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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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 with 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 2,796 patients with type 1 diabetes 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 analyzed mortality between regions where SPK transplant was the preferred intervention (80% SPK) versus regions where a kidney transplant alone was favored (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 1 year (91%) had the highest survival (median 17.4 years). Compared with 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 favoring 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 with living- or deceased-donor kidney transplantation, SPK transplant was associated with improved patient survival, especially in recipients with a long-term functioning pancreatic graft, and resulted in an almost twofold lower 10-year mortality rate.

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The global population with type 1 diabetes 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, and angiopathy and a threefold increased mortality risk as compared with individuals without diabetes (2). As such, type 1 diabetes is accompanied by considerable health care costs, estimated at ~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 patients, 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 diabetes 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 randomized clinical trials have compared survival after SPK versus kidney transplantation alone. We previously showed, in Dutch patients with type 1 diabetes between 1985 and 1996, that a treatment strategy favoring SPK over a deceased-donor kidney transplant alone was associated with a 47% lower 10-year mortality risk (8). In a U.S. registry study among 18,549 patients with type 1 diabetes during 1987–1996, 8-year survival after SPK or a living-donor kidney transplant was similar at 72% and better as compared with 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 6-year survival as compared with patients who received an SPK transplant, although others have found no clinically relevant 10-year survival benefit for SPK versus kidney transplantation alone (10,11). Weiss et al. (12) showed that SPK recipients who survived the first year posttransplant with a functioning pancreas graft had a superior 7-year survival as compared with patients with type 1 diabetes with a living-donor kidney transplant (89% vs. 80%).

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 with kidney transplantation alone, either from a living or deceased donor, on long-term survival in a nationwide cohort including all Dutch patients with type 1 diabetes who have required renal replacement therapy in the past 30 years.

RESEARCH DESIGN AND METHODS

Study Population

We included consecutive (n = 2,833) patients with type 1 diabetes aged at least 18 years, who started on chronic dialysis or received a first kidney transplant in the Netherlands between 1 January 1986 and 1 January 2016. We excluded patients who received a pancreas transplantation alone (n = 17) or a pancreas after kidney transplantation (n = 20); thus, 2,796 patients were eligible for the present analysis. In total, 1,800 patients were on chronic dialysis only, and 414, 161, and 421 patients received a deceased- or living-donor kidney or SPK, respectively (Supplementary Fig. 1). We used data from two mandatory nationwide Dutch registries. The Netherlands Organ Transplant Registry includes patients who received a kidney transplant from all eight Dutch kidney transplant centers, 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 center–specific data and is updated annually. Registration of each organ transplantation is mandatory and coordinated by the government via the Dutch Transplant Foundation. The Dutch Renal Registry (Registratie Nierfunctievervanging Nederland) collects information on all patients requiring chronic dialysis, registration for whom is also mandatory for all dialysis centers in order to receive funding. Data quality of both registries is periodically audited by onsite polls, application rules, and cross-checks between the registries. Organs were allocated according to the standard Eurotransplant guidelines. Because patients with type 1 diabetes on dialysis have a poor prognosis, Eurotransplant applies mandatory exchange rules for SPK transplants to prioritize this patient category in case of a potential SPK donor. These rules explain the shorter waiting time for SPK as compared with kidney transplantation alone, as well as the relatively large proportion of preemptive 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 patient with type 1 diabetes strictly determines treatment in a defined dialysis center, and each dialysis center is affiliated with a specific transplant center. Since the first pancreas transplant in the Netherlands in 1984, the Dutch Ministry of Health considered SPK transplantation an experimental and restricted procedure. The results have been that the vast majority of the SPK transplants have been performed in Leiden, which is only one of eight Dutch transplant centers. These policies created regional differences in the assignment of SPK transplantation to patients with type 1 diabetes, 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 center, the primary intention is to treat patients with type 1 diabetes with end-stage renal disease with an SPK transplant. Thus, SPK transplant was offered to the majority of patients with type 1 diabetes. In contrast, in the non-Leiden area, consisting of seven transplantation centers, a kidney transplant alone has been the preferred treatment, and SPK transplantation 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 transplant in 80% of cases, compared with 30% for patients living in the non-Leiden area.

Importantly, immunosuppressive treatment for patients receiving a kidney transplant has changed over time. Until 1995, recipients of an SPK transplant 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 onward, induction therapy with intravenous antithymocyte 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.

End Points

The primary end point 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 (1 January 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 among different types of transplantation. Crude survival was presented by Kaplan-Meier curves. Adjusted hazard ratios (HRs) with 95% 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 5-year interval). We adjusted for year of transplantation to account for changes in treatment protocols and medical care. To visualize 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 recipients of an SPK transplant. We therefore chose to compare 10-year all-cause mortality of SPK recipients transplanted in the periods 1986–1999 and 2000–2015. We also investigated the influence of a long-term (defined as at least 1 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 1 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 versus kidney transplant alone by analyzing 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 patients receiving a transplant 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 analyzed 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% of 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 5-year interval). We compared survival on dialysis for the Leiden versus 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 patients on dialysis on the waiting list for transplantation were included to increase comparability of clinical characteristics between patients on dialysis and transplanted patients. Patients on dialysis and transplantation patients were matched for dialysis vintage to avoid immortal time bias and minimize confounding by dialysis vintage. Survival time in transplanted patients was counted from the date of transplantation, and for matched patients on dialysis, 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 5- 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 5-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 3 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, College Station, TX) and SPSS 25.0 (IBM Corp., Armonk, NY).

RESULTS

Baseline Characteristics

Of all 2,796 patients with type 1 diabetes, 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

Table 1—Baseline characteristics of 2,796 patients with type 1 diabetes according to type of renal replacement therapy

	Dialysis (n = 1,800)	DDKT (n = 414)	LDKT (n = 161)	SPKT (n = 421)
Age at dialysis, years	59 ± 13	47 ± 10	46 ± 11	40 ± 8
Age at transplantation, years	—	50 ± 11	48 ± 11	42 ± 8
Men, %	53	63	58	62
Donor age, years	—	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
Preemptive Tx	—	15	35	42
Dialysis vintage, months[a]	36 ± 34	26 ± 24	12 ± 18	12 ± 19
Cold ischemic time, h	—	23 ± 9	2 ± 1	13 ± 4
Place of residence, %				
Leiden area	14	8	9	45
Non-Leiden area	86	92	91	55

Data are mean ± SD unless otherwise indicated. DDKT, deceased-donor kidney transplant; LDKT, living-donor kidney transplant; SPKT, SPK transplantation; Tx, transplantation. [a]Excluding patients receiving preemptive transplant.

42% of living-donor kidney and SPK recipients were preemptively 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 transplant, both recipients at transplantation and donors were younger as compared with 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 with 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 with 6% and 2% for recipients of a living-donor kidney or SPK transplant, respectively. Patients from the Leiden versus non-Leiden area had comparable age and sex distribution (Supplementary Table 1).

SPK Transplantation Compared With Kidney Transplantation Alone

Crude survival was highest in SPK recipients and lowest in recipients of a deceased-donor kidney (Fig. 1*A*). Compared with the latter patient group, adjusted HRs (95% CIs) 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 HRs (95% CIs) for 10-year and 20-year all-cause mortality for SPK compared with living-donor kidney recipients were 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 (Fig. 1*B*). Compared with deceased-donor kidney recipients, the adjusted HRs (95% CIs) for 10-year death-censored kidney graft failure were 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 patients with type 1 diabetes who survived the first 3 months after initiation of dialysis or kidney transplantation yielded similar results.

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 and 2015 were 77% and 63% for those transplanted between 1986 and 1999 (Supplementary Fig. 2). The HR (95% CI) for 10-year mortality was 0.48 (0.30; 0.76) for SPK recipients transplanted between 2000 and 2015, as compared with the period 1986–1999 (Supplementary Table 2). Comparable but slightly attenuated HRs were observed for deceased- and living-donor transplant recipients (Supplementary Table 2).

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 1 year had a 10-year survival of 80%, while patients who experienced pancreas graft failure showed survival comparable to that of recipients of a deceased-donor kidney transplant, which was <50% (Supplementary Fig. 3). 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 1 year (Table 3). In patients who survived the first postoperative year, SPK recipients who experienced pancreas graft failure had a survival comparable to that of recipients of a deceased-donor kidney transplant alone (Table 3).

Regional Differences in Intended Treatment

In total, 238 patients were transplanted in the Leiden and 758 patients in the non-Leiden area (Supplementary Table 1).

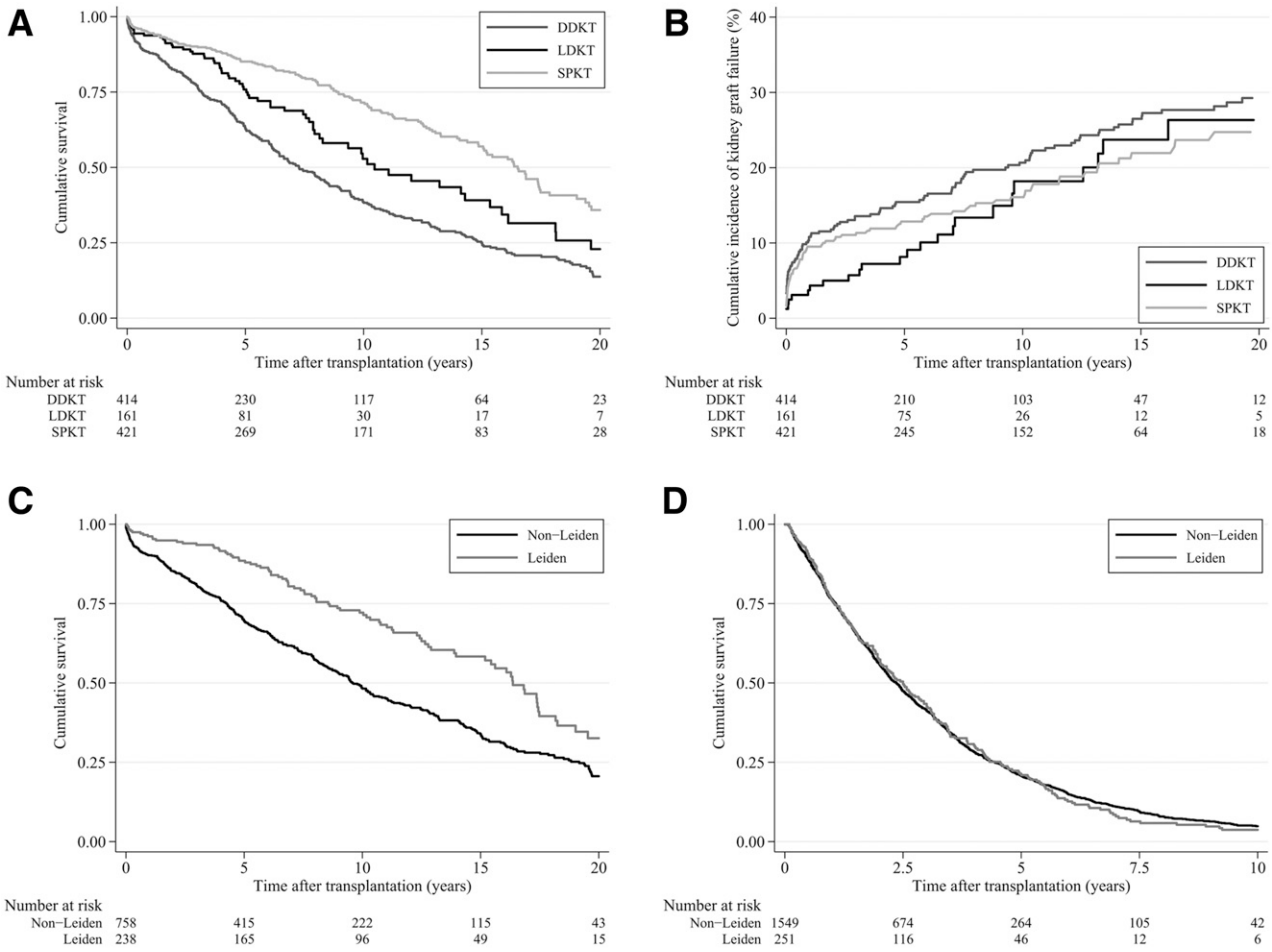

Figure 1—*A*: Overall survival of patients with type 1 diabetes after DDKT, LDKT, or SPKT. Median (95% CI) survival time was 7.3 (6.2; 8.3) years for patients with DDKT, 10.5 (7.2; 13.7) years for patients with LDKT, and 16.5 (15.1; 17.9) years for patients with SPKT. *B*: Cumulative incidence of kidney 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.

Survival for transplanted patients with type 1 diabetes was higher in the Leiden compared with non-Leiden area (Fig. 1*C*). 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 versus non-Leiden area. After multivariable adjustment, the HRs (95% CIs) for 10-year and 20-year all-cause mortality for Leiden versus non-Leiden were 0.56 (0.40; 0.78) and 0.69 (0.52; 0.90), respectively (Supplementary Table 3), and quite similar to unadjusted estimates.

Exclusion of preemptively transplanted patients yielded comparable results, with an 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 was 0.88 (95% CI 0.55; 1.39) for patients living in the Leiden versus non-Leiden area. Survival on chronic dialysis was similar in both regions (Fig. 1*D*), reflected by an adjusted HR for 5-year mortality of 0.97 (95% CI 0.83; 1.13).

Dialysis Compared With Kidney Transplantation

Compared with patients on the waiting list, patients receiving dialysis not on the waiting list for transplantation had a 1.54 (95% CI 1.34; 1.78) times higher 5-year mortality risk (Supplementary Table 4). Survival was better for transplanted patients compared with patients receiving chronic dialysis on the waiting list (Supplementary Fig. 4). Five-year survival was 32% for patients waitlisted for dialysis versus 76% for transplanted patients. The adjusted HR for 5-year all-cause mortality was 0.25 (0.19; 0.32) for transplanted patients compared with patients receiving dialysis on the waiting list (Supplementary Table 4). HRs for 10-year mortality were comparable.

CONCLUSIONS

In this Dutch nationwide cohort including all patients with type 1 diabetes who started renal replacement therapy between 1986 and 2016, those who received an SPK transplant had a 20–30% lower 10- and 20-year all-cause mortality risk compared with 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 1 year. In

Table 2—HRs (95% CIs) for 10-year and 20-year all-cause mortality and death-censored kidney graft failure for living-donor kidney transplantation or deceased-donor kidney transplantation with or without SPK transplantation

	Crude	Model 1	Model 2	Model 3
10-year all-cause mortality				
DDKT (reference)	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 (reference)	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 (reference)	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 (reference)	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)

Model 1 is adjusted for recipient age and sex; model 2 is model 1 plus adjustment for donor age; and model 3 is model 2 plus adjustment for dialysis vintage, dialysis modality, and transplantation era. DDKT, deceased-donor kidney transplant; LDKT, living-donor kidney transplant; SPKT, SPK transplantation.

contrast, survival for SPK recipients who lost their pancreas graft within 1 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 ~50% reduction in 10-year all-cause mortality risk compared with a kidney transplant alone.

We performed the present analyses to aid in the ongoing controversy of whether an SPK transplant as compared with a kidney transplant alone lowers mortality risk in patients with type 1 diabetes and end-stage renal failure, especially in the long term. This is the first study that clearly shows that patients with type 1 diabetes, both 10 and 20 years after SPK transplant, had a substantially higher life expectancy as compared with those who received a living- or deceased-donor kidney transplant alone (17,18). Most previous studies have followed patients for <10 years, providing conflicting results (9–12). Moreover, posttransplant health care 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 SPK transplantation. Alemtuzumab, for instance, is, since 2007, part of our SPK transplant protocol and resulted in the most pronounced improvement in outcome parameters (19).

The HRs (95% CIs) for 10- and 20-year all-cause mortality for SPK versus living-donor kidney transplant recipients were 0.85 (0.53; 1.38) and 0.81 (0.57; 1.16), respectively. 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

Table 3—HRs (95% CIs) of 10-year and 20-year all-cause mortality for different types of kidney transplantation with or without SPK transplantation, conditional on surviving the first year after transplantation

	Crude	Model 1	Model 2	Model 3
10-year all-cause mortality				
DDKT (reference)	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 (+) (reference)	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 (reference)	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 (+) (reference)	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)

Model 1 is adjusted for recipient age and sex; model 2 is model 1 plus adjustment for donor age; model 3 is model 2 plus adjustment for dialysis vintage, dialysis modality, and transplantation era. DDKT, deceased-donor kidney transplant; LDKT, living-donor kidney transplant; panc (+), with functioning pancreatic graft after 1 year; panc (−), with pancreatic graft failure within 1 year; SPKT, SPK transplantation.

explained by the eliminated need for exogenous insulin and reduction of nonrenal diabetes complications. Indeed, we showed that median survival of SPK recipients with a functioning pancreas graft 1 year after transplantation was 17.4 versus 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 current study, Ojo et al. (18) observed comparable 10-year crude survival rates for SPK and living-donor kidney transplant recipients of 67% and 65%, respectively. Comparable survival rates were found by others (9,20–23). Sung et al. (11) concluded that, up to 10 years, SPK transplantation as compared with 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 with kidney transplant alone (11,24). Previous studies investigated patient cohorts with, at most, 10 years of follow-up.

The overall 5-year survival of SPK recipients in general improved from 75% to 90% between 1990 and 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 >80% acute rejections after SPK transplantation. Ringers et al. (28) showed that ATG induction or interleukin-2 receptor blockade reduced the rate of acute rejection to ~40%. Induction with alemtuzumab instead of ATG from 2007 onward 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 current study is more generalizable to current clinical practice. Indeed, we showed that 10-year mortality risk was about halved for patients with type 1 diabetes who received an SPK between 2000 and 2015, as compared with 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 favoring SPK had superior 10- and 20-year survival as compared with one advocating kidney transplantation alone. Because 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 with kidney transplantation alone led to improved patient survival, which is in line with an earlier comparable Dutch study analyzing 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 diabetes 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 with kidney transplantation alone, owing to the more complicated nature of the procedure. However, most studies assessing short-term survival for transplanted patients with type 1 diabetes reported comparable short-term survival for SPK and living-donor kidney recipients (35).

The survival benefit of a kidney transplant as compared with remaining on dialysis is well known (36). Others have shown that adjusted HRs for 5-year mortality, using waitlisted patients on dialysis as a reference, were 0.40, 0.45, and 0.75 for SPK, living-donor, and deceased-donor kidney transplants, respectively (18). Transplanted patients with type 1 diabetes compared with those on the waiting list while on dialysis had a fourfold reduction in 5-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 current 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 patients with type 1 diabetes eligible for kidney transplantation. However, all patients with type 1 diabetes in the Netherlands with renal insufficiency are managed according to the latest Kidney Disease: Improving Global Outcomes (KDIGO) guidelines (37). In addition, the approval for kidney or SPK occurs in each transplantation center according to a nationwide consensus based on international guidelines (38).

The main strength of the current study is the nationwide sample, including all patients with type 1 diabetes 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 patients with type 1 diabetes with end-stage renal disease, a treatment strategy favoring SPK compared with 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 ~50% reduced mortality risk as compared with those with a failed pancreas

graft in the first year and also experienced better survival in comparison with living-donor kidney transplant recipients. These results encourage care providers and guidelines to adopt SPK transplantation as the preferred treatment option for patients with type 1 diabetes with or approaching end-stage renal disease.

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