Pancreas Transplant Alone

A procedure coming of age

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The goal of this review is to highlight the significant improvements, over the past four decades, in outcomes after a pancreas transplant alone (PTA) in patients with brittle diabetes and recurrent episodes of hypoglycemia and/or hypoglycemic unawareness. A successful PTA—in contrast to intensive insulin regimens and insulin pumps—restores normoglycemia without the risk of hypoglycemia and prevents, halts, or reverses the development or progression of secondary diabetes complications. In this International Pancreas Transplant Registry (IPTR) analysis, we reviewed the records of 1,929 PTA recipients from December 1966 to December 2011. We computed graft survival rates according to the Kaplan-Meier method and used uni- and multivariate analyses. In the most recent era (January 2007–December 2011), patient survival rates were >95% at 1 year posttransplant and >90% at 5 years. Graft survival rates with tacrolimus-based maintenance therapy were 86% at 1 year and 69% at 3 years and with sirolimus, 94 and 84%. Graft survival rates have significantly improved owing to marked decreases in technical and immunologic graft failure rates ($P < 0.05$). As a result, the need for a subsequent kidney transplant has significantly decreased, over time, to only 6% at 5 years. With patient survival rates of almost 100% and graft survival rates of up to 94% at 1 year, a PTA is now a highly successful long-term option. It should be considered in nonuremic patients with brittle diabetes in order to achieve normoglycemia, to avoid hypoglycemia, and to prevent the development or progression of secondary diabetes complications.

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The Diabetes Control and Complications Trial (DCCT) demonstrated, in patients with type 1 diabetes mellitus (T1DM), that intensive insulin therapy may slow the rate of secondary complications of diabetes at the expense of causing (life-threatening) iatrogenic hypoglycemia (1,2). The definitive treatment for these patients, a successful pancreas transplant, restores normal glucose homeostasis without exposing recipients to the risks of severe hypoglycemia and prevents, halts, or reverses the development or progression of secondary diabetes complications (3–5).

Pancreas transplants are performed in patients who require insulin administration because of T1DM, T2DM, or total pancreatectomy. Since the first pancreas transplant in December 1966, performed by Drs. William Kelly and Richard Lillehei, the majority (almost 80%) of pancreas transplants have been performed simultaneously with a kidney (SPK) in diabetic and uremic patients (6,7). An additional 15% of pancreas transplants have been performed after a kidney transplant (PAK) in diabetic and posturemic patients. Only ~8% of all pancreas transplants have been a pancreas transplant alone (PTA), performed in nonuremic patients with brittle (or labile) diabetes (including recurrent episodes of hypoglycemia and/or hypoglycemic unawareness).

The reason that SPK transplants are most common is that SPK recipients are already obligated to immunosuppressive therapy by the kidney graft, so they incur only the added surgical risk of the pancreas transplant. A PTA is less commonly performed because only a relatively small percentage of insulin-dependent patients truly have brittle diabetes that cannot be controlled despite their own best efforts and the help of diabetologists, endocrinologists, and other health professionals. In general, PTA candidates have not yet developed advanced secondary complications of diabetes; yet, halting the development or progression of such complications significantly improves both quality of life and life expectancy (more so for PTA recipients than for SPK or PAK recipients).

PTA recipients, in addition to the surgical risk of the pancreas transplant procedure itself, also incur the risk of immunosuppressive therapy (in the absence of a transplanted kidney graft). Immunosuppression in PTA recipients is required to prevent rejection (in order to establish insulin independence), to avoid hypoglycemic episodes, and to prevent the progression of secondary diabetes complications. Because of the required immunosuppressive therapy and its side effects—in the absence of advanced diabetic nephropathy—the PTA option has not been widely accepted. Moreover, in the first two decades after the first PTA was performed in 1968, its surgical risk was high, with considerable technical morbidity and poor outcomes (7). Only after the introduction of calcineurin inhibitors (and, specifically, tacrolimus) did the immunologic graft failure rates significantly decrease in PTA recipients. Despite improvements in exogenous insulin therapy, including the use of devices such as insulin pumps, the risk of hypoglycemic episodes (and their detrimental side effects) remains substantial in patients with brittle diabetes (8).

We present herein the significantly improved PTA results as reported to the International Pancreas Transplant Registry (IPTR) over a 43-year period.

RESEARCH DESIGN AND METHODS

—The IPTR, maintained at the University of Arizona, has information on >26,000 U.S. pancreas transplants in diabetic recipients performed from 17 December 1966 to 31 December 2011. Of those transplants, 1,929 (7.7%) were PTA transplants. In this IPTR analysis, we estimated patient survival and pancreas graft function rates using the Kaplan-Meier method, with pancreas function being defined as complete insulin independence. Partial pancreas graft function (irrespective of the amount of the insulin dose) was counted as graft failure, as was death with a functioning graft. For univariate

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comparisons, depending on the data type, we used the Kruskal-Wallis or the χ^2 test. We defined early technical failure as occurring during the first 90 days posttransplant. To assess the impact of immunologic failure, we performed additional analyses (excluding early technical failure). We defined graft survival as long-term if the graft had functioned at least 5 years. To estimate any differences in recipient and donor risk factors between early technical failure and long-term graft survival, as well as risk factors for graft loss and patient death, we used a Cox regression model. For all computations, we used SAS 9.3 (SAS, Cary, NC).

To assess the impact of changes over time, we analyzed six different eras: era 0 (December 1966–September 1987, the very early transplants); era 1 (October 1987–December 1993, inception of the United Network for Organ Sharing); era 2 (January 1994–December 1997, introduction of widespread use of tacrolimus); era 3 (January 1998–December 2001, use, for the most part, of nondepleting antibody induction); era 4 (January 2002–December 2006, widespread use of depleting antibody induction and rapid steroid avoidance), and era 5 (January 2007–December 2011, the most recent transplants).

Limitations of any registry analysis include some inaccurate data and some missing data. For our IPTR study, the rate of missing data is provided in Tables 1 and 2. However, the advantage of a registry analysis is completeness of cases (i.e., the exact number of transplants).

RESULTS

Recipient and donor characteristics

Table 1 shows the characteristics of all primary PTA recipients for all eras. The number of centers offering a PTA increased, over time, from 20 centers in era 0 to 68 centers in era 5. Yet, even in era 5, less than one-half of all pancreas transplant centers performed one or more PTA.

We found a significant increase, over time, in the median PTA recipient age: from 31 years (range 17–52) in era 0 to 41 years (14–64) in era 5. Of note, we also found an increase in the rate of PTA recipients ≥45 years old: from 7% in era 0 to 36% in era 5. Likewise, we found a significant increase in median duration of diabetes: from 23 years (range 1–46) in era 1 to 27 years (2–59) in era 5.

For all eras combined, ~60% of the total number of PTA recipients were female (in contrast to SPK and PAK recipients, of whom ~60% were male). The difference in sex distribution by transplant category (PTA, SPK, and PAK) did not change significantly over time (data not shown). However, the rate of sensitized PTA recipients did increase over time.

Donor characteristics also changed significantly over time. In era 1, 57% of all primary PTA donors were <30 years of age; this rate increased to 73% in era 5. Of particular interest is the initially high rate of living donors in era 0—almost 30% of that era's PTA total; in contrast, living donors were not used in era 5, and only one was used in era 4 (Table 2).

In each era, the most common cause of death in deceased donors was trauma. Pancreas preservation time decreased significantly, over time, to <12 h in 51% of PTA donors in era 5.

More attention was paid to HLA matching in the early eras: five or six HLA mismatches accounted for 26% of the PTA total in era 2 but only for 49% in era 5. Like HLA matching, the technique for managing exocrine secretions also significantly changed since era 0 (because of improved outcomes): in era 5, enteric drainage was used in 80% of all primary PTA recipients and bladder drainage in only 20%. For PTA recipients with enteric drainage, the use of portal vein drainage peaked in era 3, accounting for almost 60% of venous drainage, but subsequently declined to 10% in era 5.

In era 5, induction therapy was used in 88% of all primary PTA recipients; the vast majority received depleting antibodies (79%), but ~7% received nondepleting antibodies or a combination of depleting and nondepleting antibodies. For maintenance therapy in era 5, almost 70% of primary PTA recipients received a combination of tacrolimus (TAC) and mycophenolate mofetil (MMF); <4%, TAC monotherapy; and <4%, MMF monotherapy. Approximately 20% of primary PTA recipients received sirolimus (SRL)-based maintenance therapy (Table 3).

Patient survival

Significantly, PTA patient survival rates at 1 year posttransplant have remained excellent. Since era 1, patient survival rates at 1 year have been ≥96% and as high as 98% (era 3) (Fig. 1). In eras 4 and 5, patient survival rates at 5 years were ≥90% and at 10 years, >78%. In each era, PTA recipients' patient survival rates were similar at 1 and 5 years to the rates in SPK or PAK recipients—but were higher at 10 years. In each era, the most common cause of death in primary PTA recipients was a cardio- or cerebrovascular event.

Graft survival

Graft survival rates at 1 year in primary PTA recipients significantly improved from 23% in era 0 to >80% in era 5 (Fig. 2). In eras 3, 4, and 5, graft survival rates at 5 years were between 50 and 60% and at 10 years, almost 40%. Those improvements were primarily due to two developments: *1*) a significant reduction in the 3-month technical complication rate, from 25% in era 0 to 8% in era 5, and *2*) a significant reduction in the 1-year immunologic graft loss rate: from 61% in era 0 to 4% in era 5 (Figs. 3 and 4).

Because a PTA is considered a highly "immunogenic" transplant, effective induction and maintenance protocols are essential for good outcomes. In era 5, PTA graft function was highest in recipients on anti–T-cell induction therapy with depleting antibodies and on SRL-based maintenance therapy ($n = 75$): graft survival rates were 94% at 1 year and 84% at 3 years. In our study, we analyzed only de novo SRL immunosuppression; conversions to SRL were very rare (<5%).

We conducted a subanalysis comparing PTA versus SPK recipients on depleting antibody induction therapy and maintenance immunosuppressive therapy with either TAC/MMF or SRL/TAC/MMF. In the TAC/MMF group, outcome was significantly better for SPK recipients. But in the SRL/TAC/MMF group, we found no difference in outcome between PTA and SPK recipients. The overall improved results for both groups were due to the decreased rates of early acute rejection episodes and of immunologic graft losses.

Causes of pancreas graft failure in era 5 differed by time posttransplant: within the first 3 months, technical failure was most common (≥70%); from 3 to 12 months posttransplant, acute rejection; and after 12 months, chronic and acute rejection as well as death with a functioning graft.

The most common cause of early technical failure in PTA recipients in era 5 was graft thrombosis (2.4%), followed by infection (0.4%) and leakage (also 0.4%). We found no difference in the

Table 1—*Primary PTA recipient characteristics by era*

	Era 0: 1966–1987	Era 1: 1987–1993	Era 2: 1994–1997	Era 3: 1998–2001	Era 4: 2002–2006	Era 5: 2007–2011
Recipients	136 (8)	143 (8)	158 (9)	332 (20)	507 (30)	424 (25)
Centers	20 (47)	26 (30)	31 (30)	40 (33)	64 (45)	68 (48)
Age (years)						
<30	57 (42)	47 (33)	33 (21)	53 (16)	76 (15)	63 (15)
30 to <45	72 (53)	81 (57)	103 (65)	189 (57)	269 (53)	209 (49)
≥45	7 (7)	15 (10)	22 (14)	90 (27)	162 (32)	152 (36)
Male sex	50 (37)	49 (34)	66 (42)	142 (43)	193 (38)	166 (39)
Race						
White	—	139 (97)	150 (95)	315 (95)	488 (96)	389 (92)
African American	—	0 (0)	2 (1)	6 (2)	7 (1)	19 (5)
Other	—	2 (1)	3 (2)	9 (2)	12 (3)	16 (3)
Missing	136 (100)	2 (1)	3 (2)	2 (1)	0 (0)	0 (0)
Diabetes type						
Type 1	—	4 (3)	137 (86)	137 (86)	473 (93)	401 (95)
Type 2	—	0 (0)	4 (3)	4 (3)	19 (4)	5 (1)
Other	—	2 (1)	4 (3)	4 (3)	15 (3)	18 (4)
Missing	136 (100)	137 (96)	13 (8)	13 (8)	0 (0)	0 (0)
Duct management						
Enteric drainage	69 (51)	5 (4)	50 (32)	158 (48)	359 (71)	339 (80)
Bladder drainage	38 (28)	138 (96)	106 (67)	173 (52)	137 (27)	76 (20)
Duct injection	18 (13)	0 (0)	2 (1)	0 (0)	5 (1)	1 (0)
Other	10 (8)	0 (0)	0 (0)	0 (0)	0 (0)	4 (1)
Missing	0 (0)	0 (0)	0 (0)	1 (0)	6 (1)	4 (1)
Enteric drainage: venous management						
Systemic	—	4 (80)	31 (62)	70 (44)	278 (77)	304 (90)
Portal	—	1 (20)	19 (38)	88 (56)	81 (23)	34 (10)
Missing	69 (100)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)
PRA (%)						
0–19	— (0)	124 (87)	144 (91)	300 (90)	444 (88)	342 (81)
≥20	— (0)	5 (3)	5 (3)	13 (4)	36 (7)	58 (14)
Missing	136 (100)	14 (10)	9 (6)	19 (6)	27 (5)	24 (5)
Induction therapy						
None	104 (76)	111 (78)	46 (29)	73 (22)	81 (16)	36 (8)
Nondepleting ABs	0 (0)	0 (0)	1 (1)	48 (14)	22 (4)	30 (7)
Depleting ABs	32 (58)	30 (31)	108 (68)	88 (27)	339 (67)	335 (79)
Both types of ABs	0 (0)	0 (0)	0 (0)	111 (33)	49 (10)	7 (2)
Missing	0 (0)	2 (1)	3 (2)	12 (4)	16 (0)	16 (4)
Maintenance protocol						
TAC and MMF	0 (0)	0 (0)	55 (35)	221 (67)	301 (59)	293 (69)
CSA and AZA	78 (57)	133 (93)	27 (17)	0 (0)	1 (0)	0 (0)
CSA and MMF	0 (0)	0 (0)	15 (9)	13 (4)	5 (1)	3 (1)
AZA alone	30 (22)	5 (4)	44 (29)	13 (4)	1 (0)	0 (0)
SRL based	0 (0)	0 (0)	0 (0)	22 (7)	101 (20)	77 (18)
Other	28 (21)	3 (2)	14 (9)	51 (15)	82 (16)	35 (8)
Unknown	0 (0)	2 (1)	3 (2)	12 (4)	12 (4)	16 (4)
Steroid-free protocol						
Yes	—	—	—	268 (81)	283 (56)	172 (41)
No	—	—	—	52 (16)	208 (41)	236 (56)
Missing	136 (100)	143 (100)	158 (100)	12 (4)	16 (3)	16 (3)

Data are *n* (%). ABs, antibodies; AZA, azathioprine.

early technical failure rate between recipients with enteric versus bladder drainage ($P = 0.51$). Because the demand for a PTA has traditionally not been as high as for an SPK transplant, PTA donors were younger, had fewer (if any) comorbidities, and underwent an even more stringent selection process. The most important risk factors for early technical failure were pancreas graft preservation time ≥12 h ($P = 0.05$), donor BMI >30 kg/m^2 ($P = 0.02$), and a low-volume transplant center (<10

Table 2—*Primary PTA donor characteristics by era*

	Era 0: 1966–1987	Era 1: 1987–1993	Era 2: 1994–1997	Era 3: 1998–2001	Era 4: 2002–2006	Era 5: 2007–2011
Donors	136 (8)	143 (8)	158 (9)	332 (20)	507 (30)	424 (25)
Age (years)						
<15	1 (1)	17 (12)	21 (13)	28 (8)	49 (10)	35 (8)
15 to <30	5 (4)	65 (45)	96 (61)	172 (52)	315 (62)	274 (65)
30 to <45	4 (2)	36 (25)	30 (19)	89 (27)	111 (22)	87 (21)
45 to <60	3 (2)	16 (11)	8 (5)	40 (12)	29 (6)	28 (7)
≥60	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Missing	122 (89)	8 (6)	3 (2)	3 (1)	3 (1)	0 (0)
Type						
Deceased	96 (71)	135 (94)	157 (99)	330 (99)	506 (100)	424 (100)
Living	40 (29)	8 (6)	1 (1)	2 (1)	1 (0)	0 (0)
Deceased donors: cause of death						
Trauma	—	97 (68)	130 (82)	202 (61)	353 (70)	291 (69)
Cardio- or cerebrovascular	—	36 (25)	22 (14)	95 (29)	86 (17)	74 (17)
Other	—	0 (0)	2 (1)	2 (1)	6 (1)	2 (0)
Missing	136 (100)	10 (7)	4 (3)	33 (9)	62 (12)	57 (13)
Pancreas preservation time (h)						
0 to <12	93 (68)	35 (24)	30 (19)	57 (17)	131 (26)	215 (51)
12 to <24	24 (18)	86 (60)	105 (66)	184 (55)	263 (52)	164 (39)
≥24	3 (2)	13 (9)	12 (8)	29 (9)	22 (4)	3 (0)
Missing	16 (12)	9 (6)	11 (7)	62 (19)	91 (18)	42 (10)
HLA-A, -B, -DR mismatches (*n*)						
0	3 (2)	4 (3)	2 (1)	6 (2)	10 (2)	3 (1)
1	1 (1)	4 (3)	7 (4)	20 (6)	17 (3)	6 (1)
2	0 (0)	17 (12)	35 (22)	51 (15)	46 (9)	21 (5)
3	5 (4)	42 (29)	42 (27)	77 (23)	104 (21)	55 (13)
4	3 (2)	33 (23)	24 (15)	66 (20)	106 (21)	95 (22)
5	4 (3)	23 (16)	30 (19)	70 (21)	144 (28)	100 (24)
6	4 (3)	9 (6)	11 (7)	37 (11)	80 (16)	73 (17)
Missing	116 (85)	11 (8)	7 (4)	5 (2)	0 (0)	71 (17)

Data are *n* (%).

PTA recipients in 5 years). Of note, some transplants may be incorrectly classified as an early technical failure (thus resulting in an overestimate) because of severe early rejection and associated thrombosis.

Major risk factors for immunologic graft loss included early acute rejection episodes ($P = 0.02$), African American race ($P = 0.04$), recipient age <30 years ($P < 0.001$), and female sex ($P = 0.05$). The use of TAC/MMF or SRL significantly lowered the risk of immunologic graft loss. However, the risk was not affected by any of the following: type of drainage (bladder vs. enteric), late acute rejection episodes, steroid avoidance, HLA matching, panel-reactive antibody (PRA) class 1 ≥ 20%, and transplant center volume. In era 5, the incidence of acute rejection episodes was significantly lower for primary PTA recipients on SRL/TAC/MMF maintenance therapy than for those on TAC/MMF.

Retransplants

The PTA retransplant rate decreased from 17% in era 1 to 11% in era 5. Nonetheless, in era 5, the pancreas graft function rate in retransplant recipients was not as favorable as the rate in primary PTA recipients. The graft survival rate at 1 year in retransplant recipients in era 5 was 55% (comparable to the rate in primary PTA recipients in era 1).

The cause of primary graft failure had no impact on retransplant outcomes, but the timing of the retransplant did have an impact. PTA recipients who underwent a PTA retransplant within 2–12 months after primary graft failure had a significantly higher graft survival rate (76% at 1 year after their retransplant) than those who did so either very early (<2 months after primary graft failure: 58% at 1 year after retransplant) or later (>1 year after primary graft failure: 49% at 1 year after retransplant).

Kidney transplant rate

Thanks largely to improvements in patient care and immunosuppressive therapy, the need for a subsequent kidney transplant has significantly decreased in primary PTA recipients: from a rate of 21% at 5 years in era 2 to only 6% in era 4 (Fig. 5). In addition, in eras 4 and 5, more PTA recipients had creatinine clearance

Table 3—*Outcome by immunosuppressive protocol, 2005–2009*

	TAC/MMF		SRL/TAC/MMF	
	PTA	SPK	PTA	SPK
n	255	2,339	55	129
Technical failure rate, 3 months posttransplant	3.1	6.1	5.5	4.6
Graft survival rate (months posttransplant)				
6	93.1	88.9	92.5	91.5
12	87.7	86.8	90.2	90.6
24	75.2	82.8	83.1	88.7
Immunologic graft loss rate (months posttransplant)				
6	1.3	1.4	0.0	0.8
12	4.7	2.4	2.5	0.8
24	10.6	3.7	10.2	1.9
Acute rejection episode rate (months posttransplant)				
1 to <6	17.0	5.8	2.1	2.5
6 to <12	7.4	3.1	2.5	0.9
Kidney transplant or pancreas retransplant rate, 24 months posttransplant	1.9	0.4	0.0	0.0

Data are percent.

>70 mL/min/1.73 m^2 pretransplant (increasing their ability to tolerate the nephrotoxic side effects of lifelong maintenance immunosuppression).

CONCLUSIONS—The significant improvement in outcomes for PTA recipients over the past four decades has gone almost unnoticed: it has received little attention from diabetologists, endocrinologists, and other health professionals involved in the care of diabetic patients. Since 1966, only ~8% of all pancreas transplants have been in PTA recipients. Even though 103 transplant centers (62% of the total number of such centers) have performed at least one PTA, only a few have published their results (9,10).

It is important to emphasize that a PTA is not a procedure for every nonuremic, insulin-dependent patient. Most transplant centers offer a PTA only to patients with labile or brittle diabetes, defined as patients with *1*) recurrent hypoglycemic episodes and/or hypoglycemic unawareness and *2*) failure to improve on intensive exogenous insulin administration, including insulin pumps and other devices.

Despite its invasive surgical nature, a PTA has become an extremely safe procedure. The risk of death within the first year posttransplant is now <2%—less than the risk of death on the waiting list while waiting for a PTA (11,12). According to the newest analysis of the large population-based Allegheny County Type 1 Diabetes Registry (for patients diagnosed with T1DM from 1965 to 1979), the overall mortality rate is 812 deaths/100,000 person-years and for PTA recipients, only 320 deaths/100,000 (13).

The PTA surgical technique has undergone significant changes since 1966. Enteric drainage, as in the early eras, is now again the most common technique for managing exocrine secretions, as a consequence of improved immunosuppressive therapy with TAC and MMF. In contrast, in era 1, which was dominated by cyclosporine (CSA) maintenance immunosuppression, the less physiologic bladder drainage was the preferred technique; the reason was that exocrine rejection precedes endocrine rejection by several days, so a diagnosis of hypoamylasuria allowed successful rejection treatment before hyperglycemia could occur. By era 5, the vast majority of PTA recipients underwent systemic drainage—not portal drainage (despite systemic drainage's association with hyperinsulinemia).

Historically, graft survival rates in PTA recipients had trailed the rates in SPK recipients, in part because of the absence of a simultaneous kidney transplant in PTA recipients. In SPK recipients, kidney graft function is frequently used as a harbinger of rejection, allowing initiation of successful rejection treatment before the pancreas graft is affected. However, in era 5 (2007–2011), graft survival rates in PTA recipients on SRL were as high as 94% at 1 year and 84% at 3 years—most definitely comparable with the rates in SPK recipients (7).

In light of the most recent IPTR data (era 5), a PTA should be proactively

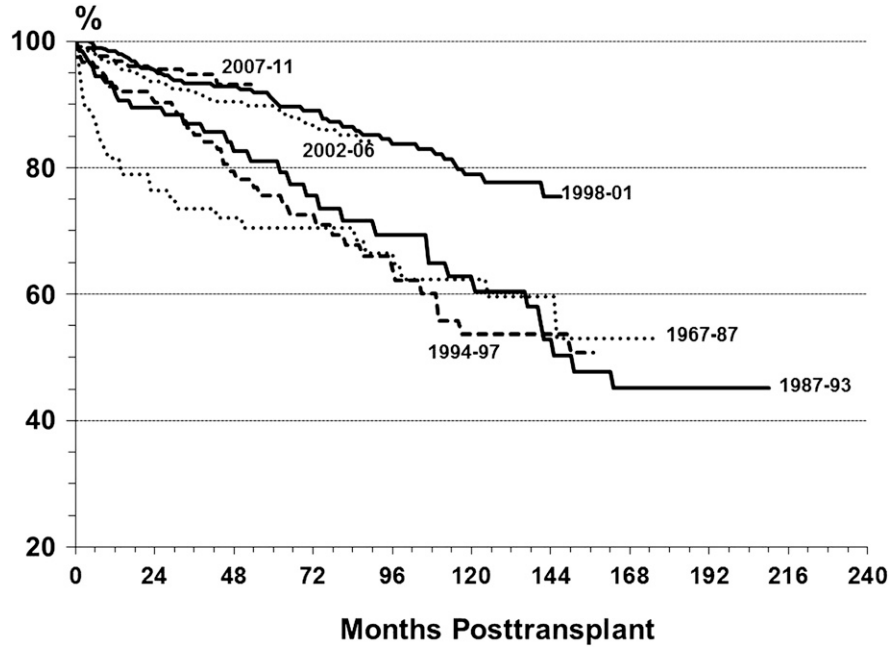

Figure 1—*Patient survival rates in primary deceased donor PTA recipients by era.*

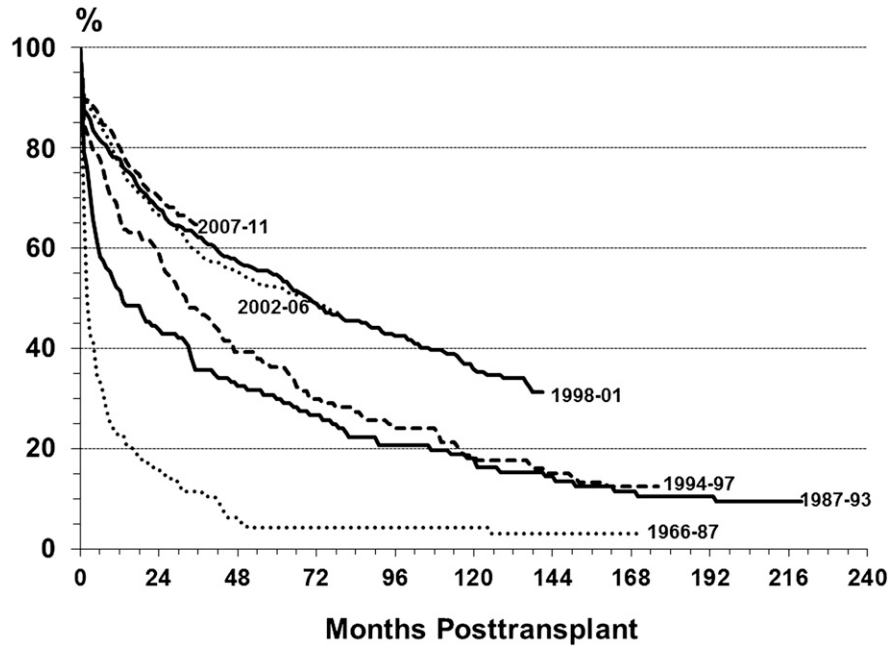

Figure 2—*Pancreas graft survival rates in primary deceased donor PTA recipients by era.*

offered to patients with brittle diabetes at an early stage of their disease. Once secondary complications develop, the timeline of nephropathy progression until end-stage renal disease is difficult to predict, but end-stage renal disease greatly increases the risk of death on the waiting list: at 4 years, the waiting list mortality for SPK candidates is >40% compared with ~10% for nonuremic PTA candidates (11). The development of (advanced) secondary diabetes complications not only decreases life expectancy but also impairs quality of life of transplant candidates. Thus, once intensive insulin treatment attempts fail for a patient with brittle diabetes, he or she should be listed early, in order to avoid progression of diabetic nephropathy and to allow for selection of an optimal donor.

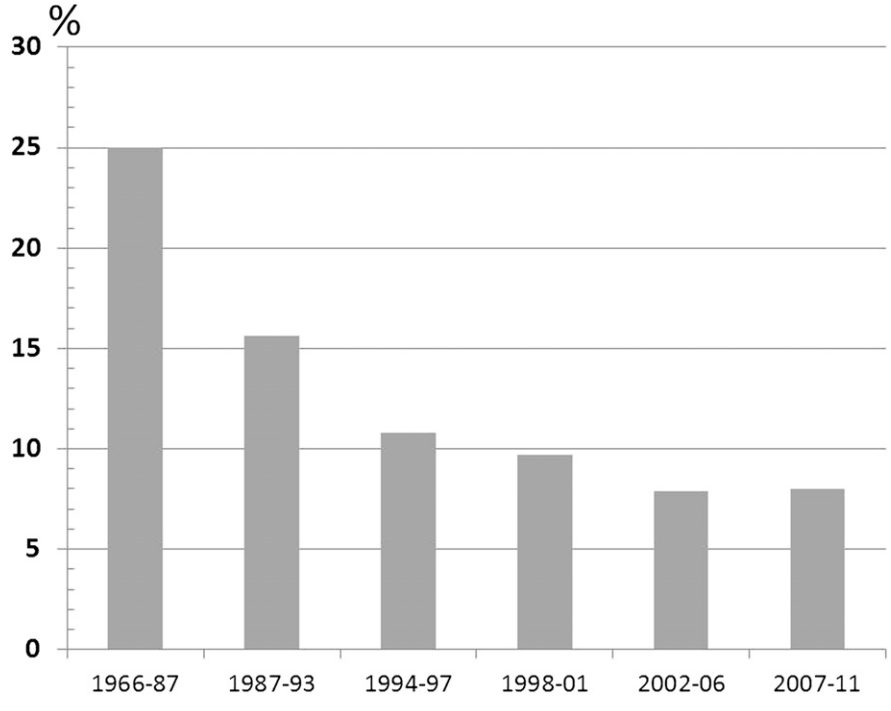

Figure 3—*Technical failure rates in the first 3 months posttransplant by era.*

Limited data are available on avoiding the development of, or halting the progression of, secondary complications in PTA recipients because of the pretransplant paucity of symptoms and findings in this category. For SPK and PAK recipients, a plethora of literature demonstrates a significant posttransplant improvement in diabetes complications, but similar reports on nephropathy, neuropathy (autonomic and peripheral), retinopathy, and cardiac and vascular disease are scarce for PTA recipients (5,12–18).

The financial benefits of a successful PTA have not been systematically studied but, in our view, must be taken into consideration. Most PTA recipients do not require a subsequent kidney transplant or cardiovascular procedure. As more transplant centers have started to offer a PTA to patients with creatinine clearance >70 mL/min/1.73 m^2, the risk of a subsequent kidney transplant has also diminished; in the past, an average decrease in creatinine clearance of 29–38% at 1 year posttransplant was reported in single-center studies (15,19). In the most recent eras (eras 4 and 5) of our study, the need for a subsequent kidney transplant because of nephrotoxic immunosuppressants decreased to 6% at 5 years after a PTA. In PTA recipients, long-term normoglycemia (>10 years) has been reported to reverse glomerular and cortical lesions of diabetic nephropathy. One long-term follow-up study of PTA recipients, in fact, revealed that glomerular structure had returned to normal at 10 years posttransplant (14).

In our IPTR study, we found that the significant reduction in the technical and immunologic failure rates (due to improved operative procedures and immunosuppressive therapies) resulted in a significantly diminished graft loss rate: in era 5, only 6% of PTA recipients on SRL and 16% on TAC had lost their graft at 1 year. The reduction in the immunologic graft loss rate resulted from evolving immunosuppressive regimens, beginning with the introduction of TAC and MMF in the 1990s and continuing with the more recent addition of SRL. In our experience, we have learned that most PTA recipients believe that managing immunosuppression is easier and more satisfactory than repeated daily glucose measurements and insulin injections (and, even more important, than the constant worry about pronounced hypoglycemia).

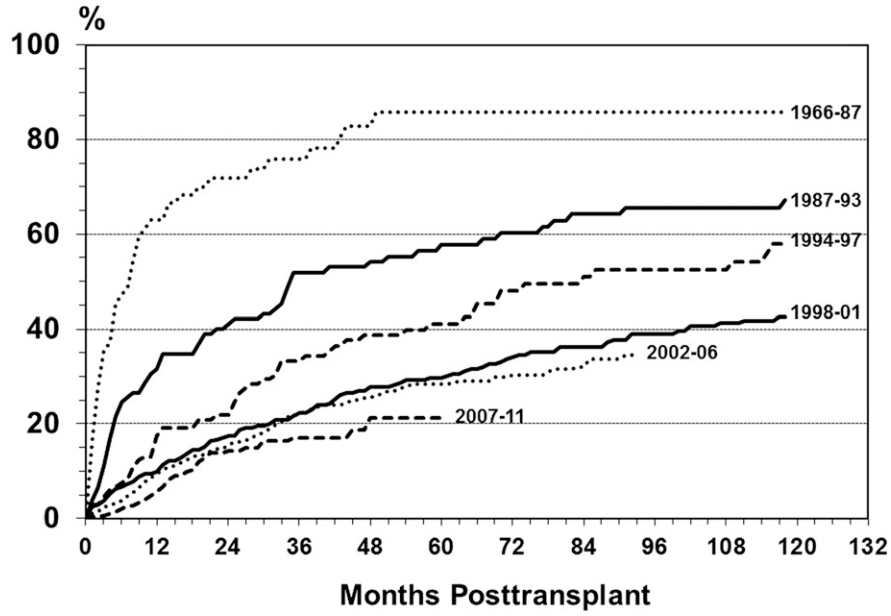

Figure 4—*Immunologic graft failure rates in primary deceased donor PTA recipients by era.*

With regard to outcomes and quality of life, pancreas transplants are frequently compared with islet transplants, which are less invasive. It is important to emphasize that these two types of transplants are not mutually exclusive but, rather, complementary. The results of islet transplants have undoubtedly improved over the past decade, but overall islet graft function (specifically, long-term function) still trails overall pancreas graft function (20,21). We recommend an algorithm that favors an islet transplant in a patient with brittle diabetes who has a high surgical risk but favors a pancreas transplant in a patient who has a low surgical risk. Solitary donor pancreases are not in short supply, yet only one donor organ is required for a successful PTA; in contrast, up to four donor pancreases have been used for a single islet recipient and, unfortunately, with a less favorable long-term outcome.

Note also that the primary end point for current islet transplant trials is not insulin independence; instead, the primary end points are a reduction in the incidence and severity of hypoglycemic events, a reduction in exogenous insulin requirements, and an amelioration of HbA_{1c} levels (22). Islet transplants rarely result in long-term insulin independence. Recently, Maffi et al. (23) reported a higher rate of insulin independence in PTA recipients (75%) than in islet transplant alone recipients (59%)—despite the use of up to three donor pancreases for each islet transplant alone recipient.

In conclusion, PTA results since the first such procedure more than four decades ago have significantly improved, with patient survival rates of almost 100% and graft function rates of up to 94% at 1 year. Despite improvements in intensive insulin therapy, in insulin-delivering devices, and in islet transplants, a PTA is currently the only treatment option for patients with brittle diabetes who can achieve long-term normoglycemia and avoid not only hypoglycemia but also, possibly, the development or progression of secondary diabetes complications.

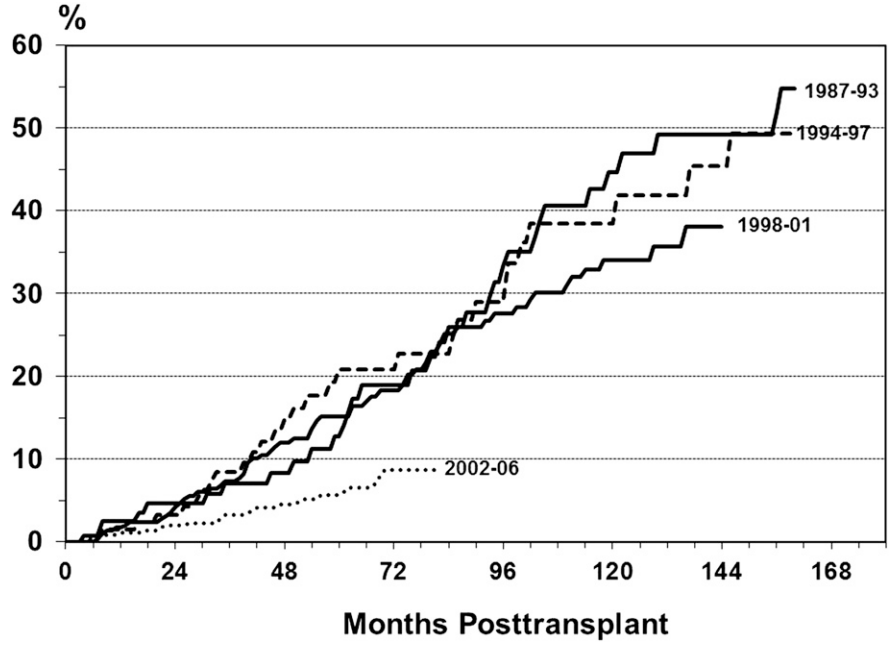

Figure 5—*Kidney transplant rates in primary deceased donor PTA recipients by era.*

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R.W.G.G. and A.C.G. researched data and wrote the manuscript. R.W.G.G. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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