# Survival After Pancreas Transplantation in Patients With Diabetes and Preserved Kidney Function

Jeffrey M. Venstrom, BS
Maureen A. McBride, PhD
Kristina I. Rother, MD
Boaz Hirshberg, MD
Trevor J. Orchard, MD, MMedSci
David M. Harlan, MD

**Context** Solitary pancreas transplantation (ie, pancreas alone or pancreas-after-kidney) for diabetes mellitus remains controversial due to procedure-associated morbidity/mortality, toxicity of immunosuppression, expense, and unproven effects on the secondary complications of diabetes. Whether transplantation offers a survival advantage over conventional therapies for diabetes is unknown.

**Objective** To determine the association between solitary pancreas transplantation and survival in patients with diabetes and preserved kidney function.

**Design, Setting, and Patients** Retrospective observational cohort study conducted at 124 transplant centers in the United States, in 11572 patients with diabetes mellitus on the waiting list for pancreas transplantation (pancreas alone, pancreas-after-kidney, or simultaneous pancreas-kidney) at the United Network for Organ Sharing/Organ Procurement and Transplantation Network between January 1, 1995, and December 31, 2000. All patients receiving a multiorgan (other than simultaneous pancreas-kidney) transplant were excluded, as were those listed for solitary pancreas transplantation who had a serum creatinine level greater than 2 mg/dL (176.8 μmol/L) at time of listing, or who ultimately received a simultaneous pancreas-kidney transplant.

**Main Outcome Measure** All-cause mortality within 4 years following transplantation (or within a comparable time on the waiting list for the group not undergoing transplantation).

**Results** Overall relative risk of all-cause mortality for transplant recipients (compared with patients awaiting the same procedure) over 4 years of follow-up was 1.57 (95% confidence interval [CI], 0.98-2.53; $P=.06$) for pancreas transplant alone, 1.42 (95% CI, 1.03-1.94; $P=.03$) for pancreas-after-kidney transplant, and 0.43 (95% CI, 0.39-0.48) for simultaneous pancreas-kidney transplant. Transplant patient 1- and 4-year survival rates were 96.5% and 85.2% for pancreas transplant alone, respectively, and 95.3% and 84.5% for pancreas-after-kidney transplant, while 1- and 4-year survival rates for patients on the waiting list were 97.6% and 92.1% for pancreas transplant alone, respectively, and 97.1% and 88.1% for pancreas-after-kidney transplant.

**Conclusion** From 1995-2000, survival for those with diabetes and preserved kidney function and receiving a solitary pancreas transplant was significantly worse compared with the survival of waiting-list patients receiving conventional therapy.

*JAMA. 2003;290:2817-2823* www.jama.com

PANCREATIC TRANSPLANTATION IS a therapeutic option for patients with complicated diabetes mellitus. The American Diabetes Association supports the procedure for patients with diabetes who have had, or need, a kidney transplant. In the absence of kidney failure, pancreas transplantation may be considered for patients with diabetes and severe and frequent metabolic instability (ie, hypoglycemia, ketoacidosis).[1] Despite current controversy, and while the annual number of simultaneous pancreas-kidney transplants remained stable from 1995 to 2002, over that same interval the annual number of solitary pancreas transplants (ie, pancreas transplant alone or pancreas-after-kidney transplant) increased 5-fold (United Network for Organ Sharing/Organ Procurement and Transplantation Network [UNOS/OPTN] data as of May 2, 2003).

Specific US transplant numbers document this trend: 910 simultaneous pancreas-kidney transplants were performed in 1995 and 902 were performed in 2002. In contrast, in 1995

**For editorial comment see p 2861.**

**Author Affiliations:** Transplantation and Autoimmunity Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Department of Health and Human Services, Bethesda, Md (Mr Venstrom and Drs Rother, Hirshberg, and Harlan); Vanderbilt University School of Medicine, Nashville, Tenn (Mr Venstrom); United Network for Organ Sharing, Richmond, Va (Dr McBride); Graduate School of Public Health, University of Pittsburgh, Pittsburgh, Pa (Dr Orchard); and Uniformed Services University of the Health Sciences, Bethesda, Md (Dr Harlan).
**Corresponding Author and Reprints:** David M. Harlan, MD, Transplantation and Autoimmunity Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Department of Health and Human Services, 10 Center Dr, Bldg 10, Room 8N307, Bethesda, MD 20892 (e-mail: DavidMH@intra.niddk.nih.gov).

©2003 American Medical Association. All rights reserved.



Downloaded From: http://jama.jamanetwork.com/ on 05/03/2015

only 37 pancreas transplant–alone procedures were performed but in 2002 that number increased to 141; and in 1995, 65 pancreas-after-kidney transplants were performed but the number had increased to 363 in 2002 (UNOS/OPTN data as of May 2, 2003).

Outcome studies have documented that the majority of pancreas transplant recipients have improved glycemic control, enhancing their quality of life.[2-7] Moreover, since the Diabetes Control and Complications Trial (DCCT) demonstrated that improved glycemic control significantly decreased diabetes-associated microvascular complications,[8] one would predict that improved glycemia associated with pancreas transplantation should have a similar salutary effect on complications of diabetes. Yet this has not been shown conclusively.[9,10]

Against possible benefits, one must weigh the fact that both the pancreas transplant procedure and the immunosuppression required to prevent rejection pose significant risks. In fact, the surgical complication rate for pancreas transplantation has historically been higher than the rate for other abdominal organ transplant procedures.[11,12] Although studies report a 1-year patient survival rate greater than 90%,[13] it remains unknown whether transplantation offers a survival advantage over continued therapies for diabetes. We therefore compared the survival of pancreas transplant recipients with that of similar patients on the waiting list for a pancreas transplant. Since cadaveric pancreas allocation is not based on diabetes severity but rather is based primarily on blood type and time on the waiting list, we reasoned that patients on the waiting list would most closely approximate those who underwent the transplant procedure. Similar analyses have recently been reported for kidney and lung transplantation.[14,15]

## METHODS

We analyzed data from all approved US transplant programs as collected by UNOS/OPTN. Since the pancreas transplant procedure and immunosuppressive therapies are constantly evolving, we limited our analysis to the recent period from January 1, 1995, through December 31, 2000. During this period, and after excluding a few individuals as specified below, 11 572 patients with diabetes were listed for a pancreas transplant, of which 6595 received a pancreas transplant at 124 different centers. Of those receiving a transplant, 5379 received a simultaneous pancreas-kidney transplant, 838 received a pancreas-after-kidney transplant, and 378 received a pancreas transplant alone. Of note, due in part to the lag time between listing and transplantation, most transplants were quite recent: the proportion during or after 1998 was 65% for simultaneous pancreas-kidney transplant, 72% for pancreas-after-kidney transplant, and 74% for pancreas transplant alone. All patients on the waiting list for pancreas transplant alone who received a kidney prior to the pancreas transplant were included in the pancreas-after-kidney group for analysis. We excluded patients listed for a multiorgan (other than simultaneous pancreas-kidney) transplant (n=135), patients listed for a pancreas transplant alone (n=50) or pancreas-after-kidney transplant (n=265) who had a serum creatinine level greater than 2 mg/dL (176.8 μmol/L) at the time of listing, and patients listed for a pancreas transplant alone who at the time of the pancreas transplant also received a kidney transplant (n=44) (because these patients are similar to recipients of simultaneous pancreas-kidney transplants, but are also unique since the organs are often from different donors). The Social Security Death Master File (SSDMF) was used to supplement the UNOS/OPTN database for complete follow-up. All patients (regardless of transplantation status) matched in the SSDMF were included as study deaths; patients not located in the SSDMF were assumed to be alive and were censored at 1460 days (transplant group) or at the sum of 1460 days plus the median waiting list time for the corresponding surgical procedure (those not receiving a transplant). Data for any patient not yet at any end point were censored on December 31, 2002.

Patients were subdivided according to the anticipated transplant procedure (ie, pancreas alone, pancreas-after-kidney, or simultaneous pancreas-kidney). We calculated unadjusted waiting-list and posttransplantation survival rates using Kaplan-Meier methods. Patient characteristics were compared using the $\chi^2$ test. In order to correctly account for all time from listing until death, a piecewise time-dependent proportional hazards analysis was used to assess the effect of transplantation. This method allowed us to compare the mortality risk for a transplant recipient with the risks for those surviving without a transplant by enrolling all patients at the time of their listing and accounting for patients switching from the waiting list group to the transplant group at the time of transplantation. So designed, the model's piecewise nature allowed for risk assessments over 3 clinically distinct time intervals relative to the surgical group's transplantation date (0-90 days, 91-365 days, and 366-1460 days). The follow-up duration for both groups was identical relative to their listing date. For the surgical groups, follow-up was until death or until 1460 days posttransplantation. For the waiting-list groups, follow-up was until death or until the sum of 1460 days plus the median waiting-list time for the corresponding surgical procedure. The mortality risk was calculated within each interval by comparing the average mortality risk for patients receiving a transplant with the average mortality of patients on the waiting list for a comparable period of time (ie, the time since listing for both the transplant and the nontransplant groups was comparable) but who did not receive a transplant. Each analysis was adjusted for the year of listing; the pancreas-after-kidney transplant analysis also controlled for kidney donor type (cadaveric or living) and the simultaneous pancreas-kidney analysis controlled for whether the patient had received a previous kidney transplant.

We evaluated prognostic factors for mortality among transplant recipients

 ©2003 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 05/03/2015

using a multivariable Cox proportional hazards analysis for solitary pancreas transplant recipients with preserved kidney function (ie, serum creatinine ≤2 mg/dL [176.8 µmol/L]) at the time of listing and for simultaneous pancreas-kidney recipients with at least 7 days of follow-up between January 1, 1995, and December 31, 2000. We examined the influence of donor (age, cause of death), recipient (age, diabetes duration), transplant characteristics (exocrine and endocrine drainage procedures, ischemia time, year of transplant, and pancreas transplant volume by center [ie, total number of pancreas transplants performed at each center during the previous 365 days]), and posttransplant characteristics (treatment for rejection and complications prior to discharge).

Statistical analyses were performed using SAS version 8.2 (SAS Institute Inc, Cary, NC); $P<.05$ was used to determine statistical significance.

## RESULTS

Patient demographic and clinical characteristics are listed in TABLE 1. For the solitary pancreas subgroups (ie, pancreas alone, pancreas-after-kidney), the transplant and nontransplant groups were statistically indistinguishable ($P\geq.05$) with respect to age, sex, coronary artery disease, diabetes duration, symptomatic cerebrovascular disease, New York Heart Association status, baseline serum creatinine level, and age at diabetes onset. For all 3 procedures, nonwhite patients received transplants less frequently than did white patients. In addition, for the simultaneous pancreas-kidney analysis, the transplant and nontransplant groups slightly differed in their age, sex, ethnicity, and diabetes duration, while their cardiovascular and cerebrovascular status was similar. Simultaneous pancreas-kidney transplant recipients waited a mean of 313 (median, 234) days prior to receiving their transplants; recipients of pancreas transplant alone, a mean of 193 (median, 103) days; and pancreas-after-kidney recipients, a mean of 276 (median, 152) days.

FIGURE 1 displays the relative risk of death among transplant recipients compared with patients on the waiting list for the same procedure and followed up for equal periods of time. For the first 90 days posttransplantation, recipients of pancreas transplant alone had a 2.27-fold higher risk of death compared with patients continuing on the waiting list for that additional 90 days (95% confidence interval [CI], 0.84-6.13; $P=.11$). From 91 through 365 days posttransplantation the relative risk was 0.99 (95% CI, 0.41-2.39; $P=.99$), and after 365 days (ie, 366-1460 days) the relative risk was 1.70 (95% CI, 0.97-2.98; $P=.06$). For recipients of pancreas alone, the overall relative risk for death for the first 4 years following transplantation was 1.57 (95% CI, 0.98-2.53; $P=.06$). Pancreas-after-kidney recipients had a 2.89-fold higher risk of death for the first 90 days following transplantation (95% CI, 1.67-5.00; $P<.001$). From 91 through 365 days posttransplantation, the relative risk was 1.12 (95% CI, 0.67-1.88; $P=.66$), and after 365 days the relative risk was 1.28 (95% CI, 0.87-1.89; $P=.21$). For pancreas-after-kidney recipients, the overall relative risk for death was 1.42 compared with patients placed on the waiting list who never received a pancreas transplant (95% CI, 1.03-1.94; $P=.03$).

Simultaneous pancreas-kidney recipients had a 1.52-fold higher risk of death for the first 90 days following transplantation compared with patients continuing on the waiting list

**Table 1.** Patient Characteristics, Stratified by Waiting-List Outcome Within 2 Years of Listing

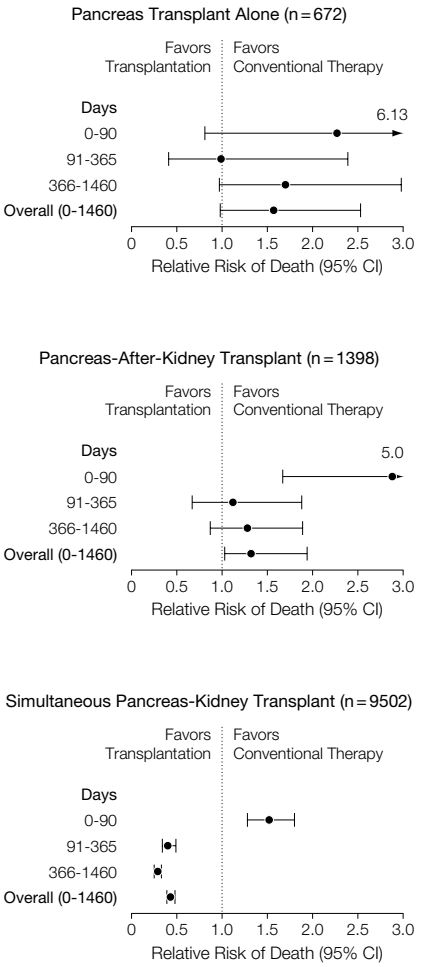
| | Waiting List-Outcome Within 2 Years, No. (%)* | | | | | |
|---|---|---|---|---|---|---|
| | Pancreas Alone (n = 672) | | Pancreas-After-Kidney (n = 1398) | | Simultaneous Pancreas-Kidney (n = 9502) | |
| Characteristic at Time of Listing | Transplant (n = 361) | No Transplant (n = 311) | Transplant (n = 753) | No Transplant (n = 645) | Transplant (n = 4876) | No Transplant (n = 4626) |
| Age, y | | | | | | |
| 0-17 | 4 (1.1) | 5 (1.6) | 0 | 0 | 8 (0.2) | 11 (0.2) |
| 18-49 | 319 (88.4) | 284 (91.3) | 676 (89.8) | 565 (87.6) | 4476 (91.8) | 4131 (89.3) |
| ≥50 | 38 (10.5) | 22 (7.1) | 77 (10.2) | 80 (12.4) | 392 (8.0) | 484 (10.5) |
| Men | 144 (39.9) | 133 (42.8) | 409 (54.3) | 363 (56.3) | 2854 (58.5) | 2591 (56.0) |
| White | 344 (95.3) | 283 (91.0) | 685 (91.0) | 561 (87.0) | 4048 (83.0) | 3730 (80.6) |
| Duration of diabetes, y | | | | | | |
| 0-10 | 34 (10.3) | 23 (8.8) | 13 (2.0) | 12 (2.1) | 86 (1.9) | 87 (2.1) |
| 11-20 | 94 (28.6) | 80 (30.4) | 102 (15.4) | 107 (19.1) | 1337 (29.9) | 1145 (27.5) |
| 21-30 | 122 (37.1) | 102 (38.8) | 329 (49.8) | 278 (49.6) | 2150 (48.0) | 2008 (48.2) |
| ≥31 | 79 (24.0) | 58 (22.1) | 217 (23.8) | 163 (29.1) | 904 (20.2) | 924 (22.2) |
| Angina | 29 (8.9) | 28 (9.7) | 107 (15.6) | 79 (13.3) | 551 (12.2) | 639 (15.2) |
| Cerebrovascular disease | 1 (0.3) | 1 (0.4) | 21 (3.1) | 19 (3.2) | 126 (2.8) | 112 (2.6) |
| NYHA functional status | | | | | | |
| Class I or II | 215 (85.7) | 208 (84.5) | 496 (86.0) | 448 (86.8) | 3879 (87.4) | 3508 (88.1) |
| Class III or IV | 36 (14.3) | 38 (15.5) | 81 (14.0) | 68 (13.2) | 560 (12.6) | 474 (11.9) |

Abbreviation: NYHA, New York Heart Association.
*Comparisons limited to 2 years because most events occur within this time period. Percentages calculated using known values.

©2003 American Medical Association. All rights reserved.


Downloaded From: http://jama.jamanetwork.com/ on 05/03/2015

**Figure 1.** Relative Risk of Mortality, by Transplant Type




Days are posttransplant (recipients) or additional days waiting (patients not transplanted). Relative risk of 1.0 indicates that the risk of transplantation equals the risk for those not transplanted. CI indicates confidence interval.

(95% CI, 1.28-1.80; $P<.001$). From 91 through 365 days posttransplantation the relative risk was 0.40 (95% CI, 0.34-0.49; $P<.001$), and after 365 days the relative risk was 0.29 (95% CI, 0.25-0.33; $P<.001$). For simultaneous pancreas-kidney recipients, the overall relative risk for death was 0.43 compared with patients on the waiting list (95% CI, 0.39-0.48; $P<.001$).

In an effort to further understand these relative risks, and as shown in FIGURE 2, the 1- and 4-year survival rates of patients on the waiting list for a pancreas transplant alone were 97.6% and 92.1%, respectively; for a pancreas-after-kidney transplant, 97.1% and 88.1%; and for a simultaneous pancreas-kidney transplant, 92.8% and 63.8%. These data are consistent with survival rates observed in the Allegheny County database (T.J.O., personal communication), which since 1965 has captured and followed data from all county residents diagnosed with type 1 diabetes mellitus.[16] For the patients diagnosed between 1965-1974, with a current mean age of 33 years and diabetes duration of 20 to 24 years (regardless of kidney function), the annual mortality was 1.6%. In contrast, overall patient survival rates for all pancreas transplant recipients transplanted between 1995 and 2000 at 1-year posttransplantation were 96.5% for recipients of pancreas transplant alone, 95.3% for pancreas-after-kidney recipients, and 94.4% for simultaneous pancreas-kidney recipients. At 4 years posttransplantation, the survival rates were 85.2% for recipients of pancreas transplant alone, 84.5% for pancreas-after-kidney recipients, and 87.5% for simultaneous pancreas-kidney recipients.

The multivariable analysis (TABLE 2) identified several factors potentially associated with posttransplant mortality, including recipient age; donor cause of death; enteric drainage; complications including pancreatitis, abscess, or anastomotic leak; and rejection before discharge.

## COMMENT

Solitary pancreas transplantation for patients with diabetes mellitus and preserved kidney function remains controversial due to associated morbidity and mortality, the requirement of lifelong immunosuppression, and questions about whether secondary complications are prevented.[10] We asked whether mortality in patients with complicated diabetes who are thus listed for a pancreas transplant was decreased by transplantation. Similar discussions have assumed a patient mortality rate ranging between 5% and 10% at 1 year for those with complicated diabetes but preserved kidney function.[17] Our data suggest that this assumption is incorrect. Indeed, previous data evaluating patients with type 1 diabetes mellitus of at least 20 years' duration suggest that the annual mortality rate is lower than is commonly assumed,[18,19] and appears to be decreasing as therapies improve.[16] As shown in Figure 2, we now report that patients awaiting a solitary pancreas transplant (ie, pancreas alone and pancreas-after-kidney) added to the waiting list between 1995 and 2000 had a 1-year survival of 97.6% and 97.1%, respectively, and a 4-year survival of 92.1% and 88.1%. Thus, even this cohort with complicated diabetes demonstrates relatively low mortality.

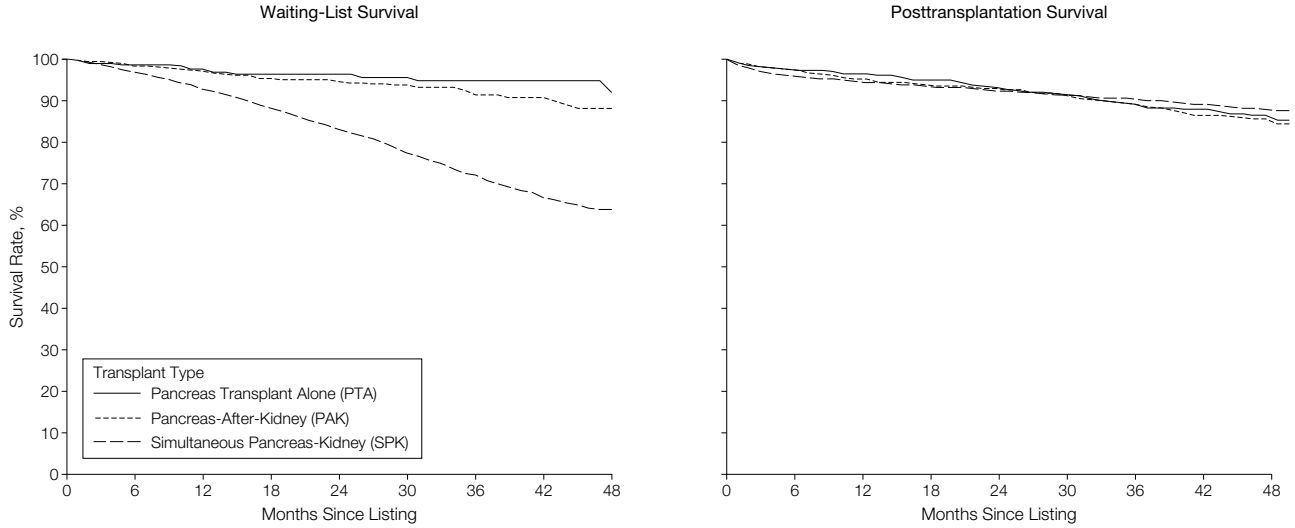
Since the elevated relative risk associated with solitary pancreas transplantation may be due to differences between transplant recipients and the nontransplanted group, we screened for potential confounding variables listed in Table 1, revealing that only ethnicity slightly differed. Patients also appear to have an equal opportunity for transplantation. In a subpopulation of our sample for which data were available (n=848), we tabulated organ offers: transplant recipients averaged 5 offers and nontransplanted patients averaged 7. These data suggest that the care team was not offering the organs to a "sicker" group, and that the slightly greater number offered to the nontransplanted group probably reflects the fact that additional offers cease once a patient receives a transplant.

In an effort to test whether the waiting-list cohort is representative of the general population of patients with diabetes, we compared the UNOS/OPTN waiting-list mortality rate with the mortality rate from the Allegheny County type 1 diabetes mellitus database.[16] The registry documents an annual mortality rate of 1.6% for a cohort with similar age and diabetes duration. This Allegheny County population-based mortality rate includes those who have developed end-stage renal disease and a small minority who received a transplant. The Epidemiology of Diabetes Interventions and Complications (EDIC) study, also based on childhood cases (di-


©2003 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 05/03/2015

**Figure 2.** Waiting-List and Posttransplantation Patient Survival Rates, 1995-2000




No. at Risk

| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| PTA | 346 | 244 | 189 | 147 | 107 | 64 | 46 | 35 | 364 | 360 | 354 | 342 | 281 | 231 | 181 | 143 |
| PAK | 845 | 617 | 488 | 391 | 281 | 166 | 117 | 90 | 687 | 672 | 658 | 652 | 526 | 406 | 297 | 244 |
| SPK | 6229 | 4087 | 2687 | 1856 | 1206 | 715 | 422 | 290 | 5176 | 5090 | 5027 | 4971 | 4491 | 4048 | 3563 | 3118 |

**Table 2.** Prognostic Factors Among Transplant Recipients, 1995-2000

| | Transplant Type | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Pancreas Alone (n = 374) | | | Pancreas-After-Kidney (n = 706) | | | Simultaneous Pancreas-Kidney (n = 5375) | | |
| Variable | No. (%) | RR (95% CI) | *P* Value | No. (%) | RR (95% CI) | *P* Value | No. (%) | RR (95% CI) | *P* Value |
| **Donor Characteristics** | | | | | | | | | |
| Age ≥45 y vs <45 y | 37 (10.0) | 0.96 (0.33-2.76) | .94 | 72 (10.4) | 0.51 (0.22-1.17) | .11 | 502 (9.4) | 1.11 (0.88-1.41) | .36 |
| CVA as donor cause of death | 27 (7.3) | 3.04 (1.41-6.56) | .005 | 52 (7.5) | 1.44 (0.74-2.79) | .29 | 361 (6.7) | 1.28 (0.99-1.65) | .06 |
| **Recipient Characteristics** | | | | | | | | | |
| Age 41-50 y vs ≤40 y | 112 (30.3) | 1.12 (0.61-2.08) | .71 | 264 (38.0) | 1.95 (1.28-2.98) | .002 | 1741 (32.5) | 1.28 (1.10-1.49) | .001 |
| Age ≥51 y vs ≤40 y | 30 (8.1) | 0.66 (0.15-2.86) | .58 | 58 (8.3) | 2.67 (1.29-5.52) | .008 | 350 (6.5) | 1.54 (1.18-2.02) | .002 |
| Diabetes duration >20 y vs ≤20 y | 262 (70.8) | 0.75 (0.42-1.35) | .34 | 615 (88.5) | 0.94 (0.50-1.77) | .86 | 4176 (78.1) | 1.12 (0.94-1.34) | .21 |
| **Transplant Characteristics** | | | | | | | | | |
| Enteric with Roux-en-Y vs bladder drainage | 81 (21.9) | 1.85 (0.78-4.36) | .16 | 127 (18.3) | 0.92 (0.46-1.85) | .82 | 965 (18.0) | 0.84 (0.68-1.05) | .13 |
| Enteric without Roux-en-Y vs bladder drainage | 72 (19.5) | 0.92 (0.39-2.19) | .85 | 211 (30.4) | 0.98 (0.58-1.66) | .95 | 1811 (33.9) | 0.73 (0.60-0.88) | <.001 |
| Portal vascular vs systemic management | 89 (24.1) | 0.84 (0.35-1.99) | .69 | 115 (16.5) | 1.12 (0.57-2.18) | .75 | 763 (14.3) | 1.33 (1.08-1.65) | .009 |
| Ischemia time >12 h vs ≤12 h | 284 (76.8) | 1.09 (0.56-2.09) | .80 | 512 (73.7) | 1.04 (0.66-1.63) | .88 | 3156 (59.0) | 1.07 (0.93-1.24) | .33 |
| Center volume, transplants/y, vs ≤25 | | | | | | | | | |
| 26-50 | 67 (18.1) | 1.66 (0.80-3.42) | .17 | 84 (12.1) | 0.53 (0.26-1.07) | .07 | 955 (17.9) | 1.01 (0.84-1.21) | .92 |
| 51-75 | 85 (23.0) | 1.31 (0.58-2.96) | .51 | 95 (13.7) | 0.86 (0.48-1.55) | .61 | 446 (8.3) | 0.85 (0.64-1.13) | .26 |
| ≥76 | 114 (30.8) | 0.73 (0.29-1.84) | .51 | 153 (22.0) | 0.66 (0.37-1.16) | .15 | 211 (3.9) | 1.26 (0.89-1.80) | .19 |
| Transplant year 1995-1997 vs 1998-2000 | 126 (34.1) | 1.46 (0.75-2.82) | .26 | 196 (28.2) | 1.98 (1.25-3.13) | .003 | 2581 (48.3) | 1.14 (0.96-1.35) | .13 |
| **Posttransplant Characteristics** | | | | | | | | | |
| Treated for rejection by discharge | 25 (6.8) | 1.75 (0.78-3.92) | .17 | 38 (5.5) | 1.54 (0.77-3.09) | .23 | 598 (11.2) | 1.44 (1.19-1.74) | <.001 |
| Any complications* | 26 (7.0) | 2.91 (1.31-6.48) | .009 | 61 (8.8) | 2.63 (1.55-4.48) | <.001 | 616 (11.5) | 1.45 (1.19-1.75) | <.001 |

Abbreviations: CI, confidence interval; CVA, cerebrovascular accident; RR, relative risk.
*Includes pancreatitis, abscess, or anastomotic leak.

©2003 American Medical Association. All rights reserved.



Downloaded From: http://jama.jamanetwork.com/ on 05/03/2015

agnosed between 1950-1980), has similar data: patients with diabetes for 25 years (mean age, 33 years) experienced an overall mortality of 1.8% per year (T.J.O., unpublished data). These data closely approximate the mortality rates of this study's waiting-list comparison group. Consistent with the assumption that those being listed for a pancreas transplant have more advanced disease, the mortality in the waiting-list groups is higher than that observed in the population-based studies.

We attempted to eliminate biases that might artificially lower waiting-list mortality and/or heighten the risk following transplantation. For instance, for the pancreas transplant alone and pancreas-after-kidney analyses, we excluded all patients who at listing had a serum creatinine level greater than 2 mg/dL (176.8 μmol/L), since those patients clearly have an increased risk of mortality. Yet 44 patients categorized in the database as not having abnormal kidney function and listed for a solitary pancreas transplant nevertheless received a kidney transplant with their pancreas transplant (see "Methods" section), indicating that these 44 patients clearly did not have normal kidney function. Thus, we likely overestimated the mortality rate for patients awaiting a solitary pancreas transplant by incompletely excluding patients with diabetes and abnormal kidney function. Moreover, our inclusion of all study patient deaths captured by the SSDMF (including deaths of inactivated patients, patients removed from the waiting list, and deaths unrelated to diabetes) may have falsely increased diabetes-associated mortality for the patients in the waiting-list cohort. For example, another approach would have been to censor patients removed from the waiting list for comorbidities unrelated to diabetes and clearly irremediable by transplant (eg, a waiting-list patient taken off the list due to imminent death from cancer). In our analysis, these patients would be classified as waiting-list deaths when clearly they could not have benefited from a pancreas transplant.

Our transplant survival rates are comparable to national and international pancreas transplant registry data. The International Pancreas Transplant Registry for pancreas transplant recipients in all categories and locations during a similar time period (1996-2000) reported a 1-year patient survival rate of 94% or greater.[20] University of Minnesota transplant recipient survival data are also quite similar.[21] We also looked for a transplant-center effect by analyzing data from the 2 centers with the largest pancreas transplant volume and found that their experience mirrored the national trends. These data suggest that even in the centers with the most experience, solitary pancreas transplantation increases mortality risk above that for patients treated medically.

We have been particularly intrigued by the greater mortality observed in the patients who received a pancreas transplant after a preceding kidney transplant when that group's survival was compared with survival for those who received a kidney transplant and were listed for a subsequent pancreas transplant but never received it. The excess deaths in that pancreas-after-kidney group, especially the excess mortality that persists long after the pancreas transplant procedure, are difficult to explain since both groups require immunosuppression. While we have no data from which to judge, one possibility is that the pancreas-after-kidney group could be given larger doses of immunosuppressive agents or could suffer more frequent acute rejection episodes (of the pancreas or the kidney), prompting antirejection rescue attempts with negative long-term consequences.

Our conclusions regarding the benefit of simultaneous pancreas-kidney transplantation differ markedly from the analyses of pancreas-after-kidney transplantation or pancreas transplantation alone, and yet the postsurgical survival for each procedure is quite similar (Figure 2). The reason appears to be that, while patients with diabetes and kidney failure awaiting a simultaneous pancreas-kidney transplant have a remarkably high annual death rate, patients awaiting a solitary pancreas transplant have a much better prognosis. Wolfe et al[15] recently demonstrated an independent survival benefit associated with a solitary kidney transplant for patients with end-stage renal disease. Similarly, our data confirm that a kidney transplant confers a great survival benefit for patients with diabetes and kidney failure. The survival rate for patients awaiting a pancreas-after-kidney transplant (ie, patients with a functioning kidney allograft) is dramatically higher than the rate for those patients with both diabetes and kidney failure awaiting a simultaneous pancreas-kidney transplant. We cannot further comment on whether a pancreas transplant independently contributes to the survival advantage following a simultaneous pancreas-kidney transplant, but several analyses in patients with both diabetes and end-stage renal disease who receive either a kidney transplant alone, or a simultaneous pancreas-kidney transplant, have recently been published. These reports come to different conclusions as to whether the pancreas transplant provides additional survival benefit above that achieved by the kidney transplant, and the studies are confounded by multiple donor and recipient variables.[22-24] Thus, it remains unclear whether the pancreas transplant adds to the clear survival advantage conferred by a kidney transplant for patients with diabetes and kidney failure.

In our statistical model, we adjusted for the year of listing to minimize the potential bias from an improved outcome over time. We focused only on the modern transplantation era, beginning in 1995, after the widespread use of tacrolimus as an immunosuppressant. Posttransplant mortality included all patients receiving a transplant, independent of allograft function.

In addition to the limitations imposed by the retrospective design, and despite our capture of all national data since 1995, our analyses were performed using relatively small patient numbers after dividing the study population into appropriate transplant subgroups (pancreas alone, pancreas-after-kidney, simultaneous pancreas-kidney). Due to this limi-

 ©2003 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 05/03/2015

tation, in our assessment of posttransplant risk we could not study smaller posttransplant time intervals. The transplants were also performed at multiple transplant centers with varying experience, technique, and immunosuppressive approaches—any of which could influence postoperative mortality. In addition, since UNOS/OPTN does not collect serial clinical data for patients on the waiting list, it is not possible to determine whether the patients who remain on the waiting list for many years are different from patients who quickly receive a transplant or are quickly removed from the list. Similarly, the database did not maintain indices of glycemic control, preventing us from analyzing the relationship between glucose control and patient mortality. Although we intentionally limited our study to 4 years posttransplantation to capture the most recent advances in surgical and medical techniques, longer follow-up may be needed before potential transplant benefits become evident. In our review of the literature, however, we find no definitive evidence that pancreas transplantation prevents or ameliorates important long-term diabetes complications such as retinopathy, neuropathy, and nephropathy.[10] We are aware, however, of reports suggesting that histologically assessed nephropathy may be reversed in the native kidney following pancreas transplantation.[25]

Mortality associated with long-term diabetes is markedly lower than that associated with other conditions similarly amenable to transplantation, such as end-stage renal disease and liver failure. Our data suggest that patients with complicated diabetes who are considering a solitary pancreas transplant must weigh the potential benefit of insulin independence against an apparent increase in mortality for at least the first 4 years posttransplantation. Benefits not accounted for in this analysis (eg, improved quality of life) may justify pancreas transplantation, and it is possible that transplant recipients may show a survival advantage with longer-term follow-up. Even if that is true, however, it is at best difficult to weigh the cost of an early excess mortality (spanning the first 4 years posttransplant) against what at this point is a hypothetical survival advantage beyond the 4 years we have analyzed. A randomized controlled clinical trial would be the most appropriate way to evaluate the effect of pancreas transplantation on survival, but this design may not be feasible or ethical.[10] At this point, clinicians and patients considering the pancreas transplant option must understand the actual risks and benefits, the expense, and the uncertainties associated with this surgical therapy. Our data suggest that the increasingly frequent application of the solitary pancreas transplantation option for those with normal kidney function warrants a second look.

**Author Contributions:** Dr Harlan, as principal investigator of this study, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analyses.
*Study concept and design:* Venstrom, McBride, Rother, Hirshberg, Harlan.
*Acquisition of data:* Venstrom, McBride, Harlan.
*Analysis and interpretation of data:* Venstrom, McBride, Rother, Hirshberg, Orchard, Harlan.
*Drafting of the manuscript:* Venstrom, McBride, Harlan.
*Critical revision of the manuscript for important intellectual content:* Venstrom, McBride, Rother, Hirshberg, Orchard, Harlan.
*Statistical expertise:* Venstrom, McBride, Orchard.
*Obtained funding:* Harlan.
*Study supervision:* Rother, Harlan.
**Funding/Support:** This work was supported in part by intramural funds of the National Institute of Diabetes and Digestive and Kidney Diseases/National Institutes of Health/Department of Health and Human Services and Health Resources and Services Administration contract 231-00-0115.
**Role of Sponsor:** The National Institute of Diabetes and Digestive and Kidney Diseases had no involvement in, or control over, the conduct of the study, the decision to publish, or the content of this article.

## REFERENCES

**1.** Robertson RP, Davis C, Larsen J, Stratta R, Sutherland DE, American Diabetes Association. Pancreas transplantation for patients with type 1 diabetes. *Diabetes Care*. 2003;26(suppl 1):S120.
**2.** Gross CR, Zehrer CL. Health-related quality of life outcomes of pancreas transplant recipients. *Clin Transplant*. 1992;6(3 pt 1):165-171.
**3.** Gross CR, Limwattananon C, Matthees BJ. Quality of life after pancreas transplantation: a review. *Clin Transplant*. 1998;12:351-361.
**4.** Katz H, Homan M, Velosa J, Robertson P, Rizza R. Effects of pancreas transplantation on postprandial glucose metabolism. *N Engl J Med*. 1991;325:1278-1283.
**5.** Landgraf R. Impact of pancreas transplantation on diabetic secondary complications and quality of life. *Diabetologia*. 1996;39:1415-1424.
**6.** Piehlmeier W, Bullinger M, Kirchberger I, Land W, Landgraf R. Evaluation of the quality of life of patients with insulin-dependent diabetes mellitus before and after organ transplantation with the SF 36 health survey. *Eur J Surg*. 1996;162:933-940.
**7.** Piehlmeier W, Bullinger M, Nusser J, et al. Quality of life in type 1 (insulin-dependent) diabetic patients prior to and after pancreas and kidney transplantation in relation to organ function. *Diabetologia*. 1991;34(suppl 1):S150-S157.
**8.** Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med*. 1993;329:977-986.
**9.** Luzi L. Pancreas transplantation and diabetic complications. *N Engl J Med*. 1998;339:115-117.
**10.** Robertson RP, Holohan TV, Genuth S. Therapeutic controversy: pancreas transplantation for type I diabetes. *J Clin Endocrinol Metab*. 1998;83:1868-1874.
**11.** Gruessner RW, Sutherland DE, Troppmann C, et al. The surgical risk of pancreas transplantation in the cyclosporine era: an overview. *J Am Coll Surg*. 1997;185:128-144.
**12.** Humar A, Kandaswamy R, Granger D, Gruessner RW, Gruessner AC, Sutherland DE. Decreased surgical risks of pancreas transplantation in the modern era. *Ann Surg*. 2000;231:269-275.
**13.** Sutherland DE, Cecka M, Gruessner AC. Report from the International Pancreas Transplant Registry–1998. *Transplant Proc*. 1999;31:597-601.
**14.** Hosenpud JD, Bennett LE, Keck BM, Edwards EB, Novick RJ. Effect of diagnosis on survival benefit of lung transplantation for end-stage lung disease. *Lancet*. 1998;351:24-27.
**15.** Wolfe RA, Ashby VB, Milford EL, et al. Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. *N Engl J Med*. 1999;341:1725-1730.
**16.** Nishimura R, LaPorte RE, Dorman JS, Tajima N, Becker D, Orchard TJ. Mortality trends in type 1 diabetes: the Allegheny County (Pennsylvania) Registry 1965-1999. *Diabetes Care*. 2001;24:823-827.
**17.** Gruessner RW, Sutherland DE, Najarian JS, Dunn DL, Gruessner AC. Solitary pancreas transplantation for nonuremic patients with labile insulin-dependent diabetes mellitus. *Transplantation*. 1997;64:1572-1577.
**18.** Deckert T, Poulsen JE, Larsen M. Prognosis of diabetics with diabetes onset before the age of thirty-one, II: factors influencing the prognosis. *Diabetologia*. 1978;14:371-377.
**19.** Deckert T, Poulsen JE, Larsen M. Prognosis of diabetics with diabetes onset before the age of thirty-one, I: survival, causes of death, and complications. *Diabetologia*. 1978;14:363-370.
**20.** Gruessner AC, Sutherland DE. Report for the international pancreas transplant registry-2000. *Transplant Proc*. 2001;33:1643-1646.
**21.** Sutherland DE, Gruessner RW, Dunn DL, et al. Lessons learned from more than 1,000 pancreas transplants at a single institution. *Ann Surg*. 2001;233:463-501.
**22.** Bunnapradist S, Cho YW, Cecka JM, Wilkinson A, Danovitch GM. Kidney allograft and patient survival in type I diabetic recipients of cadaveric kidney alone versus simultaneous pancreas/kidney transplants: a multivariate analysis of the UNOS database. *J Am Soc Nephrol*. 2003;14:208-213.
**23.** Ojo AO, Meier-Kriesche HU, Hanson JA, et al. The impact of simultaneous pancreas-kidney transplantation on long-term patient survival. *Transplantation*. 2001;71:82-90.
**24.** Reddy KS, Stablein D, Taranto S, et al. Long-term survival following simultaneous kidney-pancreas transplantation versus kidney transplantation alone in patients with type 1 diabetes mellitus and renal failure. *Am J Kidney Dis*. 2003;41:464-470.
**25.** Fioretto P, Steffes MW, Sutherland DE, Goetz FC, Mauer M. Reversal of lesions of diabetic nephropathy after pancreas transplantation. *N Engl J Med*. 1998;339:69-75.

©2003 American Medical Association. All rights reserved.



Downloaded From: http://jama.jamanetwork.com/ on 05/03/2015

Because cycle abnormalities may reflect hormonal disturbances, we repeated the analysis among the 40 389 women (with 557 twin deliveries) who reported regular menstrual cycles (26-30 days). Compared with a BMI of 20 to 24.9, the odds ratio associated with a BMI below 20 was 0.71 (95% confidence interval [CI], 0.54-0.92) and that associated with a BMI of 30 or more was 1.39 (95% CI, 1.05-1.84).

In Denmark, stillbirths are registered after 28 completed gestational weeks. Earlier deliveries in which 1 twin is stillborn thus may be wrongly registered as singleton. When we included only live births (55298 deliveries with 708 twin pairs), the odds ratios were 0.72 (95% CI, 0.57-0.91) and 1.44 (95% CI, 1.13-1.83) for women with a BMI below 20 and those with a BMI of 30 or more, respectively, compared with women with a normal BMI.

**Comment.** We found that a BMI of less than 20 was associated with a lower risk of twinning, and that a BMI of 30 or more was associated with a higher risk. The association was slightly stronger for opposite-sex twins. We found a similar trend for height.

Given the widespread increase in obesity, especially in developed countries,[7,8] this association may explain part of the observed increase in twinning. In the early 1960s, 9.3% of US women aged 20 to 39 years had a BMI of 30 or more, but this proportion increased to 28.4% in 1999-2000.[8] In Denmark, the proportion of women with a BMI of 30 or more in the general population increased from 5.5% in 1987 to 9.5% in 2000.[9]

Treatment of some obese women who might have conceived naturally could alter the magnitude of the association, but probably not to any large degree. Furthermore, the BMI-twinning association had been reported when use of infertility drugs was not as widespread.[3,4]

**Olga Basso, MD, PhD**
**ob@soci.au.dk**
**Ellen Aagaard Nohr, MHS**
**Danish Epidemiology Science Centre**
**University of Århus**
**Århus, Denmark**

**Kaare Christensen, MD, PhD**
**Epidemiology, Institute of Public Health, and the Danish Twin Registry**
**University of Southern Denmark**
**Odense**

**Jørn Olsen, MD, PhD**
**Danish Epidemiology Science Centre**
**University of Århus**

**Funding/Support:** Dr Basso is supported by a grant from the Danish Medical Research Council (No. 22-00-0008). The Danish National Research Foundation has established the Danish Epidemiology Science Centre that initiated and created the Danish National Birth Cohort. The cohort is furthermore a result of a major grant from this foundation. Additional support for the Danish National Birth Cohort is obtained from the Pharmacy Foundation, the Egmont Foundation, the March of Dimes Birth Defects Foundation, and the Augustinus Foundation.

**Role of the Sponsors:** The Danish Medical Research Council, the Danish National Research Foundation, the Pharmacy Foundation, the Egmont Foundation, the March of Dimes Birth Defects Foundation, and the Augustinus Foundation played no role in the study design; in the collection, analysis, or interpretation of data; or in the writing and the decision to submit the manuscript for publication.

**1.** Tong S, Short RV. Dizygotic twinning as a measure of human fertility. *Hum Reprod*. 1998;13:95-98.
**2.** Rachootin P, Olsen J. Secular changes in the twinning rate in Denmark 1931 to 1977. *Scand J Soc Med*. 1980;8:89-94.
**3.** MacGillivray I, Campbell DM, Thompson B, eds. *Twinning and Twins*. London, England: John Wiley & Sons; 1988.
**4.** Hemon D, Berger C, Lazar P. The etiology of human dizygotic twinning with special reference to spontaneous abortions. *Acta Genet Med Gemellol (Roma)*. 1979;28:253-258.
**5.** Olsen J, Melbye M, Olsen SF, et al. The Danish National Birth Cohort—its background, structure and aim. *Scand J Public Health*. 2001;29:300-307.
**6.** Dansk Selskab for Obstetrik og Gynekologi (Danish Society of Obstetrics and Gynecology) Web site. Available at: http://www.dsog.dk/. Accessed February 25, 2004.
**7.** Seidell JC, Flegal KM. Assessing obesity: classification and epidemiology. *Br Med Bull*. 1997;53:238-252.
**8.** Flegal KM, Carroll MD, Ogden CL, Johnson CL. Prevalence and trends in obesity among US adults, 1999-2000. *JAMA*. 2002;288:1723-1727.
**9.** Danish Institute of Public Health. The Danish Health and Morbidity Survey 2000: summary. Available at: http://susy.si-folkesundhed.dk/menu.asp. Accessed February 18, 2004.

## CORRECTION

**Incorrect Study Name:** In the Original Contribution entitled "Survival After Pancreas Transplantation in Patients With Diabetes and Preserved Kidney Function" published in the December 3, 2003, issue of THE JOURNAL (2003;290:2817-2823), the name of a study was incorrectly cited. On page 2820, the Epidemiology of Diabetes Intervention and Complications (EDIC) study should have been cited as the Epidemiology of Diabetes and Complications (EDC) study.


©2004 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 05/03/2015