). The weights can then be 'stabilised' by multiplying them by the proportion of the population treated to reduce the variability of the weights and thus the influence of patients with extreme weights on the results. [302] The stabilisation process should result in an approximate mean weight for the population of 1.

To understand which patients had a larger propensity score weight, and thus a greater influence on results, screened and unscreened patients with stabilised propensity score weights greater than or equal to 2 were compared to screened and unscreened patients with stabilised propensity score weights of under 2.

A multivariable Cox regression model was then performed examining the association between screening and MACE at 90 days, 1 year and 5 years post-transplant.

5.3.5.3 Assumptions of propensity score techniques

Propensity score techniques rely on the following assumptions:

1. Exchangeability. [303] [304] This means the treatment which a patient receives should be unrelated to their potential outcome i.e. the patients in treated and untreated groups have the same distribution of outcome predictors, and have the same distribution of outcomes if they all received the treatment of interest. This assumption is violated if individuals who are likely to have a good outcome regardless of treatment are more likely to receive treatment.
2. Positivity. [305] All subgroups of individuals in a covariate stratum have a non-zero chance of receiving either treatment option i.e. within each covariate subgroup, it must be possible for patients to receive either of the treatment options.
3. Consistency. [306] [307] This assumes that the exposure is well defined and has a stable or consistent impact on outcome. This could be violated if, for example, the outcome varies depending on how the treatment is delivered.

The likelihood of these assumptions holding are discussed in Section 5.4.7.

5.3.5.4 Limitations of propensity score matching and weighting

There are limitations to propensity score methods which should be considered when performing and interpreting analyses. These include:

- The propensity score only encompasses measured confounders. Confounders that are unknown, poorly recorded, or not easily measurable cannot be controlled for and may not be balanced between groups, leading to unmeasured confounding.
- In propensity score matching, unmatched patients are 'lost', reducing the study size. Patients with the highest and lowest propensity scores (the 'always treated' and 'never treated') are less likely to be matched and are therefore under-represented in the regression models, meaning estimates may only be relevant to the matched population and not those seen in clinical practice.
- In propensity score weighting, data from all participants is retained. However, if patients receiving an unexpected treatment contribute very large weights to analyses, results may be unstable. There is no consensus on what a large weight is, but it is common practice to stabilise the weights, as performed here. Some also advocate truncating weights to a maximum of 10 to produce more precise estimates, [308] but this may re-introduce some of the confounding that the method is designed to remove.

5.3.5.5 Instrumental variable analyses

Instrumental variable (IV) analyses were developed for economic studies and subsequently adopted in medical research. They aim to minimise confounding by indication by examining individuals based on an 'instrumental variable': a variable that influences treatment and has no common confounder with the outcome, as shown in Figure 5.2. This allows the IV to be capitalised on as a type of natural randomisation. [309] Patients are analysed according to the IV rather than by the treatment they receive, similar to an intention to treat analysis, where patients in randomised control trials are analysed according to their randomisation group rather than by received treatment. The advantage of IV analyses is they do not assume an absence of unmeasured confounders, allowing an isolated independent treatment effect to be estimated.

The IV must meet key assumptions (Figure 5.2): [310]

1. It must be strongly associated with the exposure (relevance assumption).

2. It must only affect outcome through its association with the exposure (exclusion restriction).
3. There must be no common unmeasured confounders to the instrumental variable and the outcome (independence assumption).
4. A fourth assumption is that there should be either effect homogeneity or effect monotonicity. Effect homogeneity states that the treatment should have a constant effect on the outcome across all individuals. Effect monotonicity states that no patients should receive the opposite treatment to expected at all levels of the instrument i.e. at both the instrument to which the patient was assigned and instrument(s) to which they were not assigned (so called 'defier' patients). Identifying 'defier' patients however is complex or even impossible, making this assumption difficult to define or test which can limit the clinical applicability of results.

A potential IV is initially identified using empirical evidence. Transplant centre is determined by geographical location so can be thought of as being randomly allocated. Transplant centre was determined as being a potential IV as it (at least partly) met the key assumptions:

1. Relevance assumption: the likelihood of undergoing screening is associated with transplant centre, even after adjustment for patient-level characteristics (shown in Table 5.2 and in Appendix D).
2. Exclusion restriction: transplant outcomes are similar between centres [48] and centre is not independently associated with MACE (shown in Appendix D). This means that after adjusting for patient level characteristics, any association between centre and MACE could reflect differences in screening. This assumption cannot be guaranteed as non-screening differences in centre-level practice could also influence outcome.
3. Independence assumption: transplant centre and MACE should not have any shared unmeasured confounders. This assumption cannot be proven, as acknowledged in IV analysis literature. [311] Whilst it may be assumed that if measured confounders are balanced across IV groups, unmeasured confounders will be too, this is purely speculative.
4. Homogeneity or monotonicity assumption: screening may not have a uniform effect on individuals. For example, it could benefit those with high cardiovascular risk but not low risk patients, thus violating homogeneity. Monotonicity (no patients receiving the opposite treatment to what would be expected at any level of the instrument) may be

more likely to hold as patients receive screening based on defined protocols at their transplant centre. This assumption however cannot be proven.

The analysis then involves a two-stage regression model. In the first stage, screening (the treatment) was predicted from a linear regression model containing transplant centre (the instrument) and other covariables (determined *a priori* to be those used in the propensity score analyses) as independent variables. This generated a 'predicted treatment' value, representing the likelihood of each patient being screened.

In the second stage, Cox regression models were used to examine MACE at 90 days, 1 year and 5 years post-transplant. In this model the 'predicted treatment' value generated in the first stage was included as an independent variable instead of screening, alongside other patient-level measured covariables.

It should be noted that whilst a second-stage Cox model using the 'predicted treatment' value is a straightforward method for time-to-event analyses, IV methods are not well developed for regression analyses with censored survival outcomes due to the non-collapsibility of the hazard ratio. Subsequently, Cox models are not universally recommended in IV analyses unless the outcome is rare due to their potential to introduce bias. [312] [313] [314] [315] [316] The presented analysis in Section 5.4.8 therefore should be thought of as a simplified use of IV methodology which has potential limitations.

As the analysis was performed, potential violations of the IV assumptions were assessed. The relevance assumption can be examined by calculating how strong the correlation between the instrument and exposure is; the stronger the correlation, the more unmeasured confounding can be reduced. [317] This is examined using the F statistic and partial R-squared values. An F statistic under 10 typically signifies a weak instrument. [318] In general, a greater partial R-squared value indicates a greater contribution of the IV to treatment allocation, but there is no consensus on what a 'satisfactory' value is. [319] Testing violations of the exclusion restriction, independence assumption and monotonicity assumption are more difficult, with no single statistical test determining whether they hold. [320]

5.3.5.6 Limitations of instrumental variable analyses

Finding a suitable IV can be challenging and if its correlation to the exposure is not sufficiently strong any association is diluted. Large multicentre studies are often required for these analyses. Ensuring all assumptions of the IV are met may not be possible. [321] Whilst IV analyses can overcome unmeasured confounding, they are less precise as patients are examined based on estimated not actual exposure. [322] Finally, in situations where variation is determined by the healthcare provider, the technique may be better at addressing policy rather than individual patient level questions. [323]

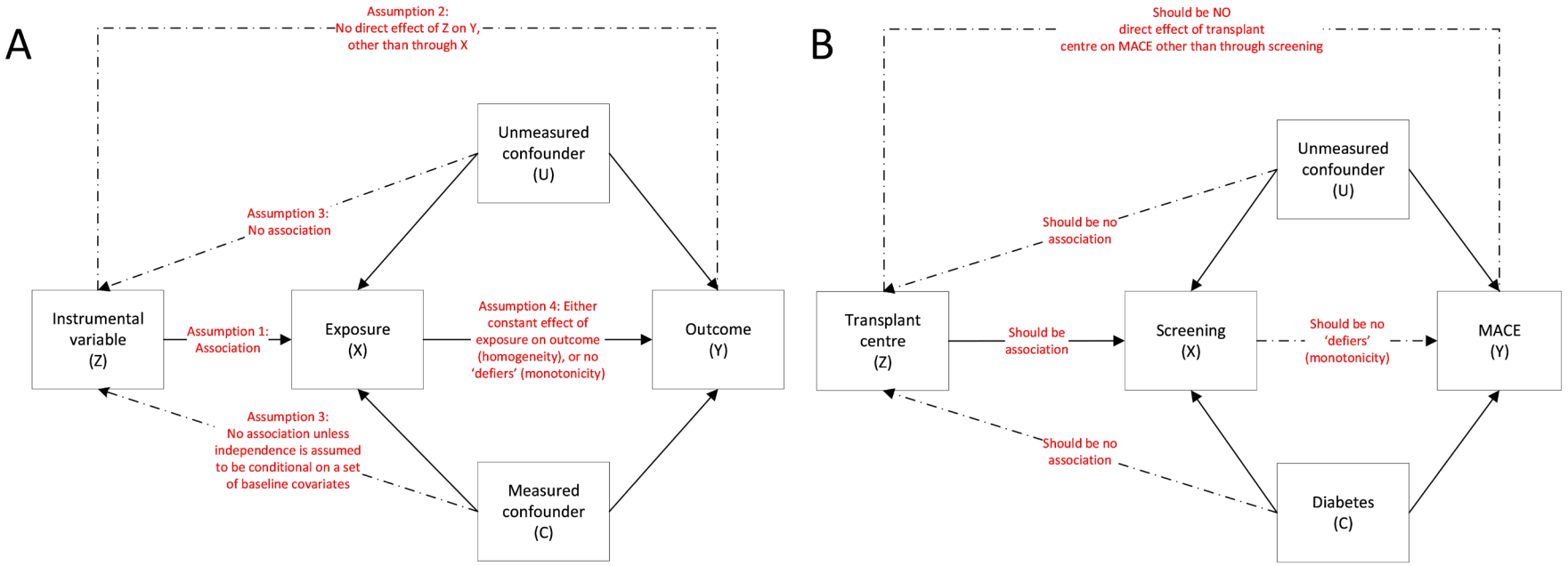


Figure 5.2. Instrumental variable analysis assumptions.

A: Assumptions and associations between the instrumental variable (Z), exposure (X), outcome (Y), measured confounders (C) and unmeasured confounders (U).

B: Assumptions and associations between screening as the exposure (X) and MACE as the outcome (Y) with transplant centre as the instrumental variable (Z) and diabetes as an example of a measured confounder (C).

5.3.5.7 Average treatment effects

When comparing results from different causal inference techniques, it must be considered which groups of patients the causal effect is applicable to. Terms used include the 'average treatment effect' (ATE), 'average treatment effect on the treated' (ATT) and 'local average treatment effect' (LATE).

ATE refers to the effect of treatment on the whole population. This is typically estimated by propensity score weighted techniques, which include all study participants. ATT refers to the effect of treatment on only those individuals potentially eligible to receive it, typically estimated by propensity score matched analyses. In IV analyses, the causal effect depends on whether effect homogeneity or monotonicity hold. If homogeneity is assumed, the estimate refers to the ATE. If monotonicity is assumed, the estimate refers to the LATE. The LATE reflects the effect of treatment on the subgroup of 'complier' patients i.e. those patients who receive the expected treatment given their instrument. As complier patients cannot be identified from within the study population, the LATE has limitations in informing practice and policy decisions. [324]

As the ATE, ATT and LATE refer to different groups of patients, their effect sizes can differ. Differences can aid the interpretation of study findings by providing insights into the effect of treatment on different groups of patients, and do not necessarily signify failure of a technique.

5.3.5.8 Sensitivity analyses

Four sensitivity analyses were performed. Three involved the propensity score matched population. These comprised:

1. Examining only the ATTOM incident transplant cohort, excluding patients recruited to the ATTOM waitlisted cohort given that pre-transplant screening in these patients could have occurred after transplant waitlisting/ATTOM recruitment and therefore not be recorded in the ATTOM dataset.
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, [325] given that there may be shared characteristics that predict both screening and death from non-cardiovascular causes such as infection and cancer.

3. An assessment of how robust the 1 year results were with respect to unmeasured confounding by calculating the E-value. [326] 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 fourth sensitivity analysis was:

4. A propensity score-stratified analysis. This examined the effect of screening on MACE in sub-groups of patients stratified by their propensity score. Patients were divided into 5 groups (quintiles). This analysis aimed to explore whether certain groups of patients, some of whom could have been excluded from the propensity score matched analysis, derive a benefit from screening.

5.4 Results

5.4.1 Patient population

In total, 2853 patients received a kidney transplant in England and 2723 were matched to their HES record. Of those unmatched, 49 had non-English postcodes and are likely to have received treatment elsewhere in the UK. The 151 patients receiving multi-organ transplants were excluded. Overall, 2572 patients were examined: 1661 (64.6%) from the incident transplant group and 911 (35.4%) from the waitlisted group (Figure 5.3). Median time from ATTOM recruitment to transplant in the waitlisted group was 17 months [IQR 9-29]. Median age at transplant was 51 years (range 20-76 years).

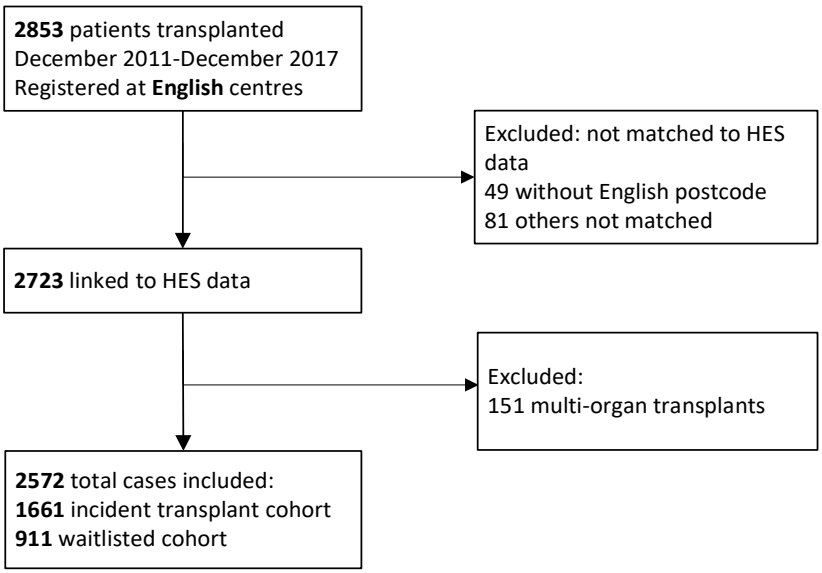


Figure 5.3. Flow chart depicting patients included in this chapter.

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, only 2.8% of individuals underwent first screening investigations after recruitment to ATTOM (full details in Appendix D).

5.4.2 Incidence of MACE

Median follow-up was 61 months [IQR 46-67], over which time 202 patients had a MACE event (145 from the incident transplant group and 57 from the waitlisted group). The incidence of MACE in this cohort was similar to that described in Chapter 4 (which also included patients from the ATTOM incident dialysis cohort, Figure 3.2), with an incidence of 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 (full details in Appendix D). Only 4% of MACE were based on a clinical diagnosis of AMI 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 of these patients experienced another MACE event during the terminal admission.

5.4.3 Patterns of coronary artery screening investigation

There was variation in the combinations of screening investigations pre-transplantation. Overall, 1252 (49%) had no screening test (440 had no investigation and 812 had an echocardiogram alone). Of the 1320 (51%) patients who underwent screening, 977 underwent a stress test with or without echocardiogram, and 343 had a CT or invasive coronary angiogram, with or without an echocardiogram or stress test (Figure 5.4).

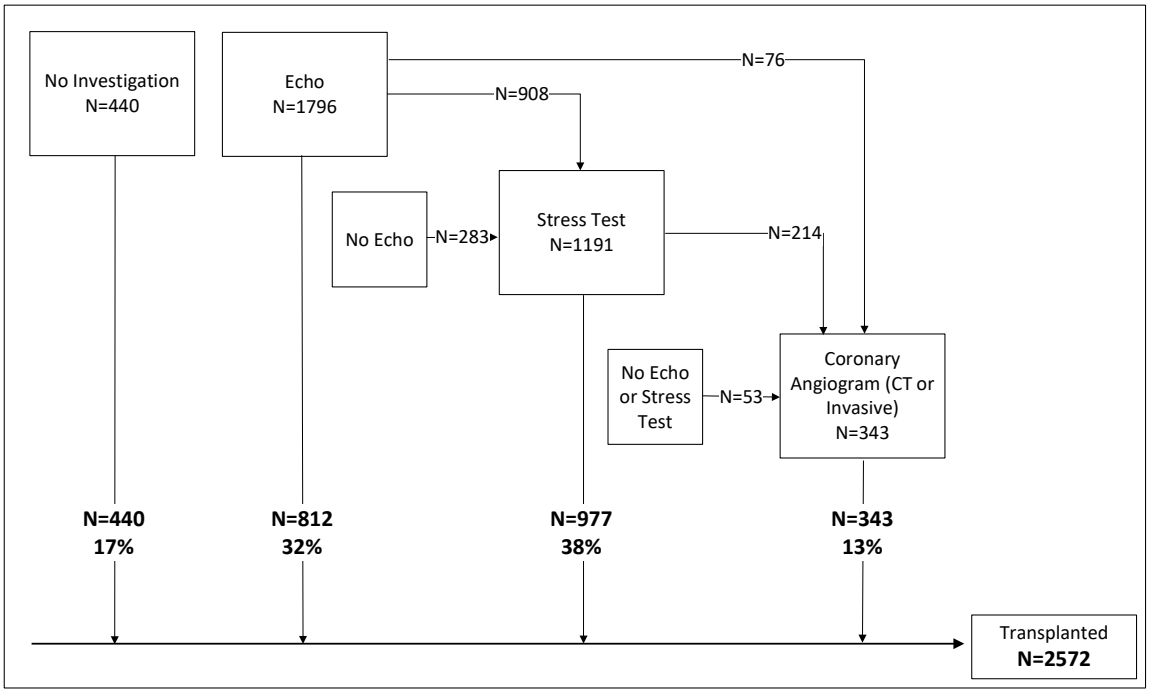


Figure 5.4. Patterns of pre-transplant screening investigations.

Abbreviation: echo; **transthoracic echocardiogram.**

Overall, 279 patients underwent a coronary angiogram before transplantation, equating to 11% of the total transplanted cohort. Of these, 59% (n=165) had undergone a non-invasive screening test prior to angiography. This equates to 14% of patients undergoing an initial non-invasive screening test subsequently undergoing a coronary angiogram. On interrogation of the HES dataset, of the 279 patients who underwent an angiogram, 32 underwent coronary stent insertion

or balloon angioplasty prior to transplantation (11.4% of those undergoing angiography, and 1% of the overall cohort) and 12 patients underwent coronary artery bypass grafting (4.3% of those undergoing angiography, and 0.5% of the overall cohort) (Figure 5.5).

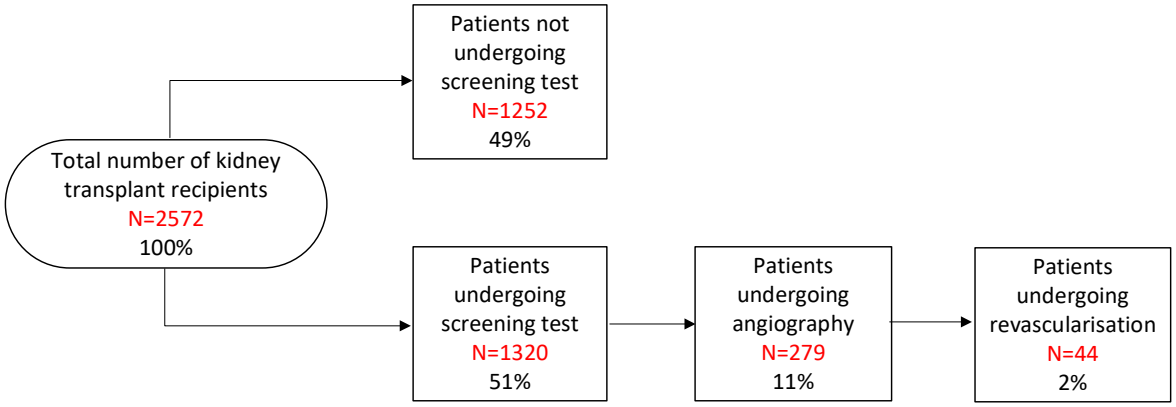


Figure 5.5. Flow diagram demonstrating patients undergoing revascularisation prior to transplantation.

The proportion of patients undergoing screening was similar between the incident transplant (n=840, 51%) and waitlisted (n=480, 53%) groups.

5.4.4 Factors associated with CAD screening

By univariable analysis, patients 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 5.1). Significant variation was also observed with ethnicity, socioeconomic status, and PRD. The highest likelihood of screening was observed in those of White ethnicity, higher socioeconomic status and renovascular disease.

The proportion of patients undergoing screening also varied by centre: the median percentage of patients screened was 58% [IQR 26-68] but ranged from 5-100% (Figure 5.6).

Given the variation in screening practice in transplant recipients between centres, the characteristics of the ATTOM incident dialysis patients by centre were also examined and are shown in Appendix D. Centres with higher use of screening had a dialysis population of higher socioeconomic status.

	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)	**<0.001**
Asian	210 (17)	147 (11)	
Black	122 (10)	101 (8)	
Mixed	23 (2)	18 (1)	
PRD (n=2555)			
Glomerulonephritis	325 (26)	286 (22)	**<0.001**
Other	283 (23)	259 (20)	
Polycystic kidney disease	196 (16)	229 (17)	
Uncertain	156 (12)	151 (12)	
Pyelonephritis	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**
KRT modality (n=2556)			
Haemodialysis	707 (57)	785 (60)	0.06
Peritoneal dialysis	263 (21)	241 (18)	
Transplant	13 (1)	5 (1)	
Pre-emptive	260 (21)	282 (21)	
IMD (n= 2572)			
1 – Most deprived	344 (27)	263 (20)	**<0.001**
2	247 (20)	271 (21)	
3	234 (19)	256 (19)	
4	218 (17)	287 (22)	
5 – Least deprived	209 (17)	243 (18)	

	No CAD Screening Test N=1252	CAD Screening Test N=1320	P
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)	
9	25 (2)	119 (9)	**<0.001**
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	99 (8)	95 (7)	
16	16 (1)	38 (3)	
17	111 (9)	6 (1)	
18	38 (3)	53 (4)	
First transplant (n=1842)	795 (88)	826 (88)	0.86
Years KRT pre-transplant (n=1592)	1.7 [0.0 – 4.0]	1.9 [0.17 – 4.28]	0.10
Living 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 5.1. Factors associated with undergoing CAD screening. Data are expressed as number (%) or median [interquartile range].
Abbreviations: IHD, ischaemic heart disease; IMD index of multiple deprivation; PVD, peripheral vascular disease; CeVD cerebrovascular disease.

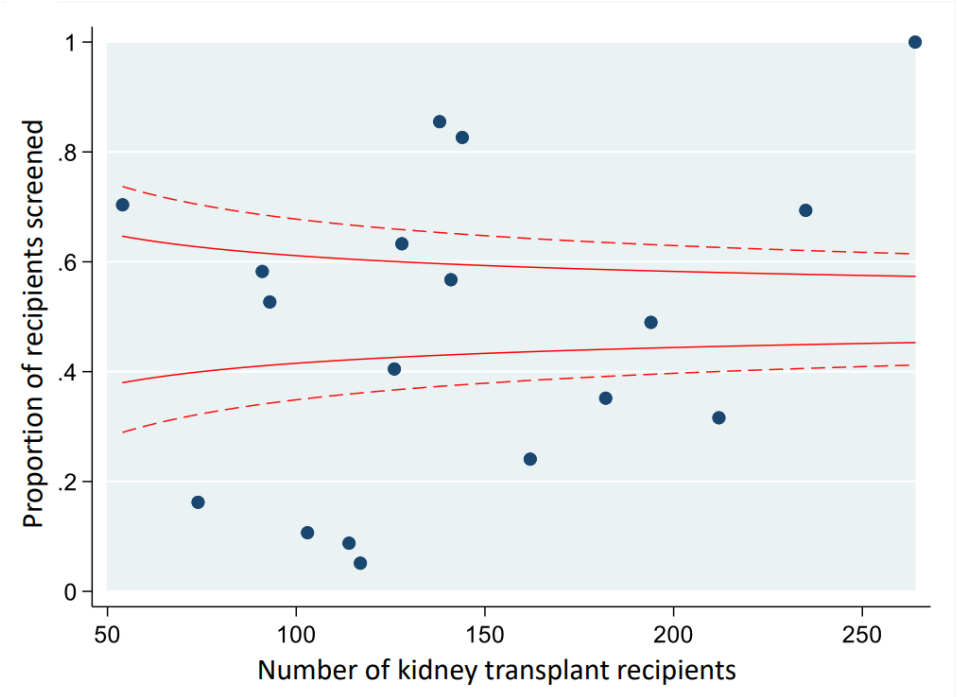


Figure 5.6. Funnel plot demonstrating proportion of patients undergoing screening by centre. The x axis reflects the number of patients from each centre receiving a kidney transplant.

By multivariable analysis, factors that remained independently associated with screening comprised increased 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) (Table 5.2). Significant variation between centres persisted following adjustment for all other factors. There was no association between screening and prior KRT modality, socioeconomic status, or PRD.

	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)				
Glomerulonephritis	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
Polycystic kidney disease	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
KRT modality (Ref: HD)				
Peritoneal dialysis	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: anonymous)				
1	0.41 (0.26 – 0.65)	**<0.001**	0.35 (0.20 – 0.61)	<**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 5.2. Logistic regression of factors associated with CAD screening. One transplant centre was removed as all patients underwent screening.
Abbreviations: PN pyelonephritis, IHD ischaemic heart disease, PVD peripheral vascular disease, CeVD cerebrovascular disease, HD haemodialysis.

5.4.5 Association between screening and MACE: propensity score matching

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 5.1).

5.4.5.1 Non-propensity score matched patients

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 detail in Appendix D and are visually represented alongside those patients who were propensity matched in Figure 5.7.

Of the non-propensity score matched patients, 440 underwent screening. Non-propensity score matched patients 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. There were no statistically significant differences in age, smoking history or prior KRT modality.

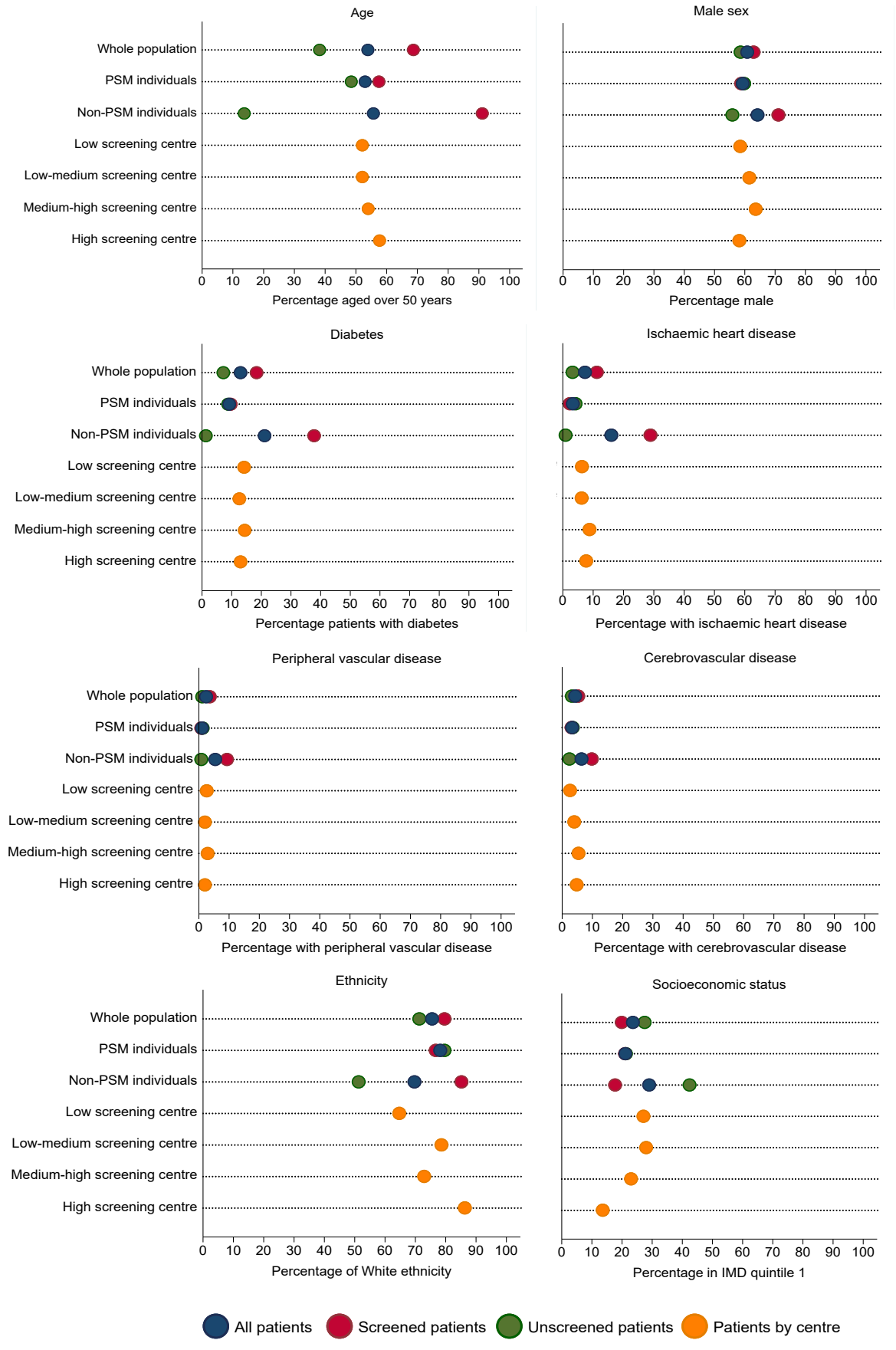

Age
Whole population
PSM individuals
Non-PSM individuals
Low screening centre
Low-medium screening centre
Medium-high screening centre
High screening centre
0 10 20 30 40 50 60 70 80 90 100
Percentage aged over 50 years
Male sex
Percentage male
Diabetes
Percentage patients with diabetes
Ischaemic heart disease
Percentage with ischaemic heart disease
Peripheral vascular disease
Percentage with peripheral vascular disease
Cerebrovascular disease
Percentage with cerebrovascular disease
Ethnicity
Percentage of White ethnicity
Socioeconomic status
Percentage in IMD quintile 1
All patients
Screened patients
Unscreened patients
Patients by centre

Figure 5.7. Characteristics of screened and unscreened groups in the whole population and propensity score matched and unmatched groups, followed by characteristics by centre screening use: low screening (<25% of transplant patients screened; n=570), low-medium (25-49% screened; n=714), medium-high (50-74% screened; n=742) or high screening (>74% screened; n=546). There is variation in patient characteristics by those screened or unscreened, but this reduces when patients are stratified by centre screening volume. Abbreviation: PSM propensity score matching.

The balance of propensity scores in the whole population and in the propensity matched cohort are shown in Figure 5.8. This shows the more even balance in propensity scores following matching but also the under-representation of patients with the highest propensity scores in the propensity matched cohort. The non-matched patients disproportionately present the patients with the highest likelihood of undergoing screening and thus those assumed to be at the highest cardiac risk.

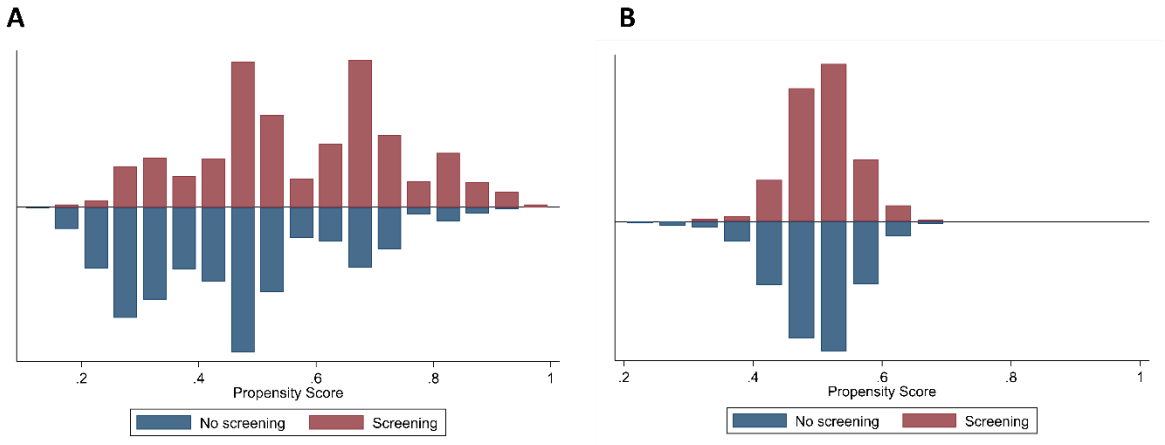


Figure 5.8. Distribution of propensity scores, indicating the propensity to undergo screening in patients who were and were not screened. A: before propensity score matching and B: after propensity score matching.

5.4.5.2 Propensity score matched analysis

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 (Appendix D). There was

variation in SMD, though all variables were more evenly balanced following the propensity score matching process (Figure 5.7). Ethnicity, PRD, index of multiple deprivation, smoking and history of ischaemic heart disease each had an SMD of greater than 0.1 (shown in Appendix D), 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 had a MACE event by 90 days (cumulative incidence 0.9%), 32 by 1 year (cumulative incidence 1.9%) and 117 by 5 years (cumulative incidence 8.0%). 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 CT or invasive 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), 1 year (HR 1.12, 95% CI 0.51-2.47) or 5 years post-transplant (HR 1.31, 95% CI 0.86-1.99) (Table 5.3 and Figure 5.9).

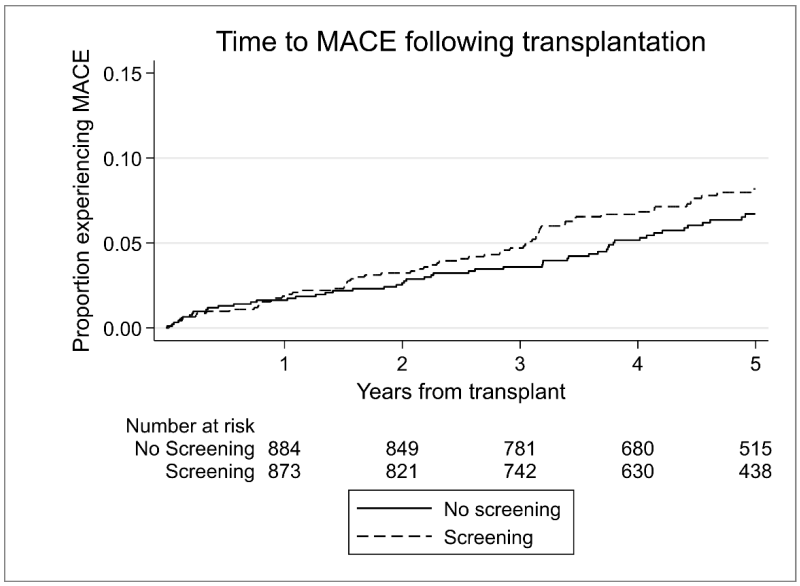


Figure 5.9. Kaplan-Meier estimator curve demonstrating MACE after transplantation in patients undergoing screening for coronary artery disease versus those who did not.

		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

		90 day Unadjusted	90 day Adjusted	1 year Unadjusted	1 year Adjusted	5 year Unadjusted	5 year Adjusted
IMD 5 (Ref: 1)	HR (95% CI) *P*	6.09 (0.84 – 43.74) 0.07	4.62 (0.61 – 34.74) 0.14	2.46 (0.81 – 7.47) 0.11	2.17 (0.74 – 6.36) 0.16	1.24 (0.64 – 2.41) 0.53	1.12 (0.63 – 1.98) 0.69
Ever smoker	HR (95% CI) *P*	0.35 (0.08 – 1.62) 0.18	0.38 (0.08 – 1.74) 0.21	0.71 (0.29 – 1.73) 0.45	0.74 (0.30 – 1.85) 0.52	0.90 (0.58 – 1.39) 0.63	0.96 (0.65 – 1.41) 0.82
History of cerebrovascular disease	HR (95% CI) *P*	- - -	- - -	0.96 (0.11 – 8.42) 0.97	0.92 (0.11 – 7.82) 0.94	0.84 (0.24 – 2.91) 0.79	0.74 (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 5.3. Factors associated with MACE 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. Hazard ratios marked with a dash reflect no events within the specified time period in this patient subgroup.

In the multivariable Cox model, factors independently associated with MACE at 1 year were age and history of ischaemic heart disease. 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, male sex, and history of ischaemic heart disease were positively associated with MACE (Table 5.3). The incidence of MACE at 5 years did not correlate with transplant centre (Appendix D).

As it is possible for post-transplant events to modify the risk of MACE, post-transplant risk factors were compared between screened and unscreened patients 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).

5.4.6 Association between screening and MACE: propensity score weighting

In the propensity score weighted analysis, a total of 2502 patients were examined; 70 patients were excluded due to missing data in variables used to generate the propensity score.

Propensity score weights were calculated and stabilised by multiplying the weight by the proportion of individuals who underwent screening. The mean of the stabilised weights was 1.00 (SD 0.47), range 0.53-8.45. The weights were deemed to not be great enough to require truncating; some advocate allowing a maximum weight of 10 to produce more precise estimates.[308] Characteristics of the 57 patients with a weight greater than or equal to 2 are shown in Appendix D. These patients were more likely to be unscreened. Higher-weighted unscreened patients were older and more likely to have a history of diabetes, ischaemic heart disease and peripheral vascular disease than those with weights under 2.

A multivariable Cox regression model was performed incorporating the weights (Table 5.4). There was no association between screening and MACE at 90 days (HR 0.95, 95% CI 0.44-2.05) or 1 year

(HR 1.28, 95% CI 0.72-2.26). The 5-year analysis did not meet the Cox proportionality assumption due to a greater rise in MACE in the screened group over time.

5.4.7 Propensity score assumptions

Potential violations of propensity score assumptions need to be considered when interpreting the results from propensity score analyses. Deviation from the exchangeability assumption could occur through the exclusion of variables such as obesity from the propensity score model, though obesity did not associate with MACE in the analyses in Chapter 4 (Section 4.5.2). Further, the consistency assumption states that the exposure should be well defined. Screening methods vary between centres, and differences in screening modalities or the way in which test results are interpreted or acted upon mean it is possible for these different 'versions' of the intervention to have varying impacts on outcomes. These possible violations of the propensity score assumptions could lead to bias in the results.

5.4.8 Association between screening and MACE: instrumental variable analysis

Transplant centre was deemed to be a good instrumental variable for screening, with a first stage F statistic of 70 and partial R squared value of 0.33. In total 2502 patients were included in the instrumental variable analysis; 70 patients were excluded due to missing data in the variables used to predict screening. There was no association between screening and MACE at 90 days (HR 1.37, 95% CI 0.29-6.55), 1 year (HR 1.85, 95% CI 0.65-5.29) or 5 years (HR 1.21, 95% CI 0.72-2.02), though confidence intervals were wide (Table 5.4).

5.4.9 Differences in results

Whilst all three statistical techniques showed no statistically significant association between screening and MACE and had overlapping confidence intervals, there was variation in estimates between the methods. The hazard ratios using propensity score methods rose over time, crossing 1 between 90 days and 1 year, whilst in the instrumental variable analysis the hazard ratio was above 1 throughout. These differences can help the interpretation of results by considering which patients are included in each analysis (and thus which treatment effect is estimated by the model; Section 5.3.5.7) and may not solely reflect a fault of the methods or residual bias.

Whilst the propensity score matched analysis suggests no benefit to screening, this cannot be directly applied to the highest risk patients (estimates reflect the ATT). The propensity score weighted analysis includes all patients and so is the treatment effect is more representative of the whole population (estimates reflect the ATE). The non-proportionality of the 5-year model however raises the possibility that a subgroup of patients excluded from the propensity score matched model but retained in the weighted method derived an early benefit from screening. Their MACE rate may have been reduced to that of the general population for the first post-transplant year before subsequently rising.

Whilst the instrumental variable technique aims to minimise unmeasured confounding, the hazard ratio was above one throughout which raises the possibility that unmeasured patient level characteristics associate with centre and outcome (i.e. clinicians screen their patients as they are in some way inherently higher risk), or there are unmeasured differences in centre level practice e.g. use of best medical therapy that could make the instrument inadequate. Alternatively, given that the propensity score analyses are prone to bias due to unmeasured confounding, this bias could explain the difference in results, and the instrumental variable analysis could provide a result that is closer to the truth.

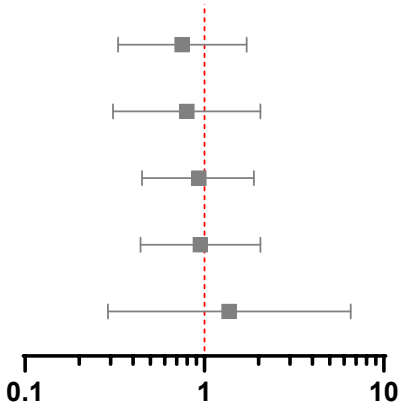
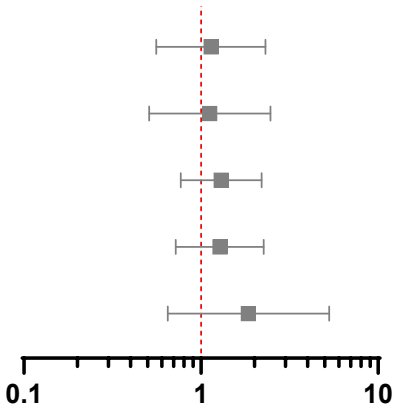
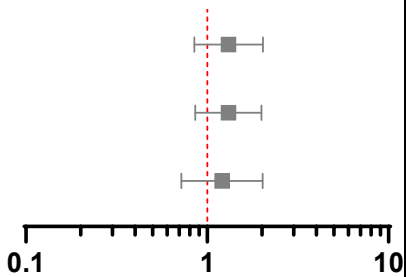
Association between screening and MACE at 90 days post-transplant 14 events in propensity score matched group, 23 events in whole population				
Method	**HR**	**95% CI**	**P value**	**HR with 95% CI**
Propensity score matched	0.75	0.33 - 1.72	0.50	
Propensity score matched "doubly robust"	0.80	0.31 - 2.05	0.64	
Propensity score weighted	0.93	0.45 – 1.89	0.83	
Propensity score weight "doubly robust"	0.95	0.44 – 2.05	0.90	
IV	1.37	0.29 – 6.55	0.69	
Association between screening and MACE at 1 year post-transplant 32 events in propensity score matched group, 52 events in whole population				
Method	**HR**	**95% CI**	**P value**	**HR with 95% CI**
Propensity score matched	1.14	0.56 – 2.31	0.72	
Propensity score matched "doubly robust"	1.12	0.51 – 2.47	0.77	
Propensity score weighted	1.30	0.77 – 2.20	0.33	
Propensity score weight "doubly robust"	1.28	0.72 – 2.26	0.40	
IV	1.85	0.65 – 5.29	0.25	
Association between screening and MACE at 5 years post-transplant 127 events in propensity score matched group, 199 events in whole population				
Method	**HR**	**95% CI**	**P value**	**HR with 95% CI**
Propensity score matched	1.31	0.85 – 2.03	0.22	
Propensity score matched "doubly robust"	1.31	0.86 – 1.99	0.20	
IV	1.21	0.72 – 2.02	0.48	

Table 5.4. Association between screening and post-transplant MACE at 90 days, 1 year and 5 years using propensity score matching, weighting and instrumental variable

techniques. The 5-year propensity score weighted analysis is not shown as it did not meet the Cox proportionality assumption.

5.4.10 Sensitivity analyses

The sensitivity analyses are included in Appendix D. These comprised:

1. Examining the ATTOM incident transplant cohort only using the propensity score matching technique. There was no significant difference in results when examining the incident transplant cohort only compared to the analyses here which included ATTOM waitlisted patients who were subsequently transplanted.
2. A competing risk model for non-cardiac death using the propensity score matching technique. Again, there remained no association between screening and MACE when accounting for non-cardiac deaths.
3. Calculation of the E-value to determine the likelihood that an unmeasured confounder eliminated a 'true' protective effect of screening in the propensity score matched analysis. 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.
4. Performing a propensity score stratified analysis by dividing patients into quintiles based on their propensity score. Screening was not associated with a reduction in MACE in any quintile; in fact, screening associated with a greater occurrence of MACE in the quintile containing the 20% of patients with the highest propensity scores. The small number of patients and events in each quintile mean this analysis is likely underpowered, but the

increased occurrence of MACE in screened individuals with the highest propensity scores raises the possibility of unmeasured confounding in the propensity score analyses.

5.5 Discussion

In this large cohort of kidney transplant recipients in England, there was no association between screening for asymptomatic CAD and the development of MACE up to 5 years post-transplantation. By examining a national cohort and adjusting for factors associated with screening through three different statistical techniques (propensity score matching, propensity score weighting and instrumental variable analysis), the results are less subject to regional and selection bias than previous observational studies which report variable associations between cardiac screening and MACE. [160 161 163 327 328 329] The uncertainty over the utility of screening is highlighted by the variation in uptake between centres, ranging from 5-100% of recipients.

5.5.1 Incidence of MACE

The low incidence of post-transplant MACE is reassuring and lower than that reported in US studies. [146 270] This suggests patients 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. Age, male sex and history of ischaemic heart disease were positively associated with MACE in the propensity matched analysis, as previously reported, [146 270] adding weight to their use in risk-stratified algorithms. [139 137] The smaller sample size in this analysis may explain why associations between MACE and diabetes, peripheral vascular disease, smoking and ethnicity were not observed, as seen in Chapter 4.

5.5.2 Associations with screening

Patients were more likely to undergo screening if they were older and had a history of heart disease or diabetes. However, variation was also seen with ethnicity, with patients of White ethnicity being more likely to be screened than those of Black ethnicity, and variation in practice between centres persisting after adjustment for patient characteristics. Centres caring for a lower proportion of White kidney transplant recipients and patients with lower socioeconomic status were less likely to perform screening. These factors are associated with reduced access to transplantation in the UK, [330] and work to identify whether there are interactions between access

to screening and access to transplantation is needed. If screening pathways are indicative of structures which promote inequity, by removing unnecessary investigations it is possible that inequities in access to transplantation could be reduced.

Similar associations with screening have been reported in US studies. In one study of 27,000 transplant recipients from 217 centres, patients were more likely to be screened if they were older, of White ethnicity, and had a history of cardiomyopathy, valvular heart disease, CAD, peripheral vascular disease, or diabetes. Similar variation in proportion of screened transplant patients by centre was observed: ranging from 11-96%. Further, of those patient factors associated with increased likelihood of screening, transplant centre was second only to prior history of CAD – suggesting practice is influenced largely by hospital culture rather than individual patient characteristics. [151] A second multi-centre US study found 46% of patients were screened prior to transplantation, with women and those of Black ethnicity less likely to undergo screening, despite Black ethnicity being associated with a higher rate of post-transplant MACE in their cohort. [152]

Whilst variation in practice is frequently attributed to differences in case-mix between centres, [331] this may not be the case based on the results presented here and the US studies reported above. The lack of robust evidence on the benefit of screening prior to transplantation likely leads to differing views between transplant clinicians and transplant centres and may contribute to the variability in screening practice. Variation may therefore be unwarranted, and the association between screening and sociodemographic factors requires further examination.

5.5.3 Association between screening and MACE

There are several possible explanations for the lack of association between screening and MACE. First, performing and interpreting non-invasive investigations is challenging in patients with CKD. The low exercise capacity of patients with CKD, [168 185] moderate sensitivity and specificity of non-invasive screening tests [170 172] and high pre-test probability of underlying CAD mean non-invasive tests may not adequately risk stratify patients, with a substantial proportion of people with normal tests still developing MACE.

Second, even if non-invasive tests accurately identified individuals with significant CAD, revascularisation may not improve outcomes. [141 186] The ISCHEMIA-CKD trial examined patients with an eGFR<30ml/min/1.73m^2 or on dialysis with moderate to severe ischaemia on stress

testing. Whilst patients were excluded if they had unprotected left main stem disease or an ejection fraction below 35%, they found no reduction in death or AMI with angioplasty over best medical therapy. [121] There is therefore a move away from performing coronary revascularisation in asymptomatic patients prior to kidney transplantation solely to reduce perioperative risk. [332]

Third, the absence of a clear benefit from revascularisation suggests the different aetiology of cardiovascular disease in people with CKD is important. The high prevalence of left ventricular hypertrophy, systolic and diastolic dysfunction, myocardial fibrosis, arteriosclerosis and electrical instability [333] may explain why half of cardiovascular deaths in transplant recipients relate to dysrhythmias as opposed to atherosclerotic events. [334] [335] The screening tools used to identify atheromatous disease may be less suited to the CKD population and other dynamic investigations e.g. coronary artery calcium scores or functional cardiopulmonary exercise testing may provide superior risk information in this cohort. [336] [337] Other explanations for the lack of benefit observed with revascularisation include altered blood coagulation in patients with advanced CKD, or the presence of competing risks that influence the occurrence of the primary outcome. [338]

Fourth, even if revascularisation of a critical coronary lesion prevented further events at that site, up to three quarters of coronary events post-transplant relate to new coronary artery lesions that were not present on pre-transplant angiography. [162] Plaque progression is common in patients with ESKD, but it is difficult to predict which non-severe coronary stenoses will rapidly progress or rupture, meaning pre-emptive revascularisation may not target the most at-risk lesions.

Finally, MACE post-transplantation may be influenced by transplant-specific cardiovascular risk factors such as renal function and acute rejection episodes. [339] However, the data here suggested these did not play a clear role in predicting MACE over follow-up: 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 was observed in the screened group.

These results suggest that the presence of individual risk factors may be better at predicting MACE, irrespective of the screening strategy adopted and whether revascularisation was performed. Optimisation of modifiable risk factors in transplant candidates may therefore be more important in managing MACE risk than screening or screening-associated interventions.

5.5.4 Strengths and limitations

These analyses have several strengths. The prospective cohort of patients from all transplant centres in England allowed evaluation of a large population through dataset linkage. The causal inference techniques were possible because of variation in practice between centres with no inter-centre difference in incidence of MACE; by examining patients with a similar likelihood for screening they are estimated as having comparable degrees of underlying CAD. The 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 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 [340] and dysrhythmia-related deaths should be captured. The population is also broadly representative of other high-income countries with respect to renal [341] and cardiovascular outcomes [342] making results generalisable.

There are however limitations:

- Data were observational so only associations can be described. The causal inference techniques aimed to increase confidence in results. Whilst there is potential for unmeasured confounding in the propensity score analyses, no association between screening and MACE was observed in the instrumental variable analysis which should minimise impact from unmeasured confounders.
- Patients included in the study were presumed to be asymptomatic and their exercise tolerance was not known.
- The time between screening and transplantation was not known. It could be argued that screening too far in advance of surgery is ineffective. However, this was a real-world study, with screening patterns determined by transplant centres. As such it is likely that some patients underwent repeated testing whilst on the waitlist and not all tests would have been far in advance of transplantation. This chapter did not aim to identify the optimal timing of screening, though similar propensity score matched work showed no benefit from surveillance stress tests whilst on the waitlist. [329]
- In the propensity score matched analysis, patients with the highest propensity for screening (and thus greatest prevalence of cardiovascular risk factors) were less likely to

be included in the models. The highest-risk individuals are thus under-represented, and caution should be exercised extrapolating findings to this group (Figure 5.10). The propensity score stratified, weighted and instrumental variable analyses go some way to mitigate this.

- The number of patients who underwent screening and were not waitlisted due to cardiac screening abnormalities is unknown. In the UK, single centre reports suggest the proportion of patients not listed who begin transplant workup range from 13-26% [141] [186] [192] but screening results are just one factor in a complex clinical assessment and the relative impact of these in transplant preclusion is unclear. The proportion excluded predominantly due to screening abnormalities is probably lower, reported as 4% by Kumar et al, [141] 1% by Kianda et al. [343] and 0.6% by Kanigicherla et al. [192] There may be subgroups of patients who benefit from screening, potentially through appropriate non-listing, but the causal inference techniques adopted here were chosen to address this issue as far as possible.
- It is not known whether screening tests met agreed diagnostic thresholds, but there is no reason to suspect that investigations would not meet established quality standards. [155] [344] [345]
- Investigation results are not known, but it is assumed that patients listed for transplantation following screening were deemed to have acceptable test results that ruled out significant cardiovascular risk. Studies in similar populations describe stress test abnormalities in 25-30% of transplant recipients, [346] and the population studied here are unlikely to be substantially different to previous reports. Although undergoing screening did not associate with MACE, it is still possible that test results could provide information on who is higher risk, which could aid patient decision making or alter peri-operative management e.g. being planned to have an initial period of post-operative management in intensive care.
- 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 it was reassuring that no difference was seen over 5 years with a greater number of events observed.
- Data on medical management of CAD, and whether this differed between groups, is unknown. However, if patients undergoing screening were identified as having CAD it could be hypothesised that they would be more rather than less likely to be on best medical therapy. This would enhance any beneficial effect of screening, not minimise it.

- Data on all post-transplantation cardiovascular risk factors such as maintenance immunosuppression and other biochemical parameters are not known, but these may impact more on long-term cardiovascular risk so are less likely to be clinically relevant.
- Waitlisted and incident transplant cohorts were combined to increase sample size. Waitlisted patients were matched to the incident transplant cohort based on time on the waitlist (within 100 days) and so it is likely that waitlisted patients (who were transplanted later) had a longer duration of ESKD prior to transplantation. However, half of waitlisted patients were transplanted by 31st March 2014 (1 year after the end of ATTOM recruitment) and waitlisted patients were evenly distributed between screened and unscreened groups so should not influence outcome.
- 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.

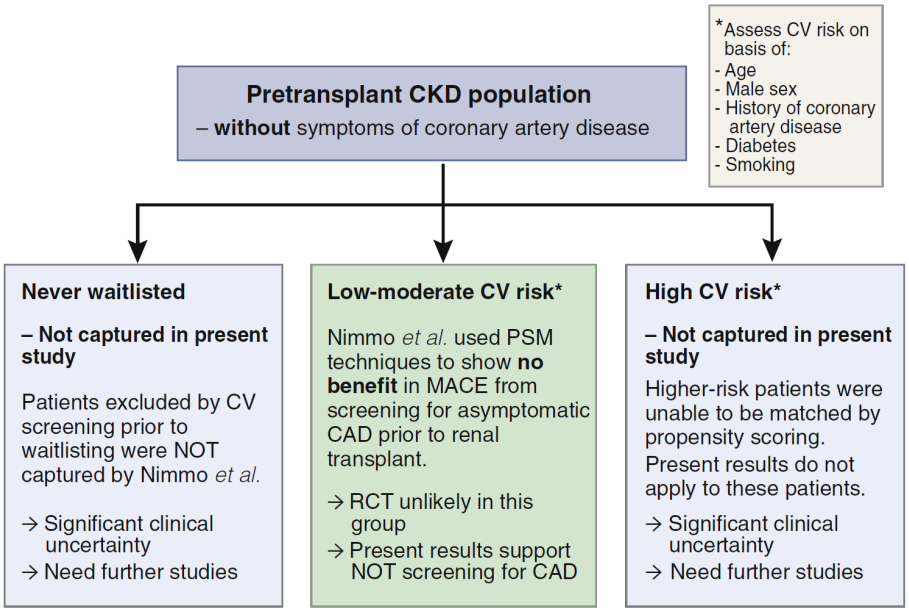


Figure 5.10. Relevance of results to patients based on individual cardiac risk factors. From Rankin and Mark. [347]

5.5.5 Risks and benefits of reducing screening

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 [52] with more being investigated and not listed. A stress echocardiogram costs £280 and an angiogram £2500, [348] 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. [158] 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 [349] 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 [141] and minimises delays to listing with potential to reduce time on dialysis. Further, given patients can benefit from transplantation even in the presence of coronary artery disease (2 vessel stenoses of over 50%), [201] high comorbidity [350] and low physical functioning, [351] reducing screening could prevent the preclusion of patients from transplantation who still benefit from this treatment.

5.6 Conclusion

This analysis suggests that screening for CAD does not reduce cardiac events post-transplantation in a large national cohort of kidney transplant recipients, using statistical techniques to minimise the risk of confounding bias. As the ideal statistical technique to use in this situation is uncertain, analyses using propensity score matching, propensity score weighting, and instrumental variables are presented together and show consistent results. While it is important not to downplay the significant risk and impact of cardiovascular events on kidney transplant recipients (Chapter 4), these results suggest that unselected screening of asymptomatic patients prior to kidney transplantation does not effectively mitigate cardiac risk, especially when balanced against the

potential risks of screening. Clinical equipoise still exists for the patients with a higher burden of cardiovascular risk factors and further work is needed to identify if screening processes result in appropriate selection of patients for the waitlist, or whether they unnecessarily deny transplantation to those patients who could achieve the greatest cardiovascular risk reduction with transplantation. A large-scale prospective 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. However, the design of such a trial is not simple. The practicalities of such a trial, alongside the results of initial scoping work in the UK, are described in the following chapters.

Chapter 6: Pre-transplant cardiac screening in 2021: a survey of UK transplant centres

6.1 Introduction

Whilst the analyses in Chapter 5 are novel, using unique observational data with long follow up times allowing an adequate assessment of outcomes, they represent pre-transplant screening practice in 2011 to 2013. At this time, surveys of UK transplant clinicians showed that although there was uncertainty in the benefit of pre-transplant cardiac screening, this practice was still frequently performed. [55] [352] It is not known whether clinical practice or clinician opinion on the utility of screening or feasibility and acceptability of a randomised control trial has changed since this time. Specifically, published results in 2020 both from the ISCHEMIA-CKD trial, [121] and from the observational analysis presented in Chapter 5 [353] may have changed clinician opinions, [347] although not all agree that screening should be reduced. [354] [355]

If a UK randomised control trial to investigate whether pre-transplant screening reduces peri-transplant MACE were to be considered, it would first be necessary to understand (1) which patients currently receive screening in the UK, (2) how the multi-professional transplant team are involved in the work up of potential transplant recipients, and (3) whether there would be an appetite amongst clinicians and patients to take part in such a trial.

Following the publication of the work in Chapter 5, I have been fortunate to be involved in national meetings with key stakeholders to discuss the potential of such a trial on pre-transplant screening. This chapter outlines a survey I designed and completed with support from the Kidney Research UK Transplantation Clinical Study Group (CSG) to progress this issue. The aim of the survey was to report on the current screening practice and pathways in the UK and examine the appetite for a clinical trial in this small but geographically representative group of clinicians. This forms part of the scoping work required to understand the practicalities, feasibility, and potential design of a trial. The survey was sent to transplant nephrologists in June 2021 representing each of the 23 transplanting centres in the UK.

Results in this chapter have been published as:

Nimmo A, Graham-Brown M, Griffin S, Sharif A, Ravanan R, Taylor D. Pre-kidney transplant screening for coronary artery disease: current practice in the UK. *Transplant International*. 2022; 35:4.

The published paper can be found in Appendix F.

6.2 Methods

An online questionnaire was developed in collaboration with three members of the Kidney Research UK Transplantation CSG (full questionnaire in Appendix E and at bit.ly/transplant_screening). The Transplantation CSG is a network of nephrologists with an academic interest in kidney transplantation from across the UK, a subgroup of which forms a working group examining pre-transplant cardiac screening.

The questionnaire was uploaded onto the SurveyMonkey (www.surveymonkey.co.uk) online platform. The initial distribution was via the UK Kidney Association Clinical Directors newsletter (an email sent to clinical directors at all 71 UK renal units) but no responses were received. Subsequently, the survey was distributed via a personal email with an embedded survey link to one transplant nephrologist from each of the 23 transplant centres in the UK. One reminder email was sent at 2 weeks. Nephrologists were identified through their representation on the NHSBT Kidney Advisory Group or through involvement in the Transplantation CSG. Responses were accepted from 22nd June 2021 to 12th July 2021. Consent was implied, responses were voluntary and optional, and no pecuniary or gift incentive was offered for taking part.

Questions were grouped into three sections to provide an overview of pre-transplant cardiac assessment:

1. Current cardiac screening practice
2. Pathways for cardiac assessment
3. Clinician opinion on current practice

The start of the questionnaire stated that questions related to current practice for asymptomatic individuals, defined as a being able to climb a flight of stairs without cardiac symptoms (chest pain or shortness of breath). Respondents were asked not to include either an ECG or echocardiogram as a screening investigation. There was a predominance of closed questions with optional free-text responses. A decision tree configuration allowed respondents to skip questions not relevant to them.

Quantitative data are presented using descriptive statistics with proportions, the denominator being the total number of eligible responses. Analyses were performed in Stata version 15 (Statacorp, College Station, TX).

6.3 Results

6.3.1 Current practice

Responses were received from all 23 transplant centres. Of these, 22 had a protocol for cardiac assessment prior to transplant listing. In 3 centres (13%), no asymptomatic individuals were required to undergo additional cardiac investigation beyond an ECG or echocardiogram prior to transplantation. The remainder of centres followed a risk-stratified approach; no centres adopted universal screening.

In the 20 centres following a risk-stratified screening protocol, factors used to screen patients included a history of ischaemic heart disease (100% of centres), diabetes (100%), peripheral vascular disease (50%), smoking (50%), stroke (35%), limited exercise capacity (35%) and hyper/hypotension (15%) (Figure 6.1). Other criteria included an abnormality on echocardiogram (95%) or ECG (70%). Two centres (10%) used the Newcastle Risk Index to stratify patients (Table 6.1). [356] In 1 centre each a longer duration of KRT and a body mass index of $\geq$35kg/m^2 were used to identify patients for screening. There were differences in the age at which screening was commenced: 15 centres out of the 18 who responded (83%) had specific age cut-offs (most frequently screening patients aged greater than or equal to 50 or 60 years), whilst the other centres based the age at which they commenced screening on clinical judgement or the Newcastle Risk Index score (Table 6.2).

The Newcastle Risk Index score that necessitated patients to be screened at 1 centre was 4 and above (score 4-8 required myocardial perfusion scan or stress echocardiogram, whilst scores of 9 above additionally required formal lung function studies and assessment of walking distance with discussion regarding suitability of transplantation). At the other centre, the score was used as a guide only with no set score requiring screening.

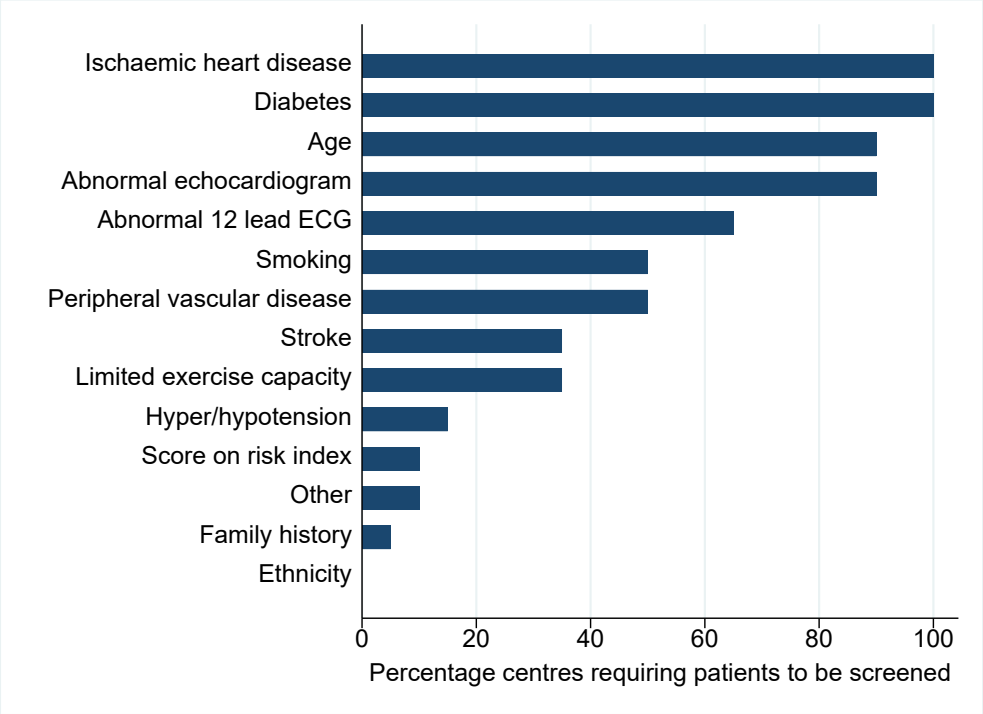


Figure 6.1. Factors used to identify patients for risk-stratified screening (n=20 centres).

Variable	Score
Age (years)	
<45	0
45-64	2
≥65	4
Diabetes	
Present	3
Blood pressure assessment	
Hypotension: Systolic blood pressure <110mmHg	4
Hypertension: BP <150/90 but >110mmHg systolic	0
Controlled with medication	2
Uncontrolled (BP>150/90) with or without medication	3
Angina	
Not present	0
Stable	3
Variable or on minimal exertion (40-50m)	4
Coronary vascular surgery and AMI	
One AMI or one CABG; 2 vessel disease or angioplasty	3
Two AMI or CABG with triple vessel disease or 2 surgical procedures with CABG	4
Cardiac valve disease	
Valve disease – mitral/tricuspid/pulmonary or surgery	2
Aortic valve surgery or disease	3
Exercising distance	
50-200m or slowing on stairs	3
<50m or stops on stairs	4
Cerebrovascular disease	
Previous stroke or transient ischaemic attack	3
Peripheral vascular disease	
Present	3
Body mass index	
<18 or >30 kg/m^2	3
Total score	0-36

Table 6.1. Newcastle cardiovascular risk score.

Age criteria for screening	Responses (n=18)
≥40 years	1
≥50 years	6
≥60 years	7
≥65 years	1
50-60 years, with room for clinical judgement	1
Age does not trigger screening, but is considered alongside other risk factors	1
No specific age, but age incorporated into the Newcastle Risk Index	1

Table 6.2. Age at which centres commence screening. This refers to the age which triggers screening based on age alone, not alongside other risk factors such as diabetes.

The most frequent initial screening investigation was a myocardial perfusion scan (55%, 11/20) followed by stress echocardiogram (20%, 4/20) and exercise tolerance test (15%, 3/20). Coronary angiography and cardiopulmonary exercise testing were the initial investigation in only 1 centre (5%) each.

Indications for coronary angiography following the initial screening test varied. In 39% (9/23) of centres, angiography was performed if the screening test was abnormal, and in a further 34% (8/23) of centres the decision for angiography was based on the opinion of a cardiologist. It was noted in free-text boxes that the cardiology decision on revascularisation was not made based solely on the possibility of transplant surgery, in-keeping with the 2020 KDIGO guidelines. [6] One centre performed angiography on all patients with diabetes. The remaining 22% (5/23) of centres had no specific policy relating to coronary angiography. No centres routinely delayed angiography until patients were on dialysis, though this happened occasionally in 64% (14/23) of centres.

The estimated time between requesting and completion of an initial screening test was under 8 weeks in 64% of centres (14/22), 8-12 weeks in 27% of centres (6/22), and over 12 weeks in 9% of centres (2/22). The missing response to this question was from a centre which does not routinely screen patients.

Out of 23 centres, 10 (43%) had updated their screening protocol within the past 2 years, with a further 3 (13%) currently in the process of updating theirs.

6.3.2 Pathways for cardiac assessment

The location from which screening tests were requested varied between centres and could occur in more than 1 setting. In 14 centres each, tests were requested from general nephrology clinics or low clearance clinics, or in the transplant assessment clinic by either a nephrologist or transplant surgeon. In 6 centres the screening test would be recommended by the doctor reviewing the patient in transplant assessment clinic but was to be actioned by the named nephrologist. In 7 centres, tests could also be requested in a cardiology clinic by a cardiologist. Less frequent routes of requesting were by transplant co-ordinators when the patient was referred for transplant assessment (n=2) or following recommendation by a cardio-renal multidisciplinary meeting (n=1).

All 23 transplant centres had services to perform screening tests within their centre. At 11 centres (48%), tests could be performed at a referring renal centre and at 9 centres (39%) tests could be performed at the patient's local acute hospital i.e. a hospital without an on-site renal

service. If a patient underwent a screening test at a referring renal centre, it was infrequent for transplant centres to repeat the test ('never' 36%, 8/22; 'rarely' 55%, 12/22; 'sometimes' 9%, 2/22).

Nine centres (39%) had a dedicated cardio-renal multidisciplinary meeting to discuss challenging cases, whilst 14 (61%) had a designated cardiologist to provide advice and review of transplant candidates. In 70% of centres (16/23) cardiology review was only needed for patients with an abnormal screening test, whilst 3 centres (13%) required all patients being screened to be reviewed.

In all centres, transplant nephrologists and transplant surgeons were involved in transplant listing meetings. In 13 centres (57%), nephrologists from the referring centre and anaesthetists were also involved, and in 9 centres (39%) cardiologists took part. The decision on whether to accept a patient onto the waiting list was a shared decision by the multidisciplinary team in 17 centres (74%), whilst the cardiology decision was deemed most important in 3 centres, and the decision of the nephrologist, surgeon or anaesthetist deemed most important in 1 centre each.

In 19 centres (83%) there was experience of patients who had been referred for transplant assessment who were declined from listing based primarily on an abnormal screening test result. It was difficult to quantify how many patients this equated to; 4 centres (21%) were unsure, whilst 11 centres (58%) estimated this to be less than 1 patient per month, and in 4 centres (21%) it was estimated to be 1-5 patients per month.

6.3.3 Clinician opinion on current evidence base

Of the 23 respondents, 14 (61%) felt there was insufficient evidence to support pre-transplant cardiac screening, whilst 2 respondents were unsure (9%) and 2 respondents (9%) felt there was sufficient evidence. The remaining 5 respondents gave free-space responses commenting on issues including screening investigations being used for reasons other than intended purpose (stating they should be used to determine the risk benefit ratio for that patient rather than determining if pre-transplant interventions are required), outdated evidence, reliance on observational data, and differences between real-world cohorts and study populations in published randomised control trials when assessing the evidence for cardiac screening.

Following on, 22 out of 23 respondents expressed an interest in participating in a clinical trial to examine the effect of screening on peri-transplant cardiac events. Of these, 12 stated they would be supportive of recruiting a risk-stratified cohort of patients and 12 were supportive of recruiting

event the highest risk cardio-metabolic patients. A visual summary of survey results is shown in Figure 6.2.

Additional free-text comments from respondents are shown in Table 6.3. These highlighted a desire to align current practice, reduce inter-centre variation, and involve experienced professionals from other specialties in decision making, but also recognised the challenges in designing a suitably powered clinical trial.

Centre	Free text comments
A	There are two questions being asked when we perform assessment of cardiac 'suitability' for transplant – will they make it through the op and will they survive long enough to make the transplant worthwhile for them and for society. Our unit has long felt that our assessment is focussed on the first of these questions because we think that, if the answer to the first question is yes, then almost certainly the answer to the second is yes as well since transplant is likely the best intervention to reduce cardiac risk in patients with ESRD. We think the key is having an interested anaesthetist at the MDT who will see high risk patients in advance so that the anaesthetist on the night has confidence that their decision to proceed is supported by the decision of the MDT that included an expert anaesthetist. In that respect our anaesthetist takes a pragmatic, minimalist approach based on walking them in clinic, what they tell us about how much exercise they can do and recent experience of operations e.g. a big AV graft operation is regarded as better than any cardiac test for assessing 'fitness' for the op. That said we would be interested in participating in a trial. I think the challenge will be designing a trial with sufficient power to answer the question.
B	It is a rapidly evolving field thankfully and within the pan London Tx collaborative we are working to see if we can come to an amalgamated protocol or at least to agree to certain principles together!
C	I think the practicalities of a trial are likely to be very challenging, and the initial premise of the survey - that 'can climb a flight of stairs' equates to asymptomatic is a very poor place to start.

Table 6.3. Free text responses to survey.

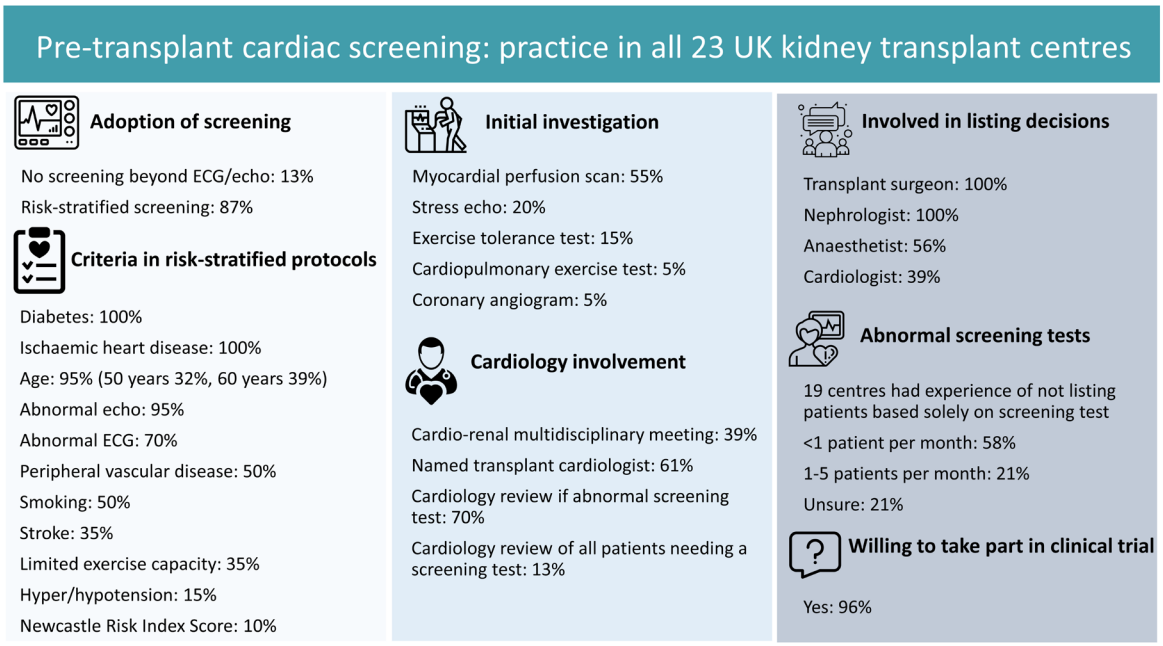


Figure 6.2. Summary of survey results.

6.4 Discussion

The results from this survey highlight variation in screening pathways across the UK. Whilst most centres adopt a risk-stratified approach to screening, identifying patients most frequently on the presence of diabetes, ischaemic heart disease or an abnormality on echocardiogram, there is variation in the other clinical characteristics used to risk-stratify patients for screening, as well as variation in initial screening modality. Further, the involvement of multi-professional colleagues such as cardiologists and anaesthetists in patient assessment and listing decision making varied between centres, with some respondents commenting on the benefits of having support from engaged specialists with different areas of expertise.

In the past 2 years, over half of transplant centres have updated their screening protocol. Whilst respondents were not asked to specify what recent changes were, no centres performed universal screening of potential recipients, contrasting to the practice described in Chapter 5. It is possible these updates represent a trend away from routine screening. Alongside survey responses, 3 centres provided their cardiac screening protocols. Two of these were updated in 2021 and made reference to the ISCHEMIA-CKD trial [121] and the observational data outlined in Chapter 5 [353] when explaining their rationale for stratified screening. However, despite these recent publications, results highlight that many nephrologists still have concerns over the evidence upon which practice is based and there was a high level of interest in participating in a future clinical trial.

This contrasts to the results from a survey of Canadian kidney transplant centres performed during the design of the CARSK study, when 13 out of 15 (87%) of centres did not support randomisation to a 'no screening' arm prior to transplant listing, [158] suggesting there is now greater debate on the utility of screening.

There are several potential reasons for the observed inter-centre variation in screening practice. First, structural differences between centres, such as whether they have an on-site cardiology service, may influence management or the timing of investigations or specialist review. [357] Second, there may be variation in risk appetite between centres. Differences in risk tolerance towards the acceptance of higher risk deceased donor organs is recognised between UK centres, [358] and this variation may extend to cardiac workup. Finally, the absence of conclusive evidence over which patients benefit of screening is likely to contribute to the variation, with practice that may instead be influenced by local opinion. [359]

A 2020 survey of transplant centres in the USA also showed heterogenous screening practice between centres. [360] Whilst non-invasive tests were the most common initial investigation, patients on dialysis were more likely to undergo coronary angiography and revascularisation than pre-emptively listed patients even in cases of a mildly positive stress. This survey was performed prior to the publication of the ISCHEMIA-CKD trial [121] but suggests a more intense approach to screening than that adopted in the UK. A thematic analysis of free-text responses raised similar points to those identified in this survey, including uncertainties over the goal of screening, difficulties in decision making in the absence of high-quality evidence and the limited predictive ability of current screening tests, and the challenges of performing a clinical trial due to high costs and long follow up time. [360]

There are limitations to this survey. Information was only collected from one transplant nephrologist at each centre. The aim of this was to avoid repetition with multiple individuals from the same centre answering identical questions on their unit's practice but means the subjective responses including willingness to participate in a future clinical trial may not be representative of all nephrologists at their centre, although the transplant lead for each unit is likely to represent unit opinion. It was not possible to capture information on practice at non-transplanting referral centres, nor the views of other transplant professionals involved in listing decisions including surgeons, anaesthetists, cardiologists, and patients. As these individuals are all involved in the listing process, understanding their views is essential. A Delphi study to examine whether there is consensus on which patients to screen across all these groups is planned and discussed in Chapter 7.

It should also be noted that while 22 out of 23 transplant nephrologists expressed willingness to enrol patients to a clinical trial in this area, half stated that this would be limited to a risk-stratified cohort of patients. However, based on the results of this survey, the patients currently undergoing screening already represent a higher-risk cohort with centres not routinely screening younger patients without cardiovascular comorbidities. The higher cardio-metabolic risk patients are the group under-represented in the analyses in Chapter 5 and in whom there is greatest clinical equipoise, and perceptions of the transplant multidisciplinary team towards recruiting these patients to a clinical trial needs to be examined (Chapter 7).

6.5 Conclusions

This survey highlights the variation in screening practice across the UK, suggests a trend towards more selected screening or no screening, and highlights the multi-professional involvement in the work up of potential transplant recipients. The responses will inform methodological discussions around a future clinical trial (Chapter 7) and suggests support for this from transplant nephrologists, though understanding the views of other transplant professionals and patients is essential before a trial can be considered to evidence the utility of screening.

Chapter 7: Conclusions

7.1 Main thesis findings

The findings of this thesis are as follows:

7.1.1 Quality of Hospital Episode Statistics data (Chapter 3)

- The linkage of the routinely collected Hospital Episode Statistics dataset to records of patients with advanced chronic kidney disease from the ATTOM study was successful, with a high linkage rate of 97%. There was demographic inequity in likelihood of successful linkage, with reduced linkage rates in patients of Black ethnicity compared to patients of White ethnicity.
- Among patients with advanced CKD, including those with kidney transplants and on the transplant waitlist, the accuracy in recording of comorbid medical conditions within the HES dataset is variable, with sensitivities ranging from 30-98% and positive predictive values ranging from 22-90%. Recording is most robust for ischaemic heart disease, diabetes, malignancy, and heart valve replacement. Ischaemic heart disease recording was sufficient to allow investigation into the utility of pre-transplant cardiac screening.

7.1.2 Incidence and impact of cardiac events post-transplant (Chapter 4)

- The cumulative incidence of major adverse cardiac events (MACE) following kidney transplantation in England is 1.5%, 2.6%, 5.9% and 9.6% at 90 days, 1-, 3- and 5-years post-transplant respectively. These rates are lower than those reported in the USA. MACE occurred in 0.7% of index admissions for kidney transplantation. The incidence of MACE after kidney transplantation exceeded the risk for waitlisted patients for around 9 months, after which cardiac risk in transplant recipients fell below the level of waitlisted patients. The incidence rate of MACE at 1 year was 25.7 and 33.0 events per 1000 patient years in kidney transplant recipients and waitlisted patients respectively.
- In a landmark analysis, patients with a MACE event within 6 months of transplantation had increased mortality and lower transplant survival than patients without MACE events, including after adjustment for patient demographics, primary renal diagnosis, and baseline comorbidity. Such an association was not seen when the landmark point was

extended to 1 year, suggesting that cardiac events which occur early in the post-transplant period have a greater impact on long-term outcomes. In patients suspended from the transplant waitlist within 30 days of a MACE event, suspension episodes had a median duration of 312 days.

7.1.3 Utility of screening for asymptomatic CAD prior to transplantation (Chapter 5)

- There is significant variation in pre-transplant coronary artery disease screening practice between transplant centres in England, even after adjustment for case mix.
- In a propensity score matched analysis, undergoing screening prior to kidney transplantation is not associated with post-transplant MACE at 90 days, 1 year or 5 years post-transplant. Findings were similar in propensity score weighted and instrumental variable analyses. These findings suggest the utility of screening, at least for low and medium risk transplant candidates, is uncertain.

7.1.4 Screening practice in the UK in 2021 (Chapter 6)

- Between 2011-2013 and present, there appears to be a shift in screening practice in the UK, with 3 out of 23 kidney transplant centres now not performing routine screening investigations of any kidney transplant candidates, and 10 centres updating their screening protocol within the past 2 years. This may result from recently published evidence, including that presented in Chapter 5.
- In those centres performing risk stratified screening, the most frequent factors used to select patients for screening were ischaemic heart disease, diabetes, peripheral vascular disease, smoking history, and abnormalities on ECG or echocardiogram.
- Out of the 23 kidney transplant centres in the UK, 22 reported willingness to recruit patients to a randomised control trial to examine the effect of screening on post-transplant MACE, but only half of these would agree to recruit the highest-risk patients. Recruiting the highest-risk patients however would be vital to the success of a randomised controlled trial, given their higher MACE rate and the greatest clinical equipoise on the utility of screening within this group.

7.2 Recommendations for clinical practice

This work provides contemporary data on cardiac risk after kidney transplantation in the UK. Clinicians should be aware that MACE occurs in 1.5% of kidney transplant recipients within 90 days of transplantation, 1.8% of recipients by 6 months, and 2.6% of recipients by 1 year. Transplant recipients of older age, Asian ethnicity and with a history of diabetes, ischaemic heart disease, peripheral vascular disease and smoking are at increased risk of MACE, and these factors should be considered when informing patients of their risk. Patients with MACE within 6 months of transplantation have greater long-term mortality.

While measures to prevent MACE should be performed if they are effective, findings from this thesis show that pre-transplant screening for CAD does not appear to reduce post-transplant MACE, and this practice should be reviewed by transplant centres. In fact, published results presented in this thesis have already influenced cardiac screening protocols. Published work presented in Chapter 5 [353] was cited in 2021 cardiac screening guidelines from Coventry and Belfast renal centres, [361] [362] in addition to changing practice in Bristol where the age threshold for recommending screening has increased from 50 years to 60 years.

Rationalising the selection process for pre-transplant CAD screening could reduce healthcare resource use and avoid unnecessary delay in the transplant assessment process. The 2021 Renal 'Getting It Right First Time' national report provided recommendations to improve kidney care in England, including to: [363]

'Streamline renal transplant pathways to increase access and reduce unwarranted variation in deceased and living donor transplantation'

The report noted that current transplant assessment pathways are complex and inconsistent, requiring multiple hospital visits and lacking sufficient evidence base. Further, delays in getting specialist tests and opinions were frequently encountered. The report recommended that the time from initiation of workup to transplant waitlisting should be under 18 weeks. Minimising unnecessary screening in low and medium cardiac risk patients could allow transplant assessment pathways to be streamlined and ensure resources are appropriately focused on those patients at the highest cardiac risk, in whom the lack of benefit from screening processes is less clear.

The work in this thesis has not been able to examine the impact of screening on access to transplantation. Ensuring equitable use of donated organs, a finite resource, is a key principle of kidney transplant programmes, [149] but must be balanced against improving the care of individual

patients who could still benefit from transplantation despite having cardiac risk factors or pre-existing CAD. [364] [350] Lower rates of screening in non-White kidney transplant recipients (Chapter 5) were seen, a population who are already known to have both a higher incidence of cardiovascular disease and reduced access to transplantation. [330] [365] [366] Whilst it is not known if screening practices and access to transplantation interlink, the sociodemographic associations with screening are potentially concerning as a pathway to inequity. It could be hypothesised that putting patients forward for screening indicates willingness to consider transplantation in an older White population of higher socioeconomic status, whilst the non-White population may not be offered the same chance. Further work is required to examine whether screening pathways drive inequity. Members of transplant multidisciplinary teams should assess their practice to ensure that they provide their patients with equitable access to the best available treatments.

7.3 Recommendations for future research

7.3.1 Comorbidity data validation by examining ATTOM, HES and UKRR data

The UKRR has had an established linkage agreement with HES since 2018 to improve the assessment of comorbidity-adjusted outcome measures in the UK ESKD population. Prior to this point, the UKRR relied on renal centres returning comorbidity data, which was labour intensive and resulted in missing data in half of patients. [218] The 2020 UKRR annual report (reporting data to the end of 2018) used HES for the first time to augment centre-returned comorbidity data within survival analyses. [19] It is hoped the ongoing use of HES will further reduce the amount of data required to be reported by renal centres to the UKRR each year. [37]

The work in this thesis showed variation in comorbidity recording accuracy within HES, and the results will provide context for researchers working with HES data in the ESKD population. However, it is not known how the quality of UKRR (i.e. renal centre-returned), HES, and research-nurse (the presumed gold standard) comorbidity information differs, nor whether discrepancies in comorbidity recording between sources influences comorbidity-adjusted survival outcomes. Work comparing UKRR, HES, and ATTOM derived comorbidities would allow an assessment of recording concordance between sources and determine whether adjusted survival outcomes differ based on which dataset comorbidities were derived from. Whilst it is possible that the quality of HES data has changed over time (the HES and ATTOM data examined in this thesis is approaching 10 years old), [240] this work would provide information on whether unit comorbidity returns could be confidently minimised.

7.3.2 Research on the utility of screening for asymptomatic CAD prior to transplantation

Studies examining the utility of screening for asymptomatic coronary artery disease prior to transplantation were highlighted as research priorities in the 2019 report of the Kidney Disease: Improving Global Outcomes Controversies Conference on Coronary Artery Disease and Chronic Kidney Disease [332] and by the American College of Cardiology (Figure 7.1). [89] Recommendations for future research from these sources include:

'Observational studies and trials evaluating whether transplant recipients should be screened for CAD. If so, in which patients and at what frequency?

Observational studies and trials evaluating whether screening strategies should be different in deceased donor transplantation versus living donors.'

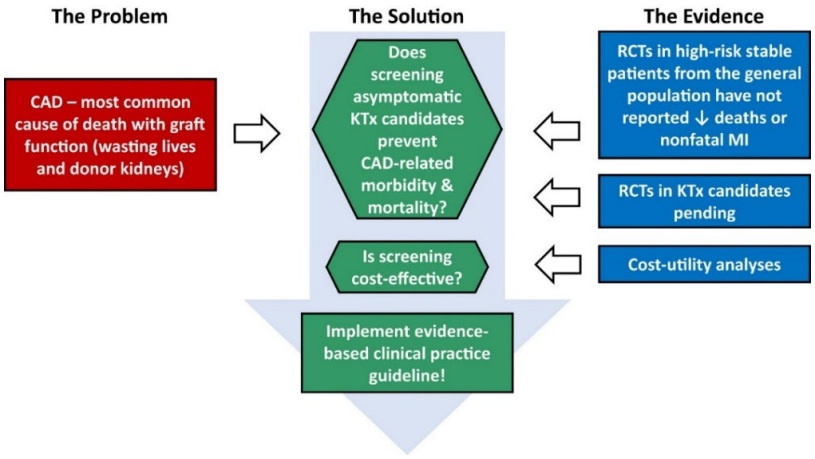


Figure 7.1. The requirement for studies to inform screening for asymptomatic coronary artery disease in high-risk kidney transplant candidates. From Hart et al. [367]

The data in this thesis showed no association between screening and MACE, but its observational nature means it is not able to make strong recommendations against screening and subgroups of patients may still benefit from this practice. Further strategies to assess whether patients should undergo CAD screening prior to transplantation are discussed in the sections below.

7.3.2.1 A randomised control trial to investigate utility of CAD screening

The feasibility of a prospective randomised control trial (RCT) to evaluate the impact of screening prior to joining the transplant waitlist on post-transplant MACE should be considered. The design,

inclusion and exclusion criteria, and primary and secondary outcomes of such an RCT are complex. Initial discussions with the NHSBT Clinical Trials Unit have taken place, with a proposed trial design shown in Figure 7.2, but it remains uncertain whether this is feasible.

The kidney community was invited to submit grant proposals to influence the NIHR Health Technology Assessment (HTA) calls in 2022. These are awards for large studies of an intervention that is ready to be tested in a clinical setting with immediate translational potential. An intervention can also represent the removal of an established treatment if this has potential for large cost-savings without impacting quality of care. A model for an RCT on screening for CAD before joining the transplant waitlist was submitted to the NIHR HTA committee in May 2021 by myself and others from the Kidney Research UK Transplantation CSG in a PICO (Patient group, Intervention, Comparator, Outcome) format based on the initial NHSBT discussions, as outlined below.

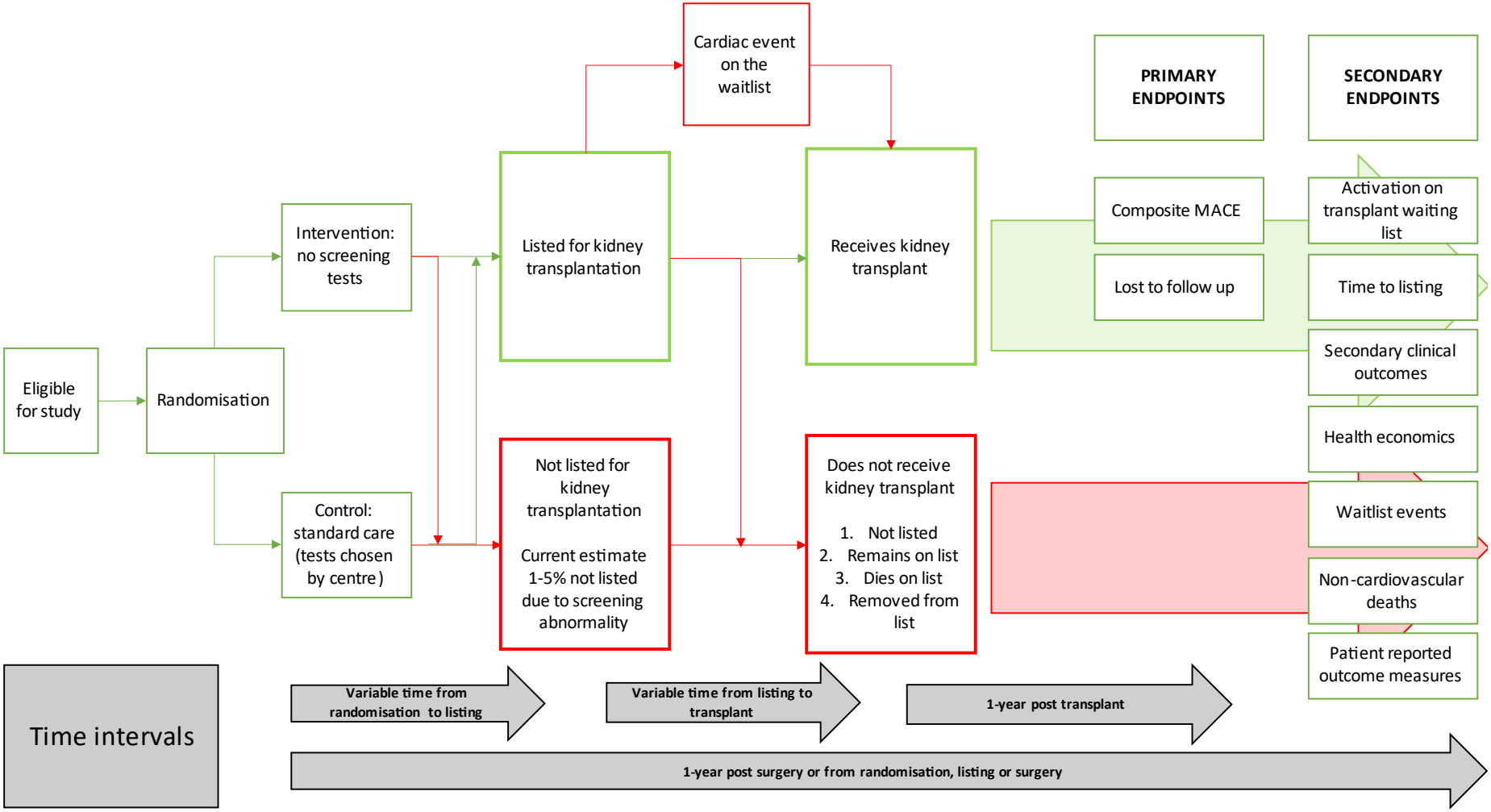


Figure 7.2. Proposed design of a randomised control trial designed for discussions with NHSBT.

Patient group

The target patient group would be adults with CKD G4-5 or established ESKD who have no symptoms of cardiac disease, who are under assessment for kidney transplantation, and who are deemed to be at increased cardiovascular risk and therefore would currently be considered for CAD screening in most UK kidney transplant centres.

Intervention

The study would assess the clinical impact and cost-effectiveness of removing routine screening tests for CAD for asymptomatic patients before kidney transplant listing. It would be envisaged as having a non-inferiority randomised control design.

Comparator

The comparator arm would be 'usual care' based on the current screening practice within that patient's transplant centre. It would therefore be expected for most patients in the 'control' arm to be allocated to undergo CAD screening tests as part of the routine assessment for determination of transplantation suitability.

Outcomes

The primary study outcome would be the occurrence of post-transplant MACE, a composite of cardiovascular death, non-fatal acute myocardial infarction, non-fatal unstable angina, coronary revascularisation procedure, and hospitalisation with heart failure in the peri- and early post-transplant period. There is debate as to what an appropriate post-transplant timeframe would be, for example 6 or 12 months.

Secondary outcomes to assess the impact of screening on other patient outcomes or on transplant process measures could include:

- Activation on the transplant waitlist and time to listing. Removing screening may impact the likelihood of being activated on the transplant waitlist, for example if it allowed the 1-5% of patients currently excluded due to cardiac screening abnormalities to join the list. [141 192 343] Further, observational studies have shown patients being screened take longer to be activated on the transplant waitlist from time of initial assessment. [192] Delays to listing may have a greater impact on those who present late to renal services, such as those from socioeconomically deprived areas, [368] exacerbating inequities in access to transplantation, and therefore is an important outcome to capture.

- Time to transplantation. Any delay to waitlisting that relates to screening is likely to be in the region of months [192] and it is not known if this would impact on time to deceased donor transplantation, particularly given the 2019 UK kidney offering scheme uses waiting time (which starts from the earliest date out of dialysis initiation or activation on the waitlist) in the prioritisation process. [369] Screening may have a greater impact on time of transplantation in patients worked up before initiation on dialysis, who could lose the opportunity for pre-emptive transplantation, or for patients planned to receive a living donor kidney in which an operation date can be planned.
- Waitlist MACE. Screening is not designed to prevent cardiac events on the waitlist, but if such an association were observed it is possible that any associated suspension episodes could impact the time to transplant or chance of receiving a transplant.
- Health economic outcomes. Whilst reducing investigations could lead to cost savings, the number of patients being listed or transplanted could increase. This has potential to increase overall net costs relating to improved patient survival, as suggested by the evaluation of the CARSK Study, [158] and a formal health economic evaluation would be required.
- Patient reported outcome measures and patient satisfaction.

7.3.2.1.1 Challenges to a randomised control trial

Such a trial would come with significant challenges. These include:

- Achieving sufficient statistical power. The low rate of post-transplant MACE in the UK means that achieving sufficient statistical power would be challenging, even with a national study. Work in the USA, where the incidence of post-transplant MACE is higher than that in the UK, estimated that 4000 patients would need to be enrolled to an RCT to detect a 20% reduction in MACE with screening with 80% power. [370] A non-inferiority study design may be more appropriate, but large participant numbers are still required. Preliminary work with the NHSBT Clinical Trials Unit shows that for a non-inferiority trial with a baseline rate of MACE of 2.6% at 1-year, an anticipated rise in MACE to 3.25% if screening were removed, and a 100% increment in MACE as the non-inferiority limit, 1990 patients would need to be receive a kidney transplant to power the study at 80% for a 5% significance level. As not all patients who begin transplant work up ultimately receive an organ, and 5% of patients on the waitlist die before receiving a transplant, [48] the number of patients recruited would need to be greater than this. Around 3600

patients are transplanted in the UK each year, [48] so high recruitment rates would be needed to achieve study size targets within a reasonable timeframe. To put this in perspective, the largest UK renal RCT performed to date is PIVOTAL: a study examining the optimal dosing of intravenous iron in haemodialysis patients. [371] This recruited 2141 patients from three quarters of UK renal centres, equating to around 10% of incident haemodialysis patients. If 10% of incident transplant patients were recruited, half of transplant recipients were at high cardiovascular risk and therefore eligible for inclusion in the study, and 2000 transplant recipients were required, recruitment would take over 10 years.

- Long follow up time and associated costs. Patients would need to be randomised early in the transplant assessment process, and given the unpredictable time spent on the waitlist prior to deceased donor transplantation the follow up time for such a trial would be long. Examining only living donor transplant recipients could shorten follow up times, as the transplant date can be planned, giving preliminary results on the feasibility and safety of reducing screening without removing an organ from the deceased donor pool. However, patients receiving living donor kidneys experience less delayed graft function, [372] and are younger and less comorbid than patients receiving deceased donor kidneys. [365] A reduced rate of MACE could therefore be expected, reducing trial efficiency. [260 373]
- Potential for increased discards of organs. There is likely to be apprehension around anaesthetising and operating on higher-risk patients who have not undergone screening, especially if some recipients would have otherwise been excluded from transplantation. These concerns could increase last-minute cancelled transplant operations, which could increase cold ischaemic times and organ discard rate if kidneys could not be reallocated in a timely manner.
- Off-protocol screening tests. It is possible for there to be apprehension about not screening patients with reduced ejection fraction or other cardiac risk factors allocated to the 'no screening' group prior to transplantation and this may lead to off-protocol screening tests being performed, which could limit applicability of results.
- Varying times to transplantation. The follow up times between screened and unscreened groups could differ, and additional randomisation methods such as using the calculated chance of transplant tool may be required. [374] This tool is still being developed for the 2019 organ offering scheme, but previous versions have been used to estimate the likelihood of a patient receiving a transplant within specified timeframes given their age,

blood group, ethnicity, transplant centre, matchability, sensitisation status, and transplant history. [374]

- Ability to remove bias. Even well-designed RCTs are not always able to fully remove bias. In the ISCHEMIA-CKD trial, patients were not included if there was suspicion of left main stem disease or a low ejection fraction. [121] First, these are common findings in patients with ESKD, and second it may be that clinician bias would influence recruitment to such a trial, meaning patients recruited may not be truly representative of the transplant population. Recruitment interventions may be required to understand and overcome recruitment challenges. [375]
- The impact of alternative methods to mitigate cardiac risk. If screening were abandoned, other methods to evaluate cardiac risk should be considered. The centres that have abandoned routine CAD screening (Chapter 6) have introduced other interventions to ensure integrity in their system, such as cardio-renal multidisciplinary team meetings, and the relative impact of these other complex interventions on cardiac events would need to be considered.

Ongoing work with clinical trials units will help assess whether a study of this design is feasible and what the optimal methodology would be e.g. an adaptive trial design. [376] A meeting to explore the views of nephrologists, surgeons, anaesthetists, cardiologists and patients on study design and their willingness to participate in such a trial is being planned for summer 2022.

7.3.2.2 An expert consensus statement on CAD screening prior to transplantation

An exercise to gain expert consensus on who should undergo CAD screening prior to transplantation should also be considered. This could aid the design of an RCT, or, if such a trial were not possible, could guide screening practice and policy within the constraints of the current evidence base:

- If an RCT was possible, the results of a consensus exercise could help inform the eligibility criteria for such a trial. As transplant centres largely adopt risk-stratified screening criteria, including patients that are not currently offered screening in a trial would be inappropriate. Given the inter-centre variation in how patients are identified as 'higher risk', defining the patients the transplant multi-professional team believe should undergo screening could be used to inform which patients to include in such a trial.
- If an RCT were not feasible, a consensus statement based on the current available evidence would have uses in helping streamline and standardise existing screening

pathways and could guide health policy. Given variation in screening uptake has also been observed in Europe [377] and the USA, [151] [152] such a statement could benefit the wider transplant community. A consensus on which patients are high risk could result in screening being rationalised to fewer patients.

A Delphi study involving nephrologists, transplant surgeons, anaesthetists and cardiologists could be performed to create a consensus statement. The Delphi methodology involves sequential questionnaire rounds being administered to experts in the field, followed by a stakeholder meeting. Respondents would be asked to rank their agreement with statements on which patients should undergo screening using a Likert scale. Statements not reaching consensus would then be re-distributed in a second questionnaire round, with respondents able to view their own response and the response from the overall cohort from the previous round, with the potential to then revise their answer. The questionnaire rounds are following by a stakeholder meeting which provides an opportunity for areas of disagreement to be discussed and resolved in person. [378] I applied for funding for this study from the Southmead Hospital Charity in August 2021 but was not successful; a further funding application has been submitted to the Bristol Health Partners Kidney Disease Health Integration Team Resourcing Application in January 2022.

7.3.2.3 Observational studies to assess the impact of changes to screening practice

With recent changes to screening practice (Chapter 6), the impact of screening on MACE could also be examined using observational data in a clinical setting where practice has changed, for example using a time-trend analysis. [379]

Time-trend analyses allow the comparison of event rates over time and could be performed spanning periods over which changes in CAD screening pathways have occurred. This analysis would be complicated by the lag-time between transplant assessment and the transplant operation, making it difficult to know which patients were worked up before any change in practice, uncertainty over the use of off-protocol screening tests (for example if patients with high cardiac risk underwent tests outwith those normally recommended), and whether any change in event rate could be attributed to other changes in practice over time e.g. improved medical management or the use of a cardio-renal multidisciplinary meeting. It may also need to be performed on a local level given that screening investigations are not currently collected or reported on a national scale, though other methods of data collection could be considered such as utilising national audit and research initiatives such as the NephWork renal registrar network. [380] It is also possible that the development of new resources containing more granular

information, such as the NIHR Health Informatics Collaborative cardiovascular and renal datasets, [381] could allow such analyses to be performed.

Given changes to screening practice have largely occurred over the last 2 years, and therefore patients being transplanted at present likely underwent screening based on historical guidelines, such an observational study may be best performed several years down the line.

7.3.2.4 Patient perceptions of screening and risk appetite

Patients' perception of screening for CAD prior to transplantation have not been explored. In the UK Kidney Week 2021 virtual conference, I co-chaired a session on the views of different stakeholders on pre-transplant CAD screening, with the patient participant in the session commenting on their perception of cardiac risk in the peri-transplant period:

'..if I was offered it as percentages, if the risk was 10%, then I'm afraid I would take it. I've been in an unpleasant state at times, not very comfortable, worrying about kidney levels. You take an opportunity like that when you're in that situation. Particularly when CKD affects your ability to exercise properly. I used to quite active, and it does restrict your ability to get about with the enthusiasm as you did previously. In my case, if I was given a percentage chance of 10%, I would have snapped off [my nephrologists] hand'

How people make decisions about risk is complex and multidimensional and depends on personal views and reflections on potential losses and gains. Risk perception is influenced by demographic factors, personal beliefs, previous experiences and how situations are framed to them. [382] A study examining risk appetite in the context of organ acceptance from donors at increased risk for viral infections found that older patients and those on dialysis were less risk averse than pre-emptive and younger patients. [383] Whilst qualitative studies have shown that transplant recipients view returning to dialysis after graft failure as being worse than death, [384] [385] it is not known how patients view their risk of peri-operative MACE.

The experiences of patients on the transplant listing process were examined through the qualitative workstream of the ATTOM study. Some patients expressed dissatisfaction with the listing process, feeling they received minimal information or were excluded from transplantation based on set criteria, such as age, without further assessment. [386] The psychological impact of investigations was also noted, demonstrated by one patient describing their concerns of abnormalities being detected:

'I used to dread, obviously, going for the tests because – never having had so many extensive tests done – I had a slight worry in the back of my mind that something might impact on having a transplantation; so obviously having the tests, I'd always worry unnecessarily.' [386]

Work is required to understand patients' perceptions of the risk they would be willing to take, how this compares to their clinicians' view, and how risk appetite should be balanced against ensuring equitable use of limited donor organ pool. General risk perceptions could be examined in potential transplant recipients, e.g. using the Domain-Specific Risk-Taking Scale, [387] followed by an assessment of the peri-transplant cardiac risk and associated adverse outcomes they would be willing to accept, or qualitative interviews could be performed to examine how patients balance the risks and benefits of a treatment such as transplantation.

7.4 Conclusion

This thesis expands on the knowledge of the incidence and impact of major adverse cardiac events on kidney transplant recipients and questions the utility of the cardiac screening investigations adopted to manage cardiac risk. The novel research using linked data from Hospital Episode Statistics and the ATTOM study represents the first large scale examination of screening practice in the UK, with previous single centre reports having greater potential for confounding bias. The detrimental effect of peri-transplant MACE on longer term patient survival has been demonstrated but screening investigations to identify asymptomatic coronary artery disease do not appear to minimise this risk. The clinical equipoise in the field is highlighted through both the persistent variation in screening practice in the UK and the appetite for an RCT amongst nephrologists. The feasibility of such a study is being considered. Planned future work includes a Delphi study to assess the views of the wider transplant multidisciplinary team on screening, with the potential to create a consensus document on the optimal pre-transplant workup of higher cardiac risk patients and reduce unwarranted variation in practice between centres. National discussions regarding a clinical trial are ongoing, including liaison with adaptive trial design methodologists and clinical trials units, and could be guided by results from the Delphi study.

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Appendices: Table of Contents

Appendix A ATTOM data collection documents

A.1 ATTOM research nurse data collection sheet

ATTOM data sheet

DEMOGRAPHICS

Patient group:
Choose one of 3 options. Groups self explanatory

Cohort:
Choose from one of 2 options. 'Detailed PROMs cohort' will only be relevant to patients in certain centres + centres undertaking pancreas transplantation

Name/DOB/Sex:
Self explanatory. System limit – no later than 31/12/1994, no earlier than 01/01/1935

Ethnicity:
Choose one of 5 options.
White – patient appears or is recorded as being of white ethnicity
Black – patient appears black or is recorded as being of black ethnicity
Mixed – patient appears or is recorded as being of mixed (any combination) of ethnic parentage
Asian – patient appears or is recorded as being of Indian/Pakistani/Bangladeshi ethnicity
Chinese – patient appears or is recorded as being of Chinese ethnicity

Height:
Height in centimeters – system limit of 100 – 240 cms

Weight:
Weight in kilograms – dry weight/target weight as far as possible
System limit 30-220 kgs
Decimal places not allowed

Patient email id:
Entry only required if patient requests e-access for completing questionnaires.
Entering email id will generate an auto-email to patient with a password to enable access to the web site

Centre:
Transplant centre where nurse is employed. Not related to centre caring for patient

Renal unit:
Name of renal unit (transplanting or non-transplanting) to which patient belongs

Hospital number:
Unique id number (with or without alphabets) in the hospital with primary care for patient (hospital that undertakes the patient's dialysis treatment)
Other number – unique id number in secondary hospital (for ex: transplant centre) where the patient may have had tertiary care

NHS number (for patients in England, Wales and Northern Ireland only):
Invalid NHS numbers will not be accepted / saved (internal modulus 11 algorithm check)

CHI number (for patients in Scotland only)
Invalid CHI number will not be accepted / saved

Address/Post code:
Address as listed in the IT system of the hospital that provides primary care for the patient.

Date first seen by Nephrologist:
Date when first seen by Nephrologist (either in clinic or as an in-patient)
If information on all 3 variables day/month/year – enter exact date
If information on only month/year available – enter 15th of that month
If information on only year available – enter 30th June for that year

Date of data entry:
Date when you started filling in the demographics page for this patient for the first time (may or may not be the same date as obtaining consent from the patient for study participation)

Mandatory data items for the demographics page:
Patient group
Cohort
First name
Surname
DOB
Address & Post code

SOCIOECONOMIC DATA

(cannot save data on this page without entering details on demographic page first)

Language

Is English your first language? Self explanatory yes/no. If no chosen - pop up of 'what is your first language?' self explanatory – free text box for writing language
Pop up box of 'Please rate your fluency in English?' – ask patient to choose from 'basic/moderate/good fluency' as reported by the patient

Leading question ("How often do you need ……") on help required for medical instructions – give patients the 5 choices and record patient preference

Place of birth
Self explanatory question. No follow up questions

Ethnicity
Record patient reported preferences from choices listed. If 'other' is chosen from any category – pop up free text box

Education
Record patient reported educational qualifications. More than 1 and a maximum of 5 options can be ticked. Highest achieved qualification must be selected.

Employment status
Record patient preference from list of 8 options. Patient must report status from the preceding 4 weeks

Car ownership
Self explanatory question. Only 3 or 4 wheeled motorised vehicles to be counted. If 'yes' ticked pop up question of 'How many vehicles'. No system limit to number of vehicles

Housing
Record patient preference for self explanatory question. If 'other' chosen pop up free text box

Civil status
Record patient preference for self explanatory question.

Dependants
Question implies number of people living in the same household and not necessarily dependant in financial or social terms. Children classified as <18years and adults as aged 18 or over. No system limits to number entered

Smoking
Record patient preference for self explanatory question. If 'yes' is ticked pop up question on number of cigarettes. If 'no' is ticked pop up question on previous smoking habit. If 'yes' ticked for previous smoker pop up question on duration since last smoked (aim to get the closest number of years unless it is <12 months since smoking cessation)

COMORBIDITY

(cannot save data on this page without entering details on demographic page first)

For the following data items, please read case notes (admission clerking notes, inter-specialty referral letters, discharge summaries are particularly useful), clinic letters, local renal IT systems or based on reports from patient/patient's named consultant. Record data items as per information gathered from above sources. If in doubt for any item check with the patient's named consultant nephrologist. For each item – if both month and year known, enter exact month/year. If only year known enter June as default month. Exact date of diagnosis for long term conditions (for ex: Diabetes, Asthma/COPD etc) is difficult to ascertain and in such situations ask patient how many years they have had this diagnosis and then choose that year in 'year' box and then choose default options of '15th' and 'June' for day and month respectively.
For each data item – if more than one entry is needed, please click on the 'add' button to the right of the 'Month/Year' tabs to open a new box. Up to a maximum of 3 boxes can be opened for each data item.

Primary Renal diagnosis
This data item indicates cause of kidney failure. Usually specified in clinic letters, local renal IT systems, patient reported cause etc. If 'other' is chosen, please fill pop up free text box Code numbers help link presumed diagnosis to registry records.
Diabetes
This data item indicates whether the patient has diabetes or not (irrespective of whether the diabetes caused kidney failure or not)
If 'yes' is checked pop up box of type I or II
Type I – diagnosis must be before age 30 years, must be on Insulin from day 1 of diabetes, may have had previous episodes of diabetic ketoacidosis. Type II – diagnosed after the age of 30, may have had diet/tablets/insulin as treatment for diabetes. This includes diabetes induced by drugs such as Ciclosporin/Tacrolimus, patients who developed diabetes after pancreatectomy/pancreatitis etc.

Ischaemic heart disease
This data item indicates whether the patient suffers from / has suffered from Ischaemic/coronary heart disease.
Angina – diagnosis of angina as recorded in case notes or reported by patient. Usually implies typical sounding cardiac chest pain, often on exertion, relieved by GTN/rest etc.
NSTEMI – diagnosis of non-ST segment elevation MI or acute coronary syndrome without ECG changes (i.e. raised troponin levels). Can only be diagnosed following blood test + ECG and therefore cannot be reported as an event by patient
STEMI/MI – diagnosis of ST elevation MI with obvious ECG changes. Can only be diagnosed with an ECG
Coronary intervention – patient has had an intervention for presumed ischaemic heart disease (with or without previous history of angina/NSTEMI/STEMI). Please choose between PCI (coronary angioplasty with or without stent insertion) or CABG (bypass operation)

Heart failure
This data item indicates whether the patient suffers from heart failure. Indicate 'yes' if any of the following items appear to have been diagnosed according to the case notes/clinic letters
Congestive cardiac failure or CCF
Left ventricular failure or LVF
Right ventricular failure of RVF
LV or RV dysfunction on ECHO
Ejection fraction or EF <30% on ECHO

Atrial Fibrillation
This data item indicates whether the patient is in atrial fibrillation currently. Do not choose 'yes' if patient had previous episodes of atrial fibrillation but is not in AF currently.

Cardiac valve replacement
This data item indicates whether the patient had a previous cardiac valve replacement or valve repair surgery. If 'yes' ticked, pop up box of which valve was replaced/repaired and month/year of procedure.

Permanent pacemaker
This data item indicates whether the patient currently has a permanent pacemaker in-situ. If 'yes' is ticked, pop up box of month/year of insertion
Cerebrovascular disease
This data item indicates whether the patient has had symptomatic cerebrovascular disease or cerebrovascular intervention. If 'yes' is ticked pop up box of type of event.
TIA – Indicate if TIA(transient ischaemic accident) /mini-stroke/transient stroke appears in case notes/letters
CVE/Stroke – Indicate if CVE or CVA (cerebro-vascular event or accident) /Stroke/hemiplegia/cerebral haemorrhage/sub-arachnoid haemorrhage/sub-dural haemorrhage appears in case notes/letters
Carotid intervention – indicate if carotid endartrectomy or carotid angioplasty or carotid operation appears in case notes

Peripheral vascular disease
This data item indicates whether the patient suffers from peripheral (usually lower limb) vascular disease. If 'yes' is ticked pop up box of type of event.
Claudication – indicate if claudication (lower limb pain on walking) appears in case notes
Radiological or surgical intervention – indicate if iliac or femoral or popliteal or profunda or anterior tibial or posterior tibial artery intervention (angioplasty, endartrectomy, bypass etc) appears in case notes
Amputation – indicate if any amputation of any part of any limb (except traumatic amputation or penile amputation) appears in case notes

Abdominal Aortic Aneurysm
This data item indicates whether the patient has ever been diagnosed as having or treated for a AAA. If AAA is indicated any where in case notes tick 'yes' and specify whether the AAA is just being monitored or whether radiological (EVAR) or open surgical procedure (AAA repair) has been undertaken.

Respiratory disease
This data item indicates whether the patient suffers from any form of respiratory disease. If any of the terms including 'Asthma', 'COPD', 'Emphysema' or 'Bronchiectasis' appears in the case notes tick 'yes' and specify which/how many of the 3 diagnoses is relevant to the patient. Emphysema can be coded as COPD.
Liver Disease
This data item indicates whether the patient suffers from any form of liver disease. If the term 'Cirrhosis', 'Non Alcoholic steato-hepatitis or NASH', 'Drug induced (for ex: paracetamol poisoning' liver disease and 'Alcoholic liver disease' appears in the case notes tick 'yes'. If the word cirrhosis is used in the case notes choose 'cirrhotic liver disease' from the drop down menu. If liver disease is mentioned without the term cirrhosis then choose 'non-cirrhotic liver disease'.
Note – cholecystitis / gall stones etc does not constitute liver disease

Blood Borne Viruses
This data item indicates whether the patient suffers/has suffered from BBV infection. If Hepatitis C/B/HIV infection (past or present) or Hep C/B PCR or antibody positive

or HIV PCR/antibody positive is recorded in case notes tick 'yes' and then indicate which/how many viral infections is relevant to the patient.

Malignancy
This data item indicates whether the patient has been diagnosed with one or more malignancies in the past. If any malignancy has been recorded in the case notes, tick 'yes' and then specify which type of malignancy from the drop down menu. Please note – tick 'yes' only for a malignancy. Benign tumours (such as breast adenoma, colon polyp, skin warts/actinic keratosis etc do not count as malignancy).

Mental illness
This data item indicates whether the patient has suffered from/suffers from any recorded mental illness in the case notes. Tick 'yes' if the term 'Depression', 'Psychosis/Psychotic disorder', 'Bipolar disorder', 'substance abuse' (usually indicates poisoning with one or more drugs – not alcohol or recreational drugs) and 'deliberate self harm' (usually indicates physical attempts at self harm – not chemical means which should be classified under 'substance abuse') or related terms such as 'Schizophrenia' (should be classified as a psychotic disorder) appears in the case notes. If in doubt ask the patient / consultant nephrologist/ named psychiatric nurse.

Dementia
This data item indicates whether the patient suffers from any form of dementia. Tick 'yes' if the term 'dementia', 'vascular dementia', 'Alzheimer's disease', 'memory loss' (short or long term) etc appears in the case notes. If in doubt, please check with the consultant Nephrologist.

Smoking
This data item captures whether the patient's smoking history is available in the case notes and therefore fill in the data item purely based on information available in the case notes. This may or may not contradict what the patient reports in the socio-economic questionnaire. If the term 'smoker', 'heavy smoker' etc is recorded in case notes indicate patient is a current smoker. If the case notes indicate that patient is an 'ex-smoker' , 'quit xx years ago' etc indicate patient is an ex-smoker. If the notes indicate that the patient has never smoked indicate 'non-smoker'. If there is no mention of smoking anywhere in the notes – indicate 'don't know'.

Other illness
3 x free text boxes to indicate any other illness that does not come under the above topic headings.

Incident dialysis

(cannot save data on this page without entering details on demographic page first)
(Demographic, comorbidity and socio-economic data same as for all patients)

Start date of dialysis

Indicated when the patient commenced long term / permanent dialysis treatment. For many patients it will be planned start on dialysis (for ex: after PD catheter insertion or AVF formation). This should be the date of the first ever dialysis session (PD or HD) even if the patient subsequently changed modalities. If the patient started dialysis as an 'acute patient' recovered renal function for a little while and then re-started dialysis, indicate date when dialysis was re-started. For patient crash landing on dialysis treatment (starting dialysis without prior planning – usually during an in-patient admission) record date of first dialysis session (usually HD session and rarely PD) as date of first dialysis. If in doubt check with local renal IT system or ask consultant nephrologist / dialysis unit sister.

Type of dialysis

This should be the dialysis modality that the patient started on when dialysis first commenced. The type of dialysis modality is self explanatory and if not clear please check with the HD unit sister to confirm between HD-v-HDF and PD unit sister between APD-v-CAPD.
If patient has been on more than one type of modality between start of treatment and time of consenting to participate in this research project, tick the modality that the patient has spent most time on.
If HD or HDF is chosen, pop up menu of type of dialysis access. This indicates the type of HD access at the start of HD/HDF (first ever HD/HDF session). The types of access are self explanatory. Non-tunnelled lines are also often referred to as 'Vascath' and tunnelled lines are often referred to as 'Permcath' or 'Tesio'.
If the patient has used more than one type of access between start of HD/HDF and time of consenting the patient for participation in the research project, tick the access type that was most used since starting HD/HDF. If patients were using one needle in AVF/AVG and one needle in tunnelled line/non-tunnelled line – tick tunnelled line/non-tunnelled line as access used.

Previous transplant

This data item indicates whether the patient has had a previous organ transplant (any solid organ and not just kidney only). The previous organ transplant may or may not be still working (for ex: working liver transplant as compared to failed kidney transplant). Indicate number of previous transplants and then indicate type of organ transplant. If exact day/month/year of previous transplant known, enter exact date. If only month/year known – enter 15th of the month/year. If only year known – enter 30th June of the year.

Incident transplant patient
Transplant work up

(cannot save data on this page without entering details on demographic page first)
(Demographic, comorbidity and socio-economic data same as for all patients)

Cardiac
Indicates whether the patient had any cardiac investigations were undertaken as part of the work up / declaration of fitness for kidney (or kidney + pancreas transplant). The investigations undertaken are likely to be listed in the case notes or described in clinic letters (either from the nephrologist or cardiologist). The result of the test is not relevant to this data item but just whether any tests were done or not done. Please include only tests done as part of work up for transplantation (usually done prior to transplant wait-listing or prior to transplant) and not include tests done in the past. If no tests are apparent then please tick 'none'.
More than one option can be ticked.

Pulmonary
Indicates whether the patient had any pulmonary function tests (includes lung function tests and CPEX or cardio-pulmonary exercise testing). If no tests are apparent then please tick 'none'.

Vascular
Indicates whether the patient had any vascular investigations (iliac/lower limb and carotid only – upper limb vascular investigations should not be included). Clinic letters from the vascular surgeons / transplant surgeons are likely to be the best sources of information. If no tests are apparent, then please click 'none'. More than one option can be ticked.

Other tests
If any other tests (for ex: genetic tests, CT/MRI scans of other organs, other radiological tests, blood tests such as Glucose Tolerance Tests etc) were undertaken exclusively for the purpose of confirming fitness for transplantation, please list then the free text box. Up to 3 items can be entered.

Incident transplant information

Date of transplant
Indicates date of renal (or renal + pancreas) transplant that triggered entry into the ATTOM study. Please enter exact date of transplant.

Transplanted organ
Indicates whether this was a kidney only or kidney + other organ transplant.

Transplant type
Indicates whether the organ/s came from a live donor or brain dead (DBD/HBD) or non-heart beating (DCD/NHBD) donor.

Treatment modality
Indicates what form of dialysis if any the patient was having just before the transplant.

If any modality (other than preemptive or failing transplant) is chosen please fill in date when the patient started dialysis for the first time. This helps calculate total time on dialysis before transplant. If HD/HDF was chosen, please also complete additional pop up menu of type of dialysis access.

Patient has had a previous transplant?
This data item indicates whether the patient has had any previous organ transplant (not just kidney). Please indicate type of transplant and date (using default options of 15th for the day and June for the month if either not known).

Induction immune suppression
Indicates the type of drug given just before the transplant operation. This is usually an IV drug and the common drugs used are listed. If 'other' is chosen – please fill in name of drug in the free text box

Maintenance CNI
CNI stands for 'Calcineurin inhibitor' and can only be Ciclosporin or Tacrolimus. Please indicate 'Tacrolimus' or 'ciclosporin' irrespective of whether the primary brand or generic brand of the drug is used. Maintenance therapy usually indicates that the patient is likely to remain on this drug for the foreseeable future.

Maintenance anti-proliferative
This data item captures whether the patient is likely to continue on any anti-proliferative agent for the foreseeable future. This is usually an oral medication and the common drugs are listed. Please pick from the drop down menu.

Maintenance steroid
This data item captures whether the patient is likely to be on short or long term steroid (usually Prednisolone) treatment. If unit policy is that for all/most patients to be weaned off steroids at 1 or 3 months, then please tick this option. If unit policy is for steroid continuation for >3 months but not indefinitely (say 6 or 12 months) please tick 'long term continuation'.

Maintenance other
This data item captures whether the patient is on any other long term immune suppression using drugs not in any of the above categories. This maybe a oral drug or IV/SC drug (Belatacept) and the common drugs are listed. Please tick any appropriate choice.

Matched control for transplant patient

(cannot save data on this page without entering details on demographic page first)
(Demographic, socio-economic info and comorbidity same as for all patients)
Transplant work up information – same as above

Wait-listing information

Date of activation on the waiting list
Please indicate the date of very first activation on the waiting list (irrespective of any subsequent suspensions etc). Data should normally be available with the transplant coordinators, renal IT system and less rarely in the notes.

Organ
The data item captures which organ/s the patient was first listed for. If the patient was listed for a kidney only and subsequently listed for a kidney + other organ – please tick 'kidney only' as this was the choice at time of first listing.

Dialysis modality at time of data collection
Data item captures type of dialysis at the time the patient was recruited to the ATTOM study. If HD/HDF chosen, please indicate type of access. Please leave blank if patient is currently not on any form of dialysis (preemptively listed or has a failing transplant but not yet back on dialysis)
Please do not fill in 'supervising hospital'. This data field is not required.

Patient had a previous transplant
This data item captures if the patient has had a previous organ (not kidney only) transplant. Please indicate exact date of transplant if known, and if not use default options of 15th if day not known and 30th June if month not known.

A.2 ATTOM patient questionnaire

Access to Transplant and Transplant Outcome Measures
(ATTOM study)
Socio-demographic questionnaire

This questionnaire asks about you and your household.

Please answer each question by putting a 'R' in the box that applies, or entering details in the spaces provided

1. Is English your first language? Yes | No

If 'No', please answer 1a and 1b below
1a What is your first language?……..

1b Please tick one box below to show your fluency in English

Very basic / no fluency
Moderately fluent
Very fluent

2. How often do you need someone's help to read instructions, leaflets, or other written material from your doctor or pharmacy?

Never
Rarely
Sometimes
Often
Always

3. Were you born in the UK? Yes | No

If 'No' how long have you lived in the UK.....years

4. Which one of the following ethnic groups best describes the one you belong to? Please choose ONE section from A to E, then tick the appropriate box to indicate your ethnic group.

A : White
British
Irish
Any other white background (please state .....)

B : Mixed
White and Black Caribbean
White and Black African
White and Asian
Any other mixed background (please state.....)

C : Asian or Asian British
Indian
Pakistani
Bangladeshi
Any other Asian background (please state… .....)

D : Black or Black British
Caribbean
African
Any other Black background (please state.....)

E : Chinese or other ethnic group
Chinese
Any other (please state .....)

5. In the last 4 weeks which of the following best describes your employment status?

Working full-time
Working part-time
Unemployed
Student (includes pupil at school, those in training)
Looking after family home
Long-term sick or disabled
Retired from paid work
Not in paid work for some other reason (please state… .....)

6. If you are not currently working have you been actively looking for work in the last 4 weeks?

Yes	No

7. Which of these qualifications do you have?

O/GCSE/CSE/School Certificate level
A level /Higher School Certificate
First degree (eg BA, BSc)

Higher degree (eg MSc, PhD, PGCE)
NVQ 1-03
NVQ 4-5
Other qualifications (e.g: City and Guilds) (please state……)
No qualification

8. Do you, or any members of your household, at present own or have continuous use of any motor vehicles (car, light van, including company vehicles if available for private use)?

Yes | No

If 'Yes', how many motor vehicles
1
2
3
4 or more

9. Which of the following best describes the accommodation you live in?

Owned by you (outright or with a mortgage)
Part rent, part owned (shared ownership)
Rented privately from council/housing association
Other (please specify .....)

10. Which of the following best describes your marital status?

Single – never married
Married
Separated (but still legally married)
Divorced Widowed

11.

How many adults (age >18 years) live in your household including you? ☐

How many children (age <18 years) live in your household? ☐

12. Do you currently smoke cigarettes, cigar or a pipe?

No
Yes: cigar
Yes: pipe
Yes: cigarettes

If you smoke cigarettes, approximately how many do you smoke per day?

If 'No' are you an ex-smoker?

Yes	No

If you are an ex-smoker - how long ago did you stop?

Years ☐ Months ☐

Appendix B Additional material for Chapter 3

B.1 HES Data Sharing Agreement

Data Sharing Agreement

DARS-NIC-14342-Q8W0X-v2.2

NHS Digital

Annex A: Application Summary

1a: General

Request Number:	DARS-NIC-14342-Q8W0X-v2.2
Request Title:	Request for HES Data to analyse outcomes in the NIHR-funded ATTOM study
DSA Start Date:	13/09/2021
DSA End Date:	12/09/2022

1b: Data Controller(s)

- **NHS Blood and Transplant (NHSBT)**

Data Controller: NHS Blood and Transplant (NHSBT)

39, Victoria Street
Filton
London
LS1 6AE
United Kingdom

Organisation Type: Agency/Public Body

Data Controller Type: Sole Data Controller

Processing the data: Yes

NHS Digital Framework Contract Reference: CON-321455-Q0T3Y

Contract Expiry Date: 28/07/2024

Security Assurances for Data Controller

Type: DSP Toolkit

Latest Status: Standards Met

Date Published: 29/06/2021

ODS Code: T1460

Comments:

DSPT 20/21 Standards Met (published 29/06/2021; not yet reviewed)
DSPT 19/20 Standards Met (published 08/10/2020; reviewed by NHS Digital 04/03/2021)

Date Reviewed: 04/03/2021

Date Checked by NHS Digital: 02/09/2021

DPA Registration

DPA Registration Number: Z9210360

DPA Organisation Name: NHS Blood and Transplant

Expiry Date: 27/09/2022

DPA Checked On : 07/09/2021

Where the Data Controller named in section 1b is processing Data, it is only entitled to process the Data at the location(s) specified in section 2a for the Purpose(s) outlined in section 5 subject to the Special Conditions in section 6, unless otherwise specified in section 6. Any processing of Data by an agreed Data Processor specified in section 1c shall be subject to the same restrictions. These details are therefore not repeated in section 1c.

Data Sharing Agreement

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NHS Digital

1c: Data Processor(s)

NHS Blood and Transplant (NHSBT) are permitted to process the data.

2. Locations

2a. Processing Location(s)

NHS Blood and Transplant

Location Area:	England & Wales
Organisation Address:	Fox Den Road Bristol Avon BS34 8RR

2b. Storage Location(s)

NHS Blood and Transplant

Location Area:	England & Wales
Organisation Address:	Fox Den Road Bristol Avon BS34 8RR UK

2c. Territory of use

England & Wales

3. Datasets Held/Requested

Common Law Duty of Confidentiality

The common law duty of confidentiality is addressed by :
Section 251 NHS Act 2006

3a. Data Access Already Given

Dataset	Extract Type	Identifiability	Sensitivity	Periods	Legal Basis	Frequency
Hospital Episode Statistics Admitted Patient Care	Extract	Pseudo/Anonymised	Non Sensitive	2005/06 2006/07 2007/08 2008/09 2009/10 2010/11 2011/12 2012/13 2013/14 2014/15 2015/16 2016/17 2017/18_M08	Processing : General Data Protection Regulation Article 9 (2) (h), General Data Protection Regulation Article 6 (1) (e) Dissemination : Health and Social Care Act 2012 - s261 - 'Other dissemination of information'	One-off
Data Minimisation						

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Restricted to cohort size 5703 15% of available fields selected						
Hospital Episode Statistics Outpatients	Extract	Pseudo/Anonymised	Non Sensitive	2005/06 2006/07 2007/08 2008/09 2009/10 2010/11 2011/12 2012/13 2013/14 2014/15 2015/16 2016/17 2017/18_M08	Processing : General Data Protection Regulation Article 9 (2) (h), General Data Protection Regulation Article 6 (1) (e) Dissemination : Health and Social Care Act 2012 - s261 - 'Other dissemination of information'	One-off
Data Minimisation						
Restricted to cohort size 5703 17% of available fields selected						
Hospital Episode Statistics Accident and Emergency	Extract	Pseudo/Anonymised	Non Sensitive	2007/08 2008/09 2009/10 2010/11 2011/12 2012/13 2013/14 2014/15 2015/16 2016/17 2017/18_M08	Processing : General Data Protection Regulation Article 9 (2) (h), General Data Protection Regulation Article 6 (1) (e) Dissemination : Health and Social Care Act 2012 - s261 - 'Other dissemination of information'	One-off
Data Minimisation						
Restricted to cohort size 5703 21% of available fields selected						

3b. Additional Data Access Requested

Dataset	Extract Type	Identifiability	Sensitivity	Periods	Legal Basis	Frequency

3c. Patient objections

Patient Objections applied? Yes

-

4. Privacy Notice

The data controller(s) listed within this agreement in Section 1 confirm that they will ensure that a GDPR compliant, publicly accessible transparency notice is maintained throughout the life of this agreement.

6. Special Conditions

MANDATORY UPDATES FOR COMPLIANCE WITH DATA SHARING STANDARDS:

Should NHS Blood and Transplant (NHSBT) wish to retain the data beyond the End Date of this Data Sharing Agreement, by no later than 31st March 2022, NHS Blood and Transplant (NHSBT) is required to submit an application to amend this Data Sharing Agreement and within that application, the following actions must have been completed:

1. The 'Objectives for processing' section should be rewritten to meet all of the requirements specified in the relevant data sharing standard for (see: https://digital.nhs.uk/services/data-access-request-service-dars/dars-guidance/objective-for-processing) .

2. With regard to NHS Digital's data sharing standard for Expected Outcomes (see: https://digital.nhs.uk/services/data-access-request-service-dars/dars-guidance/expected-outputs), the applicant must have updated the section 'Specific Outputs Expected, Including Target Date' to clearly articulate any expected outputs from the processing described in the preceding sections and to provide updates on outputs already produced including those previously described for which the expected delivery date has since passed.

3. With regard to NHS Digital's data sharing standard for Expected Measurable Benefits (see: https://digital.nhs.uk/services/data-access-request-service-dars/dars-guidance/expected-measurable-benefits), the applicant must have updated the sections 'Expected Measurable Benefits to Health and/or Social Care Including Target Date' and 'Yielded Benefits' to clearly articulate the benefits to patients, the public and/or the health or social care system which are expected and/or have been achieved as a result of the delivery of the outputs described.

Should NHS Blood and Transplant (NHSBT) wish to retain the data beyond the End Date of this Data Sharing Agreement, by no later than 31st March 2022, NHS Blood and Transplant (NHSBT) must confirm it has notified HRA CAG of any ongoing requirement for section 251 support to permit processing of confidential data without informed consent and must confirm whether or not section 251 remains in place.

SECURITY ASSURANCE:

All data controllers and processors which rely on the annual completion and publication of the Data Security and Protection Toolkit (DSPT) to demonstrate security assurance for the purpose of this Agreement must ensure:
1. Their organisation/department has completed the latest available version of the DSPT assessment or has produced the previous version of the DSPT within the last 12 months;
2. The self-assessment outcome must be 'Standards Met' or 'Standards Exceeded' or, if not, an improvement plan must be reviewed and approved by the DSPT team within NHS Digital's Data Security Centre;
3. If an improvement plan has been agreed, the organisation must carry out improvements (as stipulated in the review) within the agreed time frame determined in the organisation's remediation plan agreed with the NHS Digital DSPT team.

7. Approval Considerations

Ethics Approval

Ethics approval is required and in place

Materials Reviewed	Version	Date of Document	Date of Approval	Expiry / Review Date	Comments	CAG Reference
Consent Form	3.0	29/01/2012			SD4 - Original ATTOM PIS Consent Form v3 29.01.12	

Protocol	6.4	04/01/2017			SD1 - ATTOM v6.4 protocol	
Ethics Review		14/03/2017			SD3 - Ethics Committee Substantial Amendment Favourable Opinion 14.03.17; REC Reference: 11/EE/0120	
Section 251 Support		10/04/2017			SD2 - CAG Approval S251 10.04.17	16/CAG/0102

8. Period and Funding

8a. Data Retention

For the Data Recipient to give an indication of the duration that the Data Recipient would wish to retain the data (however if this period exceeds the Term a new DSA would need to be in place).

Indicative Data Retention Period: 12/09/2022

Reason for this Period: This is in line with the Data Sharing Agreement end date.

8b. Funding Sources

Type of Funding Source: Public

Awarding Institution: National Institute for health research (NIHR) PG f Ar

EU/International programme:

Reference and title of project/activity: RP-PG-0109-10116, ATTOM :Access to Transplantation and Transplant Outcome Measures

Year of submission/award: 04/10/2010

Applicant or Partner: Partner

Funding evidence URL:

9. Approved Users

10. Sub-licensing

Does sub-licensing apply? No

The Data Recipient is responsible for entering into a Sub-Licence that meets the requirements set out in Clause 3.3 and Schedule 4 of the Data Sharing Framework Contract.

11. Charges

Set up and first year service charge £0.00

Data Sharing Agreement

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Annual Service Charge

Principles of charging: NHS Digital operates on a cost recovery basis and does not seek to make an operating profit from providing its services. The following costs to NHS Digital are included in the Service Charges and Annual Charges below:

- all design and/or implementation specific services required to generate bespoke datasets or extracts;
- all administration services associated with providing access to the same;
- delivery and maintenance services to support the ongoing provision of bespoke datasets or extracts;
- administration costs associated with carrying out annual reviews of Data Recipients.

These charges do not include the costs associated with the investigation of a breach, planning and performance of audit(s), and any prosecution activity.

Service Charge: setup, licence, service and annual review charges

The Service Charge is a one-off fee per DSA, and is payable in advance. The Annual Review charges included in the Service Charge are based on the number of annual reviews to be carried out during the Term of the DSA.

Audit fees are payable where NHS Digital undertakes an audit or investigation which in NHS Digital's reasonable opinion, reveals that the Data Recipient either has not complied, or is not complying, with any of its obligations under the Data Sharing Framework Contract and / or this DSA. The audit fees stated in the table below are an estimate only and the Data Recipient is responsible for promptly reimbursing NHS Digital for all reasonable costs of the audit and the full cost of any investigation which NHS Digital may commence prior to an audit taking place in accordance with Clause 7 (Audit and specific rights) of the Data Sharing Framework Contract. Audit fees are payable at cost, and shall include the costs for all activity for investigation, as well as activities associated with the performance of the audit:

Estimated audit fees per audit:	**£15,000 (variable depending on circumstances).**

B.2 Comparison of 2012 UKRR incident dialysis patients to ATTOM cohort

	UK Renal Registry incident dialysis 2012 (<75 years)		ATTOM Recruited Cases		P value
Sex	**N**	**%**	**N**	**%**	
Male	3366	62.36	1701	64.90	0.03
Female	2032	38.64	920	35.10	
Age group	**N**	**%**	**N**	**%**	
18 -< 35	443	8.21	243	9.27	0.04
35 -< 50	1068	19.79	537	20.49	
50 -< 60	1219	22.58	637	24.30	
60 -< 70	1702	31.53	781	29.80	
70 -< 75	966	17.90	423	16.14	
Ethnicity	**N**	**%**	**N**	**%**	
Asian	591	10.95	247	9.42	<0.001
Black	395	7.32	179	6.83	
Other	126	2.33	53	2.02	
White	3701	68.56	1984	75.70	
Missing	591	10.95	158	6.03	
Modality	**N**	**%**	**N**	**%**	
HD	4054	75.1	2064	79.08	<0.001
PD	1344	24.9	546	20.92	
Diabetes as PRD	**N**	**%**	**N**	**%**	
Non-diabetic	1892	52.38	1914	73.03	<0.001
Diabetic	1720	47.62	707	26.97	

Characteristics of incident dialysis patients in 2012 from the UK Renal Registry and those recruited to ATTOM. Comparisons are performed using the Chi-square test.

B.3 Comorbidity recording in ATTOM and corresponding ICD-10 and OPCS-4 codes in HES

ATTOM study comorbidity	ICD-10 Code	OPCS-4 Code
Diabetes (Type 1 or type 2)	E10.0-9 E11.0-9 E12.0-9 E13.0-9 E14.0-9	
Ischaemic heart disease (Angina, non-ST elevation or ST elevation myocardial infarction, coronary angioplasty or coronary artery bypass graft)	I20.0-9 121.0-9 I22.0-9 I25.8	K40-47.1, K48.3 K49-50 K63 K75
Heart failure (Congestive cardiac failure, right or left ventricular failure, left or right ventricular dysfunction on echocardiogram, ejection fraction below 30% on echocardiogram)	I11.0 I13.2 I50.0-1 I42.0 I42.5-9	
Cardiac valve replacement (Previous valve replacement or repair)	Z95.2-4	K25-29
Permanent pacemaker (Currently in situ)	Z95.0	K60.1-9 K61.1-9
Cerebrovascular disease (Transient ischaemic attack, stroke, hemiplegia, cerebral haemorrhage, sub-arachnoid haemorrhage, subdural haemorrhage, carotid endarterectomy, carotid angioplasty or carotid operation)	I60.0-9 I61.0-9 I62.0-9 I63.0-9 I64 I65.0-9 I66.0-9 I67.0 I68.0-8 I69.0-8 G45.0-9 G46.0-9 S06.5 S06.6	L29 L31.1-2
Peripheral vascular disease (Claudication; angioplasty, endarterectomy or bypass to iliac, femoral, popliteal, profunda, anterior tibial or posterior tibial artery; non-traumatic amputation to any limb)	I73.9	L16 L20-21 L23 L25 L27.1-3, L27.6-9 L51-52 L54 L59-60 L634 X07-11
Abdominal aortic aneurysm (Monitored, radiological or surgical repair)	I71.3-6	L18-19
Respiratory Disease	J40 – J47	

(Asthma, COPD, emphysema, bronchiectasis)	J60-67 J68.4 J70.1, J70.3	
Liver Disease (Cirrhotic or non-cirrhotic of any cause, excludes cholecystitis and gallstone disease)	K70.0-9 K71.0-9 K72.0-9 K73.0-9 K74.0-9 K76.0 Z94.4	
Blood Borne Viruses (Past or present infection with hepatitis B, hepatitis C or HIV either PCR or antibody positive)	B16.0-9 B17.1 B18.0-2 B20-24 Z21 R75	
Malignancy (Any type excluding benign tumours)	C00-C97	
Mental Illness (Depression, psychosis, bipolar disorder, substance abuse, deliberate self-harm, schizophrenia)	F10-F16 (excluding .0) F17.2-F19 (excluding .0) F20-25, F28-29 F30-F39 X60-X84	
Dementia (Any form)	F00-F04 G30.0-9 G31.1	

Conditions recorded within the ATTOM dataset including advice to research nurses, and corresponding ICD-10 and OPCS-4 codes used to extract information from the HES dataset.

B.4 ATTOM and HES dataset linkage by renal centre

Renal Centre	Individuals with linked datasets N=5506	Individuals with non-linked datasets N=148
Addenbrookes Hospital	268 (98)	6 (2)
Arrowe Park Hospital, Wirral	63 (100)	0 (0)
Barts and the London Hospital	207 (95)	11 (5)
Basildon Hospital	9 (100)	0 (0)
Broomfield Hospital, Chelmsford	8 (89)	1 (11)
Colchester	25 (100)	0 (0)
Cumberland Infirmary, Carlisle	16 (100)	0 (0)
Derriford Hospital	83 (100)	0 (0)
Doncaster Royal Infirmary	38 (100)	0 (0)
Dorset County Hospital	9 (100)	0 (0)
Freeman Hospital & Royal Victoria	153 (98)	3 (2)
Gloucester Royal Hospital	33 (100)	0 (0)
Guy's and St Thomas's Hospital	304 (95)	16 (5)
Heartlands Hospital	63 (97)	2 (3)
Hope Hospital, Salford	50 (98)	1 (2)
Hull Royal Infirmary	25 (96)	1 (4)
Ipswich Hospital	47 (100)	0 (0)
James Cook University Hospital	44 (100)	0 (0)
Kent & Canterbury Hospital	41 (87)	6 (13)
King's College Hospital	115 (100)	0 (0)
Leicester General Hospital	158 (100)	0 (0)
Lister Hospital, Stevenage	118 (97)	4 (3)
London - Royal Free	215 (96)	9 (4)
London - WLRaTC	313 (97)	10 (3)
New Cross Hospital, Wolverhampton	32 (100)	0 (0)
Norfolk & Norwich University Hospital	73 (100)	0 (0)
North Staffordshire - Stoke	109 (98)	2 (2)
Northern General Hospital	220 (98)	5 (2)
Nottingham City Hospital	145 (99)	2 (1)
Oxford Radcliffe Hospital	271 (99)	4 (1)
Queen Alexandra Hospital	255 (98)	6 (2)
Queen Elizabeth Hospital	349 (97)	9 (3)
R D & E Exeter	45 (98)	1 (2)
Royal Berkshire Hospital, Reading	7 (100)	0 (0)
Royal Cornwall Hospital	15 (94)	6 (1)
Royal Derby Hospital	42 (100)	0 (0)
Royal Infirmary Manchester	252 (97)	7 (3)
Royal Liverpool University Hospital	222 (97)	7 (3)
Royal Preston Hospital	44 (92)	4 (8)
Royal Shrewsbury Hospital	16 (100)	0 (0)
Royal Sussex County Hospital	91 (96)	4 (4)
Russells Hall Hospital	38 (100)	0 (0)
Southend	9 (90)	1 (10)
Southmead Hospital	222 (97)	8 (3)

St George's Hospital	85 (91)	8 (9)
St Helier Hospital, Carshalton	193 (97)	5 (3)
St James's University Hospital	202 (99)	1 (1)
St Lukes Hospital, Bradford	15 (100)	0 (0)
Sunderland Royal Hospital	18 (100)	0 (0)
University Hospital Aintree	78 (100)	0 (0)
Walsgrave Hospital, Coventry	38 (93)	3 (7)
York District General Hospital	15 (100)	0 (0)

Number (%) of individuals whose ATTOM dataset was successfully linked to HES data at each renal centre.

Appendix C Sensitivity landmark analysis for Chapter 4

C.1 Landmark analysis at 1 year

A sensitivity analysis was performed when examining the association between early post-transplant MACE and patient and graft outcomes, using an alternative landmark point of 1 year post-transplant.

Of the 3251 transplanted patients, 63 died (12 of whom had a MACE event) and 139 experienced graft failure (29 of whom had a MACE event – 3 pre-graft failure and 26 post-graft failure) within the first post-transplant year. There were 87 patients with under 1 year of follow up (2 of whom had a MACE event). These 289 patients were excluded from the landmark analysis. This resulted in 43% of patients identified as experiencing post-transplant MACE in the first year being excluded. This section examines the remaining 2962 patients who were alive with a functioning graft at 1 year, at which point 57 (1.9%) had a MACE event. In each of the Cox models, proportionality assumptions were met.

Whilst early post-transplant MACE is referred to in this section, patients who had a cardiac death within the first post-transplant year are excluded from these analyses. MACE therefore refers to patients who experienced non-fatal cardiac events (unstable angina, myocardial infarction, or coronary revascularisation procedures) with Section C.1.1 to Section C.1.3.

C.1.1 Patient survival

Over follow up, 285 patients died. By univariable analysis, MACE in the first post-transplant year associated with an increased risk of death (HR 2.57, 95% CI 1.44-4.58) but this association was not seen in the adjusted model (HR 1.58, 95% CI 0.86-2.91) (Table C.1, Figure C.1). Factors associated with increased risk of death in the multivariable model included older age (HR 1.06, 95% CI 1.05-1.07) and higher comorbidity (Charlson score greater than $\geq$1 vs. 0). Higher socioeconomic status (IMD 5) compared to lower socioeconomic status (IMD 1) were associated with a reduced risk of death. There was no association between death and sex, ethnicity, PRD and donor type in adjusted analyses.

	Unadjusted HR (95% CI)	P	Adjusted HR (95% CI)	P
Year 1 MACE (Ref: no MACE)	2.57 (1.44 – 4.58)	**0.001**	1.58 (0.86 – 2.91)	0.14
Age (years)	1.06 (1.05 – 1.07)	**<0.001**	1.06 (1.05 – 1.07)	**<0.001**
Male sex (Ref: Female)	1.04 (0.82 – 1.33)	0.73	0.94 (0.73 – 1.20)	0.62
Ethnicity (Ref: White)				
Asian	0.71 (0.49 – 1.04)	0.08	0.68 (0.46 – 1.01)	0.06
Black	1.03 (0.67 – 1.56)	0.90	0.85 (0.54 – 1.35)	0.50
IMD (Ref: 1)				
2	0.96 (0.68 – 1.35)	0.82	0.91 (0.64 – 1.30)	0.61
3	0.87 (0.61 – 1.24)	0.45	0.76 (0.52 – 1.12)	0.16
4	0.90 (0.63 – 1.27)	0.54	0.69 (0.48 – 1.01)	0.06
5	0.73 (0.50 – 1.08)	0.11	0.54 (0.36 – 0.81)	**0.003**
PRD (Ref: Non-diabetic) Diabetes	2.25 (1.65 – 3.06)	**<0.001**	1.05 (0.72 – 1.54)	0.79
Charlson Score (Ref: 0)				
1-2	2.31 (1.79 – 2.97)	**<0.001**	1.84 (1.36 – 2.47)	**<0.001**
2-3	4.78 (3.18 – 7.21)	**<0.001**	3.26 (2.06 – 5.15)	**<0.001**
≥5	3.93 (1.73 – 8.88)	**0.001**	3.21 (1.41 – 7.31)	**0.005**
Donor type (Ref: LD)				
DBD	1.33 (0.97 – 1.82)	0.07	1.01 (0.74 – 1.39)	0.94
DCD	1.90 (0.41 – 2.57)	**<0.001**	1.19 (0.87 – 1.62)	0.27

Table C.1. Associations with death post-transplant. Mixed ethnicity is not shown as no patients experienced events in this group.

C.1.2 Graft survival

Over follow up, 264 (8.9%) out of 2962 patients experienced graft failure. There was no association between MACE within the first post-transplant year and graft failure by univariable (HR 1.10, 95% CI 0.45-2.66) or multivariable (HR 1.27, 95% CI 0.52-3.12) analyses (Table C.2, Figure C.1). Factors associated with graft failure by multivariable analysis included being of Black (HR 1.78, 95% CI 1.21-2.63) or Mixed (HR 2.62, 95% CI 1.07-6.41) ethnicity compared to White ethnicity and having higher comorbidity (Charlson score 1-2 vs. 0, HR 1.58, 95% CI 1.14-2.19). Increased age was associated with a lower risk of graft loss (HR 0.99, 95% 0.98-0.99).

	Unadjusted HR (95% CI)	P	Adjusted HR (95% CI)	P
Year 1 MACE (Ref: no MACE)	1.10 (0.45 – 2.66)	0.83	1.27 (0.52 – 3.12)	0.60
Age (years)	0.99 (0.98 – 0.99)	0.009	0.98 (0.97 – 0.99)	**0.001**
Male sex (Ref: Female)	1.08 (0.84 – 1.38)	0.56	1.08 (0.83 – 1.40)	0.57
Ethnicity (Ref: White)				
Asian	0.95 (0.66 – 1.36)	0.77	0.79 (0.53 – 1.18)	0.25
Black	1.83 (1.28 – 2.63)	0.001	1.78 (1.21 – 2.63)	**0.004**
Mixed	2.39 (0.98 – 5.81)	0.06	2.62 (1.07 – 6.41)	**0.04**
IMD (Ref: 1)				
2	0.88 (0.62 – 1.26)	0.49	0.98 (0.67 – 1.42)	0.90
3	1.05 (0.74 – 1.49)	0.79	1.23 (0.84 – 1.80)	0.28
4	0.75 (0.51 – 1.09)	0.13	1.01 (0.68 – 1.52)	0.95
5	0.72 (0.49 – 1.08)	0.11	0.97 (0.63 – 1.48)	0.90
PRD (Ref: Non-diabetic) Diabetes	1.13 (0.75 – 1.72)	0.54	0.82 (0.49 – 1.36)	0.44
Charlson Score (Ref: 0)				
1-2	1.43 (1.09 – 1.88)	0.10	1.58 (1.14 – 2.19)	**0.007**
2-3	1.62 (0.88 – 2.97)	0.12	1.71 (0.84 – 3.49)	0.14
≥5	0.53 (0.07 – 3.80)	0.53	0.66 (0.09 – 4.77)	0.68
Donor type (Ref: LD)				
DBD	1.25 (0.91 – 1.70)	0.16	1.29 (0.93 – 1.77)	0.26
DCD	1.27 (0.93 – 1.74)	0.14	1.38 (0.99 – 1.93)	0.06

Table C.2. Associations with graft loss. Abbreviations: DBD: Donor after Brainstem Death; DCD: Donor after Cardiac Death; LD: Living donor; IMD: Index of Multiple Deprivation; PRD Primary Renal Disease.

C.1.3 Transplant survival

Over follow up, 492 out of 2962 patients died or lost their graft. There was an association with MACE in the first post-transplant year and transplant loss by univariable analysis (HR 1.93, 95% CI 1.17-3.17) but this was lost by multivariable analysis (HR 1.53, 95% CI 0.91-2.58) (Table C.3, Figure C.1). Factors associated with a lower risk of transplant loss were being of higher (IMD 5) compared to lower socioeconomic status (IMD 1). Factors associated with increased transplant loss were increased age, higher baseline comorbidity (Charlson score 1-2 and 3-4) compared to lower baseline comorbidity (Charlson score 0) and receiving a DCD kidney compared to a living donor kidney (Table 3).

	Unadjusted HR (95% CI)	P	Adjusted HR (95% CI)	P
Year 1 MACE (Ref: no MACE)	1.93 (1.17 – 3.17)	**0.01**	1.53 (0.91 – 2.58)	0.11
Age (years)	1.02 (1.01 – 1.03)	**<0.001**	1.02 (1.01 – 1.02)	**<0.001**
Male sex (Ref: Female)	1.05 (0.88 – 1.26)	0.59	1.00 (0.82 – 1.20)	0.96
Ethnicity (Ref: White)				
Asian	0.86 (0.66 - 1.14)	0.30	0.76 (0.57 – 1.02)	0.07
Black	1.36 (1.02 – 1.83)	**0.04**	1.23 (0.90 – 1.68)	0.20
Mixed	1.22 (0.50 – 2.95)	0.66	1.55 (0.64 – 3.75)	0.34
IMD (Ref: 1)				
2	0.94 (0.72 – 1.21)	0.63	0.96 (0.73 – 1.26)	0.78
3	0.95 (0.73 – 1.24)	0.72	0.98 (0.74 – 1.30)	0.90
4	0.81 (0.62 – 1.06)	0.12	0.84 (0.63 – 1.12)	0.24
5	0.72 (0.53 – 0.96)	**0.03**	0.71 (0.52 – 0.97)	**0.03**
PRD (Ref: Non-diabetic) Diabetes	1.65 (1.27 – 2.14)	**<0.001**	0.94 (0.68 – 1.29)	0.19
Charlson Score (Ref: 0)				
1-2	1.81 (1.49 – 2.20)	**<0.001**	1.69 (1.34 – 2.13)	**<0.001**
2-3	2.92 (2.04 – 4.18)	**<0.001**	2.44 (1.62 – 3.67)	**<0.001**
≥5	1.96 (0.87 – 4.39)	0.10	1.95 (0.86 – 4.39)	0.11
Donor type (Ref: LD)				
DBD	1.33 (1.06 – 1.68)	**0.02**	1.17 (0.92 – 1.49)	0.19
DCD	1.58 (1.25 – 1.98)	**<0.001**	1.30 (1.02 – 1.65)	**0.03**

Table C.3. Associations with death or loss of graft. Abbreviations: DBD: Donor after Brainstem Death; DCD: Donor after Cardiac Death; LD: Living donor; IMD: Index of Multiple Deprivation; PRD Primary Renal Disease.

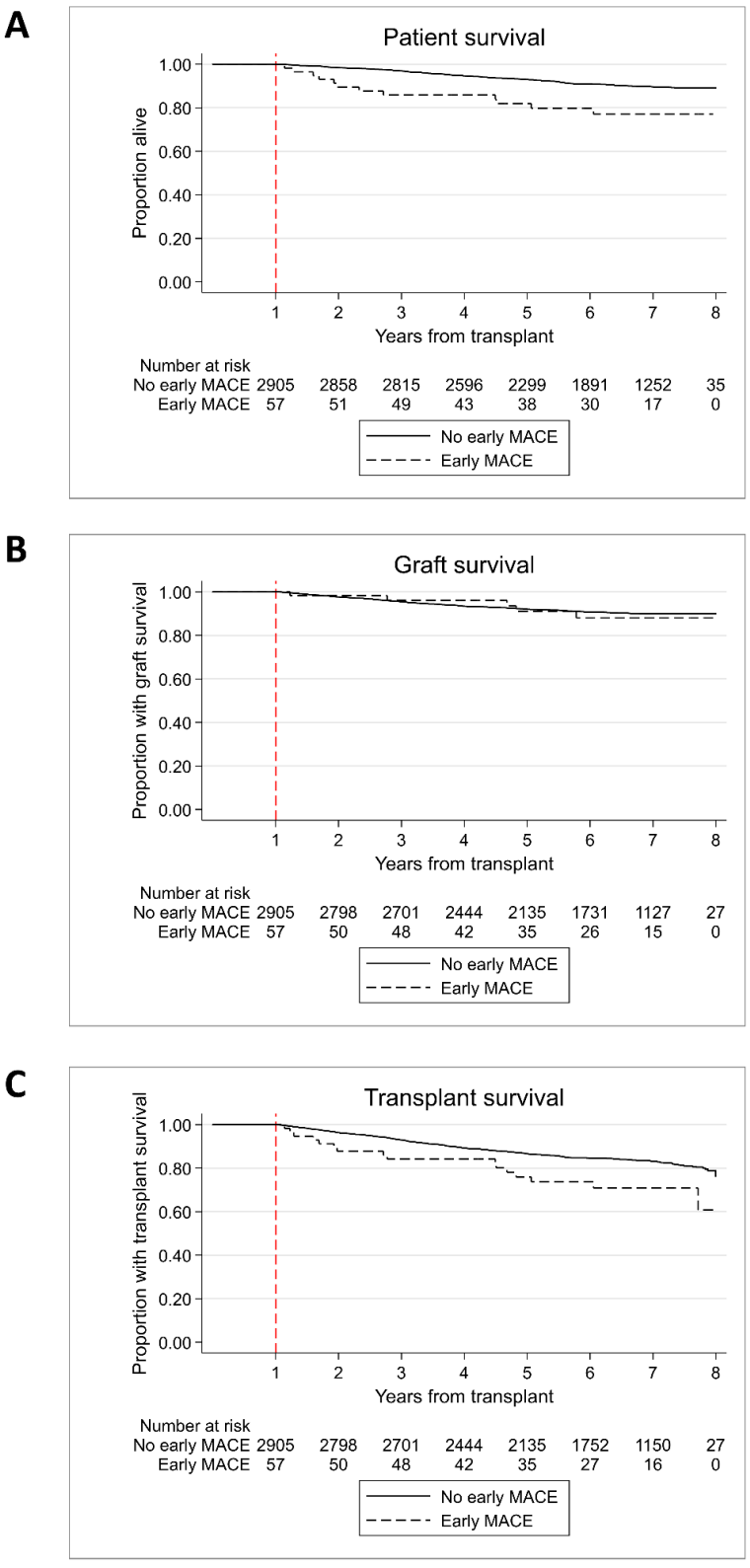


Figure C.1. Kaplan-Meier curves examining (A) patient survival, (B) graft survival and (C) transplant survival following the landmark point of 1 year post-transplant (represented by red dashed line).

Appendix D Additional material for Chapter 5

D.1 Additional tables for propensity score matching analyses

D.1.1 Comparison of characteristics of propensity score matched and unmatched patients using the Chi-square test.

	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
KRT 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)	<0.001
3	360 (20)	130 (16)	
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)	<0.001
4	119 (7)	43 (5)	
5	49 (3)	25 (3)	
6	85 (5)	41 (5)	

	Propensity matched N=1760	Not propensity matched N=812	P value
7	59 (3)	44 (5)	
8	162 (9)	73 (9)	
9	80 (5)	34 (4)	
10	98 (6)	46 (6)	
11	76 (4)	52 (6)	
12	161 (9)	51 (6)	
13	97 (6)	41(5)	
14	53 (3)	40 (5)	
15	111 (6)	83 (10	
16	35 (2)	19 (2)	
17	92 (50	25 (3)	
18	62 (4)	29 (4)	
First transplant (n=1842)	157 (14)	64 (13)	0.77
Living 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

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; KRT, kidney replacement therapy; HD, haemodialysis; PD, peritoneal dialysis; IMD, Index of Multiple Deprivation; MACE major adverse cardiovascular event.

D.1.2 Balance of characteristics of patients pre- and post-matching based on their propensity score for screening using standardised mean differences.

		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
KRT 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

Data expressed as percentages unless otherwise specified. 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; SMD, standardised mean difference.

D.1.3 Cox regression model examining 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: Anonymous centre)		
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

Cox regression of factors associated with MACE at 5 years in the propensity matched group (n=1760) with the inclusion of transplant centre.

D.2 Sensitivity analyses using the propensity score matched cohort

D.2.1 Cox regression model examining factors associated with MACE following propensity score matching in the ATTOM incident transplant cohort only (n=1156).

		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

Measures of effect are expressed as hazard ratios (HR) and confidence interval (CI). Adjusted analyses include all variables used to generate the propensity score.

D.2.2 Adjusted regression analysis using competing risk methodology (Fine and Gray) 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

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.

D.3 Sensitivity analysis using propensity score stratification

Quintile of propensity score (%)	Screened patients (n=1215)			Unscreened patients (n=1287)			HR (95% CI)
	Mean propensity score in percentile	Number of patients	Number with MACE	Mean propensity score in percentile	Number patients	Number with MACE	
80 to 100	0.775	363	63	0.748	131	13	**1.88 (1.11 – 3.16)**
60 to <80	0.631	326	33	0.616	173	21	0.87 (0.48 – 1.59)
40 to <60	0.497	242	16	0.496	238	10	1.61 (0.70 – 3.73)
20 to <40	0.420	230	15	0.412	298	11	1.78 (0.80 – 3.99)
0 to <20	0.284	126	4	0.266	375	9	1.33 (0.57 – 3.12)

Propensity score stratification, dividing patients into quintiles based on their propensity score. Quintiles were chosen to maintain sample size in each group, as has been performed previously in the literature. [388] *An unadjusted Cox regression model examined time to MACE at up to 5 years post-transplant in each quintile; this time point was selected to maximise the number of MACE events. Analyses were not adjusted for the variables used to create the propensity score to avoid increasing the number of variables in the model when the number of outcome events were small. Quintiles vary in size due to patients with identical values of propensity score being placed within the same quintile.*

D.4 Additional tables for the propensity score weighted model

D.4.1 Comparison of characteristics of screened patients (n=1287) with stabilised weights under 2 and 2 or greater within the propensity score weighted model using the Chi-square test.

	Screened patients stabilised weight <2 N= 1272	Screened patients stabilised weight ≥ 2 N= 15	P value
Age (years) (n=1287)	56 [47-63]	33 [26-36]	<0.001
Male Sex (n=1287)	798 (63)	6 (40)	0.07
Ethnicity White Asian Black Mixed	 1027 (81) 134 (11) 95 (7) 16 (1)	 2 (13) 7 (47) 5 (33) 1 97)	 <0.001
History of Diabetes (n=1287)	240 (19)	0 (0)	0.06
History of IHD (n=1287)	145 (11)	0 (0)	0.17
History of PVD (n=1287)	48 (4)	0 (0)	0.44
History of CeVD (n=1287)	67 (5)	(0)	0.36
Ever smoker (n=1287)	464 (36)	1 (7)	0.02
IMD (n=1287) 1 – Most deprived 2 3 4 5 – Least deprived	 244 (19) 264 (21) 247 (19) 280 (22) 237 (19)	 8 (53) 2 (13) 2 (13) 2 (13) 1 (7)	 0.03

Data are expressed as number (%) or median [interquartile range]. Abbreviations: IMD, index of multiple deprivation; IHD, ischaemic heart disease; PVD, peripheral vascular disease; CeVD, cerebrovascular disease.

D.4.2 Comparison of characteristics of unscreened patients (n=1215) with stabilised weights under 2 and 2 or greater within the propensity score weighted model using the Chi-square test.

	Unscreened patients stabilised weight <2 N=1173	Unscreened patients stabilised weight ≥ 2 N=42	P value
Age (years) (n=1215)	45 [35-54]	65 [63-68]	<0.001
Male Sex (n=1215)	681 (58)	30 (71)	0.08
Ethnicity (n=1215)			
White	834 (71)	31 (74)	
Asian	199 (17)	8 (19)	0.73
Black	117 (10)	3 (7)	
Mixed	23 (2)	0 (0)	
History of Diabetes (n=1215)	58 (5)	30 (71)	<0.001
History of IHD (n=1215)	21 (2)	17 (40)	<0.001
History of PVD (n=1215)	7 (1)	6 (14)	<0.001
History of CeVD (n=1215)	37 (3)	3 (7)	0.16
Ever smoker (n=1215)	342 (29)	15 (36)	0.36
IMD (n=1215)			
1 – Most deprived	327 (28)	7 (17)	
2	225 (19)	12 (29)	0.09
3	225 (19)	4 (9)	
4	204 (17)	8 (19)	
5 – Least deprived	192 (16)	11 (26)	

Data are expressed as number (%) or median [interquartile range]. Abbreviations: IMD, index of multiple deprivation; IHD, ischaemic heart disease; PVD, peripheral vascular disease; CeVD, cerebrovascular disease.

D.5 Additional table for the instrumental variable analysis

D.5.1 Comparison of transplant recipients based on the prevalence of screening pre-transplant by centre using the Kruskal-Wallis and Chi-square tests.

	Percentage of patients screened by centre				
	<25% 4 centres n=570	**25-49% 5 centres n=714**	**50-74% 6 centres n=742**	**≥75% 3 centres n=546**	**P value**
Median age (years)	50 (40-60)	50 (41-59)	52 (40-60)	52 (42-62)	0.22
Male sex (%)	58.8	61.5	63.6	58.2	0.17
White ethnicity (%)	64.7	78.6	72.9	86.3	<0.001
IMD quintile 1 (%)	27.1	28.0	23.0	13.6	<0.001
Diabetic nephropathy (%)	23.2	22.0	23.9	23.8	0.29
Diabetes (%)	14.2	12.5	14.4	10.2	0.12
Ischaemic heart disease (%)	6.3	6.2	8,8	7.7	0.20
Peripheral vascular disease (%)	2.6	2.0	2.9	2.0	0.56
Cerebrovascular disease (%)	2.6	4.0	5.4	4.8	0.09
Pre-emptive transplant (%)	20.9	20.9	24.1	20.7	0.34

The Kruskal-Wallis test was used to examine continuous variables and the Chi square test for categorical variables.

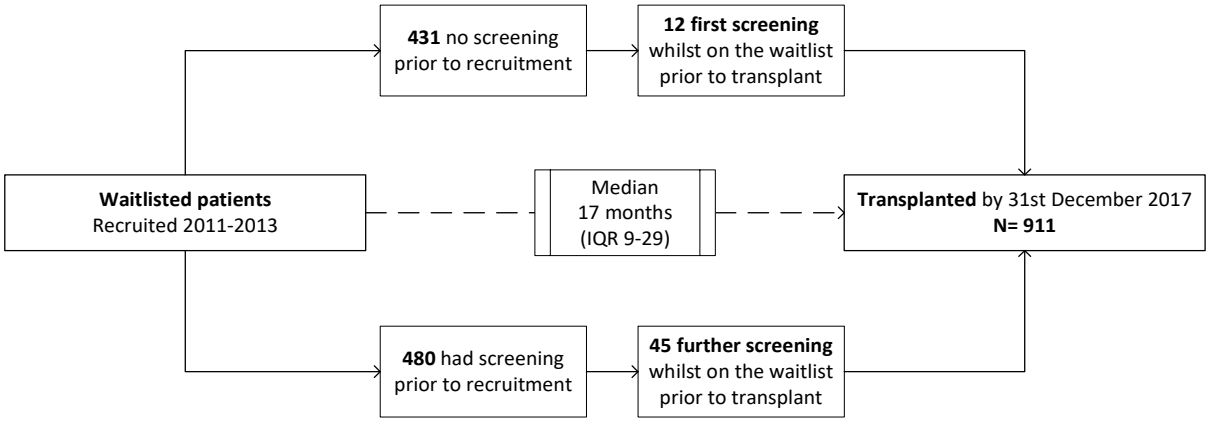
D.6 Characteristics of dialysis patients by their corresponding transplanting centre's screening practice

D.6.1 Linear regression model examining the association between dialysis patient characteristics and screening uptake in the transplant recipients at their local transplant centre.

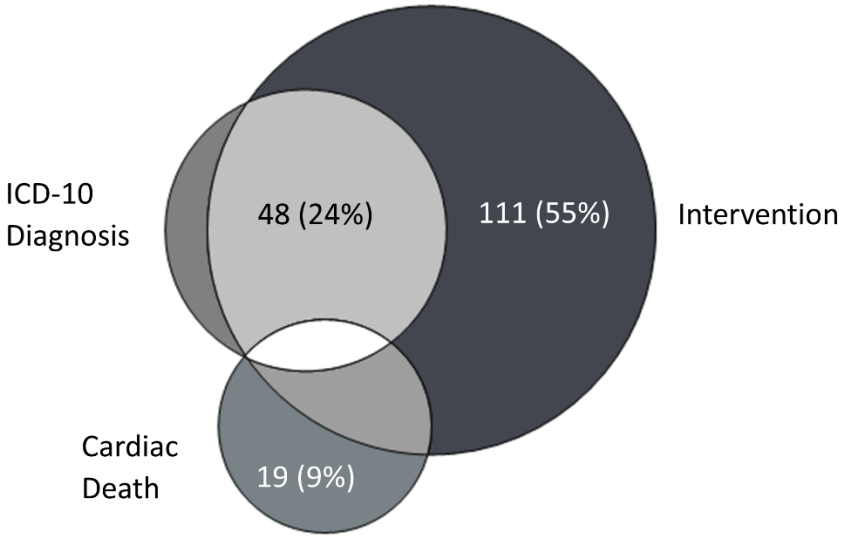
	Univariable linear regression			Multivariable linear regression		
	β	95% CI	P	β	95% CI	P
Age (Ref: <40 years)						
40-60	0.03	-0.01 to 0.07	0.19	0.02	-0.02 to 0.06	0.36
60-75	0.04	-0.003 - 0.08	0.07	0.02	-0.02 to 0.07	0.27
Male sex (Ref: Female)	-0.01	-0.04 - 0.02	0.70	-0.01	-0.04 to 0.02	0.45
Asian (Ref: White)	0.05	0.01 – 0.09	**0.007**	0.05	-0.04 to 0.03	0.64
Black (Ref: White)	-0.01	-0.05 - 0.04	0.82	0.02	-0.04 to 0.05	0.93
Mixed (Ref: White)	-0.07	-0.22 - 0.08	0.34	-0.06	-0.09 to 0.02	0.21
Diabetic nephropathy as PRD	0.04	0.002 - 0.06	0.04	0.03	-0.001 to 0.07	0.05
Charlson score (Ref: 0)						
1-2	0.01	-0.02 - 0.04	0.45	-0.01	-0.04 to 0.03	0.64
3-4	0.03	-0.02 - 0.07	0.22	0.01	-0.04 to 0.05	0.93
≥5	-0.03	-0.08 - 0.02	0.27	-0.04	-0.10 to 0.02	0.21
IMD (Ref: 3)						
1	-0.12	-0.25 to -0.08	<0.001	-0.12	-0.16 to -0.09	**<0.001**
2	-0.03	-0.07 – 0.01	0.09	-0.04	-0.08 to -0.001	**0.04**
4	-0.04	-0.09 to -0.002	0.04	-0.04	-0.09 - 0.0004	0.06
5	-0.03	-0.08 – 0.01	0.13	-0.03	-0.08 to 0.01	0.18

D.7 Additional figures

D.7.1 Screening patterns in the ATTOM waitlisted group between ATTOM recruitment and transplantation.



D.7.2 Combinations of MACE components post-transplantation.



Combinations of MACE components in the 202 individuals experiencing MACE 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.

Appendix E Cardiac screening questionnaire for Chapter 6

Screening for asymptomatic coronary artery disease prior to kidney transplantation

Thank you for taking the time to complete this short questionnaire regarding pre-transplant cardiac screening practice at your unit.

If you have any questions please contact us at ailish.nimmo@nhs.net.

Best wishes,
The DARWIN study investigators

1. What is your role within the renal unit?

- ◯ Clinical director/clinical lead
- ◯ Consultant nephrologist (not clinical director)
- ◯ Transplant surgeon (not clinical director)
- ◯ Other (please specify)

2. Please select the name/location of your renal unit.

Screening for asymptomatic coronary artery disease prior to kidney transplantation

Current practice and protocol (1)

For these questions, asymptomatic patients refer to those who are able to climb a flight of stairs without cardiac symptoms.

Cardiac screening investigations are tests to investigate for underlying coronary artery disease e.g. a stress test or coronary angiogram. It does not refer to an ECG or echocardiogram alone.

1. Does your unit have a guideline or protocol for pre-transplant cardiac investigation for asymptomatic individuals?

- ◯ Yes
- ◯ No

2. In asymptomatic patients, aside from an ECG and echocardiogram, are further investigations such as a stress test or a coronary angiogram required prior to listing?

- ◯ Yes - universal testing is required for all potential recipients
- ◯ Yes – there is a risk-stratified screening protocol
- ◯ No

Screening for asymptomatic coronary artery disease prior to kidney transplantation

Current practice and protocol (2)

1. At your centre, which risk factors do you use to select patients who need cardiac screening? Please tick all that apply.

- ☐ Age over certain threshold
- ☐ History of ischaemic heart disease
- ☐ History of diabetes
- ☐ History of stroke
- ☐ History of peripheral vascular disease
- ☐ Smoking history
- ☐ Ethnicity
- ☐ Other (please specify)
- ☐ Blood pressure (hyper/hypotension)
- ☐ Significant family history
- ☐ Limited exercise capacity e.g. due to amputation or musculoskeletal disorder
- ☐ Abnormal 12 lead ECG
- ☐ Abnormality on transthoracic echocardiogram e.g. regional wall motion abnormality
- ☐ Score on a specific risk index e.g. Duke Activity Index

2. If you have an age at which you start screening, please specify what this is.

3. If you have a different age at which you start screening patients with diabetes, please specify what this is.

Screening for asymptomatic coronary artery disease prior to kidney transplantation

Current practice and protocol (3)

1. What is the first line investigation for asymptomatic individuals undergoing cardiac stress testing at your centre (not including ECG or echocardiogram)? If practice has changed due to COVID-19, please give the investigation performed prior to the pandemic.

Please answer based on practice at your centre as opposed to referring units.

- ◯ Exercise tolerance test
- ◯ Stress echocardiogram
- ◯ Cardiac MRI
- ◯ Myocardial perfusion scan
- ◯ CPEX
- ◯ CT coronary angiogram
- ◯ Invasive coronary angiogram
- ◯ Other (please specify)

2. When was the last update to your cardiac workup protocol? Please specify year if known.

3. If a coronary angiogram is deemed necessary for listing a patient with advanced CKD not on dialysis, would your unit usually delay angiogram until the patient has started dialysis?

- ◯ Always
- ◯ Sometimes
- ◯ Never

4. What are the indications for coronary angiography in asymptomatic patients at your unit?

- ☐ All patients with a history of ischaemic heart disease
- ☐ All patients with a positive stress test
- ☐ All patients with diabetes
- ☐ All patients over a certain age
- ☐ All patients deemed to be at 'increased cardiovascular risk'
- ☐ No specific policy
- ☐ Other (please specify)

5. Do you think there is satisfactory evidence to support your unit's cardiac screening practice?

- ◯ Yes
- ◯ No
- ◯ Don't know
- ◯ Other (please specify)

Screening for asymptomatic coronary artery disease prior to kidney transplantation

Pathways of care

1. If a patient requires a cardiac screening investigation, in what settings are these requested? Please tick all that apply.

- ☐ In their usual general nephrology clinic by their named nephrologist
- ☐ In a low clearance clinic by the nephrologist reviewing them
- ☐ In a specific transplant assessment clinic by a nephrologist with additional transplant experience
- ☐ By a transplant surgeon in the transplant assessment clinic
- ☐ Recommended by the transplant assessment clinic, but to be actioned by the named nephrologist
- ☐ In a cardiology clinic by a cardiologist
- ☐ Other (please describe your units organisation if not included in the above options)

2. Does your unit have a cardio-renal multidisciplinary meeting?

- ◯ Yes
- ◯ No

3. If a patient requires a cardiac screening investigation, where are they performed? Please tick all that apply.

- [ ] Local acute hospital
- [ ] Non-transplanting renal unit hospital
- [ ] Transplanting renal unit hospital
- [ ] Other (please specify)

4. Does your unit have a named cardiologist to provide advice/review of patients undergoing transplant assessment?

- ◯ Yes
- ◯ No

5. Do patients who require cardiac screening investigations get reviewed by a cardiologist?

- ◯ No
- ◯ Yes – irrespective of the test result
- ◯ Yes – but only if they have an abnormal test result
- ◯ Yes – if for other reasons the patient is considered high risk (please specify)

6. If cardiac investigations or a cardiology opinion are performed by a referring non-transplanting centre, are these ever repeated at the transplanting unit?

- ◯ Often
- ◯ Sometimes
- ◯ Rarely
- ◯ Never

7. How long on average do you expect to wait between requesting and completion of initial cardiac workup? Please suggest pre-pandemic waiting times.

- ◯ 0-2 weeks
- ◯ 2-4 weeks
- ◯ 4-6 weeks
- ◯ 6-8 weeks
- ◯ 8-10 weeks
- ◯ 10-12 weeks
- ◯ >12 weeks

8. Which of the following staff members are routinely involved in the final decision-making regarding listing of potential transplant candidates?

- [ ] Consultant nephrologists from transplanting centre
- [ ] Transplant surgeon
- [ ] Consultant nephrologists from referring centre
- [ ] Anaesthetist
- [ ] Consultant cardiologist

9. For those individuals undergoing cardiac screening, who makes the principal decision at the transplant MDT on whether a patient has an acceptable peri-operative cardiovascular risk?

- ◯ Nephrologist
- ◯ Anaesthetist
- ◯ Transplant surgeon
- ◯ Shared decision through MDT
- ◯ Cardiologist
- ◯ Don't know

10. Are you aware of patients who have been discussed at transplant listing meetings, who were not listed for transplantation based on an abnormal cardiac screening test?

- ◯ Yes
- ◯ No

11. Roughly how many patients would not get listed based on an abnormal cardiac screening test each month?

- ◯ <1 patient/month
- ◯ 1-5 patients/month
- ◯ >5 patients/month
- ◯ Don't know

* 12. Do you think your unit be interested in participating in a randomised control clinical trial investigating whether cardiac screening affects peri-transplant cardiac events in asymptomatic patients?

- ◯ Yes – would be happy to participate and recruit all potential transplant recipients
- ◯ Yes – would be happy to participate and recruit a risk-stratified cohort of potential transplant recipients
- ◯ No – would not be happy to participate
- ◯ Don't know

Screening for asymptomatic coronary artery disease prior to kidney transplantation

Current practice and protocol (1)

For these questions, asymptomatic patients refer to those who are able to climb a flight of stairs without cardiac symptoms.

Cardiac screening investigations are tests to investigate for underlying coronary artery disease e.g. a stress test or coronary angiogram. It does not refer to an ECG or echocardiogram alone.

1. Does your unit have a guideline or protocol for pre-transplant cardiac investigation for asymptomatic individuals?

- ◯ Yes
- ◯ No

2. In asymptomatic patients, aside from an ECG and echocardiogram, are further investigations such as a stress test or a coronary angiogram required prior to listing?

- ◯ Yes - universal testing is required for all potential recipients
- ◯ Yes – there is a risk-stratified screening protocol
- ◯ No

Screening for asymptomatic coronary artery disease prior to kidney transplantation

Current practice and protocol (2)

1. At your centre, which risk factors do you use to select patients who need cardiac screening? Please tick all that apply.

- ☐ Age over certain threshold
- ☐ History of ischaemic heart disease
- ☐ History of diabetes
- ☐ History of stroke
- ☐ History of peripheral vascular disease
- ☐ Smoking history
- ☐ Ethnicity
- ☐ Other (please specify)
- ☐ Blood pressure (hyper/hypotension)
- ☐ Significant family history
- ☐ Limited exercise capacity e.g. due to amputation or musculoskeletal disorder
- ☐ Abnormal 12 lead ECG
- ☐ Abnormality on transthoracic echocardiogram e.g. regional wall motion abnormality
- ☐ Score on a specific risk index e.g. Duke Activity Index

2. If you have an age at which you start screening, please specify what this is.

3. If you have a different age at which you start screening patients with diabetes, please specify what this is.

Screening for asymptomatic coronary artery disease prior to kidney transplantation

Current practice and protocol (3)

1. What is the first line investigation for asymptomatic individuals undergoing cardiac stress testing at your centre (not including ECG or echocardiogram)? If practice has changed due to COVID-19, please give the investigation performed prior to the pandemic.

- ○ Exercise tolerance test
- ○ Stress echocardiogram
- ○ Cardiac MRI
- ○ Myocardial perfusion scan
- ○ CPEX
- ○ CT coronary angiogram
- ○ Invasive coronary angiogram
- ○ Other (please specify)

2. When was the last update to your cardiac workup protocol? Please specify year if known.

3. What are the indications for coronary angiography in asymptomatic patients at your unit?

- ☐ All patients with a history of ischaemic heart disease
- ☐ All patients with a positive stress test
- ☐ All patients with diabetes
- ☐ All patients over a certain age
- ☐ All patients deemed to be at 'increased cardiovascular risk'
- ☐ No specific policy
- ☐ Other (please specify)

4. If a coronary angiogram is deemed necessary for listing a patient with advanced CKD not on dialysis, would your unit routinely delay angiogram until the patient has started dialysis?

- ◯ Always
- ◯ Sometimes
- ◯ Never

5. Do you think there is satisfactory evidence to support your unit's cardiac screening practice?

- ◯ Yes
- ◯ No
- ◯ Don't know
- ◯ Other (please specify)

Screening for asymptomatic coronary artery disease prior to kidney transplantation

Pathways of care

1. If a patient requires a cardiac screening investigation, in what setting are these requested? Please tick all that apply.

- ☐ In their usual general nephrology clinic by their named nephrologist
- ☐ In a low clearance clinic by the nephrologist reviewing them
- ☐ In a specific transplant assessment clinic by a nephrologist with additional transplant experience
- ☐ By a transplant surgeon in the transplant assessment clinic
- ☐ Recommended by the transplant assessment clinic, but to be actioned by the named nephrologist
- ☐ In a cardiology clinic by a cardiologist
- ☐ Other (please describe your units organisation if not included in the above options)

2. Does your unit have a cardio-renal multidisciplinary meeting?

- ◯ Yes
- ◯ No

3. If a patient requires a cardiac screening investigation, where are they performed?

- [ ] Local acute hospital
- [ ] Non-transplanting renal unit hospital
- [ ] Transplanting renal unit hospital
- [ ] Other (please specify)

4. Does your unit have a named cardiologist to provide advice/review of patients undergoing transplant assessment?

- ◯ Yes
- ◯ No

5. Do patients who require cardiac screening investigations get reviewed by a cardiologist?

- ◯ No
- ◯ Yes – irrespective of the test result
- ◯ Yes – but only if they have an abnormal test result
- ◯ Yes – if for other reasons the patient is considered high risk (please specify)

6. How long on average do you expect to wait between requesting and completion of initial cardiac workup? Please suggest pre-pandemic waiting times.

- ◯ 0-2 weeks
- ◯ 2-4 weeks
- ◯ 4-6 weeks
- ◯ 6-8 weeks
- ◯ 8-10 weeks
- ◯ 10-12 weeks
- ◯ >12 weeks

* 7. Do you think your unit would be interested in participating in a randomised control clinical trial investigating whether cardiac screening affects peri-transplant cardiac events in asymptomatic patients?

- ◯ Yes – would be happy to participate and recruit all potential transplant recipients
- ◯ Yes – would be happy to participate and recruit a risk-stratified cohort of potential transplant recipients
- ◯ No – would not be happy to participate
- ◯ Don't know

Screening for asymptomatic coronary artery disease prior to kidney transplantation

Thank you for completing this questionnaire.

If you have a unit protocol on pre-transplant cardiac assessment we would be grateful if you could email it to ailish.nimmo@nhs.net.

Appendix F Publications arising from this work

The following pages contain copies of published papers arising from work in this thesis, the citations for which are as follows:

- **Nimmo, A., Steenkamp, R., Ravanan, R. *et al.* Do routine hospital data accurately record comorbidity in advanced kidney disease populations? A record linkage cohort study. *BMC Nephrol* 2021; 22, 95.**
- **Nimmo A, Forsyth J, Oniscu G, Robb M, Watson C, Fotheringham J, Roderick P, Ravanan R, Taylor D. A propensity score-matched analysis indicates screening for asymptomatic coronary artery disease does not predict cardiac events in kidney transplant recipients. Kidney International 2021; 99(2): 431-442.**
- **Nimmo A, Ravanan R, Taylor D. The authors reply. Kidney International 2021; 99(3): 772-773**
- **Nimmo A, Graham-Brown M, Griffin S, Sharif A, Ravanan R, Taylor D. Pre-kidney transplant screening for coronary artery disease: current practice in the UK. Transplant International. 2022; 35:4.**

RESEARCH ARTICLE Open Access

Do routine hospital data accurately record comorbidity in advanced kidney disease populations? A record linkage cohort study

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Abstract

Background: Routine healthcare datasets capturing clinical and administrative information are increasingly being used to examine health outcomes. The accuracy of such data is not clearly defined. We examine the accuracy of diagnosis recording in individuals with advanced chronic kidney disease using a routine healthcare dataset in England with comparison to information collected by trained research nurses.

Methods: We linked records from the Access to Transplant and Transplant Outcome Measures study to the Hospital Episode Statistics dataset. International Classification of Diseases (ICD-10) and Office for Population Censuses and Surveys Classification of Interventions and Procedures (OPCS-4) codes were used to identify medical conditions from hospital data. The sensitivity, specificity, positive and negative predictive values were calculated for a range of diagnoses.

Results: Comorbidity information was available in 96% of individuals prior to starting kidney replacement therapy. There was variation in the accuracy of individual medical conditions identified from the routine healthcare dataset. Sensitivity and positive predictive values ranged from 97.7 and 90.4% for diabetes and 82.6 and 82.9% for ischaemic heart disease to 44.2 and 28.4% for liver disease.

Conclusions: Routine healthcare datasets accurately capture certain conditions in an advanced chronic kidney disease population. They have potential for use within clinical and epidemiological research studies but are unlikely to be sufficient as a single resource for identifying a full spectrum of comorbidities.

Keywords: Comorbidity, Chronic kidney disease, Routine healthcare datasets, Record linkage, Secondary care

Introduction

Over 50% of individuals receiving kidney replacement therapy (KRT) have a comorbid medical condition in addition to their kidney disease [1]. Comorbidity is associated with increased hospitalisation [2], reduced quality of life [3], and mortality [4, 5]. It is therefore essential to adjust for comorbidity when comparing clinical outcomes, without which confounding due to differences in case-mix may bias results [6, 7]. Further, inaccurate or incomplete data may result in bias, so robust methods of collecting comorbidity information are required.

In clinical research studies, data are often extracted from clinical notes by specially trained staff. Benefits of this approach include collection of high-quality, consistent information with minimal missing data. However, this is resource-intensive and the economic implications of directly gathering information that is already routinely collected elsewhere need to be considered. Disease-specific registries, including the UK Renal Registry (UKRR) record comorbidity

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information through clinician reporting but with low data-completeness: the UKRR only captures comorbidity in half of individuals [1].

One way of improving the completeness of comorbidity data is through linkage to routinely collected healthcare datasets such as Hospital Episode Statistics (HES) [6]. These contain information recorded at the point of care delivery, are cheaper than direct data collection and of minimal burden to study participants and researchers. Long-term follow up of large populations across geographical areas can be efficiently captured with reduced attrition, no recall bias and the ability to adjust for residual confounding relating to the accrual of comorbidity over time [8–10]. If data are of sufficient quality, these datasets are an appropriate resource for use within clinical research.

HES records detailed information on National Health Service (NHS) funded hospital care in England and Wales to inform reimbursement of health providers [11]. HES data are increasingly used in research to identify participants and record outcomes [12–14], and the UKRR established HES linkage to supplement its comorbidity information in 2018 [15].

Although the accuracy of HES in recording individual medical conditions has been compared to various disease registries [16–18], its accuracy in people with advanced chronic kidney disease (CKD) is less well documented. Clustering of comorbidities [19] and higher hospitalisation rates [20] may lead to differences in the quality of data compared to the general population and merits further exploration.

The aim of this study was to investigate the accuracy of HES comorbidity data in a cohort of individuals with advanced CKD with reference to information collected by trained research nurses. This is to identify whether this resource can be reliably used within epidemiological and clinical research in the KRT population.

Materials and methods

Data sources and study population

We used data from the Access to Transplant and Transplant Outcome Measures (ATTOM) observational cohort study linked to the HES dataset. ATTOM recruited individuals aged 18 to 75 years in the United Kingdom between 2011 and 2013. Patients had started dialysis or received a kidney transplant within the preceding 90 days or were active on the deceased-donor waitlist, and entered 'incident dialysis', 'incident transplant' or 'waitlisted' cohorts respectively. Study methodology has been described previously [21].

Research nurses collected data on patient demographics, socioeconomic indicators, primary renal disease (PRD) and comorbidity (Supplementary table 1) at recruitment. Demographic and clinical data were collected from case notes whilst ethnicity and socioeconomic information were obtained from self-completed patient questionnaires. Research nurses underwent data collection training and received documentation with clear definitions against which to gather information. Independent data validation was performed by a senior nurse in a randomly selected 5% of cases with a concordance of over 98% for all collected variables [21].

Data from HES were available from 1st January 2006 to 31st December 2017, containing demographic and clinical information from NHS secondary care encounters. Encounters are recorded as admitted patient care (APC), outpatient (OP) or emergency department (ED) attendances.

Diagnoses and procedures from APC and OP episodes are coded using International Classification of Diseases 10th revision (ICD-10) and Office for Population Censuses and Surveys Classification of Interventions and Procedures version 4 (OPCS-4) criteria. Up to 20 diagnosis and 24 operation codes are recorded for each APC episode. Information in the primary position reflects the principal diagnosis, with subsequent positions documenting comorbidities collated by professional clinical coders [11].

Data were obtained by NHS Digital, stored at NHS Blood and Transplant, and linked to the ATTOM database by unique patient identifiers (Data Sharing Agreement Number DARS-NIC-14342-Q8W0X-v1.4). Ethical approval for ATTOM was obtained from the National Health Service Health and Social Care Research Ethics Committee (Ref: 11/EE/0120). Patients provided informed consent at ATTOM recruitment for subsequent analysis of outcomes. All data were stored in line with the United Kingdom Data Protection Act 1998 requirements. Study methodology was performed in line with the aforementioned ethical guidelines and regulations.

HES data were only available from hospitals in England, so ATTOM participants from elsewhere in the UK were excluded. From here we refer to ATTOM and HES as 'study data' and 'hospital data' respectively.

Data completeness and healthcare utilisation

To determine the completeness of HES data, the dataset linkage rate and number of HES entries per individual were determined. Methodology on dataset linkage rate is described within Supplementary Material. As diagnosis recording is most detailed within HES APC [11, 22] only these episodes were used to extract comorbidity information (over 95% of OP episodes were coded as 'unspecified morbidity'). The number of patients with an APC episode prior to study recruitment was calculated and number of admissions determined. Comorbidities among individuals with and without an APC episode were compared.

Comorbidity recording

The comorbidities recorded by study nurses are shown in Supplementary table 1, alongside corresponding ICD-10 and OPCS-4 codes. Codes were identified from a systematic search of data dictionaries alongside consultation of established algorithms [23]. Comorbidities were extracted from all diagnosis and operation positions from hospital admissions between January 2006 and study recruitment. If a condition was recorded once, it was considered to persist on subsequent attendances in-keeping with established methodology [24]. The prevalence of comorbidities were calculated using the denominator of all individuals with dataset linkage and complete study comorbidity records.

To maximise their statistical power, studies need to identify conditions with an adequate sensitivity (proportion of true 'cases' identified), specificity (proportion of true 'controls' identified) and positive predictive value (PPV; proportion of identified cases that truly have the condition). A higher PPV leads to greater statistical power through low misclassification of positive cases which could 'dilute' any observed effect. False negatives have less impact on power for conditions with a relatively low prevalence as they join the larger control population. If the condition of interest is rare, specificity and negative predictive value (NPV) are generally high.

The study comorbidity dataset was taken to represent 'gold standard'. The sensitivity, specificity, PPV and NPV of comorbidities derived from hospital data were calculated. Cohen's kappa statistic was used to compare the agreement of recording between sources. Accepted values were taken to indicate poor (< 0.2), fair (0.21–0.40), moderate (0.41–0.6), substantial (0.61–0.8) and good (> 0.8) agreement [25]. The ICD-10 and OPCS-4 codes of comorbidities with a PPV below 50% were scrutinised to identify diagnoses giving false positive results. To examine whether disease prevalence associates with recording accuracy, pooled sensitivities and PPVs were calculated using a subgroup meta-analysis.

Operations preferentially generate cost codes for hospital episodes and the condition being treated by an operation could be more likely to be 'truly' present if requiring an intervention. A subgroup meta-analysis compared the sensitivity and PPV of conditions identified using ICD-10 criteria alone to those also derived from OPCS-4 codes. A random-effects model was used due to heterogeneity in the prevalence of comorbidities and variation in the sensitivity and PPV of comorbidities derived from hospital data reported previously [17, 18].

The renal modified Charlson score was calculated using comorbidities derived from study and hospital data (Supplementary table 2) [26]. The sensitivity, specificity, PPV and NPV of the Charlson score derived from hospital data were calculated.

Statistical analyses

Descriptive statistics were used to report baseline characteristics with non-parametric continuous variables expressed as median [interquartile range, IQR] and categorical variables as frequency (percentage). The Chi-square test and Mann-Whitney U test were used to compare categorical and non-parametric continuous variables respectively. Results of regression analyses were presented as odds ratios with 95% confidence intervals. Statistical significance was defined as a p-value < 0.05. Analyses were performed using Stata 15 (Statacorp, College Station, TX).

Results

Data sets and study population

In total, 5703 patients were recruited to ATTOM from an English renal centre. Study and hospital records were linked for 5506 (97%) individuals. Of the 197 individuals whose records did not link, 49 had non-English postcodes and likely received treatment elsewhere in the UK, leaving 148 (2.6%) unmatched (Fig. 1). Factors associated with dataset linkage are described in the Supplementary Material and shown in Supplementary table 3 and Supplementary table 4.

Of those individuals with linked datasets, the median age was 53 years [IQR 43–63], 62% of individuals were male and 76% were of white ethnicity. Overall, 20% of individuals had a PRD classified as 'other', with a further 19% each having diabetes and glomerulonephritis (Table 1).

Healthcare utilisation

The median time covered by hospital data prior to study recruitment was 6.7 years [IQR 6.4–7.0]. Of the 5506 individuals whose datasets linked, 5437 (99%) had an APC episode prior to recruitment. The median number of APC episodes was 9 [IQR 5–16] and median time from last admission to recruitment was 58 days [IQR 19–258]. Of those individuals with an admission, 89% had an admission within 1 year of recruitment and 95% within 2 years. Details of the 69 individuals without an admission prior to study recruitment are shown in the Supplementary Material; these individuals are included in subsequent analyses and counted as having no comorbidity in hospital records.

Comorbidity recording

There was variation in the sensitivity, specificity, PPV and NPVs of comorbidities (Table 2). Diabetes, ischaemic heart disease and malignancy were most prevalent (Fig. 2) and recorded with a high sensitivity and PPV of 97.7 and 90.4% for diabetes, 82.6 and 82.9% for ischaemic heart disease and 62.8 and 71.9% for malignancy (Figs. 3 and 4). Alongside heart valve replacement, these

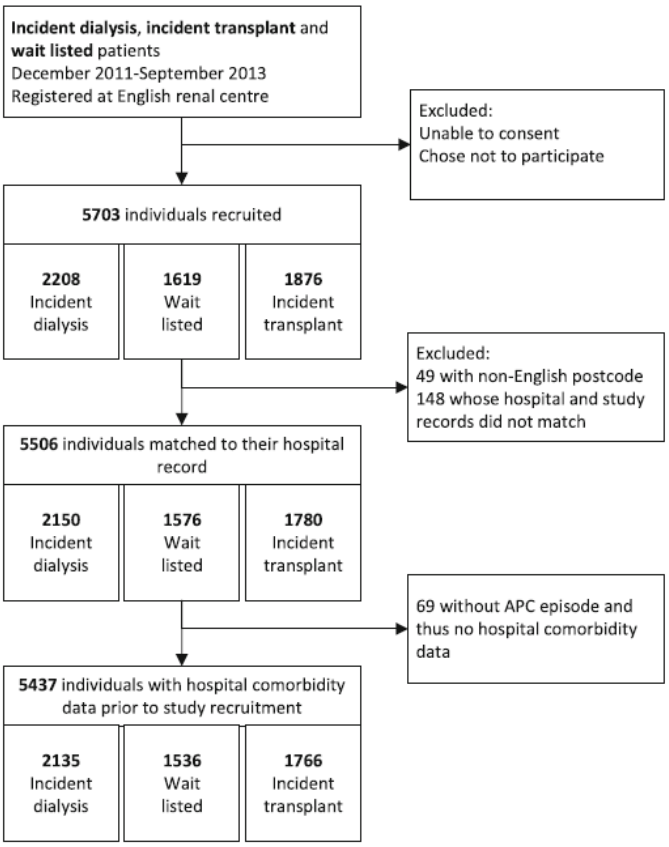

Fig. 1 Flow chart depicting individuals included in the study. There were 69 individuals without an admitted patient care episode prior to study recruitment, but 67 of these had a subsequent admitted patient care episode after recruitment

conditions had a kappa statistic over 0.6 indicating adequate agreement.

Heart failure, chronic lung disease, mental illness and peripheral vascular disease each had greater sensitivities relative to their PPV, reflecting a greater proportion of false positive cases in hospital data. False positive cases of chronic lung disease reflected recordings of asthma or COPD in 85% of cases, and false positive cases of mental illness were recorded as depression in 46% and harmful or dependent use of alcohol in 32% of cases (Supplementary table 5). Peripheral vascular disease was identified using both ICD-10 and OPCS-4 codes and had a sensitivity of 67.2% and PPV of 47.7%. Examining the ICD-10 code alone gave a similar sensitivity (51.2, 95% CI 45.3–57.1) and PPV (51.5, 95% CI 45.6–57.4).

Blood borne viruses and abdominal aortic aneurysm had the lowest sensitivities but proportionately greater PPVs reflecting a higher rate of false negative cases. Liver disease and dementia both had poor sensitivities and PPVs under 50%. False positive liver disease cases were due to coding of liver transplant, fatty change of the liver and liver failure otherwise unspecified.

To examine whether disease prevalence was associated with the accuracy of comorbidity recording, pooled sensitivities and PPVs were calculated. The three most prevalent comorbidities comprising diabetes, heart disease and malignancy had a greater pooled PPV than all other conditions combined at 81.8% (95% CI 70.1–93.6) versus 48.1% (95% CI 37.1–59.0) ($p < 0.001$) but the association between recording accuracy and disease prevalence was not linear.

The conditions identified through ICD-10 codes alone or a combination of ICD-10 and OPCS-4 codes are shown in Supplementary table 1. There was no variation in sensitivity or PPV with coding system. The pooled sensitivity of conditions identified from ICD-10 and OPCS-4 criteria was 69.6% (95% CI 56.4–82.8), and from ICD-10 codes alone 59.8% (95% CI 39.7–80.0) ($p = 0.43$). The pooled PPV of ICD-10 and OPCS-4 diagnoses was

Table 1 Study dataset linkage by patient demographic and clinical factors. Data are expressed as number (%) or median [IQR]. Standardised differences of 0.2, 0.5 and 0.8 reflect small, medium and large standardised differences respectively

Variable	Linked dataset N = 5506	Non-linked dataset N = 148	P	Standard diff.
Age (n = 5654)	53 [43–63]	51 [41–61]	0.09	0.15
Sex (n = 5654)				
Male	3422 (62)	84 (57)	0.18	0.11
Ethnicity (n = 5632)				
White	4192 (76)	100 (69)	< 0.001	0.47
Black	497 (9)	35 (24)		
Asian	750 (14)	10 (7)		
Mixed	48 (1)	0 (0)		
Index of Multiple Deprivation (n = 5654)				
1 – Most deprived	1420 (26)	31 (21)	0.51	0.11
2	1169 (21)	29 (20)		
3	1052 (19)	35 (24)		
4	983 (18)	27 (18)		
5 – Least deprived	882 (16)	26 (17)		
ATTOM cohort (n = 5654)				
Dialysis	2150 (39)	49 (33)	0.14	0.16
Transplant	1780 (32)	59 (40)		
Wait listed	1576 (28)	40 (27)		
PRD (n = 5590)				
Polycystic kidney disease	676 (13)	22 (15)	0.005	0.38
Diabetes	1026 (19)	14 (10)		
Glomerulonephritis	1057 (19)	36 (24)		
Pyelonephritis	460 (8)	15 (10)		
Hypertension	340 (6)	9 (6)		
Renovascular disease	97 (2)	7 (5)		
Other	1090 (20)	33 (22)		
Uncertain	697 (13)	11 (8)		
Charlson comorbidity index (n = 5571)				
0	3031 (56)	100 (68)	0.007	0.33
1–2	1518 (28)	37 (25)		
3–4	583 (11)	7 (5)		
5+	292 (5)	3 (2)		

Abbreviations: *PRD* Primary renal diagnosis

58.1% (95% CI 43.3–73.0) and for ICD-10 diagnoses alone was 53.5% (95% CI 29.5–77.5) ($p = 0.74$).

The sensitivity and PPV of Charlson comorbidity scores derived from hospital data are shown in Table 3. These declined with rising Charlson score. The sensitivity and PPV of a Charlson score of 0 were 88.2 and 82.9% respectively, and for a Charlson score of 1–2 were 83.9 and 66.6%.

Discussion

This observational study of over 5000 individuals with advanced CKD describes the accuracy of comorbidity recording in the Hospital Episode Statistics dataset compared to data collected by trained research nurses. The record linkage rate and proportion of individuals with comorbidity data before starting kidney replacement therapy are high, but there is variation in the sensitivity and positive predictive values of conditions derived from the hospital dataset. We suggest hospital data are adequate for capturing comorbidities including diabetes, ischaemic heart disease and malignancy but caution should be used if using this resource to identify a full spectrum of conditions.

Table 2 Sensitivity, specificity, positive and negative predictive values and Kappa statistic of hospital data comorbidity as compared to study data. Conditions are ordered by prevalence

Comorbidity	Sensitivity (95% CI)	Specificity (95% CI)	PPV (%) (95% CI)	NPV (%) (95% CI)	Kappa
Diabetes (*n* = 5461)	97.7 (96.8–98.4)	96.1 (95.4–96.7)	90.4 (88.9–91.8)	99.1 (98.7–99.4)	0.91
Ischaemic heart disease (*n* = 5450)	82.6 (79.6–85.4)	93.4 (92.7–94.1)	82.9 (77.3–87.6)	90.2 (89.4–91.0)	0.68
Malignancy (*n* = 5453)	62.8 (58.3–67.2)	97.7 (97.2–98.1)	71.9 (67.3–76.2)	96.5 (96.0–97.0)	0.64
Chronic lung disease (*n* = 5450)	86.0 (82.3–89.2)	90.4 (89.5–91.2)	41.9 (38.6–45.4)	98.8 (98.4–99.1)	0.52
Cerebrovascular disease (*n* = 5448)	56.6 (51.2–61.9)	96.7 (96.2–97.2)	53.6 (48.3–58.9)	97.1 (96.6–97.5)	0.52
Mental illness (*n* = 5451)	55.1 (49.7–60.5)	94.0 (93.3–94.7)	38.1 (33.8–42.6)	96.9 (96.4–97.5)	0.41
Peripheral vascular disease (*n* = 5452)	67.2 (61.5–72.6)	95.8 (95.2–96.3)	47.7 (42.8–52.6)	98.1 (97.7–98.5)	0.53
Heart failure (*n* = 5450)	68.4 (61.3–75.0)	91.4 (90.6–92.1)	22.3 (18.9–25.9)	98.8 (98.4–99.1)	0.30
Blood borne viruses (n = 5450)	15.5 (10.2–22.2)	100 (99.9–100)	96.0 (79.6–99.9)	97.6 (97.1–98.0)	0.26
Liver disease (*n* = 5452)	44.2 (34.0–54.8)	98.0 (97.6–98.4)	28.4 (21.3–36.4)	99.0 (98.7–99.3)	0.33
Heart valve replacement (*n* = 5448)	92.6 (82.1–97.9)	99.5 (99.3–99.7)	65.8 (54.0–76.3)	99.9 (99.8–100)	0.77
Permanent pacemaker (*n* = 5449)	84.9 (72.4–93.3)	98.6 (98.3–98.9)	37.5 (28.8–46.8)	99.8 (99.7–99.9)	0.51
Abdominal aortic aneurysm (*n* = 5447)	29.5 (16.8–45.2)	99.9 (99.7–99.9)	61.9 (38.4–81.9)	99.4 (99.2–99.6)	0.40
Dementia (*n* = 5453)	44.4 (13.7–78.8)	99.9 (99.7–99.9)	36.4 (10.9–69.2)	99.9 (99.8–100)	0.40

Abbreviations: *PPV* Positive predictive value, *NPV* Negative predictive value

There are several possible explanations for the variation in recording accuracy. First, accuracy may be influenced by the likelihood of a condition being directly implicated in hospital admission. Acute coronary syndromes and the management of malignancy are likely to require hospitalisation and were accurately recorded, whilst conditions predominantly monitored as an outpatient such as blood borne viruses and aortic aneurysms had lower sensitivities. Whilst the working diagnosis will influence the likelihood of hospital admission, this will also vary with clinician, social and geographical factors. We were not able to examine variation in recording accuracy between hospitals due to individuals having admissions across multiple sites and the small number of individuals attending certain hospitals, but inter-centre variation may also exist.

Second, variations in diagnostic criteria may lead to discrepancies in recording. For example, echocardiogram abnormalities are common in people on dialysis in the context of volume overload but there may not structural or functional cardiac dysfunction when the patient is at their dry weight [27]. Extracellular fluid overload could

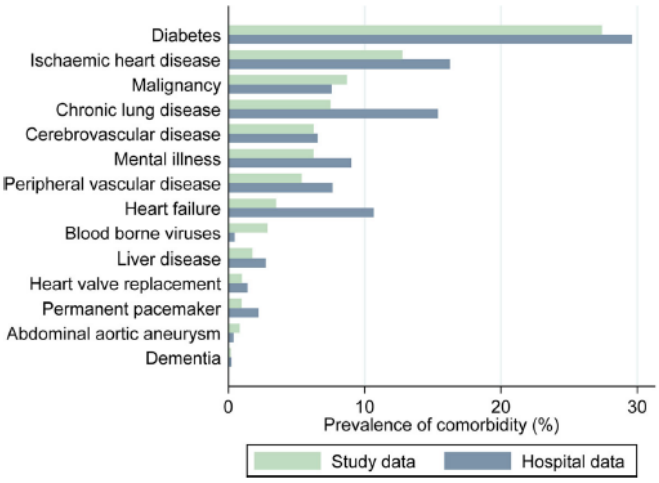

Fig. 2 Prevalence of comorbidities derived from study and hospital datasets

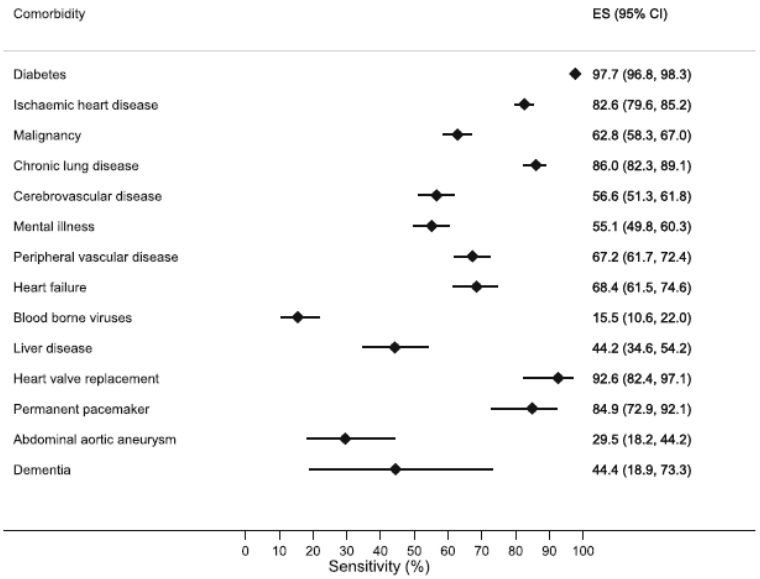

Fig. 3 Forest plot displaying sensitivity (%) with 95% confidence intervals for individual comorbidities derived from hospital data. Comorbidities are ordered by prevalence. ES: effect size, represents sensitivity (%)

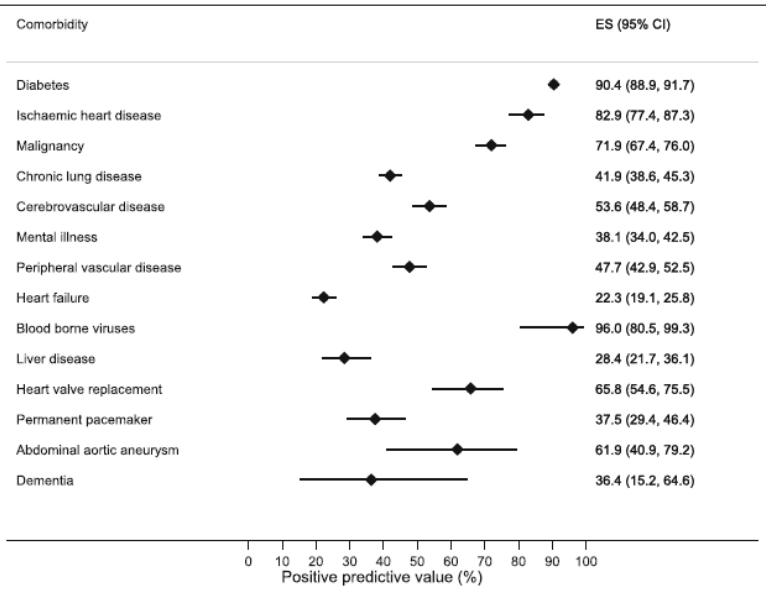

Fig. 4 Forest plot displaying positive predictive values (%) with 95% confidence intervals for individual comorbidities derived from hospital data. Comorbidities are ordered by prevalence. ES: effect size, represents positive predictive value (%)

Table 3 Sensitivity, specificity, positive and negative predictive values and Kappa statistic of hospital data Charlson comorbidity index as compared to study data

Charlson comorbidity index	Sensitivity (95% CI)	Specificity (95% CI)	PPV (%) (95% CI)	NPV (%) (95% CI)	Kappa
0 ($n = 3031$)	88.2 (86.8–89.5)	87.2 (86.1–88.4)	82.9 (81.3–84.4)	91.3 (90.3–92.3)	0.74
1–2 ($n = 1518$)	83.9 (82.3–85.4)	70.9 (69.3–72.5)	66.6 (64.8–68.3)	86.5 (85.1–87.7)	0.53
3–4 ($n = 583$)	73.1 (69.6–76.5)	84.7 (83.6–85.7)	39.3 (36.6–42.1)	95.9 (95.2–96.4)	0.42
5+ ($n = 292$)	67.9 (61.9–73.5)	93.0 (92.2–93.6)	32.8 (28.9–36.9)	98.3 (97.9–98.6)	0.40

Abbreviations: *PPV* Positive predictive value, *NPV* Negative predictive value

be misinterpreted as heart failure and recorded as such in clinical notes, but stricter diagnostic criteria were used in the study proforma. Variation may also reflect how 'presumed' diagnoses are recorded e.g. malignancy without histological confirmation.

Third, the granularity of ICD-10 and OPCS-4 coding systems should be considered. Amputations are coded as a procedure within hospital data but the reason for amputation is not documented. We assumed lower limb amputations related to peripheral vascular disease, though some may have traumatic, infective, or malignant aetiologies. Examining ICD-10 diagnosis codes for peripheral vascular disease alone did not substantially improve the PPV. Previous studies have suggested that severe disease is more likely to be correctly recorded [28], so it might have been expected that individuals with peripheral vascular disease requiring amputation to also have ICD-10 coding.

Previous studies have assessed the accuracy of hospital coding with reference to primary care and disease registry data, and recommended ways to maximise data quality. Herrett et al. examined the recording of acute myocardial infarction, reporting a PPV of 91.5% in hospital data with reference to a myocardial infarction registry. However, a third of cases were missed and they suggest linked datasets from more than one source can reduce biased estimates [16, 29]. Careful selection of ICD-10 codes is also important: a meta-analysis examining stroke recording found a wide variation in PPV, with the most accurate studies using stroke-specific as opposed to general cerebrovascular disease codes [17]. Finally, the PPV can be increased if diagnoses are recorded only if they correlate to the treating specialty, are in the primary diagnosis position or documented more than once [30]. These techniques will however reduce sensitivity so a balance must be found.

Lessons on improving routine healthcare data quality can also be taken from countries which successfully gather this information [31]. Denmark has a similar healthcare system to the UK and has excellent routine healthcare data which is easily accessible for research purposes. Consultants prospectively enter medical diagnoses in clinical databases that record the quality of healthcare delivered, and as these are used to assess treatment effectiveness and in research there are constant efforts to ensure the data is valid [32].

One study has previously examined the accuracy of HES comorbidity data in individuals on KRT, using UKRR comorbidity returns as their reference [6]. They reported overall 'good' concordance between sources, but the information was not as granular as is presented here and 50% of individuals had missing UKRR comorbidity information. HES comorbidity was however predictive of mortality and partially explained variation in outcomes between centres [6]. It is therefore possible that hospital data could minimise bias arising from comorbidity accrual in longitudinal observational studies [33, 34].

Using routine healthcare data for research purposes comes with economic and practical advantages: it is of low burden to participants and researchers, captures a large study population with high data completeness (96% in our study) and allows longitudinal follow up of individuals. Datasets used for hospital reimbursement also provide a 'real-world' view of hospitals care and insight into the financial impact of treatment.

Challenges however do exist. First, not all individuals are represented within hospital data and 2.6% of datasets in our study were not linked. This could be explained by individuals opting-out of record sharing between NHS Digital and third parties which results in the loss of 2% of hospital episodes [11].

Second, HES does not capture treatment in primary care, in the private sector or outside of England. The development of comorbidity is often associated with hospitalisation and nearly 90% of individuals had an admission within a year of KRT start, so for this population it seems unlikely for significant uncaptured community comorbidity accrual to have occurred. It is also not known if the absence of hospital data reflects no hospital contact or a loss to follow up. Similarly, hospital data cannot code conditions as absent, so lack of documentation does not definitively confirm absence of disease.

Third, the data inputted into HES are extracted from patient notes often completed by junior members of the medical team, with trained medical coders selecting the best aligned ICD-10 and OPCS-4 codes. The quality of the data depends on the documented information [35],

experience of the coder and whether any systematic errors occur during the data collection process.

Finally, whilst cheaper than employing staff to gather patient information, the time and cost in gaining access to hospital data may be a barrier to its use. A new application for HES data costs £1030 and linking a bespoke dataset costs £2060 [36]. The time to receive data varies depending on the information required, but for this project took 2 years.

Our study has several strengths. We examine a large cohort of individuals with advanced CKD who are broadly representative of the UK KRT population [21] and report the accuracy of national hospital data with greater granularity and a lower rate of missing reference data than previous studies [37]. Our reference data collected by trained research nurses is likely to be accurate and reflects standard practice in most clinical research studies.

We acknowledge this study's limitations. Study comorbidity was used as a gold standard, and although data validation suggested a high concordance between staff this source may still contain errors. Current HES data quality may differ from the 2006–2013 dataset used here. A rise in the number of completed coding fields in HES over time could yield greater data accuracy, but the possibility of over-diagnosis should be considered [37, 38].

In conclusion, the routinely collected HES dataset captured comorbidity information in 96% of individuals before the start of KRT, but there is variation in data accuracy. HES data were accurate for more prevalent conditions, but less suitable for recording a full complement of comorbidities. Understanding patterns of comorbidity among people with advanced kidney disease is crucial in informing policy and service planning, and in shared decision-making with patients. Our work will inform the use of routinely collected data to improve the efficiency of future research.

Abbreviations

APC: Admitted patient care; ATTOM: Access to Transplant and Transplant Outcome Measures study; CKD: Chronic kidney disease; ED: Emergency department; HES: Hospital Episode Statistics; ICD-10: International Classification of Diseases version 10; IQR: Interquartile range; NHS: National Health Service; NPV: Negative predictive value; KRT: Kidney replacement therapy; OP: Outpatient; OPCS-4: Office for Population Censuses and Surveys Classification of Interventions and Procedures version 4; OR: Odds ratio; PPV: Positive predictive value; PRD: Primary renal disease; UKRR: UK Renal Registry

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12882-021-02301-5.

Additional file 1.

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Authors' contributions

AN performed the analyses, produced the tables, and wrote the manuscript under the supervision of DMT and RR. RS assisted with statistical analyses and contributed to manuscript preparation. All authors read and approved the final manuscript.

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Availability of data and materials

The HES dataset analysed during the current study is not publicly available and cannot be shared at a patient level as per the NHS Digital data sharing agreement. Analysis codes and ATTOM summary datasets are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Ethical approval for the ATTOM study was obtained from the National Health Service Health and Social Care Research Ethics Committee (Ref: 11/EE/0120). Patients provided informed consent at ATTOM recruitment that they were happy for subsequent analysis of outcomes. All data were stored in line with the United Kingdom Data Protection Act 1998 requirements. HES data were stored securely in NHS Blood and Transplant as per the data sharing agreement with NHS Digital (Data Sharing Agreement Number DARS-NIC-14342-Q8W0X-v1.4).

Consent for publication

Not applicable.

Competing interests

The authors, other than RS, 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. RS declares no conflicts of interest.

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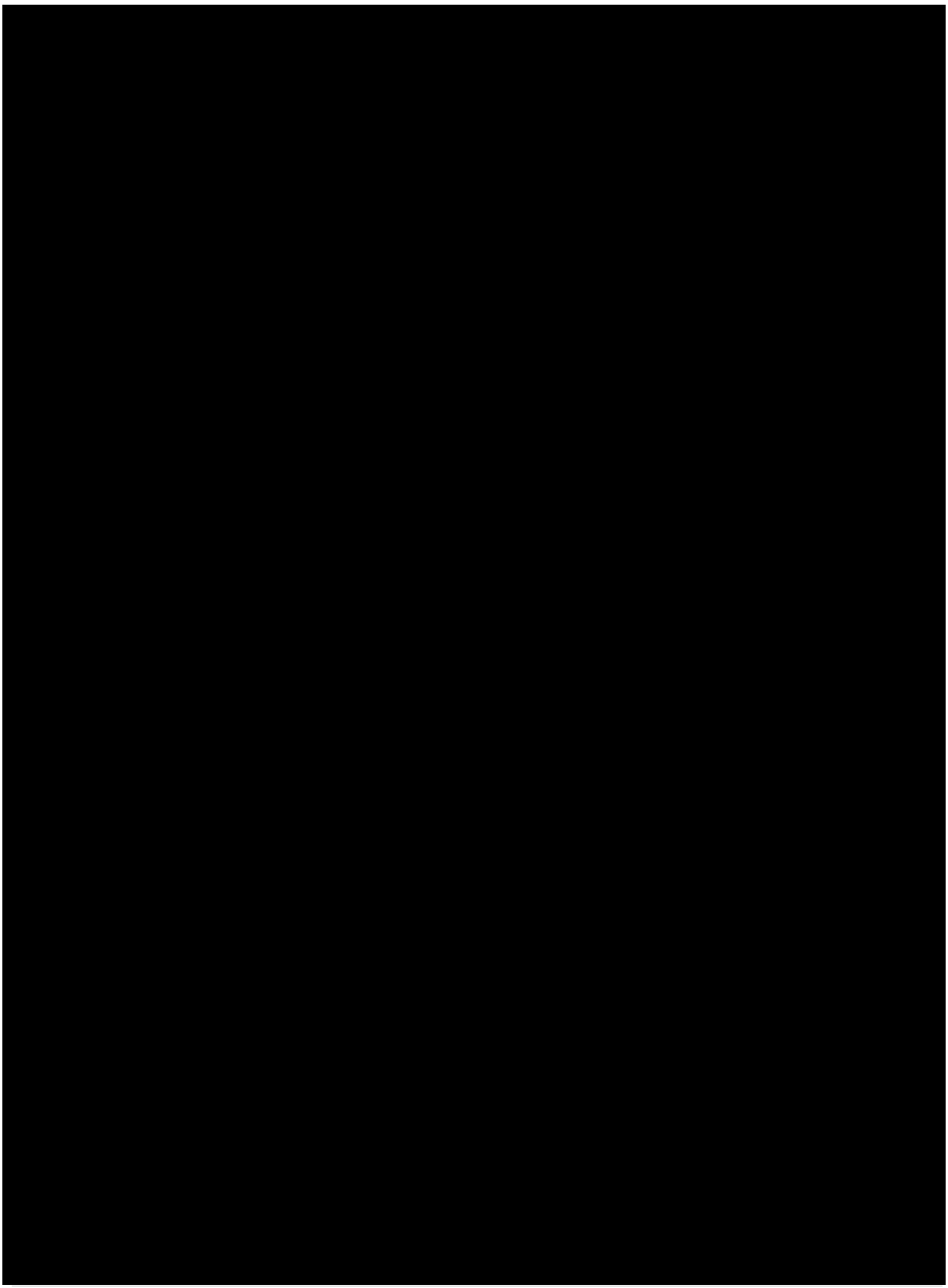

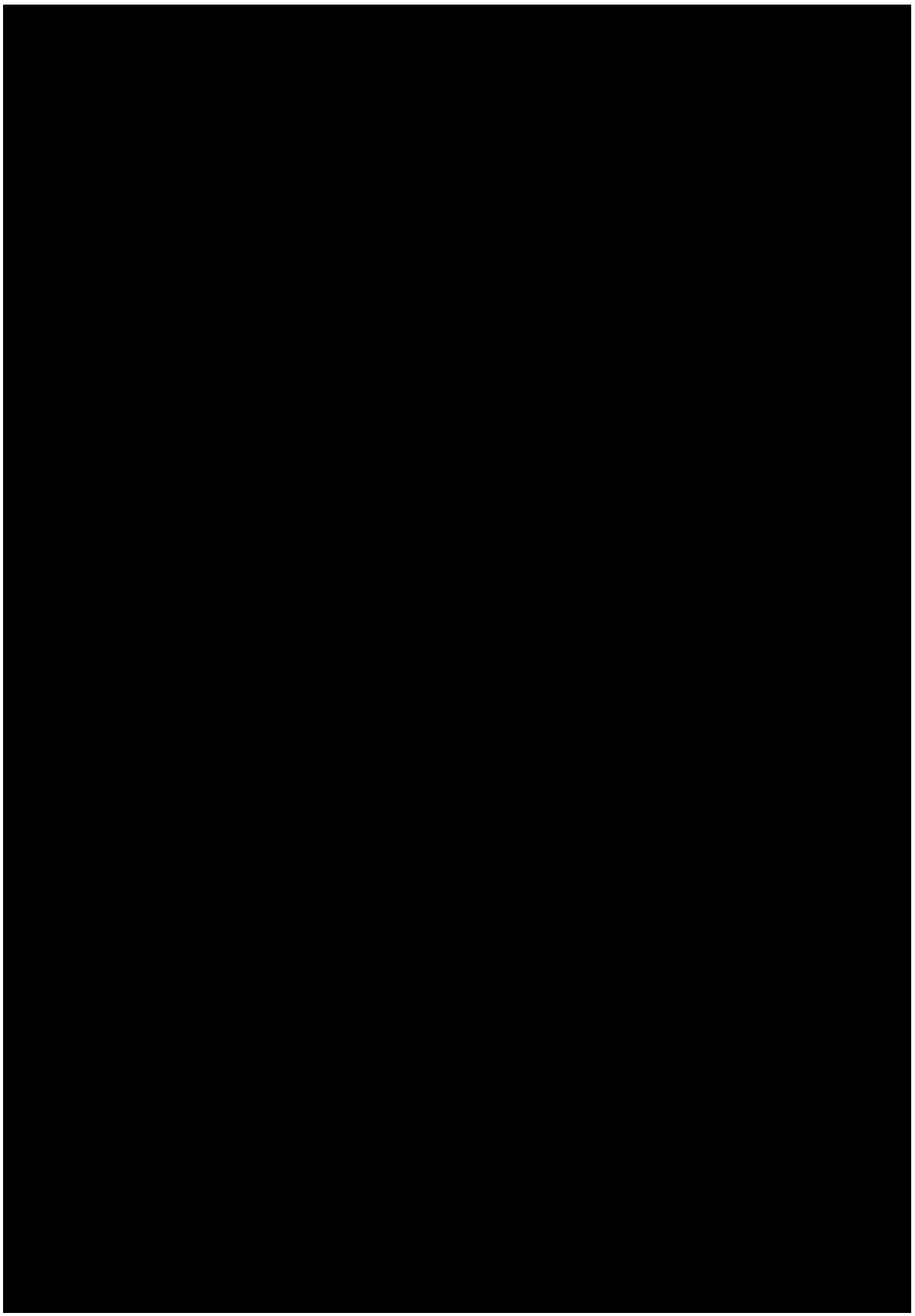

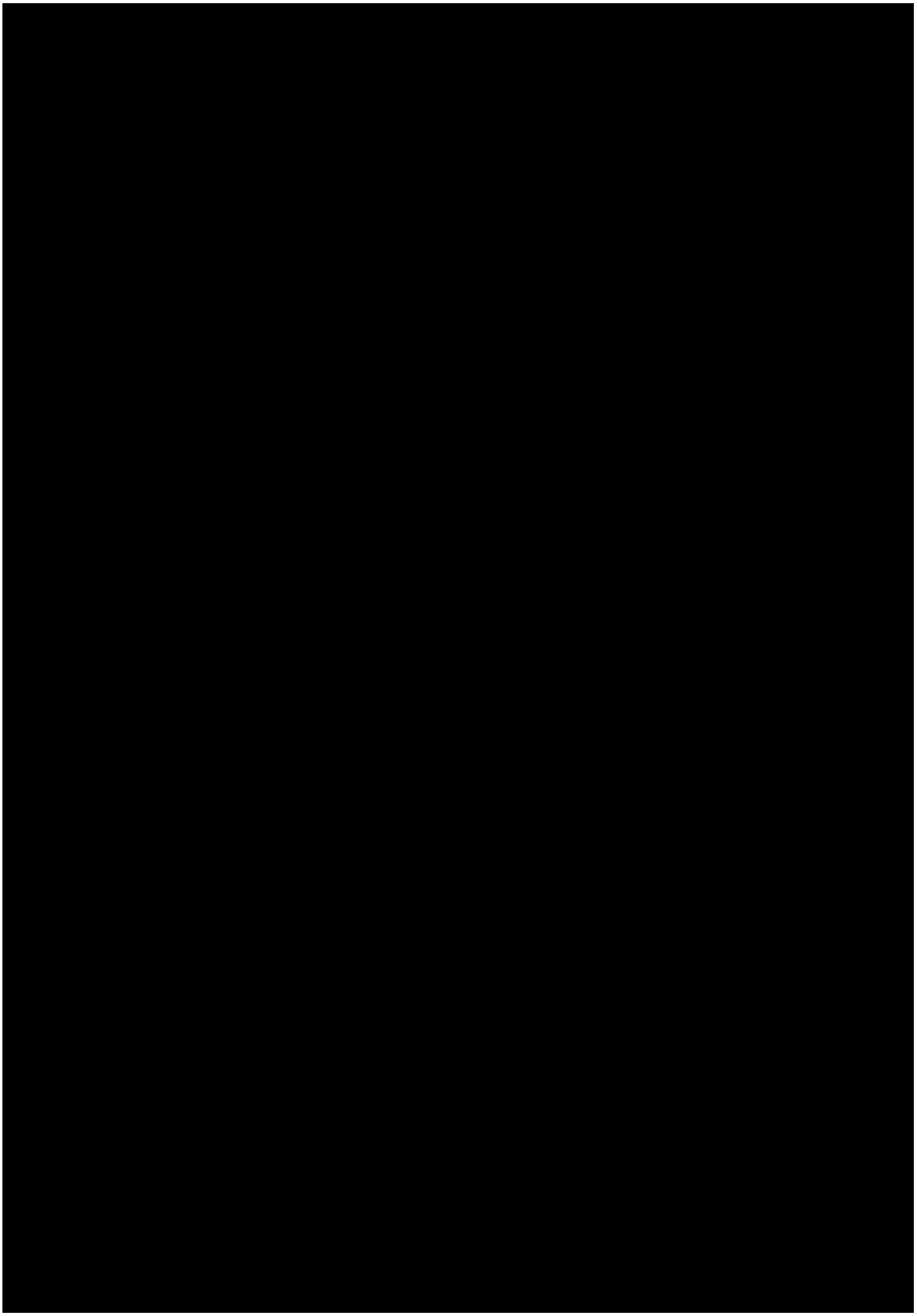

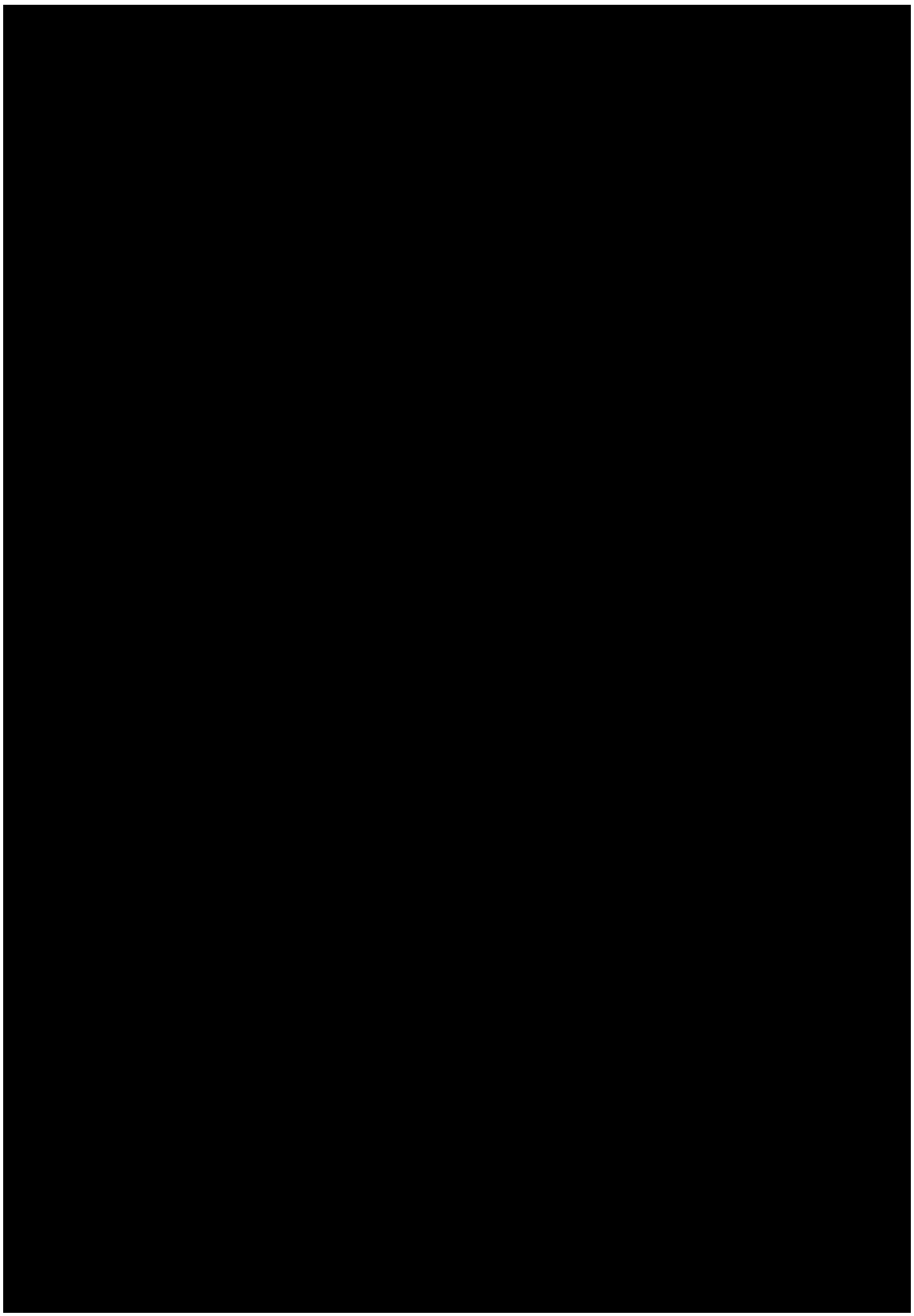

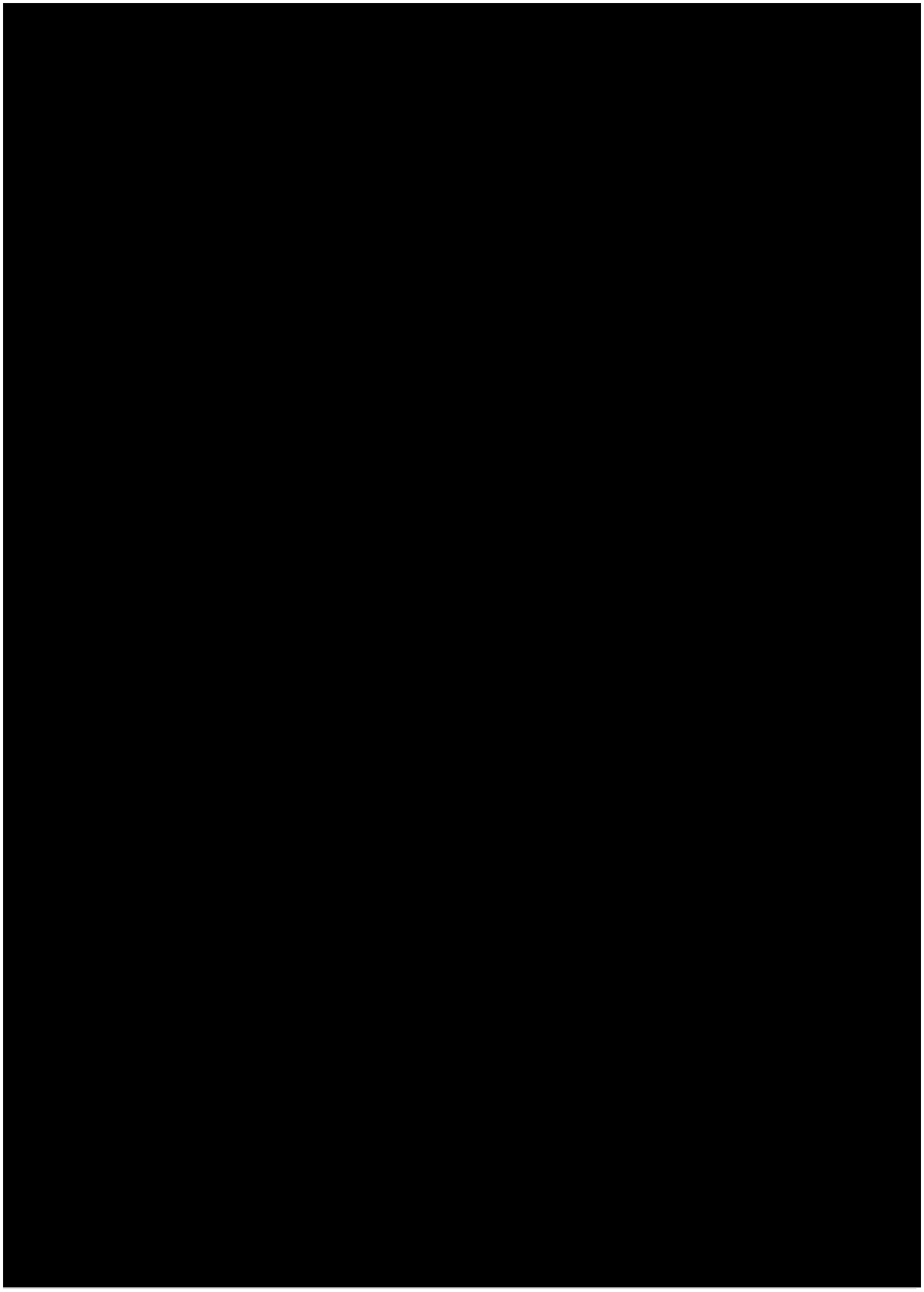

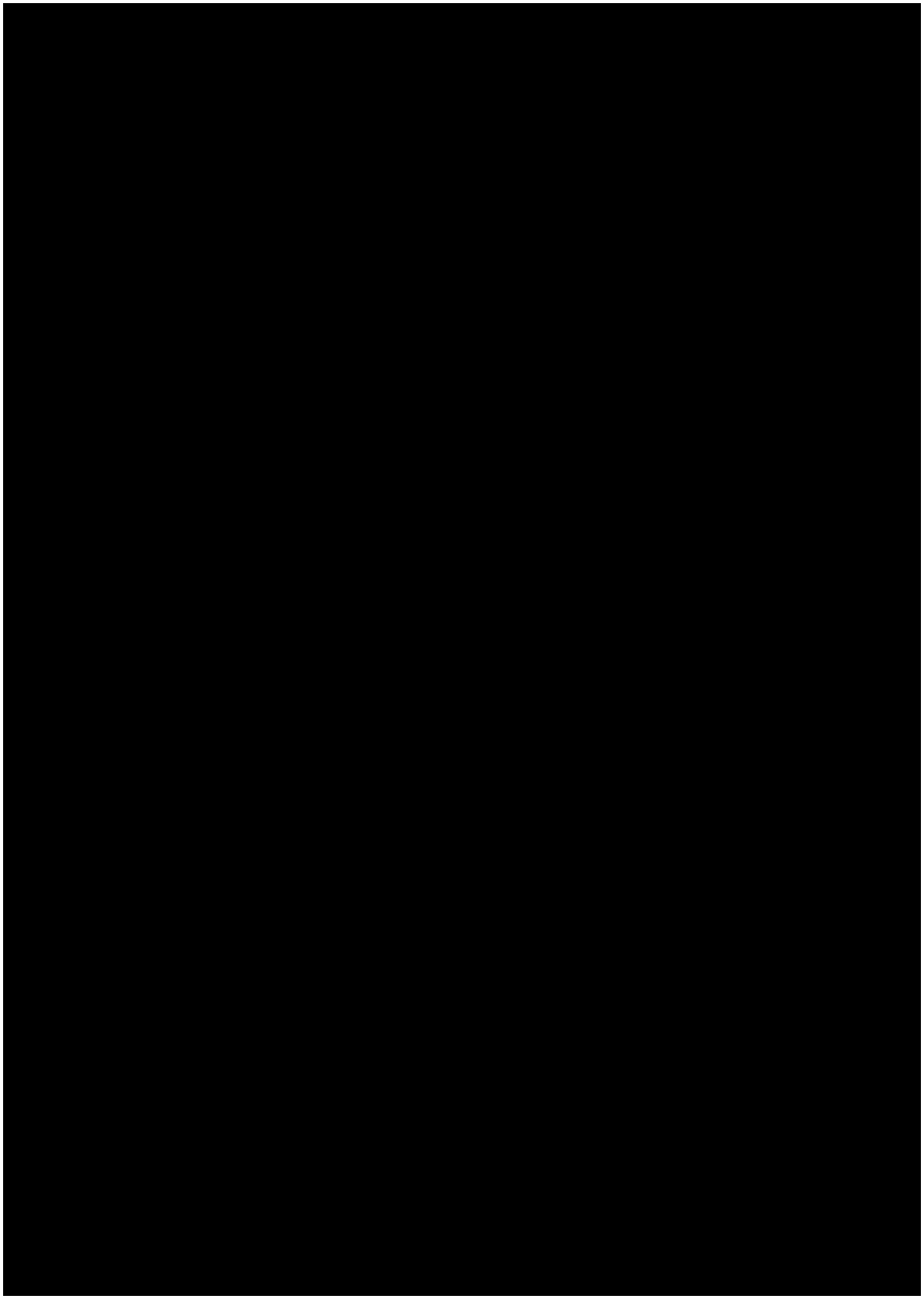

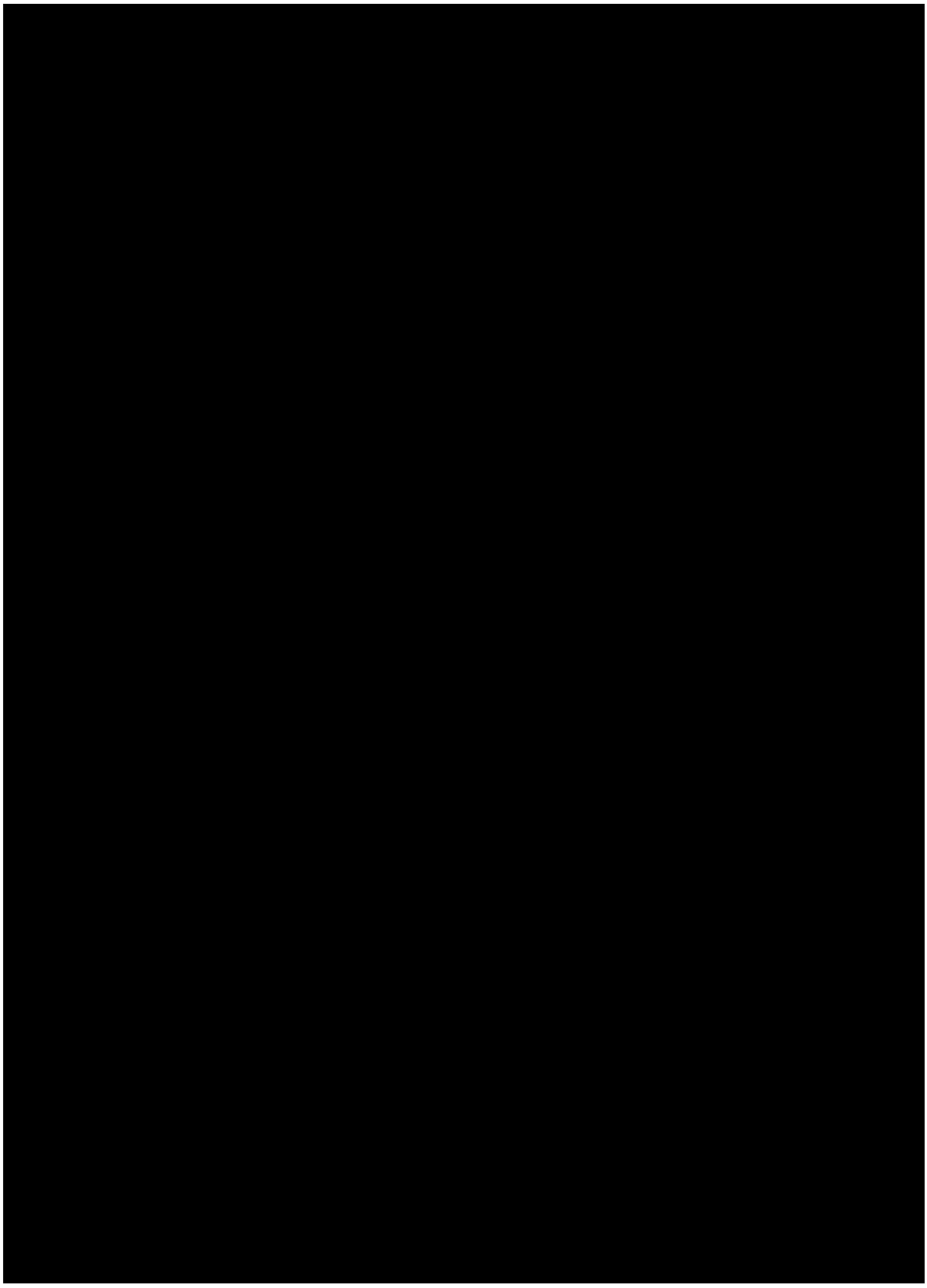

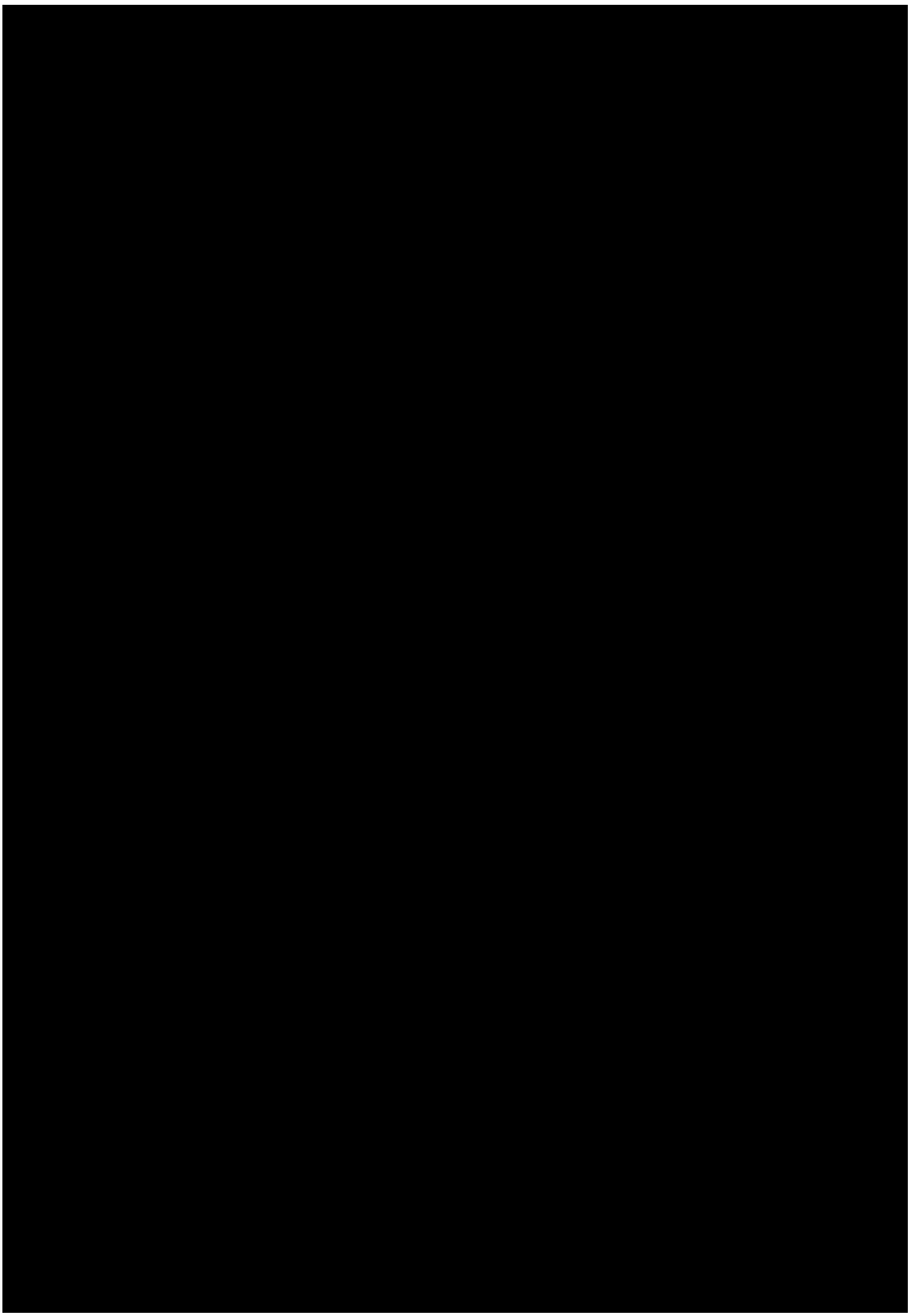

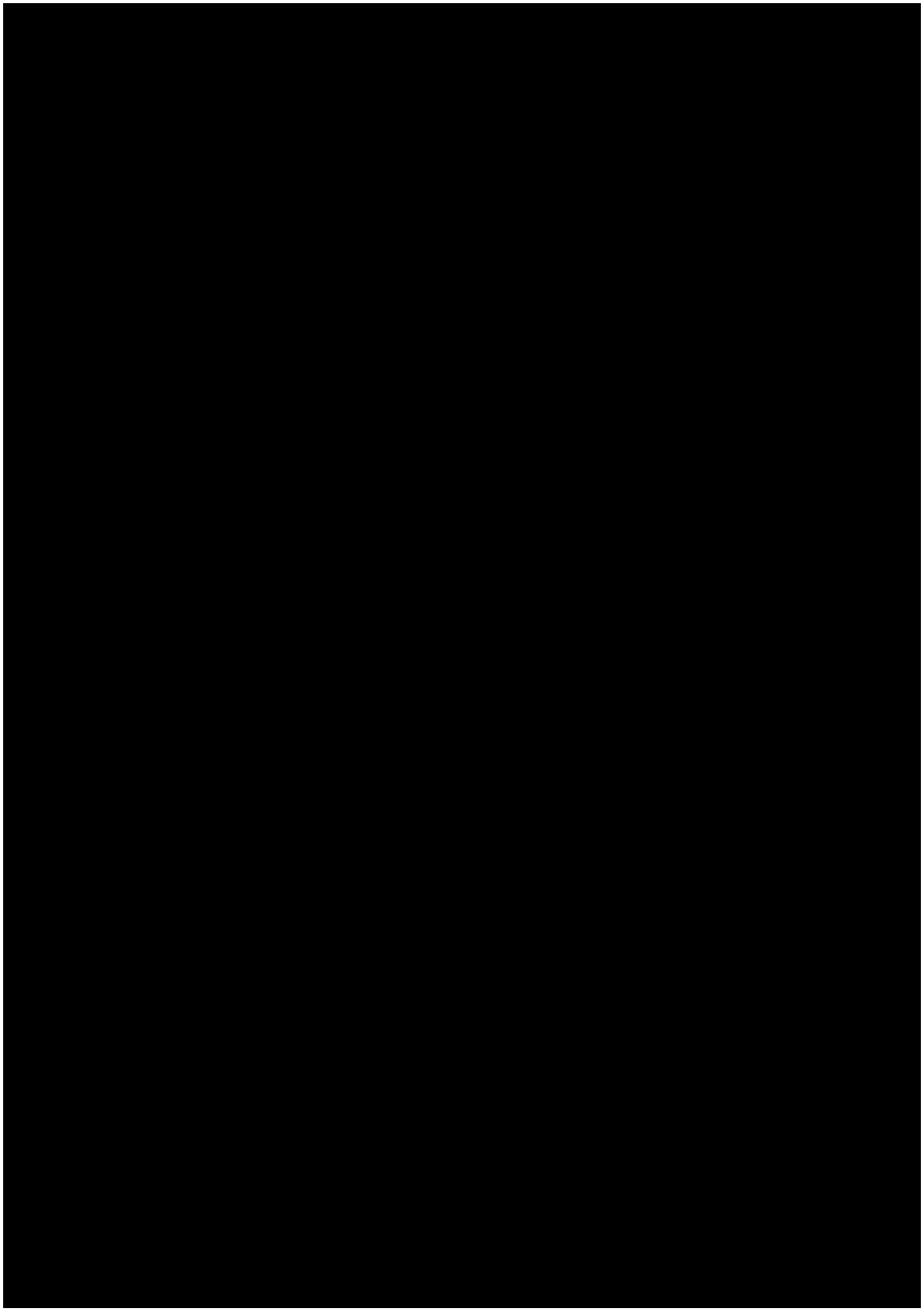

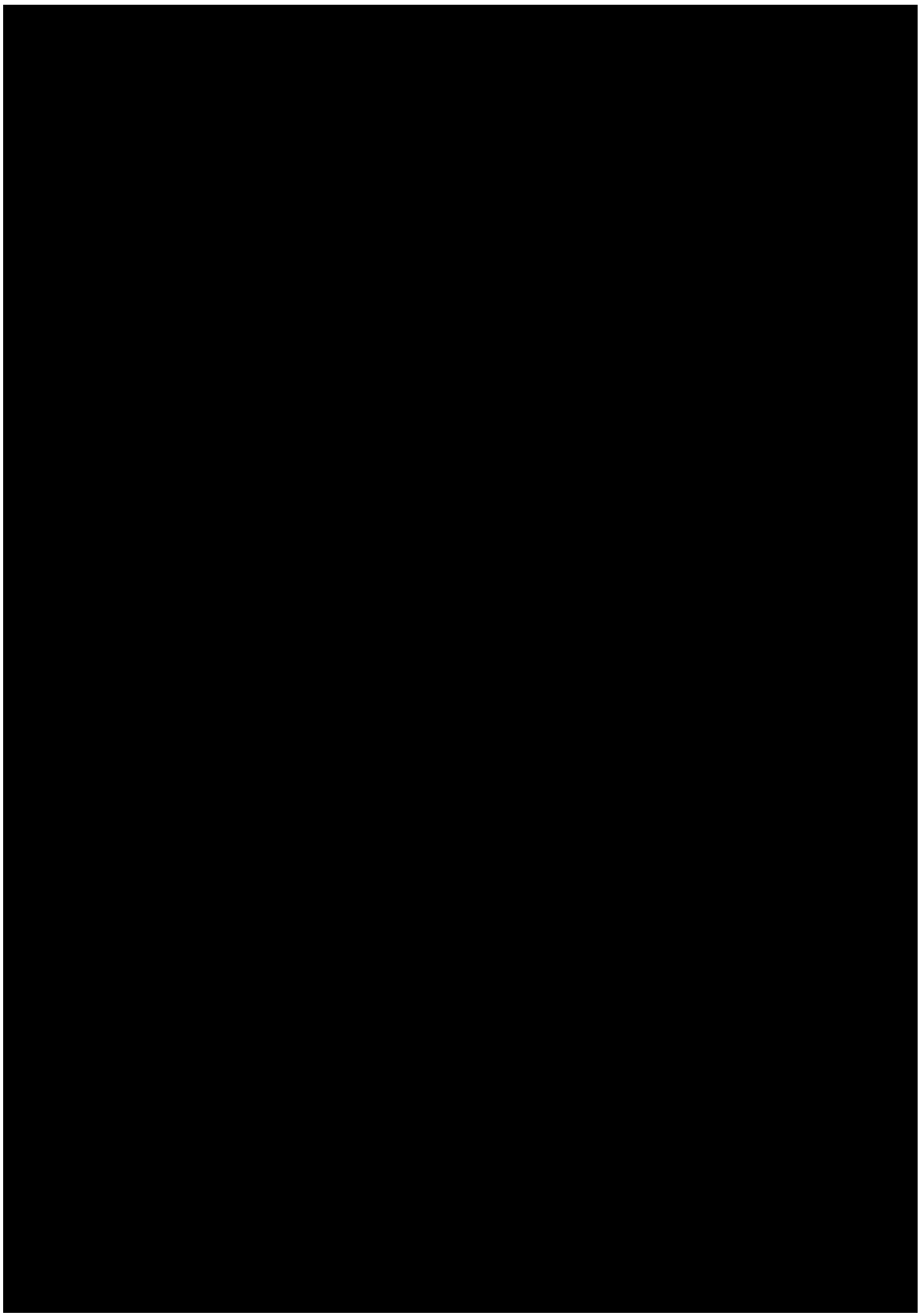

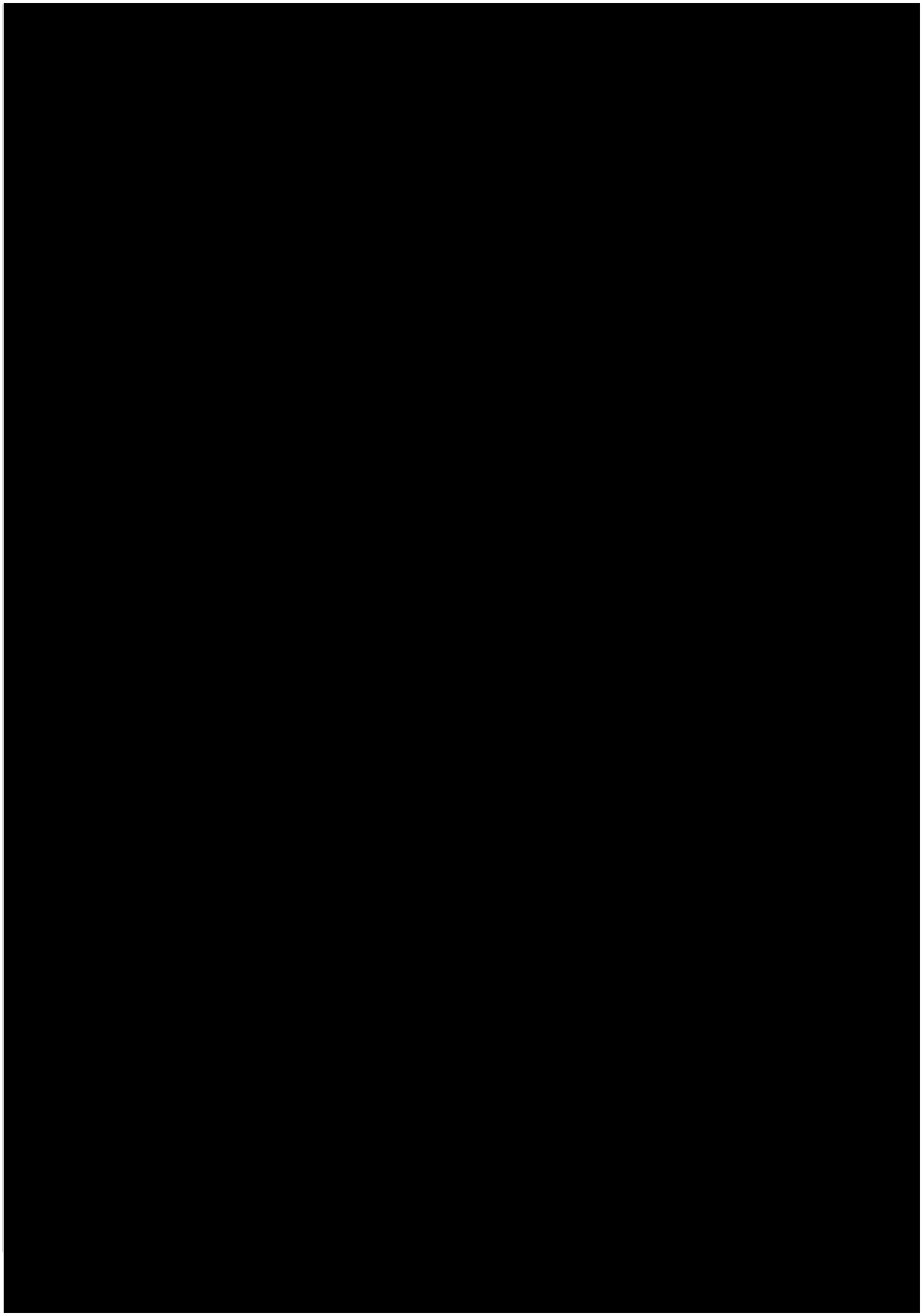

Letters to the editor

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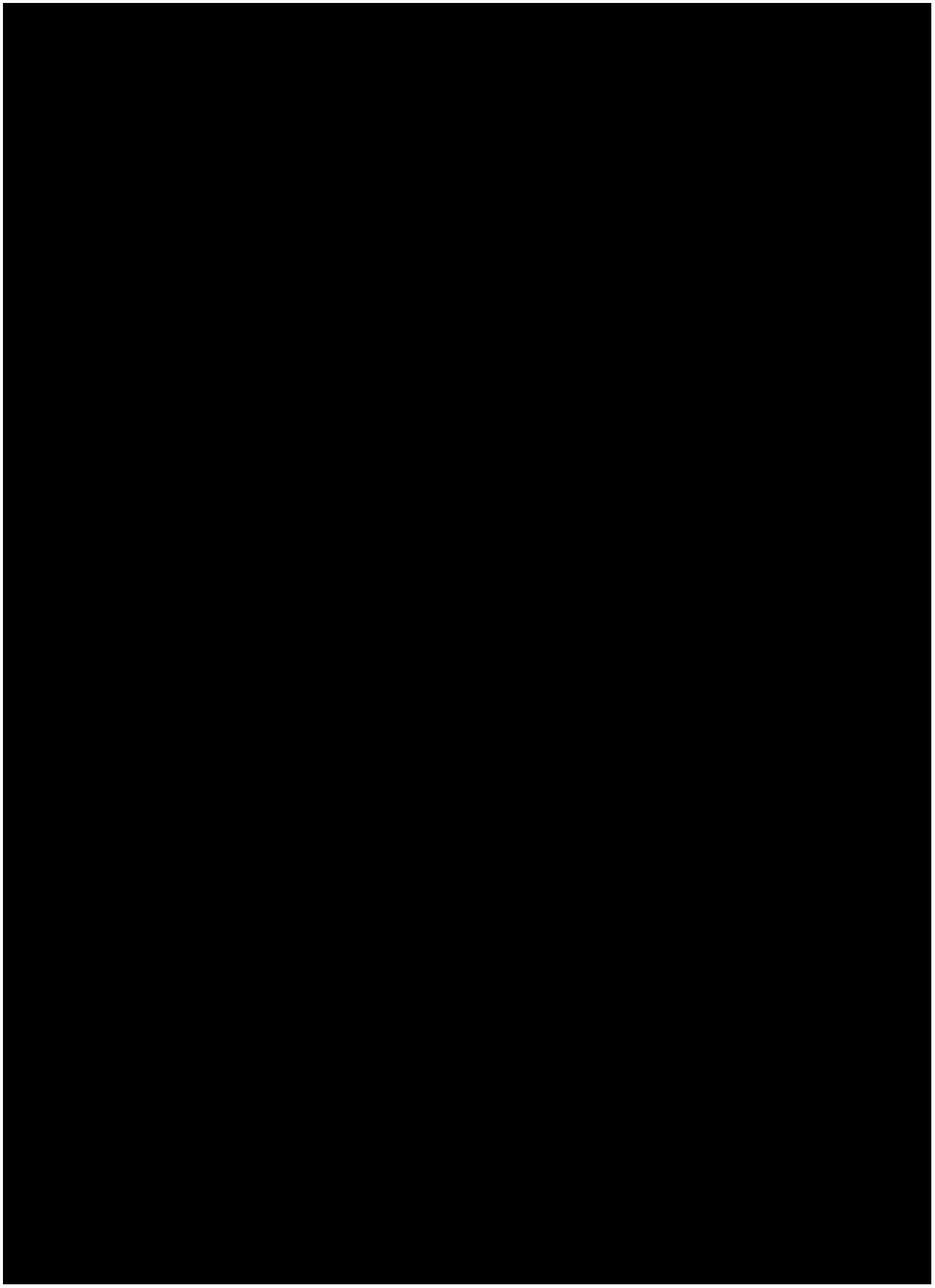

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LETTER TO THE EDITOR
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Pre-Kidney Transplant Screening for Coronary Artery Disease: Current Practice in the United Kingdom

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Dear Editors,

Randomised control trial (RCT) evidence is not available to guide screening for asymptomatic coronary artery disease before kidney transplantation [1]. United Kingdom observational data show no clear benefit from screening [2]. To gain data representative of current practice in the United Kingdom, we invited a lead transplant nephrologist from each kidney transplant centre to complete a survey examining cardiac screening practice, work-up pathways, and appetite for a national RCT in June 2021. Ethical approval was not required.

Responses were received from all 23 (100%) centres, of which 22 had a protocol for cardiac assessment prior to listing. In three centres, asymptomatic individuals were not required to undergo cardiac investigation beyond an ECG or echocardiogram prior to transplantation. The remainder followed a risk-stratified approach; no centres performed universal screening.

In centres adopting risk-stratified screening, factors used to screen patients included a history of ischaemic heart disease (100% of centres), diabetes (100%), peripheral vascular disease (50%), smoking (50%), stroke (35%), limited exercise capacity (35%), hyper/hypotension (15%), or an abnormal echocardiogram (95%) or ECG (70%). Two centres stratified using the Newcastle Risk Index [3]. Thirteen centres had a specific age threshold (mostly 50 or 60 years), whilst others included age in combination with additional risk factors or Newcastle Risk Index scores.

The most frequent screening investigation was a myocardial perfusion scan (55%) followed by stress echocardiogram (20%). Coronary angiography and cardiopulmonary exercise testing were the initial investigation in one centre each. Other indications for coronary angiography included an abnormal initial screening test (39%) or on cardiology advice (35%). In one third of centres, the waiting time for investigations was over 10 weeks.

Nine centres had cardio-renal multidisciplinary meetings, whilst 14 had a designated cardiologist providing transplant candidate assessments. In 16 centres cardiology review was only needed for patients with abnormal screening tests, whilst in three cardiologists reviewed all screened patients.

Of 23 centres, 10 had updated their screening protocol within the past 2 years and three were in the process of an update. Whilst 19 centres reported experience of patient declines from listing based on an abnormal screening test, this amounted to one patient per month or less in 11 centres.

Respondents commented on the challenges of outdated evidence, reliance on observational data, and differences between real-world cohorts and RCT study populations when assessing the evidence for cardiac screening. The importance of cardio-renal meetings was noted in units not adopting

Abbreviations: ECG, Electrocardiogram; RCT, Randomised controlled trial.

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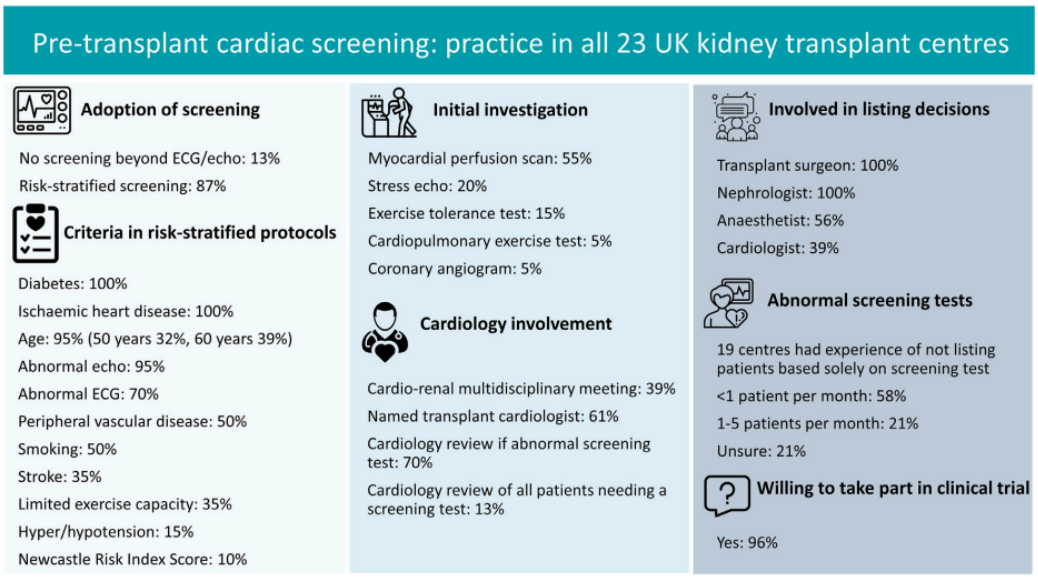

FIGURE 1 | Summary of findings from survey of pre-transplant cardiac screening.

screening. Of 23 centres, 22 expressed interest to participate in an RCT to examine the utility of screening, 12 of whom supported recruiting the highest cardiac risk candidates.

Our survey highlights variation in screening practice across the United Kingdom (**Figure 1**). Similar heterogenous practice has been shown in the United States [4], although our survey was undertaken following publication of ISCHEMIA-CKD [5]. Whilst no centres perform universal screening and many have recently updated their protocols, which may represent a trend away from routine screening, responses highlight nephrologists' concerns over the evidence upon which practice is based. Capturing views of other transplant professionals and patients is essential, but this survey suggests support for an RCT to evidence utility of screening.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

All authors contributed to study design and writing of the survey questions. AN performed the analyses, produced the figure and wrote the letter under the supervision of RR and DT. All authors contributed to manuscript preparation.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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