



***Scientific Summary of the  
Collaborative Islet Transplant Registry (CITR)  
2010 (Seventh) Annual Report***

## **BACKGROUND AND PURPOSE**

Pancreatic islets of Langerhans contain insulin producing beta cells that regulate the utilization of dietary sugars by all cells in the body. In persons with Type 1 diabetes mellitus (T1DM), most of the beta cells are destroyed by an autoimmune attack, resulting in the need for pharmaceutical insulin delivered by injection or pump to avoid diabetes-related illness and death. About 5% of the 25.8 million people in the US with diabetes have T1DM, or an estimated 1.5 million people. The only alternatives to daily insulin injections or pump currently available are solid organ pancreas transplant or transplantation of islets of Langerhans isolated from a donated pancreas.

Islet transplantation in the US is experimental and available only at sites that have received exemption from the US Food and Drug Administration (US-FDA) for clinical research of islet transplantation in T1DM. In the US, individual transplant centers may initiate their own independent research protocols or participate in Clinical Islet Transplant Consortium ([www.CITIsletStudy.org](http://www.CITIsletStudy.org)) to advance the field of islet transplantation. At the Canadian, European and Australian sites, both research and standard of care protocols have been available. Research investigators in clinical islet transplantation and islet science at the various programs contribute data and collaborate on the data analysis to advance knowledge about the risks and benefits of islet transplantation. Each center may publish the results of their local protocols or aggregate experience, and disseminate information regarding their open and recruiting protocols through their own means and/or at the National Library of Medicine's developed website [www.clinicaltrials.gov](http://www.clinicaltrials.gov). In addition, CITR maintains interactive maps of North American and JDRF European and Australian islet transplant programs at [www.citregistry.org](http://www.citregistry.org).

In 2001, the National Institute of Diabetes & Digestive & Kidney Diseases established the Collaborative Islet Transplant Registry (CITR) to compile data from all islet transplant programs in North America from 1999 to the present. The Juvenile Diabetes Research Foundation (JDRF) granted additional funding to include the participation of JDRF-funded European and Australian centers. The cumulated North American and JDRF European and Australian data are pooled into an annual report. CITR Annual Reports are publically available and can be downloaded or requested in hard copy at [www.citregistry.org](http://www.citregistry.org). This Scientific Summary highlights results from the CITR 2010 (7<sup>th</sup>) Annual Report, either by direct inclusion or by reference.

## **PATIENTS AND METHODS**

At the time of their first Islet transplant, CITR allograft recipients were 18-67 years of age (mean  $45 \pm 10$ SD), had T1DM for 1-61 ( $28 \pm 12$ ) years, and had very poor diabetes control including hypoglycemia unawareness and severe hypoglycemic events. Poor glyceemic control can

manifest as frequent episodes of critically low blood sugar levels (which often result as a reaction to injected insulin, requiring the assistance of another person to avert a possibly life-threatening loss of consciousness), wide swings in blood sugar levels (blood glucose lability), or consistently high HbA<sub>1c</sub> levels (>8% of total hemoglobin).

Data reported to the Registry are abstracted from medical information that is routinely collected by investigators in the course of their research protocols or clinical practice, and for reports to the multiple agencies and entities required by US-FDA regulated trials or according to the requirements of the respective nation.

Detailed follow-up data are abstracted pre-infusion and at Days 7, 75 and Month 6, Month 12, and annually post infusion. At each new infusion, a new follow-up schedule is established.

All grade 3, 4 and 5 adverse events, according to the Clinical Islet Transplant Consortium (CIT) Terminology Criteria for Adverse Events (TCAE), and all serious adverse events (regardless of grade) are reported to CITR. A copy of the CITR data collection forms may be requested from the CITR Coordinating Center ([citr@emmes.com](mailto:citr@emmes.com)), or viewed at the CITR Website ([www.citregistry.org](http://www.citregistry.org)).

CITR utilizes the Coordinating Center's (The EMMES Corporation, Rockville, MD) web-based data entry and management systems to capture data on recipients and donors. Additional data have been obtained through data sharing agreements with the United Network for Organ Sharing (UNOS), the Administrative and Bioinformatics Coordinating Center (ABCC, 2001-2009) of the Islet Cell Resource Centers (ICR), and the Data Coordinating Center (DCC) of the Clinical Islet Transplant Consortium (CIT, 2008-).

The Registry data exists because of the voluntary participation of the transplanting centers, with written informed consent for participation in the Registry by the islet recipients. While the Registry represents the most comprehensive collection of the human islet transplantation experience since 1999, there may exist uncontrollable biases and imbalances including selective reporting and differences in clinical care and decision-making. Even with the diligent efforts of the participating centers, the total number of cases and outcomes remains relatively small. Hence, the aggregate results should be interpreted cautiously.

**Statistical analysis.** The database for the 7<sup>th</sup> Annual Report was closed for analysis on March 21, 2011 for data on recipients that were transplanted as of December 31, 2009.

The major focus of the present analyses is to identify factors of patient selection, islet processing and islet transplantation management factors that result in the best possible clinical outcomes of islet transplantation. Reduced data reporting, particularly in long-term follow-up, has posed a challenge for the present analyses. The primary endpoints of insulin use, hence independence or not, and fasting C-peptide levels are the most completely available outcomes data. Monitoring site visits have been performed as scheduled and have included data audits for key recipient baseline and primary outcome data. Additionally, since 2008, site-by-site semi-annual reviews have been conducted by teleconference to maximize reporting of primary endpoints.

Descriptive analyses include tabular or graphical displays of sample means and their standard deviations (SD) or standard errors (SE), and whole-distribution statistics such as median, interquartile range and extremes. Primary outcomes -- analyzed at study time points post first or last infusion -- include percent insulin independent ( $\geq 14$  consecutive days), C-peptide  $< 0.3$  ng/mL, HbA<sub>1c</sub>  $< 6.5\%$  or drop by  $\geq 2\%$ , fasting blood glucose of 60-140, and severe

hypoglycemic events (Yes/No). First achievement and final loss of insulin independence, as well as complete graft failure, are analyzed by Kaplan-Meier time-to-event analysis with proportional hazards investigation of predictive factors, employing multivariate models to adjust for correlated or confounding factors. Secondary outcomes include whole-distribution description of these and other laboratory measurements, metabolic test results, liver and kidney function measures, and complications of diabetes. Safety is monitored by incidence rates of new adverse events classified by TCAE criteria and related to either infusion procedure or immunosuppression as determined by the local investigator.

Statistical comparisons are observational in nature: reported p-values are not based on controlled, experimental design but on the available data as a sample of convenience. The results should be used to direct future research as well as guide current clinical practice.

## RESULTS

**Islet Allograft Transplantation Activity 1999-2009.** As of December 31, 2009, the CITR Registry included data on 571 allogeneic islet transplant recipients (481 islet transplant alone, ITA) and 90 islet after or simultaneous with kidney (IAK/SIK), who received 1,072 infusions from 1,187 donors. The North American sites contributed 66% and the JDRF European and Australian sites contributed 34% of the recipients. Combining the ITA and IAK/SIK recipients, 31% received a single islet infusion, 47% received two, 20% received three, and 2% received 4-6 infusions.

### Exhibit A CITR Recipients, Infusions and Donors by NIDDK/JDRF Sites and by ITA/IAK-SIK Consented, Registered and First Infused in 1999-2009

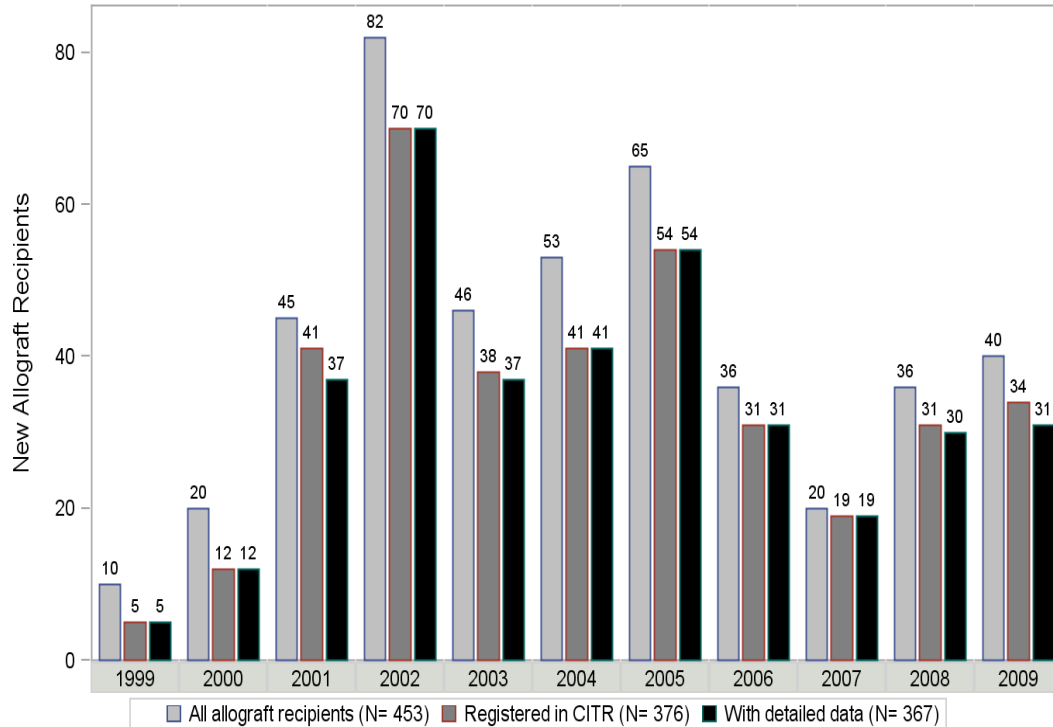
	Islet Transplant Alone (ITA)			Islet After Kidney or Simultaneous Islet-Kidney (IAK-SIK)			GRAND TOTALS
	Total	North America	Europe/Australia	Total	North America	Europe/Australia	
<b>Recipients</b>	<b>481</b>	341	140	<b>90</b>	35	55	<b>571</b>
<b>Infusions</b>	<b>897</b>	650	247	<b>175</b>	66	109	<b>1,072</b>
<b>Donors</b>	<b>988</b>	693	295	<b>199</b>	73	126	<b>1,187</b>

Exhibits B-1 and B-2 display the data collected from the islet transplant programs in North America and the JDRF European and Australian sites from 1999 through 2009. Of the 453 total North American recipients reported by general survey of the sites to have received an islet allograft in 1999-2009, 376 (83%) consented to and were registered in CITR. Detailed data was available on 367 of these recipients, representing 81% of the overall 453. While islet transplantation declined dramatically in 2006-2007 in North America and less so at the JDRF European and Australian sites, it has seen a definite resurgence in 2008-2009, not only in the CIT trials cases but also in local protocols.

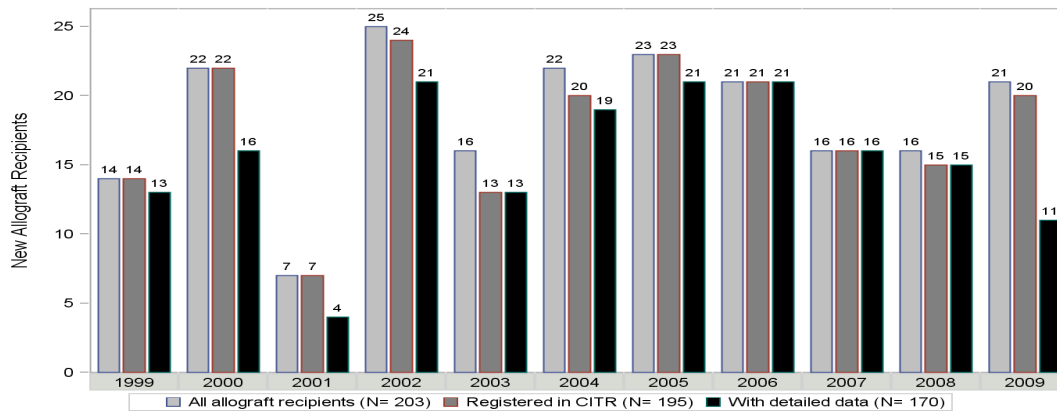
**Exhibit B**

**Total Number of Islet Allograft Recipients, Recipients at CITR-Participating Centers, and Recipients with Detailed Data Reported to CITR by Year of First Islet Allograft Infusion**

**1. Allograft recipients at CITR North American Centers 1999-2009**



**2. Allograft recipients at CITR European and Australian JDRF Centers 1999-2009**



**Islet Transplant Recipient Characteristics.** Mean age of islet allograft transplant recipients in CITR has risen over the decade from 42±9 SD to 49±9 years and the mean duration of diabetes has risen from 26±12 to 32±13 years. Mean recipient body mass index (BMI) has remained steady at 23.4±0.1 SE kg/m<sup>2</sup>. About 60% of the recipients were female. There has been limited racial and ethnic diversity in islet transplantation. Prior insulin pump use rose from 30% to 45% over the decade while daily insulin requirement dropped from 36.3±1.1 SE to 31.5±1.5. Pre-infusion mean HbA1c has remained steady at 7.8±0.1%, while fasting blood glucose decreased from 199±8.3 to 163±9.3 mg/dL and basal C-peptide fell from 0.3±0.01 SE to 0.1±0.01 ng/mL,

with very few recipients in the recent era (2007-2009) transplanted with a basal C-peptide >0.3 ng/mL. The percent of recipients taking lipid-lowering medications has increased over the eras 1999-2003, 2004-2006 and 2007-2009, from 24% to 47%. About 43% were CMV-positive, and 15% were PRA Class I positive.

**Donor Information.** All donors were deceased, at a mean age that rose from  $42.1 \pm 0.5$  SE to  $44.8 \pm 0.8$  years with mean BMI rising from  $28.0 \pm 0.3$  to  $30.3 \pm 0.4$  over the decade. About 58% of the donors were male, and in North America, <10% were Hispanic and 90% were white. About 47% of the donors had cerebrovascular/stroke cause of death while 25% experienced head trauma. Approximately 36% of the donors had a history of hypertension and 19% had a history of alcohol dependency.

Thirty-two percent (32%) of the donors received a transfusion during their terminal hospitalization, while only 6% received a transfusion intraoperatively. Fifty nine percent (59%) of the donors received steroids and 95% received at least one vasopressor during the terminal hospitalization. Peri-recovery insulin use rose from 32% to 60% over the decade. A total of 10 donors tested positive for anti-HBC, one tested positive for RPR-VDRL and one for HCV. Mean serum creatinine of the donors remained steady at 1.1 mg/dL, while mean maximum stimulated blood glucose decreased from  $245 \pm 5.9$  SE to  $214 \pm 5.4$  mg/dL.

**Pancreas Procurement and Processing.** Mean time from cross clamp to pancreas recovery was  $44 \pm 22$  SD minutes while mean cold ischemia time was 7.3 hours (range 1 to 27). Pancreas preservation with UW-only fell from 56% to 19% while HTK use rose from 0% to 23% and preservation other than UW, 2-layer, HTK, Eurocollins and Celsior rose from 15% to 31% over the decade. For digestion, use of Liberase HI dropped from 86% in 1999-2003 to 6% in 2007-2009, while Serva/NB1 use rose from 1% to 47%, and other collagenase rose from 1% to 13%. Thermolysin use increased from 1% to 13% and pulmozyme use rose from 19% to 45%. Culturing of the islets for >6 hours rose from 29% to 49%, with mean culture time rising from  $12 \pm 17$  SD to  $26 \pm 19$  hours. All of the pancreata processed used a density gradient for islet purification. Of the 1,072 islet preparations, sixteen showed a positive aerobic culture (1.5%), five showed a positive anaerobic culture (0.5%), five showed a positive fungal culture (0.5%), and one tested positive for mycoplasma (0.1%).

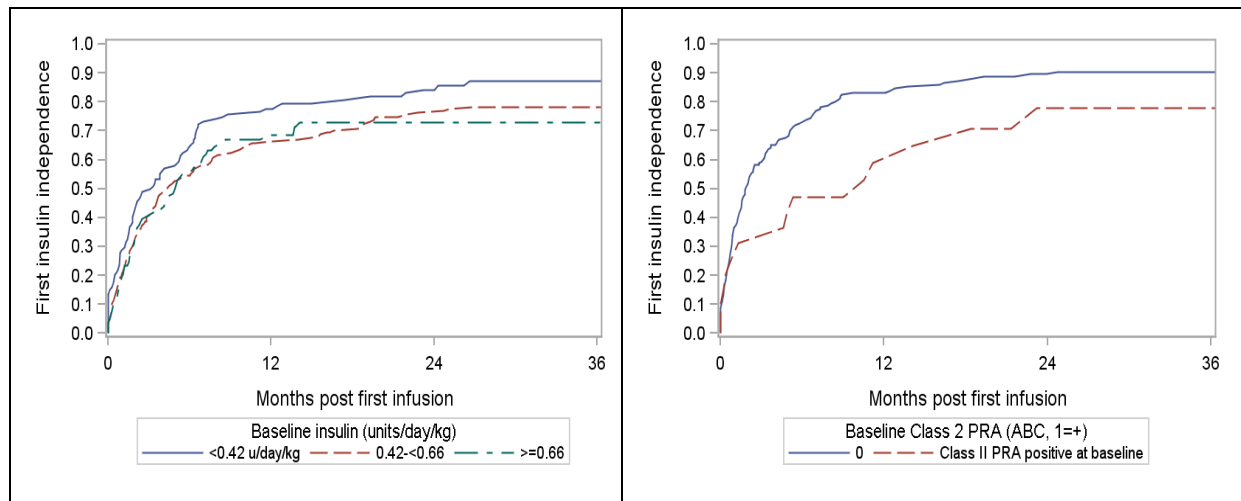
**Islet product characteristics.** Mean total IEQs infused per infusion rose from  $417 \pm 7.5$  SD 1000s to  $463 \pm 11.2$ , beta cells rose from  $217 \pm 17$  to  $335 \pm 32$  1000s, endotoxin/kg fell from  $0.3 \pm 0.001$  EU to  $0.1 \pm 0.001$ , and total DNA rose from  $8.3 \pm 0.9$   $\mu$ g to  $14.2 \pm 1.3$ .

**Immunosuppression Therapy.** Induction with IL2R antagonists only, which comprised about 80% of all initial infusions in 1999-2003, was replaced or supplemented with regimens that included T-cell depletion with/without TNF antagonists in over 80% of the infusions performed in 2007-2009. In 1999-2003, maintenance immunosuppression was predominantly (~75%) calcineurin+mTOR inhibitor combinations. It was increasingly replaced or supplemented in 2004-2009 by a calcineurin-inhibitor (CNI) and IMPDH-inhibitor combination, which was also increasingly used in long-term follow-up of early era transplants.

**Graft Function.** First achievement of insulin independence measured from initial islet infusion (Exhibit C), with or without subsequent infusion, is an indicator of the rate of engraftment under the real-time conditions of competing events including early graft loss, islet resource availability, patient/doctor decisions and myriad other factors, some of which are characterized in the CITR data and others not. It is notable that the cumulative rate of achievement of insulin independence follows the general shape of engraftment curves for solid organs, but with a slower initial slope, indicative of multiple infusions. Overall, non-stratified achievement of insulin

independence was 65% in the first year post first infusion (with or without reinfusion), and by Year 2 this increased to 75%. Among the most predictive factors of first achievement of insulin independence were lower baseline insulin requirement and negative Class II PRA (Exhibit C). Multivariate analysis including time-dependent factors such as re-infusion and changes in immunosuppression over time is deferred to a focus topic analysis.

**Exhibit C**  
**First Achievement of Insulin Independence**  
**Post First Infusion (Censored at final graft loss or end of follow-up)**

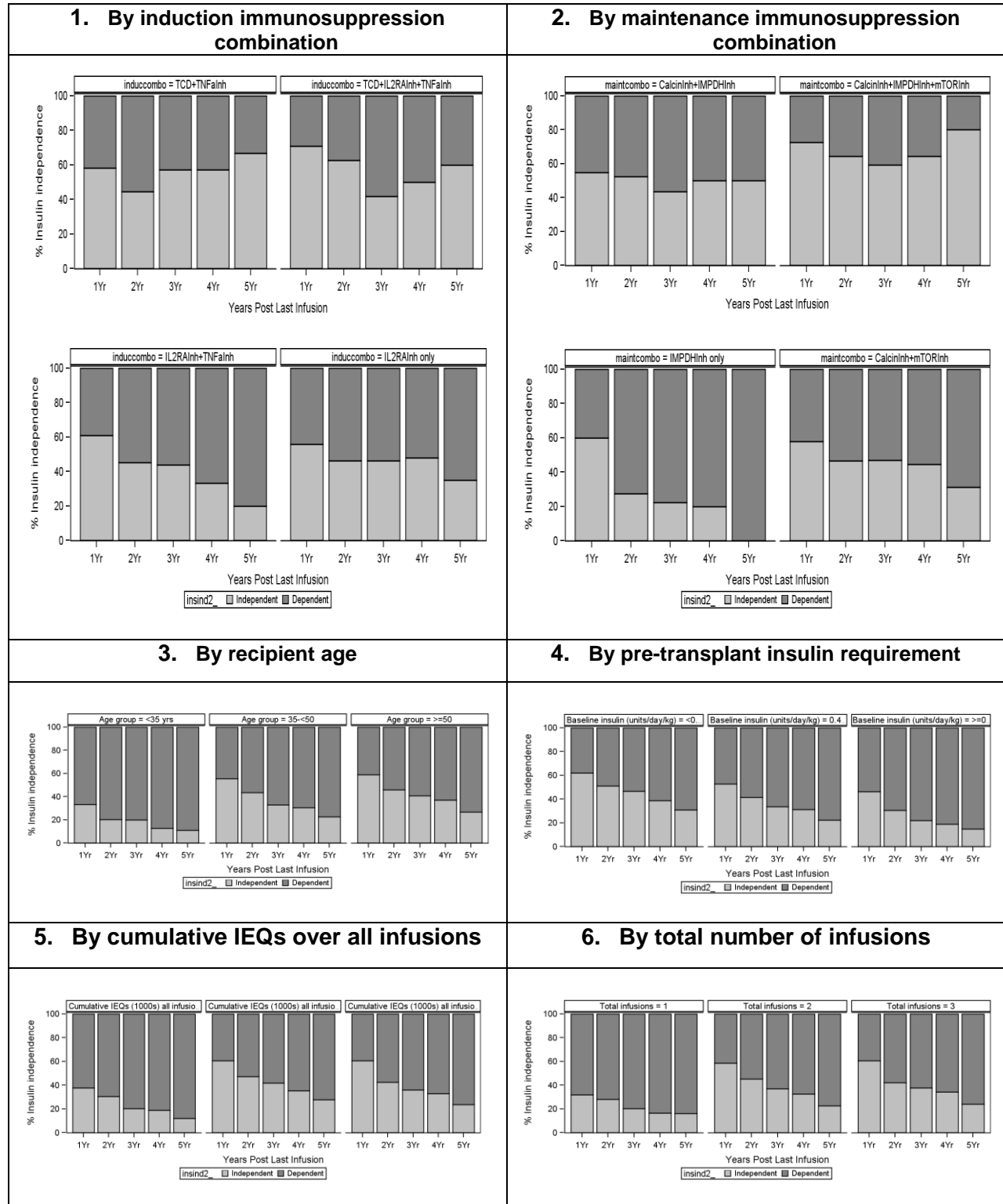


Among factors potentially predictive of successful long-term islet function are induction and maintenance immunosuppression, with 5-year insulin independence rates of 60-70% seen with combinations utilizing T-cell depletion and TNF antagonism compared with IL2RA alone (Exhibit D1,  $p=0.07$ ), and maintenance combinations that included CNI and IMPDH inhibitors compared with CNI+mTOR inhibitors (Exhibit D2,  $p=0.02$ ).

Improved insulin independence rates are seen also with older recipient age ( $p<0.01$ , Exhibit D3), lower insulin requirements ( $p=0.004$ , Exhibit D4), even in this patient population with high rates of hypoglycemia unawareness and severe hypoglycemic events. Additional beneficial factors include higher total IEQs infused over all infusions ( $p=0.01$ , Exhibit D5), 2 (but not  $\geq 3$ ) total infusions ( $p<0.01$  Exhibit D6), and lower recipient cholesterol. Beneficial donor factors include age<35 yrs, use of vasopressors and insulin pre-recovery. Beneficial islet recovery and processing factors include HTK preservation, use of pulmozyme and/or thermolysin, and culturing at least 6 hours. The beneficial effect of these factors, including the immunosuppression regimens employed since the 2004-2006 era, is also seen for HbA1c<6.5% or a drop by 2%, and absence of severe hypoglycemic events (see full report). All of the foregoing results are based on univariate analysis.

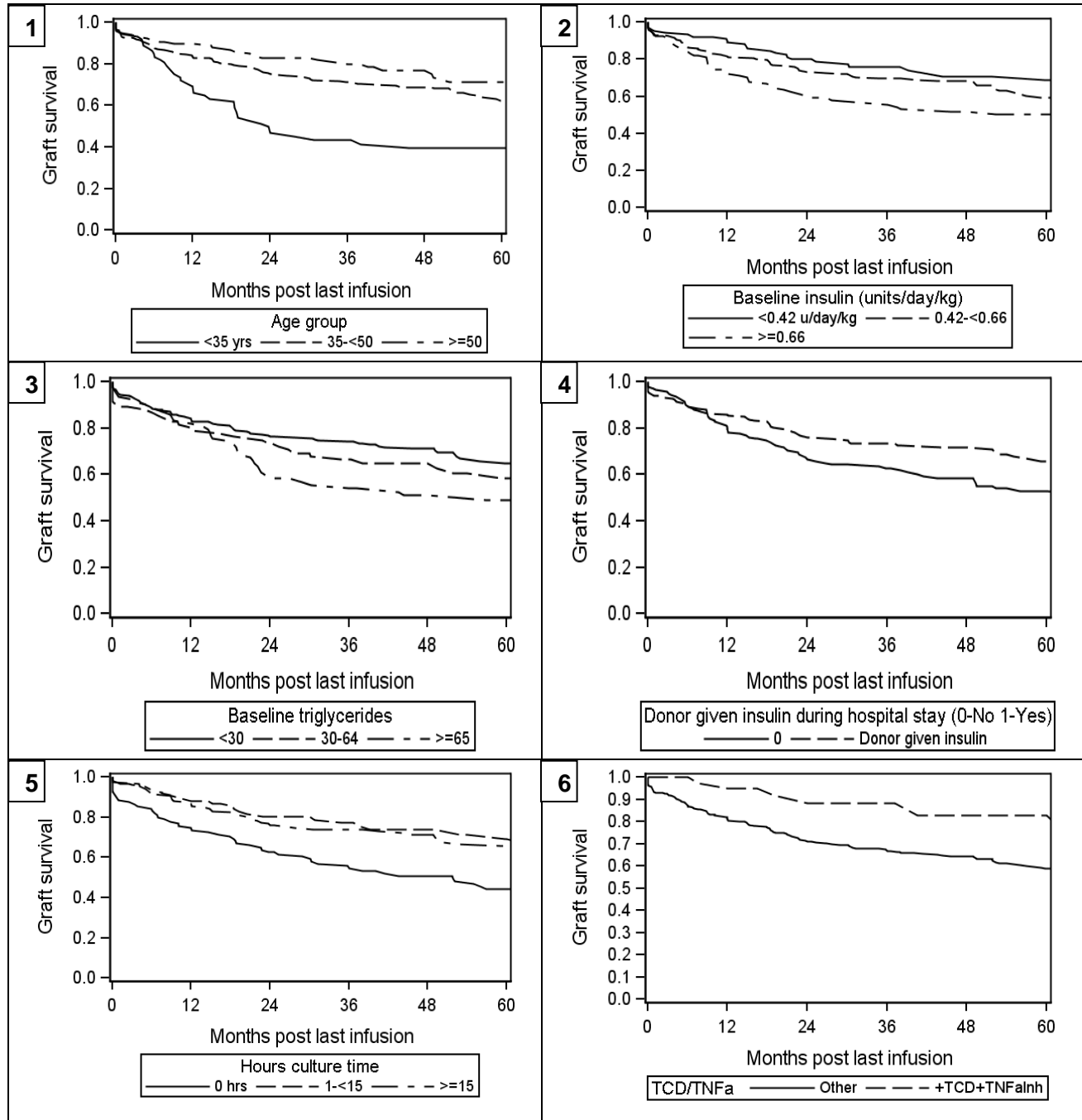
Although sustainability of insulin independence declines over long-term follow-up, the rates of long-term graft function improved over the decade. Recipients transplanted in 2004-2007 retained insulin independence significantly longer than those transplanted in 1999-2003 ( $p=0.009$ , see full report). This is only partially accounted for by changes over the decade in the most significant factors associated with long-term benefit (Exhibit D).

### Exhibit D Percent insulin independence post last infusion by predictive factors



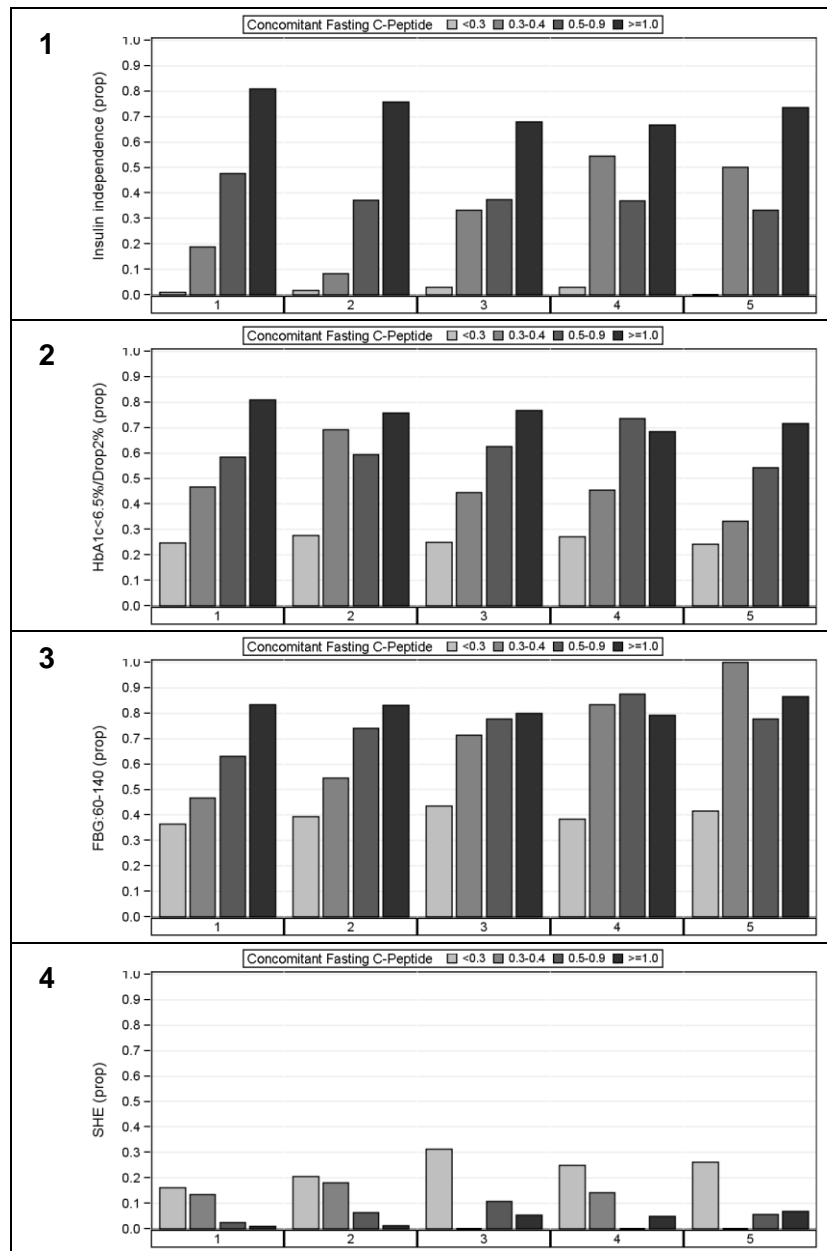
Similarly, graft function is lost over long-term follow-up, although it too varies substantially according to various factors. By Kaplan-Meier and Cox proportional hazards analysis, graft survival (fasting C-peptide $\geq$ 0.3 ng/mL) can range as low as 40% at 5-years with unfavorable factors (e.g., recipient age <35 years,  $p<0.001$ , Exhibit E1), or islets not cultured ( $p<0.001$ , Exhibit E4), to upwards of 80% at 5 years with favorable factors (e.g., T-cell depletion plus TNF- $\alpha$  inhibition,  $p=0.04$ , Exhibit E6).

**Exhibit E**  
**Time to complete graft failure post last infusion**



Even partial graft function, i.e., fasting C-peptide of 0.3-0.5 ng/mL usually requiring some level of exogenous insulin use, is associated with improved HbA1c, greater glycemic control, and lower levels of severe hypoglycemia (Exhibit F): the higher the fasting C-peptide level, the higher the likelihood of insulin independence, HbA1c<6.5% or drop by 2%, FBG of 60-140, and the lower the likelihood of severe hypoglycemia. Even with C-peptide<0.3 ng/mL, severe hypoglycemia occurs less than 30% at any follow-up, a substantial reduction from the baseline level of about 70%.

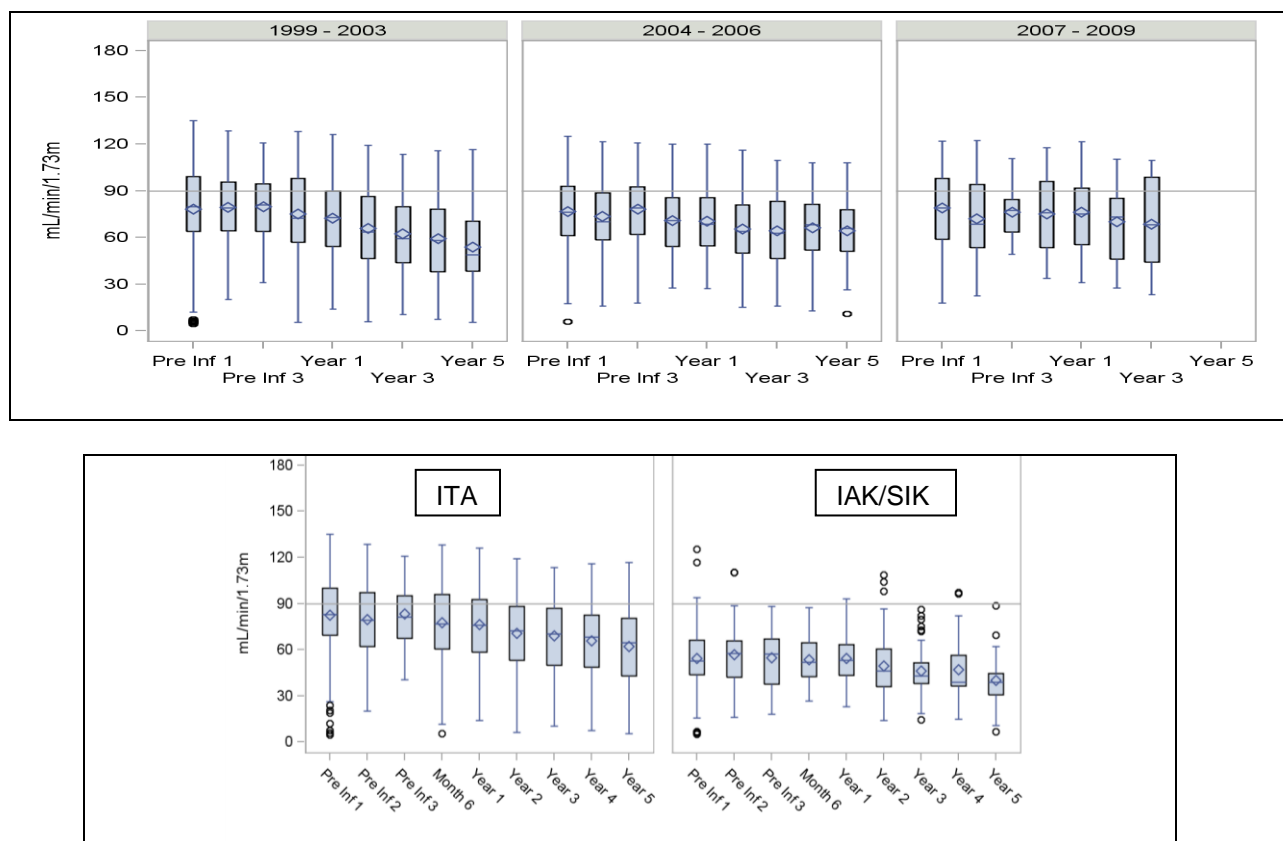
**Exhibit F**  
**Insulin independence (1), HbA1c <6.5 or drop by 2% (2), FBG 60-140 (3) and**  
**Severe hypoglycemic events (4)**  
**By concurrent C-peptide level, at annual follow-up post last infusion**



**Adverse Effects.** The post-transplant increases in ALT and AST levels seen in the early era (1999-2003), followed by return to pre-transplant levels by 1 year, were virtually eliminated in

the most recent era (see full report Exhibits 6-1 & 6-2). The steady rise in serum creatinine over 5 years post transfusion in the early era was also virtually eliminated in the 2004-2006 era (see full report Exhibit 6-9). The decline in CKD-EPI calculated GFR (eGFR) seen in 1999-2003 was less steep in 2004-2006 and 2007-2009 (Exhibit A). Compared with an age-unadjusted cohort of 1,141 T1D followed by the Diabetes Control and Complications Trial and then by the Epidemiology of Diabetes Interventions and Complications (EDIC) (The DCCT/EDIC Research Group, 2011) who started with mean eGFR levels of 126 ml/min/1.73m<sup>3</sup>, CITR allograft recipients had much lower mean eGFR (83±24SD for ITA and 54±23 for IAK/SIK) at their first transplant. CITR ITA recipients exhibited a decline in eGFR of 16.5±20.3 and IAK/SIK experienced a mean decline of 7.7±32.6 ml/min/1.73m<sup>3</sup> in 5 years from first infusion, compared to a mean decline of about 9 ml/min/1.73m<sup>3</sup> over the first 5 years in the DCCT.

### Exhibit G Chronic Kidney Disease Collaboration (CKD-EPI) Estimated GFR (mL/min/1.73m<sup>2</sup>)



**Neoplasms.** A total of 29 instances of neoplasm have been diagnosed in 27 of the 571 islet recipients who collectively represent a total of about 1,800 person-years of observed follow-up. This equates to about 0.02 neoplasms per person-year. Twenty-one (72%) were classified as benign: 16 instances in 13 patients (1 in 11 patients, 2 in one patient, and 3 in another) of basal or squamous cell carcinoma of the skin; the 11 patients with a single instance recovered completely, and the other two recovered with sequelae. There were 6 instances of malignant ovarian cysts, three instances of breast cancer (once in one patient and twice in another); two instances of lung cancer; and two instances of thyroid cancer. Of the 12 patients developing non-skin cancers, six (50%) recovered completely, 2 recovered with sequelae, 3 did not recover, and 1 died (lung).

**Deaths.** There have been 18 reports of death to the Registry for islet allograft recipients, for 3% crude mortality over a mean of 6 years elapsed follow-up per patient (including periods after complete graft failure and loss to observed follow-up). Causes of death were (# cases): infection (5); cerebral hemorrhage (3); cardiovascular (2); acute respiratory distress syndrome (1); diabetic ketoacidosis (1); lung carcinoma (1); multi-organ failure of unknown etiology (1); acute toxicity (1); and unknown/unreported causes (3).

## CONCLUSIONS

In the years since 2005, fewer North American centers performed islet transplantation, with half as many islet transplant recipients in 2007 as in each year from 2001 to 2005. Notably, both center activity and recipient numbers increased in 2008-2009 compared to 2007. With the continuation of Clinical Islet Transplantation (CIT) Consortium protocols that began in 2008, the number of new islet cell recipients has risen somewhat in North America, and remained steady in Europe and Australia in 2008-2009.

The safety-risk profile indicates that over 1999-2009, recipients of allogeneic islet transplantation were much more impacted by their disease than either of the DCCT-EPIC T1D cohorts, being substantially older, having diabetes for many more years, exhibiting much more impaired kidney function at initial transplant, and suffering from very poor glycemic control marked by frequent episodes of severe hypoglycemia. Despite the burden of immunosuppression, CITR allograft recipients exhibited substantial benefit with acceptable risk as evidenced by low levels of infusion-related complications, and relatively few events of immunosuppression-related cancer and death. Increased cancer risk is associated with both diabetes (Hemkens, et al., 2009; Suh, 2011; Noto, Osame, Sasazuki, and Noda 2010) and solid organ transplantation (Engels, et al., 2011), making it difficult to predict expected rates of neoplasm in T1D islet transplant recipients. Declining kidney function, while of concern, is not comparable to the full DCCT-EPIC cohorts: in CITR allograft recipients, eGFR started much lower relative to the DCCT-EPIC cohorts, declined at higher rates in the ITA group and declined at similar rates in the IAK/SIK group, which were very low to start with.

Islet transplantation continues to show improved long-term benefits of insulin independence, normal or near normal HbA<sub>1c</sub> levels, sustained marked decrease in severe hypoglycemic episodes and a return of hypoglycemia awareness. The accumulated experience in islet transplantation indicates that the best candidates for islet transplantation are recipients  $\geq 35$  years of age in relatively better glycemic control. The use of vasopressors and insulin in the donor at pre-recovery, as well as use of T-cell depletion with TNF antagonism for induction, and CNI with IMPDH inhibitors for maintenance immunosuppression, are associated with improved outcomes.

### **Acknowledgments and Disclaimers**

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