Congresso Regionale SID-AMD
Sezione Marche

FANO (PU) Centro Pastorale Diocesano 28 ottobre 2023

Il trapianto di insule e la medicina rigenerativa nel diabete tipo 1: le cellule staminali pluripotenti

Federico BERTUZZI
SC Diabetologia
Grande Ospedale Metropolitano Niguarda

L'EVOLUZIONE DELLA DIABETOLOGIA:
un ricco passato, uno sfidante presente, un affascinante futuro

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

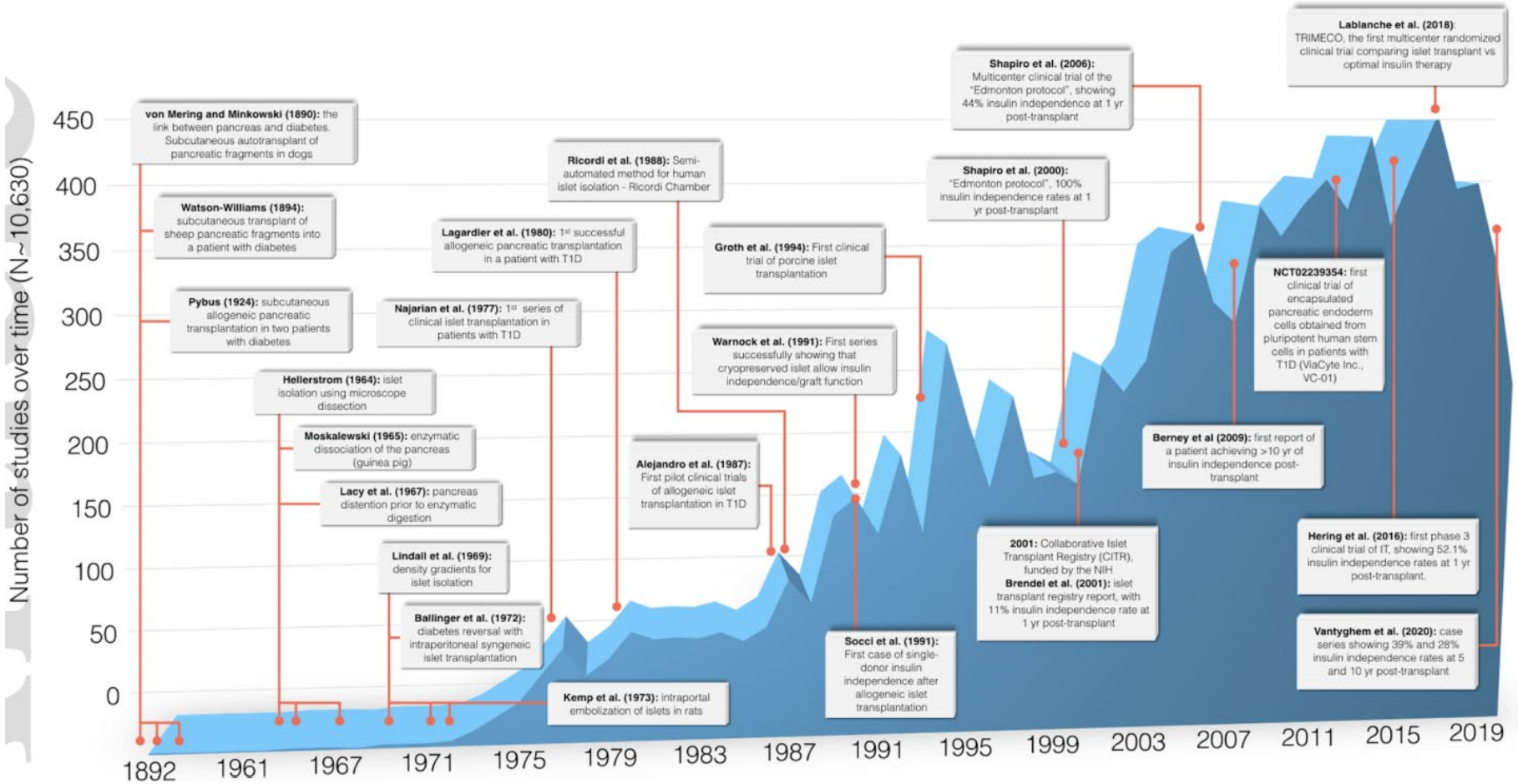
- **BD**
- **Lilly**
- **Abbott**

Congresso Regionale **SID-AMD**

Sezione Marche

FANO (PU) Centro Pastorale Diocesano 28 ottobre 2023

La terapia cellulare



L'EVOLUZIONE DELLA DIABETOLOGIA:

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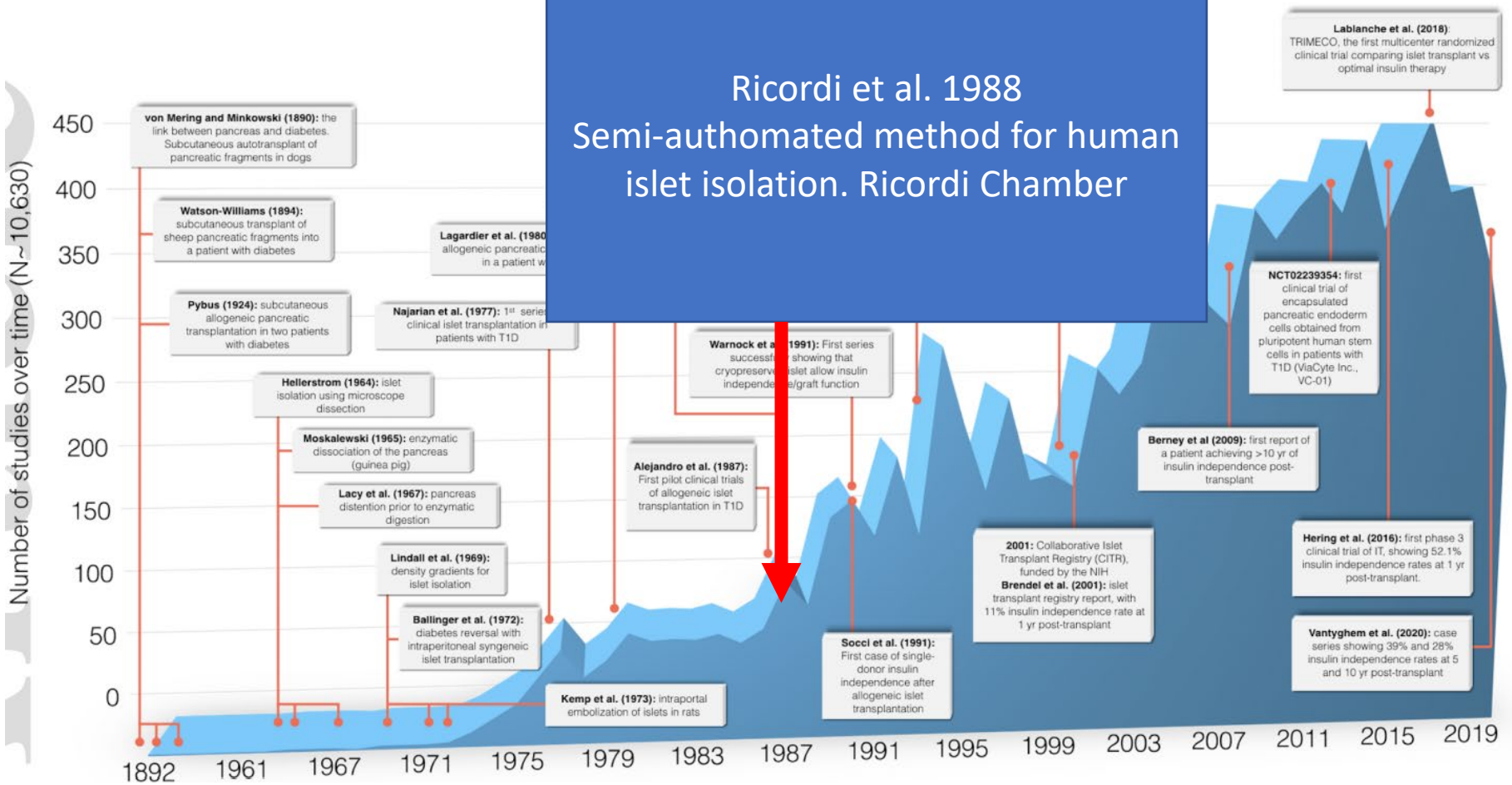
La terapia cellulare

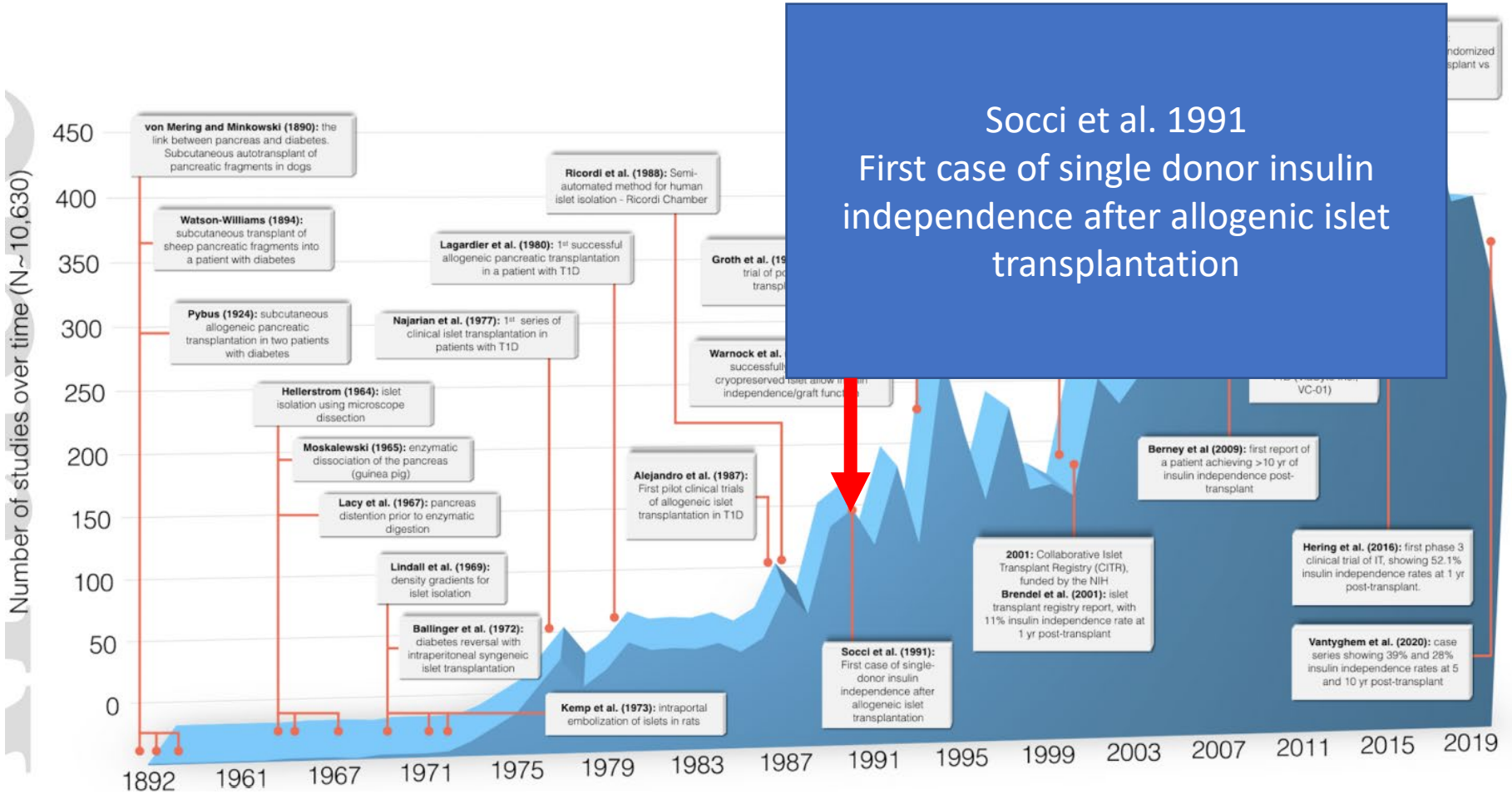
Ricordi et al. 1988
Semi-authomated method for human islet isolation. Ricordi Chamber



L'EVOLUZIONE DELLA DIABETOLOGIA:
un ricco passato, uno sfidante presente, un affascinante futuro

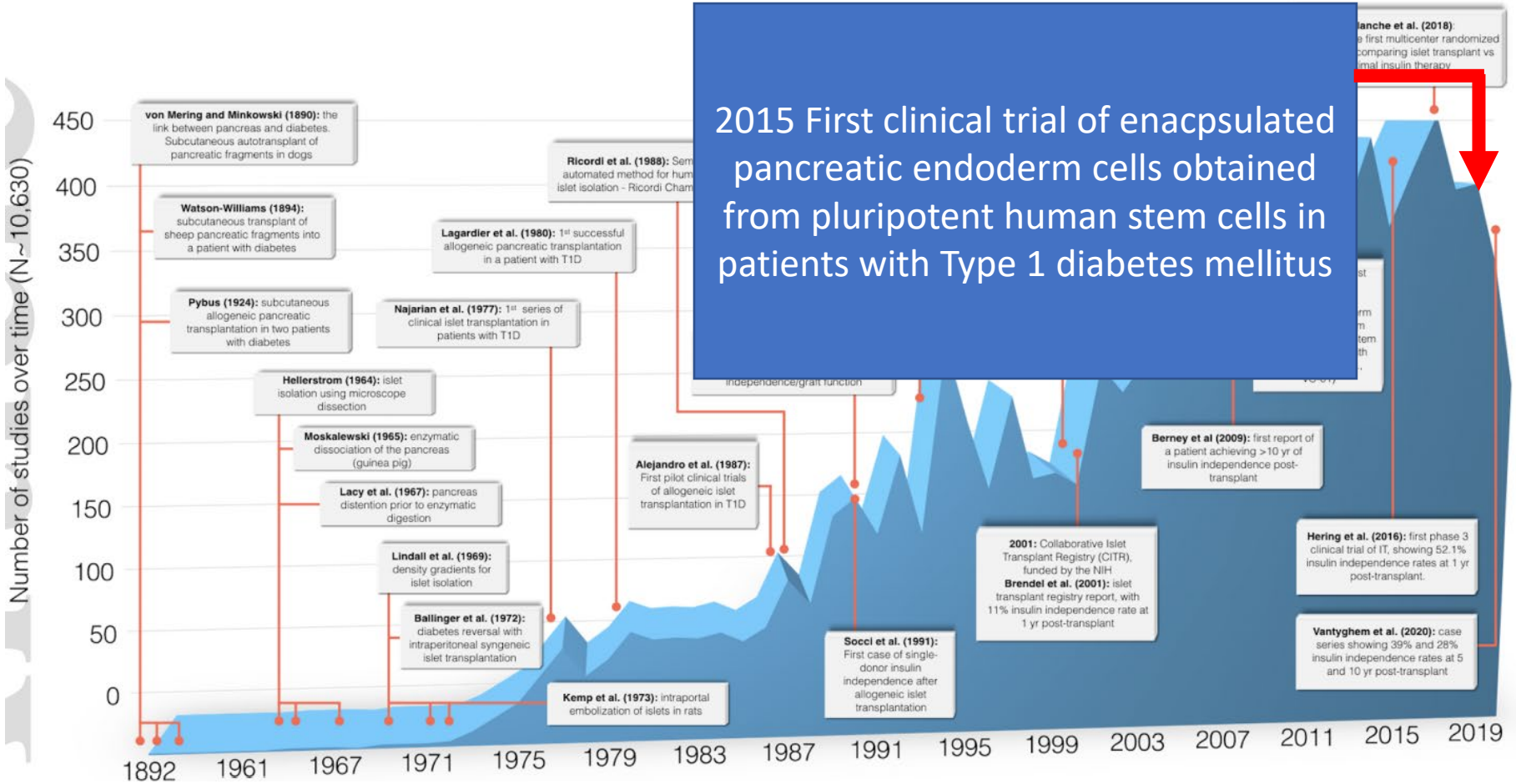
La terapia cellulare

Socci et al. 1991
First case of single donor insulin independence after allogenic islet transplantation



La terapia cellulare

2015 First clinical trial of enacpsulated pancreatic endoderm cells obtained from pluripotent human stem cells in patients with Type 1 diabetes mellitus



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Sezione Marche

FANO (PU) Centro Pastorale Diocesano 28 ottobre 2023

Il trapianto di isole è una opzione terapeutica nel diabete mellito di tipo 1

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

L'EVOLUZIONE DELLA DIABETOLOGIA:

un ricco passato, uno sfidante presente, un affascinante futuro

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.

Diabetes Care Volume 44, November 2021

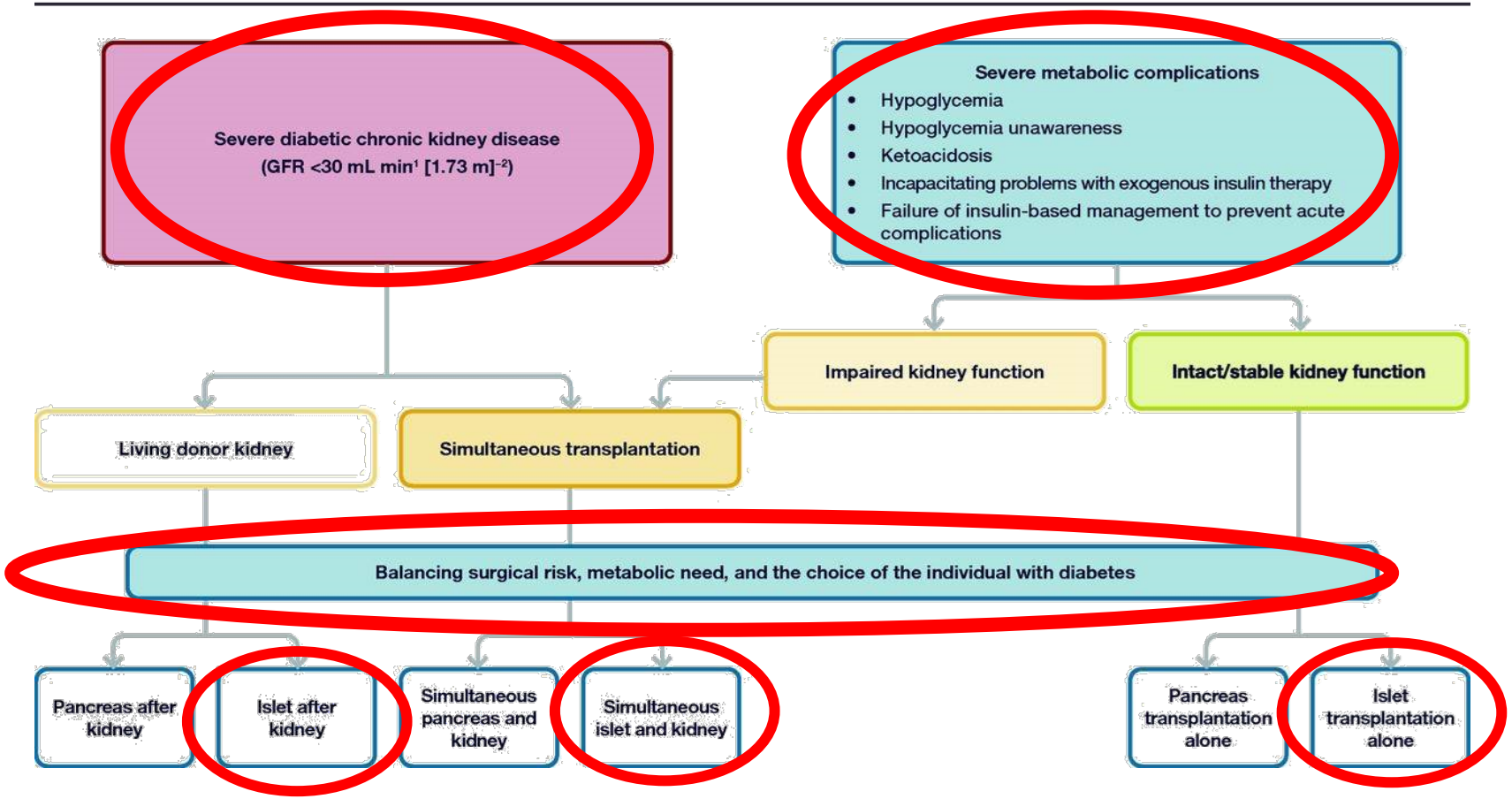
Check for updates

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



American Diabetes Association.

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

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

Lancet Diabetes Endocrinol 2018; 6: 527-37

*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**

	Immediate islet transplantation group (n=25)	Insulin group (n=22)	Total (n=47)
Type of patient (based on inclusion criteria)			
Severe glycaemic lability (with severe hypoglycaemia)	18 (72%)	18 (82%)	36 (77%)
Severe glycaemic lability (with hypoglycaemia unawareness)	2 (8%)	0	2 (4%)
Kidney graft recipients with poor glycaemic control	5 (20%)	4 (18%)	9 (19%)
Sex			
Male	13 (52%)	7 (32%)	20 (43%)
Female	12 (48%)	15 (68%)	27 (57%)
Age (years)	52 (40 to 57)	51 (42 to 58)	51 (41 to 58)
BMI (kg/m²)	22·9 (21·9 to 25·5)	23·9 (22·2 to 25·5)	23·7 (21·9 to 25·5)
Duration of diabetes (years)	34 (25 to 41)	30 (24 to 37)	30 (24 to 38)
HbA_{1c} (%)	8·1% (7·4 to 8·9)	8·1% (7·7 to 8·6)	8·1 (7·4 to 8·9)
HbA_{1c} (mmol/mol)	65 (57·4 to 73·8)	65·5 (60·7 to 70·3)	65·0 (57·4 to 73·8)
Fasting blood glucose (mmol/L)	8·1 (5·4 to 12·6)	9·8 (6·3 to 13·6)	9·1 (5·9 to 13·0)
Insulin requirements			
Units per day	[illegible]	30 (27 to 38)	32 (27 to 40)
Units per kg bod[illegible] per day	0·53 (0·42 to 0·66)	0·46 (0·41 to 0·[illegible])	0·47 (0·41 to 0·63)
[illegible] pump use	15 (60% [39 to 79])	14 (64% [41 to 83])	29 (62% [46 to [illegible]])
Continuous glucose monitoring	4 (16% [4 to 36])	3 (14% [3 to 35])	7 (15% [6 to 28])
Carbohydrate counting	11 (44% [24 to 65])	11 (50% [28 to 72])	22 (47% [32 to 62])
C-peptide (ng/mL)	0·00 (0·00 to 0·02)	0·01 (0·00 to 0·10)	0·00 (0·00 to 0·09)
Modified β-score	0 (0 to 2)	0 (0 to 1)	0 (0 to 1)
0	13 (52% [31 to 72])	13 (59% [36 to 79])	26 (55% [40 to 70])
1	5 (20% [7 to 41])	7 (32% [14 to 55])	12 (26% [14 to 40])
2	6 (24% [9 to 45])	2 (9% [1 to 29])	8 (17% [illegible] to 31])
3	1 (4% [<1 to 20])	0	1 (2% [<1 to 11])
Clarke score	5·0 (4·0 to 6·0)	4·5 (3·0 to 7·0)	5 (3 to 6)
At least two severe hypoglycaemic events in the year before randomisation	18 (72%)	18 (82%)	36 (77%)

Data are n (%), median (IQR), n/N (%), or n (% [95% CI]).

Table 1: **Baseline characteristics**

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

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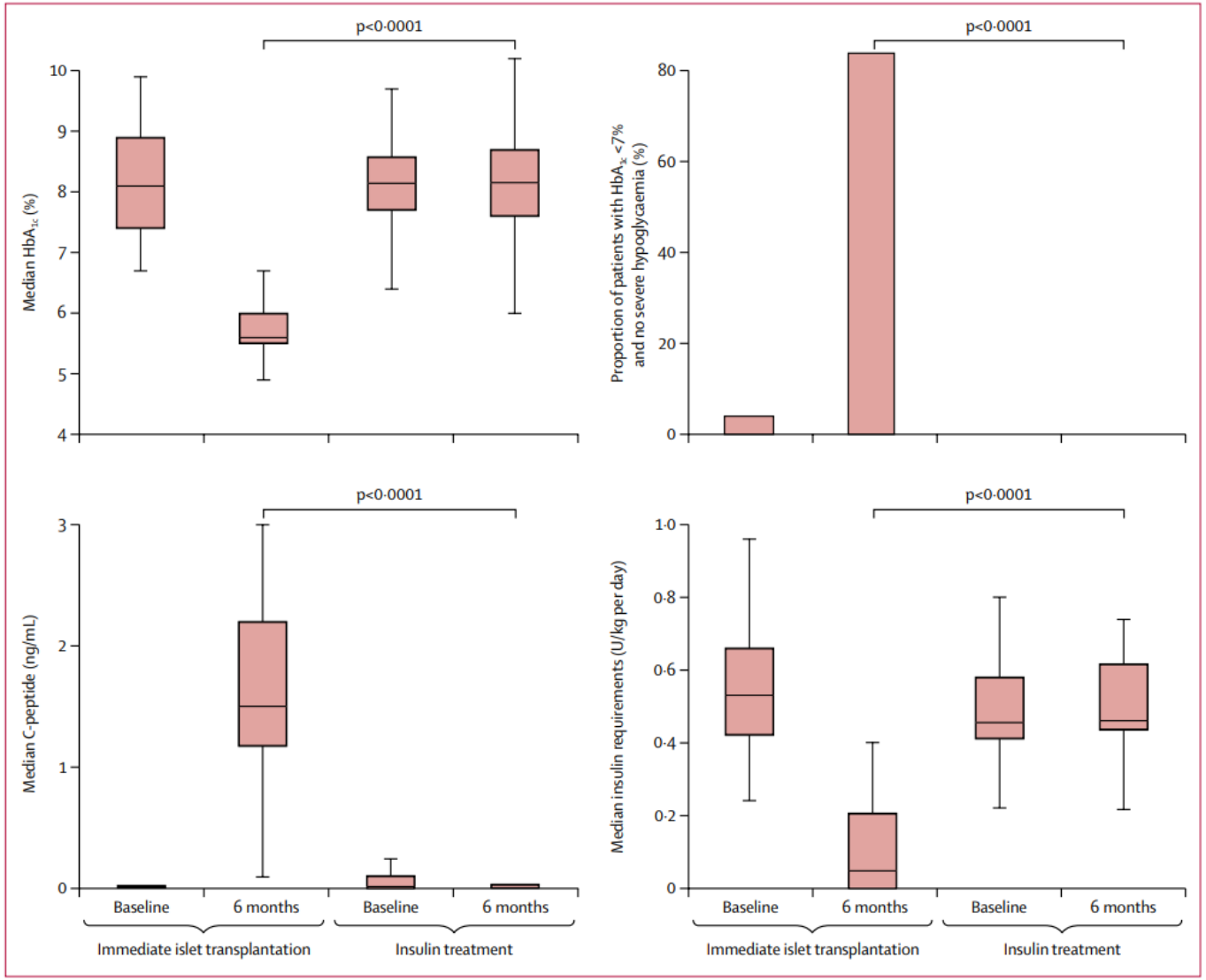


Figure 3: **Metabolic outcomes at baseline and 6 months**

	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%)

Data are number of patients (%). Serious adverse events that occurred in more than 10% of patients in either group are reported. *Number of patients differs from baseline because one patient in the insulin group died while on the islet transplantation waiting list.

Lancet Diabetes Endocrinol 2018; 6: 527-37

***Table 3*: Serious adverse events**

- 135 SAEs occurred during our study, of which 92 were in the 6 months after first islet infusion. One patient died from severe hypoglycaemia while on the waiting list for islet transplantation.
- Immunosuppression was responsible for two-thirds of the SAEs. Bleeding complications were associated with 6·3% of islet infusions. However, bleeding complications can be severe, as evidenced by the patient in our study who had a transient cardiac arrest after an islet infusion complicated by a haemorrhage. A decrease in glomerular filtration rate after islet transplantation, mainly due to calcineurin inhibitor therapy and reduction of hyperfiltration driven by the improvement in glycaemic control. Notably, a high proportion of patients in our study had HLA sensitization.

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**

Lancet Diabetes Endocrinol
2018; 6: 527–37

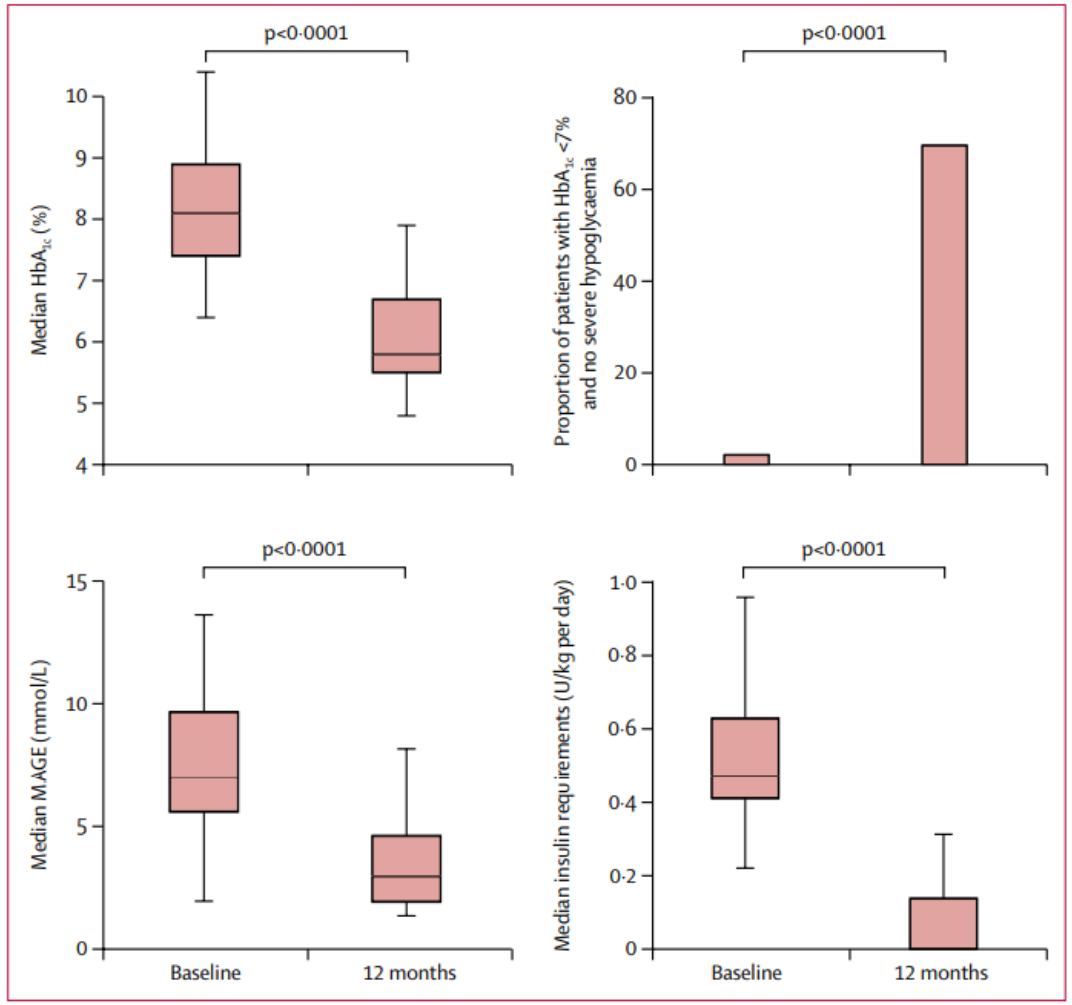
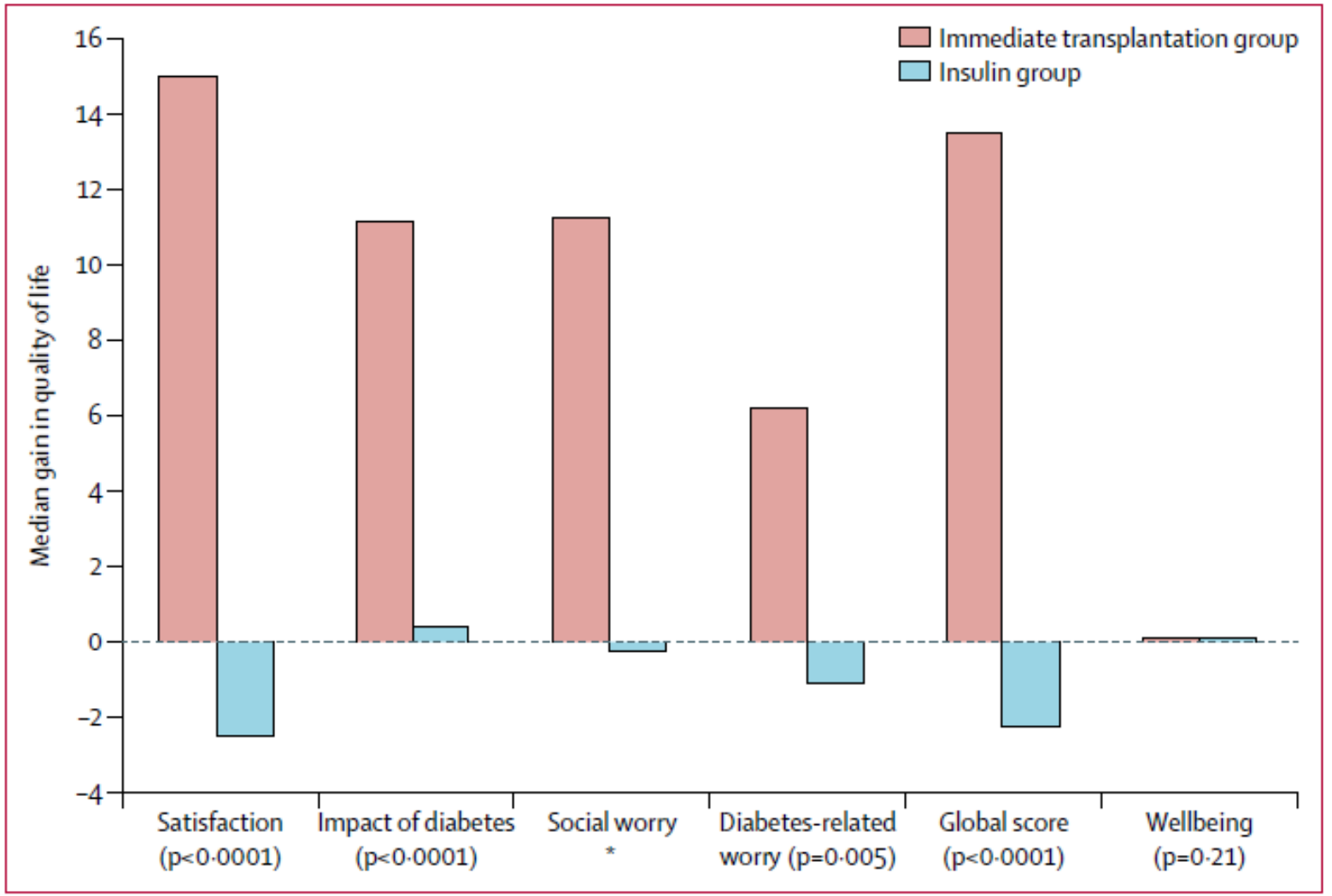


Figure 5: **Outcomes in the entire cohort at 12 months after first islet transplantation**
Boxes show IQRs, with bands within the boxes indicating medians. The error bars indicate ranges. MAGE=mean amplitude of glycaemic excursions.



www.thelancet.com/diabetes-endocrinology
Published online May 15, 2018
http://dx.doi.org/10.1016/S2213-8587(18)30078-0

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]

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

Limiti

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**

citr
Collaborative Islet Transplant Registry

Tenth Annual Report

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

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

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

January 6, 2017

Transplant type ITA

		Total	Related to Infusion?					Related to Immunosuppression?				
				Not related	Unlikely related	Possibly related	Related		Not related	Unlikely related	Possibly related	Related
		N	%	%	%	%	%	%	%	%	%	%
Infections and infestations	Appendicitis	4	.	.	100	.	.	.	.	100	.	.
	Appendicitis perforated	2	100	.	.	.	.	100	.	.	.	.
	Arthritis bacterial	1	.	100	.	.	.	.	.	.	100	.
	Bacillus infection	2	.	100	.	.	.	.	100	.	.	.
	Clostridium difficile colitis	1	100	.	.	.	.	100	.	.	.	.
	Cystitis	2	.	100	.	.	.	.	.	50.0	50.0	.
	Cytomegalovirus infection	2	.	.	50.0	50.0	.	.	50.0	.	.	50.0
	Ear infection	1	.	100	.	.	.	.	.	100	.	.
	Enterocolitis infectious	1	.	100	.	.	.	.	.	100	.	.
	Gastroenteritis viral	2	.	.	50.0	.	50.0	50.0	.	50.0	.	.
	Gastrointestinal infection	1	.	100	.	.	.	.	.	.	100	.
	H1N1 influenza	1	100	.	.	.	.	100	.	.	.	.
	Herpes simplex	1	100	.	.	.	.	100	.	.	.	.
	Infection	**65**	26	64.6	16.9	7.7	6.2	4.6	16.9	7.7	**67.7**	**3.1**
	Influenza	1	.	.	.	100	.	.	.	.	100	.
	Laryngitis	1	.	100	.	.	.	.	100	.	.	.
	Metapneumovirus infection	1	.	100	.	.	.	.	100	.	.	.
	Opportunistic infection	1	.	100	.	.	.	.	.	.	.	100
	Periorbital cellulitis	1	.	100	.	.	.	.	.	.	100	.
	Pneumococcal infection	1	100	.	.	.	.	100	.	.	.	.
	Pneumonia	**10**	30.0	10.0	50.0	10.0	.	30.0	.	.	**60.0**	**10.0**
	Pulmonary tuberculosis	1	.	100	.	.	.	.	100	.	.	.
	Pyelonephritis	1	.	100	.	.	.	.	.	.	100	.
	Respiratory tract infection	1	.	.	.	100	.	.	.	.	100	.
	Urinary tract infection	1	100	.	.	.	.	100	.	.	.	.
	Vestibular neuronitis	1	.	100	.	.	.	.	.	.	100	.
	Viral encephalitis	1	.	100	.	.	.	.	.	.	100	.

citr
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Bethesda, MD

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

January 6, 2017

Exhibit 7-1 (continued)
All AEs Classified and by relatedness to infusion or IS

Transplant type ITA

		Total	Related to Infusion?					Related to Immunosuppression?				
				Not related	Unlikely related	Possibly related	Related		Not related	Unlikely related	Possibly related	Related
		N	%	%	%	%	%	%	%	%	%	%
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**Basal cell carcinoma**	**7**	57.1	42.9	.	.	.	28.6	.	.	**42.9**	**28.6**
	Lobular breast carcinoma in situ	1	.	100	.	.	.	.	.	.	100	.
	Lymphoma	1	100	.	.	.	.	100	.	.	.	.
	Metastases	1	.	100	.	.	.	.	.	.	100	.
	Mucinous adenocarcinoma of appendix	1	100	.	.	.	.	100	.	.	.	.
	Neoplasm malignant	**18**	.	61.1	33.3	5.6	.	.	5.6	.	**94.4**	.
	Papillary thyroid cancer	1	.	100	.	.	.	.	.	.	100	.
	Post transplant lymphoproliferative disorder	1	100	.	.	.	.	100	.	.	.	.
	Skin cancer	1	100	.	.	.	.	100	.	.	.	.
	Squamous cell carcinoma	**6**	66.7	33.3	.	.	.	50.0	.	.	**33.3**	**16.7**
	Treatment related secondary malignancy	1	.	100	.	.	.	.	.	.	100	.

Le indicazioni

Congresso Regionale **SID-AMD**

Sezione Marche

FANO (PU) Centro Pastorale Diocesano 28 ottobre 2023

A) DIABETE INSTABILE

L'EVOLUZIONE DELLA DIABETOLOGIA:

un ricco passato, uno sfidante presente, un affascinante futuro

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

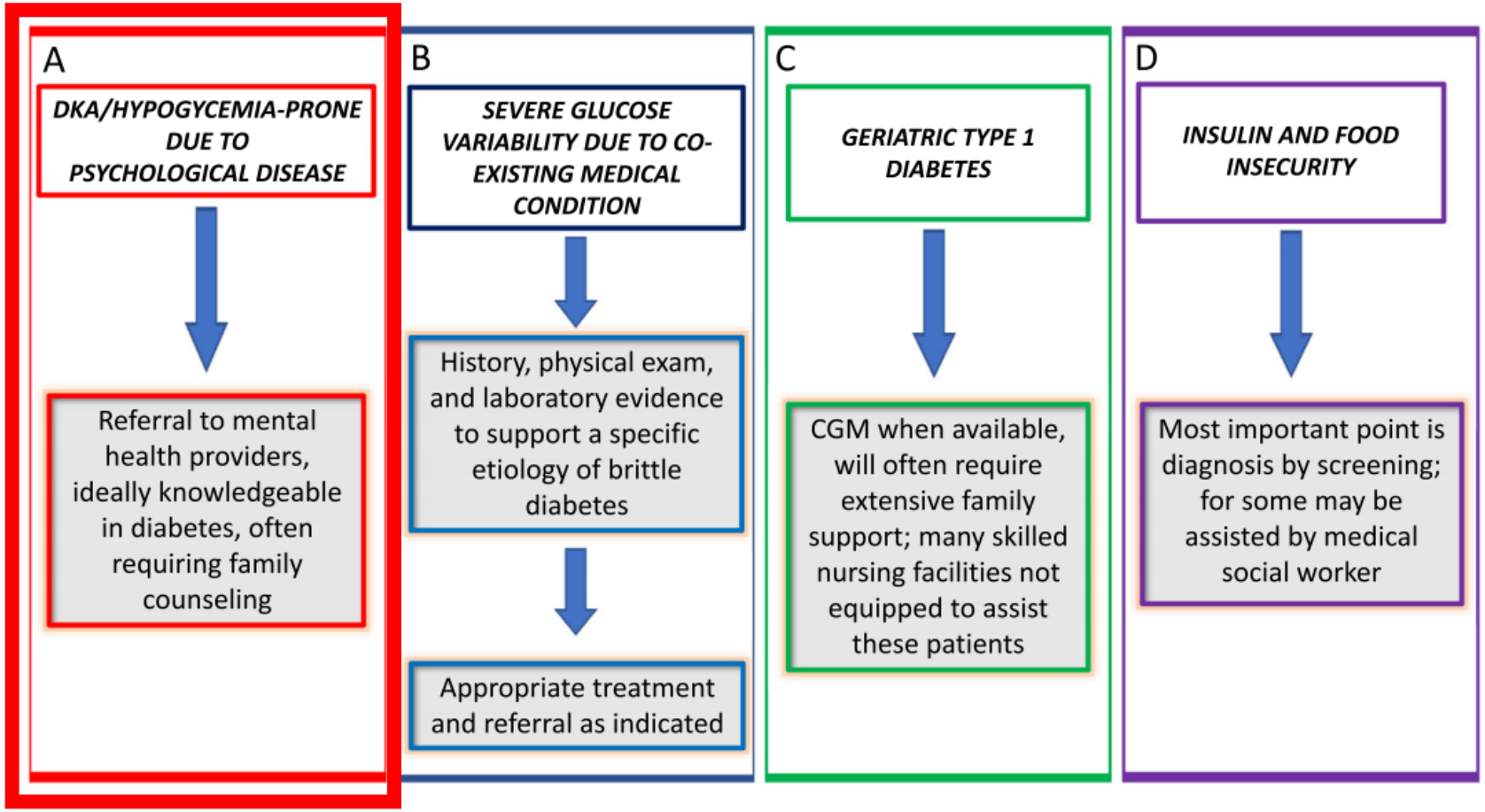

Fig. 4. Overall approach to the treatment of brittle diabetes divided into the four groups: A. DKA and hypoglycemia due to psychological disease; B. severe glucose variability due to medical condition; C. geriatric type 1 diabetes; D. insulin and food insecurity. CGM = continuous glucose monitoring.

Congresso Regionale SID-AMD
Sezione Marche

FANO (PU) Centro Pastorale Diocesano 28 ottobre 2023

B) DIFFICOLTÀ NELL'USO DELLA TECNOLOGIA

L'EVOLUZIONE DELLA DIABETOLOGIA:
un ricco passato, uno sfidante presente, un affascinante futuro

DIABETES TECHNOLOGY & THERAPEUTICS
Volume 21, Number 4, 2019

DOI: 10.1089/dia.2019.0007

ORIGINAL ARTICLE

Skin Problems Due to Treatment with Technology Are Associated with Increased Disease Burden Among Adults with Type 1 Diabetes

Maria O. Christensen, BSc,[1,2] Anna K. Berg, BSc,[1,3] Karen Rytter, RN,[2] Eva Hommel, DMSc,[2] Jacob P. Thyssen, DMSc,[4] Jannet Svensson, PhD,[1,3] and Kirsten Nørgaard, DMSc[2,5]

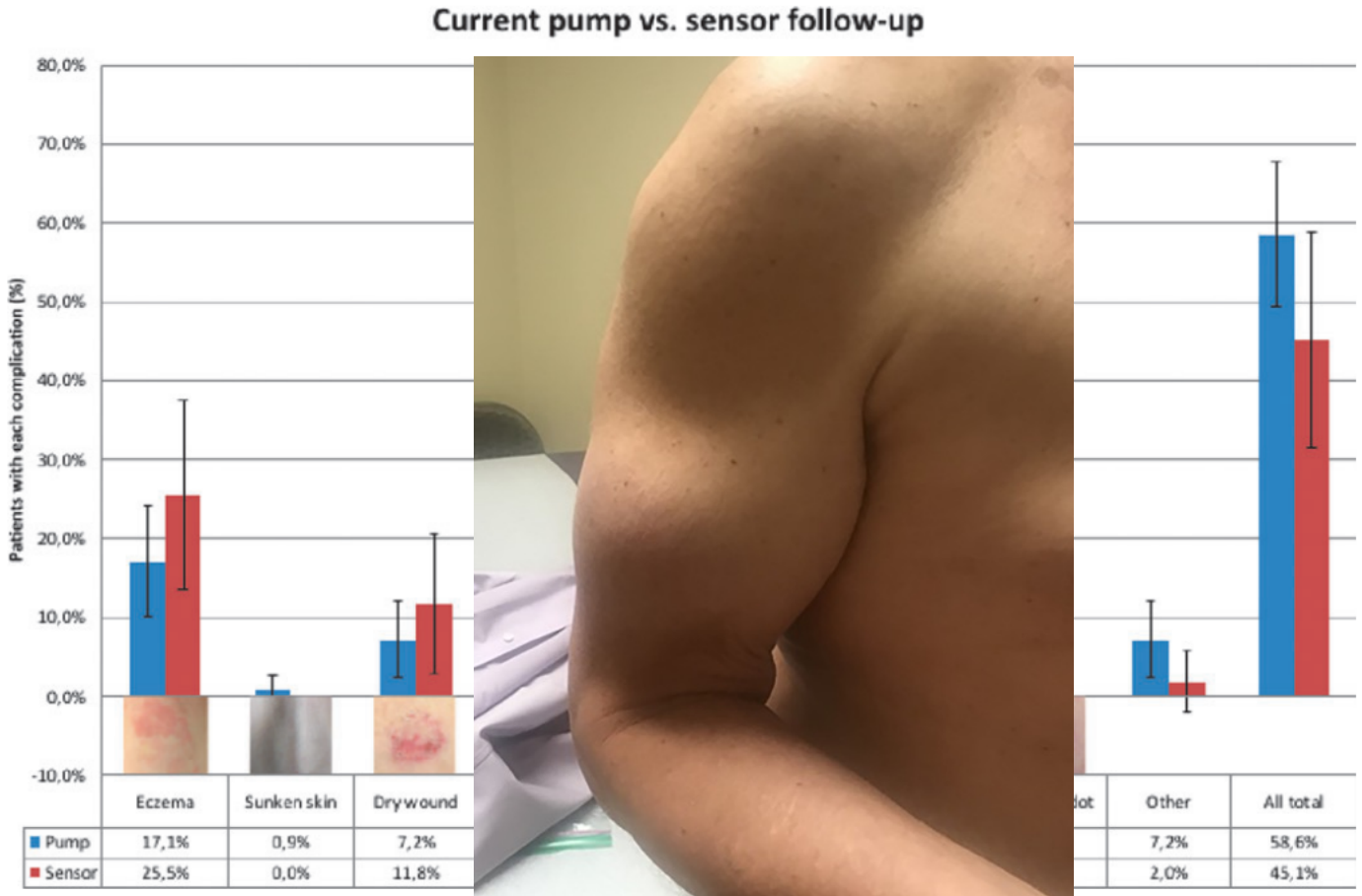

FIG. 1. Distribution of current skin pro e intervals. Blue columns represent skin problems because of CSII u CGM use. Both columns represent the proportion of skin problems ategories of skin problems were translated directly from Danish to English and represent how skin problems were presented in the questionnaire. CGM, continuous glucose monitoring; CSII, continuous subcutaneous insulin infusion.

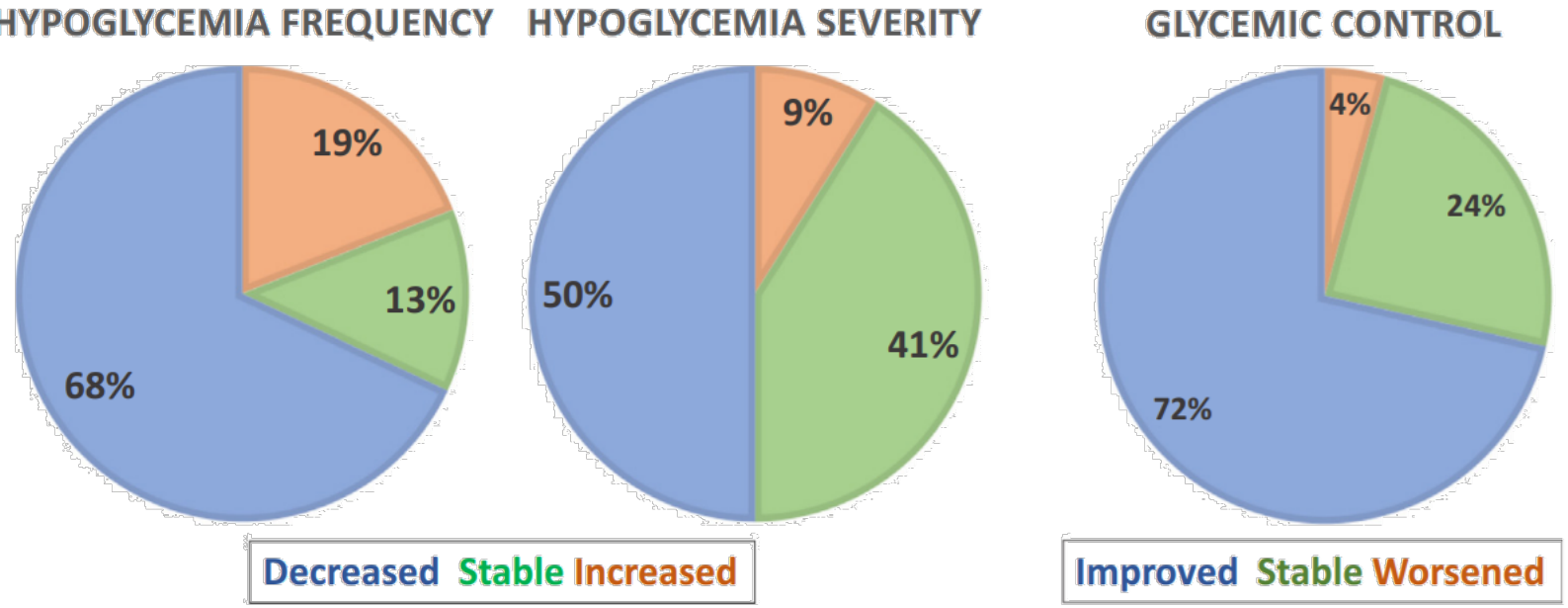

Fig. 1 – Metabolic control reporting after switching from MDI regimens to CSII therapy.

DIABETES RESEARCH AND CLINICAL PRACTICE 144 (2018) 42–50

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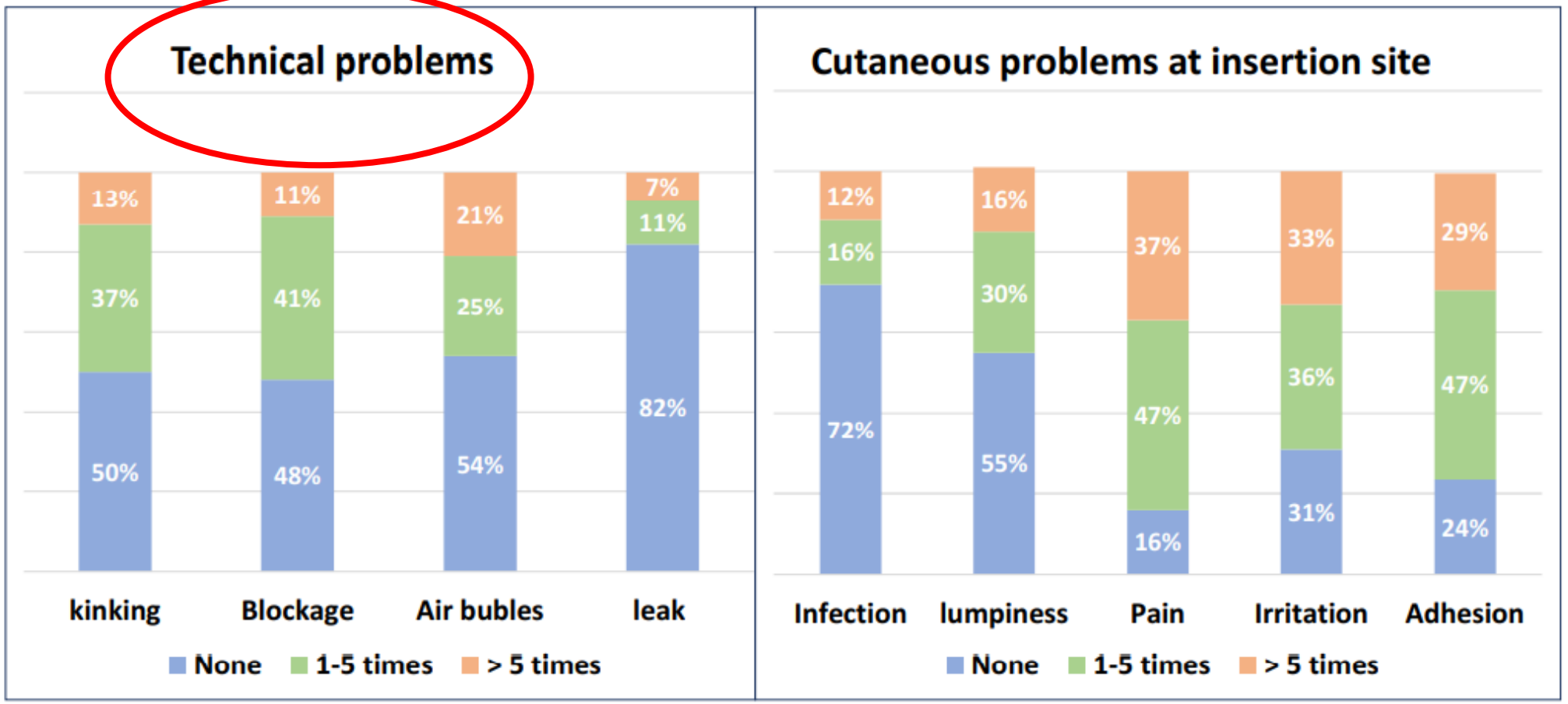
ELSEVIER

International Diabetes Federation

Perceptions and experiences of adult patients with type 1 diabetes using continuous subcutaneous insulin infusion therapy: Results of an online survey

Nadine Taleb [a,b], *Virginie Messier* [a], *Sylvie Ott-Braschi* [a,c], *Jean-Luc Ardilouze* [d], *Rémi Rabasa-Lhoret* [a,c,e,f,*]




Diabetes Research and Clinical Practice
International Diabetes Federation
Perceptions and experiences of adult patients with type 1 diabetes using continuous subcutaneous insulin infusion therapy: Results of an online survey
Nadine Taleb, Virginie Messier, Sylvie Ott-Braschi, Jean-Luc Ardilouze, Rémi Rabasa-Lhoret

Frequency of perfusion set/catheter change is 3.3 ± 0.9 day

Fig. 2 – Technical and cutaneous problem encountered with infusion set/catheter over the past year of CSII use.

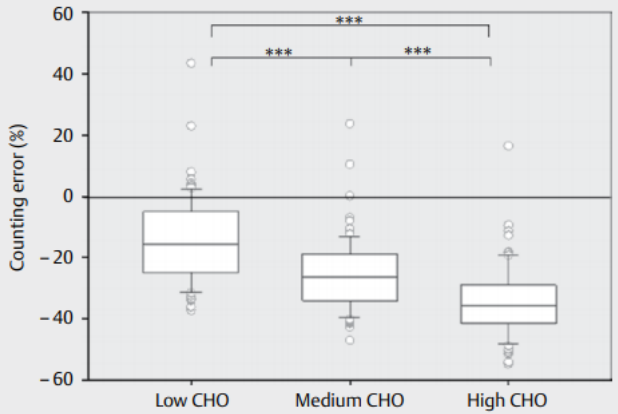
Exp Clin Endocrinol Diabetes | © 2021.

Article

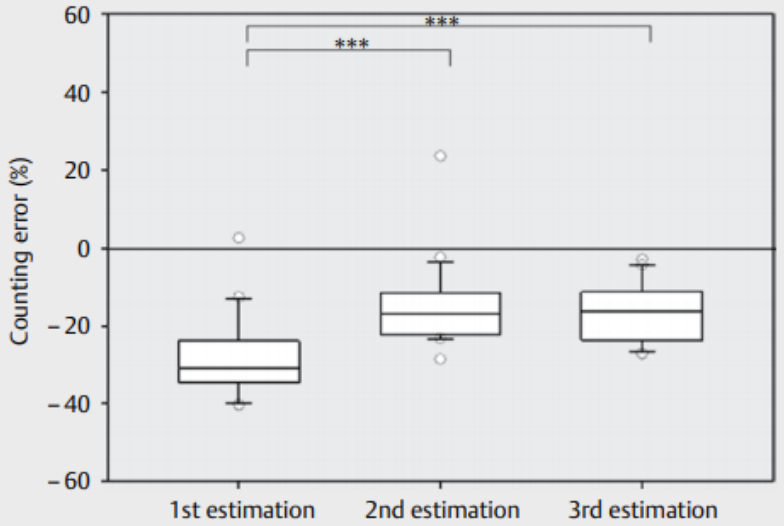
Thieme

Evaluation of Meal Carbohydrate Counting Errors in Patients with Type 1 Diabetes

Authors
Sina Buck[1], Collin Krauss[1], Delia Waldenmaier[1], Christina Liebing[1], Nina Jendrike[1], Josef Högel[2], Boris M. Pfeiffer[3], Cornelia Haug[1], Guido Freckmann[1]



▶ **Fig. 2** Median counting error (%) of the 24 test meals with low, medium, and high CHO content; n = 74. Values outside the 10th and 90th percentile are presented as outliers (grey circles); *** = p < 0.001 (Friedman Repeated Measures Analysis of Variance on Ranks).



▶ **Fig. 3** Median counting error (%) of the 24 test meals (%) after the first, second, and third estimation; n = 22. Values outside the 10th and 90th percentile are presented as outliers (grey circles); * * * = p < 0.001 (One Way RM ANOVA).

Congresso Regionale **SID-AMD**

Sezione Marche

FANO (PU) Centro Pastorale Diocesano 28 ottobre 2023

C) IPOGLICEMIA NON AVVERTITA

L'EVOLUZIONE DELLA DIABETOLOGIA:

un ricco passato, uno sfidante presente, un affascinante futuro

Congresso Regionale **SID-AMD**

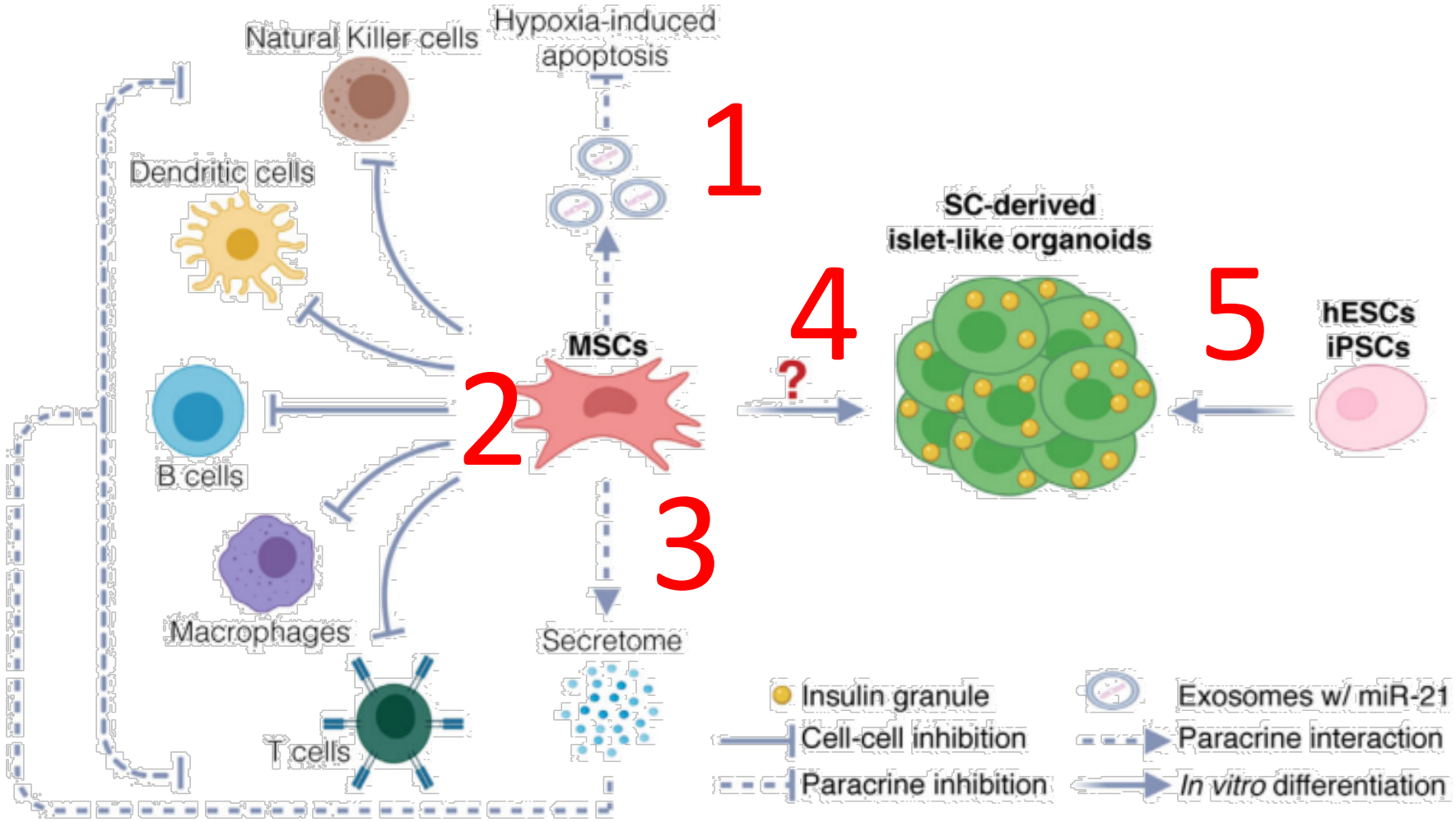
Sezione Marche

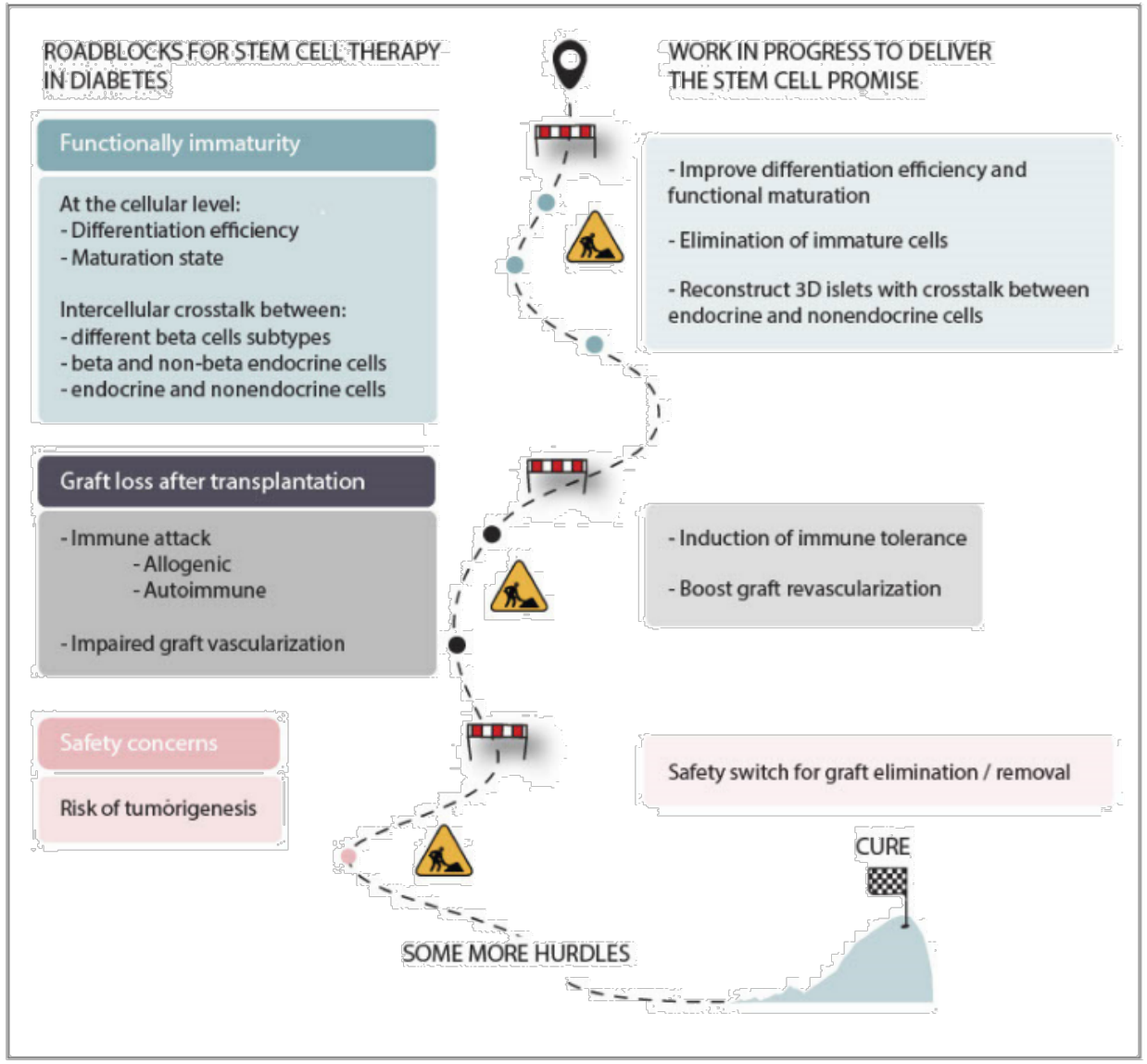
FANO (PU) Centro Pastorale Diocesano 28 ottobre 2023

L'evoluzione:
Il trapianto di cellule staminali

L'EVOLUZIONE DELLA DIABETOLOGIA:

un ricco passato, uno sfidante presente, un affascinante futuro


Natural Killer cells
Hypoxia-induced apoptosis
1
Dendritic cells
SC-derived islet-like organoids
4
5
hESCs iPSCs
MSCs
2
?
B cells
3
Macrophages
Secretome
T cells
Insulin granule
Cell-cell inhibition
Paracrine inhibition
Exosomes w/ miR-21
Paracrine interaction
In vitro differentiation



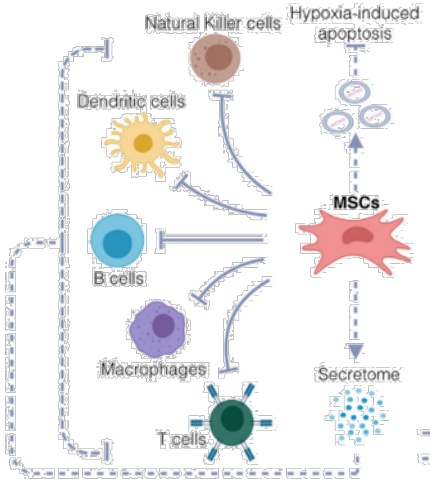
cells
MDPI
Review

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,*]

PLOS ONE

1-4



RESEARCH ARTICLE

Clinical Efficacy of Stem Cell Therapy for Diabetes Mellitus: A Meta-Analysis

Ahmed El-Badawy, Nagwa El-Badri*

Center of Excellence for Stem Cells and Regenerative Medicine (CESC), Zewail City of Science and Technology, 6th of October City, Egypt

2016

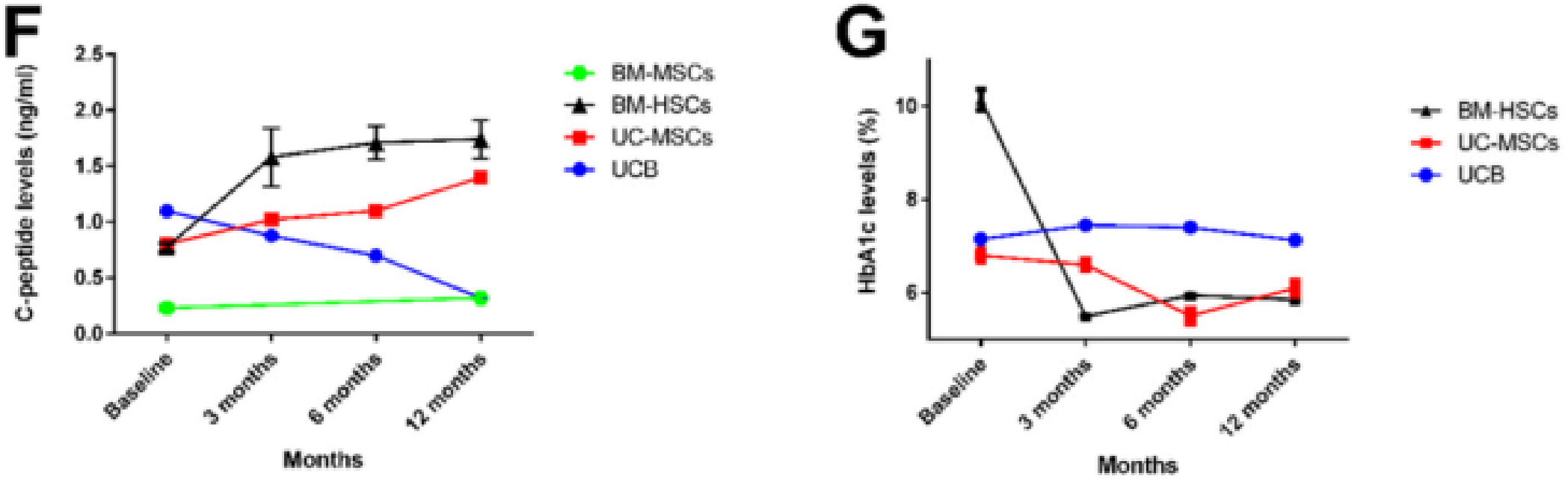


Fig 2. Stem cell therapy for type 1 DM. (A-C) Comparison of the outcome of different types of stem cells in T1DM by Intravenous administration of Umbilical Cord Blood (UCB, $n = 61$), Umbilical Cord-Mesenchymal Stem Cells (UC-MSCs, $n = 15$) and Bone Marrow Hematopoietic Stem Cells (BM-HSCs, $n = 82$) (D-E) Bar graphs depicting the change in C-peptide and HbA1c levels from baseline and 12 months after intravenous administration of different types of stem cells. (F-G) Line graphs showing changes in C-peptide and HbA1c levels over time at baseline, 3, 6 and 12 months after stem cell therapy in T1DM patients. All data are expressed as the mean ± SEM. **** $P < 0.0001$.

doi:10.1371/journal.pone.0151938.g002

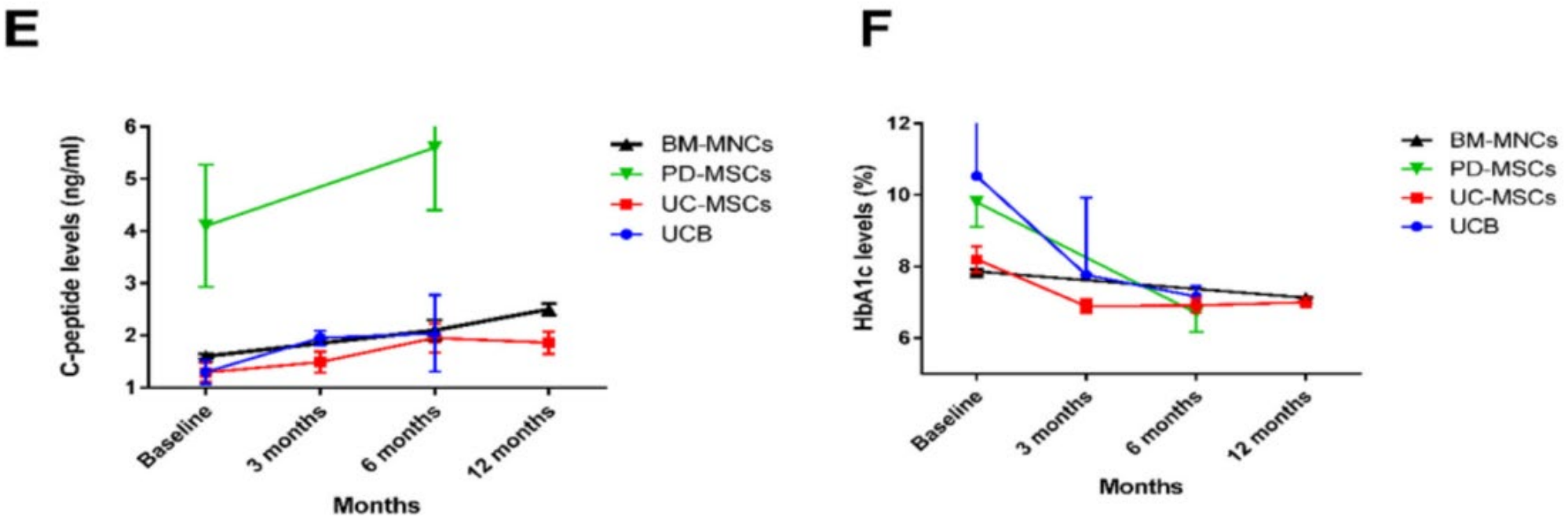


Fig 4. Stem cell therapy for type 2 DM. (A-D) Bar graphs depicting the change in C-peptide and HbA1c levels from baseline and 12 months after administration of different types of stem cells. UCB and BM-MNCs were injected intra-pancreatically (*n* = 3 and *n* = 107, respectively), while UC-MSCs and PD-MSCs were injected intravenously (*n* = 22 and *n* = 10, respectively). (E-F) Line graphs showing changes in C-peptide and HbA1c levels over time at baseline, 3, 6 and 12 months after stem cell therapy in T2DM patients. All data are expressed as the mean ± SEM. **** P < 0.0001.

doi:10.1371/journal.pone.0151938.g004

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,*]

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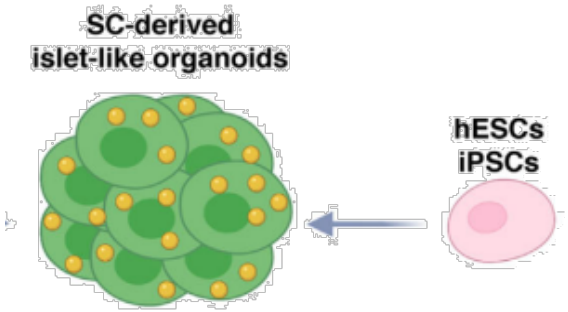
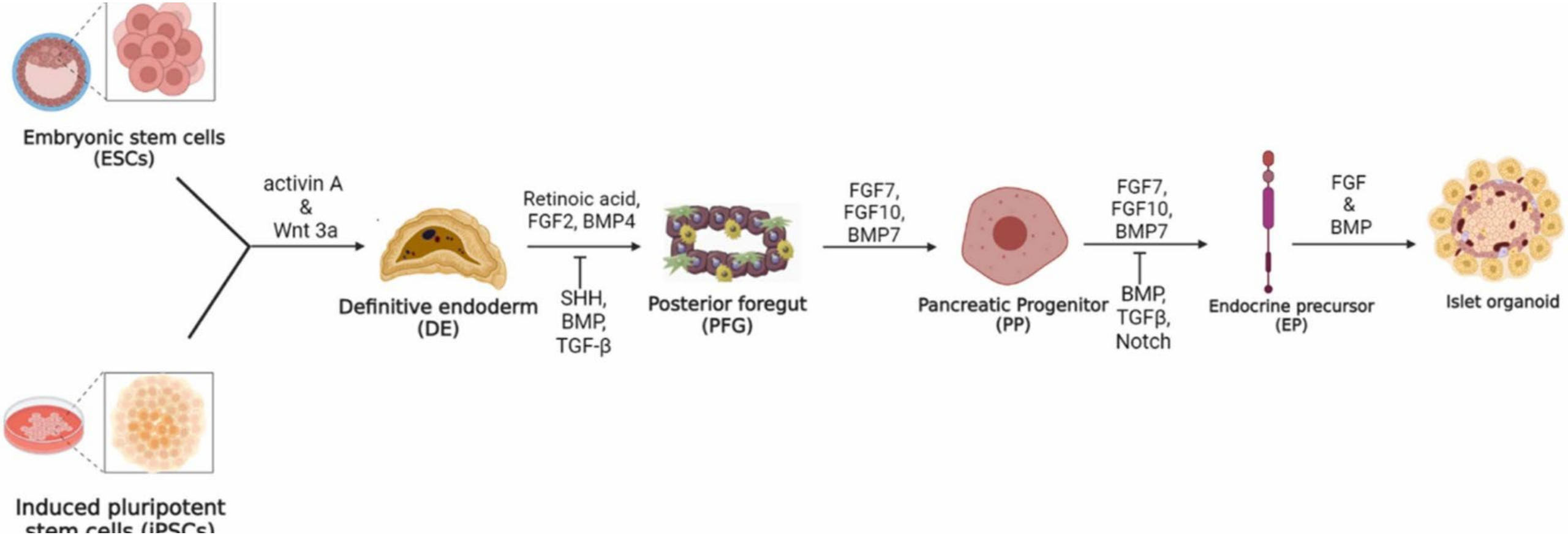


Table 1. Overview of protocols for the generation of stem cell-derived beta cells.

Report	Approach	Outcome to Beta-Cell Function	Reference
Pagliuca et al., 2014	Protocol for generation of beta-like cells by modifying and combining three previous protocols [70–72]	Expression of key markers of mature pancreatic beta-cells, glucose-induced Ca^{2+} influx, insulin secretion in response to multiple sequential glucose challenges	[52]
Rezania et al., 2014	7-stage protocol for generation of beta-like cells based on previous own protocol [70]	Expression of key markers of mature pancreatic beta-cells, insulin secretion in response to high glucose	[53]
Russ et al., 2015	Protocol for generation of beta-like cells based on two previous protocols [70] by culture without additional growth factors after endocrine progenitor stage	Expression of key markers of mature pancreatic beta-cells, insulin secretion in response to high glucose	[51]
Millman et al., 2016	Addition of ROCK inhibitor and Activin A based on [52] at pancreatic progenitor stage	Similar to their previous studies [52], beneficial effect on insulin expression and secretion	[56]
Zhu et al., 2016	Addition of vitamin C and BayK-8644 at final stage	Increased insulin expression and secretion	[55]
Ghazizadeh et al., 2017	ROCKII inhibition at pancreatic progenitor stage	Generation and maturation of glucose-responsive cells	[54]
Nair et al., 2019	Reaggregation/clustering after FACS at final stage	Robust dynamic insulin secretion, metabolic maturation by driving mitochondrial oxidative respiration	[57]
Velazco-Cruz et al., 2019	Allowing TGF-β signaling during the final stage and reaggregation/clustering	Pure populations of beta-like cells that secrete high levels of insulin and express key beta cell markers	[58]
Yoshihara et al., 2020	Allowing WNT4 signaling during the final stage	Metabolic maturation with robust insulin secretion and high mitochondrial oxidative respiration	[63]
Li et al., 2020	Combination of three previous protocols [52], and reaggregation/clustering after negative sorting by CD9	High glucose-responsiveness and insulin production	[65]

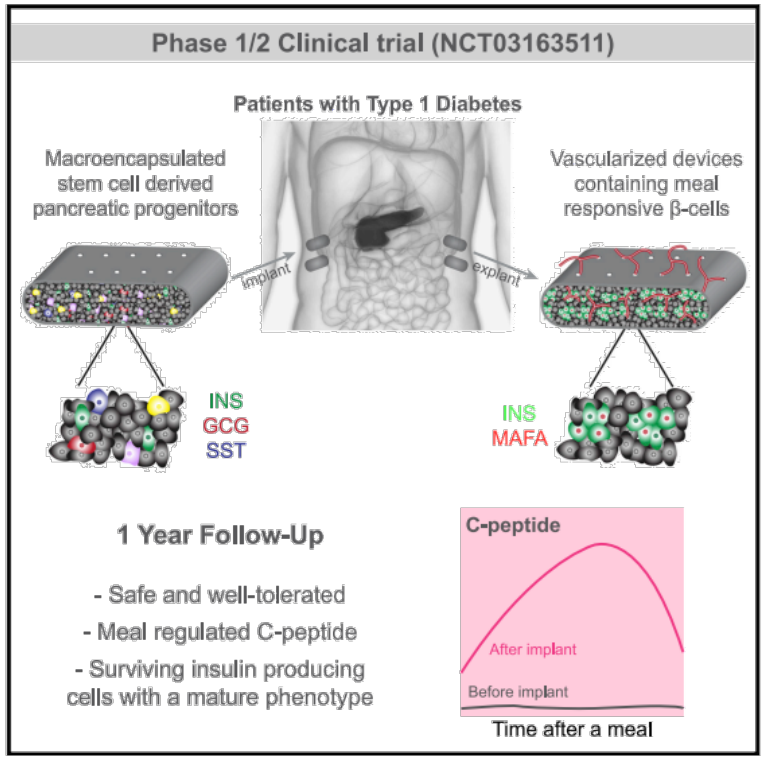
ROCK: Rho-associated protein kinase, TGF-β: transforming growth factor β, FACS: fluorescence-activated cell sorting, WNT4: wingless-type murine-mammary-tumour virus integration site family member 4, CD9: cluster of differentiation 9.


Embryonic stem cells
(ESCs)
activin A
&
Wnt 3a
Definitive endoderm
(DE)
Retinoic acid,
FGF2, BMP4
SHH,
BMP,
TGF-β
Posterior foregut
(PFG)
FGF7,
FGF10,
BMP7
Pancreatic Progenitor
(PP)
FGF7,
FGF10,
BMP7
BMP,
TGFβ,
Notch
Endocrine precursor
(EP)
FGF
&
BMP
Islet organoid
Induced pluripotent
stem cells (iPSCs)

Cell Stem Cell
Clinical and Translational Report

Implanted pluripotent stem-cell-derived pancreatic endoderm cells secrete glucose-responsive C-peptide in patients with type 1 diabetes

Graphical abstract



Authors

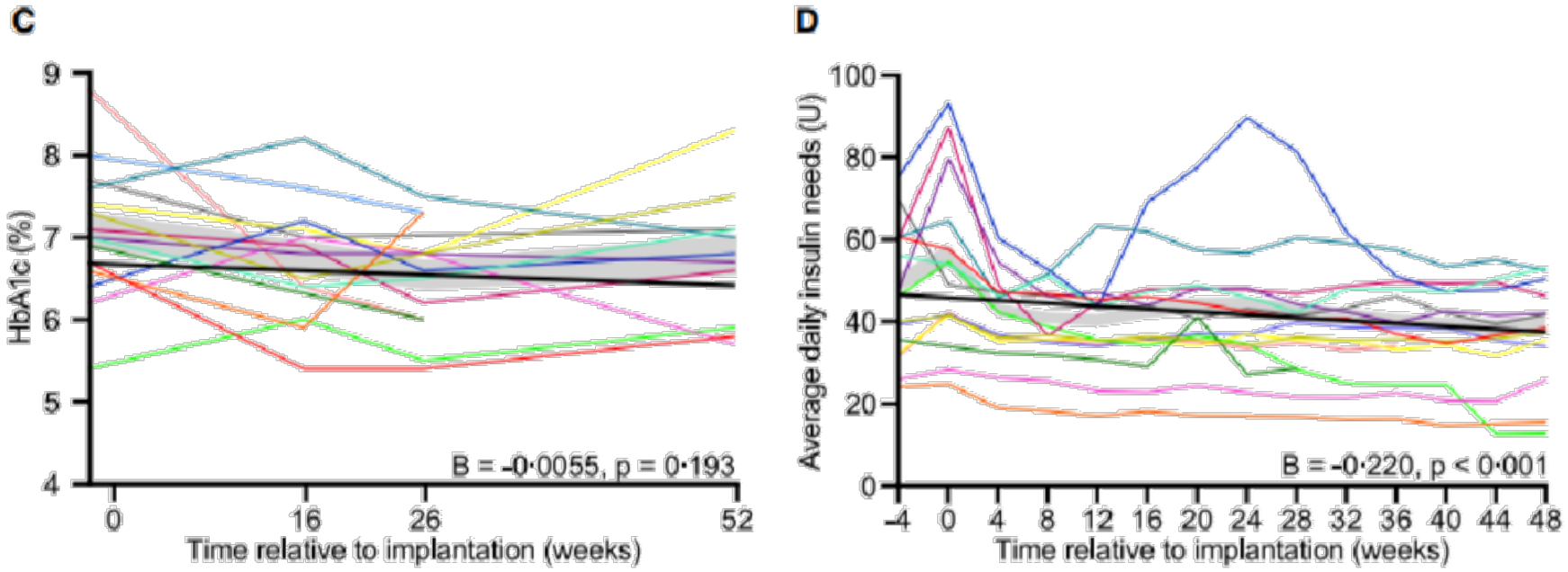
Adam Ramzy, David M. Thompson, Kirsten A. Ward-Hartstonge, ..., Garth L. Warnock, Megan K. Levings, Timothy J. Kieffer

Correspondence

tim.kieffer@ubc.ca

In brief

Kieffer and colleagues assessed the implant of stem-cell-derived pancreatic cells for the treatment of type 1 diabetes. Patients developed meal-responsive insulin secretion post-implantation and retrieved grafts contained cells with a mature β cell phenotype. Stem-cell-derived cells can mature into glucose-responsive functional β cells in patients with diabetes.

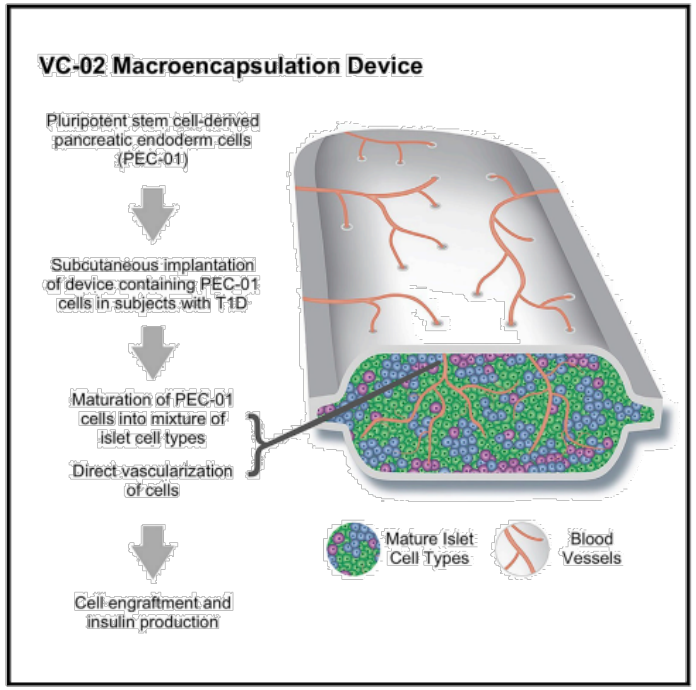

C
HbA1c (%)
9
8
7
6
5
4
B = -0·0055, p = 0·193
0
16
26
52
Time relative to implantation (weeks)
D
Average daily insulin needs (U)
100
80
60
40
20
0
B = -0·220, p < 0·001
-4
0
4
8
12
16
20
24
28
32
36
40
44
48
Time relative to implantation (weeks)

Cell Reports
Medicine

Article

Insulin expression and C-peptide in type 1 diabetes subjects implanted with stem cell-derived pancreatic endoderm cells in an encapsulation device

Graphical abstract



Authors

A.M. James Shapiro, David Thompson, Thomas W. Donner, ..., Evert J. Kroon, Kevin A. D'Amour, Howard L. Foyt

Correspondence

hfoyt@viacyte.com

In brief

Shapiro et al. report preliminary proof-of-concept that in 17 people with type 1 diabetes, pancreatic endoderm cells in an investigational subcutaneous device (VC-02) achieved engraftment and insulin expression in 63% of units at 3–12 months post-implant. Pluripotent stem cells may be a scalable, renewable alternative to pancreatic islet transplants.

Table 3. Summary of stimulated C-peptide and histology analysis of graft explants

		Post-implant Maximum stimulated [C-peptide] (ng/mL)							Histology (Number of insulin-positive graft cells per section)	
	Pre-implant									
Subject	**Screening**[a]	**6 m**[b]	**9 m**[c]	**12 m**[b]	**15 m**[c]	**18 m**[c]	**21 m**[c]	**24 m**[b]	**3 m**	**9-12 m**
A-006	C-peptide negative	BQL	BQL	0.3	0.2	n/a	*TBD*	*TBD*	202	25
B-004		BQL	BQL	0.1	BQL	0.2	*TBD*	*TBD*	758	20
D-001		0.1	BQL	0.1	*TBD*	*TBD*	*TBD*	*TBD*	461	1419
E-002		0.1	OUT	OUT	OUT	OUT	OUT	OUT	56	387
E-006		BQL	0.1	0.2	ND	0.2	0.2	0.2	70	132
E-007		BQL	0.1	0.2	0.2	0.2	*TBD*	*TBD*	346	1123
p value Responders (N = 6) versus Non-Responders (N = 11)									0.0348	0.0514
A-001	C-peptide negative	BQL	BQL	BQL	OUT	OUT	OUT	OUT	4	17
A-002		BQL	BQL	BQL	OUT	OUT	OUT	OUT	18	43
A-003		BQL	BQL	BQL	OUT	OUT	OUT	OUT	2	41
A-004		BQL	BQL	BQL	OUT	OUT	OUT	OUT	5	ND
A-005		BQL	BQL	BQL	OUT	OUT	OUT	OUT	38	25
B-003		BQL	BQL	BQL	OUT	OUT	OUT	OUT	19	34
C-001		BQL	BQL	BQL	OUT	OUT	OUT	OUT	75	1
D-002		BQL	BQL	BQL	OUT	OUT	OUT	OUT	2230	ND
E-003		BQL	BQL	BQL	OUT	OUT	OUT	OUT	46	57
E-005		BQL	BQL	BQL	OUT	OUT	OUT	OUT	227	1
E-008		BQL	BQL	BQL	OUT	OUT	OUT	OUT	72	0

Data from the 17 subjects in Cohort 2 are shown; the six subjects who exhibited *de novo* stimulated C-peptide measurements (peak measurement in ng/mL) are sorted to the top of the table.
Letters A-E in the subject number represent different clinical sites.

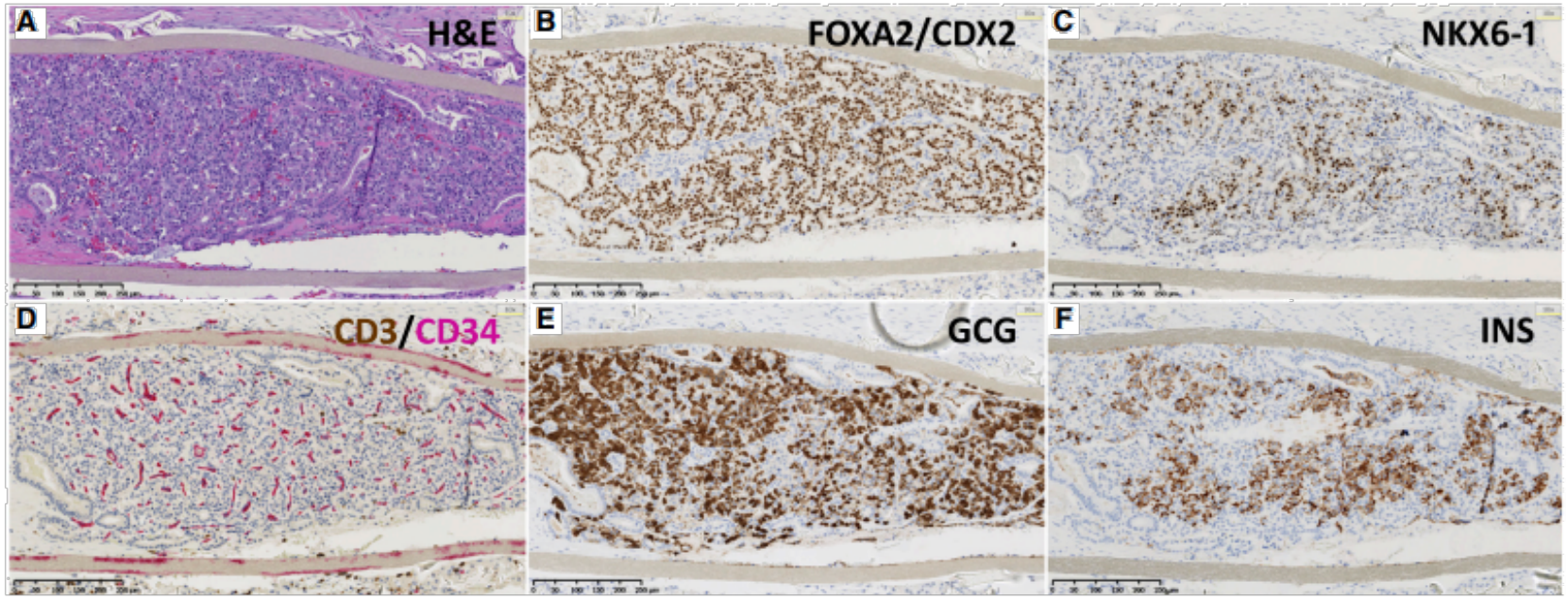


Figure 4. Histology of cross-sections from an explanted dose-finding unit at approximately 11 months from "Subject E-002"

Several panels illustrate the histological features routinely observed in the cellular regions of VC-02 grafts. Shown are "nearly adjacent" sections. Gray strips seen at the top and bottom of each image are the delivery device membranes.

(A) H&E staining reveals densely packed cells reminiscent of human endocrine islet morphologies, albeit without the macro-anatomical "islet" nature.

(B) Nearly all graft-derived cells are endodermal in nature as demonstrated by nuclear staining to the transcription factors FOXA2 and CDX2. The open structure lined with endodermal cells, exemplified in the lower left of each image, is not a prominent feature but observed occasionally in the cellular regions of the grafts.

(C) A subset of graft-derived cells coincident with insulin-expressing cells show nuclear immunoreactivity for NKX6-1, a transcription factor specific to β cells in mature human islets.

(D) The cellular regions are well vascularized with microcapillary structure, demonstrated with the endothelial cell marker CD34 (magenta). CD3 staining (brown) marks T cells, not abundant but observed occasionally outside the device lumen, but rarely inside the lumen among graft-derived cells.

(E) Many cells show glucagon (GCG) immunoreactivity.

(F) Many cells show insulin (INS) immunoreactivity in regions coincident with NKX6-1 expression. Scale bars, 250 μm. Counterstain is hematoxylin.

Vertex Shares "Unprecedented" Results in Early-Stage Type 1 Diabetes Trial

Published: Oct 18, 2021 | By Mark Terry

VX-880, formerly known as STx-02, is an investigational allogeneic human stem cell-derived islet cell therapy that is being evaluated for patients who have T1D with impaired hypoglycemic awareness and severe hypoglycemia.

VX-880 involves an infusion of fully differentiated, functional islet cells, as well as the chronic administration of concomitant immunosuppressive therapy, to protect the islet cells from immune rejection.

RECRUITING Phase 1, Phase 2

A Safety, Tolerability, and Efficacy Study of VX-880 in Participants With Type 1 Diabetes

This study will evaluate the safety, tolerability and efficacy of VX-880 infusion in participants with Type 1 diabetes mellitus (T1D) and impaired awareness of hypoglycemia (IAH) and severe hypoglycemia.

ClinicalTrials.gov Identifier

NCT04786262

Key inclusion criteria

- Clinical history of T1D with > 5 years of duration
- At least two episodes of documented severe hypoglycemia in the 12 months prior to enrollment
- Stable diabetic treatment
- Consistent use of continuous glucose monitor (CGM) for at least 3 months before Screening and willingness to use CGM for the duration of the study

Key exclusion criteria

Other protocol defined Inclusion/Exclusion criteria may apply.

Study Overview

Brief Summary

This study will evaluate the safety, tolerability and efficacy of VX-880 infusion in participants with Type 1 diabetes mellitus (T1D) and impaired awareness of hypoglycemia (IAH) and severe hypoglycemia.

Official Title

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

Conditions

Study Start (Actual)

2021-03-29

Primary Completion (Estimated)

2024-01

Study Completion (Estimated)

2028-01

VX-880 Phase 1/2 Study Enrolled Participants with T1D, History of Recurrent Severe Hypoglycemia, and High HbA1c

Study design:

- 3-part, open-label, Phase 1/2 study
- Part A completed enrollment and sequential dosing (half target dose)
- Part B completed enrollment and sequential dosing (target dose)
- Part C is ongoing with concurrent dosing (target dose)

Key inclusion criteria:

- Diagnosis of T1D and 18 to 65 years of age
- Impaired hypoglycemic awareness
- ≥2 SHEs in year before screening

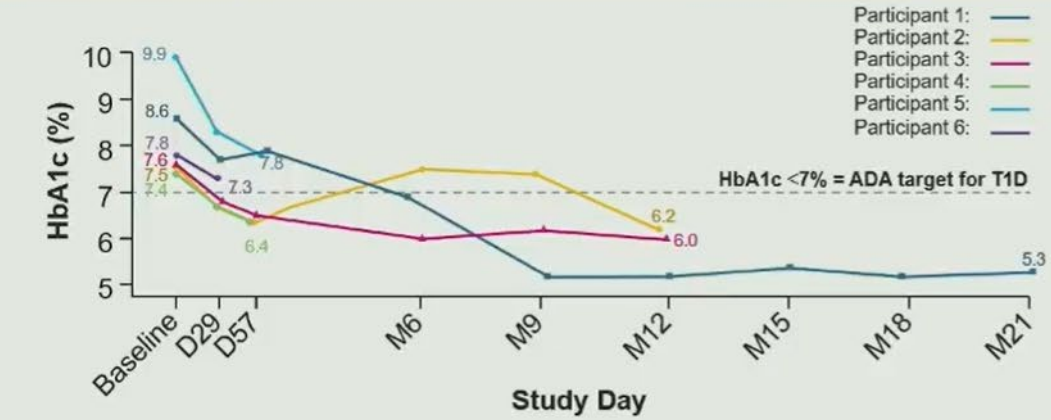
Primary efficacy endpoint:

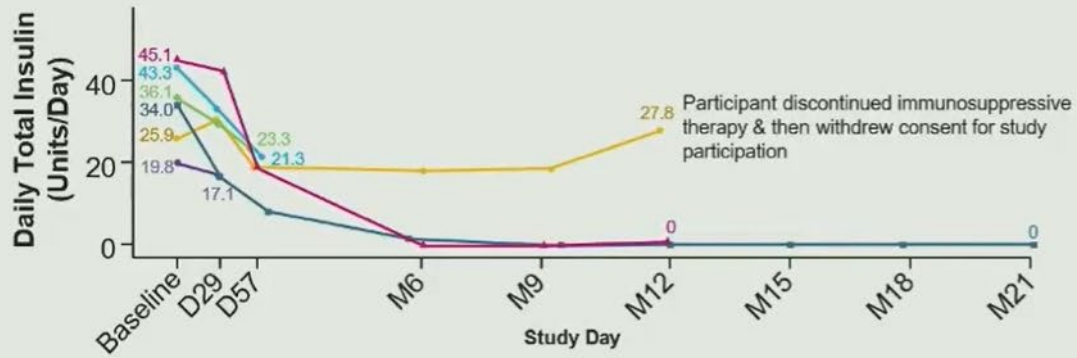
- Proportion of participants free from SHEs from Day 90 through Month 12 with Hb1Ac <7% or ≥1% reduction in HbA1c from baseline between Day 180 and Month 12

Baseline Demographics

Category, mean (min, max)	N = 6
Age (years)	44.0 (33, 64)
Sex (F/M)	3F/3M
BMI (kg/m^2)	23.5 (21.3, 28.0)
Duration of diabetes (years)	23.0 (7.8, 47.4)
HbA1c (%)	8.13 (7.4, 9.9)
Fasting C-peptide (pmol/L)	undetectable
Total daily insulin (unit/day)	34.0 (19.8, 45.1)
SHEs in year prior to infusion	3.3 (2, 5)

All Participants Engrafted Islet Cells, Had Improved Glycemic Control (HbA1c), and Reduction in Insulin Use After VX-880 Infusion



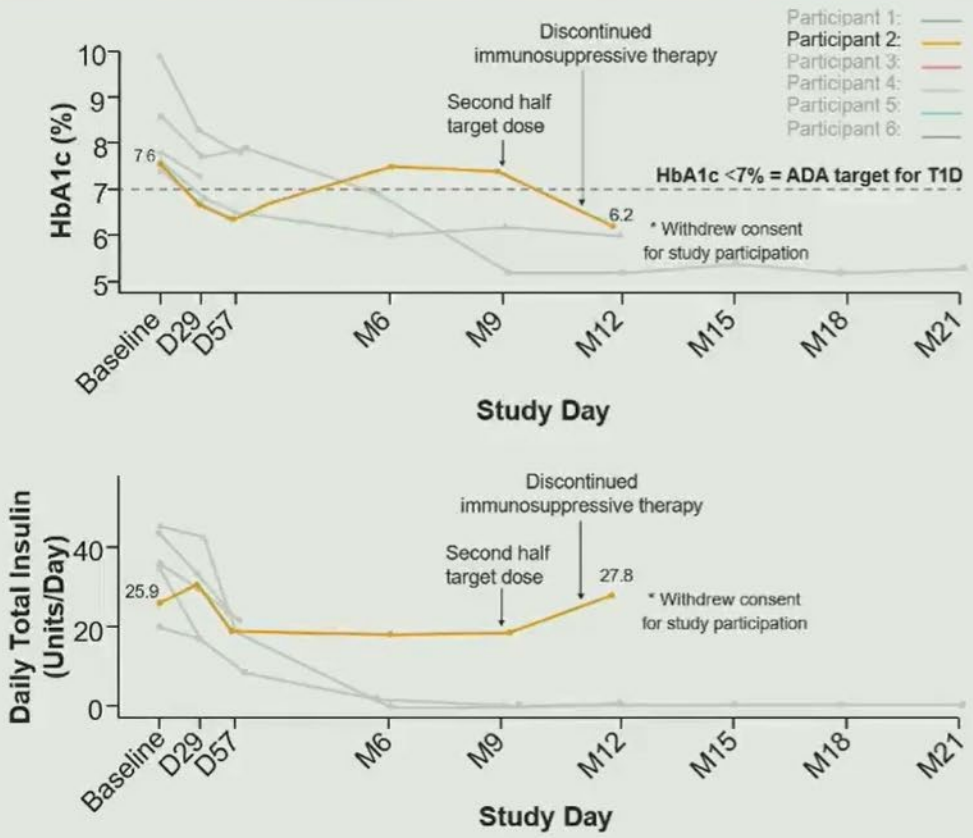


All 6 participants had undetectable fasting C-peptide at enrollment

After VX-880 infusion, all 6 participants demonstrated:

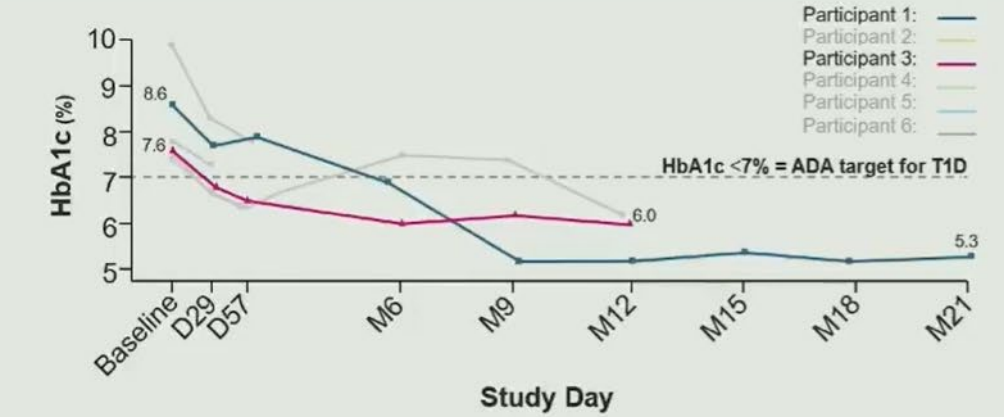
- Production of endogenous insulin (C-peptide)
- Reduction in HbA1c
- Reductions in insulin use
- Elimination of SHEs during the evaluation period (Day 90 onwards)

One Participant Stopped Immunosuppressive Therapy and Withdrew Consent Following Second Half Dose of VX-880



- Participant received half target dose of VX-880 in Part A and demonstrated improved glycemic control
- At Day 269, the participant received a second half target dose of VX-880, per protocol
- Participant discontinued immunosuppressive therapy on Day 75 after the second half target dose of VX-880 (Day 343)
- Participant withdrew consent (not due to AE) after the Day 90 visit following second half target dose of VX-880 (Day 370)

Both Participants with >1 Year of Follow-up Met the Criteria for the Primary Endpoint and are Insulin Independent

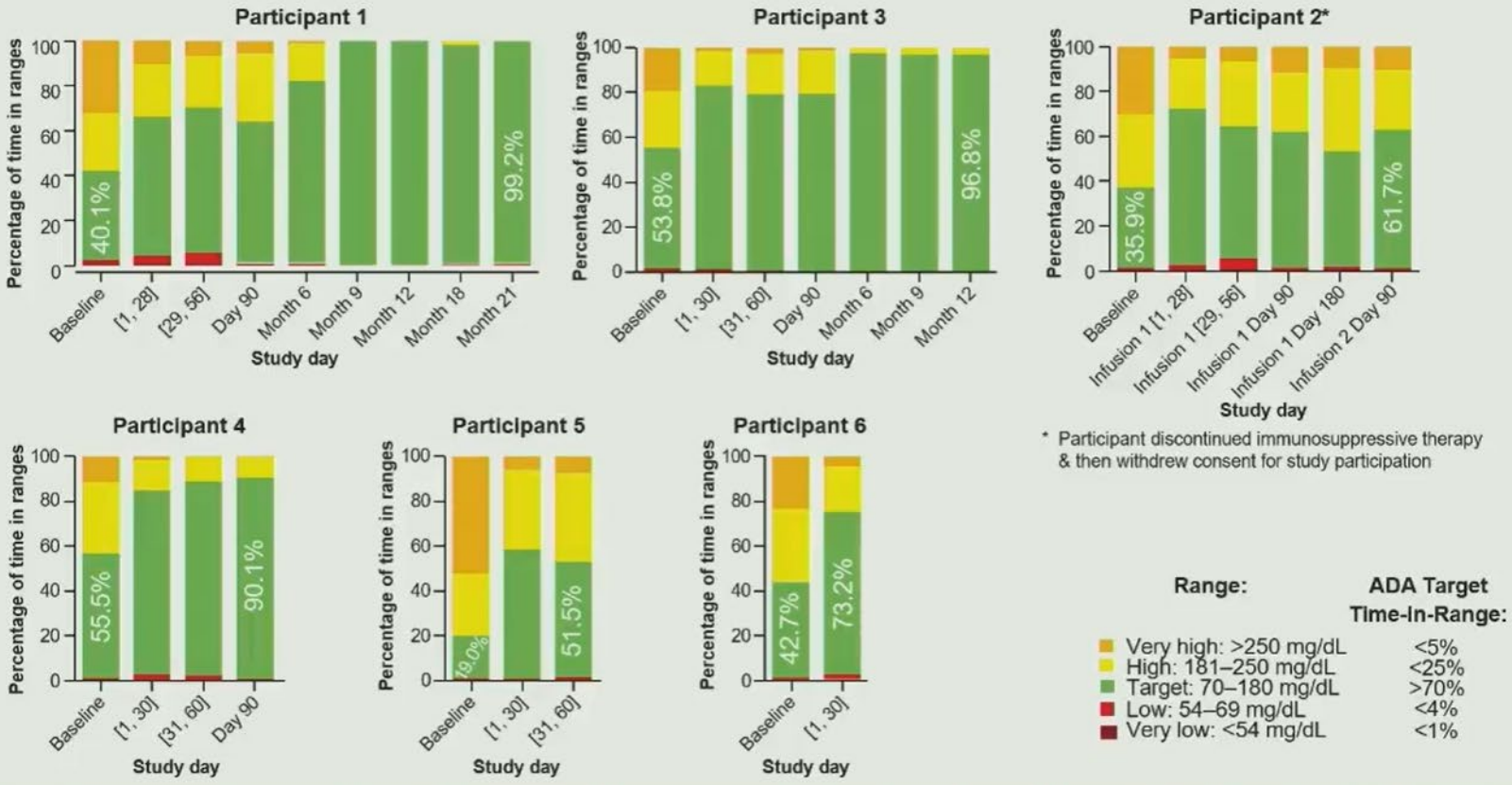


Both participants met the criteria for the primary endpoint of eliminating SHEs with HbA1c <7%

Both participants achieved insulin independence

- One participant maintained insulin independence from Month 9 to the data cut-off time point (Month 21) with HbA1c of 5.3%
- A second participant maintained insulin independence from Month 6 to data cut-off time point (Month 12) with HbA1c of 6.0%

All Participants Had Improved Time-in-Range After VX-880 Infusion



Safety Profile of VX-880 is Consistent with Immunosuppressive Therapy and Deceased Donor Islet Cell Therapy

	Participants with AEs (N=6) n (%)	Total AEs (N=6)
Any AEs	6 (100)	110
AEs by severity		
Mild	5 (83)	57
Moderate	5 (83)	41
Severe	3 (50)	12
Life threatening	0	0
AEs related to VX-880	2 (33)	2
AEs related to immunosuppressive therapy	5 (83)	44
Serious AEs	3 (50)	7
Serious AEs related to VX-880	0	0
AEs leading to study discontinuation	0	0

- Most AEs were **mild or moderate** in severity
  - One participant had SHEs in the peri-operative period; considered unrelated to VX-880
- Of the **AEs with a causal relationship,** most were **attributed to immunosuppressive therapy**
- Two nonserious AEs were related to VX-880; both were transaminase elevations that occurred shortly after VX-880 infusion, were transient and resolved
- SAEs included dehydration, rash, confusional state, neutropenia, small intestinal obstruction, and migraine events
- **No SAEs** were considered **related to VX-880**

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

Participation Criteria

Researchers look for people who fit a certain description, called eligibility criteria. Some examples of these criteria are a person's general health condition or prior treatments.

For general information about clinical research, read Learn About Studies.

Eligibility Criteria

Description

Key Inclusion Criteria:

- Clinical history of T1D with greater than (>) 5 years duration
- Participant is on a stable diabetic treatment
- Consistent use of continuous glucose monitoring (CGM) for at least 4 weeks before Screening and willingness to use CGM for the duration of the study

Key Exclusion Criteria:

- Prior islet cell transplant, organ transplant, or cell therapy...

Ages Eligible for Study

18 Years to 65 Years (Adult, Older Adult)

Sexes Eligible for Study

All

Accepts Healthy Volunteers

No

A 30 anni dal primo trapianto di isole .....

Grazie per l'attenzione!

Ospedale Niguarda

Sistema Socio Sanitario
Regione Lombardia