Sostituzione e rigenerazione cellulare nel Diabete di Tipo 1: nuove prospettive per una cura definitiva

- Federico Bertuzzi
- SC Diabetologia
- Ospedale Niguarda Milano

Conflitto di interesse

Dichiaro di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

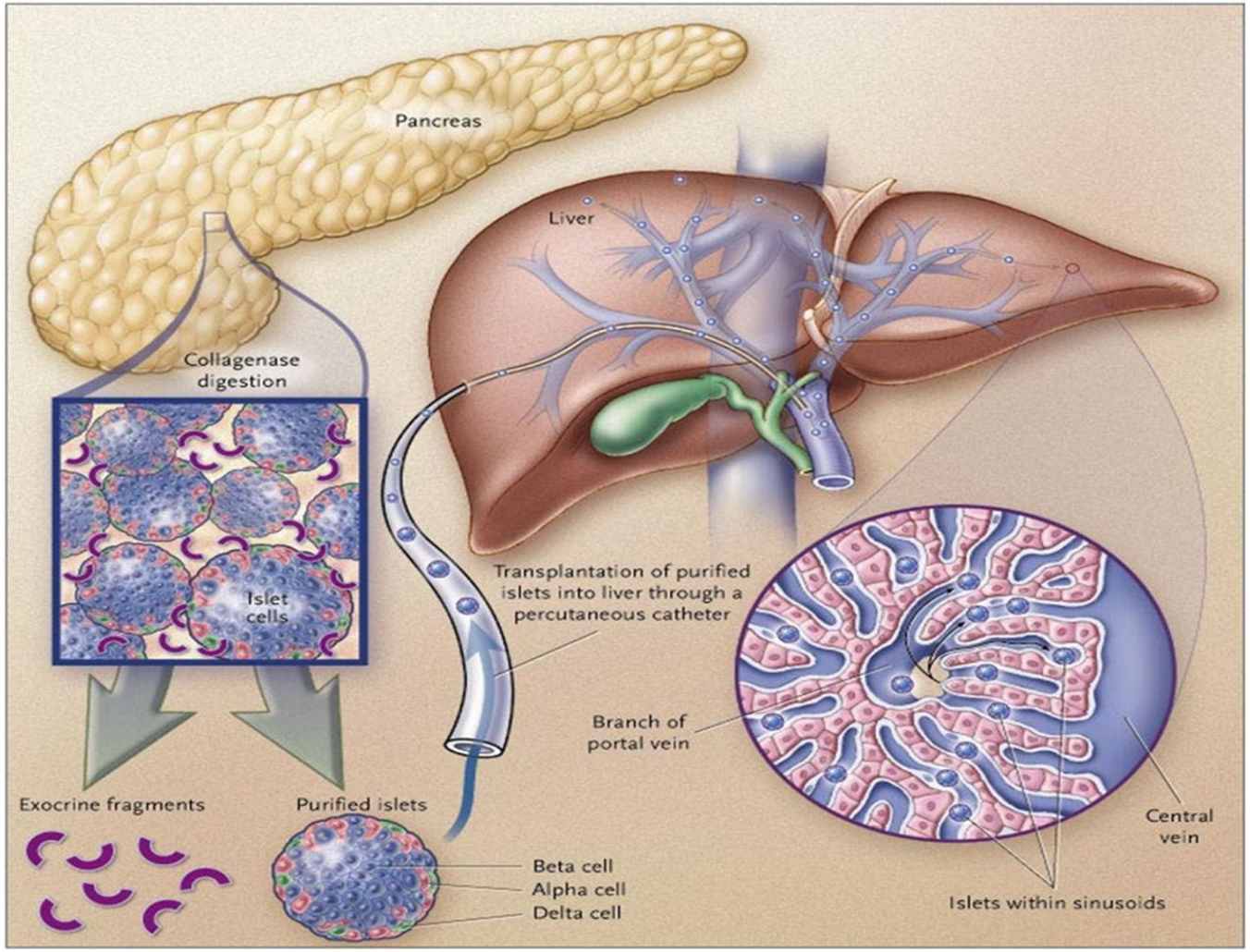
- BD
- Lilly
- Theras
- Movi
- Abbott

LA TERAPIA CELLULARE

-Il trapianto di isole

-Il trapianto di cellule staminali

Il trapianto di isole



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

American Diabetes Association.

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

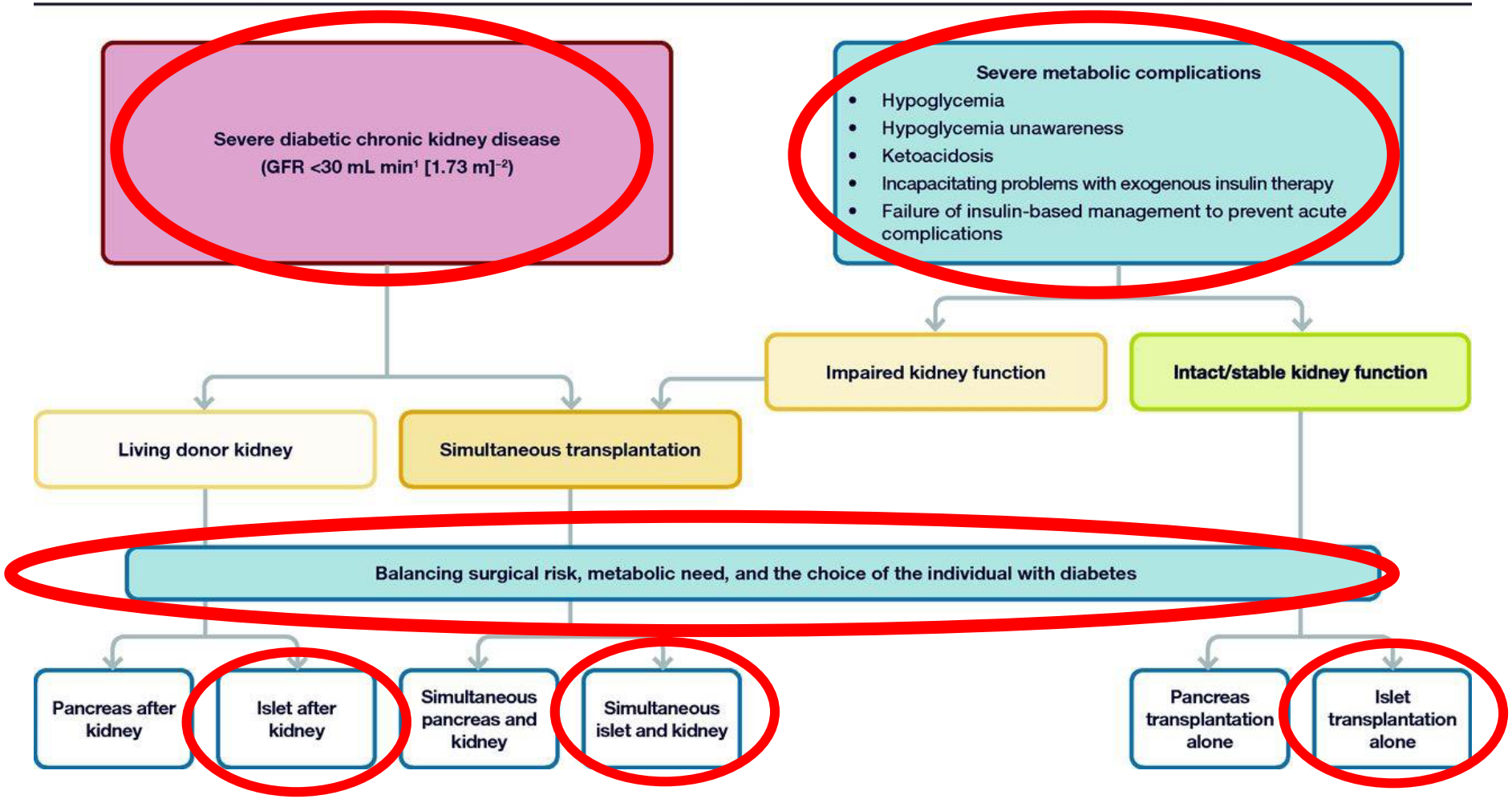
Qualità delle prove: moderata.

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

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

American Diabetes Association.

Perché si

Il trapianto di isole è l'unica terapia in grado di

-normalizzare i valori glicemici

-senza il rischio di ipoglicemia

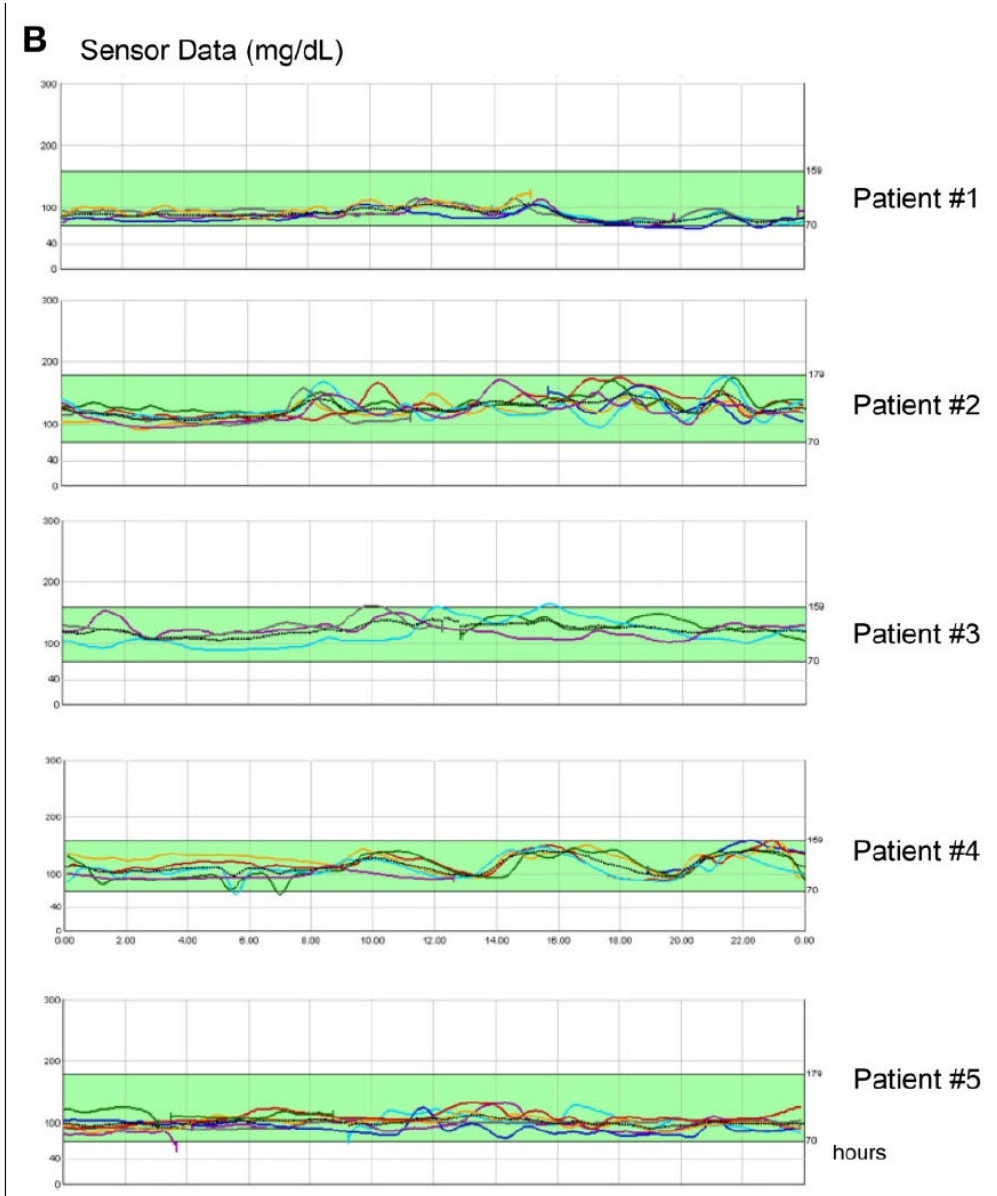
-con una procedura non chirurgica

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]

Cell Transplantation
1–7

DOI: 10.1177/0963689718
journals.sagepub.com/hom
SAGE



Il trapianto di isole:

-migliora HbA1c, TIR, riduce le ipoglicemie

-migliora la qualità di vita

-rallenta la progressione delle complicanze croniche

anche in caso di funzione parziale

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**

Reduced Progression of Diabetic Microvascular Complications With Islet Cell Transplantation Compared With Intensive Medical Therapy

David M. Thompson,[1,5] Mark Meloche,[2] Ziliang Ao,[2] Breay Paty,[1] Paul Keown,[1] R. Jean Shapiro,[1] Stephen Ho,[3] Dan Worsley,[3] Michelle Fung,[1] Graydon Meneilly,[1] Iain Begg,[4] Mohammed Al Mehthel,[1] Joma Kondi,[1] Claire Harris,[1] Blake Fensom,[1] Sharon E. Kozak,[1] Suet On Tong,[1] Mary Trinh,[1] and Garth L. Warnock[2]

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

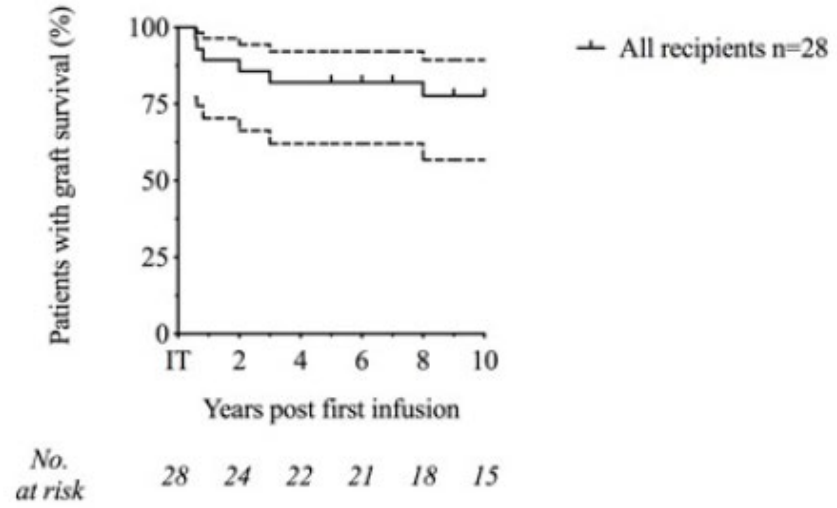
Marie-Christine Vantyghem,[1,2,3] Mikael Chetboun,[1,3,4] Valéry Gmyr,[1,3] Arnaud Jannin,[2] Stéphanie Espiard,[2] Kristell Le Mapihan,[2] Violeta Raverdy,[1,3] Nathalie Delalleau,[1,3] François Machuron,[5] Thomas Hubert,[1,3] Marie Frimat,[6] Eric Van Belle,[7] Marc Hazzan,[6] Pascal Pigny,[8] Christian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

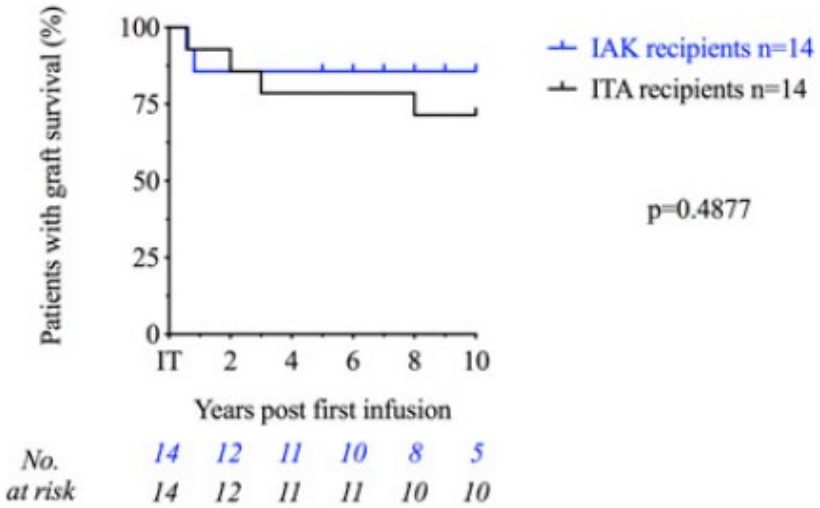
Diabetes Care 2019;42:2042–2049 | https://doi.org/10.2337/dc19-0401

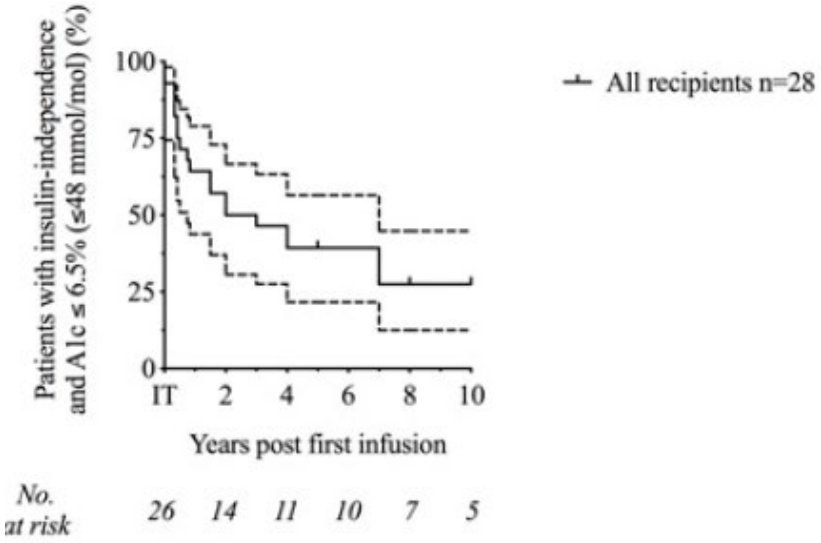
Table 2—Metabolic and renal long-term outcomes in the entire study group

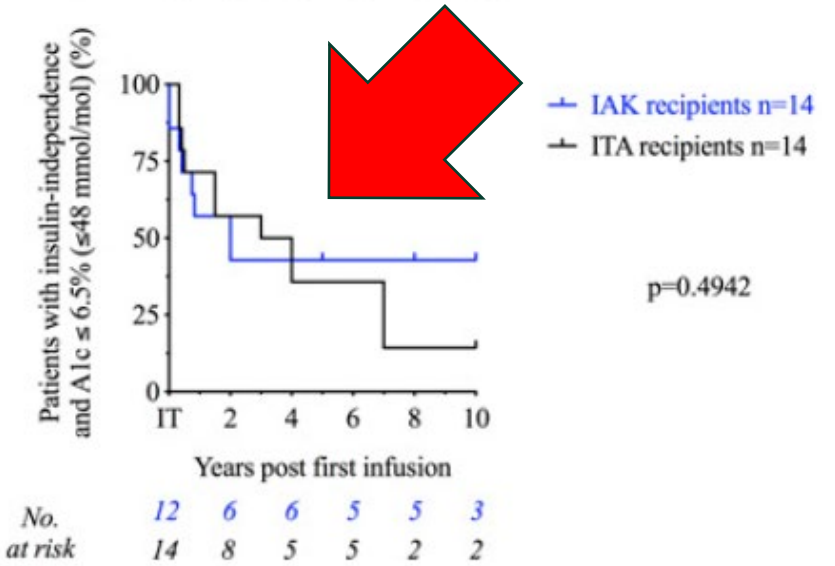
	1 year	*P* value vs. baseline	5 years	*P* value vs. baseline	10 years	*P* value vs. baseline
Patients followed	28		27		20	
No. of severe hypoglycemia events in previous year	0 (0–0)	<0.0001	0 (0–0)	<0.0001	0 (0–0)	<0.0001
Glycated hemoglobin (%) (mmol/mol)	5.9 (5.5–6.7) 41 (37–50)	<0.0001	6.9 (6.1–7.5) 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

Values expressed as medians (interquartile range) or frequencies (percentages).


Patients with graft survival (%)
100
75
50
25
0
IT 2 4 6 8 10
Years post first infusion
All recipients n=28
No. at risk
28 24 22 21 18 15


Patients with graft survival (%)
100
75
50
25
0
IT 2 4 6 8 10
Years post first infusion
IAK recipients n=14
ITA recipients n=14
p=0.4877
No. at risk
14 12 11 10 8 5
14 12 11 11 10 10

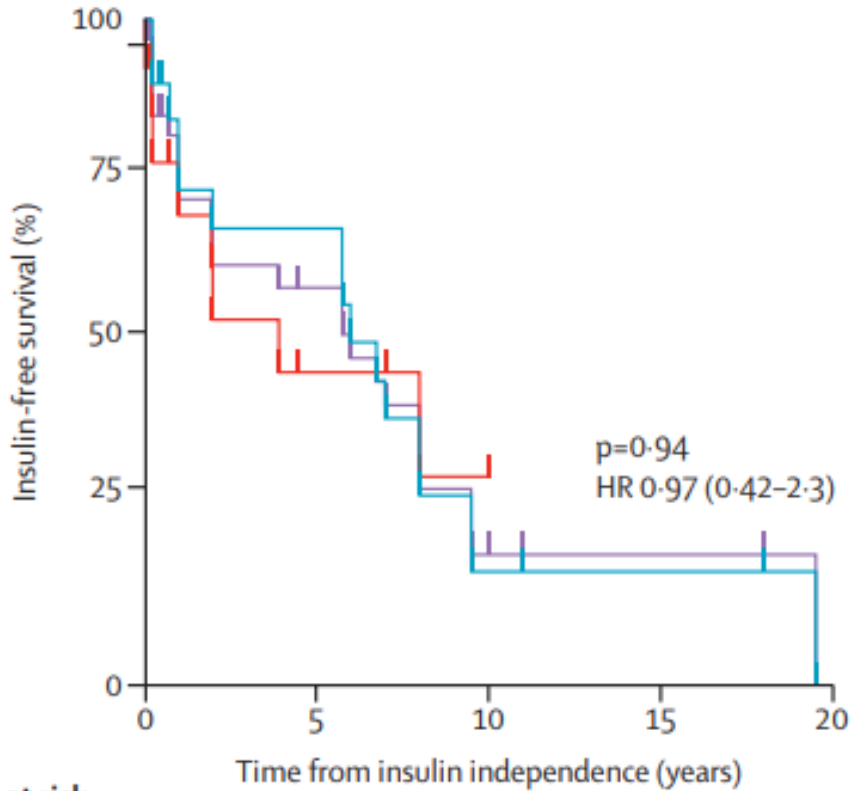

Patients with insulin-independence and A1c ≤ 6.5% (≤48 mmol/mol) (%)
100
75
50
25
0
IT 2 4 6 8 10
Years post first infusion
All recipients n=28
No. at risk
26 14 11 10 7 5


Patients with insulin-independence and A1c ≤ 6.5% (≤48 mmol/mol) (%)
100
75
50
25
0
IT 2 4 6 8 10
Years post first infusion
IAK recipients n=14
ITA recipients n=14
p=0.4942
No. at risk
12 6 6 5 5 3
14 8 5 5 2 2

Lancet Diabetes Endocrinol
2025; 13: 279–93
Published Online
February 7, 2025
https://doi.org/10.1016/
S2213-8587(24)00341-3
See Comment page 264

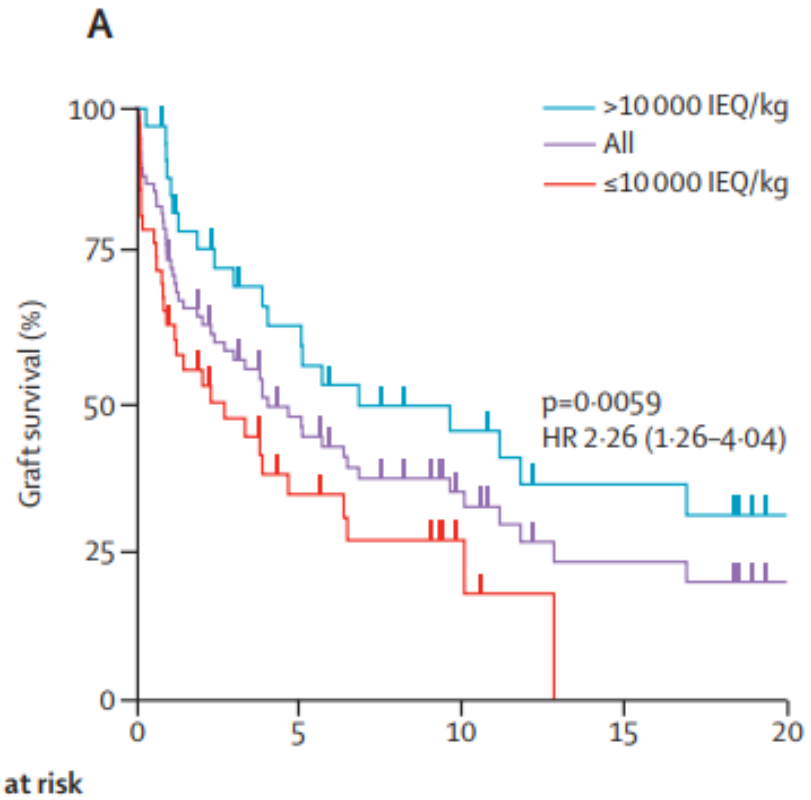
Long-term outcomes of pancreatic islet transplantation alone in type 1 diabetes: a 20-year single-centre study in Italy

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

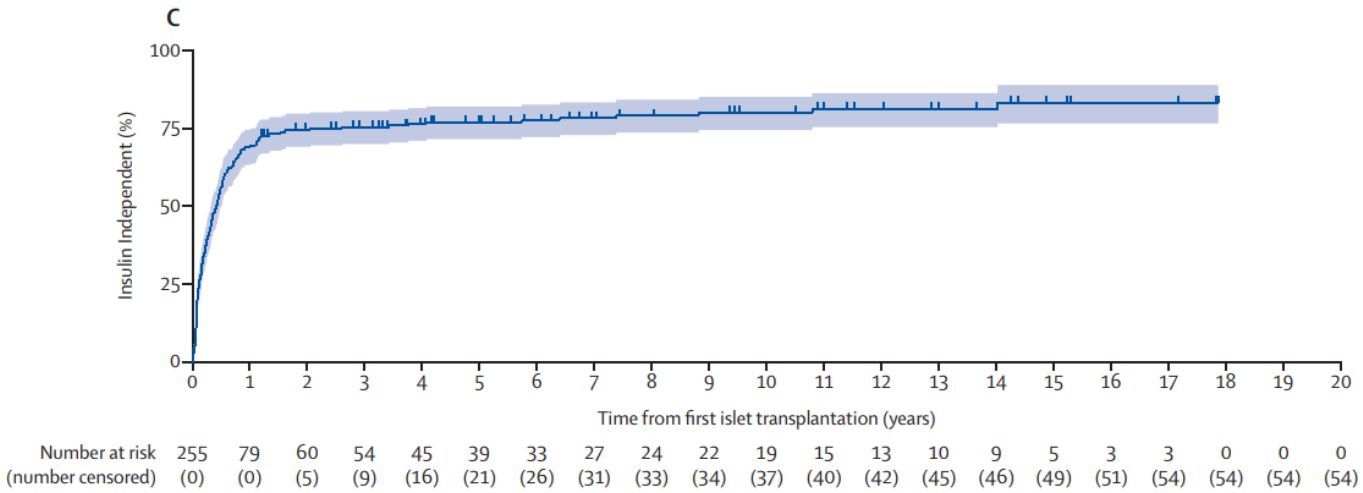


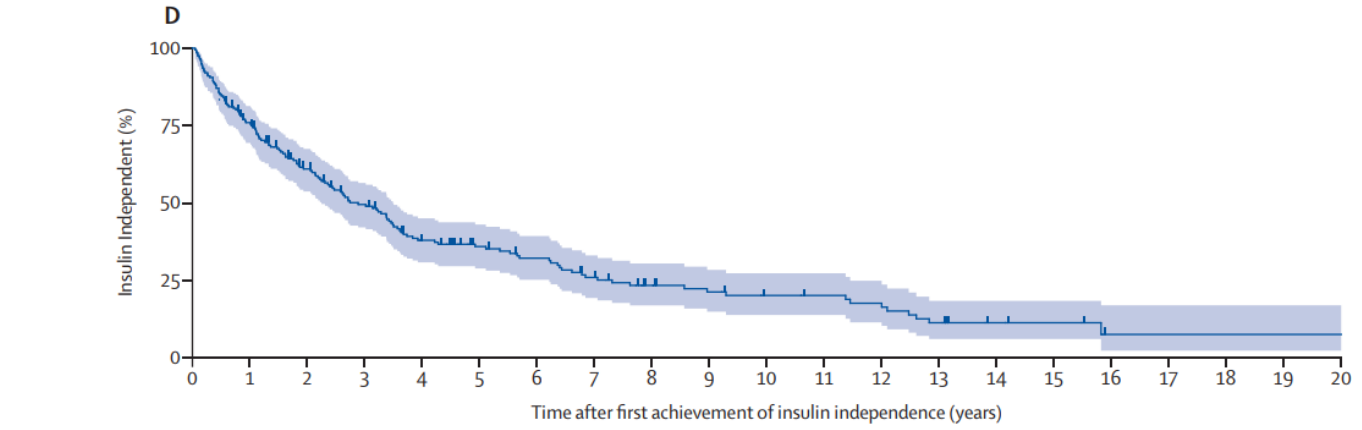
Number at risk

All	79	31	16	8	4
>10 000 IEQ/kg	35	20	12	8	4
≤10 000 IEQ/kg	44	11	4	0	0

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,





(79%) recipients had insulin independence

61% (95% CI 54–67) at 1 year

32% (25–39) at 5 years

20% (14–27) at 10 years

11% (6–18) at 15 years

8% (2–17) at 20 years.

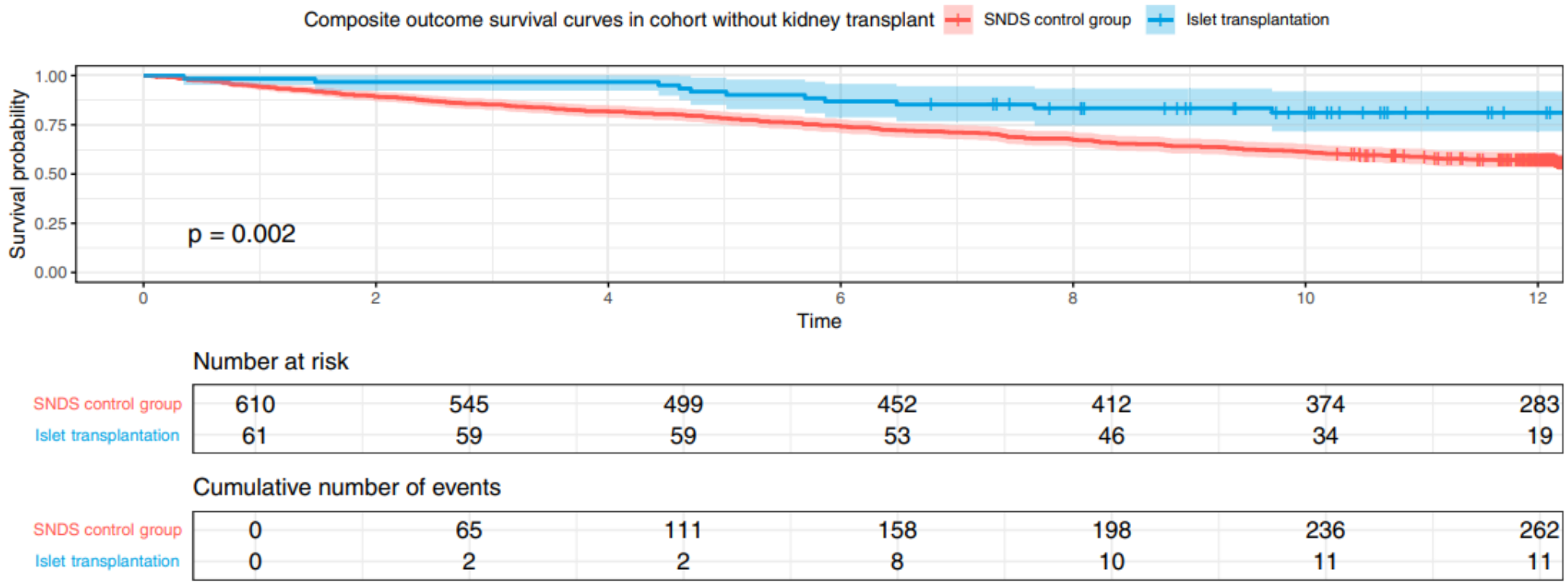
Diabetes Care 1

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

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]

https://doi.org/10.2:

A

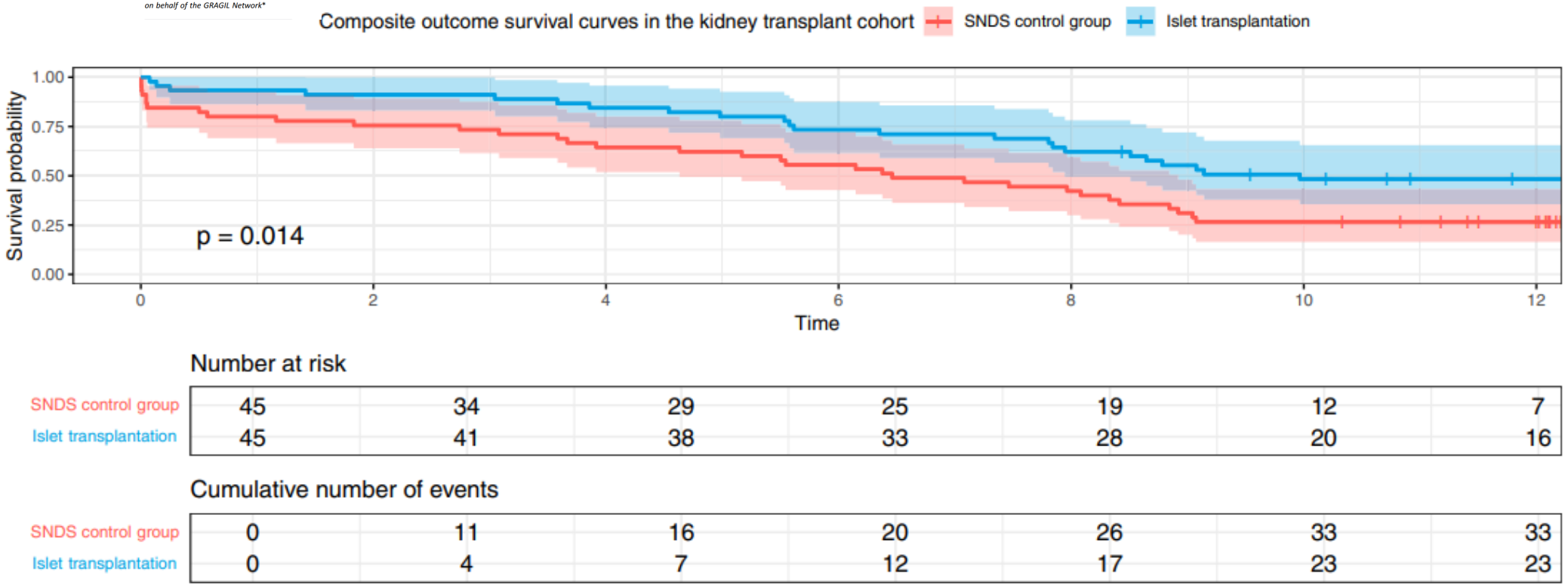


Diabetes Care 1

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

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*



Number at risk

SNDS control group	45	34	29	25	19	12	7
Islet transplantation	45	41	38	33	28	20	16

Cumulative number of events

SNDS control group	0	11	16	20	26	33	33
Islet transplantation	0	4	7	12	17	23	23

Figure 1—Kaplan-Meier survival curves of the primary composite outcome in the ITA (*A*) and IAK (*B*) groups. Time is given in years.

Islet-after-kidney transplantation versus kidney alone in kidney transplant recipients with type 1 diabetes (KAIAK): a population-based target trial emulation in France

Mehdi Maanaoui, Rémi Lenain*, Yohann Foucher, Fanny Buron, Gilles Blancho, Corinne Antoine, Sophie Caillard, Laurence Kessler, Moglie Le Quintrec, Orianne Villard, Dany Anglicheau, Matthias Büchler, Albane Brodin-Sartorius, Luc Frimat, Paolo Malvezzi, Sandrine Lablanche, Lionel Badet, Laure Esposito, Mikael Chetboun, Aghiles Hamroun, Julie Kerr-Conte, Thierry Berney, Marie-Christine Vantyghem, Marc Hazzan, François Pattou, on behalf of the TREPID-ABM study group†*

www.thelancet.com/diabetes-endocrinology **Vol 12 October 2024**

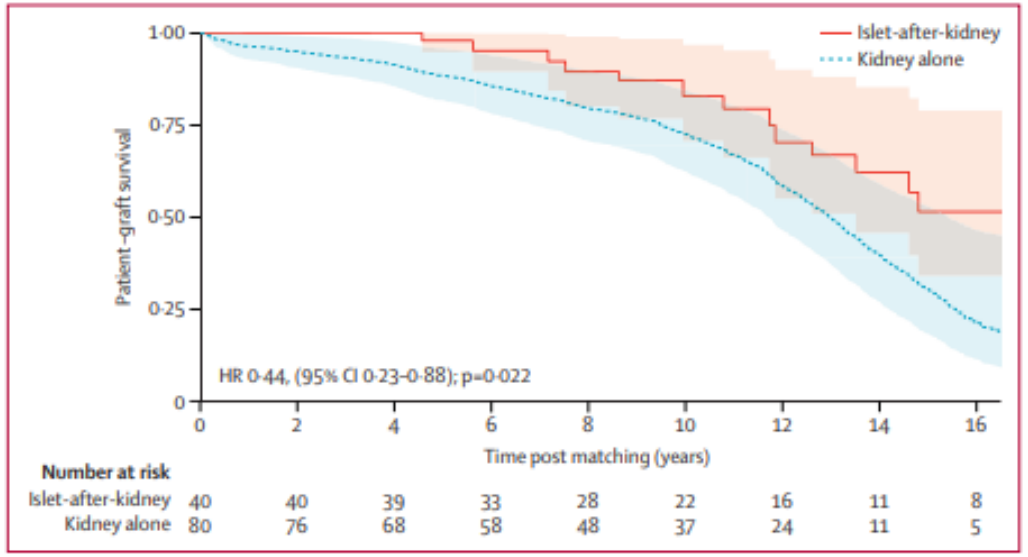


***Figure 3*: Patient-graft survival in patients with type 1 diabetes treated with islet-after-kidney transplantation or kidney transplantation alone**
Representation of bootstrapped Kaplan–Meier survival curves after matching of patients with islet-after-kidney transplantation and patients with kidney transplantation alone (1000 bootstrapped samples). Shaded areas represent 95% CI.

	n/N	10-year survival (95% CI)	Hazard ratio (95% CI)
Patient-graft survival			
Kidney alone	36/80	72·7% (57·4–88·0)	1·00 (reference)
Islet-after-kidney	13/40	82·9% (66·6–99·2)	0·44 (0·23–0·88)
Death-censored graft survival			
Kidney alone	16/80	81·6% (70·2–93·1)	1·00 (reference)
Islet-after-kidney	8/40	85·5% (70·7–100)	0·73 (0·30–1·89)
Patient survival			
Kidney alone	25/80	73·0% (57·4–88·5)	1·00 (reference)
Islet-after-kidney	8/40	90·7% (80·5–100)	0·41 (0·13–0·91)

By design, origin and start times of the survival analysis were identical for each outcome (islet transplantation for islet-after-kidney and the equivalent time of follow-up after kidney transplantation for controls). End time for patient-graft survival was death, return to dialysis, re-transplantation, or end of follow-up. End time for patient survival was death or end of follow-up. End time for death-censored graft survival was death, return to dialysis, re-transplantation, or end of follow-up.

***Table 2*: Effect of islet-after-kidney transplantation on the risk of death**

Perché no

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*

Il trapianto di isole:

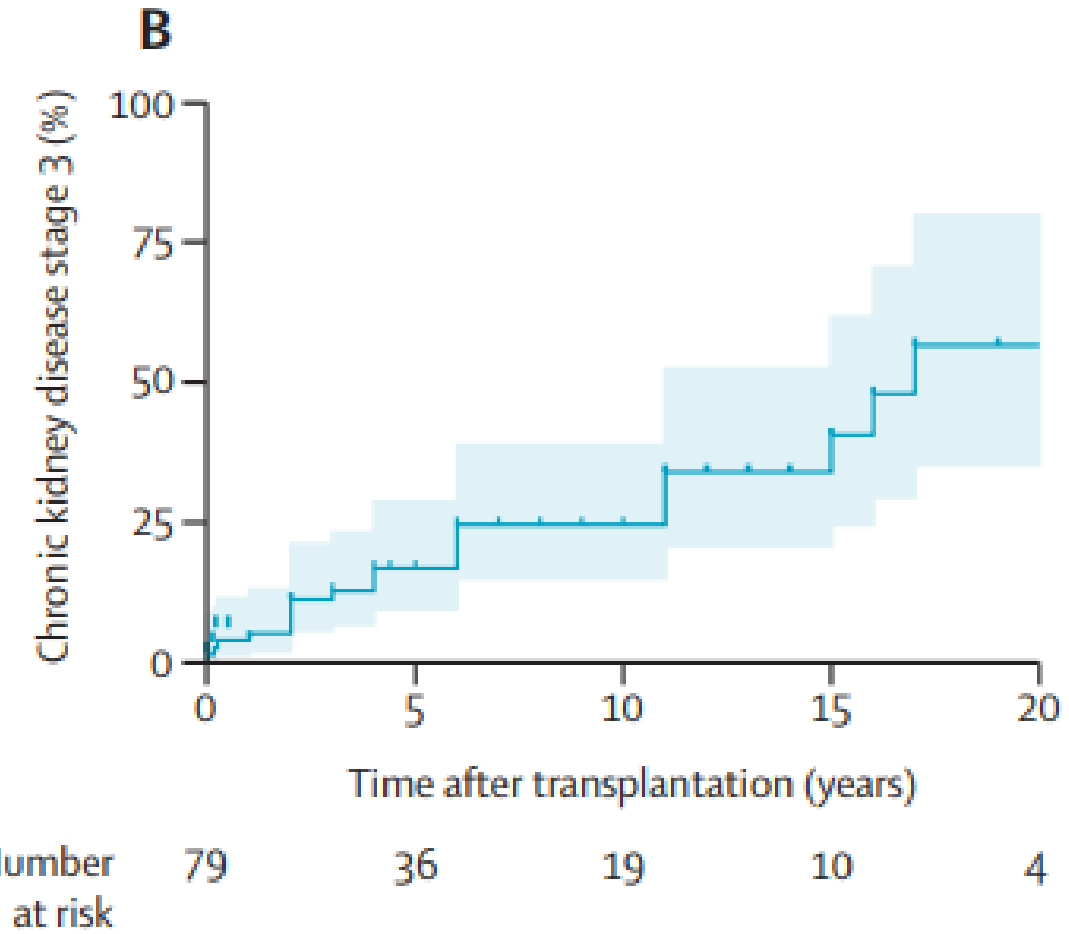
-effetti collaterali della procedura (sanguinamento, trombosi) clinicamente significativi

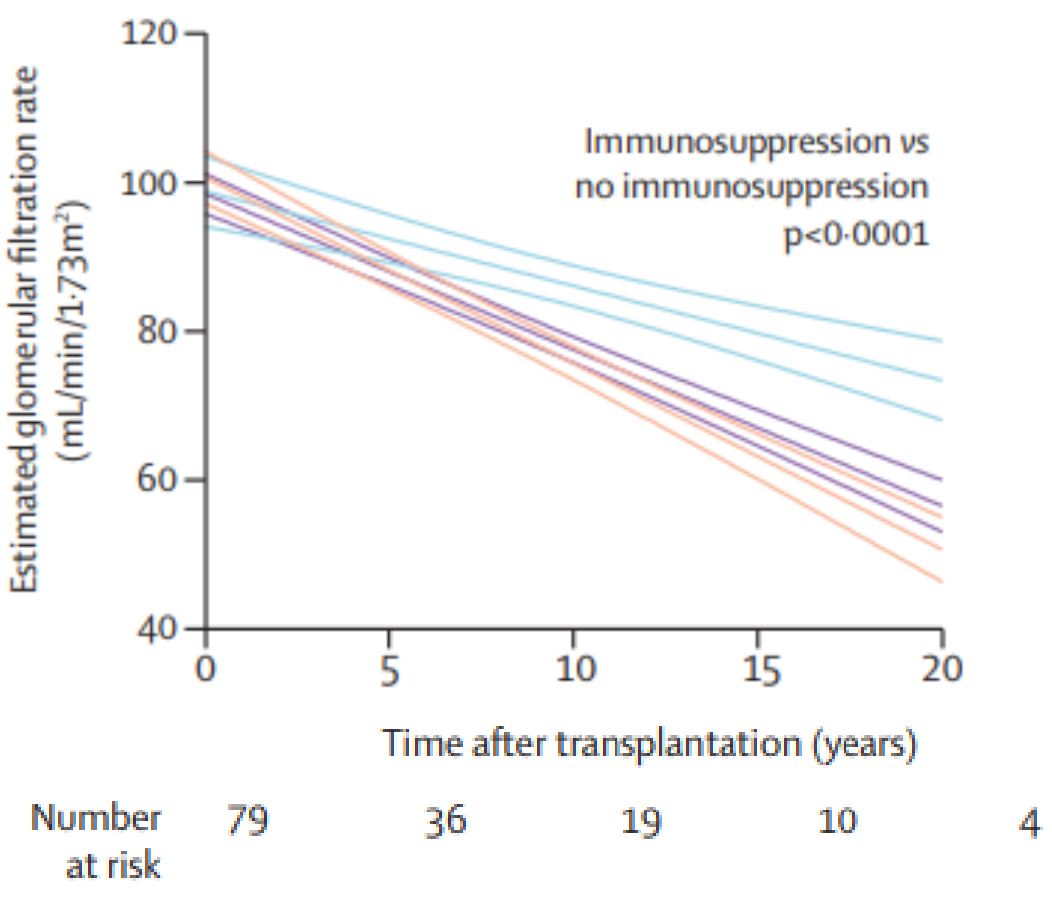
-effetti collaterali della terapia immunosoppressiva (infezioni, nefrotossicità, neoplasie)

-sensibilizzazione antigeni HLA

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*





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

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*

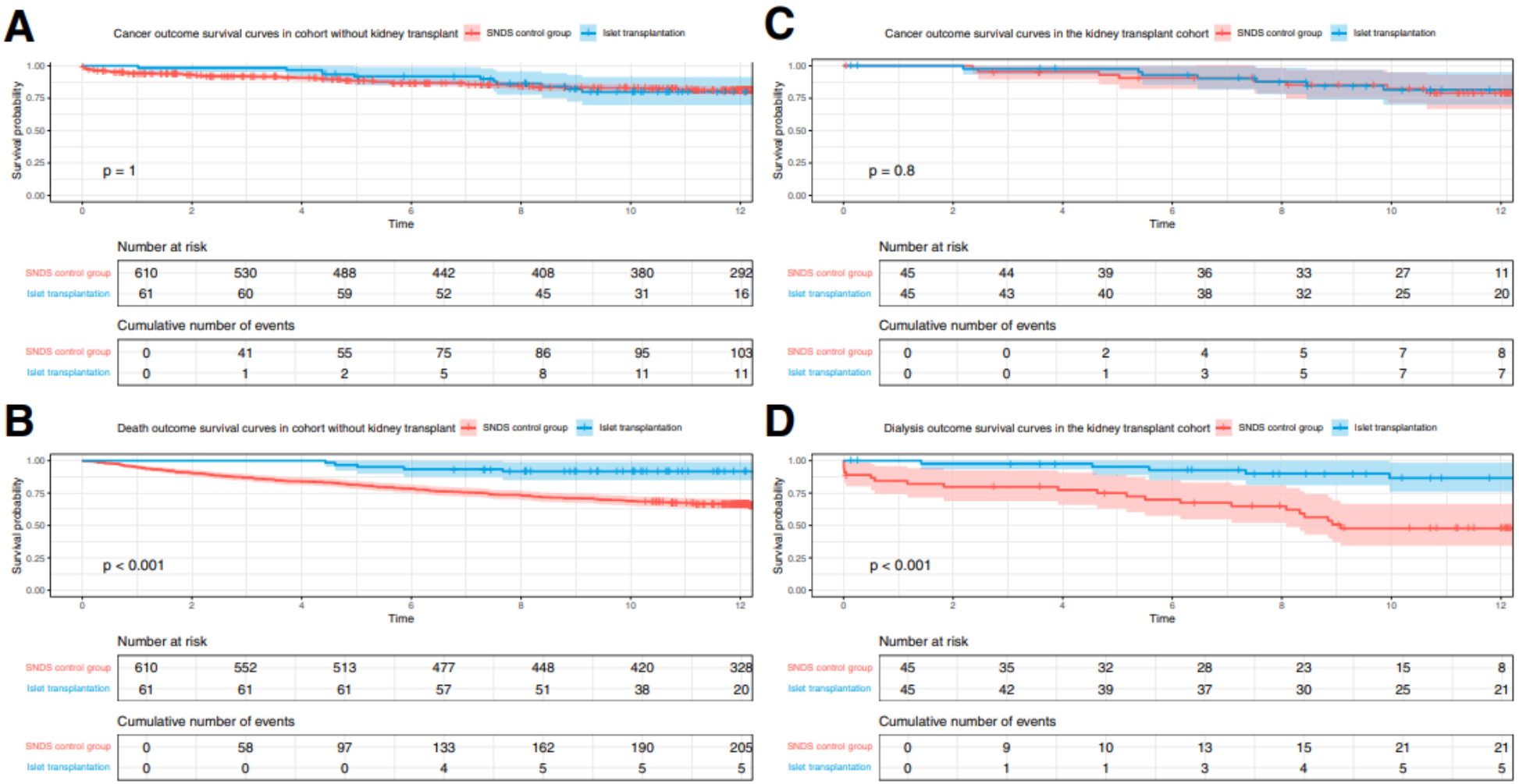
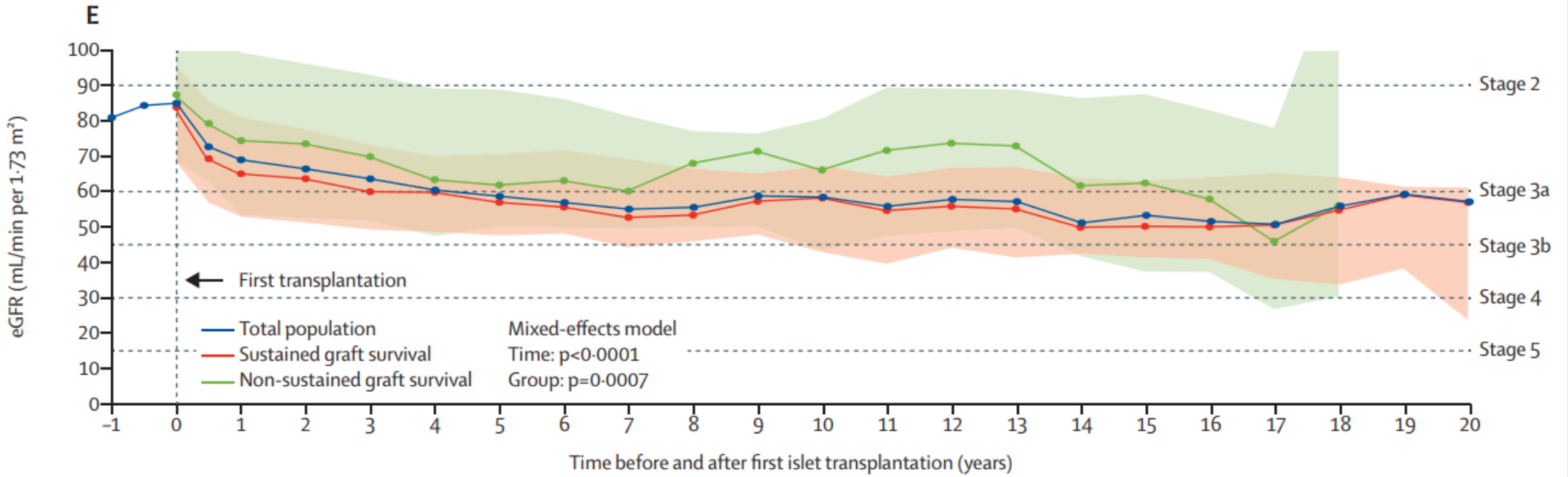


Figure 2—Kaplan-Meier survival curves of the secondary cancer (*A*) and death (*B*) outcomes in the ITA group and the secondary cancer (*C*) and dialysis (*D*) outcomes in the IAK group. Time is given in years.


E
eGFR (mL/min per 1·73 m²)
100
90
80
70
60
50
40
30
20
10
0
Stage 2
Stage 3a
Stage 3b
Stage 4
Stage 5
First transplantation
Total population
Sustained graft survival
Non-sustained graft survival
Mixed-effects model
Time: p<0·0001
Group: p=0·0007
–1
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
Time before and after first islet transplantation (years)

frontiers | Frontiers in Transplantation
TYPE Review
PUBLISHED 20 March 2025
DOI 10.3389/frtra.2025.1514956

TABLE 1 Immunosuppressive and anti-inflammatory drugs used in islet transplantation and associated mechanism of action (MoA).

Brand name/ pharma name	Route of administration/ formulation	Class	MoA	Notable side effects	Reference
Rapamune/Rapamycin (sirolimus)	Oral tablet and oral solution	mTOR inhibitor	Arrest T cell activation and proliferation by inhibiting progression from G1 to S phase	Latent viral infections Nephrotoxicity Hyperlipidemia	(38)
Prograf/Tacrolimus	Oral capsules and intravenous use	Calcineurin inhibitor	Inhibits IL-2 receptor expression and nitric oxide release on T cells	Increased risk of cancer Increased risk of infection	(39)
Zinbryta/Daclizumab (anti-CD25)	Subcutaneous use	IL-2 receptor blocking antibody	Binds to CD25 and prevents IL-2 mediated T cell activation	Autoimmune liver problems Inflammatory brain disorders	(40)
Thymoglobulin/ Antithymocyte globulin	Intravenous use	Immunoglobulin	T cell clearance and modulation of T cell activation	Anaphylactic reaction Low platelet and white blood cell count	(41)
Medrol/ Methylprednisolone	Intravenous and Intramuscular use	Glucocorticoid	Binds to the intracellular glucocorticoid receptor and blocks the transcription of inflammatory genes in immune cells	Gastritis Gastrointestinal bleeding	(42)
CellCept/Mycophenolate mofetil	Oral tablets, oral suspension and intravenous use	IMPDH inhibitor	Prevents guanine nucleotides synthesis critical for T and B cell proliferation	Low blood cell count Stomach problems	(43)
Kineret/Anakinra	Subcutaneous use	IL-1 receptor antagonist	Binds to the IL-1 receptor on macrophages and lymphocytes and suppresses inflammation	Worsening of rheumatoid arthritis Upper respiratory tract infection	(44)
Enbrel/Etanercept	Subcutaneous use	TNF blocker	Prevents TNF cytokines from binding its receptor on macrophages and lymphocytes	Infection risk Injection site reaction	(45)

OPEN ACCESS
EDITED BY
Anca Dana Dobrian,
Eastern Virginia Medical School, United States
REVIEWED BY
Alice Tomei,
University of Miami, United States
Joseph Sushil Rao,
University of Minnesota Medical Center, United States
Derfogail Delcassian,
University of California, Berkeley, United States

From Edmonton to Lantidra and beyond: immunoengineering islet transplantation to cure type 1 diabetes

El Hadji Arona Mbaye[1], Evan A. Scott[1,2] and Jacqueline A. Burke[3]*
[1]Department of Biomedical Engineering, Northwestern University, Evanston, IL, United States, [2]Department of Biomedical Engineering, NanoSTAR Institute, University of Virginia School of Medicine, Charlottesville, VA, United States, [3]SNC Therapeutics Inc., Evanston, IL, United States

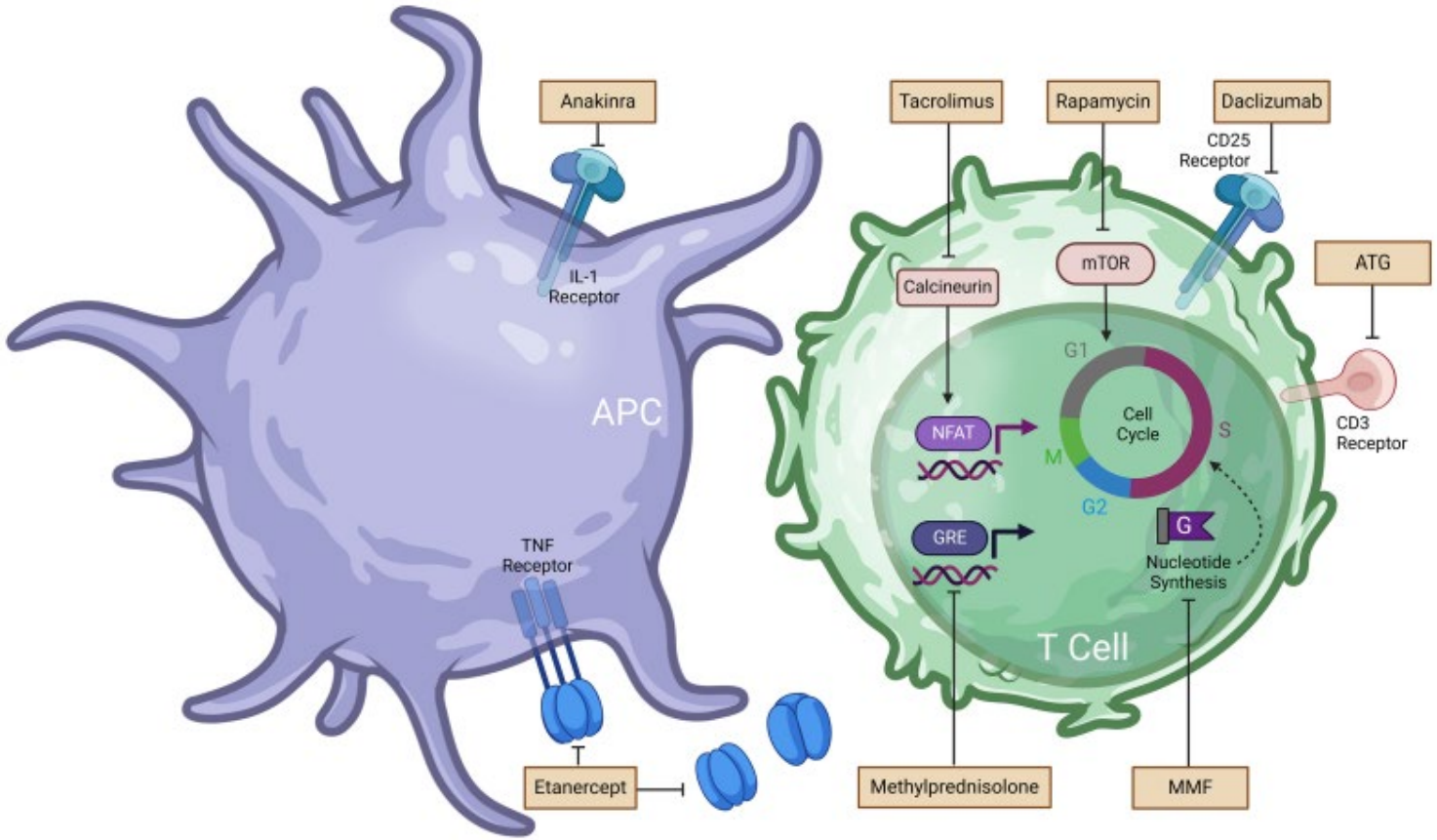


FIGURE 1
Immunosuppressive and anti-inflammatory drugs used in islet transplantation and associated mechanism of action (MoA). Further details regarding MoA are summarized in Table 1. Anakinra prevents the binding of interleukin-1 (IL-1) to the IL-1 receptor. Etanercept blocks the action of tumor necrosis factor (TNF). Tacrolimus inhibits calcineurin activity and downstream nuclear factor of activated T cells (NFAT), resulting inhibition of T cell activation. Rapamycin binds to the protein kinase mammalian target of rapamycin (mTOR) and arrest T cell activation and proliferation. Daclizumab binds to the CD25 receptor on T cells and impedes IL-2 mediated T cell activation. Methylprednisolone hinders the transcription of inflammatory genes. Mycophenolate mofetil (MMF) prevents *de novo* guanine nucleotides synthesis required for T cell and B cell proliferation.

Islet source

Deceased donors

Challenges
- Insufficient yield
- Low purity

Solutions
- Optimizing donor selection criteria
- Optimizing enzymatic digestion, tissue recovery and purification

Xenotransplant

Challenges
- Strong immune responses
- Infectious complications (i.e., zoonosis)

Solutions
- Gene-editing
- Human-animal chimeras
- Cellular encapsulation

Pluripotent stem cells

Challenges
- Cost and scalability
- Uncertain potential for autoimmunity and malignancy
- Suboptimal metabolic capacity

Solutions
- Stem cell master cell banks
- Immature cell products, in vivo terminal differentiation
- Cell-sorting to improve purity
- Gene-editing

Islet culture

Cell death

Challenges
- Islet loss
- Contamination

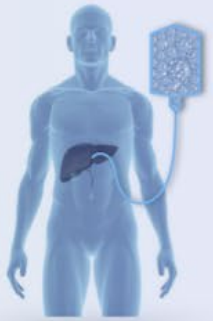
Solutions
- Anti-apoptotic agents
- Improved culture media
- Microfluidic perfusion

Infusion

IBMIR

Challenges
- Islet loss
- Multiple donors
- Micro thrombosis

Solutions
- Anticoagulation
- Anti-inflammatory agents
- Complement inhibitors
- Alternative implantation sites



Procedural complications

Challenges
- Bleeding
- Portal vein thrombosis

Solutions
- Thrombostatic paste
- Low packed cell volume → increasing islet purity
- Alternative implantation sites

Engraftment

Hypoxia

Challenges
- Delayed vascularization
- Low-oxygen tension

Solutions
- Islet preconditioning
- Pre-vascularization strategies
- Pro-angiogenic agents
- Gene and/or soluble factor delivery
- *In situ* oxygen delivery or generation

Immune response

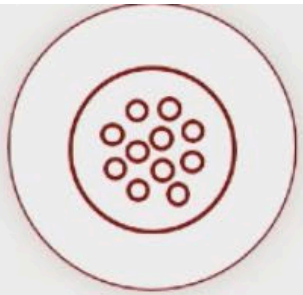
Autoimmunity

Alloimmunity

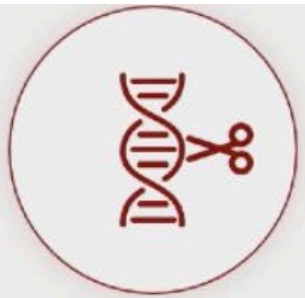
Challenges
- Autoimune recurrence
- Alloimmune responses
- Reciprocal facilitation
- Sensitization
- Chronic immunosuppression (systemic and local adverse effects)

Solutions
- Cell-based therapies (i.e., Tregs)
- Cellular encapsulation
- Gene-editing
- Immune reset (i.e., HSCT)
- Immunosuppression minimization strategies (e.g., Treg-centric)
- Personalized hiPSC-derived β-cell replacement therapies

In prospettiva



Encapsulation (physical barrier)



Immune evasion via gene editing

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

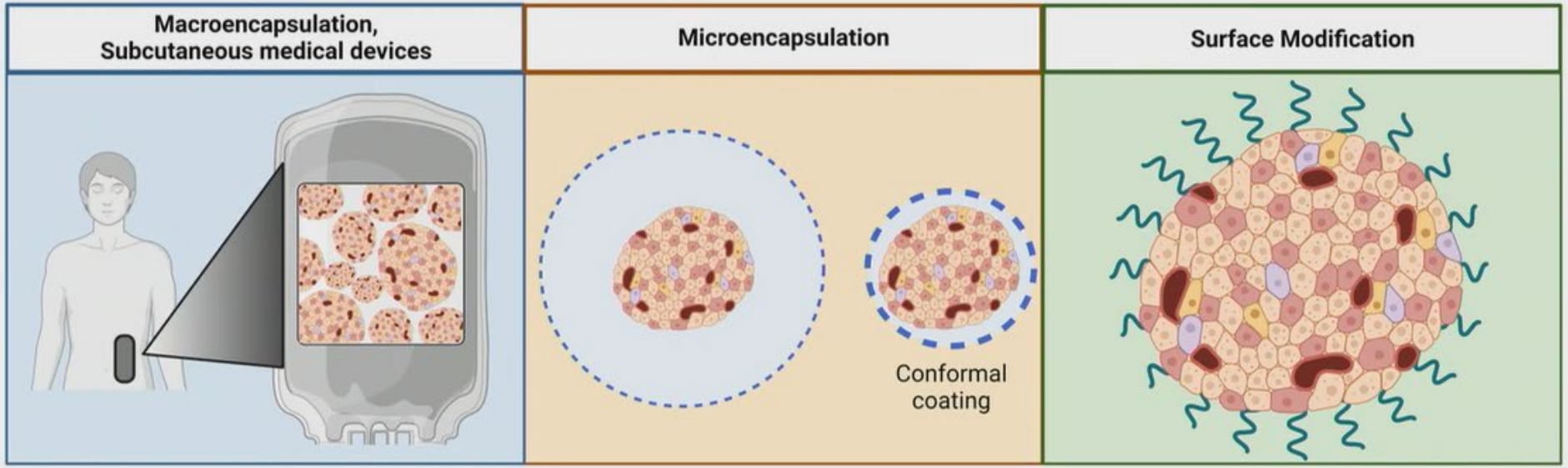
Key inclusion criteria: Adults with T1D (no recurrent SHEs)
Locations: USA (Miami, Chicago, Boston, Penn, Pittsburgh, Wisconsin) Canada (Toronto, Vancouver, Edmonton), Europe (Dresden, Milan, Leiden, Geneva, Oxford, Newcastle)

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)

Islet Encapsulation Strategies – Different Designs

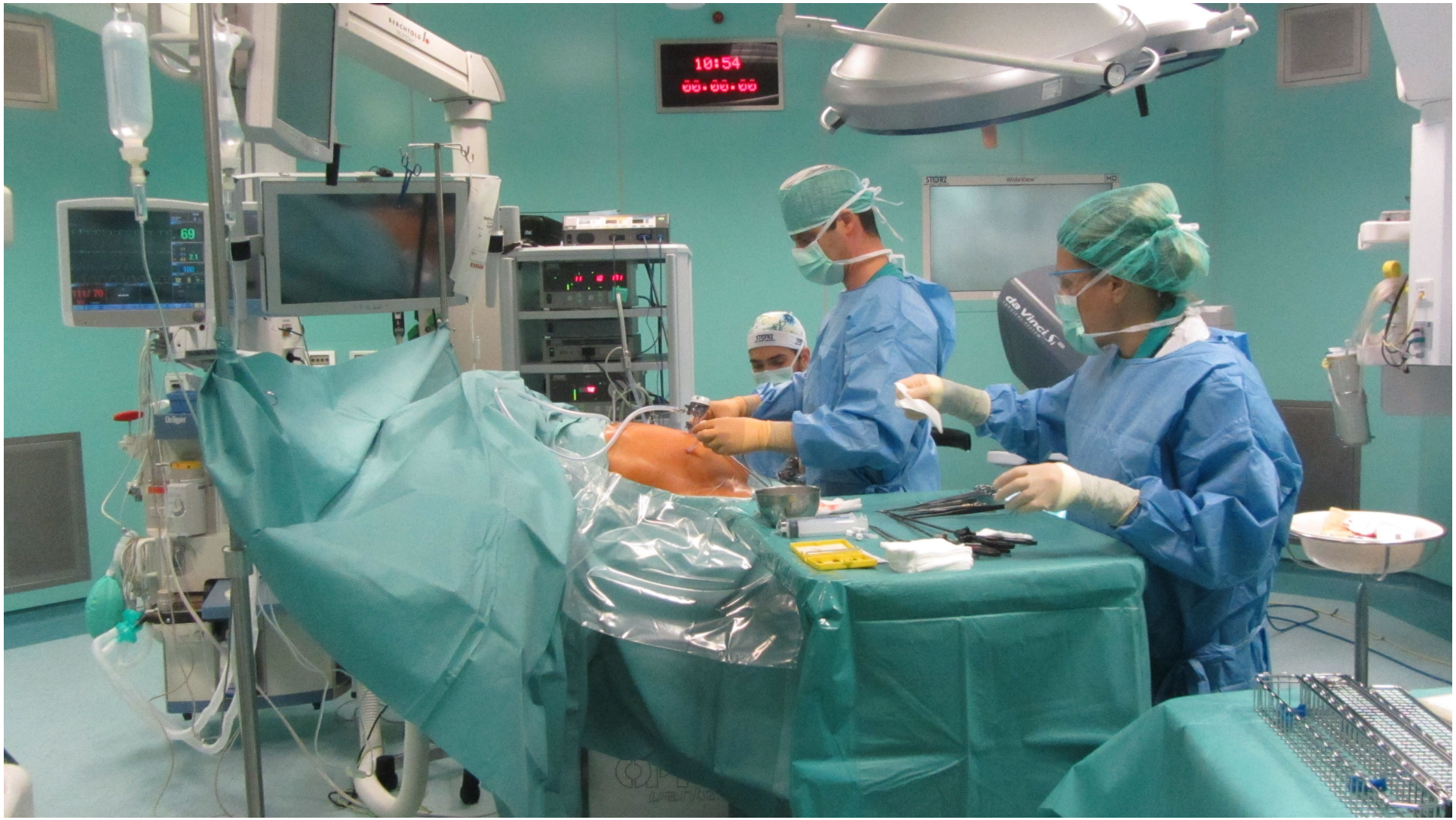


Adapted from SoRelle *et al.*
Intech. 2011

CONGRESSO REGIONALE
SID-AMD MARCHE 2025

SID
Società Italiana di Diabetologia

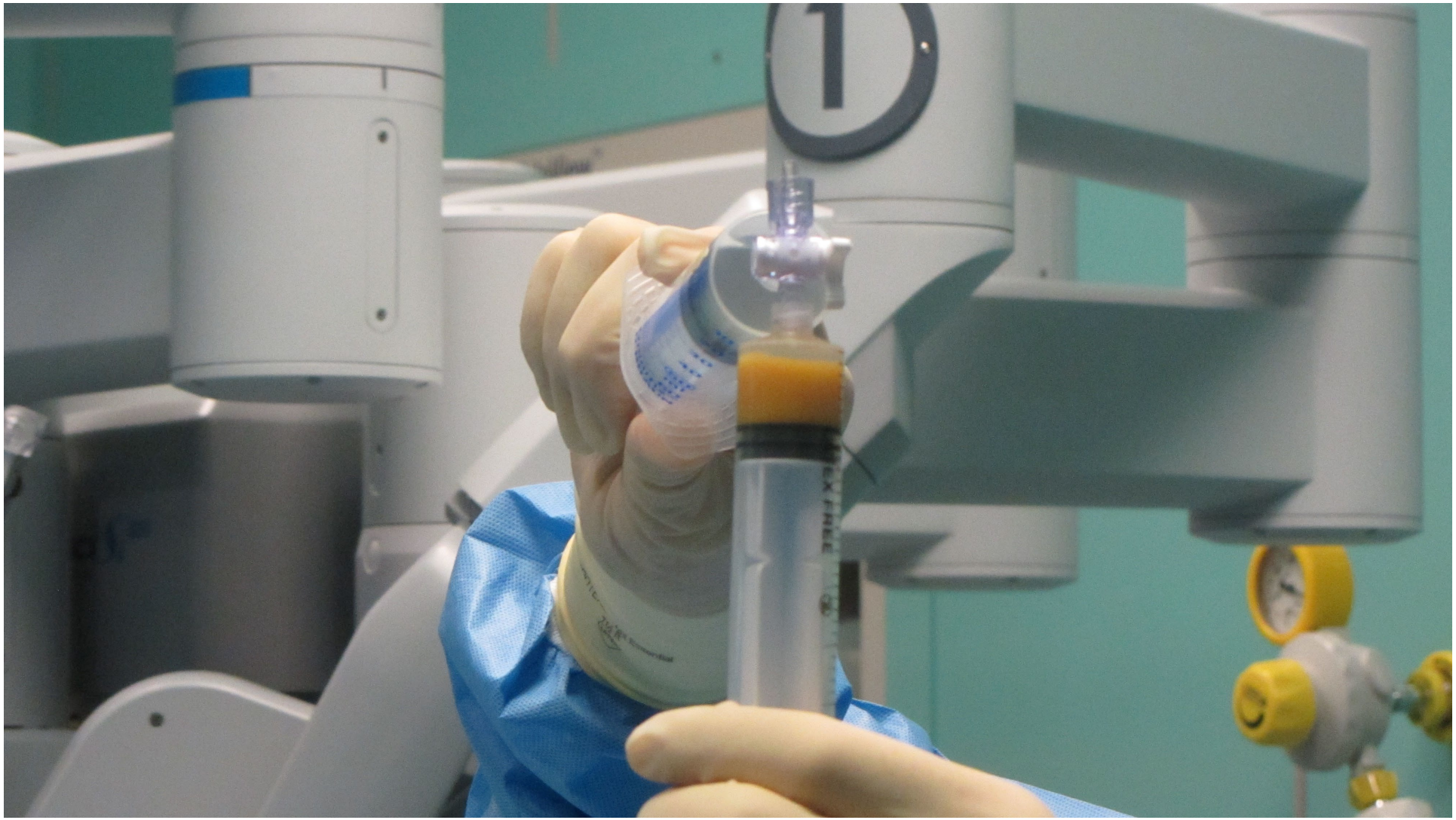
AMD
MARCHE
ASSOCIAZIONE MEDICI DIABETOLOGI



CONGRESSO REGIONALE
SID-AMD MARCHE 2025

SID
Società Italiana di Diabetologia

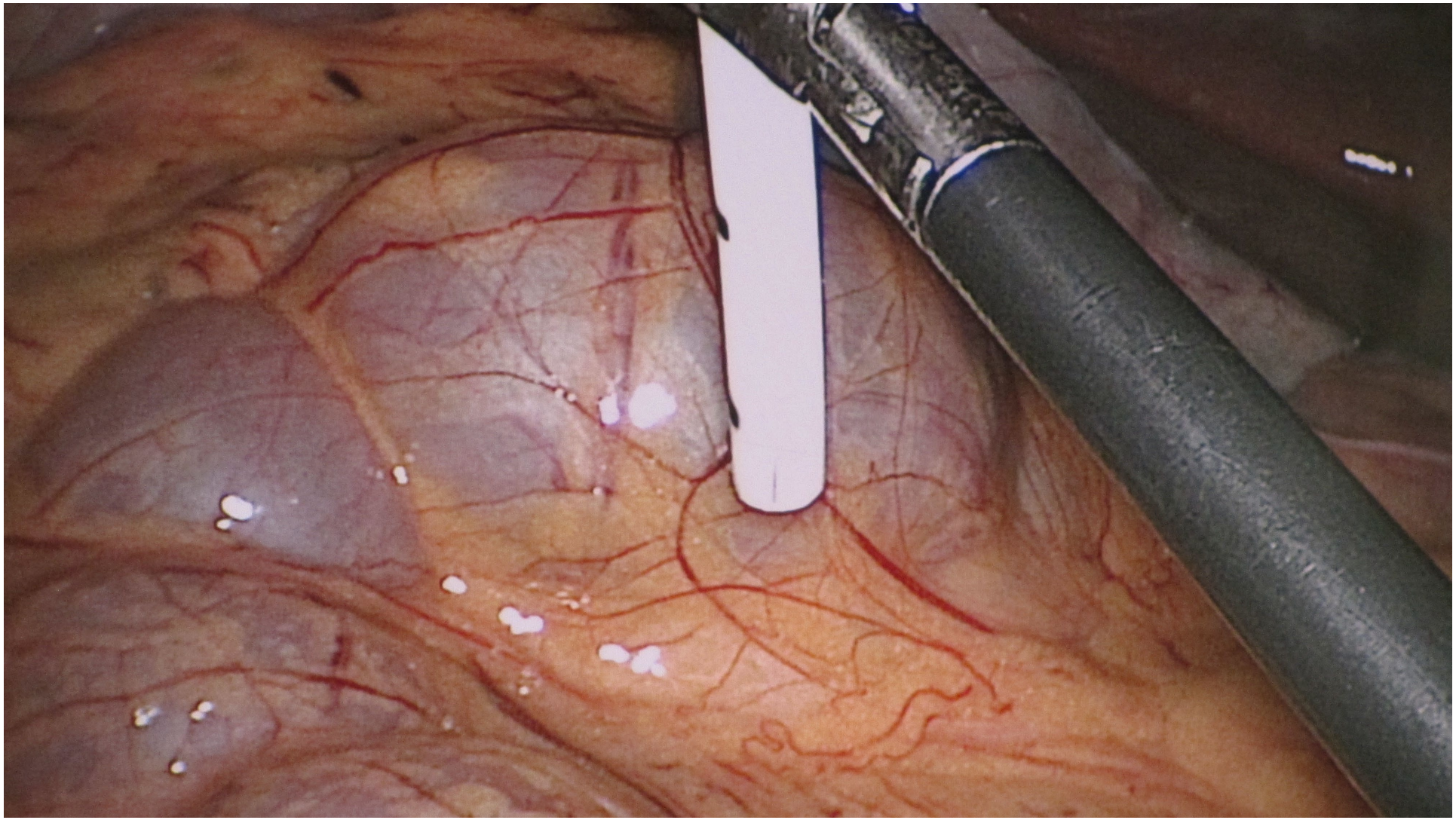
AMD
MARCHE
ASSOCIAZIONE MEDICI DIABETOLOGI

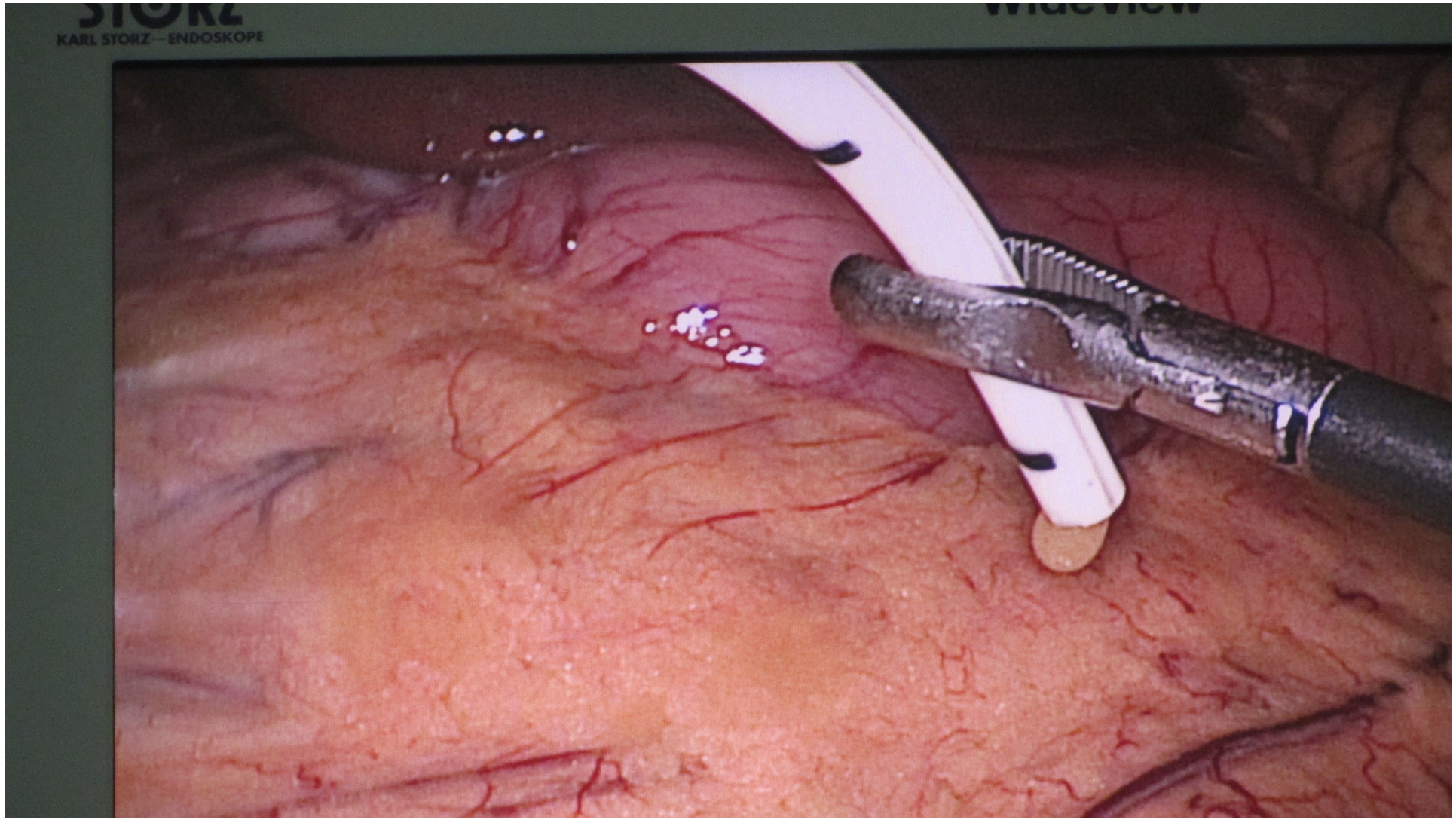


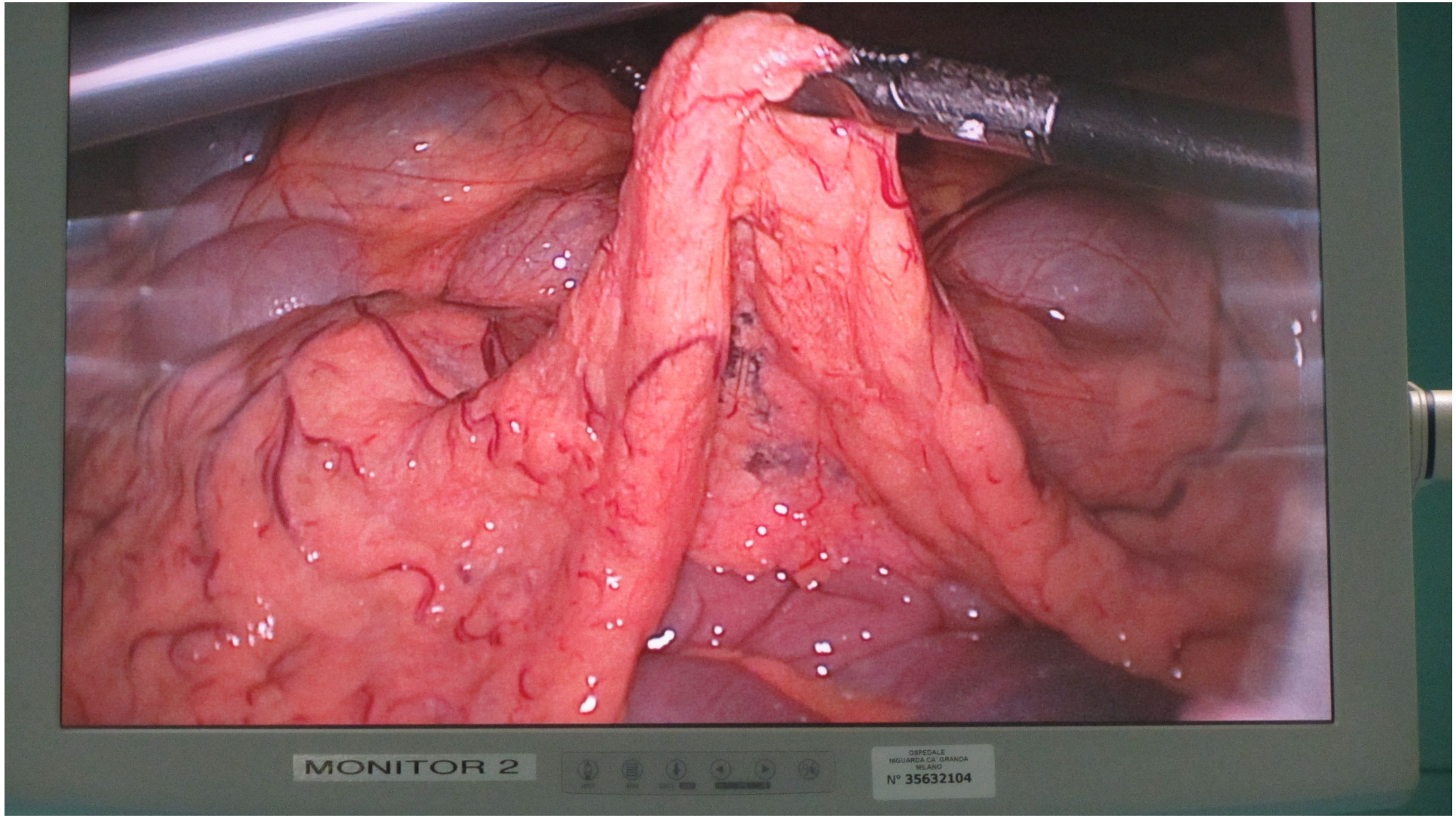
CONGRESSO REGIONALE
SID-AMD MARCHE 2025

SID
Società Italiana di Diabetologia

AMD
MARCHE
ASSOCIAZIONE MEDICI DIABETOLOGI



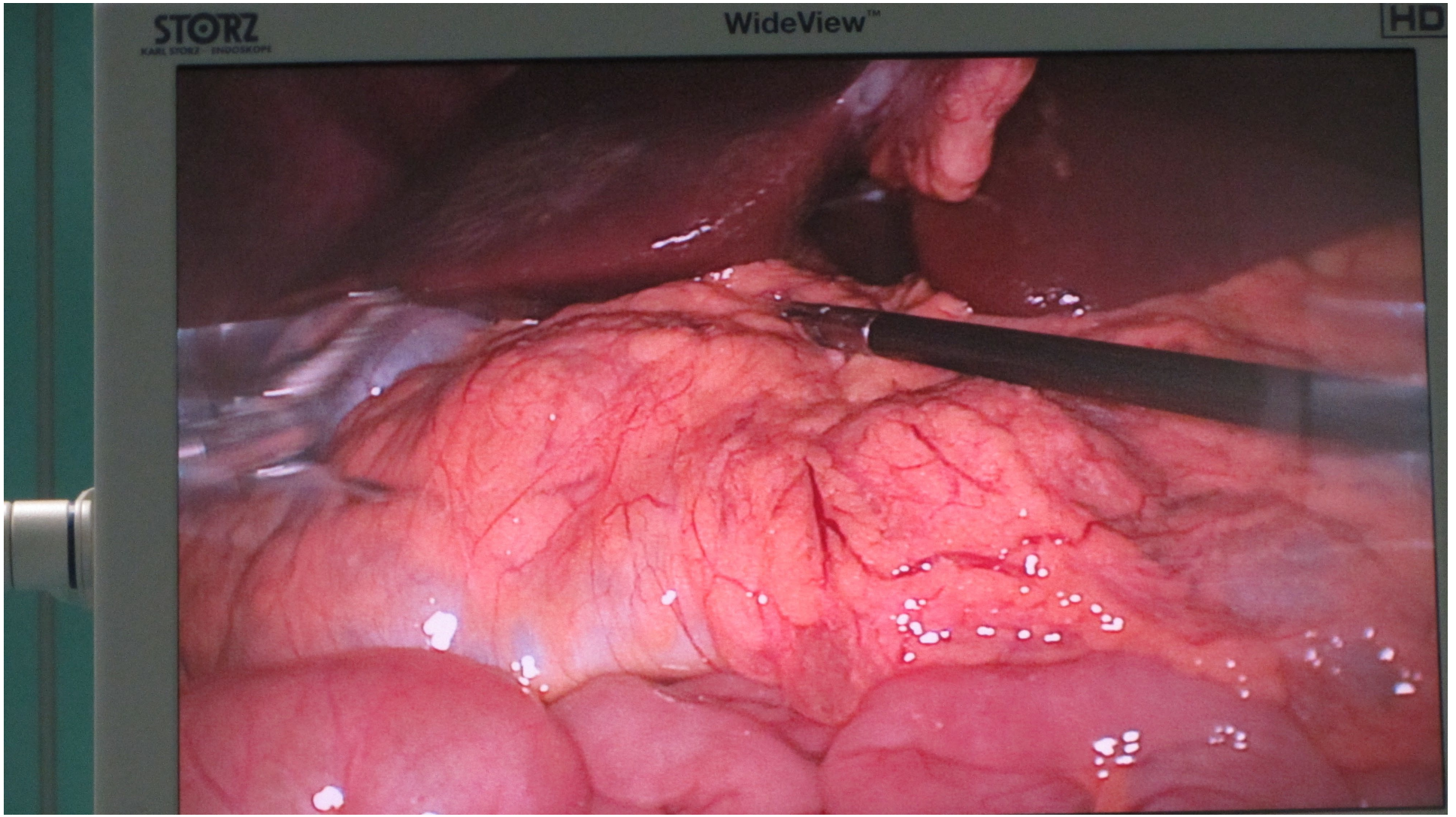

KARL STORZ — ENDOSKOPE


MONITOR 2
OSPEDALE
NIGUARDA CA' GRANDA
MILANO
N° 35632104

CONGRESSO REGIONALE
SID-AMD MARCHE 2025

SID
Società Italiana di Diabetologia

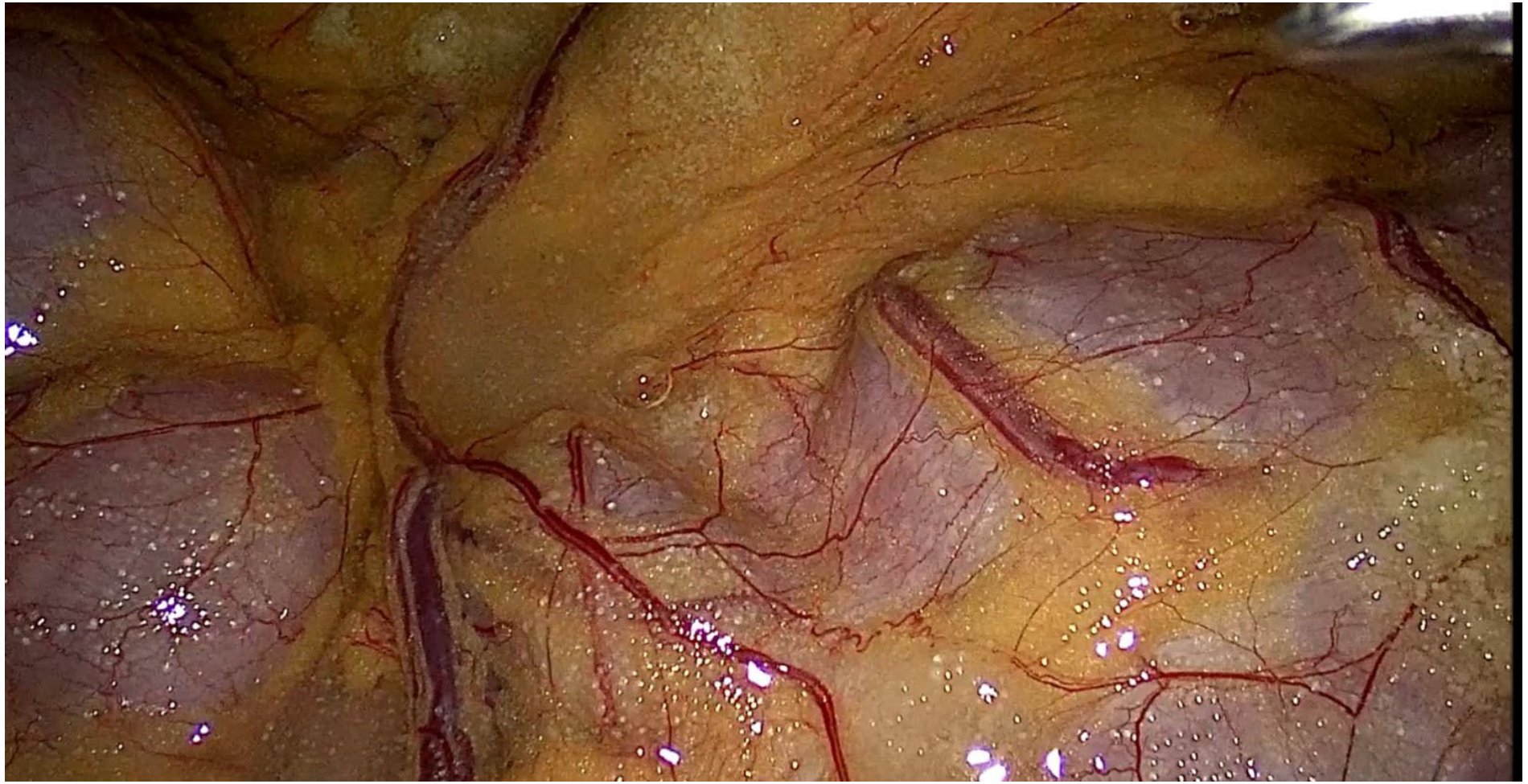
AMD
MARCHE
ASSOCIAZIONE MEDICI DIABETOLOGI



CONGRESSO REGIONALE
SID-AMD MARCHE 2025

SID
Società Italiana di Diabetologia

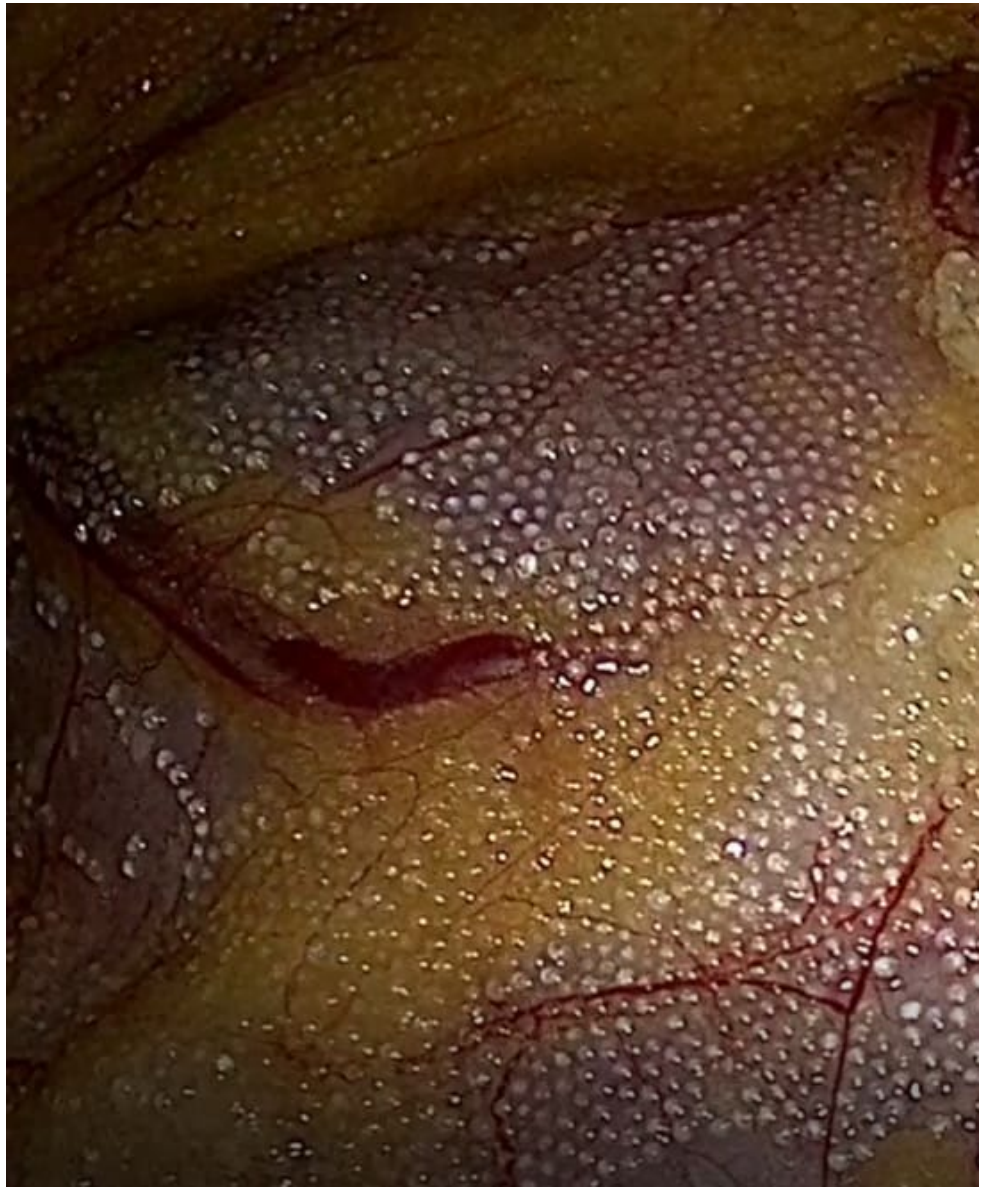
AMD
MARCHE
ASSOCIAZIONE MEDICI DIABETOLOGI



CONGRESSO REGIONALE
SID-AMD MARCHE 2025

SID
Società Italiana di Diabetologia

AMD
MARCHE
ASSOCIAZIONE MEDICI DIABETOLOGI



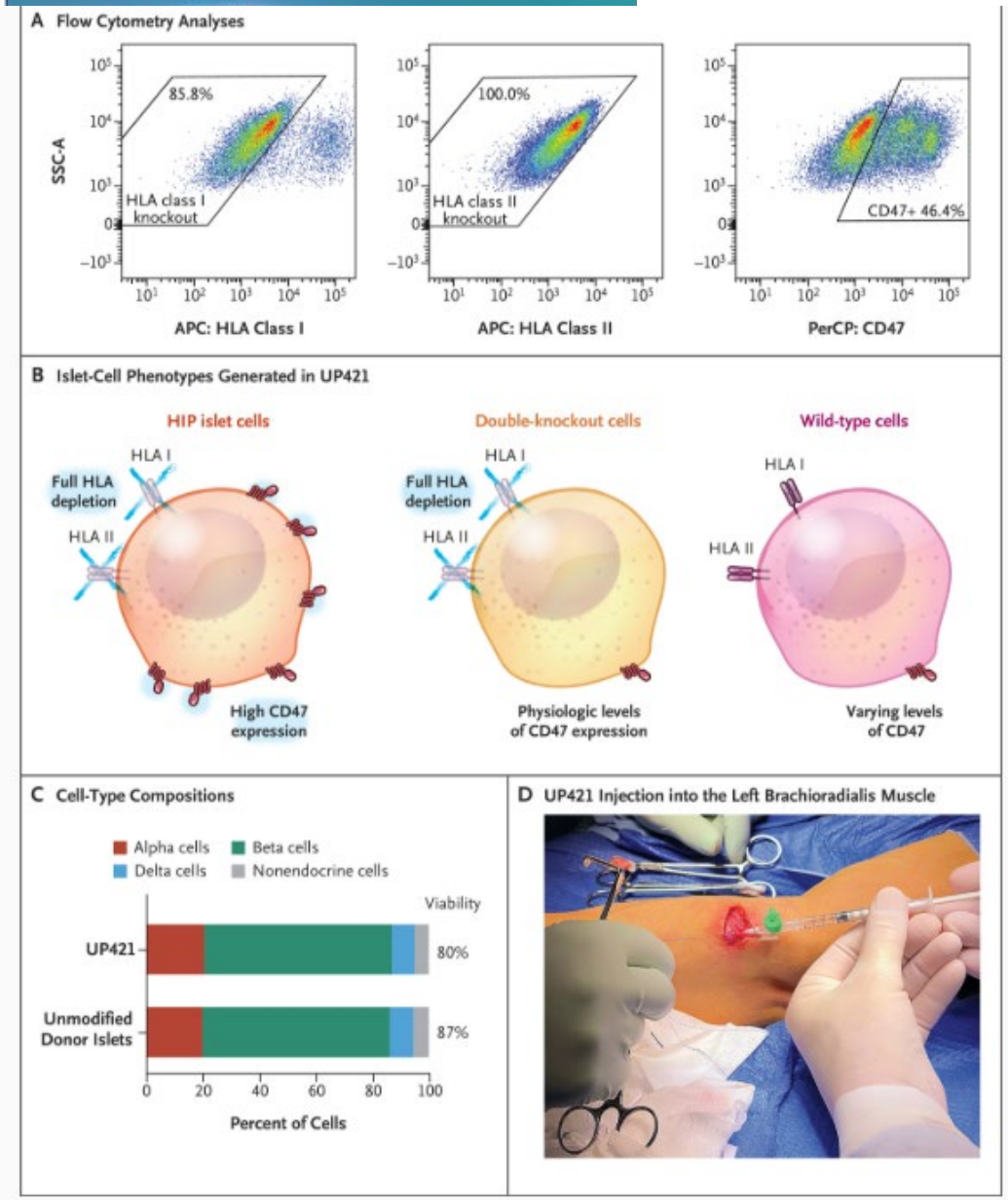
The NEW ENGLAND JOURNAL of MEDICINE

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

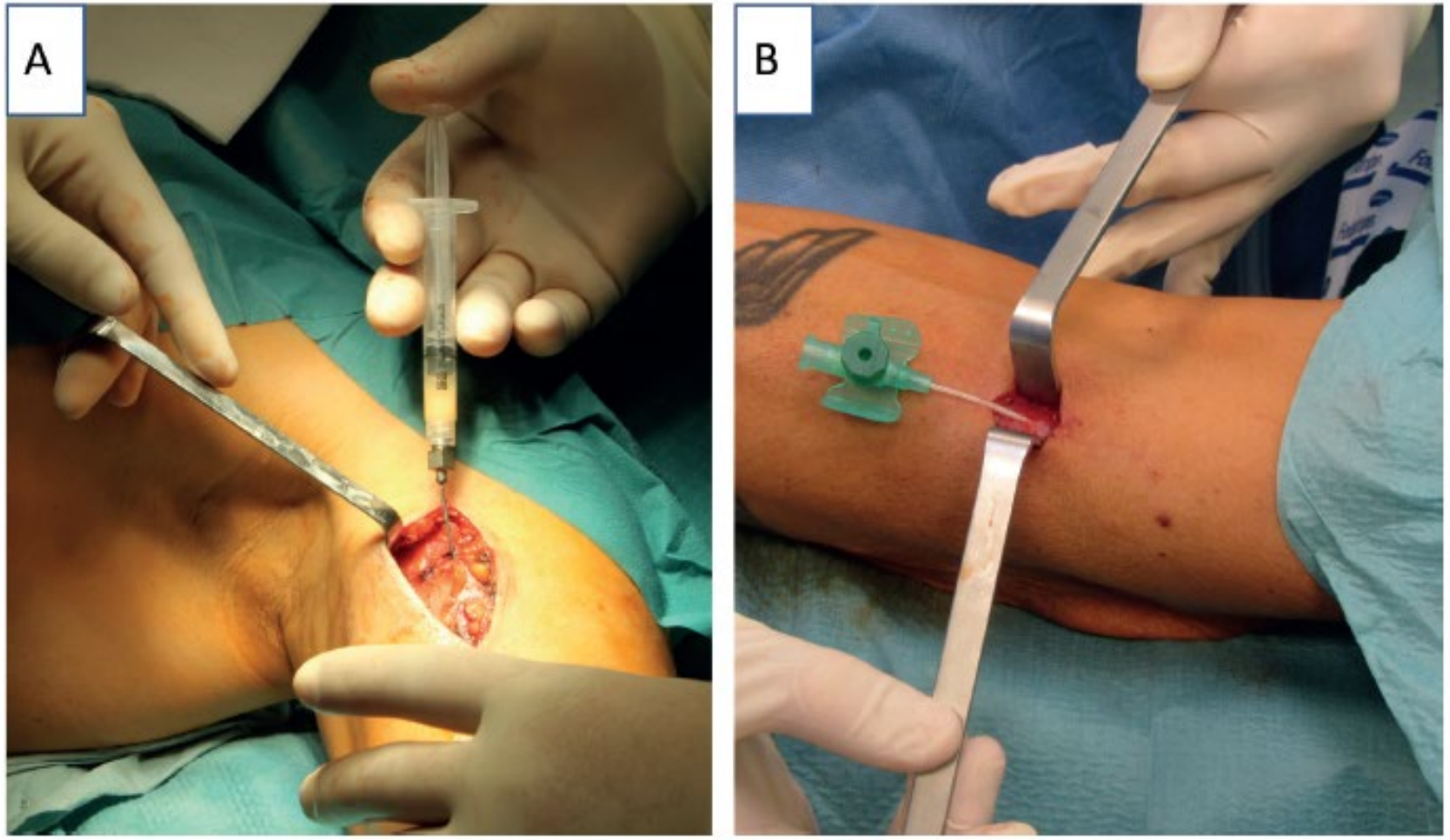
Published August 4, 2025 | N Engl J Med 2025;393:887-894 | DOI: 10.1056/NEJMoa2503822 | VOL. 393 NO. 9

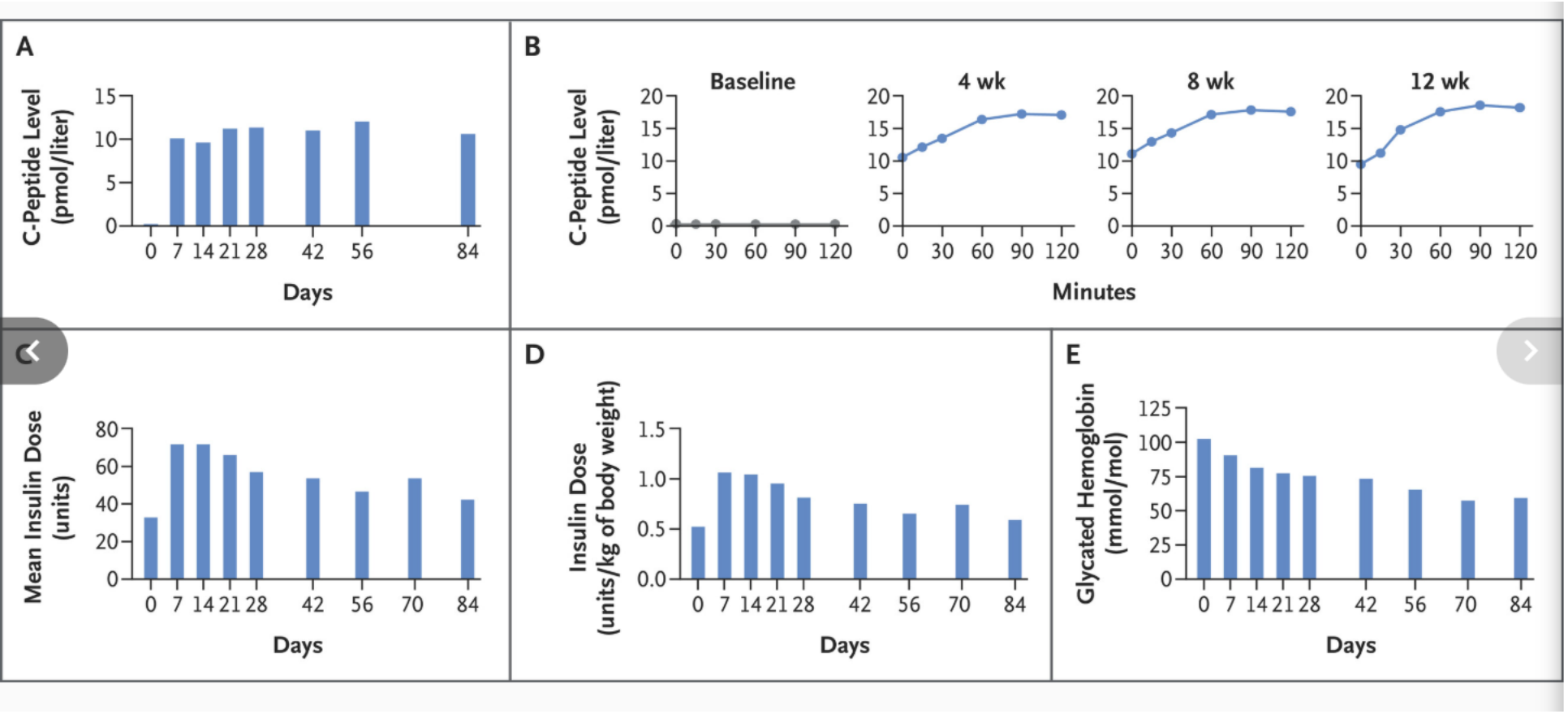


European Review for Medical and Pharmacological Sciences 2018; 22: 1731-1736

Intramuscular islet allotransplantation in type 1 diabetes mellitus

F. BERTUZZI[1], G. COLUSSI[2], A. LAUTERIO[3], L. DE CARLIS[3]

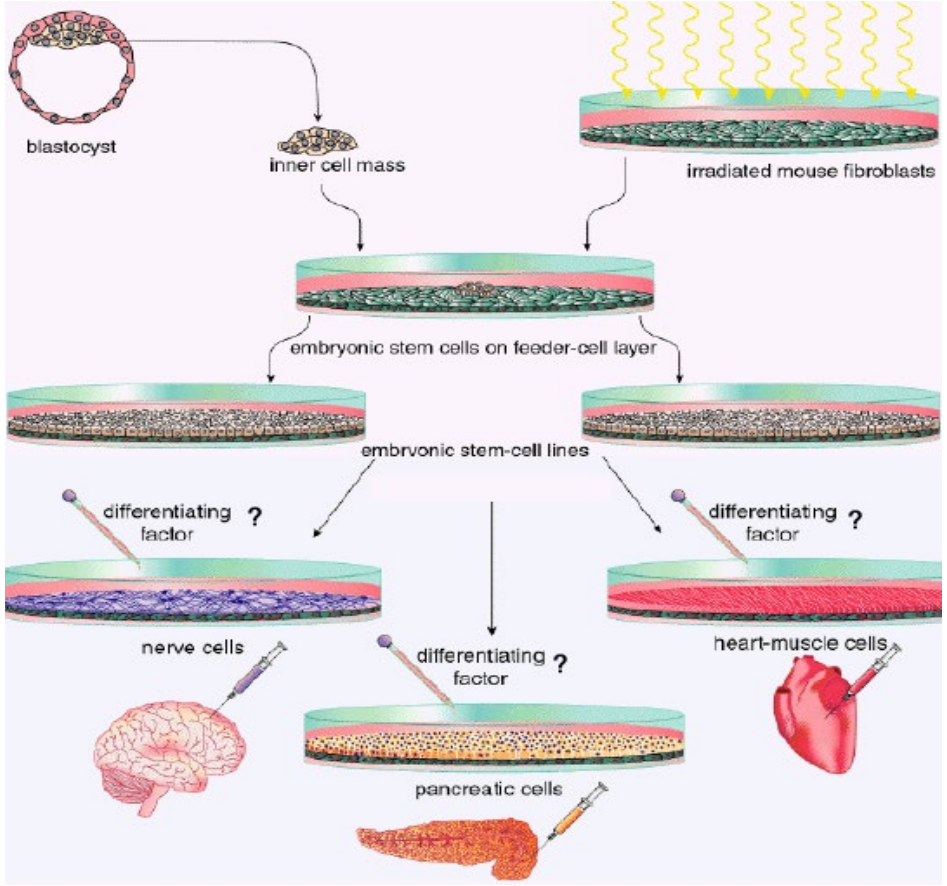


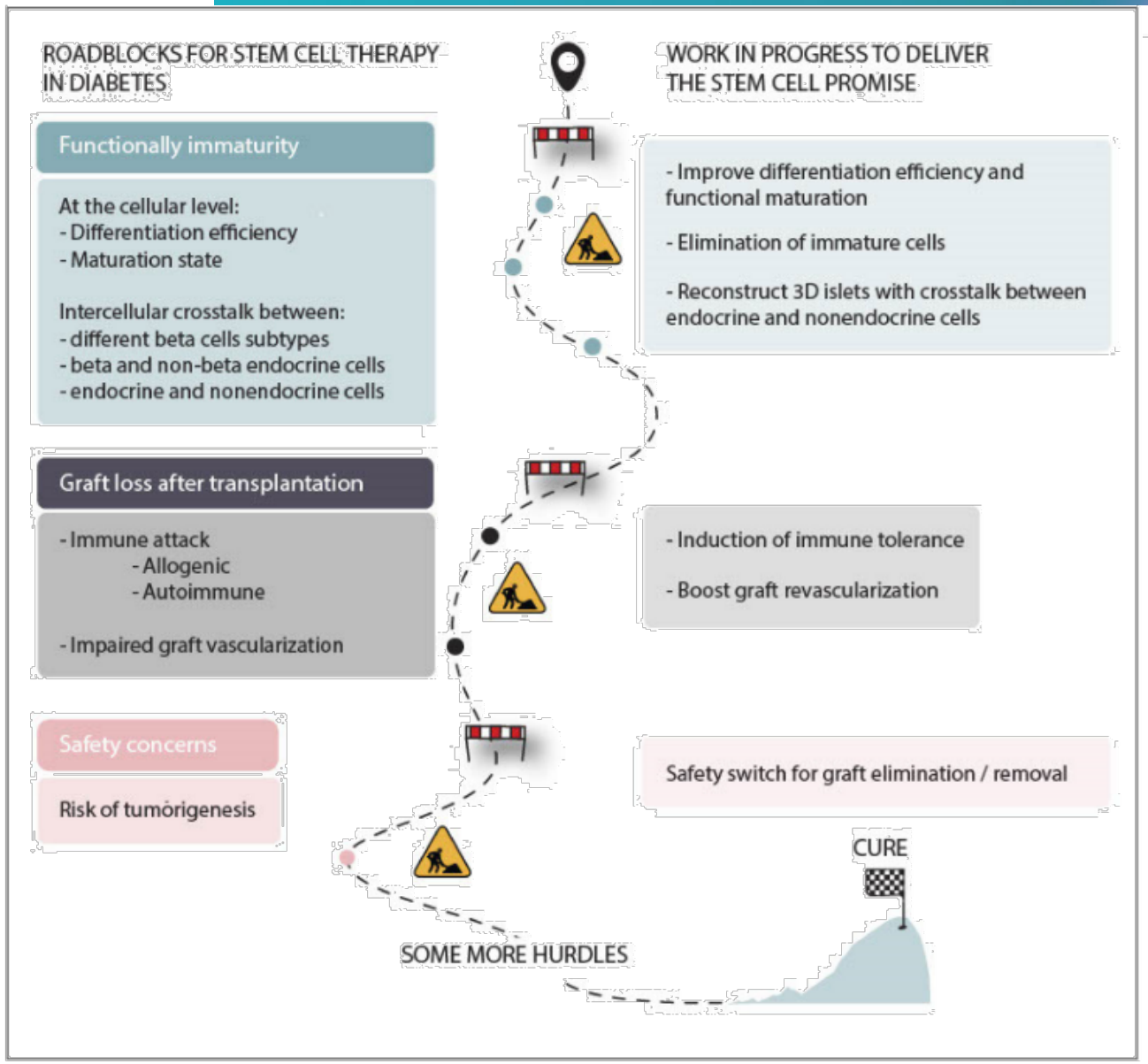


Postoperative Persistence and Function of HIP Islet-Cell Allografts.

Panel A shows that the participant did not have measurable C-peptide levels before receiving the UP421 islet-cell product. C-peptide levels were measured over the 12-week follow-up period with a high-sensitivity assay, which showed that the levels remained stable near or above 10 pmol per liter. Panel B shows that the participant did not have any C-peptide response to a mixed-meal tolerance test before transplantation, but at 4, 8, and 12 weeks after transplantation, an increase in the C-peptide level was observed, a finding suggestive of functional beta-cell grafts. Panels C and D show the mean insulin doses (the total dose and the dose per kilogram of body weight, respectively) that were administered during the study period. Panel E shows glycated hemoglobin levels over the 12-week follow-up period.

B) Il trapianto di cellule staminali





cells
MDPI

Review

Towards a Functional Cure for Diabetes Using Stem Cell-Derived Beta Cells: Are We There Yet?

Stephanie Bourgeois [1,†], Toshiaki Sawatani [2,†], Annelore Van Mulders [1], Nico De Leu [1,3,4], Yves Heremans [1], Harry Heimberg [1], Miriam Cnop [2,5] and Willem Staels [1,6,*]

1) Allotrapianto di stem cells embrionali

2) Autotrapianto di IPS nel diabete di tipo 2

3) Autotrapianto di IPS nel diabete di tipo 1

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*

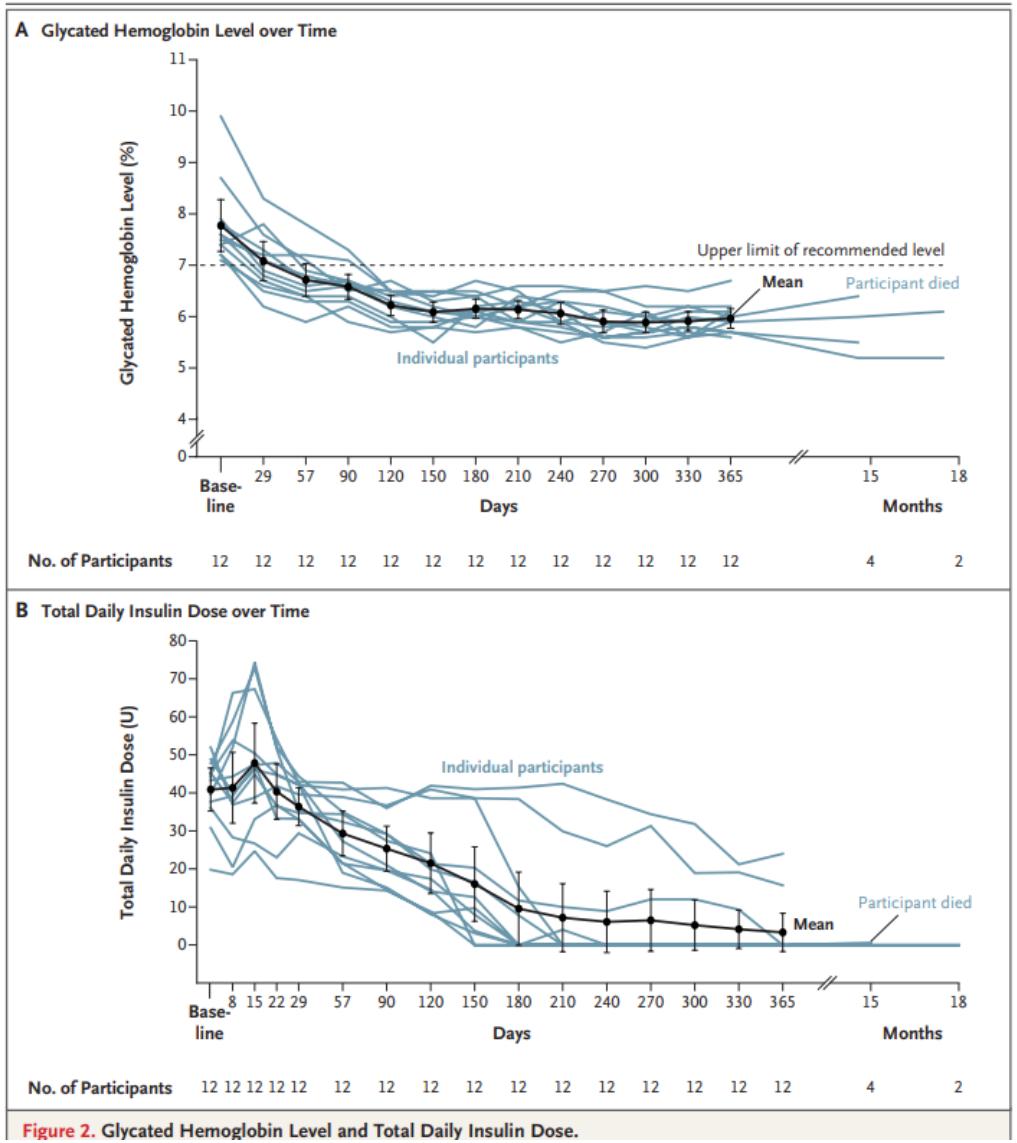
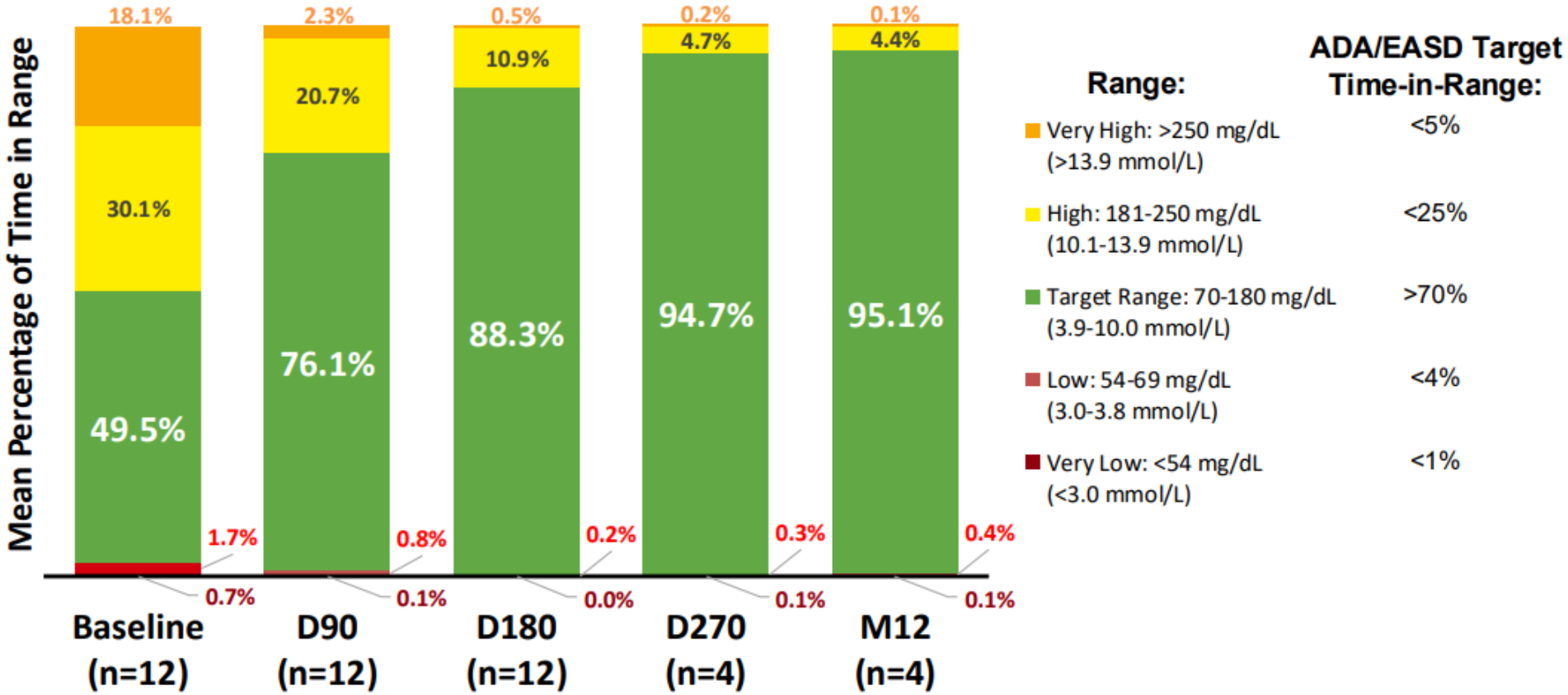


Figure 2. Glycated Hemoglobin Level and Total Daily Insulin Dose.

Mean time in range for all participants over time



erican Diabetes Association; **CGM,** continuous glucose monitoring; **D,** day; **EASD,** European Association for the Study of Diabetes; **M,** month

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

Wu et al. *Cell Discovery* (2024)10:45
https://doi.org/10.1038/s41421-024-00662-3

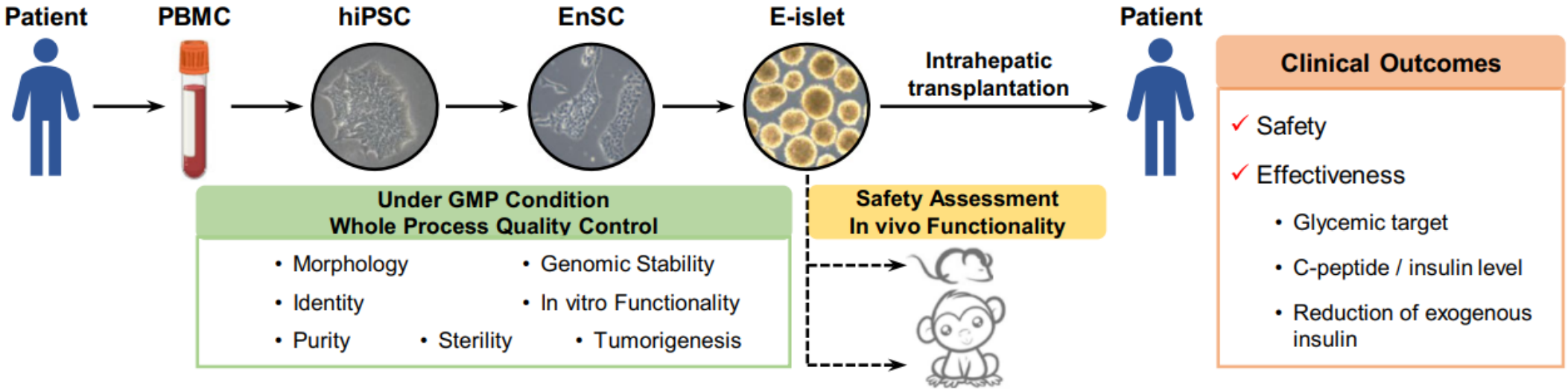
Cell Discovery
www.nature.com/celldisc

2)

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



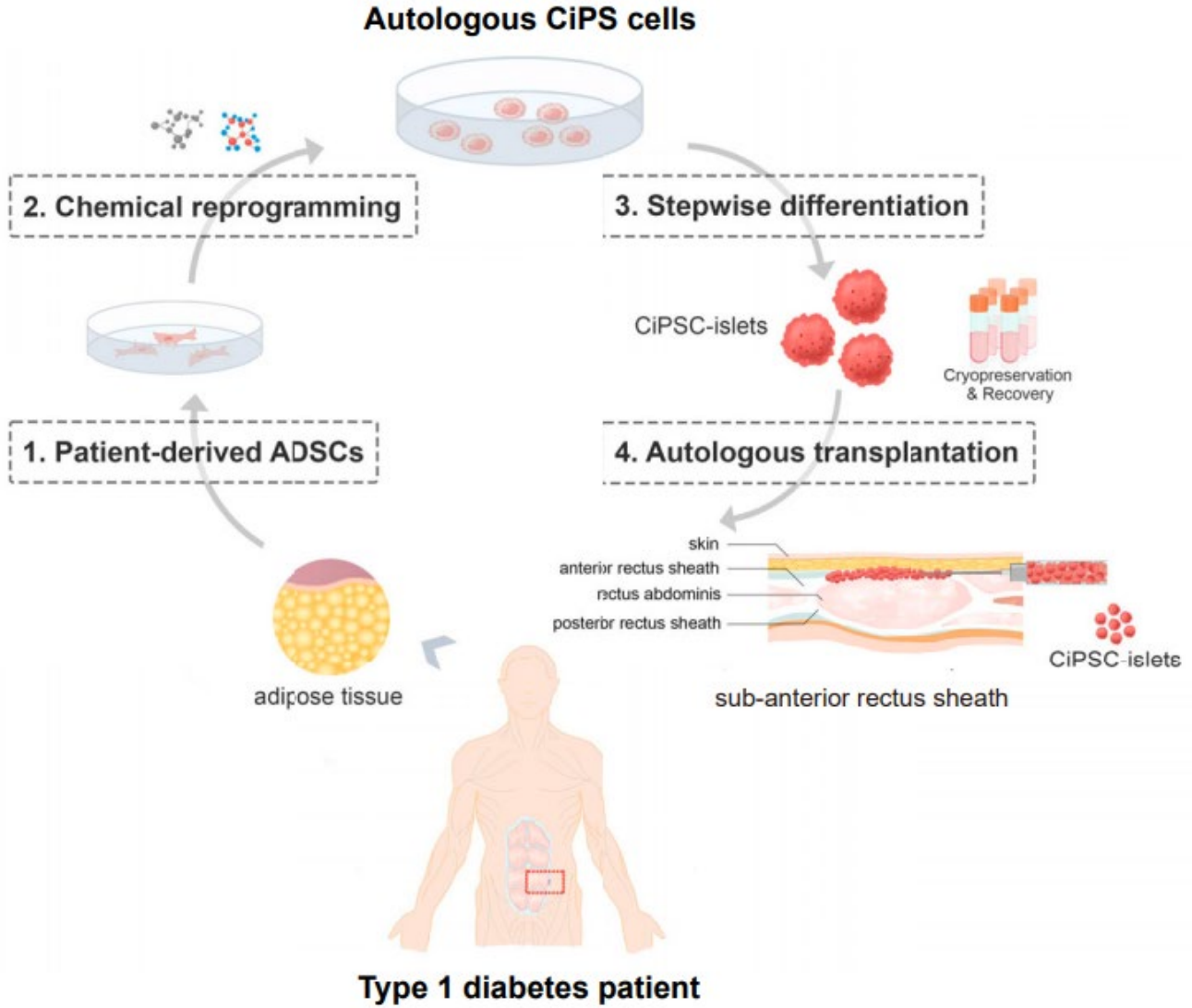
Cell

CellPress

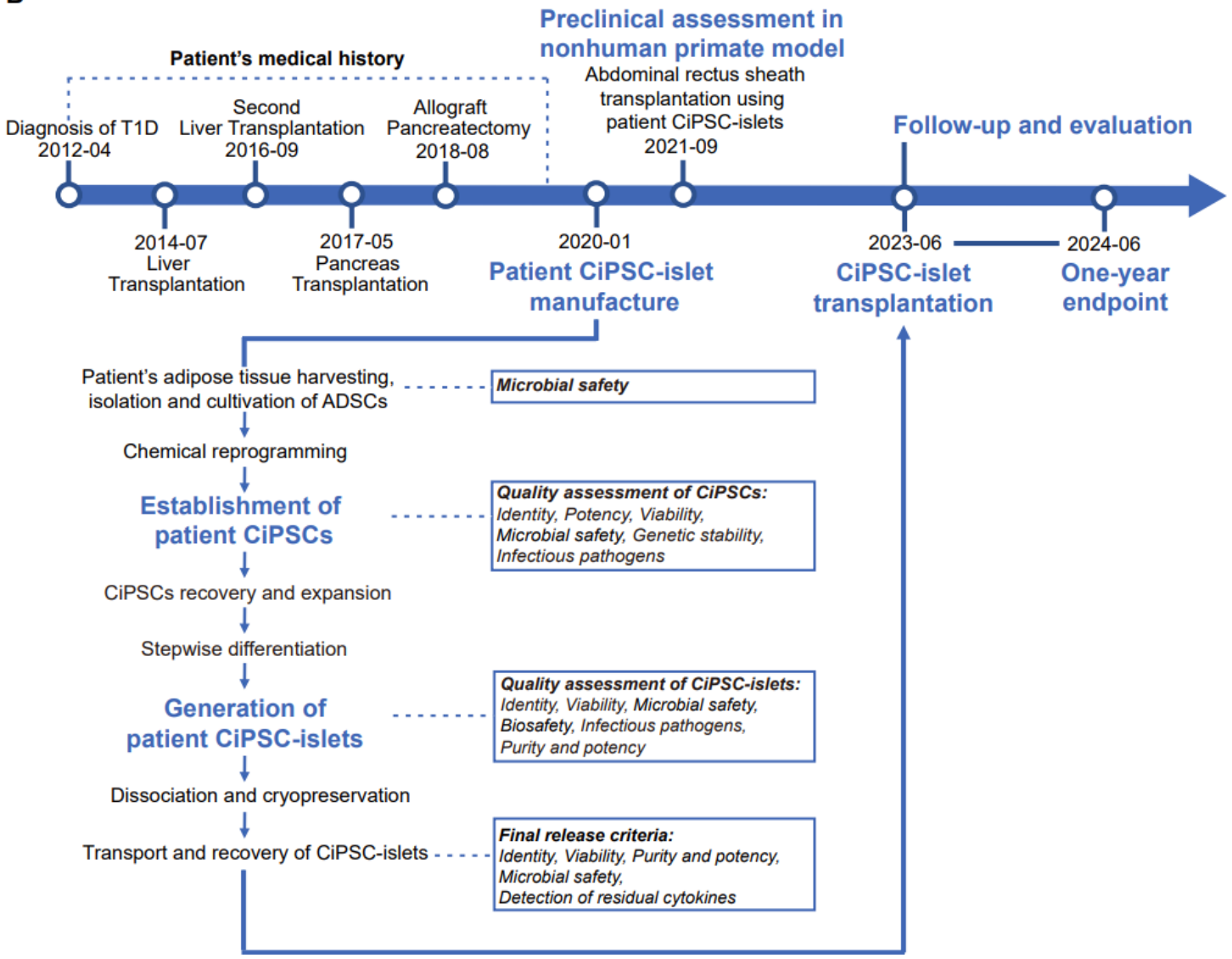
Article

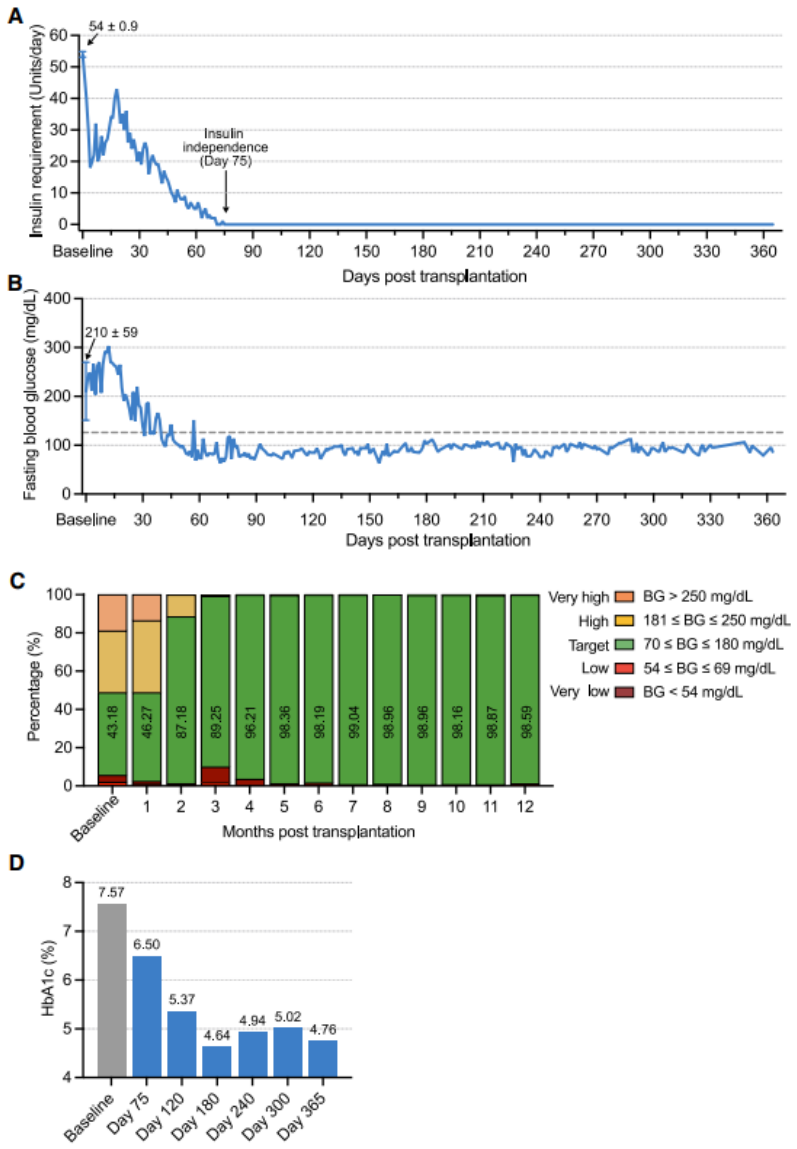
Transplantation of chemically induced pluripotent stem-cell-derived islets under abdominal anterior rectus sheath in a type 1 diabetes patient

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,*]



B


Patient's medical history
Diagnosis of T1D
2012-04
Second
Liver Transplantation
2016-09
Allograft
Pancreatectomy
2018-08
Preclinical assessment in nonhuman primate model
Abdominal rectus sheath transplantation using patient CiPSC-islets
2021-09
Follow-up and evaluation
2014-07
Liver
Transplantation
2017-05
Pancreas
Transplantation
2020-01
Patient CiPSC-islet manufacture
2023-06
CiPSC-islet transplantation
2024-06
One-year endpoint
Patient's adipose tissue harvesting, isolation and cultivation of ADSCs
Microbial safety
Chemical reprogramming
Establishment of patient CiPSCs
Quality assessment of CiPSCs:
Identity, Potency, Viability,
Microbial safety, Genetic stability,
Infectious pathogens
CiPSCs recovery and expansion
Stepwise differentiation
Generation of patient CiPSC-islets
Quality assessment of CiPSC-islets:
Identity, Viability, Microbial safety,
Biosafety, Infectious pathogens,
Purity and potency
Dissociation and cryopreservation
Transport and recovery of CiPSC-islets
Final release criteria:
Identity, Viability, Purity and potency,
Microbial safety,
Detection of residual cytokines


A
54 ± 0.9
Insulin requirement (Units/day)
Insulin independence (Day 75)
Baseline 30 60 90 120 150 180 210 240 270 300 330 360
Days post transplantation
B
210 ± 59
Fasting blood glucose (mg/dL)
Baseline 30 60 90 120 150 180 210 240 270 300 330 360
Days post transplantation
C
Percentage (%)
43.18 46.27 87.18 89.25 96.21 98.36 98.19 99.04 98.96 98.96 98.16 98.87 98.59
Baseline 1 2 3 4 5 6 7 8 9 10 11 12
Months post transplantation
Very high BG > 250 mg/dL
High 181 ≤ BG ≤ 250 mg/dL
Target 70 ≤ BG ≤ 180 mg/dL
Low 54 ≤ BG ≤ 69 mg/dL
Very low BG < 54 mg/dL
D
HbA1c (%)
7.57 6.50 5.37 4.64 4.94 5.02 4.76
Baseline Day 75 Day 120 Day 180 Day 240 Day 300 Day 365

Regolatorio e accesso

Terapie avanzate da 1 milione di dollari. Come renderle sostenibili?

Sono le terapie più costose al mondo e, senza una corretta gestione, potrebbero causare discriminazioni socioeconomiche per l'accesso ai trattamenti

Secondo i dati riportati da un articolo del mese di febbraio 2019, solo 367 su 4603 malattie rare registrate sul NIH Genetic and Rare Disease Information Center hanno a disposizione **almeno una terapia approvata dalla Food and Drug Administration** (FDA) e quasi **il 70%** - stando alle caratteristiche della patologia - **potrebbe essere trattato con la terapia genica**.

L'editing genomico sembrerebbe offrire una soluzione a molte malattie, avvicinandoci alle terapie personalizzate. CRISPR ha senza dubbio

Grazie per l’attenzione!