Risk factors of chronic kidney disease progression: Dutch cohort studies

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Chapter 5 –

Superior long-term survival for simultaneous pancreas-kidney transplantation as renal replacement therapy: 30-year follow-up of a nationwide cohort

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Diabetes Care 2020, 43: 321-328

ABSTRACT

Objective: In patients with type 1 diabetes and end-stage renal disease, it is controversial whether a simultaneous pancreas-kidney (SPK) transplantation improves survival compared to kidney transplantation alone. We compared long-term survival in SPK and living or deceased donor kidney transplant recipients.

Research Design and Methods: We included all 2796 type 1 diabetes patients in The Netherlands, who started renal replacement therapy between 1986 and 2016. We used multivariable Cox regression analyses adjusted for recipient age and sex, dialysis modality and vintage, transplantation era, and donor age to compare all-cause mortality between deceased or living donor kidney and SPK transplant recipients. Separately, we analysed mortality between regions where SPK was the preferred intervention (80% SPK) *vs* regions where a kidney transplant alone was favoured (30% SPK).

Results: Of 996 transplanted patients, 42%, 16%, and 42% received a deceased or living donor kidney, or SPK transplant, respectively. Mean (SD) age at transplantation was 50 (11), 48 (11), and 42 (8) years, respectively. Median (95%-CI) survival time was 7.3 (6.2; 8.3), 10.5 (7.2; 13.7), and 16.5 (15.1; 17.9) years, respectively. SPK recipients with a functioning pancreas graft at one year (91%) had the highest survival (median 17.4 years). Compared to deceased donor kidney transplant recipients, adjusted hazard ratios (95%-CI) for 10- and 20-year all-cause mortality were 0.79 (0.49; 1.29) and 0.98 (0.69; 1.39) for living donor kidney, and 0.67 (0.46; 0.98) and 0.79 (0.60; 1.05) for SPK recipients, respectively. A treatment strategy favouring SPK over kidney transplantation alone showed 10- and 20-year mortality hazard ratios of 0.56 (0.40; 0.78) and 0.69 (0.52; 0.90), respectively.

Conclusions: Compared to living or deceased donor kidney transplantation, SPK was associated with improved patient survival, especially in recipients with a long-term functioning pancreatic graft, and resulted in an almost two-fold lower 10-year mortality rate.

INTRODUCTION

The global type 1 diabetes mellitus population approaches 40 million. Approximately 78,000 children are diagnosed with type 1 diabetes annually, and the incidence is expected to rise by 3% per year.[1] Micro- and macrovascular damage due to impaired glucose regulation leads to diabetic retinopathy, nephropathy, neuropathy, angiopathy and a three-fold increased mortality risk as compared to non-diabetic individuals.[2] As such, type 1 diabetes is accompanied by considerable health care costs, estimated at about 10,000 US dollars per patient per year.[3]

Patients with type 1 diabetes have a high cumulative risk of 7% to develop end-stage renal disease requiring renal replacement therapy within 30 years.[4] Compared with dialysis, kidney transplant recipients have a substantially improved survival and quality of life.[5, 6] In contrast to a kidney transplant alone, a simultaneous pancreas-kidney (SPK) transplantation may also restore endogenous insulin production and, at least partially, reverses progression of diabetic micro- and macrovascular complications.[7] Controversy remains however as to whether an SPK compared with a kidney transplant alone improves patient survival. Specifically, it is unknown whether an SPK should be preferred over a living donor kidney transplant.

For practical or ethical reasons, no randomised clinical trials have compared survival after SPK *vs* kidney transplantation alone. We previously showed, in Dutch type 1 diabetes patients between 1985 and 1996, that a treatment strategy favouring SPK over a deceased donor kidney transplant alone was associated with a 47% lower 10-year mortality risk.[8] In a US registry study among 18,549 type 1 diabetes patients during 1987-1996, eight-year survival after SPK or a living donor kidney transplant was similar at 72%, and better as compared to 55% in deceased donor kidney transplant recipients.[9] In the same registry during 2000-2007, recipients of a living donor kidney transplant had a better six-year survival as compared to SPK transplant patients, although others have found no clinically relevant 10-year survival benefit for SPK *vs* kidney transplantation alone.[10, 11] Weiss *et al* showed that SPK recipients who survived the first year post-transplant with a functioning pancreas graft, had a superior seven-year survival as compared to type 1 diabetes patients with a living donor kidney transplant (89% *vs* 80%).[12]

Taken together, there is no consensus on whether SPK compared with kidney transplantation alone actually improves mortality risk in patients with type 1 diabetes, especially in the long term. Therefore, we investigated the effect of SPK in comparison to kidney transplantation alone, either from a living or deceased donor, on long-term survival, in a nationwide cohort including all Dutch type 1 diabetes patients who have required renal replacement therapy in the past 30 years.

METHODS

Study population

We included consecutive (n=2833) type 1 diabetes mellitus patients aged at least 18 years, who started on chronic dialysis or received a first kidney transplant in the Netherlands between January 1, 1986 and January 1, 2016. We excluded patients who received a pancreas transplantation alone (n=17) or a pancreas after kidney transplantation (n=20); thus 2796 patients were eligible for the present analysis. In total, 1800 patients were on chronic dialysis only and 414, 161 and 421 patients received a deceased or living donor kidney, or SPK, respectively (Supplementary Figure S1). We used data from two mandatory nationwide Dutch registries. The Netherlands Organ Transplant Registry includes kidney transplant patients of all eight Dutch kidney transplant centres, containing information on donor and recipient characteristics as well as outcome parameters. The registry combines the donor, procurement and allocation data from the Eurotransplant Network Information System with transplant centre-specific data, and is updated annually. Registration of each organ transplantation is mandatory and is coordinated by the government via the Dutch Transplant Foundation. The Dutch Renal Registry (RENINE: Registratie Nierfunctievervanging Nederland) collects information on all chronic dialysis patients, registration for whom is also mandatory for all dialysis centres in order to receive funding. Data quality of both registries is periodically audited by on-site polls, application rules, and cross checks between the registries. Organs were allocated according to the standard Eurotransplant guidelines. Since type 1 diabetes patients on dialysis have a poor prognosis, Eurotransplant applies mandatory exchange rules for SPK, to prioritise this patient category in case of a potential SPK donor. These rules explain the shorter waiting time for SPK as compared to kidney transplantation alone, as well as the relatively large proportion of pre-emptive SPK transplant procedures (36%).[13] Deceased donor kidney and SPK transplants were performed following donation after brain death procedures in 95% of cases.

Regional differences in treatment strategy

The postal code of the type 1 diabetes patient strictly determines treatment in a defined dialysis centre, and each dialysis centre is affiliated to a specific transplant centre. Since the first pancreas transplant in the Netherlands in 1984, the Dutch Ministry of Health considered simultaneous pancreas-kidney transplantation an experimental and restricted procedure. The results has been that the vast majority of the simultaneous pancreas-kidney transplants have been performed in Leiden, which is only one of eight Dutch transplant

centres. These policies created regional differences in the assignment of simultaneous pancreas-kidney transplantation to patients with type 1 diabetes mellitus in essence largely based on their place of residence. We therefore defined two transplant areas: the Leiden area, with an average population of 2.5 million inhabitants during the 30-year follow-up period, and the rest of the Netherlands, with 14.0 million inhabitants. In the Leiden area, consisting of one transplantation centre, the primary intention is to treat type 1 diabetes patients with end-stage renal disease with an SPK. Thus, SPK was offered to the majority of type 1 diabetes patients. In contrast, in the non-Leiden area, consisting of seven transplantation centres, a kidney transplant alone has been the preferred treatment and SPK is performed in a significantly lower proportion of patients. Of all SPK transplants, 87% were performed in the Leiden area. Patients living in the Leiden area received an SPK in 80% of cases, compared with 30% for patients living in the non-Leiden area.

Importantly, immunosuppressive treatment for kidney transplant patients has changed over time. Until 1995 SPK recipients were treated with cyclosporine, azathioprine and prednisolone. From 1996 onward azathioprine was replaced by mycophenolate mofetil, and in 2003 cyclosporine was structurally replaced by tacrolimus. From 1997 induction therapy with intravenous anti-thymocyte globulin (ATG) was given, and beyond 2007 this was switched to subcutaneous alemtuzumab. For patients receiving a kidney transplant alone, immunosuppressive therapy changed comparably, although these patients do not receive ATG or alemtuzumab as induction therapy.

Endpoints

The primary endpoint was all-cause mortality. Patients were censored in case of loss to follow up, recovery of kidney function on dialysis, or end of follow-up (January 1, 2016), whichever came first. We defined patient survival as the time between start of dialysis or first kidney transplantation with or without pancreas transplant and the date of death from any cause. Pancreatic graft failure was defined as pancreas graft loss, need for exogenous insulin, or serum C-peptide levels <0.3 nmol/L. The secondary outcome was kidney graft failure, defined as kidney graft loss after transplantation and return to dialysis. We defined graft survival as the time between the date of transplantation and the date of graft failure or death. We investigated both graft failure including all-cause mortality, and death-censored graft failure. Finally, we assessed the occurrence of delayed graft function, defined as the need for dialysis within the first week after surgery, for the three different types of transplantation (deceased or living donor kidney, and SPK). Kidney grafts that never functioned were not considered as delayed graft functioning.

Statistical analyses

Baseline recipient and donor characteristics are presented as mean (SD) or number (%), when appropriate; data are presented for all patients, for different types of renal replacement therapy, and for different regions. There were no missing data for the most important clinical parameters; nine patients (0.3%) were lost to follow-up.

First, survival was compared between different types of transplantation. Crude survival was presented by Kaplan-Meier curves. Adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) for 10- and 20-year all-cause mortality were estimated by Cox regression. Analyses were adjusted for recipient age and sex, donor age, dialysis vintage and modality, and year of transplantation (per five-year interval). We adjusted for year of transplantation to account for changes in treatment protocols and medical care. To visualise the cumulative incidence of kidney graft failure, taking into account death as a competing risk, we used competing risk regression according to Fine and Gray.[14] Adjusted cause-specific HRs for kidney graft failure were calculated using standard Cox regression analyses, censoring patients in case of death.[15] Additionally, we investigated the influence of changes in immunosuppressive therapy over time on survival of SPK recipients. We therefore chose to compare 10-year all-cause mortality of SPK recipients transplanted in the period 1986-1999 and 2000-2015. We also investigated the influence of a long-term (defined as at least one year) functioning pancreas graft in SPK recipients on mortality. Information on date of pancreatic graft failure was only available for patients transplanted in the Leiden area (367 patients, 87% of all SPK recipients). We included all transplanted patients alive one year after transplantation, and stratified SPK recipients on having a functioning or failed pancreas graft.

Second, we performed analyses at the regional level (Leiden *vs* non-Leiden), to mimic an "intention-to-treat" analysis.[8] We provide effect estimates of SPK *vs* kidney transplant alone, by analysing patients according to their region of residence, and not according to the region where they were actually transplanted. Under the assumption that medical care for transplant patients is similar in the Leiden and non-Leiden areas, and that prognostic factors are similar for patients in both areas, confounding is dealt with by design. For example, a patient living in the non-Leiden area, but who received an SPK transplant in Leiden, was analysed according to the intended treatment belonging to the non-Leiden area.[8] Patients living in the Leiden and non-Leiden areas received an SPK transplant in 80% and 30% cases, respectively. Overall survival of transplanted patients was compared between the Leiden and non-Leiden areas. HRs for 10- and 20-year all-cause mortality were calculated using Cox regression, adjusted for recipient age and sex, donor age, dialysis vintage

and modality, and year of transplantation (per five-year interval). We compared survival on dialysis for the Leiden *vs* non-Leiden areas, censoring patients when transplanted.

Finally, survival was compared in patients who received any form of kidney transplantation (deceased or living donor kidney, or SPK) versus chronic dialysis treatment. In these analyses only dialysis patients on the waiting list for transplantation were included, to increase comparability of clinical characteristics between dialysis and transplanted patients. Dialysis and transplantation patients were matched for dialysis vintage, to avoid immortal time bias and minimise confounding by dialysis vintage. Survival time in transplanted patients was counted from the date of transplantation, and for matched dialysis patients we subtracted the dialysis vintage of the transplanted match, thereby creating a similar start of follow-up. Differences in crude survival were tested by the Log-rank test. HRs for five- and 10-year all-cause mortality were calculated using Cox regression, adjusted for recipient age and sex, and year of renal replacement therapy initiation (per five-year interval).

In all Cox regression analyses, the proportional hazards assumption was not violated, demonstrated by parallel log-survival curves in log-minus-log plots.[16] We repeated all analyses in patients who survived the first three months without graft loss. We thus excluded surgically- and immunologically-related death. We considered two-sided *p*-values <0.05 statistically significant. All analyses were performed using STATA Statistical Software version 14 (Statacorp, Texas, USA) and SPSS 25.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Baseline characteristics

Of all 2796 type 1 diabetes patients, 996 (36%) received a first kidney transplant from either a deceased (42%) or living (16%) donor, and 42% received an SPK (Table 1). Approximately 35% and 42% of living donor kidney and SPK recipients were pre-emptively transplanted. Mean (SD) age at start of dialysis was 59 years (13) for patients who stayed on chronic maintenance dialysis, and was 44 years (10) for transplant recipients. For SPK, both recipient age at transplantation and donor age were younger as compared to deceased or living donor kidney transplant recipients. Recipients of a deceased donor kidney had the longest dialysis vintage before transplantation and a longer cold ischemic period as compared to recipients of a living donor kidney or SPK. Delayed graft function occurred in 122 (12%) of all transplanted patients. For deceased donor kidney recipients the incidence of delayed graft failure was 25%, compared to 6%

and 2% for recipients of a living donor kidney or SPK transplant. Patients from the Leiden *vs* non-Leiden area had comparable age and sex distribution (Supplementary Table S1).

Table 1: Baseline characteristics 2796 type 1 diabetes mellitus patients, according to type of renal replacement therapy.

	Dialysis n=1800	**DDKT** n=414	**LDKT** n=161	**SPKT** n=421
Age at dialysis, y	59 ± 13	47 ± 10	46 ± 11	40 ± 8
Age at transplantation, y	-	50 ± 11	48 ± 11	42 ± 8
Men, %	53	63	58	62
Donor age, y	-	42 ± 16	51 ± 12	34 ± 12
Dialysis modality, %				
Hemodialysis	71	37	35	26
Peritoneal dialysis	29	34	23	31
Missing	0.1	14	7	1
Pre-emptive Tx, %	-	15	35	42
Dialysis vintage, mo [a]	36 ± 34	26 ± 24	12 ± 18	12 ± 19
Cold ischaemic time, h	-	23 ± 9	2 ± 1	13 ± 4
Place of residence, %				
Leiden area	14	8	9	45
Non-Leiden area	86	92	91	55

[a] Excluding pre-emptive transplant patients
Numbers are presented as mean ± SD or percentage.
DDKT, deceased donor kidney transplant; LDKT, living donor kidney transplant; SPKT, simultaneous pancreas kidney transplantation; Tx, transplantation.

Simultaneous pancreas-kidney transplantation compared to kidney transplantation alone

Crude survival was highest in SPK recipients, and lowest in recipients of a deceased donor kidney (Figure 1A). Compared to the latter patient group, adjusted HRs (95%-CI) for 10-year all-cause mortality for living donor kidney and SPK recipients were 0.79 (0.49; 1.29) and 0.67 (0.46; 0.98), and for 20-year all-cause mortality were 0.98 (0.69; 1.39) and 0.79 (0.60; 1.05), respectively (Table 2). The HR (95%-CI) for 10-year and 20-year all-cause mortality for SPK compared to living donor kidney recipients was 0.85 (0.53; 1.38) and 0.81 (0.57; 1.16), respectively. Overall graft loss, defined as death or kidney graft failure,

was dominated by patient mortality, and therefore results were comparable to those for all-cause mortality alone. Recipients of a living donor kidney had the lowest cumulative incidence of death-censored kidney graft failure, while death-censored graft failure was comparable for deceased donor kidney and SPK recipients (Figure 1B). Compared with deceased donor kidney recipients, the adjusted HR (95%-CI) for 10-year death-censored kidney graft failure was 0.52 (0.28; 0.98) and 1.05 (0.66; 1.67) for living donor kidney and SPK recipients, respectively (Table 2). Repeating analyses restricted to type 1 diabetes patients who survived the first three months after initiation of dialysis or kidney transplantation, yielded similar results.

Table 2: Hazard ratios (95%-CIs) for 10-year and 20-year all-cause mortality and death-censored kidney graft failure for living kidney transplantation or deceased kidney transplantation with or without simultaneous pancreas transplantation.

	Crude	Model 1	Model 2	Model 3
10-year all-cause mortality				
DDKT (ref)	1	1	1	1
LDKT	0.57 (0.37; 0.86)	0.64 (0.42; 0.98)	0.56 (0.36; 0.86)	0.79 (0.49; 1.29)
SPKT	0.34 (0.25; 0.45)	0.41 (0.30; 0.56)	0.44 (0.32; 0.61)	0.67 (0.46; 0.98)
10-year death-censored graft failure				
DDKT (ref)	1	1	1	1
LDKT	0.61 (0.35; 1.06)	0.59 (0.34; 1.02)	0.38 (0.21; 0.67)	0.52 (0.28; 0.98)
SPKT	0.67 (0.46; 0.97)	0.60 (0.41; 0.89)	0.76 (0.50; 1.15)	1.05 (0.66; 1.67)
20-year all-cause mortality				
DDKT (ref)	1	1	1	1
LDKT	0.69 (0.51; 0.94)	0.75 (0.55; 1.03)	0.70 (0.50; 0.96)	0.98 (0.69; 1.39)
SPKT	0.44 (0.36; 0.56)	0.55 (0.44; 0.71)	0.58 (0.45; 0.74)	0.79 (0.60; 1.05)
20-year death-censored graft failure				
DDKT (ref)	1	1	1	1
LDKT	0.63 (0.38; 1.03)	0.60 (0.37; 0.98)	0.40 (0.24; 0.67)	0.50 (0.29; 0.88)
SPKT	0.59 (0.42; 0.83)	0.52 (0.37; 0.74)	0.62 (0.43; 0.89)	0.79 (0.53; 1.20)

DDKT, deceased donor kidney transplant; LDKT, living donor kidney transplant; SPKT, simultaneous pancreas kidney transplantation.
Model 1: Adjusted for recipient age and sex.
Model 2: Model 1, plus adjustment for donor age.
Model 3: Model 2, plus adjustment for dialysis vintage, dialysis modality, and transplantation era.

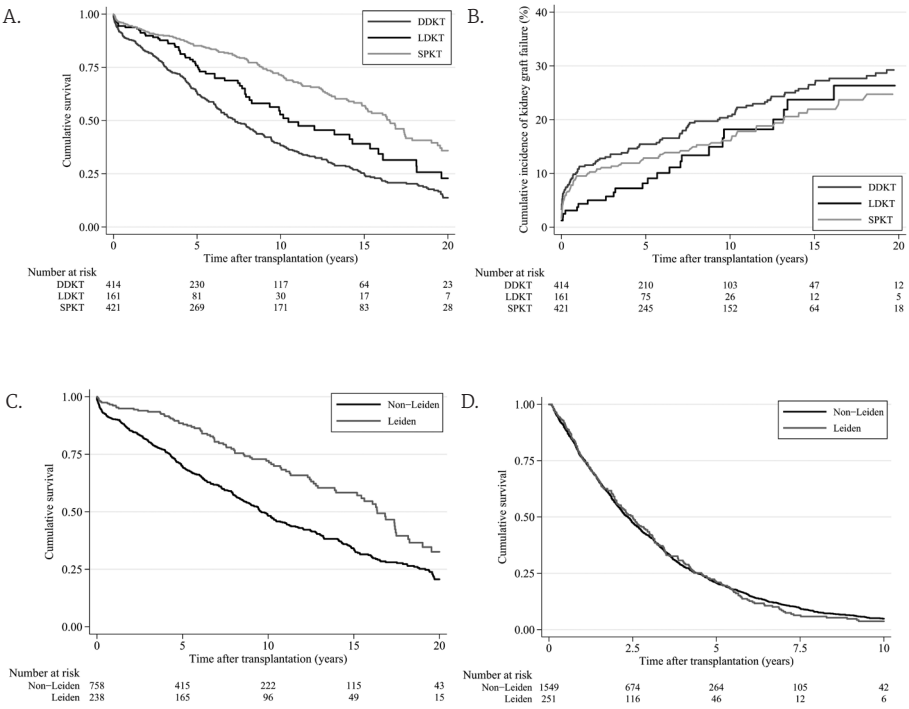

Figure 1. Crude Survival curves. A: Overall survival of patients with type 1 diabetes after DDKT, LDKT, or SPKT. Median (95% CI) survival time was 7.3 (6.2; 8.3) years for patients with DDKT, 10.5 (7.2; 13.7) years for patients with LDKT, and 16.5 (15.1; 17.9) years for patients with SPKT. **B:** Cumulative incidence of kidney graft failure, taking into account the competing risk of death. **C:** Survival of patients with type 1 diabetes after transplantation in the Leiden area vs. the non-Leiden area. Median (95% CI) survival was 9.6 (8.6; 10.6) years for the non-Leiden area and 16.4 (14.9; 17.8) years for the Leiden area. **D:** Survival of patients with type 1 diabetes during dialysis in the Leiden area vs. the non-Leiden area. Median (95%CI) survival was 3.1 (3.0; 3.3) years for the non-Leiden area and 3.2 (2.8; 3.5) years for the Leiden area. DDKT, deceased-donor kidney transplant; LDKT, living-donor kidney transplant; SPKT, SPK transplantation.

In total, 137 and 284 SPK transplantations were performed between 1986-1999 and 2000-2015, respectively, with mean (SD) recipient age 39 (7) years and 43 (8) years, and donor age 30 (11) years and 35 (12) years, respectively. Kaplan-Meier estimates for 10-year survival for SPK recipients transplanted between 2000-2015 was 77%, and 63% for those transplanted between 1986-1999 (Supplementary Figure S2). The HR (95%-CI) for 10-year mortality was 0.48 (0.30; 0.76) for SPK recipients transplanted between 2000-2015, as compared to the period 1986-1999 (Supplementary Table S2). Comparable but slightly attenuated HRs were observed for deceased and living donor transplant recipients (Supplementary Table S2).

Of all 367 SPK recipients transplanted in the Leiden area who survived the first postoperative year, 34 experienced pancreas graft failure. Patients with a functioning pancreas graft at one year had a 10-year survival of 80%, while patients who experienced pancreas graft failure showed survival comparable to recipients of a deceased donor kidney transplant, being less than 50% (Supplementary Figure S3). Median (95%-CI) survival for SPK recipients with a functioning pancreas graft, or recipients of a living or deceased donor kidney was 17.4 (15.4; 19.5), 12.0 (8.0; 16.0), and 8.6 (7.4; 9.7) years, respectively. SPK recipients with pancreas graft failure had a 2.15 (95%-CI: 1.09; 4.27) and 1.42 (95%-CI: 0.77; 2.62) times higher 10-year and 20-year all-cause mortality risk than those with a functioning pancreas at one year (Table 3). In patients who survived the first postoperative year, SPK recipients who experienced pancreas graft failure had a comparable survival to recipients of a deceased donor kidney transplant alone (Table 3).

Table 3: Hazard ratios (95%CI) of 10-year and 20-year all-cause mortality for different types of kidney transplantation with or without simultaneous pancreas transplantation, conditional on surviving the first year after transplantation.

	Crude	Model 1	Model 2	Model 3
10-year all-cause mortality				
DDKT (ref)	1	1	1	1
LDKT	0.67 (0.46; 0.99)	0.72 (0.49; 1.07)	0.59 (0.39; 0.88)	0.74 (0.48; 1.15)
SPKT panc (+)	0.26 (0.18; 0.38)	0.32 (0.22; 0.47)	0.35 (0.24; 0.52)	0.44 (0.29; 0.68)
SPKT panc (–)	0.82 (0.46; 1.44)	0.99 (0.55; 1.79)	1.01 (0.56; 1.83)	1.10 (0.60; 2.05)
SPKT panc (+) (ref)	1	1	1	1
SPKT panc (–)	3.15 (1.67; 5.93)	2.91 (1.50; 5.63)	2.60 (1.34; 5.05)	2.15 (1.09; 4.27)
20-year all-cause mortality				
DDKT (ref)	1	1	1	1
LDKT	0.76 (0.54; 1.06)	0.82 (0.59; 1.15)	0.72 (0.51; 1.03)	0.94 (0.65; 1.37)
SPKT panc (+)	0.38 (0.28; 0.50)	0.45 (0.33; 0.61)	0.48 (0.35; 0.65)	0.62 (0.45; 0.87)
SPKT panc (–)	0.73 (0.43; 1.24)	0.88 (0.51; 1.50)	0.88 (0.51; 1.51)	1.04 (0.59; 1.83)
SPKT panc (+) (ref)	1	1	1	1
SPKT panc (–)	1.99 (1.14; 3.47)	1.83 (1.01; 3.30)	1.64 (0.90; 2.97)	1.42 (0.77; 2.62)

DDKT, deceased donor kidney transplant; LDKT, living donor kidney transplant; SPKT, simultaneous pancreas kidney transplantation; panc (+), with functioning pancreatic graft after 1 year; panc (–), with pancreatic graft failure within one year.
Model 1: Adjusted for recipient age and sex.
Model 2: Model 1, plus adjustment for donor age.
Model 3: Model 2, plus adjustment for dialysis vintage, dialysis modality, and transplantation era.

Regional differences in intended treatment

In total, 238 patients were transplanted in the Leiden and 758 patients in the non-Leiden area (Supplementary Table S1). Survival for transplanted type 1 diabetes patients was higher in the Leiden compared to non-Leiden area (Figure 1C). Median (95%-CI) survival time was 16.4 (14.9; 17.8) and 9.6 (8.6; 10.6) years for the patients residing in the Leiden *vs* non-Leiden area. After multivariable adjustment, the HR (95%-CI) for 10-year and 20-year all-cause mortality for Leiden *vs* non-Leiden was 0.56 (0.40; 0.78) and 0.69 (0.52; 0.90), respectively (Supplementary Table S3), and quite similar to unadjusted estimates. Exclusion of pre-emptively transplanted patients yielded comparable results, with a HR for 10-year all-cause mortality of 0.52 (0.34; 0.80). We found no significant difference with regard to death-censored graft failure: 10-year cause-specific HR 0.88 (95%-CI: 0.55; 1.39) for patients living in the Leiden *vs* non-Leiden area. Survival on chronic dialysis was similar in both regions (Figure 1D), reflected by an adjusted HR for five-year mortality of 0.97 (95%-CI: 0.83; 1.13).

Dialysis compared to kidney transplantation

Compared to patients on the waiting list, dialysis patients not on the waiting list for transplantation, , had a 1.54 (95%-CI: 1.34; 1.78) times higher five-year mortality risk (Supplementary Table S4). Survival was better for transplanted patients compared with chronic dialysis patients on the waiting list (Supplementary Figure S4). Five-year survival was 32% for wait-listed dialysis patients *vs* 76% for transplanted patients. The adjusted HR for five-year all-cause mortality was 0.25 (0.19; 0.32) for transplanted patients, compared with dialysis patients on the waiting list (Supplementary Table S4). HRs for 10-year mortality were comparable.

DISCUSSION

In this Dutch nationwide cohort including all type 1 diabetes patients who started renal replacement therapy between 1986 and 2016, those who received an SPK had a 20-30% lower 10- and 20-year all-cause mortality risk compared to recipients of a deceased donor kidney transplant. The risk of 20-year all-cause mortality for SPK compared with living donor kidney recipients was 20% lower, despite the fact that living donor kidney recipients had better kidney graft survival. Patient survival was highest for SPK recipients with a functioning pancreas graft at one year. In contrast, survival for SPK recipients who lost their pancreas graft within one year was comparable to recipients of a deceased donor kidney transplant alone. Most importantly, a treatment

strategy with the primary intention of treating patients with an SPK resulted in an almost 50% reduction in 10-year all-cause mortality risk compared to a kidney transplant alone.

We performed the present analyses to aid in the ongoing controversy whether a SPK transplant as compared to a kidney transplant alone lowers mortality risk in patients with type 1 diabetes and end-stage renal failure, especially on the long term. This is the first study that clearly shows that type 1 diabetes patients, both 10 and 20 years after simultaneous pancreas-kidney transplant, had a substantially higher life expectancy, as compared to those who received a living or deceased donor kidney transplant alone.[17, 18] Most previous studies have followed patients for less than 10 years providing conflicting results.[9-12] Moreover, post-transplant healthcare rapidly improved in the past decades, while most previous studies reported data up to 2010. We followed patients up to 2016 and separately report the results obtained before and after 2000. For example, the wide introduction of the different forms of induction therapy markedly improved outcomes for both kidney and simultaneous pancreas-kidney transplantation. Alemtuzumab, for instance, is since 2007 part of our SPK protocol and resulted in the most pronounced improvement in outcome parameters.[19]

The HR (95%-CI) for 10- and 20-year all-cause mortality for SPK *vs* living donor kidney transplant recipients was 0.85 (0.53; 1.38) and 0.81 (0.57; 1.16). Importantly, living donor kidney transplant recipients less often experienced death-censored kidney graft failure. This implies that the improved survival after SPK transplantation may be explained by the eliminated need for exogenous insulin and reduction of non-renal diabetic complications. Indeed, we showed that median survival of SPK recipients with a functioning pancreas graft one-year after transplantation was 17.4 *vs* 10.7 years for those with pancreas graft failure. Median survival was 8.6 years for deceased and 12.0 years for living donor kidney recipients. These results confirm previous data by Weiss *et al*.[12] In contrast to the present study, Ojo *et al* observed comparable 10-year crude survival rates for SPK and living donor kidney transplant recipients of 67% and 65%, respectively.[18] Comparable survival rates were found by others.[9, 20-23] Sung *et al* concluded that, up to 10 years, SPK transplantation as compared to kidney transplantation alone was associated with a clinically irrelevant survival benefit of 0.17 years. Using the same data registry, a subsequent analysis found that with a follow-up extended beyond 10 years, the survival benefit for SPK increased as compared to kidney transplant alone.[11, 24] Previous studies investigated patient cohorts with, at most, 10 years of follow-up.

The overall five-year survival of SPK recipients in general improved from 75% to 90% between 1990-2009.[25] Differences in treatment regimens, especially introduction of T-cell depleting agents such as induction therapy, have drastically reduced the incidence of acute rejection episodes in SPK

recipients.[26, 27] Until 1997, no induction therapy was given, leading to over 80% acute rejections after SPK transplantation. Ringers *et al* showed that ATG induction or interleukin-2 receptor blockade reduced the rate of acute rejection to about 40%.[28] Induction with alemtuzumab instead of ATG from 2007 onwards further reduced the incidence of acute rejection.[19] A therapy regimen including tacrolimus instead of cyclosporine was introduced in 2003, and resulted in fewer and less severe kidney and pancreas rejections.[29] The more recent sample of patients included in the present study is more generalisable to current clinical practice. Indeed, we showed that 10-year mortality risk was about halved for type 1 diabetes patients who received an SPK between 2000-2015, as compared to those transplanted in the period 1986-1999, despite increased mean donor and recipient ages during the latter period.

Using regional differences in treatment strategies, we showed that the approach favouring SPK had superior 10- and 20-year survival as compared to one advocating kidney transplantation alone. Since we did not expect origin-related variables, we used these regional differences to mimic an intention-to-treat approach, reducing the influence of confounders such as age and dialysis vintage. On average, recipients and donors for SPK were younger than those for a living or deceased donor kidney transplant. We showed that our intention-to-treat approach resulted in more similar patient groups as opposed to comparing transplant by type, which is also reflected by the similar mortality rates for patients on dialysis in both regions. Importantly, we showed that survival while on dialysis was almost identical between the two regions (HR 0.97), suggesting that differences in care are unlikely to explain our results. These results imply that SPK compared to kidney transplantation alone led to improved patient survival, which is in line with an earlier comparable Dutch study analysing patients until 1996.[8]

The main advantage of a pancreas transplantation in addition to a kidney transplantation is the improved quality of life due to resolving the need for exogenous insulin.[5, 7] Furthermore, curing diabetes halts an otherwise ongoing progression of diabetic complications, in particular nephropathy, retinopathy, and neuropathy.[30-32] Finally, pancreas transplantation was shown to attenuate progression of atherosclerosis and improve cardiac functioning.[33, 34] In contrast, short-term mortality may be higher for SPK as compared to kidney transplantation alone, owing to the more complicated nature of the procedure. However, most studies assessing short-term survival for transplanted type 1 diabetes patients reported comparable short-term survival for SPK and living donor kidney recipients.[35]

The survival benefit of a kidney transplant as compared to remaining on dialysis is well known.[36] Others have shown that adjusted hazard ratios for

5-year mortality, using wait-listed dialysis patients as reference, were 0.40, 0.45, and 0.75 for SPK, living, and deceased kidney transplants, respectively.[18] Transplanted type 1 diabetes patients compared to those on the waiting list while on dialysis had a four-fold reduction in five-year mortality risk.

This study has several limitations. First, data collection in a registry study may have led to misclassification, measurement error, and missing data. However, in the present study the proportion of missing data of key variables was negligible, and regular quality cross-checks between the two mandatory registries reduced the risk of misclassification. Additionally, inherent to using registry data, we had limited information about important patient characteristics, such as lifestyle, comorbidity, and medical history. Second, we compared several interventions in an observational study. Despite adjusting for confounders, residual confounding may remain. We aimed to limit the influence of confounding by also using regional differences to compare intended treatment strategies. Because our main analysis was based on a comparison of two treatment strategies (preferably SPK *vs* preferably non-SPK), our study did not clarify which patients actually benefited most from an SPK transplant. Third, we had no detailed data on the cardiovascular risk profile of the type 1 diabetes patients eligible for kidney transplantation. However, all type 1 diabetes patients in The Netherlands with renal insufficiency are managed according to the latest KDIGO guidelines.[37] In addition, the approval for kidney or SPK occurs in each transplantation centre according to a nationwide consensus based on international guidelines.[38]

The main strength of the present study is the nationwide sample, including all type 1 diabetes patients in The Netherlands requiring renal replacement therapy during a 30-year period. Furthermore, we used regional differences to mimic an intention-to-treat principle, reducing the influence of confounding.

In conclusion, in type 1 diabetes patients with end-stage renal disease, a treatment strategy favouring SPK compared to kidney transplantation alone, was associated with a 44% and 31% reduction of 10- and 20-year all-cause mortality, respectively. SPK recipients with a functioning pancreas graft had an approximately 50% reduced mortality risk as compared to those with a failed pancreas graft in the first year, and also experienced better survival in comparison to living donor kidney transplant recipients. These results encourage care providers and guidelines to adopt SPK transplantation as the preferred treatment option for type 1 diabetes patients with or approaching end-stage renal disease.

DISCLOSURES

We declare no conflicts of interest.

FUNDING

This study did not receive external funding.

AUTHORS' CONTRIBUTIONS

Research idea and study design: JF, OD, PB, KE; data acquisition: KE, MM, PB, CK, Dutch Transplantation Foundation; data analysis/interpretation: JF, EH, OD, KE; statistical analysis: KE, OD; supervision and mentorship: JF, EH, OD. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

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SUPPLEMENTARY DATA

Supplementary Table S1: Baseline characteristics 2796 type 1 diabetes patients, according to area of residence and type of renal replacement therapy.

	Dialysis		Transplantation	
	Leiden n=251	Non-Leiden n=1549	Leiden n=238	Non-Leiden n=758
Age at dialysis, y	58 ± 13	59 ± 13	43 ± 10	44 ± 10
Age at transplantation, y			44 ±10	46 ± 11
Men, %	53	53	59	63
Donor age, y	-	-	36 ± 14	41 ± 16
Dialysis modality, nr (%)				
Haemodialysis	68	72	22	35
Peritoneal dialysis	32	28	21	34
Missing	0	0.1	0	10
Pre-emptive Tx, %			57	21
Dialysis vintage, mo	9 ± 6	8 ± 6	23 ± 24	20 ± 22
Cold ischaemic time, h	-	-	15 ± 8	16 ± 11
DDKT, nr (%)	-	-	14	50
LDKT, nr (%)	-	-	6	20
SPKT, nr (%)	-	-	80	30

[a] Excluding pre-emptive transplant patients
Numbers are presented as mean ± SD or percentage.
DDKT, deceased donor kidney transplant; LDKT, living donor kidney transplant; SPKT, simultaneous pancreas kidney transplantation; Tx, transplantation.

Supplementary Table S2: Hazard ratios of 10-year mortality of patients transplanted until the year 2000, compared with patients transplanted afterwards.

	Crude	Model 1	Model 2	Model 3
DDKT				
1986 to 1999 (ref)	1	1	1	1
2000 to 2015	0.74 (0.54; 1.03)	0.62 (0.44; 0.87)	0.57 (0.40; 0.81)	0.54 (0.37; 0.78)
LDKT				
1986 to 1999 (ref)	1	1	1	1
2000 to 2015	0.95 (0.47; 1.90)	0.58 (0.27; 1.24)	0.57 (0.27; 1.21)	0.56 (0.26; 1.19)
SPKT				
1986 to 1999 (ref)	1	1	1	1
2000 to 2015	0.60 (0.39; 0.94)	0.51 (0.32; 0.81)	0.48 (0.30; 0.76)	0.48 (0.30; 0.76)

Model 1: Adjusted for recipient age and sex.
Model 2: Model 1, plus adjustment for donor age.
Model 3: Model 2, plus adjustment for dialysis vintage and dialysis modality.

Supplementary Table S3: Hazard ratios (95%CI) of 10- and 20-year all-cause mortality and death-censored graft failure for kidney transplanted patients living in the Leiden area compared to the non-Leiden area.

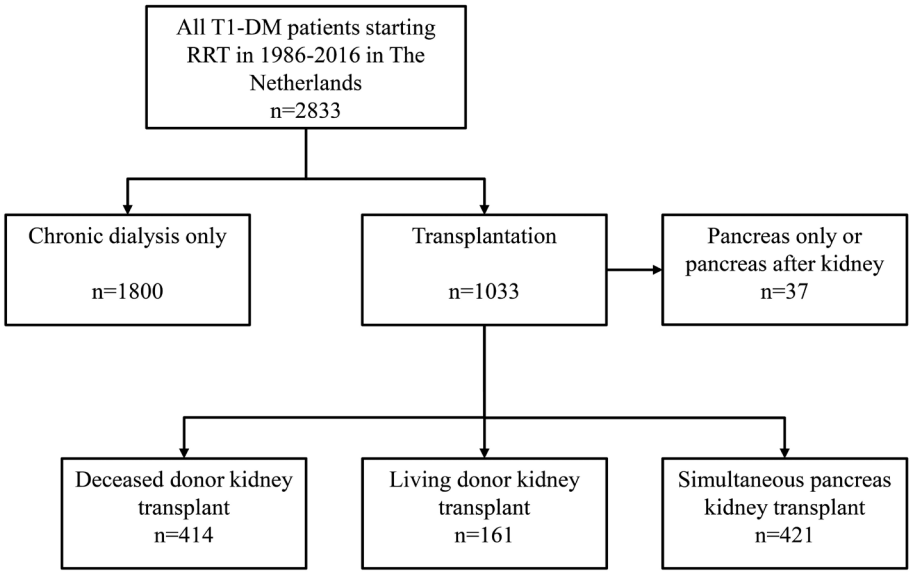
	Crude	Model 1	Model 2	Model 3
10-year all-cause mortality				
Non-Leiden area (ref)	1	1	1	1
Leiden area	0.47 (0.34; 0.64)	0.50 (0.37; 0.69)	0.54 (0.39; 0.73)	0.56 (0.40; 0.78)
10-year death-censored graft failure				
Non-Leiden area (ref)	1	1	1	1
Leiden area	0.74 (0.49; 1.11)	0.73 (0.48; 1.09)	0.87 (0.57; 1.33)	0.88 (0.55; 1.39)
20-year all-cause mortality				
Non-Leiden area (ref)	1	1	1	1
Leiden area	0.56 (0.44; 0.72)	0.60 (0.47; 0.78)	0.63 (0.48; 0.81)	0.69 (0.52; 0.90)
20-year death-censored graft failure				
Non-Leiden area (ref)	1	1	1	1
Leiden area	0.69 (0.48; 1.00)	0.68 (0.47; 0.99)	0.80 (0.55; 1.16)	0.79 (0.52; 1.19)

Model 1: Adjusted for recipient age and sex.
Model 2: Model 1, plus adjustment for donor age.
Model 3: Model 2, plus adjustment for dialysis vintage, dialysis modality, and transplantation era.

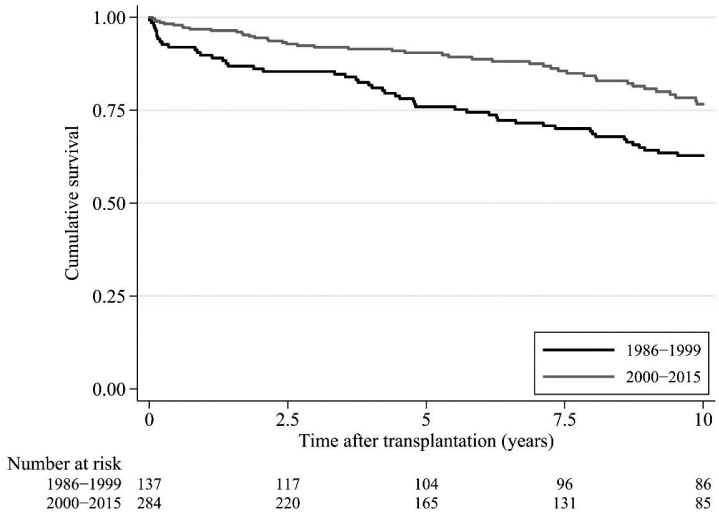
Supplementary Table S4.: Hazard ratios (95%CI) of 5-year and 10-year mortality for type 1 diabetes after kidney transplantation compared with dialysis, matched for dialysis vintage.

	Crude	Model 1	Model 2
5-year mortality			
Dialysis (on waiting list)	1	1	1
Dialysis (not on waiting list)	1.70 (1.50; 1.93)	1.59 (1.38; 1.83)	1.54 (1.34; 1.78)
Transplantation*	0.23 (0.18; 0.30)	0.24 (0.18; 0.31)	0.25 (0.19; 0.32)
10-year mortality			
Dialysis (on waiting list)	1	1	1
Dialysis (not on waiting list)	1.62 (1.44; 1.81)	1.50 (1.32; 1.70)	1.46 (1.29; 1.66)
Transplantation*	0.21 (0.17; 0.26)	0.22 (0.18; 0.28)	0.23 (0.18; 0.28)

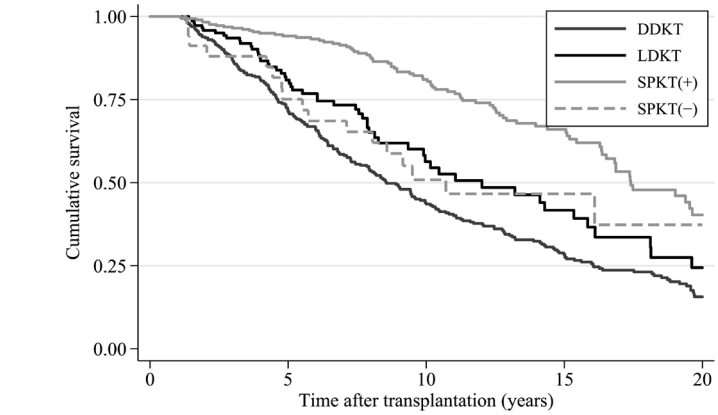
*Transplantation included both living kidney donor transplant, or deceased donor transplant with or without simultaneous pancreas transplantation.
Model 1: Adjusted for age and sex.
Model 2: Model 1, plus adjustment for calendar time.



Supplementary Figure S1: Flow diagram of 2833 type 1 diabetes mellitus (TI-DM) patients with end-stage renal disease, and different types of renal replacement therapy (RRT).



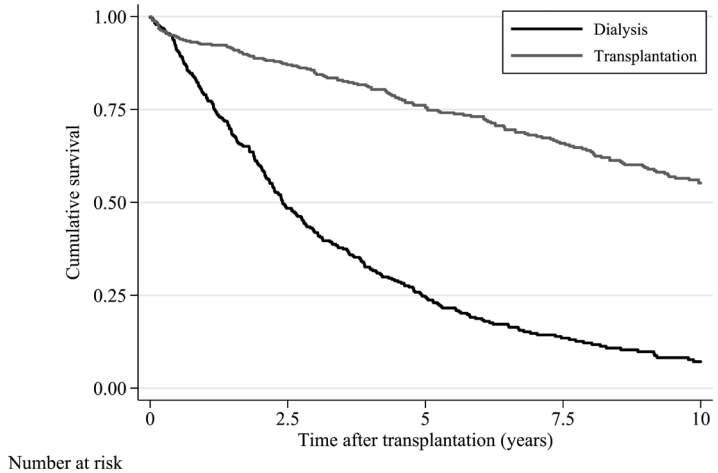
Supplementary Figure S2: Survival of simultaneous pancreas kidney transplantation (SPKT) patients transplanted in the period 1986-1999 and 2000-2015.



Number at risk

DDKT	361	230	117	64	23
LDKT	150	81	30	17	7
SPKT(+)	305	217	137	67	20
SPKT(−)	34	23	12	5	4

Supplementary Figure S3: Type 1 diabetes mellitus patient survival conditional on survival of the first year after transplantation, according to transplantation type: living donor kidney transplant (LDKT), deceased donor kidney transplant (DDKT), and simultaneous pancreas kidney transplantation (SPKT). SPKT patients were divided into patients with a functioning pancreatic graft after one year, SPKT(+), and those with pancreatic graft failure in the first year, SPKT(-). Median survival was 8.6 (7.4; 9.7) years for DDKT, 12.0 (8.0; 16.0) years for LDKT, 17.4 (15.4; 19.5) years for SPKT(+), and 10.7 (3.5; 17.9) years for SPKT(-). DDKT, deceased donor kidney transplant; LDKT, living donor kidney transplant; SPKT, simultaneous pancreas kidney transplantation.



Number at risk

Dialysis	379	157	70	31	12
Transplantation	379	301	226	177	131

Supplementary Figure S4: Patient survival after start dialysis or kidney transplantation. Each transplanted patient was matched on dialysis vintage with a chronic dialysis patient on the waiting list for transplantation. Median survival was 2.4 (2.1; 2.7) years for dialysis patients, and 11.3 (9.6; 12.9) years for transplanted patients.