Studying the short-term complications of kidney transplantation: from bed to bench
Kok, M.J.C. de

Chapter 3

Improving outcomes for donation after circulatory death kidney transplantation: Science of the times

Michèle J.C. de Kok, Alexander F.M. Schaapherder, Ian P.J. Alwayn, Frederike J. Bemelman, Jacqueline van de Wetering, Arjan D. van Zuilen, Maarten H.L. Christiaans, Marije C. Baas, Azam S. Nurmohamed, Stefan P. Berger, Esther Bastiaannet, Rutger J. Ploeg, Aiko P.J. de Vries, Jan H.N. Lindeman

Abstract

The use of kidneys donated after circulatory death (DCD) remains controversial due to concerns with regard to high incidences of early graft loss, delayed graft function (DGF), and impaired graft survival. As these concerns are mainly based on data from historical cohorts, they are prone to time-related effects and may therefore not apply to the current timeframe. To assess the impact of time on outcomes, we performed a time-dependent comparative analysis of outcomes of DCD and donation after brain death (DBD) kidney transplantations.

Data of all 11,415 deceased-donor kidney transplantations performed in The Netherlands between 1990-2018 were collected. Based on the incidences of early graft loss, two eras were defined (1998-2008 [n=3,499] and 2008-2018 [n=3,781]), and potential time-related effects on outcomes evaluated. Multivariate analyses were applied to examine associations between donor type and outcomes. Interaction tests were used to explore presence of effect modification.

Results show clear time-related effects on posttransplant outcomes. The 1998-2008 interval showed compromised outcomes for DCD procedures (higher incidences of DGF and early graft loss, impaired 1-year renal function, and inferior graft survival), whereas DBD and DCD outcome equivalence was observed for the 2008-2018 interval. This occurred despite persistently high incidences of DGF in DCD grafts, and more adverse recipient and donor risk profiles (recipients were 6 years older and the KDRI increased from 1.23 to 1.39 and from 1.35 to 1.49 for DBD and DCD donors). In contrast, the median cold ischemic period decreased from 20 to 15 hours.

This national study shows major improvements in outcomes of transplanted DCD kidneys over time. The time-dependent shift underpins that kidney transplantation has come of age and DCD results are nowadays comparable to DBD transplants. It also calls for careful interpretation of conclusions based on historical cohorts, and emphasises that retrospective studies should correct for time-related effects.

Introduction

In the past decades, organs retrieved from donation after brain death (DBD) donors have provided the majority of solid organ transplants globally. Due to the medical success of transplantation as an effective therapy for patients with end stage organ failure, the increased need of donor organs created a persistent shortage which has resulted in the death of many patients while waiting for a transplant.

For many years now, kidneys donated after circulatory death (DCD) have been proposed as an effective means of addressing this severe organ shortage.[1,2] Despite emerging reports indicating that mid-term and long-term outcomes of DCD procedures are better than commonly thought,[3-5] only some countries have fully embraced this opportunity.[6] For various reasons, others have been reluctant or even outspoken adverse towards the introduction of a controlled DCD programme that could alleviate the shortage and save many lives within a healthcare system.[7-8] While for some countries reasons to not or only slowly allow DCD programmes relate to ethical issues, legal restrictions or logistical concerns,[9] for the majority of countries the reticent attitude generally reflects medical concerns that are based on reported high incidences of early graft loss, delayed graft function (DGF), and an assumed impaired graft survival for DCD kidneys.

Since the concerns regarding the inferior DCD outcomes are mainly based on historical analyses, they are prone to time-related effects as time-varying confounding and effect modification by time.[10,11] Time-varying confounding is the phenomenon that the values of confounding variables, such as donor and recipient age, change over time.[10] Effect modification by time occurs when the effect of donor type on outcomes is modified by time (e.g. due to changes in procedural characteristics and/or medical decision-making over time).[11] Therefore, assumptions as regards inferior outcomes of DCD procedures may not apply anymore to our current timeframe.

To test whether conclusions with regard to the outcomes of DCD kidney transplant procedures are influenced by time, and to objectify the current results achieved when utilising DCD donor kidneys, we performed a longitudinal time-dependent comparative analysis of the outcomes of DBD and DCD kidney transplant procedures performed in The Netherlands, as country with a longstanding tradition of the use of DCD donor kidneys.

Materials and methods

Patient population
This national outcome evaluation was approved by the Ethics Committee of the Leiden University Medical Center, and the clinical and research activities being reported are consistent with the Principles of the Declaration of Istanbul as outlined in the 'Declaration

of Istanbul on Organ Trafficking and Transplant Tourism'. Data was fully anonymized prior to access and analysis.

In this study, we collected data of all 11,415 deceased-donor kidney transplant procedures performed in The Netherlands between 1990 and 2018. Combined organ procedures (n = 635), procedures with grafts donated after uncontrolled circulatory death (i.e. Maastricht Category I: dead on arrival and II: unsuccessful resuscitation) (n = 212), and procedures in recipients younger than 12 years old (n = 261) were excluded.

To explore a possible time-related effect, the incidence of early graft loss was mapped for the years 1990 to 2018. In this analysis, only primary kidney transplant procedures (n=8,511) were included since early graft loss after re-transplantation is potentially interfered with accumulation of recipient-related risk factors.[12] Based on the early graft loss incidences, two timeframes were defined for the time-dependent comparative analysis. This analysis included all (primary transplantations and re-transplantations) transplantations performed between 1998-2008 (n=3,499) and 2008-2018 (n=3,781). Data was retrieved from the Dutch National Organ Transplant Registry, which is a mandatory registry that contains granular data of all eight Dutch kidney transplant centres.

Definitions

Early graft loss was defined as graft loss within 90 days after transplantation. Patients who died within 90 days after transplantation with a functioning graft were not considered as early graft loss recipients. DGF was defined as the need for dialysis in the first postoperative week(s). The Modification of Diet in Renal Disease (MDRD) equation was used to estimate the glomerular filtration rate (eGFR) in the recipient. The non-scaled, donor-only version of the Kidney Donor Risk Index (KDRI) was calculated as described by Rao et al..[13] The following definitions were used for ischemic periods of the donor kidneys. The first warm ischemic period is the time following the no touch period after circulatory arrest and asystole in the DCD donor, until cold flush-out in the donor is commenced. The cold ischemic period is the time from start of cold flush-out until the start of the vascular anastomosis in the recipient. The graft anastomosis time is defined as the time from kidney removal from static cold storage or hypothermic machine perfusion until reperfusion in the recipient.

Data analysis

IBM SPSS Statistics 23.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Comparisons between DBD and DCD procedures were performed using the independent t-test for normal-distributed data, the Mann-Whitney rank test for non-parametric data, and the Chi-Square test for categorical data.

The KDRI was reported to facilitate comparison of the Dutch donor cohort with that of other countries. However, in the Dutch National Organ Transplant Registry donor hypertension and diabetes–which are included in the KDRI–are only registered from 2000 respectively 2002 onwards. As such, there was a high proportion of missing data for the 1998-2018 interval (26.6% for diabetes and 10.0% for hypertension) and multiple imputation of missing data of variables included in the KDRI was applied.

Logistic and linear regression analyses were used to examine the association between outcomes (DGF, early graft loss and 1-year eGFR) and donor type. Cox proportional hazards analyses were performed to evaluate differences in patient survival and death censored graft survival. All the multivariate models were adjusted for variables statistically relevant (p-value <0.10) in the univariate analysis (Supplemental Table 1). To avoid overcorrection the KDRI was not included in the multivariate models (as the KDRI also comprises donor age and donor type which are already included separately in the univariate and multivariate analyses). Also the type of preservation solution was not included as the inter-relationship between variables (the selection of preservation solution depends on donor type) would substantially impact the validity of the model. Results are represented as beta coefficient (β), Odds Ratio (OR) or Hazard Ratio (HR) with the corresponding 95% Confidence Interval (CI).

An interaction (Wald) test was used to explore the presence of effect modification by time. In other words, to test whether the effect of donor type on outcomes is modified by time. To specifically determine the association (R^2) between KDRI and 5-year graft survival, logistic regression analysis was performed using the data from 2002 to 2018 (non-imputed). P-values <0.05 were considered statistically significant.

Results

To explore a possible time-dependent effect on transplant outcomes, we mapped the incidence of early graft loss, as an unambiguous outcome parameter, for the years 1990 to 2018 in The Netherlands (Figure 1). Analyses of 5,895 DBD and 2,616 DCD primary kidney transplants performed in this period indicated clear time-related effects with 1998 (DBD) and 2008 (DCD) as clear transition years, after which the incidence of early graft loss dropped and stabilized at an incidence of approximately 6% (Figure 1).

Based on the transition years for early graft loss, two timeframes (1998-2008 and 2008-2018) were defined, and the outcomes of all 7,280 DBD and DCD procedures performed in these periods were compared accordingly (Table 1 and 2). This comparison showed a marked increase in donor and recipient age, and in KDRI over time: donors and recipients were respectively 6.5 and 6 years older in the recent (2008-2018) timeframe and the KDRI increased from 1.23 to 1.39 for DBD donors and from 1.35 to 1.49 for DCD

donors (Table 1). Although the KDRI for this Dutch cohort was significantly associated with 5-year graft survival (p<0.001), the Nagelkerke R^2 for the KDRI and 5-year graft loss was only 1.7% suggesting a limited impact of donor characteristics on graft survival. In contrast to the increase in donor and recipient age over time, there was a clear decrease in the cold ischemic period from a mean value of 20 hours in the 1998-2008 era to approximately 15 hours in the 2008-2018 era (Table 1). Also, the proportion of procedures with excessive cold ischemic periods (>24 hours) substantially decreased over time (from 25.7% to 7.8% and from 20.1% to 3.2% for DBD respectively DCD donors).

Furthermore, the type of preservation solution changed over time. Whereas histidine-tryptophan-ketoglutarate (HTK) solution was most common for DCD donor kidneys between 1998 and 2008 (86.1%), University of Wisconsin solution was most commonly used between 2008 and 2018 (57.8%) (Table 1).

The comparative outcome analysis showed clear time-related effects (Table 2). Whereas the 1998-2008 era associates with compromised outcomes for DCD procedures in comparison to DBD procedures (i.e. higher incidences of DGF and early graft loss, impaired 1-year renal function in patients without DGF, and inferior 1- and 5-year graft survival rates), the 2008-2018 era shows outcome equivalence for DBD and DCD procedures. Only the incidence of DGF for DCD grafts remained high in the current era (Table 2), but this did not impact graft and patient survival. Yet, for both timeframes and for both donor types, DGF resulted in a 15% reduced 1-year renal function (Table 2).

To explore whether the shift towards outcome equivalence reflects effect modification by time, an interaction (Wald) test was performed. As expected, the interaction test confirmed a significant difference in the effect of donor type on outcomes (DGF, early graft loss, 1- and 5-year graft survival) between the two time eras (p for interaction: <0.001, 0.002, 0.001 and <0.001, respectively) (Table 2).

Table 1. Baseline characteristics of deceased-donor kidney transplants in The Netherlands for the 1998-2008 and the 2008-2018 interval.

	01/1998 - 12/2007			01/2008 - 12/2017			p for interaction
	DBD n = 2361 (67.5%)	DCD n = 1138 (32.5%)	p-value	DBD n =1929 (51.0%)	DCD n = 1852 (49,0%)	p-value	
Donor age	46.2 ± 15.3	45.4 ± 15.4	0.16	52.7 ± 14.6	51.6 ± 14.5	0.03	**<0.001**
Recipient age	48.6 ± 14.3	50.7 ± 13.3	<0.001	55.0 ± 14.2	55.9 ± 12.9	0.03	**<0.001**
Time on dialysis (years)	4.1 ± 2.5	4.2 ± 2.0	0.24	3.8 ± 2.5	3.6 ± 2.1	0.001	**<0.001**
First warm ischaemic period (min.)	NA	19.0 [15.0 - 25.0]	-	NA	16.0 [13.0 - 19.0]	-	-
Cold ischaemic period (hours)	20.0 [15.6 - 24.6]	20.0 [16.0 - 23.8]	0.32	15.4 [11.8 - 19.8]	14.0 [11.5 - 17.6]	<0.001	**<0.001**
≤24 hours	1705 (74.3%)	889 (79.9%)		1589 (92.2%)	1575 (96.8%)		
>24 hours	589 (25.7%)	224 (20.1%)		135 (7.8%)	52 (3.2%)		
Graft anastomosis time (min.)	34.0 [27.0 - 41.0]	33.0 [27.0 - 40.0]	0.32	33.0 [26.0 - 41.0]	32.0 [25.0 - 40.0]	0.01	**0.01**
KDRI[1]	1.23 [1.0 - 1.5]	1.35 [1.1 - 1.6]	<0.001	1.39 [1.1 - 1.7]	1.49 [1.2 - 1.8]	<0.001	**<0.001**
Preservation solution			<0.001			<0.001	**<0.001**
- HTK	325 (13.9%)	967 (86.1%)		463 (24.4%)	719 (39.3%)		
- University of Wisconsin	2001 (85.4%)	152 (13.5%)		1383 (72.8%)	1058 (57.8%)		
- Other	17 (0.7%)	4 (0.4%)		55 (2.9%)	53 (2.9%)		

BASELINE

Data are respectively presented as mean ± standard deviation, as number (%), as median [interquartile range] or as beta coefficient (β), odds ratio or hazard ratio with the corresponding 95% confidence interval.

[1] Multiple imputation was applied for missing data of variables included in the KDRI.

DBD, donation after brain death; DCD, donation after circulatory death; HTK, histidine-tryptophan-ketoglutarate; KDRI, kidney donor risk index; min., minutes; NA, not applicable.

Table 2. Deceased-donor kidney transplant outcomes in The Netherlands for the 1998-2008 and the 2008-2018 interval.

OUTCOME	01/1998–12/2007			01/2008–12/2017			p for interaction
	DBD n = 2361 (67.5%)	DCD n = 1138 (32.5%)	p-value	DBD n =1929 (51.0%)	DCD n = 1852 (49.0%)	p-value	
Delayed graft function	**420 (17.8%)**	**511 (44.9%)**	**<0.001**	**321 (16.6%)**	**736 (39.7%)**	**<0.001**	**<0.001**
Crude OR (95% CI)	Ref.	4.04 (3.42–4.78)	<0.001	Ref.	3.85 (3.28–4.53)	<0.001	
Adjusted OR (95% CI)	Ref.	4.17 (3.45 – 5.04)	<0.001	Ref.	4.78 (3.99 – 5.70)	<0.001	*0.002*
Early graft loss (<day 90)	**194 (8.2%)**	**151 (13.3%)**	**<0.001**	**110 (5.7%)**	**114 (6.2%)**	*0.56*	
Crude OR (95% CI)	Ref.	1.71 (1.36–2.14)	<0.001	Ref.	1.09 (0.83–1.42)	0.56	
Adjusted OR (95% CI)	Ref.	1.77 (1.40 – 2.23)	<0.001	Ref.	1.24 (0.92–1.68)	0.16	
- Primary non-function	44 (22.7%)	58 (38.4%)		42 (38.2%)	43 (37.7%)		
- Rejection	58 (29.9%)	25 (16.6%)		23 (20.9%)	20 (17.5%)		
- Thrombosis or infarction	38 (19.6%)	36 (23.8%)		14 (12.7)	24 (21.1%)		
- Other	54 (27.8%)	32 (21.2%)		31 (28.2%)	27 (23.7%)		
1-year eGFR DGF -	**52.6 ± 19.7**	**49.5 ± 18.1**	**0.02**	**51.5 ± 19.7**	**52.3 ± 20.0**	*0.44*	*0.93*
Crude β (95% CI)	Ref.	-3.07 (-5.67–0.47)	0.02	Ref.	0.84 (-1.29–2.96)	0.44	
Adjusted β (95% CI)	Ref.	-4.21 (-6.57–1.86)	<0.001	Ref.	-0.11 (-2.04 – 1.82)	0.91	
1-year eGFR DGF +	**44.1 ± 19.0**	**44.4 ± 18.4**	*0.81*	**44.8 ± 18.9**	**44.6 ± 17.5**	*0.89*	*0.70*
Crude β (95% CI)	Ref.	0.32 (-2.19–2.82)	0.81	Ref.	-0.18 (-2.81–2.45)	0.89	
Adjusted β (95% CI)	Ref.	-0.69 (-3.02 – 1.63)	0.56	Ref.	-1.63 (-4.05 – 0.79)	0.19	
1-year graft loss	(10.9%)	(15.0%)		(8.0%)	(7.9%)		
Crude HR (95% CI)	**1.0**	**1.41 (1.16–1.71)**	**0.001**	**1.0**	**0.98 (0.78–1.23)**	*0.84*	*0.001*
Adjusted H R (95% CI)	1.0	1.45 (1.19–1.77)	<0.001	1.0	1.09 (0.85–1.40)	0.49	
5-year graft loss	(20.0%)	(22.8%)		(14.0%)	(13.6%)		
Crude HR (95% CI)	**1.0**	**1.18 (1.01–1.37)**	**0.04**	**1.0**	**0.96 (0.80–1.15)**	*0.66*	**<0.001**
Adjusted HR (95% CI)	1.0	1.25 (1.07 – 1.46)	0.01	1.04 (0.85–1.27)		0.69	
1-year patient survival	(95.0%)	(94.4%)		(95.2%)	(94.8%)		
Crude HR (95% CI)	**1.0**	**1.14 (0.84–1.54)**	*0.41*	**1.0**	**1.08 (0.82–1.43)**	*0.58*	*0.60*
Adjusted HR (95% CI)	1.0	1.08 (0.80–1.46)	0.62	1.0	1.08 (0.81–1.42)	0.61	
5-year patient survival	(82.8%)	(82.4%)		(82.3%)	(82.5%)		
Crude HR (95% CI)	**1.0**	**1.04 (0.88–1.23)**	*0.66*	**1.0**	**1.00 (0.85–1.17)**	*0.96*	*0.81*
Adjusted HR (95% CI)	1.0	1.08 (0.89–1.30)	0.44	1.0	1.02 (0.85–1.22)	0.83	

Data are respectively presented as mean ± standard deviation, or as number (%), and beta coefficient (β), odds ratio or hazard ratio with the corresponding 95% confidence interval.

95% CI, 95% confidence interval; DBD, donation after brain death; DCD, donation after circulatory death; DGF, delayed graft function; eGFR, estimated glomerular filtration rate; HR, hazard ratio; min., minutes; OR, odds ratio.

Discussion

This national study demonstrates a major improvement in outcomes of transplanted DCD kidneys over time. Whereas the 1998-2008 era associates with inferior outcomes for DCD kidney transplant procedures, the 2008-2018 era shows outcome equivalence between DBD and DCD kidney transplants. This shift underpins that DCD kidney transplantation has come of age and results are nowadays comparable to DBD kidney transplants. It also emphasises that conclusions based on retrospective data (i.e. based on timeframes in which outcomes of DCD procedures were inferior to DBD procedures) are interfered by time-varying confounding and effect modification, and are therefore no longer justified.

Patient- and graft survival equivalence for DBD and DCD procedures occurred despite a persistent high incidence of DGF in DCD grafts. This apparent paradox can be explained by differential impacts of DGF on DBD and DCD outcomes, with a negligible impact of DGF on patient- and graft survival in recipients with DCD grafts.[4,14] A phenomenon that presumably relates to donor type-specific molecular differences in organ resilience.[14]

A clear, univocal explanation for the improved outcomes is missing. In the context of more adverse donor and recipient risk profiles in the more recent timeframe, the improvement in DCD outcomes over time presumably involves a complex interplay of factors that includes optimized surgical procedures and immunosuppressive regimens, altered organ preservation techniques, and enhanced transport logistics.[15-19] Certainly, a significant impact has been the profound reduction in cold ischemic time.[16,20] Several studies have shown that a prolonged cold ischemic time is more deleterious in recipients receiving kidney transplants from DCD donors than in recipients from DBD donors.[21-23] This finding, with DCD grafts being more 'vulnerable' to cold ischemia than DBD grafts, has recently been confirmed by colleagues in The Netherlands,[20] and might also explain why graft survival rates have improved to a greater extent for recipients of DCD donors than for recipients of DBD donors. Another possible explanation is that–as cold ischemic periods of more than 24 hours in DCD kidneys are associated with worse graft survival–the proportion of procedures with excessive cold ischemic periods (>24 hours) decreased over time with the increasing awareness of avoiding long cold ischemic times in The Netherlands.[4] A potential contribution of hypothermic machine perfusion (HMP) to improved outcomes, however, is limited in this Dutch cohort since HMP was only fully implemented in the year 2016, and as the available data indicate that although HMP reduces the risk of DGF, it has a limited impact on the other outcome data.[24]

Improved outcomes over time may further reflect advances in immunosuppressive therapies including the conversion from cyclosporine to tacrolimus as standard

maintenance regime.[25,26] Also, the introduction of more sensitive techniques to detect anti-human leukocyte antigen antibodies, such as the LUMINEX technique may have resulted in increased graft survival.[18]

An alternative and non-exclusive explanation for the improved outcomes is the presence of a learning curve that involves the intangible and often intuitive aspects of medical decision-making processes in the context of donor and recipient selection, and organ allocation. Existence of a learning curve phenomenon is supported by the observation that outcomes of transplanted DBD kidneys improved significantly in a similar way as for DCD transplant procedures, but at an earlier (1990-1998) time era, and by the dynamics of the incidence of early graft loss over time (Figure 1). To be more specific, data for DBD procedures show a steep decline and stabilization of the incidence of early graft loss after 1998. A similar–albeit postponed–pattern is seen for the DCD procedures, for which the early graft loss incidence rate dropped and stabilized following 2008. Thus, it is likely that countries initiated a controlled DCD programme, may also experience some form of learning curve with transient inferior outcomes for this type of transplant procedure.

Remarkably, the time-related improvements in DCD outcomes occurred despite considerable increases in donor and recipient age, and in KDRI over time (Table 1). The apparent paradox of increasing KDRI values but improving graft survival rates suggests that, after the medical decision to accept a kidney for donation, there is a limited impact of donor characteristics on graft survival. This is illustrated by the remarkably low Nagelkerke R^2 for the association between KDRI and 5-year graft survival.[13] Hence, these data illustrate that graft survival reflects an interplay of donor, procedural and recipient factors.[15]
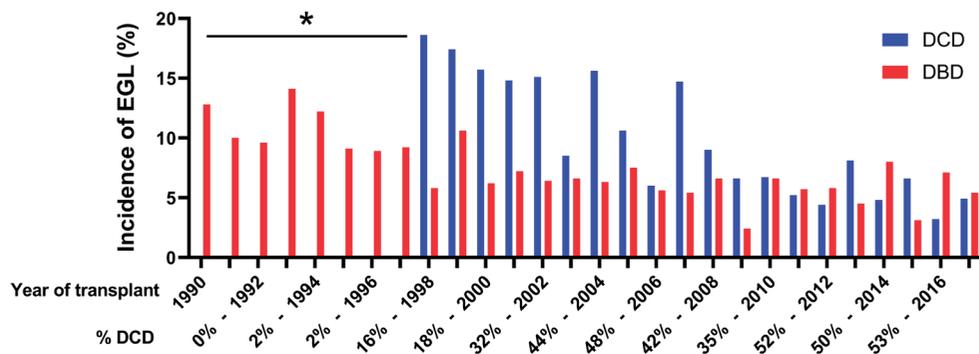
Figure 1. Time-related incidences of early graft loss in 8,511 primary kidney transplant recipients according to deceased donor type in The Netherlands. * The small number of DCD kidney transplant procedures performed in these years (n < 15), does not justify adequate power for analysis. *DBD, donation after brain death; DCD, donation after circulatory death; EGL, early graft loss.*

This study has some limitations. Firstly, it is a registry-based study, which is associated with inherent design limitations. Secondly, this is a country-specific study as outcomes are influenced by national guidelines and decision-making policies. However, considering the liberal attitude towards DCD kidneys in The Netherlands (reflected by an equal distribution in DBD and DCD procedures, comparable donor ages and KDRI values) it is unlikely that the results reflect a high threshold in accepting DCD grafts.

In conclusion, this registry-based study shows a major improvement in outcomes of transplanted DCD kidneys over time, with DBD and DCD outcome equivalence in the current timeframe. The time-related improvements for DCD outcomes not only show that DCD kidneys can be fully embraced, but also emphasise that careful interpretation is required for conclusions that are based on historical cohorts.

Acknowledgements

References

1. DeVita MA, Snyder JV, Grenvik A. History of organ donation by patients with cardiac death. Kennedy Inst Ethics J. 1993;3: 113-129.

2. Bendorf A, Kelly PJ, Kerridge IH, McCaughan GW, Myerson B, Stewart C, et al. An international comparison of the effect of policy shifts to organ donation following cardiocirculatory death (DCD) on donation rates after brain death (DBD) and transplantation rates. PLoS One. 2013;8: e62010.

3. Brook NR, White SA, Waller JR, Veitch PS, Nicholson ML. Non-heart beating donor kidneys with delayed graft function have superior graft survival compared with conventional heart-beating donor kidneys that develop delayed graft function. Am J Transplant. 2003;3: 614-618.

4. Schaapherder AF, Wijermars LG, de Vries DK, de Vries AP, Bemelman FJ, van de Wetering J, et al. Equivalent long-term transplantation outcomes for kidneys donated after brain death and cardiac death: Conclusions from a nationwide evaluation. EClinicalMedicine. 2018;4-5: 25-31.

5. Summers DM, Watson CJ, Pettigrew GJ, Johnson RJ, Collett D, Neuberger JM, Bradley JA. Kidney donation after circulatory death (DCD): state of the art. Kidney Int. 2015;88: 241-249.

6. Weiss J, Elmer A, Mahíllo B, Domínguez-Gil B, Avsec D, Nanni Costa A, et al. Evolution of deceased organ donation activity versus efficiency over a 15-year period: an international comparison. Transplantation. 2018;102: 1768-1778.

7. Weiss J, Elmer A, Béchir M, Brunner C, Eckert P, Endermann S, et al. Deceased organ donation activity and efficiency in Switzerland between 2008 and 2017: achievements and future challenges. BMC Health Serv Res. 2018;18: 876.

8. Manyalich M, Nelson H, Delmonico FL. The need and opportunity for donation after circulatory death worldwide. Curr Opin Organ Transplant. 2018;23: 136-141.

9. Jericho BG. Organ Donation After Circulatory Death: Ethical issues and international practices. Anesth Analg. 2019;128: 280-285.

10. Platt RW, Schisterman EF, Cole SR. Time-modified confounding. Am J Epidemiol. 2009;170: 687-694.

11. VanderWeele TJ. On the distinction between interaction and effect modification. Epidemiology. 2009;20: 863-871.

12. de Kok MJ, Schaapherder AF, Mensink JW, de Vries AP, Reinders ME, Konijn C, et al. A nationwide evaluation of deceased donor kidney transplantation indicates detrimental consequences of early graft loss. Kidney Int. 2020;97: 1243-1252.

13. Rao PS, Schaubel DE, Guidinger MK, Andreoni KA, Wolfe RA, Merion RM, et al. A comprehensive risk quantification score for deceased donor kidneys: the kidney donor risk index. Transplantation. 2009;88: 231-236.

14. de Kok MJ, McGuinness D, Shiels PG, de Vries DK, Tutein Nolthenius JB, Wijermars LG, et al. The neglectable impact of delayed graft function on long-term graft survival in kidneys donated after circulatory death associates with superior organ resilience. Annals of Surg. 2019;270: 877-883.

15. Kaplan B, Srinivas TR, Meier-Kriesche HU. Factors associated with long-term renal allograft survival. Therapeutic Drug Monitoring. 2002;24: 36-39.

16.   Debout A, Foucher Y, Trébern-Launay K, Legendre C, Kreis H, Mourad G, et al. Each additional hour of cold ischemia time significantly increases the risk of graft failure and mortality following renal transplantation. Kidney Int. 2015;87: 343-349.

17.   Tojimbara T, Fuchinoue S, Iwadoh K, Koyama I, Sannomiya A, Kato Y, et al. Improved outcomes of renal transplantation from cardiac death donors: a 30-year single center experience. Am J Transplant. 2007;7: 609-617.

18.   Abramowicz D, Oberbauer R, Heemann U, Viklicky O, Peruzzi L, Mariat C, et al. Recent advances in kidney transplantation: a viewpoint from the Descartes advisory board. Nephrol Dial Transplant. 2018;33: 1699-1707.

19.   Lam HD, Schaapherder AF, Kopp WH, Putter H, Braat AE, Baranski AG. Professionalization of surgical abdominal organ recovery leading to an increase in pancreatic allografts accepted for transplantation in The Netherlands: a serial analysis. Transpl Int. 2017;30: 117-123.

20.   Peters-Sengers H, Houtzager JHE, Idu MM, Heemskerk MBA, van Heurn ELW, Homan van der Heide JJ, et al. Impact of cold ischemia time on outcomes of deceased donor kidney transplantation: an analysis of a national registry. Transplant Direct. 2019;5: e448.

21.   Summers DM, Johnson RJ, Hudson A, Collett D, Watson CJ, Bradley JA. Effect of donor age and cold storage time on outcome in recipients of kidneys donated after circulatory death in the UK: a cohort study. Lancet. 2013;381: 727-734.

22.   Summers DM, Johnson RJ, Allen J, Fuggle SV, Collett D, Watson CJ, et al. Analysis of factors that affect outcome after transplantation of kidneys donated after cardiac death in the UK: a cohort study. Lancet. 2010;376:1303-1311.

23.   van der Vliet JA, Warlé MC, Cheung CL, Teerenstra S, Hoitsma AJ. Influence of prolonged cold ischemia in renal transplantation. Clin Transplant. 2011;25: E612-6.

24.   Tingle SJ, Figueiredo RS, Moir JA, Goodfellow M, Talbot D, Wilson CH. Machine perfusion preservation versus static cold storage for deceased donor kidney transplantation. Cochrane Database Syst Rev. 2019;3: CD011671.

25.   Kho M, Cransberg K, Weimar W, van Gelder T. Current immunosuppressive treatment after kidney transplantation. Expert Opin Pharmacother. 2011;12:1217-1231.

26.   Boots JM, van Duijnhoven EM, Christiaans MH, Nieman FH, van Suylen RJ, van Hooff JP. Single-center experience with tacrolimus versus cyclosporine-Neoral in renal transplant recipients. Transpl Int. 2001;14: 370-383.

Supplemental Data

Supplemental Table 1. Multivariate analyses of posttransplant outcomes.

	Donor age	Recipient age	Time on dialysis	Cold ischemic period	Graft anastomosis time
Delayed graft function					
1998-2008 (OR + 95% CI)	1.010 (1.004–1.017)**	1.002 (0.995–1.008)	1.069 (1.029–1.110)**	-	1.007 (1.001–1.014)*
2008-2018 (OR + 95% CI)	1.013 (1.007–1.020)**	-	1.106 (1.065–1.148)**	1.030 (1.015–1.046)**	-
Early graft loss (<day 90)					
1998-2008 (OR + 95% CI)	1.018 (1.010–1.027)**	-	-	1.032 (1.015–1.049)**	1.017 (1.009–1.024)**
2008-2018 (OR + 95% CI)	1.028 (1.014–1.041)**	1.002 (0.990–1.015)	1.100 (1.037–1.167)**	1.027 (1.001–1.053)*	1.018 (1.008–1.028)**
1-year eGFR DGF -					
1998-2008 (β + 95% CI)	-0.535 (-0.593–-0.476)**	-0.153 (-0.217–-0.088)**		-0.308 (-0.439–-0.176)**	-
2008-2018 (β + 95% CI)	-0.512 (-0.577–-0.448)**	-0.112 (-0.181–-0.042)**		-	-
1-year eGFR DGF +					
1998-2008 (β + 95% CI)	-0.488 (-0.566–-0.409)**	-0.061 (-0.145–0.022)		-	-
2008-2018 (β + 95% CI)	-0.527 (-0.611–-0.442)**	-0.006 (-0.093–0.080)		-	-
1-year graft loss					
1998-2008 (HR + 95% CI)	1.021 (1.014–1.028)**			1.029 (1.016–1.043)**	1.012 (1.007–1.018)**
2008-2018 (HR + 95% CI)	1.026 (1.015–1.037)**	1.001 (0.991–1.011)	1.080 (1.028–1.134)**	1.023 (1.002–1.045)*	1.012 (1.004–1.021)**
5-year graft loss					
1998-2008 (HR + 95% CI)	1.024 (1.018–1.030)**	0.986 (0.981–0.992)**		1.022 (1.011–1.033)**	1.008 (1.003–1.012)**
2008-2018 (HR + 95% CI)	1.018 (1.011–1.026)**	-	1.043 (1.001–1.087)*	1.024 (1.007–1.041)*	1.013 (1.007–1.020)**
1-year patient survival					
1998-2008 (HR + 95% CI)	1.015 (1.005–1.026)**	1.049 (1.035–1.063)**	-	-	-
2008-2018 (HR + 95% CI)	1.006 (0.995–1.017)	1.049 (1.034–1.064)**	-	-	-
5-year patient survival					
1998-2008 (HR + 95% CI)	1.018 (1.011–1.024)**	1.049 (1.040–1.058)**	1.071 (1.033–1.112)**	0.992 (0.978–1.006)	1.003 (0.997–0.010)
2008-2018 (HR + 95% CI)	1.011 (1.003–1.018)**	1.057 (1.047–1.067)**	1.083 (1.044–1.123)**	1.021 (1.005–1.036)*	1.012 (1.005–1.018)**

In total 16 multivariate analyses were performed. Each row represents a single multivariate analysis. The multivariate models were adjusted for variables that were statistically relevant in the univariate analysis (p-value <0.1).

(-) Indicates that the variable was not included in the multivariate analysis. (*) p-value <0.05, (**) p-value <0.005.

95% CI, 95% confidence interval; DGF, delayed graft function; eGFR, estimated glomerular filtration rate; HR, hazard ratio; OR, odds ratio.