Ischemia/reperfusion injury : a metabolic meltdown

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Part II

Clinical

Translation

VI

Realistic restrictions in cold ischemia time result in similar outcomes for kidneys donated after brain and cardiac death.

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ABSTRACT

Background: There are reservations with respect to the use of kidneys from cardiac death donors (DCD) in kidney transplantation. However, several outcome-based studies suggest that long-term graft survival of DCD grafts may be similar to survival of brain death donor (DBD) grafts. As such conclusions would have far reaching consequences, we considered an in-depth analysis of long-term outcomes after DBD and DCD kidney transplantations relevant.
Materials & Methods: Differences in 10-years graft survival were analysed in the Netherlands Organ Transplantation Registry (NOTR) database, for the 2000-2017 interval (DBD n=4084 (58.6%); DCD n=2891 (41.4%)), by means of calculating hazard ratios en plotting Kaplan Meier survival curves. Differences in graft survival for patients with and without DGF/PNF were calculated for the two graft types. Results were additionally stratified by intervals of cold ischemia times. For functional outcome (eGFR) we evaluated all transplantations performed in the Leiden University Medical Center (LUMC) (DBD n=370; DCD n=258) between 2007-2015.
Results: The NOTR data indicate a 50% higher incidence of primary non-function, and an almost tripled incidence of delayed graft function (DGF) in DCD grafts. After excluding the grafts with primary non-function (7,9% of all DCD and 4.5% of all DBD grafts) 10-year graft survival was similar for both donortypes (HR (DBD reference): 1.00 (95%CI 0.88-1.15); P=0.95). Further evaluation shows that duration of cold ischemia longer than 24 h disproportionally influences incident PNF and mitigates graft survival of DCD grafts (HR (DBD reference): 1.54 (1.21-1.96); P<0.001). Contrasting effects were seen for the impact of ischemia time on incident DGF. Thereby, it was shown that incident DGF negatively impacts graft survival in DBD grafts, while it does not so in DCD grafts (P=0.001). This differential impact of DGF on DBD grafts may reflect biological differences between the graft-types. Indeed, recovery of graft function is exponential in DCD grafts, resulting in long-term graft functions similar to those of DBD grafts, despite inferior initial function of DCD grafts.
Conclusion: Although DBD grafts have superior short-term outcomes, mid- and long-term graft survival is similar for DBD and DCD grafts. The increased susceptibility to longer ischemia times, in particular over 24 hours calls for stricter guidelines with respect to the logistics of DCD procedures.

INTRODUCTION

Kidney transplantation remains the only curative option for patients with end-stage renal disease. In an era of growing waiting lists for renal transplants, pressing donor shortages led to an increased use of so called "extended criteria grafts" and grafts donated following cardiac death (DCD). Transplantation procedures with DCD grafts associate with increased incidences of primary non-function (PNF) and delayed graft function (DGF). The latter phenomenon is considered to negatively influence graft function and long-term graft survival.[1-4]
Remarkably, a reticent attitude towards use of DCD grafts is not supported by data from some small cohort studies,[5-7] and follow-up data from the UK transplant registry.[8] In fact, the UK registry indicated equal 5-year graft survival rates for DCD grafts and brain-death donor (DBD) grafts. However, the registry data did signal potential concern with respect to differences in risk profiles; in particular a possible increased susceptibility of DCD grafts for (prolonged) cold-ischemia[9], thereby raising a cause of reservation on the generalizability of the observations. Nevertheless, reported similar survival outcome for DBD and DCD grafts is remarkable and lead some expert-opinions to call for a more liberal use of DCD grafts in the light of pressing donor shortages.[10] Still, use of DCD grafts is controversial[11], with many societies/countries refraining from these grafts.[12-16] In this light we considered an independent and adequately powered evaluation of outcomes of procedures with grafts donated after brain death (DCD) and DCD grafts relevant. From this perspective, the position of The Netherlands is unique as it has a long and relative liberal tradition with regard to use of DCD grafts. In fact, DCD procedures now account for 50% of the deceased donor procedures performed nationwide. The aim of this study was to compare long-term outcome (graft survival and functioning) of DBD and DCD grafts. This paper reports the outcomes for all 2891 DCD procedures performed in The Netherlands within the 2000 and 2017 interval and analyses functional outcome of 258 DCD procedures performed in our center.

MATERIALS & METHODS

The Netherlands Organ Transplant Registry (NOTR) registry is a nationwide registry of kidney transplant recipients from all eight kidney transplant centres in the Netherlands. The NOTR registry is managed by the Dutch Transplant Foundation and includes recipient and donor characteristics and a variety of outcome parameters (Table 1). In the first year after transplantation, registry follow-up is at 3 months, thereafter on a yearly basis. We retrieved data on recipient and donor characteristics, and transplantation outcomes for all transplants performed between January 1st 2000 and December 31st 2016.

DONOR CRITERIA AND PROCEEDINGS OF DONATION AFTER BRAIN AND CIRCULATORY DEATH

The NOTR collaborates with Eurotransplant, the organisation that facilitates organ allocation in Belgium, Germany, Luxembourg, Austria, Hungary, Slovenia, Croatia and the Netherlands. Donation takes places following the Eurotransplant quality standards and practices. For DBD grafts this means that a donor is diagnosed brain dead according to current national regulations and laws on transplantation. During the donation procedure the DBD donor is heparinized and after cannulation the organs are flushed with cold perfusion fluid (HTK/UW). After retrieval, organs are transported and stored by means of static cold storage preservation.
In DCD donation, the heart irreversibly stopped beating and the donor is diagnosed dead according to the respective national laws and regulations. All DCD kidneys were donated by a controlled DCD donor (category 3: awaiting cardiac arrest after withdrawal of life-supporting treatments in the ICU). After a no-touch period, organs were preserved via arterial cold perfusion generally with UW or HTK. Organs were retrieved and preserved by means of static cold storage.
All organs were matched and allocated following the Eurotransplant guidelines.

FUNCTIONAL RECOVERY RATE

Putative effects of donortype on functional (clearance) graft recovery were explored in a retrospective analysis of all deceased donor kidney transplantations (n= 628) performed between January 2007 and June 2015 in the Leiden University Medical Center (LUMC) (Sup.Table 1). All kidneys received from cardiac death donors were from the Maastricht category 3 (controlled DCD: awaiting cardiac arrest after withdrawal of life-supporting treatments in the ICU).[17] Data were retrieved from the (electronic) patient records.

STUDY END POINTS

Post transplantation outcome was classified in the following categories: primary function, delayed graft function (DGF) and primary non-function. DGF was defined by the need of dialysis because of initial non-function in the first week(s) after kidney transplantation that was followed by functional recovery. Primary non-function was defined as persistent non function of the kidney graft upon transplantation. The 'Kidney Donor Risk Index' (KDRI) was calculated using the coefficients provided[18] and creatinine clearance estimated by the Cockcroft-Gault Equation.

Weekly eGFR measurements in the first 12 weeks and at 3, 6, 9, 12, 18, 24, 36 and 48 months after transplantation were collected of all LUMC patients that showed functional graft recovery (i.e. PF and DGF). For grafts that developed DGF 'week 1', the first week of eGFR measurements, was defined as the first week following the last dialysis. Graft function recovery curves were generated up to 12 months after transplantation for the LUMC patients.

STATISTICAL ANALYSES

With respect to the NOTR database, differences between DBD and DCD donor grafts (i.e. recipient and donor characteristics and outcome parameters) were described (Table 1). A multivariate logistic regression analyses was performed to assess factors associated with primary non-function, stratified by graft type (*variables with a p-value ‹0.05 in the uni-variate analysis were entered in the multi-variate analysis*). Results are represented as OR with 95%CI. Differences in graft survival were calculated for DCD versus DBD as reference category and expressed as HR with corresponding 95%CI and plotted in Kaplan Meier survival figures. Graft survival was truncated at 10 years of follow-up. Results were additionally stratified by intervals of cold ischemia times. Differences in graft survival for patients with and without DGF were calculated for both DBD and DCD grafts. Analyses were performed using STATA/SE version 12.0 (StataCorp, Texas, USA).

RESULTS

The NOTR registry, for the 2000-2017 interval, include data for 4084 (58.6%) DBD and 2891 (41.4%) DCD kidney transplantations. With the exception of a higher proportion of male donors in the DCD group, and a different cause of death distribution, donor characteristics were similar for the 2 donor groups (Table 1). Equivalence of the two groups is also reflected in comparable mean KDRI's for the DBD and DCD grafts (1.29 and 1.21 respectively when excluding the DCD component from the equation).

Table 1. NOTR characteristics

	DBD	DCD
	N=4084 (58.6%)	N=2891 (41.4%)
Male	1950 (47.7%)	1689 (58.4%)
Age (mean (sd))	48.2 (25.0)	48.6 (15.5)
BMI (mean (sd))	25.0 (4.3)	25.2 (4.6)
Last Creatinine [IQR]	70 [54-89]	67 [53-84]
MDRD (mean (sd))	92 (37)	101 (38)
Cause of death Trauma Stroke Cardiac arrest Other	 906 (22.2%) 2404 (58.9%) 165 (4.0%) 609 (14.9%)	 901 (31.2%) 1090 (37.7%) 536 (18.5%) 364 (12.6%)
Hypertension No Yes Unknown	 2584 (63.3%) 1005 (24.6%) 495 (12.1%)	 2172 (75.1%) 543 (18.8%) 176 (6.1%)
Smoking No Yes Unknown	 1889 (46.3%) 1859 (45.5%) 336 (8.2%)	 1372 (47.5%) 1328 (45.9%) 191 (6.6%)
Cold Ischemia Time ‹12 hrs 12-18 hrs 18-24 hrs ›24 hrs Unknown	 787 (19.3%) 1398 (34.23%) 1001 (24.5%) 536 (13.1%) 362 (8.9%)	 497 (17.2%) 1110 (38.4%) 771 (26.7%) 304 (10.5%) 209 (7.2%)
Warm Ischemia Time (min) [IQR]	33 [26-41]	32 [26-40]
KDRI [IQR]	1.29 [1.04-1.62]	1.38 [1.12-1.71] 1.21 [0.98-1.50] (minus DCD component of KDRI equation)

Early Graft Loss			
Primary non function		183 (4.5%)	227 (7.9%)
Loss between day 8-90		122 (3.0%)	86 (3.0%)
Overall Graft Loss		1577 (38.6%)	1058 (36.6%)
Procedural		86 (5.5%)	86 (8.1%)
Permanent non function		55 (3.5%)	83 (7.8%)
Hyper acute rejection		21 (1.3%)	11 (1.0%)
Death recipient		785 (49.8%)	467 (44.1%)
Rejection		426 (27%)	255 (24.1%)
DGF			
No		2772 (73.4%)	918 (35.7%)
Yes		653 (17.3%)	1230 (47.8%)
Unknown		349 (9.2%)	427 (16.6%)
Sex Recipient (male)		2361 (57.8%)	1805 (62.4%)
Age Recipient		49.9 (16.1)	53.7 (13.4)
BMI recipient		25.0 (4.5)	28.8 (4.4)
Mismatch HLA-Dr	1	2011 (49.4%)	1713 (59.7%)
	2	466 (11.4%)	231 (8.1%)
HLA-A	1	2022 (49.6%)	1589 (55.1%)
	2	589 (14.5%)	428 (14.9%)
HLA-B	1	2005 (49.2%)	1725 (59.9%)
	2	1079 (26.5%)	685 (23.8%)
Panel reactive antibodies >5%		14.8%	9%
3 months creatinine [IQR]		132 [105-167]	146 [116-188]
Year 1 creatinine [IQR]		127 [102-161]	136 [109-176]
-DGF		123 [100-154]	125 [102-159]
+DGF		145 [98-159]	145 [99-163]
Year 5 creatinine [IQR]		126 [99-166]	135 [106-180]
-DGF		124 [115-187]	126 [117-189]
+DGF		139 [108-188]	142 [112-191]

The registry data indicate an almost 50% higher incidence of primary non-function, and an almost tripled incidence of DGF in DCD grafts (Table 1). DCD procedures moderately impacted 10-year graft survival (HR for graft loss (DBD reference): 1.19 (95%CI: 1.06-1.32); P=0.002, Figure 1A). Recipient survival was similar for the two graft types (HR for recipient death after correcting for the higher recipient age in the DCD group: 0.95 (95%CI: 0.86-1.05), P=ns).
Further evaluation showed that the observed survival disadvantage of DCD grafts essentially relates to the higher incidence of primary non-function in these grafts, since exclusion of grafts with primary non-function resulted in similar 10-year graft survival (HR for graft loss (DBD is reference): 1.00 (95%CI 0.88-1.15); P=0.95), Sup.Fig.1).

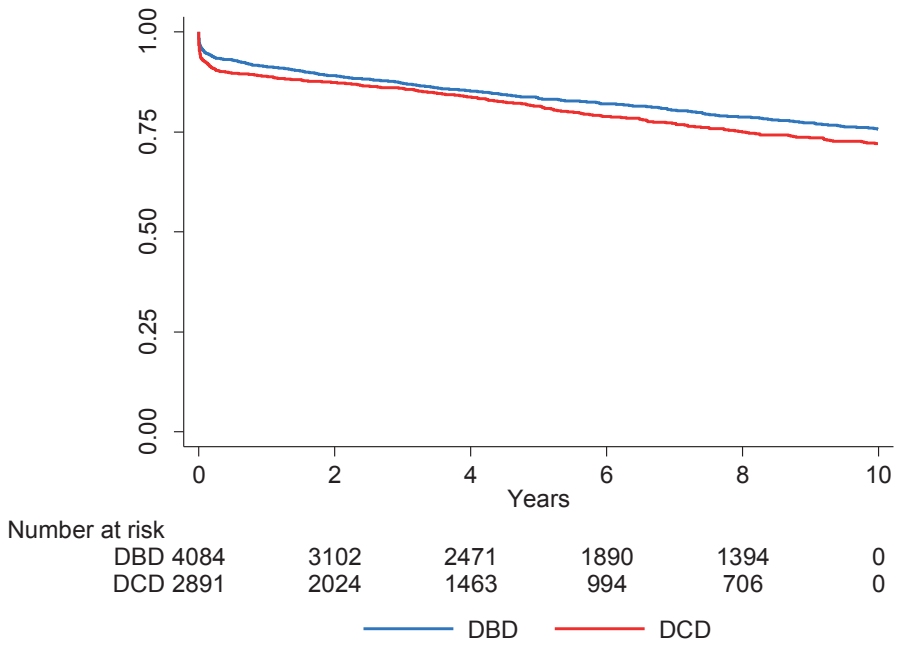


Figure 1A. 10-year graft survival of DBD(red) and DCD(blue) grafts transplanted in the Netherlands

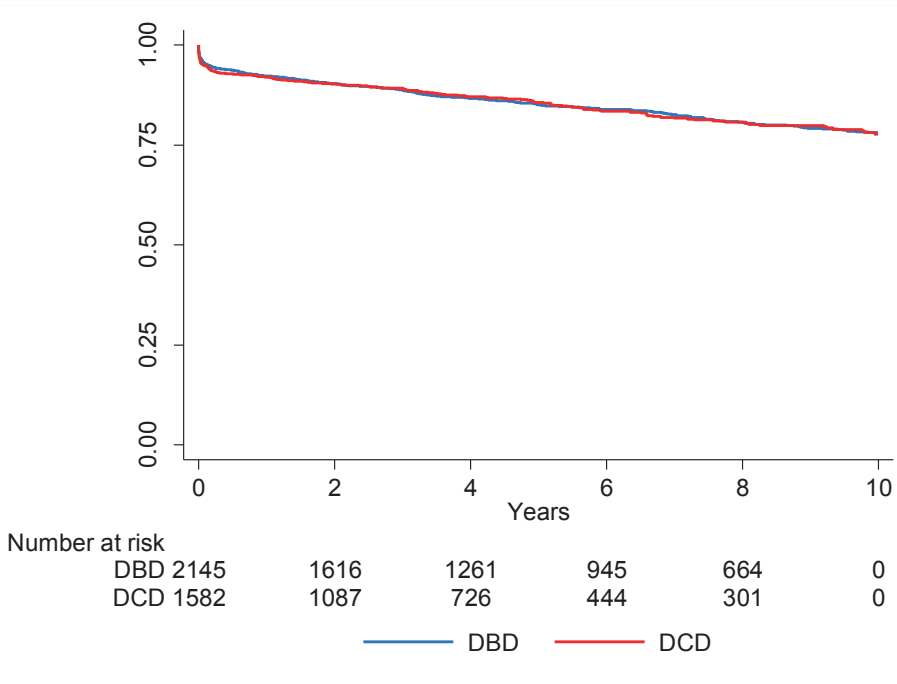


Figure 1B. 10-year graft survival of DBD(red) and DCD(blue) grafts with cold ischemia times restricted to 18 h or less

Incident primary non-function strongly associates with cold-ischemia time (P‹1.10-11, Table 2). Along similar lines the UK registry data signalled concern with regard to an impact of longer ischemia times on DCD graft survival.[8,9] We therefore specifically addressed the impact of this potentially modifiable risk factor cold-ischemia time on outcome. Table 3 shows that longer ischemia times disproportionally influence incident PNF as well as long-term graft survival in DCD grafts as compared to DBD grafts. To test the impact of a policy with restricted ischemia times, we evaluated graft survival data for all procedures with a maximum ischemia times of 18 and 24 hours. This re-evaluation showed that a stricter policy with capped maximum cold ischemia times results in 10-year outcome equivalence for DBD and DCD grafts (HR for graft loss (DBD reference) for maximum cold-ischemia times of 18 and 24 hours respectively: 1.01 (95%CI 0.85-1.19); P=0.91) and 1.12 (95% CI: 0.99-1.27); P=0.08 (Figure 1B).

Table 2. Factors associated with primary non-function (multi-variate analysis)

	DBD	DCD
Date of transplant	1.002 (0.999-1.085)	1.007 (1.003-1.010) **
Donor age	1.023 (1.011-1.034)**	1.029 (1.018-1.041) **
Donor height	0.969 (0.957-0.98) **	0.985 (0.971-0.999) *
Cold Ischemia Time (hrs)	1.031 (1.007-1.055) *	1.043 (1.016-1.072) *
Warm Ischemia Time (min)	1.014 (1.004-1.024) *	1.022 (1.013-1.031) **

*P‹0.04; **P‹0.00015

Table 3. Discordant impact of longer cold ischemia times on DCD graft survival (DBD is reference)

DBD as reference	N	HR (95%CI)	p-value	Adjusted for donor age HR (95%CI)	p-value
‹ 12 h	1194	1.08 (0.76-1.54)	0.66	1.03 (0.72-1.46)	0.88
12 – 15 h	1690	0.93 (0.73-1.19)	0.56	0.91 (0.72-1.16)	0.47
16 – 17 h	843	1.06 (0.77-1.47)	0.70	1.08 (0.78-1.49)	0.63
18 – 19 h	657	1.12 (0.80-1.57)	0.51	1.16 (0.82-1.62)	0.40
20 – 21 h	581	1.32 (0.96-1.82)	0.09	1.35 (0.98-1.86)	0.07
22 – 23 h	487	1.33 (0.93-1.88)	0.11	1.38 (0.97-1.95)	0.07
≥24 h	969	1.48 (1.17-1.88)	0.001	1.54 (1.21-1.96)	‹0.001

HR graft loss Cold ischemic time under 18h (DBD is reference) (n=3727): 1.01 (0.85-1.19); p=0.91

HR graft loss Cold ischemic time under 24h (DBD is reference) (n=5452): 1.12 (0.99-1.27); p=0.08

The almost tripled incidence of DGF in DCD grafts but comparable 10-year graft survival for DBD and DCD grafts implies a differential impact of DGF on outcome, with DBD grafts being more susceptible than DCD grafts. A discordant effect is supported by the differential impact of incident DGF on graft *survival* (HR for graft loss following DGF in the DCD group: 0.69 (95% CI: 0.59-0.86; P=0.001, Figure 2). The impact of DGF on graft *function* on the other hand, was similar for DBD and DCD grafts (Table 1: one and five year post-transplantation creatinine levels). In fact, reduced graft function in the DCD group was fully explained by the higher incidence of DGF in this group.

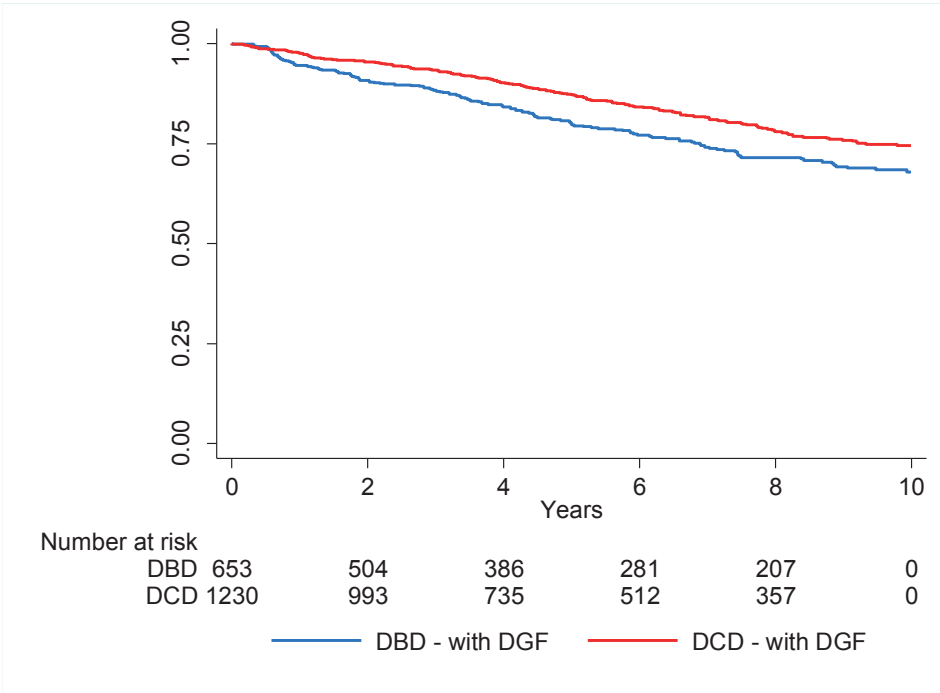


Figure 2 Differential impact of DGF on graft survival of DBD and DCD grafts (excluding grafts with primary non function) n=653 (DBD) and 1230 (DCD)). HR for graft loss (DBD reference): 0.69 (95%CI 0.55-0.86); P=0.001.

The differential impact of DGF on DBD and DCD grafts survival may imply biological differences in resilience of the two grafts types. To further explore such a difference we evaluated post-transplantation graft recovery dynamics in a subset of 628 grafts transplanted between 2010-2015 in our center (n=628, details of these grafts are provided in Supplemental Table 1) for which detailed recovery data is available. Data for DBD grafts without DGF show full functional reinstatement within the first week of transplantation (Figure 3), while DBD grafts with DGF

show a protracted recovery with an ultimate clearance that is approximate 12% less than that of grafts without DGF.
DCD grafts with and without DGF show parallel recovery dynamics that are clearly distinct from those of DBD grafts. Initial functions are profoundly inferior to those of DBD grafts, but the grafts show a catch up, with exponential recoveries in the first weeks of transplantation (Figure 3, and Table 4), ultimately resulting in long-term graft functions similar to those of DBD grafts (Table 1: similar 1 and 5-year post-transplantation creatinine levels in the full NOTR cohort)).

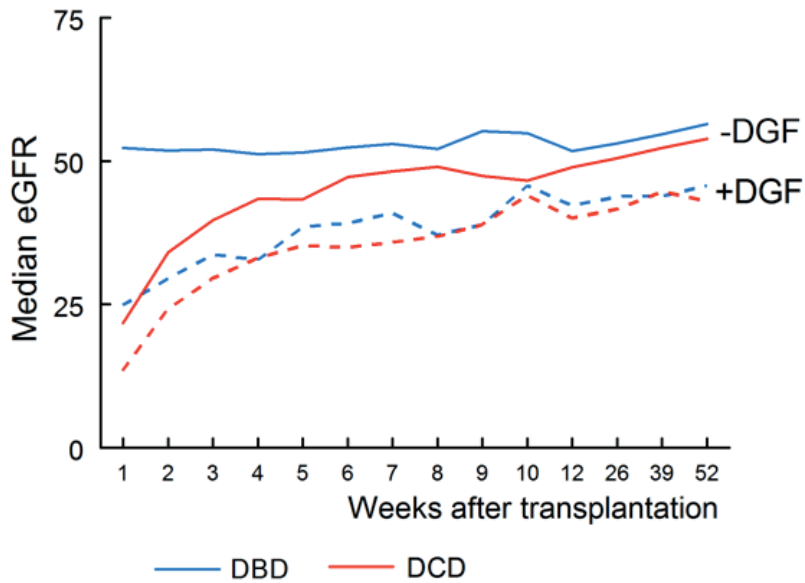


Figure 3. Graft recovery following transplantation. Solid lines: grafts without DGF, dashed lines grafts with DGF. Week 1 in the +DGF groups is defined as the first week without a need for dialysis.

Table 4. Post transplantation functional recovery of DBD and DCD grafts

	Relative eGFR recovery (week 26) vs baseline (week 1)	Mean absolute eGFR (ml/min/1,73m2) recovery at week 26 from baseline (week 1)	Number of dialysis performed because of DGF (mean(SD))
DBD -DGF	+ 1.55%	0.84 ml/min/1.73m2	
DBD +DGF	+ 55.9%	16.83 ml/min/1.73m2	4.78(3.1)
DCD -DGF	+ 95.4%	26.05 ml/min/1.73m2	
DCD+DGF	+ 155.4%	27.31 ml/min/1.73m2	5.02(2.9)

DISCUSSION

Results of this nation-wide evaluation of data from a society with an almost equal allocation of DCD and DBD renal grafts confirm and extend earlier indications of similar mid- and long-term outcomes for DCD and DBD grafts, after excluding patients with primary non-function.[6-9,19]

Pressing donor shortages in an era of progressive demand for donor kidneys have led to a progressive use of grafts from so-called marginal donors, and from DCD donors. Yet, high incidences of DGF and primary non-function in DCD grafts fuels concern on a more liberal use of this latter type of grafts.[13] In fact, in most societies including the USA, use of DCD procedures has stabilized at approximately 10% of the deceased donor procedures,[20] although some opinion leaders are now calling to amend the restrictive policy with regard to DCD grafts.
A less reticent attitude towards DCD grafts is supported by preliminary reports from small observational studies, and particularly by data from the UK registry.[5-9] Although the number of DCD procedures included in these studies remains limited, all reports indicate similar outcomes for DCD and DBD grafts. However, concern was raised with regard to a higher susceptibility of DCD grafts towards (prolonged) ischemia.[1,13] Although promising, these reports, and the reported more pronounced impact of prolonged ischemia on DCD outcomes require confirmation.

With an almost equal share of DBD and DCD grafts, the situation in the Netherlands is uniquely positioned to evaluate outcomes after DBD and DCD procedures. The context in the Netherlands not only allows for the evaluation of a large number of DCD procedures, but it also reduces selection biases that may result from a reticent attitude with regard to the use of DCD grafts (i.e. preference for DCD grafts with superior donor characteristics (i.e. young donor age; short ischemia time).[5-7]

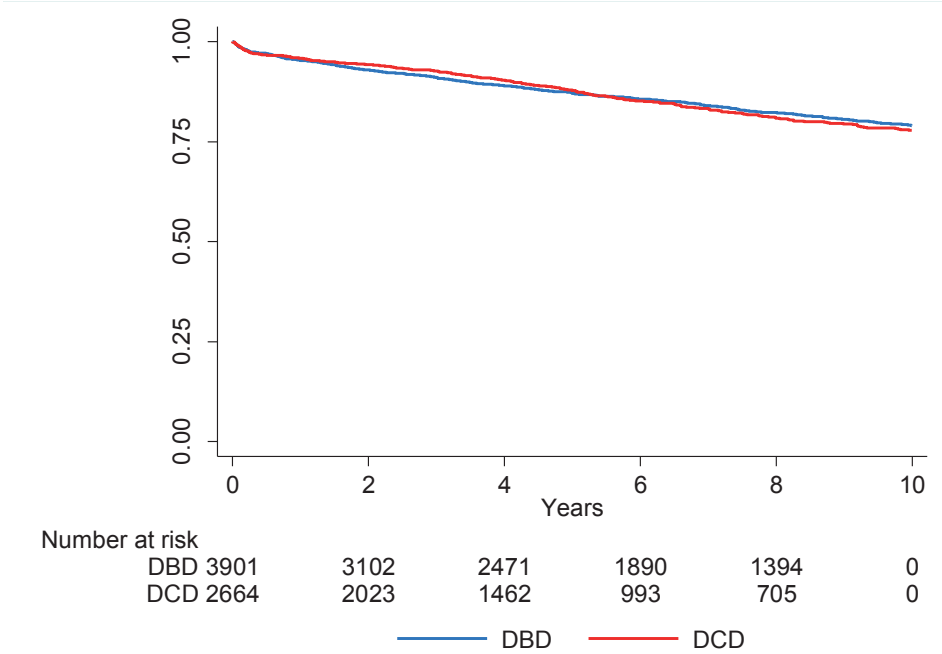
The liberal attitude towards DCD grafts for the Dutch context is reflected in the high proportion of DCD grafts (41% for the 17 year observation period in this study, 50% in 2016) and equal donor characteristics for DBD and DCD grafts. Although the cohort data confirm the higher incidence of primary non-function and DGF in-, and an (modestly) impaired 10-year survival of DCD grafts, results show that this disadvantage essentially relates to the use of DCD grafts with cold ischemia times over 24 hours. In fact we observed similar mid- and long-term outcomes for DBD and DCD grafts with cold-ischemia times less than 24 hours. Consequently, the data confirm observations from the UK registry and showed

discordant impacts of longer ischemia times on DCD graft survival for cold ischemia times in excess of 24 hours.

Discordant impact of longer ischemia times, and different impact of DGF on graft survival may imply differences in graft biology. Such a concept is supported by functional recovery analysis (eGFR) performed on all deceased donor procedures performed in our hospital. While this data extends the superior short-term outcomes for DBD grafts without DGF, it signals a remarkable recovery potential of DCD graft with an exponential catch up of kidney function in the first weeks following transplantation. This ultimately results in a functional and survival equivalence of DBD and DCD grafts, as outcomes for kidney transplantation should be based on mid- and long-term parameters
The notable recovery potential of DCD grafts, and superior survival of these grafts following DGF point to differences in graft biology. One could speculate that these differences relate to the negative impact of donor brain death on DBD grafts[21,22] and/or activation of tissue protective responses such as ischemic preconditioning,[23] and/or activation of the innate repair receptor[24] during the initial warm ischemia episode following cardiac death in DCD grafts.

In conclusion, this study that includes almost 2900 DCD procedures shows that mid- and long-term outcome after DBD and DCD kidney graft procedures is similar. A focus on short-term outcomes neglects the superior recovery potential of DCD grafts.
The increased susceptibility to longer ischemia times, in particular over 24 hours calls for stricter guidelines with respect to the logistics of DCD procedures.

SUPPLEMENTARY FIGURES



Supplemental Figure 1. Similar 10-year graft survival after excluding all grafts with primary non-function (n=410), HR (DBD reference): 1.00 (95%CI 0.88-1.15); P=0.95

SUPPLEMENTARY TABLES

Supplemental Table 1. Patient characteristics (donor, recipient and procedure) of the LUMC cohort.

Factors		*DBD*	*DCD*	*P-value*
DONOR				
Cause of death donor	CVA / SAB Trauma CA-OHCA-AMI Tumour Suicide – respiratory Miscellaneous	232 (63.6) 85 (23.3) 15 (4.1) 2 (0.6) 14 (3.8) 17 (4.7)	96 (38.1) 59 (23.4) 51 (20.2) 2 (0.8) 20 (7.9) 24 (9.5)	<0.001
Cardiac arrest donor	No Yes	259 (76.4) 80 (23.6)	147 (59.0) 102 (41.0)	<0.001
Age donor	≤40 years 41-59 years 60 or older	109 (29.9) 161 (44.1) 95 (26.0)	61 (24.2) 107 (42.5) 84 (33.3)	0.1
Sex donor	Male Female	187 (51.2) 178 (48.8)	149 (59.1) 103 (40.9)	0.05
BMI donor	Under 23 23-25 26 and higher	94 (25.9) 140 (38.6) 129 (35.5)	68 (27.0) 78 (30.9) 106 (42.1)	0.1
Diabetes donor	No Yes	320 (93.8) 21 (6.2)	231 (92.8) 18 (7.2)	0.6
Smoking status donor (Pack Years)	None Less than 25 25 or more	175 (50.7) 113 (32.8) 57 (16.5)	112 (46.7) 79 (32.9) 49 (20.4)	0.4
Duration hospital admission donor	2 or less 3-4 More than 4 days	237 (65.1) 55 (15.1) 72 (19.8)	73 (29.1) 75 (29.9) 103 (41.0)	<0.001
Hypotensive period donor	No Yes	242 (71.8) 95 (28.2)	189 (77.1) 56 (22.9)	0.15
Hypotensive minutes	0 1 or more	263 (72.1) 102 (27.9)	187 (74.2) 65 (25.8)	0.6
Terminal Creatinine Donor	<55 55-74 75 and higher	130 (35.8) 116 (32.0) 117 (32.2)	81 (32.3) 88 (35.1) 82 (32.7)	0.6
Heart or lung donor	Yes No	214 (58.9) 149 (41.1)	54 (21.8) 194 (78.2)	<0.001
Pancreatic or liver donor	Yes No	340 (93.9) 22 (6.1)	126 (51.2) 120 (48.8)	<0.001
RECIPIENT				

Age recipient	≤40 years 41–59 years 60 or older	72 (19.8) 172 (47.4) 119 (32.8)	38 (15.1) 100 (39.7) 114 (45.2)	0.007
Sex recipient	Male Female	218 (60.1) 145 (39.9)	151 (59.9) 101 (40.1)	0.9
TRANSPLANTATION PROCEDURE				
Organ	Kidney kidney Kidney pancreas Kidney liver	232 (63.6) 127 (34.8) 6 (1.6)	235 (93.3) 14 (5.5) 3 (1.2)	‹0.001
Side	Right Left	129 (35.3) 236 (64.7)	113 (44.8) 139 (55.2)	0.02
Transplantation period	2007–2010 2011–2015	182 (49.9) 183 (50.1)	96 (38.1) 156 (61.9)	0.004
Panel Reactive Antibody	0 ≥1	239 (66.9) 118 (33.1)	178 (71.2) 72 (28.8)	0.3
Warm ischaemic time (WIT1, (min))	‹15 15–19 ≥20	NA	88 (35.3) 99 (39.8) 62 (24.9)	
Lukewarm ischaemic time (LIT1, (min))	‹15 15–19 ≥20	NA	93 (39.6) 66 (28.1) 76 (32.3)	
WIT1 + LIT1 (min)	‹30 30–39 ≥40	NA	89 (38.0) 80 (34.2) 65 (27.8)	
Lukewarm ischaemic time (LIT2 (min))	≤50 51–69 ≥70	97 (26.8) 112 (30.9) 153 (42.3)	105 (41.8) 69 (27.5) 77 (30.7	‹0.001
Lukewarm ischaemic time (LIT—total (min))	‹60 60–79 ≥80	162 (44.8) 104 (28.7) 96 (26.5)	57 (24.3) 70 (29.8) 108 (45.9)	‹0.001
Cold ischaemic time (CIT (h))	≤10 11–14 ≥15	123 (34.0) 135 (37.6) 103 (28.4)	30 (12.0) 117 (46.8) 103 (41.2)	‹0.001
Warm ischaemic time (WIT2 (min))	‹30 30–34 ≥35	170 (46.8) 83 (22.9) 110 (30.3)	105 (41.8) 54 (21.5) 92 (36.7)	0.3
Perfusion fluid	HTK UW Modified UW Other	70 (19.3) 276 (76.2) 14 (3.9) 2 (0.6)	146 (57.9) 90 (35.7) 14 (5.6) 2 (0.8)	‹0.001
Perfusion fluid amount	≤6000 6000–8000 ›8000	194 (54.6) 111 (31.3) 50 (14.1)	53 (22.6) 64 (27.2) 118 (50.2)	‹0.001

Supplemental Table 1. Patient characteristics: DBD versus DCD grafts.
DCD grafts were transplanted in significantly older recipients compared to DBD grafts (resp. 55 versus 52 years) and duration of hospital admission before donation of the graft was significantly longer in DCD versus DBD grafts. Thereby, during the interval 2007-2010 significantly more DBD then DCD grafts were transplanted, this difference was not significant for the 2011-2015 interval. Significantly more DBD grafts were in the category of shortest duration of cold ischemia time (34% versus 12% in DCD grafts).

Supplemental Table 2. Functional outcome of kidney transplantations in our single center (LUMC) cohort.

Single center (LUMC) cohort (n=628)				
	PF	DGF	PNF	Unknown
DBD (n=370)	n=292 (78.9%)	n=73 (19.7%)	n=5 (1.4%)	-
DCD (n=258)	n=102 (39.5%)	n=150 (58.1%)	n=6 (2.3%)	-

Odds Ratio (OR) for DGF in DCD compared to DCD grafts: 5.88 (4.11-8.42); p<0.001).
PF = primary function, DGF = delayed graft function, PNF = primary non-function

Supplemental Table 3. Summary of the defined ischemia periods

ISCHEMIC PERIOD	TIME SLOT DEFINED
Lukewarm ischaemic time 1 (LIT1) (DCD donors)	Switch off – death
Warm ischaemic time 1 (WIT1) (DCD donors)	Death – start cold perfusion
Lukewarm ischaemic time 2 (LIT2) (DCD and DBD)	Start cold perfusion – nephrectomy
Cold ischaemic time (CIT) (DCD and DBD)	Start cold perfusion – start kidney transplantation procedure
Warm ischaemic time 2 (WIT2) (DCD and DBD)	Start kidney transplantation procedure – reperfusion of the graft

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