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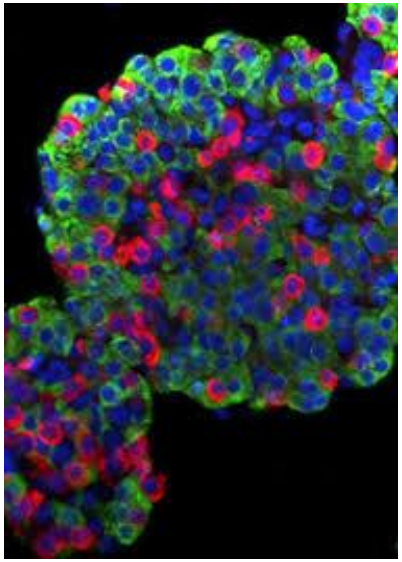
Islet Transplantation

Alistair Lumb

01.10.2025



Disclosures

- Payments for Speaking and Advisory boards
  - Abbott Diabetes Care, Dexcom, Insulet, Lilly Diabetes, Medtronic, Menarini, Novo Nordisk, Sanofi
- Institutional Research Support
  - Abbott Diabetes Care, Novo Nordisk
- Positions held
  - Chair, Diabetes Technology Network-UK
  - Member of EXTOD executive

Plan

- The process of islet transplantation
- Benefits and risks for islet transplantation alone
  - Who to refer?
- Other current indications for islet transplantation
  - Simultaneous islet kidney transplantation
  - Total Pancreatectomy with Islet Auto-Transplantation (TPIAT)
- Future directions

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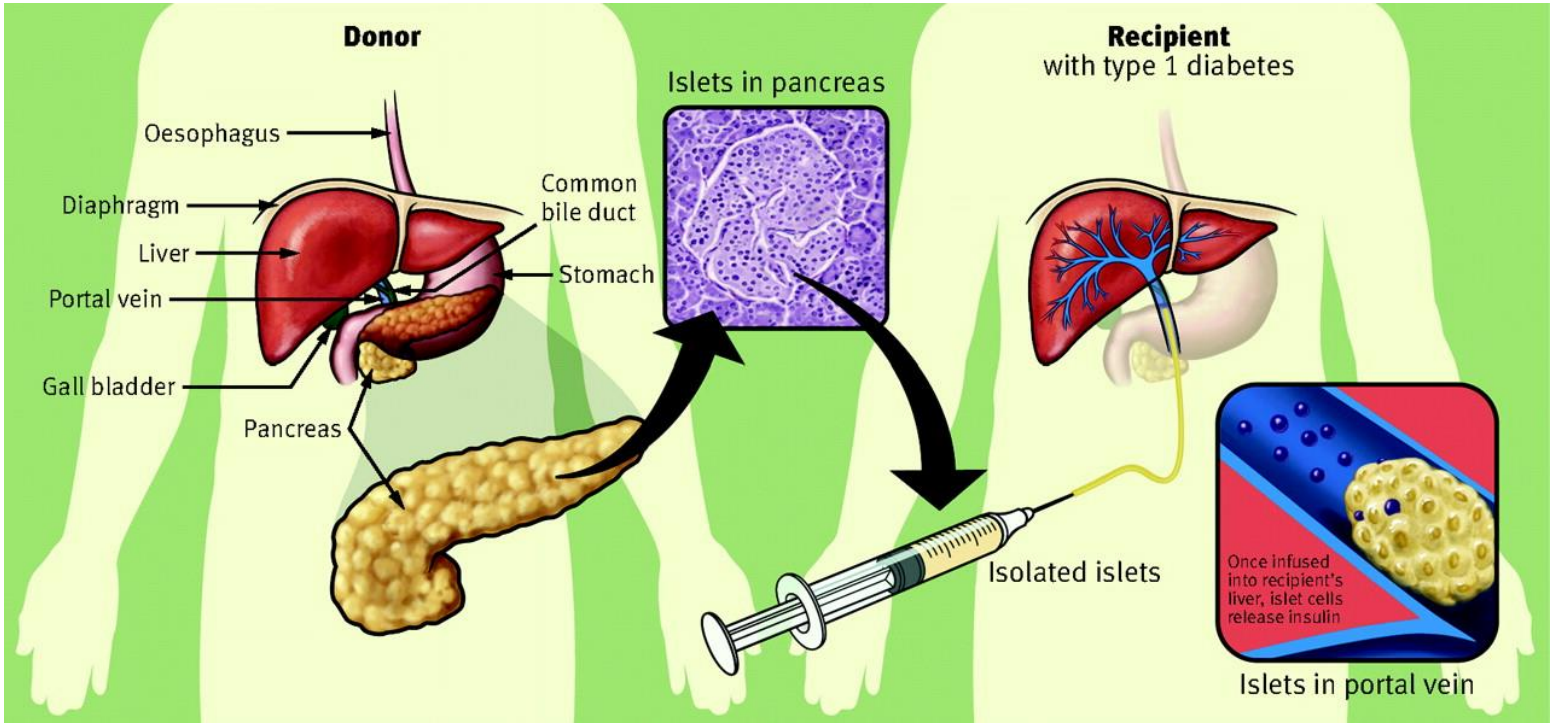
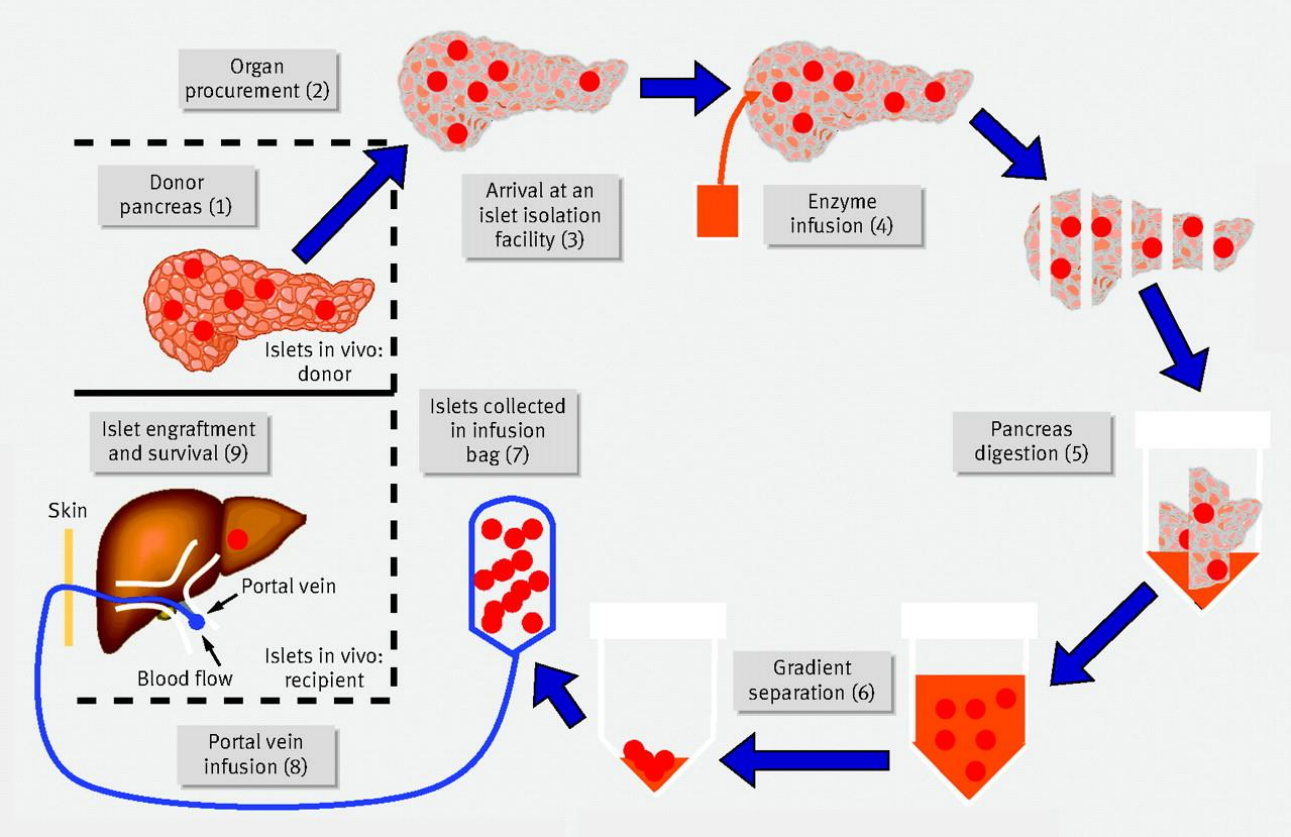
Islet transplantation – the process

Islet Transplantation



Hanneke de Kort et al. BMJ 2011;342:bmj.d217

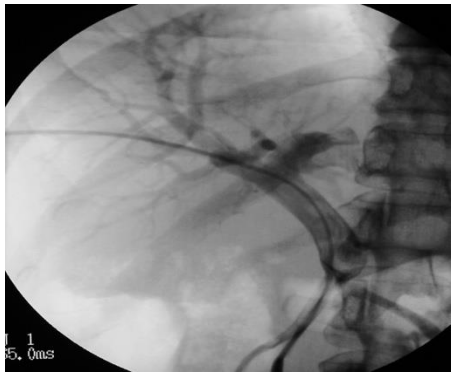
Islet Isolation



Hanneke de Kort et al. BMJ 2011;342:bmj.d217

Islet Transplantation

- Percutaneous transhepatic approach in interventional radiology
- Antibiotic and heparin cover
- Local anaesthesia ± sedation
- Infused over 30 minutes
- Tract closed with embolization (increased risk of bleeding with gelfoam)



Post-transplant management

- Tight glucose management – aiming for normoglycaemia to protect islet function (specific insulin protocol)
- No CHO first 24 hours
- After that – initially limited to 25g CHO with each meal
- Usually on pump/HCL therapy – restarted after 24 hours at previous settings and then monitored and adjusted closely
- Usually home after 72 hours when glucose stable and recovered from procedure

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The Edmonton Protocol

The New England Journal of Medicine

VOLUME 343 JULY 27, 2000 NUMBER 4

ISLET TRANSPLANTATION IN SEVEN PATIENTS WITH TYPE 1 DIABETES MELLITUS USING A GLUCOCORTICOID-FREE IMMUNOSUPPRESSIVE REGIMEN

A.M. JAMES SHAPIRO, M.B., B.S., JONATHAN R.T. LAKEY, PH.D., EDMOND A. RYAN, M.D., GREGORY S. KORBUTT, PH.D., ELLEN TOTH, M.D., GARTH L. WARNOCK, M.D., NORMAN M. KNETEMAN, M.D., AND RAY V. RAJOTTE, PH.D.

Immunosuppression

- Steroid-free maintenance immunosuppressive regimen:
    - Single dose of methylprednisolone at induction
    - Campath (alemtuzumab – anti-CD52 monoclonal antibody) at induction
    - Tacrolimus (calcineurin inhibitor) – aiming for trough level of 8-12 ng/ml first 3/12, then 5-8 ng/ml
    - Mycophenolate mofetil

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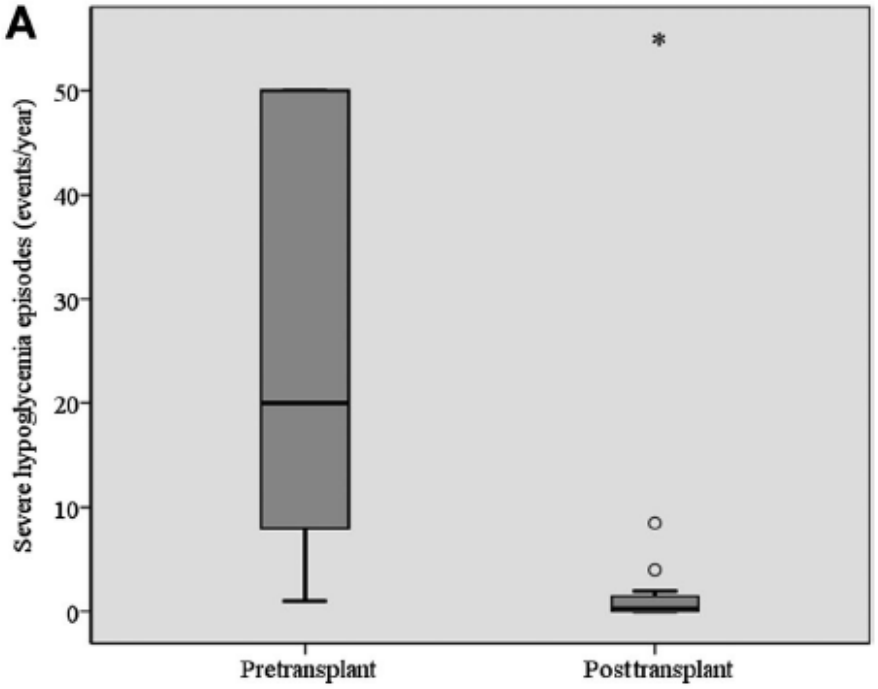
Islet transplantation – the benefits

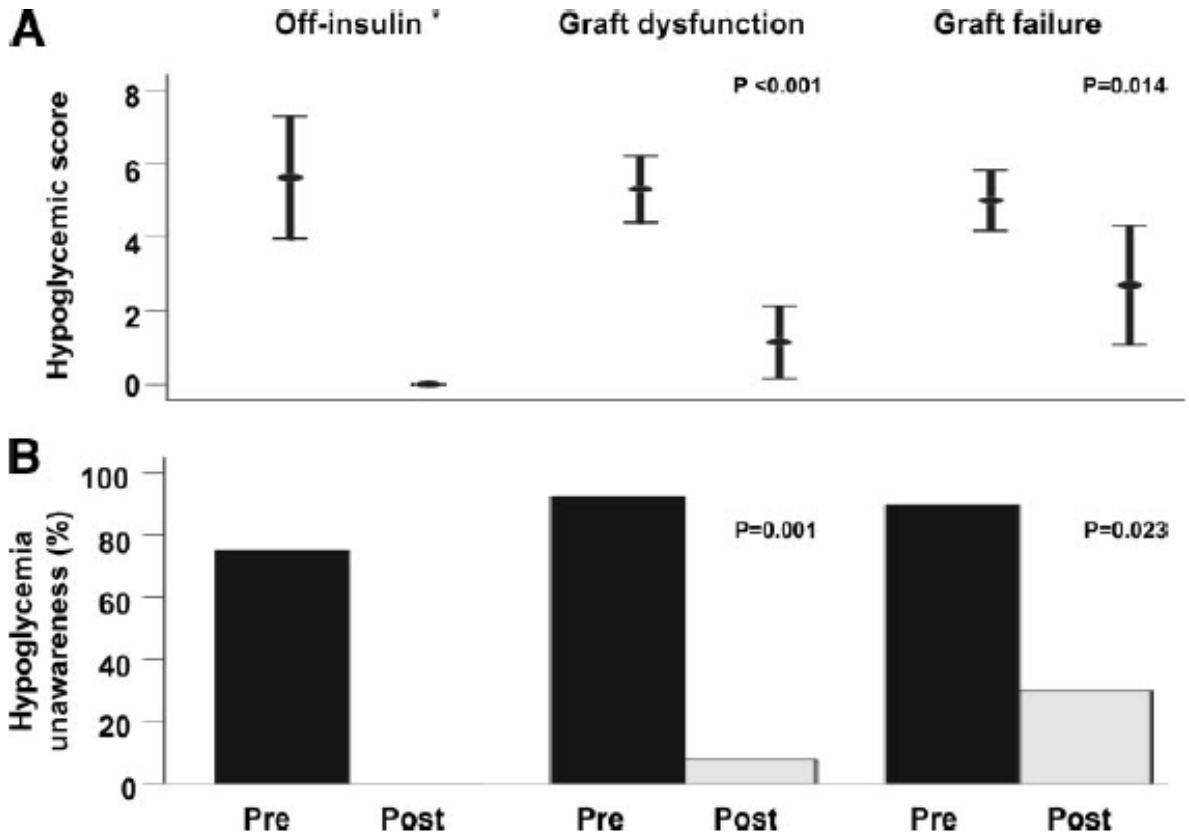
Reduction in severe hypoglycaemia

- Significant reduction in episodes of severe hypoglycaemia (requiring assistance)
- Improvement also seen in hypoglycaemia awareness (mean Gold Score reduced from 6 to 2)



American Journal of Transplantation 2013; 13:3236-3243

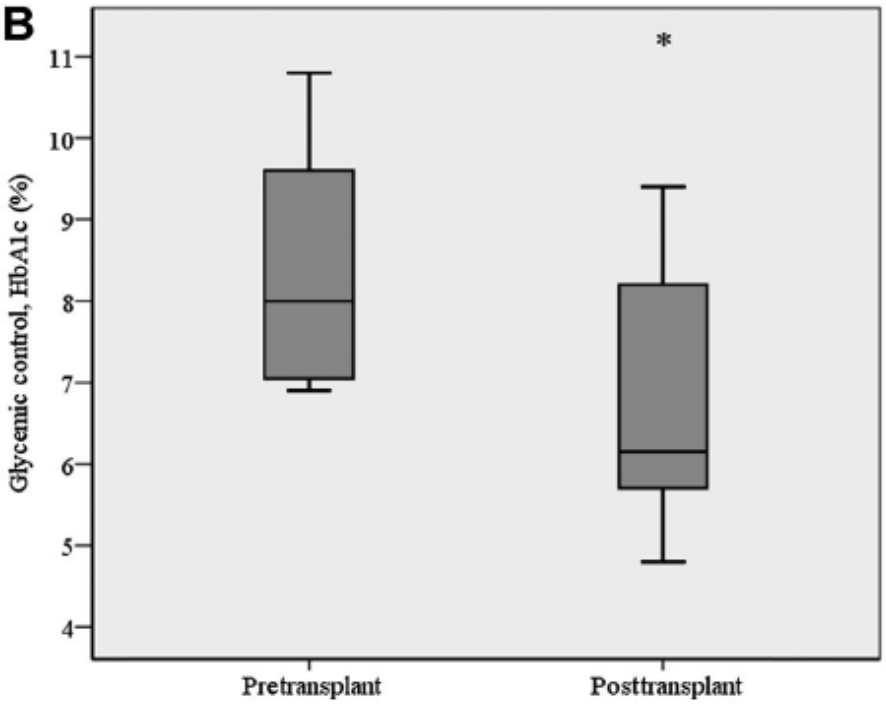
Even with graft dysfunction



Diabetes Care 2008; 31:2113-2115

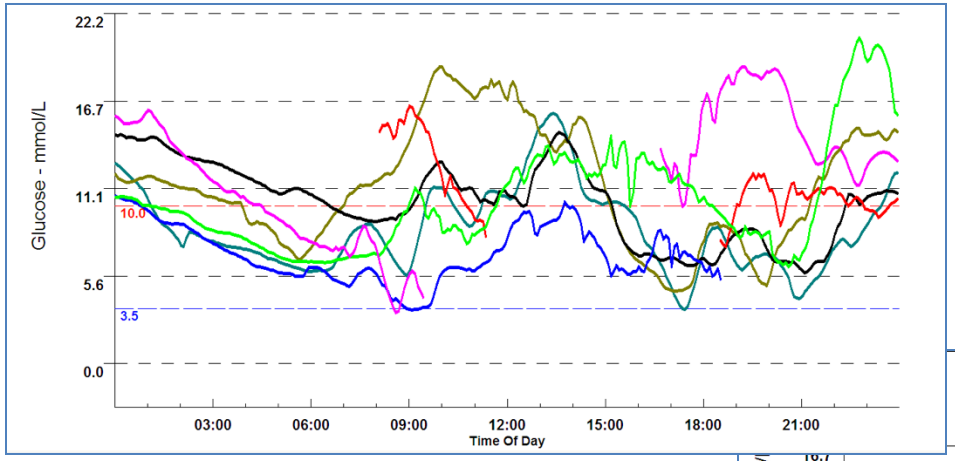
Improvement in HbA1c

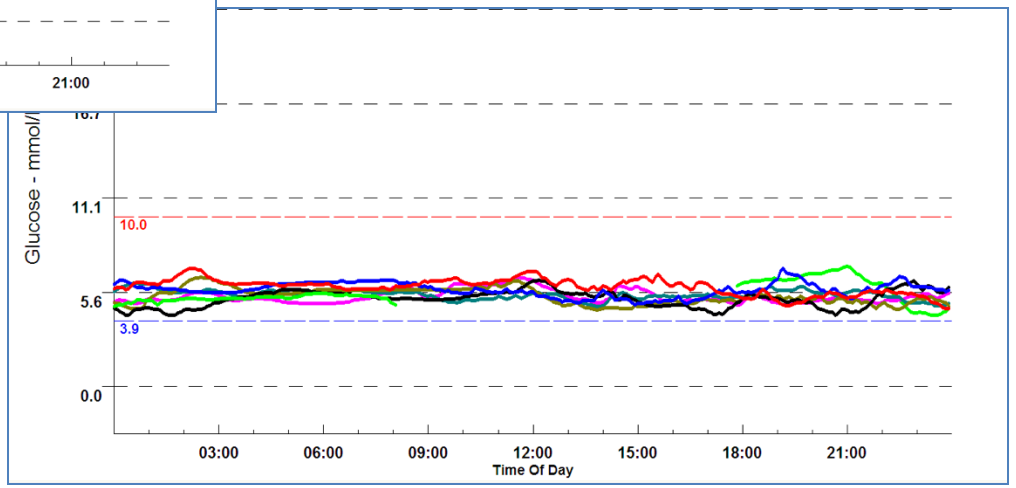
- There is a significant improvement in HbA1c post-transplant alongside the reduction in severe hypoglycaemia
- As you would expect, this reflects a significant reduction in glycaemic variability post-transplant



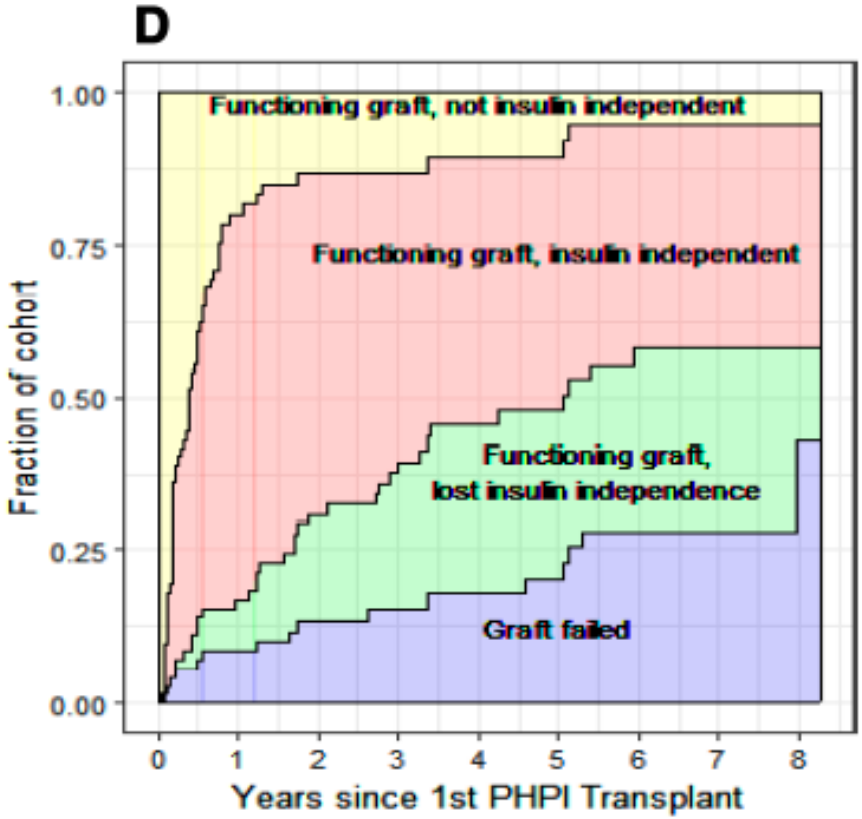
American Journal of Transplantation 2013; 13:3236-3243

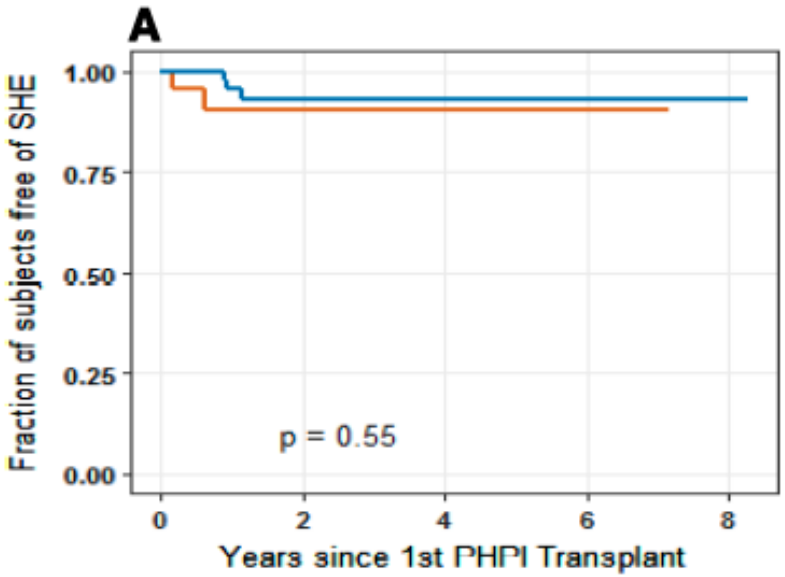
Quality of life can be transformed





Long-term outcomes





Diabetes Care 2022; 45:2967-2975

Microvascular complications

TABLE 2. Annual rate of change in GFR by ^{99m}Tc-DTPA and MDRD in the medical and post-ICT groups

Δ GFR (mL/min/1.73 m^2/yr)	Medical (95% CI)	ICT (95% CI)	*P*
^{99m}Tc-DTPA all subjects	−2.98 (−1.81 to −4.15)	−1.27 (−0.50 to −2.04)	<0.0001
≥2-yr follow-up	−4.79 (−2.44 to −7.14)	−1.42 (−0.44 to −2.40)	<0.0001
≥3-yr follow-up	−3.55 (−1.53 to −5.57)	−1.40 (−0.32 to −2.48)	<0.0001
MDRD all subjects	−3.53 (−2.49 to −4.57)	−1.49 (−1.06 to −1.92)	<0.0001

GFR, glomerular filtration rate; ICT, islet cell transplantation; DTPA, ^{99m}Tc-diethylenetriaminepentaacetate; MDRD, modification of diet in renal disease; CI, confidence interval.

TABLE 3. Progression of diabetic retinopathy in the medical and post-ICT groups

	Medical		ICT	
	No. eyes	No. progressed	No. eyes	No. progressed
Mild NPDR	16	0	8	0
Moderate NPDR	19	1	12	0
Severe NPDR	6	2	2	0
PDR	41	7	29	0
Total	82	10[a]	51	0[a]

[a] The progression is significantly more in the medical than the post-ICT group ($P<0.01$).

ICT, islet cell transplantation; NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy.

Transplantation 2011; 91:373-378

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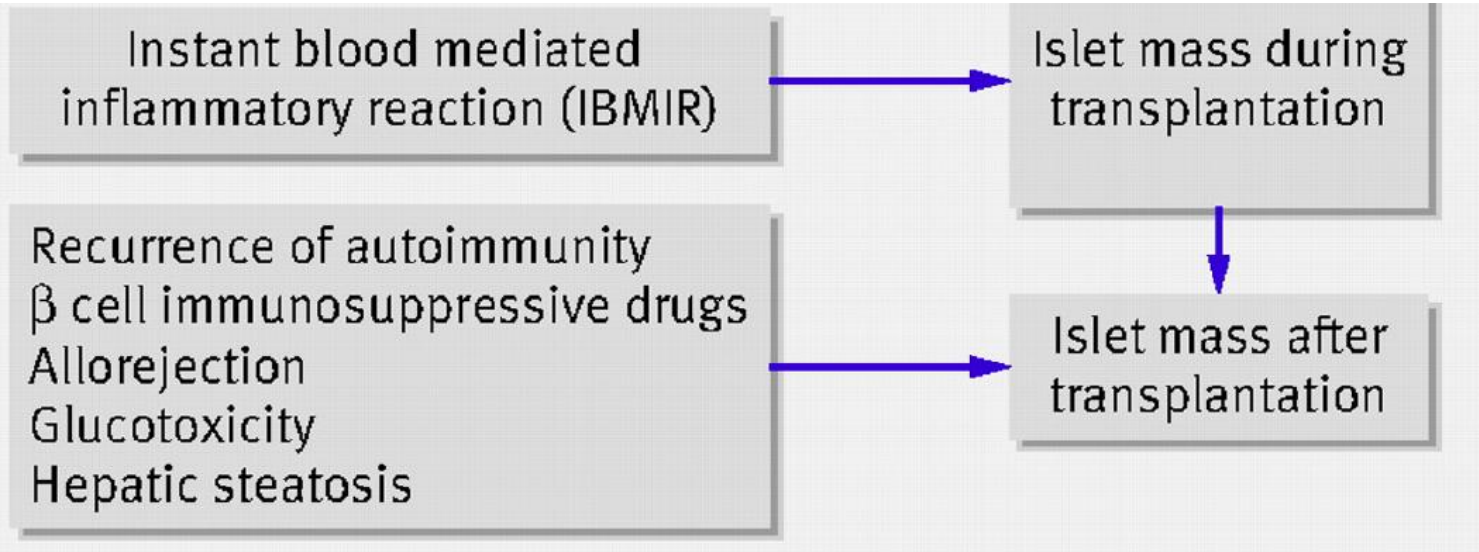
Islet transplantation – the risks

Risks of Islet Transplantation

- Procedure:
  - Bleeding and Haematoma: 10-15%
  - Infection: Rare
  - Portal vein thrombosis: rare
  - Mortality: <1%

- Immunosuppression (data from solid organ transplant recipients):
  - Life-threatening infection 2%
  - Overall cancer risk is doubled – 6 year risks
    - Cancer excluding skin cancer 4%
    - Skin cancer 8%

Risks to the transplanted islets



Hanneke de Kort et al. BMJ 2011;342:bmj.d217

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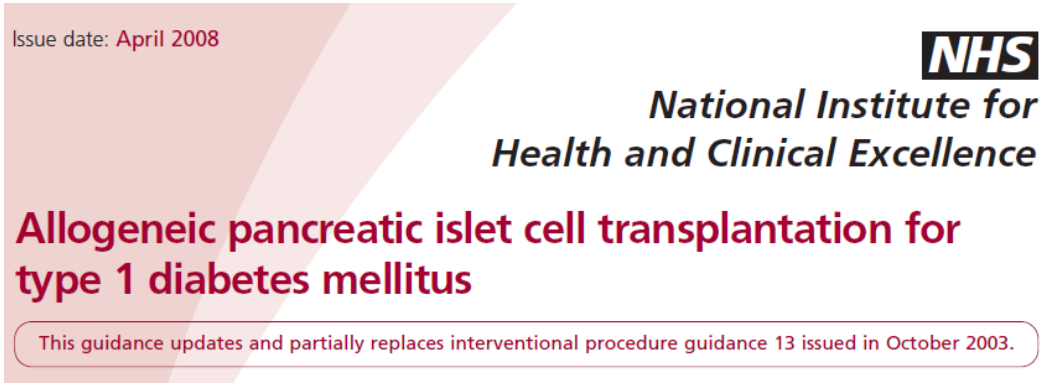
Who to refer?

Aims for Islet Transplantation Alone (ITA)


Issue date: April 2008

NHS
National Institute for Health and Clinical Excellence

Allogeneic pancreatic islet cell transplantation for type 1 diabetes mellitus

This guidance updates and partially replaces interventional procedure guidance 13 issued in October 2003.

- To improve the quality of life of people with T1DM suffering from severe, recurrent and potentially life-threatening hypoglycaemia
- To improve awareness of hypoglycaemia
- To be considered in those with a renal transplant already on immunosuppression
- Insulin independence is **not** a goal

Who to refer?

Patients with type 1 diabetes who might be suitable for islet cell transplantation
Patients with: • Two or more episodes of severe hypoglycaemia (requiring other people to help) within the last 2 years • Impaired awareness of hypoglycaemia • Severe hypoglycaemia, impaired awareness or poor glycaemic control despite best medical therapy[2] in those who have a functioning kidney transplant
Patients who are probably not suitable for islet cell transplantation
Patients who: • Require >0.7 units/kg/day of insulin (~50 units/day for a 70kg patient) • Weigh more than 85kg • Have poor kidney function (in general this means a GFR <60ml/min, and ~30ml/min in renal transplant patients)

Other current indications

SIK/IAK Transplantation

- In those with type 1 diabetes requiring renal transplant where whole pancreas transplantation would be contraindicated due to
  - Age
  - Co-morbidity
  - Fitness
  - Patient choice

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Benefit to the renal transplant

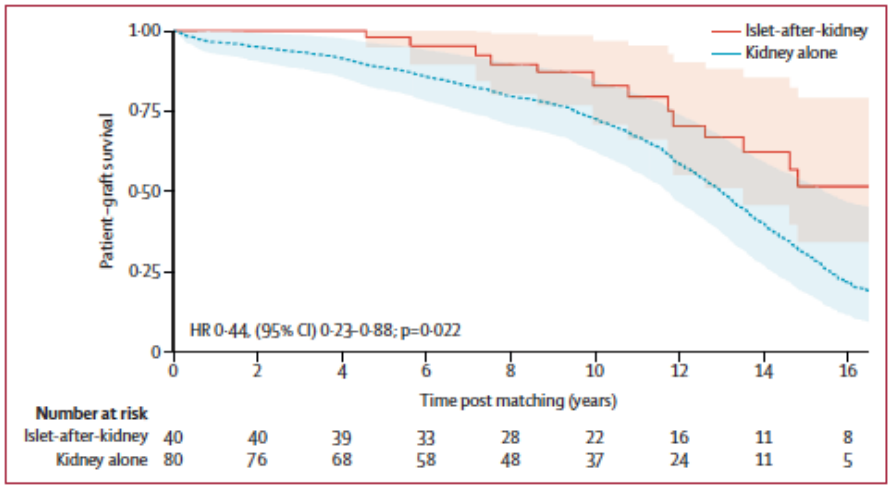


Figure 3: **Patient–graft survival in patients with type 1 diabetes treated with islet-after-kidney transplantation or kidney transplantation alone**
Representation of bootstrapped Kaplan–Meier survival curves after matching of patients with islet-after-kidney transplantation and patients with kidney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

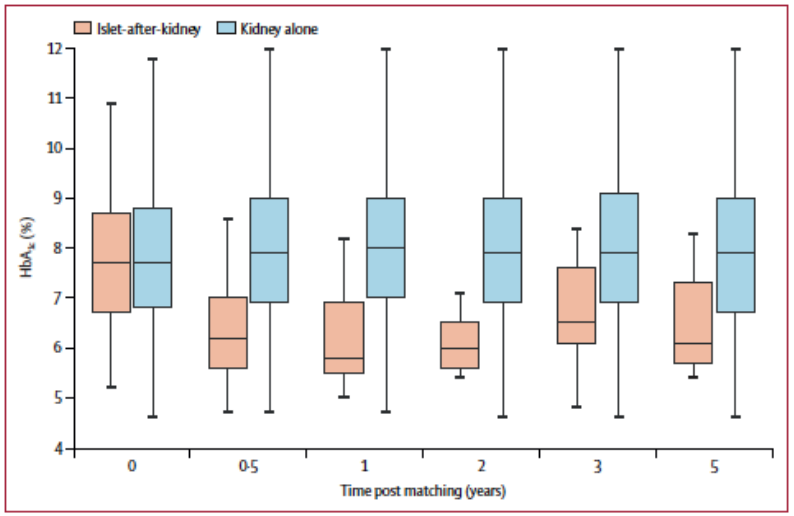


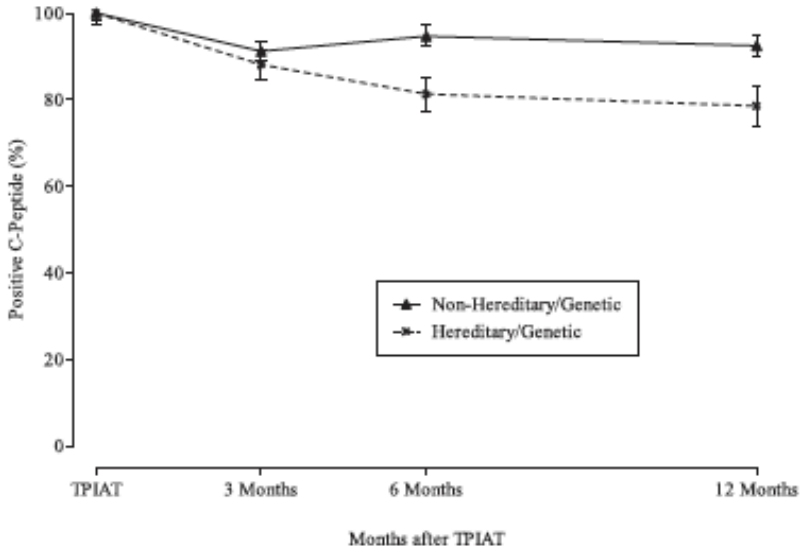
Figure 4: **HbA_{1c} after matching in patients with type 1 diabetes treated with islet-after-kidney transplantation or kidney transplantation alone**
Results were obtained on the 1000 bootstrap samples to mitigate any bias that might arise from a single matched sample. Boxes show median, 25th and 75th percentiles. Whiskers indicate 1·5 IQR.

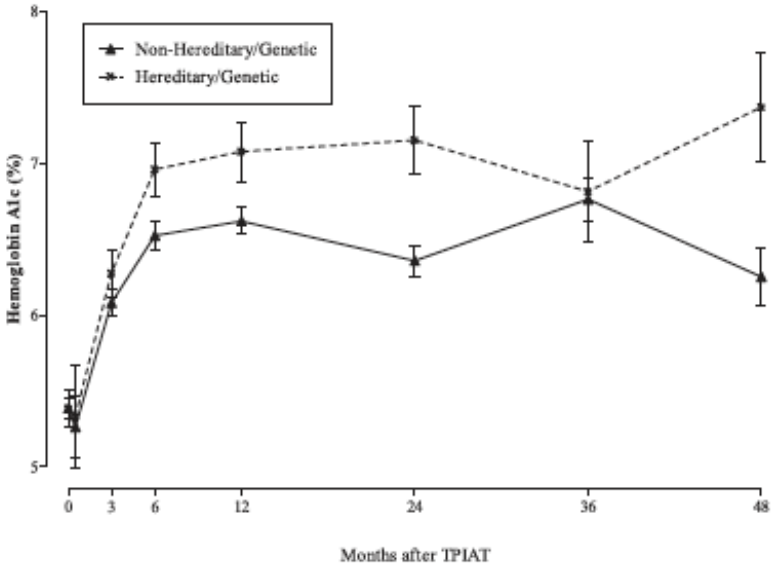
https://doi.org/10.1016/S2213-8587(24)00241-9

TPIAT

- Where total pancreatectomy is indicated as a result of chronic pancreatitis and person does **not** have diabetes pre-operatively
- Regional referral centres around the UK (King's, Leicester, Oxford, Newcastle)
- TPIAT mitigates the challenges with managing type 3c diabetes resulting from total pancreatectomy

Benefits of TPIAT





J Am Coll Surg 2014;218:530-545

GLUCOSE STATISTICS AND TARGETS

18 September 2025 - 1 October 2025	**14 Days**
Time sensor active:	**95%**

Ranges And Targets For	Type 1 or Type 2 Diabetes
Glucose Ranges	**Targets** % of Readings (Time/Day)
Target Range 3.9-10.0 mmol/L	Greater than 70% (16h 48min)
Below 3.9 mmol/L	Less than 4% (58min)
Below 3.0 mmol/L	Less than 1% (14min)
Above 10.0 mmol/L	Less than 25% (6h)
Above 13.9 mmol/L	Less than 5% (1h 12min)

Each 5% increase in time in range (3.9-10.0 mmol/L) is clinically beneficial.

Average Glucose	**5.4** mmol/L
Glucose Management Indicator (GMI)	**5.6% or 38 mmol/mol**
Glucose Variability	**15.7%**

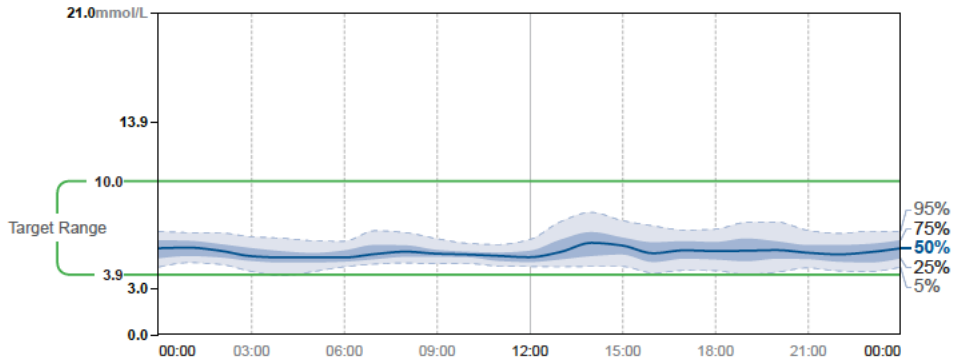
Defined as percent coefficient of variation (%CV); target ≤36%

TIME IN RANGES

Very High	>13.9 mmol/L	0% (0min)
High	10.1 - 13.9 mmol/L	0% (0min)
Target Range	3.9 - 10.0 mmol/L	98% (23h 31min)
Low	3.0 - 3.8 mmol/L	2% (29min)
Very Low	<3.0 mmol/L	0% (0min)

AMBULATORY GLUCOSE PROFILE (AGP)

AGP is a summary of glucose values from the report period, with median (50%) and other percentiles shown as if occurring in a single day.



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Future of islet transplantation

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Stem Cell-Derived Islets

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*

NEJM 2025; 393:858-868

Trial Outcomes

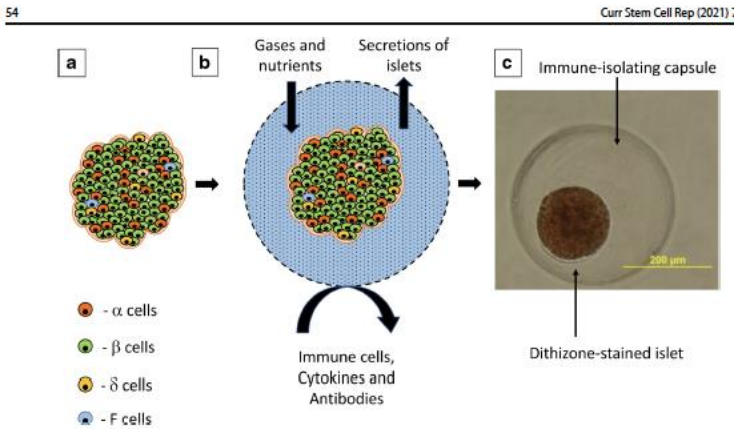
- 2 people received half dose (0.4 x 10^9 cells), followed by 12 receiving full dose (0.8 x 10^9 cells)
- Everybody receiving a full dose of cells achieved freedom from SH and HbA1c less than 7.0% (as well as TIR over 70%)
- 10/12 participants insulin independent at 1 year
- 2 deaths – 1 from cryptococcal meningitis, 1 from progressive dementia related to previous traumatic brain injury

NEJM 2025; 393:858-868

Other future directions

- Microencapsulation
- Macroencapsulation
- Immune modulation

- Aim is to reduce exposure to immunosuppression and associated risk



Curr Stem Cell Rep 2021;7:49-71

Summary

- The process of islet transplantation
- Benefits and risks for islet transplantation alone
  - Who to refer?
- Other current indications for islet transplantation
  - Simultaneous islet kidney transplantation
  - Total Pancreatectomy with Islet Auto-Transplantation (TPIAT)
- Future directions

Thanks for your attention

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