Improvement in Outcomes of Clinical Islet Transplantation: 1999–2010

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OBJECTIVE—To describe trends of primary efficacy and safety outcomes of islet transplantation in type 1 diabetes recipients with severe hypoglycemia from the Collaborative Islet Transplant Registry (CITR) from 1999 to 2010.

RESEARCH DESIGN AND METHODS—A total of 677 islet transplant-alone or islet-after-kidney recipients with type 1 diabetes in the CITR were analyzed for five primary efficacy outcomes and overall safety to identify any differences by early (1999–2002), mid (2003–2006), or recent (2007–2010) transplant era based on annual follow-up to 5 years.

RESULTS—Insulin independence at 3 years after transplant improved from 27% in the early era (1999–2002, $n = 214$) to 37% in the mid (2003–2006, $n = 255$) and to 44% in the most recent era (2007–2010, $n = 208$; $P = 0.006$ for years-by-era; $P = 0.01$ for era alone). C-peptide ≥0.3 ng/mL, indicative of islet graft function, was retained longer in the most recent era ($P < 0.001$). Reduction of HbA_{1c} and resolution of severe hypoglycemia exhibited enduring long-term effects. Fasting blood glucose stabilization also showed improvements in the most recent era. There were also modest reductions in the occurrence of adverse events. The islet reinfusion rate was lower: 48% by 1 year in 2007–2010 vs. 60–65% in 1999–2006 ($P < 0.01$). Recipients that ever achieved insulin-independence experienced longer duration of islet graft function ($P < 0.001$).

CONCLUSIONS—The CITR shows improvement in primary efficacy and safety outcomes of islet transplantation in recipients who received transplants in 2007–2010 compared with those in 1999–2006, with fewer islet infusions and adverse events per recipient.

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Allogeneic islet transplantation offers a minimally invasive option for β-cell replacement in people with type 1 diabetes complicated by recurrent severe hypoglycemia and/or marked glycemic lability. Before 1999, less than 10% of islet transplant recipients achieved insulin independence (1). In 2000, the Edmonton Protocol for islet transplantation achieved insulin independence in seven consecutive participants who received islets from more than one donor under a steroid-free immunosuppression regimen (2). After this proof-of-concept success, islet transplant programs expanded in North America and elsewhere (3). These centers have offered evolving strategies of islet preparation and immunosuppression, although the limited resources available have prevented anything but independent Phase I/II attempts to standardize processes, achieve success, and stabilize outcomes.

Even in the absence of insulin independence, an islet transplant can protect type 1 diabetic recipients from severe hypoglycemic episodes as long as residual islet graft function is maintained, as proven by restoration of C-peptide production (4). Despite this compelling rationale, islet transplantation for type 1 diabetes has produced variable success and elusive durability, has frequently required multiple donor organs, and has balanced one disease load—severe hypoglycemia—with another—long-term immunosuppression. In some countries outside the U.S., islet transplantation has been designated and funded as nonexperimental over the last decade, where the trade-off between severe hypoglycemia and the risks of immunosuppression was felt to be

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justifiable in carefully selected patients. Islet transplantation remains an experimental procedure in the U.S. and awaits formal results of ongoing Phase III trials to justify biologic licensure and transition to standard of care.

The Collaborative Islet Transplant Registry (CITR) has been established to monitor progress and safety of islet transplantation by using data from the U.S., Canada, and several centers in Europe and Australia supported by the Juvenile Diabetes Research Foundation (JDRF). The CITR represents the most complete collection of information on islet transplantation in the last decade. The purpose of the present inquiry is to describe trends of primary outcomes and safety profiles of islet transplantation according to cohorts defined by the year of first islet infusion (early: 1999–2002; mid: 2003–2006; or recent: 2007–2010). The analysis comprises allogeneic islet-alone and islet-after-kidney (IAK) transplants performed through 31 December 2010 with data updated through 4 January 2012.

RESEARCH DESIGN AND METHODS

Patients

The CITR is the comprehensive islet transplant registry for 27 National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)–funded North American and JDRF-funded European and Australian centers since 1999, comprising 81% of all allogeneic islet transplants conducted as single-arm Phase I/II trials or standard of care. Patients and methods are fully described in previous and current CITR Annual Reports (3), which are publicly available. In brief, recipients of allogeneic islet transplants typically are aged between 18 and 65 years. All have had type 1 diabetes for >5 years, and >95% had documented negative fasting C-peptide (<0.3 ng/mL) and very problematic diabetes control, including hypoglycemia unawareness complicated by episodes of severe hypoglycemia and/or marked glycemic lability characterized by wide swings of blood glucose levels, often with consistently elevated HbA_{1c} levels (>8%). This report includes no cases of islet transplantation after total pancreatectomy.

The Registry collects information on the pancreas donor(s), islet processing and testing, immunosuppression and concomitant medications, severe hypoglycemic episodes, HbA_{1c}, fasting blood glucose and C-peptide levels, daily insulin doses, vital status, islet graft dysfunction and loss, reportable adverse events graded 3, 4, and 5 according to the Terminology Criteria for Adverse Events of the Clinical Islet Transplantation Consortium (CIT) (5), and serious adverse events (6). Islet recipients enrolled in CIT protocols consenting to have their data shared with the CITR are registered in the CITR and included in the CITR reports.

CIT protocols comprise a series of Phase II and Phase III clinical trials designed to test current immunosuppressive strategies and management practices and pursue licensure for clinical islet transplantation in the U.S. The CIT data are coordinated by the University of Iowa Clinical Trials and Data Management Center, William Clarke, PhD, Director, and are made available to the CITR through collaborative agreements via the common sponsor, the U.S. NIDDK. CITR data are rigorously monitored by the Data Coordinating Center, The EMMES Corporation, Rockville, Maryland, to comply with U.S. Food and Drug Administration Part 21 Code of Federal Regulations requirements. Site participation in the Registry requires local research ethics board approval, strict assurance of patient-identifier confidentiality, and written informed consent by the islet recipients. The CITR Publications and Presentations Committee approved the manuscript.

Statistics

At preinfusion and at each scheduled follow-up visit, five coprimary end points were assessed by laboratory measurements or clinical evaluations: basal C-peptide (further divided as ≥0.3 vs. <0.3 ng/mL), including reported complete graft loss (defined as fasting C-peptide consistently undetectable with stimulated C-peptide <0.3 ng/mL by local assay without subsequent recovery to ≥0.3 ng/mL or reinfusion, also denoted as "no function"); independence from exogenous insulin for ≥14 consecutive days; HbA_{1c} (further divided as <6.5% and/or a drop by two percentage points or more); fasting blood glucose (further divided as 60–140 vs. <60 or >140 mg/dL); and absence of severe hypoglycemia episodes (requiring assistance of another person). The scheduled times for each infusion were immediately before transplant, 7 days, 1 month, 6 months, and annually thereafter, which was reset at each subsequent infusion. Annual time points from the last of one or more infusions per recipient were used in this analysis. Except for complete graft failure, each of these outcomes can occur, relapse, and then reoccur during follow-up, although with relatively long periods of stable status; hence, they are analyzed as prevalence (percentage) at each follow-up after the last infusion. Complete graft failure cannot remit by definition; therefore, this outcome was analyzed by failure-time techniques. When direct data were missing but graft function was known to have been previously lost and not restored, insulin independence was set as dependent and C-peptide was set at 0. Otherwise, missing data were omitted (i.e., treated as missing at random) in the computations and modeling.

For infusions given the same day from two to three different donors, the donor, procurement, processing, and isolation characteristics were summarized over the multiple donors (e.g., donor ages were averaged, total islet equivalents infused were summed, etc.) The information was summarized again over two to six infusion events per recipient. Trapped (embedded) islets are expressed as a percentage of total islet count in the preparation. Immunosuppression agents were noted as each given or not at each infusion and during the follow-up. Each recipient was classified into induction and maintenance combination categories as indicated in Table 1. All available recipient, donor, islet, and immunosuppression variables were used in the various analyses as possible predictors of the primary outcomes.

Generalized estimating equations with repeated measures per recipient were used to assess the effect of era (1999–2003,

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A slide set summarizing this article is available online.

Table 1—*Recipient, donor, islet, and immunosuppression characteristics, based on numbers with data*

	Era						
	1999–2002		2003–2006		2007–2010		
	N	%	*N*	%	*N*	%	*P*
Recipient characteristics	214		255		208		
ITA	183	85.5	202	79.2	190	91.4	
Female sex	123	57.5	151	59.4	127	63.2	
C-peptide ≥0.3 ng/mL	36	23.8	28	15.1	12	8.3	<0.01
Baseline hypoglycemia status							
No episodes or aware	20	11.4	16	6.8	11	10.3	
Baseline							
Insulin pump or ≥3 insulin injections/day	162	95.9	220	99.1	100	98.0	
IA-2 autoantibody (ICA 512, +)	35	17.0	35	13.9	11	9.1	
GAD 65 autoantibody (GAA, +)	47	29.9	58	34.1	24	31.6	
Insulin autoantibody (IAA, +)	64	31.1	104	41.3	30	24.8	<0.01
Blood pressure medication	76	41.3	105	44.5	58	53.2	
Lipid-lowering medication	31	17.2	97	41.1	49	45.4	<0.01
Peripheral neuropathy	71	39.7	89	38.5	32	30.5	
Autonomic neuropathy	43	24.9	46	21.2	20	20.6	
Class 1 panel reactive antibody (+)	17	12.6	31	16.6	18	22.8	

	N	Mean	SE	*N*	Mean	SE	*N*	Mean	SE	
Age at baseline (years)	214	41.8	0.6	255	44.7	0.6	202	47.8	0.7	<0.01
Diabetes duration (years)	202	27.3	0.7	251	29.6	0.6	168	31.4	1.0	<0.01
BMI (kg/m^2)	179	23.4	0.2	231	23.3	0.2	136	23.7	0.3	
Baseline daily insulin use (units/kg)	153	0.6	<0.1	219	0.5	<0.1	85	0.5	<0.1	<0.01
Baseline class 1 (%-age value)	135	1.5	0.5	185	4.3	1.1	76	2.5	0.9	
Alanine aminotransferase (units/L)	154	21.7	1.0	216	24.0	0.8	139	25.7	1.7	0.02
Aspartate aminotransferase (units/L)	161	23.5	0.7	223	25.9	0.7	135	32.5	3.3	<0.01
Alkaline phosphatase (units/L)	155	91.6	4.6	218	98.9	4.7	145	79.3	3.6	
Total bilirubin (mg/dL)	157	0.6	<0.1	217	0.6	<0.1	141	0.6	<0.1	
Creatinine (mg/dL)	185	1.4	<0.1	238	1.1	<0.1	157	1.0	<0.1	<0.01
HDL (mg/dL)	162	65.0	1.3	222	64.2	1.3	105	66.7	1.7	
LDL (mg/dL)	138	97.1	2.5	213	94.6	1.8	106	90.1	2.9	
Total cholesterol (mg/dL)	169	179.4	2.7	227	172.9	2.2	119	173.3	3.6	
Triglycerides (mg/dL)	169	55.4	2.8	226	55.6	2.7	119	50.6	2.5	

Donor, procurement & processing characteristics	1999–2002		2003–2006		2007–2010		
	N	%	*N*	%	*N*	%	
Procurement/infusion teams related	89	51.7	107	48.4	59	55.1	
Donor sex							0.006
Female	33	19.2	37	16.2	37	23.6	
Mixed	72	41.9	113	49.3	47	29.9	
Male	67	39.0	79	34.5	73	46.5	
Donor blood type O	116	67.4	150	65.5	104	67.5	
Donor given vasopressors	143	99.3	215	99.1	109	96.5	
Donor given steroid	59	69.4	103	64.0	49	77.8	
Donor given insulin	68	53.5	128	63.7	82	64.1	
Preservation*							
UW only	77	38.3	66	26.3	30	14.6	
2-layer only	18	9.0	39	15.5	10	4.9	
HTK only	—	—	13	5.2	19	9.2	
Celsior	3	1.5	2	0.8	4	1.9	
UW + 2-layer	26	12.9	52	20.7	11	5.3	
Other single or combination	77	38.3	79	31.5	132	64.1	<0.01
Gradient*							
Mixed	17	11.6	27	12.7	4	4.0	
Discontinuous	10	6.8	9	4.2	—	—	

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Table 1—*Continued*

	Era						
	1999–2002		2003–2006		2007–2010		
	N	%	*N*	%	*N*	%	*P*
Continuous	110	75.3	162	76.4	92	91.1	
Both	9	6.2	13	6.1	5	5.0	0.04
Enzyme*							
Liberase	159	100.0	181	84.6	10	10.0	
Collagenase P	2	1.3	14	6.5	2	2.0	
Serva/NB1	13	8.2	25	11.7	77	77.0	
Other	10	6.3	61	28.5	30	30.0	<0.01
Thermolysin (+ other enzyme)	6	3.8	40	18.7	5	5.0	<0.01
Pulmozyme (+ other enzyme)	56	35.2	136	63.6	69	69.0	<0.01
Islets cultured ≥6 h	77	52.7	145	74.4	82	87.2	<0.01

	1999–2002			2003–2006			2007–2010			
	N	Mean	SE	*N*	Mean	SE	*N*	Mean	SE	
Donor age (years)	140	42.3	0.8	196	43.1	0.7	133	43.8	1.0	
Donor weight (kg)	171	85.5	1.4	228	87.6	1.0	144	93.4	1.6	<0.01
Donor BMI (kg/m^2)	171	28.5	0.4	228	29.0	0.3	144	30.9	0.5	<0.01
Donor HbA_{1c} (%)	17	5.5	0.1	74	5.5	0.0	44	5.6	0.0	
Maximum donor glucose (mg/dL)	130	239.6	6.9	208	226.3	4.5	135	217.4	5.3	<0.01
Donor AST (units/L)	111	97.3	16.5	182	60.7	5.0	96	72.3	11.4	
Donor BUN (mg/dL)	97	15.3	0.7	156	14.8	0.5	72	17.1	1.2	
Donor total bilirubin (mg/dL)	107	0.9	0.1	176	0.9	0.0	95	0.8	0.1	

Islet characteristics (average or sum of all infusions)	1999–2002			2003–2006			2007–2010			
	N	Mean	SE	*N*	Mean	SE	*N*	Mean	SE	
Hours of cold ischemia	146	7.1	0.2	198	7.3	0.2	88	9.0	0.9	<0.01
Hours of culture time (0 included)	146	14.4	1.5	195	19.0	1.2	94	24.4	1.6	<0.01
Total islet particles (final preparation, 1,000s)	135	861.0	39.5	177	822.3	27.9	94	623.0	33.6	<0.01
Embedded islets (%)	93	34.5	3.6	140	34.3	2.8	79	26.8	3.0	
Purity (%)	140	58.5	1.4	205	62.2	1.0	95	65.3	1.5	<0.01
β-Cells/kg recipient (1,000s)	57	6.3	0.6	74	6.3	0.6	15	4.9	0.9	
Islet viability (%)	124	91.0	0.5	198	91.4	0.4	102	89.8	0.6	
Stimulation index	136	3.5	0.3	185	3.2	0.2	86	2.5	0.2	<0.01
Total endotoxin infused/kg recipient	113	0.7	0.1	178	0.7	0.1	83	0.2	0.1	0.02
IE-to-islet particle ratio	126	1.1	0.1	163	1.1	0.1	91	1.5	0.1	<0.01
Total DNA (μg)	65	16.7	1.8	96	17.8	1.5	24	19.5	3.5	
IEs infused (1,000s)	160	421.3	11.9	213	422.6	11.3	148	461.8	13.4	0.03
Cumulative IEs/kg recipient (1,000s)	158	6.6	0.2	207	6.7	0.2	142	7.0	0.2	

Immunosuppression	1999–2002		2003–2006		2007–2010		
	N	%	*N*	%	*N*	%	
Induction at infusion 1							
IL2RA only	105	59.3	146	62.1	25	15.6	
TCD only	14	7.9	12	5.1	32	20.0	
TNF-α inhibitor only	—	—	5	2.1	1	0.6	
TCD+TNF-α inhibitor	—	—	16	6.8	42	26.3	
IL2RA+TCD	—	—	2	0.9	3	1.9	
IL2RA+TNF-α inhibitor	14	7.9	17	7.2	8	5.0	
IL2RA+TCD+TNF-α inhibitor	7	4.0	1	0.4	3	1.9	
Other	—	—	5	2.1	31	19.4	<0.01
Not yet reported	37	20.9	31	13.2	15	9.4	
Maintenance at infusion 1							
CNI+IMPDH inhibitor	1	0.6	16	6.8	40	25.0	
CNI+IMPDH inhibitor+steroid	25	14.1	5	2.1	10	6.3	

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Table 1—*Continued*

	Era						
	1999–2002		2003–2006		2007–2010		
	N	%	*N*	%	*N*	%	*P*
CNI+mTOR inhibitor	133	75.1	184	78.3	61	38.1	
CNI+mTOR inhibitor+steroid	7	4.0	9	3.8	11	6.9	
CNI+mTOR inhibitor+IMPDH inhibitor	6	3.4	9	3.8	4	2.5	
Other combination	5	2.9	12	5.1	31	19.4	
Not yet reported	—	—	—	—	3	1.9	<0.01

HTK, histidine-tryptophan-ketoglutarate; IE, islet equivalents; IL2RA, interleukin 2 receptor antagonist; IMPDH, inosine monophosphate dehydrogenase; PRA, panel reactive antibody; UW, University of Wisconsin. *Multiple responses are possible; the sum of categories may be greater than *N*.

2003–2006, 2007–2010), follow-up time after the first infusion, and other covariates on the rate (prevalence) of the desirable outcome for each primary end point. A multivariate analysis of all available recipient, donor, islet, and medical management factors on the outcomes was also conducted to see if changes in patient selection and management practices accounted for the observed differences in outcomes over the eras.

The occurrence and outcomes of clinically reportable adverse events (CRAEs), classified as unlikely, probably, or definitely related to the infusion procedure or to the immunosuppression regimen, were analyzed according to era. Each recipient was classified and tabulated according to his or her worst outcome of all infusion-related CRAEs and immunosuppression-related CRAEs during the entire period of infusions and follow-up for the recipient. Comparisons were made with Mantel-Haenszel χ^2.

Comparisons across eras clearly were not randomized, and sample sizes were not experimentally determined. In this registry data, nominal *P* values are reported without prespecified Type I error rates.

RESULTS—This analysis was based on 677 recipients of allogeneic islet transplantation who consented to the reporting of their data to the CITR, with 214 recipients in 1999–2002 (early), 255 in mid-2003–2006, and 208 in 2007–2010 (recent); 423 (62%) came from North America, and 254 (38%) were reported from the European and Australian JDRF sites. Transplants comprised islet alone in 575 (85%) and IAK or simultaneous islet kidney (IAK/SIK) transplant in 102 (15%). The CIT enrolled 46 (7%) in 2008–2010. They received 1,375 islet infusions from 1,502 donors, of which ~10% were islets from 2 to 3 donors infused on the same day, considered here as "multiple donor infusion." Approximately 36% of the recipients received only one infusion, 44% received two, 18% received three, 1.3% received four, and one person received six infusions.

The CITR data represent 81% of all islet transplants performed in the North American and JDRF European and Australian centers between 1999 and 2010. The number of new islet allograft recipients doubled yearly between 1999 and 2002 (Fig. 1). A marked decline in activity from 2002 to 2003 reflected a saturation of then-existing protocol enrollments, combined with tempered enthusiasm for the procedure after some centers reported waning insulin independence at 2–3 years (7,8). The number of North American centers performing islet transplants continued to rise through 2005, although the annual number of islet allografts remained less than the 2002 levels. In 2007, there were fewer than half as many North American centers performing islet transplants and one-third of the total number of islet allografts performed compared with 2005 at a time when the commonly used collagenase enzyme Liberase became unavailable. A distinct resurgence in islet transplant activity occurred in 2008 with the available collagenase products and the start-up of the CIT trials.

Figure 1 also shows substantial shifts in immunosuppression strategies implemented during the 12-year period. The early and mideras were dominated by the Edmonton Protocol, which used an interleukin 2 receptor antagonist (e.g., daclizumab) for induction and a mammalian target of rapamycin (mTOR) inhibitor (e.g., sirolimus), together with a calcineurin inhibitor (CNI, e.g., tacrolimus) for maintenance immunosuppression. In the most recent era, there has been a shift to induction with a T-cell depleting (TCD) antibody, with or without an inhibitor of tumor necrosis factor-α (TNF-α; e.g., etanercept) and maintenance with an mTOR inhibitor or an inosine monophosphate dehydrogenase inhibitor (e.g., mycophenolic acid) combined with a CNI.

Table 1 summarizes the preinfusion recipient characteristics according to era. Over time, recipients with C-peptide ≥0.3 ng/mL have been excluded. Increasingly, recipients have been selected at older age and with longer type 1 diabetes duration, requiring slightly less insulin and having better kidney function, as indicated by lower serum creatinine, suggesting more appropriate patient selection. Consistent with trends in clinical practice, more were using insulin pumps for insulin delivery, which may explain the slightly lower daily insulin requirement, and more were taking lipid-lowering medications. Following national trends, donor weight increased, and consistent with trends in critical care medicine, more donors received insulin with a consequent decrease in donor glucose. Donor HbA_{1c}, when sampled, remained within normal levels in all eras. There were also definite shifts in preservation method and collagenase type, and more islet preparations were cultured. The clinical effects of procurement, processing, and final islet characteristics are the focus of a separate analysis. Recent years have seen a substantial decline in the use of daclizumab, with a substantial rise in polyclonal T-cell–depleting antibodies and/or etanercept, as well as notable declines in sirolimus use, with increased use of mycophenolic acid.

There were increasing levels of missing data with longer follow-up, which is a mixture of data unavailable from the medical record and data still pending entry into the registry. The percentages of missing data for insulin independence were 3% at 1 year, 5% at 3 years, and 7% at 5 years and for other primary end points were 10 to 20% over years 1–3.

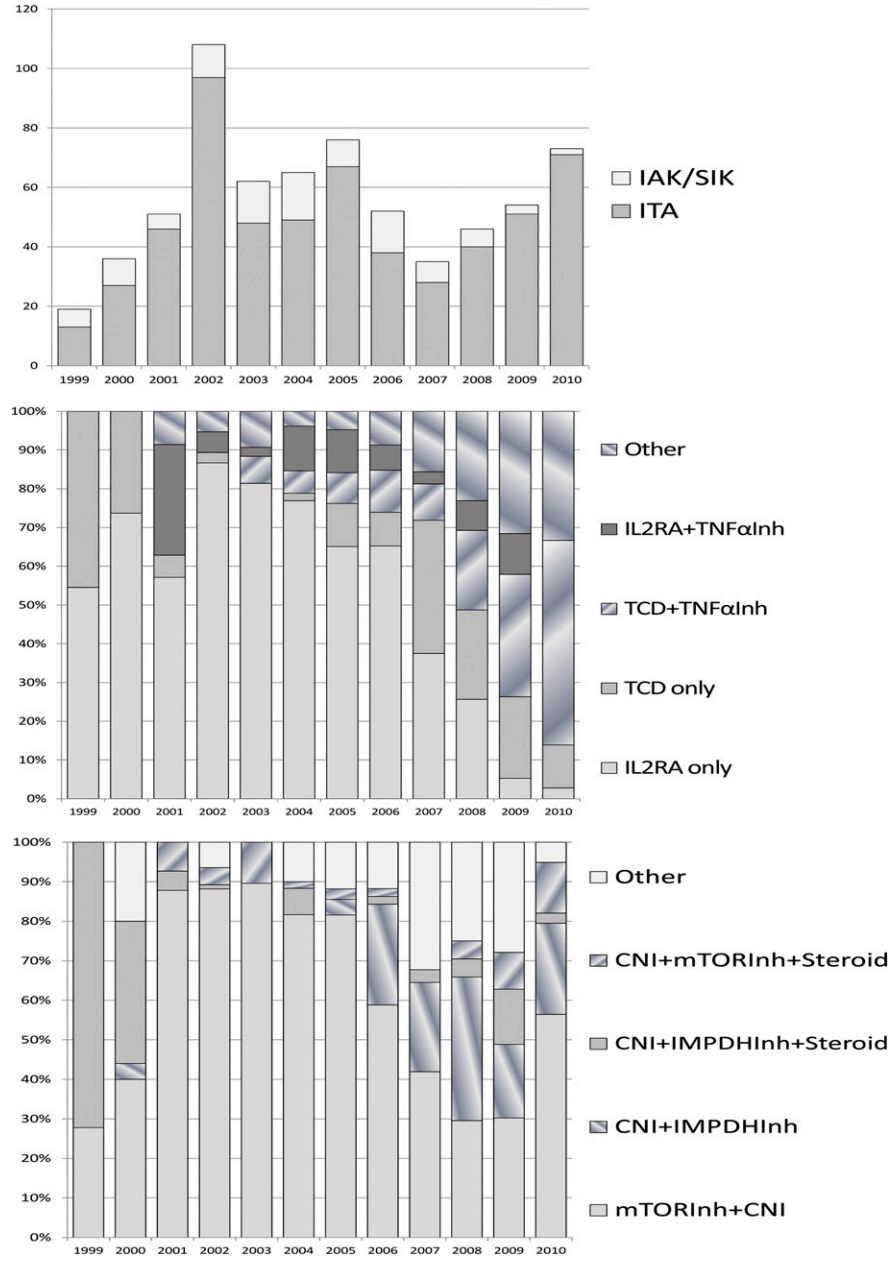

Figure 1—*Islet allograft recipients* (N = 677) *registered in CITR according to type of transplant* (n *per year;* top)*, induction immunosuppression at first infusion (% by year;* center)*, and maintenance immunosuppression at first infusion (% by year;* bottom)*. ITA, islet transplant alone.*

Of those who received transplants in the 1999–2002 era, 51% were insulin-independent at 1-year after the first infusion, regardless of reinfusion, and this declined to 36% at 2 years and to 27% at 3 years. By contrast in the 2007–2010 era, 66% were insulin-independent at 1 year, 55% at 2 years, and 44% at 3 years (P = 0.01, Fig. 2*A*). The decline in the rate of insulin independence during 5 years of follow-up in all eras is significant ($P <$ 0.001). The difference in this decline among the three eras (P = 0.006 for years-by-era) indicates that the rate of decline is less steep, showing notable improvement in durability in the most recent era. Durability of islet graft function, as measured by fasting C-peptide ≥0.3 ng/mL, improved significantly over the eras ($P <$ 0.001, Fig. 2*B*, *left*). The rate of graft function loss was significantly reduced if insulin independence was previously achieved, an effect seen in all eras (Fig. 2*B*, *right*). Nearly all islet recipients had significant improvements in HbA_{1c} and fasting blood glucose after islet transplantation. The composite end point of HbA_{1c} <6.5% or a drop by two or more percentage points shows improvement from the early era to the mid era (P = 0.03), although no further improvement in the most recent era, with 2–5-year success rates of 50–60% in the recent era (Fig. 2*C*, *left*). Fasting blood glucose showed a marked improvement from the early to mid eras ($P <$ 0.01, not shown).

Severe hypoglycemia was prevalent at first infusion in >90% of all subjects in all eras. Available data on severe hypoglycemic events, regardless of previous graft loss (C-peptide <0.3 ng/mL without recovery), shows >90% remained free of severe hypoglycemic events in all eras, and this relationship persisted through 5 years of follow-up (Fig. 2*C*, *right*). Any differences by era on resolution of severe hypoglycemic events were neither detectable nor important relative to this sustained, high level of benefit. If data on severe hypoglycemic events were missing and previous complete graft loss was counted as return to severe hypoglycemic events—an extreme assumption—there was still improvement in 2003–2006 compared with 1999–2002 at years 2–4 (P = 0.03, not shown).

Concurrent C-peptide is a strong correlate of all the other primary outcomes: the higher the C-peptide, the greater the likelihood of HbA_{1c} <6.5% or a drop by two percentage points ($P <$ 0.001; Fig. 2*D*), the greater the likelihood of absence of severe hypoglycemic events ($P <$ 0.001; Fig. 2*D*), the greater the likelihood of fasting blood glucose in the 60–140 mg/dL range ($P <$ 0.001, not shown), and the greater the likelihood of insulin independence ($P <$ 0.001, not shown).

A comprehensive model of all predictive factors—noting the shifts in patient age and immunosuppression strategies over the eras (Table 1)—largely accounted for the differences by era in insulin independence (Table 2). The effect of T-cell–depleting agents in conjunction with TNF-α inhibitors shows on enduring insulin independence (9) is confirmed: 50–62% of recipients receiving this induction regimen were insulin-independent at years 3–5 after the last infusion (Fig. 2*A*, *right*), compared with 34–43% for those not receiving TCD+TNF-α inhibitors.

Reinfusion is performed when the first graft loses function completely or declining function is proven by declining C-peptide levels. Islet reinfusion has decreased substantially during the 12-year period: 48%

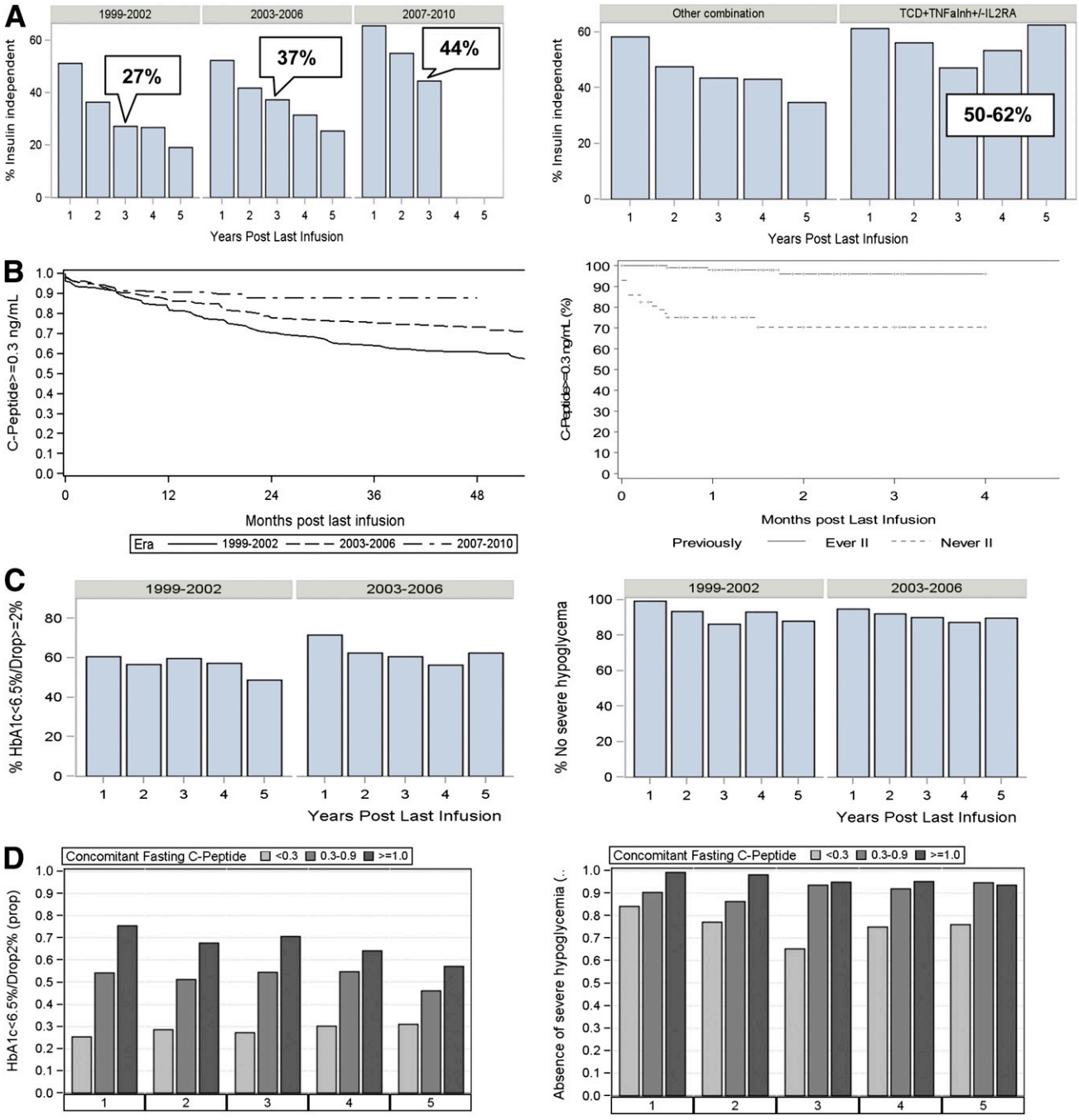

Figure 2—A: *Rates of insulin independence after allogeneic islet infusion (islet transplant alone and IAK), annually after last infusion.* Left: *By era* (P = *0.02*). Right: *By induction immunosuppression category* (P < *0.01*). B: *Durability of graft function (basal C-peptide ≥0.3 ng/mL) after the last infusion, by era* (P < *0.001*; left). *The immediate drop at time 0 is occurrences of primary nonfunction (i.e., C-peptide never ≥0.3 ng/mL). In the most recent era, 95% of those who ever achieved insulin independence (II) retained graft function through 3 years after last infusion compared with 70% for those who never achieved II* (P < *0.001*; right). C: *Percentage of patients with HbA$_{1c}$ <6.5% or drop by two percentage points* (P = *0.03*; left); *and absence of severe hypoglycemic events regardless of complete graft failure* (P = *NS by era; there were insufficient data from 2007–2010;* right). D: *The percentage with HbA$_{1c}$ <6.5% or drop by 2% increases with increasing C-peptide level* (P < *0.001*; left), *as does absence of severe hypoglycemic events* (P < *0.001*; right), *annually after the last infusion. (A high-quality color representation of this figure is available in the online issue.)*

of recipients were reinfused by 1 year in 2007–2010 vs. 60–65% in 1999–2006 ($P < 0.01$).

Mortality is low in this group of type 1 diabetic individuals with substantial disease burden, with stable event rates during the 12-year period (Fig. 3*A*). The incidence of life-threatening events has declined ($P = 0.002$; Fig. 3*B*). The incidence of any CRAE in year 1 declined from 50 to 53% in 1999–2006 and to 38% in 2007–2010 ($P = 0.02$; Fig. 3*C*). Peritoneal hemorrhage or gallbladder perforation declined from 5.4% in 1999–2003 to 3.1% in 2007–2010. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) calculated glomerular filtration rate (GFR) declined after islet

Table 2—*Factors predictive of insulin independence after last infusion*

Results from generalized estimating equations	Odds ratio (95% CI)	*P*
Total infusions	1.44 (1.06–1.98)	0.02
Recipient age (each additional year)	1.04 (1.02–1.07)	<0.001
Islets cultured ≥6 h	1.82 (1.06–3.15)	0.03
Stimulation index ≥1.5	1.83 (1.23–2.72)	0.05
T-cell depletion + TNF-α inhibitor	2.38 (0.95–5.94)	0.06

transplantation (Fig. 3*D*); however, there are no published comparable follow-up data in similar groups of type 1 diabetes. No primary efficacy or safety end points were associated with recipient or donor sex or ethnicity.

CONCLUSIONS—In North America, the number of centers performing clinical islet transplants and the total number of islet transplants declined in 2006–2007, with a distinct resurgence in 2008. The reasons for the decline are not directly captured by the Registry but likely reflect changes in the production and availability of the collagenase enzymes used for islet digestion, tempered enthusiasm with respect to long-term clinical outcomes of insulin independence (7,8,10), concern for effect of immunosuppression on kidney function in islet-alone recipients (11,12), concern for risk of sensitization to donor HLA (13–15), and saturation of the referral base for patients with the severest forms of unstable type 1 diabetes. However, with the start of the new CIT protocols in 2008, coupled with more encouraging recent trends in longer-term outcomes with novel protocols using T-cell depletion for induction (16,17), the number of new islet cell recipients has increased annually in the most recent era.

Direct evidence is presented of the importance of durable islet graft function to achieve multiple clinical benefits as a consequent effect. Positive C-peptide is strongly associated with all of the other primary clinical outcomes; hence, the factors that drive positive C-peptide necessarily lead to the other clinical benefits, although additional factors may also contribute to the other benefits. A comprehensive analysis of the effect of all available factors on these primary co-outcomes indicates that older recipient age, lower initial insulin requirement, and the use of T-cell depletion, particularly when given in conjunction with TNF-α inhibitors, are significantly associated with improved clinical outcomes. The numbers are too low to definitively assess the impact of a shift in maintenance immunosuppression, with mycophenolic acid replacing mTOR inhibitors, and both agents are still usually administered in combination with a CNI.

It must be noted that the CITR data have not been accruing in real time; rather, as sites have joined over the 12-year life of the Registry, large portions of the data, including some of the historical data, have been reported during the last 1–3 years. Hence, the current results may vary somewhat from previously published reports, including the CITR Annual Reports. The present data are the most comprehensive and up-to-date information available for the 12-year period 1999–2010.

In the present analysis, the increasing levels of missing data with increasing follow-up time pose some limitation. Strengths of the analysis are the most complete available set of data and ability to track trends during this 12-year period of steroid-free immunosuppression. Stratifying the CITR data by era of transplant shows a compelling trend toward better outcomes in the recent era ($P \leq 0.01$), despite the still relatively low total number of islet transplant recipients worldwide. There is an indication of moving toward selection of older recipients with longer-standing diabetes and absence of C-peptide to tip the risk-to-benefit ratio in their favor. The trend toward heavier donors is likely due to donor availability in the midst of a global obesity epidemic and possibly to the known association between higher donor weights and the higher number of islet equivalents isolated (18). This must be balanced against the detrimental effects of transplanting islets derived from donors with unsuspected type 2 diabetes (19), and for this reason, it is important to confirm that the HbA_{1c} of an obese donor is within the normal range before transplantation.

In the past, transplanting islets rapidly after isolation was believed to be optimal. In recent years, the preference toward transplanting islets after a short culture period emphasizes the current supposition that culturing removes the nonviable islets and decreases tissue factor expression that can lead to nonspecific inflammation and islet loss after transplant (20). The percutaneous infusion technique occasionally resulted in intraperitoneal hemorrhage and portal branch vein thrombosis early on; however, these complications have occurred less often in the present era.

Whole pancreas transplantation is an approved option for β-cell replacement in type 1 diabetes, although it is mostly limited to patients simultaneously receiving a kidney transplant for diabetic nephropathy and often excludes older patients and those with coronary artery disease due to the potential for significant surgical morbidity. Thus, islet transplantation may offer a complementary alternative to whole pancreas transplantation in patients who are not candidates for or are unwilling to accept the risks of major surgery, and so some estimation of comparative efficacy is required. In the 2007–2010 era, islet graft survival (C-peptide ≥0.3 ng/mL) of 92% at 1 year and 83% at 3 years (Fig. 2*B*) compares very favorably with whole pancreas graft survival of 80% at 1 year and 61% at 3 years (21). In the recent era, these graft survival rates translate to an unconditional 44% insulin independence at 3 years (Fig. 2*A*), the highest long-term islet transplant success rate observed to date. Although this is still short of the 61% insulin independence reported in the most successful cohort of type 1 diabetes pancreas-alone transplant recipients (22), this difference may be explained by the transplantation of 100% of a normal islet β-cell mass with a whole pancreas compared with a variable islet β-cell mass surviving the engraftment of isolated islets and resulting in a reduced β-cell secretory capacity (23). In addition, throughout the 12-year period, these data show an enduring benefit in HbA_{1c} reduction and stabilization of fasting blood glucose.

Importantly, the presence of insulin-dependent islet graft survival defined by C-peptide >0.3 ng/mL confers protection from severe hypoglycemia, and this effect persists even after the islet graft is lost. This declining rate of islet graft loss by era suggests that more recent strategies of immunosuppression, as identified in the multivariate analysis, may better protect islets from alloimmune rejection and recurrent autoimmunity. The successful strategies have all included CNIs that are known to exhibit β-cell toxicity at high doses; however, one study showed modern use of lower-dose, CNI-based

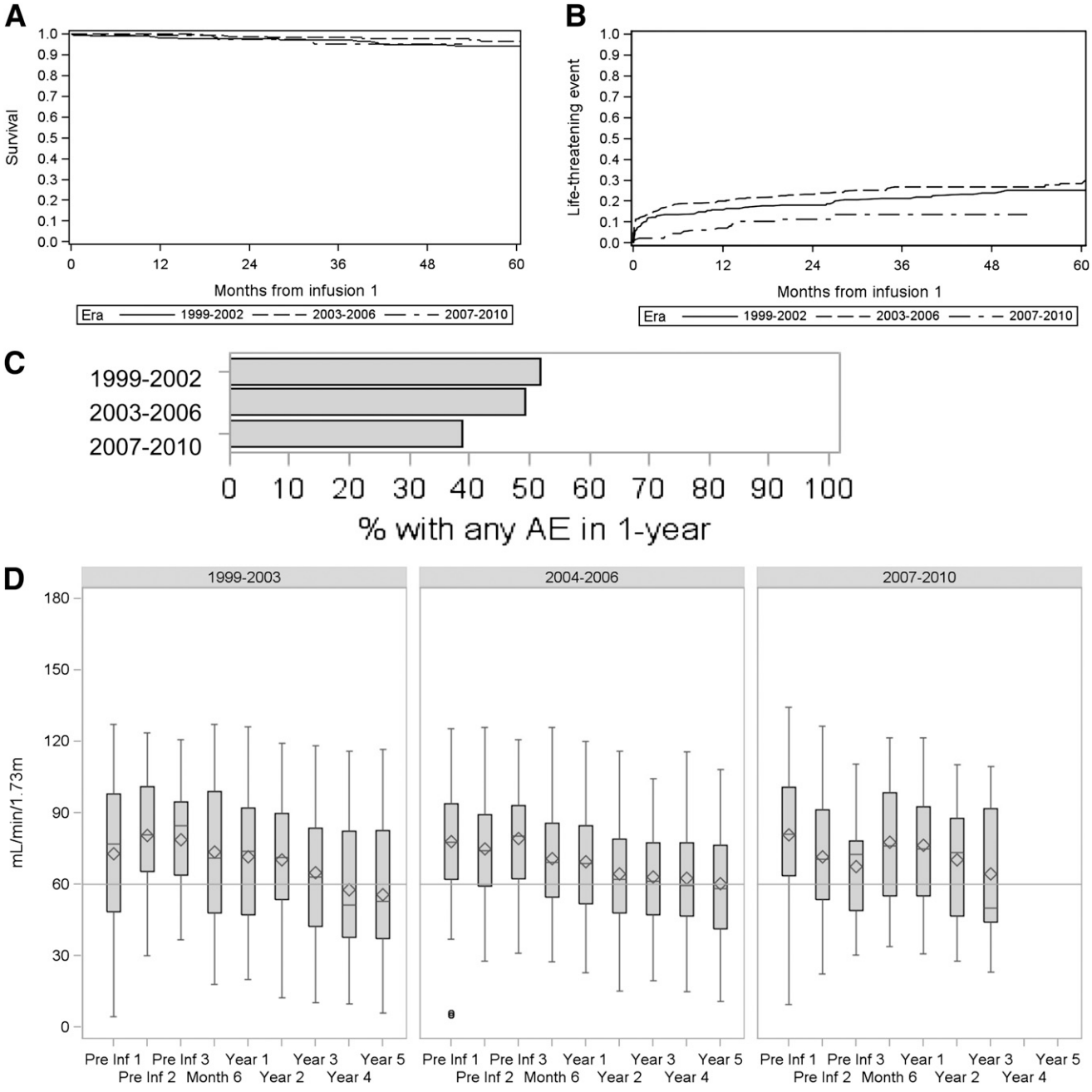

Figure 3—A: *Mortality by era* (P = *0.49*). B: *Life-threatening events by era* (P = *0.01*). C: *Incidence of any adverse event (AE) in year 1 of first infusion* (P = *0.02 by era*). D: *CKD-EPI calculated glomerular filtration rate, by era.*

immunosuppression resulted in a 100% normal β-cell secretory capacity in whole pancreas transplant recipients (23), supporting that these agents can be used and may even be necessary for successful islet transplantation. Finally, the finding that the rate of graft function loss was significantly reduced when insulin independence was previously achieved suggests that the engraftment of a sufficient islet β-cell mass to eliminate the need for exogenous insulin may mitigate nonimmunologic islet graft loss believed to occur in the setting of increased β-cell demand. Present strategies to improve the proportion of islets surviving engraftment are expected to lead to improved functional outcomes for islet recipients (24).

The CITR shows consistent trends toward improved primary outcomes of islet transplantation in the cohort who received transplants in 2007–2010 compared with those in 1999–2006. Islet transplantation currently offers substantial protection from severe hypoglycemic episodes and high rates of freedom from exogenous insulin requirements in a minimally invasive setting. Emerging innovations in islet production, processing, delivery, and immunosuppressive protection undoubtedly will advance the field. Islet transplantation has already moved from Phase I/II to Phase III evaluation, with the results from the CIT eagerly awaited to provide efficacy and safety information for a standardized

approach to islet isolation and immunosuppression management.

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F.B.B. was the principal investigator of the Registry. M.R.R., R.A., J.O., and P.A.S. contributed substantially to the analysis of the data and interpretation of the results, assumed responsibility for clinical data reported to the Registry, and reviewed and edited the manuscript. B.J.H., B.N., J.S.O., M.R.G., F.P., T.B., and A.M.J.S. contributed substantially to the analysis of the data and interpretation of the results and assumed responsibility for clinical data reported to the Registry. S.W. was the study manager of the Registry. M.L., A.P., X.L., F.K., N.A.T., P.W., P.J.O., K.L.B., M.J.A., C.L., T.W.H.K., L.A.F., and M.B. assumed responsibility for clinical data reported to the Registry and reviewed and edited the manuscript. A.S., P.M., D.B.K., P.G.S., E.C., A.N., C.G., Y.C.K., and M.-C.V. assumed responsibility for clinical data reported to the Registry. S.M. contributed to the analysis of the data and reviewed and edited the manuscript. F.B.B. and S.W. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Similar results based on 2008 Registry data were presented at the International Islet and Pancreas Transplant Association (IPITA) in October 2009, and published as an abstract (Barton FB, Wease S, Alejandro R, Hering BJ, Shapiro AMJ, Berney T, Rickels M, Pattou, F, Secchi A, and the CITR Investigators. Improvement in outcomes of islet transplantation: CITR 1999-2008. Xenotransplantation 2009; 16:293).

Parts of this study were presented at the 72nd Scientific Sessions of the American Diabetes Association, Philadelphia, Pennsylvania, 8–12 June 2012.

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