

Update on pancreas – renal transplant in diabetes mellitus

Peter J Friend
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Why transplant the pancreas?

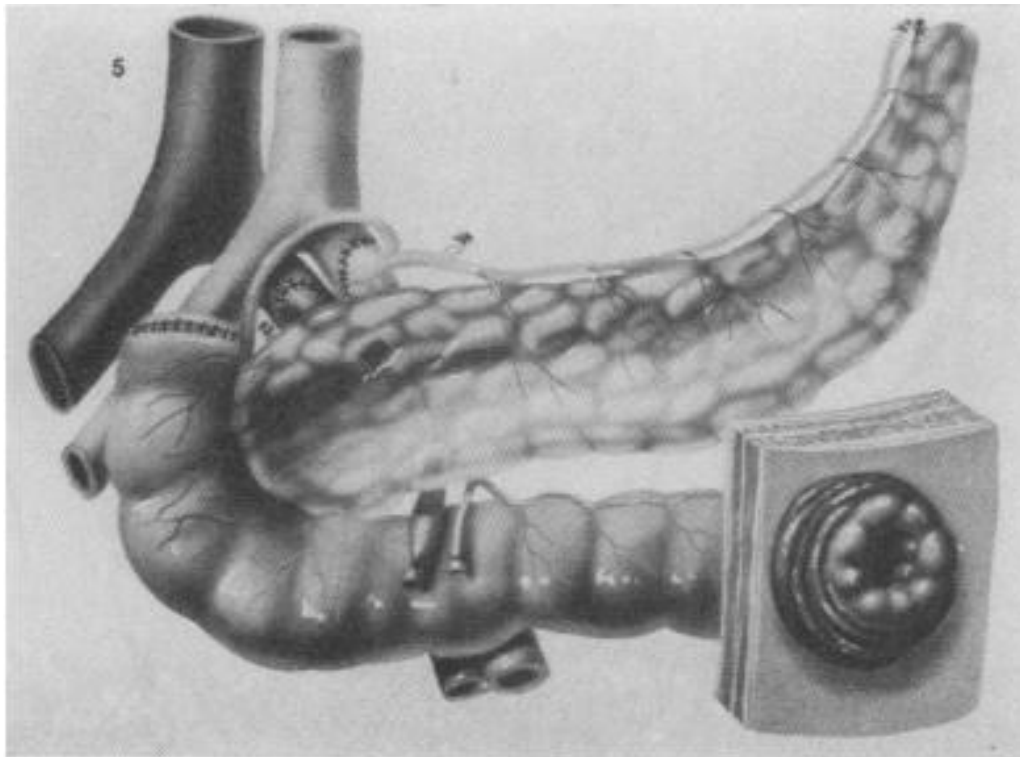
Medical treatment has come a long way...



...and so has surgery

Allotransplantation of the pancreas and duodenum
along with the kidney in diabetic nephropathy.

Kelly WD, Lillehei RC, Merkel FK, Idezuki Y, Goetz FC.
Surgery. 1967



The New England Journal of Medicine

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Number 14

THE EFFECT OF INTENSIVE TREATMENT OF DIABETES ON THE DEVELOPMENT AND PROGRESSION OF LONG-TERM COMPLICATIONS IN INSULIN-DEPENDENT DIABETES MELLITUS

THE DIABETES CONTROL AND COMPLICATIONS TRIAL RESEARCH GROUP*

Tight glycaemic control associated with:

- Delayed onset & progression of nephropathy, neuropathy, retinopathy
- Increased incidence of hypoglycaemic episodes

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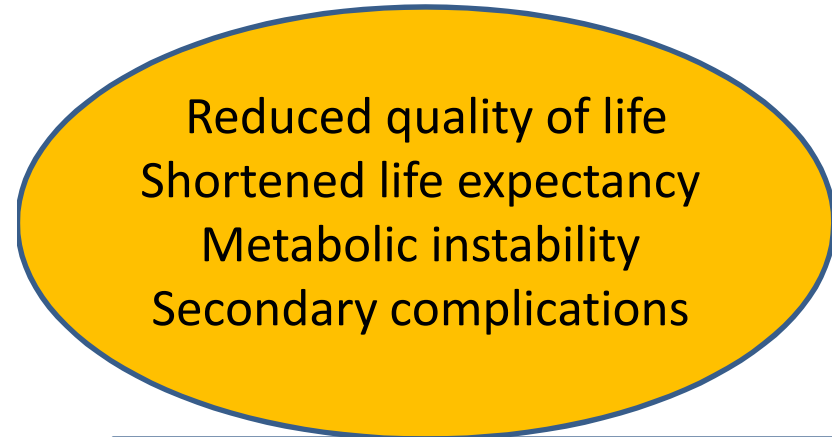
Tight glycaemic control associated with:

- Delayed onset & progression of nephropathy, neuropathy, retinopathy
- Increased incidence of hypoglycaemic episodes

Successful pancreatic transplantation is the best means to achieve good glycaemic control

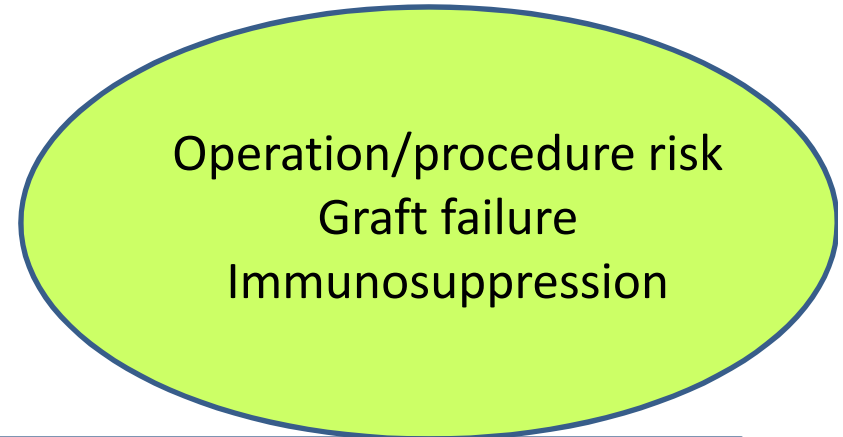
Pancreas transplantation and risk-benefit

Diabetes

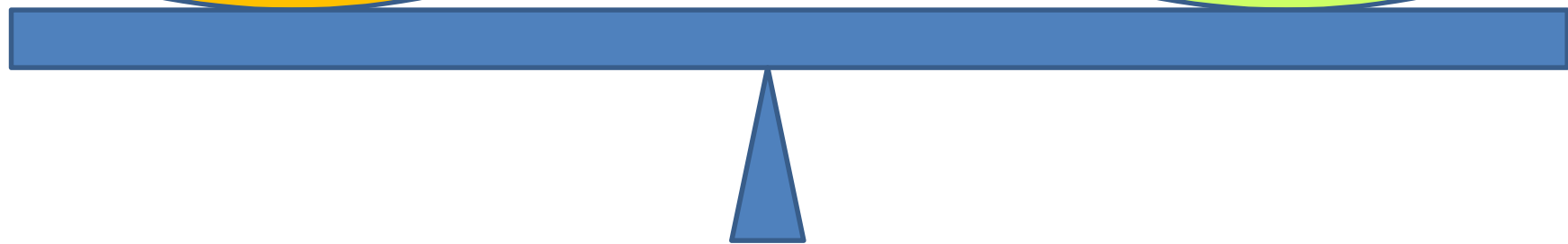


Reduced quality of life
Shortened life expectancy
Metabolic instability
Secondary complications

Transplantation



Operation/procedure risk
Graft failure
Immunosuppression



Who are the candidates for
pancreas transplantation?

Patients with debilitating/life-threatening complications of blood glucose control

- Patients with secondary complications
- Patients with poor control

Patients with debilitating/life-threatening complications of blood glucose control

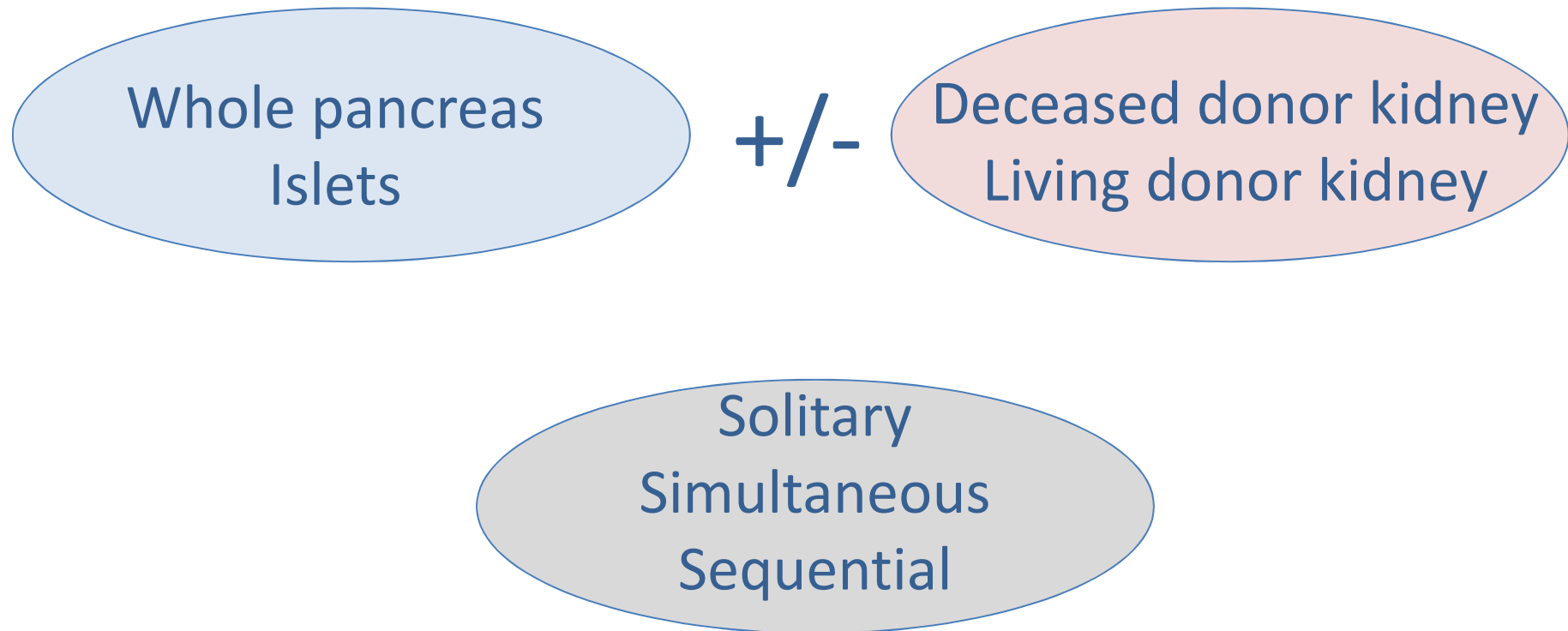
- Patients with secondary complications
 - Renal (failure)
 - Retinal
 - Cardiovascular
 - Neurological
- Patients with poor control
 - Hypoglycaemia unawareness

β -cell replacement – the transplant options

- Diabetes with renal failure
 - Simultaneous pancreas + kidney
 - Living donor kidney + pancreas after kidney
 - Simultaneous islet + kidney
 - Living donor kidney + islet after kidney
- Diabetes with hypoglycaemia-unawareness
 - Islet
 - Pancreas transplant alone

[Patients with 'intermediate' renal dysfunction are problematic]

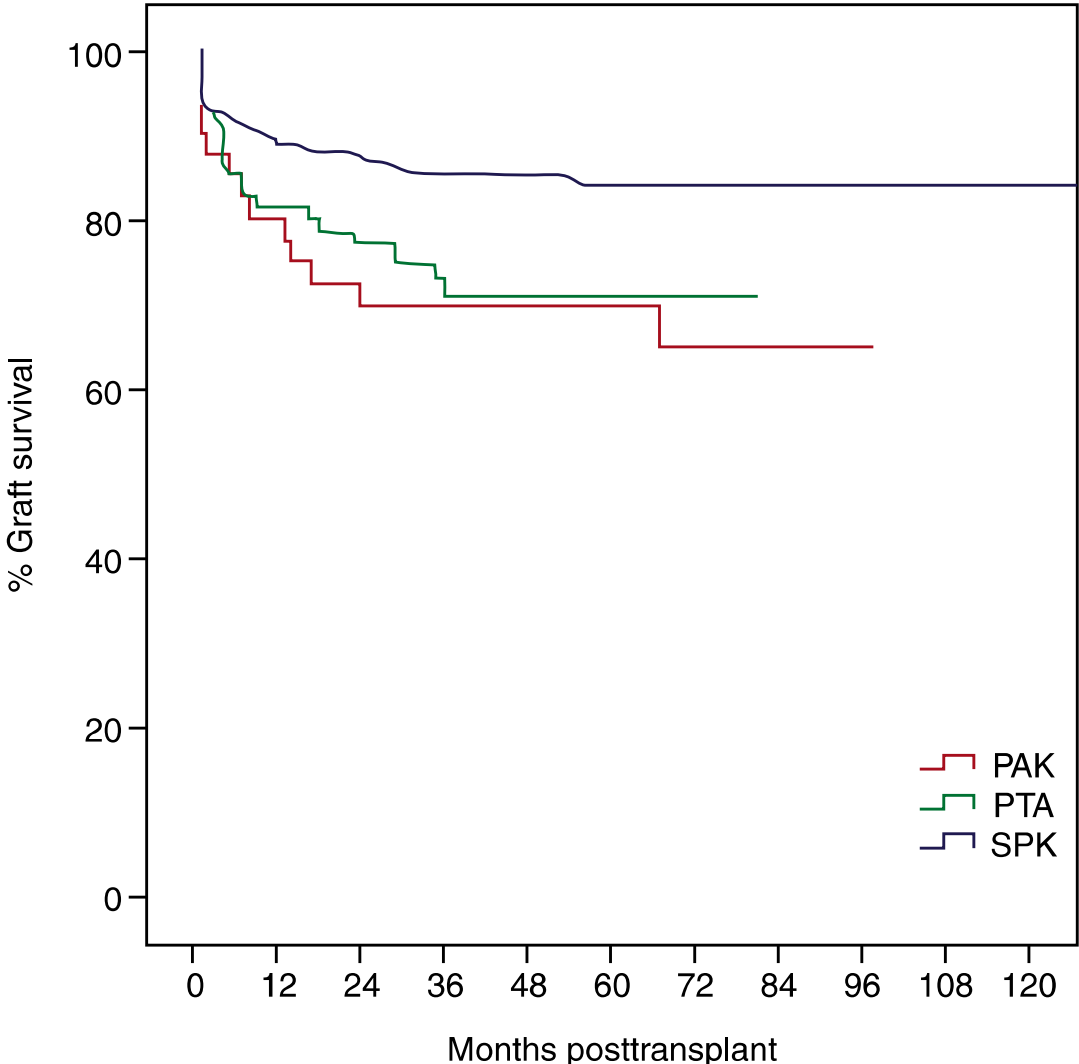
What to transplant and in what order?



Solid organ pancreas transplantation

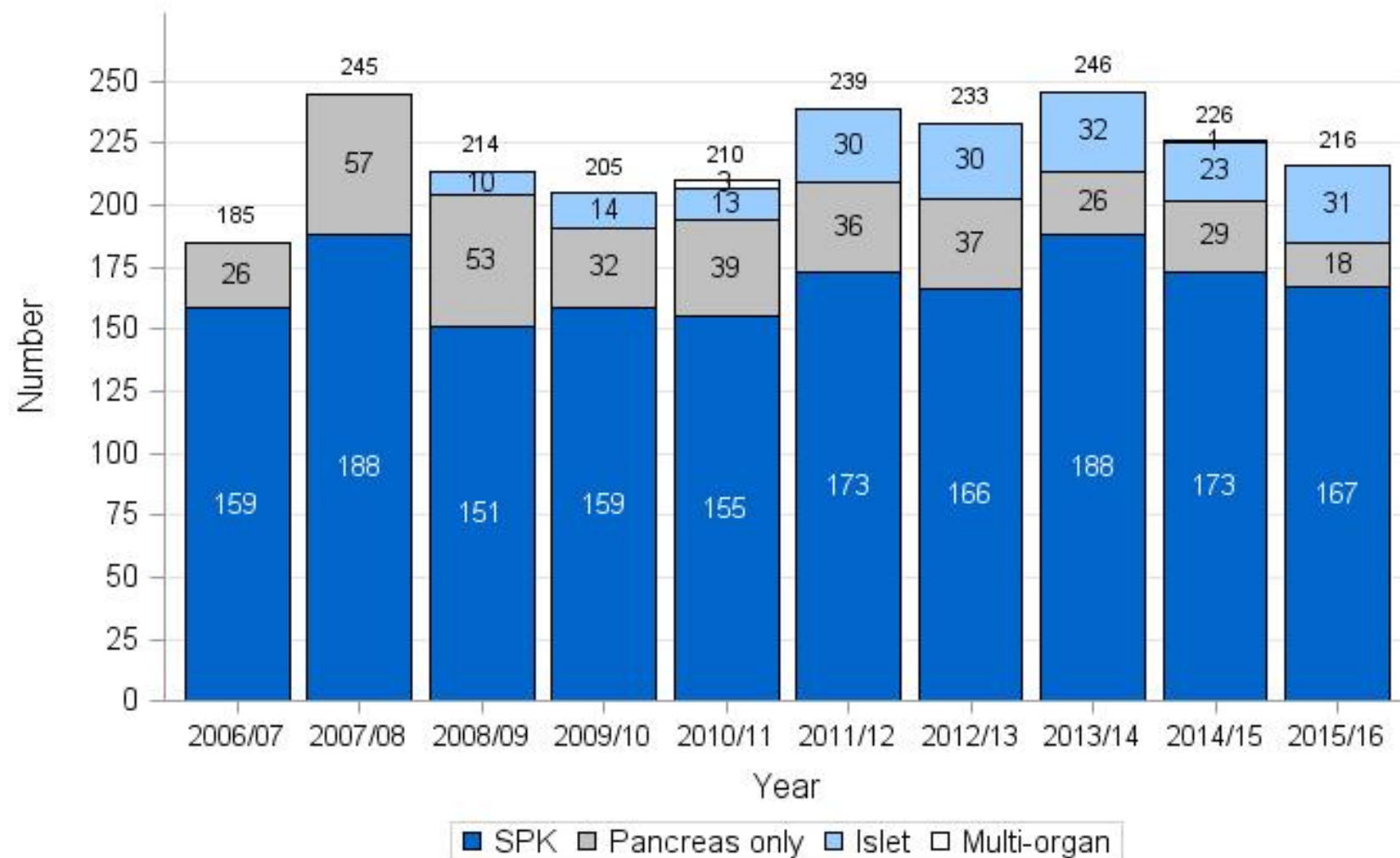
Graft survival significantly better with
simultaneous pancreas & kidney

Outcomes better in SPK than pancreas only

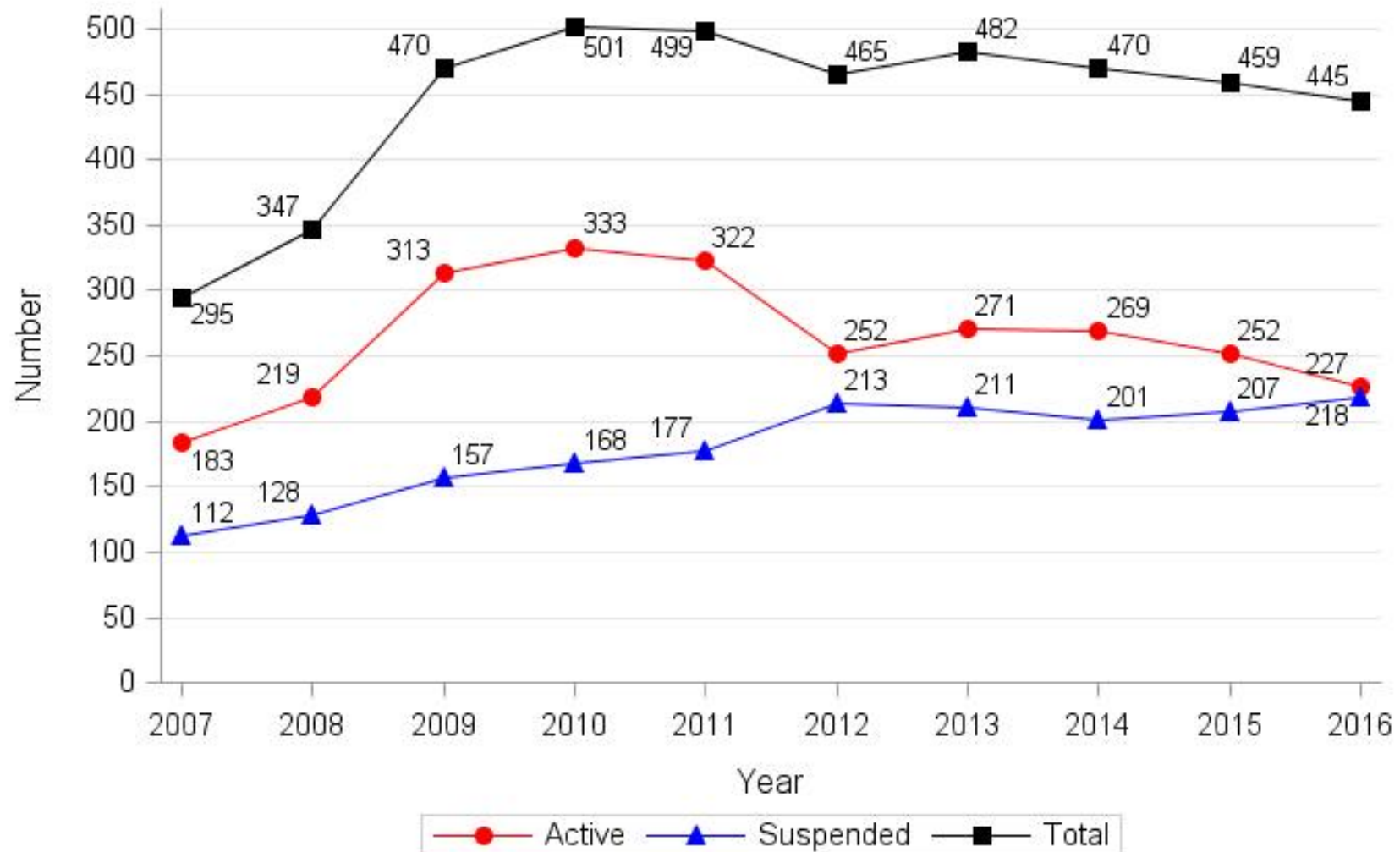


Pancreas transplantation in the UK

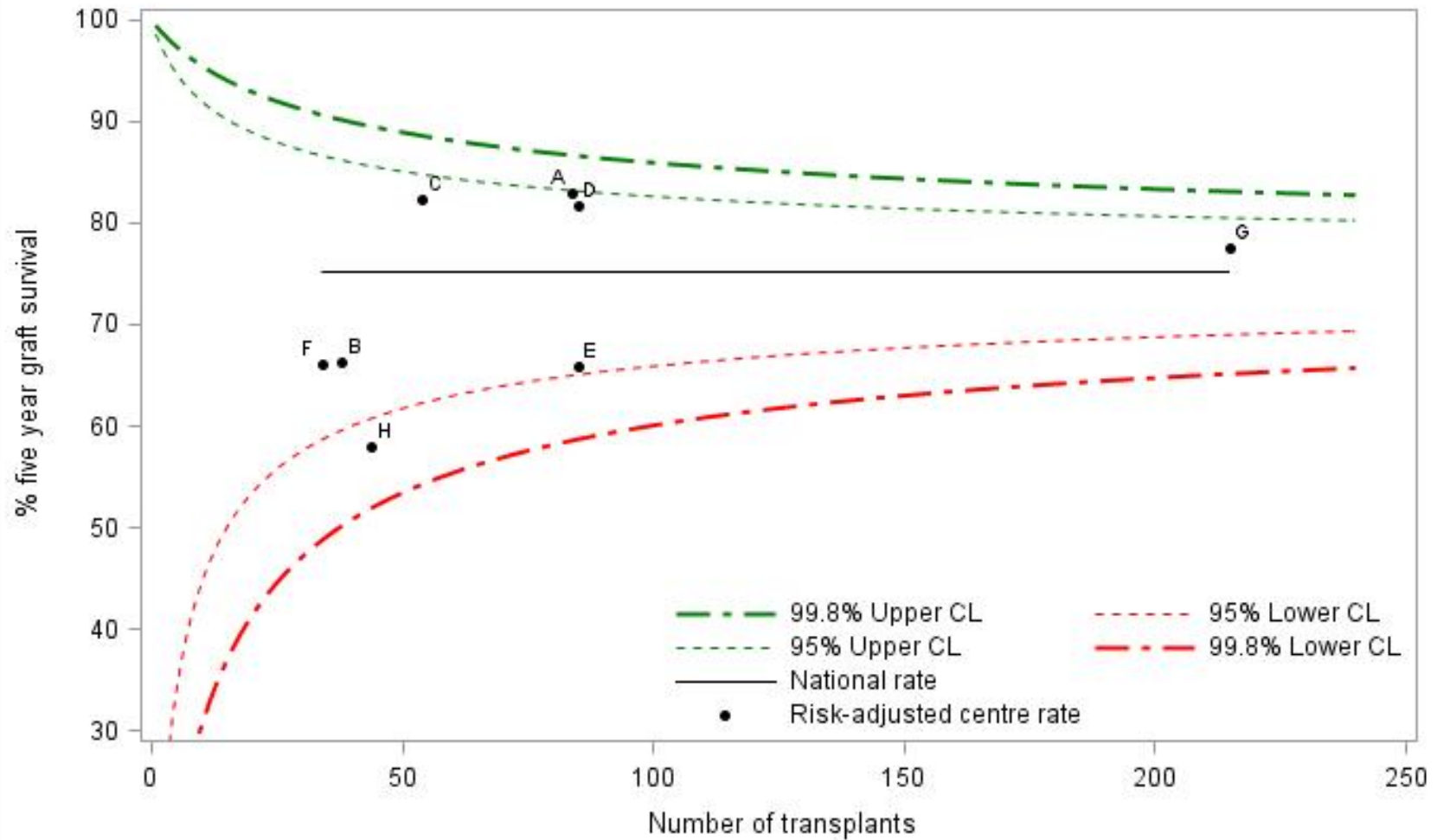
Pancreas/islet transplant activity



Pancreas/islet transplants waiting list



5-year graft survival (SPK)



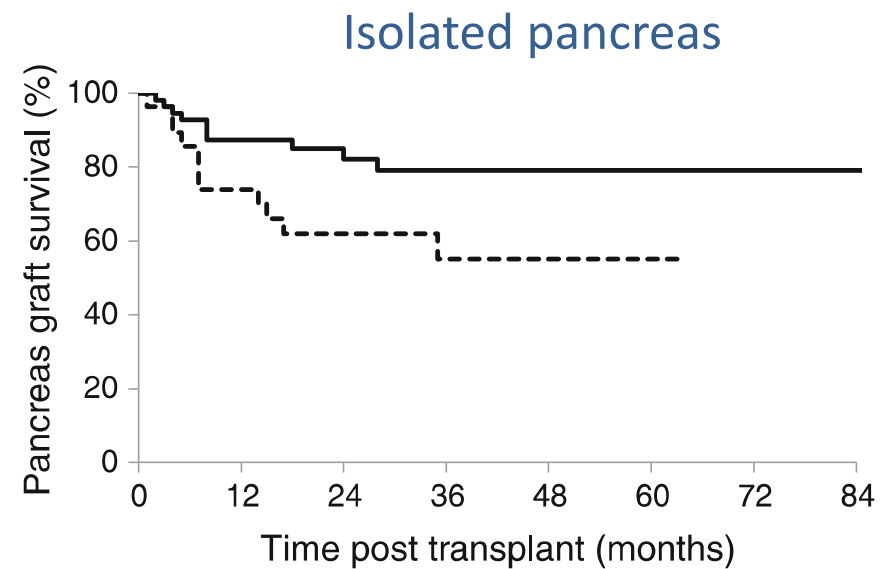
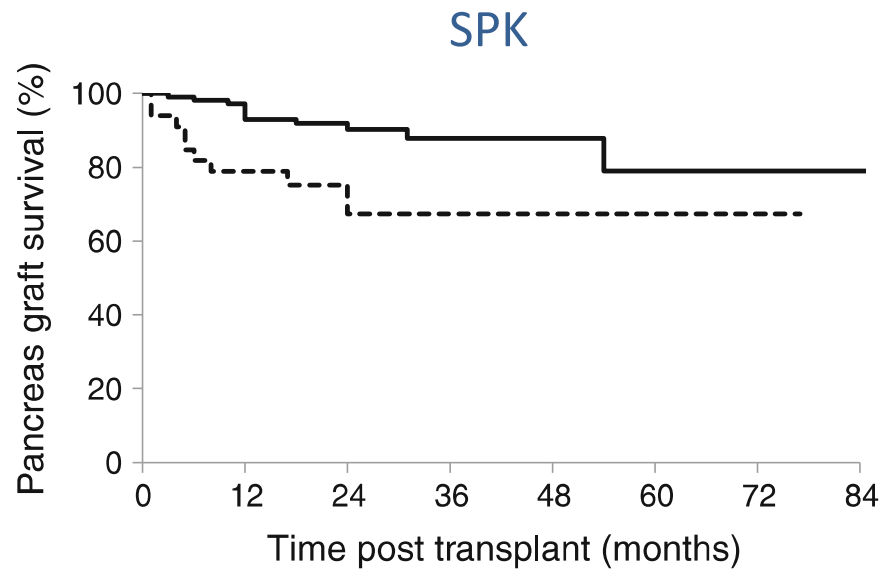
Which organs to transplant and when?

- SPK vs. LD kidney + PAK
- Advantages of SPK
 - Better pancreas survival
- Advantages of LD kidney + PAK
 - Early kidney transplant
 - Liberates deceased donor kidney
- Decision depends on local conditions
 - Waiting time for SPK (organ allocation)
 - Availability of live donor

Longer-term problems

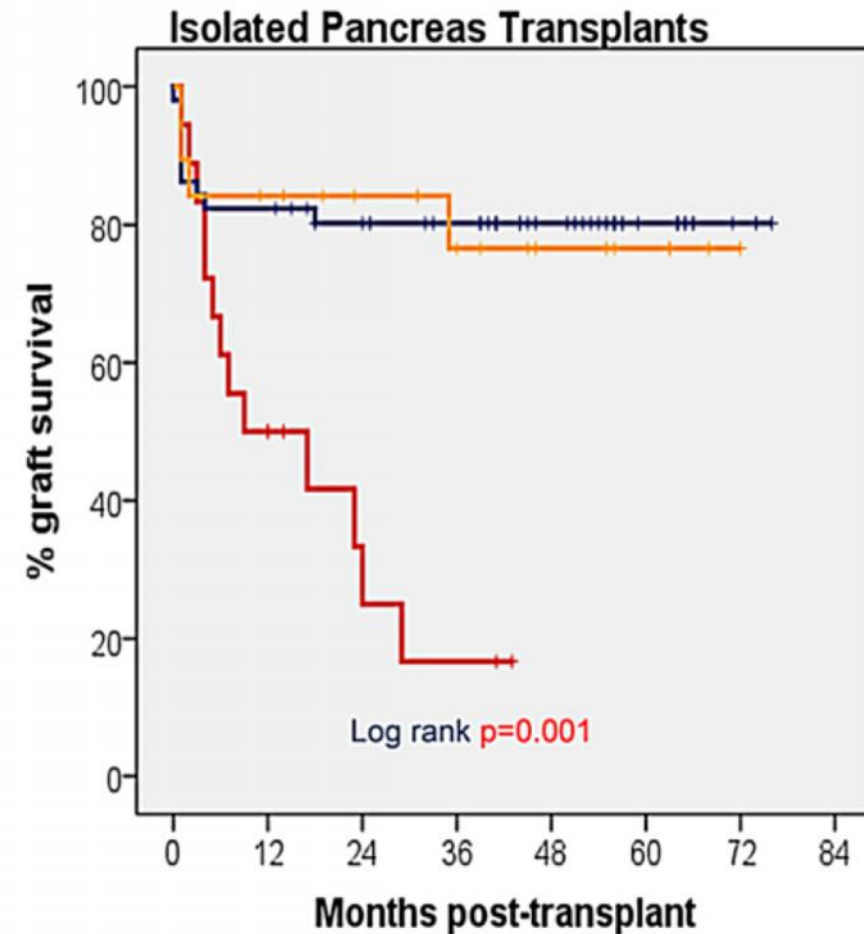
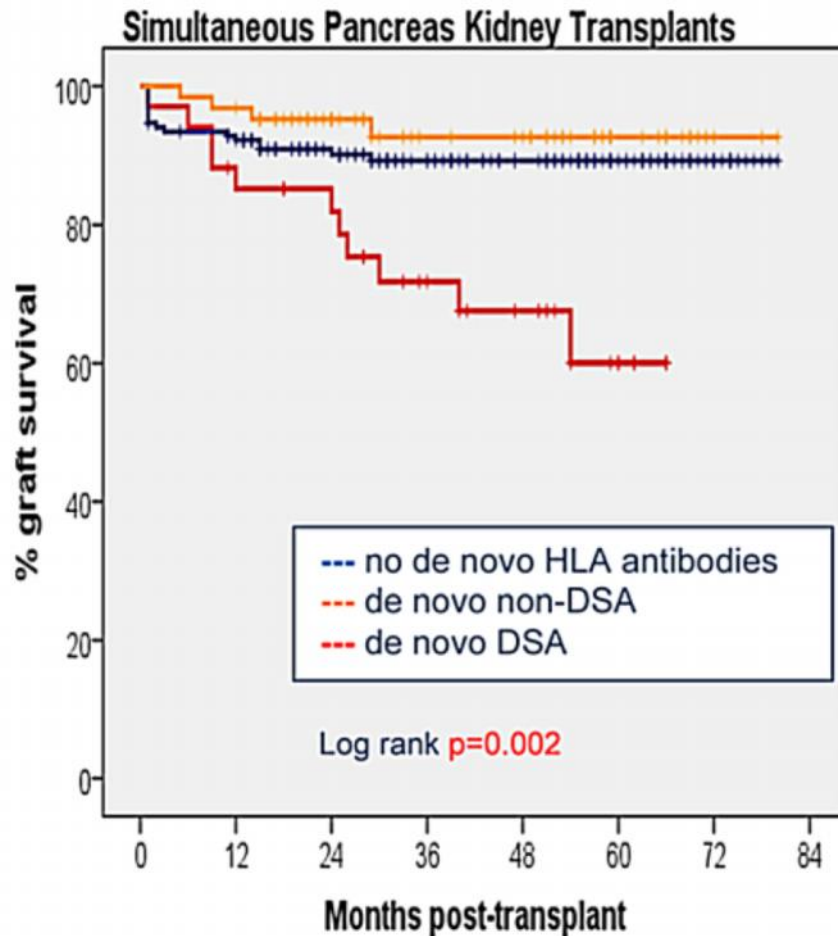
Postoperative impaired glucose tolerance is an early predictor of pancreas graft failure

Shruti Mittal • Myura Nagendran • Rachel H. Franklin •
Edward J. Sharples • Peter J. Friend •
Stephen C. L. Gough



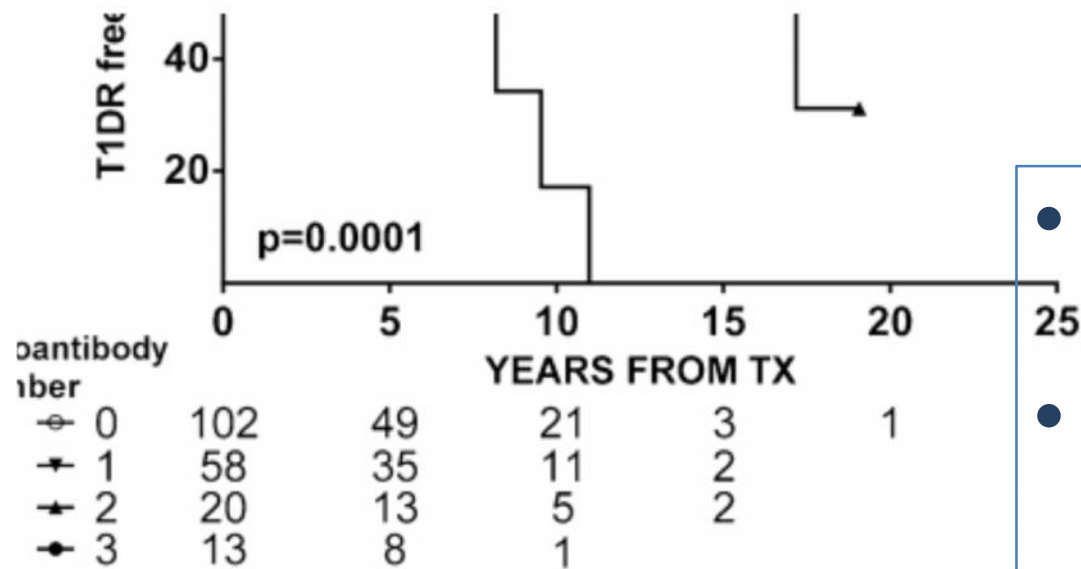
De Novo Donor-Specific HLA Antibodies: Biomarkers of Pancreas Transplant Failure

S. Mittal^{1,2,3,*}, S. L. Page⁴, P. J. Friend^{1,2},
E. J. Sharples^{1,5} and S. V. Fuggle^{1,2}



Lessons From Pancreas Transplantation in Type 1 Diabetes: Recurrence of Islet Autoimmunity

George W. Burke III^{1,3} · Francesco Vendrame⁴ · Sahil K. Viridi² · G. Ciancio^{1,3} ·
 Linda Chen^{1,3} · Phillip Ruiz^{1,3} · Shari Messinger⁶ · Helena K. Reijonen⁷ ·
 Alberto Pugliese^{2,4,5}



- 6-8% recurrent auto-antibodies
- Majority develop recurrent T1DM within 6 months

C. Autoantibody patterns conversion

Apart from insulin independence,
what are the benefits of pancreas
transplantation?

The effect of pancreas transplantation on life expectancy

There are no randomised controlled trials

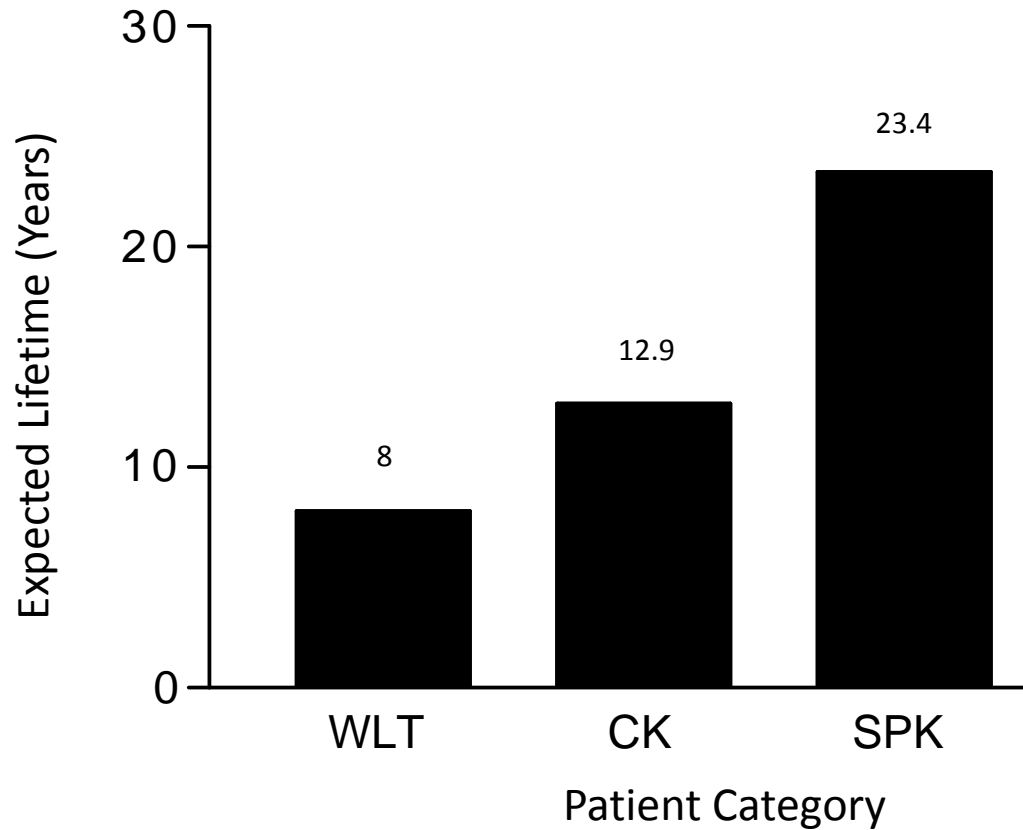
THE IMPACT OF SIMULTANEOUS PANCREAS-KIDNEY TRANSPLANTATION ON LONG-TERM PATIENT SURVIVAL¹

AKINLOLU O. OJO,² HERWIG-ULF MEIER-KRIESCHE,² JULIE A. HANSON,² ALAN LEICHTMAN,²
JOHN C. MAGEE,³ DIANE CIBRIK,² ROBERT A. WOLFE,⁴ FRIEDRICH K. PORT,^{2,5} LAWRENCE AGODOA,⁶
DIXON B. KAUFMAN,⁷ AND BRUCE KAPLAN^{2,8}

*Departments of Medicine, Surgery, Biostatistics, and Epidemiology at the University of Michigan,
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20892-5458; and Department of Surgery, Northwestern University Medical School, Chicago, IL 60611-3015*

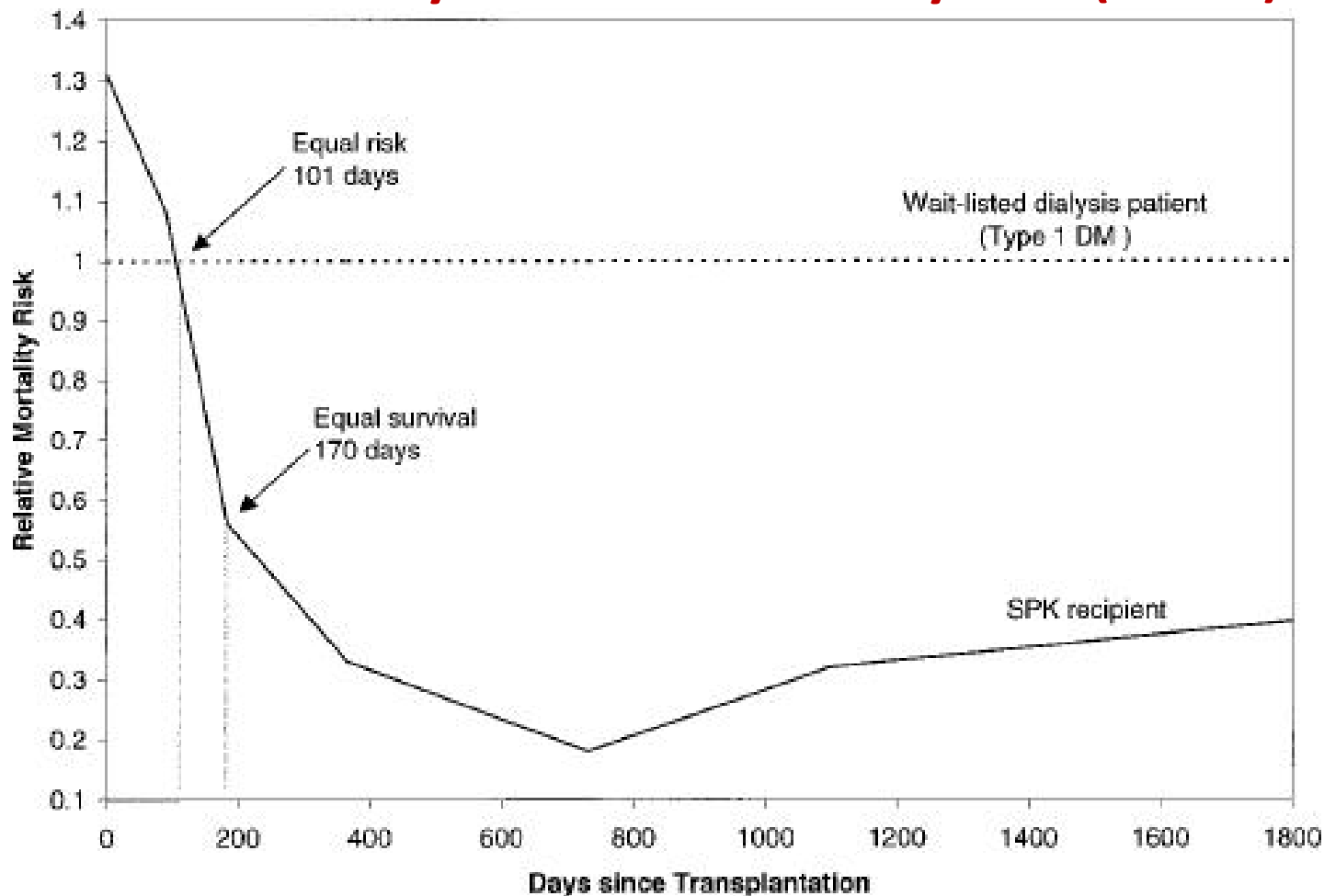
- 13,467 type 1 diabetic patients
- Transplant waiting list 1988-97
- W/L vs. DD kidney alone vs. SPK vs LD kidney

Life expectancy after transplantation



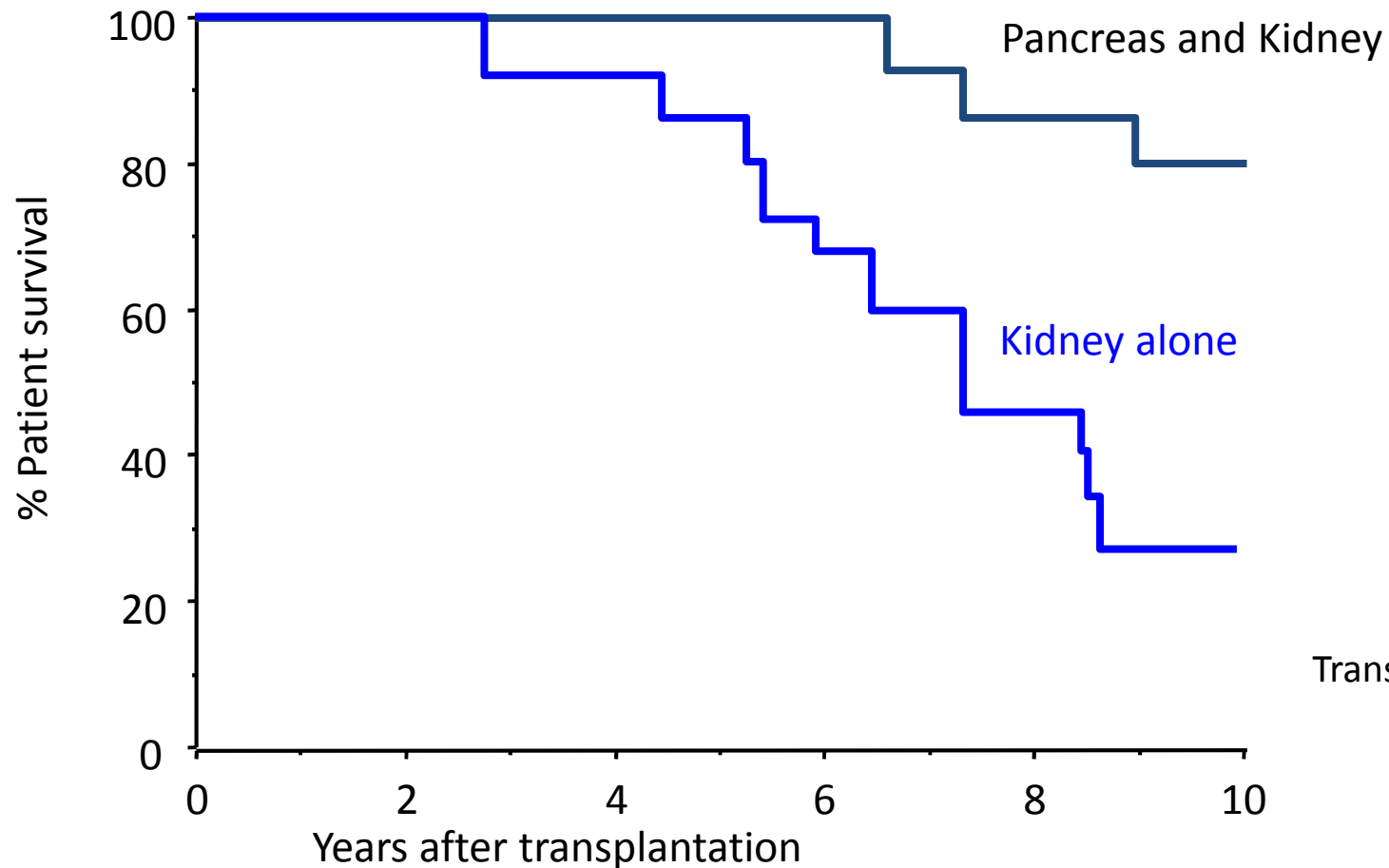
USRDS after Ojo et al. (2001)

Mortality risk vs. dialysis (SPK)



Treatment	Days to equal risk	Days to equal survival	5-yr RR
Dialysis (wait-listed) (reference)			1.00
Simultaneous pancreas-kidney	101	170	0.40
Living donor kidney	15	72	0.45
Cadaveric donor kidney	43	95	0.75

Functioning pancreas transplant improves patient survival



Tydén et al,
Transplantation 1999.

**Benefits with respect to
secondary diabetic complications**

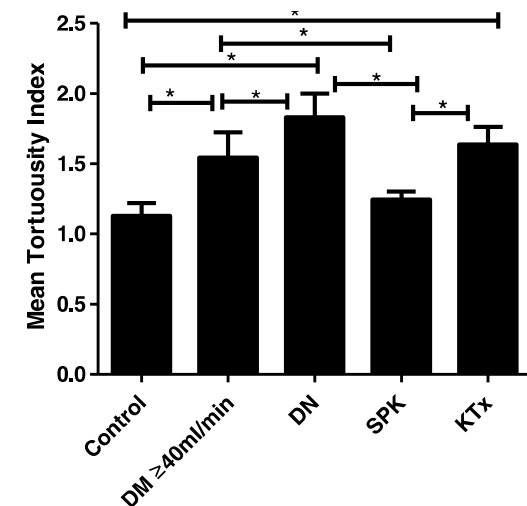
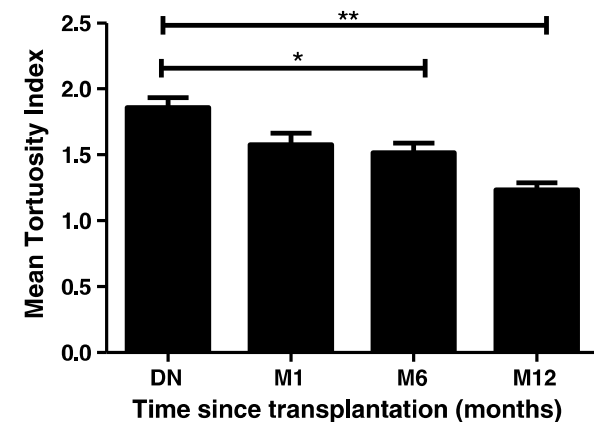
Progression of cardiovascular disease

Microvascular Damage in Type 1 Diabetic Patients Is Reversed in the First Year After Simultaneous Pancreas–Kidney Transplantation

M. Khairoun^{a,*}, E. J. P. de Koning^a,
B. M. van den Berg^{a,b}, E. Lievers^a,
H.C. de Boer^{a,b}, A. F. M. Schaapherder^c,
M. J. K. Mallat^a, J. I. Rotmans^{a,b},
P. J. M. van der Boog^a, A. J. van Zonneveld^{a,b},
J. W. de Fijter^a, T. J. Rabelink^{a,b}
and M. E. J. Reinders^{a,b}

^aDepartment of Nephrology, ^bEindhoven Laboratory for Experimental Vascular Research and ^cDepartment of Surgery, Leiden University Medical Center, the Netherlands.

- Markers of microvascular disease & endothelial dysfunction reversed by PTx within 12 months
- Capillary tortuosity (sidestream dark-field imaging of oral mucosa)
- Angiopoietin & thrombomodulin



Cardiac Assessment of Patients With Type 1 Diabetes Median 10 Years After Successful Simultaneous Pancreas and Kidney Transplantation Compared With Living Donor Kidney Transplantation

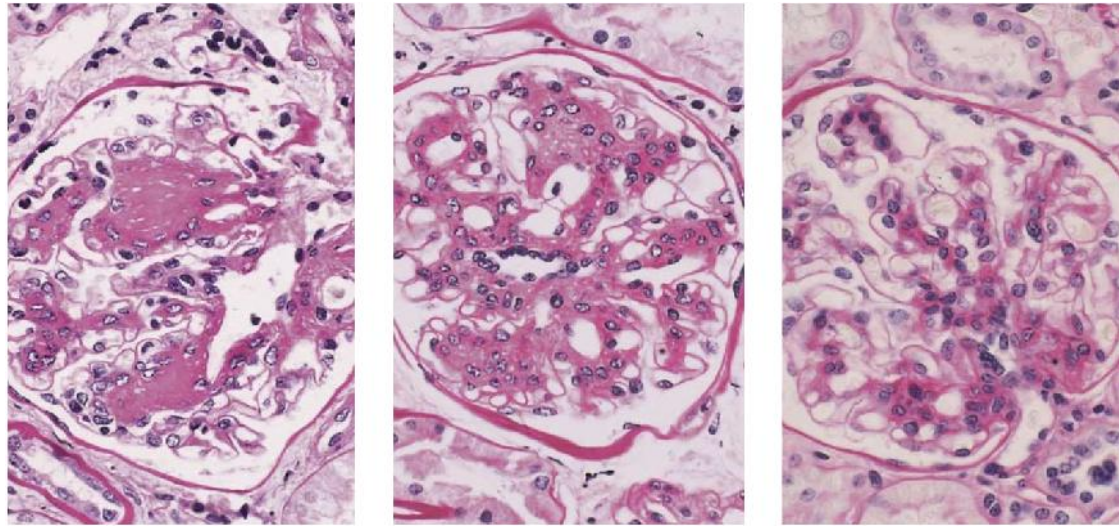
Jørn Petter Lindahl, MD,^{1,2} Richard John Massey, MSc,³ Anders Hartmann, PhD,^{1,2} Svend Aakhus, PhD,^{3,4} Knut Endresen, PhD,³ Anne Günther, MD,⁵ Karsten Midtvedt, PhD,² Halvard Holdaas, PhD,² Torbjørn Leivestad, PhD,² Rune Horneland, MD,² Ole Øyen, PhD,² and Trond Jenssen, PhD^{2,6}

- SPK (n = 25) vs. LDK (n = 17)
- CAD progression (angiographic) from pretransplant to 7 years (minimum)
- Progression in 10 SPK & 5 LDK group (p=0.49)
- No difference in systolic function

Effect on diabetic nephropathy

REVERSAL OF LESIONS OF DIABETIC NEPHROPATHY AFTER PANCREAS TRANSPLANTATION

PAOLA FIORETTO, M.D., PH.D., MICHAEL W. STEFFES, M.D., PH.D., DAVID E.R. SUTHERLAND, M.D., PH.D.,
FREDERICK C. GOETZ, M.D., AND MICHAEL MAUER, M.D.



At transplant

5 years postop

10 years postop

- Improvements in:
 - Proteinuria (5 years)
 - Basement membrane thickness (10 years)
 - Mesangial fractional volume (10 years)

8 patients reported; paper cited 1034 times

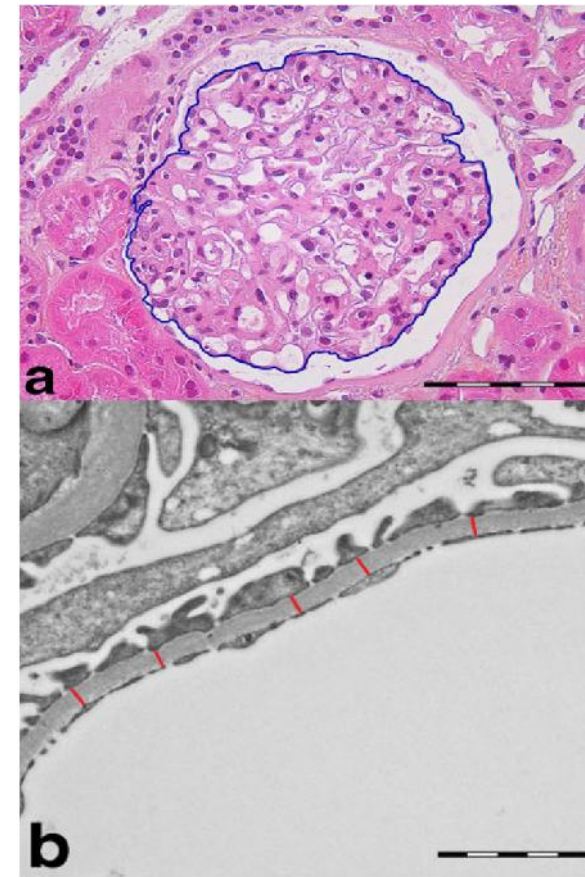
NEJM (1998): 69(2); 69-75

In patients with type 1 diabetes simultaneous pancreas and kidney transplantation preserves long-term kidney graft ultrastructure and function better than transplantation of kidney alone

Jørn P. Lindahl · Finn P. Reinholt · Ivar A. Eide · Anders Hartmann ·
Karsten Midtvedt · Hallvard Holdaas · Linda T. Dorg · Trine M. Reine ·
Svein O. Kolset · Rune Horneland · Ole Øyen · Knut Brabrand · Trond Jenssen

University of Oslo

- SPK (n=25) vs. LDKTx alone (n=17)
 - Median follow-up 10.1 years
- Significant differences:
 - HbA1c 5.5 vs. 8.3% (p<0.001)
 - GBM thickness (p=0.008)
 - Mesangial volume fraction (p=0.007)
 - eGFR gradient (-1.1 vs. -2.6) (p=0.001)

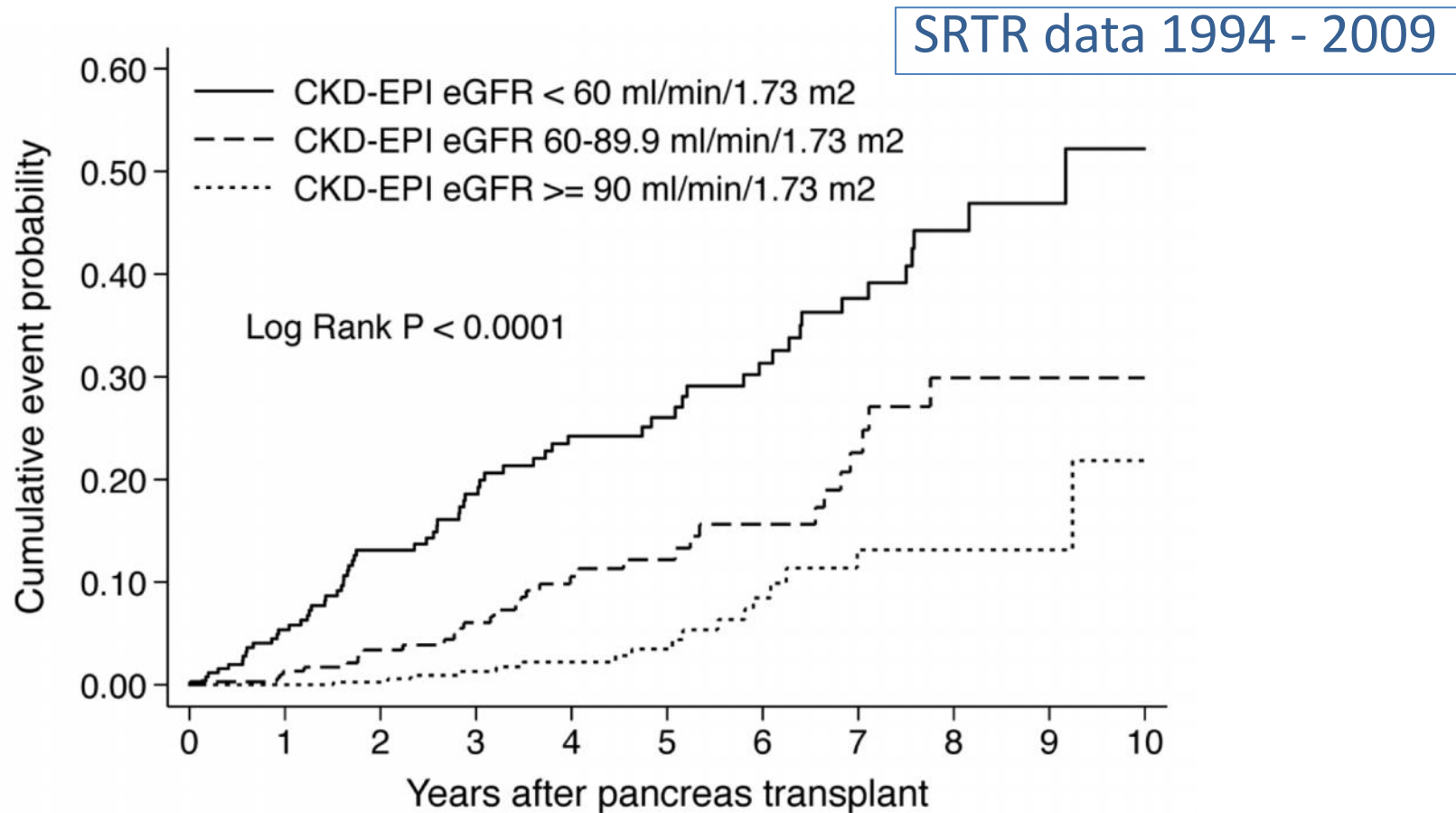


Management of the patient with 'intermediate' renal dysfunction (GFR 30-50ml/min)

- Several years from needing renal replacement
 - Does not warrant use of donor kidney
- Might successful PTx arrest progression of renal disease?
- Will immunosuppressive therapy advance the need for dialysis?

Kidney Function Before Pancreas Transplant Alone Predicts Subsequent Risk of End-Stage Renal Disease

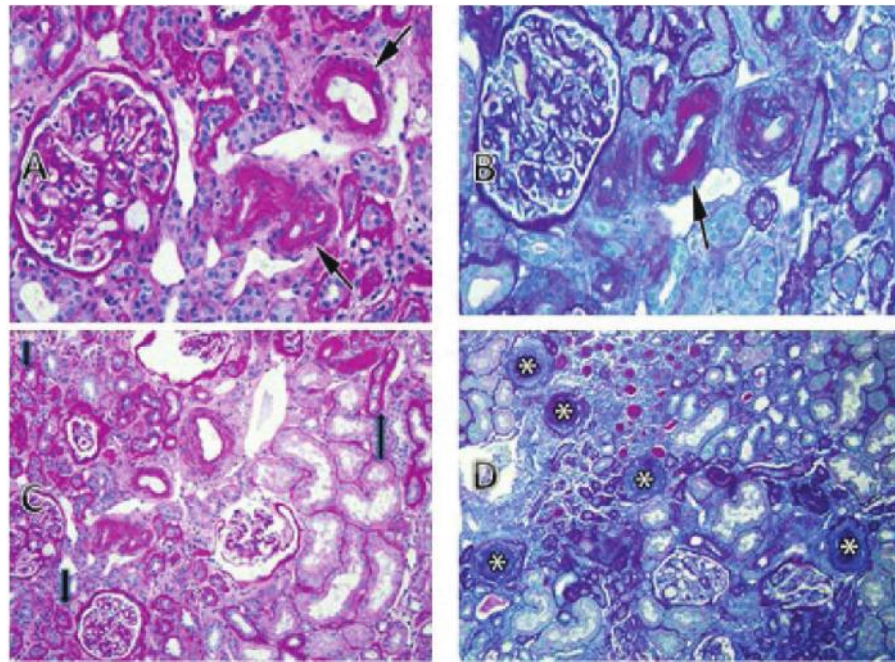
Sang Joseph Kim,^{1,2,3,6} Nassima Smail,⁴ Steven Paraskevas,⁵ Jeffery Schiff,^{1,2} and Marcelo Cantarovich⁴



26% risk of ESRF within 5 yrs of transplant with GFR below 60ml/min

Conversion From Tacrolimus to Belatacept to Prevent the Progression of Chronic Kidney Disease in Pancreas Transplantation: Case Report of Two Patients

M. A. Mujtaba^{1,†}, A. A. Sharfuddin^{1,†}, T. Taber¹,
J. Chen², C. L. Phillips¹, M. Goble³
and J. A. Fridell³



Evidence of benefit in retinal disease

Pancreas transplant alone has beneficial effects on retinopathy in type 1 diabetic patients

R. Giannarelli • A. Coppelli • M. S. Sartini •
M. del Chiaro • F. Vistoli • G. Rizzo • M. Barsotti •
S. Del Prato • F. Mosca • U. Boggi • P. Marchetti

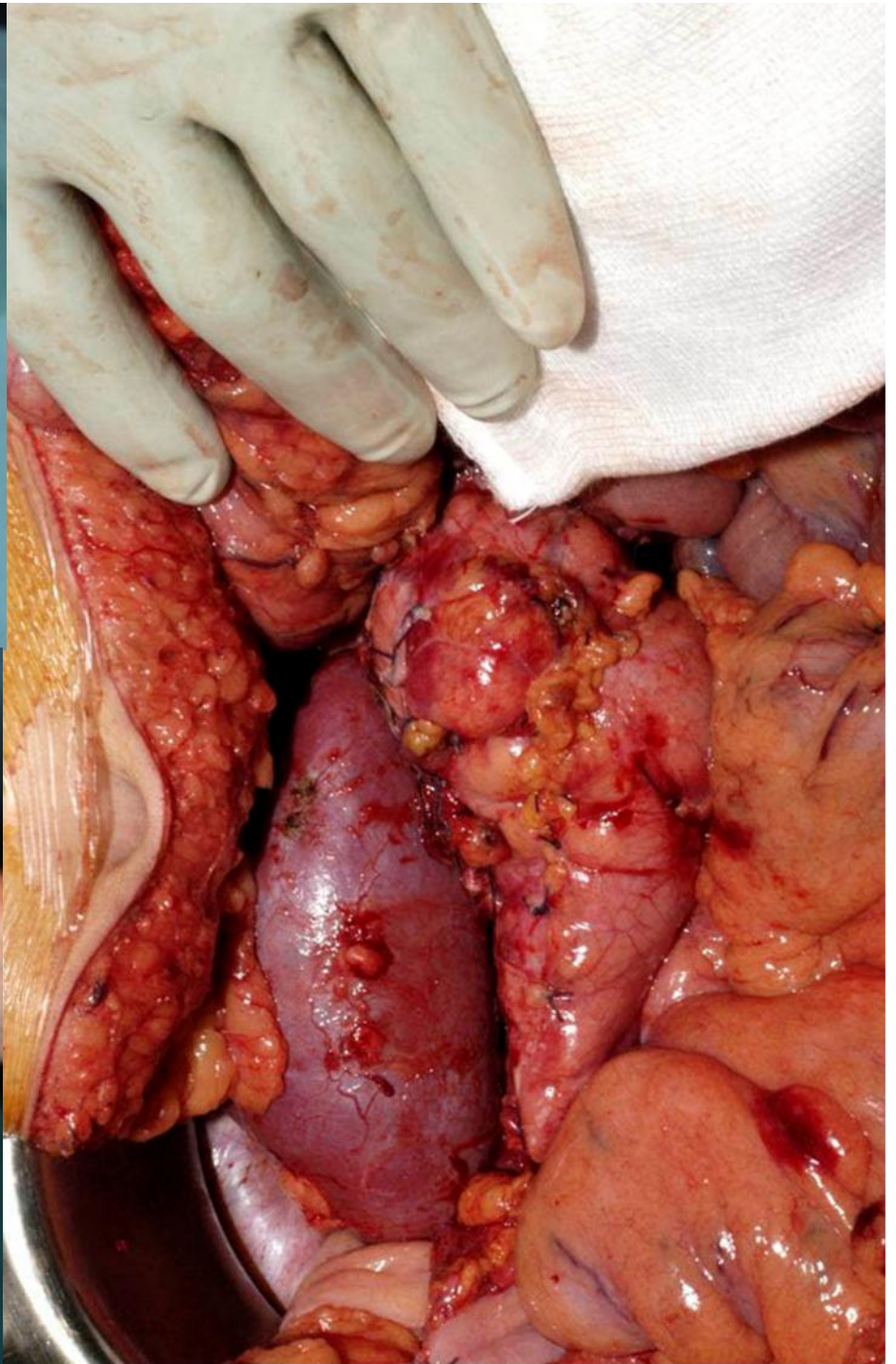
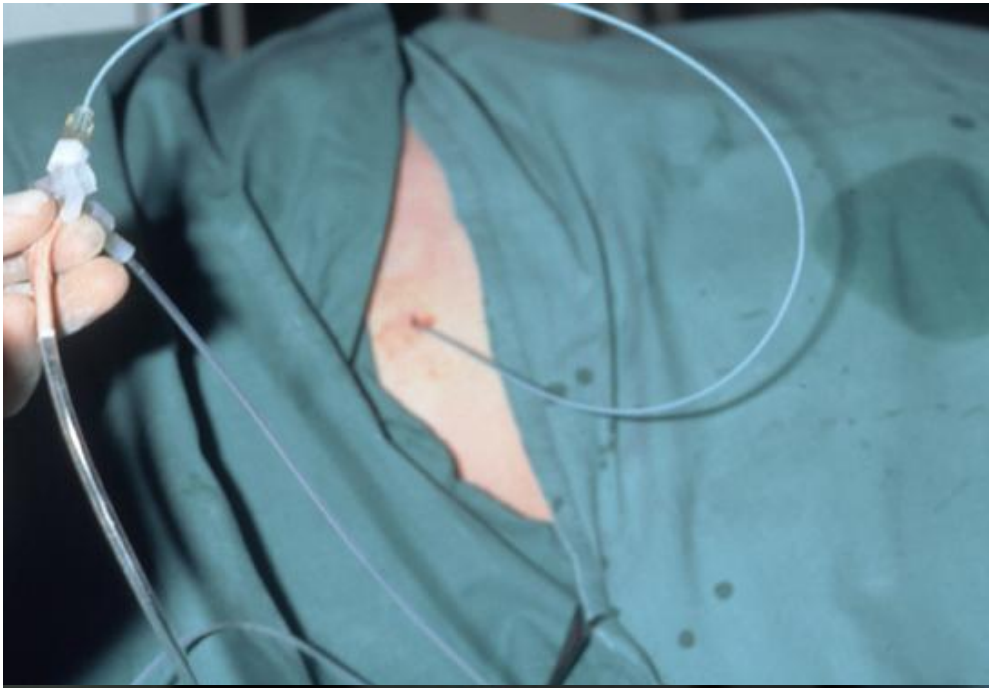
- 33 PTA versus 35 matched controls
- Median follow-up 30 vs. 28 months
- Non-proliferative disease: improved 50% vs. 20%
- Proliferative disease: stable 86% vs. 43%
- Resolution of macular oedema in PTA patients
- No change in visual acuity

Transplantation for hypoglycaemia unawareness

Islet transplantation vs. pancreas transplant alone

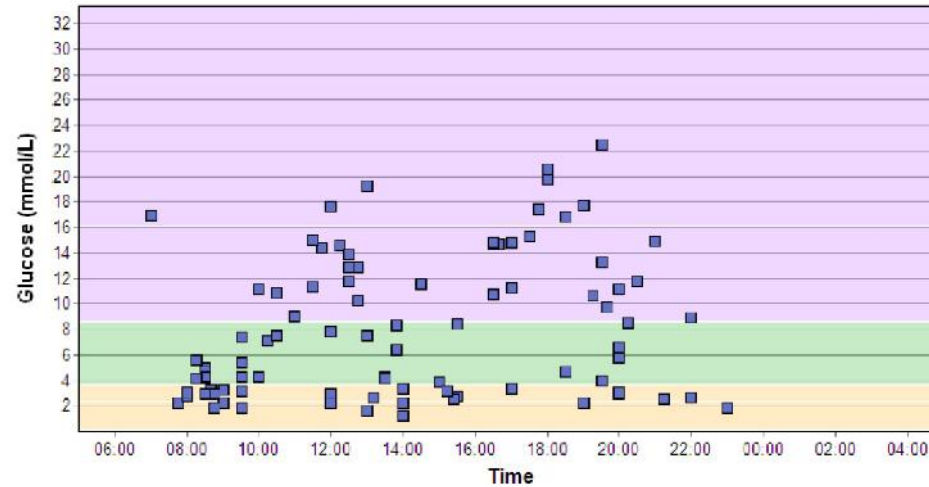
Success is measured by different parameters

- Solid organ: insulin independence
- Islet: freedom from hypoglycaemic unawareness & stabilisation of HbA1c



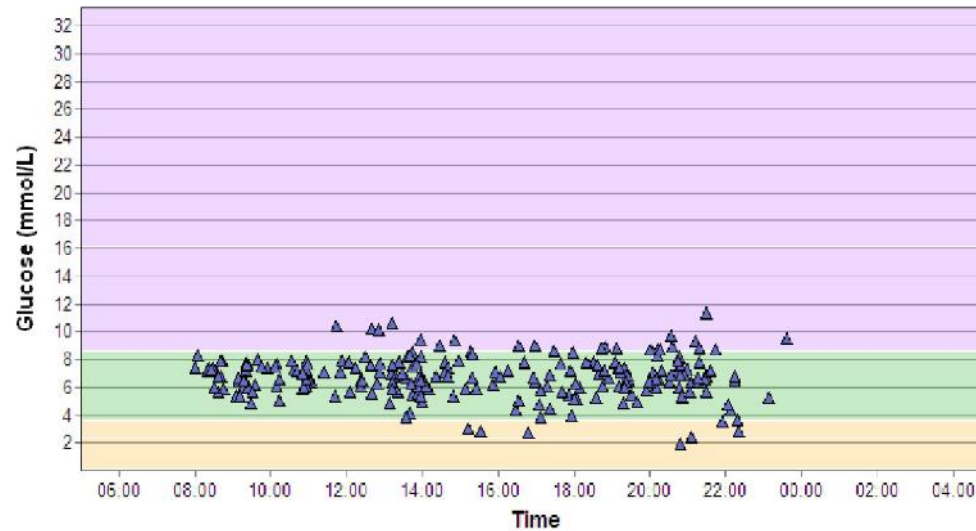
Benefits do not require insulin independence

Pre-transplant
(single patient)



36U insulin/ 24 hrs

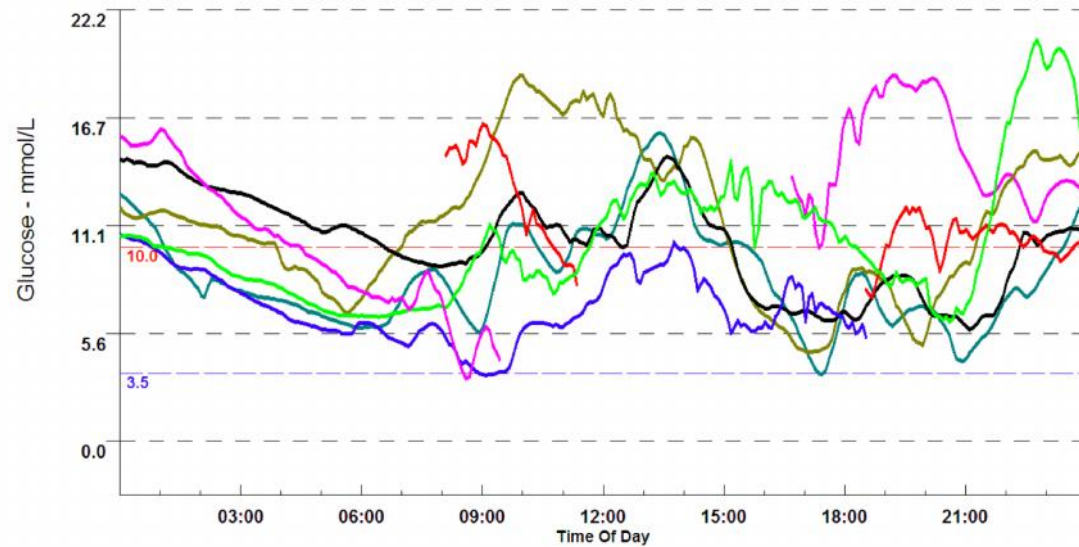
Post-transplant
3 months



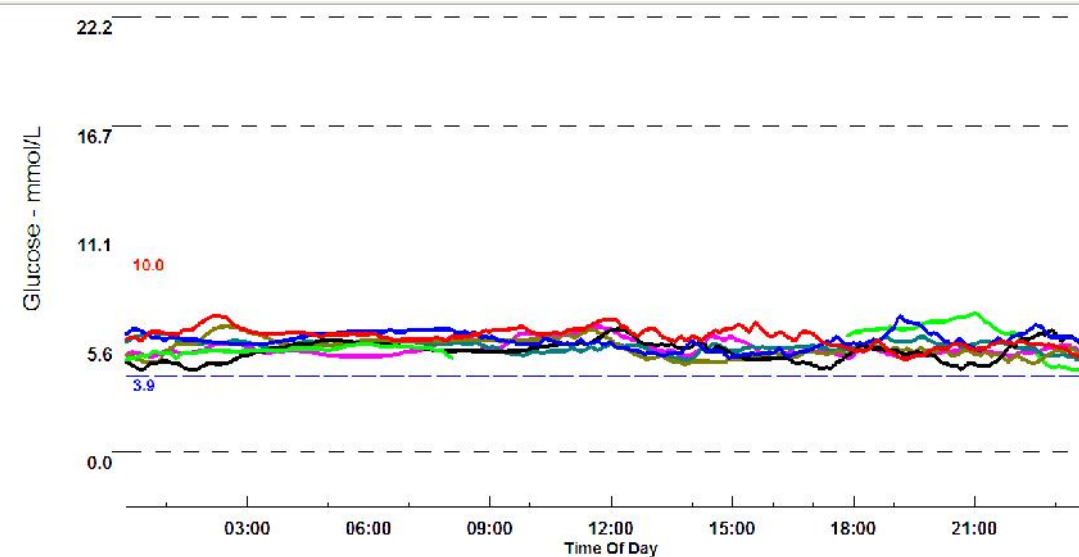
8U insulin/ 24 hrs

Post-transplant stability

Pre-transplant
(multiple patients)



6 month post-transplant
75% reduction in insulin



What is the evidence that islet transplantation improves secondary complications of diabetes?

And does it require insulin-independence?

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. Warnock²

- Prospective, one-way crossover, cohort study
 - Intensive medical therapy vs. islet Tx
 - 32 patients transplanted
- Islet transplant associated with
 - Slower decline in renal function (p=0.01)
 - Less deterioration in retinopathy (p=0.01)

Solid organ vs islets – the balance

Islets

Less procedure risk

Inferior function

Inferior survival

Donor organ use

Risk of sensitisation

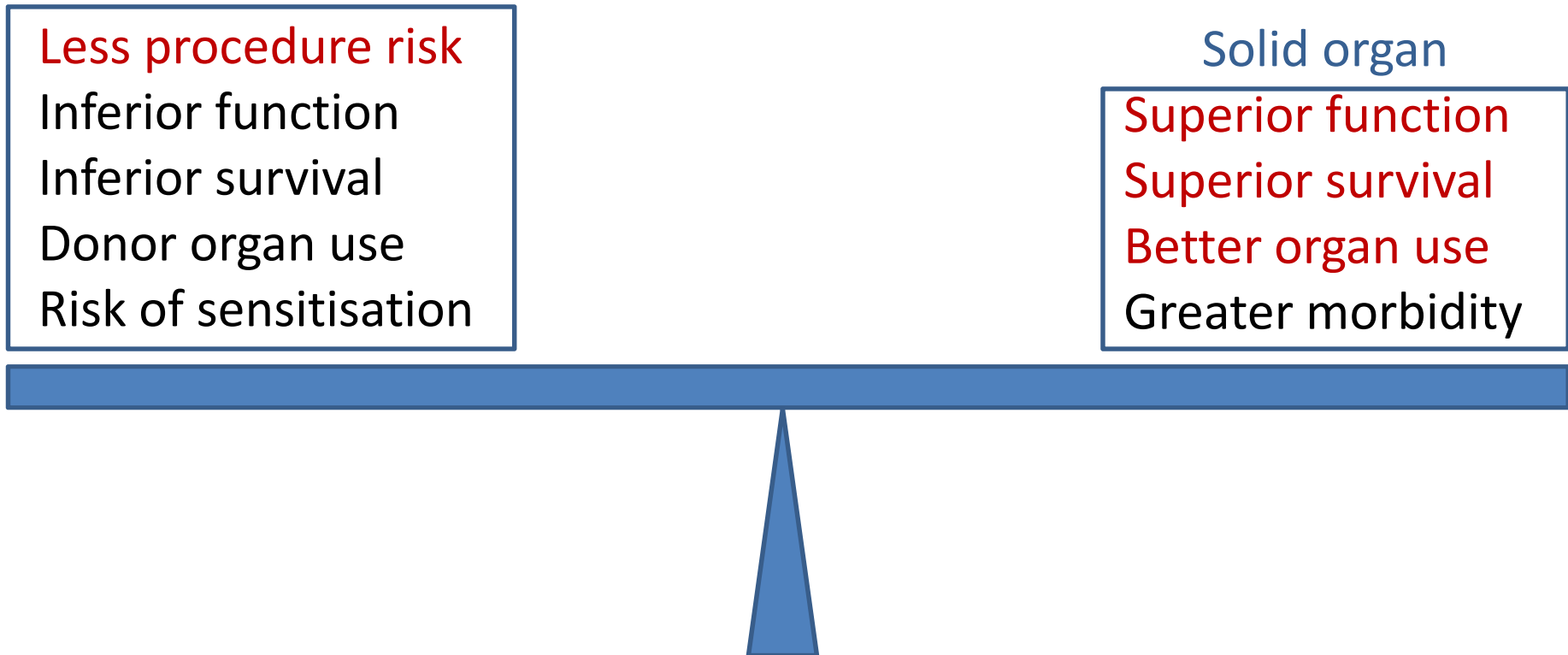
Solid organ

Superior function

Superior survival

Better organ use

Greater morbidity



Islet transplant versus solid organ PTA for hypoglycaemia unawareness

What to recommend?

Is it time for a trial?

The future

Transplant patients much earlier?

Are we are doing the wrong operation at the wrong time?

- Majority of pancreas transplants are SPK
- Secondary complications already advanced
- Prevention is better than cure

*Hypothesis: If we could safely and reliably
transplant the pancreas alone (or islets)
at an earlier stage, then complications
would be avoided*

If earlier transplantation is the solution,
then what is needed to achieve this?

- Improve safety of procedure
- Improve graft survival
- Reduce long-term morbidity
- Evidence that transplantation prevents complications, and in what time-frame

Will we still be transplanting pancreases in 20 years?

- Stem cells
- Xenotransplants
- Encapsulation
- Bioartificial organs
- Recellularised grafts

But for now, the choice is between solid organ and islet transplantation, with or without the kidney