

Scientific Summary of the Collaborative Islet Transplant Registry (CITR) 2013 (Ninth) 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 29.1 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. From 2005 through 2015 the Clinical Islet Transplant Consortium (www.CITIsletStudy.org) conducted studies designed 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 from all such programs have contributed data and collaborated 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. In addition, CITR maintains interactive maps of North American and JDRF European and Australian islet transplant programs at 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 from 2006 through 2015. The cumulated North American, European and Australian data are pooled for analyses included in the annual report. CITR Annual Reports are publically available as open access and can be downloaded or requested in hard copy at www.citregistry.org. **This Scientific Summary highlights results from the CITR 2013 (9th) Annual Report, either by direct inclusion or by reference.**

PATIENTS AND METHODS

From 1999 through 2013 – the cut-off for the 9th Annual Report – CITR has collected data on the following groups of study subjects:

- Allogeneic islet transplantation (typically cadaveric donor), performed as either islet-transplant alone (ITA) or islet-after-kidney (IAK). A small number of cases have been performed as islet simultaneous with kidney (SIK). The last group are combined with the

IAKs in Chapters 1-4, and 6-8 of the Annual Report, but omitted for the main outcomes (Chapter 5).

- Autologous islet transplantation, performed after total pancreatectomy (N=610) are also reported to CITR. They are summarized in a separate report.

The 9th Annual Report and this Summary focus on the allogeneic islet transplant recipients. The autologous islet transplant recipients are the subject of a separate report.

The database for the 9th Annual Report was closed for analysis on December 17, 2015 for data on recipients that were first transplanted as of December 31, 2013.

At the time of their first Islet transplant,

- ITA recipients were 17-74 years of age (mean 46±10.4SD), had T1DM for 2-61 (29±11) years, and 76% had very poor diabetes control including hypoglycemia unawareness. Poor glycemic 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_{1c} levels (>8% of total hemoglobin).
- IAK/SIK recipients were 6-69 years of age (mean 46±9.0SD), had T1DM for 2-57 (32±9) years, and 39% had very poor diabetes control including hypoglycemia unawareness.

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 28, 75, Month 6, 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), or viewed at the CITR website (www.citregistry.org).

CITR utilizes the Coordinating Center's (The Emmes Corporation, Rockville, MD; www.emmes.com) web-based data entry and management systems to capture data on recipients, donors and pancreata. Additional data are obtained through data sharing agreements with the United Network for Organ Sharing (UNOS) for US donor data, the Administrative and Bioinformatics Coordinating Center (ABCC, 2001-2009) of the Islet Cell Resource Centers for the islet data, and the Data Coordinating Center of the Clinical Islet Transplant Consortium (CIT, 2005-2015).

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.

Statistical Analysis.

In addition to updating information on total islet transplant procedures and descriptions of the recipient, donor, islet and immunosuppression data, a major focus of the present analyses is to continue identifying and corroborating factors of patient selection, islet processing and islet transplantation management 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 are routinely performed as scheduled and include data audits for key recipient baseline, primary outcome, and safety 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.

First achievement of insulin independence, as well as complete graft failure, were 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.

Primary outcomes, analyzed as prevalence (percent) at annual study time points post last infusion, include:

- insulin independence (≥ 14 consecutive days)
- C-peptide < 0.3 ng/mL
- HbA1c $< 6.5\%$ or drop by $\geq 2\%$
- fasting blood glucose of 60-140, and
- severe hypoglycemic events (Yes/No).

An "all-factors-on-all-outcomes" analytical approach was undertaken to uncover the most predictive recipient, donor, islet and medical management practices associated with the greatest success rates in the primary outcomes. First, every covariate available on recipient, donor, islet, and immunosuppression was analyzed univariately to determine its effect on each outcome (insulin independence, HbA1c, etc.). Those variables significant at $p < 0.10$ were then stepped into multivariate models to eliminate duplicative effects and narrow down the final effects. While some predictive variables (factors) consistently exerted a clear beneficial effect across outcomes, each outcome within ITA and IAK yielded a slightly different set of significant favorable factors. To facilitate interpretation for translation into clinical practice, the set of favorable factors that were common to all the outcomes within ITA and IAK respectively were selected, and subgroups comprising all those with the favorable common factors was compared to the remainder (who may have none, one or more, but not all the favorable factors). These final results of the common favorable factors on the primary outcomes are exhibited together (Exhibit D). Targeting the common favorable factors somewhat dilutes the largest differences seen univariately for each outcome; however, this method identifies the factors that are clinically most relevant to the recipients. These then comprise best practices in terms of patient selection and medical management for allogeneic islet transplantation.

Secondary outcomes include whole-distribution description of laboratory measurements, metabolic test results, liver and kidney function measures, and complications of diabetes.

Safety is monitored by incidence rates of adverse events classified by CIT-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.

Statistical analyses were conducted using SAS 9.4.

RESULTS

Islet Allograft Transplantation Activity 1999-2013. As of December 31, 2013, the CITR Registry included data on 1,011 allogeneic islet transplant recipients (819 islet transplant alone, ITA, and 192 islet after or simultaneous with kidney, IAK/SIK), who received 1,927 infusions from 2,421 donors (Exhibit A). The North American sites contributed 55%, while the European and Australian sites contributed 45% of the data. Combining the ITA and IAK/SIK recipients, 29% received a single islet infusion, 50% received two, 18% received three, and 3% 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 1999-2013

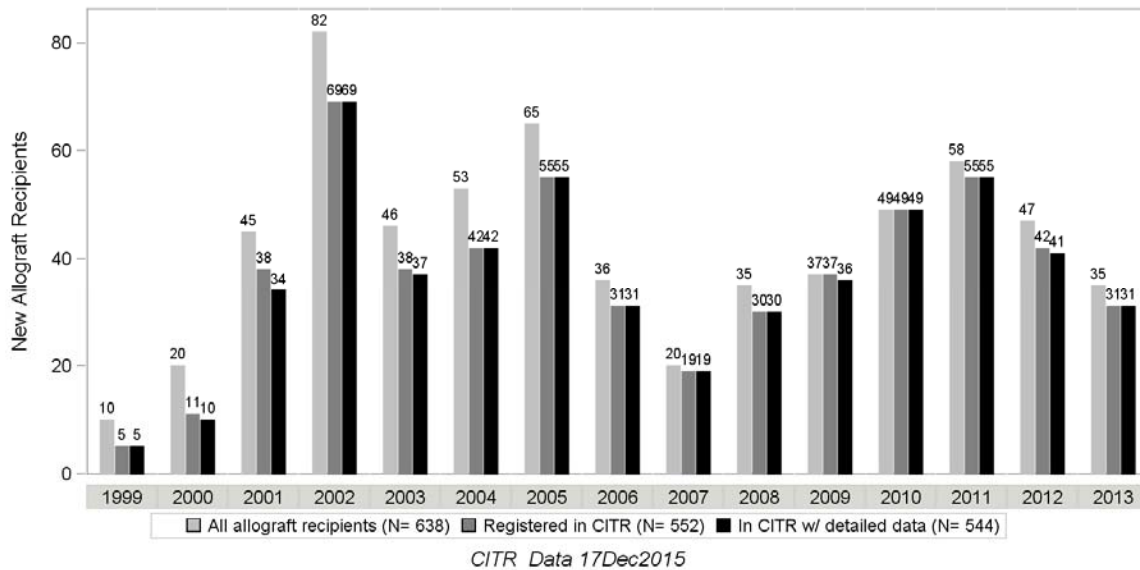
	Islet Transplant Alone (ITA)			Islet After Kidney or Simultaneous Islet-Kidney (IAK/SIK)			GRAND TOTALS
	Total	North America	Europe/Australia/Asia	Total	North America	Europe/Australia/Asia	
Recipients	819	488	331	192	64	128	1,011
Infusions	1,584	933	651	343	112	231	1,927
Donors	2,032	1,005	1,027	389	123	266	2,421

Exhibits B1 and B2 display the data collected from the islet transplant programs in North America and the JDRF European and Australian sites from 1999 through 2013. Of the 638 total North American recipients reported by general survey of the sites to have received an islet allograft in 1999-2013, 552 (87%) consented to and were registered in CITR. Detailed data was available on 544 of these recipients, representing 85% of the overall 638. Of the 473 total reported JDRF European and Australian recipients, 97% (459) were consented and registered in CITR and 79% (376) have detailed data available. Both North American and JDRF sites saw a decline in new recipients around 2007, followed by an increase in following years. In 2013, North American sites again saw a decline while JDRF sites increased the number of new recipients.

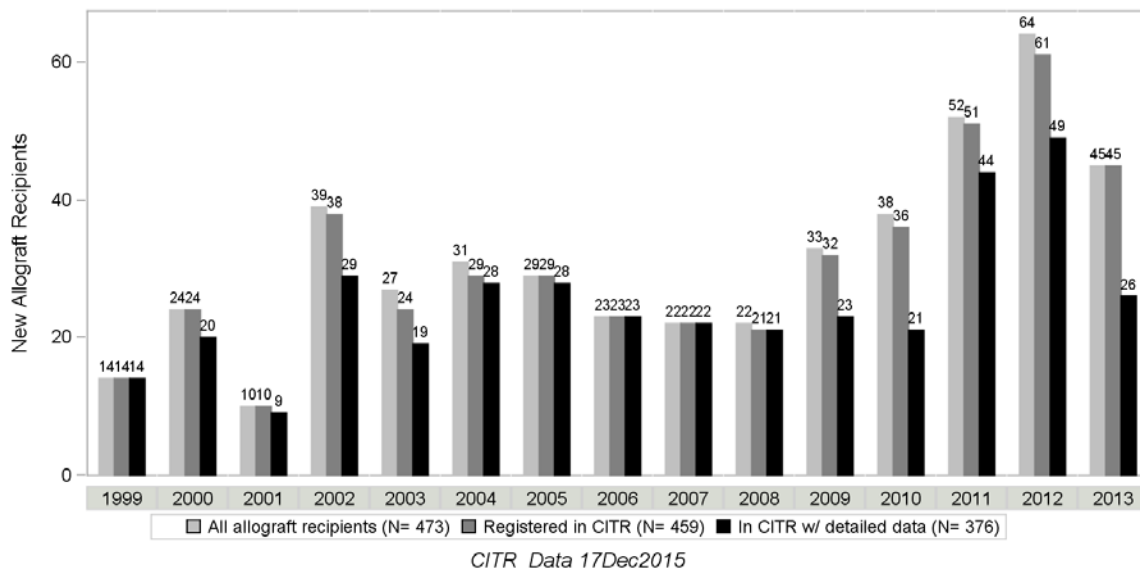
Exhibit B

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 1999-2013



2. Allograft recipients at CITR European and Australian Centers 1999-2013



Islet Transplant Recipient Characteristics. Over the eras of the Registry, the following trends are observed for recipients of allogeneic islets:

- Recipients have been selected at older age (42±0.6* to 49±0.6) and longer wait time (236.7±21.4d to 360.2±39.1d) at initial transplant
- Recipients have been selected with higher HbA1c (7.9±0.1 to 8.4±0.1), increased use of insulin pump (30% to 50%), and higher prevalence of hypoglycemia unawareness (58% to 76%)

- Greater proportions had positive GAD65 autoantibody (31% to 60%) and lower proportions had positive insulin autoantibody (32% to 13.5%)
- Recipients had lower levels of total cholesterol (181.3 ± 2.8 to 164.3 ± 3.9) and LDL cholesterol (98.5 ± 2.5 to 84.0 ± 3.2) in recent eras

*Mean \pm SE

There were also notable differences in medical characteristics between ITA and IAK/SIK recipients, most notably, a much lower initial eGFR in the IAK/SIK (58.6 ± 2.6 vs. 90.6 ± 0.8) recipients.

Donor Information. All allograft donors were deceased, at a mean age that rose from 43.8 ± 0.7 SE to 44.3 ± 0.6 years. “Infusions” (an “infusion” is defined as all islet products from one, two or three (maximum) donors given to a single recipient on a single day) were comprised of about 58% all male donors, 37% all female donors, and 5% mixed male and female donors. About 20% of infusions derived from Hispanic donors, while about 10% derived from non-white donors. About 60% of the donors had cerebrovascular accident/stroke as their cause of death while 28% experienced trauma.

About 30% of the donors received a transfusion during their terminal hospitalization, while only 6% received a transfusion intraoperatively. Sixty-two percent (62%) of the donors received steroids and 97% received at least one vasopressor during the terminal hospitalization. Insulin administration during recovery increased from 33% in the earliest era to 55% in the most recent era. A total of 12 donors tested positive for anti-HBC, one tested positive for RPR-VDRL and one for HCV. Mean serum creatinine of the donors remained steady around 1.1 mg/dL, while the mean maximum stimulated blood glucose decreased from 244 ± 6.3 SE to 202 ± 4.9 mg/dL over the eras of the registry.

The following trends are observed among donors of allogeneic islets over the eras:

- Substantial increase in donor weight and BMI (27.9 ± 0.3 to 30.0 ± 0.3)
- Lowered use of transfusion during hospitalization (33% to 15%)
- Increased use of insulin to donor during hospitalization (33% to 55%)
- Donor stimulated blood glucose (244 ± 6.3 SE to 202 ± 4.9 mg/dL) has declined

Pancreas Procurement and Processing.

The following trends were observed regarding islet preparations:

- pancreas preservation with UW-only fell from 51% to 9% and 2-layer solutions fell from 3% to 0%, while HTK use rose from 0% to 15% and preservation other than UW, 2-layer, HTK, Eurocollins and Celsior rose from 32% to 73%; data collection on these methods is under revision
- use of Liberase HI dropped from 99% in 1999-2002 to 19% in 2011-2014, while Serva/NB1 use rose from 0% to 45%, and other collagenase rose from 0.4% to 14%. Thermolysin use increased from 0% to 16%, and pulmozyme use rose from 19% to 61%.
- Islet preparations were cultured more frequently in the recent eras (from 35% in 1999-2002 to 98% in 2011-2014).
- Mean time from brain death to pancreas recovery was about 3 hours longer for ITA than IAK/SIK, and has increased over the eras by 4 hours.

All but one of the pancreata processed used a density gradient for islet purification. Of the 1,212 islet preparations, 18 (1.5%) showed a positive aerobic culture, 7 (0.6%) showed a

positive anaerobic culture, 15 (1.2%) showed a positive fungal culture, and 1 (0.1%) tested positive for mycoplasma.

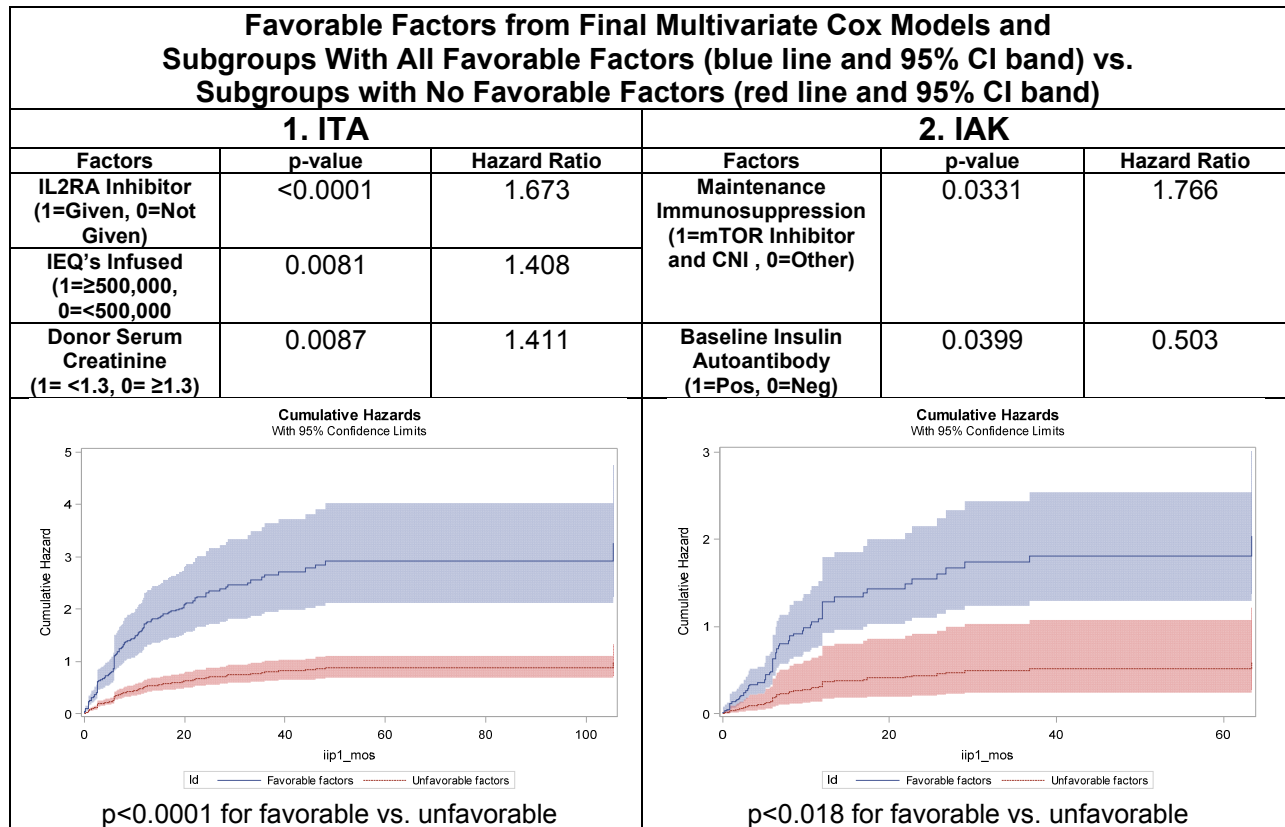
Islet product characteristics. Mean total islet equivalents (1000s) per infusion rose from 413 ± 10 SE IEQs in the first era to 423 ± 9 in the third, then decreased to 418 ± 8 in the most recent era. Total Beta cells and β -cells/kg were higher for IAK/SIK (5.5 ± 0.7 vs. 3.5 ± 0.2) and have increased over the eras (2.9 ± 0.3 to 4.3 ± 0.5). Endotoxin (both total and /kg) has declined sharply over the eras (0.5 ± 0.1 to 0.1 ± 0.05). Stimulation index has declined over the eras (3.7 ± 0.3 to 2.8 ± 0.2).

Immunosuppression therapy. Induction with IL2R antagonists only, which comprised about 54% of all initial infusions in 1999-2002, was replaced or supplemented with regimens that included T-cell depletion with/without TNF antagonists in about 61% of the new infusions performed by 2011-2014. In 1999-2002, maintenance immunosuppression was predominantly (64%) calcineurin (CNI)+mTOR inhibitors. It was increasingly replaced or supplemented throughout the eras by a CNI and IMPDH-inhibitor combination; in the most recent era, CNI+mTOR inhibitors were used in 30% of new infusions while CNI+IMPDH inhibitors were used in about 56%.

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 real-time conditions that include 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. While the overall rate of first achievement of insulin independence is, remarkably, nearly identical between ITA and IAK recipients, the most predictive factors of this endpoint in the two groups were different: for ITA, the most favorable factors were immunosuppression with IL2RA, ≥ 500 K IEQs infused overall, and donor serum creatinine < 1.3 . For IAK, the favorable factors were maintenance immunosuppression with mTOR-inhibitor, and negative recipient insulin autoantibody at baseline (Exhibit C).

Exhibit C
First Achievement of Insulin Independence Post First Infusion
ITA and IAK Recipients Separately

(Through all infusions, censored at final graft loss or end of follow-up)



The primary endpoints are analyzed as prevalence at annual time points post last infusion to isolate the factors that optimized the outcomes. Remarkably, only a handful of common favorable factors emerge, and their combined effects appear to be additive, as exhibited by the final multivariate models of the various primary endpoints (Exhibit D). For each endpoint within ITA, the subgroup with all favorable common factors had significantly and clinically higher prevalence of all outcomes at $p<0.001$, except for absence of severe hypoglycemic events, in which case the outcome prevalences are sustained at remarkably high levels ($>90\%$) throughout the five years of follow-up, hence no specific factors are predictive. For each endpoint within IAK excluding severe hypoglycemic events, the subgroup with all favorable common factors had significantly and clinically higher prevalence of all outcomes at $p<0.03$. The common favorable factors are:

For islet alone:

- Selection of patients aged 35 years or older. The remarkable consistency of this result runs across most of the primary outcomes including achievement and long-term retention of insulin independence or reduction in daily insulin requirement, higher levels of basal C-peptide, lowered HbA1c levels and/or drop by 2%, and near elimination of severe hypoglycemia. As islet transplantation is not life-saving, this selection factor helps optimize use of scarce donor pancreas resources. Obviously, clinical judgment should drive the process: all other favorable factors being in place, someone younger than 35 may still be a good candidate for an islet transplant.

- Use of T-cell depletion and/or TNF- α inhibition and MTOR inhibition with calcineurin inhibitors continue to be associated with improved clinical outcomes with accruing data in CITR. A major limitation from the CITR data is that these strategies were not assigned at random and independently of each other; hampering the ability to isolate the effects of each factor separately. Nonetheless, from analyses of each factor alone (yes/no) and as combinations of induction and maintenance immunosuppression, the benefit of these agents continues to be well supported by the data.
- Islet product characteristics have remained consistently high over the eras of the Registry (Chapter 3). Because of the consistently high levels and narrow ranges of all islet product criteria used for clinical transplantation, it is difficult to statistically evaluate the effect of low-grade vs. high-grade products. The only factor that consistently yields improved outcomes is higher total IEQs infused, whether in a single infusion or over 2-3 infusions.

For islet-after-kidney:

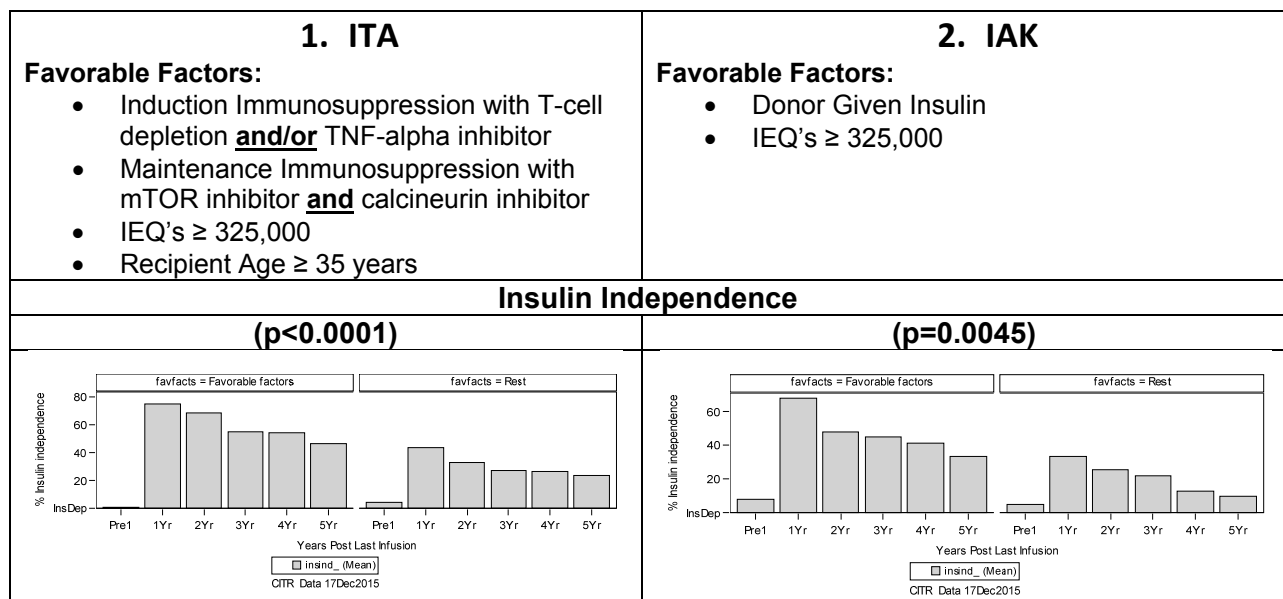
- As with ITA, total IEQs $\geq 325,000$ over one to several infusions is a primary predictor of the greatest clinical benefit of islet transplantation..
- Donor management with insulin therapy during retrieval is associated with improvements in most of the primary outcomes and now emerges as a favorable common factor for IAK.

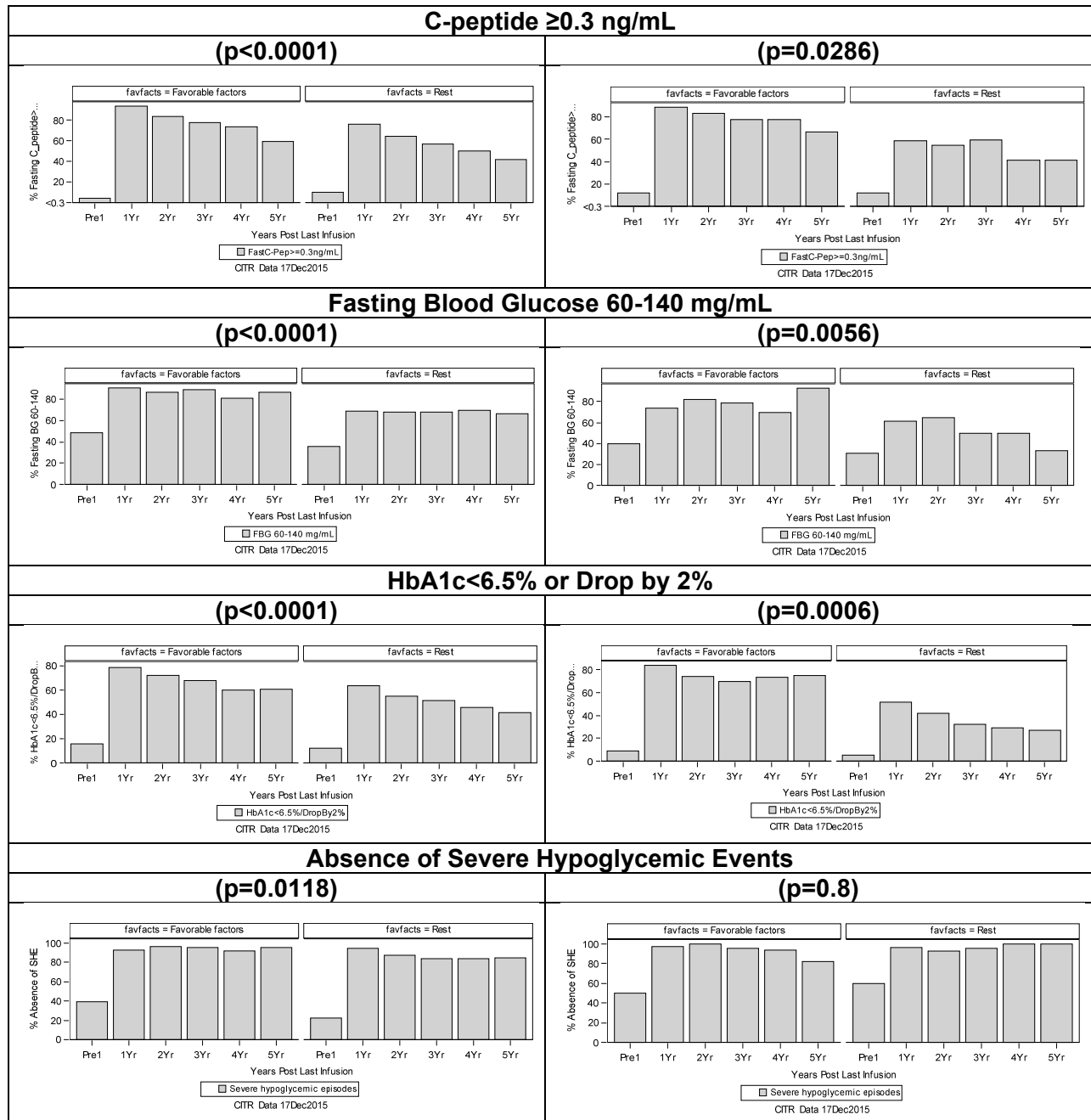
Simultaneous islet-kidney (SIK):

There were 9 cases of SIK reported to the registry as of the data lock for this report. While their data are reported in earlier chapters (IAK/SIK) of the 9th Annual Report, they were excluded from analyses of primary endpoints to keep the transplant groups clean (SIK is more similar to ITA than IAK in terms of immunosuppression, but also similar to IAK in terms of kidney transplant).

Exhibit D

Combined Effect of the Common Favorable Factors on Primary Outcomes Post Last Infusion (p-value of difference between subgroup with the common favorable factors vs. the rest for all endpoints in each transplant group)





Basic graft function as measured by retention of fasting C-peptide ≥ 0.3 ng/mL is sometimes lost over long-term follow-up, although it too varies substantially according to various factors. By Kaplan-Meier and Cox proportional hazards analysis, retention of C-peptide ≥ 0.3 ng/mL post last infusion in ITA (Exhibit E1) is maximized by recipient age ≥ 35 years ($p < 0.001$), $> 500K$ IEQs infused ($p = 0.04$), and use of TNF- α inhibitor ($p = 0.004$). For IAK recipients (Exhibit E2), in addition to IEQ $> 500K$ infused ($p = 0.0012$), maintenance with mTOR inhibitor ($p = 0.025$) is the other significant factor. With these factors combined, graft retention rates remain at 80% through 7-8 years in both transplant groups.

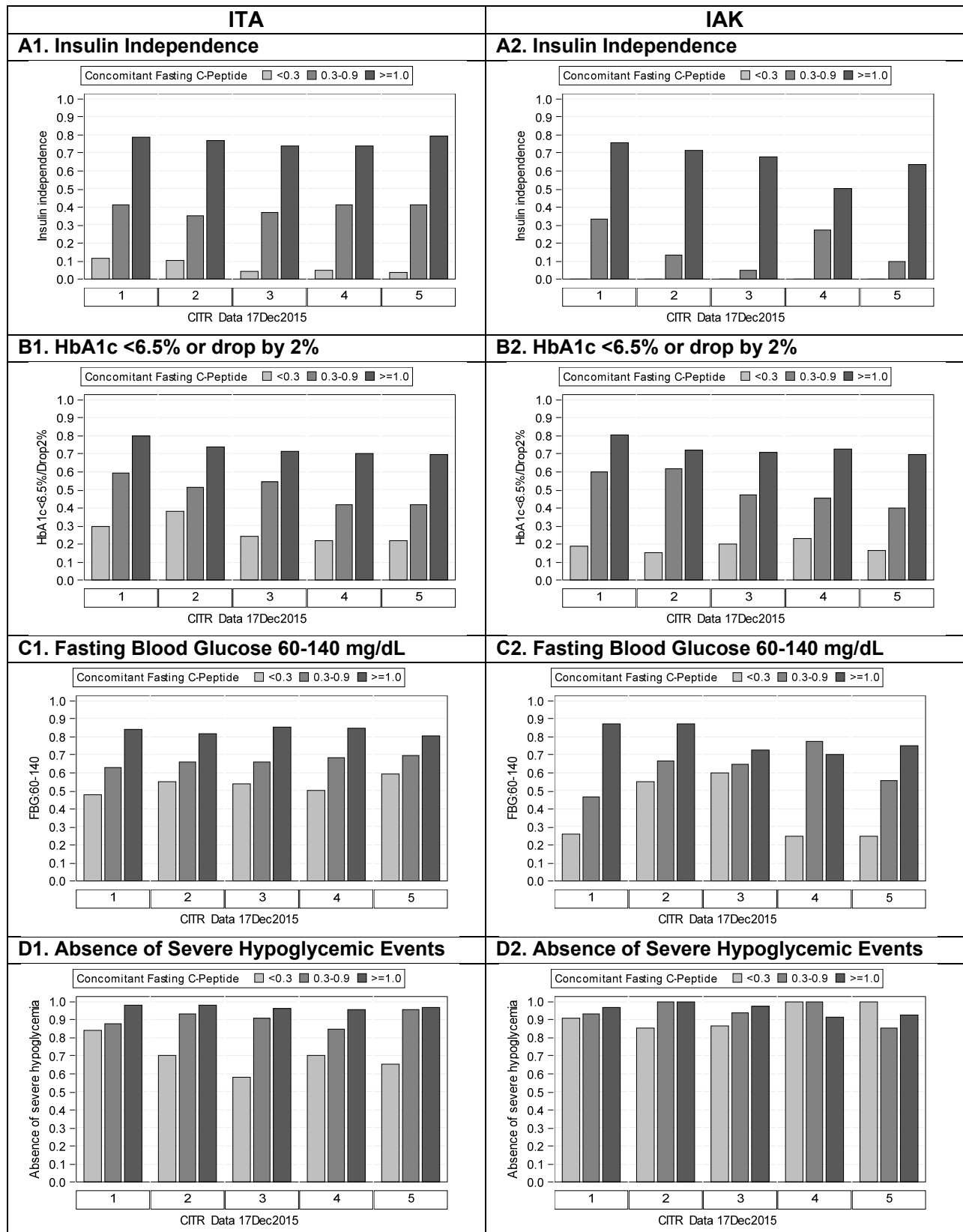
Exhibit E
Retention of C-peptide ≥0.3 ng/mL Post Last Infusion
Combined effects of most favorable factors

1. ITA			2. IAK		
Factors	p-value	Hazard Ratio	Factors	p-value	Hazard Ratio
Age (1= ≥35, 0= <35)	<0.0001	0.397	mTOR Inhibitor (1=Given, 0=Not Given)	0.0249	0.425
TNF alpha (1=Given, 0=Not Given)	0.0036	0.555			
IEQ's Infused	0.0391	0.743	IEQ's Infused	0.0012	0.416

<p align="center">Survivor Functions With 95% Confidence Limits</p> <p align="center">p<0.0001 for favorable vs. unfavorable</p>	<p align="center">Survivor Functions With 95% Confidence Limits</p> <p align="center">p=0.0001 for favorable vs. unfavorable</p>
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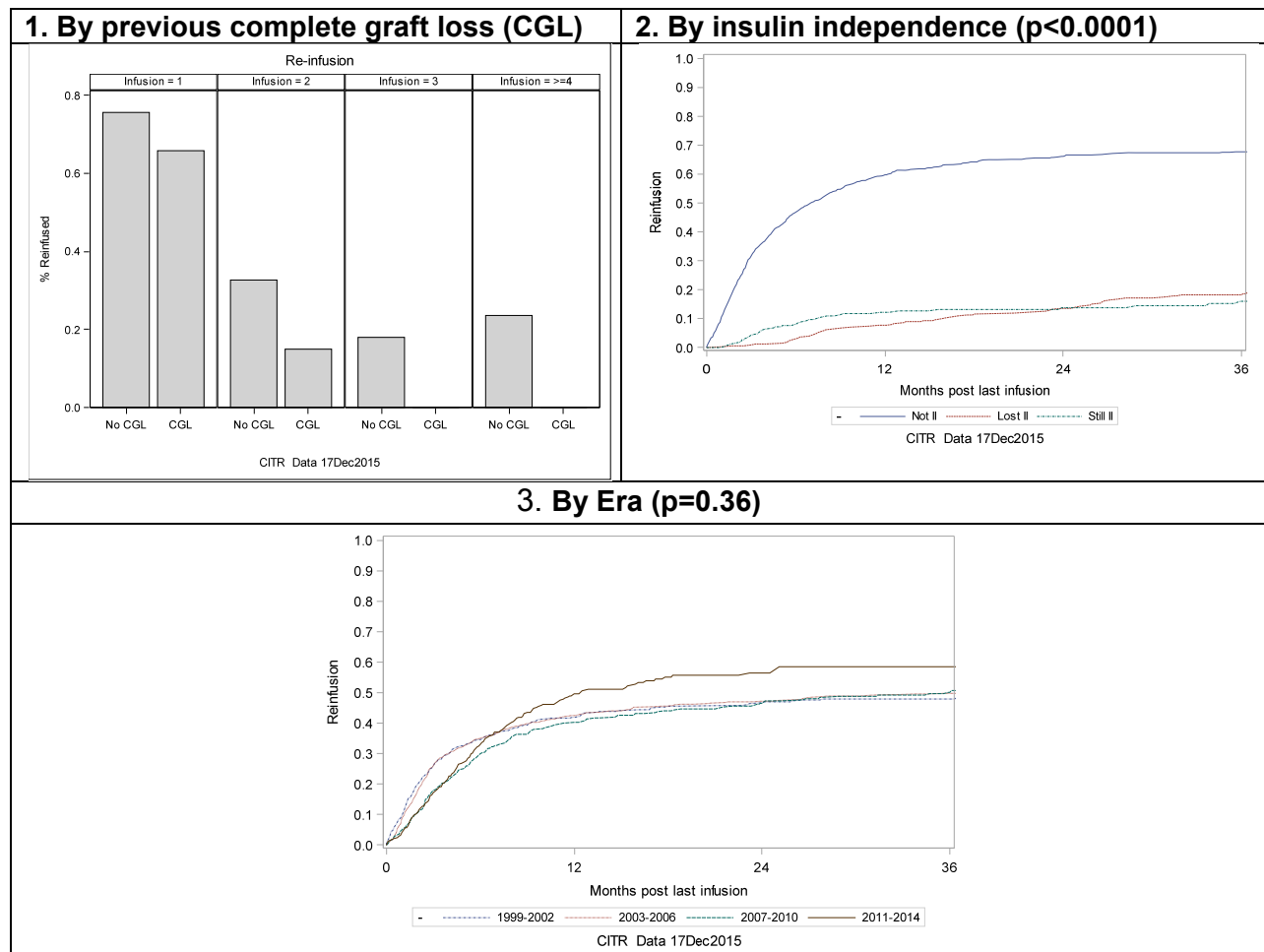
In both transplant groups, the higher the fasting C-peptide level, the higher the likelihood of insulin independence, HbA1c<6.5% or drop by 2%, FBG of 60-140, and the lower the likelihood of severe hypoglycemia (Exhibit F). Even partial graft function, i.e., fasting C-peptide of 0.3-0.5 ng/mL, is associated with lowered insulin use, improved HbA1c, greater glycemic control, and lower levels of severe hypoglycemia, which is drastically reduced over all follow-up even with C-peptide<0.3 ng/mL.

Exhibit F Association of Fasting C-Peptide Level (ng/mL) with Other Primary Outcomes at Years 1-5 Post Last Infusion



Over the years of the CITR data, reinfusion (Exhibit G) has been performed in about 71% of all allograft (ITA and IAK) recipients. It may have been performed after complete graft failure, or while the recipient still had at least some graft function (C-peptide \geq 0.3 ng/mL), or even while the patient was fully insulin independent. The group most likely to be re-infused was those who were not insulin independent (Exhibit G2). This Kaplan-Meier also shows that time to re-infusion varied substantially from days to years, with a mean \pm SD of 25 \pm 32 months. Rates of second infusion by era show a substantially uniform rate over the eras (Exhibit G3).

Exhibit G Re-infusion (Kaplan-Meier), over all infusions



Adverse Effects (laboratory determinations and reported adverse events). Data collection on adverse events and other effects of islet transplantation continues for all islet transplant recipients. The data are confirmed via regularly scheduled site visits that include 100% data audit for adverse events. The reported data are coded for system/organ class and preferred term for tabulation and summary reporting, using the Medical Dictionary for Regulatory Activities, a part of the overall data quality and assurance process integral to The Emmes Corporation's Advantage EDC system. The coding is conducted by trained Emmes medical coders. Over the years of the Registry, both the MedDRA lexicon and coding processes, as well as the data structures for reporting adverse events have evolved. Therefore, it was decided during the production of the 9th Annual Report to have the entire history of adverse events re-coded to the current MedDRA lexicon, using a uniform process and the most complete descriptions of all the reported adverse events. This process is expected to be complete by the

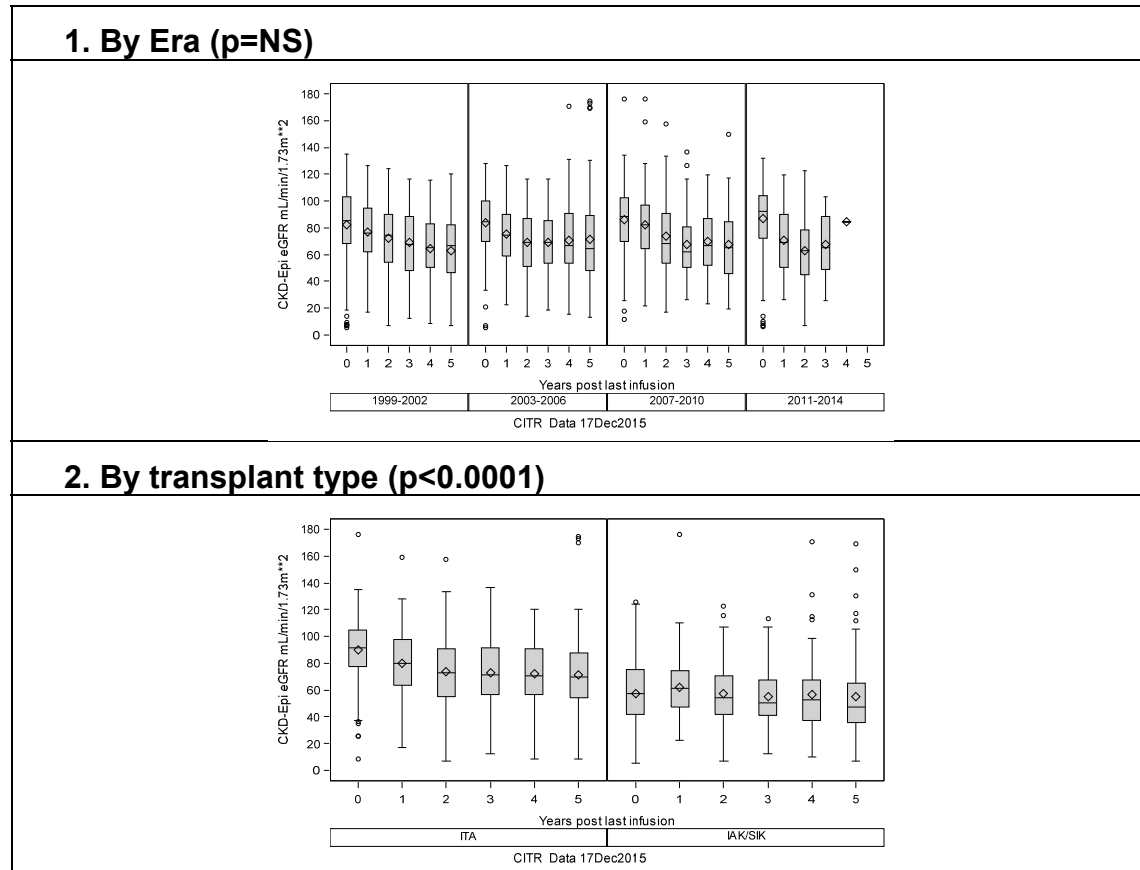
end of 2016. To avoid holding up the 9th Annual Report, the results on adverse events (Chapter 7) are being deferred until the re-coding process is complete. They will be published in the report available online, as well as in print version as an addendum.

From the laboratory determinations, ALT and AST levels typically rise after islet transplantation, then level off, with the rise being significantly lower in the recent eras ($p=0.008$), and with lower rise in those managed with TCD+TNF- α inhibition and IL2RA.

Serum creatinine rose slightly but steadily over years of follow-up after initial islet transplant, in both ITA and IAK/SIK, but started higher in IAK/SIK. Serum creatinine levels rose significantly less in patients with $\geq 325,000$ IEQ's infused.

The decline in eGFR (CKD-Epi) after islet transplantation is both statistically significant and clinically important. IAK/SIK had much lower pre-transplant levels than ITA, which then declined at a slower rate (Exhibit G2, $p<0.001$). Importantly, there were no differences in initial levels or subsequent decline over follow-up by immunosuppression regimens. 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/1.73m³, CITR allograft recipients had much lower mean eGFR (91091 \pm 0.8SE for ITA and 5959 \pm 2.6 for IAK/SIK) at their first transplant. CITR ITA recipients exhibited a decline in eGFR of 1313.6 \pm 3535.4 and IAK/SIK experienced a mean decline of 0.6 \pm 4646.5 ml/min/1.73m³ in 5 years from last infusion, compared to a mean decline of about 9 ml/min/1.73m³ over the first 5 years in the DCCT.

Exhibit H
Chronic Kidney Disease Collaboration (CKD-EPI) Estimated GFR (mL/min/1.73m²)



Neoplasms and Deaths. Tabulation and description of neoplasms and fatalities occurring in islet transplant recipients will be completed after the MedDRA recoding is complete.

CONCLUSIONS

The number of North American centers performing allogeneic islet transplantation has fluctuated over the life of the CITR, with the number of centers peaking in 2005, then declining to 2007, then leveling off at 9 active sites (1 not participating) as of 2013. With the addition of Clinical Islet Transplantation (CIT) Consortium protocols that began in 2008, the number of new islet cell recipients rose somewhat in North America from 2008 through 2011. New allograft recipients at European and Australian JDRF sites remained fairly steady up to 2008, but have seen a substantial increase in recent years.

The safety-risk profile will be updated after the MedDRA re-coding of adverse events is complete.

In terms of the clinical benefit of allogeneic islet transplantation, the cumulative CITR data now clearly points to the best patient selection and medical practices that optimize long-term outcomes: insulin independence, clinically improved HbA1c levels, achievement and durability of blood glucose levels in near-normal ranges, and the remarkable resolution of severe hypoglycemic episodes with a return of hypoglycemia awareness in the vast majority of the recipients. The accumulated experience in islet transplantation indicates that the best practices for islet are:

- For islet-alone: recipient age ≥ 35 years; $>325K$ IEQs over all infusions; and use of T-cell depletion with TNF antagonism for induction, and CNI and/or mTOR inhibitors for maintenance immunosuppression;
- For islet-after-kidney, in addition to $>325K$ IEQs over all infusions, insulin administration to the donor also is a favorable factor for optimizing outcomes.

The most remarkable clinical effect of islet transplantation are the very high levels of resolution of severe hypoglycemic events (Exhibit D, last panel), which are sustained long-term, even after complete loss of graft function (Exhibit F, last panel – while the event rates for absence of severe hypoglycemic events (ASHE) are lower when C-peptide is <0.3 ng/mL, they are still at least 60%). The fundamental determinant of clinical benefit is maintenance of C-peptide ≥ 0.3 ng/mL: the higher, the better (Exhibit F, all panels). And the most important predictors of sustained high C-peptide levels are recipient age ≥ 35 , IEQs infused $\geq 325K$, and induction with TNF- α inhibitors for ITA; and ≥ 325 IEQs infused and maintenance with mTOR inhibitors for IAKs (Exhibit E).

Acknowledgments and Disclaimers

The Collaborative Islet Transplant Registry is funded by the National Institute of Diabetes, Digestive and Kidney Diseases, National Institutes of Health, USA, and by a supplemental grant from the Juvenile Diabetes Foundation International. Additional data is made available through cooperative agreements with the US United Network for Organ Sharing, Alexandria, VA, and the Administrative and Bioinformatics Coordinating Center of the City of Hope, Duarte, CA (1999-2009). The CITR investigators (roster available at www.citregistry.org) have contributed data used in this report. The principal investigator and biostatisticians of the CITR Coordinating Center (roster available at www.citregistry.org), had full access to all the study data and assume responsibility for the integrity of the data, the accuracy of the data analysis, and the overall results and conclusions presented. Members of the CITR Publications and Presentations Committee over the life of the Registry (roster available at www.citregistry.org) contributed substantially to the analysis of the data and interpretation of the results. No collaborator discloses any conflict of interest in reporting the results presented in the CITR Annual Reports or the Scientific Summary. The voluntary participation of the islet transplant recipients is gratefully acknowledged.

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