Major Adverse Cardiovascular Events Following Simultaneous Pancreas and Kidney Transplantation in the United Kingdom

Petros Yiannoullou,[1,2] Angela Summers,[1,2] Shu C. Goh,[2] Catherine Fullwood,[3] Hussein Khambalia,[1,2] Zia Moinuddin,[1,2] Iestyn M. Shapey,[1,2] Josephine Naish,[4,5] Christopher Miller,[4,5,6] Titus Augustine,[1,2] Martin K. Rutter,[2,7] and David van Dellen[1,2]

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OBJECTIVE

People with type 1 diabetes and kidney failure have an increased risk for major adverse cardiovascular events (MACE). Simultaneous pancreas and kidney transplantation (SPKT) improves survival, but the long-term risk for MACE is uncertain.

RESEARCH DESIGN AND METHODS

We assessed the frequency and risk factors for MACE (defined as fatal cardiovascular disease and nonfatal myocardial infarction or stroke) and related nonfatal MACE to allograft failure in SPKT recipients with type 1 diabetes who underwent transplantation between 2001 and 2015 in the U.K. In a subgroup, we related a pretransplant cardiovascular risk score to MACE.

RESULTS

During 5 years of follow-up, 133 of 1,699 SPKT recipients (7.8%) experienced a MACE. In covariate-adjusted models, age (hazard ratio 1.04 per year [95% CI 1.01–1.07]), prior myocardial infarction (2.6 [1.3–5.0]), stroke (2.3 [1.2–4.7]), amputation (2.0 [1.02–3.7]), donor history of hypertension (1.8 [1.05–3.2]), and waiting time (1.02 per month [1.0–1.04]) were significant predictors. Nonfatal MACE predicted subsequent allograft failure (renal 1.6 [1.06–2.6]; pancreas 1.7 [1.09–2.6]). In the subgroup, the pretransplant cardiovascular risk score predicted MACE (1.04 per 1% increment [1.02–1.06]).

CONCLUSIONS

We report a high rate of MACE in SPKT recipients. There are a number of variables that predict MACE, while nonfatal MACE increase the risk of subsequent allograft failure. It may be beneficial that organs from hypertensive donors are matched to recipients with lower cardiovascular risk. Pretransplant cardiovascular risk scoring may help to identify patients who would benefit from risk factor optimization or alternative transplant therapies and warrants validation nationally.

Type 1 diabetes affects ~400,000 people in the U.K. (1). Type 1 diabetes significantly reduces life expectancy predominantly because of cardiovascular disease (CVD) complications (2,3). The addition of chronic kidney disease further increases CVD risk (4). We have shown that simultaneous pancreas and kidney transplantation (SPKT)

[1]Department of Renal and Pancreatic Transplantation, Manchester University NHS Foundation Trust, Manchester, U.K.
[2]Division of Diabetes, Endocrinology and Gastroenterology, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, U.K.
[3]Centre for Biostatistics, Division of Population Health, Health Services Research and Primary Care, School of Health Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester Academic Health Science Centre, Research and Innovation, Manchester University NHS Foundation Trust, Manchester, U.K.
[4]Division of Cardiovascular Sciences, School of Medical Sciences, Faculty of Biology, Medicine and Health, Manchester Academic Health Science Centre, University of Manchester, Manchester, U.K.
[5]Wellcome Centre for Cell-Matrix Research, Division of Cell-Matrix Biology and Regenerative Medicine, School of Biology, Faculty of Biology, Medicine and Health, Manchester Academic Health Science Centre, University of Manchester, Manchester, U.K.
[6]North West Heart Centre, Manchester University NHS Foundation Trust, Manchester, U.K.
[7]Manchester Diabetes Centre, Manchester University NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, U.K.

Corresponding author: Petros Yiannoullou, petros.yiann@icloud.com

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M.K.R. and D.v.D. contributed equally to this work.

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improves survival in recipients compared with those individuals on the waiting list (5). However, there are limited data on the long-term risk for major adverse cardiovascular events (MACE) in contemporary SPKT cohorts (6,7).

Cardiovascular death with a functioning graft (DWFG) accounts for a large proportion of allograft loss in transplant populations (8,9). However, the relationship between nonfatal cardiovascular events and subsequent allograft loss in SPKT recipients is unknown.

The QRISK2 calculator was developed within the U.K. general population to estimate an individual's 10-year risk of CVD, without modification of risk factors. The QRISK2 variables include modifiable and nonmodifiable factors, ethnicity, and level of social deprivation estimated from an individual's U.K. postal code (Supplementary Table 1) (10). A score of $\geq$10% is the current threshold for statin therapy; a score of $\geq$20% is considered severe risk (10). Its ability to predict MACE in SPKT recipients has never been assessed.

We aimed to assess the long-term risk for MACE and identify associated risk factors in the full U.K. cohort of SPKT recipients. We also aimed to relate posttransplant nonfatal MACE to subsequent allograft loss. In a Manchester-based subgroup, we aimed to relate a pretransplant QRISK2 score to MACE.

RESEARCH DESIGN AND METHODS

Cohort, Exposures, and Covariates

The National Health Service Blood and Transplant (NHSBT) prospectively records recipient and donor data, from all U.K. centers, into the UK Transplant Registry (UKTR) (11). All SPKT recipients with type 1 diabetes who were $\geq$18 years of age and had undergone transplantation between 2001 (the first year of robust national data) and 2015 were included.

Type 1 diabetes was confirmed using C-peptide measurement in the majority of cases; however, some centers used clinical parameters such as age of onset. Surgical technique and immunosuppressive regimens were not standardized.

To obtain more detailed patient profiling and cardiovascular risk factor data, further information for a subset of the total population was collated from the electronic patient records and case notes at a single U.K. transplant center in Manchester. Cardiovascular risk was calculated from pretransplant variables using the QRISK2-2017 calculator available at https://qrisk.org/2017/.

Current or ex–tobacco smokers were defined as having a history of tobacco smoke exposure. We defined unemployed as being able to work but not working or unable to work because of disease. Amputation was defined as limb or digit amputation. For the local cohort, retinopathy was defined as preproliferative or proliferative changes or maculopathy. An ankle-brachial pressure index score $\leq$0.9 or the presence of flow-limiting arterial stenosis on angiography was used to identify patients with peripheral arterial disease.

No ethical approval was required for this study as only restricted data were requested in accordance with NHSBT data access policy available at http://www.odt.nhs.uk/statistics-and-reports/data-access-policy/. As per the National Health Service Code of Practice on Confidentiality and in accordance with the Declaration of Helsinki (https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/), NHSBT prospectively obtained informed consent from transplant candidates for inclusion of their data in the UKTR database. Informed consent is also obtained by NHSBT for the use of restricted data (nonidentifiable data) by third parties for the purpose of transplant-related research.

Patients were excluded if they had received any prior transplant.

All cases were closed for analysis on the 27 April 2017.

Outcomes

The primary outcome measure was the first recorded MACE following transplantation. MACE was defined as fatal CVD (ICD-10 codes: I11, hypertensive heart disease; I20–I25, ischemic heart diseases; I42 + I43, cardiomyopathies [excluding infectious, familial, alcohol, and drug-related cardiomyopathies]; I44 + I45, conduction disorders; I46.1, sudden cardiac death; I50, heart failure; I51, complications of heart disease [excluding myocarditis]; and I61–I69, [cerebrovascular diseases excluding subarachnoid hemorrhage]) or nonfatal myocardial infarction (MI) and/or nonfatal stroke.

The General Register Office of the U.K. Government records the details of all U.K. deaths into the Register of Births, Deaths, and Marriages from death certificates. The Office for National Statistics (ONS) is the recognized national statistical institute of the U.K. It quality assures mortality data and provides data reports. To improve the completeness and accuracy of outcome data, cause of death data were obtained from the ONS and linked at patient level by the NHSBT.

Nonfatal MACE is recorded into the UKTR using forms that are completed annually by clinicians or transplant coordinators. The event time for nonfatal events was taken as the midpoint between annual follow-up appointments.

We analyzed a secondary outcome of fatal CVD.

A tertiary outcome of allograft loss was included for analysis. The definition of pancreas allograft failure varies among centers: some use C-peptide measurement, while others use a return to exogenous insulin use. The NHSBT records pancreas survival to the earlier of those definitions or death. Kidney allograft survival is determined as the earlier date between return to dialysis or death.

Statistical Methods

Parameters are expressed as the mean (SD) or median (interquartile range [IQR]) as appropriate. Continuous variables were compared using either the Student *t* test or Mann-Whitney *U* test. Categorical variables were compared using the Pearson χ^2 or Fisher exact test. Survival analyses were visualized using Kaplan-Meier plots.

Cox regression models were used to relate covariates to MACE and cardiovascular mortality. Covariates were tested for colinearity using the Pearson correlation coefficient or χ^2 test and were included in multivariable models if they were considered clinically important or if univariable *P* values were $\leq$0.1.

Immortal-time bias can arise from inappropriate handling of the time interval between the start of follow-up and an exposure (Supplementary Fig. 1) (12). To overcome immortal-time bias when exploring the relationship with subsequent allograft loss, we used an extended Cox model with a time-dependent definition for nonfatal MACE (12,13).

All analyses were performed using SPSS Statistics (version 22; Armonk,

NY). A two-tailed *P* value of ≤0.05 was considered to be statistically significant.

Missing Values

Aside from BMI (26.4%) and employment status (24.9%), patient-level data were missing in <5% of individuals. For the local cohort, patient-level data were missing in ≤4% of individuals. All missing values were considered missing at random and complete case analyses were performed.

RESULTS

We identified 1,699 patients with type 1 diabetes who received their first SPKT between 2001 and 2015 (mean age 41.6 [SD 8.3] years; 59% male; 6.3% with prior MI or stroke) with a median follow-up of 5.0 years (IQR 2.7–8.4 years). During the observation period, the use of alemtuzumab induction immunosuppression increased from 12.1% of recipients in 2001–2005 to 68.7% in 2011–2015, while the use of other agents decreased. Furthermore, the use of maintenance immunosuppression regimens containing prednisolone decreased (Supplementary Table 2).

MACE occurred in 133 individuals (7.8%) in the total UKTR cohort (1.4% per annum [p.a.]). CVD accounted for 31.2% of deaths (74 of 237 deaths; 4.4% overall; 0.8% p.a.). Ischemic heart disease accounted for the majority of MACE (56.4%) (Supplementary Table 3). The median time to MACE was 913 days (IQR 138–1,606 days). The peak frequency of events occurred 133 days following transplantation. A second peak occurred 866 days posttransplant (Supplementary Fig. 2). There was no significant difference in the types of events experienced at each time point (peak 1 vs. peak 2 $P = 0.391$).

Table 1 shows the recipient and donor characteristics by MACE outcomes. In the UKTR cohort, those individuals experiencing a MACE were older and more likely to have had a history of MI or stroke. They had an earlier year of transplant and longer pancreas cold ischemia time (CIT), and more individuals had received organs from hypertensive donors. A smaller proportion of individuals received alemtuzumab induction immunosuppression, while more received maintenance immunosuppressive regimens containing prednisolone. Furthermore, fewer individuals in the MACE group had received organs donated after cardiac death (DCD) and expanded criteria donor (ECD) kidneys.

Recipients of DCD and ECD organs had a more recent year of transplantation compared with recipients of organs from donors with brainstem death and standard criteria donors (DCD vs. donors with brainstem death 2012 [range 2010–2014] vs. 2009 [range 2006–2012], $P < 0.001$; ECD vs. standard criteria donor 2015 [range 2015–2015] vs. 2009 [range 2007–2012], $P < 0.001$).

Within the Manchester subgroup ($n = 306$), 23 patients (7.5%) experienced a MACE, of which 8 MACE (34.7%) were fatal. The median time to a MACE was 905 days (IQR 116–2,000 days). Patients were followed for a median of 5.7 years. Those experiencing a MACE were more likely to be older; to be receiving treatment with antihypertensive and antiplatelet medications; to have an earlier year of transplantation, a history of MI, and a higher QRISK2 score; and to have received prednisolone-based maintenance immunosuppression therapy. Patients were less likely to have received alemtuzumab induction immunotherapy (Table 1). The QRISK2 score was ≥20 in 205 patients (67.0%) in the Manchester cohort, of whom 85 (41.5%) were receiving antiplatelet medications, 110 (53.7%) were receiving lipid-lowering treatment, and 171 (83.7%) were receiving treatment with antihypertensive medications. In patients with a systolic blood pressure (SBP) of ≥130 mmHg, 74.0% (94 of 127) were receiving antihypertensive treatment. Patients receiving antiplatelet treatment were more likely to have a history of CVD at baseline (57.9% [22 of 38 patients] vs. 32.5% [87 of 268 patients], $P < 0.001$).

In the full UKTR cohort, the univariable predictors of MACE were recipient age, prior MI, prior stroke, prior amputation, donor history of hypertension, pancreas CIT, and prednisolone-based maintenance immunosuppression therapy. Advancing year of transplantation was associated with a 10% lower risk for MACE per year (Table 2). Tobacco smoking (hazard ratio [HR] 1.3 [95% CI 0.8–2.0], $P = 0.248$), sex (female vs. male 1.0 [0.7–1.4], $P = 0.994$), and ethnicity (nonwhite vs. white 0.9 [0.4–1.4], $P = 0.669$) were not significant. DCD and ECD organs were not included in the Cox regression models as they were highly correlated with the year of transplantation (Pearson correlation coefficient = 0.992 and 0.991, respectively; $P < 0.001$). In the multivariable model, waiting time became a significant hazard (2% increase in risk per month), while pancreas CIT and prednisolone lost significance (Table 3).

The predictors of fatal CVD were recipient age and history of MI, stroke, and amputation. In the multivariable model, unemployment and a donor history of hypertension remained significant hazards, while blindness became a significant factor. Prednisolone was not related to fatal CVD (Table 4).

Pancreas allograft loss was recorded in 507 of patients (29.8%), of which 155 incidents of loss were due to DWFG. Kidney allograft loss was recorded in 371 patients (21.8%; 149 DWFG). A nonfatal MACE conferred an additional 60% risk for subsequent all-cause kidney allograft failure (HR 1.6 [95% CI 1.06–2.6], $P = 0.027$) and 70% for all-cause pancreas allograft failure (1.7 [1.09–2.6], $P = 0.018$).

Table 2 shows the univariable predictors for MACE in the Manchester subgroup ($n = 306$). Again, recipient age, prior MI, and year of transplantation were significant factors. A history of peritoneal dialysis was associated with a fivefold increase in MACE risk, while receiving antiplatelet therapy was associated with four times the risk. Alemtuzumab reduced MACE risk by 80%, while prednisolone-based maintenance immunosuppression therapy was associated with three times the risk. Each 1% increase in the pretransplant QRISK2 score was associated with a 4% increase in posttransplant MACE risk. A QRISK2 score >20% conferred an 11-fold increased risk (Table 2 and Supplementary Fig. 3). In age-adjusted models, a history of MI, peritoneal dialysis, antiplatelet therapy, alemtuzumab therapy, prednisolone therapy, and year of transplantation remained significant. The HR for total cholesterol/HDL ratio (1.3 [95% CI 0.998–1.7], $P = 0.052$) approached significance (Supplementary Table 4). Alemtuzumab and prednisolone became insignificant factors in models adjusting for the year of transplantation (0.6 [0.1–3.2], $P = 0.534$; 1.3 [0.3–6.0], $P = 0.774$, respectively).

The QRISK2 score demonstrated acceptable discrimination for MACE with an area under the receiver operating

Table 1—Recipient and donor characteristics in UKTR SPKT recipients and the Manchester subgroup by MACE outcome

	All UKTR SPKT recipients (n = 1,699)			Manchester SPKT subgroup (n = 306)		
Characteristic	MACE (133 [7.8])	No MACE (1,566 [92.2])	P value	MACE (23 [7.5])	No MACE (283 [92.5])	P value
Recipient factors						
Age at transplant, years [mean (SD)]	43.1 (8.4)	41.5 (8.3)	0.034	47.5 (7.8)	41.0 (9.2)	0.008
Male	79 (59.4)	920 (58.7)	0.884	12 (52.2)	172 (60.8)	0.418
Nonwhite ethnicity	8 (6.0)	117 (7.5)	0.633	4 (17.4)	19 (6.7)	0.082
BMI, kg/m^2	25.0 (22.3–27.4)	24.6 (22.1–27.2)	0.920	26.2 (22–27)	24.8 (22–27)	0.491
Tobacco smoke exposure	57 (42.8)	615 (39.3)	0.561	3 (13.0)	34 (12.0)	0.748
Unemployed	64 (48.1)	675 (43.1)	0.371	NA	NA	
Registered blind	18 (13.5)	136 (8.7)	0.065	3 (13.0)	36 (12.7)	1.000
Retinopathy	NA	NA		20 (87.0)	238 (84.1)	1.000
MI	13 (9.8)	44 (2.9)	<0.001	8 (34.8)	30 (10.6)	0.001
Stroke	9 (6.8)	49 (3.2)	0.043	2 (8.7)	13 (4.6)	0.313
Amputation	12 (9.0)	81 (5.2)	0.072	3 (13.0)	15 (5.3)	0.136
Peripheral vascular disease	NA	NA		3 (13.0)	32 (11.3)	0.736
Peripheral neuropathy	NA	NA		14 (60.9)	139 (49.1)	0.386
Autonomic neuropathy	NA	NA		10 (43.5)	95 (33.5)	0.365
Antihypertensive treatment	NA	NA		21 (91.3)	202 (71.4)	0.049
SBP, mmHg	NA	NA		154 (120–163)	143 (123–158)	0.901
Total cholesterol/HDL ratio	NA	NA		3.0 (2.3–4.9)	2.8 (2.1–4.0)	0.217
Lipid-lowering treatment	NA	NA		10 (43.5)	141 (49.8)	0.069
Antiplatelet treatment	NA	NA		12 (52.2)	97 (34.3)	0.006
Duration of diabetes, years [mean (SD)]	NA	NA		25.5 (8.2)	25.8 (8.3)	0.869
Number receiving dialysis at listing	67 (50.4)	893 (57.0)	0.383	17 (73.9)	176 (62.3)	0.369
Number receiving dialysis at transplant	82 (61.6)	1,087 (69.4)	0.286	21 (91.3)	207 (73.1)	0.078
Hemodialysis	48 (36.1)	628 (40.1)		6 (26.1)	109 (38.5)	
Peritoneal dialysis	33 (24.8)	456 (29.1)	0.531	15 (65.2)	98 (34.6)	0.011
QRISK2 score, %	NA	NA		35.2 (28–48)	24.4 (16–36)	0.001
QRISK2 ≥20%	NA	NA		22 (95.7)	183 (64.6)	0.002
Donor factors						
Age, years	35 (23–44)	36 (23–45)	0.871	34 (24–42)	34 (21–43)	0.989
DCD	6 (4.5)	222 (14.2)	0.002	0 (0.0)	29 (10.2)	0.144
ECD	1 (0.8)	73 (4.7)	0.026	0 (0.0)	10 (3.5)	1.000
Hypertension	18 (13.5)	123 (7.9)	0.033	0 (0.0)	8 (2.8)	1.000
Transplant factors						
Waiting time, months	10.0 (3.8–25.1)	12.5 (4.8–20.8)	0.849	10.0 (6.6–23.6)	15.5 (4.4–20.8)	0.138
Year of transplant	2006 (2004–2010)	2010 (2007–2013)	<0.001	2005 (2004–2008)	2010 (2007–2012)	<0.001
CIT, hours	12.6 (10.5–15.0)	11.6 (9.7–13.8)	0.002	14.0 (12.8–15.7)	13.0 (10.3–15.1)	0.102
HLA mismatch group 4*	80 (60.2)	968 (61.8)	0.513	10 (43.5)	79 (27.9)	0.696
Immunosuppression						
Alemtuzumab	52 (39.1)	842 (53.8)	0.003	3 (13.0)	147 (51.9)	<0.001
Basiliximab	56 (42.1)	555 (35.4)	0.056	20 (87.0)	136 (48.1)	<0.001
Prednisolone	85 (63.9)	691 (44.1)	<0.001	19 (82.6)	129 (45.6)	0.001

Data are n (%) or mean (IQR) unless otherwise indicated. NA, not available. *HLA mismatch group 4 = (1DR + 2B) or (2DR) mismatches.

Table 2—Univariable HRs (95% CI) for predictors of MACE in the UKTR SPKT recipients and the Manchester-based subgroup of SPKT recipients using variables measured at baseline

	All UKTR SPKT recipients (n = 1,699)		Manchester SPKT subgroup (n = 306)	
Predictor	HR (95% CI)	P value	HR (95% CI)	P value
Recipient				
Age	1.03 (1.01–1.05)	0.004	1.07 (1.02–1.1)	0.005
BMI, kg/m^2	1.0 (0.9–1.1)	0.799	1.03 (0.9–1.2)	0.645
Prior MI	3.5 (2.0–6.1)	<0.001	4.0 (1.7–9.4)	0.002
Prior stroke	2.4 (1.2–4.7)	0.012	2.4 (0.6–10.4)	0.229
Prior amputation	2.0 (1.1–3.7)	0.019	2.8 (0.8–9.4)	0.104
Prior peripheral artery disease			0.99 (0.3–3.3)	0.986
Registered blind	1.5 (0.9–2.5)	0.091	1.09 (0.3–3.7)	0.892
Retinopathy			1.2 (0.4–4.1)	0.747
Antihypertensive treatment			3.8 (0.9–16.1)	0.073
SBP, mmHg			0.99 (0.98–1.02)	0.799
Total cholesterol/HDL ratio			1.3 (0.99–1.6)	0.053
Lipid-lowering treatment			1.2 (0.5–3.4)	0.668
Antiplatelet treatment			4.4 (1.4–13.7)	0.010
RRT	0.9 (0.6–1.3)	0.457	3.9 (0.9–16.6)	0.067
Hemodialysis*	1.0 (0.6–1.4)	0.807	2.4 (0.5–11.8)	0.289
Peritoneal dialysis*	0.8 (0.5–1.2)	0.257	5.2 (1.2–22.7)	0.029
Duration of diabetes, years			1.0 (0.95–1.05)	0.995
QRISK2 score, %			1.04 (1.02–1.06)	<0.001
QRISK2 ≥20%			11.4 (1.5–84.6)	0.017
Transplant				
Waiting time, months	1.01 (0.999–1.02)	0.076	0.99 (0.96–1.02)	0.537
HLA group	1.0 (0.7–1.2)	0.723	1.2 (0.5–2.9)	0.655
CIT, hours	1.06 (1.002–1.1)	0.042	1.1 (0.9–1.2)	0.288
Year of transplant	0.9 (0.8–0.9)	<0.001	0.8 (0.7–0.9)	0.004
Donor history of hypertension	2.0 (1.2–3.2)	0.008	4.6 (0–4,713)	0.668
Immunosuppression				
Alemtuzumab	0.7 (0.5–1.1)	0.108	0.2 (0.1–0.8)	0.024
Prednisolone	1.8 (1.2–2.5)	0.002	3.4 (1.1–10.2)	0.032

The QRISK2 score assesses the 10-year risk of a cardiovascular event based on several cardiovascular risk factors measured at baseline; a risk >10% is considered high risk and a risk >20% is considered to be very high risk. Data are HR (95% CI) from Cox regression. *Predialysis as reference category.

characteristic curve of 0.715 (95% CI 0.616–0.815; P = 0.001).

CONCLUSIONS

Prior Studies of Event Rates in Relation to the National Cohort

Very few studies have assessed the long-term risks for cardiovascular events in SPKT recipients (6,14–16). We report the largest study of long-term CVD risk in this cohort and demonstrate a large residual risk for CVD events following SPKT. This is particularly relevant because it occurs despite the young age and careful selection of recipients. It also occurs in the context of potential CVD benefits from SPKT (17).

Table 3—Multivariable-adjusted HRs (95% CI) for predictors of MACE in UKTR SPKT recipients at baseline

Predictor	HR (95% CI)	P value
Recipient		
Age, years	1.04 (1.01–1.07)	0.002
Prior MI	2.6 (1.3–5.0)	0.006
Prior stroke	2.3 (1.2–4.7)	0.018
Prior amputation	2.0 (1.02–3.7)	0.044
Registered blind	1.5 (0.9–2.5)	0.136
Transplant		
Waiting time, months	1.02 (1.0–1.03)	0.046
Donor history of hypertension	1.8 (1.05–3.2)	0.034
CIT, hours	1.0 (0.95–1.06)	0.847
Year of transplant	0.9 (0.8–0.9)	<0.001
Prednisolone	1.1 (0.7–1.8)	0.544

Data are HR (95% CI) from Cox regression.

Prior studies in patients with type 1 diabetes and renal failure have shown that SPKT improves several CVD risk factors including glucose, blood pressure, and lipid levels when compared with kidney transplant alone (18). In our study, MACE occurred in 7.8% of patients over 5 years. This compares favorably to the rate in kidney transplant recipients with diabetes in Japan (n = 1,614; 19.6% over 6 years) and a single U.S. center (n = 212; 26.9% over 3.4 years) (19,20). However, direct comparison with these studies is limited because they also included people with type 2 diabetes. Also, the selection criteria for transplantation of kidney alone are different from those for SPKT.

The UKTR rate is higher than that in other SPKT cohorts. Kim et al. (6) reported events in 5.5% in the U.S., but their study was limited to perioperative cardiovascular complications. The CVD event rate in our study also contrasts with findings reported in SPKT recipients in Poland (n = 66; 0.2% p.a. over 6.7 years)

Table 4—Univariable and multivariable-adjusted HRs (95% CI) for predictors of cardiovascular death in UKTR SPKT recipients

Predictor	Univariable HR (95% CI)	*P* value	Adjusted HR* (95% CI)	*P* value
Age, years	1.06 (1.03–1.09)	<0.001		
Prior MI	4.9 (2.5–9.6)	<0.001		
Prior stroke	3.2 (1.4–7.5)	0.006		
Prior amputation	3.1 (1.6–6.3)	0.001		
Unemployed	1.4 (1.06–6.3)	0.020	1.8 (1.03–3.2)	0.041
Donor history of hypertension	2.4 (1.3–4.5)	0.006	2.2 (1.2–4.2)	0.012
Registered blind	1.8 (0.98–3.3)	0.056	1.9 (1.02–3.6)	0.042
Year of transplant	0.99 (0.91–1.07)	0.729		
Prednisolone	1.3 (0.8–2.0)	0.361	1.3 (0.8–2.1)	0.358

Data are HR (95% CI) from Cox regression. *Adjusting for age, prior MI, stroke and amputation.

(14). These findings may have been influenced by sample size and being a single-center study, with specific patient selection criteria/management.

The proportion experiencing fatal CVD in our study also compares favorably to that reported in living donor kidney transplant recipients with type 1 diabetes in the U.K. (6.2% over 3.9 years) and in Norway (34.3% over 7.9 years) (7,21). Although differences between recipient/donor characteristics and selection criteria for SPKT and living donor kidney transplantation may account for this, the benefits of a functioning pancreas allograft might also contribute to these findings.

A consistent finding in our analyses was that CVD outcomes improved over time. This observation is consistent with trends in the general population and a Norwegian cohort of SPKT recipients (3,7). This likely arises from improved recipient/donor selection, operative technique, perioperative care, and immunosuppression as our national program has matured, in addition to improvements in population health and the management of CVD risk factors (22,23).

Prior Studies of CVD Risk Factors in Relation to the National Cohort

Our study adds to the work by Kim et al. (6). They reported significant relationships with age, nonwhite ethnicity, male sex, previous cardiac surgery or coronary intervention, valvular disease, pulmonary circulatory disorder, and anemia. Our study focused on longer-term follow-up and supported some of these findings. Differences in results could be explained by differences in time frames of observation and recipient and donor characteristics, especially since the study by Kim et al. (6) reported on all pancreas transplant recipients whereas our study focused on SPKT recipients.

We show an adverse effect of advancing age on CVD risk. This is unsurprising as atherosclerosis and plaque rupture are age-related processes (24).

We demonstrate strong relationships between the presence of known CVD prior to transplant (MI and stroke), amputation, and the risk for subsequent MACE or fatal CVD. In a previous mortality study (25) involving 78 German SPKT recipients, prior MI (relative risk 5.1) and amputation (relative risk 3.7) were strongly associated with a reduced patient survival. These risk factors are surrogates for prevalent vascular disease and are considered markers of "diabetes severity." They have been shown to be potent risk factors for CVD events in other clinical contexts (26–29).

The relationship between BMI and CVD outcomes was not significant in our study, which is contrary to outcomes in large population-based studies (10). This may be explained in part by the U.K. selection criteria for SPKT, which list BMI of $\geq$30 kg/m^2 as a relative contraindication, and cohort studies (30,31) that report nonlinear relationships between BMI and CVD in people with diabetes, which could be missed using conventional Cox models.

The results of our unadjusted model for MACE suggest a significant adverse effect of increasing pancreas CIT. Pancreas CIT is related to adverse allograft outcomes (32). It is possible that this relationship reflects the effect that adverse allograft outcomes may have on MACE. However, one must also consider that a longer pancreas CIT may arise from differences in recipient and donor selection, transplant volume, logistics, and surgical technique among transplant centers. In addition, the U.K. average pancreas CIT has been declining over the study period, potentially confounding our unadjusted results (11). This is supported by the loss of significance in adjusted models. Our results also show that prednisolone immunosuppression is related to a higher risk for MACE in unadjusted models. We also show that there has been a decline in the use of prednisolone-containing immunosuppression regimens over time, possibly as a result of the increased use of T cell–depleting agents at induction such as alemtuzumab (Supplementary Table 2). It is possible that our unadjusted results may reflect the effect of an earlier year of transplantation. Although the relationship between steroid use and higher risk for MACE in our data was no longer significant after covariate adjustment, a previous large population-based study (33) from the Netherlands reported that oral glucocorticoids were adversely related to cardiovascular outcomes in fully adjusted models. Taken together, and noting the known side effects of steroid therapy, these data suggest that avoiding glucocorticoid immunosuppression in SPKT recipients may be beneficial.

The relationship between increasing waiting time and MACE is unsurprising. Patients waiting longer have prolonged dialysis exposure, which increases the risk of all-cause and cardiovascular mortality (34).

Over the observation period, we observed a gradual increase in the use of organs from DCD and ECD donors. A lower proportion of MACE patients received DCD and ECD organs, suggesting a protective relationship; however, we identified strong correlations between donor type and the year of transplantation, leading us to exclude donor type from regression models. Receiving organs from a donor with a history of hypertension conferred a twofold higher risk of MACE and fatal CVD. It is known that recipients of a kidney from a donor with hypertension have a 10-fold higher risk of the development of hypertension (35). Donor hypertension also relates to

adverse renal allograft outcomes (36). We speculate that inducing or exacerbating recipient hypertension and adverse renal allograft survival may contribute to our findings.

Unemployment was a significant hazard for fatal CVD. Previous population-based studies (37) have reported associations between voluntary or involuntary unemployment and CVD in general populations. Because of the definition we used for unemployment, it is likely that our findings indicate disease severity. However, it is important to consider other factors associated with unemployment that may influence cardiovascular outcomes, such as deprivation and psychological factors.

A high proportion of recipients were current or ex-smokers (39.5%). Although this was not a significant hazard in our analyses, it may have contributed toward the CVD event rate because it is a strong CVD risk factor in large population-based studies (10).

Prior Studies of Allograft Failure Following Nonfatal CVD Events

We are the first to report an association between nonfatal MACE and subsequent allograft loss in SPKT recipients. Previous studies (8,9,38) of renal and SPKT recipients have focused upon DWFG secondary to fatal CVD. Nonfatal MACE increase mortality risk, and this is likely to be reflected in our findings given that we included DWFG in our analyses. However, SPKT recipients experiencing events are likely to have abnormal levels of modifiable CVD risk factors, such as blood pressure and lipid profile, which may also influence allograft outcomes (16,39). The relationship we report is important because CVD risk is modifiable and continued efforts should be made to minimize this following transplantation. In our local experience, CVD events in SPKT recipients are often managed in nontransplant centers. This is likely the case across the U.K. because pancreas transplantation takes place in a small number of centers. We suggest that SPKT recipients experiencing events are transferred to transplant centers to receive joint cardiology and transplant team treatment, ensuring that transplant factors such as immunosuppression are optimized during the CVD episode.

Prior Studies in Relation to the Local Cohort

We demonstrate a relationship between renal replacement therapy (RRT) and worse MACE outcomes. However, the relationship between RRT and MACE was not observed in the national data set, which is likely to be the more robust analysis considering the relative sample sizes.

We did not observe significant relationships between individual modifiable CVD risk factors and outcome events, with only the HR for total cholesterol/HDL ratio approaching significance. We speculate that the modest sample size accounts for this, as these factors are validated predictors of CVD outcomes in large cohort studies (10). We found that antiplatelet therapy was a significant hazard, associated with an approximately fourfold increase in risk, and we suspect that this relationship is explained by confounding by indication because antiplatelet treatment was strongly related to the presence of established CVD at baseline.

Each 1% increment in the QRISK2 score conferred an additional 4% increase in the risk for MACE following SPKT and demonstrated acceptable discrimination (area under the curve 0.715). However, 64.6% had a QRISK2 score of $\geq$20% but did not experience a MACE, raising concerns about the specificity of using a 20% threshold in this cohort. Our follow-up period was 5.7 years, whereas the QRISK2 calculator was designed to predict 10-year CVD risk, partly explaining this finding. We suggest that the QRISK2 score is validated in the national cohort to determine a better threshold. We believe that QRISK2 may facilitate the identification of individuals who might benefit from enhanced cardiovascular investigation prior to listing, risk factor modification, or alternative transplant pathways such as living donor kidney transplantation or simultaneous islet and kidney transplantation.

We observed that only 74.0% of patients meeting National Institute for Health and Care Excellence criteria for receiving antihypertensive treatment (SBP $\geq$130 mmHg) were receiving any (40). Furthermore, only 49.3% of those meeting National Institute for Health and Care Excellence criteria for lipid management and only 53.7% of those with a QRISK2 score $\geq$20% were receiving lipid-lowering treatment. Our findings suggest that local SPKT recipients are receiving suboptimal risk factor management while awaiting transplantation, and this needs urgent attention for patient benefit.

Strengths and Limitations

This study has several strengths based on the comprehensive nature of the data. It augments the national transplant registry with ONS mortality data. As with most registry data sets, there are some limitations, which include the absence of markers of cardiac function, modifiable CVD risk factor levels, and changes and interventions in the national cohort. The frequency of annual follow-up data returned to NHSBT varies from 90% to 100% per year, and only allograft failure and death are separately validated (11). Therefore, our report likely underestimates the rate of nonfatal MACE. When compared with outcome data for the local Manchester subgroup, the UKTR outcomes were accurate in 92% of cases.

The local subgroup had a modest sample size/event number, which limited the ability to perform multivariable modeling. Although the subgroup was similar in age, ethnicity, and sex to the entire national cohort, a larger proportion had a history of MI and were receiving dialysis at baseline and thus the subgroup may not be representative of the full UKTR cohort. Because of the U.K. selection criteria for SPKT, we had a limited range of BMIs. It is unlikely that this affected the performance of the QRISK2 calculator in our cohort, because QRISK2 was developed using BMI as a continuous variable (10).

Finally, our findings may not apply to other populations.

Clinical Implications

This study has several clinical implications, including that these patients have a high risk for fatal and nonfatal CVD events. A nonfatal cardiovascular event following transplantation significantly increases the risk of subsequent allograft failure, suggesting that those experiencing events should be jointly managed by cardiology and transplant teams, preferably at transplant centers. In so doing, allograft factors can be optimized in patients while undergoing CVD investigations or treatment. In our local cohort we report that the QRISK2 score predicted MACE, suggesting that it may be

of clinical use to identify potential SPKT recipients who might benefit especially from more active management of CVD risk factors or who could be offered alternative innovative treatment pathways such as simultaneous islet and kidney transplantation. These findings highlight an opportunity to expand the national data set to include information on modifiable CVD risk factors, because currently these data are not collected and some patients may not have adequate risk factor control, as we report in our local cohort. Efforts to further reduce the use of prednisolone-based maintenance immunosuppression therapy should be continued. Finally, it may be beneficial that organs from hypertensive donors are matched to recipients with a lower risk of hypertension to minimize future CVD risk.

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Author Contributions. P.Y. is an approved researcher with the ONS (Approved Researcher number: ONSF20308; valid until 23 June 2022). P.Y., A.S., J.N., M.K.R., and D.v.D. designed the study. P.Y., S.C.G., H.K., Z.M., and I.M.S. participated in acquisition of data for the national and local cohorts. P.Y., A.S., and C.F. analyzed the data. P.Y., A.S., C.M., T.A., M.K.R., and D.v.D. interpreted the data. P.Y. wrote the manuscript. All authors reviewed and edited the manuscript before approving its submission. P.Y. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Data Availability. The data presented herewith were provided by NHSBT and the ONS. Individuals wishing to access the raw data would require proof of permission from NHSBT and the ONS. Data sharing will only take place upon receipt of verified permission from NHSBT and the ONS.

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