Analysis of factors that affect outcome after transplantation of kidneys donated after cardiac death in the UK: a cohort study

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Summary

Background A third of all kidneys from deceased donors in the UK are donated after cardiac death, but concerns have been raised about the long-term outcome of such transplants. We aimed to establish these outcomes for kidneys donated after controlled cardiac death versus brain death, and to identify the factors that affect graft survival and function.

Methods We used data from the UK transplant registry to select a cohort of deceased kidney donors and the corresponding transplant recipients (aged ≥18 years) for transplantations done between Jan 1, 2000, and Dec 31, 2007. Kaplan-Meier estimates were used to assess graft survival, and multivariate analyses were used to identify factors associated with graft survival and with long-term renal function, which was measured from estimated glomerular filtration rate (eGFR).

Findings 9134 kidney transplants were done in 23 centres; 8289 kidneys were donated after brain death and 845 after controlled cardiac death. First-time recipients of kidneys from cardiac-death donors (n=739) or brain-death donors (n=6759) showed no difference in graft survival up to 5 years (hazard ratio 1·01, 95% CI 0·83 to 1·19, p=0·97), or in eGFR at 1–5 years after transplantation (at 12 months –0·36 mL/min per 1·73 m², 95% CI –2·00 to 1·27, p=0·66). For recipients of kidneys from cardiac-death donors, increasing age of donor and recipient, repeat transplantation, and cold ischaemic time of more than 12 h were associated with worse graft survival; grafts from cardiac-death donors that were poorly matched for HLA had an association with inferior outcome that was not significant, and delayed graft function and warm ischaemic time had no effect on outcome.

Interpretation Kidneys from controlled cardiac-death donors provide good graft survival and function up to 5 years in first-time recipients, and are equivalent to kidneys from brain-death donors. Allocation policy for kidneys from cardiac-death donors should reduce cold ischaemic time, avoid large age mismatches between donors and recipients, and restrict use of kidneys poorly matched for HLA in young recipients.

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Introduction

The demand for kidney transplantation far exceeds the supply of donor organs and the shortfall is becoming more severe as donor numbers fail to keep pace with increasing numbers of patients listed for transplantation.[1,2] Most deceased-donor kidneys are from donors with brain-stem death whose hearts were beating (brain-death donors).[1,2] During the past decade, the number of brain-death donors has declined in the UK for reasons that include a reduction in deaths from trauma and changes in neurosurgical practice.[3–5] By contrast, use of kidneys from non-heart-beating donors (cardiac-death donors) has risen steeply from 3% of all deceased donors in 2000 to 32% in 2009,[6] and if the present pattern continues, they will become the dominant type of deceased donor by 2015. In the UK, most cardiac-death donors are controlled donors (Maastricht category 3)[7] who have suffered massive irreversible brain injury but do not fulfil the criteria for brain-stem death; death is instead certified by cessation of cardiopulmonary function after a decision to withdraw life-supporting treatment.

Kidneys donated after brain death or cardiac death inevitably acquire a variable degree of injury during donation, but the nature of injury differs according to donor type. Kidneys from brain-death donors are exposed to substantial metabolic and hormonal disturbances that accompany brain-stem death,[8–10] whereas kidneys from cardiac-death donors incur a variable period of warm ischaemia between cessation of cardiopulmonary function and perfusion with cold preservation solution. Warm ischaemic injury increases the incidence of delayed graft function, suggesting that kidneys from cardiac-death donors are inferior to those from brain-death donors. Little information is available about long-term renal function in recipients of kidneys from controlled cardiac-death donors,[11–13] but the outcome in terms of graft survival seems to be broadly similar to that recorded in recipients of kidneys from brain-death donors.[14,15]

To make best use of kidneys from deceased donors, the factors that affect outcome after transplantation need to be understood so that resources within transplant centres are used effectively, and decisions about organ allocation are evidence-based. For kidneys from brain-death donors these factors are well established.[16–19] In the UK, all kidneys from brain-death donors are allocated according to an evidence-based national organ sharing scheme that aims to keep inequity of access to a minimum, and to allocate kidneys to the most suitable recipients. Kidneys are allocated according to a points-based scoring system that prioritises long waiting time, HLA match, and age match.[20] By contrast, the factors that affect outcome after transplantation with kidneys from cardiac-death donors are largely unknown. In view of the nature of renal injury acquired during donation, the types and relative effects of risk factors in recipients of these kidneys might differ from the factors identified in recipients of kidneys from brain-death donors. In the UK, because of this absence of adequate information, kidneys from cardiac-death donors are not allocated through the national organ sharing scheme, but are instead allocated locally according to the policy in individual transplant centres.

To inform future transplant policy, particularly with respect to kidney allocation, we undertook a comprehensive UK-wide cohort analysis of the outcome of kidney transplants from controlled cardiac-death donors to identify the factors that affect survival of graft and patient and transplant function up to 5 years after transplantation.

Methods

Study population

The UK transplant registry is held by National Health Service (NHS) Blood and Transplant, and 23 UK adult renal transplant centres provide mandatory data to this registry. We used the registry to identify all renal transplantations from deceased donors between Jan 1, 2000, and Dec 31, 2007. We selected for analysis all transplants of kidneys from controlled cardiac-death donors of Maastricht category 3, defined as donors awaiting cardiac arrest after withdrawal of life-supporting treatment in the intensive care unit.[7] We excluded transplants of kidneys from uncontrolled cardiac-death donors of Maastricht categories 1 (dead on arrival at hospital) and 2 (resuscitation attempted without success in the emergency department), and from controlled cardiac-death donors of Maastricht category 4 (undergone brain death). The comparator group comprised all transplants of kidneys from brain-death donors. Recipients were excluded if they were younger than 18 years at transplantation or had received a non-renal organ transplant. No age restrictions were placed on donors.

All-cause graft failure was taken as the time from transplantation to graft nephrectomy or return to dialysis, whichever was earlier, or to death of the patient with a functioning graft. Survival of the patient was defined as the time from transplantation until death. Primary non-function was defined as failure of a graft to ever function, irrespective of cause. Delayed graft function was defined as need for dialysis after transplantation; recipients with primary non-function were excluded from this category. Recipient sensitisation was defined as HLA antibody reaction frequency, which we calculated by comparison of unacceptable HLA specificities with HLA types of donors of identical ABO blood group in a pool of 10 000 donors on the UK transplant database. Graft function was measured from the estimated glomerular filtration rate (eGFR, adjusted for 1·73 m² body surface area), which was calculated with the abbreviated modified diet in renal disease equation[21] from creatinine measurements obtained at 3 months, and then yearly after transplantation. Acute rejection was defined as treatment for rejection within the first 3 months. We defined warm ischaemic time as the time from cardiac arrest to cold perfusion, and cold ischaemic time as the time from start of cold perfusion to reperfusion after implantation. HLA mismatch level was defined according to UK allocation policy for kidneys from brain-death donors and was based on the mismatch between donor and recipient at the HLA-A, HLA-B, and HLA-DR loci: level 1 was a 000 HLA-A, HLA-B, and HLA-DR mismatch; level 2 was a 0 HLA-DR plus 0/1 HLA-B mismatch; level 3 was a 0 HLA-DR plus 2 HLA-B mismatch or a 1 HLA-DR plus 0/1 HLA-B mismatch; and level 4 was a 2 HLA-DR or a 1 HLA-DR plus 2 HLA-B mismatch.

Statistical analysis

Follow-up analysis of the entire transplant study cohort of deceased donors included all data submitted to NHS Blood and Transplant by Dec 29, 2009. The median period of follow-up was 6·10 years (IQR 4·14–8·07), and graft survival was censored at 5 years. The multivariate analysis included only recipients with complete data on: graft survival; cold ischaemic time; donor's and recipient's age and sex, ethnic group, and blood group; HLA mismatch; and sensitisation. A separate subgroup was created for the multivariate analysis for other variables with missing data for some recipients. Univariate comparisons of transplants from brain-death versus cardiac-death donors were done with χ^2 tests for categorical data, *t* tests for parametric continuous data, and Wilcoxon tests for non-parametric continuous data. Cox proportional hazards regression models were fitted by a stepwise variable selection method to analyse the combined effect of factors on all-cause graft survival. Variables of interest that were not found to have significant effects were added individually to the final model and are presented for illustrative purposes. Log cumulative hazard plots showed no evidence of non-proportionality of hazards.

Kaplan-Meier curves were used to show graft survival. Associated p values were derived from the univariate log-rank test. Multiple linear regression was used to

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identify factors associated with eGFR. Donor-related variables included in the multivariate model were: age, sex, ethnic group, terminal creatinine concentration, and medical history (diabetes, hypertension, liver disease, cardiac disease, drug abuse, and smoking status). Recipient-related factors included in the multivariate model were: age, sex, ethnic group, sensitisation, ABO blood group, cytomegalovirus seroconversion status, and primary renal disease. Other variables included were: HLA mismatch, cold ischaemic time, warm ischaemic time, and use of machine perfusion preservation. All tests were two-sided and p values of less than 0·05 were judged to be significant. Analyses were done with SAS (version 9.1).

Role of funding source

NHS Blood and Transplant holds the database for transplantation in the UK. NHS Blood and Transplant and Cambridge National Institute for Health Research (NIHR) Biomedical Centre had no other role in the study design, data collection, data analysis, data interpretation, or writing of the report other than that listed in the statement of authors' contributions at the end of the paper. The corresponding author had full access to all data and final responsibility for submission for publication.

Results

9134 recipients of renal transplants from deceased donors were recorded during the 8-year study period, of whom 845 (9%) received kidneys from controlled (Maastricht category 3) cardiac-death donors, and 8289 (91%) received kidneys from heart-beating brain-death donors. Table 1 shows the characteristics of donors and recipients. Cardiac-death donors were younger, more predominantly male and white, and less likely to have smoked than were brain-death donors. The most common cause of death in both donor groups was stroke, but stroke caused a lower proportion of cardiac deaths than brain deaths, and trauma caused a higher proportion of cardiac deaths than brain deaths. The serum creatinine concentration in donors immediately before organ procurement was slightly lower in cardiac-death than in brain-death donors.

Compared with recipients of kidneys from brain-death donors, recipients from cardiac-death donors were older, were less likely to have received a previous renal transplant (1401 [17%] *vs* 97 [11%], p<0·0001), and received kidneys that were less well matched for HLA (table 1). Unlike kidneys from brain-death donors, those from cardiac-death donors underwent a variable period of warm ischaemia, but they had a shorter cold ischaemic time than did kidneys from brain-death donors and were more often preserved by cold machine perfusion before transplantation.

For analysis of outcome, transplant recipients were stratified according to whether or not they had received a previous kidney transplant (table 2). First-time recipients of kidneys from the two donor types had a low incidence

	Transplants from cardiac-death donors (n=845)*	Transplants from brain-death donors (n=8289)	p value
Donors			
Age (years)	43·5 (15·3)	45·7 (15·1)	<0·0001†
Sex‡	..	..	<0·0001§
Men	529 (63%)	4196 (51%)	..
Women	316 (37%)	4086 (49%)	..
Ethnic group‡	..	..	0·02§
White	828 (99%)	7976 (97%)	..
Other	12 (1%)	235 (3%)	..
Smoking status‡	..	..	0·001§
Smoker	106 (36%)	3929 (49%)	..
Non-smoker	187 (64%)	4112 (51%)	..
Cause of death‡	..	..	<0·0001§
Stroke	509 (61%)	6206 (75%)	..
Trauma	213 (25%)	1271 (15%)	..
Other	117 (14%)	801 (10%)	..
Terminal creatinine (μmol/L)	78 (61–98)	81 (66–101)	0·002¶
Recipients			
Age (years)	49·3 (12·8)	46·8 (13·0)	<0·0001†
Sex‡	..	..	0·09§
Men	542 (64%)	5065 (61%)	..
Women	303 (36%)	3222 (39%)	..
Ethnic group‡	..	..	0·04§
White	695 (83%)	6925 (85%)	..
Asian	78 (9%)	734 (9%)	..
Other	69 (8%)	489 (6%)	..
Cause of renal failure‡	..	..	0·04§
Glomerulonephritis	186 (30%)	1476 (28%)	..
Polycystic kidney disease	138 (22%)	947 (18%)	..
Pyelonephritis	90 (15%)	788 (15%)	..
Diabetes mellitus	57 (9%)	532 (10%)	..
Other	148 (24%)	1467 (28%)	..
HLA mismatch level[20]	..	..	<0·0001§
1	24 (3%)	1467 (18%)	..
2	183 (22%)	3939 (48%)	..
3	457 (54%)	2308 (28%)	..
4	181 (21%)	575 (7%)	..
Graft number	..	..	0·0002§
1	748 (89%)	6888 (83%)	..
2	89 (11%)	1168 (14%)	..
3	7 (1%)	210 (3%)	..
4	1 (<1%)	23 (<1%)	..
Process			
Cold ischaemic time (h)	17·7 (14·5–21·4)	18·0 (15·3–22·3)	<0·0001¶
Warm ischaemic time (min)	15·0 (12·0–19·0)	NA	..
Method of kidney storage‡	..	..	<0·0001§
Cold storage	551 (75%)	7222 (99·6%)	..
Machine perfusion	181 (25%)	29 (<1%)	..

Data are mean (SD), number (%), or median (IQR). NA=not applicable. *Only recipients of kidneys from cardiac-death donors of Maastricht category 3 were included in the analysis. During the study period four transplants of Maastricht category 1, 84 transplants of Maastricht category 2, and 65 transplants of Maastricht category 4 were done in the UK. †t test. ‡Data are missing for some participants who were excluded from percentage calculations. §χ^2 test. ¶Wilcoxon test.

Table 1: **Demographic and clinical characteristics of transplant donors and recipients**

	Recipients of first grafts			Recipients of second grafts		
	Transplants from cardiac-death donors (n=748)	Transplants from brain-death donors (n=6888)	p value	Transplants from cardiac-death donors (n=89)	Transplants from brain-death donors (n=1168)	p value
Primary non-function	20 (3%)	174 (3%)	0·89*	6 (7%)	40 (3%)	0·12*
Graft failure up to 30 days (death censored)	31 (4%)	334 (5%)	0·39*	7 (8%)	70 (6%)	0·50*
Immediate function	297/581 (51%)	3462/4564 (76%)	<0·0001*	29/71 (41%)	534/767 (70%)	<0·0001*
Acute rejection up to 3 months	107/649 (16%)	1399/5773 (24%)	<0·0001*	14/74 (19%)	247/1020 (24%)	0·30*
eGFR (mL/min per 1·73m²)						
3 months	44 (34–57)	46 (36–57)	0·16†	45 (31–58)	48 (36–59)	0·14†
1 year	46 (35–58)	47 (36–59)	0·26†	49 (32–59)	47 (35–59)	0·81†
3 years	45 (34–59)	46 (35–58)	0·83†	48 (36–62)	45 (34–58)	0·41†
Sensitisation at transplantation‡	104 (14%)	991 (14%)	0·77*	76 (85%)	1021 (87%)	0·59*
Graft survival up to 5 years (death censored)	85·1%	83·2%	0·16§	64·6%	79·0%	0·007§
Graft survival up to 5 years (all-cause failure)	76·2%	76·4%	0·72§	50·6%	73·1%	0·001§
Survival of patients up to 5 years	86·4%	88·0%	0·31§	76·5%	90·2%	0·026§
HLA mismatch level	..	..	<0·0001*	..	..	<0·0001*
1	13 (2%)	1028 (15%)	..	6 (7%)	327 (28%)	..
2	158 (21%)	3361 (49%)	..	25 (28%)	510 (44%)	..
3	410 (55%)	1996 (29%)	..	45 (51%)	270 (23%)	..
4	167 (22%)	503 (7%)	..	13 (15%)	61 (5%)	..

Data are number (%), median (IQR), or percentages; denominators are presented for outcomes with missing data . eGFR=estimated glomerular filtration rate. *χ^2 test. †Wilcoxon test. ‡Patients with HLA antibody reaction frequency of more than 10%. §Log-rank test.

Table 2: **Unadjusted transplant outcomes**

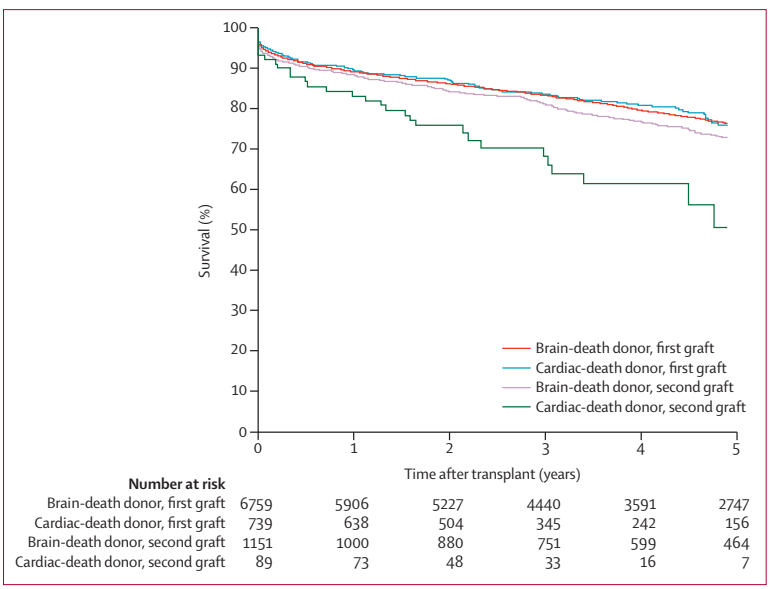

Figure 1: **Kaplan-Meier estimates of graft survival after renal transplantation in recipients of kidneys from cardiac-death or brain-death donors, stratified according to receipt of first or second grafts**
Nine recipients of their first grafts from cardiac-death donors, 123 recipients of their first grafts from brain-death donors, and 17 recipients of their second grafts from brain-death donors were excluded from the analysis because they had missing data for: graft survival; cold ischaemic time; donor's and recipient's age or sex, ethnic group, or blood group; HLA mismatch; or sensitisation.

of primary non-function and 30-day death-censored graft failure. For recipients of kidneys from cardiac-death donors, occurrence of primary non-function was higher for repeat than for first transplants (p=0·04), with a similar pattern for kidneys from brain-death donors (p=0·07; table 2). With inclusion of all recipients irrespective of number of previous grafts, delayed graft function occurred in 50% (332/659) of kidneys from cardiac-death donors and 25% (1386/5474) of kidneys from brain-death donors (p<0·0001). Acute rejection occurred in 17% (121/723) of recipients of kidneys from cardiac-death donors and 24% (1646/6793) of recipients of kidneys from brain-death donors during the first 3 months after transplantation (p<0·0001). For first-time recipients, graft survival up to 5 years (including death of a patient as graft failure) was very similar between recipients of kidneys from the two donor types (table 2, figure 1). Graft survival (all-cause failure) in recipients of second grafts was clearly inferior to that of recipients of first grafts for recipients of kidneys from both cardiac-death donors (p<0·0001) and brain-death donors (p=0·0243; table 2, figure 1). From 3 months onwards, eGFR was similar between recipients of kidneys from the two donor types (table 2).

Transplant characteristics of recipients of kidneys from the two donor types differed in ways that might have affected transplant outcome, so Cox proportional hazards regression was done to control for potentially confounding variables by use of data obtained from first-time recipients. Multivariate analysis included 98% (8738/8893) of recipients of first or second grafts (figure 1). For first-time recipients of kidneys from cardiac-death donors, increasing age of donor, age of

recipient, and cold ischaemic time were all associated with inferior transplant outcome at 5 years after transplantation (table 3). After use of Cox analysis to account for the effects of these variables, graft failure (including recipient death) at 5 years was equivalent for first-time recipients of kidneys from cardiac-death donors (n=739) versus brain-death donors (n=6759; hazard ratio [HR] 1·01, 95% CI 0·83–1·19, p=0·97). Although delayed graft function was not associated with transplant outcome in recipients of kidneys from cardiac-death donors (table 4), it was strongly predictive of inferior transplant survival for recipients of kidneys from brain-death donors (1·70, 1·45–1·98). Application of the Cox model to all recipients of kidneys from cardiac-death donors showed that graft survival was worse in recipients of second grafts (2·22, 1·49–3·32) than in recipients of first grafts.

We assessed eGFR by use of multiple linear regression to control for differences between first-time recipients of kidneys from cardiac-death versus brain-death donors. Factors associated with inferior eGFR at 3 months in recipients of kidneys from cardiac-death donors included increasing age of donors, age of recipients, and cold ischaemic time, and non-traumatic cause of death in donors (table 5). HLA mismatch, warm ischaemic time, and recipient sensitisation were not associated with eGFR. Control for these four variables showed that at 3 months, kidneys from cardiac-death donors had inferior eGFR compared with those from brain-death donors (–2·49 mL/min per 1·73 m², 95% CI –3·76 to –1·23, p=0·0001). But adjustment for similar variables associated with outcome at 12 months onwards showed no significant difference in eGFR between recipients of kidneys from the two donor types (–0·36 mL/min per 1·73 m², –2·00 to 1·27, p=0·66).

	Number of patients (n=739)	Hazard ratio (95% CI)	p value
Age of donors (years)			
<40	264	1·00	..
40–59	371	1·28 (0·84–1·93)	0·24
≥60	104	2·13 (1·30–3·51)	0·003
Age of recipients (years)			
18–39	178	1·00	..
40–59	372	1·13 (0·69–1·87)	0·63
≥60	189	2·14 (1·27–3·62)	0·0045
Cold ischaemic time (h)			
<12	97	1·00	..
≥12 and <18	287	1·99 (0·98–4·02)	0·057
≥18 and <24	244	1·82 (0·89–3·73)	0·10
≥24	111	2·00 (0·92–4·28)	0·08

Data are censored at 5 years. Graft failure includes patient's death.

Table 3: **Cox proportional hazards regression model for graft failure in first-time recipients of kidneys from cardiac-death donors, adjusted for age of donors and recipients, and cold ischaemic time**

In first-time recipients of kidneys from cardiac-death donors, the factors associated with graft outcome (censored at 5 years) were assessed by Kaplan-Meier survival analysis (figure 2), and then by Cox proportional hazards regression (table 3). Donors aged 60 years or older were associated with twice the risk of graft failure relative to donors younger than 40 years, and recipients of 60 years or older at transplantation were twice as likely to have graft failure compared with those younger than 40 years (table 3). Increasing cold ischaemic time showed a strong association with inferior graft survival; graft failure doubled at a cold ischaemic time of 12 h or more, although this difference was not significant (table 3). HLA matching was not associated with graft survival; the most poorly matched grafts had an association with inferior outcome that was not significant (table 4). Recipient sensitisation, warm ischaemic time, and machine perfusion had no effect on graft survival when these variables were individually added to the final Cox model (table 4).

	Number of patients (n=739)	Hazard ratio (95% CI)	p value
HLA mismatch level[20]			
1–2	170	1·00	..
3	405	1·35 (0·84–2·15)	0·21
4	164	1·55 (0·91–2·62)	0·11
Number of HLA mismatches*			
0–1	61	1·00	..
2–4	602	1·01 (0·53–1·95)	0·97
5–6	76	1·39 (0·64–3·02)	0·40
HLA-DR mismatches			
0	260	1·00	..
1	407	1·06 (0·73–1·55)	0·76
2	72	1·28 (0·71–2·30)	0·41
Machine perfusion			
Yes	162	0·96 (0·63–1·47)	0·84
No	477	1·00	..
Missing	100	0·74 (0·43–1·29)	0·29
Sensitisation†	739	1·00 (0·99–1·00)	0·92
Warm ischaemic time (min)‡			
<10	47	1·00	..
≥10 and <15	270	0·79 (0·38–1·65)	0·53
≥15 and <20	244	0·94 (0·46–1·93)	0·86
≥20	173	1·02 (0·48–2·14)	0·96
Delayed graft function§			
Immediate function	293	1·00	..
Delayed function	280	0·77 (0·48–1·24)	0·29

Data are censored at 5 years. *Total number of mismatches at HLA-A, HLA-B, and HLA-DR loci. †Data were analysed as a continuous variable. ‡Data are missing for some participants who were excluded from hazard ratio calculations. §Patients with primary non-function were excluded.

Table 4: **Cox proportional hazards regression model for individual factors affecting graft failure in first-time recipients of kidneys from cardiac-death donors, adjusted for age of donors and recipients, and cold ischaemic time**

	Transplants from cardiac-death donors			Transplants from brain-death donors		
	Number of patients (n=627)	eGFR (mL/min per 1·73 m²)	p value	Number of patients (n=5593)	eGFR (mL/min per 1·73 m²)	p value
Age of donors (years)						
<40	232	1	..	1740	1	..
40–59	307	−10·55 (−13·33 to −7·77)	<0·0001	2873	−9·32 (−10·30 to −8·35)	<0·0001
≥60	88	−14·66 (−18·68 to −10·64)	<0·0001	980	−16·01 (−17·28 to −14·74)	<0·0001
Age of recipients (years)						
18–39	157	1	..	1609	1	..
40–59	324	−5·65 (−8·61 to −2·70)	0·0002	2871	−3·26 (−4·21 to −2·33)	<0·0001
≥60	146	−6·24 (−9·88 to −2·61)	0·0008	1113	−3·91 (−5·11 to −2·72)	<0·0001
Cold ischaemic time (h)						
<12	82	1	..	304	1	..
≥12 and <18	251	−0·43 (−4·24 to 3·38)	0·83	2455	−3·65 (−5·45 to −1·84)	<0·0001
≥18 and <24	198	−1·43 (−5·36 to 2·50)	0·48	1777	−4·04 (−5·88 to −2·20)	<0·0001
≥24	96	−4·71 (−9·21 to −0·21)	0·04	1057	−5·08 (−7·01 to −3·14)	<0·0001
Cause of death in donors						
Trauma	158	1	..	868	1	..
Stroke	377	−3·29 (−6·28 to −0·31)	0·03	4198	−4·37 (−5·55 to −3·19)	<0·0001
Other	88	−4·93 (−8·97 to −0·89)	0·02	525	−3·82 (−5·47 to −2·18)	<0·0001
Missing	4	−5·52 (−20·79 to 9·75)	0·48	2	17·00 (−4·04 to 38·03)	0·11

Graft function is measured from estimated glomerular filtration rate (eGFR) at 3 months after transplantation. Data for eGFR are estimate (95% CI).

Table 5: **Multiple linear regression model of graft function in first-time recipients of kidneys, adjusted for age of donors and recipients, cold ischaemic time, and cause of death in donors**

Multiple linear regression modelling was used to assess the variables associated with eGFR at 3 months in first-time recipients of kidneys (table 5). For kidneys from cardiac-death donors, a reduction in eGFR was associated with donors aged 60 years or older relative to younger than 40 years, and with recipients of 60 years or older compared with younger than 40 years. Further, in kidneys from cardiac-death donors, cold ischaemic time of 24 h or more relative to less than 12 h, and donor death from stroke relative to death from trauma, were associated with a reduction in eGFR.

Discussion

This study is a comprehensive analysis of outcome in recipients of kidneys from controlled cardiac-death donors, providing two important findings. First, for recipients of their first grafts, kidneys from controlled cardiac-death donors had excellent results that were equivalent to results for kidneys from heart-beating brain-death donors. Second, important variables were associated with transplant outcome in recipients of kidneys from cardiac-death donors, and these variables could be used to improve organ allocation. Kidneys from uncontrolled cardiac-death donors were not included in our analysis because too few transplantations had been done for meaningful conclusions to be drawn. Changes to UK legislation in 2004 have allowed in-situ cooling of kidneys in uncontrolled cardiac-death donors, and if the necessary additional resources are made widely available, the number of such donors might increase in the future.

Widespread enthusiasm for expansion of kidney transplant programmes that use controlled cardiac-death donors has been tempered by concerns that transplant outcome might be inferior to that with kidneys from brain-death donors, with a worryingly high incidence of primary non-function and reports of poor long-term graft function.[12–14,22,23] Our results show that for controlled cardiac-death donors, such concerns are unfounded: although kidneys from cardiac-death donors had a higher rate of delayed graft function than did those from brain-death donors, the incidence of primary non-function was similar in recipients of kidneys from either donor type, and graft survival and function (eGFR) did not differ between the donor types up to 5 years after transplantation.

Factors associated with outcome of kidney transplants from brain-death donors are well established,[16–19] but for cardiac-death donors information is scarce. We based our study on a fairly complete national dataset that had been validated on many variables, enabling the evaluation of the potential factors affecting outcome in recipients of kidneys from cardiac-death donors to be more detailed than had previously been possible. The results show that for recipients of a first transplant, the main variables associated with transplant survival and function are age of donor, age of recipient, and cold ischaemic time. HLA mismatch, warm ischaemic time, and recipient sensitisation did not significantly affect transplant outcome in terms of graft survival up to 5 years after transplantation or eGFR. For consistency with previously published studies of transplant outcome, the follow-up data in our study were censored at 5 years; only 16% (133/845) of recipients had longer follow-up data for graft function, and analysis of the complete dataset beyond 5 years continued to show no difference in transplant outcome between recipients of kidneys from cardiac-death versus brain-death donors. Long-term follow-up to 10 years will be of interest, but we have no reason to suspect that longer-term transplant outcome in the two groups will diverge.

Increasing age of the donor is a well established independent risk factor for poor graft outcome in recipients of kidneys from brain-death donors, and is also a risk factor for graft survival in recipients of kidneys from cardiac-death donors,[14,23] although little is known about its effect on graft function.[12] Our findings show that in recipients of kidneys from cardiac-death donors, graft survival and function reduce as age of the donor increases, presumably

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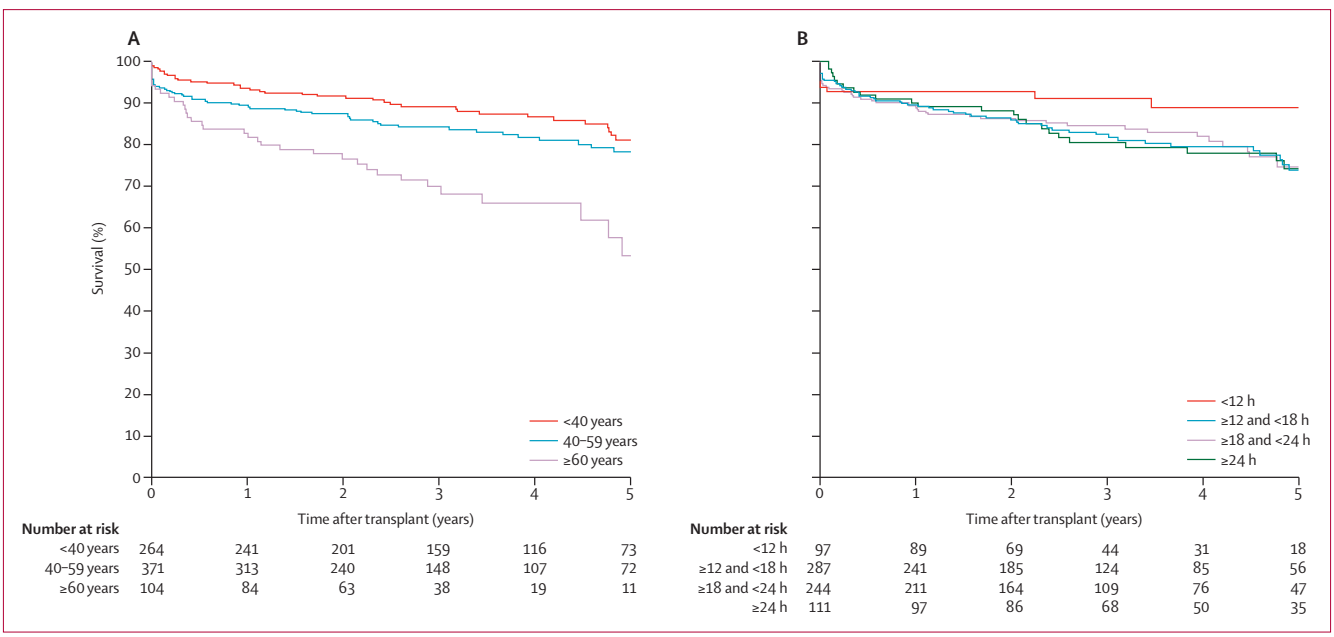

Figure 2: **Kaplan-Meier estimates of graft survival for first-time recipients of kidneys from cardiac-death donors, stratified by age of donor (A) and cold ischaemic time (B)**

because these kidneys have less functional reserve, have more vasculopathy, and are less able to withstand the injury that accompanies transplantation than are kidneys from younger donors.[24,25] The UK allocation policy for kidneys from brain-death donors aims to avoid large disparities in age between donor and recipient, and in view of our findings, a similar policy should be adopted for kidneys from cardiac-death donors.

Cold ischaemic time is a potential risk factor for graft survival in recipients of kidneys from cardiac-death donors,[14] and it was the only modifiable variable associated with transplant outcome in our study. A cold ischaemic time of less than 12 h was strongly associated with superior graft survival, but few kidneys from cardiac-death donors had such a short cold ischaemic time. Our findings suggest that increased efforts are needed to restrict the cold ischaemic time of these kidneys by reduction of the time taken for crossmatch testing before transplantation,[26] shortening of organ transport times, and ensuring adequate infrastructure in transplant centres. In addition to a potential benefit in terms of graft survival, our results suggest that reduction of cold ischaemic time could improve long-term graft function.

HLA matching affects transplant outcome for kidneys from brain-death donors and is an important component of the UK kidney allocation algorithm.[20,27] Kidneys from cardiac-death donors are not allocated through the national sharing scheme, and, unsurprisingly, many are given to recipients who are poorly matched for HLA. Poor graft matching was associated, but not significantly, with inferior graft survival in first-time recipients of kidneys from cardiac-death donors. In older recipients, therefore, HLA matching need not be the major factor in organ allocation, but in younger recipients, grafts that are poorly matched for HLA might be best avoided to prevent sensitisation to HLA that could restrict access to a further transplant.

In our study, about 10% of kidneys from cardiac-death donors were transplanted into second-time recipients, and graft survival in this group was notably reduced compared with first-time recipients of kidneys from cardiac-death donors and second-time recipients of kidneys from brain-death donors. Routine allocation of kidneys from cardiac-death donors to recipients with a failed kidney transplant might be inadvisable until the explanation for the poor outcome in this group of patients is better understood. Because second grafts in recipients of kidneys from cardiac-death donors were much less well matched for HLA than were second grafts in recipients of kidneys from brain-death donors, the poor outcome for second-time recipients of kidneys from cardiac-death donors might be attributable, at least in part, to poor HLA matching in an HLA-sensitised recipient population.[28,29]

Warm ischaemic time and the use of machine perfusion were not associated with transplant outcome in our study. However, these findings should be interpreted with caution because of the difficulties in ensuring accurate measurement of warm ischaemic time and controlling for potentially confounding variables in machine perfusion, such as selection bias and perfusion protocol. The use of machine perfusion for the storage of kidneys from cardiac-death donors holds much interest, and the

results of randomised controlled trials of machine perfusion versus simple cold storage are awaited. In keeping with previous reports, we recorded delayed graft function in many kidneys from cardiac-death donors, but graft survival was not affected.[14,22] By contrast, in kidneys from brain-death donors, delayed graft function is strongly associated with inferior graft outcome.[14,30–32] We speculate that in a proportion of kidneys from these two donor types, delayed graft function is indicative of clinically significant and irreversible pathology that results in poor graft outcome. However, the excess incidence of delayed graft function in kidneys from cardiac-death donors is indicative of reversible warm ischaemic injury that has little or no effect on long-term transplant outcome.

Information about immunosuppressive therapy was not available in our study, and we are unable to comment, therefore, on potential differences in the immunosuppressive regimens given to recipients of kidneys from cardiac-death or brain-death donors. The UK guidelines relating to kidneys from cardiac-death donors emphasise the potential advantage of avoiding exposure to nephrotoxic immunosuppressive agents in the early period after transplantation, especially if graft function is delayed.[33] Many recipients of kidneys from cardiac-death donors in this study probably received aggressive induction regimens to allow reduced exposure to calcineurin inhibitors in the early period after transplantation. This possibility could account for the unexpected finding that acute rejection was reduced in recipients of kidneys from cardiac-death donors, which contrasts with reports that the incidence of acute rejection is the same or even higher than in recipients of kidneys from brain-death donors.[11,12,31] Interestingly, experimental evidence suggests that kidneys from brain-death donors provoke a heightened inflammatory response that accelerates allograft rejection.[9]

Kidneys from controlled cardiac-death donors provide a good outcome in terms of both graft survival and graft function in first-time recipients and should be regarded as equivalent to kidneys from brain-death donors. The factors shown to affect transplant outcome for kidneys from cardiac-death donors will help to guide clinical decision making and inform future allocation policy.

Contributors

All authors contributed to the study design and data interpretation. DMS, RJJ, JA, and DC undertook the analysis and validation of the data. DMS and JAB drafted the initial report, and all authors contributed to the final draft. Data was provided for the UK NHS Blood and Transplant registry by staff from the UK renal transplant centres, and compiled from the reigstry by DMS and JA.

Conflicts of interest

JAB is a trustee of Roche Organ Transplant Foundation; his department has received grants from pharmaceutical companies which market immunosuppressive therapy, notably Astellas, Novartis, Roche, and Wyeth, and from machine preservation manufacturers Organ Recovery Systems; and he has received travel and accommodation costs from Astellas to attend a training course. CJW has received research grants and honoraria for travel, accommodation, and registration to transplant conferences from Astellas, Novartis, Roche, and Wyeth; and research grants from Organ Recovery Systems. All other authors declare that they have no conflicts of interest.

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