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Similar 5-Year Estimated Glomerular Filtration Rate Between Kidney Transplants From Uncontrolled and Controlled Donors After Circulatory Death—A Dutch Cohort Study

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Background. Organ shortage persists despite a high rate of donation after circulatory death (DCD) in the Netherlands. The median waiting time for a deceased donor kidney in 2013 was 3.5 years. Most DCD kidneys are from controlled DCD (cDCD; Maastricht category III). Experience with uncontrolled donors after cardiac death (uDCD), that is, donors with an unexpected and irreversible cardiac arrest (Maastricht categories I and II), is increasing; and its effect on transplant outcomes needs evaluation. **Methods.** We used the Dutch Organ Transplantation Registry to include recipients (≥18 years old) from all Dutch centers who received transplants from 2002 to 2012 with a first DCD kidney. We compared transplant outcome in uDCD (n = 97) and cDCD (n = 1441). **Results.** Primary nonfunction in uDCD was higher than in the cDCD (19.6% vs 9.6%, $P < 0.001$, respectively). Delayed graft function was also higher in uDCD than in cDCD, but not significantly (73.7% vs 63.3%, $P = .074$, respectively). If censored for primary nonfunction, estimated glomerular filtration rates after 1 year and 5 years were comparable between uDCD and cDCD (1 year: uDCD, 44.3 (23.4) mL/min/m^2 and cDCD, 45.8 (24.1) mL/min/m^2; $P = 0.621$; 5 years: uDCD, 49.1 (25.6) mL/min/m^2 and cDCD, 47.7 (21.7) mL/min/m^2; $P = 0.686$). The differences in primary nonfunction between kidneys from uDCD and cDCD were explained by differences in the first warm ischemic period, cold ischemic time, and donor age. **Conclusions.** We conclude that uDCD kidneys have potential for excellent function and can constitute a valuable extension of the donor pool. However, further efforts are necessary to address the high rate of primary nonfunction.

(*Transplantation* 2017;101: 1144–1151)

In 2013 in the Netherlands, 60% of all deceased donor kidney transplantations were performed with kidneys from donation after circulatory death (DCD) donors.[1] During the past decade, the number of transplantations with DCD kidneys has been steadily increasing. By comparison, the number of transplantations with donations after brain death (DBD) kidneys remained the same. Besides the Netherlands, DCD kidneys substantially contribute to the donor pool in several other European countries.[2] Despite the valuable expansion of the donor pool by these DCD kidneys, organ shortage

Received 18 August 2015. Revision received 3 February 2016.

Accepted 5 February 2016.

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The Dutch Organ transplantation Registry (NOTR) was funded and administered by the Dutch Transplantation Foundation (NTS), with initial additional funding from the Dutch Health Care Insurance Board (CVZ).

The authors declare no conflicts of interest.

All Dutch transplant centers were involved in collection of the data registered in the Dutch Organ Transplantation Registry. H.P.S., J.J.H.H., F.J.B., M.B.A.H., and S.P.B. were involved in the design of the study. H.P.S. did the statistical analysis and drafted the article, whereas all authors took part in its revision. H.P.S. had final responsibility for the decision to submit for publication and is the guarantor for the study.

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Supplemental digital content (SDC) is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's Web site (www.transplantjournal.com).

ISSN: 0041-1337/17/10106-1144

DOI: 10.1097/TP.0000000000001211

remains a problem. Dutch dialysis patients wait for more than 3 years for a deceased donor kidney, and more than 10% of patients die while on the waiting list in 2013.[1]

Most DCD kidneys in the Netherlands are classified as controlled (cDCD), whereas only a small proportion consists of uncontrolled (uDCD). According to the Maastricht classification, uDCD corresponds to category I and category II, and controlled donation is classified as category III and category IV.[3] Controlled DCD donors are patients in intensive care units in whom further treatment is futile. Within the hospitalized setting of the controlled donor, preparations can be made to retrieve the organs immediately after death, keeping the warm ischemic time as short as possible. Uncontrolled DCD donors are patients for whom resuscitation failed. This difference in context implies major logistical effort, both inside and outside the hospital. Critical information, such as the period between circulatory arrest and organ preservation and the efficacy of cardiopulmonary resuscitation, is sometimes difficult to obtain. Furthermore, uncontrolled DCD kidneys are potentially subjected to greater injury caused by a more prolonged warm ischemic time, which may result in a higher incidence of primary nonfunction (PNF) and delayed graft function. Consequently, uDCD kidneys in the Netherlands have been accepted with some reluctance in the past. However, lately, there has been growing interest in the potential of uDCD kidneys.[4-7] In some European countries like Spain and France, transplantation with uDCD kidneys is a more common practice, and promising results with uDCD have been reported.[8-15] After the pioneering work of the Maastricht Transplantation Center, the practice of transplanting uDCD kidneys has been implemented throughout all Dutch transplant centers. Up to now, the results of this nationwide implementation have not been investigated.

This study is the first to report nationwide results of renal outcome with 5-year follow-up of all Dutch DCD kidney transplantations from January 2002 to January 2012. We aimed to compare renal outcome, especially the 5-year renal function, between the cDCD and uDCD.

MATERIALS AND METHODS

Study Population

Data were retrieved from the Dutch Organ Transplantation Registry (NOTR), which records follow-up data for kidney transplantations derived from all 8 Dutch renal transplantation academic centers. We included all recipients (n = 1538) of a first renal allograft from a DCD Maastricht category I-III[3] donor between the January 5, 2002, and January 5, 2012. Excluded were Maastricht category IV donors, managed and treated as brain-death donors beforehand. Patients were followed for at least 6 months, and the last follow-up date was July 5, 2012.

Measures

We evaluated several end points after transplantation: PNF (graft never functioned, recipient lived for at least 10 days after transplantation), delayed graft function (DGF; dialysis within 7 days after transplantation), graft survival, death-censored graft survival, and patient survival (at 5 years' posttransplantation). One-year and 5-year renal functions were analyzed with the estimated glomerular filtration rate (eGFR) in milliliter per minute per 1.73 m^2.[16] Graft survival was defined as time from transplantation to either graft nephrectomy, return to dialysis, or patient death. We censored the latter in death-censored graft survival.

The following donor-related characteristics were included: age, sex, smoking status (yes/no), body mass index, use of inotropics before donation (yes/no), atherosclerosis (yes/no), terminal Modification of Diet in Renal Disease and cause of death (circulatory arrest, cardiovascular accident, suicide, trauma, other). Recipient characteristics were age, dialysis vintage (in days), primary renal disease (polycystic kidney disease, glomerulonephritis, renal vascular disease, diabetes, chronic renal failure (etiology unknown), pyelonephritis, other), dialysis modality (peritoneal dialysis, center dialysis, other), and induction therapy (yes/no). Initial immunosuppressive therapy in cDCD and uDCD consisted of steroids combined with mycophenolate mofetil or mycophenolic acid and a calcineurin inhibitor, mostly tacrolimus but also cyclosporine. Alternatively, a combination of steroids, tacrolimus, and sirolimus was used. Other than the fact that this combination was used more frequently in uDCD than in cDCD (32.9% vs 5.9%, respectively), the immunosuppressive regimen in the 2 groups was identical. Some recipients of grafts from both uDCD and cDCD were also treated with induction therapy consisting of antithymocyte globulin or basiliximab. Transplant-related variables considered for inclusion were: first warm ischemic time (1st WIT), cold ischemic time (CIT), second warm ischemic time (2nd WIT), and human leukocyte antigen (HLA) mismatch levels (no mismatch; 1 mismatch; 2 mismatches; 3 mismatches; 4 or more mismatches). First WIT was defined as time from circulatory arrest (or time of cessation of cardiac pulmonary resuscitation in uDCD donation) to cold perfusion within the hospital. Cold ischemic time was defined as the time from start of cold perfusion to removal from ice for implantation. Second WIT was the time during implantation, from removal of the organ from ice until reperfusion. Mismatches were defined as the number of mismatches between donor and recipient of HLA-A, HLA-B, and HLA-DR combined.

Donor Criteria and Proceedings of Donation After Circulatory Death

Figure 1 shows the timeline and order of events from switch-off for cDCD and from unsuccessful resuscitation for uDCD. The controlled and uncontrolled DCD differ in the setting where circulatory arrest takes place, the preservation technique, and the extended acceptable 1st WIT for the uDCD (maximum of 45 minutes for uDCD vs maximum of 30 minutes for cDCD). After an obligatory 5-minute no-touch period, the preferred Dutch preservation technique for uDCD is in-situ perfusion, the insertion of a double-balloon triple-lumen catheter via the femoral artery followed by a cold flush-out with histidine-tryptophan-ketoglutarate solution (Custodiol), described elsewhere.[17,18] After starting the in-situ perfusion, donor nephrectomy is initiated within 2 hours. Other donor criteria for uDCD are age younger than 65 years, resuscitation of less than 90 minutes, and no systemic signs of infection or evidence of sepsis. Furthermore, in uDCD category 1, advanced life support should be initiated within 20 minutes after witnessed cardiac arrest, and donor age should be younger than 55 years. Age limit for the cDCD is younger than 75 years. In cDCD, rapid laparotomy with direct cannulation of the aorta is the preferred

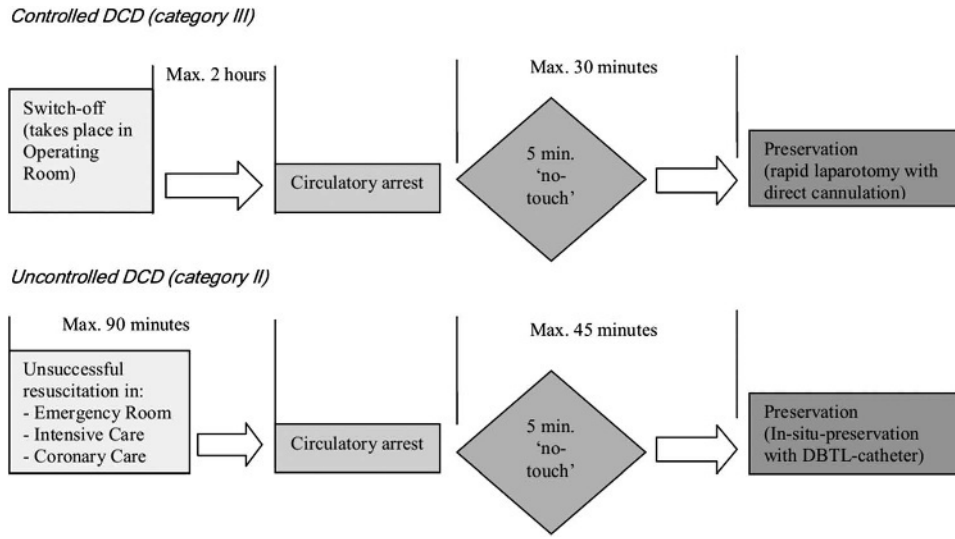


FIGURE 1. Scheme of controlled (from switch-off period) and uncontrolled (from unsuccessful resuscitation) kidney donation after cardiac circulatory death.[19] DBTL, double balloon triple lumen catheter.

preservation technique, and the permissible time between switch-off and cardiac arrest is restricted to 120 minutes.

Data Analysis

We compared the donor and recipient characteristics of patients who underwent a transplant across the uDCD and cDCD using independent *t* tests for continuous variables and the Fisher exact statistics for categorical variables. Kaplan-Meier curves were used, censored at 5 years, to estimate cumulative graft survival (all-cause failure), stratified by uDCD and cDCD. Loss to follow-up was handled by censoring at the last known date. We used logistic regression for the short-term transplant outcomes PNF and DGF, linear regression to compare eGFR, and Cox regression for survival analyses. We searched the literature for known donor and recipient risk factors that were associated with transplant outcomes of transplanting kidneys from donors after circulatory death. In addition, these variables had to be documented in the Dutch national registry. Then, we investigated in an association model whether the risk factors confounded the relationship between the 2 DCD groups and the designated transplant outcome.[20] The contribution of all risk factors

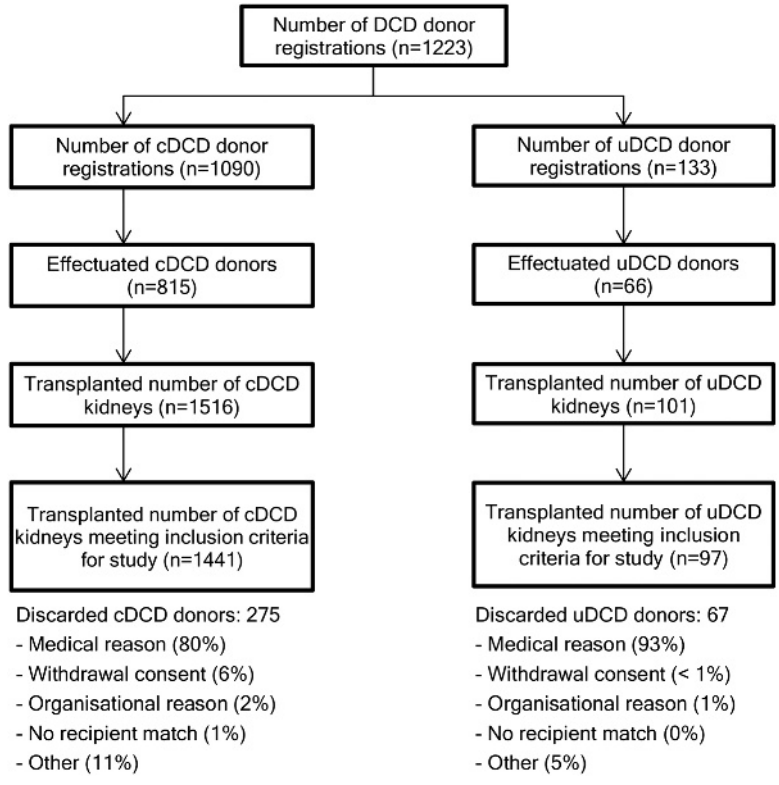


FIGURE 2. Selection process from registration to acceptance for transplantation of cDCD and uDCD donor kidneys.

was explored by using a stepwise forward selection procedure by adding the variables separately, one by one, to the model. A variable was considered a confounder when it effected a change of more than 10% in the regression coefficient of the 2 DCD groups. Additional interaction analysis was tested by adding the product term (risk factor × DCD groups).

The rate of missing data across all baseline variables was below 10.0%, except for macroscopic atherosclerosis. Although atherosclerosis was missing in 30.2% of cases, we included this variable because the degree of atherosclerosis is used as an easy and quick criterion to assess donor quality. When the degree of atherosclerosis was not reported, we considered this missing value as not present ("no"). With the exception of atherosclerosis, all missing values of other possible confounders were imputed by using the multivariate imputation by chained equations (MICE) algorithm with a predictive mean matching modeling type. Each missing variable in MICE is treated as an outcome, and missing data are predicted from the remaining variables, incorporating a random element to allow for the uncertainty in this variable's true

TABLE 1.

Descriptive statistics of kidney transplantations categorized by controlled and uncontrolled circulatory death donors

	All data	Controlled	Uncontrolled	Group differences
Characteristic	**N (%) / M (SD)**	**N (%) / M (SD)**	**N (%) / M (SD)**	***P***
N (%)	1538 (100%)	1441 (93.7%)	97 (6.3%)	
Donor age, y*	47.2 (15.4)	47.6 (15.3)	40.9 (15.5)	<0.001
Donor sex, male*	884 (57.5%)	814 (56.5%)	70 (72.2%)	0.003
Smoking donor (yes)[a]	636 (44.1%)	611 (44.7%)	25 (25.8%)	0.057
Body mass index donor	25.2 (4.7)	25.2 (4.8)	24.4 (3.8)	0.093
Inotropic before donation, yes*	325 (21.1%)	313 (21.7%)	12 (12.4%)	0.029
Atherosclerosis, y[b]*	504 (47.0%)	488 (48.1%)	16 (27.6%)	0.001
Terminal donor eGFR[c]*	103.8 (52.2)	105.9 (52.6)	69.1 (27.9)	<0.001
Donor cause of death*				
CVA	635 (41.3%)	619 (43.0%)	16 (16.5%)	<0.001
Circulatory arrest	239 (15.5%)	197 (13.7%)	42 (43.3%)	
Suicide	64 (4.2%)	60 (4.2%)	4 (4.1%)	
Trauma	454 (29.5%)	424 (29.4%)	30 (30.9%)	
Other	146 (9.5%)	141 (9.8%)	5 (5.2%)	
Recipient age, y	52.6 (12.8)	52.4 (12.8)	54.8 (13.0)	0.079
Recipient dialysis vintage, y[d]*	4.3 (2.4)	4.3 (2.4)	3.5 (1.5)	<0.001
Cause of renal failure				0.893
Polycystic kidney disease	243 (15.8%)	224 (15.5%)	19 (19.6%)	
Glomerulonephritis	381 (24.8%)	358 (24.8%)	23 (23.7%)	
Renal vascular disease	234 (15.2%)	220 (15.3%)	14 (14.4%)	
Diabetes	170 (11.1%)	158 (11.0%)	12 (12.4%)	
Chronic renal failure, etiology unknown	220 (14.3%)	205 (14.2%)	15 (15.5%)	
Pyelonephritis	101 (6.6%)	96 (6.7%)	5 (5.2%)	
Other	189 (12.3%)	180 (12.5%)	9 (9.3%)	
HLA mismatch level[e]				0.835
No mismatch	79 (5.5 %)	74 (5.5%)	5 (5.2%)	
1 mismatch	178 (12.3%)	164 (12.2%)	14 (14.4%)	
2 mismatch	466 (32.2%)	439 (32.5%)	27 (27.8%)	
3 mismatch	475 (32.8%)	440 (32.6%)	35 (36.1%)	
4 or more mismatches	249 (17.2%)	232 (17.2%)	16 (16.5%)	
Cold ischemia time, h[f]*	18.5 (5.4)	18.2 (5.3)	23.0 (5.4)	<0.001
Warm ischemic period 1, min[g]*	19.4 (8.3)	18.7 (7.6)	29.4 (10.6)	<0.001
Warm ischemic period 2, min [h]	35.0 (13.2)	35.0 (13.3)	34.9 (10.7)	0.948
Machine perfusion (yes)	230 (15.0%)	170 (11.8%)	60 (61.8%)	<0.001
Dialysis modality[i]				0.714
Peritoneal dialysis	510 (33.3%)	474 (33.1%)	36 (37.1%)	
Center dialysis	924 (60.1%)	868 (60.4%)	56 (57.7%)	
Other	99 (6.5%)	94 (6.5%)	5 (5.2%)	
Induction therapy (yes)[j]	456 (29.7%)	447 (32.0%)	9 (9.3%)	<0.001

[a] Ninety-five missing values (cDCD = 74; uDCD = 21); [b] 465 missing values (cDCD = 426; uDCD = 39); [c] 68 missing values (cDCD = 55; uDCD = 13); [d] 15 missing values (cDCD = 14; uDCD = 1); [e] 92 missing values (cDCD = 92); [f] 112 missing values (cDCD = 109; uDCD = 3); [g] 148 missing values (cDCD = 141; uDCD = 7); [h] 55 missing values (cDCD = 51; uDCD = 4); [i] 5 missing values (cDCD = 5); [j] 42 missing values (cDCD = 42).

*$P < 0.05$.

Original data shown. Mean with corresponding standard deviation are shown for continuous variables. Induction therapy used was antithymocite globulin or basiliximab.

y, years; min, time in minutes; h, time in hours; m, length in meters; eGFR, estimated glomerular filtration rate.

value.[21] We preferred MICE imputation because complete-case analysis may lead to bias in results.[22] The predictive mean matching method ensures that imputed values are plausible, as this method might be more appropriate than the regression method if the normality assumption is violated.[21] We created 5 imputed data sets and pooled the regression results to take different imputed values into account.

Relative risks are reported as odds ratios (ORs) or hazard ratios (HRs) with 95% confidence intervals (95% CIs). To interpret relative risks, we also calculated crude and adjusted absolute risk differences as percentage risk difference with 95% CI by using GLM with an identity link function and binomial distribution.[23] The clinically favorable controlled DCD served as a reference category. Significance levels were set at the 5% level; for interaction, they were set at the 10% level. All analyses were conducted using SPSS (version 21.0), and Kaplan-Meier curves were plotted using GraphPad Prism (version 5.0).

RESULTS

Between January 5, 2002, and January 5, 2012, 97 uDCD (n = 9 category I, and n = 88 category II) and 1441 cDCD (category III) primary kidney transplants were identified in the Dutch Organ Transplantation Registry (NOTR) in the Netherlands. Figure 2 shows that a higher percentage of uncontrolled donors were discarded in the selection process for transplantation compared with cDCD donors (50.4% vs 25.2%, respectively). We excluded category IV DCD donors (n = 3). The number of uncontrolled transplantations was lowest in the year 2011 (1 transplantation) and highest in 2004 (19 transplantations).

Baseline Characteristics

Table 1 shows an overview of the donor, recipient, and transplant-related characteristics. Donor mean (SD) age was significantly lower in uDCD compared with cDCD (40.9 [15.5] vs 47.6 [15.3], respectively; $P < 0.001$). Of the uDCD donors, 72.2% were males compared to 56.5% of the cDCD donors; $P = 0.003$. Less inotropic agents before donation were given in uDCD (12.4% vs 21.9%); $P = 0.029$. Atherosclerosis was less prevalent in uDCD (27.6% vs 48.0%; $P < 0.001$). The mean (SD) terminal eGFR of the donor was significantly lower in uDCD (69.1 [27.9] mL/min/m^2 vs 105.9 [52.6]); $P < 0.001$. The uDCD differed from the cDCD across categories of donor cause of death, mainly because circulatory arrest was noted more frequently as a cause of death (43.3% vs 13.7%) instead of cardiovascular accidents (16.5% vs 43.0%); $P < 0.001$. The mean (SD) dialysis vintage in years of the recipients was significantly lower in the uDCD (3.5 [1.5] years vs 4.3 [2.4] years; $P < 0.001$). The uDCD had a longer 1st WIT in minutes than the cDCD (29.4 [10.6] minutes vs 18.7 [7.6] minutes, respectively; $P < 0.001$). The CIT in hours was longer in the uDCD than the cDCD (23.0 [5.4] hours vs 18.2 [5.3] hours; $P < 0.001$). The number of machine-perfused kidneys was higher in the uDCD than the cDCD (61.8% vs 11.8%: $P < 0.001$). A smaller number of recipients of uDCD received induction therapy as most commonly chosen therapy (9.3% vs 32.0%; $P < 0.001$).

Clinical Outcomes

Table 2 shows the unadjusted multivariate transplant outcomes of the DCD groups. Primary nonfunction was 10.1% in all DCDs. In the uDCD, PNF was higher than in the cDCD (19.6% vs 9.6%, respectively). The odds of having PNF was 2.45 (95% confidence interval [CI], 1.46-4.13; $P = 0.001$) higher for the uDCD compared with the cDCD. Of the 19 recipients of uDCD kidneys who had PNF, 16 patients were actively—screened by a nephrologist—relisted again, 2 patients died while being in the process of rescreening, and 1 patient returned to the waiting list but was inactive and removed shortly hereafter for unknown reasons (**Table S1, SDC**, http://links.lww.com/TP/B267). Eleven of 16 actively relisted patients had retransplantation before November 22, 2015.

Kidneys from uDCD had a higher rate of delayed graft function (73.7% vs 63.3%); however, this difference was not significant (OR, 1.61; 95% CI, 0.95-2.72; $P = 0.074$). Graft-function (eGFR) was comparable 12 months after transplantation between the uDCD and the cDCD (44.3 (23.4) and 45.8 (24.0) mL/min/m^2; $P = 0.621$; n = 71 uDCD, n = 1118 cDCD), and also after 5 years (49.1 ± 25.6 mL/min/m^2 and 47.7 ± 27.6 mL/min/m^2; $P = 0.686$, n = 42 uDCD, n = 485 cDCD).

Figure 3 shows separate Kaplan-Meier curves for the graft survival, death-censored graft survival, and patient survival curves at 5 years for both DCD groups. The 5-year graft survival of all DCDs was 66.4%. Within the 2 groups, graft survival was 60.0% in uDCD and 66.8% in cDCD, with an HR of 1.41 (95% CI, 1.01-1.98; $P = 0.044$).

TABLE 2.

Comparison of transplant outcomes between grafts from uncontrolled and controlled circulatory-death donors

Outcome	Uncontrolled DCD	Controlled DCD	Coefficient (CI-95%)	P
Primary nonfunction	19/97 (19.6%)	139/1441 (9.6%)	OR 2.45 (1.46-4.13)	0.001
Delayed graft function[a]	56/76 (73.7%)	791/1247 (63.4%)	OR 1.61 (0.95-2.72)	0.074
1-year eGFR (mL/min 1.73 m^2)[b]	44.3 (23.4)	45.8 (24.1)	RE –1.45 (–7.21 to 4.31)	0.621
5-year eGFR (mL/min 1.73 m^2)[c]	49.1 (25.6)	47.7 (21.7)	RE 1.42 (–5.48 to 8.32)	0.686
5-year graft survival (all-cause failure)[d,e]	60.0%	66.8%	HR 1.41 (1.01-1.98)	0.044

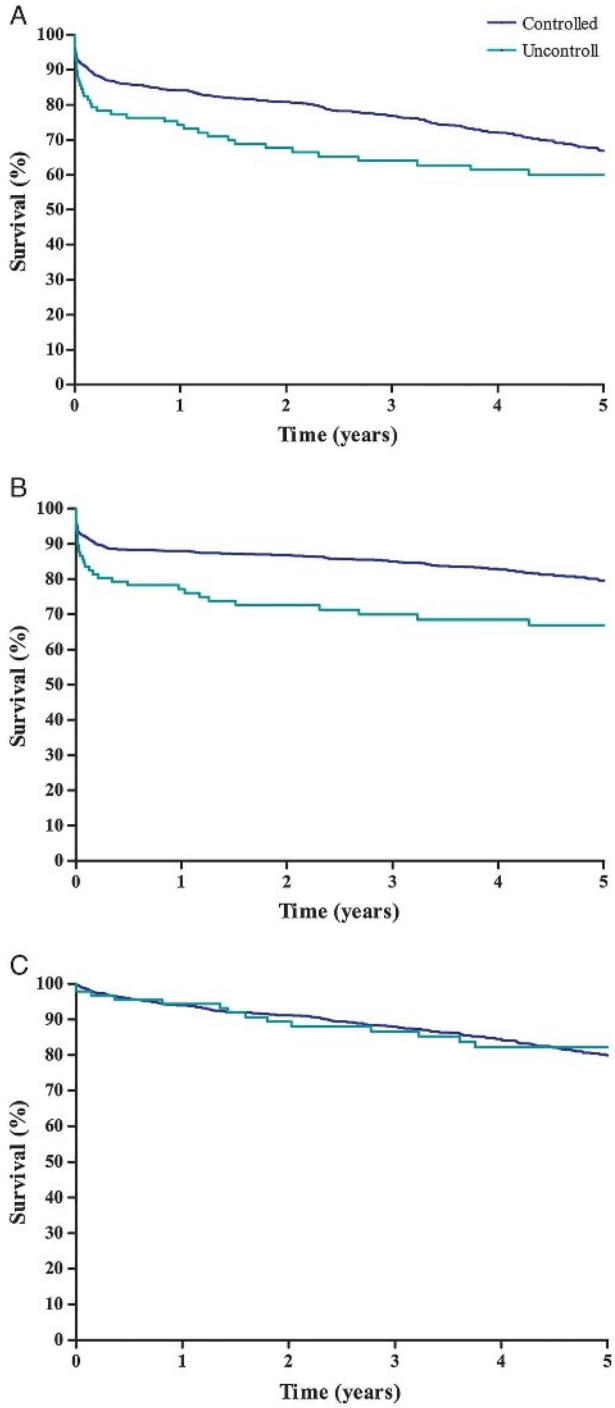
[a] Two hundred fifteen recipients were excluded due to PNF (uDCD = 19; cDCD = 139) or missing on DGF (uDCD = 2; cDCD = 55); [b] 349 recipients were excluded owing to graft loss (uDCD = 21; cDCD = 170), patient death (uDCD = 4; cDCD = 54), followed up <1 year (uDCD = 1; cDCD = 13) or missing eGFR (only cDCD = 13); [c] 1010 recipients were excluded owing to graft loss (uDCD = 30; cDCD = 235), patient death (uDCD = 7; cDCD = 143), followed-up <5 years (uDCD = 16; cDCD = 545) or missing eGFR (uDCD = 1; cDCD = 33); [d] 8 were missing in the time variable of the controlled DCD; [e] cumulative proportional survival percentages are shown.

For all outcomes, the controlled DCD was chosen as reference category. All analyses are unadjusted for other variables.

DCD, donation after circulatory death; eGFR, estimated glomerular filtration rate; OR, odds ratio from logistic regression; RE, regression coefficient from linear regression; HR, hazard ratio from Cox proportional hazards regression. For all outcomes, the controlled DCD was chosen as reference category. All analyses are unadjusted for other variables.

Association Between DCD Groups and Primary Nonfunction

Table 3 shows the results of potential risk factors confounding the relationship between the DCD groups, with cDCD as reference category, and outcome PNF in multiple logistic regression analysis. Evaluating the forward stepwise selection of the risk factors, the 1st WIT (adjusted model 1), CIT (adjusted model 2), and donor age (adjusted model 3) were considered confounders. After including 1st WIT only, DCD groups were not significantly different in risk of PNF (OR, 1.68; 95% CI, 0.94-2.98; $P = 0.074$), with a reduction of the risk difference of PNF risk from 10.0% to 7.0% (95% CI, −1.6 to 15.6). The inclusion of only CIT led to a decreased OR and risk difference, but DCD groups remained significantly different in risk of PNF (OR, 1.95; 95% CI, 1.14-3.35; $P = 0.015$). The OR increased after including donor age only (OR, 2.96; 95% CI, 1.73-5.06; $P < 0.001$), and the risk difference of uDCD increased from 10.0% to 12.4% (95% CI, 4.3-20.6) for having PNF. This increase was due to a remarkably lower donor age in the uDCD group. In adjusted model 4, all relevant confounders were included. As a result, the risk of experiencing PNF in uDCD was not statistically different from cDCD (OR, 1.72; 95% CI, 0.94-3.10; $P = 0.075$), and the risk difference between the DCD groups was reduced to 6.4% (95% CI,–2.3 to 15.1). Additionally, all 3 risk factors, namely, 1st WIT, CIT, and donor age, remained independently associated with PNF. In adjusted model 5, including other characteristics, uDCD was also not statistically different from cDCD (OR, 1.85; 95% CI, 0.95-3.61; $P = 0.072$). None of the risk factors interacted significantly between the DCD groups and the outcome of PNF. We also compared the DCD groups on the event of delayed graft function (**Table S1, SDC**, http://links.lww.com/TP/B267). In line with the previous analysis, 1st WIT, CIT, and donor age were relevant confounders as well as terminal donor eGFR for the association between the DCD groups and DGF.



Number at risk Graph 3A and Graph 3B [a]	0	1	2	3	4	5
Controlled	1433	1123	912	758	512	380
Uncontrolled	97	72	62	52	47	39

Number at risk Graph 3C [b]	0	1	2	3	4	5
Controlled	1433	1364	1326	1279	1249	1210
Uncontrolled	97	92	88	86	83	83

FIGURE 3. Kaplan-Meier curves of 5-year graft survival (A), death-censored graft survival (B), and 5-year patient survival (C) for the uncontrolled (green line) and the controlled (blue line) donors after circulatory death (DCD). Log-rank (Mantel-Cox) test (A), $P = 0.008$. Log-rank (Mantel-Cox) test (B), $P < 0.001$. Log-rank (Mantel-Cox) test (C), $P = 0.683$. [a]Eight recipients were excluded owing to missing data in the time variable of the controlled DCD group; mean follow-up uDCD, 2.9 years; cDCD, 2.8 years. [b]Mean follow-up uDCD, 4.5 years; cDCD, 4.5 years.

DISCUSSION

This study shows that once a uDCD donor kidney starts functioning, renal transplant function at 1 year and 5 years after transplantation is comparable to a cDCD kidney. If censored for PNF, 5-year graft survival rates were comparable between uDCD and cDCD. The main difference between the groups was the almost 2-fold higher incidence of PNF in uDCD. Three variables seem to influence the incidence of PNF between the DCD groups: 1st warm ischemic time, CIT, and donor age.

Our study underpins the importance of a short first warm ischemic period, a short period of CIT, and careful selection of the uDCD for age. In our study, the 1st WIT and CIT were longer in uDCD compared with cDCD. The longer 1st WIT is due to the unplanned nature of uDCD. The longer CIT might be explained as due to a later initialization of HLA typing and matching and possibly the reluctant acceptance by some centers of such a kidney in the allocation process.

TABLE 3.

Association between DCD groups and primary nonfunction

	Odds ratio	95% CI	*P*	Risk difference %	95% CI
Crude model	2.45	1.46-4.13	0.001	10.0	2.9-19.4
Adjusted model 1[a]	1.68	0.94-2.98	0.074	7.0	−1.6 to 15.6
Adjusted model 2[b]	1.95	1.14-3.35	0.015	8.7	0.3-17.0
Adjusted model 3[c]	2.96	1.73-5.06	<0.001	12.4	4.3-20.6
Adjusted model 4[d]	1.72	0.94-3.10	0.075	6.4	−2.3 to 15.1
Adjusted model 5[e]	1.85	0.95-3.61	0.072	6.6	−2.1 to 15.3

[a] Adjusted for 1st warm ischemic time; [b] adjusted for cold ischemic time; [c] adjusted for donor age; [d] adjusted for 1st warm ischemic time, cold ischemic time, donor age; [e] additional adjusted for donor atherosclerosis, inotropic before donation, donor BMI, smoking, terminal donor eGFR, dialysis vintage, donor sex, donor cause of death, HLA mismatch, 2nd warm ischemic time, dialysis modality, recipient's age, recipient's sex, recipient's cause of renal failure, induction therapy, year of transplantation.

DCD groups consist of controlled donation after circulatory death (reference category) and uncontrolled donation after circulatory death; cDCD versus uDCD.

The mean donor age was already significantly lower in uDCD, which mitigated the PNF incidence in uDCD. Most recipients of uDCD kidneys with PNF were relisted and had retransplantation.

These results partially corroborate earlier findings by Hoogland et al[7] who concluded that donor age, 1st WIT, CIT, anastomosis time, and immunosuppressive therapy were risk factors for PNF, regardless of whether the donor was cDCD or uDCD. A major difference between their findings and ours is the decreased incidence of PNF in our controlled DCD group, which was 21% in Maastricht vs 9.4% in the Dutch cohort including Maastricht. The high rate of PNF in cDCD might have been due to the liberal policy of the Maastricht Transplantation Center in accepting donors at the time.[24] When we compared our results with the UK, the prevalence of PNF in both cDCD and uDCD is higher.[11] This may be explained by the longer CIT in both DCD groups as well as a higher 1st WIT. Summers et al[25] reported a median CIT of 14.0 hours within cDCD in the UK, whereas the Dutch cohort reports a median CIT of 18.0 hours. Cold ischemic time is even higher in uDCD and consequently leads to more PNF. We used a higher cutoff of 1st WIT in the uDCD compared to other studies.[10,11,26] In addition, our 1st WIT is higher in the cDCD compared with the UK.[25] According to our data, when transplanting a uDCD kidney from a 40-year-old donor with a CIT of 12.0 hours and 1st WIT of 25 minutes as compared to a uDCD kidney transplanted with the same donor age, but an increased CIT of 23 hours and 1st WIT of 29.4 minutes, the predicted chance of PNF is reduced to 10.7 % (0.1873-0.1067 × 100 = 8.1% risk difference within uDCD). Reduction of CIT seems feasible, as the mean CIT already declined from 21.8 hours in 2002 to 16.6 hours in 2011, and is expected to decrease further.

Once a uDCD kidney functions, good long-term results are achieved. Several small clinical studies support that uDCD kidneys perform comparably to expanded criteria donor grafts,[9,11] and the 3-month and 1-year histological assessments of graft biopsies from uDCD and expanded criteria donor grafts revealed no differences in interstitial fibrosis and tubular atrophy.[10] Viglietti et al[26] in France showed longitudinal data from sequential biopsies of transplanted uDCD kidneys. They concluded that in uDCD recipients with a no-flow time of less than 10 minutes, 1-year eGFR and the degree of interstitial fibrosis were similar to those of DBD recipients. Good long-term results were also reported in a study from Switzerland, in which 66 cDCD and 56 uDCD procedures were compared and no significant differences in graft survival with a 15-year follow-up was found.[12] Pioneering centers in Spain have also shown encouraging results of uDCD kidneys, mostly category I uDCD, but comparison with cDCD is limited.[8,27,28] Sanchez-Fructuoso et al[8] compared the survival rates of 273 kidneys from category I uDCD, 47 kidneys from category II uDCD, and 584 kidneys from DBD. Primary nonfunction was highest among category II uDCD (8.5%) as well as delayed graft function (60.9% for both categories I and II uDCD). The 5-year graft survival of uDCD and DBD (donor age younger than 60 years) did not differ statistically. Dominguez-Gil et al[14] investigated the current status of DCD donors in 27 countries and compared several renal outcomes between 2343 cDCD donors and 649 uDCD donors. Primary nonfunction differed marginally (5.0% vs 6.4%, respectively), delayed graft function was significantly higher (50.2% vs 75.7%, respectively), and 1-year death-censored survival curves seemed to be advantageous (85.9% vs 88.9%, respectively). However, with different DCD practices across different countries and the strict selection of uDCD, one should be cautious in interpreting pooled results.[29,30] For instance, in the Spanish opt-out donation system, perfusion catheters and normothermic extracorporeal membrane oxygenation can be started before consent is obtained from the family of the deceased donor.[31] In the opt-in system in the Netherlands, preservation techniques are started after obtaining the consent of the donor in the national donor registry, and always after the obligatory 5-minute no-touch period.[19] Therefore, 1st WIT is likely to be increased in the Dutch cohort.

Our study has some limitations. First, uDCD donors probably present a selected group because we were unable to reliably match the baseline risk factors of the uDCD with the cDCD group, also due to the relatively small sample size of uDCD. As a result of the small sample size, we were unable to detect the thresholds of uDCD donor criteria to accomplish an acceptable rate of PNF. Some factors, which may influence ischemic injury, such as the duration and efficacy of resuscitation, hypoxia by cardiac arrest before initiation of resuscitation, and data about machine perfusion (yes/no) are not registered in the national database. Although static cold storage has been much more commonly used, more recent data show that hypothermic machine perfusion is associated with reduced delayed graft function.[7,32] Consequently, machine perfusion could have confounded the association between donor type and PNF; however, machine-perfused uDCD kidneys were not associated with PNF rate in the

Maastricht Transplantation Center.[7] In our cohort, roughly 60 uDCD kidneys and 170 cDCD were machine perfused between 2002 and 2012. Management of machine perfusion of DCD was done as described by Hoogland et al.[4,7] Viability testing was not used to determine organ suitability.

In summary, our results show that graft and recipient survival of uDCD are acceptable and similar to that in cDCD, whereas the high PNF rate is a reason for major concern. The challenge is to decrease the incidence of PNF by mitigating the risk factors. Bringing down 1st WIT by strict protocols and well-trained professionals, and decreasing CIT by local center allocation might contribute to decrease the PNF rate. If WIT and CIT are improved on uDCD donors, these donors can be a valuable expansion of the donor pool. Furthermore, other factors that influence warm ischemic injury, such as the time between cardiac arrest and resuscitation, and the hemodynamic profile and oxygen saturation of the donor in the agonal phase, may be improvable targets. Another target could be the use of machine perfusion characteristics for strict selection of uDCD kidneys. An alternative method to reduce the number of discarded donors could be dual transplantation. A recent report showed a case series of dual transplanted uDCD kidneys that would have been discarded for single transplantation.[33] Future research and larger cohorts are required to establish reliable thresholds of uDCD donor criteria.

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