

28^o Congresso Interassociativo AMD-SID Lombardia 2022

Trapianto Isole/Pancreas



I.R.C.C.S. Ospedale
San Raffaele
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Milano



14-15 ottobre 2022

Auditorium Giorgio Gaber - Grattacielo Pirelli
Piazza Duca d'Aosta, 3 - Milano

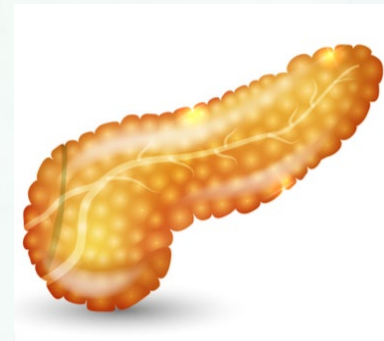


Beta cell replacement to 'cure' Type 1 Diabetes

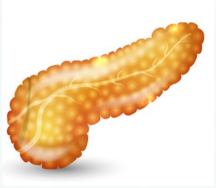
Islet of Langerhans



Whole Pancreas



Criteria of Transplant Indication – Pancreas with kidney



1° choice:
all T1D patients
who need kidney
transplant

Simultaneous Pancreas-Kidney

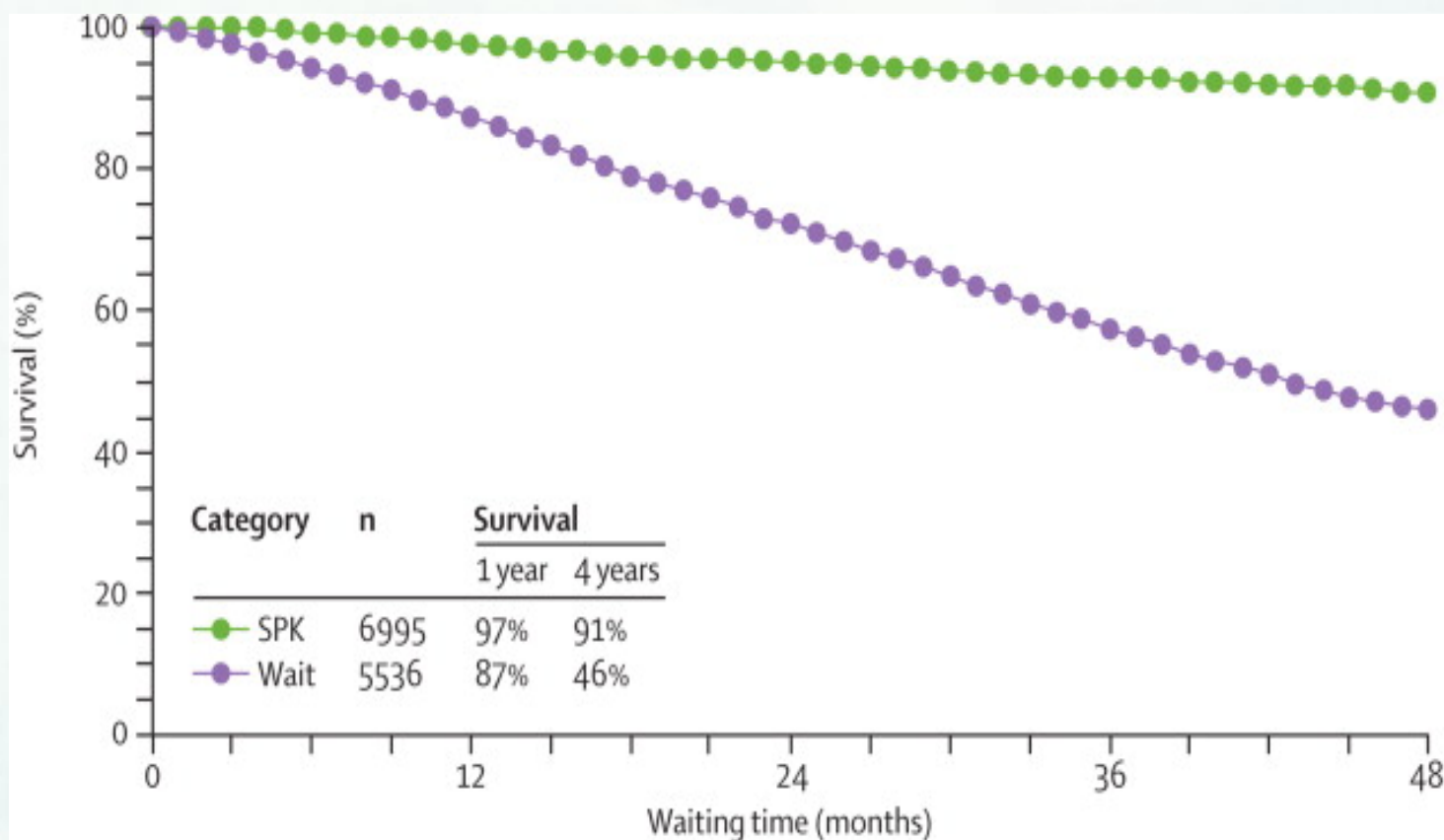
- Uremic or **pre-uremic** T1D without major advanced cardiovascular disease

Pancreas after Kidney

- T1D who received kidney transplant alone or SPK and lost the pancreas

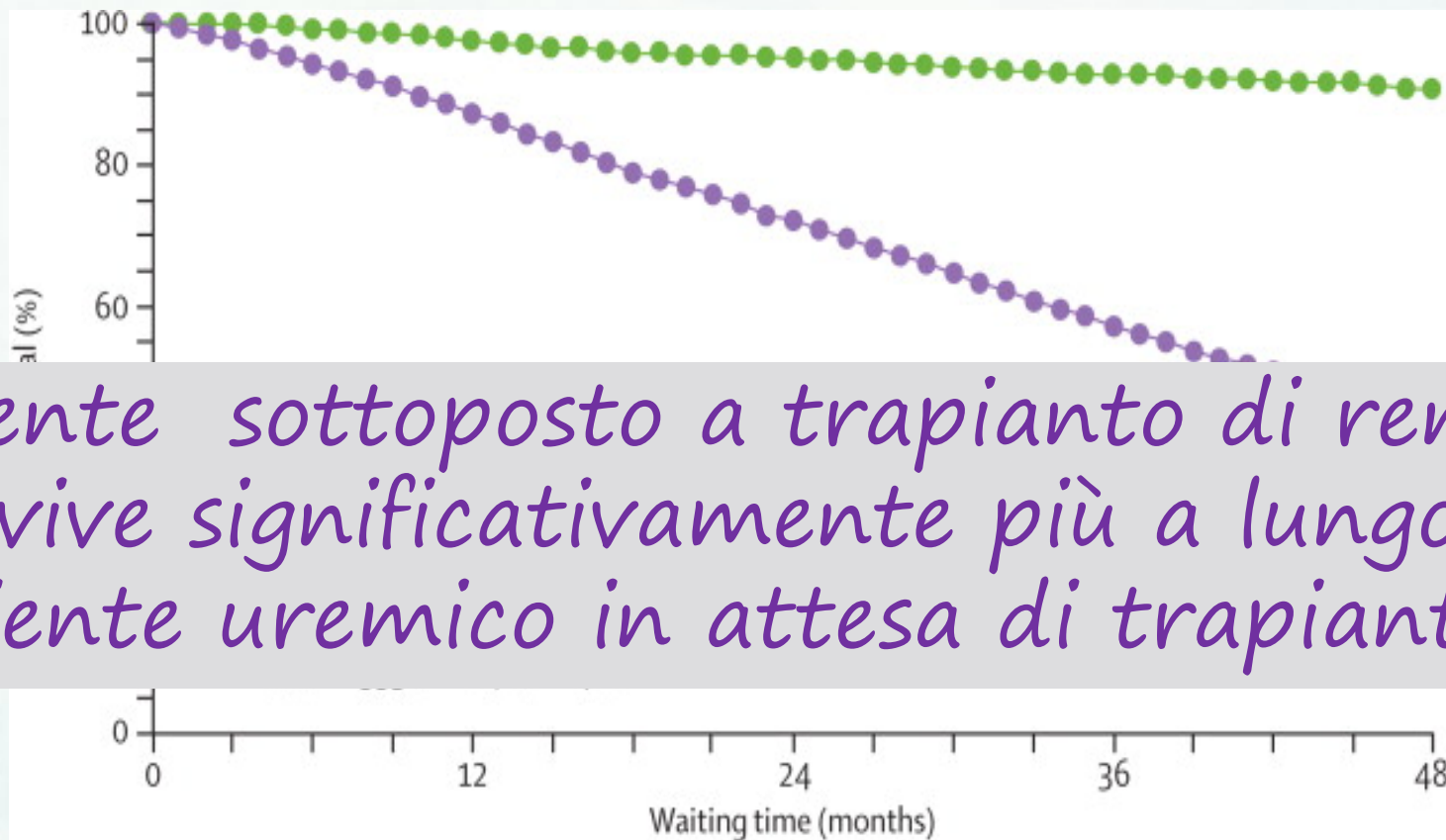
Criteria of Transplant Indication – Pancreas with kidney

Il paziente diabetico può essere inserito in lista di attesa per un trapianto rene, associato o meno a pancreas, in fase pre uremica, $eGFR \leq 30 \text{ mL/min/1.73m}^2$



*Simultaneous pancreas-kidney transplant improves survival in
Pts with Type 1 Diabetes and end stage renal disease*

Morath C et al. CJASN 5, 2010

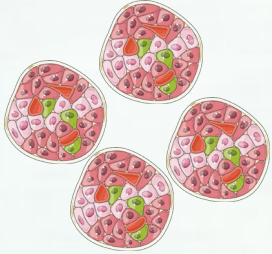


Il Paziente sottoposto a trapianto di rene-pancreas sopravvive significativamente più a lungo rispetto al Paziente uremico in attesa di trapianto di rene

Simultaneous pancreas-kidney transplant improves survival in Pts with Type 1 Diabetes and end stage renal disease

Morath C et al. CJASN 5, 2010

Criteria of Transplant Indication – Islets with kidney



*all T1D patients
who need kidney
transplant but....*

Simultaneous Islet – Kidney (SIK):

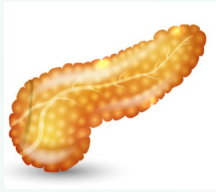
T1D excluded from simultaneous pancreas-kidney because of major cardiovascular disease

Donor unsuitable for whole pancreas transplant, suitable for isolation

Islet After Kidney (IAK):

T1D who received kidney transplant alone (recipient excluded from whole pancreas; kidney donor unsuitable for whole pancreas)

Criteria of Transplant Indication – Pancreas alone

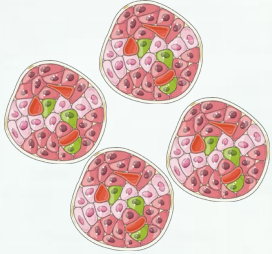


T1D patients, when advanced insulin therapy has failed

- Clinical and emotional problems with exogenous insulin therapy that are so **severe as to be incapacitating**
- History of frequent, **acute and severe** metabolic complications (**hypoglycaemia, hyperglycaemia, ketoacidosis**) **requiring medical attention**
- Consistent failure of insulin - based management to prevent acute complications

ADA, Diabetes Care 27, 2004

Criteria of Transplant Indication – Islets alone



T1D patients, when advanced insulin therapy has failed

- ✓ **low awareness to hypoglycemia**
- ✓ metabolic lability with **severe hypoglycemic crisis** or ketoacidosis which lead to hospitalization, despite intensive insulin management
- ✓ progressive secondary complications as retinopathy and neuropathy despite intensive insulin management

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

Pratik Choudhary,¹ Michael R. Rickels,²
Peter A. Senior,³
Marie-Christine Vantyghem,⁴
Paola Maffi,⁵ Thomas W. Kay,⁶
Bart Keymeulen,⁷ Nobuya Inagaki,⁸
Frantisek Saudek,⁹ Roger Lehmann,¹⁰
and Bernhard J. Hering¹¹

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

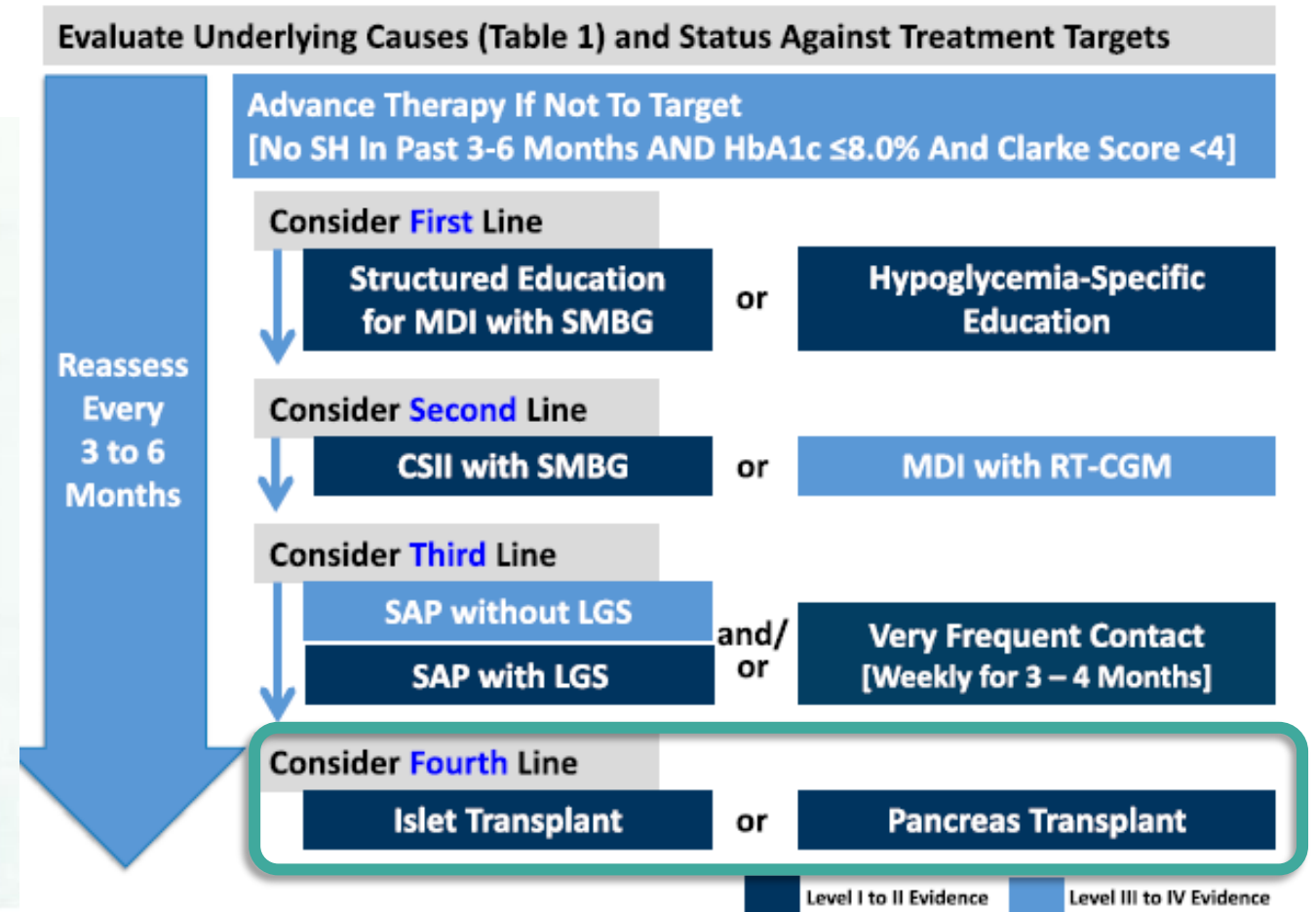
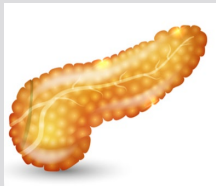
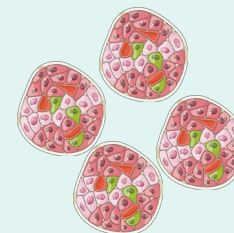


Figure 1—Proposed treatment algorithm for patients with T1D and problematic hypoglycemia.

Methos: sources of organ / tissue

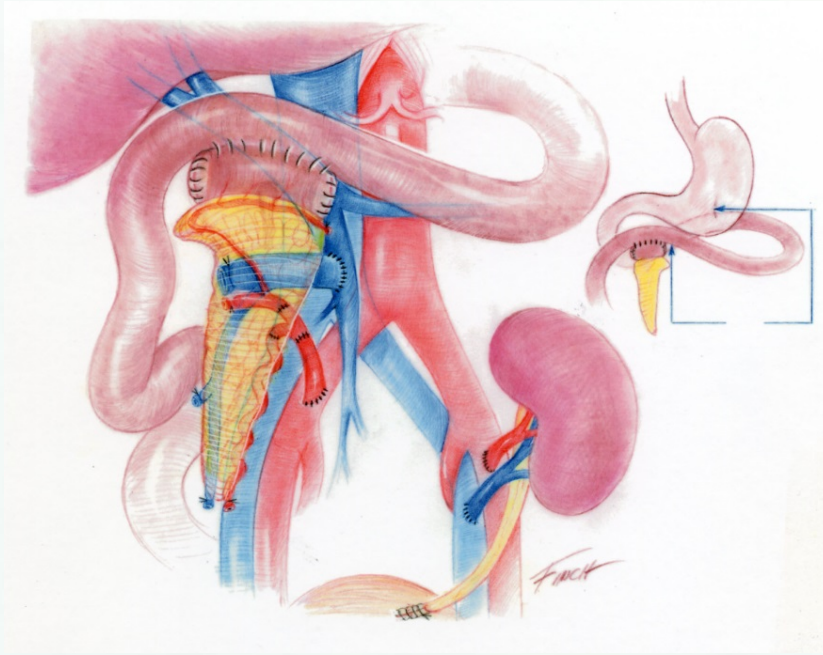


- ✓ Brain death donors aged ≤ 45 yrs, also pediatric donors
- ✓ Intensive care unit staying < 3 days
- ✓ Obese donors BMI ≥ 32 excluded
- ✓ No spleen trauma

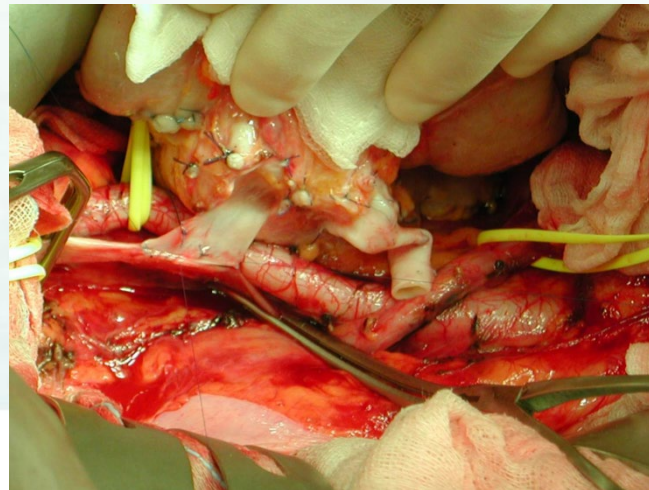
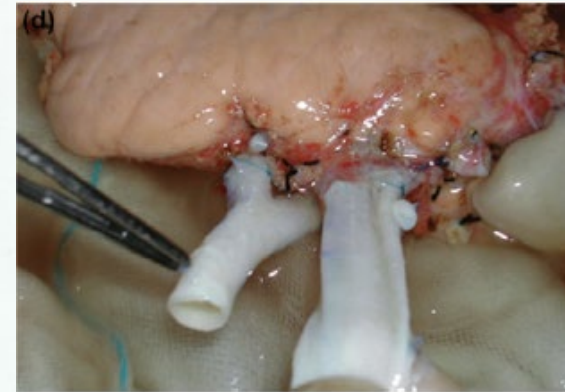


- ✓ Brain death donors aged 18-65 yrs
- ✓ Intensive care unit staying < 4 days
- ✓ Better obese donors BMI ≥ 30

Methos: Pancreas and kidney / Pancreas alone

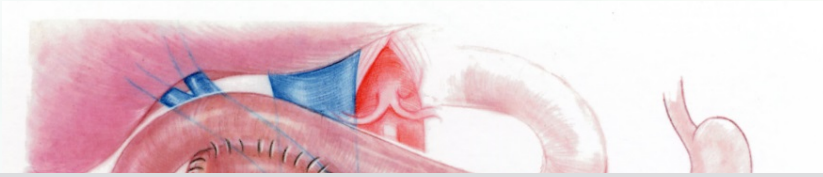


✓ The pancreas is reconstructed with a Y graft from the donor iliac artery sutured onto the donor superior mesenteric and splenic arteries



- ✓ Arterial anastomosis to the recipient's common iliac artery
- ✓ Venous drainage to the recipient's portal vein or to common iliac vein or to inferior vena cava.

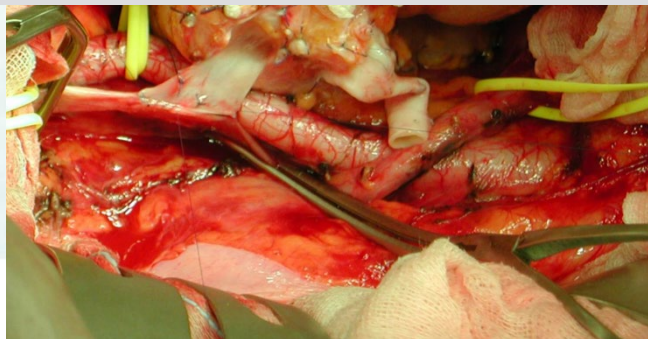
Methos: Pancreas and kidney / Pancreas alone



✓ The pancreas is reconstructed with a Y graft from the donor iliac artery sutured onto the

Il trapianto di Pancreas è un intervento di Chirurgia maggiore, che deve essere effettuato in Centri qualificati, selezionati, da Chirurghi esperti:

- ✓ Pacreas con un sistema artero-venoso ad alto rischio di trombosi
- ✓ Posizionamento intraperitoneale
- ✓ Apertura del tenue
- ✓ Anastomosi vascolari difficili per la frequente presenza di aterosclerosi



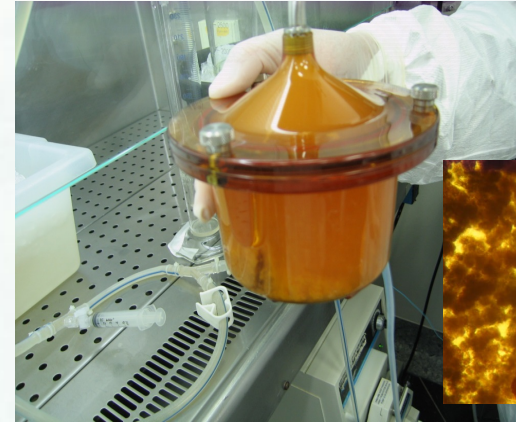
arterial anastomosis to the recipient's common iliac artery

✓ Venous drainage to the recipient's portal vein
or to common iliac vein
or to inferior vena cava.

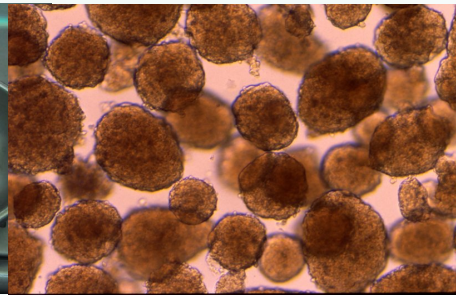
Methos: Islet isolation and Infusion



Pancreas harvested from
brain death donors



Digestion



Purification
Final product

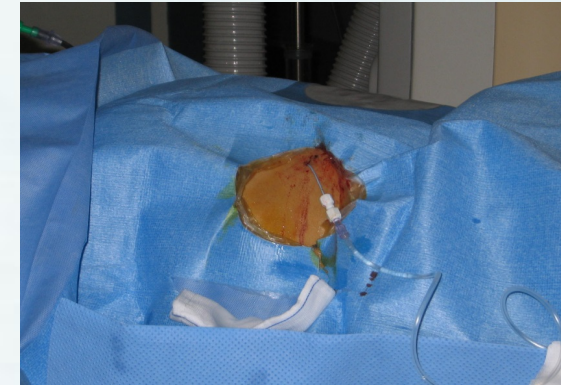
Methos: Islet isolation and Infusion

Intra Hepatic Infusion

Percutaneous transhepatic portal vein catheterization

Ultrasonography and fluoroscopic guidance

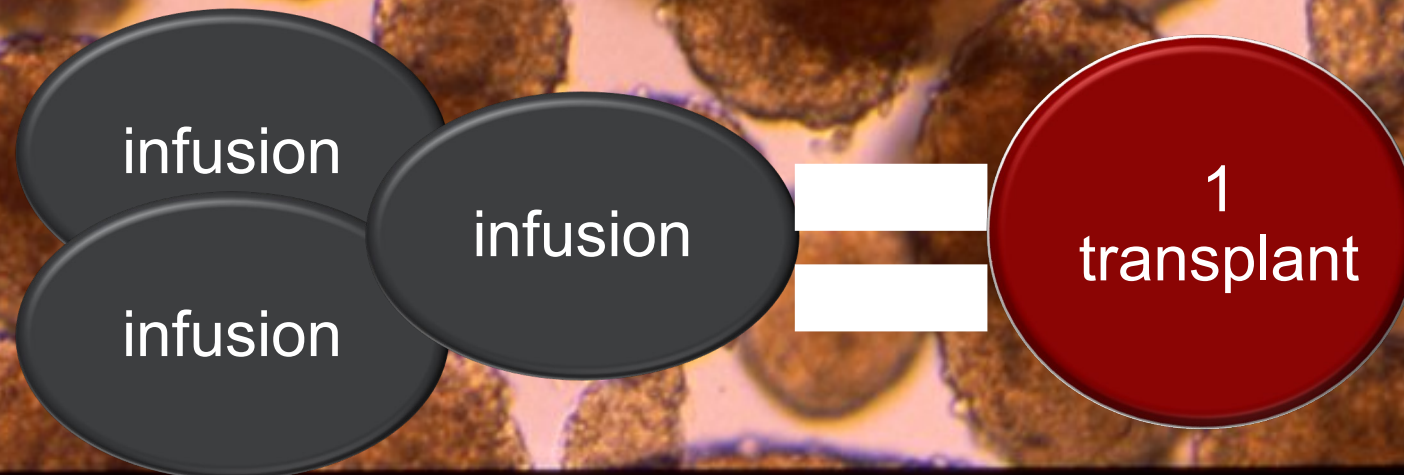
Local anesthesia



Ideal Final Product to Transplant

Islet number 10,000 IEq/kg body weight

Transplant: multiple infusion



Ideal Final Product to Transplant

Islet number 10,000 IEq/kg body weight

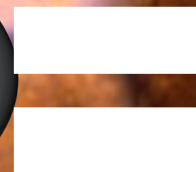
Il trapianto di isole è una procedura a basso rischio.

Il problema principale è relativo al numero di pancreas necessari per raggiungere i criteri di un preparato 'ideal'

infusion

infusion

infusion



1
transplant

IMMUNOSUPPRESSION

Induction - Anti acute rejection

Induction therapy: at the time of surgery/infusion

- Steroids (high dose, single bolus)
+
- Anti Tymocyte Globulin (ATG)
or
- Anti IL2 receptor Antibody
(basiliximab, anti CD25)

IMMUNOSUPPRESSION

Maintenance

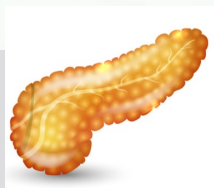
Chronic therapy: every day, for all graft life



- Steroids
- Calcineurin inhibitors (tacrolimus, cyclosporine)
- Purine synthesis inhibitors (MMF, Aza)
- mTOR inhibitors (sirolimus, everolimus)

Immunosuppression Therapy

With kidney or alone:



- ✓ Steroids (high dose, single bolus)
+
- ✓ Anti Tymocyte Globulin (ATG), 7-10 days,
max dosage 6mg/kg
- ✓ Steroids
- ✓ Tacrolimus
- ✓ Micofenolate Mofetil

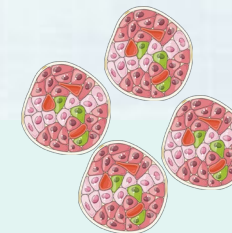
With kidney:

- The kidney transplant is leading; no changes for islet

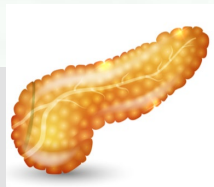
Alone

- ✓ Anti IL2 receptor Antibody (basiliximab, anti CD25)
- ✓ Tacrolimus
- ✓ Sirolimus

* steroids free



Immunosuppression Therapy



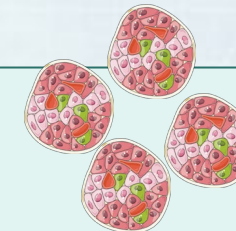
With kidney or alone:

Induction

- ✓ Steroids (high dose, single bolus)
- ✓ Anti Tymocyte Globulin (ATG), 7 days, max dosage 6mg/kg

Chronic

- ✓ Steroids
- ✓ Tacrolimus
- ✓ Micofenolate Mofetil



With kidney:

The kidney transplant is leading; no changes for islet

Alone

Induction (at each infusion)

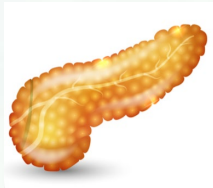
- ✓ Anti IL2 receptor Antibody (basiliximab, anti CD25)

Chronic

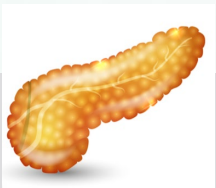
- ✓ Tacrolimus
- ✓ Sirolimus

* steroids free

Metabolic Results

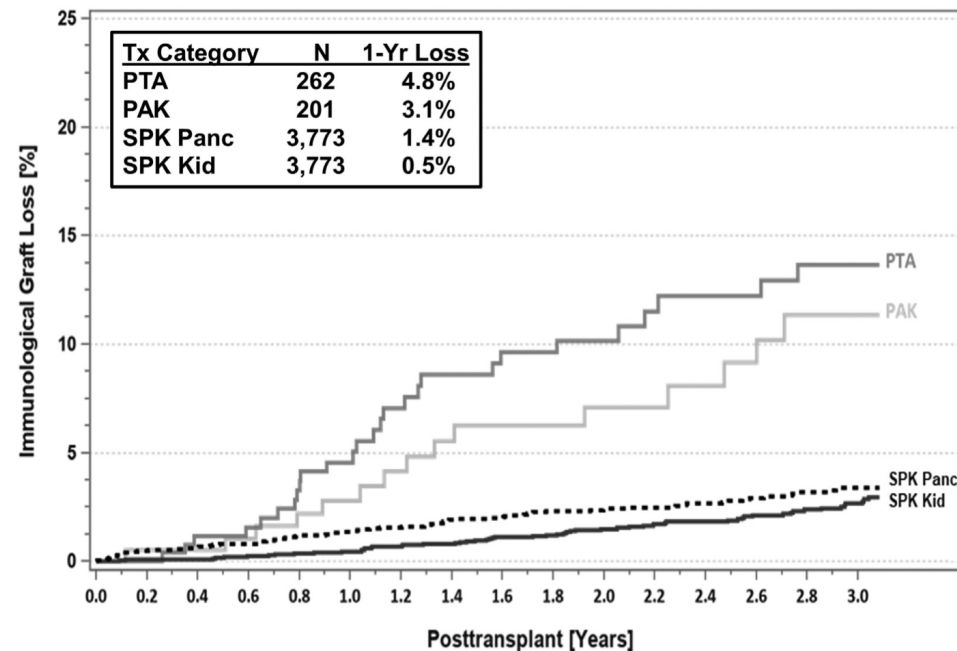
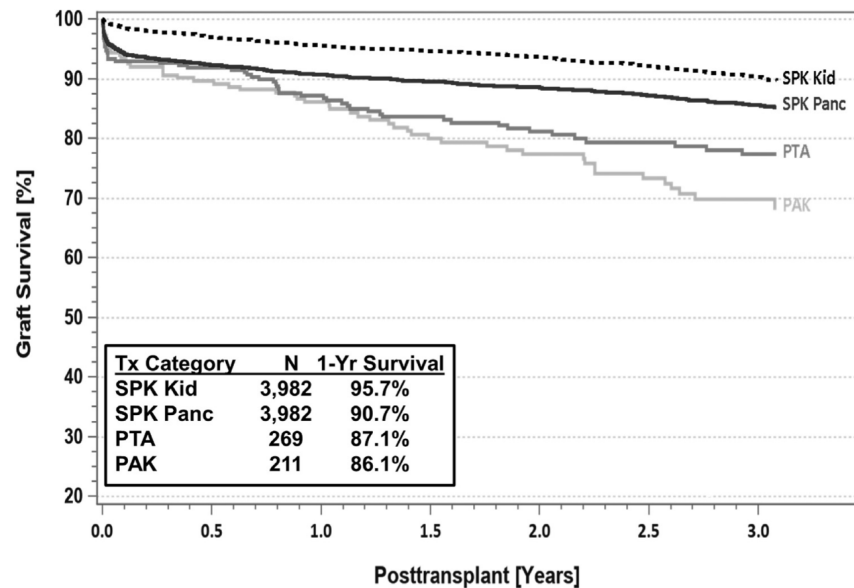


Metabolic Results



- ✓ Normal glycaemia immediately after surgery
- ✓ Normal glycaeted haemoglobin
- ✓ No diet





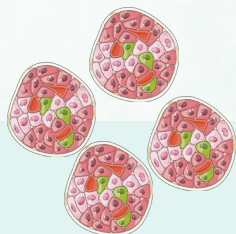
The 2022 International Pancreas Transplant Registry Report—A Review

Angelika C. Gruessner*, and Rainer W.G. Gruessner

0041-1345/20

<https://doi.org/10.1016/j.transproceed.2022.03.059>

Metabolic Results



- ✓ Progressive, slow reduction in exogenous insulin requirement
- ✓ Flat glycaemia despite exogenous insulin therapy
- ✓ Withdrawl of exogenous insulin therapy after 2-3 infusions (several months)

Functional Outcome of beta cells replacement therapy: Igl's Criteria

β -Cell graft functional status	HbA1c, % (mmol/mol)	Severe Hypoglycemia, events per year	Insulin requirements, U/kg/day	C-peptide	Treatment success	
Optimal	≤ 6.5 (48)	None	None	>Baseline; >0.5 ng/mL	Yes	
Good	<7.0 (53)	None	<50% baseline; <0.5 U/kg/day	>Baseline; >0.5 ng/mL	Yes	
Marginal	Baseline	<Baseline	$\geq 50\%$ baseline	>Baseline; >0.5 ng/mL	No	
Failure	Baseline	Baseline	Baseline	Baseline	No	

Piemonti L. et al , Diabetologia 2108, 61: 1273

Rickels, M. R. et al. , Transplant International 2018 31, 343



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Islet Transplantation Program

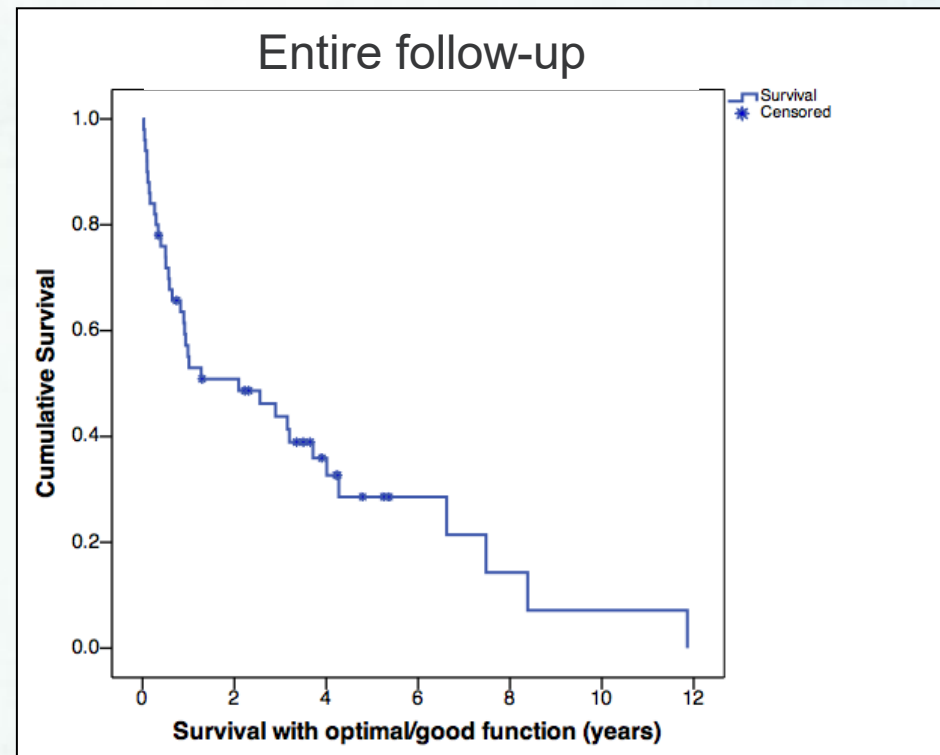
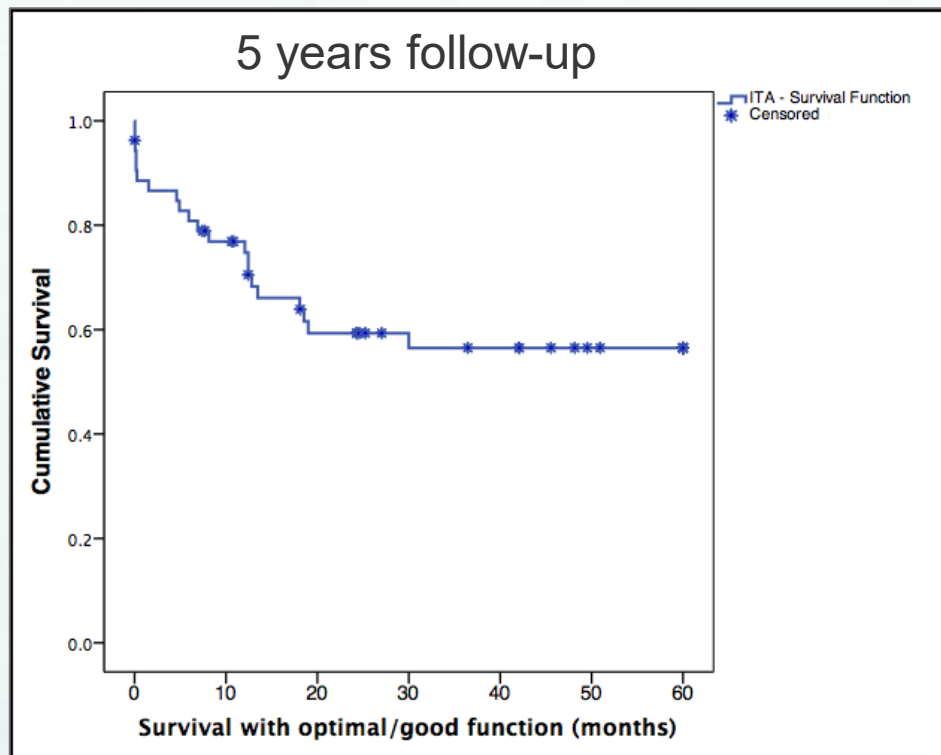
Dec 1989 – 10 Oct 2022



	Transplants	Infusions
Islet tx alone	88	167
Islet and kidney	66	88
Auto Islet tx	79	79
Total	233	334



Islet Alone functional status: optimal - good

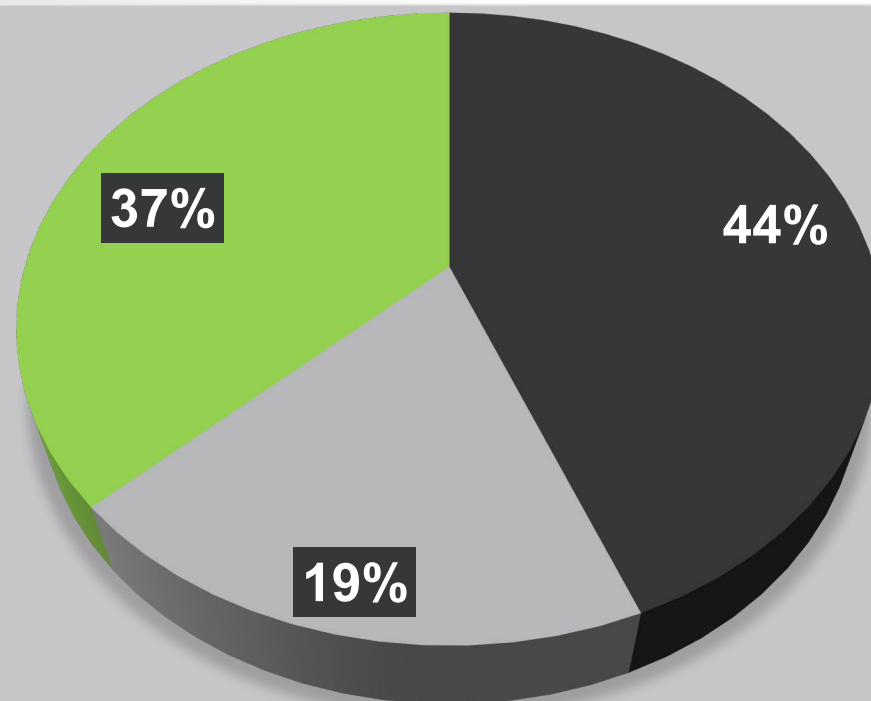




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Outcome of Islet Transplant Alone

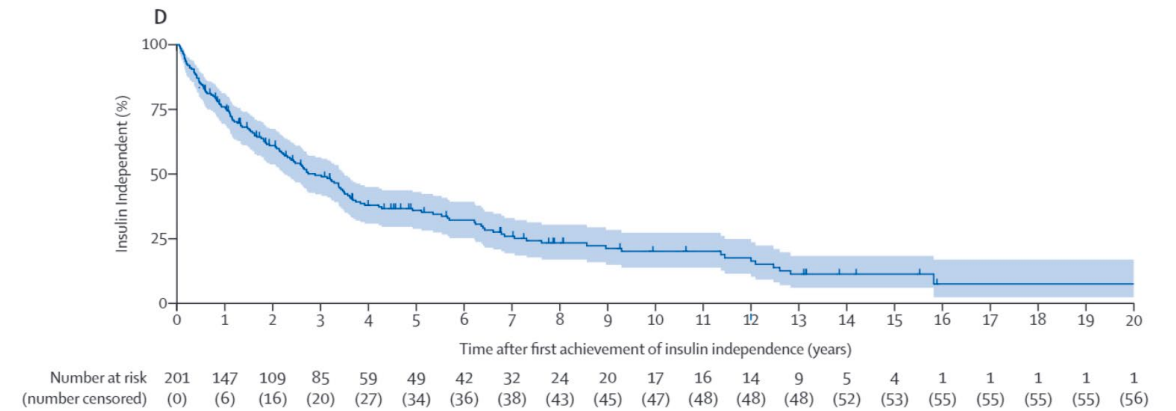
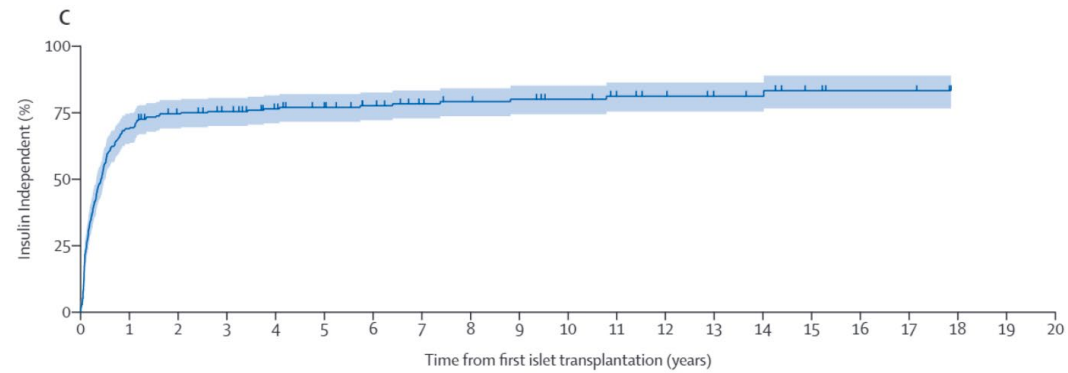
Pts: 88; Infusions: 167



Optimal
Good
Marginal
+
failure



Longest insulin-independence: **133 months**

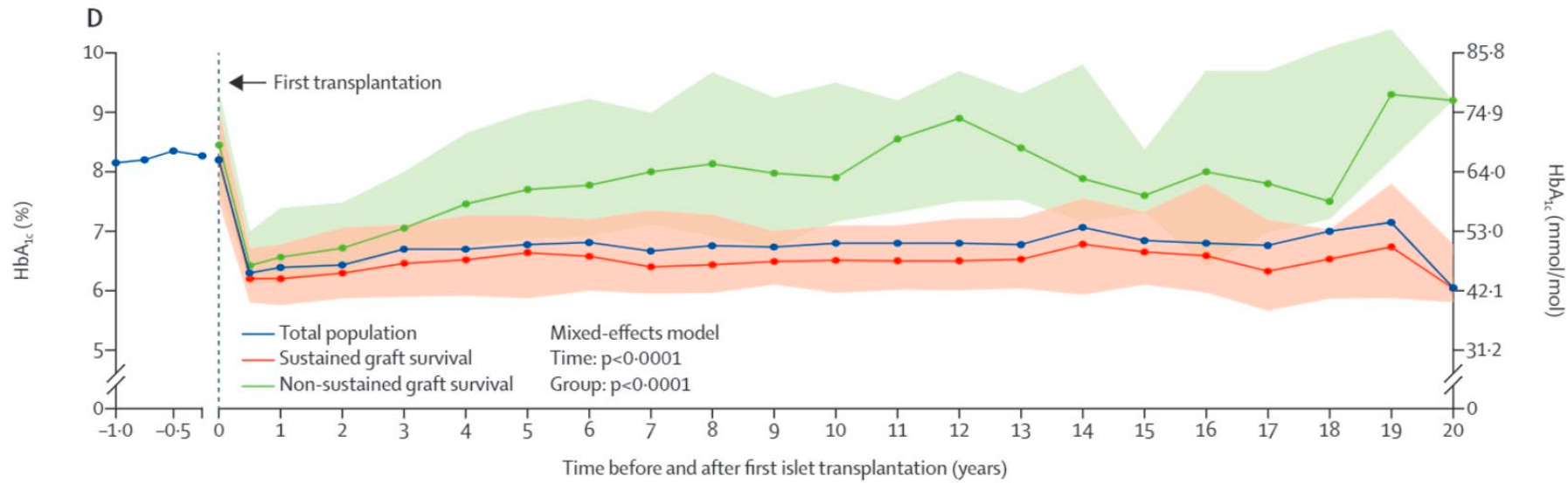


Pancreatic islet transplantation in type 1 diabetes: 20-year experience from a single-centre cohort in Canada



Braulio A Marfil-Garza, Sharleen Imes, Kevin Verhoeff, Joshua Hefler, Anna Lam, Khaled Dajani, Blaire Anderson, Doug O'Gorman, Tatsuya Kin, David Bigam, Peter A Senior, A M James Shapiro

www.thelancet.com/diabetes-endocrinology Published online May 16, 2022



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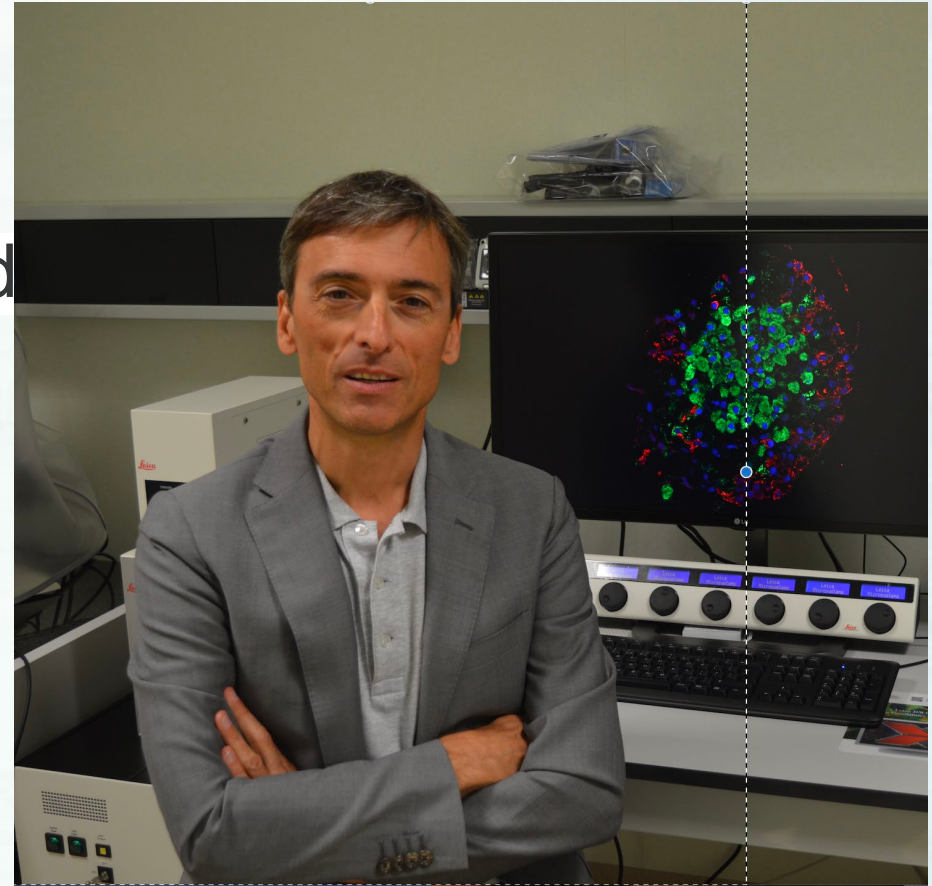
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Pub Med.gov

Pancreas Islet Transplant and Chronic d

Search



Transplant and Chronic diabetes complications

Diabetes Care. 2000 Dec;23(12):1804-10.

doi: 10.2337/diacare.23.12.1804.

Reversal of left ventricular diastolic dysfunction after kidney-pancreas transplantation in type 1 diabetic uremic patients

P Fiorina

Cell Transplant. 2000 Nov-Dec;9(6):929-32.

doi: 10.1177/096368970000900621.

Patient survival and cardiovascular events after kidney-pancreas transplantation: comparison with kidney transplantation alone in uremic IDDM patients

E La Rocca¹, P Fiorina,

J Am Soc Nephrol. 2003 Aug;14(8):2150-8.

doi: 10.1097/01.asn.0000077339.20759.a3.

Islet transplantation is associated with improvement of renal function among uremic patients with type I diabetes mellitus and kidney transplants

Paolo Fiorina¹

Diabetes Care. 2003 Apr;26(4):1129-36.

doi: 10.2337/diacare.26.4.1129.

Long-term beneficial effect of islet transplantation on diabetic macro-/microangiopathy in type 1 diabetic kidney-transplanted patients

Paolo Fiorina¹

Kidney Int. 2001 Nov;60(5):1964-71.

doi: 10.1046/j.1523-1755.2001.00008.x.

Cardiovascular outcomes after kidney-pancreas and kidney-alone transplantation

E La Rocca¹, P Fiorina

Diabetes. 2001 Mar;50(3):496-501.

doi: 10.2337/diabetes.50.3.496.

Effects of kidney-pancreas transplantation on atherosclerotic risk factors and endothelial function in patients with uremia and type 1 diabetes

P Fiorina¹,

Transplantation. 2003 Apr 27;75(8):1296-301.

doi: 10.1097/01.TP.0000061788.32639.D9.

Islet transplantation improves vascular diabetic complications in patients with diabetes who underwent kidney transplantation: a comparison between kidney-pancreas and kidney-alone transplantation

Paolo Fiorina¹,

Diabetes. 2004 Sep;53(9):2291-300.

doi: 10.2337/diabetes.53.9.2291.

Normalization of multiple hemostatic abnormalities in uremic type 1 diabetic patients after kidney-pancreas transplantation

Paolo Fiorina

Transplant and Chronic diabetes complications

Diabetes Care. 2004 Apr;27(4):947-54.

doi: 10.2337/diacare.27.4.947.

L-arginine-induced vasodilation of the renal vasculature is preserved in uremic type 1 diabetic patients after kidney and pancreas but not after kidney-alone transplantation

Francesco De Cobelli¹, Paolo Fiorina,

Diabetes Care. 2005 Jun;28(6):1303-10.

doi: 10.2337/diacare.28.6.1303.

Natural history of kidney graft survival, hypertrophy, and vascular function in end-stage renal disease type 1 diabetic kidney-transplanted patients: beneficial impact of pancreas and successful islet cotransplantation

Paolo Fiorina

Transplantation. 2006 May 15;81(9):1274-7.

doi: 10.1097/01.tp.0000208631.63235.6a.

Early increase of retinal arterial and venous blood flow velocities at color Doppler imaging in brittle type 1 diabetes after islet transplant alone

Massimo Venturini¹, Paolo Fiorina,

Am J Transplant. 2010 Dec;10(12):2690-700.

doi: 10.1111/j.1600-6143.2010.03309.x.

Improved function of circulating angiogenic cells is evident in type 1 diabetic islet-transplanted patients

A Petrelli-----P Fiorina

Diabetes Care. 2014;37(1):267-76.

doi: 10.2337/dc13-1663. Epub 2013 Sep 11.

Islet transplantation stabilizes hemostatic abnormalities and cerebral metabolism in individuals with type 1 diabetes

Francesca D'Addio-----Paolo Fiorina

Diabetes Care. 2005 Jun;28(6):1358-65.

doi: 10.2337/diacare.28.6.1358.

Islet transplantation is associated with an improvement of cardiovascular function in type 1 diabetic kidney transplant patients

Paolo Fiorina¹,

Diabetes Care. 2007 Dec;30(12):3063-9.

doi: 10.2337/dc07-0206. Epub 2007 Sep 5.

Evaluation of polyneuropathy markers in type 1 diabetic kidney transplant patients and effects of islet transplantation: neurophysiological and skin biopsy longitudinal analysis

Ubaldo Del Carro¹, Paolo Fiorina,

Transplantation. 2011 Oct 15;92(7):802-8.

doi: 10.1097/TP.0b013e31822c6eb8.

Kidney-pancreas transplantation is associated with near-normal sexual function in uremic type 1 diabetic patients

Andrea Salonia-----Paolo Fiorina

Diabetes Care. 2012 Feb;35(2):367-74.

doi: 10.2337/dc11-1697. Epub 2011 Dec 21.

Near normalization of metabolic and functional features of the central nervous system in type 1 diabetic patients with end-stage renal disease after kidney-pancreas transplantation

Paolo Fiorina¹

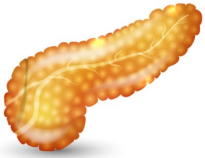


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To sum up focused analysis overview: beneficial effects of transplant on chronic diabetes complications

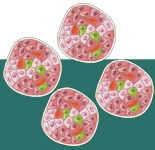
- Better cerebral metabolism
- Improvement of polineuropathy
- Improvement of kidney transplanted function
- Better survival in diabetic Patients with end stage renal disease
- Improvement of cardiovascular function
- Improvement of macro-microangiopathy
- Improvement of early stage retinopathy

Transplant related complications



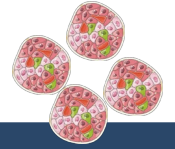
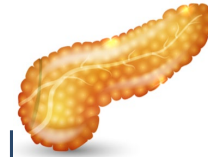
Surgery

- Pancreas thrombosis
- Peritoneal emorragy
- Leak of duodenum graft
- Acute abdomen



Infusion

- Portal vein thrombosis
- Peritoneal bleeding



Immunosuppression

- Infection
- Cancer/PTLD*
- kidney function deterioration

* Post Transplant Lymphoprolifertative Disease



Risks and Benefits of Transplantation in the Cure of Type 1 Diabetes: Whole Pancreas Versus Islet Transplantation. A Single Center Study

Maffi P., Secchi A



Table 2. Transplantation procedure: hospital stay and procedure-related adverse events

Characteristic	PTA (n = 33)	ITA (n = 33)	p-value
Hospitalization (days)	19 (16-24)	16 (9-19)	0.009
RBC transfusion	14	2	< 0.001
Relaparotomy	18	0	< 0.001
Transplantectomy	12	NA	
Thrombosis (total)	13	3*	
Medical therapy	4	3	
Fogarty	2	NA	
Transplantectomy	7	NA	
Bleeding (total)	5	12	
Medical therapy	2	2	
Surgical revision	2	NA	
Transplantectomy	1	NA	
Acute rejection (total)	9		
Transplantectomy	4		
Medical therapy	4	NA	
Chronic rejection	1		



Risks and Benefits of Transplantation in the Cure of Type 1 Diabetes: Whole Pancreas Versus Islet Transplantation. A Single Center Study

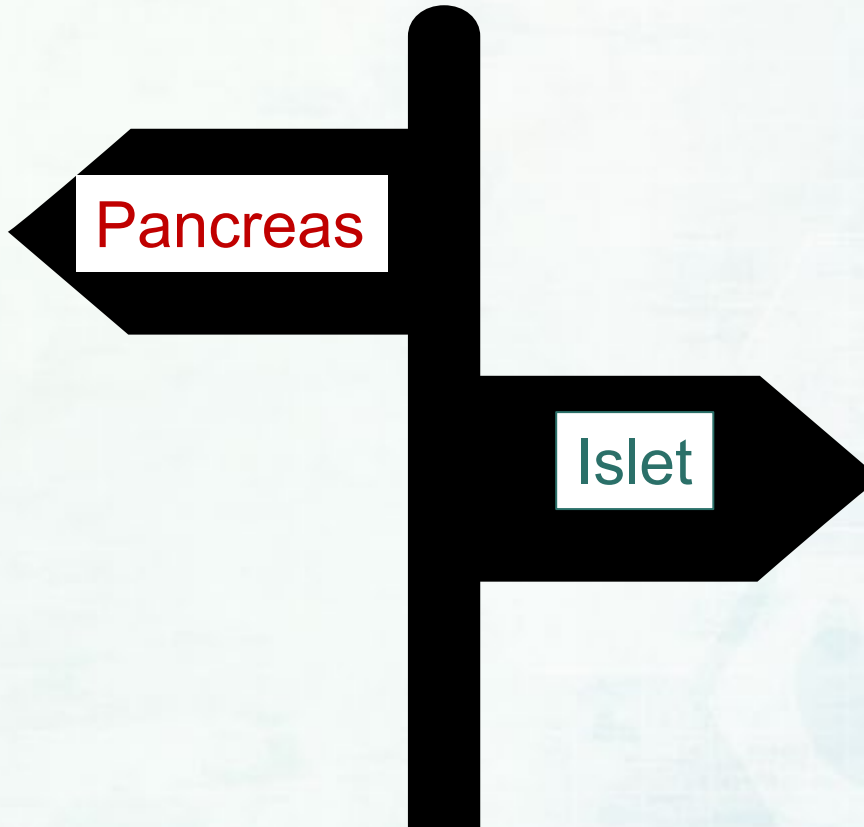
Maffi P., Secchi A



Table 3. Adverse events during long-term follow-up

Characteristic	PTA (n = 33)	ITA (n = 33)	p-value
CMV reactivation	21	2	< 0.001
Other infections	5	2	
Urinary tract infection	3	0	
Bacterial sepsis	2	0	
Viral myocarditis	0	2	
Necrotizing fasciitis	1*	0	
Worsening kidney function	4	5	
End-stage RD	1	2	
Worsened DN	3	1	
Resolved after TW	0	2	
Other medical complications	2	1	
Thrombotic TP	1	0	
Toxic hepatitis	0	1	
TAC-ind. optic neuritis	1	0	

Beta cell replacement to 'cure' Type 1 Diabetes





Islet Transplantation Alone Versus Solitary Pancreas Transplantation: an Outcome-Driven Choice?

Paola Maffi¹ · Antonio Secchi²

Fig. 1 Flowchart proposal to define when to carry out pancreas (PTA) or islet (ITA) transplantation alone

ADA: Indications for PTA and suggestions for ITA

- hypoglycemia unawareness
- extreme glycemic lability
- failure of advanced insulin therapy (CGM/CSII technologies)

Clinical Assessment

- cardiovascular examination (surgical risk)
- hypoglycemia severity grade
- progression of chronic complications (retinopathy, neuropathy)
- expectations of the patient

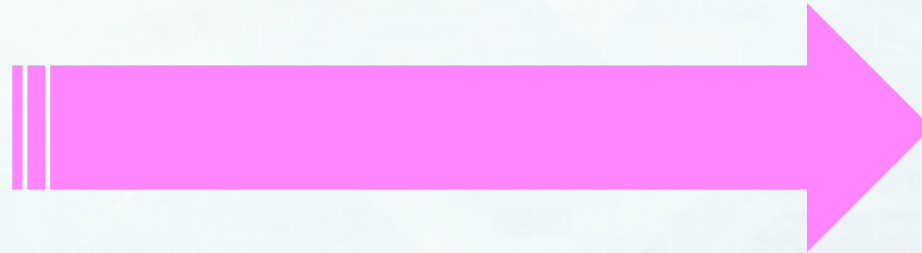
cardiovascular disease*	No	No	Yes
hypoglycemia severity grade**	Yes	Yes	Yes/No
fast progression of chronic complications (potential reversal with PTA)**	Yes	No	Yes/No
patient's willingness**	High	Mild	Yes/No
propensity risk**	High	Mild	Yes/No
Choice	PTA	ITA	ITA

* not outcome-driven

** outcome-driven

28^o Congresso Interassociativo AMD-SID Lombardia 2022

Take home message



14-15 ottobre 2022

Auditorium Giorgio Gaber - Grattacielo Pirelli
Piazza Duca d'Aosta, 3 - Milano



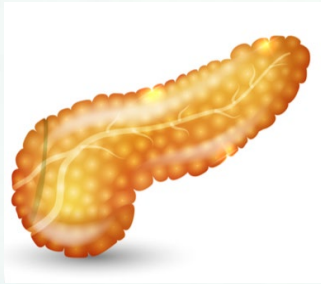
SID

Società Italiana
di Diabetologia

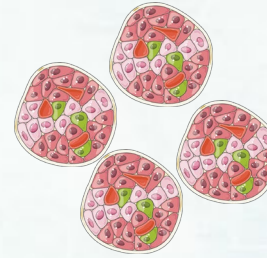


Beta cell replacement to 'cure' Type 1 Diabetes

Whole Pancreas

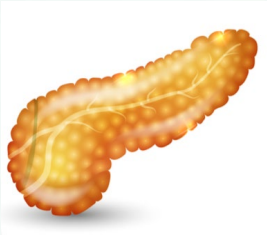


Islet of Langerhans

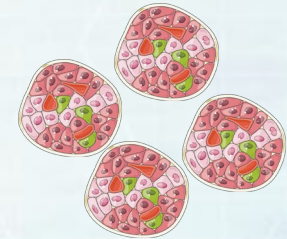


Beta cell replacement to 'cure' Type 1 Diabetes

Whole Pancreas



Islet of Langerhans



Statement of indications to transplant in Type 1 Diabetes is well confirmed

Efficiency

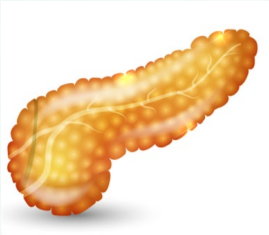
High potential to cure type 1 diabetes / insulin independence for long time

Safety, when performed in experienced centres

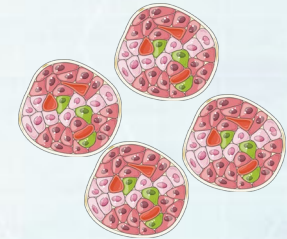


Beta cell replacement to 'cure' Type 1 Diabetes

Whole Pancreas



Islet of Langerhans



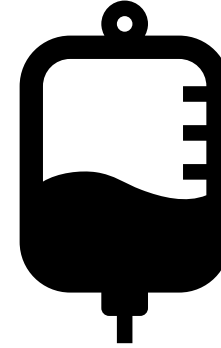
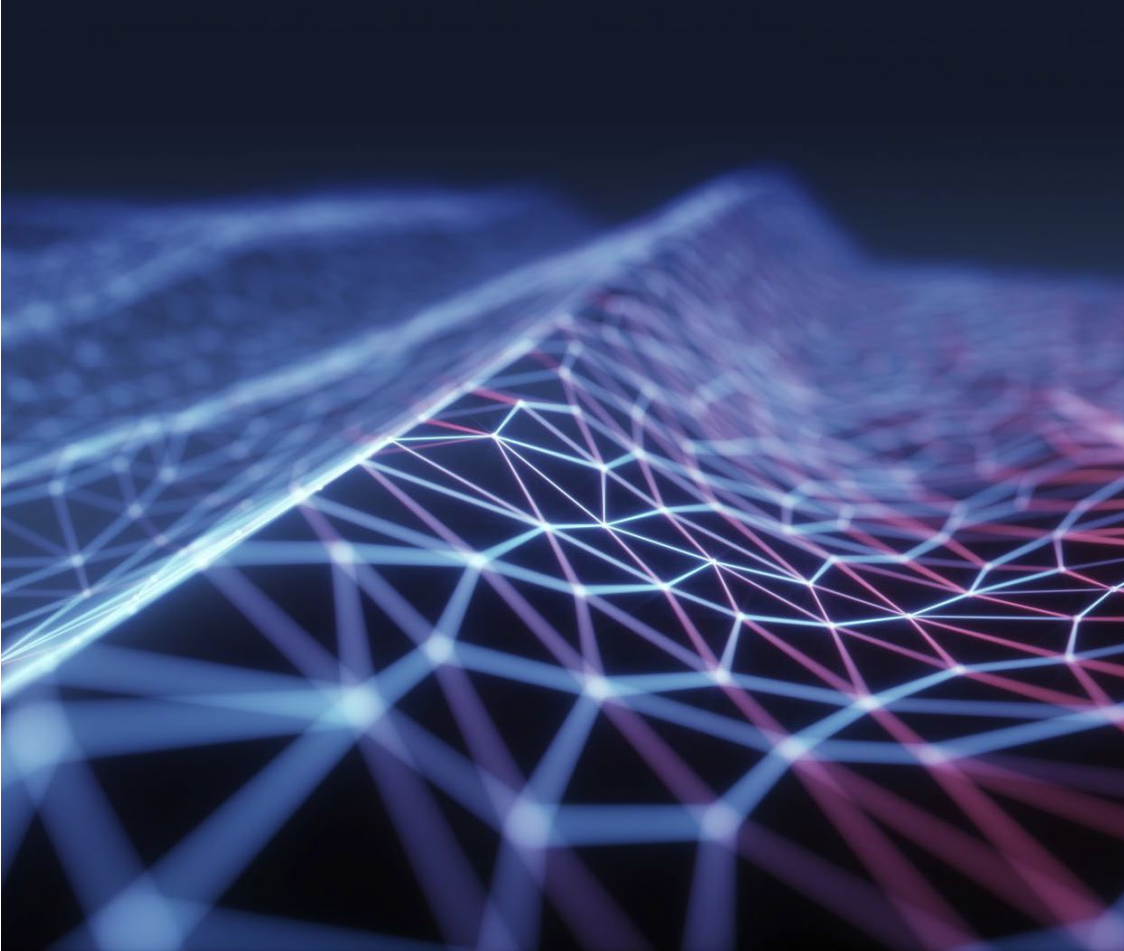
Problems still open

Pancreas procurement – sufficient organs

Production of adequate islet mass

Immunosuppressive therapy balance between efficacy and low side effects (better tolerance)

The future



infusion of allogeneic human embryonic stem cell (hESC)-derived islets into the portal vein

A Phase 1/2 Study to Evaluate the Safety, Tolerability, and Efficacy of VX-880 in Subjects Who Have Type 1 Diabetes Mellitus with Impaired Hypoglycemic Awareness and Severe Hypoglycemia

VX-880 drug substance (DS)

- Suspension of aggregated hESC-derived pancreatic islet cells
- Predominantly chromogranin A⁺ (CHGA⁺) fully differentiated endocrine cells
- No detectable residual embryonic stem cells

Description: infusion of allogeneic human embryonic stem cell (hESC)-derived islets into the portal vein in the context of a steroid-free immunosuppressive regimen (akin to cadaveric islet transplantation)

Advantages: compared to cadaveric islet transplantation, treatment with VX-880

- 
- Overcomes the limited supplies of cadaveric tissue availability issue, allowing higher doses to be delivered in single infusion
 - Provides more homogeneous cell preparations with the potential for a more consistent leading to improved outcomes

Immunosuppression:

- Standard as for islet transplant



**“No man is an island, entire of
itself...”**

John Donne - *Meditation XVII*

...or is he?