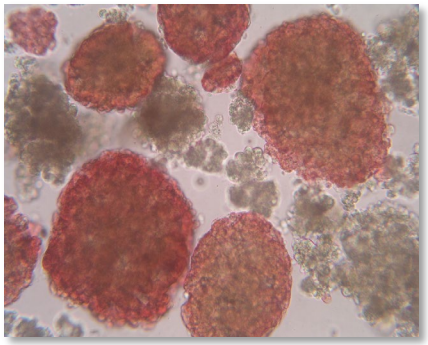


Trapianto di pancreas/isole: quando e a chi

Piero Marchetti
Università di Pisa



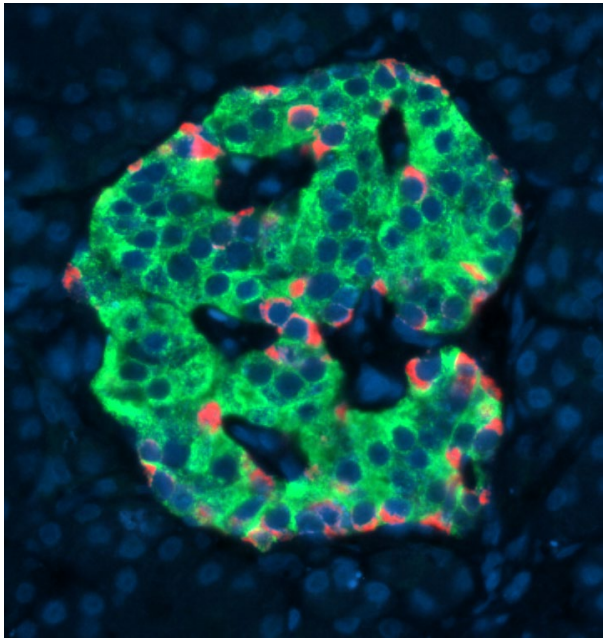


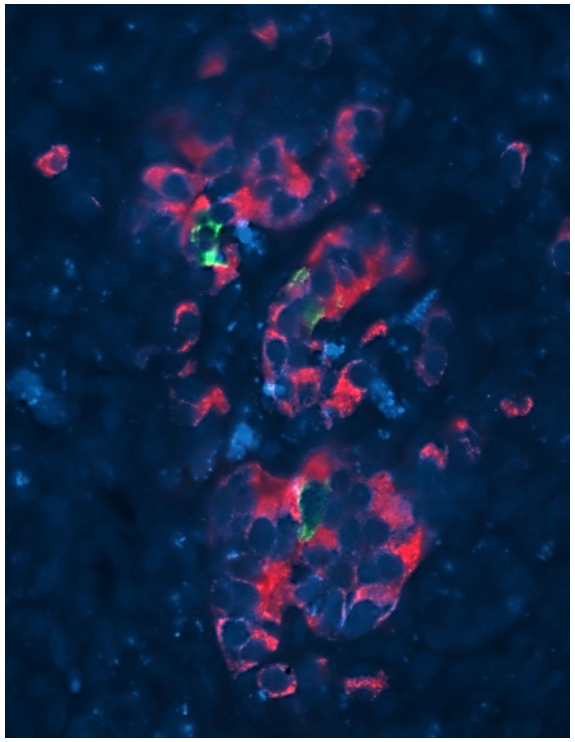


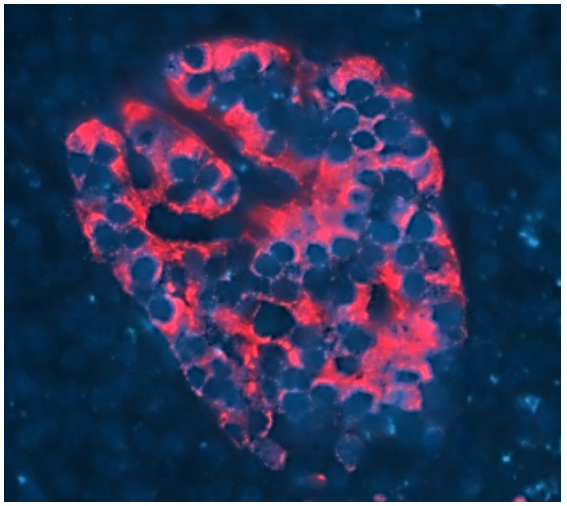
Piero Marchetti:

Nessuno conflitto di interessi per quanto riguarda gli argomenti trattati in questa presentazione

Beta cells in pancreatic islets

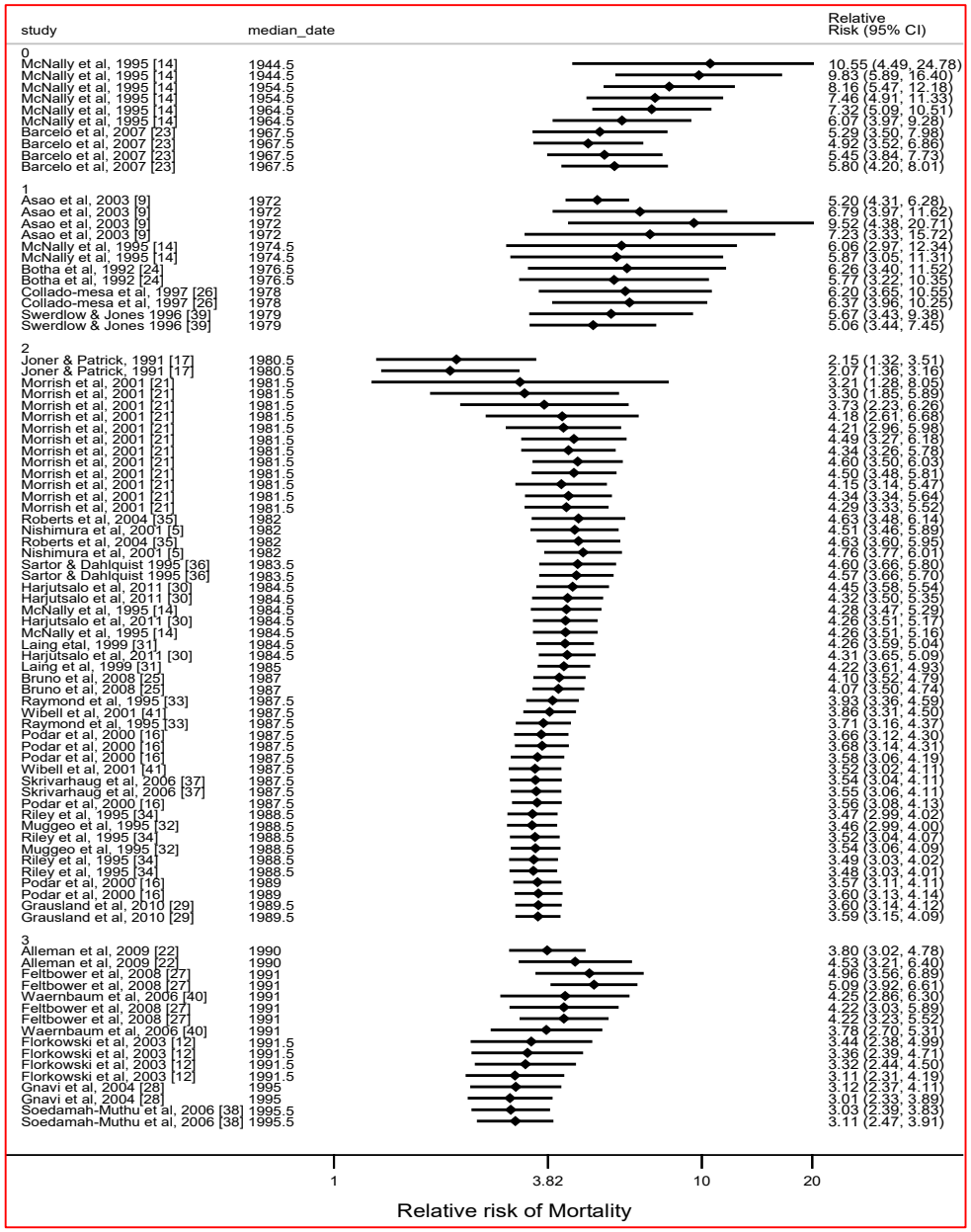






DAPI
INSULIN
GLUCAGON

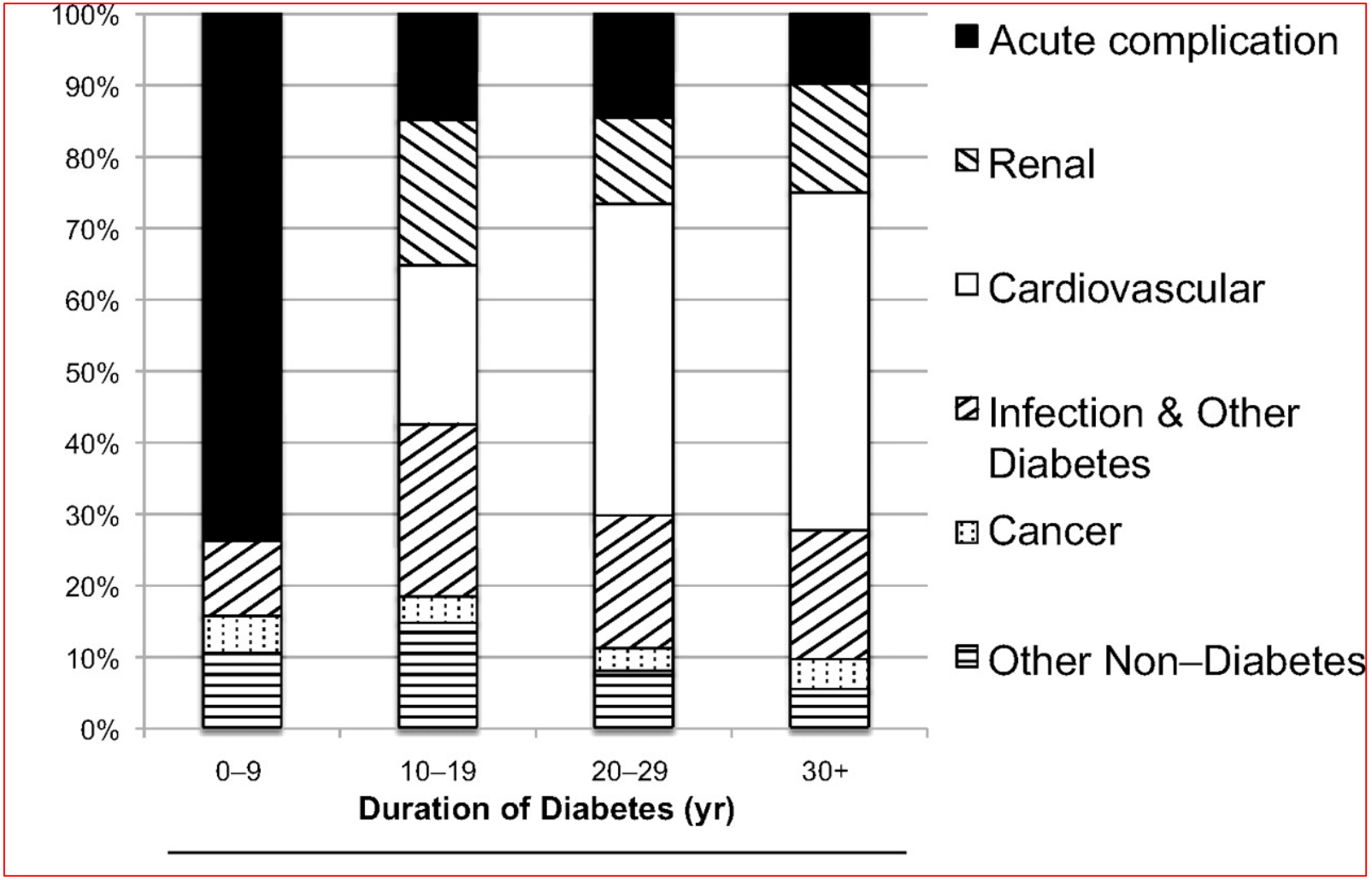
Mortality in type 1 diabetes



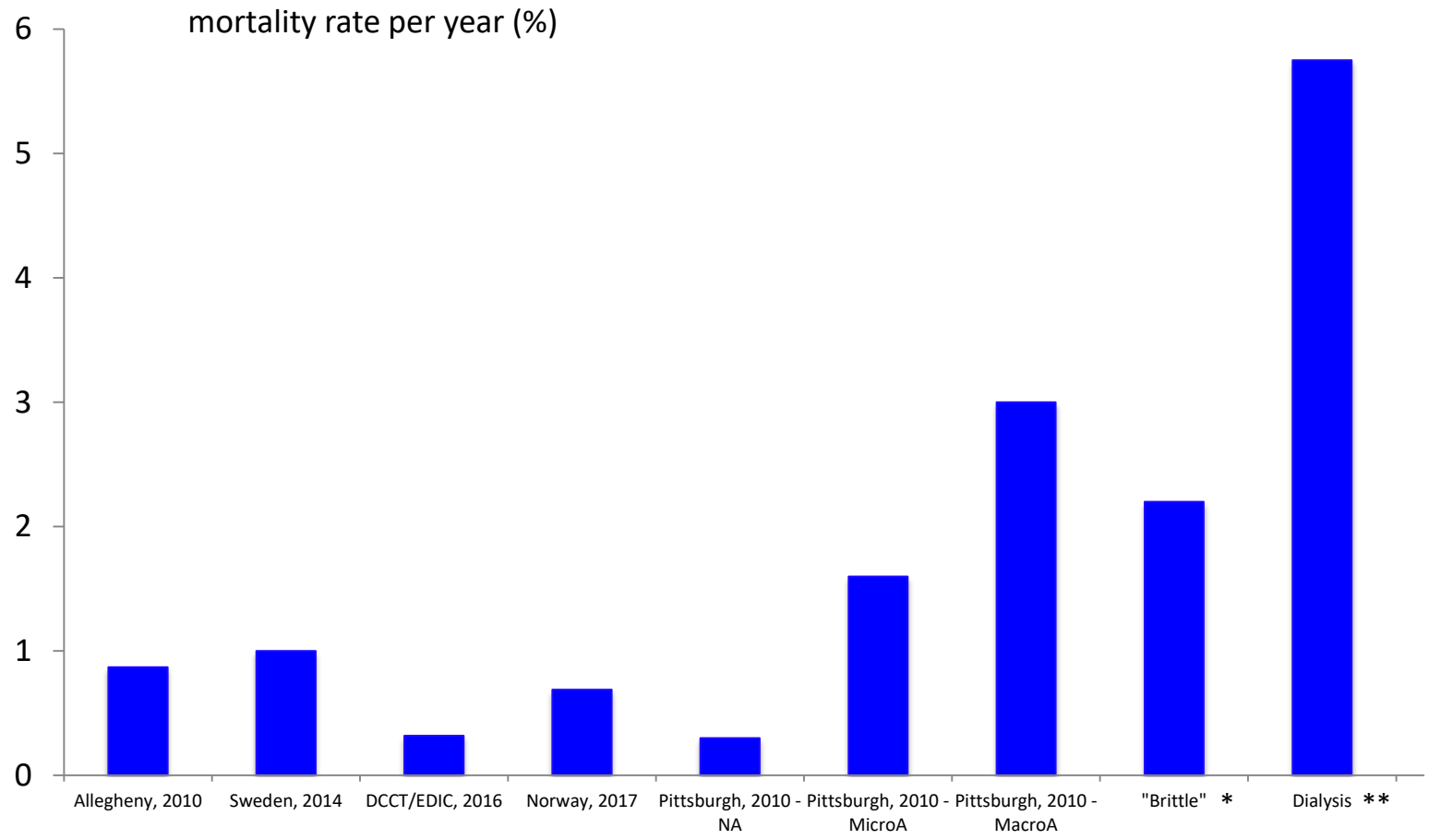
Lung TWC et al, PLoS ONE 2014

Cause-Specific Mortality Trends in a Large Population-Based Cohort With Long-Standing Childhood-Onset Type 1 Diabetes

Aaron M. Secrest,[1] Dorothy J. Becker,[2] Sheryl F. Kelsey,[1] Ronald E. LaPorte,[1] and Trevor J. Orchard[1] Diabetes 2010



Mortality in type 1 diabetes

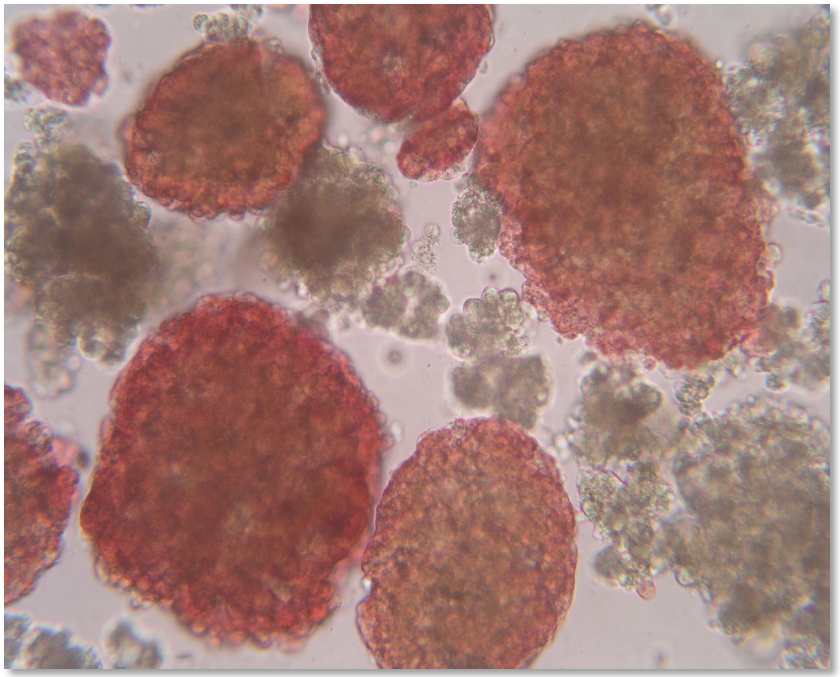


* Cartwright A et al, Q J Med 2011

** Haapio M et al, Diabetes Care 2010

The role of pancreas/islet Tx



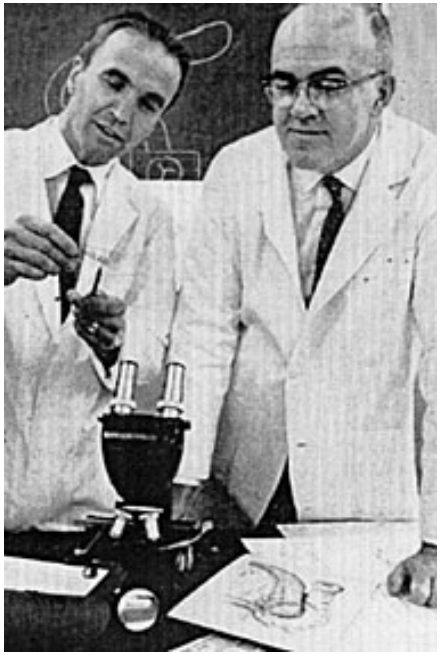


First pancreas transplant

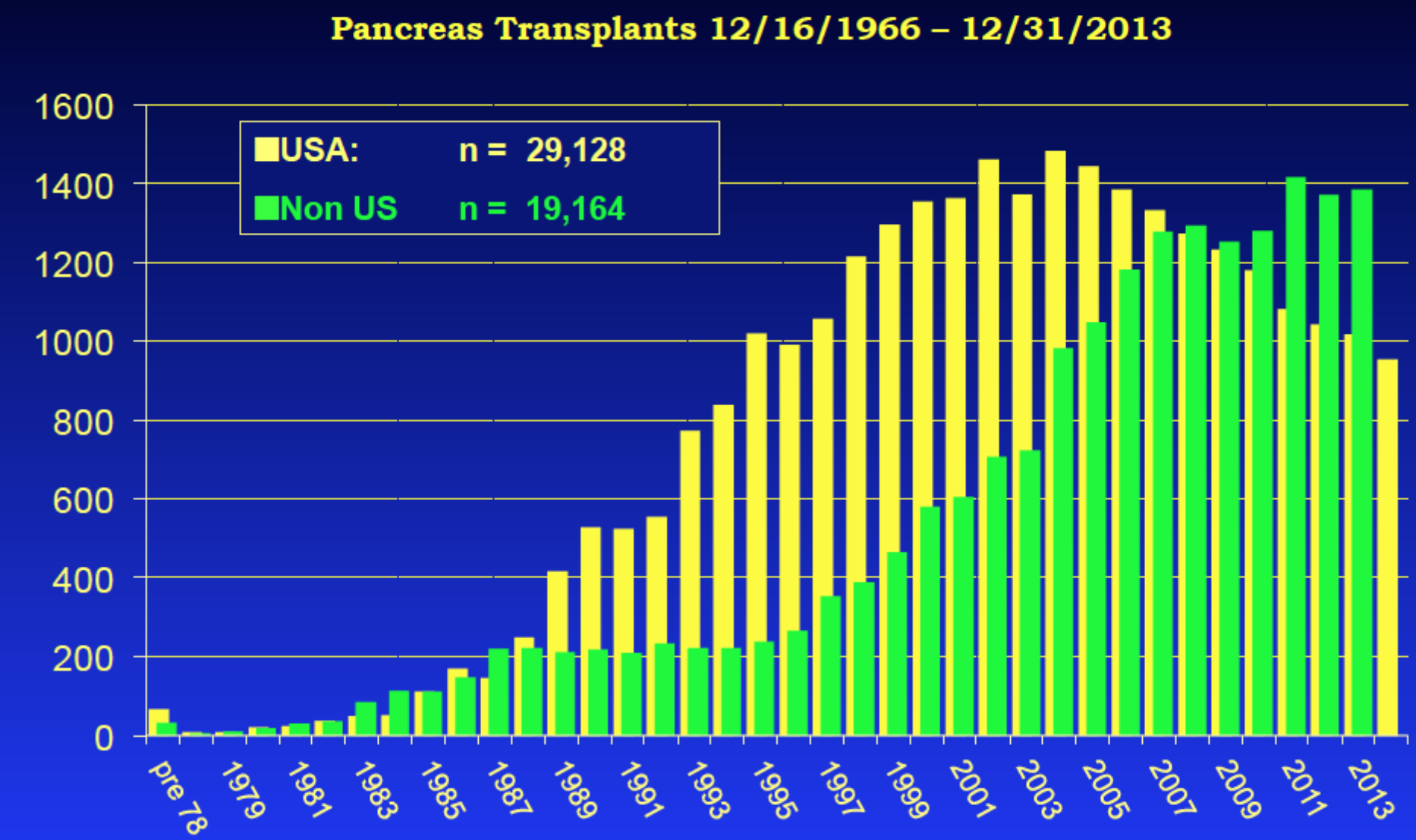
Surgery. 1967 Jun;61(6):827-37.

Allotransplantation of the pancreas and duodenum along with the kidney in diabetic nephropathy.

Kelly WD, Lillehei RC, Merkel FK, Idezuki Y, Goetz FC.



Worldwide Pancreas Transplants



IPTR/UNOS

Pancreas transplantation in Italy

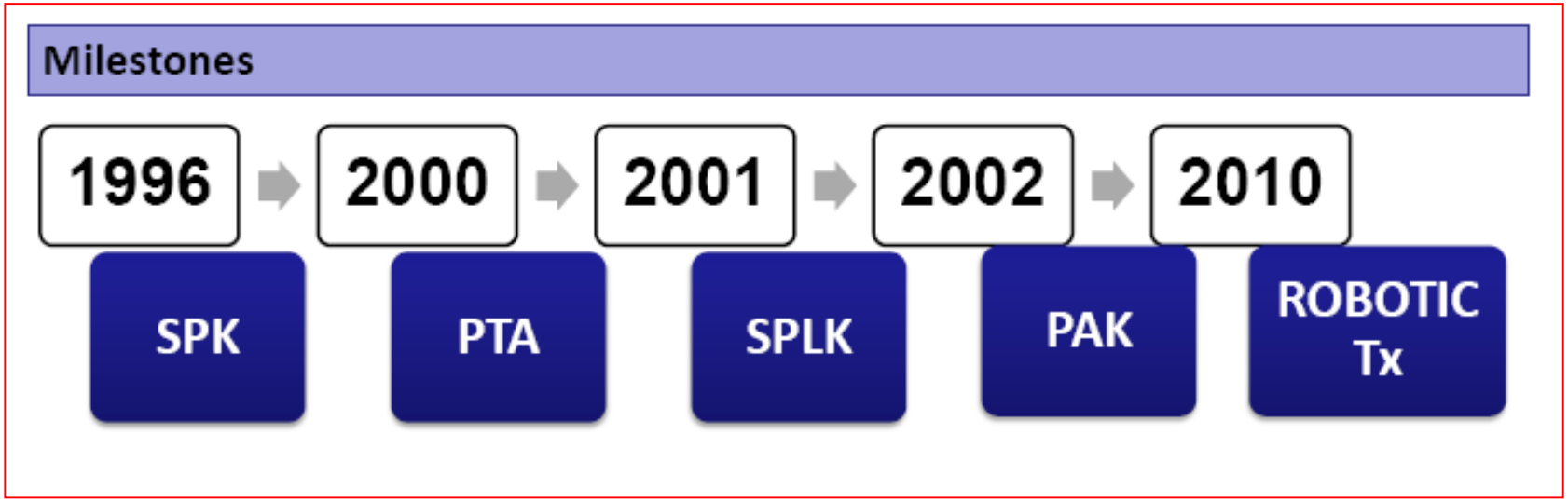
- First pancreas transplants in Rome (prof. Cortesini) and Milan (prof. Di Carlo, prof. G. Pozza) in 1985

Pancreas transplantation in Italy

- First pancreas transplants in Rome (prof. Cortesini) and Milan (prof. Di Carlo, prof. G. Pozza) in 1985

- 17 centres activated:
  - Ancona
  - Bergamo
  - Bologna
  - Catania
  - **Cagliari**
  - **Milano HSR**
  - **Milano Niguarda**
  - **Padova**
  - **Palermo**
  - Parma
  - **Pisa**
  - Roma S. Camillo
  - Roma P. Umberto I
  - Genova
  - **Torino**
  - Varese
  - Udine

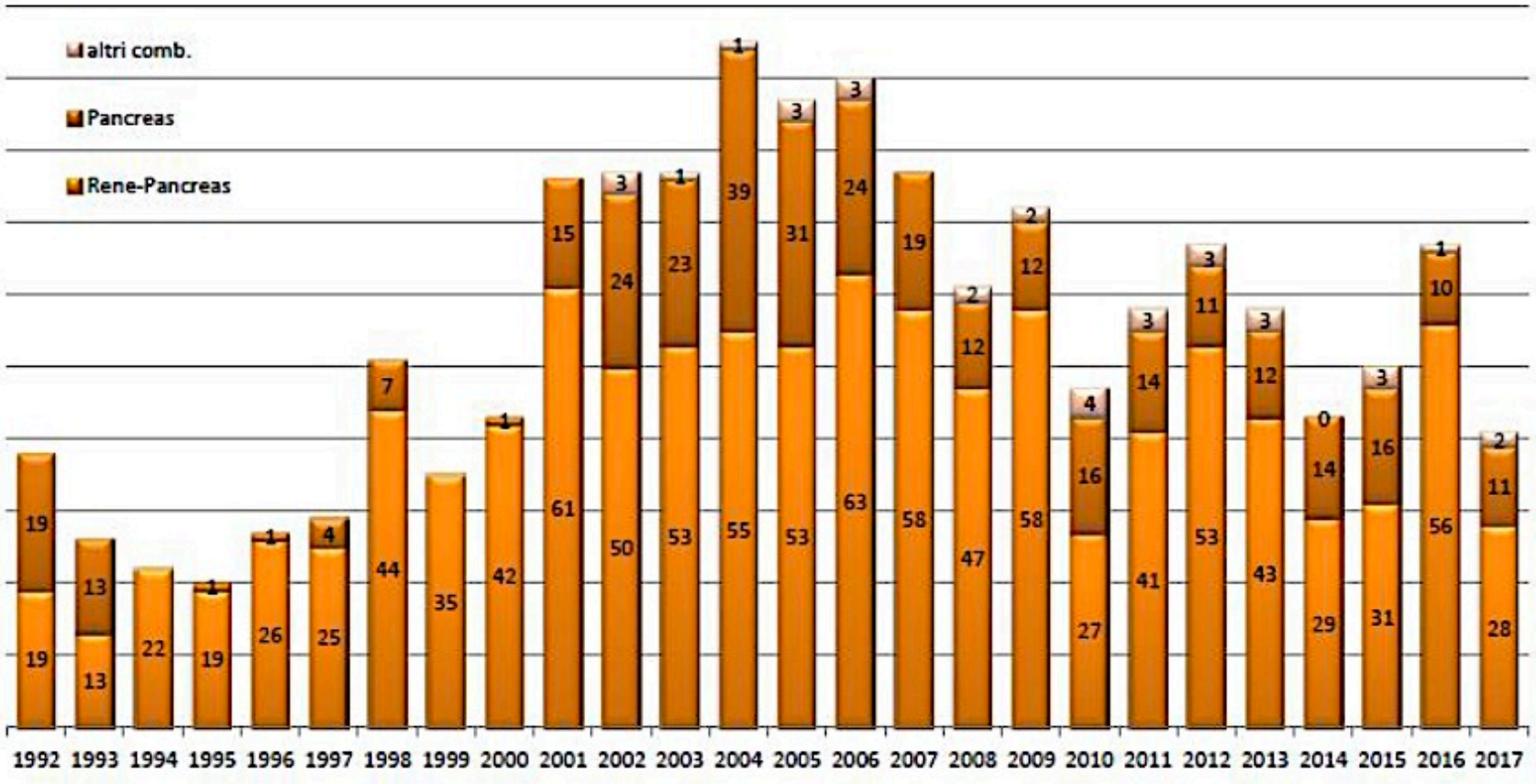
Pancreas Transplantation: the Pisa experience



Occhipinti M et al, OP, EASD 2016

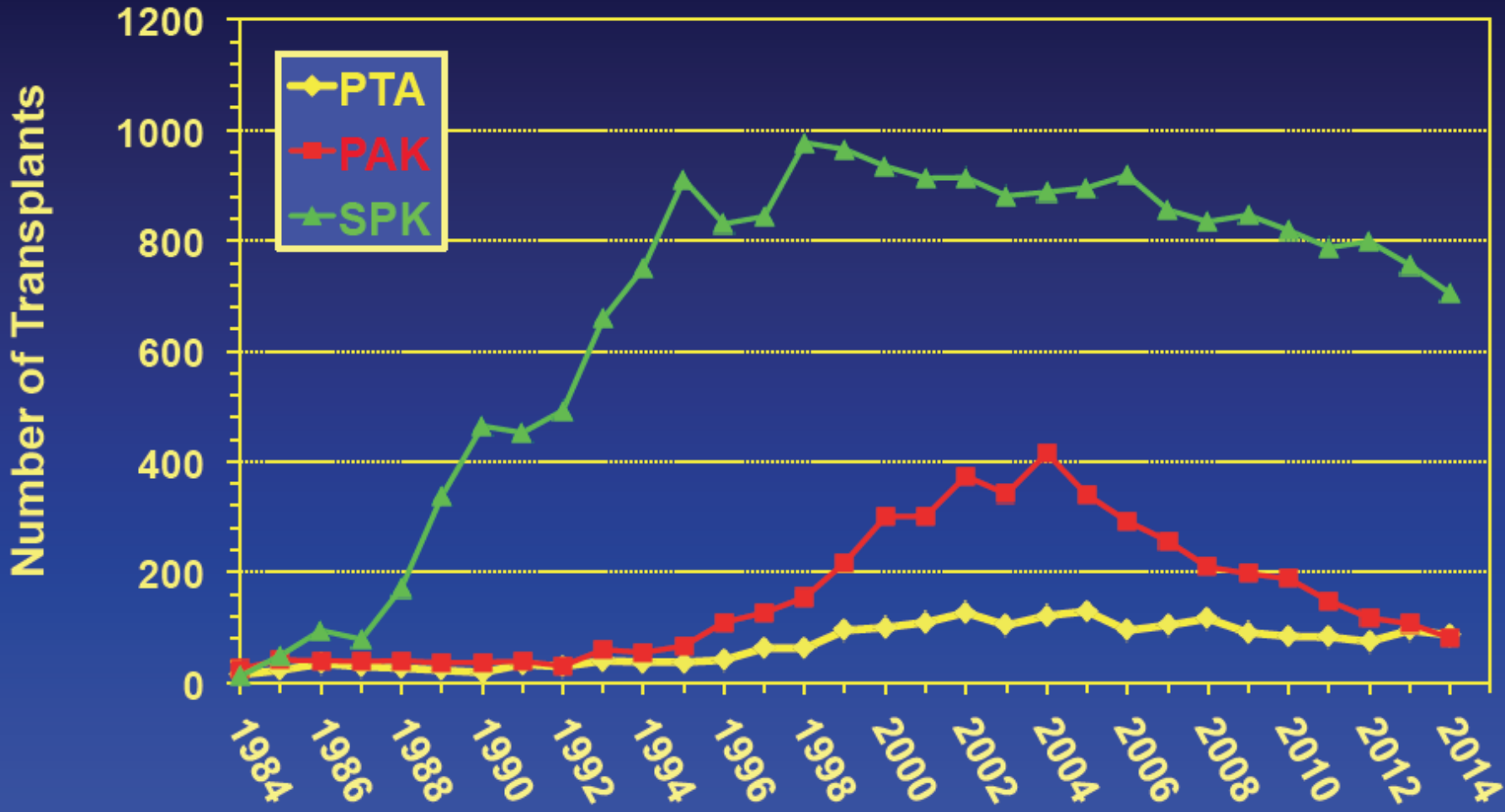
SIT- Sistema Informativo Trapianti (CRT)

Trapianti di Pancreas – Anni 1992-2017



Transplant Categories

USA SPK, PAK and PTA Transplants 1/1/1984 – 12/31/2014

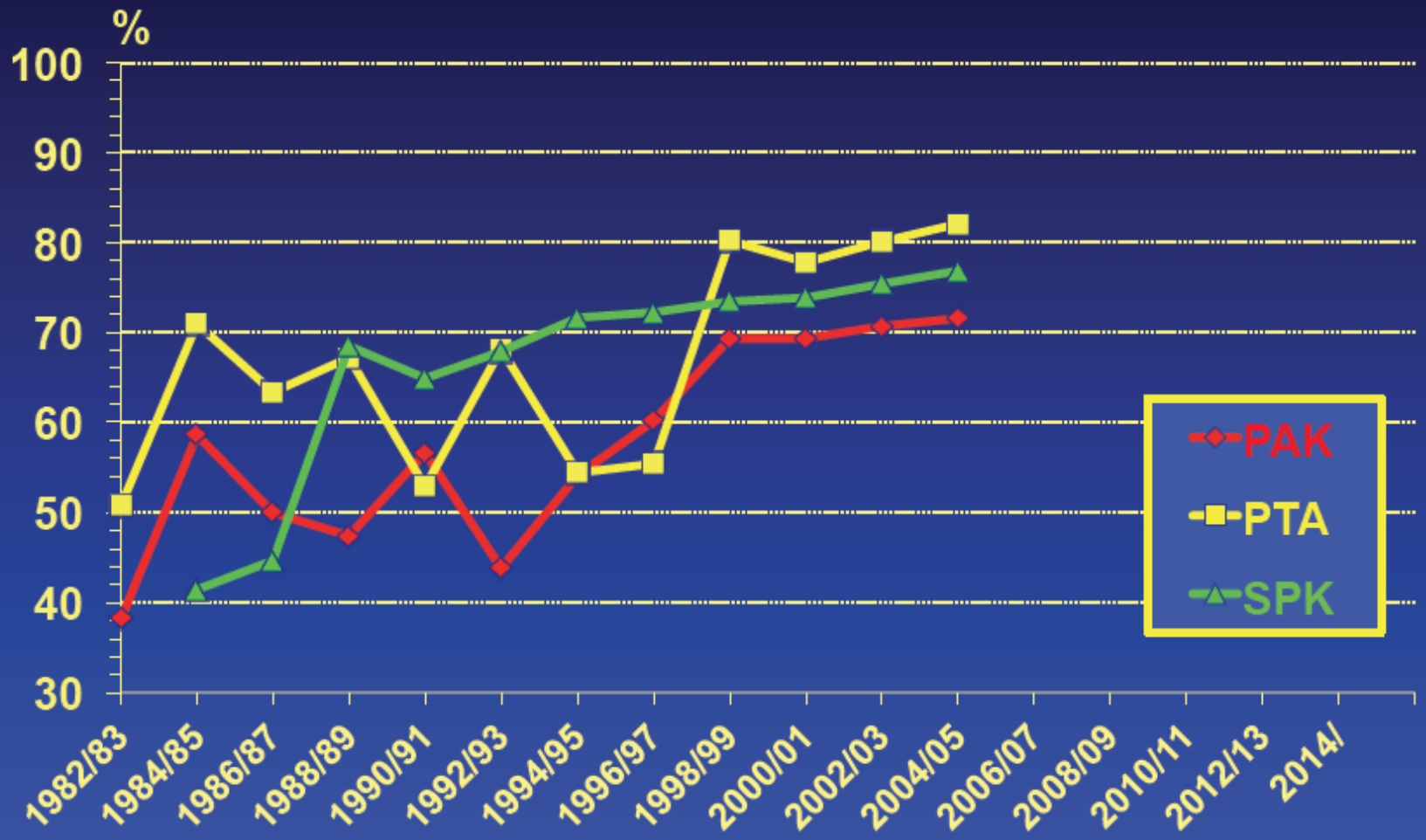


IPTR/UNOS

02/15

10-Year Unadjusted Patient Survival

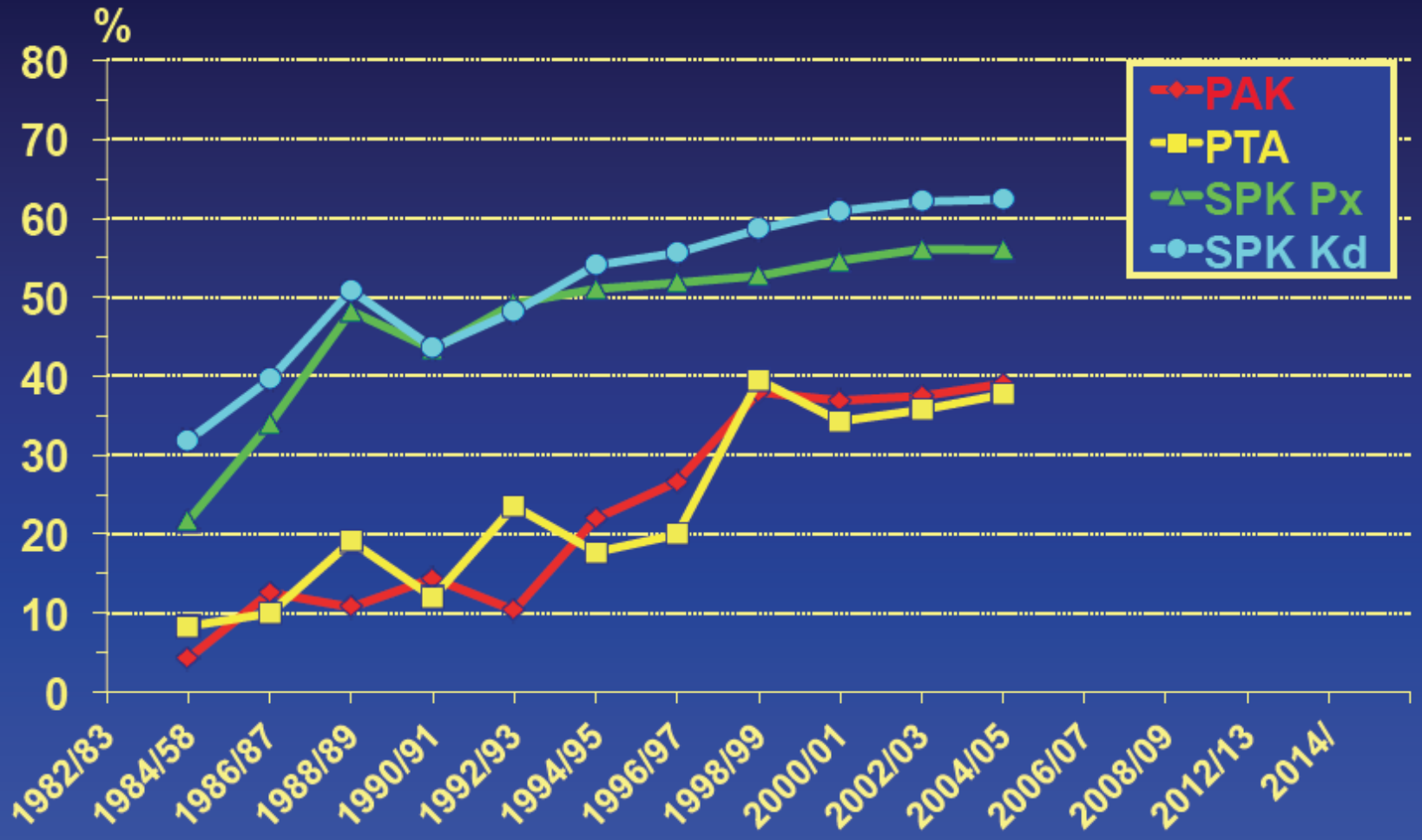
USA DD Primary Pancreas Transplants, 1 /1/1982 – 12/31/2014



IPTR/UNOS

10-Year Pancreas/Kidney Graft Function

USA Primary DD Pancreas Transplants, 1/1/1982 – 12/31/2014



IPTR/UNOS

Survival benefit of solid organ transplantation

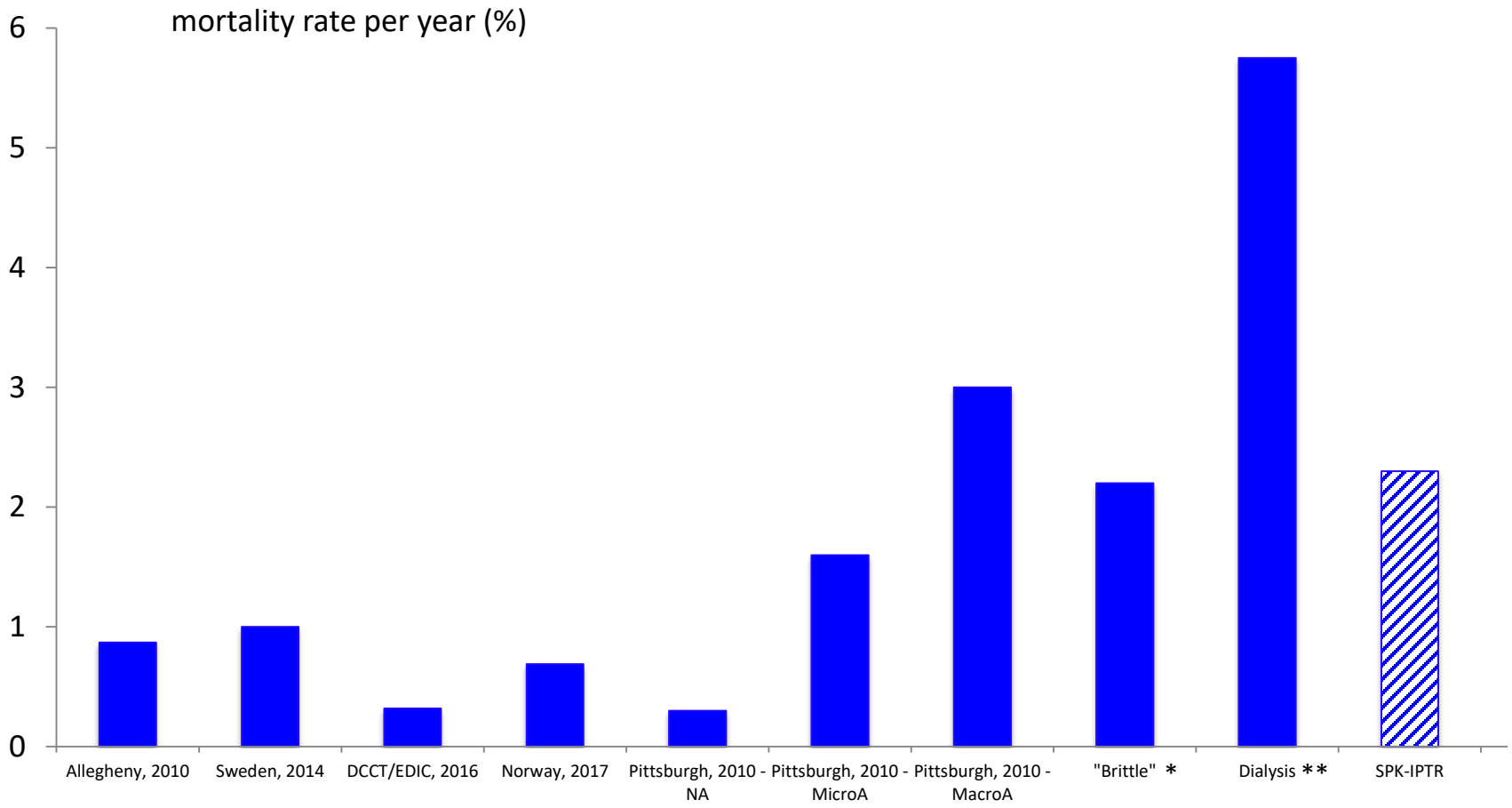
Table 2. Survival Benefit of Solid-Organ Transplant After Propensity Score Matching

Transplant Type and Patient Category	No. of Patients	Unadjusted Median Survival, y	No. of Patients After Matching	Median Survival After Matching, y
Kidney				
Waiting list	355 189	5.4	173 086	5.3
Transplant	314 561	12.4	112 049	12.1
Liver				
Waiting list	134 826	3.1	86 050	2.9
Transplant	112 319	11.6	64 011	10.1
Heart				
Waiting list	38 578	2.3	31 086	2.7
Transplant	54 039	9.5	53 173	9.5
Lung				
Waiting list	24 688	2.3	8960	2.1
Transplant	26 943	5.2	9934	4.9
Pancreas-kidney				
Waiting list	14 195	4.2	7134	3.7
Transplant	16 995	14.5	6713	14.4
Pancreas				
Waiting list	8568	8	7010	7.8
Transplant	6177	13.3	6042	14.5
Intestine				
Waiting list	1787	1.8	1185	1.9
Transplant	1588	5.1	802	5.0
Total				
Waiting list	577 831	...[a]	314 511	...
Transplant	532 622	...	252 724	...

Pancreas-Kidney
median survival:
WL 3.7 yrs
Tx 14.4 yrs

Rana A et al, JAMA Surgery 2015

Mortality in type 1 diabetes



* Cartwright A et al, Q J Med 2011

** Haapio M et al, Diabetes Care 2010



Il trapianto di pancreas e rene è consigliabile, dopo esclusione della presenza di controindicazioni, nei pazienti con diabete tipo 1 e insufficienza renale cronica (in fase di trattamento dialitico o in fase predialitica); tale trapianto ha effetti positivi sull'aspettativa di vita dei pazienti e può contribuire a rallentare la progressione delle complicanze vascolari croniche del diabete

II A

Pancreas Transplant Alone

A procedure coming of age

RAINER W.G. GRUESSNER, MD
ANGELIKA C. GRUESSNER, PHD

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

Diabetes Care 36:2440–2447, 2013

1,929 PTA
from Dec. 1966
to Dec. 2011

Survival benefit of solid organ transplantation

Table 2. Survival Benefit of Solid-Organ Transplant After Propensity Score Matching

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Waiting list	577 831	...[a]	314 511	...
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Pancreas-Kidney
median survival:
WL 3.7 yrs
Tx 14.4 yrs

Pancreas alone
median survival:
WL 7.8 yrs
Tx 14.5 yrs

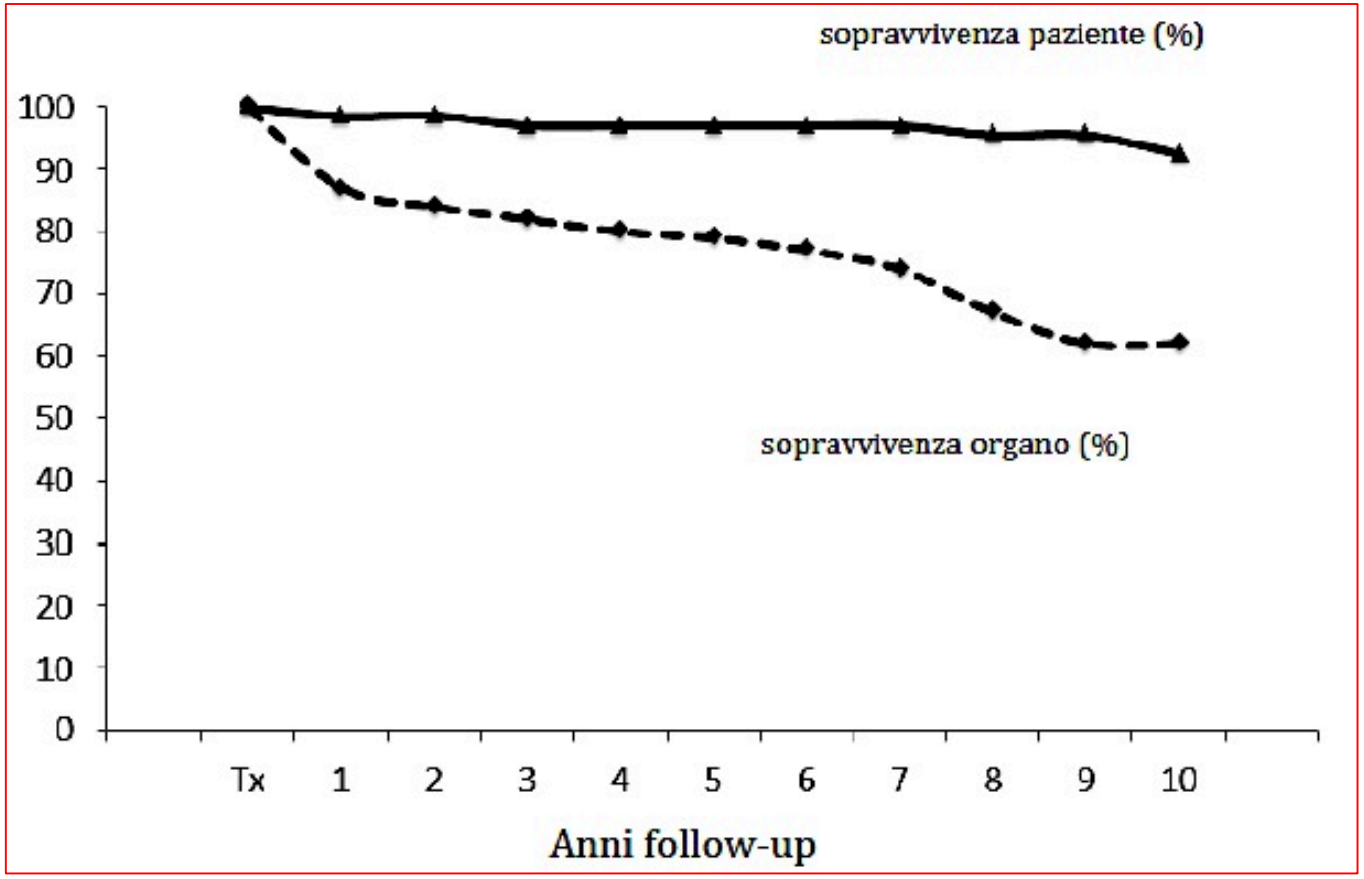
Rana A et al, JAMA Surgery 2015

PTA: the Pisa experience

Numero pazienti	Età al trapianto (anni)	Età insorgenza DM1 (anni)	Genere (M/F)	BMI (kg/m^2)	Durata diabete (anni)	Dose insulina (UI/die)	C-peptide (ng/ml)	HbA1c (%)	eGFR (ml/min/ 1.73m^2)
66	38.1 ±8.2	14.2 ±8.8	30M/36F	23.8 ±2.9	23.9 ±9.1	44.6 ±11.8	0.1±0.2	9.2±1.6	89.98 ±26.68

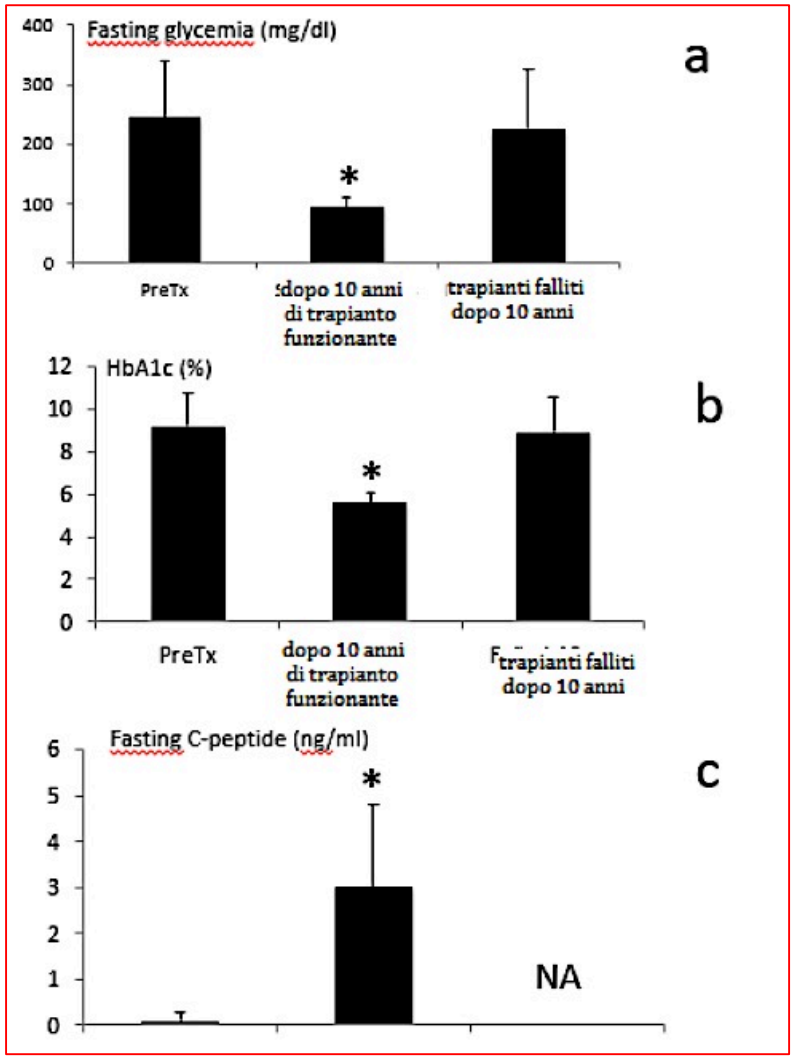
- 19/66 soggetti (28%) avevano scarso controllo glicemico, di cui 14 presentavano ipoglicemie frequenti e/o inavvertite
- La maggior parte dei pazienti presentava vari gradi di complicanze croniche del diabete, spesso associate.
  - 49 pz retinopatia laser trattata
  - 29 pz neuropatia periferica
  - 6 pz neuropatia autonomica sintomatica (gastroparesi)

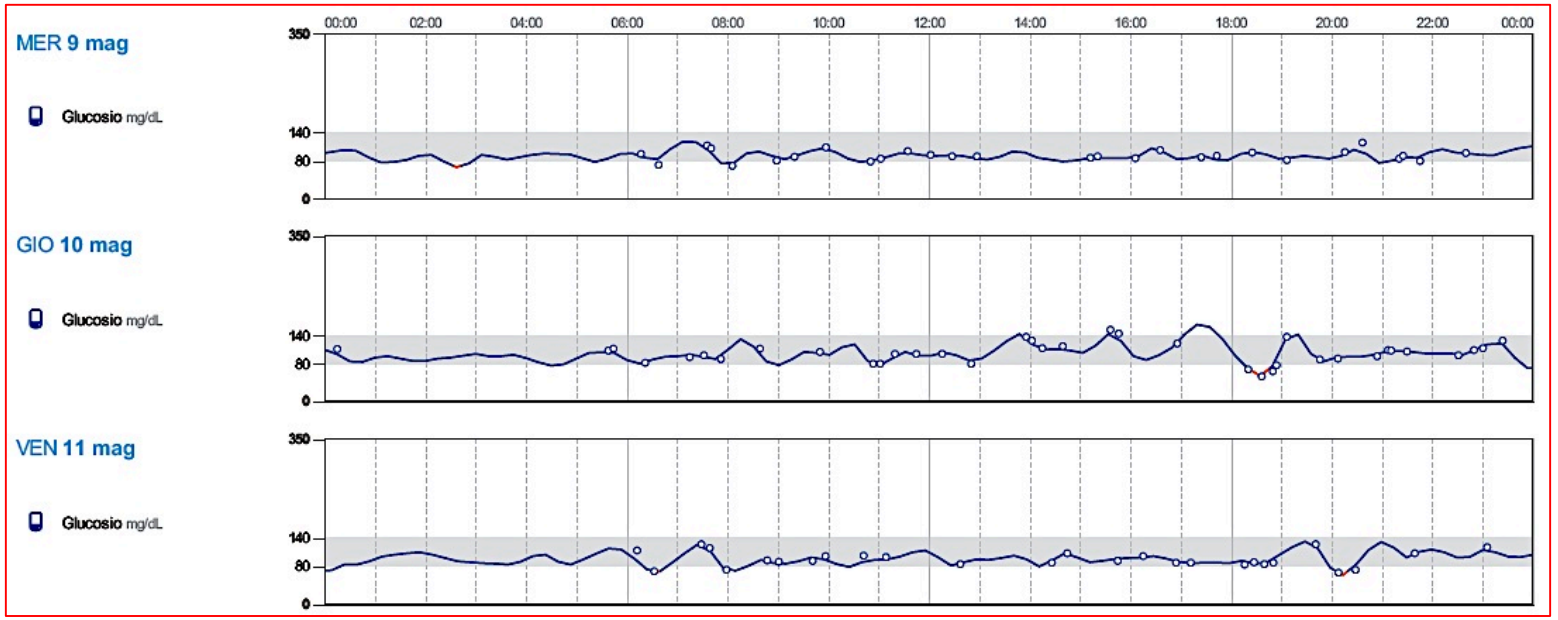
PTA: the Pisa experience



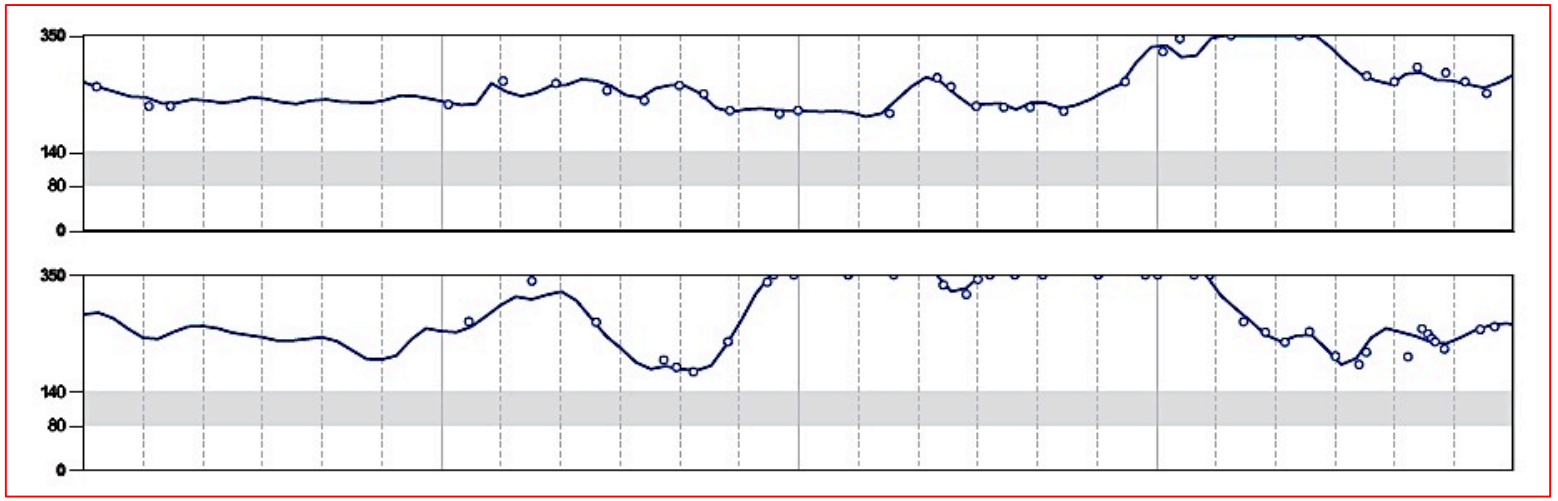
Decessi: infezioni 2 casi, MCV 3 casi (3 con pancreas funzionante)

PTA: the Pisa experience



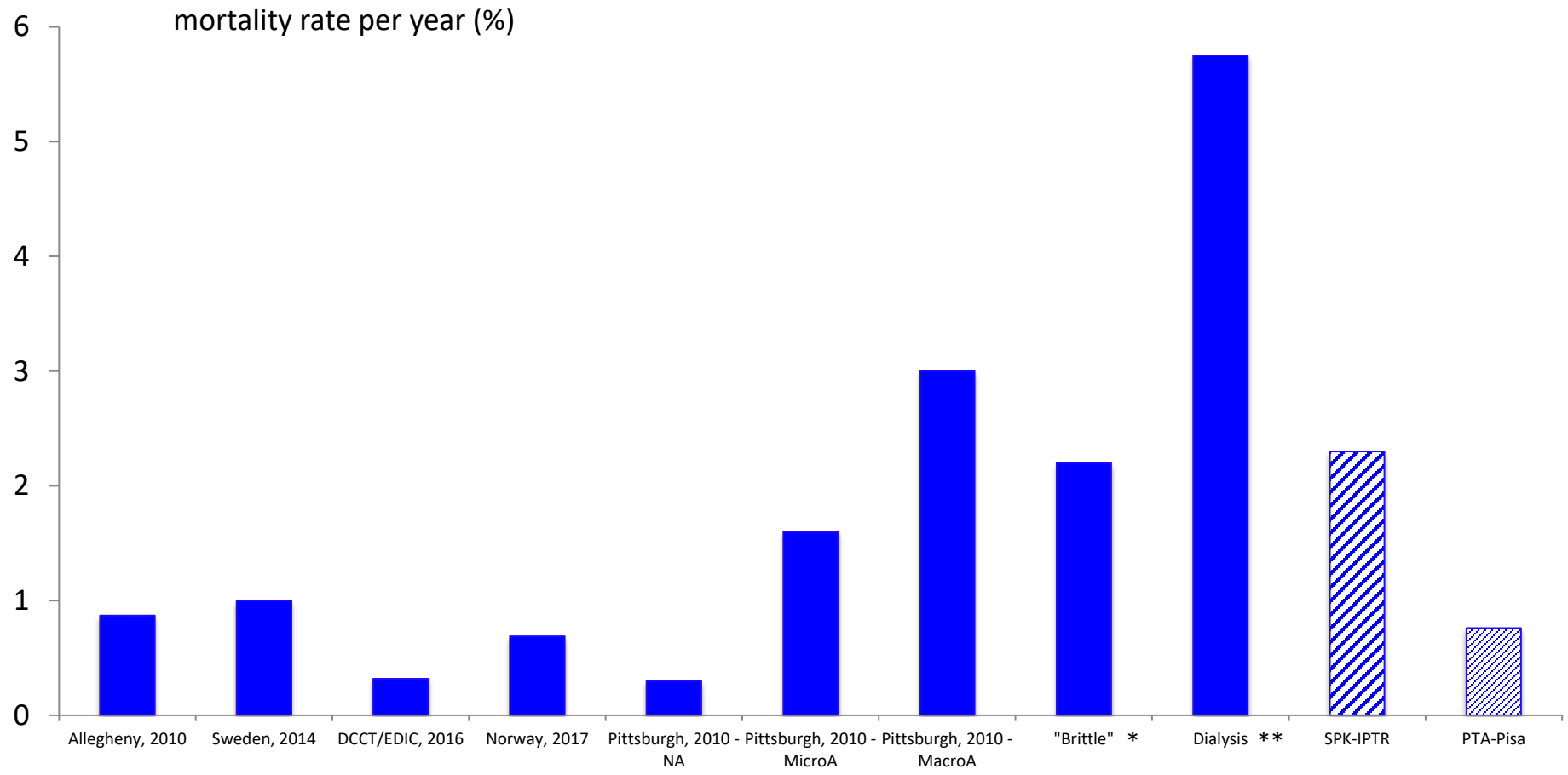

MER 9 mag
Glucosio mg/dL
GIO 10 mag
Glucosio mg/dL
VEN 11 mag
Glucosio mg/dL
00:00
02:00
04:00
06:00
08:00
10:00
12:00
14:00
16:00
18:00
20:00
22:00
00:00
350
140
80
0

R.B.


350
140
80
0
350
140
80
0

F.R.

Mortality in type 1 diabetes

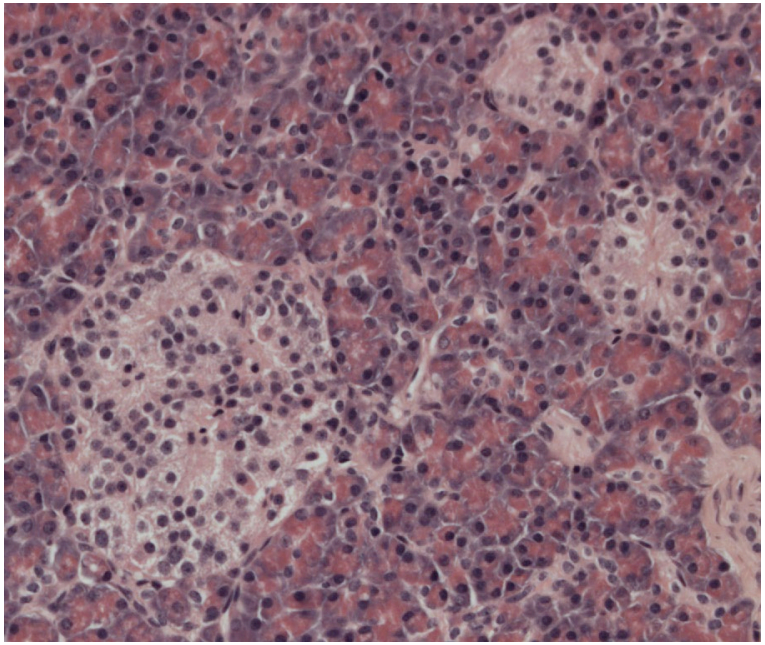


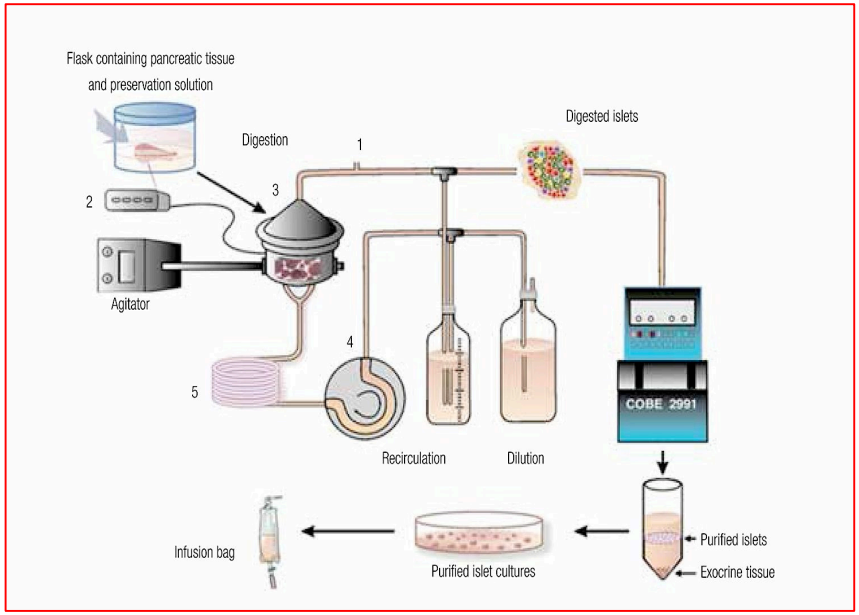
* Cartwright A et al, Q J Med 2011

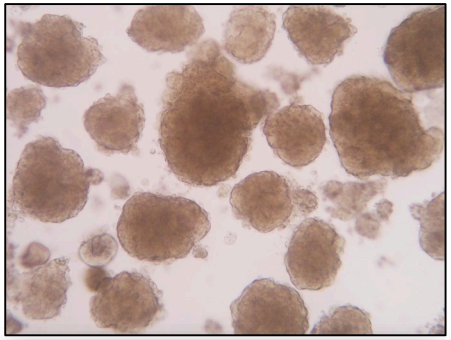
** Haapio M et al, Diabetes Care 2010



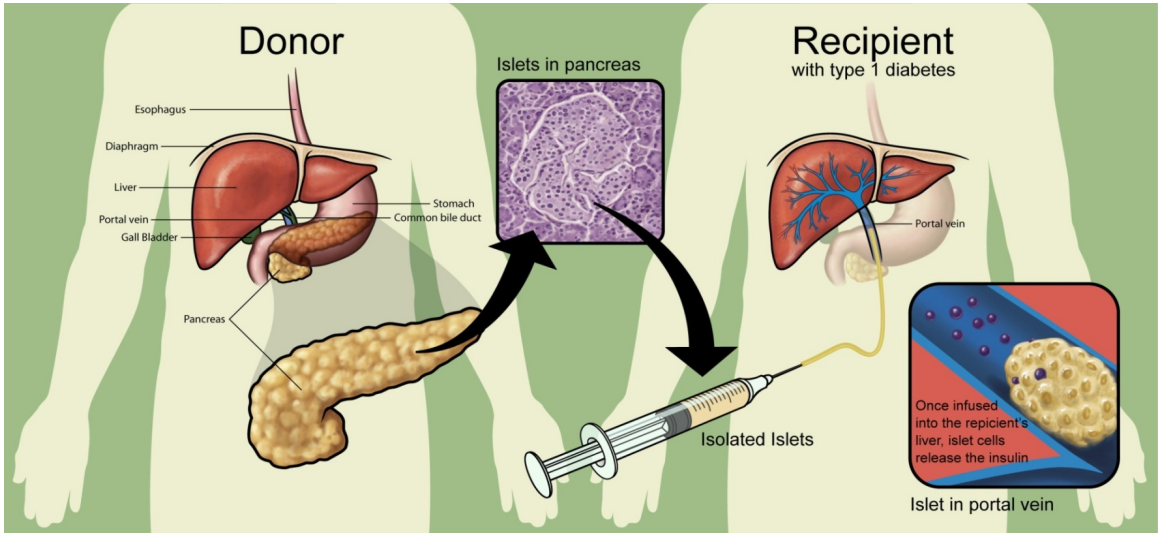
Il trapianto di pancreas isolato può essere consigliabile, dopo esclusione della presenza di controindicazioni e verifica di una adeguatamente conservata funzione renale, nei pazienti con DM1 e grave instabilità glicemica e/o complicanze croniche in evoluzione; tale trapianto ha effetti positivi sulle complicanze acute del diabete e può contribuire a rallentare la progressione delle complicanze croniche della malattia. ***III B***




Flask containing pancreatic tissue
and preservation solution
Digestion
Digested islets
1
2
3
4
5
Agitator
COBE 2991
Recirculation
Dilution
Infusion bag
Purified islet cultures
Purified islets
Exocrine tissue

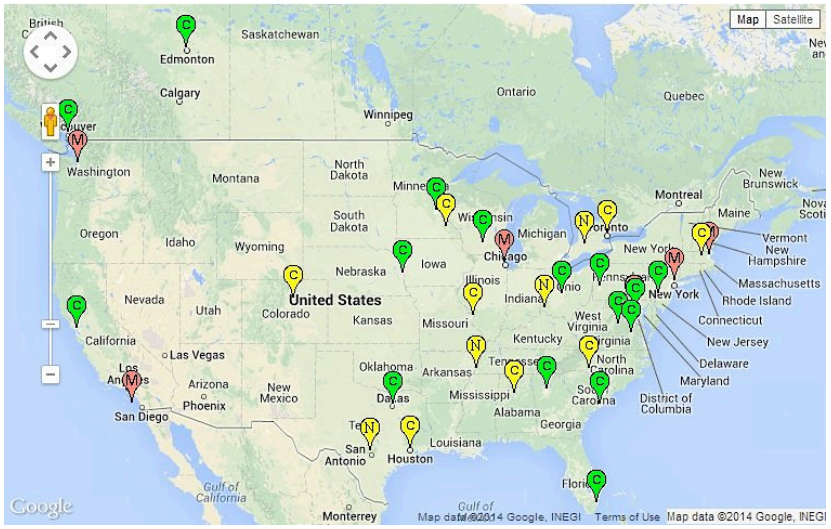


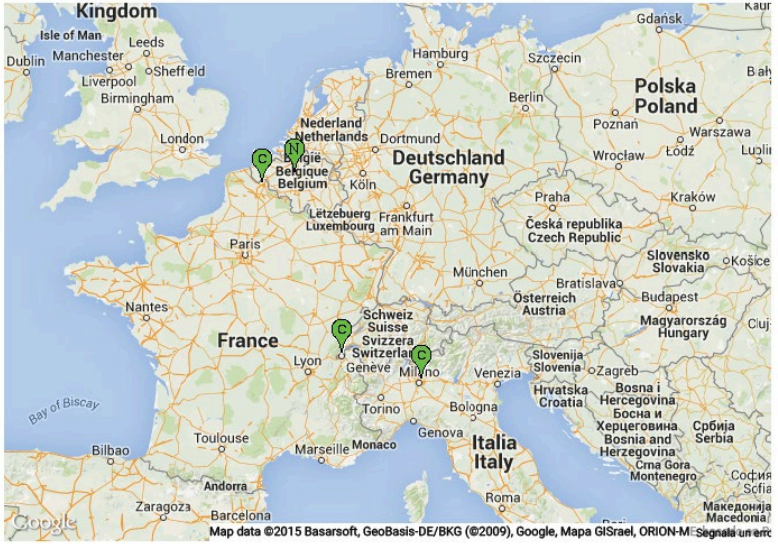


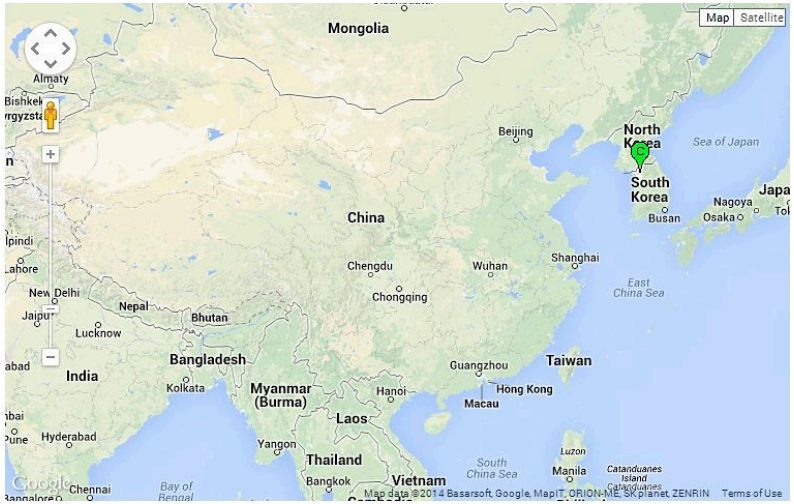

Donor
Islets in pancreas
Recipient
with type 1 diabetes
Esophagus
Diaphragm
Liver
Portal vein
Gall Bladder
Stomach
Common bile duct
Pancreas
Portal vein
Isolated Islets
Once infused into the repicient's liver, islet cells release the insulin
Islet in portal vein

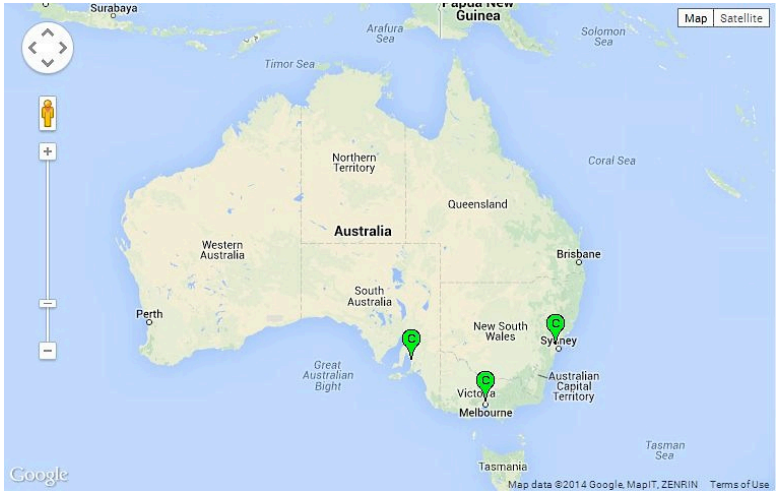
citr
Collaborative Islet Transplant Registry

Transplant Centers









citr

Collaborative Islet Transplant Registry

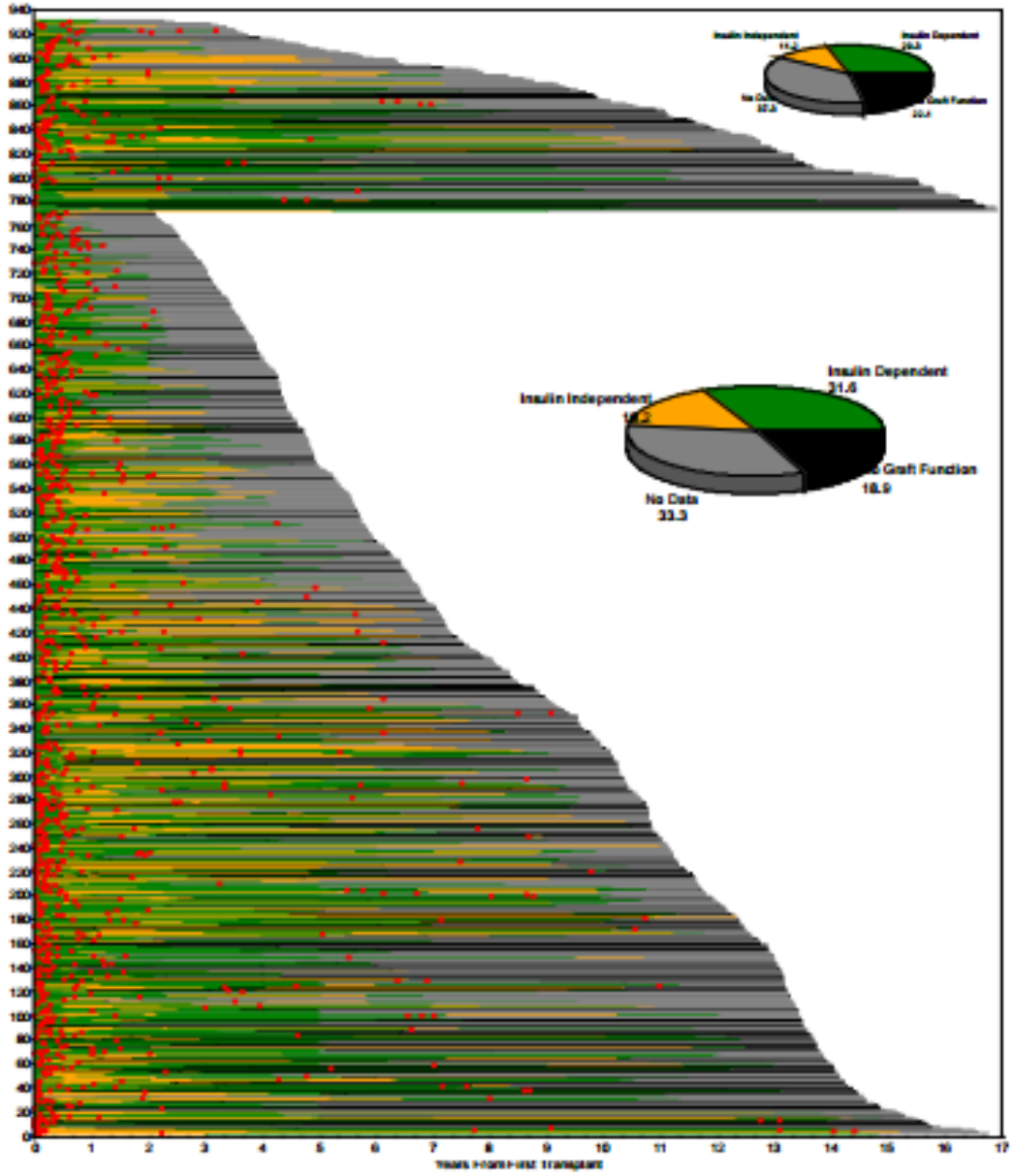
Ninth Annual Report

Prepared by:
CITR Coordinating Center
The Emmes Corporation
Rockville, MD

Sponsored by:
National Institute of Diabetes and Digestive and Kidney Diseases
National Institutes of Health
US Department of Health and Human Services
Bethesda, MD

Additional support from:
The Juvenile Diabetes Research Foundation International
New York, NY

December 8, 2016



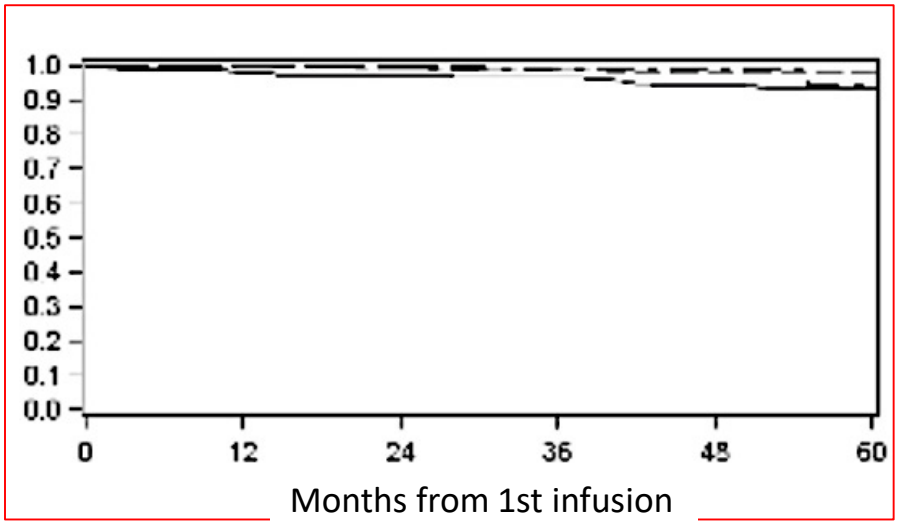
Collaborative Islet Transplant Registry 2013
TOP: Islet after kidney or simultaneous islet-kidney (IAK/SIK, N=192)
BOTTOM: Islet transplant alone (ITA, N=819)
Yellow: insulin independent; Green: insulin-using with graft function (50% average reduction in daily insulin use);
Black: no islet function (C-peptide<0.3 ng/ml); Gray: missing data; Red: re-infusions.
Pie charts show percent of all follow-up time.

citr
Collaborative Islet Transplant Registry

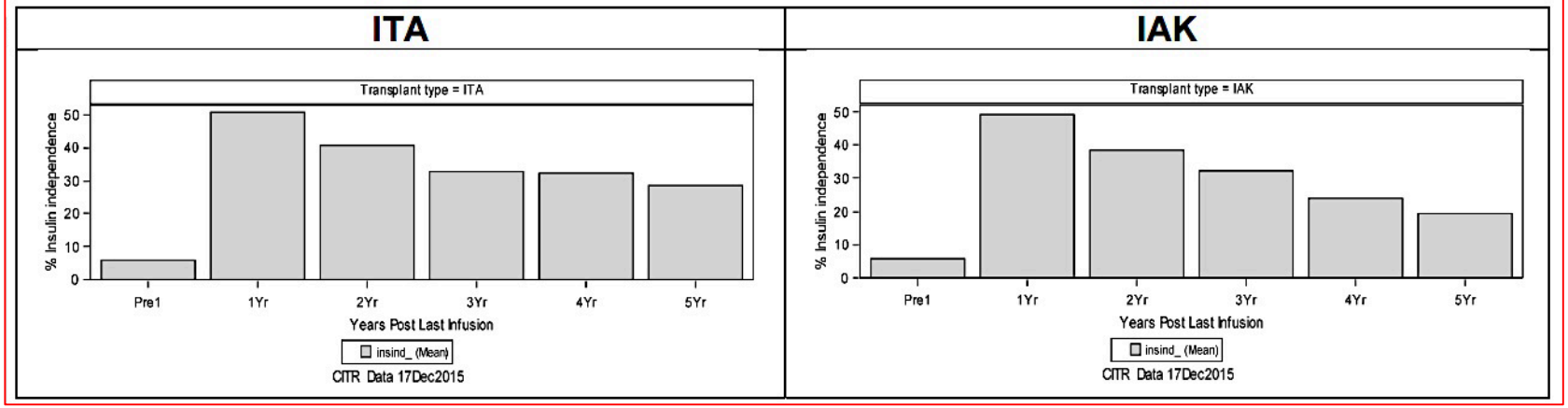
CITR Recipients, Infusions and Donors by NIDDK/JDRF Sites and by ITA/IAK/SIK Consented, Registered and First Infused in 1999-2013

	Islet Transplant Alone (ITA)			Islet After Kidney or Simultaneous Islet-Kidney (IAK/SIK)			
	Total	North America	Europe/ Australia/ Asia	Total	North America	Europe/ Australia/ Asia	GRAND TOTALS
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**

survival



Unadjusted Prevalence of Insulin Independence Post Last Infusion



Islet transplantation in selected centres

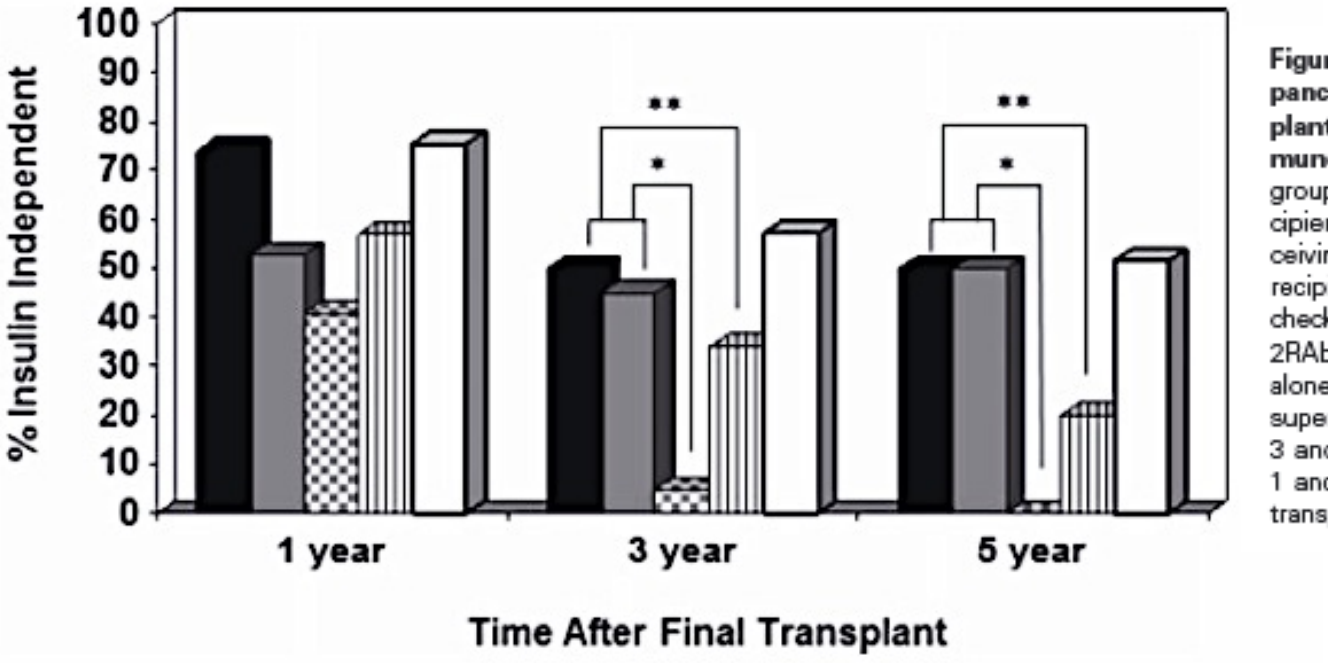


Figure 1: Observed insulin independence in pancreas transplant alone and in islet transplant alone recipients based on induction immunosuppression administered. Islet transplant groups are indicated as follows: group 1 (UMN recipients, solid black), group 2 (CITR recipients receiving TCDAb +TNF-α-i, solid gray), group 3 (CITR recipients receiving TCDAb without TNF-α-i, gray checkered), group 4 (CITR recipients receiving IL-2RAb, vertical lines), group 5 (pancreas transplant alone recipients, white). Insulin independence was superior in groups 1 and 2 compared to groups 3 and 4 at 3 and 5 years posttransplant; groups 1 and 2 did not differ statistically from pancreas transplant alone (group 5). * $p<0.01$; ** $p\leq0.05$.

Hering BJ et al, Am J Transplant 2012

Five-Year Metabolic, Functional, and Safety Results of Patients With Type 1 Diabetes Transplanted With Allogenic Islets Within the Swiss-French GRAGIL Network

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*Members of the GRAGIL Network can be found in the Supplementary Data online.

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OBJECTIVE

To describe the 5-year outcomes of islet transplantation within the Swiss-French GRAGIL Network.

RESEARCH DESIGN AND METHODS

Retrospective analysis of all subjects enrolled in the GRAGIL-1c and GRAGIL-2 islet transplantation trials. Parameters related to metabolic control, graft function, and safety outcomes were studied.

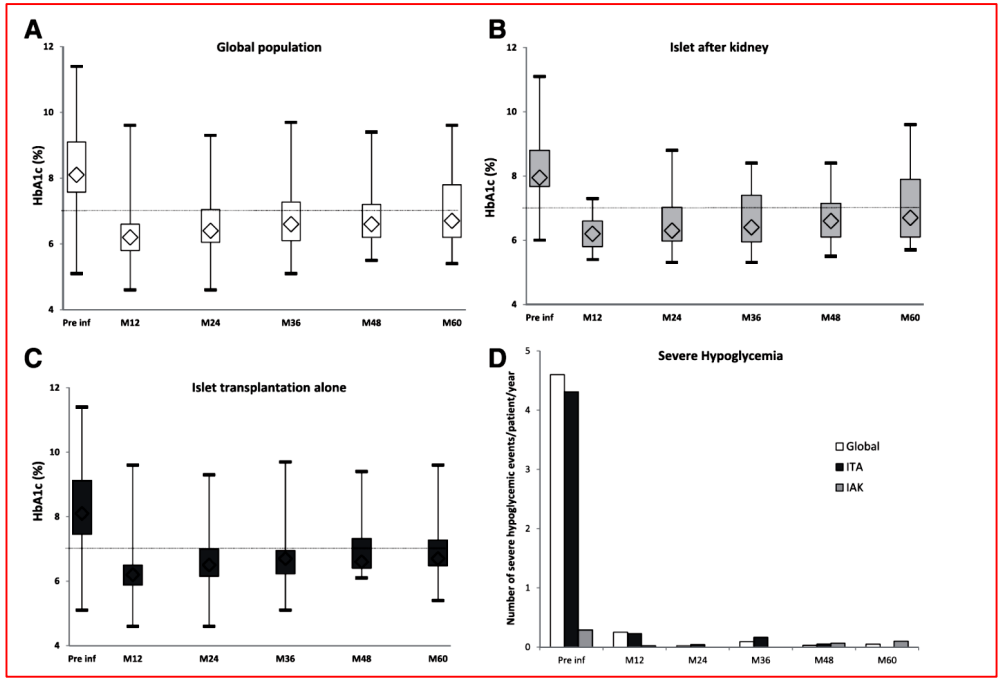
RESULTS

Forty-four patients received islet transplantation (islet transplantation alone [ITA] 24 patients [54.5%], islet after kidney [IAK] transplantation 20 patients [45.5%]) between September 2003 and April 2010. Recipients received a total islet mass of 9,715.75 ± 3,444.40 IEQ/kg. Thirty-four patients completed a 5-year follow-up, and 10 patients completed a 4-year follow-up. At 1, 4, and 5 years after islet transplantation, respectively, 83%, 67%, and 58% of the ITA recipients and 80%, 70%, and 60% of the IAK transplant recipients reached HbA_{1c} under 7% (53 mmol/mol) and were free of severe hypoglycemia, while none of the ITA recipients and only 10% of the IAK transplant recipients met this composite criterion at the preinfusion stage. Thirty-three of 44 patients (75%) experienced insulin independence during the entire follow-up period, with a median duration of insulin independence of 19.25 months (interquartile range 2–58). Twenty-nine of 44 recipients (66%) exhibited at least one adverse event; 18 of 55 adverse events (33%) were possibly related to immunosuppression; and complications related to the islet infusion (n = 84) occurred in 10 recipients (11.9%).

CONCLUSIONS

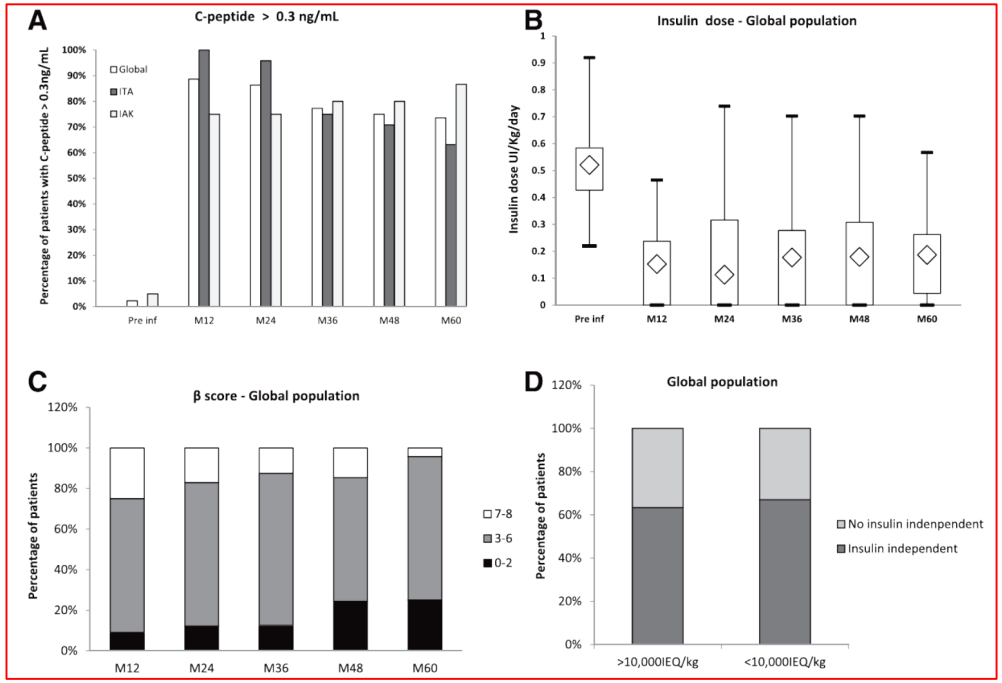
In a large cohort with a 5-year follow-up and in a multicenter network setting, islet transplantation was safe and efficient in restoring good and lasting glycemic control and preventing severe hypoglycemia in patients with type 1 diabetes.

Over the last decade, islet transplantation has emerged as a promising treatment for type 1 diabetes. Currently, islet transplantation can be offered to patients with type 1 diabetes who are experiencing major glucose variability and lack of predictability and unawareness of hypoglycemic episodes despite intensive insulin therapy and



40 recipients

Insulin independence at 5 yrs: 29%



Phase 3 Trial of Transplantation of Human Islets in Type 1 Diabetes Complicated by Severe Hypoglycemia

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OBJECTIVE

Impaired awareness of hypoglycemia (IAH) and severe hypoglycemic events (SHEs) cause substantial morbidity and mortality in patients with type 1 diabetes (T1D). Current therapies are effective in preventing SHEs in 50–80% of patients with IAH and SHEs, leaving a substantial number of patients at risk. We evaluated the effectiveness and safety of a standardized human pancreatic islet product in subjects in whom IAH and SHEs persisted despite medical treatment.

RESEARCH DESIGN AND METHODS

This multicenter, single-arm, phase 3 study of the investigational product purified human pancreatic islets (PHPI) was conducted at eight centers in North America. Forty-eight adults with T1D for >5 years, absent stimulated C-peptide, and documented IAH and SHEs despite expert care were enrolled. Each received immunosuppression and one or more transplants of PHPI, manufactured on-site under good manufacturing practice conditions using a common batch record and standardized lot release criteria and test methods. The primary end point was the achievement of HbA_{1c} <7.0% (53 mmol/mol) at day 365 and freedom from SHEs from day 28 to day 365 after the first transplant.

RESULTS

The primary end point was successfully met by 87.5% of subjects at 1 year and by 71% at 2 years. The median HbA_{1c} level was 5.6% (38 mmol/mol) at both 1 and 2 years. Hypoglycemia awareness was restored, with highly significant improvements in Clarke and HYPO scores ($P > 0.0001$). No study-related deaths or disabilities occurred. Five of the enrollees (10.4%) experienced bleeds requiring transfusions (corresponding to 5 of 75 procedures), and two enrollees (4.1%) had infections attributed to immunosuppression. Glomerular filtration rate decreased significantly on immunosuppression, and donor-specific antibodies developed in two patients.

CONCLUSIONS

Transplanted PHPI provided glycemic control, restoration of hypoglycemia awareness, and protection from SHEs in subjects with intractable IAH and SHEs. Safety events occurred related to the infusion procedure and immunosuppression, including bleeding and decreased renal function. Islet transplantation should be considered for patients with T1D and IAH in whom other, less invasive current treatments have been ineffective in preventing SHEs.

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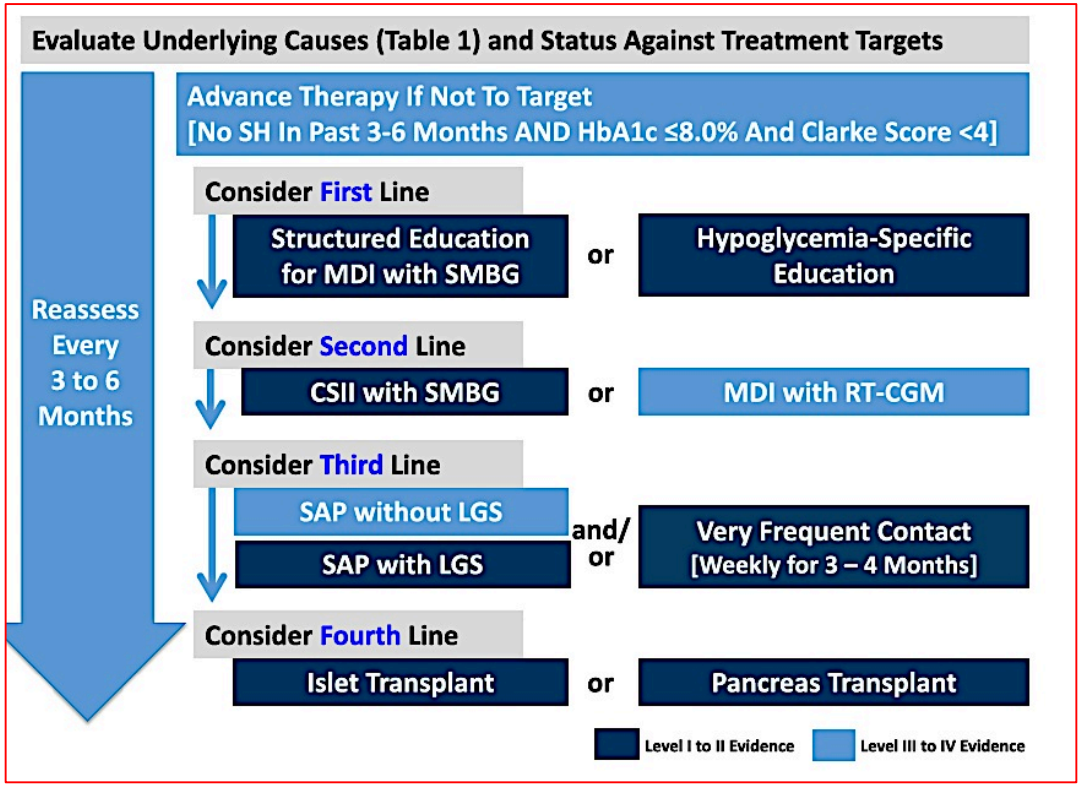
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Evidence-Informed Clinical Practice Recommendations for Treatment of Type 1 Diabetes Complicated by Problematic Hypoglycemia

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Diabetes Care 2015;38:1016–1029 | DOI: 10.2337/dc15-0090





Il trapianto di isole pancreatiche insieme o dopo un altro trapianto di organo (ad esempio, trapianto di rene) può essere consigliabile in alternativa al trapianto di pancreas insieme o dopo un altro organo (più comunemente rene) quando il pancreas non è fattibile (trapianto combinato). Le indicazioni cliniche del trapianto combinato di isole sono pertanto le stesse del trapianto combinato di pancreas. Il trapianto di pancreas non è fattibile in caso di complicanze cardiovascolari, pregressi multipli interventi chirurgici addominali, o volontà del paziente che rifiuta un aggiuntivo intervento di chirurgia maggiore. ***V B***

Il trapianto di isole pancreatiche da sole può essere consigliabile in alternativa al trapianto di pancreas isolato quando questo non è fattibile. Le indicazioni cliniche rimangono pertanto le stesse del trapianto di pancreas isolato. I casi in cui il trapianto di pancreas non è fattibile includono: complicanze cardiovascolari, pregressi multipli interventi chirurgici addominali, la volontà del paziente che rifiuta un intervento di chirurgia maggiore. ***V B***

Pancreas/islet transplantation

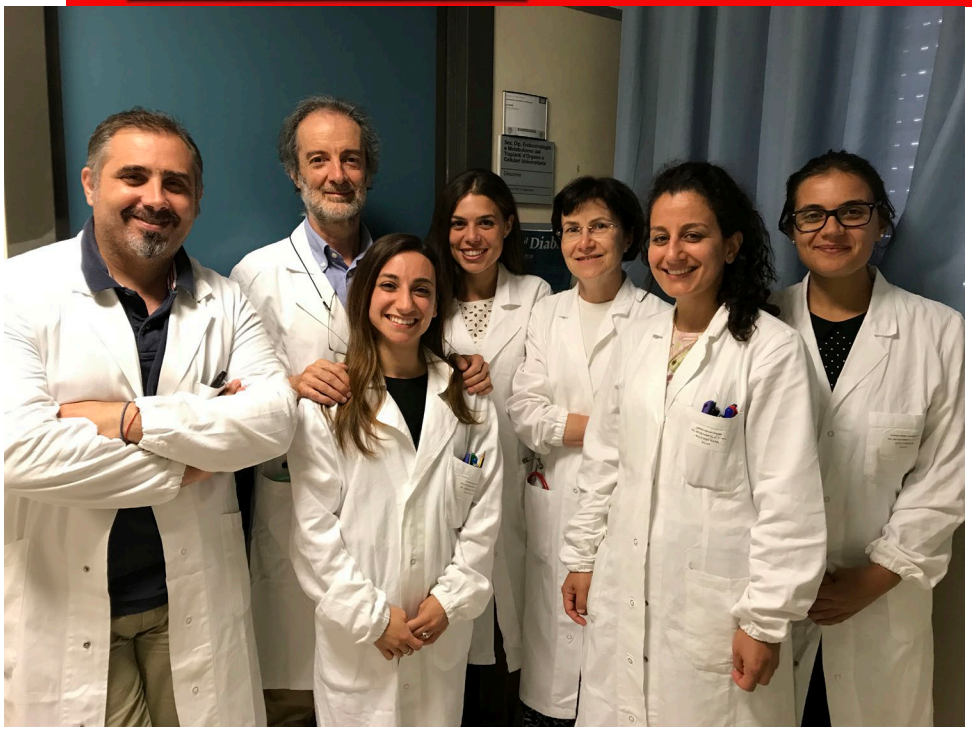
	Clinical efficacy (insulin-independence)	Clinical efficacy (reduction acute complications)	Surgical risks	Immuno-suppression therapy risks
Pancreas Tx	++++	++++	++++	++
Islet Tx	++	++++	++	++



Nessun uomo è un'isola*, completo in se stesso; ogni uomo è una parte del tutto.

John Donne (Londra, 1572 – Londra, 31 marzo 1631)

* … e neanche un pancreas…

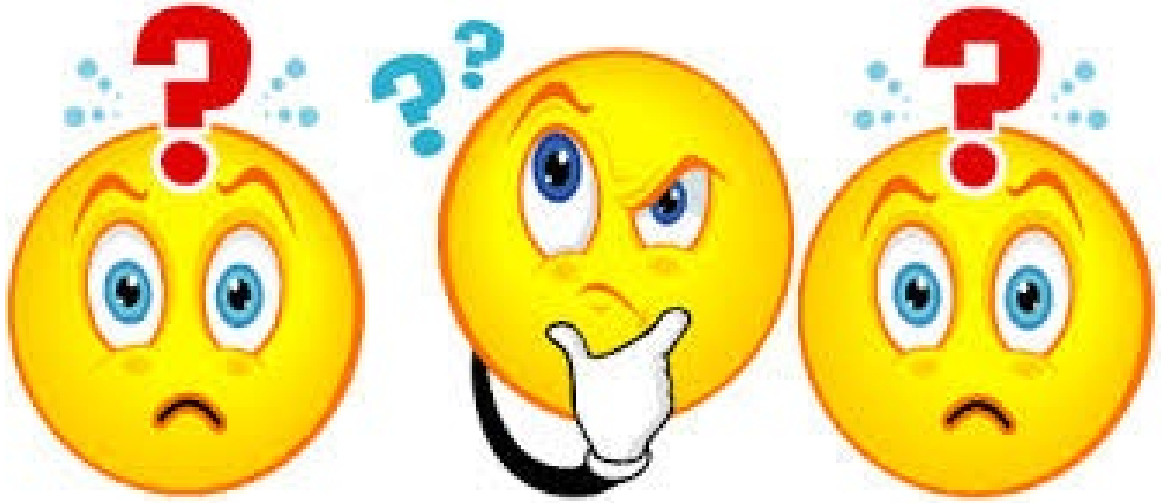








Grazie per la vostra attenzione!

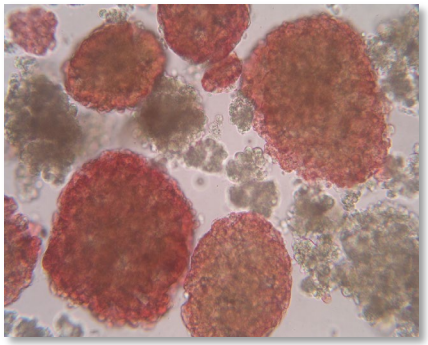




Trapianto di pancreas/isole: quando e a chi

Piero Marchetti
Università di Pisa







Excess mortality and cardiovascular disease in young adults with type 1 diabetes in relation to age at onset: a nationwide, register-based cohort study

Araz Rawshani*, Naveed Sattar*, Stefan Franzén, Aidin Rawshani, Andrew T Hattersley, Ann-Marie Svensson, Björn Eliasson, Soffia Gudbjörnsdottir

Summary

Background People with type 1 diabetes are at elevated risk of mortality and cardiovascular disease, yet current guidelines do not consider age of onset as an important risk stratifier. We aimed to examine how age at diagnosis of type 1 diabetes relates to excess mortality and cardiovascular risk.

Methods We did a nationwide, register-based cohort study of individuals with type 1 diabetes in the Swedish National Diabetes Register and matched controls from the general population. We included patients with at least one registration between Jan 1, 1998, and Dec 31, 2012. Using Cox regression, and with adjustment for diabetes duration, we estimated the excess risk of all-cause mortality, cardiovascular mortality, non-cardiovascular mortality, acute myocardial infarction, stroke, cardiovascular disease (a composite of acute myocardial infarction and stroke), coronary heart disease, heart failure, and atrial fibrillation. Individuals with type 1 diabetes were categorised into five groups, according to age at diagnosis: 0–10 years, 11–15 years, 16–20 years, 21–25 years, and 26–30 years.

Findings 27 195 individuals with type 1 diabetes and 135 178 matched controls were selected for this study. 959 individuals with type 1 diabetes and 1501 controls died during follow-up (median follow-up was 10 years). Patients who developed type 1 diabetes at 0–10 years of age had hazard ratios of 4·11 (95% CI 3·24–5·22) for all-cause mortality, 7·38 (3·65–14·94) for cardiovascular mortality, 3·96 (3·06–5·11) for non-cardiovascular mortality, 11·44 (7·95–16·44) for cardiovascular disease, 30·50 (19·98–46·57) for coronary heart disease, 30·95 (17·59–54·45) for acute myocardial infarction, 6·45 (4·04–10·31) for stroke, 12·90 (7·39–22·51) for heart failure, and 1·17 (0·62–2·20) for atrial fibrillation. Corresponding hazard ratios for individuals who developed type 1 diabetes aged 26–30 years were 2·83 (95% CI 2·38–3·37) for all-cause mortality, 3·64 (2·34–5·66) for cardiovascular mortality, 2·78 (2·29–3·38) for non-cardiovascular mortality, 3·85 (3·05–4·87) for cardiovascular disease, 6·08 (4·71–7·84) for coronary heart disease, 5·77 (4·08–8·16) for acute myocardial infarction, 3·22 (2·35–4·42) for stroke, 5·07 (3·55–7·22) for heart failure, and 1·18 (0·79–1·77) for atrial fibrillation; hence the excess risk differed by up to five times across the diagnosis age groups. The highest overall incidence rate, noted for all-cause mortality, was 1·9 (95% CI 1·71–2·11) per 100 000 person-years for people with type 1 diabetes. Development of type 1 diabetes before 10 years of age resulted in a loss of 17·7 life-years (95% CI 14·5–20·4) for women and 14·2 life-years (12·1–18·2) for men.

Interpretation Age at onset of type 1 diabetes is an important determinant of survival, as well as all cardiovascular outcomes, with highest excess risk in women. Greater focus on cardioprotection might be warranted in people with early-onset type 1 diabetes.

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See Comment page 453

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Swedish Diabetes Register
27195 T1D
135178 matched controls
Median follow-up: 10 yrs

Mortality in type 1 diabetes

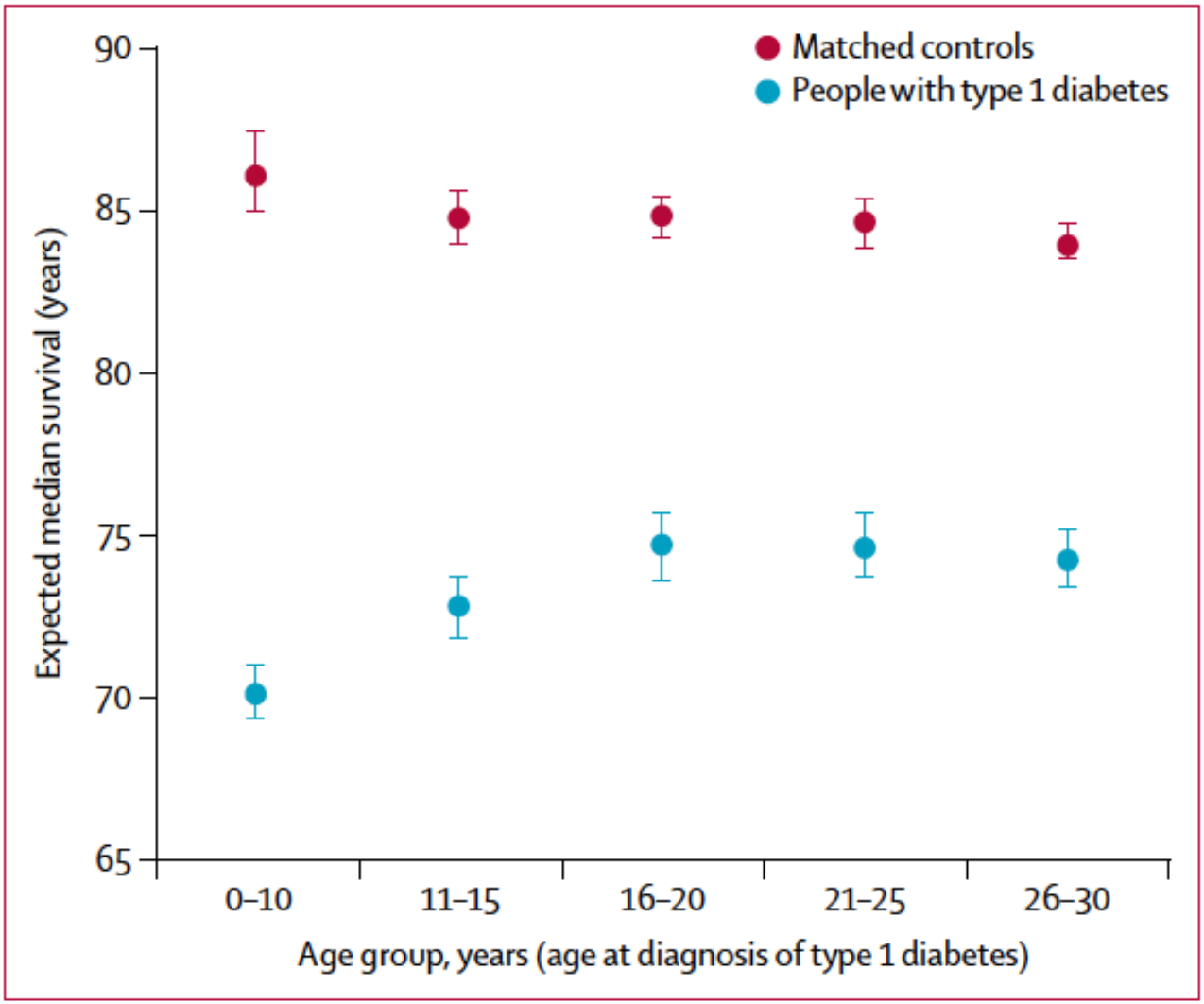
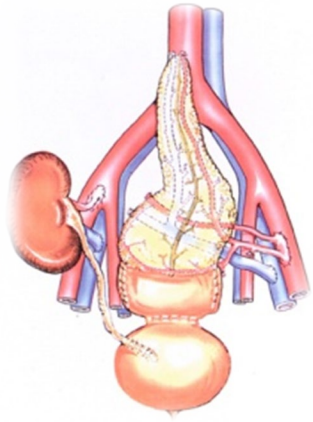


Figure 1: **Life-years lost in relation to age at onset of type 1 diabetes**

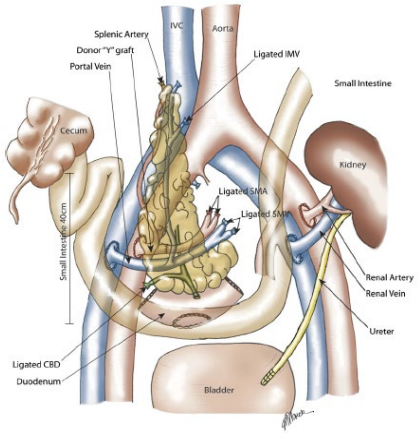
Pancreas transplantation

Surgical Techniques

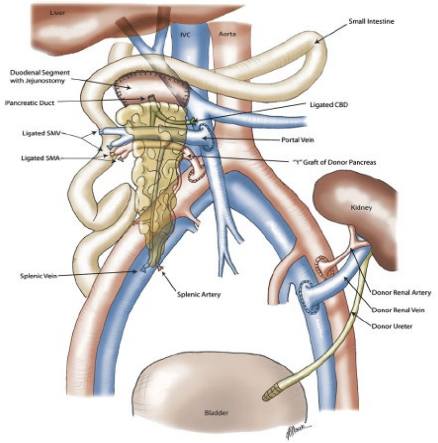
Systemic-bladder



Systemic-enteric

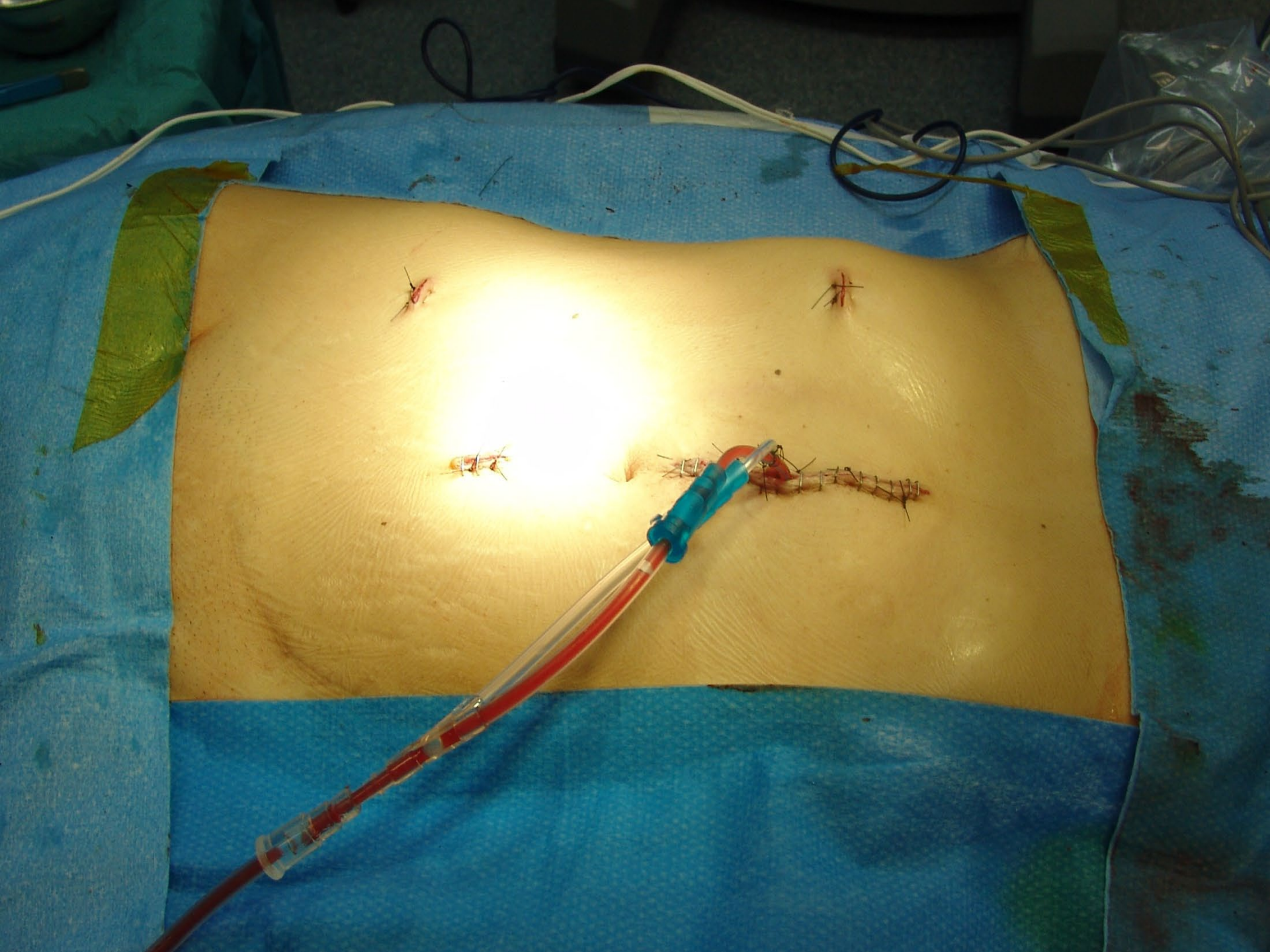


Portal-enteric





Robot assisted



Pancreas Tx perspectives





Reduce/avoid the risks
of immunosuppression

Se volete…

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Do the best you can until you know better. Then when you know better, do better.

- Maya Angelou



PTA in DM1

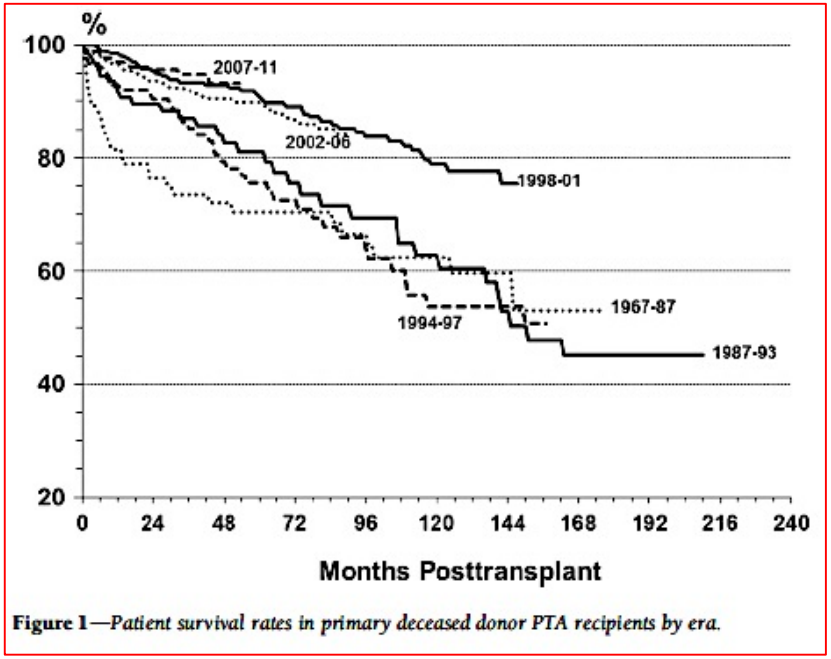


Figure 1—*Patient survival rates in primary deceased donor PTA recipients by era.*

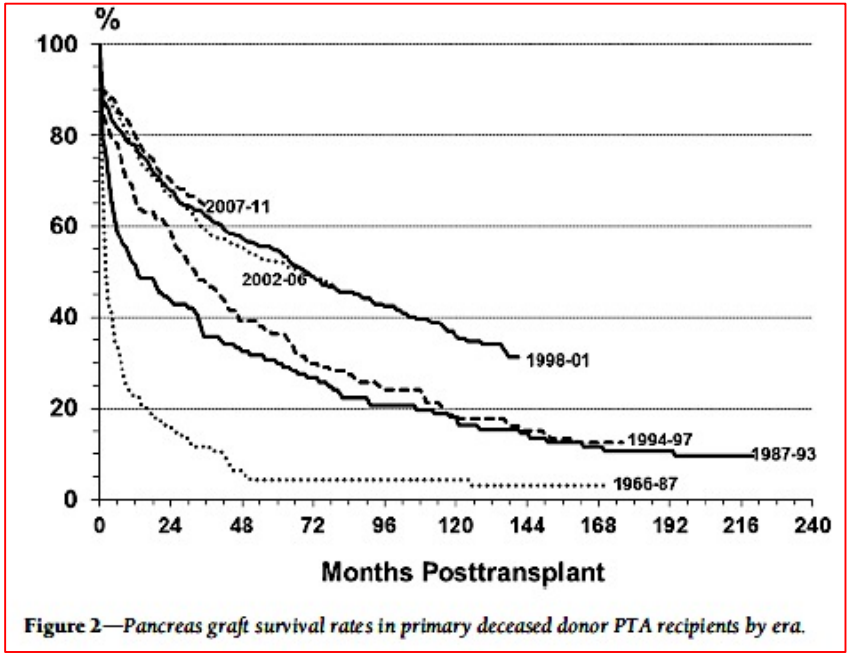


Figure 2—*Pancreas graft survival rates in primary deceased donor PTA recipients by era.*

Gruessner RWG and Gruessner AC, Diabetes Care 2013

PTA in DM1

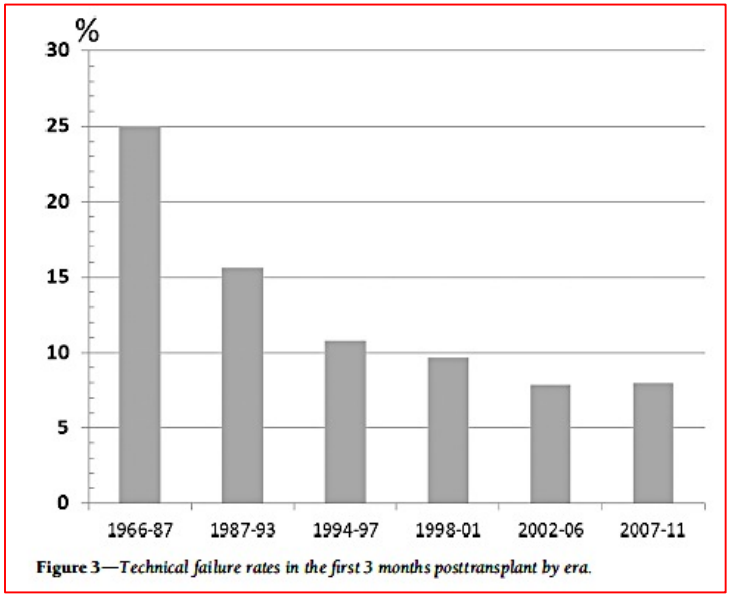


Figure 3—*Technical failure rates in the first 3 months posttransplant by era.*

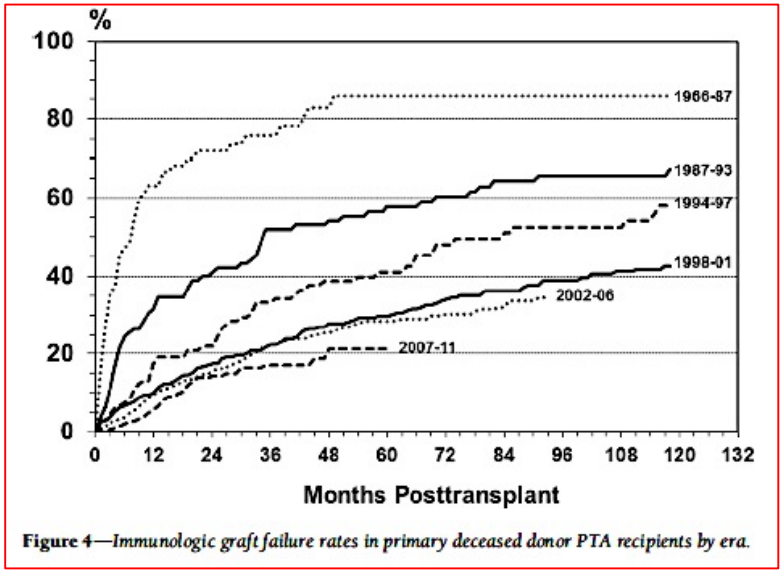


Figure 4—*Immunologic graft failure rates in primary deceased donor PTA recipients by era.*

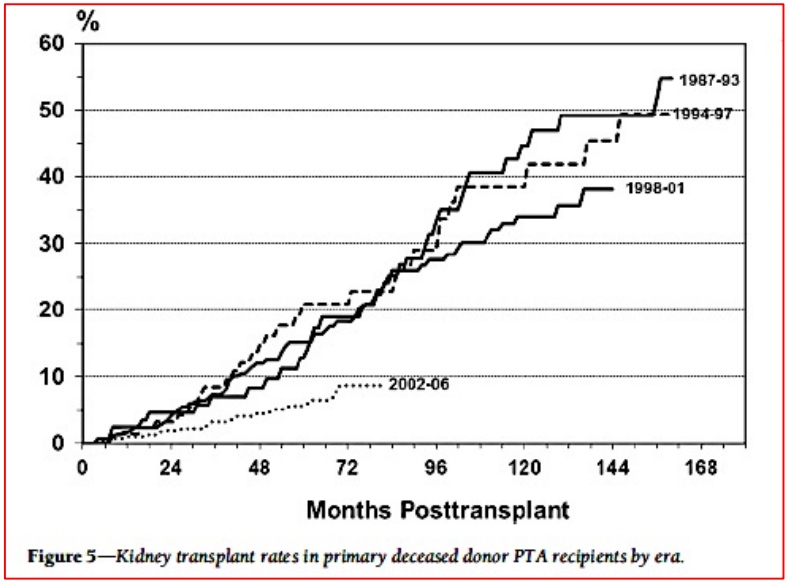


Figure 5—*Kidney transplant rates in primary deceased donor PTA recipients by era.*

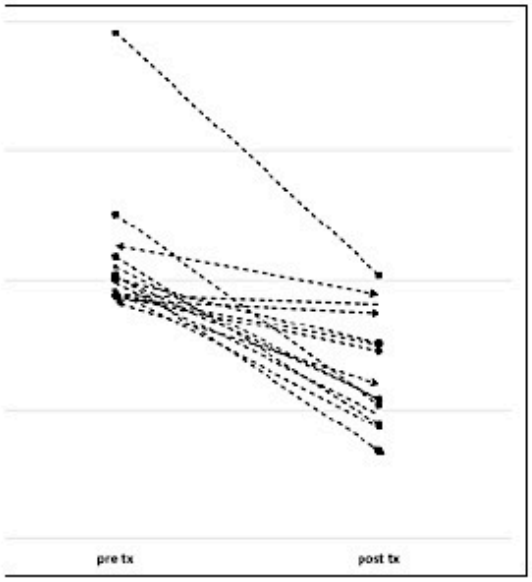
Gruessner RWG and Gruessner AC, Diabetes Care 2013

PTA: the Pisa experience

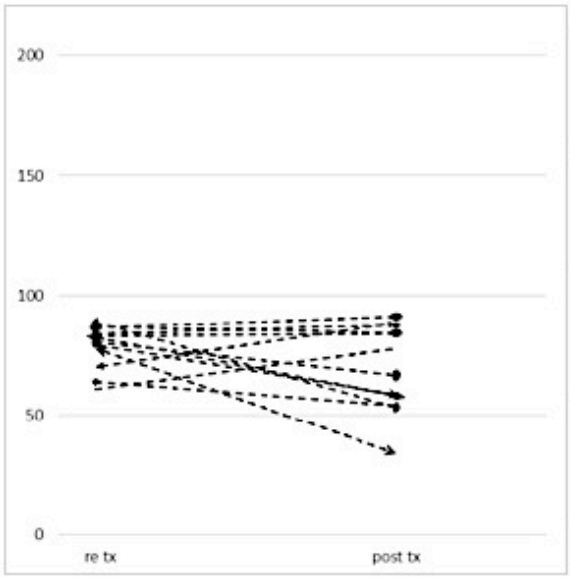
- 4 riceventi stadio 5 IRC (RRT a 1, 2, 8 e 9 anni post-tx); eGFR al momento del Tx: 48.0, 52.0,79.2 e 148.7 ml/min/1.73 m^2
- 2 riceventi stadio 4 IRC a 10 anni; eGFR al momento del Tx: 58.8 e 94.0 ml/min/1.73 m^2

PTA: the Pisa experience

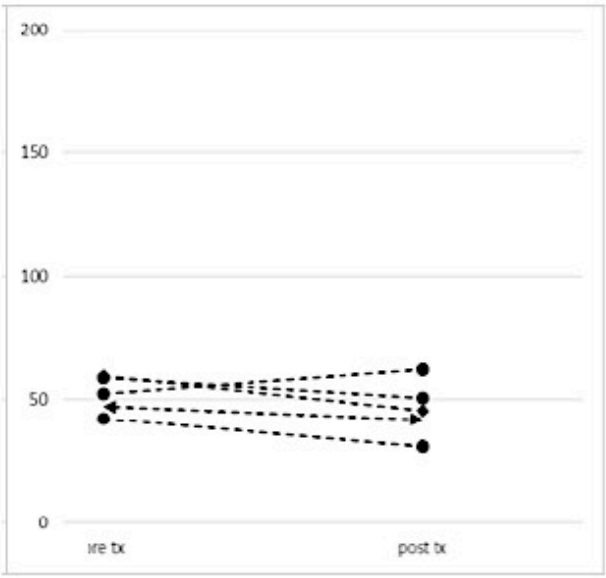
Variazione eGFR nel gruppo di pazienti con filtrato basale≥ 90 ml/min/1,73m².



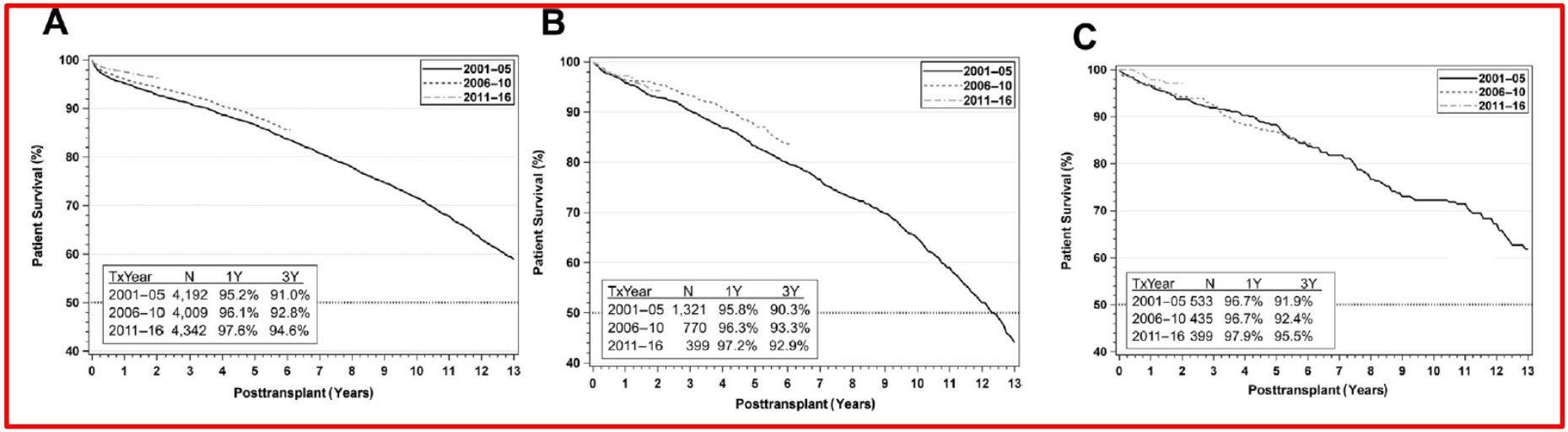
Variazione eGFR nel gruppo di pazienti con filtrato basale tra 60-89 ml/min/1,73m².



Variazione eGFR nel gruppo di pazienti con filtrato basale≤59 ml/min/1,73m².



IPTR: patient survival



SPK PAK PTA

Tx period: 2011 – 2016

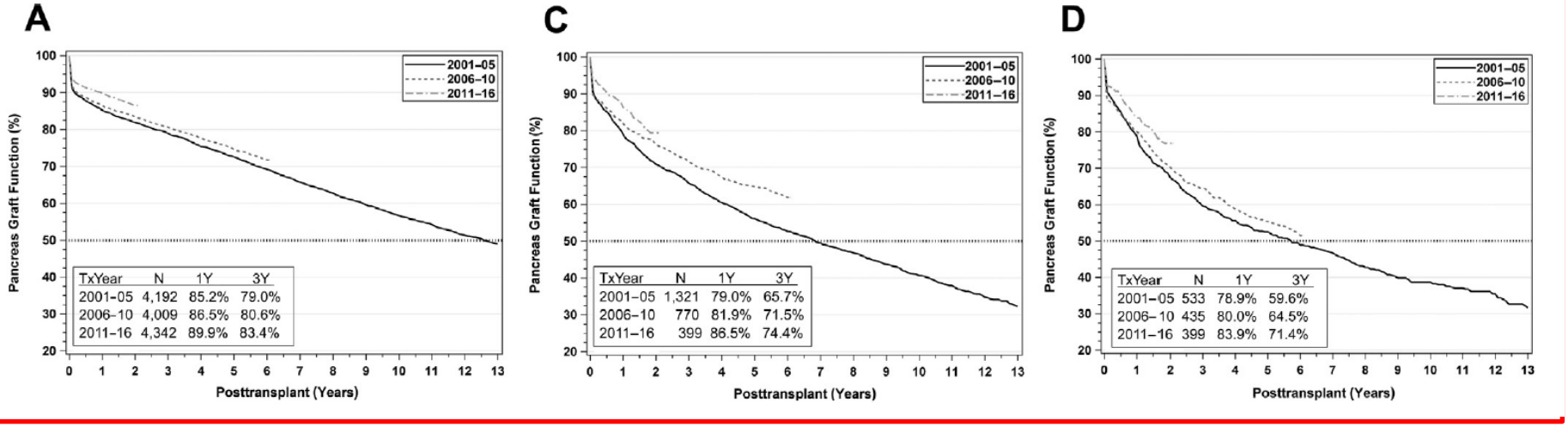
3 yr pt survival

SPK 94.6%

PAK 92.9%

PTA 95.6%

IPTR: pancreas survival



SPK PAK PTA

Tx period: 2011 – 2016

3 yr pancreas survival

SPK 83.4%

PAK 74.4%

PTA 71.4%