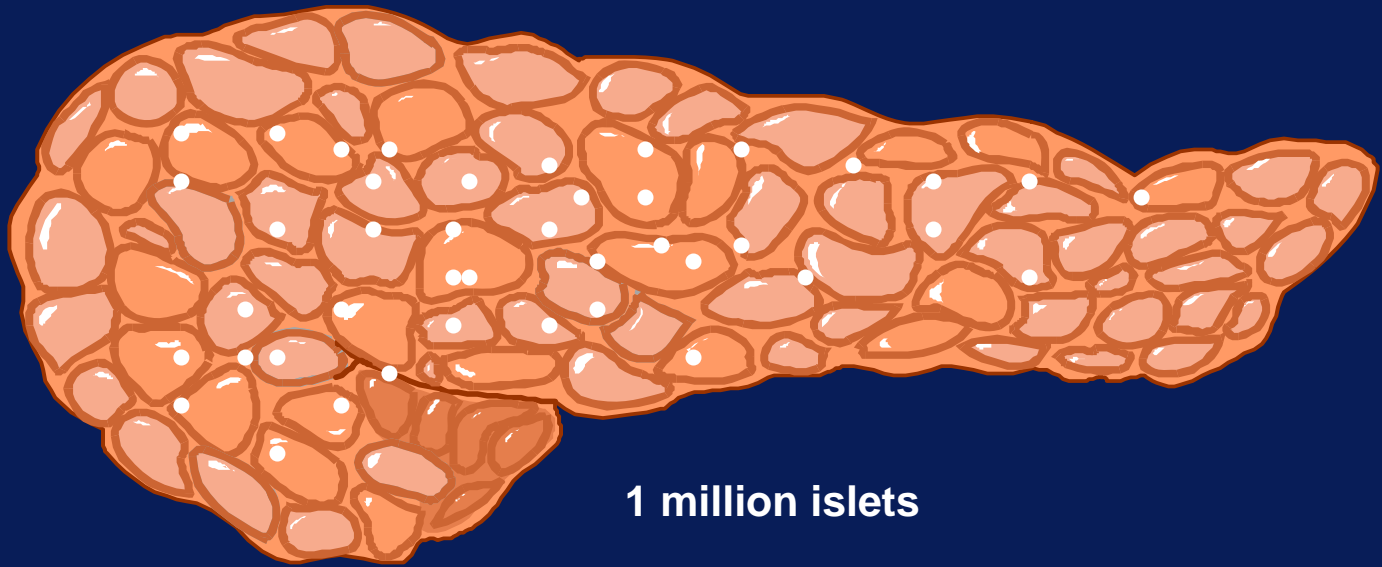


Pancreas or islets?

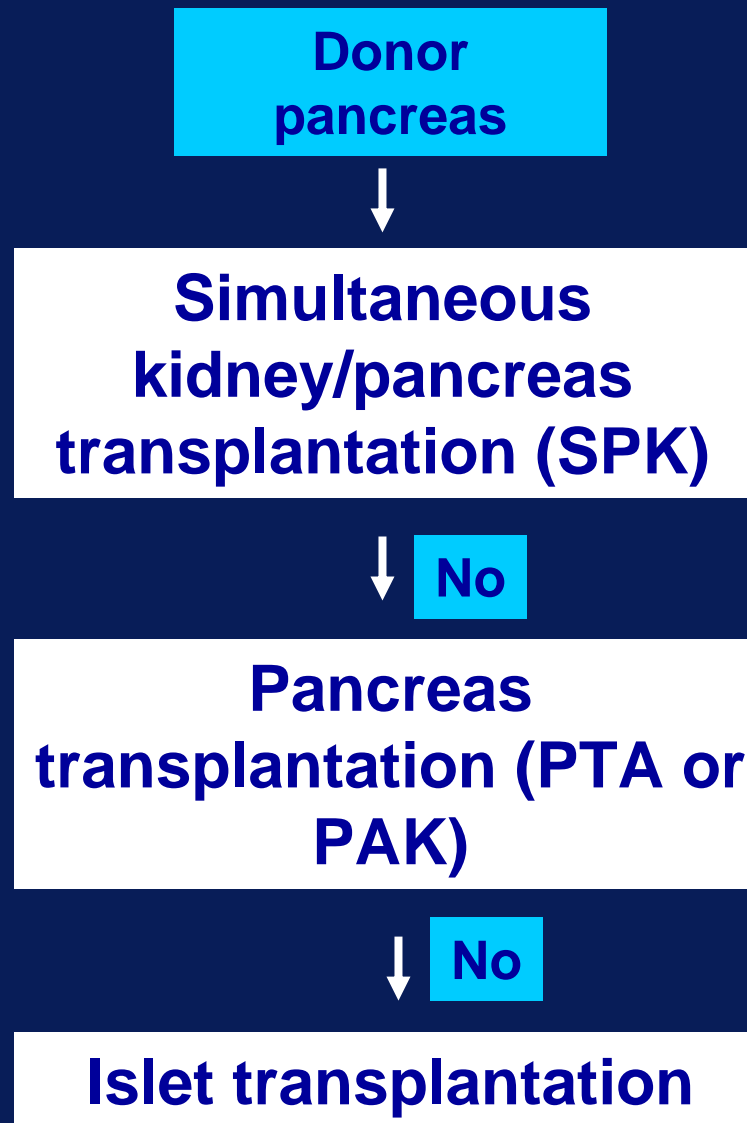
- What tissue do we wish to transplant?
- Is there competition for donor pancreas?
- How does the islet isolation and transplantation procedure compare to pancreas transplantation?
- What are the complications?
- What is the outcome of islet transplantation for
 - Glycemic control?
 - Mortality?
 - Kidney graft survival?
- Which patients?

**Pancreas consists of only 1-2%
endocrine tissue (islets of
Langerhans)**



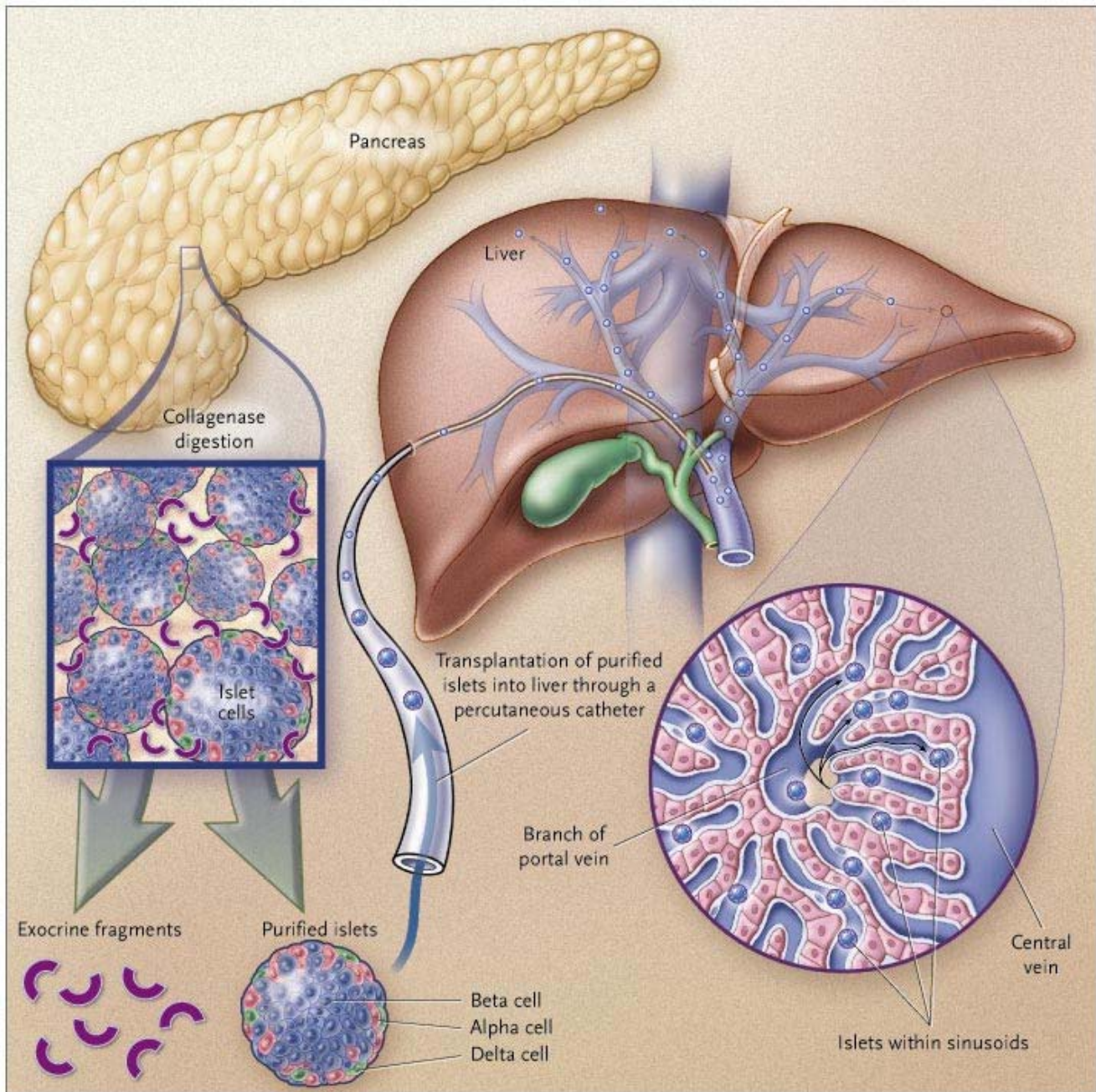
Competition for donor pancreas?

Pancreas allocation (Eurotransplant)

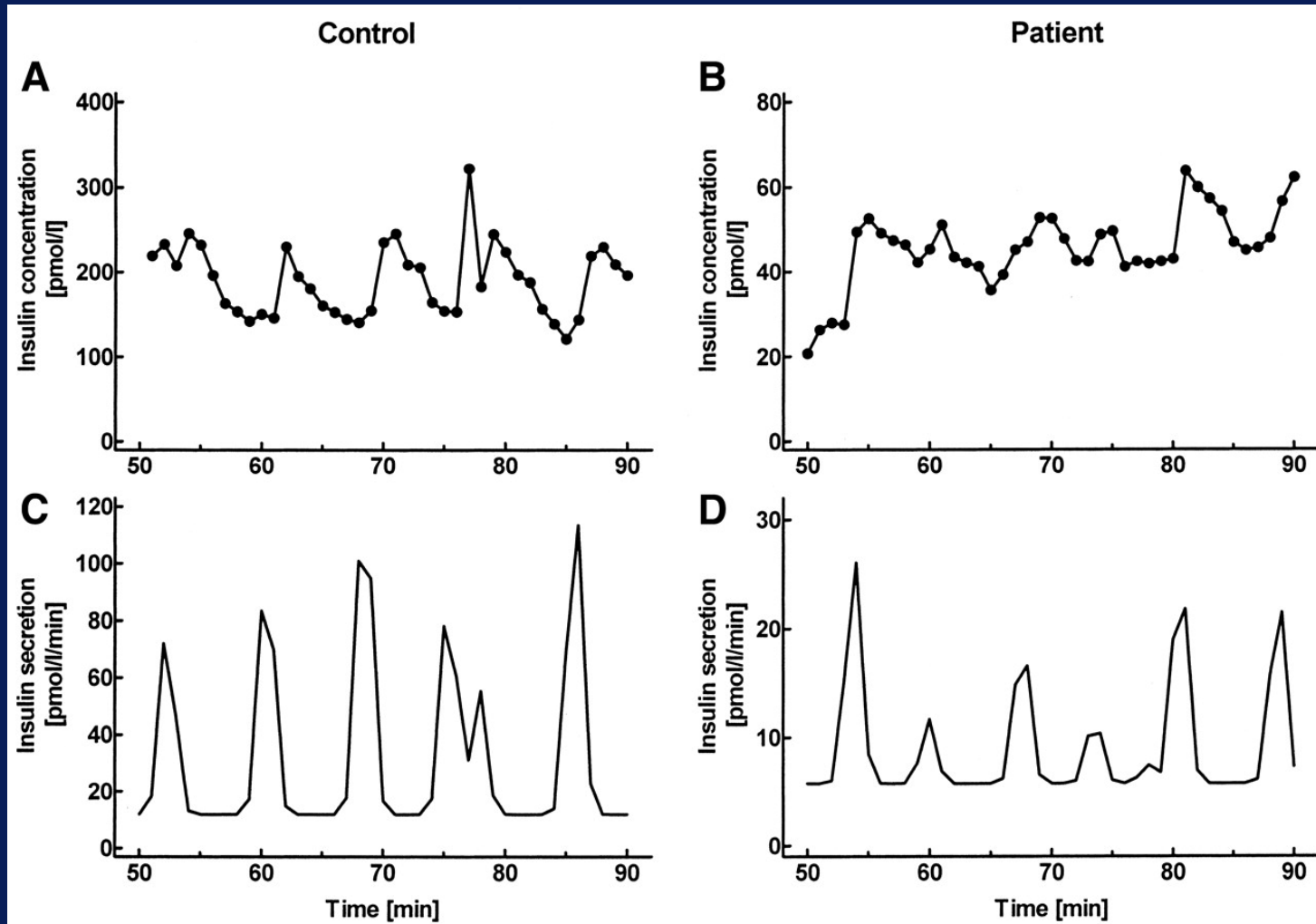


Where to transplant pancreatic islets?

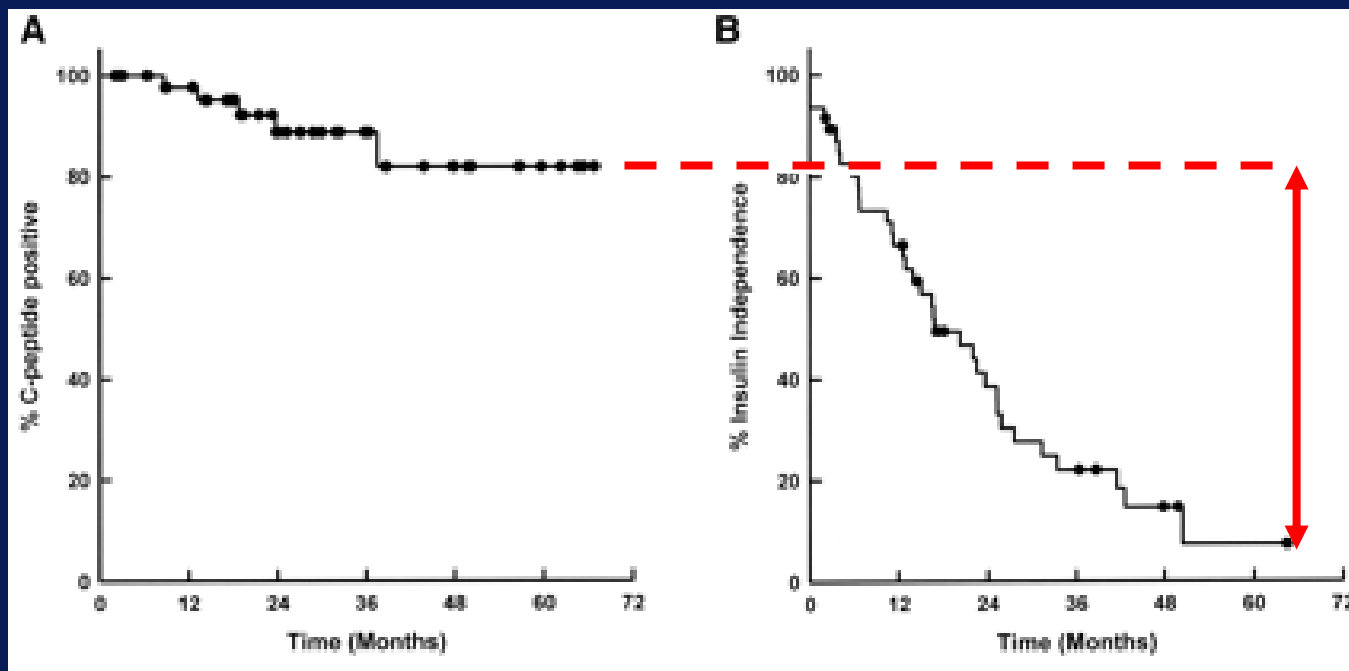




Islet transplantation restores insulin pulsatility



Persistent C-peptide secretion despite loss of insulin independence after 5 years: Edmonton single center study



Multifactorial events leading to loss of islet mass

- Recurrent autoimmunity?
- Allograft rejection?
- Chronic islet toxicity by immunosuppressive drugs (most drugs diabetogenic)
- Early islet loss (IBMIR - instant blood-mediated inflammatory reaction)

Table 2. Mechanisms of the Adverse Effects of Immunosuppressant Drugs on Beta Cells.

Adverse Effect	Corticosteroids	Cyclosporine	Tacrolimus	Sirolimus	Mycophenolate Mofetil
	<i>Source</i>				
Decreased insulin gene transcription		Oetjen et al. ^{67,68}	Redmon et al., ⁶³ Oetjen et al. ^{67,68}		
Decreased level of stability of insulin messenger RNA	Phillippe and Missotten ⁵⁷		Redmon et al. ⁶³		
Decreased insulin synthesis	Gold et al. ⁵³	Chandrasekar and Mukherjee, ⁵⁵ Gillison et al. ⁵⁶			
Decreased insulin synthesis in vitro	Davani et al., ⁶⁵ Paty et al. ⁶⁶	Robertson, ⁵¹ Nielsen et al., ⁵² Draznin et al., ⁵⁴ Chandrasekar and Mukherjee, ⁵⁵ Gillison et al., ^{56,58} Philippe and Missotten, ⁵⁷ Ishizuka et al., ⁶¹ Paty et al. ⁶⁶	Ishizuka et al., ⁶¹ Redmon et al., ⁶³ Paty et al. ⁶⁶	Fabian et al., ⁶² Paty et al. ⁶⁶	Meredith et al., ⁶⁴ Paty et al. ⁶⁶
Decreased insulin secretion in vivo	Billaudel and Sutter ⁵⁰		Ricordi et al., ⁵⁹ Strasser et al. ⁶⁰		

Robertson RP, N Engl J Med 350: 694-705, 2004

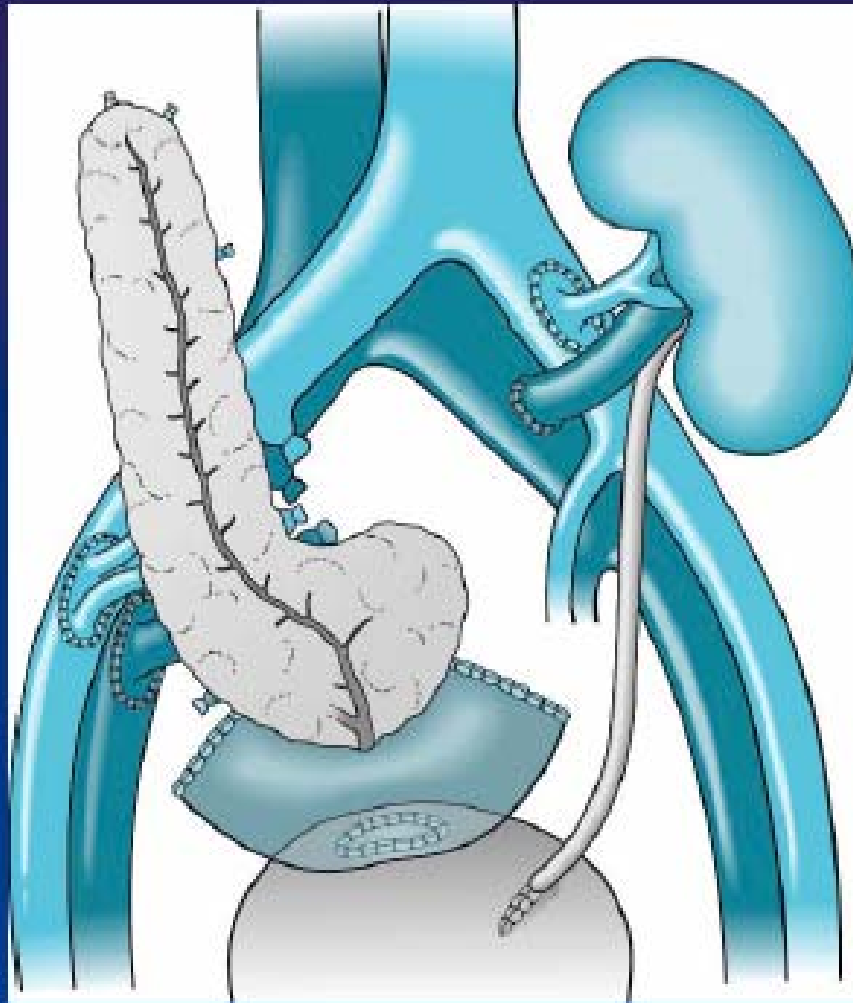
Islet transplantation and chronic diabetic complications

- Stabilizes diabetic retinopathy
- Improves cardiovascular function and vascular structure (Forina P et al., Diab Care 28: 1358-1365, 2005)
 - Kidney-islet vs kidney alone
 - Improves diastolic function
 - Reduces progression in IMT
 - Reduces BNP concentrations
- Stabilization of diabetic neuropathy in > 50% of patients

Complications of islet transplantation

- **Procedure-related**
 - **Bleeding liver (1%)**
 - **Thrombosis portal vein (5 %) – heparin**
 - **(2-3 procedures usually necessary)**
- **Long-term**
 - **Related to immunosuppressive agents (infections, cancer)**
 - **Risk of immunisation**

Complications?



Complications after pancreas or islet transplantation

Characteristic	SPK	SIK	<i>p</i> value
Total number of patients in each group	25	13	–
Patients with complications (pancreas/islets)	12 (48)	2 (15)	0.19
Patients with complications (kidney)	5 (20)	3 (23)	1.00
Patients with (re)laparotomy because of the pancreas/islet Tx	10 (40)	0 (0)	0.04
Patients with revision because of the kidney transplantation	2 (8)	2 (15)	0.61

Values are *n* (%)

Tx, transplantation

Islet transplantation in the Netherlands

Permission for
islet isolation

LUMC

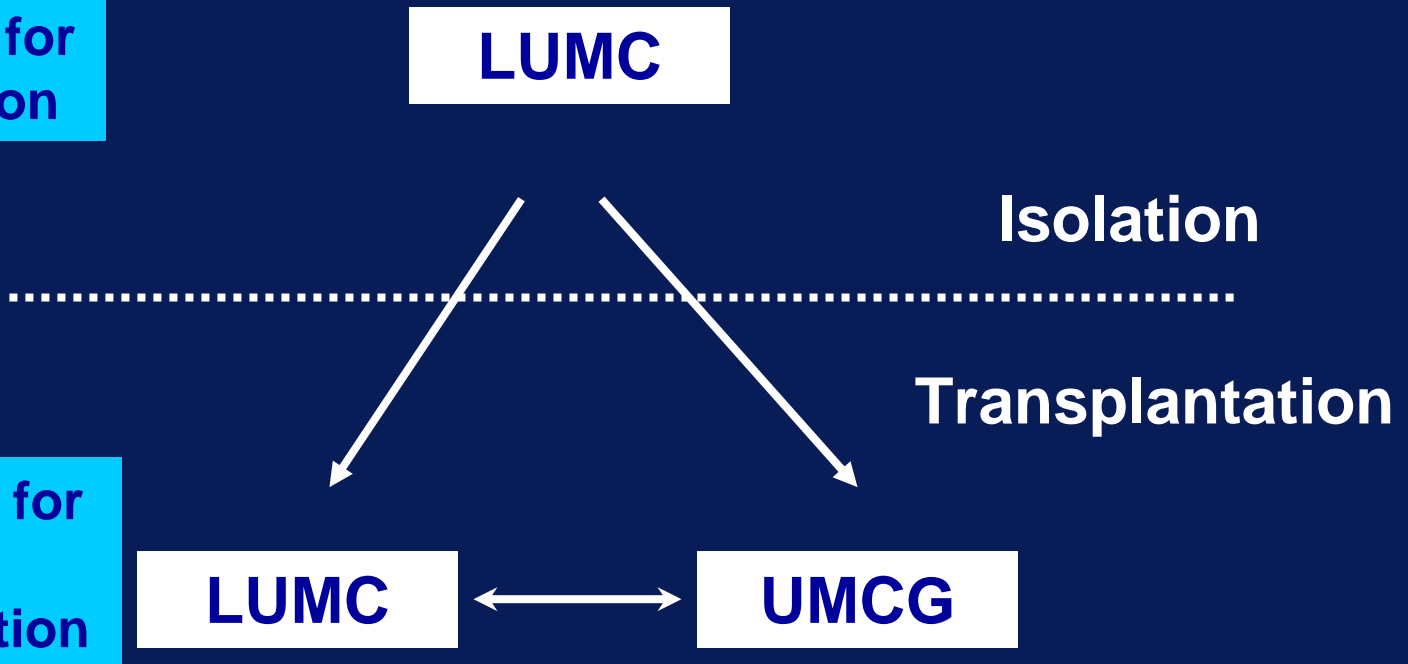
Isolation

Transplantation

Permission for
islet
transplantation

LUMC

UMCG



Islet transplantation outcome

- **Major improvement in glucose fluctuations**
- **Strong reduction in hypoglycemic episodes and restoration of hypoglycemia awareness**
- **Improvement in quality of life**

...even if not insulin-independent

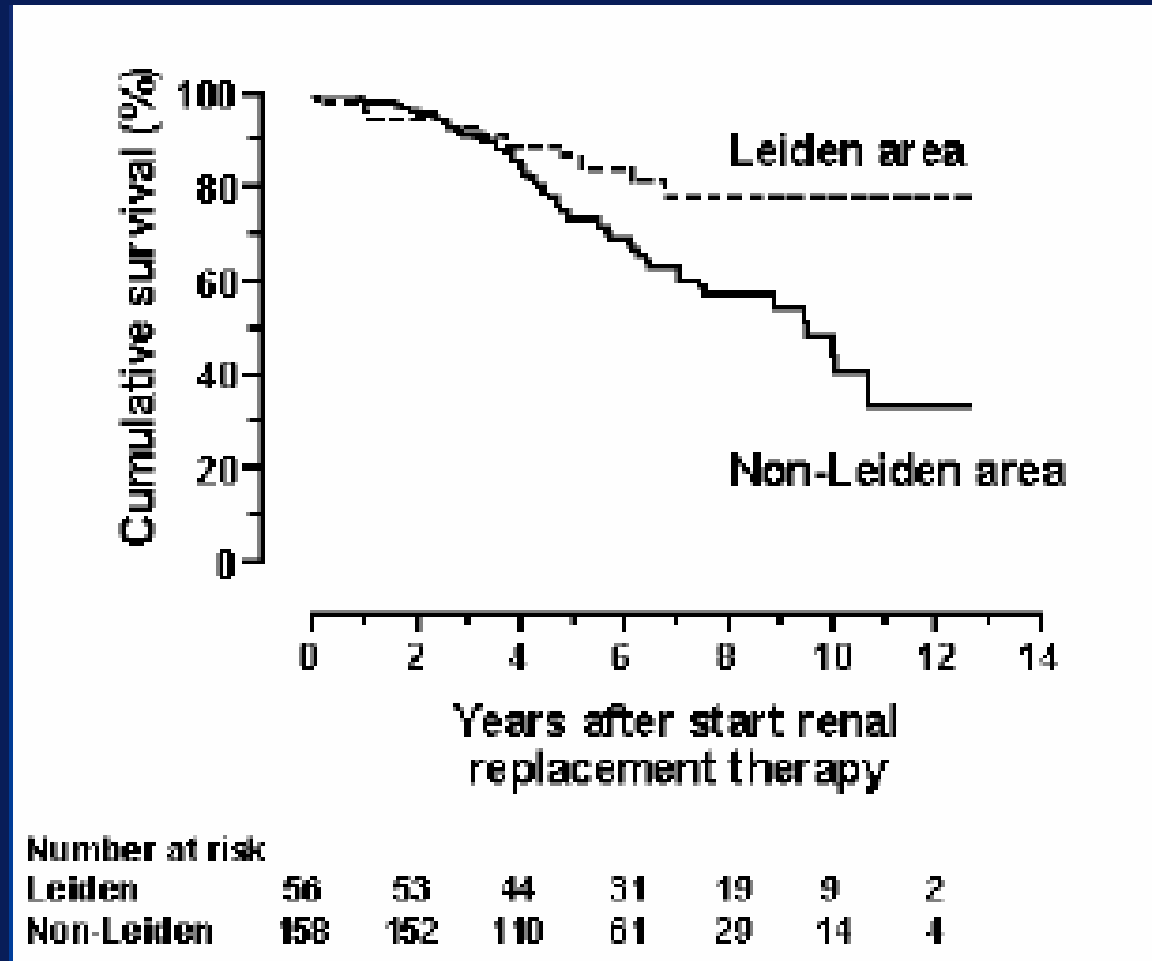
Pancreas or islets?

- **What is the goal of treatment?**
 - **Reduction in mortality?**
 - **Improvement in kidney graft survival?**
 - **Improvement in glycemic control?**

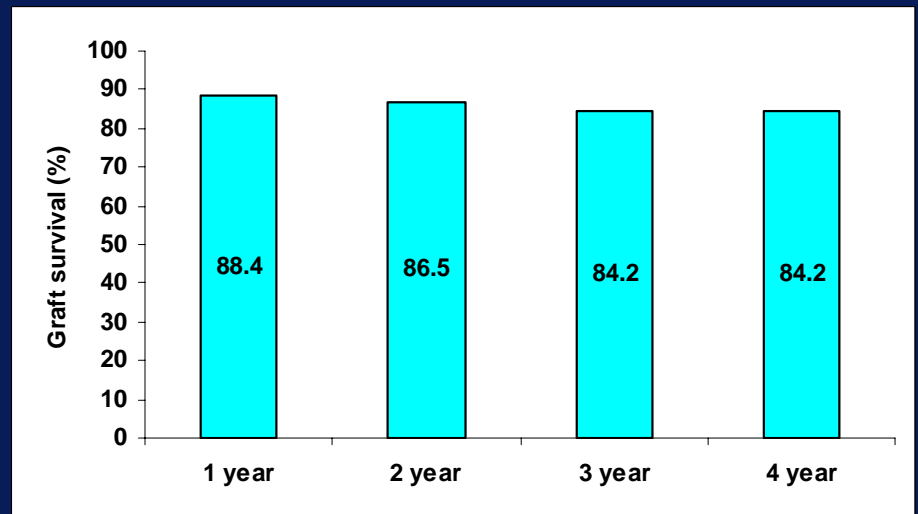
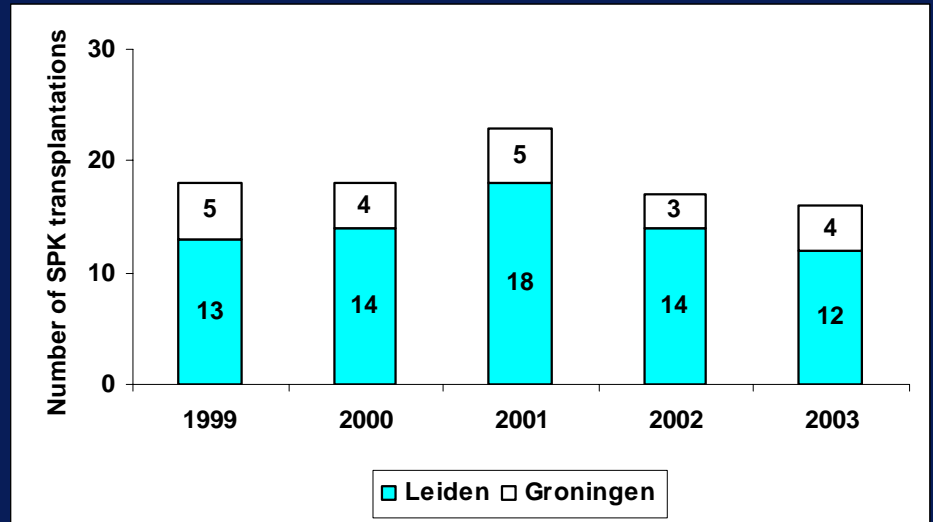
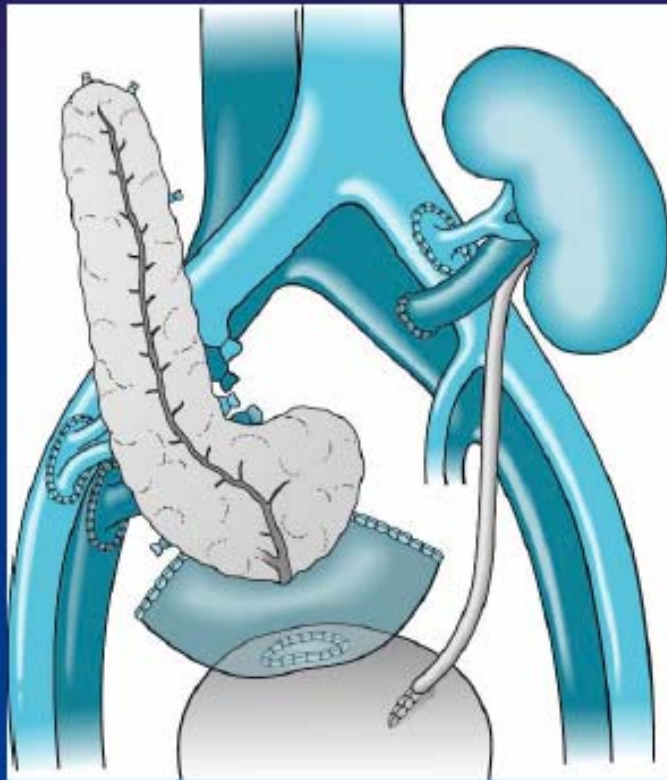
Cumulative survival after simultaneous pancreas-kidney (SPK) transplantation in type 1 diabetes and renal failure (1985-1996)

Leiden: SPK 75%

Non-Leiden: SPK 37%



Simultaneous-pancreas kidney transplantation in the Netherlands

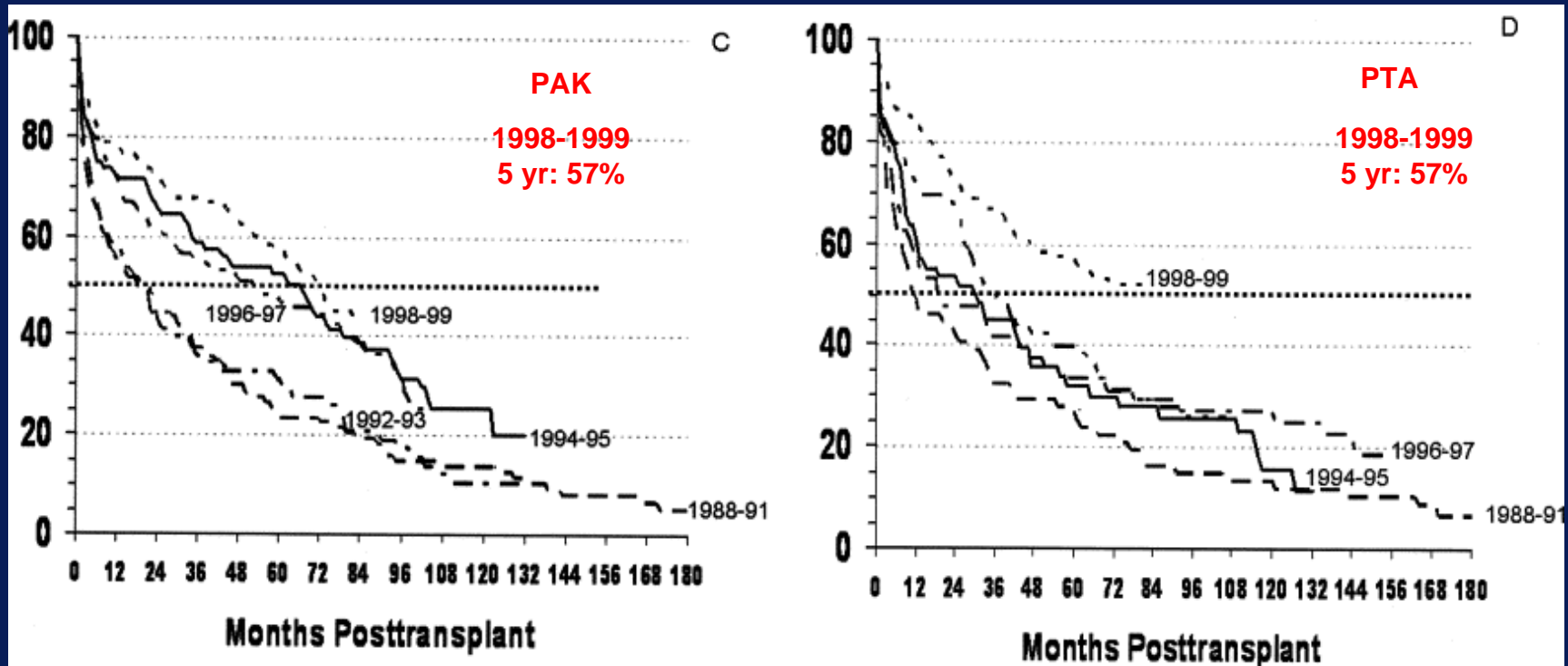


**Type 1
diabetes with
renal failure**



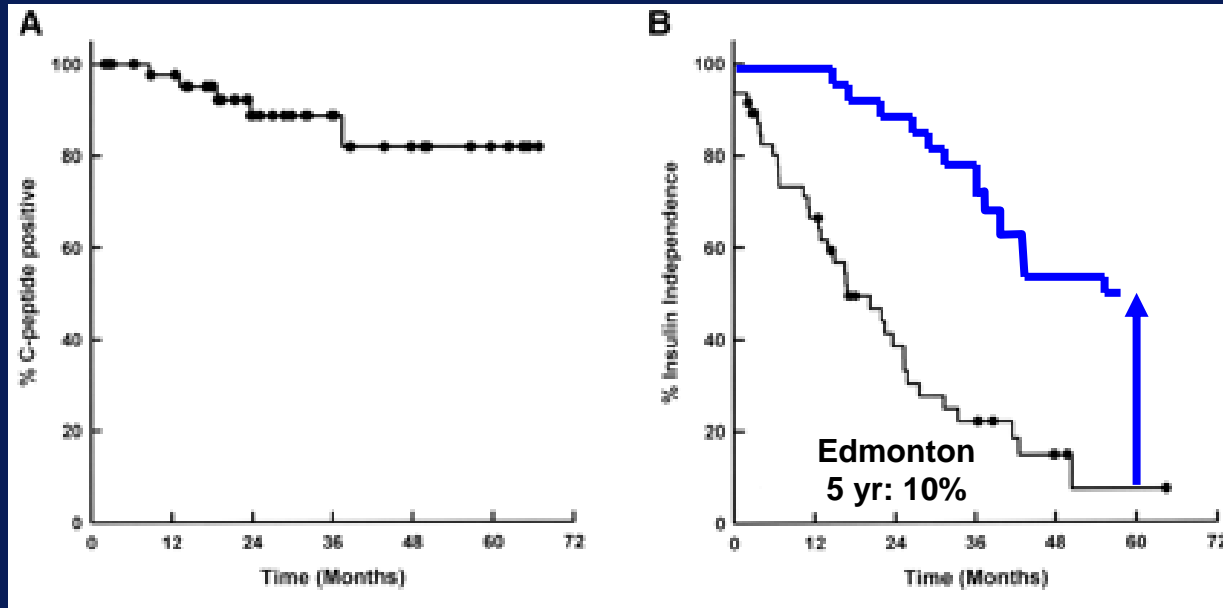
**Simultaneous
pancreas-kidney**

Pancreas graft survival in PAK and PTA

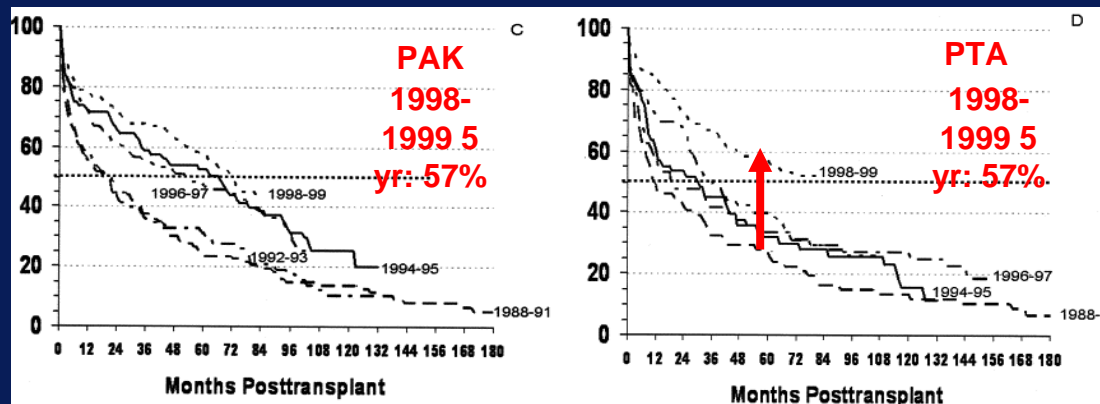


A matter of experience?

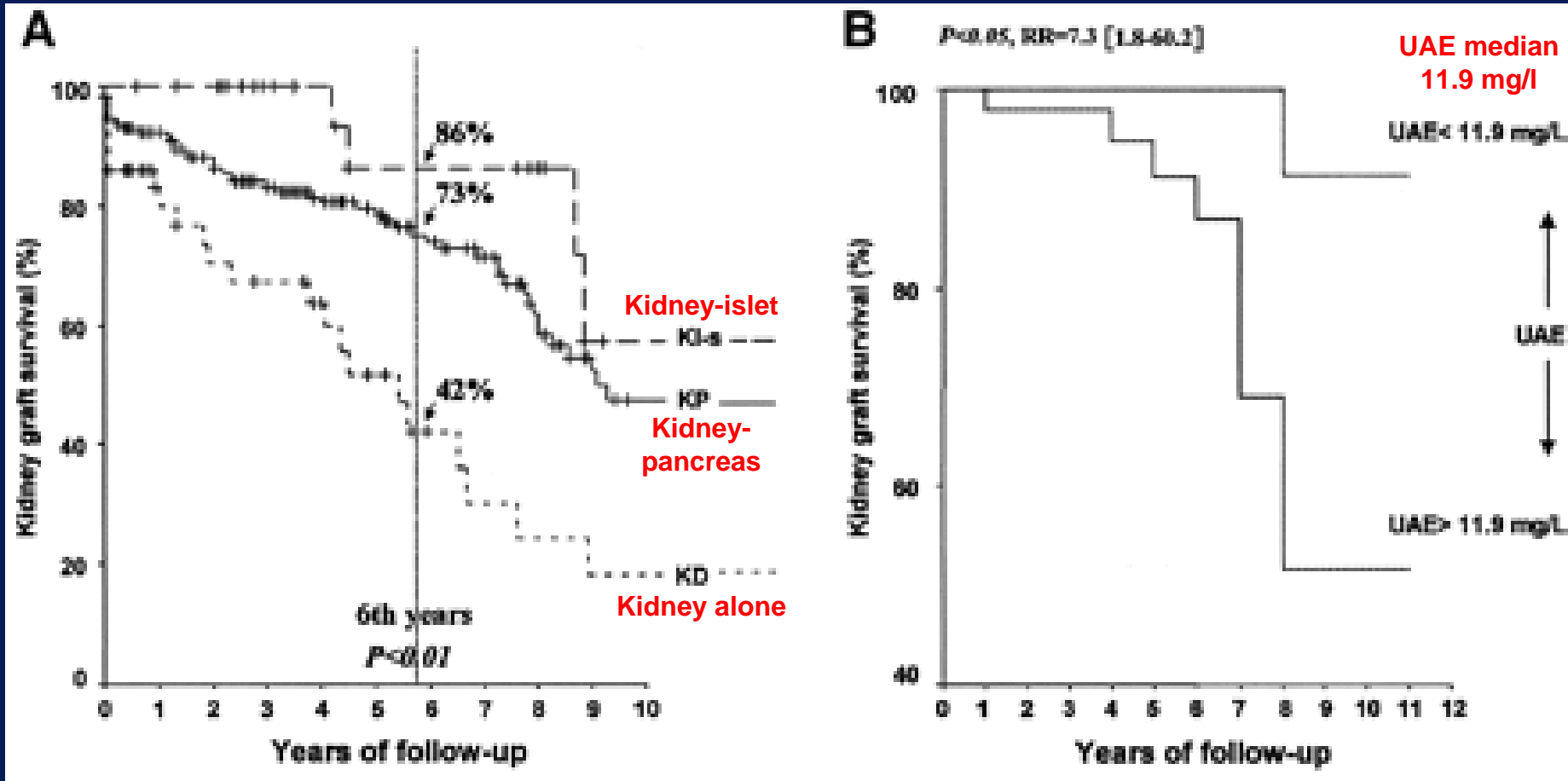
Graft survival
(islets)
Worldwide
700 Tx



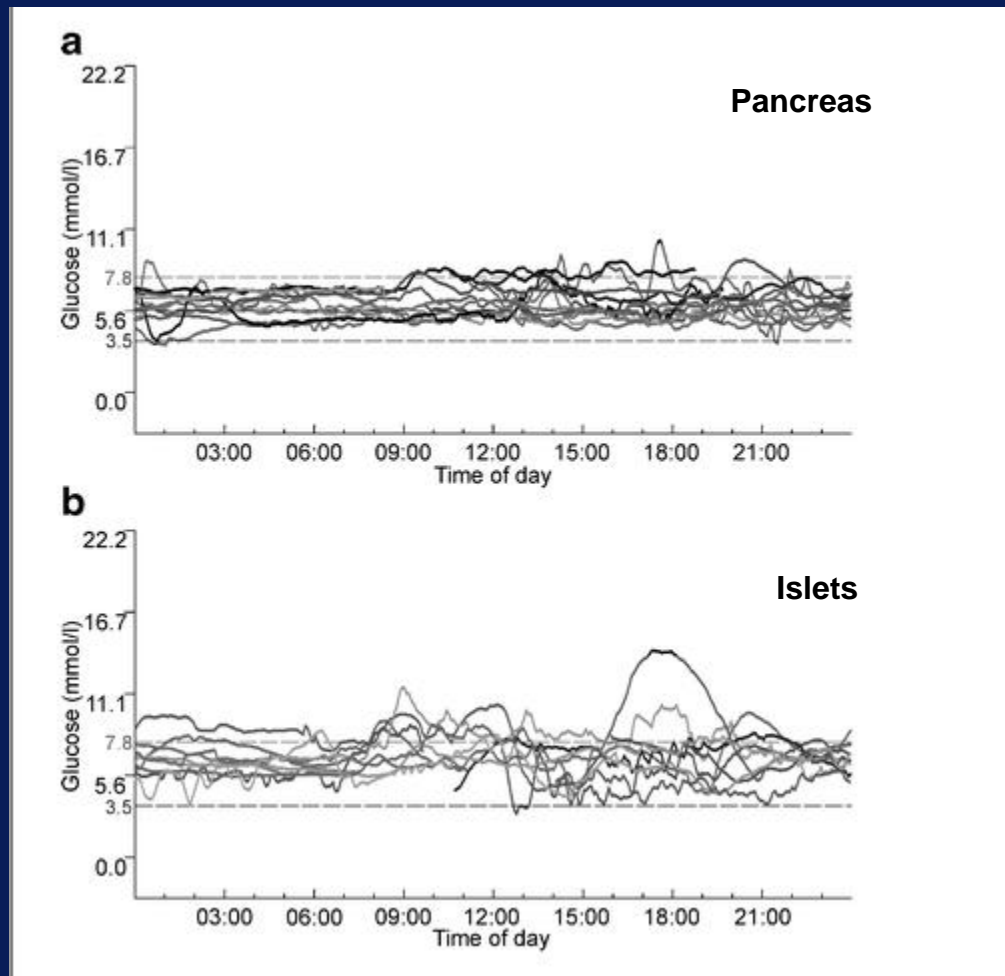
Graft survival
(pancreas)
Worldwide
>25.000 Tx



Islet transplantation improves kidney graft survival in T1DM



Continuous glucose monitoring after pancreas or islet transplantation



**Type 1
diabetes with
renal failure**



**Simultaneous
pancreas-kidney
(SPK) transplantation**

**Type 1
diabetes with
previous renal
transplantation**



**Pancreas after kidney
(PAK)
transplantation**



**Islets after kidney
(IAK) transplantation
(LUMC, UMCG)**

Type 1 diabetes and previous kidney transplantation: what to do?

- **Case 1:**
 - Male 53 yrs, T1DM since 31 yrs
 - Admission for SPK, during operation too many adhesions for pancreas transplantation
- **Case 2**
 - Male 68 yrs, T1DM since 45 yrs, previous kidney transplantation
 - Deterioration of vision due to DR
 - Strict glycemic control, 4-5 per month severe hypoglycemia
- **Case 3**
 - Male 48 yrs, T1Dm since 26 yrs, previous SPK, pancreas graft failed
 - Poor glycemic control, progressive DR
 - Diffuse coronary abnormalities, PTCA, chest pain during low-impact exercise
- **Case 4**
 - Female 30 yrs, T1DM since 22 yrs
 - Blind
 - Severe hypoglycemia 2-3 x per week

**Type 1
diabetes with
renal failure**



**Simultaneous
pancreas-kidney
(SPK) transplantation**

**Type 1
diabetes with
previous renal
transplantation**



**Pancreas after kidney
(PAK)
transplantation**



**Islets after kidney
(IAK) transplantation
(LUMC, UMCG)**

**Type 1
diabetes
without renal
failure**



**Islets or pancreas?
No referral?**

Transplantation in patients with type 1 diabetes without renal insufficiency?

A doctor's dilemma

- **Severe glycemic instability despite optimal insulin treatment (hypoglycemia unawareness and/or recurrent hypoglycemia)**
- **Severe autonomic neuropathy (postural hypotension, gastroparesis)**
- **Morbidity related to the pancreas transplantation**
- **Side-effects of immunosuppressive drugs**

Islet transplantation the future?

- We only need the islets
- We do not want the procedure-related complications
- We can improve glycemic control and reduce microvascular complications
- But still suboptimal function in the long term
- But what does the patient want?