Pancreas-kidney transplantation in diabetes mellitus: Benefits and complications

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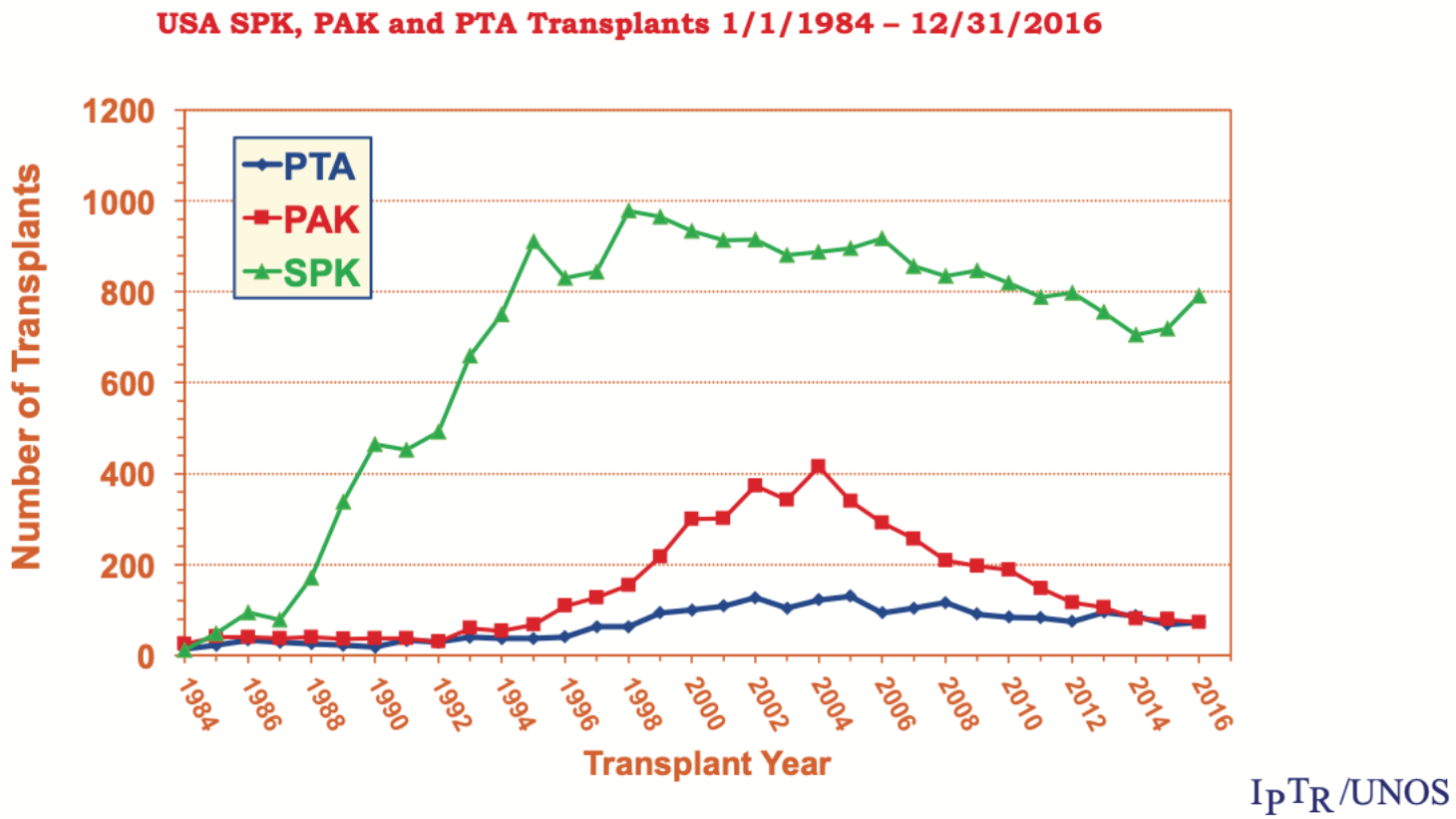
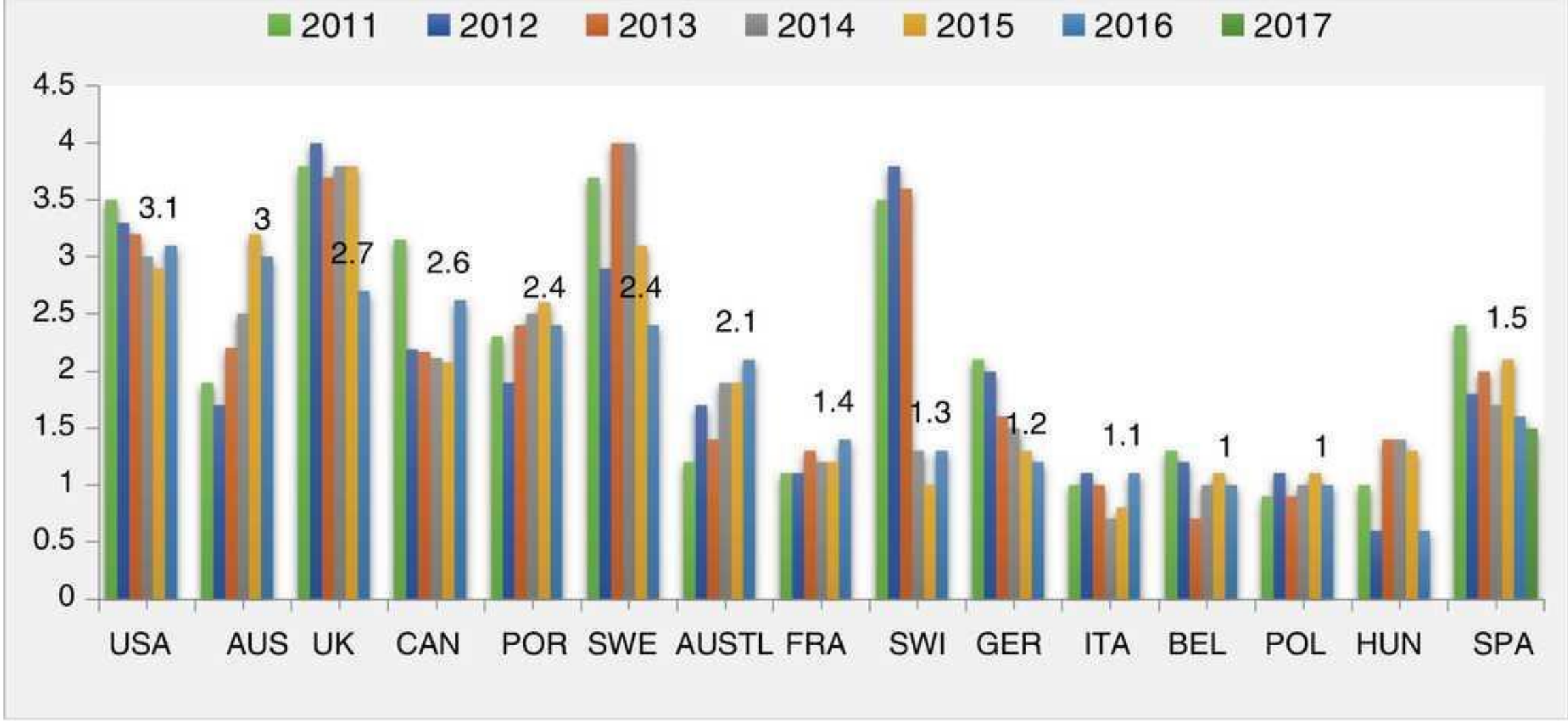
SUMS

- SPK transplantation is an established treatment for selected insulin-requiring diabetic patients with either (CKD) or (ESKD).

Transplant Categories



Organ Transplant. 2015 Feb;20(1):94-102



Pancreas transplants PMP: Spain and other countries. 2011-2017

Nefrologia (English Version). 2019;39:455-7

BENEFITS

- The major benefits of simultaneous pancreas-kidney (SPK) transplantation are decreased mortality and improved quality of life.
- The improved quality of life is due to:
  - freedom from frequent blood sugar monitoring
  - insulin therapy
  - glucose variability
  - dialysis

- Glucose metabolism
- Nephropathy
- Lipid metabolism and atherosclerosis
- Retinopathy
- Circulation
- Fertility
- Fracture risk

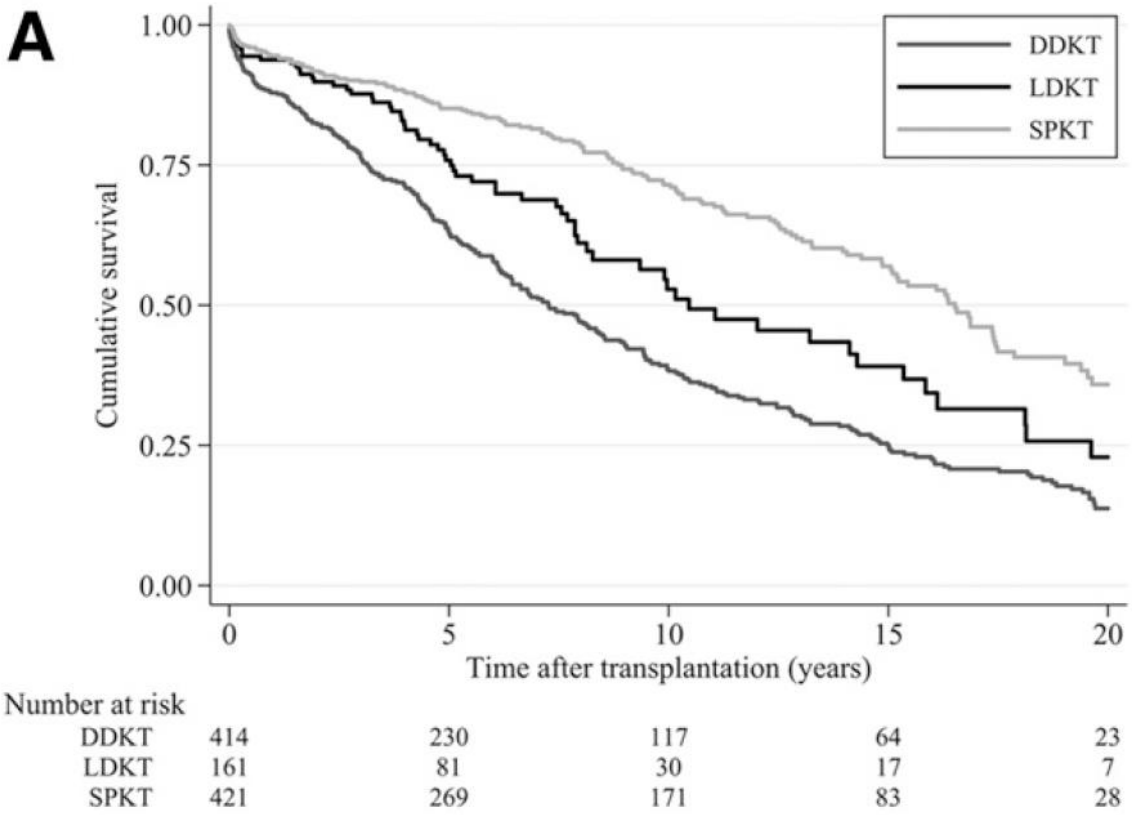
Superior Long-term Survival for Simultaneous Pancreas-Kidney Transplantation as Renal Replacement Therapy: 30-Year Follow-up of a Nationwide Cohort

Kevin Esmeijer [1], Ellen K Hoogeveen [2 3], Paul J M van den Boog [2], Cynthia Konijn [4], Marko J K Mallat [2], Andre G Baranski [5], Olaf M Dekkers [3 6], Johan W de Fijter [2], Dutch Transplant Centers; Dutch Kidney Transplant Centres

- cohort of kidney replacement therapy in patients with type 1 diabetes, included all 2,796 patients with type 1 diabetes in the Netherlands between 1986 and 2016.

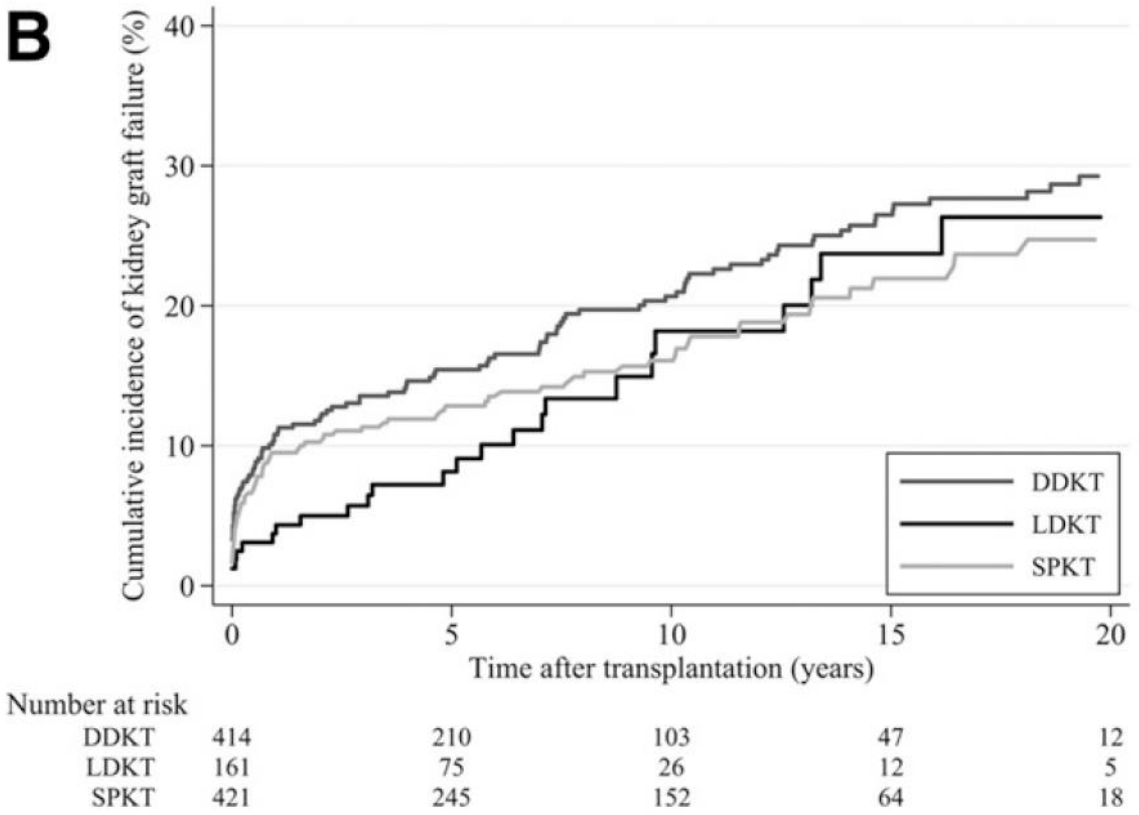
- SPK transplant recipients with a functioning graft at one year (91 percent) compared with either deceased-donor or living-donor KTA recipients

Compared with living- or deceased-donor kidney transplantation, SPK transplant was associated with improved patient survival, especially in recipients with a longterm functioning pancreatic graft, and resulted in an almost twofold lower 10-year mortality rate.



Number at risk

DDKT	414	230	117	64	23
LDKT	161	81	30	17	7
SPKT	421	269	171	83	28

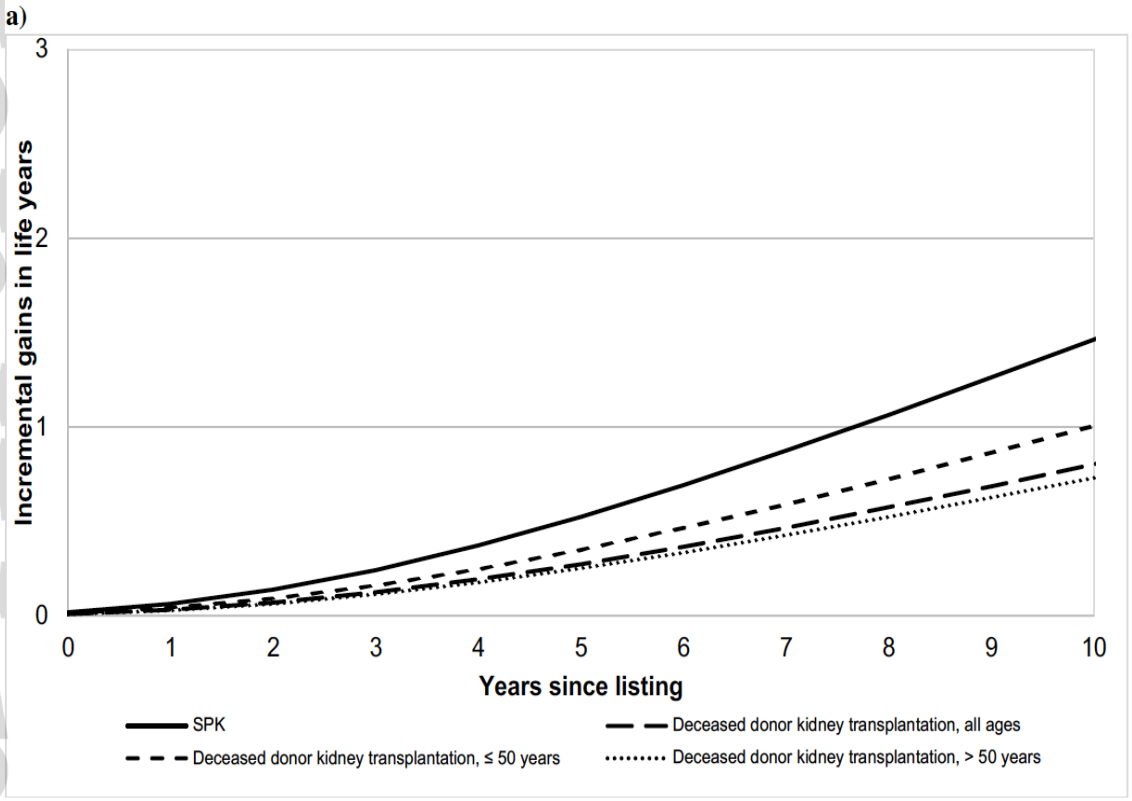


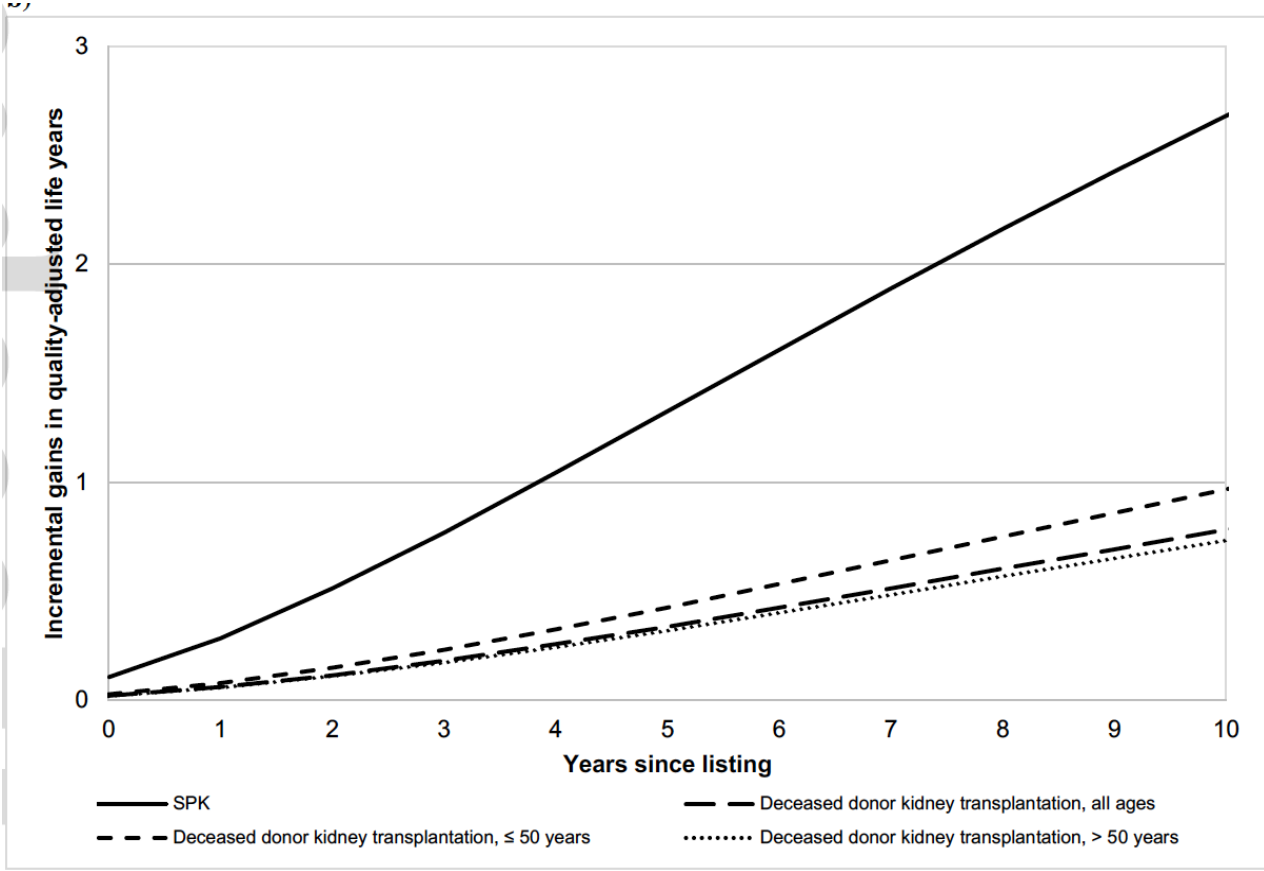
Number at risk

DDKT	414	210	103	47	12
LDKT	161	75	26	12	5
SPKT	421	245	152	64	18

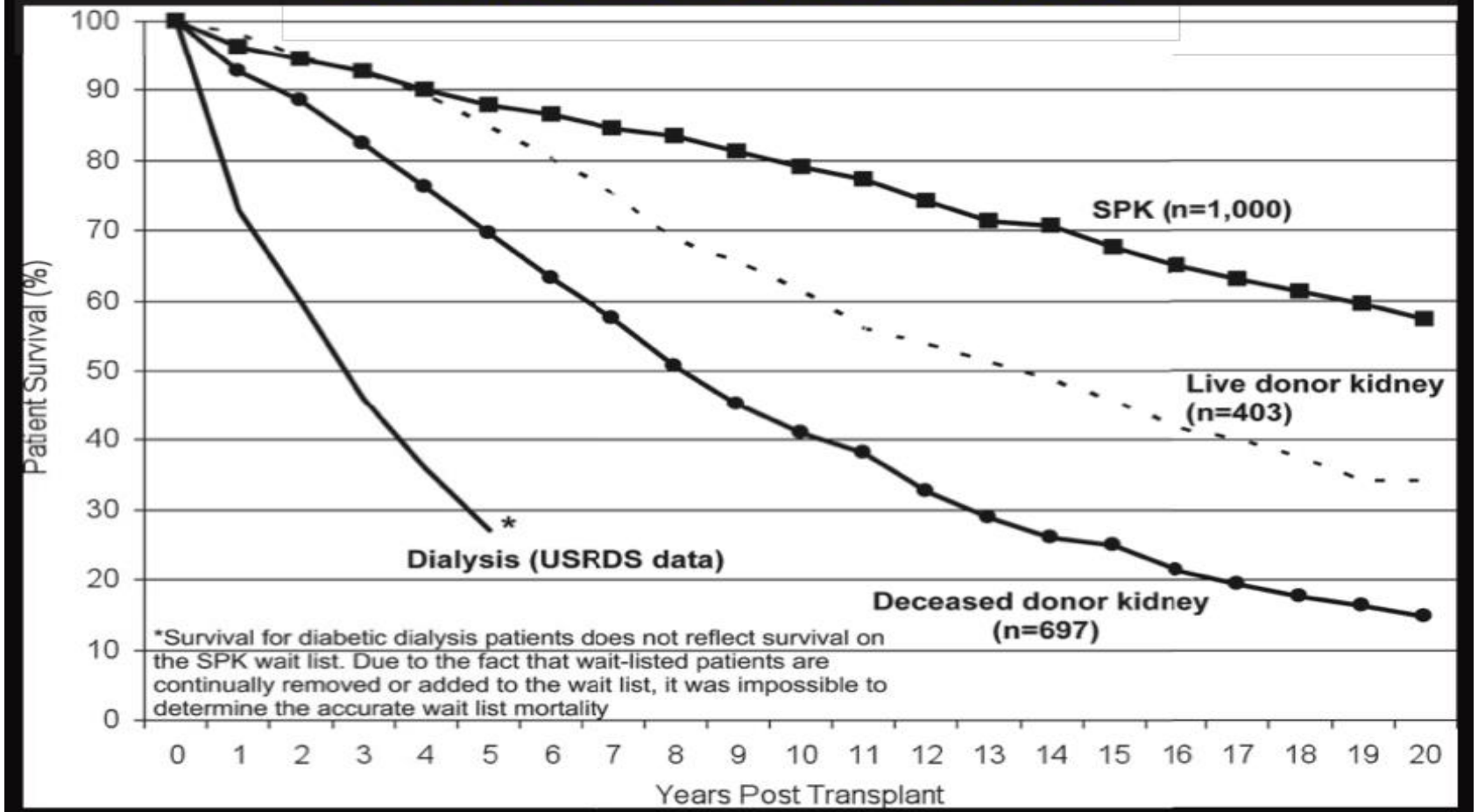
Relative survival and quality of life benefits of pancreas–kidney transplantation, deceased kidney transplantation and dialysis in type 1 diabetes mellitus–a probabilistic simulation model

Figure 3. The cumulative incremental benefits of SPK and deceased donor kidney transplantation compared with being listed on dialysis, in a) life years, and b) quality-adjusted life years

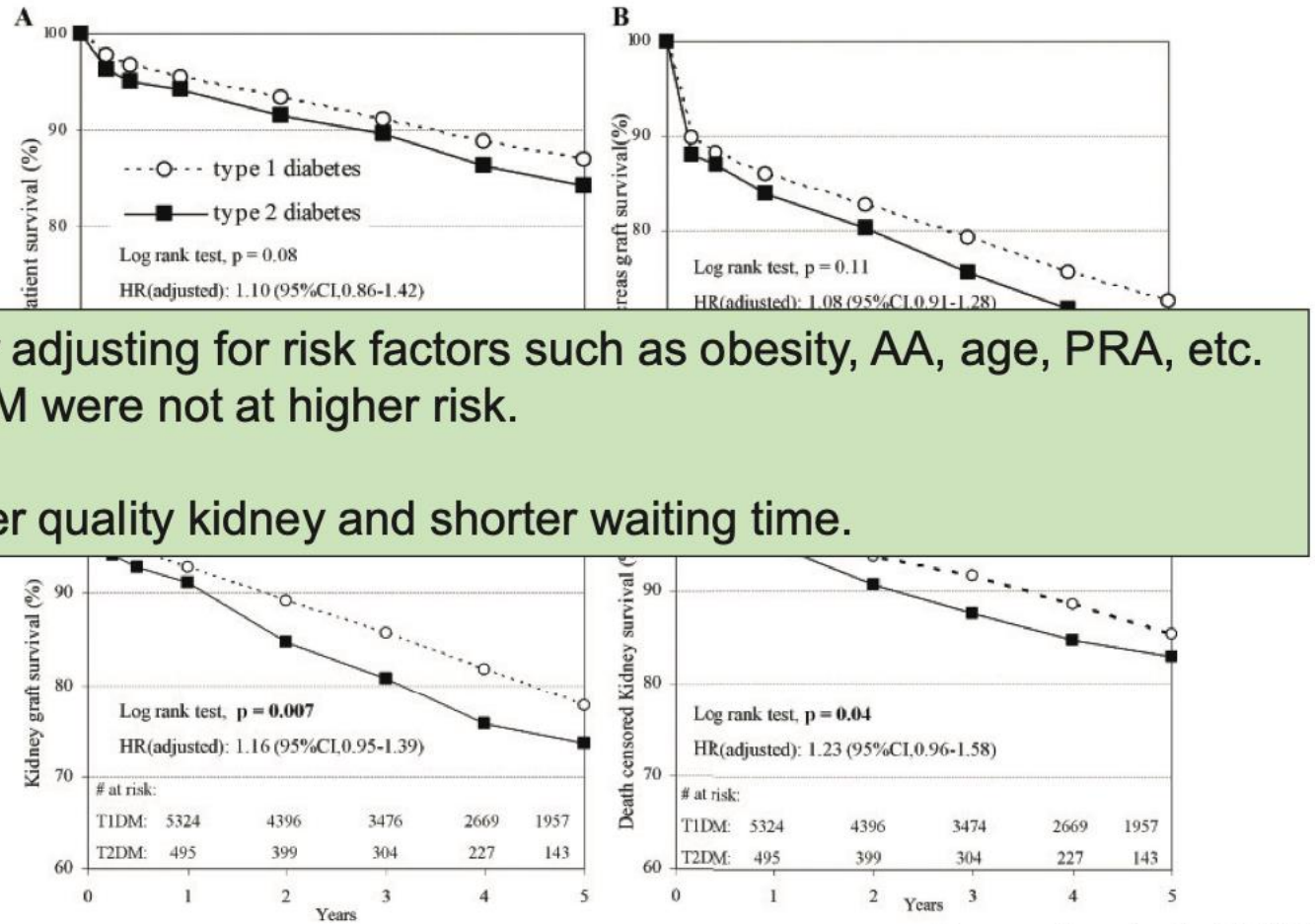




Patient Survival in Uremic Type 1 Diabetes
SPK vs. LD vs. DD vs. HD



Comparable outcomes in SPK transplantation – T1DM v. T2DM



After adjusting for risk factors such as obesity, AA, age, PRA, etc. T2DM were not at higher risk.

Better quality kidney and shorter waiting time.

Sampaio et al. CJASN 2011

Glucose metabolism

- Successful pancreas transplantation is defined as restoration of normoglycemia without the need for exogenous insulin.

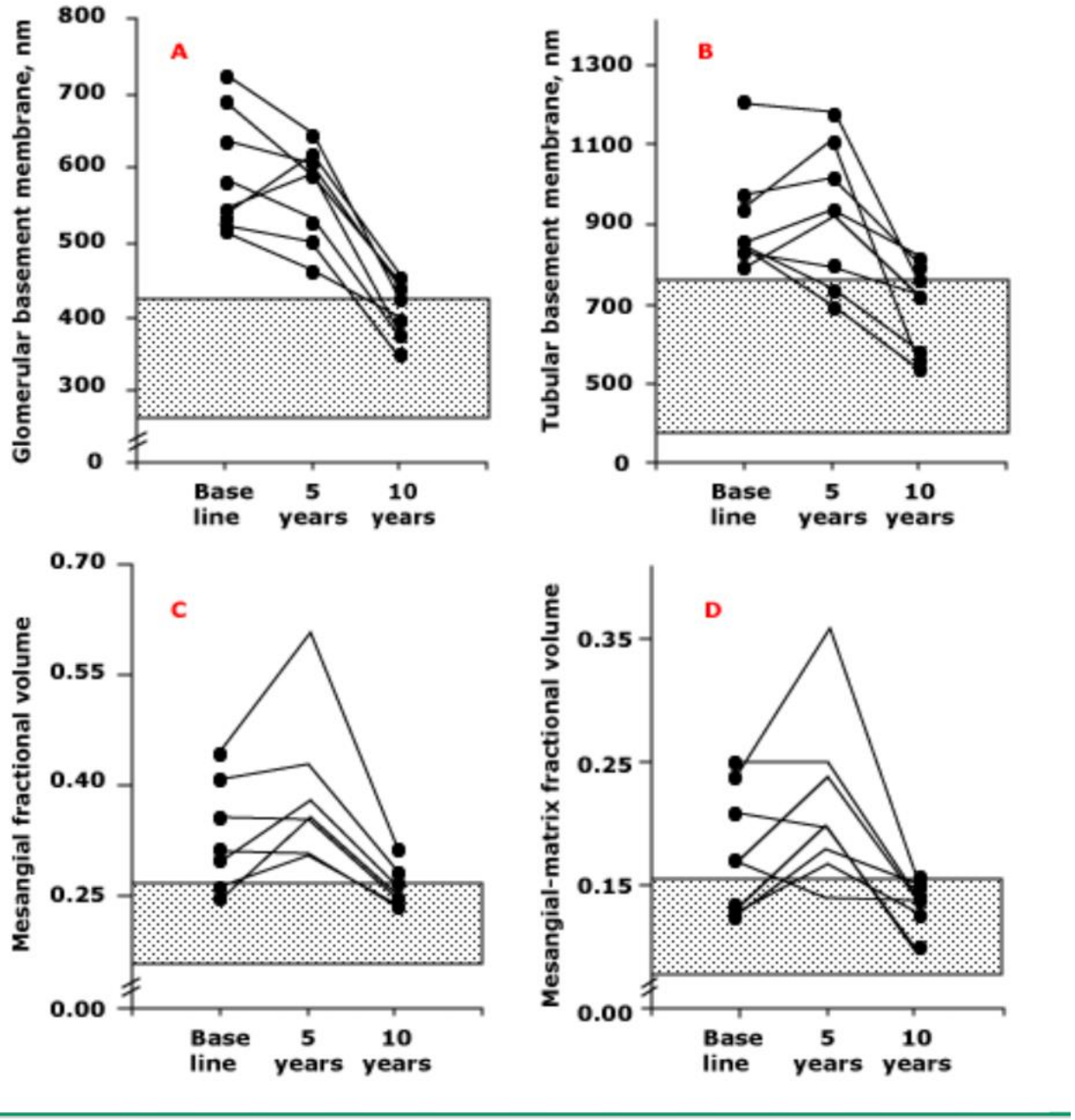
- Glucose counter regulation also improves after pancreas transplantation because the transplanted pancreas produces not only insulin but also glucagon.
- symptom recognition of hypoglycemia is restored and occurs at higher blood glucose concentrations.

Lipid metabolism and atherosclerosis

- Serum triglyceride and low-density lipoprotein cholesterol (LDL-C) concentrations tend to fall and serum high-density lipoprotein cholesterol (HDL-C) concentrations tend to rise in recipients of pancreas transplants.

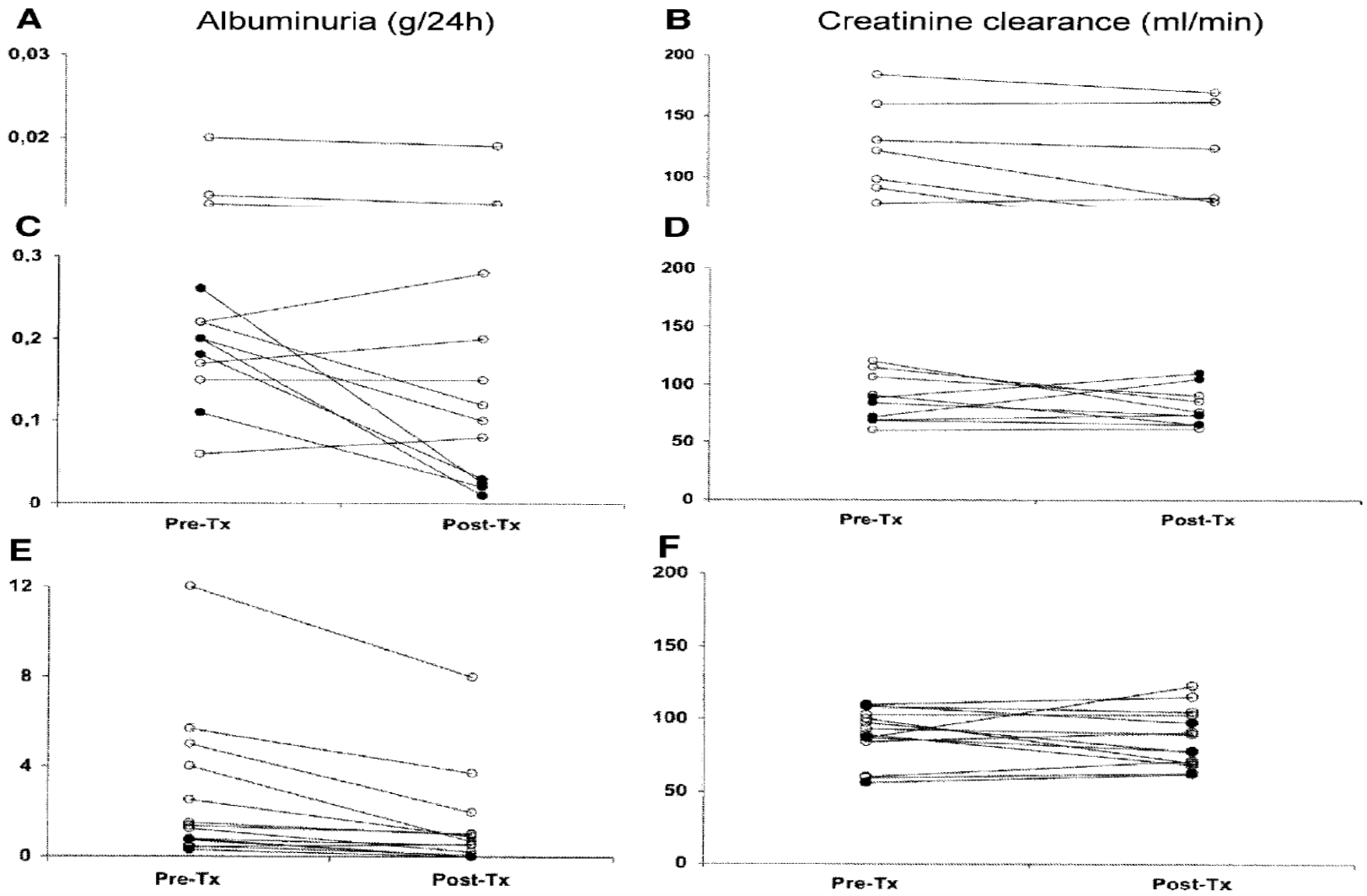
Diabetic nephropathy

- Recurrent and de novo diabetic nephropathy is prevented by successful pancreas transplantation .
- PTA may reverse established diabetic lesions in patients with early diabetic nephropathy.



N Engl J Med 1998; 339:69

The beneficial effects of pancreas transplant alone on diabetic nephropathy



Diabetes Care 28:1366–1370, 2005

- **Diabetic neuropathy:**
  - There is stabilization and, in some cases, improvement in peripheral and autonomic diabetic neuropathy after pancreas transplantation.
- **Diabetic retinopathy:**
  - The effect of pancreas transplant on diabetic retinopathy is **not clear.**
  - Some studies have found no benefit in terms of halting or reversing the progression of advanced retinopathy after pancreas transplantation .

- **Fracture risk:**
  - The risk of fracture may be lower following SPK transplant compared with that after KTA.
  - The protective effect of SPK transplant on fracture was particularly evident among men.
- **Reproductive health**
- **Quality of life**

COMPLICATIONS

- Complications are generally more severe and common in the first year posttransplant in (SPK) transplant compared with (KTA).

Pancreas failure

- The new definition of pancreas graft failure includes any of the following criteria:
  - A recipient's transplanted pancreas is removed
  - A recipient re-registers for a pancreas
  - A recipient registers for an islet transplant after receiving a pancreas transplant
  - A recipient's insulin use is ≥0.5 units/kg/day for 90 consecutive days
  - A recipient dies

➢ Donor factors:

- Donor risk factors for technical failure were :
  - age >50 years, BMI ≥30 kg/m^2, serum creatinine ≥2.5 mg/dL, and preservation time >20 hours.
- pancreas donor risk index (PDRI) to estimate the risk of early pancreas failure.

➢ Recipient factors:

- Recipients over age 45 years carry a twofold greater risk of graft loss, most often due to technical failure, and a threefold greater risk of dying than younger patient
- Other recipient factors that have been associated with inferior pancreas outcomes are obesity (defined as BMI >30 kg/m^2) and African-American race (compared with White American).

Variable	Median	IQR
Recipient characteristics		
Age at transplantation [years]	44.3	38.2–50.4
BMI [kg/m²]	23.1	21.5–25.6
Time on waiting list [months]	14.8	7.9–26.7
Time on dialysis [years]	2.5	1.3–4.2
Follow-up [months]	51	26–80
Donor characteristics		
Age at explantation [years]	35	20–42
BMI [kg/m²]	23.3	21–25
Graft travel distance [km]	156	91–284
Cold ischemia time [hours]	12.0	10–14.1
P-PASS	17	14–20
pDRI	1.198	0.961–1.382

Infection

- Increased risk of bacterial, fungal, and viral infections
- CMV
- BK: tubulointerstitial nephritis and ureteral stenosis
- UTI

Metabolic disturbances

- **Metabolic acidosis:**
  - bladder exocrine drainage:normal anion gap metabolic acidosis, hyponatremia, and volume depletion.
- **Hyperglycemia:**
  - result from pancreatic dysfunction due to rejection or technical problems, to calcineurin inhibitor toxicity, glucocorticoids or to recurrent diabetes.
  - CNI induced:decreased insulin gene expression, decreased stability of insulin messenger RNA (mRNA), decreased insulin synthesis, and decreased insulin

Posttransplant erythrocytosis

- PTE is defined as persistently elevated hemoglobin and hematocrit levels that occur following kidney transplantation and persist for more than six months in the absence of thrombocytosis, leukocytosis.
- with the advent of enteric exocrine drainage, the incidence of PTE has decreased dramatically.

ADVANTAGES

Improved long-term patient survival*¥
(Compared to KTA)

Long-term Insulin-independence#
(Up to 75% at 10years)

Lower risk of MACE*¥
(Compared to KTA)

Improved QoL*¥
(Improvement in Health--related QoL)

DISADVANTAGES

Surgical risk¥#
(e.g. bleeding, leaks, fistulas)

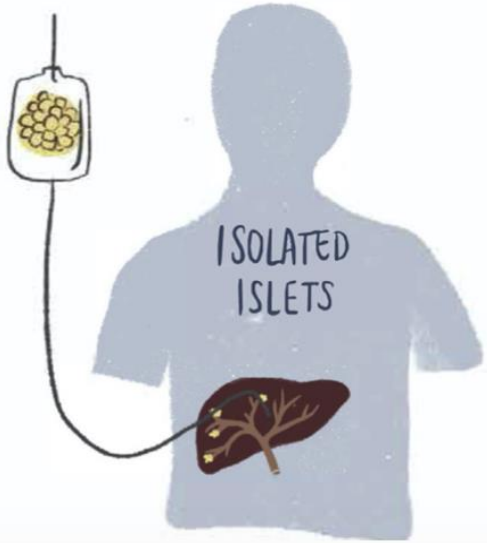
Early graft failure
(Thrombosis and pancreatitis are the leading causes; incidence up to 8%)

Contraindication due to technical reasons
(Potencial candidates ineligible due to vascular disease/iliac artery calcification)

Minimally invasive procedure&
(Potential benefit in older patients and those with established CVD)

Long-term graft function*
(Up to 75% at 10 years with improved glycemic control)

Improved QoL¥$
(Improvement in IAH in up to 100% of patients at 3 years)



Insulin-independence$&
(only up to 53% at 5 years)

Multiple donors&
(more than one pancreas often required to achieve sufficient islet engraftment following transplantation)

Sensitization risk*$
(requirement of multiple donors may increase sensitization)

Study	Population	Design	FU Period	Time on Wait List and/or Dialysis	Patient Survival	Graft Survival	
						Pancreas/ Islet	Kidney
SPK vs KTA							
Lindahl (2016)[62]	SPK (n = 256) vs LDKT (n = 230)	Single center	7.9 y	Wait list: ND Dialysis: SPK: 0.9 y, LDKT: 0.6 y	Survival on FU: 61% for SPK vs 44% for LDKT HR for mortality,[a] SPK vs LDKT CVD related: 0.63 (0.4-0.99); $P = 0.047$ All-cause: 0.81 (0.57-1.16); $P = 0.25$ CAD related: 0.63 (0.36-1.12); $P = 0.12$	—	—
Sollinger (2009)[55]	SPK (n = 1,000) vs LDKT (n = 403) vs DDKT (n = 697)	Single center	20 y	ND	At 10 y: 80% for SPK; 50%-60% for LDKT; 40%-50% for DDKT	—	At 10 y: 38% for SPK; ND for LDKT, DDKT
Barlow (2017)[60]	SPK (n = 1,739) vs LDKT (n = 370)	Registry analysis	13 y	Wait list: SPK, 0.87 y; LDKT, 0.90 y Dialysis: ND	Better in SPK (with functioning pancreas at 90 d) vs LDKT ($P = 0.042$)	—	DGF: 15.5% for SPK vs 7.3% for LDKT ($P < 0.001$) Graft survival at 10 y: 77% for SPK vs 80% for LDKT ($P = 0.25$)
Fridell (2018)[61]	SPK (n = 19,725) vs PAK (n = 5636)	Registry analysis	10 y	Wait list: SPK, 1.2 y; KTA, ND	At 10 y: 70.3% for SPK; 86.3% for KTA[b]	—	69.8% for PALK vs 61.0% for LDKT; 66.0% for PADK vs 50.4% for DDKT

Study	Population	Design	FU Period	Time on Wait List and/or Dialysis	Patient Survival	Graft Survival	
						Pancreas/ Islet	Kidney
SPK vs PAK							
Fridell (2018)[61]	SPK (n = 19,725) vs PAK (n = 5,636)	Registry analysis	10 y	Wait list: SPK, 1.2 y; PAK, 1.3 y Dialysis: ND	70.3% for SPK vs 63.2% for PAK ($P < 0.001$)	58.7% for SPK vs 44.4% for PALK vs 41.7% for PADK ($P < 0.001$)	61% for SPK vs 69.8% for PALK vs 66.0% for PADK ($P < 0.001$)
Ventura-Aguiar (2018)[63]	SPK (n = 139) vs PALK (n = 18) vs PADK (n = 28)	Single center	10 y	Wait list: SPK, 1.6 y; PALK, 0.5 y; PADK, 0.3 y Dialysis: SPK, 2.9 y; PALK, 1.0 y; PADK, 2.8 y	$P > 0.05$ for SPK vs PALK vs PADK	PALK & PADK inferior to SPK ($P < 0.05$)	$P > 0.05$ for SPK vs PALK vs PADK
Parajuli (2019)[81]	SPK (n = 611) vs PALK (n = 12) vs PADK (n = 12)	Single center	15 y	Wait list: SPK, 0.5 y; PAK, 1.2 y Dialysis: ND	68% for SPK vs 71% for PAK ($P = 0.79$)	62% for SPK vs 71% for PAK ($P = 0.38$); $P = 0.68$ for SPK vs PALK vs PADK	66% for SPK vs 50% for PAK ($P = 0.11$); $P = 0.59$ for SPK vs PALK vs PADK
SIK/IAK vs SPK/PAK							
Frank (2004)[86]	IAK (n = 4) vs SPK/PAK (n = 30)	Single center	IAK: 1.4 y; SPK/PAK: 1.2 y	ND	At FU: 96.6% for SPK/PAK vs 100% for IAK	Graft function (as per C-peptide secretion): no difference Insulin independence: superior for SPK/PAK ($P < .04$)	ND
Lehmann (2015)[19]	SPK/PAK (n = 94) vs SIK/IAK (n = 38)	Single center	SPK/PAK: 5.6 y; SIK/IAK: 6.4 y	Wait list: SPK/PAK, 0.9 y SIK/IAK, 1.4 y	At 10 y: 88.5% for SPK/PAK vs 65.4% for SIK/IAK	Insulin independence at 5 y: 73.6% for SPK/PAK vs 9.3% for SIK/IAK	ΔeGFR at 13 y: −9.5 ± 23 for SPK/PAK vs −13.3 ± 13.8 for SIK/IAK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