ORIGINAL ARTICLE

Increased risk of graft failure and mortality in Dutch recipients receiving an expanded criteria donor kidney transplant

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SUMMARY

Survival of expanded criteria donor (ECD) kidneys and their recipients has not been thoroughly evaluated in Europe. Therefore, we compared the outcome of ECD and non-ECD kidney transplantations in a Dutch cohort, stratifying by age and diabetes. In all first Dutch kidney transplants in recipients ≥18 years between 1995 and 2005, both relative risks (hazard ratios, HR) and adjusted absolute risk differences (RD) for ECD kidney transplantation were analysed. In 3062 transplantations [recipient age 49.0 (12.8) years; 20% ECD], ECD kidney transplantation was associated with graft failure including death [HR 1.62 (1.44–1.82)]. The adjusted HR was lower in recipients ≥60 years of age [1.32 (1.07–1.63)] than in recipients 40–59 years [1.71 (1.44–2.02) $P = 0.12$ for comparison with ≥60 years] and recipients 18–39 years [1.92 (1.42–2.62) $P = 0.03$ for comparison with ≥60 years]. RDs showed a similar pattern. In diabetics, the risks for graft failure and death were higher than in the nondiabetics. ECD kidney grafts have a poorer prognosis than non-ECD grafts, especially in younger recipients (<60 years), and diabetic recipients. Further studies and ethical discussions should reveal whether ECD kidneys should preferentially be allocated to specific subgroups, such as elderly and nondiabetic individuals.

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Introduction

In patients with end-stage renal disease, kidney transplantation is the optimal renal replacement therapy (RRT) with regard to survival [1], quality of life [2] and costs [3]. As a consequence, the demand for donor kidneys exceeds the more or less constant supply of organs donated after death [4]. To reduce the number of patients waiting for a kidney transplant, many transplant centres over the world started to accept suboptimal organ donors, referred to as expanded criteria donors (ECD) or marginal donors [5]. Results of these ECD kidney transplantations differ across studies in different regions: some studies reveal no differences in outcome between ECD and non-ECD kidney transplants [6–10], whereas other studies, including a systematic review and a meta-analysis, tend to show higher rates of graft failure and mortality in ECD kidney

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transplantations, especially in recipients with diabetes or recipients younger than 40 years of age [11–13]. In the Eurotransplant (ET) kidney exchange program, facilitating cross-border organ exchange from both ECD and non-ECD donors in eight European countries including the Netherlands, graft and patient survival according to ECD status have not been investigated.

Analysing outcome of ECD kidney transplantation in several regions is relevant as kidney transplant procedures across the world differ, among other things, in allocation strategies, cold ischaemia times, human leucocyte antigen (HLA) matching and (initial) immunosuppressive regimens. In addition, a recent meta-analysis shows differences in outcome of ECD kidney transplantation between Europe and North America [13]. If results of a certain region appear to be better, it possibly provides clues for improving ECD kidney transplantation in other areas. If, however, outcome of ET ECD kidneys is similar as in other areas, ET could consider to adapt its allocation policy and allocate ECD kidneys to recipients in whom the influence of ECD status on outcome is minimal. The last decades, other adaptations of the ET-allocation strategy have proven to be successful. First, the acceptable mismatch program, giving priority to highly immunized kidney recipients over the standard allocation procedure based on ABO matching, optimal HLA matching and short cold ischaemia times, has considerably reduced waiting times in these patients [14]. Second, more recently, the ET Senior Program (ESP; 'Old for old') was implemented and its results are successful as well [15,16].

Therefore, the aim of this study was to evaluate outcome of ECD kidney donations in the Netherlands, part of the ET region, in subgroups of patients. In the Netherlands, data on kidney transplantations have been prospectively and retrospectively registered in the Dutch Organ Transplant Registry (NOTR) database. Besides patient and donor characteristics at the moment of kidney transplantation, this registry contains yearly follow-up data. The question of this study is whether graft and patient survival after deceased ECD kidney donations in the Netherlands, between 1995 and 2005, in adult recipients receiving their first kidney transplantation differ from deceased non-ECD kidney donations in general, and in specific subgroups of kidney recipients, stratified by age and diabetes.

Methods

This study was performed on NOTR data containing baseline and follow-up data on kidney transplants in the Netherlands. All Dutch kidney transplant centres have committed themselves to provide the required data to this registry. Additional data of kidney transplants and kidney recipients from the ET and the Renine (Dutch Renal Replacement Registry) registries are routinely incorporated in the NOTR registry. As ET allocates all kidney grafts of deceased donors in its region, all deceased donor kidney transplants are registered in the NOTR database; because of the link with Renine, information on renal replacement therapy (RRT) in the recipient before transplantation and death on RRT after graft failure is available in the NOTR.

In this study, all deceased donor kidney transplantations performed in recipients of 18 years and older receiving their first kidney transplant between 1 January 1995 and 31 December 2004 in the Netherlands were included. The inclusion period was chosen to affirm a long follow-up period (up to 2013, at least 8 years). Combined kidney and pancreas transplantations were excluded. Both baseline data and annual follow-up data till February 2013 were used for this study. Most variables used in the analyses were without additional calculations available in the NOTR database, such as dates for graft failure and death. The primary endpoints of this study were time to graft failure and time to death. For graft failure, first both failure of the graft (need of renal replacement therapy) and death were considered as graft failure, and second, failure of the graft alone (with censoring for death). Delayed graft function was not considered as graft failure. The determinant of our analyses was ECD (yes/no). Donor kidneys were retrospectively classified as ECD kidneys if donor characteristics met one of the following criteria: (i) donor age ≥60 years at the moment of donation; (ii) donor age 50–59 years at the moment of donation and two out of (a) history of hypertension, (b) donor creatinine value ≥132 μmol/l/1.5 mg/dl (if more than one donor creatinine value was available, the lowest value was taken for this criterion), and (c) donor death caused by a cerebrovascular accident (CVA) [5,17]. A donor history of hypertension was considered to be present if hypertension was mentioned in the donor's medical record or in case of antihypertensive treatment before admission in the hospital. CVA was considered to be the cause of death if the European Dialysis and Transplant Association (EDTA) death cause in the NOTR database was recorded as 'CVA: Cerebro Vascular Accident Not Otherwise Specified', 'CVA: Intra Cerebral Bleeding' or 'CVA: Cerebral Ischaemia'. Diabetes in the recipients was defined as diabetic renal disease as primary kidney disease or presence of diabetes before transplantation

registered in the database. Diabetes was classified as type 1 if the primary renal disease in the database was 'Diabetes type 1'. If the primary renal disease was registered as 'diabetes type 2' or the dichotomous field 'Diabetes before transplantation' was 'Yes', diabetes was classified as type 2.

Statistical analyses

Descriptive statistics are presented as numbers, percentages and means (standard deviation; SD). Relative risks were analysed using Cox proportional hazards models and given as hazard ratios with 95% CI. In these models, ECD kidney was analysed as a dichotomous determinant of the two outcome variables. Initially, crude models with ECD kidney as determinant were constructed. Thereafter, we adjusted for baseline confounders in two steps. Model 1 was adjusted for characteristics of the recipient [recipient age, previous dialysis duration, panel-reactive antibodies (PRA), recipient blood group, diabetes]; model 2 for all characteristics of model 1 and characteristics of the transplant procedure and matching [cold ischaemia time, HLA sharing, donor blood group, donation after cardiac death (DCD) versus donation after brain death (DBD), year of transplantation]. In the Netherlands, the date of registration on the waiting list is the same as the data of initiation of dialysis. Therefore, the time on the waiting list was not added as a separate confounder. Recipient age, sharing HLA, cold ischaemia time (hours) and dialysis duration (years) were entered as continuous variables; panel-reactive antibody (PRA) category (0–5%, 6–84%, >85% PRA activity), transplant year, DCD (yes/no), gender (male/female), donor and recipient blood group and diabetes (yes/no) as categorical variables. As in these analyses few data were missing, complete case analyses were executed. Adjusted absolute risk differences (RD) at three time points (1, 5 and 10 years of follow-up) between the ECD kidney donation and the non-ECD kidney donation were calculated from the obtained Cox models using the corrected group prognosis method as described by Austin [18]. Pointwise confidence intervals of the obtained risk differences were computed via bootstrap resampling (2000 cycles).

Subgroup analyses were performed with respect to recipient age and diabetes. Age was defined as age at the moment of kidney transplantation and divided into three subgroups: 18–39, 40–59 and ≥60 years. Statistical testing of HRs among subgroups was performed by adding an interaction term between ECD kidney and age category or diabetes to the Cox models using the appropriate group as reference. Statistical testing of RDs among the groups was performed with independent *t*-tests using the standard errors obtained with bootstrap resampling.

We considered comparing kidney pairs allocated to an old and a younger recipient. However, in the ET-region kidneys of the same donor are often allocated to recipients in different countries. Therefore, these data are not available in the NOTR (Dutch) database. As a consequence, paired kidney analysis was impossible.

Survival graphs were constructed as raw Kaplan–Meier curves without adjustments.

Sensitivity analyses

To assess robustness of our results, a number of sensitivity analyses were performed. First, transplant year was replaced by confounders that possibly were more aetiologically associated with improvements over time. To this end, we used dichotomous indicators of administration of initial immunosuppressive drugs, such as antibodies (antithymocyte globulin, basiliximab, etc.), calcineurin inhibitors (ciclosporin, tacrolimus). Other factors, such as indicators of surgical techniques, the use of certain kidney preservation fluids may have contributed to improvements of the results, but are not available in the database. Second, donor kidney side was added to the confounders in the analyses of graft failure as right kidneys may have worse outcome [19]. As a third sensitivity analysis, absolute risk differences were analysed in prevalent patients in 4 periods after transplantation: 0–3 months, 3–12 months, 1–5 years and 5–10 years, to study whether absolute risk differences between the groups were present during the entire follow-up period. In these analyses, only patients without an event in the preceding period were analysed. Fourth, as graft failure and death are competing risks, which might influence the analysis of death-censored graft failure, graft failure was analysed with a competing risk analysis [20] using graft failure a primary outcome and death as competing outcome. Fifth, we analysed the effect of ECD kidney in strata of previous dialysis duration (<2 years, 2–4 years, and >4 years). Sixth, in order to avoid selection bias in type 1 diabetic patients due to the policy to preferentially execute a combined kidney and pancreas transplantation in these patients, analyses in diabetic patients were performed after exclusion of type 1 diabetic patients.

Seventh, to evaluate the robustness of the determinant, we constructed a categorical determinant indicating the four possible combinations of ECD and DBD/

DCD. Cox regression analyses were repeated with this categorical determinant using the non-ECD-DBD category as reference.

Eight, possible confounders with a high proportion of missing values, such as BMI and smoking, were analysed in a complete case analysis and after multiple imputation using chained equations (MICE) [21,22]. In the latter, weight, length and smoking were predicted with recipient age, recipient gender, previous dialysis duration, kidney disease, PRA activity, year of transplantation, donor hypertension, donor death cause CVA, DCD or DBD donor type, the dichotomous outcome indicator and the result of the cumulative hazard function [23]. In the Cox proportional hazard models, body mass index (weight/length^2) and smoking were added as confounders to model 2.

All analyses were performed using STATA® 13 and 14 statistical software (Stata Inc, College Station, TX, USA).

Results

From a total of 3901 kidney transplantations of deceased donors, we identified 3062 first procedures in recipients ≥18 years performed between 1 January 1995 and 31 December 2004 (Fig. 1, Table 1). Data were

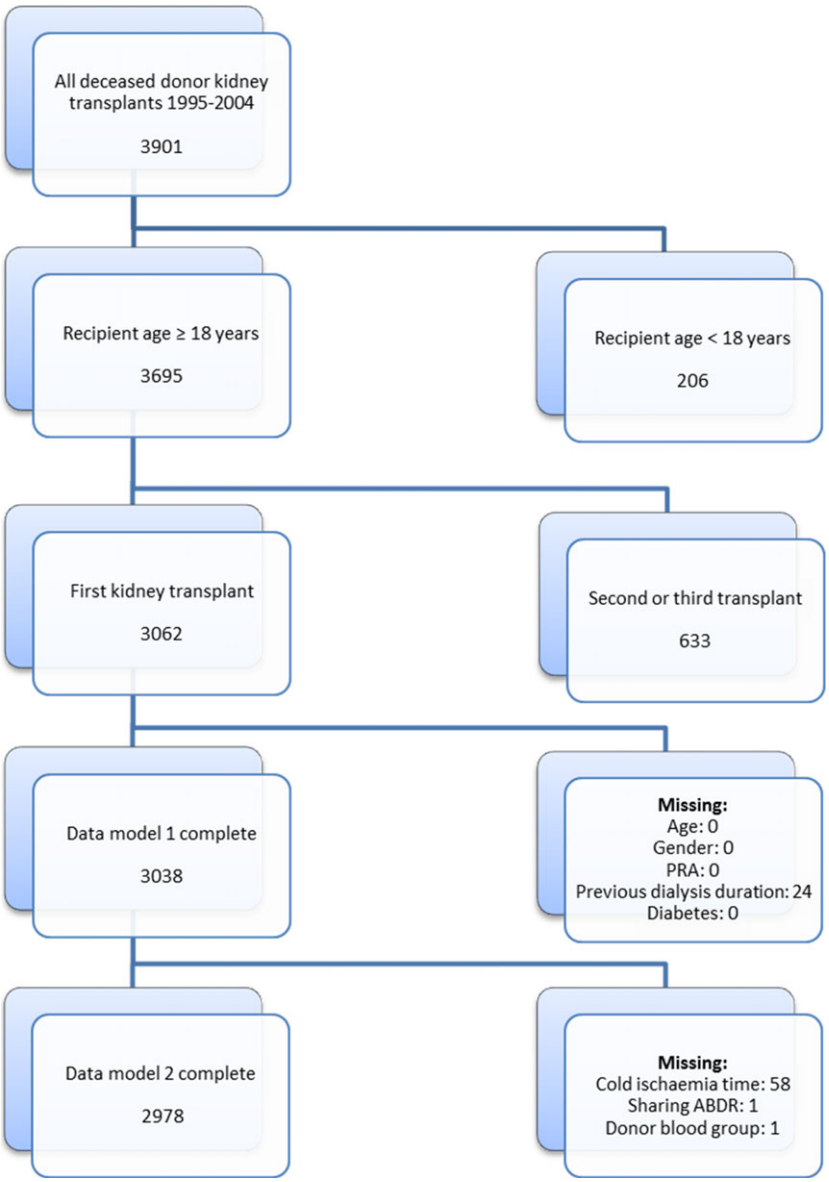

Figure 1 Selection of patients and available cases in the analyses.

Table 1. Recipient, donor, transplant procedure characteristics and events.

	All kidney transplants	ECD	Non-ECD
Kidney recipients			
N	3062	619 (20% of total)	2443 (80% of total)
Male	1814 (59%)	387 (62.5%)	1427 (58.4%)
Female	1248 (41%)	232 (37.5%)	1016 (41.6%)
Age (years)	49.0 (12.8)	53.1 (13.0)	48.0 (12.5)
18–39 years (*N*)	746	642	104
40–59 years (*N*)	1598	1312	286
≥60 years (*N*)	718	489	229
BMI (kg/m^2)*	24.0 (5.5)	24.4 (5.5)	24.0 (5.5)
Smoking (%)*			
Yes	11.7	13.3	11.3
No	35.3	37.5	34.8
Unknown	53.0	49.2	53.7
Dialysis duration (years)	3.29 (2.30)	3.14 (2.12)	3.32 (2.35)
Previous dialysis modality (%)			
HD	55.0	58.3	54.2
PD	39.3	36.8	40.0
None	3.6	2.1	3.9
Unknown	2.1	2.8	1.9
Diabetes (*N*)	333 (10.9%)	50 (8.1%)	283 (11.6%)
Blood group			
O	1282 (42%)	250 (40%)	1032 (42%)
A	1260 (41%)	247 (40%)	1013 (42%)
B	382 (12%)	90 (15%)	292 (12%)
AB	138 (5%)	32 (5%)	106 (4%)
PRA (*N*)			
0–5%	2684 (87.6%)	566 (91.4%)	2118 (86.7%)
6–84%	348 (11.4%)	49 (7.9%)	299 (12.2%)
>85%	30 (1.0%)	4 (0.7%)	26 (1.1%)
Kidney donors			
N	3062	619	2443
Male	1612 (53%)	303 (49%)	1309 (54%)
Female	1450 (47%)	316 (51%)	1134 (46%)
Age (years)	43.1 (16.1)	62.7 (5.6)	38.1 (13.9)
Kidney side (left/right)	1570/1492	306/313	1264/1179
Lowest donor creatinine (μmol/l)	77.7 (42.0)	82.8 (28.6)	76.5 (44.6)
Blood group			
O	1388 (45%)	280 (45%)	1108 (45%)
A	1268 (42%)	246 (40%)	1022 (42%)
B	317 (10)	75 (12%)	242 (10%)
AB	88 (3%)	17 (3%)	71 (3%)
Unknown	1 (0.03%)	1 (0.16%)	0 (0%)
Donor death cause			
CVA	1385 (45.2%)	417 (67.4%)	968 (39.6%)
Donation			
After brain death (DBD)	2360 (77.1%)	489 (79.0%)	1871 (76.6%)
After cardiac death (DCD)	702 (22.9%)	130 (21.0%)	572 (23.4%)
Transplant procedure/other			
Sharing HLA			
0 (%)	2.2	1.9	2.3
1 (%)	4.6	4.5	4.6
2 (%)	15.1	19.1	14.1
3 (%)	35.8	34.9	36.0
4 (%)	25.9	24.1	26.3

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Table 1. Continued.

	All kidney transplants	ECD	Non-ECD
5 (%)	11.6	11.3	11.7
6 (%)	4.9	4.2	5.0
Cold ischaemia time (h)	22.2 (7.5)	22.7 (7.4)	22.0 (7.5)
Endpoints			
Follow-up time (years) (min–max)	7.8 (4.6) (0–18)	6.5 (4.5) (0–17.4)	8.2 (4.6) (0–18)
Transplant failure (including death) (*N*)	1607 (52.5%)	414 (66.9%)	1193 (48.8%)
Graft failure	818 (26.7%)	223 (36.0%)	595 (24.4%)
Death (*N*)	1183 (38.6%)	301 (48.6%)	882 (36.1)

N, number; BMI, body mass index; HLA, human leucocyte antigen; PRA, panel-reactive antibodies; ECD, expanded criteria donor. Data are given as mean (SD).

*About 31% missing data for BMI, 50% for smoking.

extracted from the NOTR database in April 2013. Considering data quality: 6% of the cases was considered to be lost to follow-up by the treating transplant centres and NOTR; 68% of the patients without an event had their last follow-up in 2011 or later; 24% in 2008–2010. Table 1 shows the characteristics of the kidney donors, kidney recipients and the transplantation procedures. Among these, ECD criteria were met in 619 kidney transplants (20%). The number of kidney pairs, that is kidneys from the same donor, could not be derived from the database. Over time, the distribution of criteria classifying a kidney as ECD kidney did not change (data not shown).

In general, missing data at the moment of transplantation were below 5%. However, recipient smoking at the moment of transplantation was unknown in about 50% of the cases, recipient body mass index (BMI) in about 30% and donor diuresis in about 18%. Therefore, smoking and BMI were analysed as confounders in the sensitivity analyses only.

Table 2 shows the *relative risks* (hazard ratios) obtained with multivariable Cox models, adjusting for possible confounders. These analyses confirm the finding that ECD kidneys perform worse. These effects are most striking in diabetic patients and the young (18–39 years) and middle age category (40–59 years). The adjusted HR for graft failure including death in recipients ≥60 years differed statistically significantly from the HR in recipients of 18–39 years of age ($P = 0.03$). All HRs between diabetic and nondiabetic patients were statistically significant ($P \leq 0.02$).

Table 3 shows the *adjusted absolute risk differences* (RD) between ECD and non-ECD kidneys at three time points using model 2 from Table 2. In general, in these analyses, the risk of graft failure in ECD kidney recipients is higher. The RDs of graft failure between ECD and non-ECD kidneys were lowest in the oldest age group, and statistically different from the youngest and middle age groups with respect to graft failure including death ($P = 0.04$ and $P = 0.002$ respectively). RD trends for graft failure (death censored) and death were similar as those for graft failure including death among the age subgroups, but not statistically significant. Death-censored graft failure and death differ statistically significantly between the diabetic and nondiabetic groups ($P = 0.02$ and $P = 0.001$, respectively).

Table 4 shows the adjusted hazard ratios of combinations of ECD and DCD/DBD kidneys. Overall, the highest risks of graft failure and death are observed in the groups with both ECD and DCD kidneys. In the age subgroups, this risk appeared to be more dependent on graft failure than on death. The results obtained in the diabetic patients must be interpreted with caution, as the ECD-DCD group consists of only 12 diabetic kidney recipients.

Figures 2 and 3 show the crude Kaplan–Meier survival curves of kidney transplants and patients according to ECD status in all patients and after stratification for age categories or the presence of diabetes as primary kidney disease, illustrating the above-mentioned absolute and relative risk differences.

Sensitivity analyses

In the analyses with the initial immunosuppression as confounders, the confounding effect of 'transplant year' was explained in part, but not fully, by immunosuppression. Adding kidney side in the second sensitivity analysis did not change the results of model 2 (data not

Table 2. Relative risk of graft failure and mortality in patients receiving a kidney transplantations with Expanded Criteria Donor kidneys.

	ECD versus non-ECD					
	All patients	Recipient age 18–39 years	Recipient age 40–59 years	Recipient age ≥60 years	No diabetes	Diabetes
N	3062	746	1598	718	2729	333
Graft failure including death						
Crude	1.71 (1.53–1.91)	1.69 (1.26–2.27)	1.66 (1.41–1.95)	1.35 (1.13–1.63)	1.64 (1.46–1.85)	3.03 (2.16–4.24)
Model 1 (recipient characteristics)*	1.58 (1.41–1.78)	1.73 (1.29–2.33)	1.69 (1.43–2.00)	1.34 (1.10–1.62)	1.51 (1.33–1.71)	2.33 (1.63–3.34)
Model 2 (model 1 and procedure/ matching characteristics)†	1.62 (1.44–1.82)	1.92 (1.42–2.62)	1.71 (1.44–2.02)	1.32 (1.07–1.63)‡	1.53 (1.35–1.74)	2.60 (1.75–3.88)§
Graft failure – death censored						
Crude	1.75 (1.50–2.05)	1.75 (1.27–2.40)	1.92 (1.54–2.39)	1.63 (1.19–2.22)	1.67 (1.42–1.96)	3.29 (1.95–5.54)
Model 1 (recipient characteristics)*	1.85 (1.58–2.17)	1.72 (1.25–2.38)	1.95 (1.56–2.45)	1.59 (1.16–2.20)	1.76 (1.50–2.09)	3.06 (1.73–5.39)
Model 2 (model 1 and procedure/ matching characteristics)†	1.92 (1.63–2.26)	1.95 (1.40–2.71)	1.99 (1.58–2.51)	1.61 (1.13–2.29)¶	1.82 (1.53–2.15)	3.56 (1.91–6.64)**
Death						
Crude	1.73 (1.52–1.97)	1.16 (0.68–2.00)	1.58 (1.31–1.92)	1.30 (1.06–1.58)	1.66 (1.44–1.91)	3.13 (2.18–4.48)
Model 1 (recipient characteristics)*	1.43 (1.25–1.64)	1.37 (0.79–2.38)	1.65 (1.35–2.00)	1.27 (1.04–1.56)	1.35 (1.16–1.56)	2.24 (1.52–3.29)
Model 2 (model 1 and procedure/ matching characteristics)†	1.45 (1.26–1.67)	1.49 (0.83–2.66)	1.66 (1.36–2.03)	1.25 (0.99–1.56)††	1.35 (1.16–1.57)	2.55 (1.66–3.93)‡‡

Data are given as hazard ratios (95% CI) obtained with Cox proportional hazards models.

*Adjusted for recipient age, recipient gender, dialysis duration recipient, panel-reactive antibody (PRA) activity, recipient blood group, diabetes (not in analyses stratified for diabetes).

†Adjusted for model 1 and HLA sharing, donor blood group, cold ischaemia time, DCD (versus DBD), year of transplantation.

‡$P = 0.03$ versus recipients 18–39 years, $P = 0.12$ versus recipients 40–59 years.

§$P = 0.01$ versus nondiabetic recipients.

¶$P = 0.6$ versus recipients 18–39 years, $P = 0.6$ versus recipients 40–59 years.

**$P = 0.02$ versus nondiabetic recipients.

††$P = 0.8$ versus recipients 18–39 years, $P = 0.13$ versus recipients 40–59 years.

‡‡$P = 0.02$ versus nondiabetic recipients.

Table 3. Adjusted absolute risk differences (%) of graft failure and mortality at certain time points of follow-up period in subgroups of patients.

	ECD versus non-ECD					
	All patients	Recipient age 18–39 years	Recipient age 40–59 years	Recipient age ≥60 years	No diabetes	Diabetes
N	3062	746	1598	718	2729	333
Graft failure including death						
1 year	7.1 (5.2–9.2)	9.7 (4.2–17.2)	7.4 (4.7–10.4)	5.0 (0.9–8.9)	6.1 (4.3–8.2)	17.1 (8.7–30.2)
5 years	12.4 (9.2–15.7)	16.1 (7.2–26.2)	13.0 (8.5–17.8)	8.6 (1.4–15.1)	10.8 (7.6–14.2)	26.5 (14.0–42.1)
10 years	16.1 (12.3–20.2)	20.3 (9.4–31.4)	18.0 (12.0–24.0)	9.7 (1.7–16.4)*	14.3 (10.2–18.4)	28.9 (15.7–40.3)†
Graft failure, death censored						
1 year	8.1 (5.6–10.6)	9.1 (3.3–16.5)	8.0 (4.7–11.4)	6.0 (1.3–10.8)	7.4 (5.2–10.1)	15.1 (5.2–30.3)
5 years	12.8 (9.1–16.8)	15.0 (5.7–25.5)	12.6 (7.5–17.5)	9.0 (1.8–16.4)	11.8 (8.2–15.6)	23.7 (8.2–43.9)
10 years	16.9 (12.1–21.8)	19.0 (7.5–30.7)	17.2 (10.5–23.2)	11.0 (2.1–20.0)‡	15.4 (10.8–20.3)	32.8 (12.1–51.2)§
Death						
1 year	2.0 (1.2–2.9)	0.9 (−0.6 to 3.0)	2.3 (1.2–3.7)	2.2 (−0.2 to 4.7)	1.4 (0.7–2.2)	11.0 (4.6–20.6)
5 years	6.1 (3.6–8.7)	3.2 (−1.8 to 9.3)	8.0 (4.6–12.1)	5.9 (−0.4 to 12.3)	4.6 (2.3–7.2)	22.2 (10.1–37.3)
10 years	10.1 (6.1–14.2)	5.5 (−0.3 to 15.0)	14.9 (8.7–21.3)	7.8 (−0.6 to 15.5)¶	7.9 (4.0–12.0)	28.1 (13.3–42.5)**

Data are given as risk difference (95% CI) obtained with the corrected group prognosis method using Cox proportional hazard model 2 (Table 2).

All risk differences are adjusted for recipient age, recipient gender, dialysis duration recipient, panel-reactive antibody (PRA) activity, recipient blood group, diabetes (not in analyses stratified for diabetes), HLA sharing, donor blood group, cold ischaemia time, DCD (versus DBD), year of transplantation.

*P = 0.04 versus recipients 18–39 years, P = 0.002 versus recipients 40–59 years.

†P = 0.06 versus nondiabetic patients.

‡P = 0.3 versus recipients 18–39 years, P = 0.06 versus recipients 40–59 years.

§P = 0.02 versus nondiabetic patients.

¶P = 0.72 versus recipients 18–39 years, P = 0.19 versus recipients 40–59 years.

**P = 0.001 versus nondiabetic patients.

Table 4. Adjusted relative risks of ECD and DCD combinations.

	ECD/non-ECD and DBD/DCD combinations					
	All patients	Recipient age 18–39 years	Recipient age 40–59 years	Recipient age ≥60 years	No diabetes	Diabetes
N	3062	746	1598	718	2729	333
Graft failure including death						
Non-ECD-DBD	1	1	1	1	1	1
Non-ECD-DCD	1.14 (0.99–1.34)	1.46 (1.01–2.10)	1.10 (0.88–1.37)	0.94 (0.71–1.25)	1.15 (0.98–1.35)	1.03 (0.61–1.73)
ECD-DBD	1.57 (1.38–1.80)	2.01 (1.41–2.86)	1.60 (1.32–1.95)	1.28 (1.01–1.62)	1.47 (1.27–1.69)	3.20 (2.02–5.08)
ECD-DCD	2.05 (1.63–2.60)	2.42 (1.29–4.56)	2.37 (1.70–3.30)	1.39 (0.93–2.08)	2.07 (1.62–2.65)	1.49 (0.65–3.45)
Graft failure – death censored						
Non-ECD-DBD	1	1	1	1	1	1
Non-ECD-DCD	1.64 (1.35–2.01)	1.48 (1.01–2.18)	1.43 (1.07–1.92)	2.27 (1.44–3.58)	1.61 (1.31–1.98)	1.41 (0.60–3.29)
ECD-DBD	1.99 (1.65–2.41)	2.10 (1.44–3.06)	1.91 (1.46–2.51)	1.97 (1.29–3.00)	1.85 (1.52–2.26)	5.34 (2.58–11.05)
ECD-DCD	2.83 (2.10–3.83)	2.24 (1.11–4.50)	3.22 (2.12–4.88)	2.38 (1.25–4.52)	2.77 (2.03–3.79)	1.72 (0.45–6.56)
Death						
Non-ECD-DBD	1	1	1	1	1	1
Non-ECD-DCD	0.97 (0.81–1.17)	1.89 (1.02–3.53)	1.01 (0.77–1.31)	0.81 (0.60–1.09)	1.02 (0.84–1.24)	0.97 (0.55–1.70)
ECD-DBD	1.41 (1.20–1.64)	1.53 (0.78–2.98)	1.61 (1.29–2.01)	1.19 (0.93–1.52)	1.30 (1.10–1.54)	2.84 (1.73–4.67)
ECD-DCD	1.64 (1.23–2.19)	2.54 (0.76–8.44)	1.92 (1.27–2.91)	1.22 (0.78–1.92)	1.64 (1.20–2.23)	1.77 (0.72–4.41)

Data are given as hazard ratios (95% CI) obtained with Cox proportional hazards models.

Adjusted for recipient age, recipient gender, dialysis duration recipient, panel-reactive antibody (PRA) activity, recipient and donor blood group, diabetes (not in analyses stratified for diabetes), HLA sharing, cold ischaemia time, year of transplantation.

DBD, donation after brain death; DCD, donation after cardiac death.

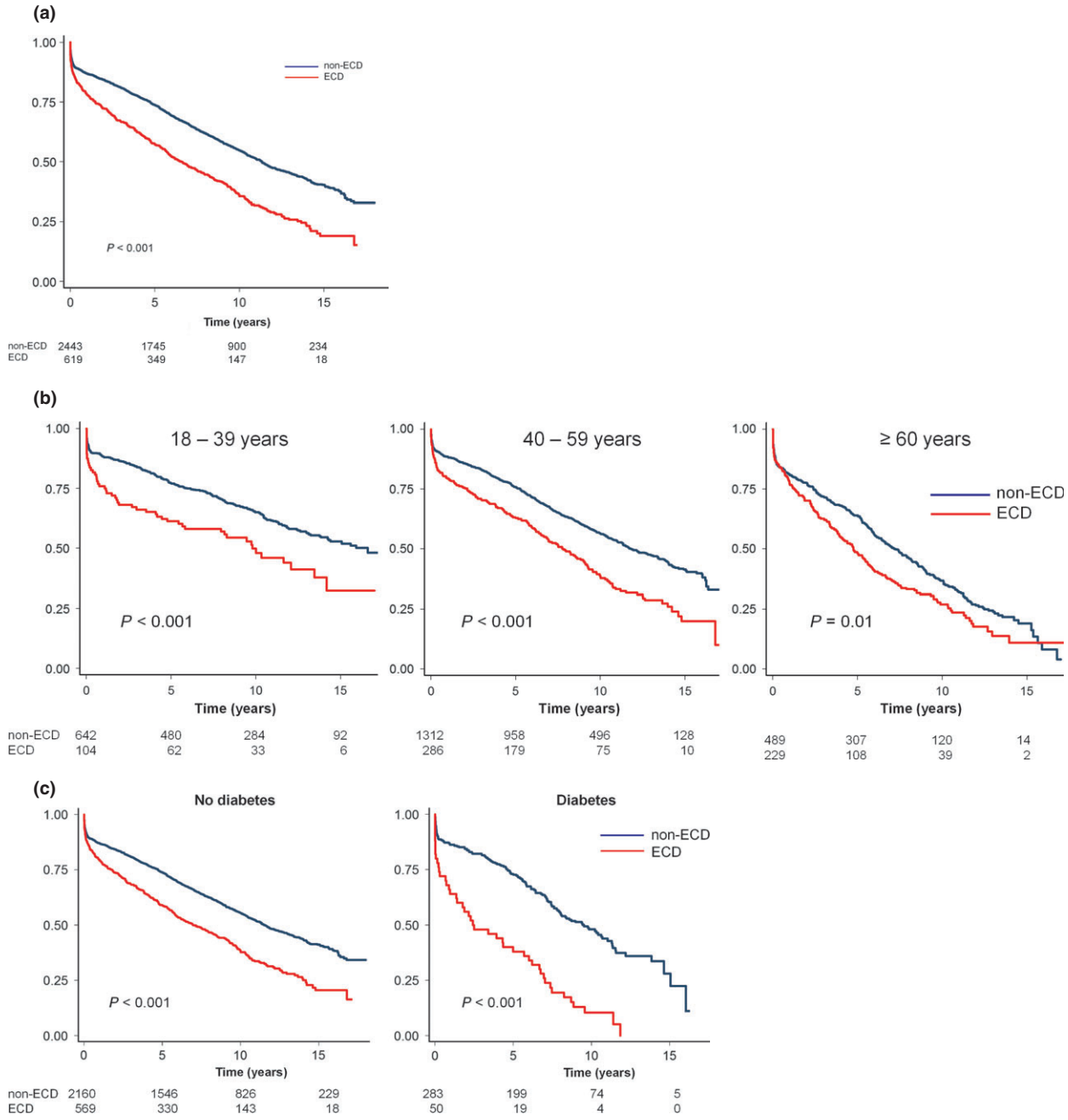

Figure 2 Crude Kaplan–Meier graft survival graphs given as proportion not reaching the endpoint graft failure or death according to expanded criteria donor (ECD) kidney donation. *P*-values indicate the difference between ECD and non-ECD recipients and are derived from model 2 (Table 2). (a) All patients. (b) Stratification by recipient age category. (c) Stratification by diabetes.

shown). The third sensitivity analysis (data not shown) looking at absolute risk differences of graft failure and mortality within time periods after transplantation (0–3 months, 3–12 months, etc.) showed that absolute risks were higher in the first months after transplantation. In all time periods, absolute risks were higher in the ECD kidney recipient group. The fourth sensitivity analysis, using competing risk analysis for graft failure and death as competing risks, showed similar patterns in the subhazard ratio of ECD kidney for graft failure as the Cox models for death-censored graft failure (data not shown). The fifth sensitivity analysis did not show differences among strata of previous dialysis duration. The sixth sensitivity analysis excluding type 1 diabetic patients showed that absolute risk differences between ECD kidney and non-ECD kidney were similar as in the

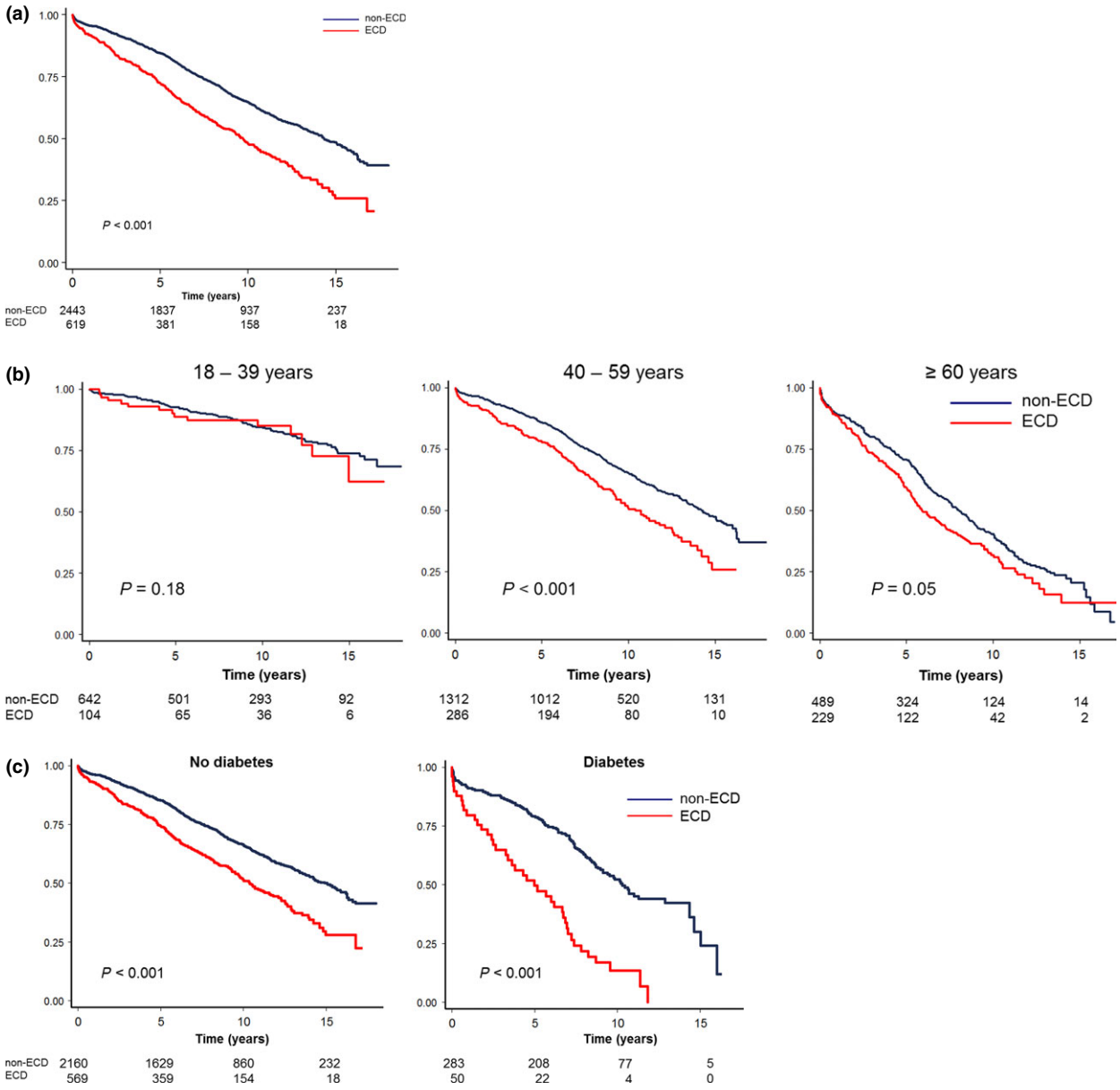

Figure 3 Crude Kaplan–Meier patient survival graphs given as proportion not reaching the endpoint death according to expanded criteria donor (ECD) kidney donation. *P*-values indicate the difference between ECD and non-ECD recipients and are derived from model 2 (Table 2). (a) All patients. (b) Stratification by recipient age category. (c) Stratification by diabetes.

analysis with all diabetics; the relative risk was slightly lower, but did not change the conclusion that the risk of graft failure and death is higher in diabetic patients than in nondiabetics. The seventh sensitivity analysis is described above (description of Table 4). Finally, both in the complete cases analyses and the imputed data sets, recipient smoking and recipient BMI did not appear to be important confounders of the association between ECD kidney and outcomes and effect estimates did not change substantially (data not shown).

Discussion

This study shows that deceased donor kidney transplantation fulfilling ECD criteria is associated with a higher risk of graft failure and (long-term) death of the recipient (even after transplant failure and a subsequent period of dialysis treatment) in the Netherlands. In particular, recipients with diabetes and recipients in the youngest and middle age groups have higher absolute and relative risks.

In the whole cohort, transplantation with ECD kidney grafts results in higher relative and absolute risks of graft failure including recipient death. After adjusting for confounders, the relative risk for graft failure and death tended to be higher in the youngest and middle age groups when compared to the highest age group (model 2, HR 1.92 and 1.71 vs. 1.32, $P = 0.03$ and $P = 0.12$ respectively). Absolute risk differences showed a similar pattern. These results suggest that the adverse outcome of ECD kidneys is at least more pronounced in the youngest age group and possibly in the middle age group than in the oldest group. This is in line with previous studies on the donor and recipient age match [24]. The oldest group has the lowest risk associated with ECD kidney transplantation. These effects are even more striking in the recipients receiving an ECD–DCD kidney. Probably, the oldest group has the highest risk for death and ECD kidney transplantation does not add substantially to this risk.

In the diabetic group, both relative and absolute risks were higher than in the nondiabetic group. The differences in HR and RD were generally statistically significant after correction for confounders in a multivariable model. It indicates that ECD kidneys perform worse in diabetic recipients. Nevertheless, the findings of this study on diabetics should be interpreted carefully, as in our analysis, only 50 diabetic patients received an ECD kidney, and, the number of diabetic patients was too low to evaluate interaction between ECD kidney and DCD kidney interaction in this subgroup (12 recipients). In case our results are not a chance finding, this means that the diabetic environment aggravates adverse consequences of ECD kidney transplantation. The mechanisms by which ECD kidney transplantations give rise to worse outcomes cannot be derived from this study. We hypothesize that ECD kidneys will have worse kidney function, even after an uncomplicated transplantation procedure and that this impaired kidney function determines outcomes of graft and patient survival. In the diabetic patients, it seems plausible that the diabetic environment impairs recovery of tubular and other renal cells from the ischaemia during the transplant procedure, thereby inducing a higher risk of rejection and impaired renal function, which, in turn, induces premature death.

The results of the present study are in line with the general conclusion of a systematic review [12], a recent report on organ quality and recipient age in the United States [25], and an analysis of ECD kidney transplantation in retransplanted patients [26]. However, in the systematic review, the results of the studies analysed were not pooled. Therefore, we cannot compare the sizes of the HRs and RDs of the present study with a pooled counterpart of previous studies. Based on our results, subgroups receiving an ECD kidney that have the lowest relative risk for graft failure and death in comparison with non-ECD kidney recipients, are patients ≥60 years and patients without diabetes. Pascual *et al.* [12] suggested that certain patients with long expected waiting times could be preferential subgroups for receiving an ECD kidney. The hypothesis of Pascual might be supported by a Dutch study on the 5-year results of DCD transplantation that showed that transplantation with DCD grafts appeared to be better than waiting a DBD kidney while remaining on dialysis [27]. Therefore, we think it is a good idea to select patient groups that would profit most from ECD transplantation with shortened waiting times, compared to the alternative, which is continuing dialysis and waiting for a higher quality kidney graft.

It has been postulated that other classifications than the ECD/non-ECD classification might be more discriminative for organ and recipient prognosis. The present study suggests that a classification using four ECD and DCD/DBD combinations is already better than ECD alone (Table 4). In the USA, the Kidney Donor Risk Index (KDRI) was developed [28] and implemented in 2014 in the UNOS kidney allocation system. In its five categories, almost all ECD donors are within one KDRI category. This means that KDRI's discriminative capacity may be better in non-ECD kidneys, but not in ECD ones [28]. In practice, KDRI does not predict results of kidney transplantation correctly in all subgroups [29]. In our additional analyses (data not shown), donor age appeared to be the most important factor associated with death and graft failure. Therefore, we agree that ECD kidney is probably not the optimal marker for poor donor quality. Further studies and refinements of classification systems, such as KDRI, are necessary to optimize risk classification before using those systems more extensively in allocation strategies.

Within the ET region, median donor age and, thereby the number of ECD kidney grafts, is steadily increasing in the ET region from 43 years in 1995 to 53 years in 2013 [30]. Based on our results, it could be advocated to allocate ECD kidneys, and especially ECD-DCD kidneys, preferentially to recipients of ≥60 years and to avoid ECD kidneys in diabetic recipients. The Eurotransplant Senior Program for kidneys from donors of 65 years and older is already an example of matching the age of donor and recipient. This concept of age matching could be extended to younger donors. Avoiding ECD kidneys in diabetic recipients will induce a longer waiting time

for diabetic patients, which might be more harmful than receiving an ECD kidney transplant. Furthermore, this strategy will result in more ECD kidney allocations in the group of nondiabetics, which also raises ethical questions. Another interesting strategy raising ethical questions in a situation of organ scarcity, is allocating a pair of ECD kidneys in younger recipients. In middle-aged and older recipients, results of this type of transplantation have proven to be successful [31–33].

From a patient perspective, it is desirable to receive the optimal renal replacement therapy in a certain situation. Possibly, refusing a kidney transplant of poor quality, continuing dialysis and waiting for another kidney transplant might be the optimal solution in some situations. However, in order to evaluate several scenarios at the moment of a kidney transplant offer, complex mathematical simulation models taking into account consequences of a poor kidney transplant, a longer episode on maintenance dialysis and the chance of getting a better transplant offer must be available. At this moment, those models have not been constructed. Two prediction models, the Deceased Donor Score and The Kidney Donor Risk Index predict survival of kidney transplants using donor characteristics [28,34–36]. These models only predict patient and graft outcomes after transplantation but do not take into account recipient characteristics, waiting time on dialysis nor chances of getting a better transplant offer. Therefore, future research should focus on prediction models combining donor, recipient and procedure characteristics. The associations found in our study suggest that recipient characteristics should be evaluated as potential predictors in future prediction models and mathematical simulation models.

Limitations and strengths of this study

The present study has some limitations and strengths. The first limitation is that, although allocation of kidney transplants by ET is executed according to several objective rules, the acceptance of the donor kidney by nephrologists is subjective. The possibility that some nephrologists induce confounding by indication by refusing ECD kidneys if allocated to recipients in a good clinical condition must be considered. As a consequence, adding an estimate of the physical condition of the recipient as a confounder to our analyses could be a reasonable solution, but is impossible as the NOTR database does not contain those data. Other estimates of physical condition such as data on comorbid conditions have a lot of, potentially nonrandom, missing values in the NOTR registry and, therefore, will not, even after data multiple imputation, alleviate this problem. On the other hand, recipient age is expected to be a strong predictor of physical condition and this variable was taken into account. Second, the number of diabetic patients receiving a ECD kidney is low (50). Especially, results of subgroups in this category (e.g. ECD-DCD subgroup) must interpreted cautiously. Third, because of many missing values, two potential confounders could not be used in the main analyses: smoking behaviour and body mass index of the recipient. However, in the complete case analyses and the analyses with imputed data, these characteristics did not emerge as important confounders. Fourth, transplant year appeared to be an important confounder. It indicates that kidney transplantation in general has become more successful over time. However, in our analyses the effects of this confounder could not be fully replaced by other confounders, such as induction immunosuppressive therapy with monoclonal antibodies and other initial immunosuppressive therapy. Maybe, other characteristics not included in our analyses, such as the use of kidney preservation fluids, surgical techniques, (early) changes in the immunosuppressive regimen and their dose during follow-up, and effectiveness of antirejection therapies, are part of the effect of 'transplant year'. The transplant period is also associated with changes in kidney allocation. Before 1996 there was only obligatory exchange of full-house HLA matches. After March 11, 1996 allocation of all recipients was regulated with computerized allocation lists (Eurotransplant Kidney Allocation System, ETKAS). In January 1999, the Eurotransplant Senior Program (ESP) was introduced. The ESP allocates kidney from postmortem donors of 65 years and older to recipients of 65 years and older, without the use of a donor HLA typing. The ESP aims at a cold ischaemic period that is as short as possible. In the Netherlands, kidneys from ESP donors are allocated to ESP recipients according to the national waiting list. Kidneys from an ESP donor that cannot be allocated nationally are allocated through the regular ETKAS after reporting of the HLA typing. In the Netherlands, ESP donor kidneys are only allocated to never-immunized recipients awaiting a first kidney transplant. Since 1 February 2001, kidneys from both DCD (donation after cardiac death) and DBD (donation after brain death) donors in the Netherlands have been indiscriminately allocated through the standard renal allocation system. Although replacement of transplant year by variables such as immunosuppressive regimens and allocation strategies would gain insight in the mechanism of improvements of outcome over the years, we do not expect this to affect the estimates of ECD donation.

Fifth, the effect of kidneys pairs, that is kidneys from the same donor, could not be analysed in our database. Finally, only variables known at the moment of kidney allocation were analysed as confounding variables. As a consequence, factors influencing graft survival, such as the number and type of acute rejections, and the presence of post-transplant anti-HLA donor specific antibodies, even if they were present in the database, were not included in the analyses. Including these covariates may be an interesting question for further research.

However, this study also has several strengths. The first strength is that all recipients of a kidney graft of a deceased donor in the Netherlands within a defined period were included. The inclusion period (1995–2005) affirms a long follow-up period of 8–18 years. Second, the main variables in the NOTR database have few missing values. Third, exchange with the Renine registry provides information on long-term death, mostly not available in transplant registries. And fourth, we analysed both relative risks and absolute risk differences. Both points into the same direction.

In conclusion, ECD, and especially ECD-DCD kidney transplantation, is associated with a higher risk of graft failure and death. This effect is most striking in young and middle-aged recipients (<60 years) and in patients with diabetes. In case of persisting scarcity of donor kidneys, further analyses should reveal whether preferential allocation of ECD kidneys to specific subgroups, such as older, nondiabetic patients, is a safe and ethically justified strategy.

Authorship

The study was designed by myself, Aline Hemke, Andries Hoitsma, friedo dekker and Merel van Diepen. Merel van Diepen and I analysed the data. Luuk Hilbrands, Maarten Christiaans and Joke Roodnat collected data for the study. All authors contributed in the interpretation of the results as given in the results and discussion sections.

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Conflicts of interest

The authors of this manuscript have no conflict of interests to disclose as described by *Transplant International*.

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