Table 1. Outcomes reported in the literature for whole-organ pancreas transplantation contrasted with kidney transplant only or medical management in patients with type 1 diabetes.

	Pancreas Transplant (+/- Kidney Transplant)	Kidney Transplant Alone	Medical Management
Hypoglycemia unawareness[a]	Return to normoglycemia avoids hypoglycemia; symptom awareness returned to near normal in hypoglycemic clamp studies	Strict glycemic control increases episodes of hypoglycemia unawareness and decreases symptom recognition	Strict glycemic control increases episodes of hypoglycemia unawareness and decreases symptom recognition
Nephropathy 5 years	No significant change[b]	Significant changes in 45.8% over 2.5 years[c]	Total mesangial volume increased significantly over 5 years[c]
10 years	Indicators returned to normal or baseline[b]		
Neuropathy Motor nerve conduction[d]			(Progression at usual rate)
% improved, 7 years	65	6	
% stable, 7 years	23	25	
Sensory nerve conduction[d]			
% improved, 7 years	41	0	
% stable, 7 years	24	37	
Cardiorespiratory reflex[d]			
% improved, 7 years	47	20	
% stable, 7 years	47	20	
% patients normotensive, 18 months[e]	34	0	0
Retinopathy[f]			
% improved, 3 years	21	6	(Progression at usual rate)
% stable, 3 years	62	49	
Tacrolimus toxicity[g]			N/A
% nephrotoxicity	20		
% neurotoxicity	19		
% gastrointestinal toxicity	12		
% diabetogenicity	12		
Mycophenolate mofetil toxicity	25 (total)[h]		
% CMV infection	7[i]		
% myelosuppression			
% gastrointestinal toxicity			

[a]Robertson, 1999
[b]Fioretto, Steffes, Sutherland, et al., 1998
[c]Fioretto, Mauer, Bilous, et al., 1993; Wilczek, Jaremko, Tyden, et al., 1995
[d]Navarro, Sutherland, and Kennedy, 1997
[e]Elliott, Kapoor, Parker, et al., 2001
[f]Koznarova, Saudek, Sosna, et al., 2000
[g]Stratta, 1999
[h]Stratta, Shokouh-Amiri, Egidi, et al., 2003
[i]Gruessner and Sutherland, 1998

allotransplant, 94 percent were alive and 19 percent retained some evidence of islet function (not shown; Islet Transplant Registry, 2001). However, the proportion remaining insulin independent at 3 years was not reported. In a later update (Brendel, Hering, Schultz, et al., 2002), the Registry reported functional graft survival in 24 percent, insulin independence in 4 percent, and overall survival in 95 percent of 235 patients followed for at least 3 years.

Table 2. Outcomes of Islet Allografts Transplanted 1990-1999[a]

Patient Group	n included	n (%) with C-peptide ≥0.5 ng/mL at 1 year	n (%) insulin independent at 1 year	n (%) patients alive at 1 year
all reported	237	98 (41)	25 (11)	227 (96)
SIK	131	61 (47)	12 (9)	126 (96)
IAK	87	34 (39)	13 (15)	85 (98)
ITA	9			
SIL	7			
≥ 6000 IEq/kg	146	63 (43)	25 (17)	
< 6000 IEq/kg	78	30 (38)	0 (0)	
≤8 hrs. cold ischemia	162	73 (45)	21 (13)	
>8 hrs. cold ischemia	62	18 (29)	3 (5)	
no T-cell AB	40	9 (23)	1 (3)	
ATG/ALG/IL-2R	162	80 (49)	23 (14)	
OKT3	30	9 (30)	1 (3)	
yes, all 4 criteria	67	35 (52)	16 (24)	
no, ≥1 criterion	170	63 (37)	9 (5)	
1990–93 transplants	82	31 (38)	7 (9)	
1994–97 transplants	118	43 (36)	9 (8)	
1998–99 transplants	37	25 (68)	5 (14)	

[a]Note: Data presented here are from pre-Edmonton protocol transplants

The overwhelming majority of patients given islet allotransplants in the pre-Edmonton era were treated either simultaneously with (simultaneous islet/kidney, SIK, 55 percent) or after (islet after kidney, IAK, 37 percent) a kidney transplant (Islet Transplant Registry, 2001). Only nine patients (4 percent) received an islet transplant alone (ITA). Immunosuppression regimens for most patients transplanted using pre-Edmonton protocols likely were primarily based on those used to manage kidney transplant recipients. The subsequent update (Brendel, Hering, Schultz, et al., 2002) included 138 SIK patients and 90 IAK patients. Among these, functional graft survival at 1 year was 51 percent and 40 percent, respectively, while insulin independence at 1 year was 9 percent and 15 percent, respectively.

Registry analyses identified several factors that influence outcomes of islet transplants (Islet Transplant Registry, 2001). These include the site of the transplant (data not tabulated; liver [n = 220] versus others [n = 17]); the number of islet equivalents transplanted per kilogram of body weight (≥6000 versus <6000); the duration of cold ischemia from cross-clamping to islet isolation (≤8 hours versus >8 hours); and the regimen used to induce immunosuppression (no anti-T cell antibody versus ATG, ALG, or antibody to IL-2R versus OKT3). A substantially greater proportion of transplants that were favorable on all four of these predictive criteria than of those that failed on one criterion or more remained functional (31 percent versus 9 percent, respectively) and maintained insulin independence (24 percent versus 5 percent, respectively) at 1 year after treatment (Table 2). Note also that success was more frequent among those patients transplanted in years 1998 and 1999 than among those transplanted earlier.

The Registry reports did not include any data on effects of insulin independence following islet allotransplantation on diabetic complications. Fiorina, Folli, Maffi, and co-workers (2003) followed 37 islet allotransplanted type 1 diabetic kidney transplant patients, of whom, 24 maintained islet function (C-peptide >0.5 ng/mL) for longer than 1 year and 13 lost or never achieved islet function during the first year, for an average of 63 months. Patients with successful islet transplants had significantly reduced: cardiovascular and all-cause mortality; microvascular-endothelial injury; atherothrombotic risk factors; and renal damage (as measured by urine albumin excretion) compared to those whose transplants were not successful (Table 3). Additionally, the cardiovascular death rate for successful islet transplant patients was similar to that of a control group of whole-organ pancreas transplant patients, and better than that of kidney-alone transplant patients. Patients with successful islet transplants had significantly lower exogenous insulin requirements than those with unsuccessful transplants at all timepoints.

Table 3. Long-term outcomes of kidney-islet, kidney-pancreas organ, kidney alone transplantation and uremic type 1 diabetes with no transplantation (Fiorina, Folli, Maffi, et al., 2003).

	Kidney-Islet Transplant (All)	Kidney-Islet Transplant, Successful	Kidney-Islet Transplant, Unsuccessful	Kidney-Pancreas Transplant	Kidney Alone Transplant	Uremic Type 1 Diabetic
Patient survival (%)						
1 year	95	100	84	93	92	94
4 years	86	100	75	86	74	67
7 years	68	90	45	74	56	37
Cardiovascular death (%)	18	5	46	8	19	16
Exogenous insulin required (units/day)						
1 year		19	46			
4 years		23	52			
7 years		18	36			
Patients with increased urine albumin excretion (%)		4	46			

An earlier small study (n = 8) reported that stable islet function after an allograft (n = 6) significantly reduced HbA_{1c} concentrations and insulin requirements (Alejandro, Lehmann, Ricordi, et al., 1997). Over 6 years of followup, these patients also remained free of the severe hypoglycemic episodes observed in the Diabetes Control and Complications Trial, even though they were not insulin independent. Other investigators also have reported that functional islets after allotransplants decrease hypoglycemia unawareness and improve hormonal counter-regulation in response to hypoglycemia (Meyer, Hering, Grosmann, et al., 1998).

Edmonton Protocol and Subsequent Research

In 2000, Shapiro, Lakey, Ryan, and co-workers at the University of Alberta in Edmonton, Canada, published the results of a patient series of islet transplants using a modified protocol, thereafter known as the Edmonton protocol. The key elements of this protocol were the minimization of cold ischemia time after pancreas removal; the preparation of islets in medium free of animal protein; the transplantation of at least 9,000 IEq/kg (which usually entails islet transplants from two donor organs**)**; and an immunosuppressive regimen that replaced

- In the U.S., islets are currently obtained from the small number of donor organs that have not been utilized for whole organ transplantation. Alternative sources of islets, such as pancreata obtained from marginal donors and rejected for whole-organ transplant (Ricordi, Fraker, Szust, et al., 2002) or nonheart beating donors (Markmann, Deng, Desai, et al., 2003), have been tried with some success. The study of xenotransplants in humans remains controversial (Valdes-Gonzalez, Elliot, Dorantes, et al., 2002), but is proceeding in animal models. Ongoing basic and clinical research is examining the potential of genetic engineering of nonpancreatic cells to produce insulin (Shen, Qin, Xiao, et al., 2002); and of transforming stem cells or pancreatic ductal cells into islets (Campbell, 2002; Lumelsky, Blondel, Laeng, et al., 2001).

- Various methods that may reduce or eliminate the need for lifelong immunosuppression are currently under study. These include costimulatory blockade of T-cell activation to induce tolerance (Parker, Greiner, Phillips, et al., 1995; Kawai, Sogawa, Koulmanda, et al., 2001; Adams, Shirasugi, Durham, et al., 2002) and immune isolation by islet encapsulation (de Vos, Hamel, Tatarkiewicz, et al., 2002; Sharp, 2002).

Trials testing various protocols are currently underway; examples are summarized in Table 4.

Table 4. Examples of ongoing clinical trials of islet transplant protocols.

Study ID Number	Phase	Location	Purpose
NCRR-M01RR00400-0672	I/II, recruiting	U Minnesota	Determine the safety, tolerability, immune activity, and pharmacokinetics of hOKT3 gamma1 (Ala-Ala) administration for the prevention of autoimmune destruction and rejection of allogeneic islet transplants
(Sponsored by NIDDK)	II	U Miami	Determine the efficacy of nonglucocorticoid, low-dose tacrolimus plus sirolimus immunosuppression with vs. without the administration of infliximab in islet-alone transplantation in type 1 diabetic patients.
NIH # DK 56953-03	II	U Miami	Determine the efficacy of islet transplantation alone and with CD34+ enriched donor bone marrow cell infusion in patients with type 1 diabetes mellitus; glucocorticoid-free regimen.
JDFI-Penn Comprehensive Islet Transplantation Program		U Pennsylvania	Application of the Edmonton protocol in patients who have already received a renal allograft. "Edmonton" immunosuppression is modified to include patients receiving low doses of glucocorticoids and other combinations of maintenance immunosuppression.
Northwestern U General Clinical Research Center #715	?	Northwestern U	Test induction with 15-deoxyspergualin (DSG) with the Edmonton protocol to determine efficacy of islet transplantation from a single donor. 15-DSG is hypothesized to inhibit factors responsible for the generation of primary islet nonfunction.
NCRR-M01RR00036-0775	I	Washington U	Determine the efficacy of oral antidiabetic drugs in conjunction with the Edmonton islet transplant protocol to allow for successful transplantation of islets from a single donor pancreas; and expand the Edmonton protocol to diabetic patients who are also receiving kidney transplantation and determine the effect on kidney function and blood glucose control.
NCRR-M01RR00036-0779	I	Washington U	Determine how immunosuppressive regimens affect glucose metabolism and insulin utilization in diabetic patients who have received both kidney and islet transplants and compare to nondiabetic patients who have received only kidney transplants

- Hypoglycemic episodes: Hypoglycemia unawareness and life-threatening hypoglycemic episodes can be a consequence of strict glucose control with exogenous insulin, and are indications for pancreas whole-organ or islet transplantation. Elimination of hypoglycemic episodes in conjunction with glycemic control is also a direct measure of transplant success.

- Quality of life: Islet transplantation can improve quality of life for patients by eliminating hypoglycemic and hyperglycemic episodes, the need for insulin injections, frequent self-monitoring of blood glucose levels, and dietary restrictions. General and specific standardized measures of quality of life may include the Health Utilities Index, SF-36, Immunosuppressant Quality of Life (QOL) Survey, and Hypoglycemia Fear Survey (Johnson, 2002). Characteristics of these instruments are briefly summarized in Table 5.

Although sustained euglycemia may be of highest clinical interest, in the absence of well-controlled studies, insulin independence may be the most persuasive measure available to establish the success of the procedure.

Table 5. Measures for evaluation of transplantation and quality of life.

Survey	Description	Reference
36-item Short Form health survey (SF-36)	Evaluates general quality of life. Survey addresses 8 areas of health status, summarized in 2 component scores: *Physical component:* physical functioning; physical limitations; pain; general health perception *Mental component:* vitality; social functioning; emotional limitations; mental health	Terada and Hyde, 2002; Ware and Sherbourne, 1992
Health Utilities Index Mark 2 (HUI2)	Comprehensive description of health status in 8 core domains: Vision; hearing; speech; ambulation; dexterity; emotion; cognition; pain.	Furlong, Geeny, Torrance, et al., 2001
Hypoglycemia Fear Survey (HFS)	Addresses behaviors and worries related to potential hypoglycemic episodes. Increased awareness of hypoglycemia correlates with decreased HFS scores in validation studies.	Cox, Irvine, Gonder-Frederick, et al., 1987
Immunosuppressant QOL Survey (Memphis Survey)	Evaluates side effects of immunosuppressive therapy for organ transplantation. Employs 4 subscales: emotional burden, life/role responsibilities, mobility, gastrointestinal distress.	Winsett, Stratta, Alloway, et al., 2001

Improvement in long-term diabetic outcomes is the measure of ultimate success of islet transplantation in type 1 diabetes. The objective is to reduce or eliminate long-term diabetic outcomes such as retinopathy, neuropathy, nephropathy, and cardiovascular disease. Transplantation after complications have already become apparent may not be able to reverse or even stabilize the process. Transplantation prior to complications is more likely to delay or preclude their occurrence, but studies will require a minimum of 5–10 years in order to collect robust data on clinical outcomes.