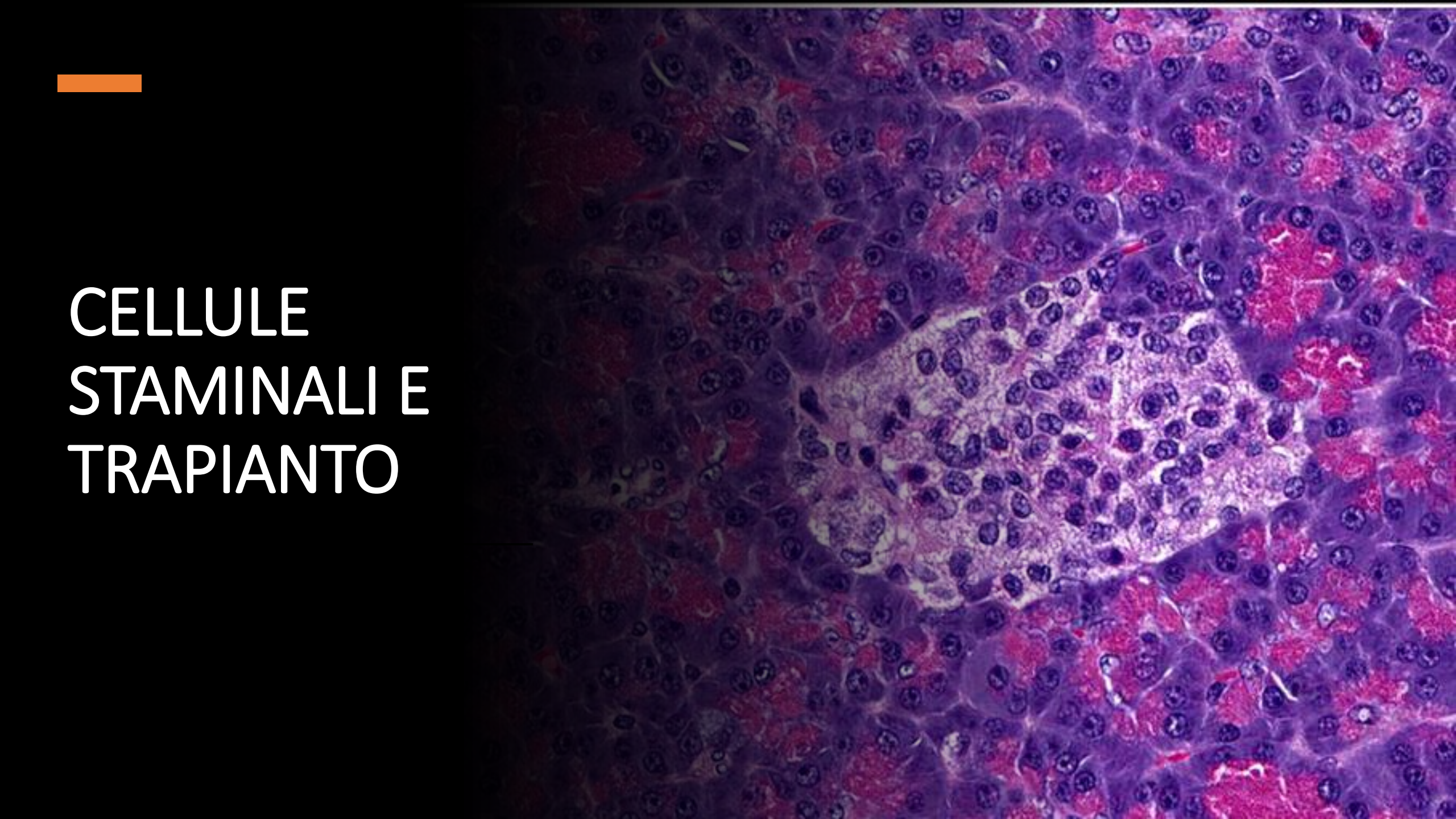
CELLULE STAMINALI E TRAPIANTO



- Il dr. Alessandro Viadana dichiara di NON aver ricevuto negli ultimi due anni compensi o finanziamenti da Aziende Farmaceutiche e/o Diagnostiche

Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico-chirurgici, ecc.).

Verso una terapia definitiva per il T1D
Perché parlare di staminali e trapianto?

Diabete instabile (*brittle diabetes)*

I limiti delle **nuove tecnologie**

Necessità di una **cura definitiva.**

Brittle Diabetes

Journal of Diabetes and Its Complications 35 (2021) 107646

Contents lists available at ScienceDirect

Journal of Diabetes and Its Complications

journal homepage: WWW.JDCJOURNAL.COM

A new look at brittle diabetes☆

Irl B. Hirsch, MD [a,*], Linda M. Gaudiani, MD [b]

[a] University of Washington School of Medicine, Seattle, WA, United States of America
[b] Braden Diabetes Center and Marin Endocrine Care and Research, Greenbrae, CA, United States of America

Table 1
Etiologies of brittle diabetes.

Generally resulting in hyperglycemia/ketoacidosis

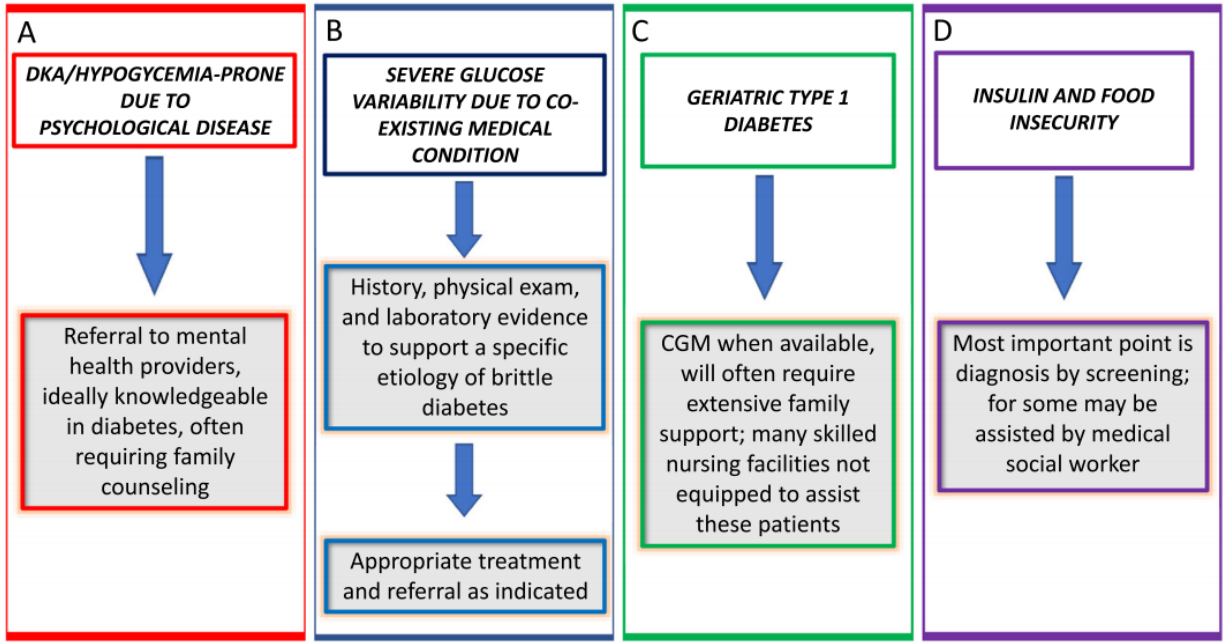
a. Endocrinopathies (thyrotoxicosis, acromegaly, Cushing's Syndrome glucagonoma, and pheochromocytoma)
b. Systemic infection
c. Stiff-Person Syndrome

Generally resulting in hypoglycemia

a. Diabetic gastroparesis
b. Syndromes of lipodystrophy
c. Insulin receptor antibody
d. Untreated Addison Disease in someone with pre-existing type 1 diabetes
e. Untreated celiac disease or other malabsorption disorders
f. Change in insulin clearance (renal failure, hypothyroidism)

Generally resulting in either hyperglycemia or hypoglycemia

a. Psychological disease including Munchausen's Syndrome, malingering, and eating disorders
b. Lipohypertrophy
c. Dementia and milder forms of cognitive impairment
d. Insulin or food insecurity
e. Drug or alcohol addiction
f. Steroid dependence, particularly when changing doses frequently required

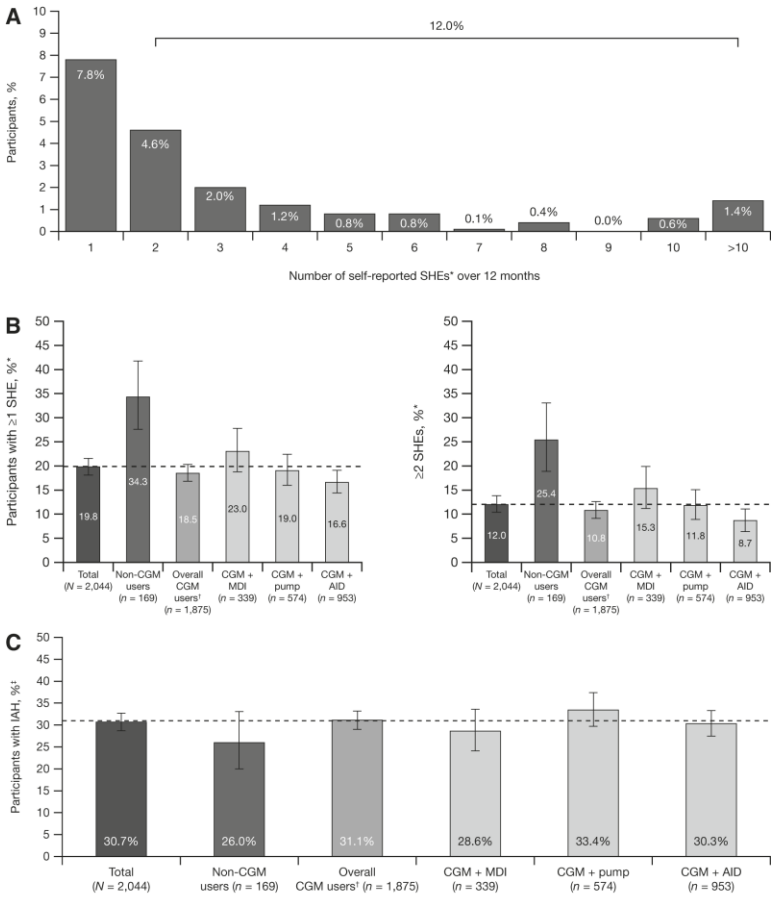


.4. Overall approach to the treatment of brittle diabetes divided into the four groups: A. DKA and hypoglycemia due to psychological disease; B. severe glucose variability due to medical ıdition; C. geriatric type 1 diabetes; D. insulin and food insecurity. CGM = continuous glucose monitoring.

I limiti della tecnologia

Severe Hypoglycemia and Impaired Awareness of Hypoglycemia Persist in People With Type 1 Diabetes Despite Use of Diabetes Technology: Results From a Cross-sectional Survey

Diabetes Care 2024;47:941–947 | https://doi.org/10.2337/dc23-1765



Key results

Only 57.7% of all respondents reported **achieving target HbA$_{1c}$ <7%**

~20% of all respondents reported having **≥1 SHEs in past 12 months** including CGM users (16.6% of AID users, 19% of pump users, and 23% of MDI users)

12% of respondents had **≥2 SHEs** in previous 12 months

Approximately one-third of all respondents **reported IAH in past 12 months**, regardless of CGM or AID usage

American Diabetes Association®

Conclusion: Despite use of currently available advanced diabetes technologies, a high proportion of people with type 1 diabetes do not achieve glycemic targets and continue to experience SHEs and IAH, suggesting an ongoing need for improved treatment strategies

Distress del diabete

Diabetes Distress and Associations With Demographic and Clinical Variables: A Nationwide Population-Based Registry Study of 10,186 Adults With Type 1 Diabetes in Norway

Ingvild Hernar,[1,2] John G. Cooper,[3] Roy M. Nilsen,[2] Timothy C. Skinner,[4,5] Ragnhild B. Strandberg,[2] Marjolein M. Iversen,[2,6] Marit Graue,[2] Tony Ernes,[3] Karianne F. Løvaas,[3] Tone V. Madsen,[3] Silje S. Lie,[7] David A. Richards,[2] Grethe Å. Ueland,[1,3] and Anne Haugstvedt[2]

Diabetes Care 2024;47:126–131 | https://doi.org/10.2337/dc23-1001

Diabetes distress data from a nationwide register-based cohort of adults with type 1 diabetes (*N* = 10,186)

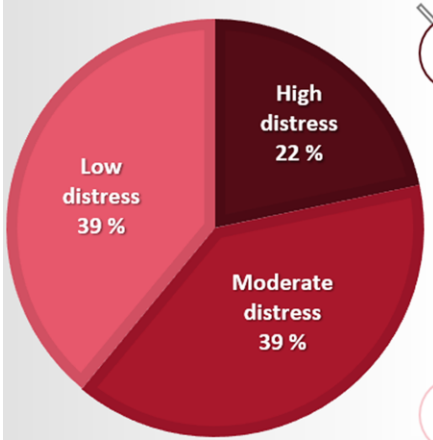
American Diabetes Association®

Prevalence of diabetes distress. Associations with demographic and clinical variables.

Data from the Norwegian Diabetes Register for Adults.

The 20-item Problem Areas in Diabetes (PAID-20) scale.

Distress levels:



The five most endorsed PAID-20 items:

1. Worry about the future and diabetes complications
2. Feel diabetes is taking up too much energy every day
3. Feel burnt out by diabetes self-management
4. Feel guilty about not self-managing "well enough"
5. Worry about hypoglycemia

Associations:

Higher distress

- Female sex
- Higher HbA1c
- Hypoglycemia
- Continuous glucose monitoring
- Daily smoking
- Treated retinopathy
- Reduced foot sensitivity

Lower distress

- Older age
- Longer diabetes duration
- European origin
- University/college education
- Employment

The findings underline the importance of addressing diabetes distress to improve the health of adults with type 1 diabetes.

Diabetes Care

Reference: Hernar I, Cooper JG, Nilsen RM et al. https://doi.org/10.2337/dc23-1001

American Diabetes Association. Connected for Life

Linee guida AMD-SID-SIEDP

Linea Guida della Associazione dei Medici Diabetologi (AMD), della Società Italiana di Diabetologia (SID) e della Società Italiana di Endocrinologia e Diabetologia Pediatrica (SIEDP)

La terapia del diabete mellito di tipo 1

Linea guida pubblicata nel Sistema Nazionale Linee Guida
Roma, 16 marzo 2022

6. Trapianto di isole pancreatiche

6.1 In soggetti con diabete mellito di tipo 1 instabile quali sono le indicazioni per il trapianto di isole pancreatiche?

In soggetti con diabete mellito di tipo 1 instabile, nonostante la migliore terapia insulinica ottimizzata possibile, si suggerisce di avviare la valutazione per trapianto di isole pancreatiche.

Raccomandazione condizionata a favore dell'intervento

Qualità delle prove: moderata.

Consensus ADA e EASD

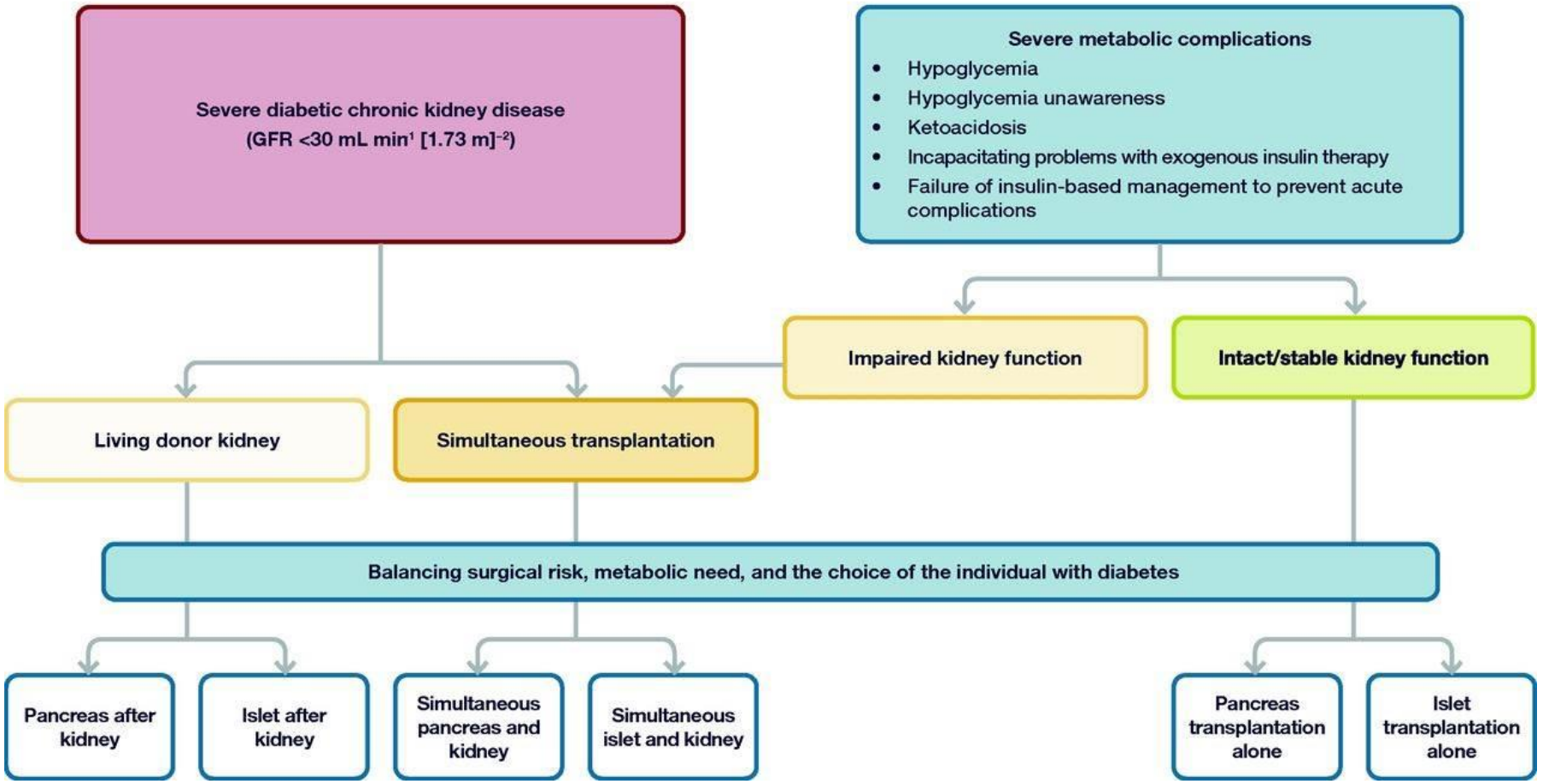
The Management of Type 1 Diabetes in Adults. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

Richard I.G. Holt,[1,2] J. Hans DeVries,[3,4] Amy Hess-Fischl,[5] Irl B. Hirsch,[6] M. Sue Kirkman,[7] Tomasz Klupa,[8] Barbara Ludwig,[9] Kirsten Nørgaard,[10,11] Jeremy Pettus,[12] Eric Renard,[13,14] Jay S. Skyler,[15] Frank J. Snoek,[16] Ruth S. Weinstock,[17] and Anne L. Peters[18]

Diabetes Care 2021;44:2589–2625 | https://doi.org/10.2337/dci21-0043

American Diabetes Association.

Simplified overview of indications for β-cell replacement therapy in people with type 1 diabetes



Richard I.G. Holt et al. Dia Care 2021;44:2589-2625

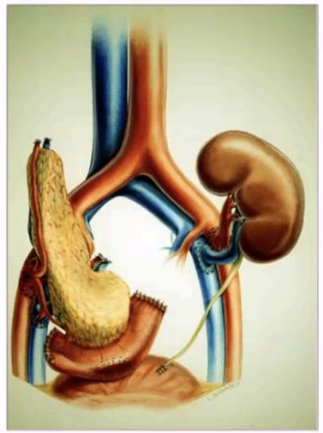
TRAPIANTO DI PANCREAS

REVIEW

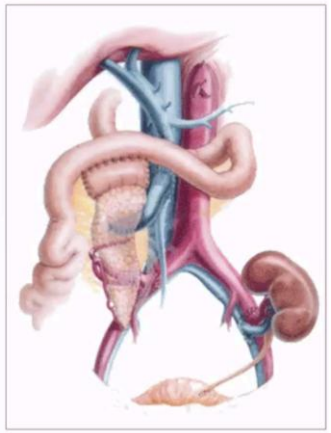
Lessons Learned From More Than 1,000 Pancreas Transplants at a Single Institution

David E. R. Sutherland, MD, PhD,* Rainer W. G. Gruessner, MD,* David L. Dunn, MD, PhD,* Arthur J. Matas, MD,* Abhinav Humar, MD,* Raja Kandaswamy, MD,* S. Michael Mauer, MD,§ William R. Kennedy, MD,‡ Frederick C. Goetz, MD,* R. Paul Robertson, MD† Angelika C. Gruessner, PhD,* and John S. Najarian, MD*

*From the Departments of *Surgery, †Medicine, ‡Neurology, and §Pediatrics, University of Minnesota, Minneapolis, Minnesot*



Bladder Drainage with Systemic Venous Anastomosis



Enteric Drainage with Portal Venous Anastomosis

Funzione d'organo a 10 anni:

- nel trapianto combinato rene-pancreas (**SPK**) → 50-60%
- nel trapianto di pancreas isolato (**PTA**) → 30-40%

NB Tasso di mortalità del 2-5% a seconda dei centri.

COMPLICANZE

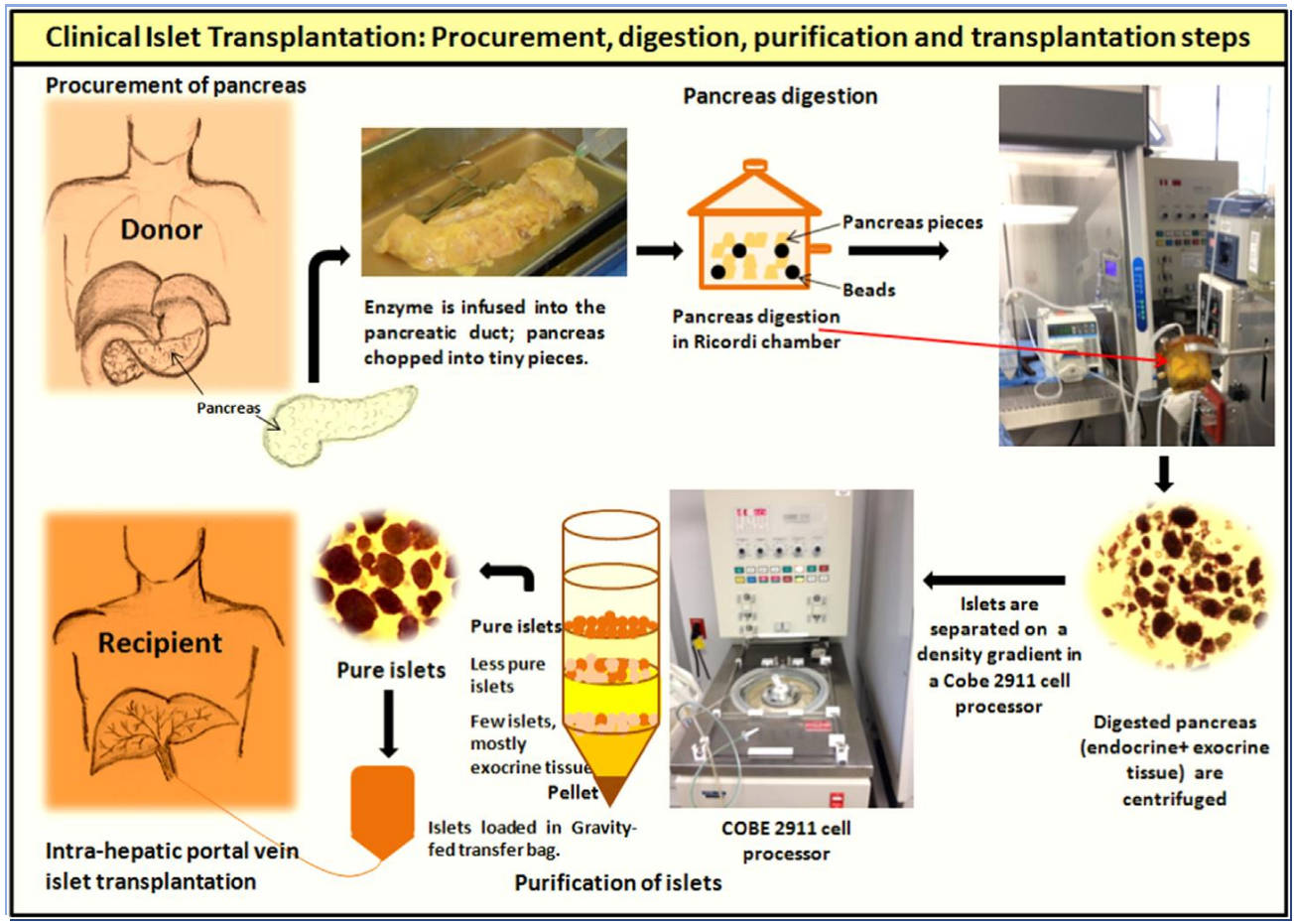
Legate alla **chirurgia maggiore**

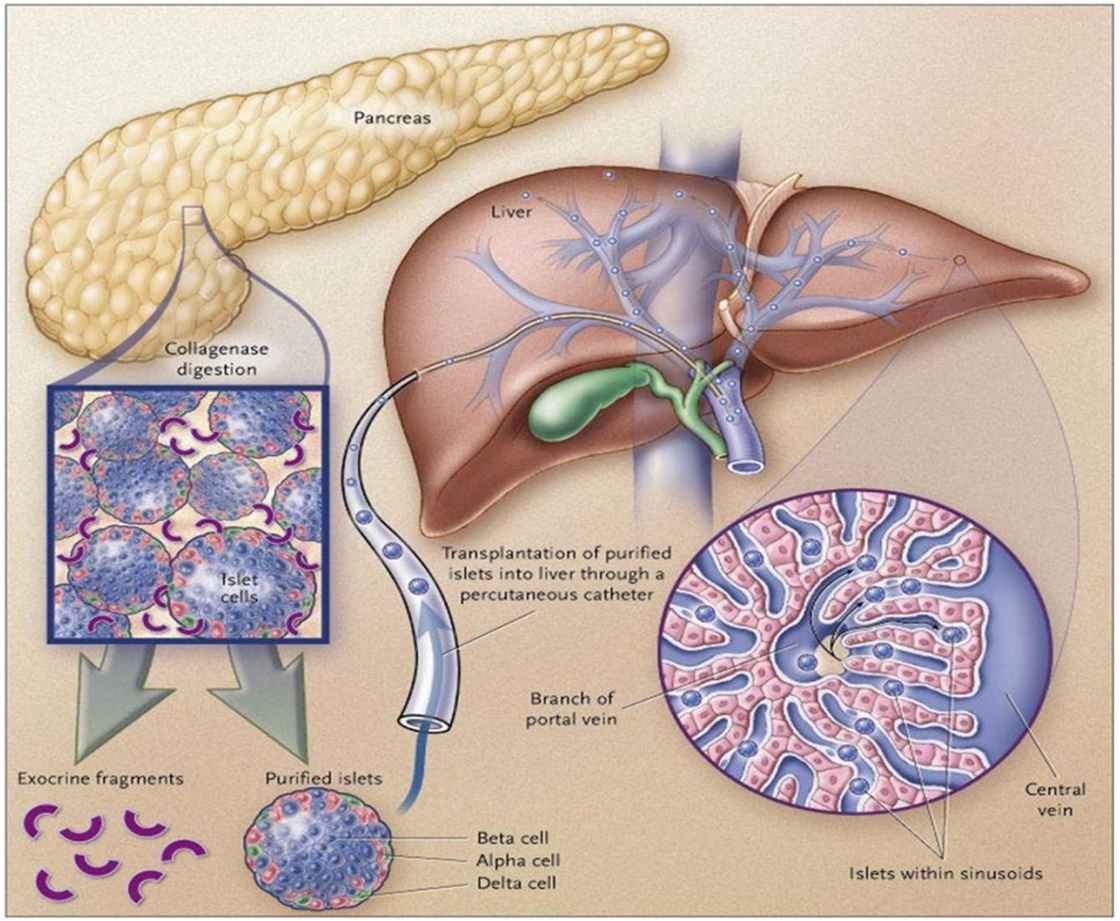
Nuova laparotomia 25.9%
Sanguinamento 26.8%
Trombosi 8.7%
Deiscenza anatomica 11.3%
Pancreatite 12.2 %

Legate alla terapia **immunosoppressiva**

Aumentato rischio di **infezioni** e di neoplasie.

TRAPIANTO DI ISOLE PANCREATICHE

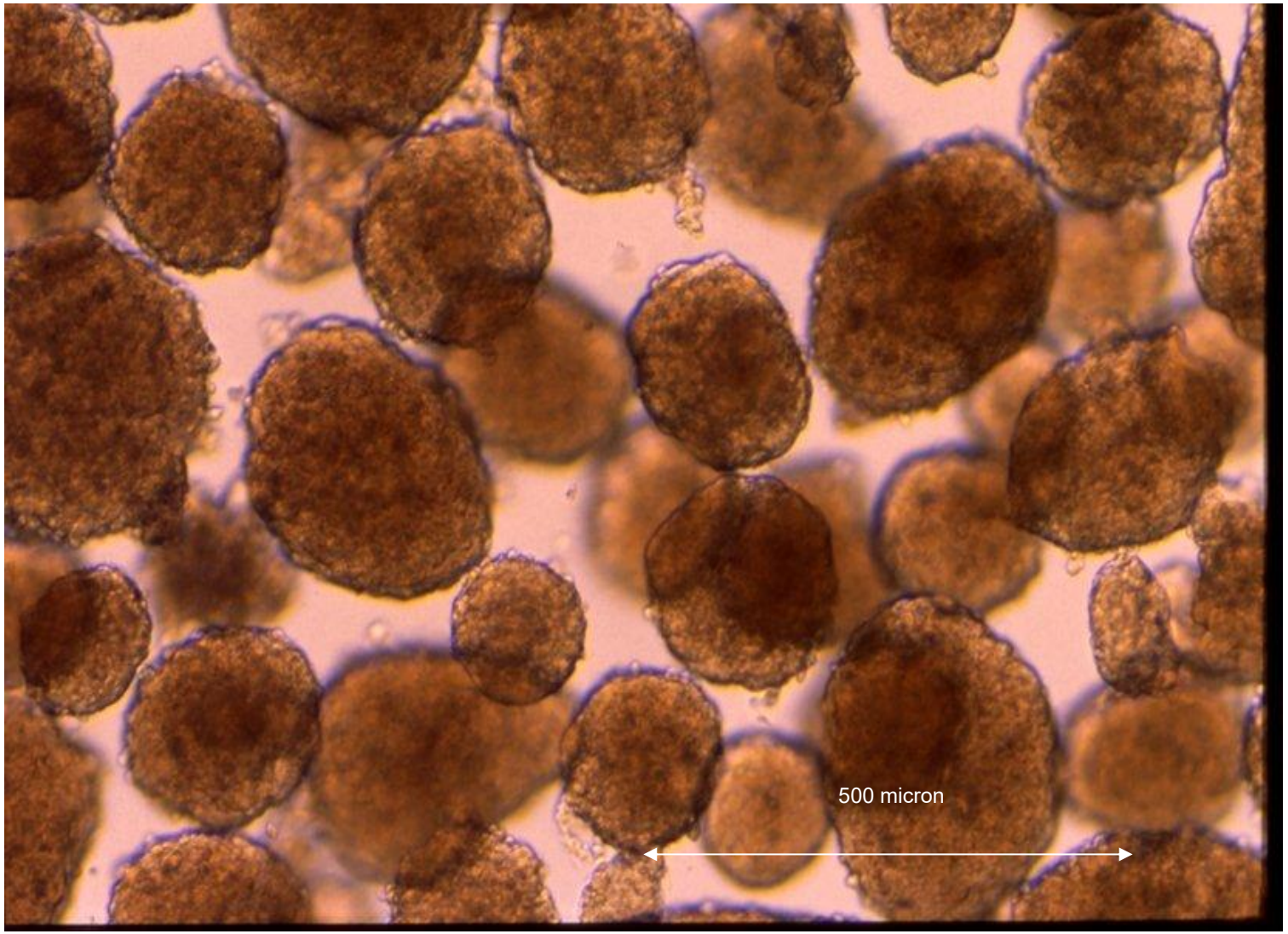




R. Paul Robertson Dia Care 2015;38:1030-1035

American Diabetes Association.

Dalle cellule…

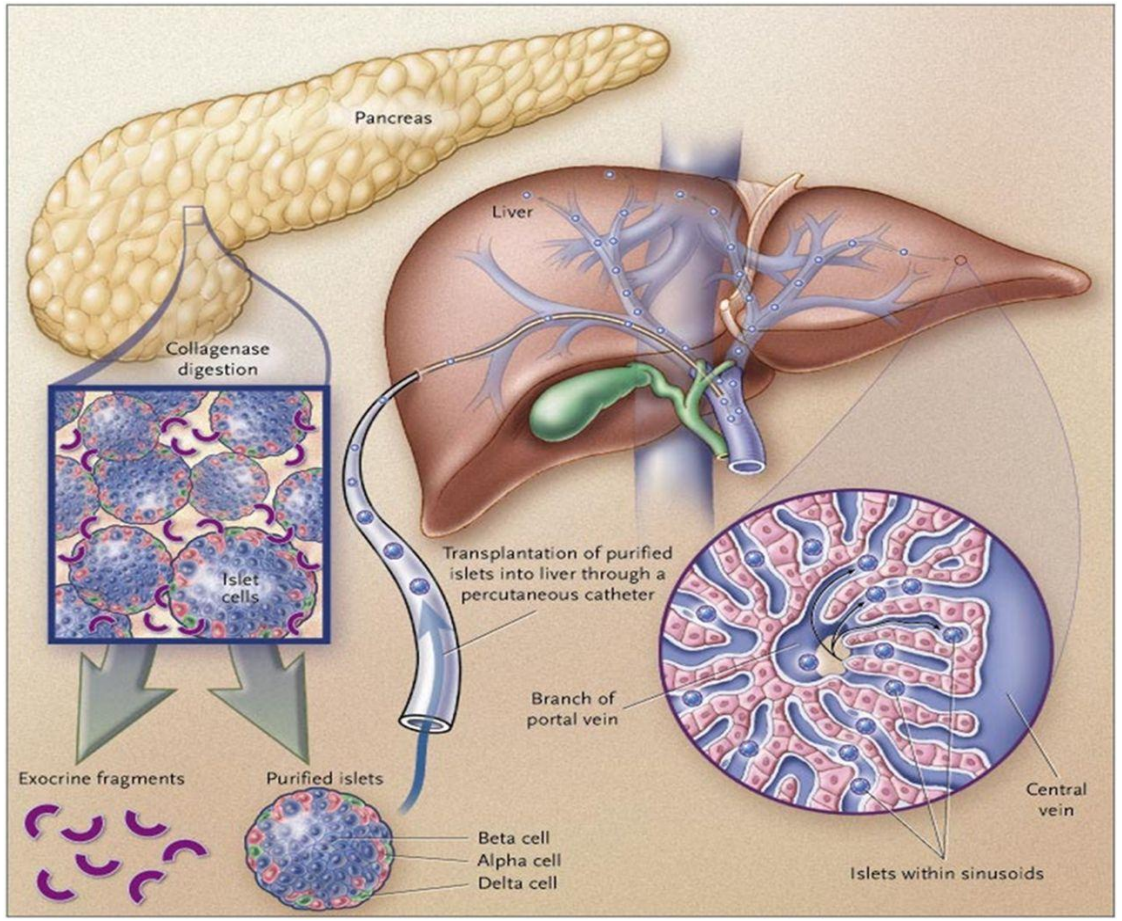


…al trapianto

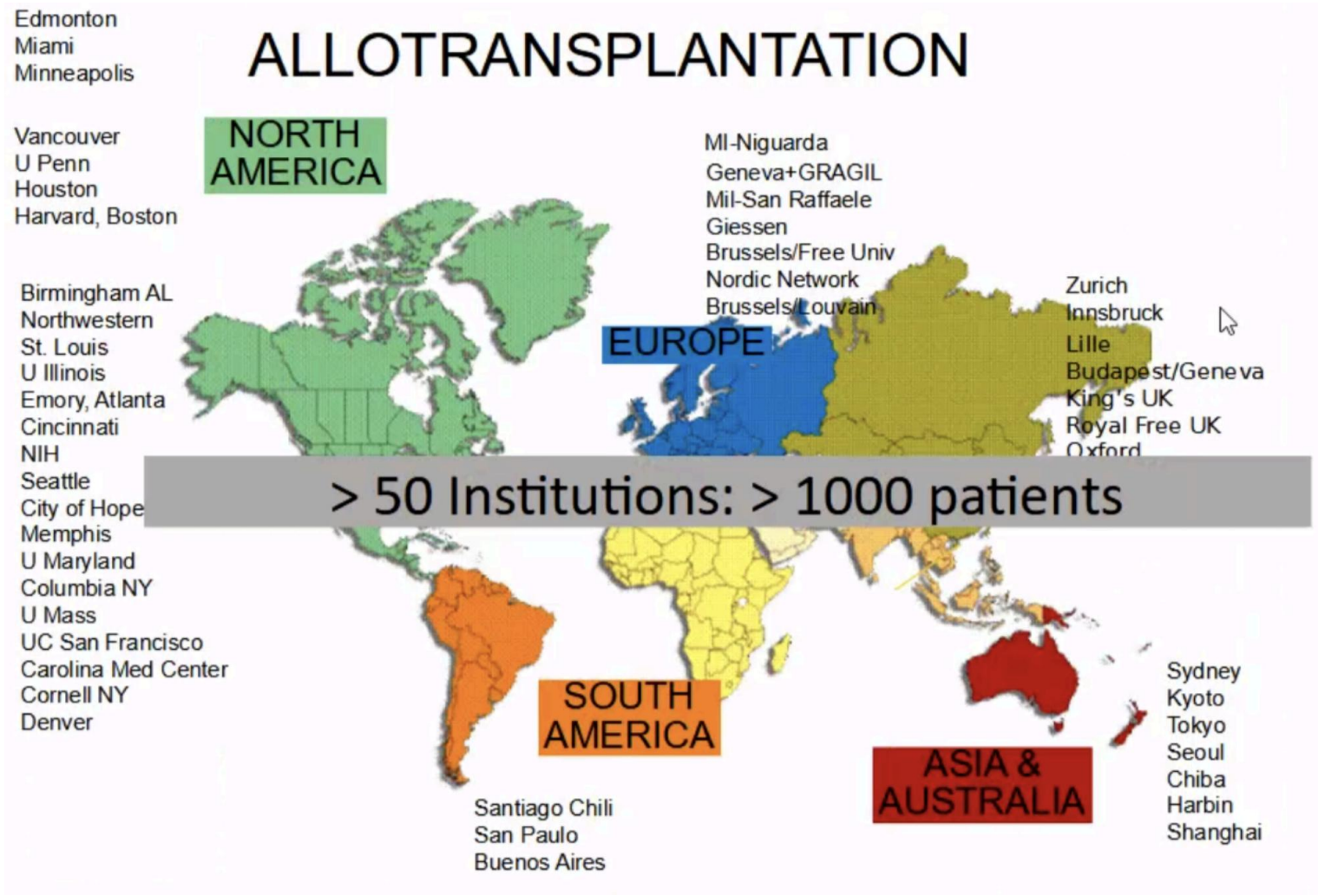
Procedura **mini invasiva:**

- In anestesia locale, a paziente sveglio
- Per via percutanea trans epatica

→ <u>Impianto **beta-cellulare** a livello dei sinusoidi epatici.</u>



Dove?


ALLOTRANSPLANTATION
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Vancouver
U Penn
Houston
Harvard, Boston
Birmingham AL
Northwestern
St. Louis
U Illinois
Emory, Atlanta
Cincinnati
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Memphis
U Maryland
Columbia NY
U Mass
UC San Francisco
Carolina Med Center
Cornell NY
Denver
EUROPE
MI-Niguarda
Geneva+GRAGIL
Mil-San Raffaele
Giessen
Brussels/Free Univ
Nordic Network
Brussels/Louvain
Zurich
Innsbruck
Lille
Budapest/Geneva
King's UK
Royal Free UK
Oxford
> 50 Institutions: > 1000 patients
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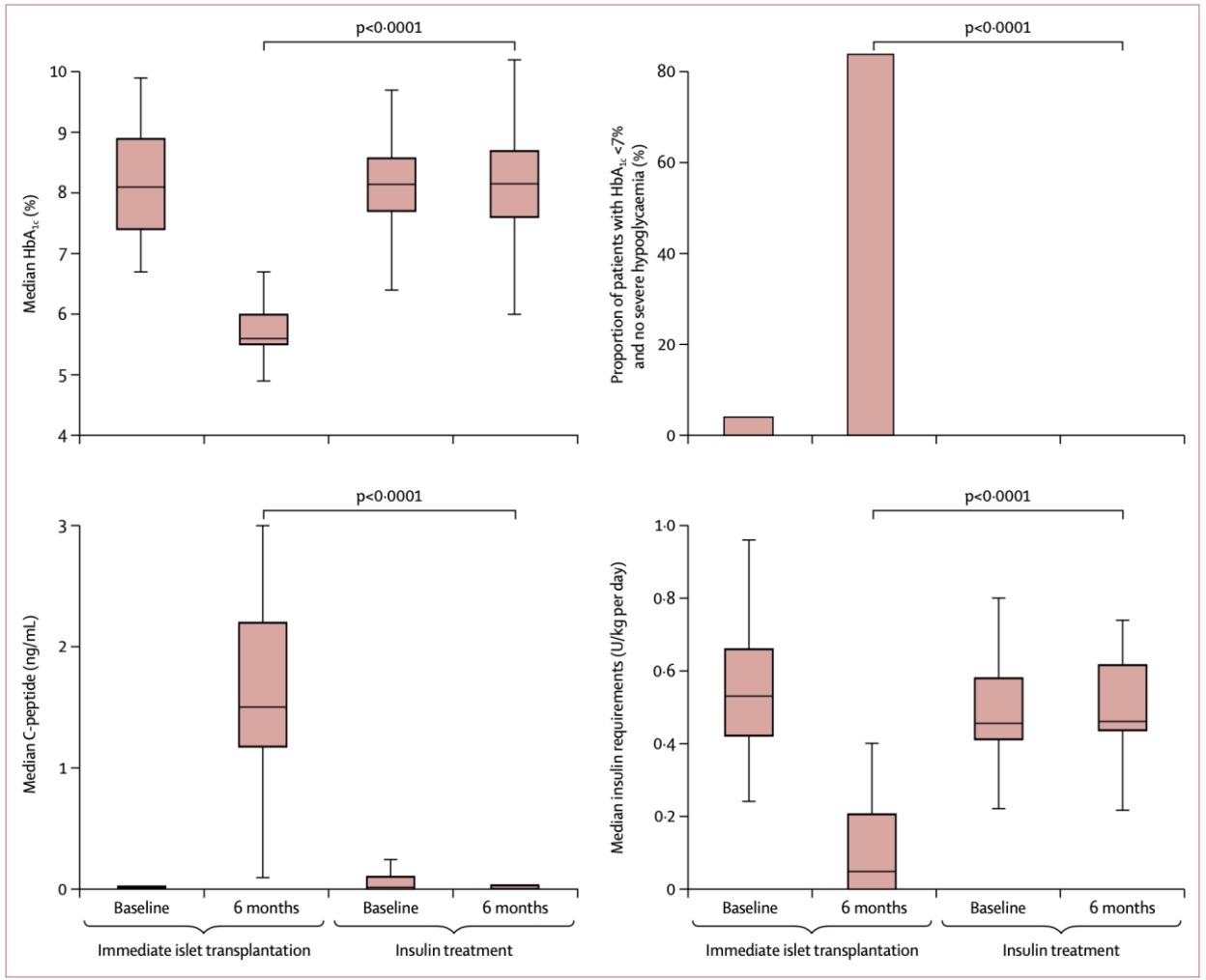
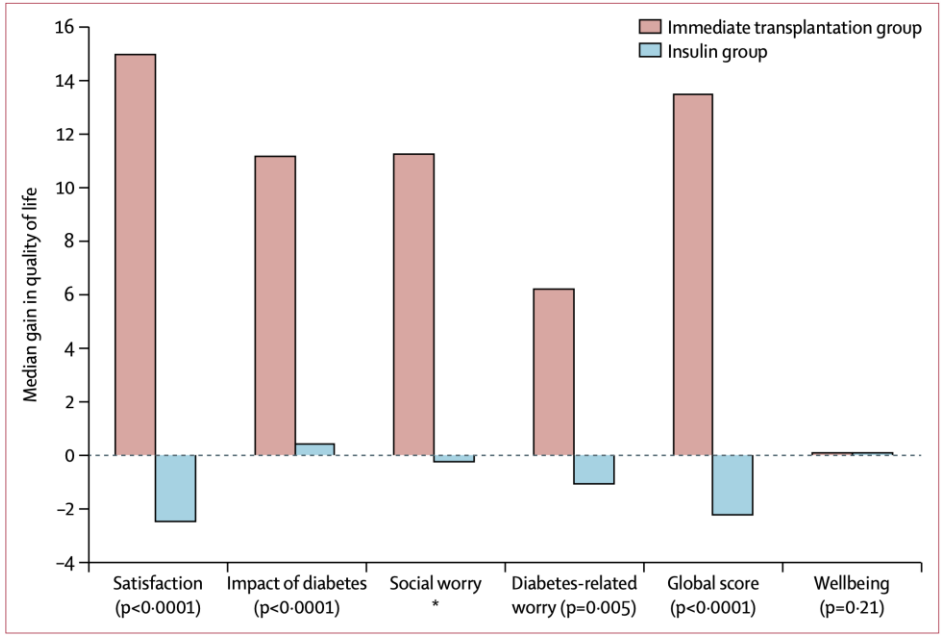
Sydney
Kyoto
Tokyo
Seoul
Chiba
Harbin
Shanghai

Studi clinici
TRIMECO

Islet transplantation versus insulin therapy in patients with type 1 diabetes with severe hypoglycaemia or poorly controlled glycaemia after kidney transplantation (TRIMECO): a multicentre, randomised controlled trial

*Sandrine Lablanche, Marie-Christine Vantyghem, Laurence Kessler, Anne Wojtusciszyn, Sophie Borot, Charles Thivolet, Sophie Girerd, Domenico Bosco, Jean-Luc Bosson, Cyrille Colin, Rachel Tetaz, Sophie Logerot, Julie Kerr-Conte, Eric Renard, Alfred Penfornis, Emmanuel Morelon, Fanny Buron, Kristina Skaare, Gwen Grguric, Coralie Camillo-Brault, Harald Egelhofer, Kanza Benomar, Lionel Badet, Thierry Berney, François Pattou, Pierre-Yves Benhamou, on behalf of the TRIMECO trial investigators**





RISULTATI A 6 MESI

- Migliora **HbA1c** (5.6% vs 8.2%)
- **HbA1c <7% senza SHEs nel 84%**
- Migliora la **qualità di vita**

Studi clinici

Ten-year outcome of ITA or IAK in T1D

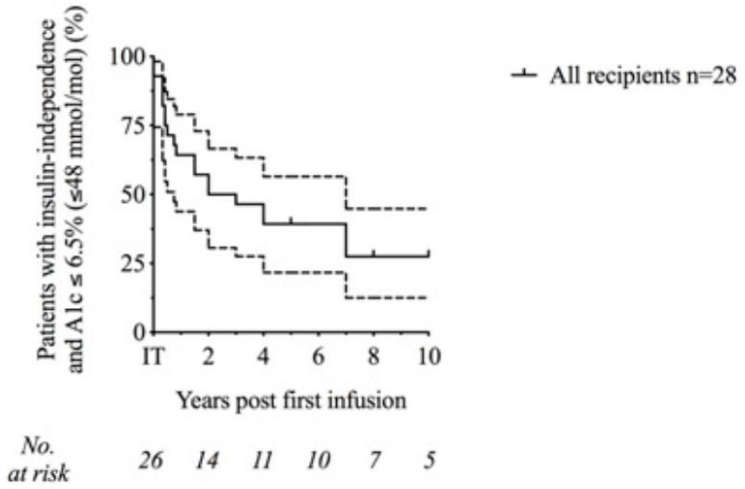
Ten-Year Outcome of Islet Alone or Islet After Kidney Transplantation in Type 1 Diabetes: A Prospective Parallel-Arm Cohort Study

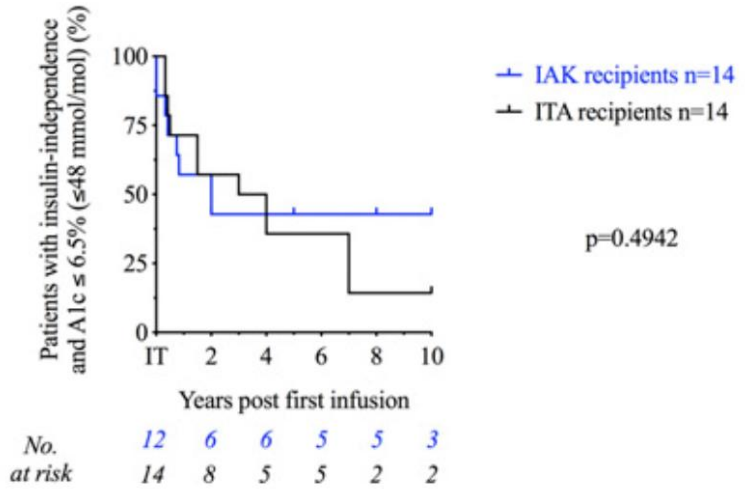
Marie-Christine Vantyghem,[1,2,3] Mikael Chetboun,[1,3,4] Valéry Gmyr,[1,3] Arnaud Jannin,[2] Stéphanie Espiard,[2] Kristell Le Mapihan,[2] Violeta Raverdy,[1,3] Nathalie Delalleau,[1,3] François Machuron,[5] Thomas Hubert,[1,3] Marie Frimat,[6] Eric Van Belle,[7] Marc Hazzan,[6] Pascal Pigny,[8] Christian Noel,[6] Robert Caiazzo,[1,3,4] Julie Kerr-Conte,[1,3] and François Pattou[1,3,4]

Diabetes Care 2019;42:2042–2049 | https://doi.org/10.2337/dc19-0401

Table 2—Metabolic and renal long-term outcomes in the entire study group

	1 year	*P* value vs. baseline	5 years	*P* value vs. baseline	10 years	*P* value vs. baseline
Patients followed	28		27		20	
No. of severe hypoglycemia events in previous year	0 (0–0)	<0.0001	0 (0–0)	<0.0001	0 (0–0)	<0.0001
Glycated hemoglobin (%) (mmol/mol)	5.9 (5.5–6.7) 41 (37–50)	<0.0001	6.9 (6.1–7.5) 52 (43–58)	<0.0001	6.7 (6.1–8) 50 (43–64)	0.0009
Exogenous insulin requirements (IU/kg per day)	0 (0–0.04)	<0.0001	0 (0–0.36)	<0.0001	0.28 (0–0.43)	<0.0001
Mean glucose (CGM) (mg/dL)	112 (102–133)	<0.0001	126 (110–144)	<0.0001	118 (113–154)	0.0007
SD of mean glucose (CGM) (mg/dL)	22 (15–41)	<0.0001	29 (17–52)	<0.0001	40 (18–54)	<0.0001
Time below range (<70 mg/dL) (CGM) (%)	0 (0–5)	<0.0001	1 (0–3)	<0.0001	3 (0–9)	0.0012
eGFR (mL/min/1.73 m^2)	68 (55–81)	0.8883	64 (51–80)	0.7926	54 (43–91)	0.252





RISULTATI A 10 ANNI

- Indipendenza insulinica con HbA1c < 6.5% nel **28% dei pazienti**
- HbA1c <7% in assenza di eventi ipoglicemici severi (SHEs) nel **50% dei pazienti.**
- Produzione di c-peptide presente nel **75% dei pazienti**

Studi clinici

Long term effect of IT on Glycemic Variability

Cell Transplantation
1–7
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DOI: 10.1177/096368971
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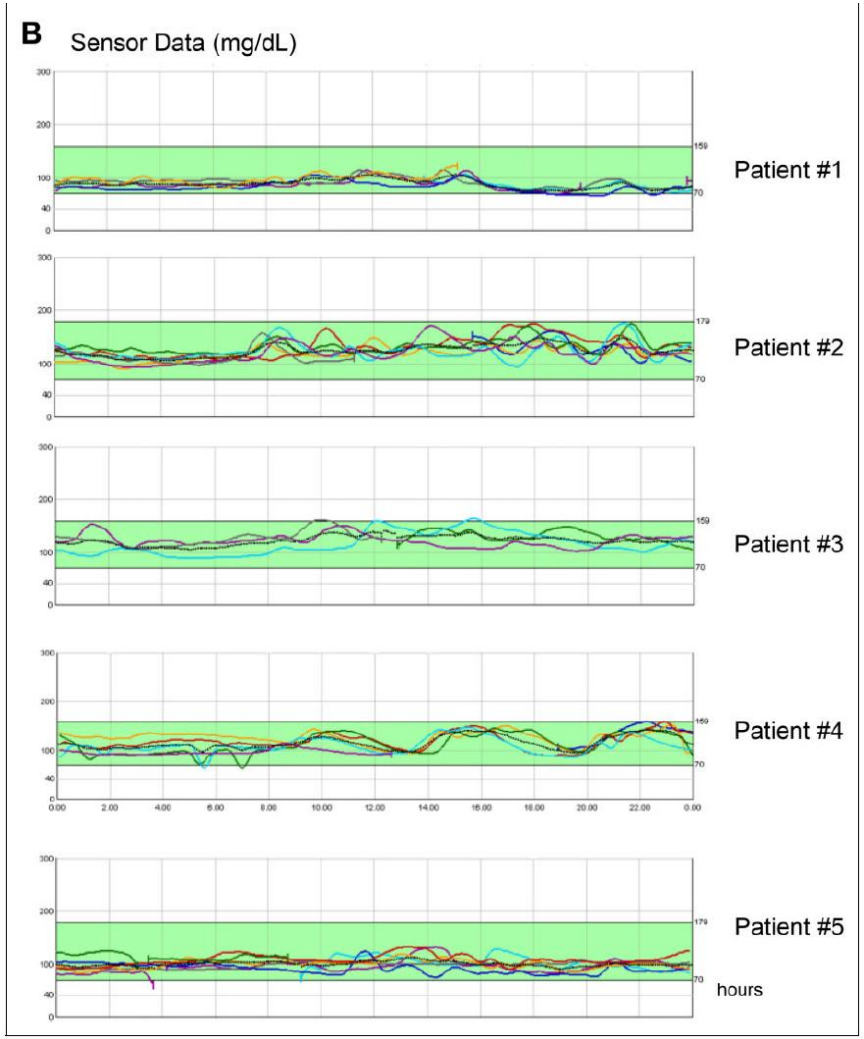
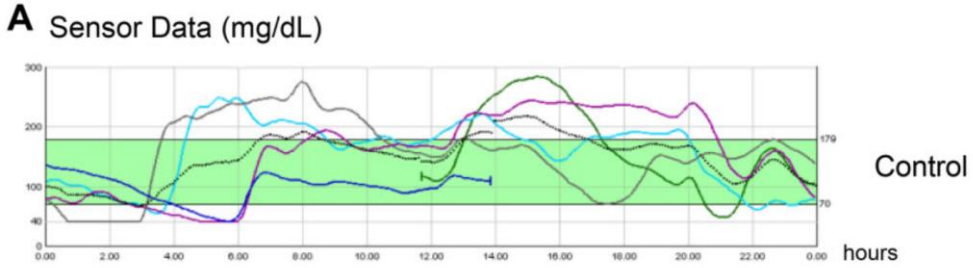
SAGE

Long-term Effect of Islet Transplantation on Glycemic Variability

Federico Bertuzzi[1], Luciano De Carlis[2], Mario Marazzi[3], Antonio Gaetano Rampoldi[4], Matteo Bonomo[1], Barbara Antonioli[3], Marta Cecilia Tosca[3], Marta Galuzzi[3], Andrea Lauterio[2], Danila Fava[5], Patrizia Dorighet[6], Andrea De Gasperi[2], and Giacomo Colussi[6]





Indexes	Control Patients	Transplanted Patients	*P* Value
HbA1c (mmol, %)	71 ± 10 (8.7 ± 1.0)	41 ± 6 (5.9 ± 0.6)	0.004*
Clarke score	5 ± 1	0	0.001*
Sensor glucose mean (mg/dL)	212 ± 47	109 ± 16	0.012*
Coefficient variation (%)	37 ± 7	13 ± 2	0.012*
Standard deviation (mg/dL)	77 ± 11	15 ± 4	0.012*
AUC (min mg/dL)	1,058 ± 235	545 ± 79	0.012*
MAGE (mg/dL)	1.2 ± 0.2	0.3 ± 0.1	0.012*
CONGA-4	94 ± 10	19 ± 8	0.012*
MODD (mg/dL)	66 ± 40	11 ± 4	0.037*
HBGI	19.8 ± 7.6	0.7 ± 0.5	0.012*
LBGI	5.9 ± 4.1	1.2 ± 1.1	0.022*
BGRI	18 ± 7	1 ± 1	0.012*
ADRR	71 ± 9	10 ± 4	0.012*
J index	86 ± 31	16 ± 5	0.012*
Time in range (%)	31 ± 15	99 ± 2	0.008*

RISULTATI

→ **Trapianto** vs Terapia insulinica

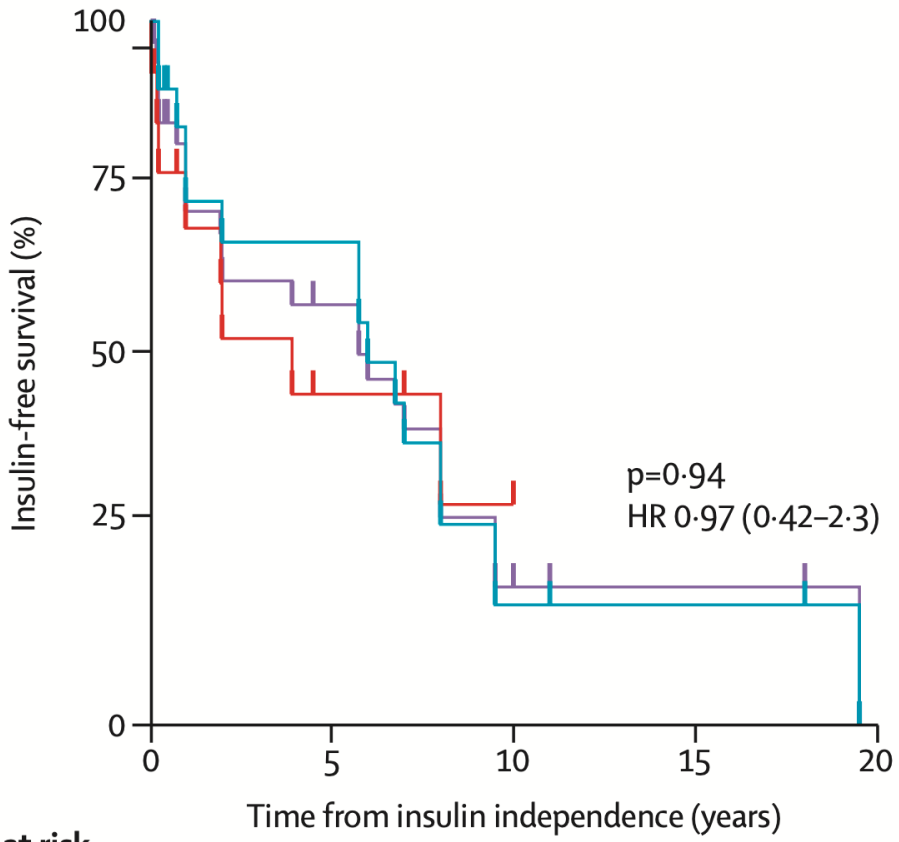
- **HbA1c 5.9%** vs 8.7%
- **CV 13+2%** vs 37+7%
- **TIR 99+2%** vs 31+15%

Studi clinici

Long term outcomes of

Long-term outcomes of pancreatic islet transplantation alone in type 1 diabetes: a 20-year single-centre study in Italy

Davide Catarinella, Raffaella Melzi, Alessia Mercalli, Paola Magistretti, Stefano Tentori, Chiara Gremizzi, Vera Paloschi, Francesco De Cobelli, Giuseppe Esposto, Sabrina Costa, Antonio Secchi, Rossana Caldara, Paola Maffi, Rita Nano*, Lorenzo Piemonti**



Number at risk

All	35	19	6	3	0
>10 000 IEQ/kg	21	13	5	3	0
≤10 000 IEQ/kg	14	6	1	0	0

- Riduzione della **HbA1c** di 10,04 mmol/mol e una diminuzione del fabbisogno insulinico giornaliero di **13,35 UI.**
- Il **44% dei pazienti** (35 su 79) ha raggiunto l'**indipendenza dall'insulina** per una durata mediana di **6 anni**.
- Nei pazienti che hanno ricevuto più di 10.000 IEQ/kg sopravvivenza mediana del trapianto di **9,7 anni** e **73% di indipendenza insulinica**.

Studi clinici

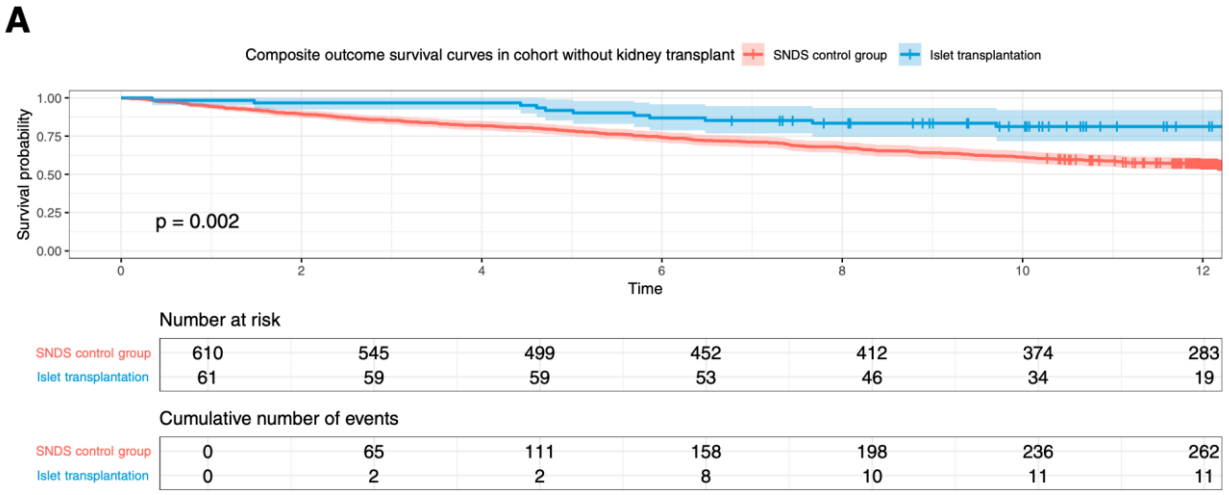
Impact of IT on Complications and Mortality

Impact of Islet Transplantation on Diabetes Complications and Mortality in Patients Living With Type 1 Diabetes

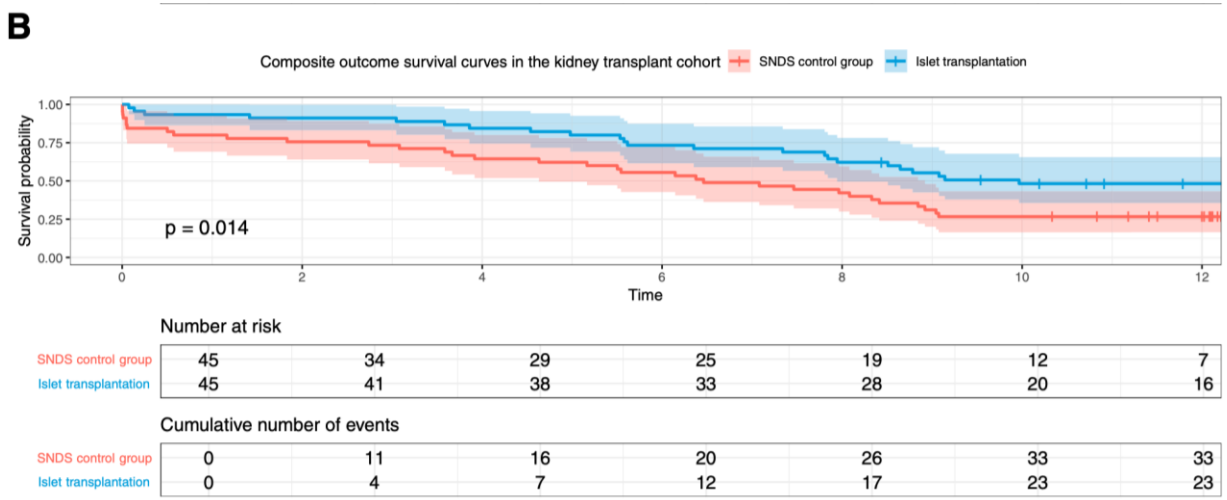
Diabetes Care 2025;48:1007–1015 | https://doi.org/10.2337/dc25-0059

*Quentin Perrier,[1] Clément Jambon-Barbara,[2] Laurence Kessler,[3] Orianne Villard,[4] Fanny Buron,[5] Bruno Guerci,[6] Sophie Borot,[7] Matthieu Roustit,[8] Ekaterine Berishvilli,[9] Luc Rakotoarisoa,[3] Marie-Christine Vantyghem,[10] Emmanuel Morelon,[5] Eric Renard,[4] Camille Besch,[3] Thierry Berney,[5,9] Pierre-Yves Benhamou,[11] and Sandrine Lablanche,[11] on behalf of the GRAGIL Network**

ITA



IAK



RISULTATI a **10 anni**:

Outcome primario → composito di mortalità, dialisi ed eventi cardiovascolari.

- **Gruppo ITA:** Riduzione del rischio del **61%** (HR **0,39**) rispetto ai controlli.
- **Gruppo IAK:** Riduzione del rischio del **48%** (HR **0,52** rispetto ai con trolli.

Studi clinici

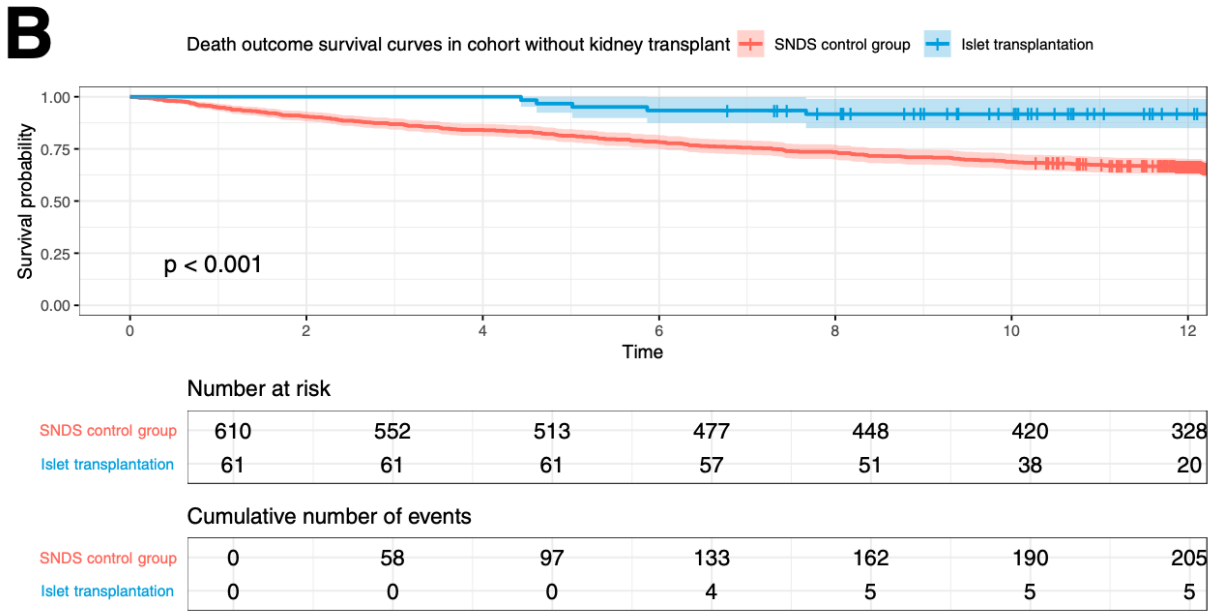
Impact of IT on Complications and Mortality

Impact of Islet Transplantation on Diabetes Complications and Mortality in Patients Living With Type 1 Diabetes

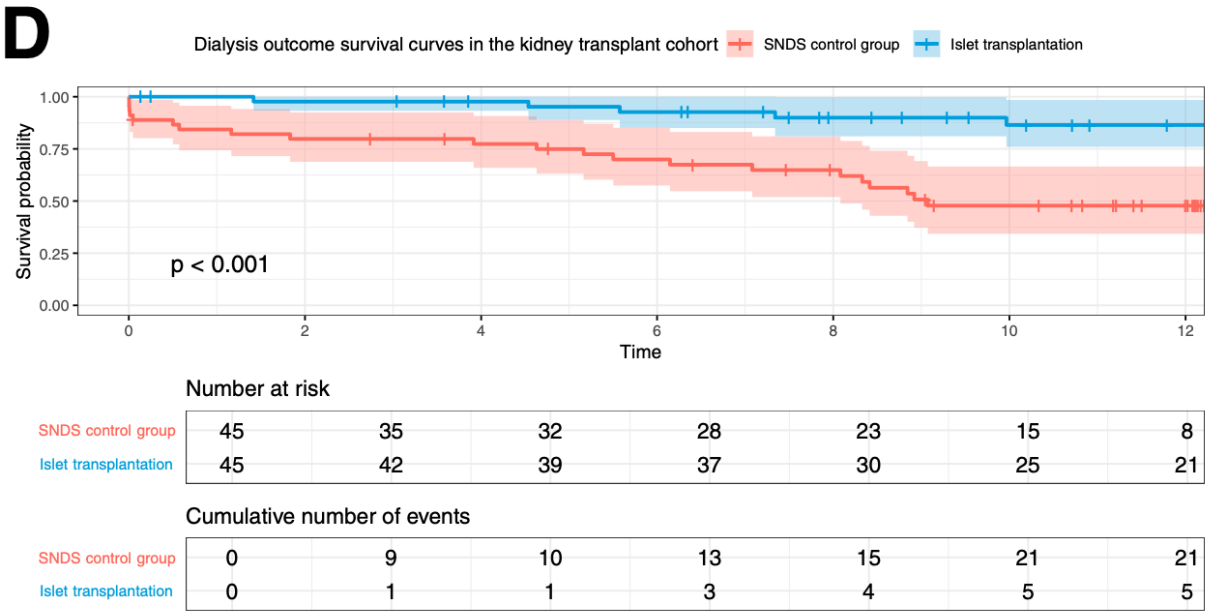
Diabetes Care 2025;48:1007–1015 | https://doi.org/10.2337/dc25-0059

*Quentin Perrier,[1] Clément Jambon-Barbara,[2] Laurence Kessler,[3] Orianne Villard,[4] Fanny Buron,[5] Bruno Guerci,[6] Sophie Borot,[7] Matthieu Roustit,[8] Ekaterine Berishvilli,[9] Luc Rakotoarisoa,[3] Marie-Christine Vantyghem,[10] Emmanuel Morelon,[5] Eric Renard,[4] Camille Besch,[3] Thierry Berney,[5,9] Pierre-Yves Benhamou,[11] and Sandrine Lablanche,[11] on behalf of the GRAGIL Network**

ITA



IAK



ITA: riduzione della **mortalità del 78%** (HR 0,22; P < 0,001).

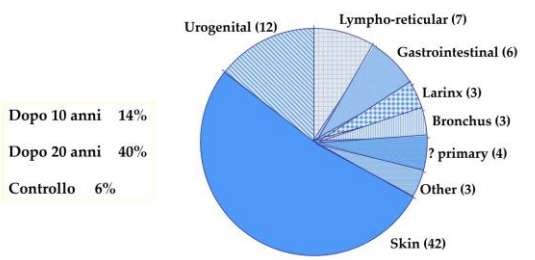
IAK: riduzione del rischio di tornare in **dialisi dell'81%** (HR 0,19; P < 0,001).

EFFETTI AVVERSI

LEGATI ALLA PROCEDURA	LEGATI ALL'IMMUNOSPPRESSIONE
Trombosi portale	Infezioni opportunistiche
Emorragia – Ematomi	Leucopenia
Dolore	Neoplasie
Vomito	Nefrotossicità

	Immediate islet transplantation group			Insulin group				Total (n=46)*
	Waiting list for transplantation (n=25)	First infusion to 6 months (n=25)	6–12 months after first infusion (n=25)	Baseline to 6 months after randomisation (n=22)	Waiting list for transplantation (n=22)	First infusion to 6 months (n=21)*	6–12 months after first infusion (n=21)*	
Infections and infestations	0	5 (20%)	4 (16%)	1 (5%)	2 (10%)	4 (19%)	4 (19%)	20 (43%)
Gastrointestinal disorder	0	7 (28%)	4 (16%)	0	0	6 (29%)	1 (5%)	18 (39%)
Blood and lymphatic system disorders	1 (4%)	5 (20%)	3 (12%)	0	0	7 (33%)	0	16 (35%)
Procedural complication	0	5 (20%)	0	0	0	4 (19%)	0	9 (20%)
Nervous disorders	2 (8%)	2 (8%)	0	0	0	2 (10%)	2 (10%)	8 (17%)
Renal and urinary disorders	2 (8%)	1 (4%)	0	0	0	3 (14%)	0	6 (13%)
Cardiac disorders	0	1 (4%)	0	0	2 (10%)	2 (10%)	0	5 (11%)
Metabolism and nutrition disorders	0	1 (4%)	1 (4%)	0	2 (10%)	2 (10%)	2 (10%)	6 (13%)

Rischi cumulativo di tumore dopo 10 anni



London, Lancet 346:403-406, 1995

Quali sono i limiti?

Immunosoppressione

Scarsità di donatori

L’immunosoppressione come ostacolo: come superarla?

- **Aumentato rischio di infezioni** (virali e fungine).
- **Aumento dell'incidenza di tumori (**carcinomi cutanei e linfomi).
- **Nefrotossicità cronica** (legata ad inibitori della calcineurina).
- **Tossicità** diretta dei farmaci **sulle stesse cellule beta trapiantate.**

Survival of Transplanted Beta Cells with No Immunosuppression

The NEW ENGLAND JOURNAL of MEDICINE

CURRENT ISSUE | SPECIALTIES | TOPICS

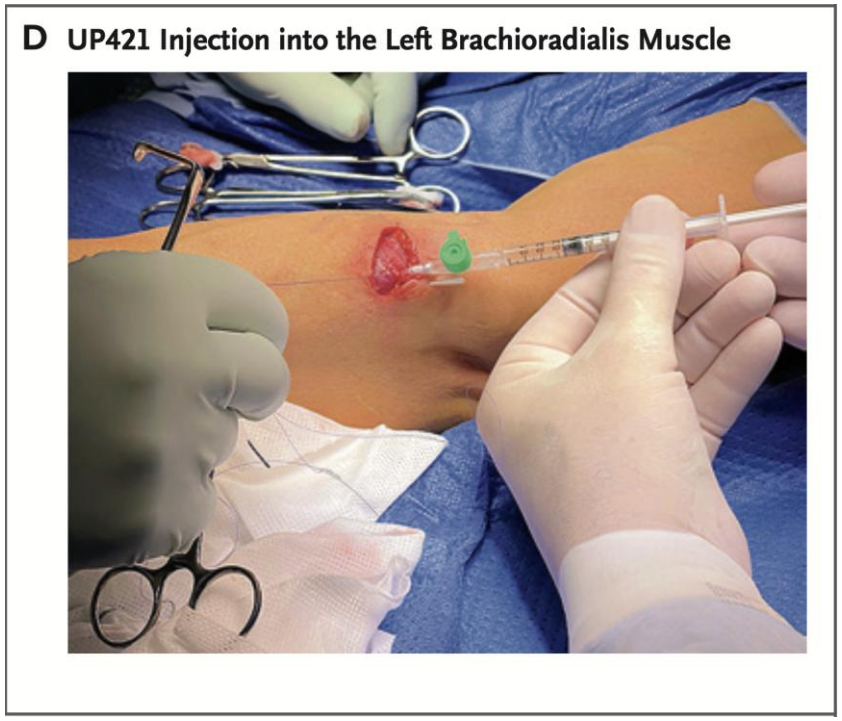
ORIGINAL ARTICLE | BRIEF REPORT

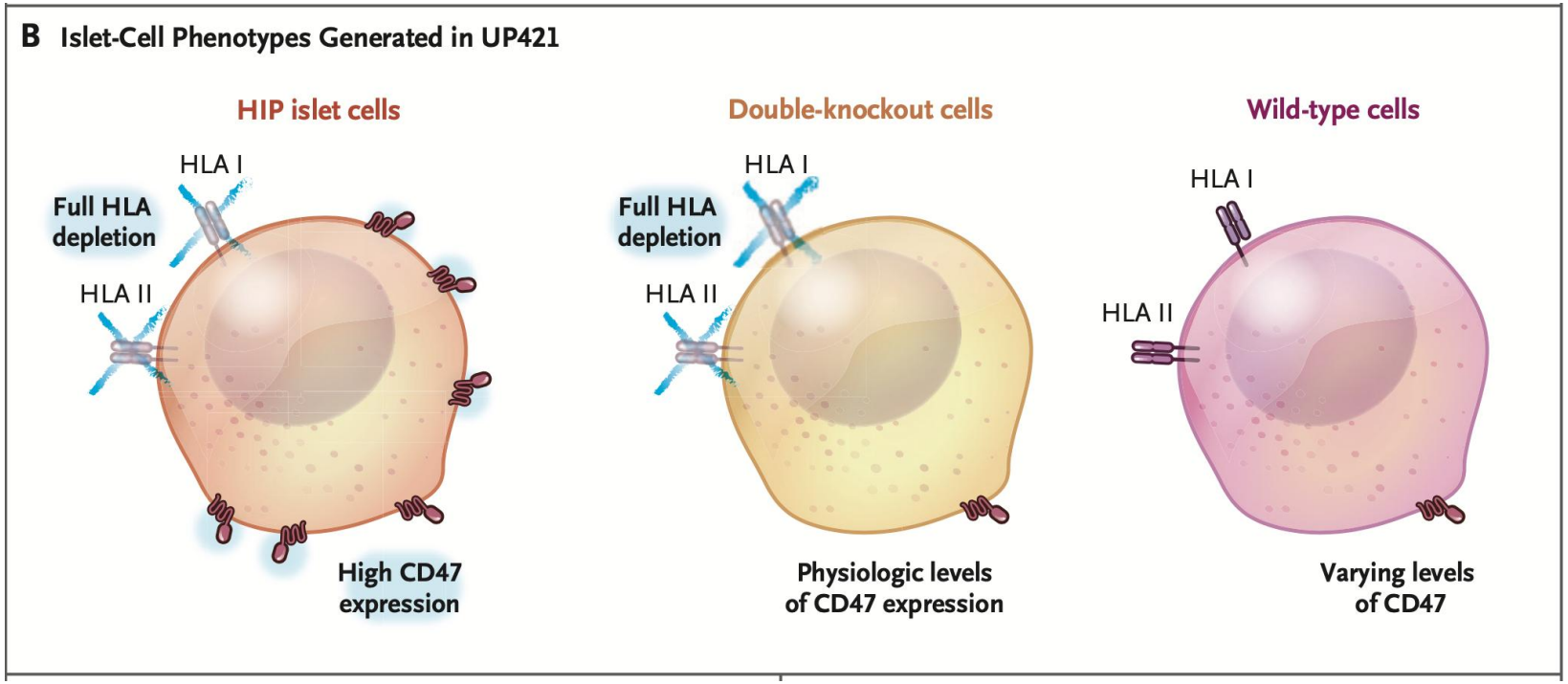
Survival of Transplanted Allogeneic Beta Cells with No Immunosuppression

Authors: Per-Ola Carlsson, M.D., Ph.D., Xiaomeng Hu, Ph.D., Hanne Scholz, Ph.D., Sofie Ingvast, B.Sc., Torbjörn Lundgren, M.D., Ph.D., Tim Scholz, M.D., Ph.D., Olof Eriksson, Ph.D., Per Liss, M.D., Ph.D., Di Yu, Ph.D., Tobias Deuse, M.D., Olle Korsgren, M.D., Ph.D., and Sonja Schrepfer, M.D., Ph.D. Author Info & Affiliations

Published August 4, 2025 | N Engl J Med 2025;393:887-894 | DOI: 10.1056/NEJMoa2503822 | VOL. 393 NO. 9

***β* cellule** da donatore cadavere processate tramite **gene editing genomico CRISPR**: ablazione di HLA





Survival of Transplanted Beta Cells with No Immunosuppression

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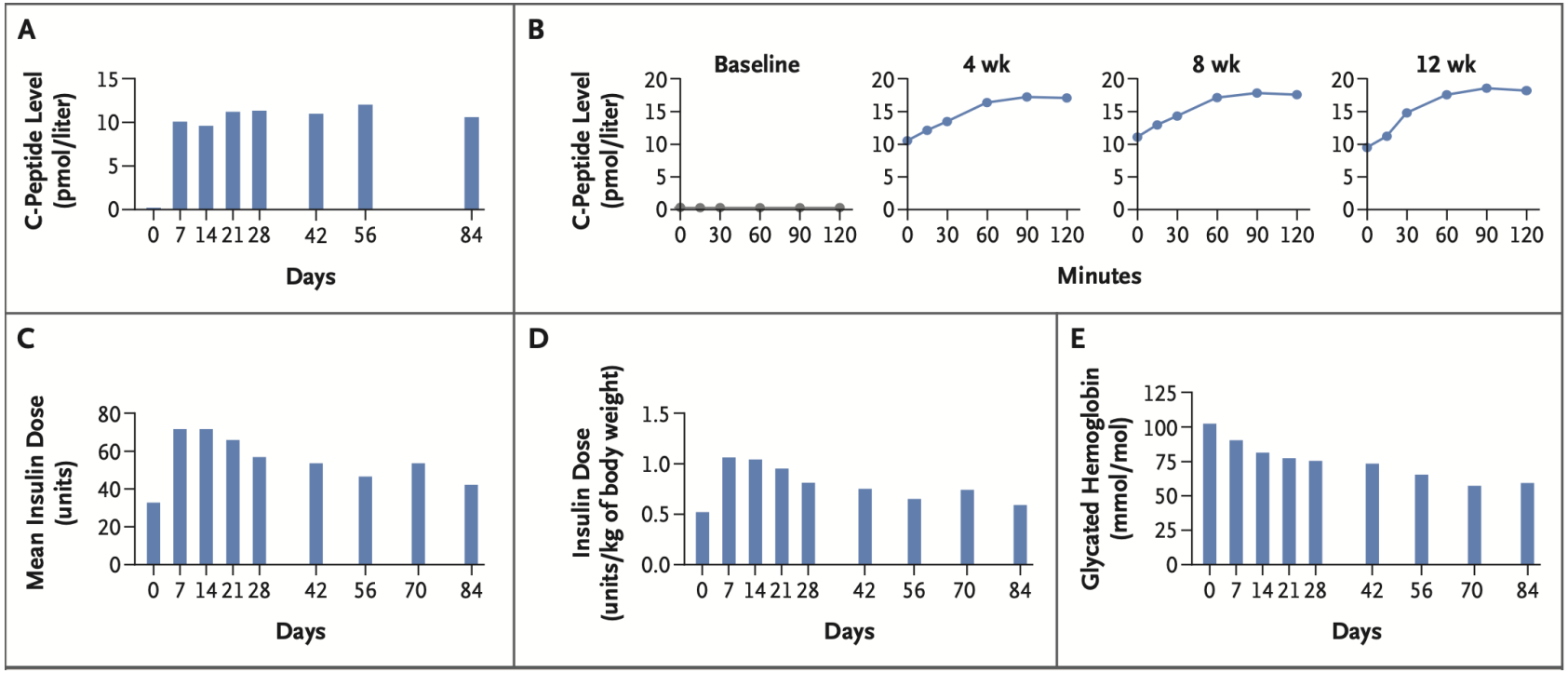


- **Assenza di rigetto** nelle cellule trapiantate
- Funzionalità conservata: livelli stabili di **C-peptide**
- **NB**: numero di cellule processate esiguo → insulino indipendenza non ottenuta

Quali sono i limiti?

Immunosoppressione

Scarsità di donatori

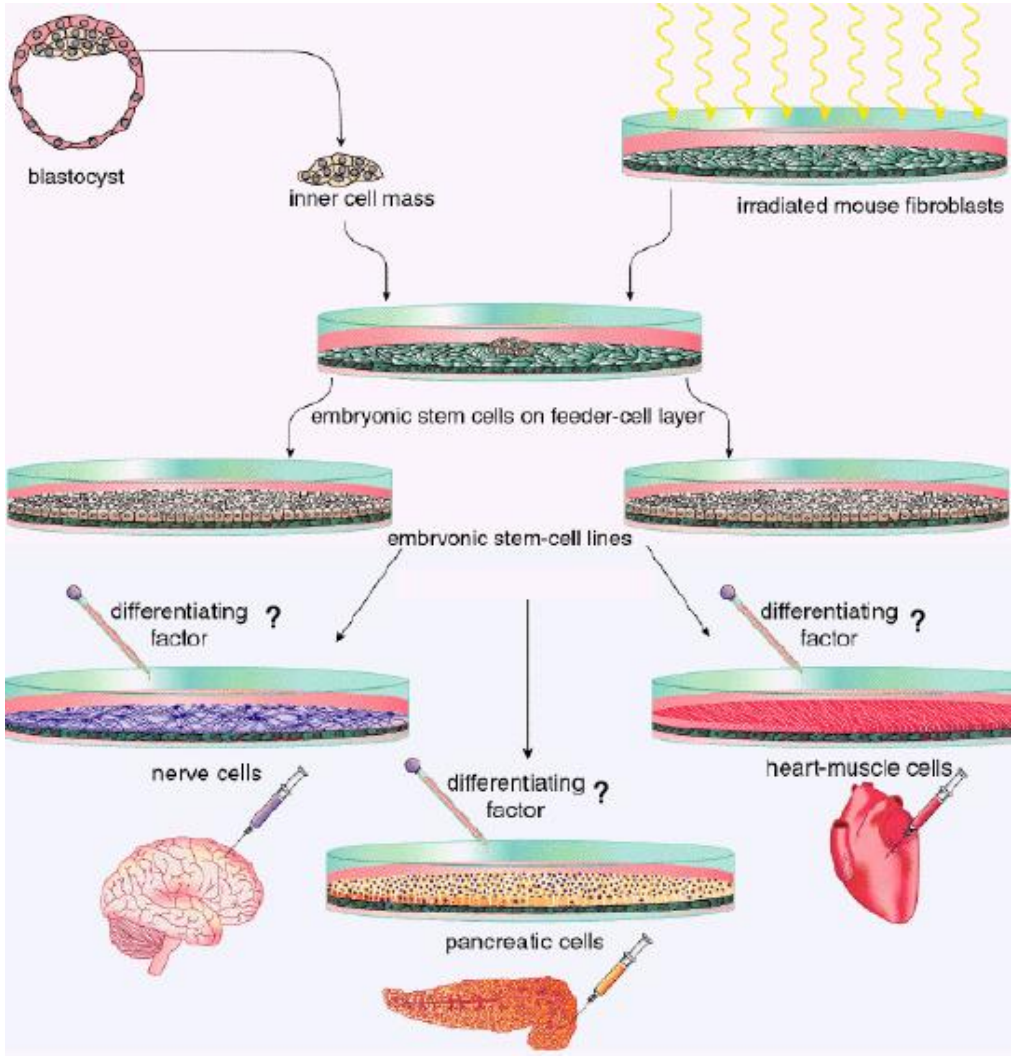
La Barriera dell'offerta

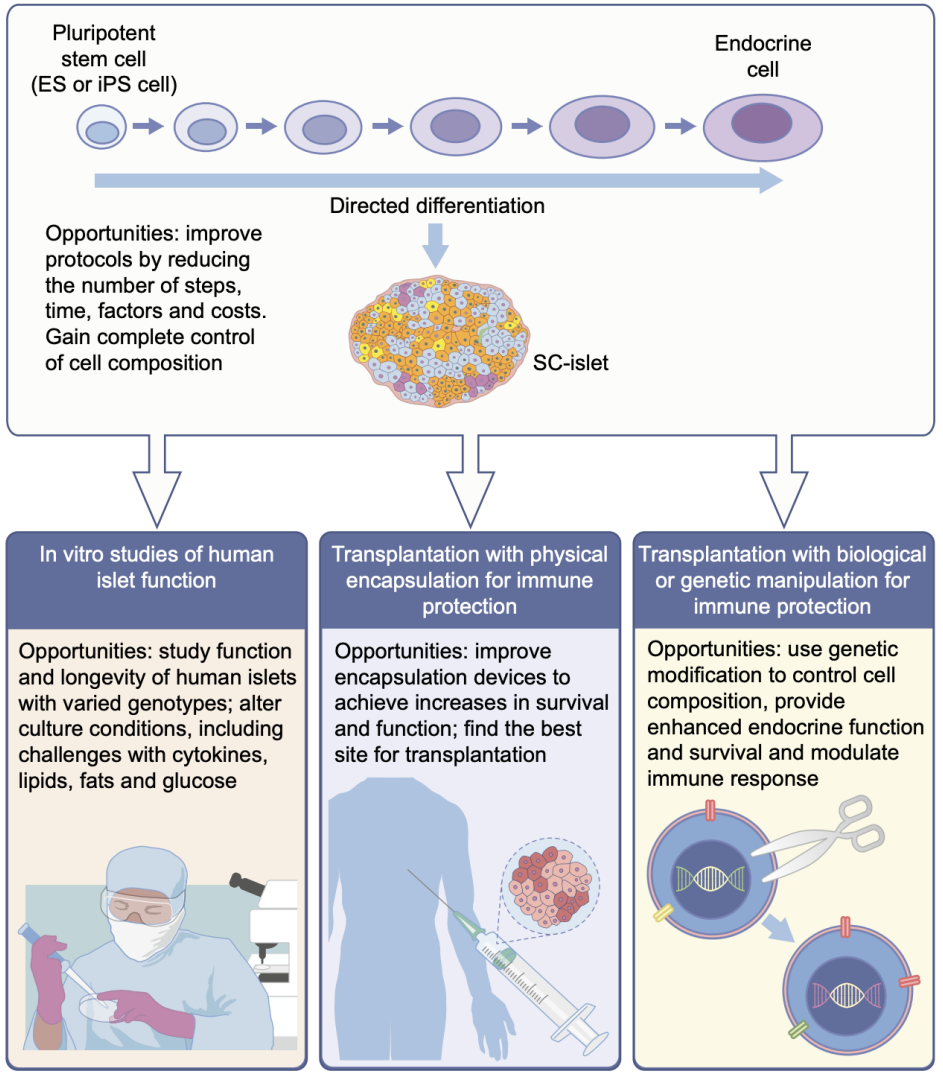
Migliaia di pazienti in Lista (T1D Instabile)

Donatori Cadavere Limitati: La scarsità di organi è un collo di bottiglia insormontabile.

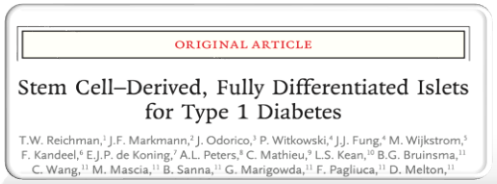
Efficienza Ridotta: Per un singolo trapianto di successo, a volte sono necessarie le isole di **2 o anche 3 pancreas** di donatori diversi.

LE CELLULE STAMINALI





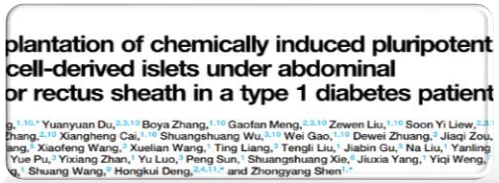
Le principali pubblicazioni


ORIGINAL ARTICLE

Stem Cell–Derived, Fully Differentiated Islets for Type 1 Diabetes

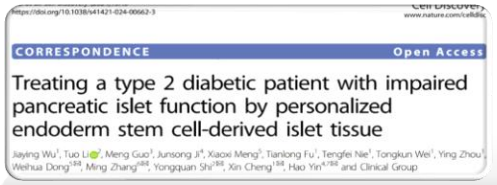
T.W. Reichman,[1] J.F. Markmann,[2] J. Odorico,[3] P. Witkowski,[4] J.J. Fung,[4] M. Wijkstrom,[5] F. Kandeel,[6] E.J.P. de Koning,[7] A.L. Peters,[8] C. Mathieu,[9] L.S. Kean,[10] B.G. Bruinsma,[11] C. Wang,[11] M. Mascia,[11] B. Sanna,[11] G. Marigowda,[11] F. Pagliuca,[11] D. Melton,[11]

1) Allotrapianto di cellule staminali embrionali (ESC)


plantation of chemically induced pluripotent
cell-derived islets under abdominal
or rectus sheath in a type 1 diabetes patient

Yuanyuan Du, Boya Zhang, Gaofan Meng, Zewen Liu, Soon Yi Liew, Xiangheng Cai, Shuangshuang Wu, Wei Gao, Dewei Zhuang, Jiaqi Zou, Xiaofeng Wang, Xuelian Wang, Ting Liang, Tengli Liu, Jiabin Gu, Na Liu, Yanling Yue Pu, Yixiang Zhan, Yu Luo, Peng Sun, Shuangshuang Xie, Jiuxia Yang, Yiqi Weng, Shuang Wang, Hongkui Deng, and Zhongyang Shen

2) Autotrapianto di IPS nel diabete di tipo 1


CORRESPONDENCE Open Access

Treating a type 2 diabetic patient with impaired pancreatic islet function by personalized endoderm stem cell-derived islet tissue

Jiaying Wu, Tuo Li, Meng Guo, Junsong Ji, Xiaoxi Meng, Tianlong Fu, Tengfei Nie, Tongkun Wei, Ying Zhou, Weihua Dong, Ming Zhang, Yongquan Shi, Xin Cheng, Hao Yin and Clinical Group

3) Autotrapianto di IPS nel diabete di tipo 2

VERTEX VX - 880

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Stem Cell–Derived, Fully Differentiated Islets for Type 1 Diabetes

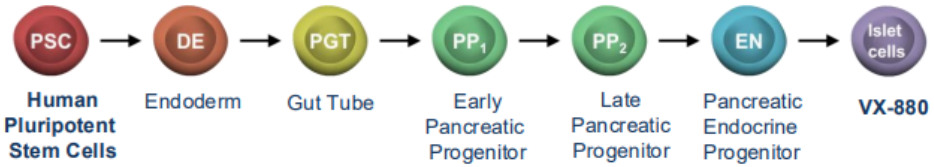
T.W. Reichman,[1] J.F. Markmann,[2] J. Odorico,[3] P. Witkowski,[4] J.J. Fung,[4] M. Wijkstrom,[5] F. Kandeel,[6] E.J.P. de Koning,[7] A.L. Peters,[8] C. Mathieu,[9] L.S. Kean,[10] B.G. Bruinsma,[11] C. Wang,[11] M. Mascia,[11] B. Sanna,[11] G. Marigowda,[11] F. Pagliuca,[11] D. Melton,[11] C. Ricordi,[12] and M.R. Rickels,[2] for the VX-880-101 FORWARD Study Group*

ABSTRACT

BACKGROUND

Zimislecel is an allogeneic stem cell–derived islet-cell therapy. Data on the safety and efficacy of zimislecel in persons with type 1 diabetes are needed.

VX-880 is an Islet Cell Therapy in Clinical Development for T1D Complicated by Recurrent Severe Hypoglycemia



VX-880 is an investigational allogeneic stem cell-derived, fully differentiated, insulin-producing **islet cell therapy**

VX-880 is delivered by **infusion** into the **hepatic portal vein**

A steroid free **immunosuppressive regimen** is used to protect the cells from the immune system:

- induction (anti-thymocyte globulin)
- maintenance (tacrolimus + sirolimus)

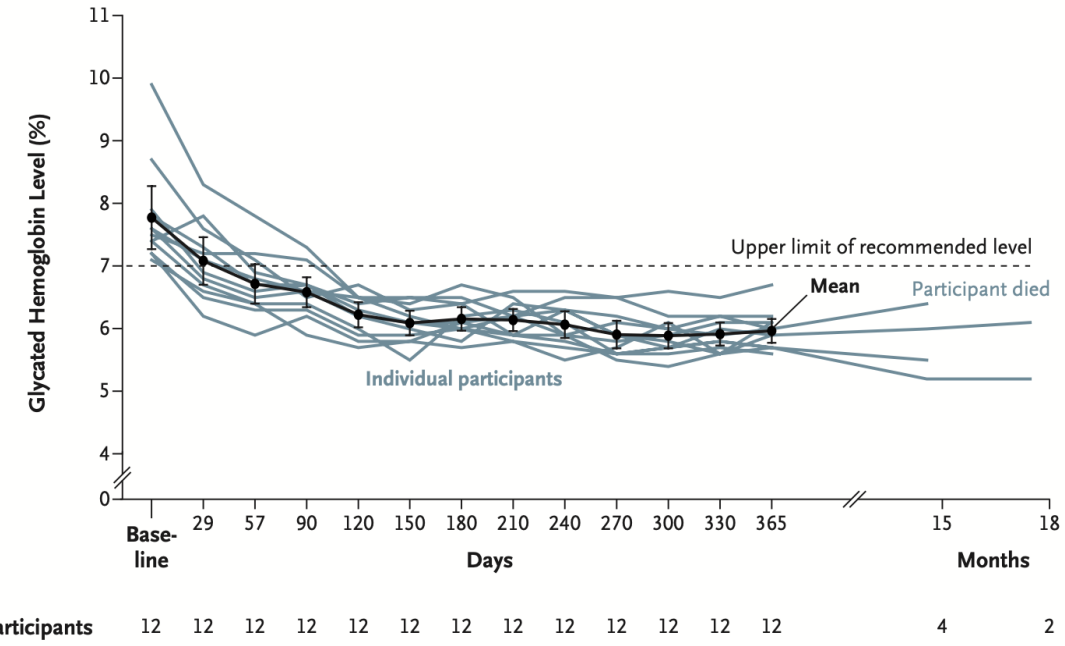
The cell infusion protocol and immunosuppressive regimen have been established with deceased donor islet cell transplants

T1D. Type 1 diabetes

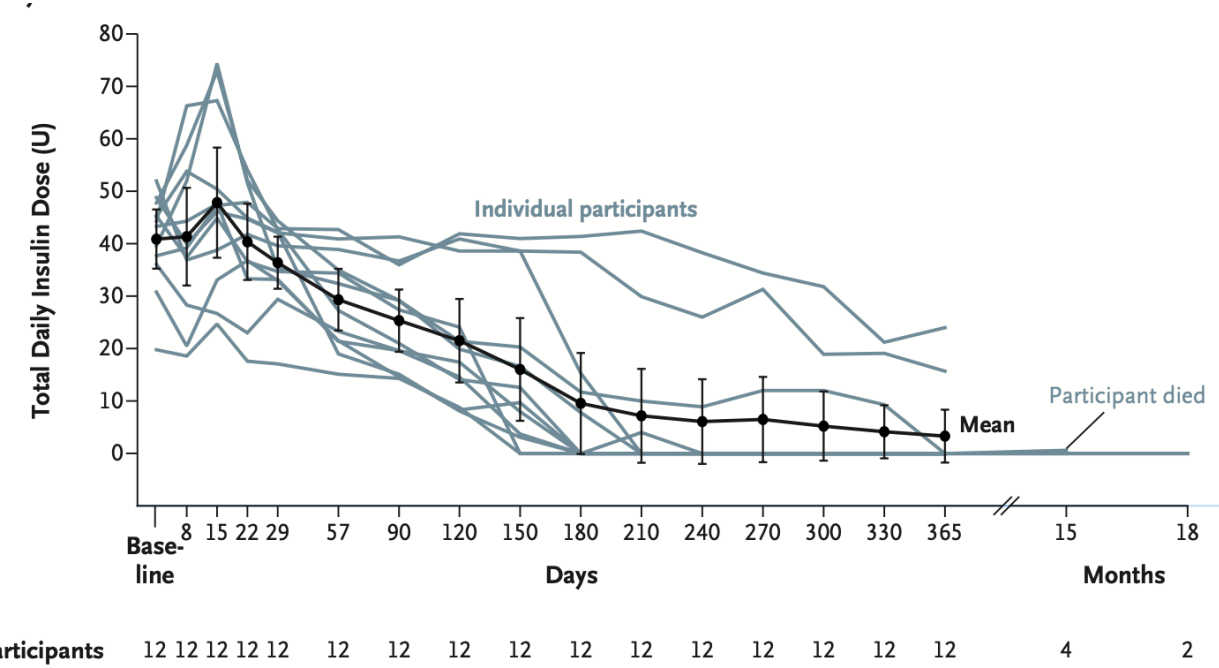
RISULTATI A UN ANNO

- Il **100%** dei **partecipanti** ha raggiunto i target clinici di emoglobina glicata (**HbA1c < 7%**) e Time in Range (**TIR > 70%**).
- Il **100% dei partecipanti** ha ottenuto la **totale eliminazione** degli eventi ipoglicemici gravi (**SHEs**).
- L'**83%** dei pazienti (10 su 12) ha raggiunto la **completa indipendenza dall'insulina** a 12 mesi dall'infusione.

HbA1c



Total daily insulin dose



Safety Profile of VX-880 is Consistent with Immunosuppressive Regimen, Infusion Procedure, and Complications from Long-Standing T1D

	Participants with AEs (N=14) n (%)	Total AEs (N=14)
Any AEs	14 (100.0)	337
AEs by severity		
Mild	14 (100.0)	219
Moderate	13 (92.9)	88
Severe	7 (50.0)	28
Life threatening	0	0
Death	2 (14.3)	2
AEs related to VX-880	6 (42.9)	17
AEs related to immunosuppressive therapy	14 (100.0)	166
SAEs	7 (50.0)	19
SAEs related to VX-880	0	0
AEs leading to study discontinuation	0	0

- Majority of **AEs** were of **mild or moderate severity**
- Of the **AEs with a causal relationship to any study drug,** most were **attributed to immunosuppressive therapy**
- **No SAEs** were considered **related to VX-880**
- **2 deaths, not related to VX-880:**
  - **Cryptococcal meningitis infection** due to complications from an elective sinus surgery (cribriform plate injury), high-dose steroids use (prohibited by protocol) in the weeks preceding and following the sinus surgery, and immunosuppressive medications
  - **Progression of pre-existing neurocognitive impairment** due to a severe traumatic brain-injury sustained in a motor vehicle accident caused by a SHE before study enrollment

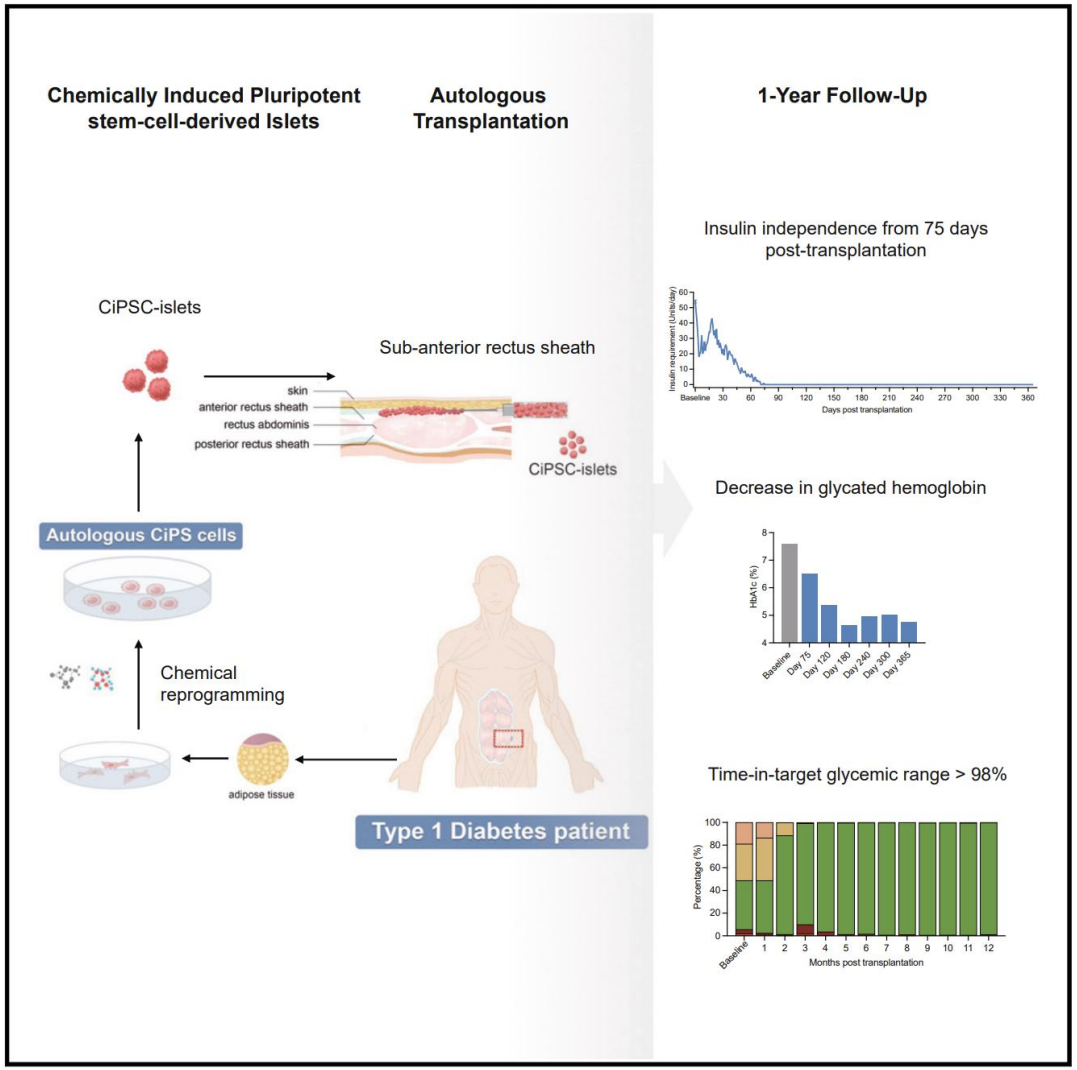
AE, adverse events; **SAEs,** serious adverse events; **SHE,** severe hypoglycemic event; **T1D,** Type 1 diabetes

cIPSC in Type 1 Diabetes

Article

Transplantation of chemically induced pluripotent stem-cell-derived islets under abdominal anterior rectus sheath in a type 1 diabetes patient

Shusen Wang,[1,10,*] Yuanyuan Du,[2,3,10] Boya Zhang,[1,10] Gaofan Meng,[2,3,10] Zewen Liu,[1,10] Soon Yi Liew,[2,3,10] Rui Liang,[1,10] Zhengyuan Zhang,[2,10] Xiangheng Cai,[1,10] Shuangshuang Wu,[3,10] Wei Gao,[1,10] Dewei Zhuang,[3] Jiaqi Zou,[1] Hui Huang,[3] Mingyang Wang,[5] Xiaofeng Wang,[3] Xuelian Wang,[1] Ting Liang,[3] Tengli Liu,[1] Jiabin Gu,[3] Na Liu,[1] Yanling Wei,[3] Xuejie Ding,[1] Yue Pu,[3] Yixiang Zhan,[1] Yu Luo,[3] Peng Sun,[1] Shuangshuang Xie,[6] Jiuxia Yang,[1] Yiqi Weng,[7] Chunlei Zhou,[8] Zhenglu Wang,[1] Shuang Wang,[9] Hongkui Deng,[2,4,11,*] and Zhongyang Shen[1,*]



Highlights

- Patient-derived islets were generated with chemically induced pluripotent stem cells
- Transplantation of these islets to an abdominal site led to engraftment in one patient
- Exogenous insulin-independent glycemic control was restored in the patient
- All safety and efficacy clinical endpoints were met at 1-year follow-up of the patient

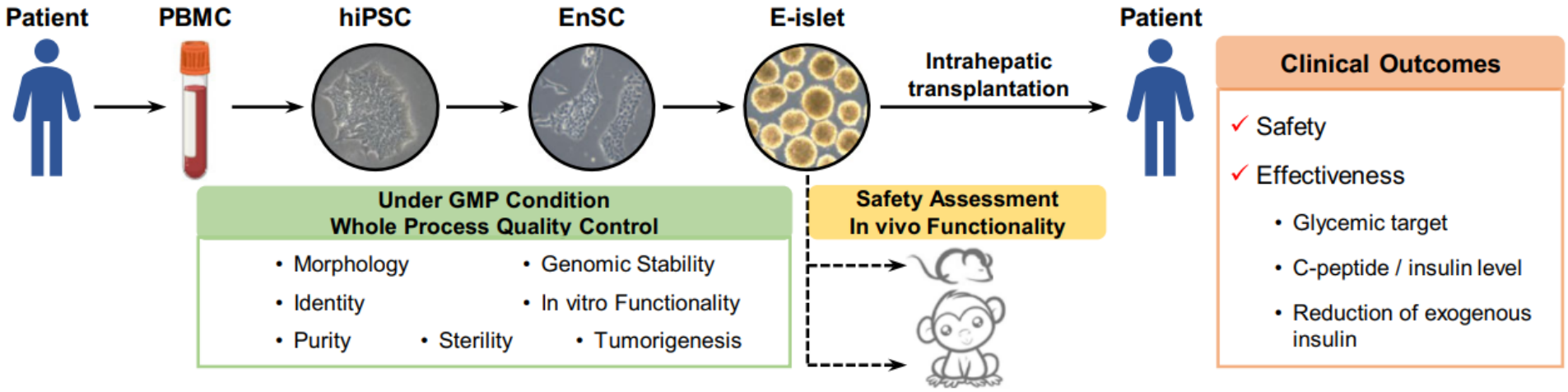
cIPSC in Type 2 Diabetes

CORRESPONDENCE Open Access

Treating a type 2 diabetic patient with impaired pancreatic islet function by personalized endoderm stem cell-derived islet tissue

Jiaying Wu[1], Tuo Li[2], Meng Guo[3], Junsong Ji[4], Xiaoxi Meng[5], Tianlong Fu[1], Tengfei Nie[1], Tongkun Wei[1], Ying Zhou[1], Weihua Dong[5]✉, Ming Zhang[6]✉, Yongquan Shi[2]✉, Xin Cheng[1]✉, Hao Yin[4,7]✉ and Clinical Group

- **TITR** (Time In Tight Range) incrementato dal 56,7% al **99%** (stabile dalla settimana 32).
- **MAGE** (variabilità) ridotto da 99 mg/dL a **29 mg/dL**: ritorno a livelli fisiologici.
- **Nessun episodio** di **ipoglicemia** (<70 mg/dL) o **iperglicemia grave** (<55 mg/dL) durante le 116 settimane di follow-up.
- Scomparsa del fabbisogno di insulina esogena e stabilizzazione dei target glicemici.



IN PROSPETTIVA

Encapsulation (physical barrier)

A Phase 1/2 Study to Evaluate the Safety, Tolerability, and Efficacy of VX-264 in Subjects With Type 1 Diabetes Mellitus (Vertex)

- Fully differentiated, stem cell-derived islet cell therapy
- Encapsulated in Vertex-developed, immunoprotective device implanted within abdominal wall
- Does not require the use of immunosuppression

Key inclusion criteria: Adults with T1D (no recurrent SHEs)
Locations: USA (Miami, Chicago, Boston, Penn, Pittsburgh, Wisconsin) Canada (Toronto, Vancouver, Edmonton), Europe (Dresden, Milan, Leiden, Geneva, Oxford, Newcastle)

Immune evasion via gene editing

An Open-Label, FIH Study Evaluating the Safety, Tolerability, and Efficacy of VCTX211 Combination Product in Subjects With T1D (CRISPR)

- Pancreatic progenitor cells (ex-Viacyte)
- Encapsulated in implantable device
- First patient dosed in Feb 2022 (press release), target N=10 (clinicaltrials.gov)

Key inclusion criteria: Adults with T1D (with recurrent SHEs)
Locations: Canada (Vancouver, Edmonton)

VERTEX VX - 264

Study Overview

Brief Summary

The purpose of the study is to evaluate the safety, tolerability, and efficacy of **VX-264** in participants with type 1 diabetes (T1D).

Official Title

A Phase 1/2 Study to Evaluate the Safety, Tolerability, and Efficacy of **VX-264** in Subjects With Type 1 **Diabetes Mellitus**

Conditions

Type 1 Diabetes

Intervention / Treatment

- Drug: **VX-264**

Other Study ID Numbers

- VX22-264-101

Study Start (Actual)

2023-05-16

Primary Completion (Estimated)

2026-05

Study Completion (Estimated)

2026-05

Enrollment (Estimated)

17

Study Type

Interventional

Phase

Phase 1
Phase 2

BOSTON--(BUSINESS WIRE)--Mar. 28, 2025-- Vertex Pharmaceuticals Incorporated (Nasdaq: VRTX) today announced several updates on the Company's type 1 diabetes (T1D) portfolio.

VX-264 Update

Vertex has completed enrollment and dosing in Parts A and B of the Phase 1/2 VX-264 (cells + device) study and the planned analysis at Day 90 for Part B. In Part B of the study, participants received the full dose of the investigational fully differentiated pancreatic islet cell therapy encapsulated in a proprietary immunoprotective device. There were two primary endpoints in Part B, safety and change in peak C-peptide during a mixed-meal tolerance test (MMTT) from baseline at Day 90. VX-264 was generally safe and well tolerated; however, the study did not meet the efficacy endpoint. Increases in C-peptide, a marker of insulin production, were not observed at levels necessary to deliver benefit. Therefore, VX-264 will not be advancing further in clinical trials. Vertex plans to conduct further analyses, including of explanted devices, to better understand these findings.

TAKE HOME MESSAGES

Indicazione Clinica: Diabete instabile (*brittle diabetes*).

Limiti del Trapianto: Scarsità donatori e immunosoppressione.

Cellule Staminali: Validazione clinica di linee ESC e iPSC.

Prospettive Future: Gene editing e ipoimmunità.

GRAZIE PER L’ATTENZIONE