Pancreas Transplantation: The Marginal Donor and Recipient

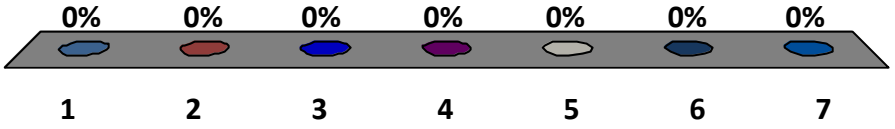
Jon Odorico, M.D., F.A.C.S.
Division of Transplantation, Dept of Surgery
University of Wisconsin School of Medicine and Public Health
Director, Pancreas and Islet Transplantation

Disclosures

- No commercial interests related to this topic

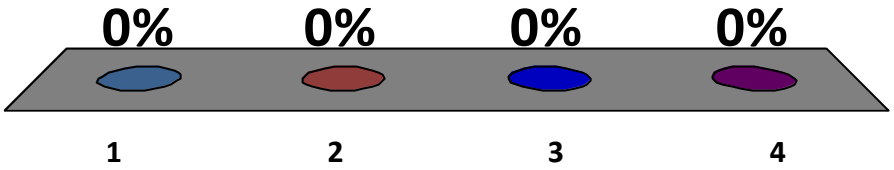
I am/will be looking for a job involving:

1. Kidney transplantation only
2. Liver transplantation only
3. Kidney & liver transplantation
4. Kidney, liver & pancreas transplantation
5. Kidney & pancreas transplantation
6. Nothing having to do with transplantation
7. Waiting tables at Applebee's

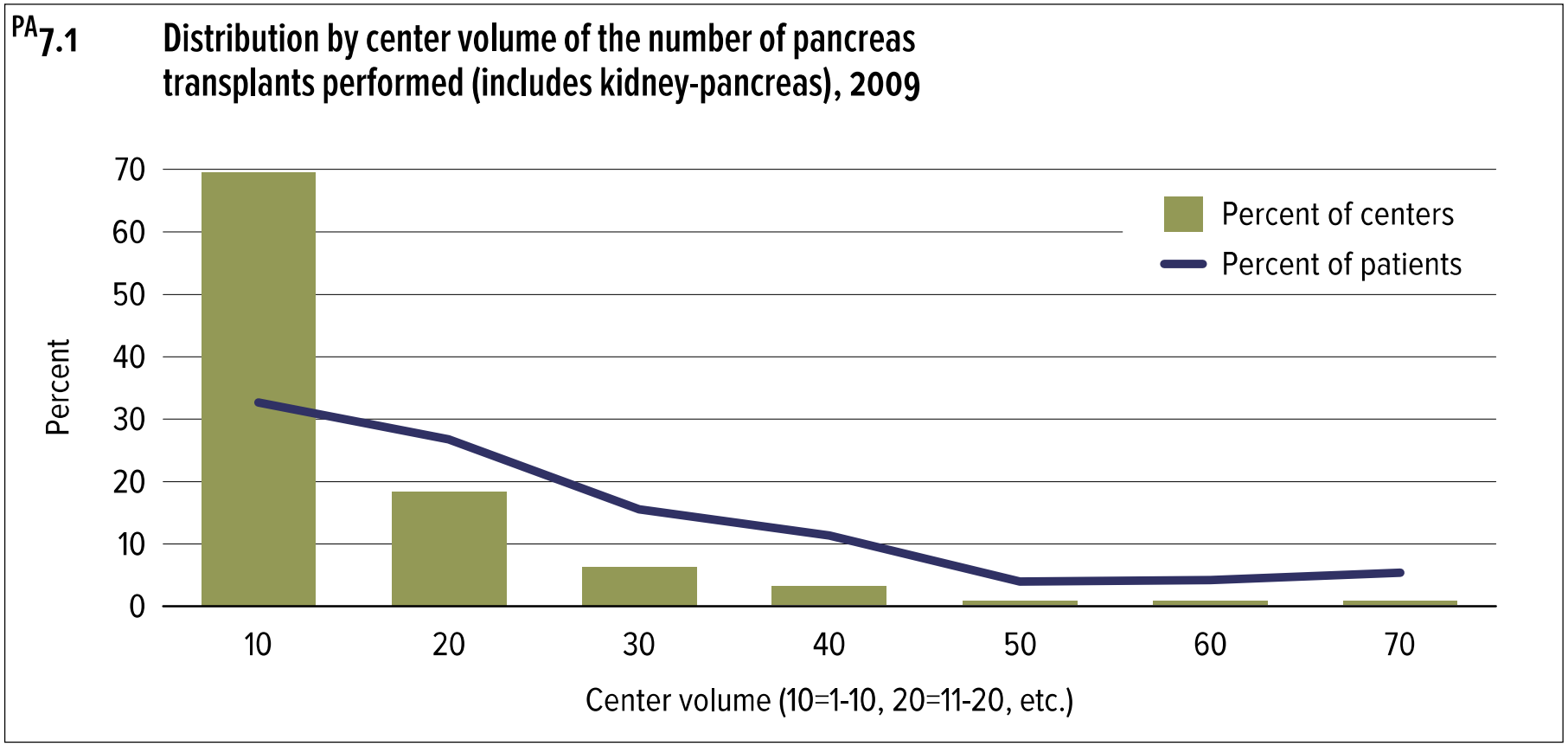


I feel most confident transplanting and taking care of:

1. Kidney transplants
2. Liver transplants
3. Pancreas transplants
4. None of the above



The majority of programs perform few pancreas transplants



UNOS SRTR Report Am J Transplant 2011

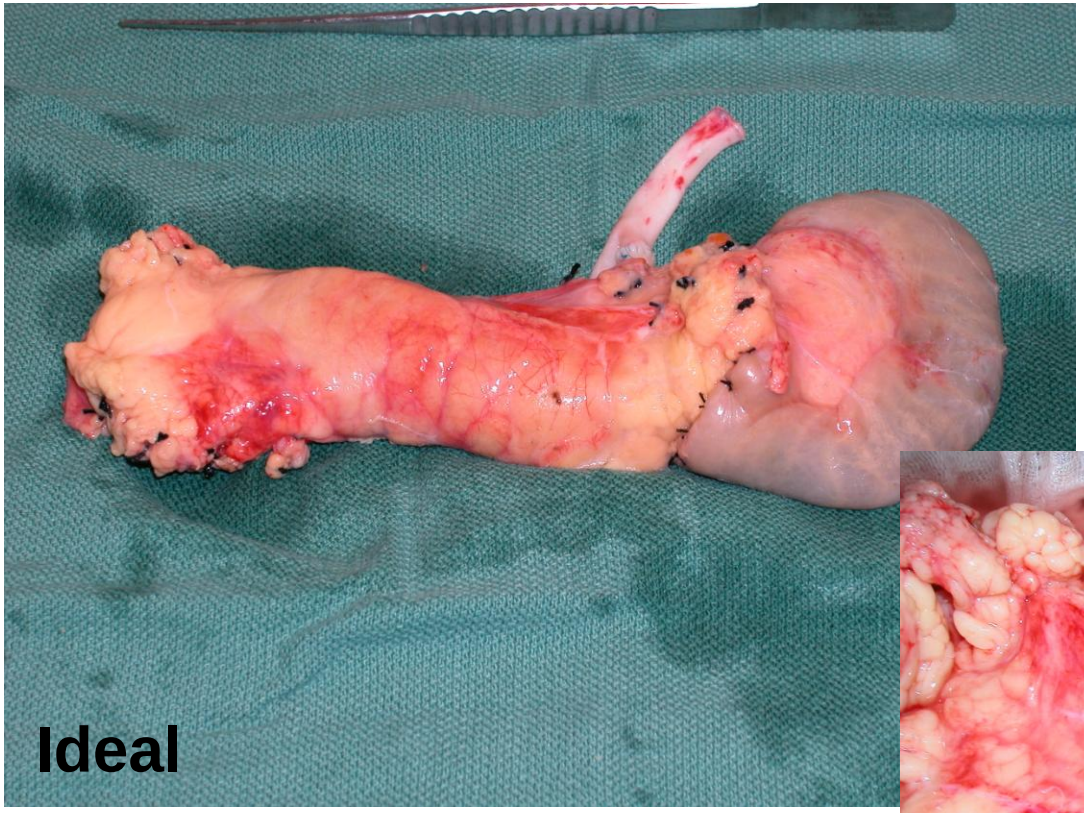
Outline

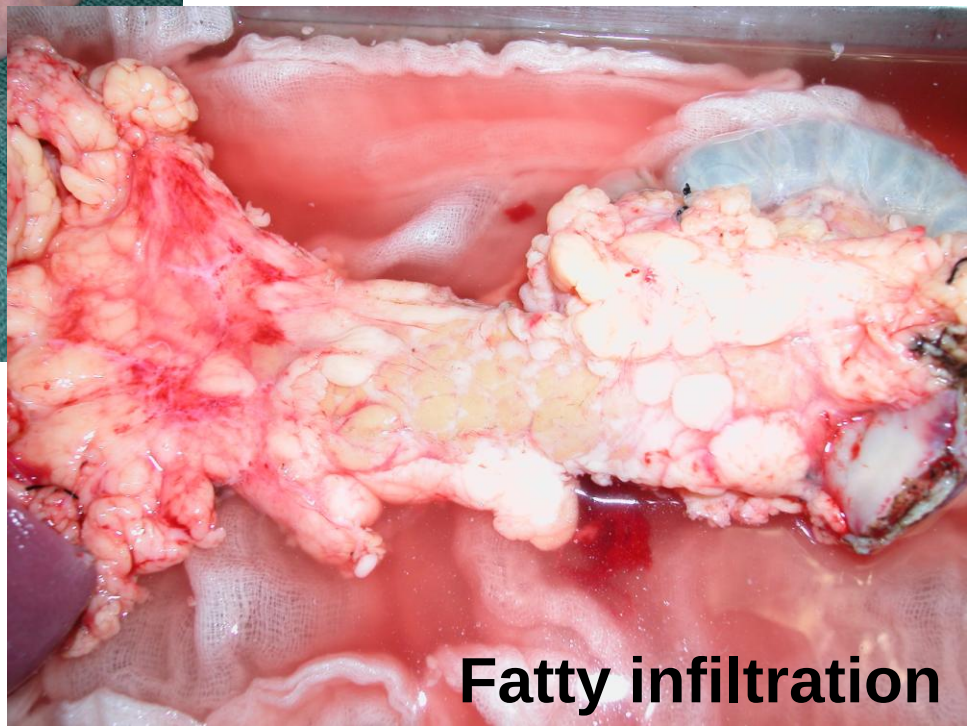
- Marginal Donor
  - Pancreas Quality
  - Donor recovery errors
  - PDRI
  - Age and BMI
  - DCD
  - Pediatric
  - HTK
- Marginal Recipient
  - Age and BMI
  - Cardiac disease
  - Vascular disease
  - Type 2 DM
  - Re-transplant

Outline

- Marginal Donor
  - Pancreas Quality
  - Donor recovery errors
  - PDRI
  - Age and BMI
  - DCD
  - Pediatric
  - HTK
- Marginal Recipient
  - Age and BMI
  - Cardiac disease
  - Vascular disease
  - Type 2 DM
  - Re-transplant

Quality of the Pancreas
!!!!! Paramount importance !!!!!



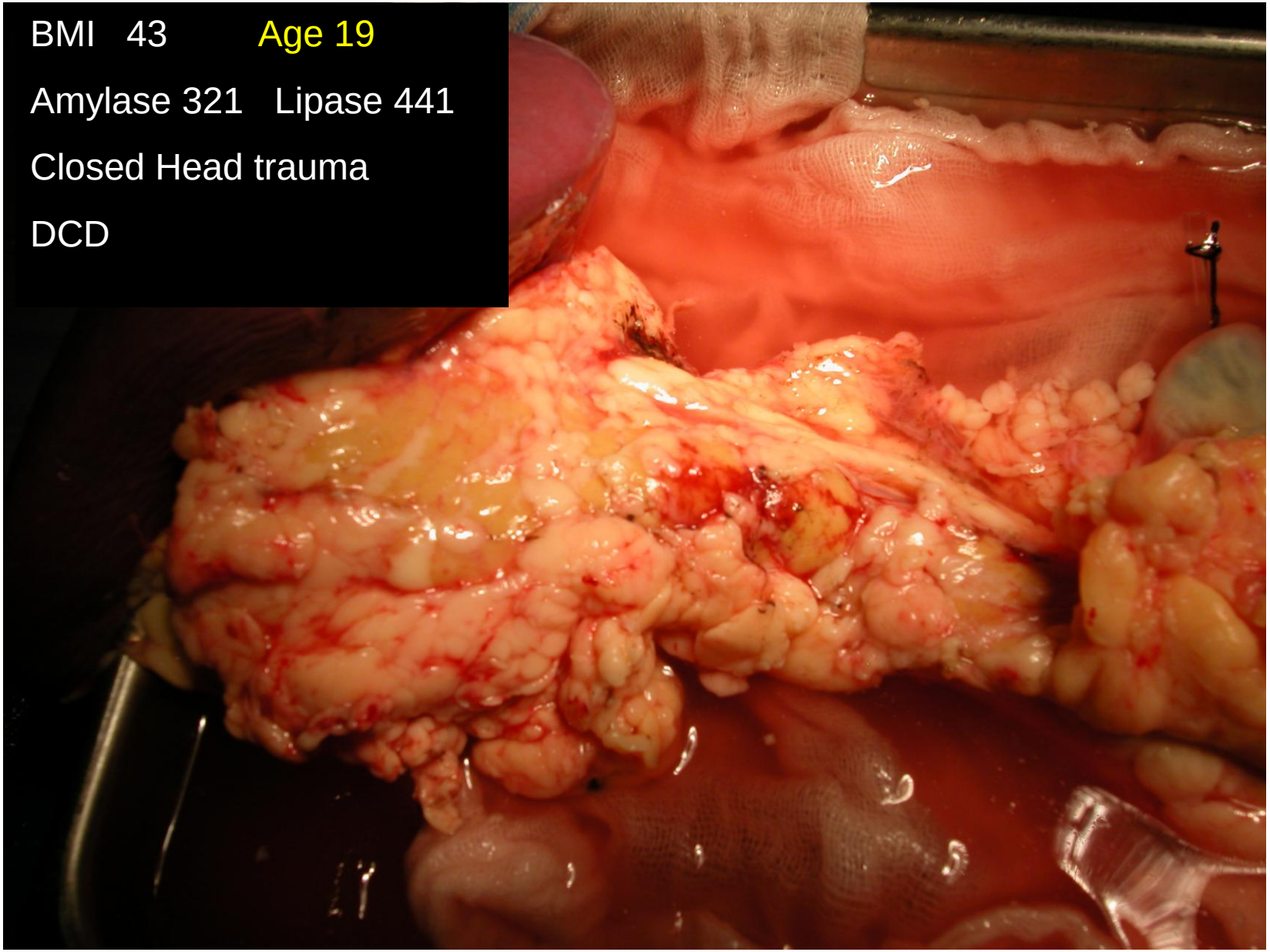


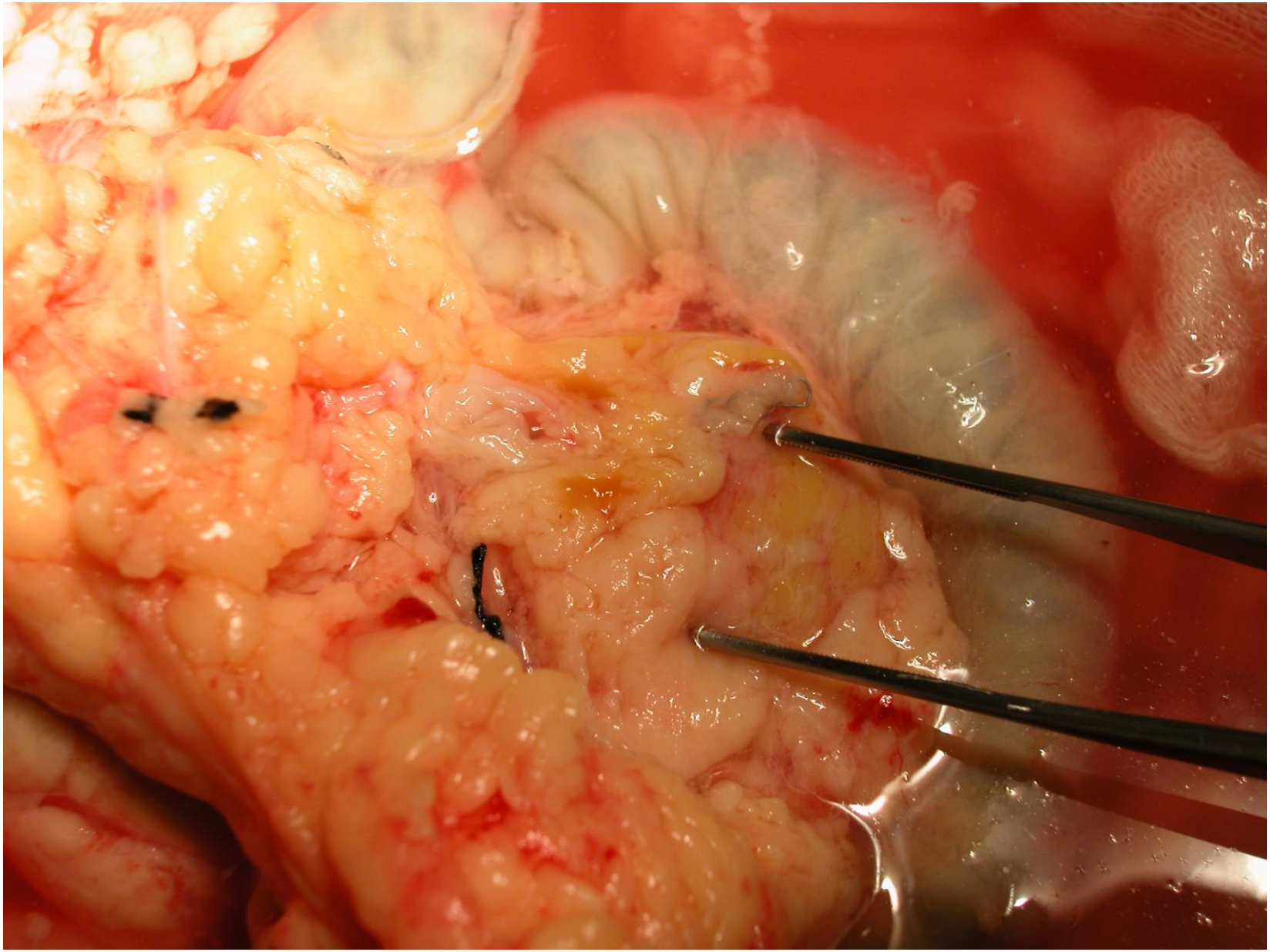
BMI 43 Age 19

Amylase 321 Lipase 441

Closed Head trauma

DCD





Pancreas Graft Quality Assessment

- Fatty infiltration, marbling
- Firmness, fibrosis
- Evidence of hemorrhagic pancreatitis
- Atrophy, nodularity, calcifications, masses

<u>Other issues:</u>

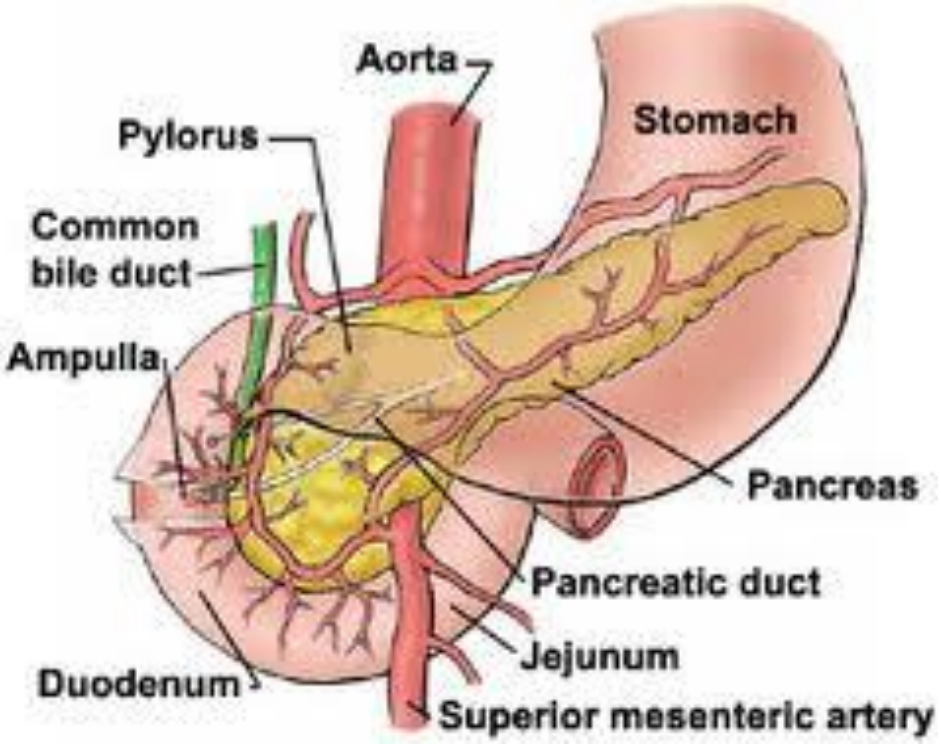
Length of PV

Replaced RHA and potentially sacrificed inferior PDA

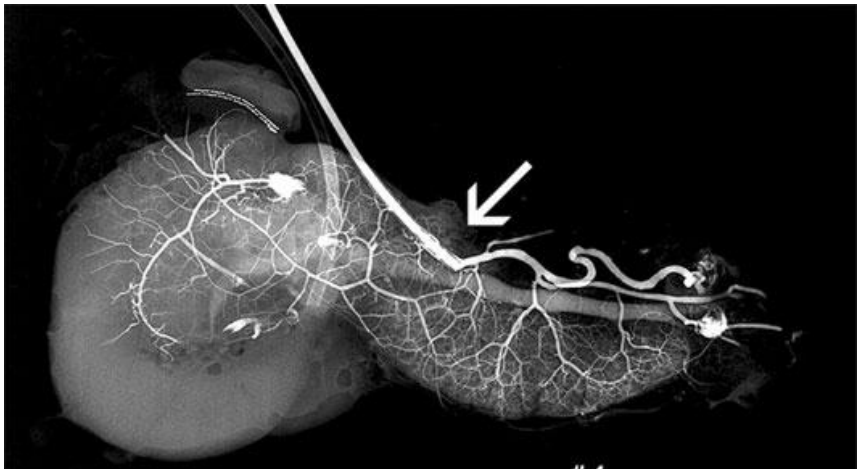
Prior trauma splenectomy

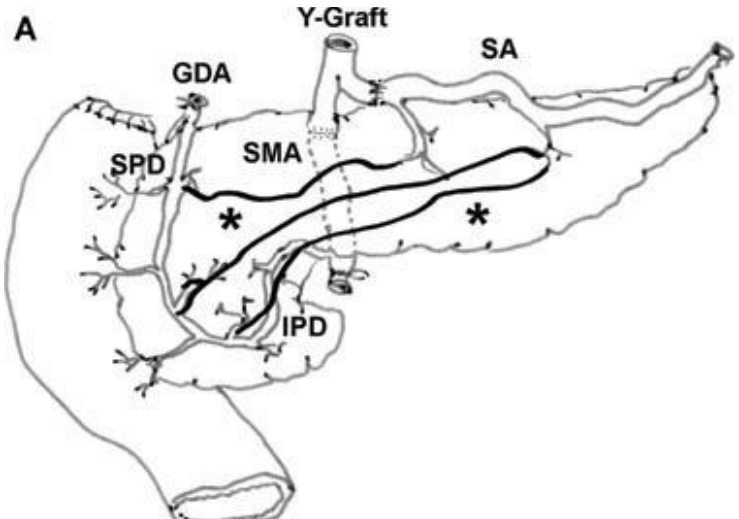
HbA1c

Replaced RHA : Is the Inferior PDA preserved after the liver is separated ?



Cross-circulation SMA - Spl A

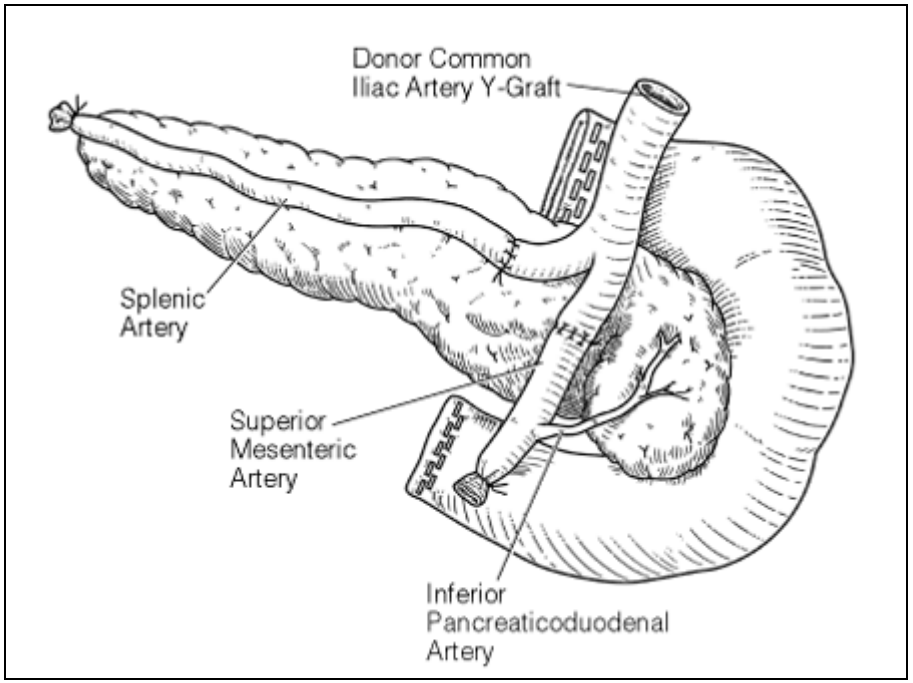




Margreiter et al. AJT 2010

Pancreas Procurement Errors

Pancreata recovered elsewhere and shipped to UW



- Ligated splenic vein at origin
- Short or non-existent portal vein
- Injury to PV (e.g. lacerated SMV-PV jcn)
- Sacrificed inferior PDA vessels
- Transected SMA at root of the mesentery proximal to the inferior PDA vessels
- Injury to the parenchyma
- Injury to the duodenal segment
- Staple line across the uncinate process
- Failure to ship/supply iliac Y graft

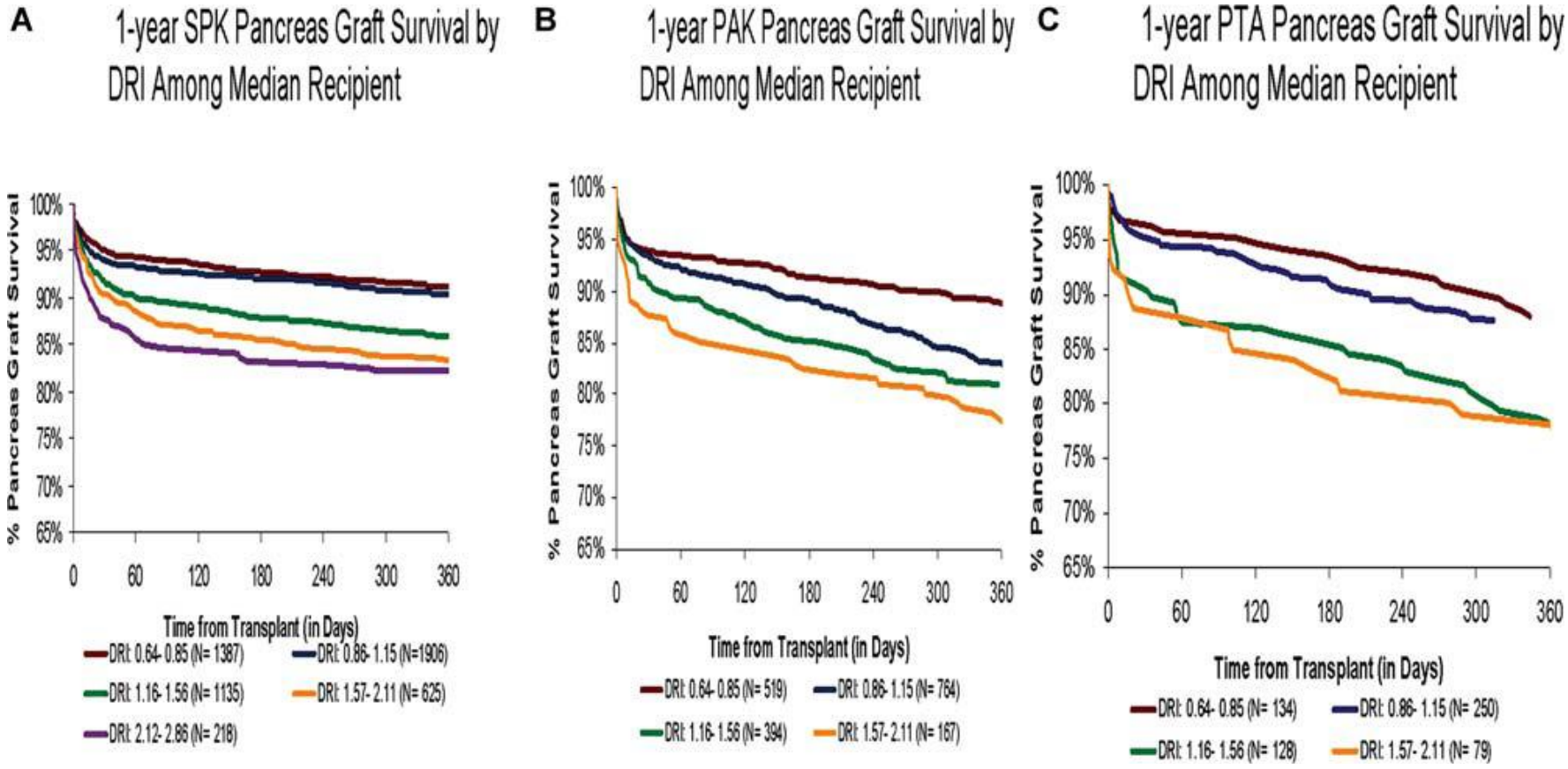
Pancreas Quality and Back Table Bench Preparation

Pancreas Donor Risk Index (PDRI)

Donor Characteristics	Reference Donor (DRI=1)	Change factor value to	DRI
Gender	male	female	0.87
Age	28	45	1.56
Black race	No	Yes	1.27
Asian race	No	Yes	1.17
BMI	24	30	1.17
Height	173	190	0.9
Cause of Death-CVA/Stroke	No	Yes	1.23
CIT (hrs)	12	20	1.13
DCD	No	Yes	1.39
SCr >2.5 mg/dL	No	Yes	1.22

- Axelrod et al. Am J Transplant 2010

Pancreas Donor Risk Index (PDRI)



- Axelrod et al. Am J Transplant 2010

Pancreas Donor Risk Index (PDRI)

- Increasing PDRI was associated with a significant graded risk of graft failure within 1 year

- PTA and PAK grafts from donors with elevated PDRI experienced a lower rate of 1 year graft survival (77%) compared with SPK recipients (88%)

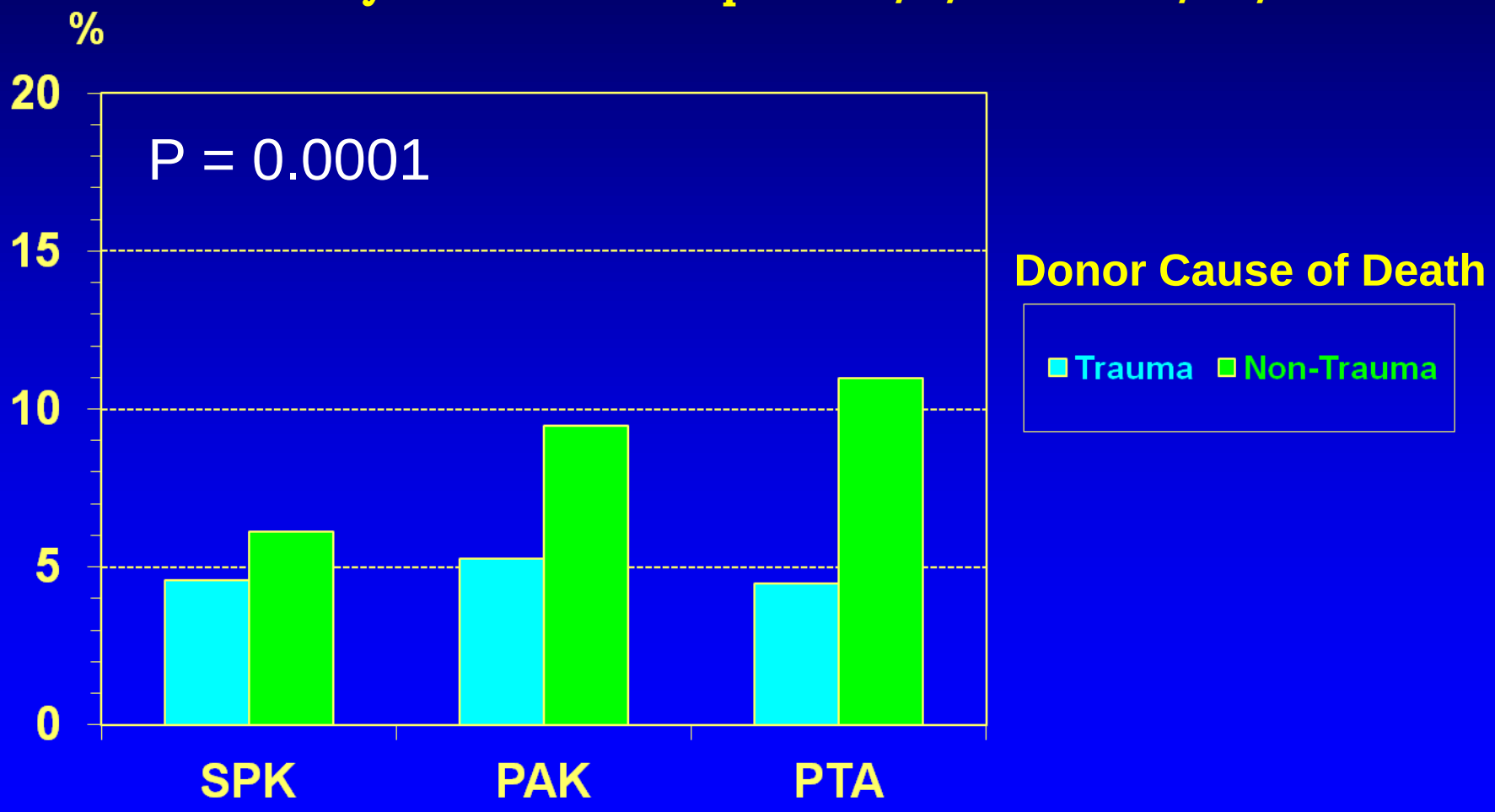
- Pancreas allograft acceptance varied significantly by region particularly for PAK/PTA ($p<0.0001$)

- Axelrod et al. Am J Transplant 2010

Donor Cause of Death

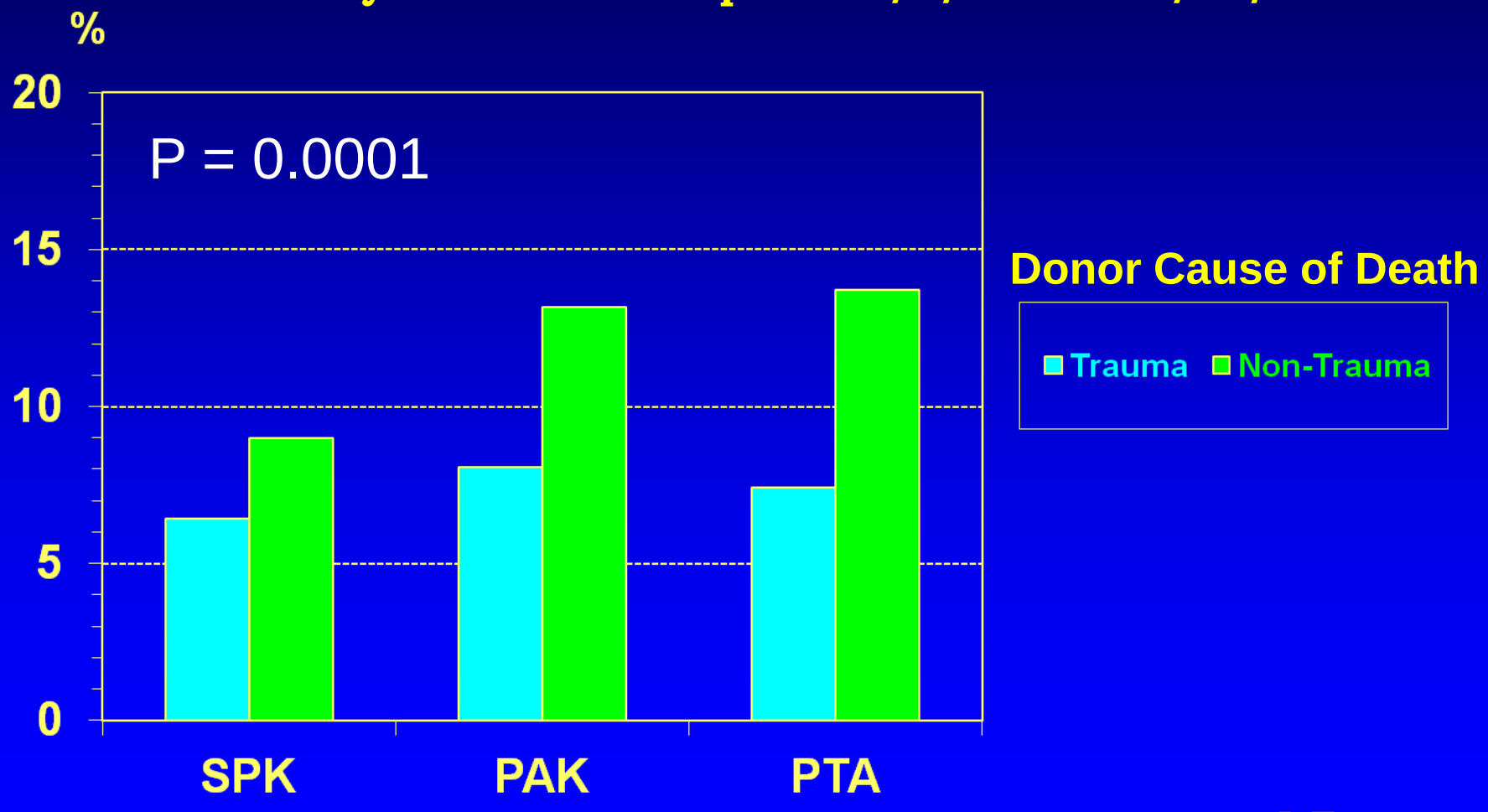
Graft Thrombosis Rate

USA DD Primary Pancreas Transplants 1/1/2000 – 12/31/2005



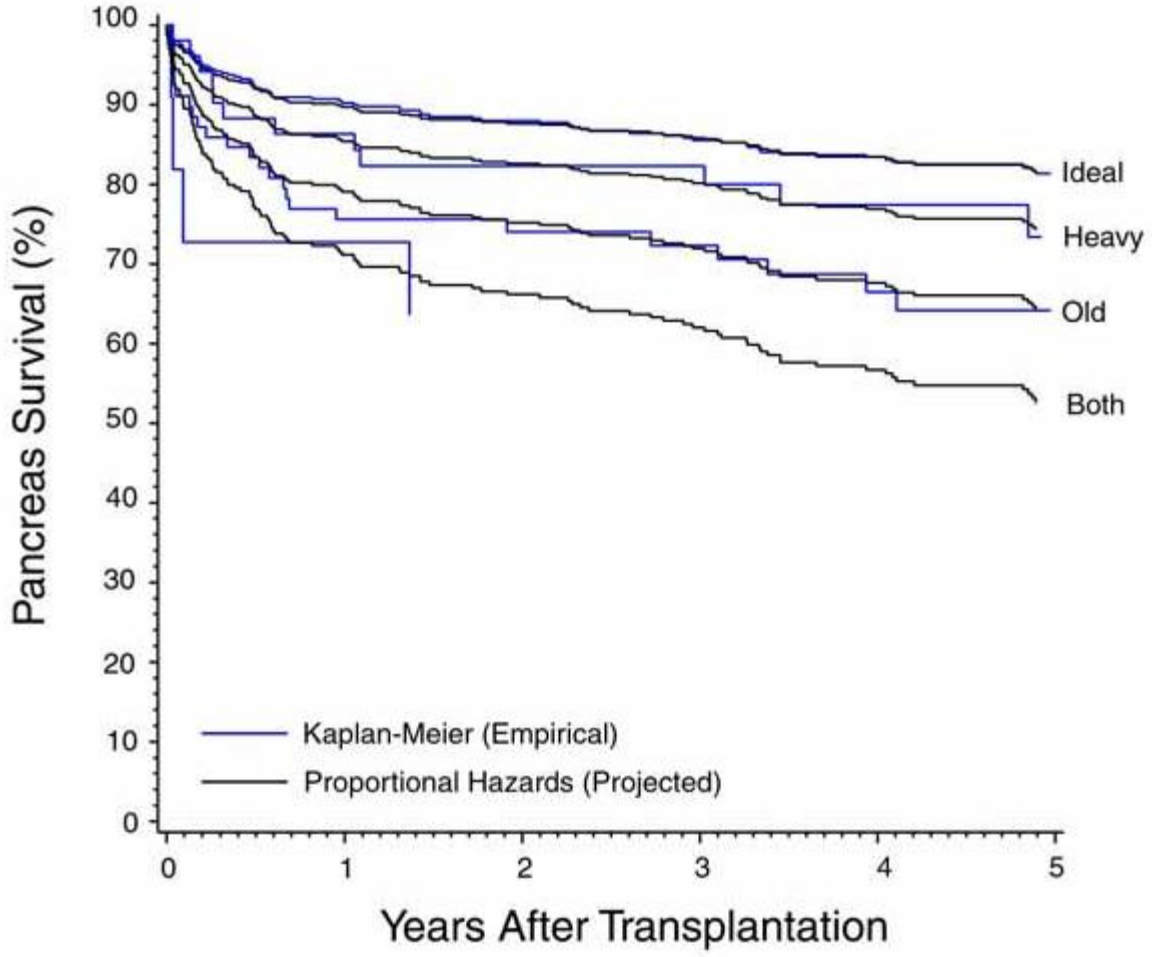
Technical Failure Rate

USA DD Primary Pancreas Transplants 1/1/2000 – 12/31/2005



IPTR/UNOS

Old and heavy donors increase the risk of pancreas graft loss



Heavy = >200 lbs
Old = >45 yrs

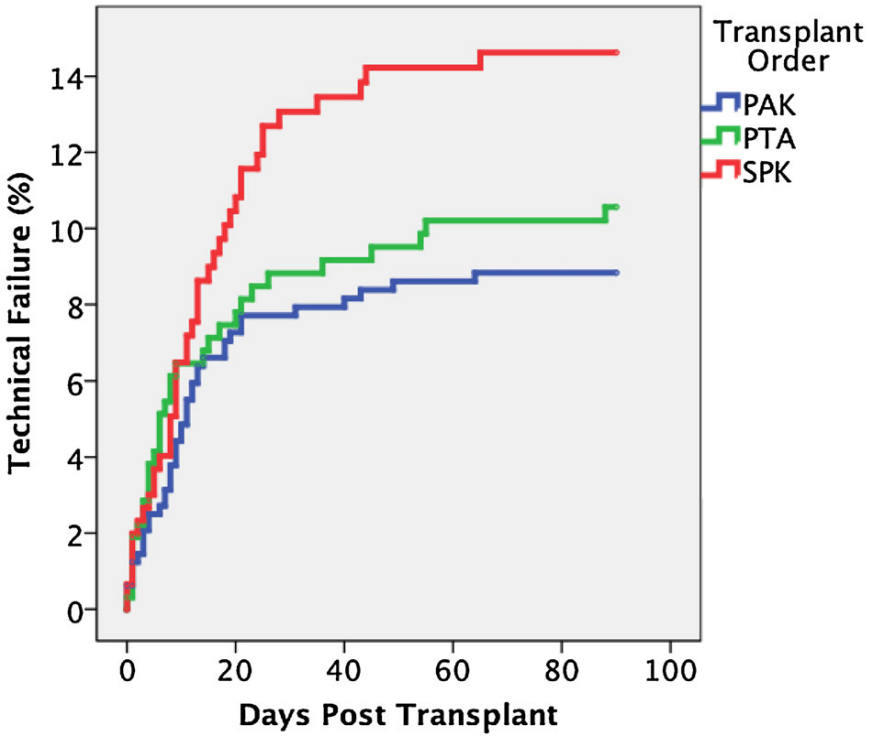
- Krieger et al Transplantation 2003

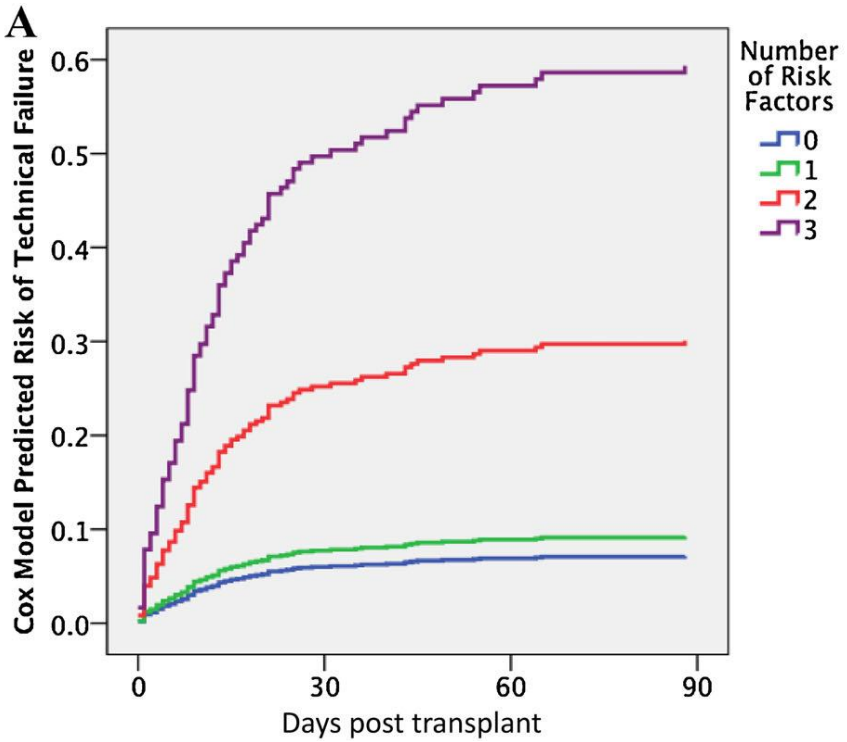
Results - Univariate Analysis

Donor Characteristic	P value
Age	0.0001
BMI	0.0037
Weight	0.0365
Height	0.1824
Serum Glucose	0.6238
Serum Amylase	0.0844
Serum Lipase	0.1750
Abdominal Trauma vs other COD	0.6585
DCD	0.7736
Vasopressor use	0.9196

➡ Multivariate analysis – only Age (p=0.0039) and BMI (p=0.021)

Factors Associated with Technical Failure

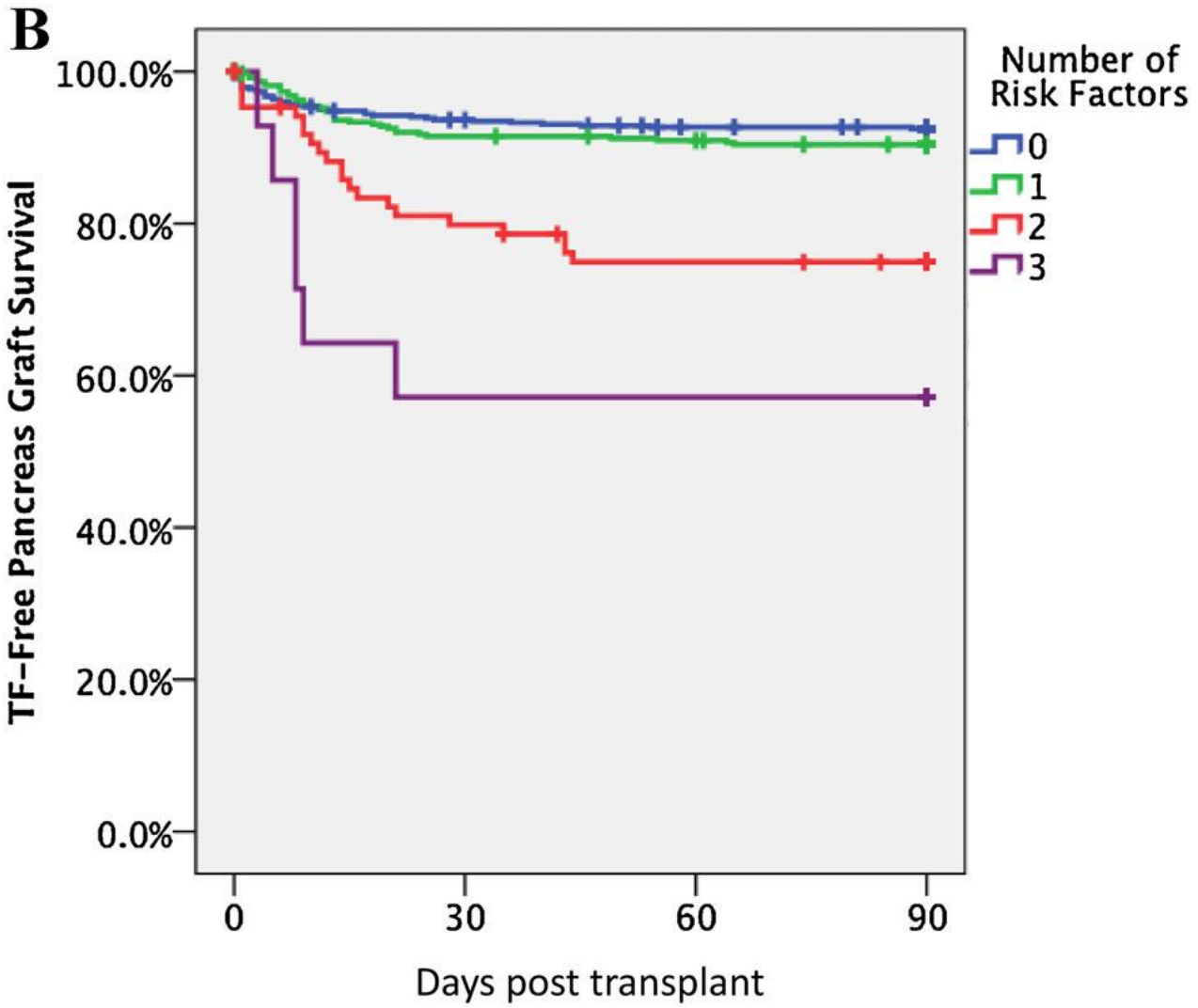




Composite Risk Model = donor age >50, donor BMI >30, donor Cr, >2.5 preservation time >20 hr and adjusted for surgical approach.

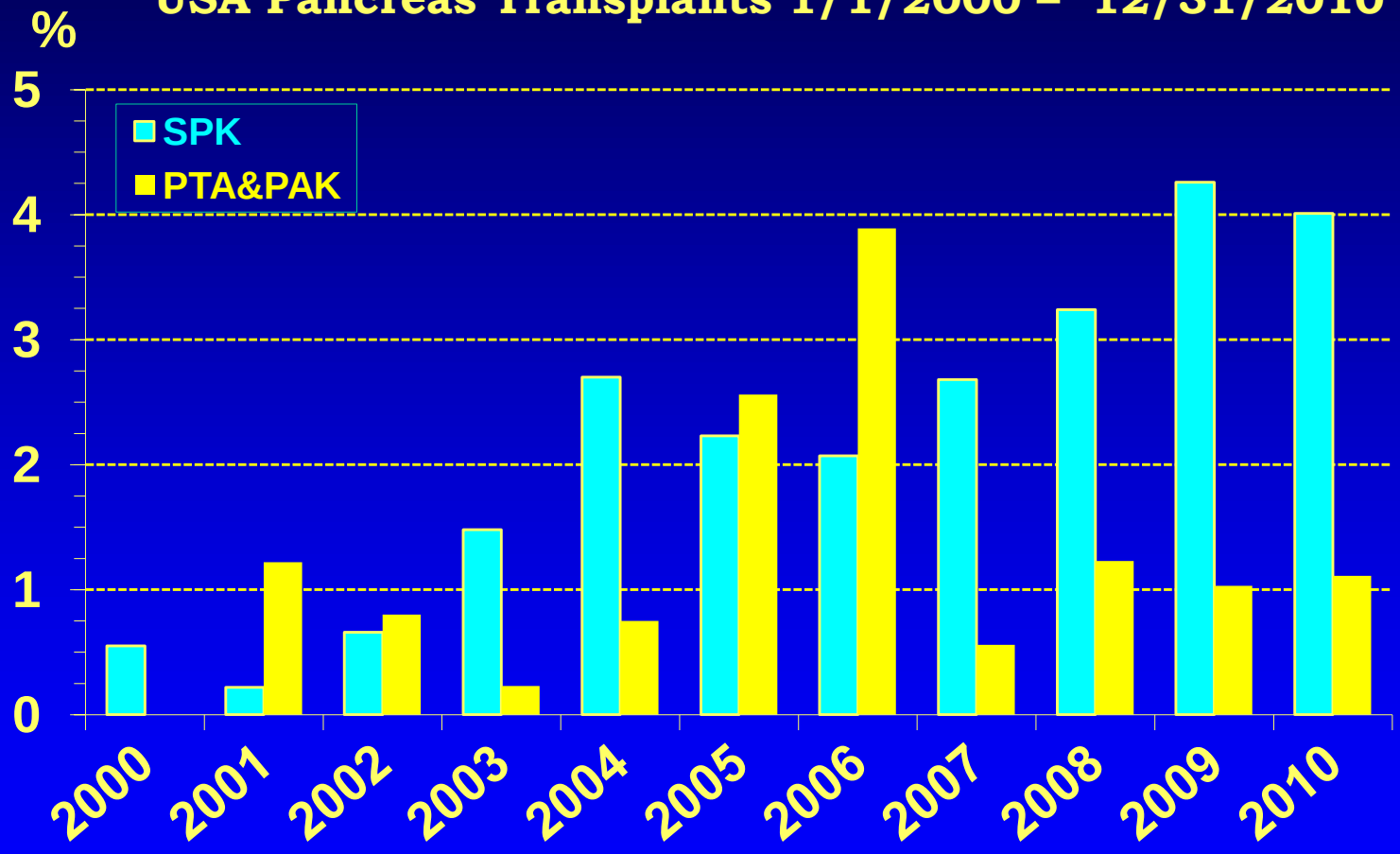
Finger et al. AJT 2013

2 or more Donor Risk Factors Increases the Risk of Technical Failure and Graft Loss

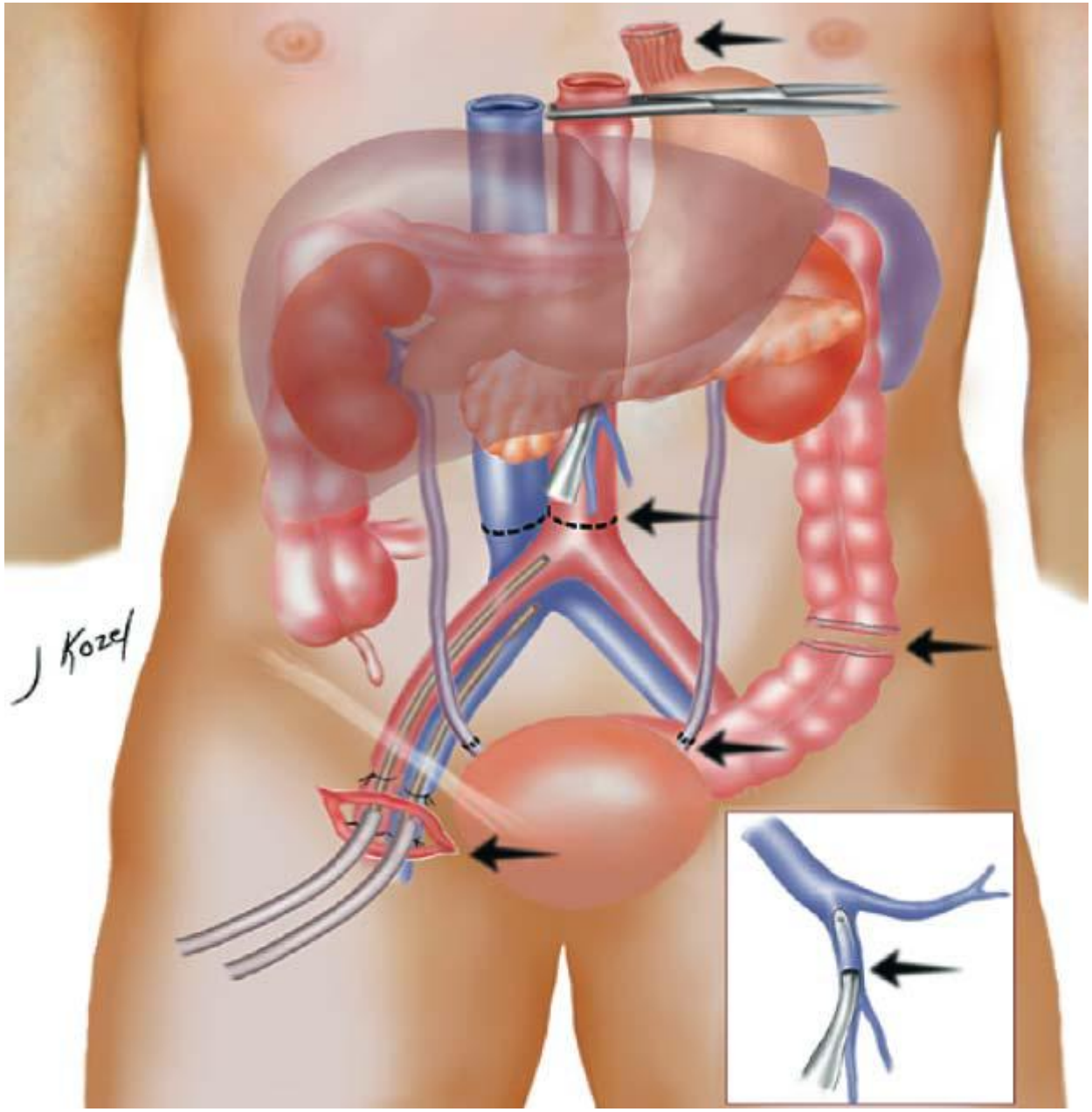


Finger et al. AJT 2013

Rate of DCD-Donors



IPTR/UNOS


J Kozel

10-year Outcomes of Simultaneous Pancreas-Kidney Transplantation from Donation After Cardiac Death

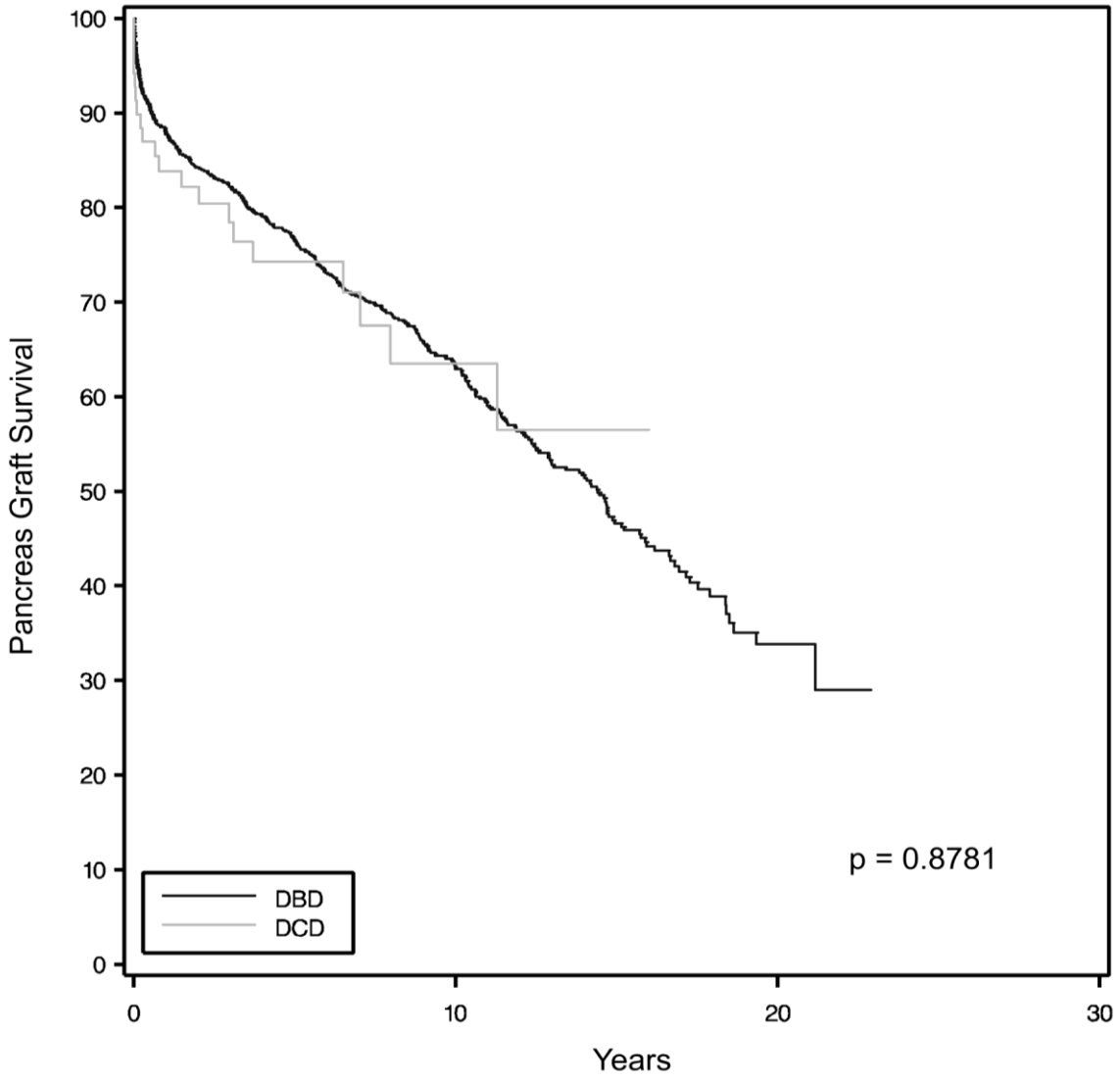
SPK transplants from 1982 - 2007

DBD donors (n=914)

DCD donors (n=56)

No specific recipients or type of immunosuppression was used for DCD pancreata

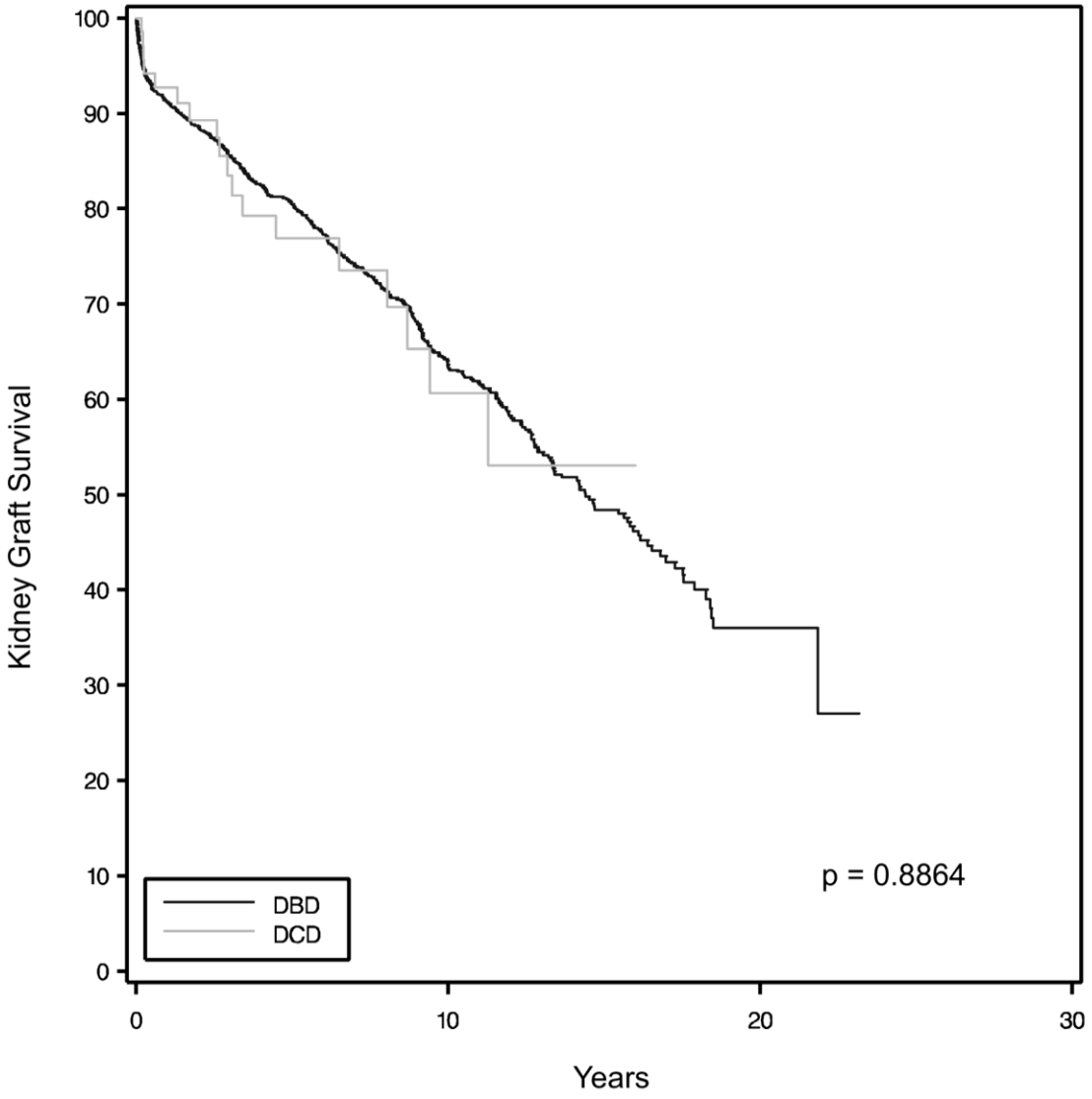
Pancreas Graft Survival for SPK Donation after Brain Death vs. Cardiac Death



Long Term Pancreas Function

Hb A1c%	DBD	DCD	p -Value
6 months	5.5 ± 0.95	5.42 ± 0.67	0.98
12 months	5.6 ± 1.0	5.58 ± 0.69	0.65
24 months	5.7 ± 0.89	5.66 ±0.65	0.68
36 months	5.7 ± 0.93	5.54 ± 0.71	0.27
48 months	5.7 ± 0.94	5.35 ± 0.6	0.26
60 months	5.7 ± 1.1	5.53 ± 0.7	0.88
84 months	5.8 ± 1.2	5.5 ± 0.5	0.92
120 months	5.7 ± 1.0	5.5 ± 0.1	0.86

Kidney Graft Survival for SPK
Donation after Brain Death vs. Cardiac Death



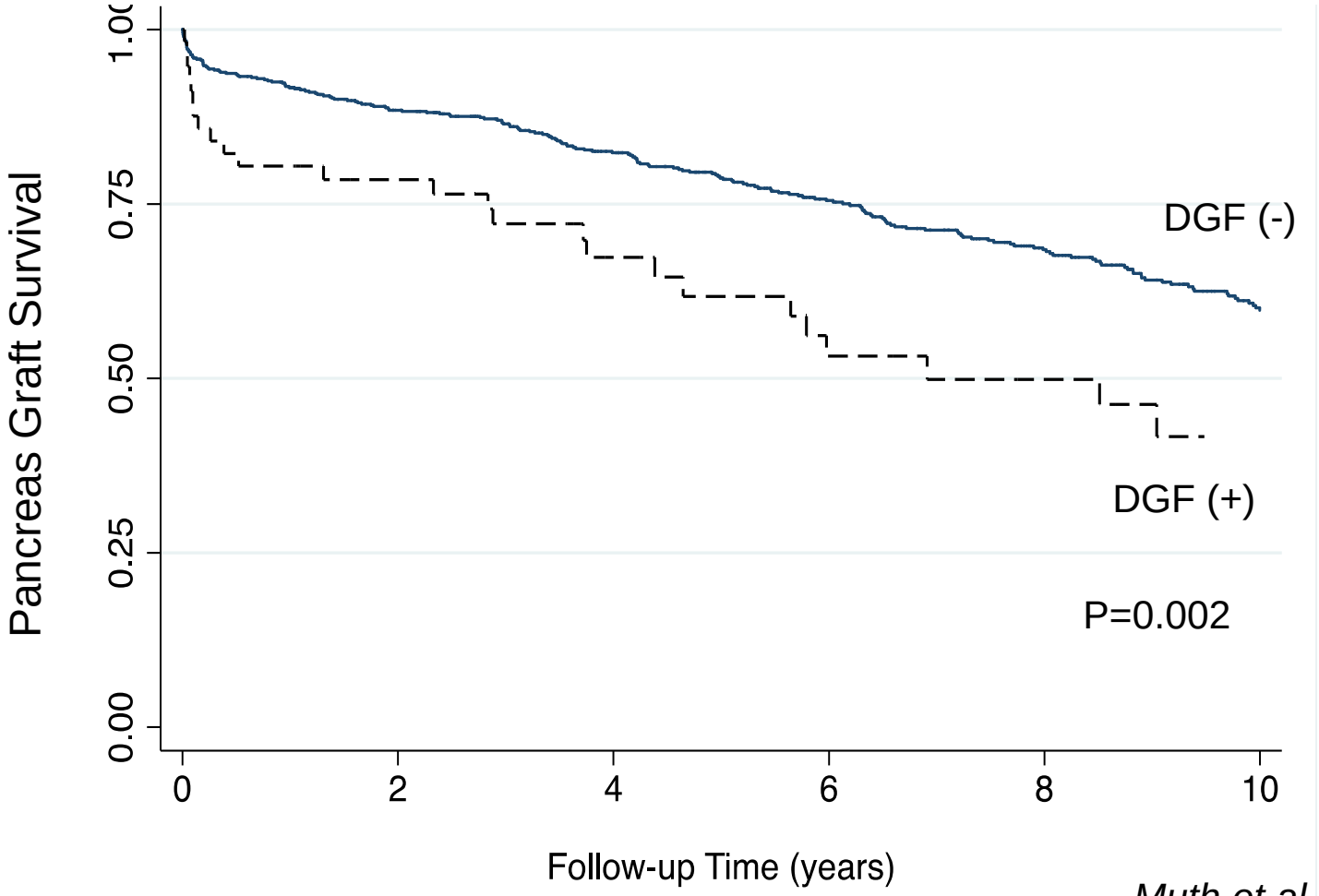
Long Term Kidney Function

Greater DGF in DCD Kidneys compared to Kidneys from DBD donors in SPK recipients P=0.001

Creatinine (mg/dl)	DBD	DCD	p -Value
POD #7	1.86 ± 1.8	2.65 ± 2.3	0.001
at time of D/C	1.42 ± 0.5	1.60 ± 0.5	0.03
6 months	1.51 ± 0.8	1.35 ± 0.4	0.23
12 months	1.54 ±0.9	1.40 ± 0.4	0.37
24 months	1.49 ± 0.7	1.52 ± 0.6	0.53
36 months	1.62 ± 0.9	1.51 ± 0.6	0.68
48 months	1.57 ± 0.8	1.43 ± 0.4	0.72
60 months	1.60 ± 0.8	1.45 ± 0.4	0.7
84 months	1.69 ± 0.9	1.57 ± 0.5	0.79
120 months	1.87 ± 1.3	1.64 ± 0.5	0.89

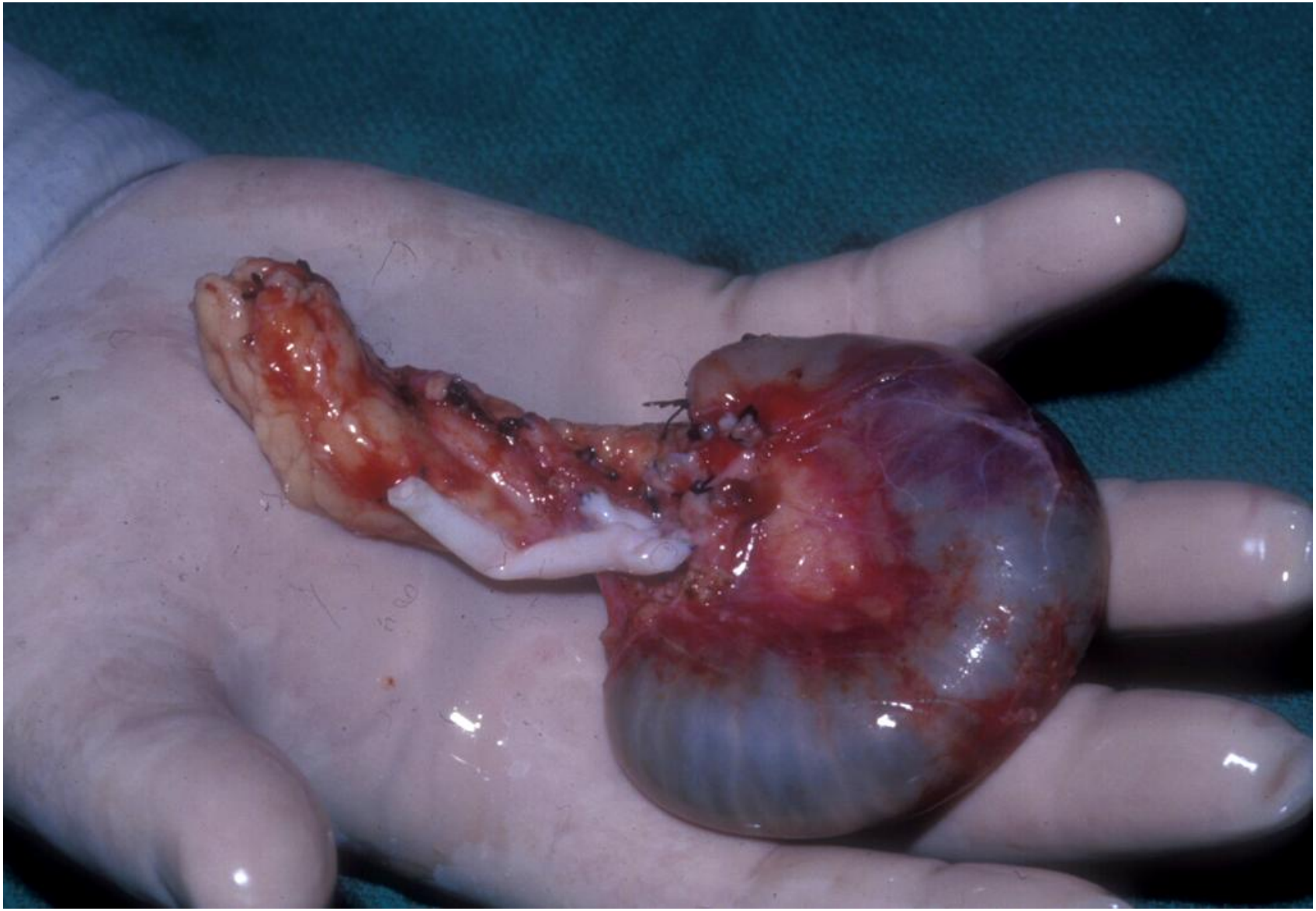
Delayed Kidney Graft Function in SPK Recipients is Associated with Poor Long Term Outcomes

733 consecutive primary SPK recipients 1994-2010



Muth et al. ATC 2013

What about the pediatric donor ?



Are Pediatric Donors Suitable for Simultaneous Pancreas / Kidney Transplantation?

**Luis A. Fernandez,M.D. ; Jon S. Odorico, MD.; Glen Leverson, PhD.;
L Thomas Chin, M.D.; Stuart J. Knechtle, M.D
Anthony D'Alessandro, MD; Yolanda Becker M.D.;
Munci Kalayoglu, M.D.; and Hans W. Sollinger, M.D., PhD.**

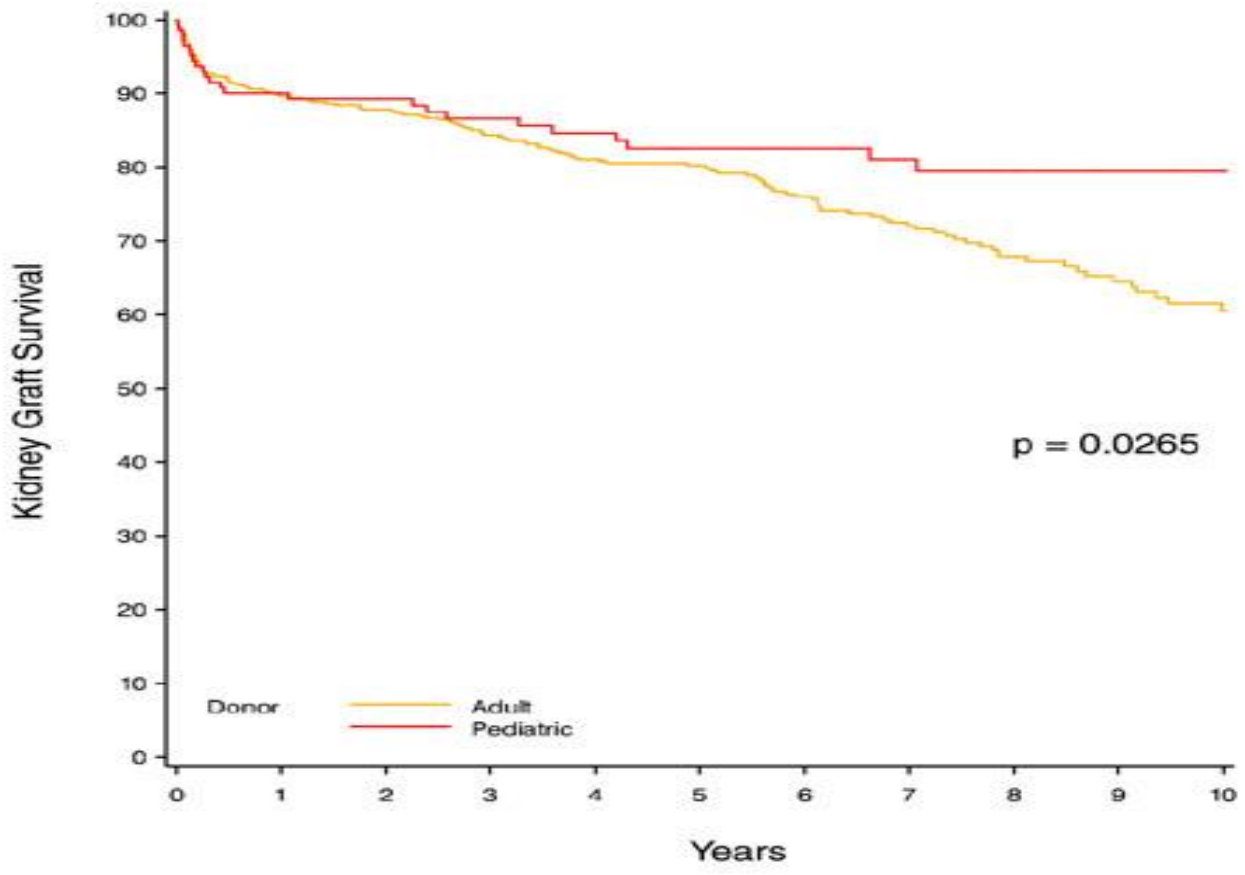
1986 -2001 680 SPK transplants

Pediatric < 18 yo (n=142)

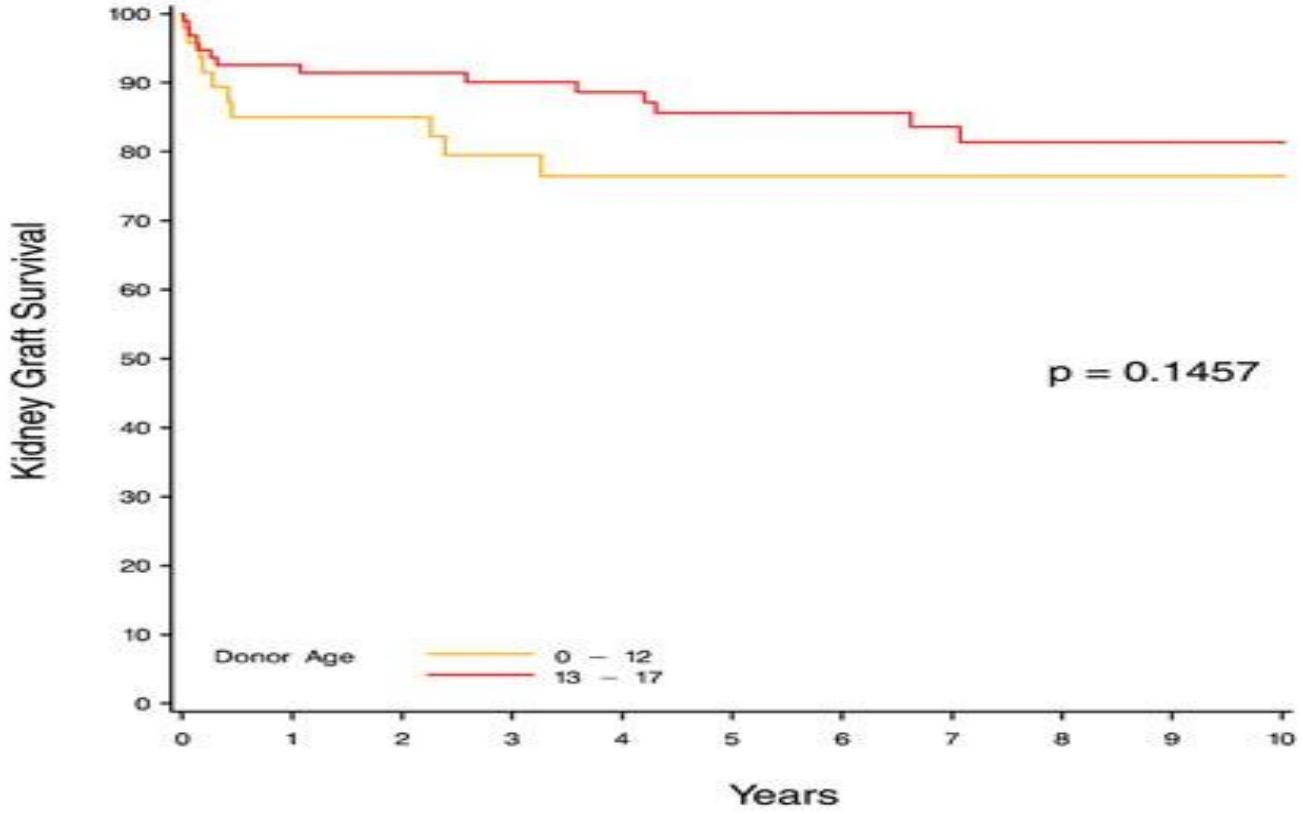
Adult ≥ 18 yo (n=538)

Fernandez et al. Am J Transplant 2006

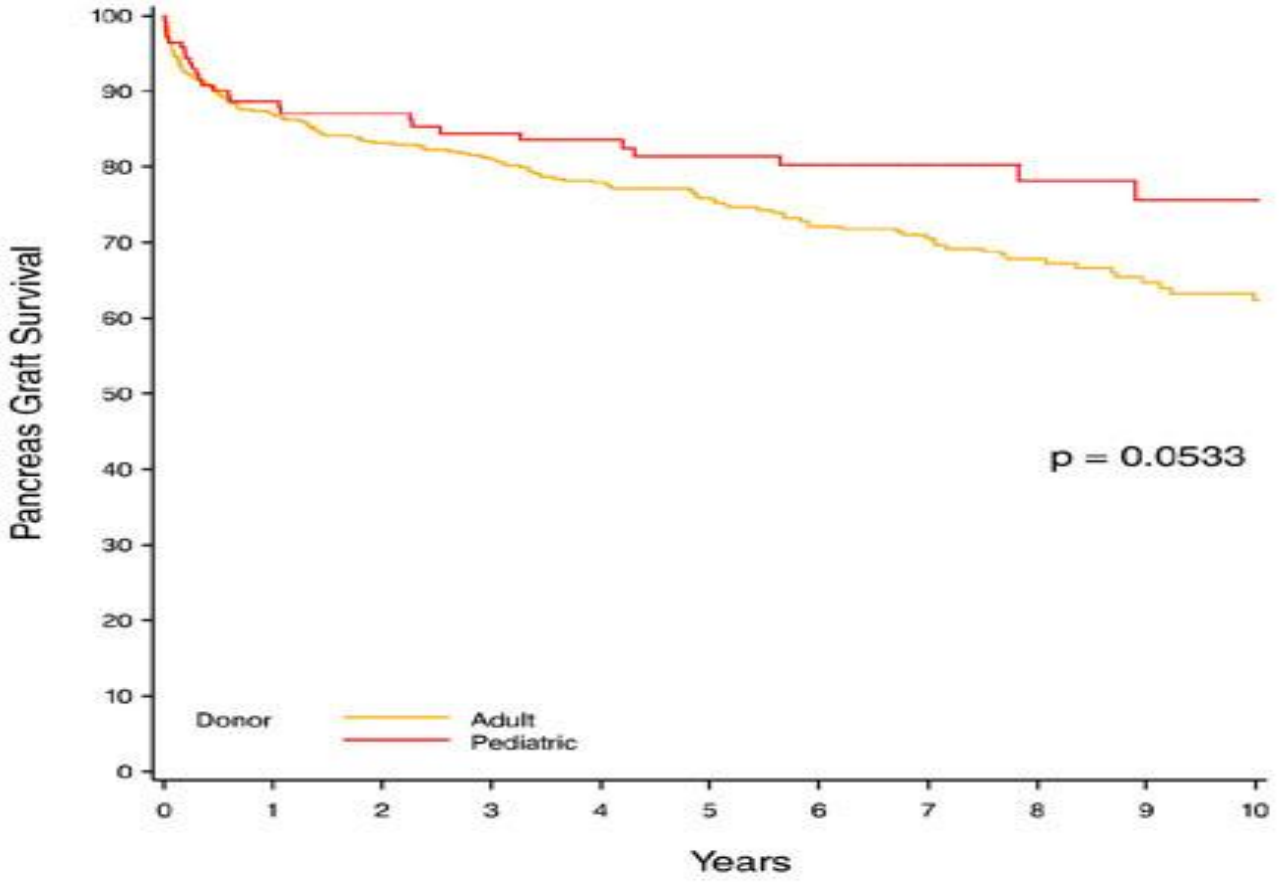
Kidney Graft Survival SPK Transplantation of Pediatrics vs Adult Donors



Kidney Graft Survival Rates SPK Transplantation of Pediatric Donors at Different Ages



Pancreas Graft Survival SPK Transplantation of Pediatric vs Adult Donors



Pancreas Graft Thrombosis

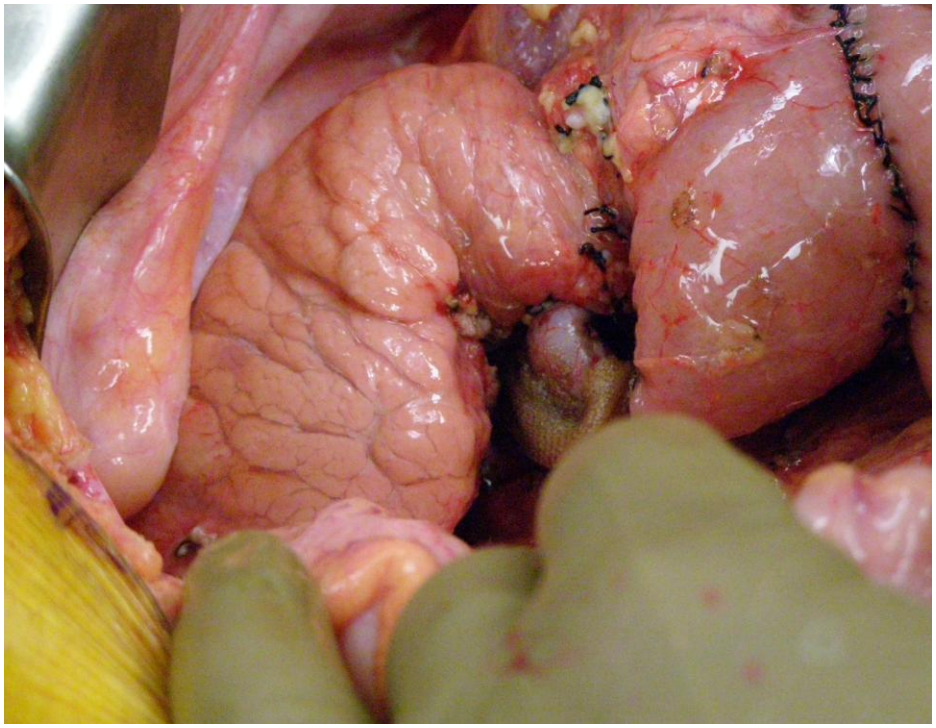
Peds	2/142	6.8%
Adult	13/538	8.4%

Comparison of Physiological Parameters
SPK Transplantation of Pediatric vs Adult Donors

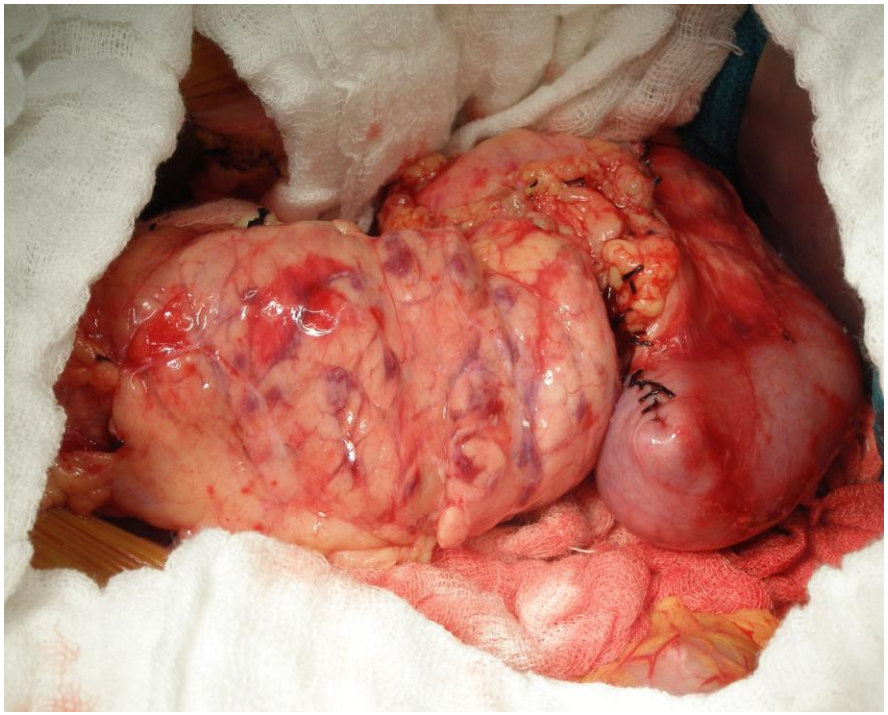
at 5 years			
	Adults	**Pediatrics**	**Statistics**
	n=237	**n=63**	
GFR	58.3 ± 17	65.6 ± 16	**0.002**
GLYCEMIA-FBG	95.16 ± 29	85.3 ± 13	**0.001**
HbA1c	5.86 ± 3.5	5.47 ± 0.98	**0.013**
at 10 years	**n=66**	**n=24**	
GFR	54+ 17.7	65.9+ 18.8	**0.015**

Debate: HTK vs UW ?

UW



HTK



UW experience with HTK (*shipped in organs*)

- 2004-2010: 85 shipped in pancreata
- 9 flushed and preserved in HTK (all CIT >12h)
- Complications in 4/9 pts

  Pseudocysts requiring intervention (n=2)
  Pancreatitis/Graft Thrombosis (n=1)
  Peripancreatic infection and enzyme leak req Lap (n=1)

Debate: HTK vs. UW ?

- Fridell et al. *AJT* 2010

Retrospective analysis of 308 pancreas transplants – 84% HTK, 16% UW

Endpoints: 7day, 90 day and 1 yr Graft survival, peak and subsequent serum amylase and lipase, HbA1c and C-peptide

Findings :No difference in any outcome variable

Limitations – non-randomized, single center, more Sol. Panc transplants in UW group, longer CIT in UW group, both CIT under 10 hrs, more import organs and non-local OPO recovery in UW group

- Schneeberger et al. *Transplant Int* 2009

Prospective randomized multicenter trial 68 pancreas transplants – 27 HTK, 41 UW

Endpoints: Graft survival at 6 mos., post-operative amylase, lipase, Cpeptide, HbA1c and insulin req

Findings: Sl.higher exogenous insulin use in UW arm resolved by 3mos.

No difference in GS at 6 mos. or any lab values

Limitations: Underpowered, mean CIT 10-11 hrs

- Alonso et al. *AJT* 2008

Retrospective analysis of 97 pancreas transplants at 2 centers – 16 HTK, 81 UW; CIT-13-15 hrs

Endpoints: Early complications-thrombosis, bleeding, abscess, pancreatitis, octreotide use, relaparotomy, LOS, amylase lipase levels, insulin independence at DC, graft survival

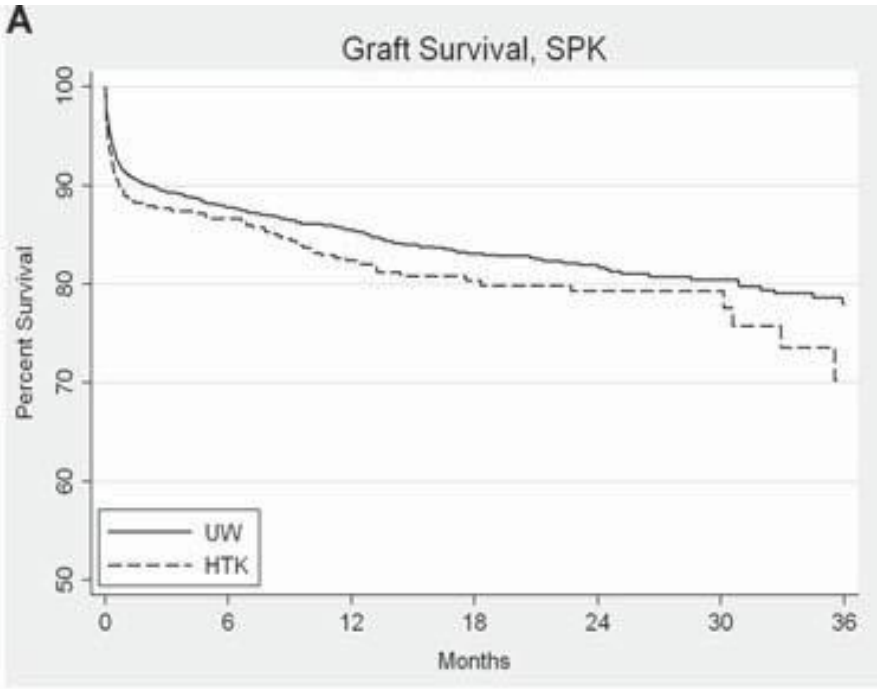
Findings: 2yr graft survival – 70%HTK, 90% UW; Graft loss due to thrombosis: 19% HTK, 4% UW; Abscess: 38%HTK, 14%UW; Post-operative peak amylase, frequency of octreotide use and pancreatitis were significantly greater in the HTK group; Insulin independence at DC: 64% HTK, 97% UW

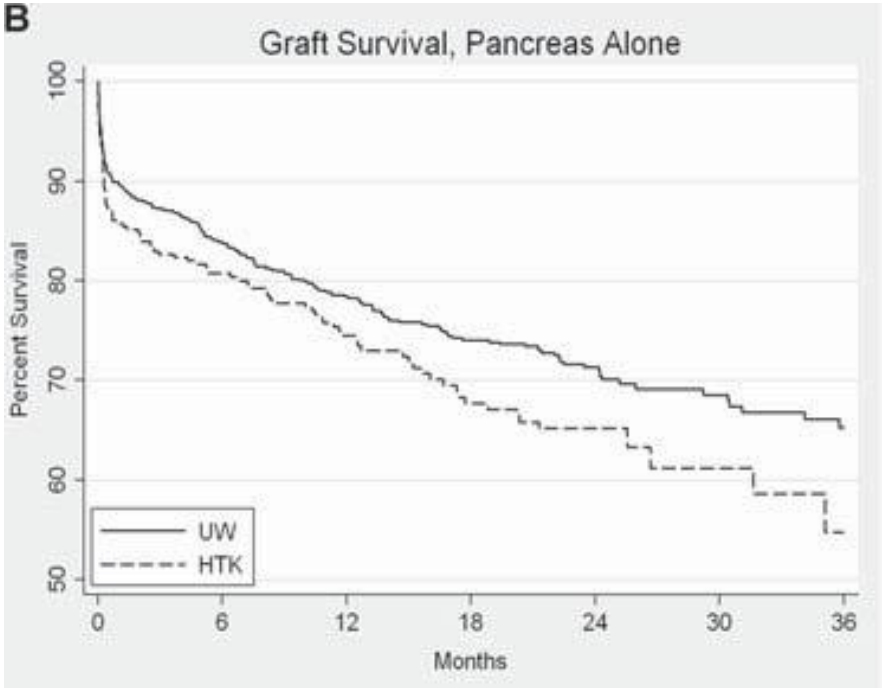
"Resumption of UW use resulted in a series of 25 transplants without serious complications with 100% graft survival at 12 months."

Limitations: mixed groups of transplants, relatively small sample size, bias in some outcome variables

HTK vs UW

UNOS 2004-2008 pancreas transplants
HTK (n=1081) and UW (n=3311)





- HTK was independently associated with an increased risk of graft loss (HR 1.30, p=0.014) especially with CIT >12 h (HR 1.42, p=0.017)
- Stratified for donors age> 40, the HRs were increased but not significant due to low power
- HTK was associated with a 1.54-fold higher risk of early, <30 days, graft loss (OR 1.54, p=0.008)

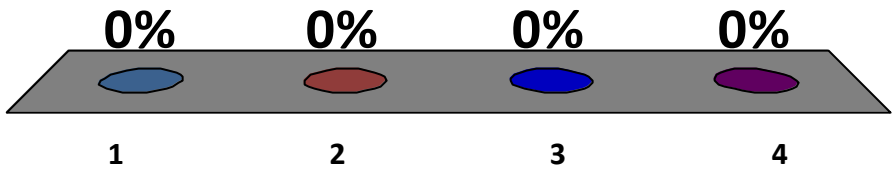
Stewart et al. AJT 2009

Conclusions

- PDRI can be used to predict outcomes but does not trump quality assessment
- Older age and high BMI are consistently risk factors for worse pancreas graft survival
- Donor risk factors primarily predict with short –term outcomes
- Two or more risk factors increase the risk of TF
- Young pediatric donors and selected controlled DCD donors are suitable for pancreas donation
- HTK solution provides suboptimal preservation in donors with long (>10-12 hrs) CIT and ? DCD donors

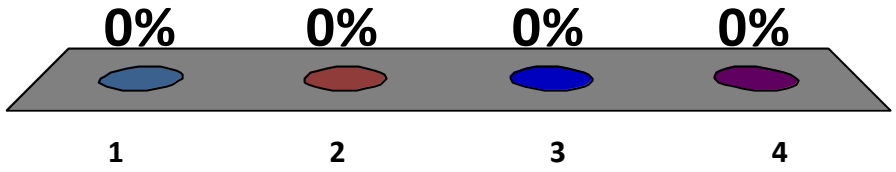
The single most important non-quantifiable donor factor predicting success in pancreas transplantation is:

1. Fibrosis
2. Pancreas quality assessment by an experienced transplant surgeon
3. Pancreas feel & size
4. Absence of atrophy



The 2 most important quantifiable donor factors correlating with pancreas graft survival are:

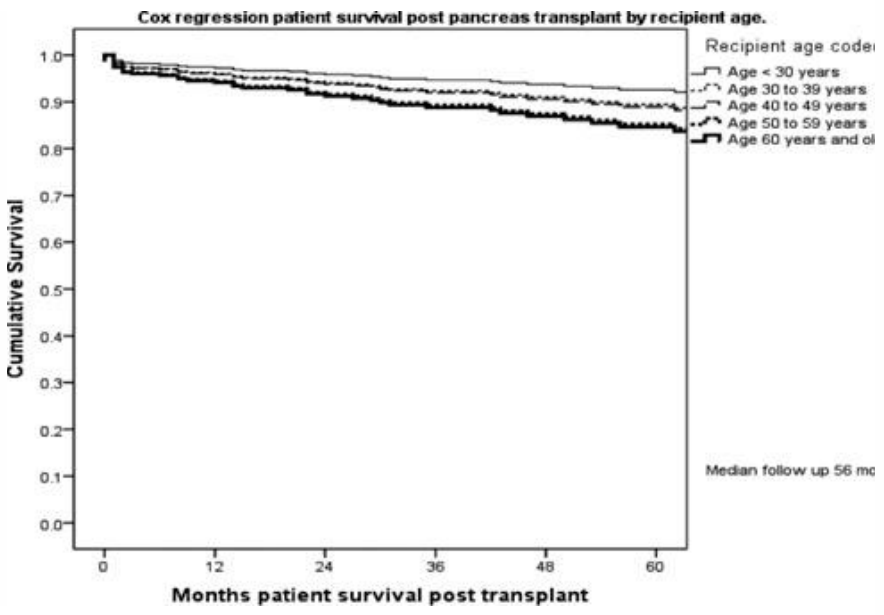
1. Presence of prior cardiac arrest and CIT
2. PDRI and % fat
3. Number of vasopressors are used and amylase level
4. Age & BMI

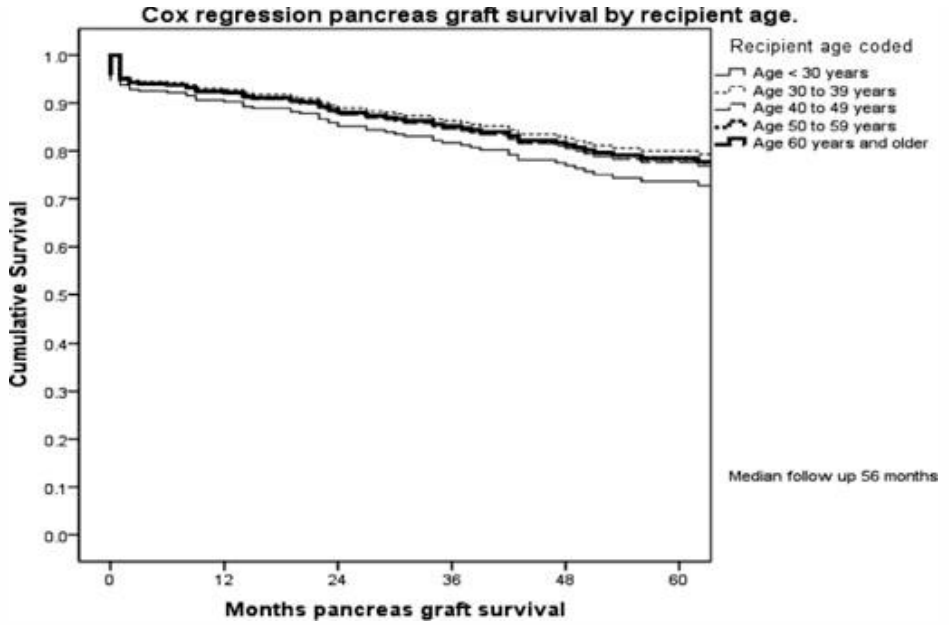


Outline

- Marginal Donor
  - Pancreas Quality
  - Donor recovery errors
  - PDRI
  - Age and BMI
  - DCD
  - Pediatric
  - HTK
- Marginal Recipient
  - Age and BMI
  - Cardiac disease
  - Vascular disease
  - Type 2 DM
  - Re-transplant

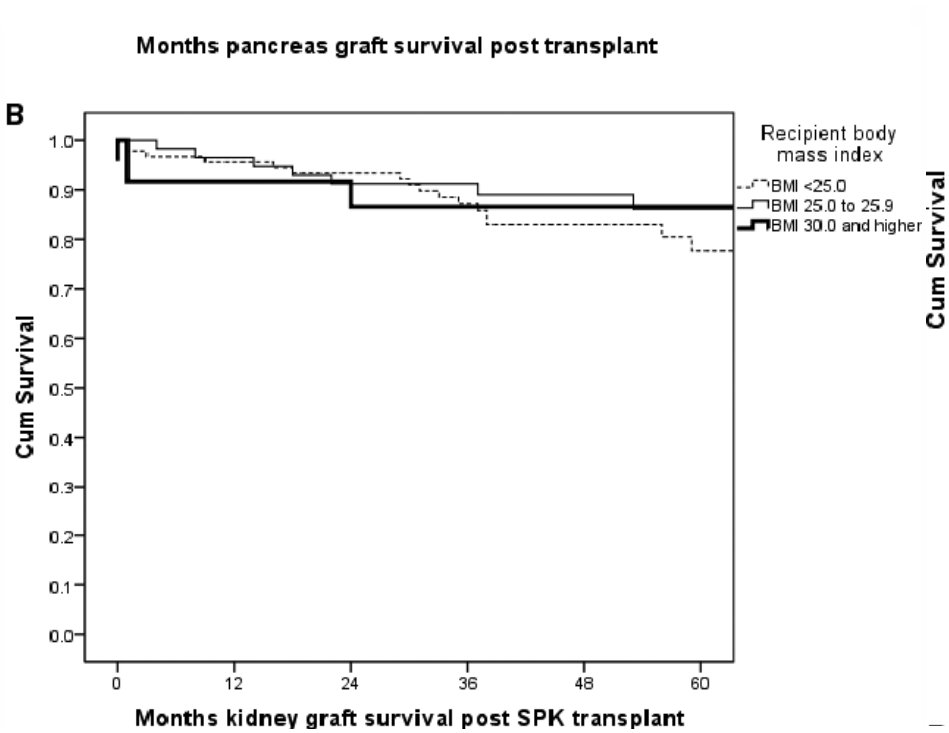
Age as Recipient Risk Factor

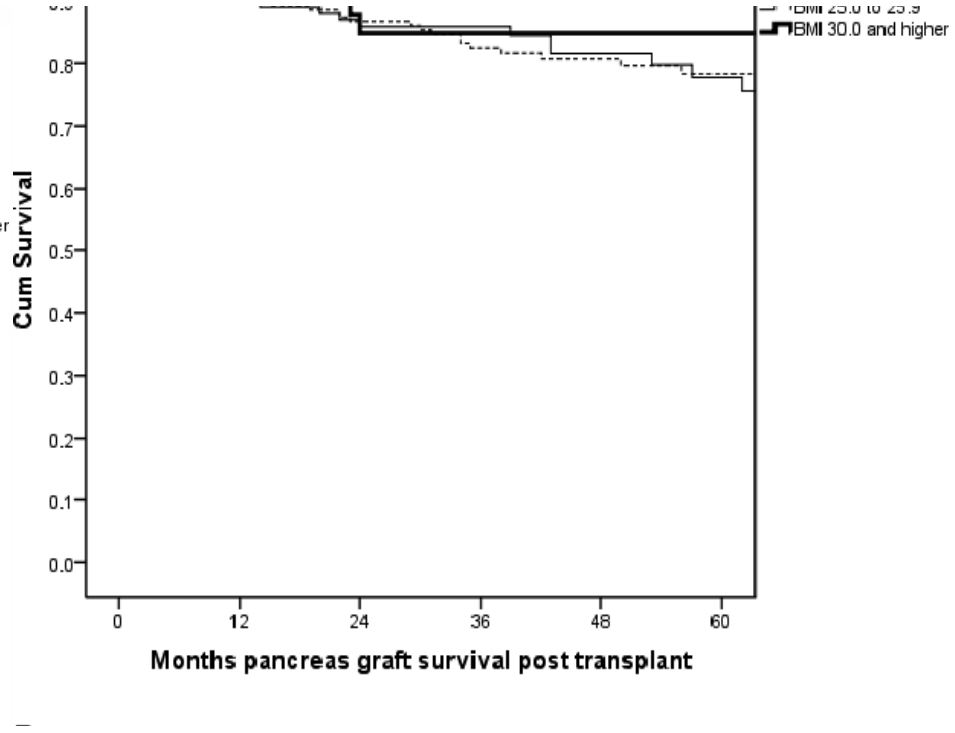




Shah et al. Clin Transplant 2013

BMI as Recipient Risk Factor

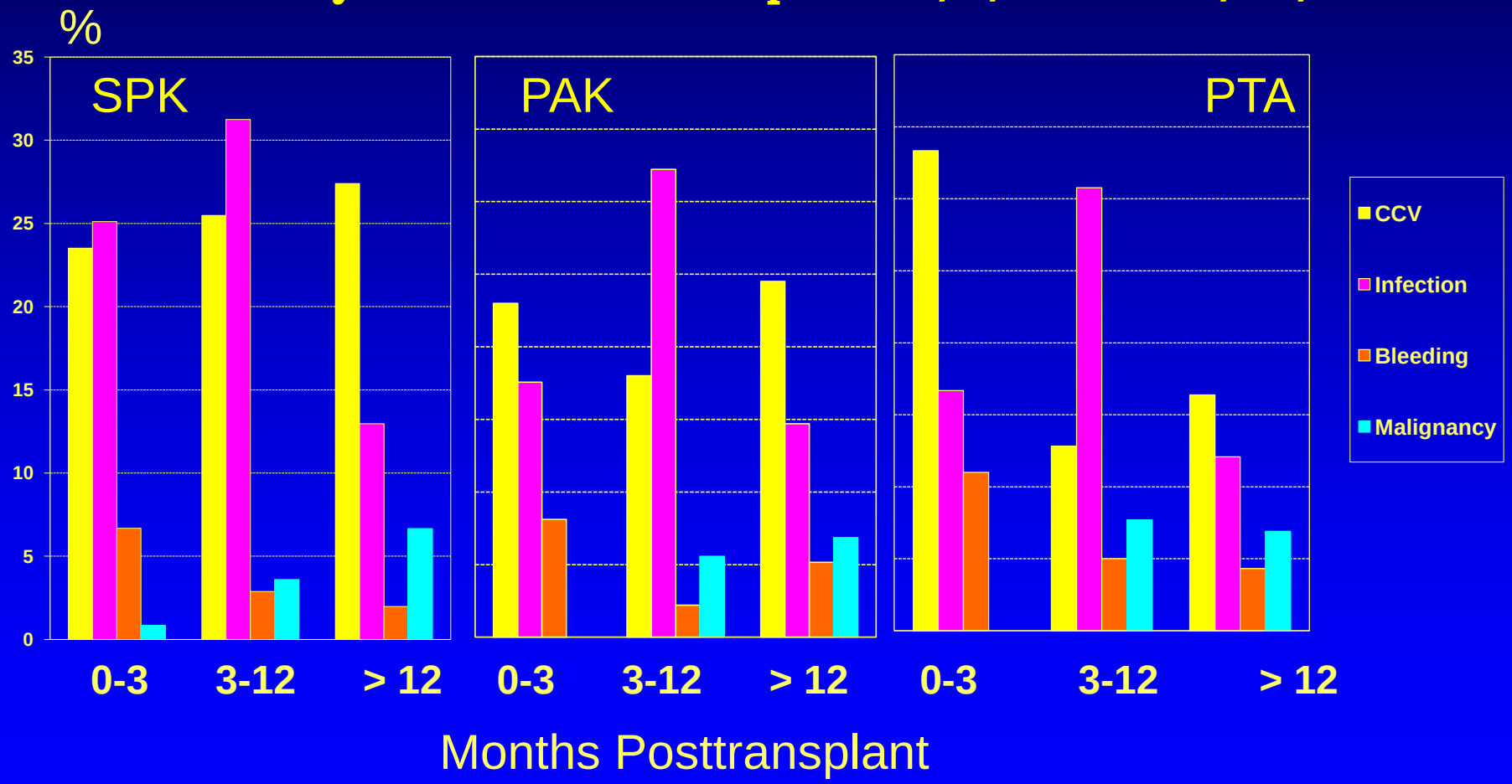




Fridell et al. Clin Transplant 2011

Major Causes of Patient Death

USA Primary DD Pancreas Transplants 1/1/2005 – 12/31/2009



IPTR/UNOS

Cardiac Disease – The Perfect Storm

- High prevalence of heart disease
- Often asymptomatic myocardial ischemia
- High false negative rate of cardiac stress tests

Prevalence of Cardiovascular Disease

Table 2. PREVALENCE OF GENERAL VASCULAR DISEASE PRETRANSPLANT FOR STUDY PATIENTS IN ERAS 3 AND 4 COMBINED

	SPK (n = 187)	PAK (n = 198)	PTA (n = 74)
Coronary artery disease			
Pretransplant MI	37%	33%	14%
CAB	40%	22%	17%
CAA	12%	14%	11%
Peripheral vascular disease			
Claudication	13%	18%	9%
Arterial bypass	8%	5%	0%
Major amputation	9%	6%	6%
Minor amputation	12%	22%	11%
≥1 manifestation	47%	42%	24%

MI, myocardial infarction; CAB, coronary artery bypass; CAA, coronary artery angioplasty; SPK, simultaneous pancreas–kidney; PAK, pancreas after kidney; PTA, pancreas transplant alone.

Sutherland et al Annals of Surgery 2000

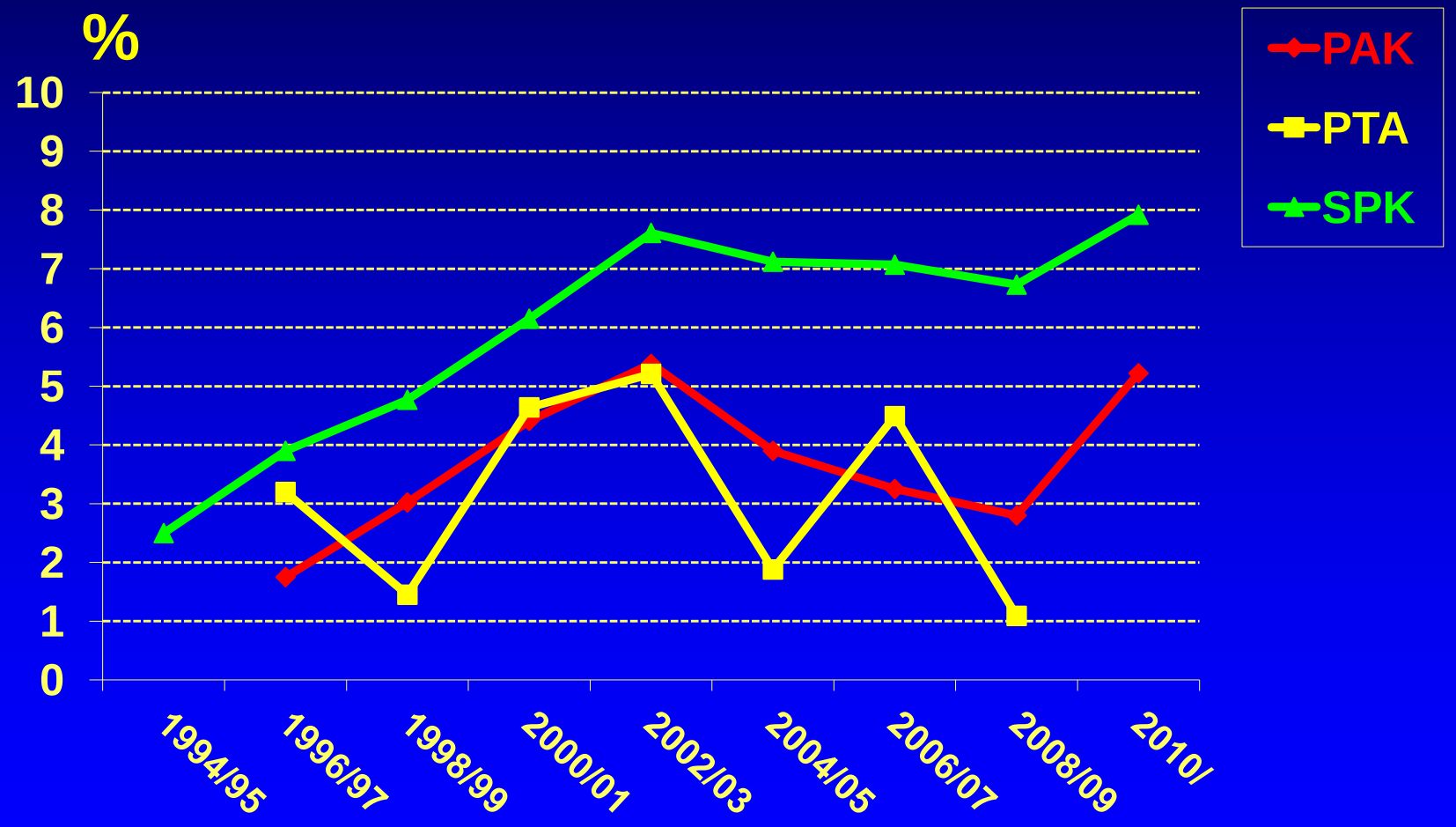
Summary: Cath vs ST?

- The prevalence of CAD in Type I diabetic patients is 63%
  - 46% Non-Critical
  - 17% Critical
- Overall, stress testing has poor sensitivity and PPV for CAD
  - Sensitivity - 26.7%
  - Specificity – 80%
  - PPV – 22.2%
  - NPV – 83.6%
- Only disease duration and time of dialysis were MV risk factors for positive cardiac cath
- Patients who did not undergo coronary angiography 2 years prior to transplantation had a trend towards worse patient and graft survival

University of Wisconsin
SCHOOL OF MEDICINE
AND PUBLIC HEALTH

Patients with Type 2 Diabetes

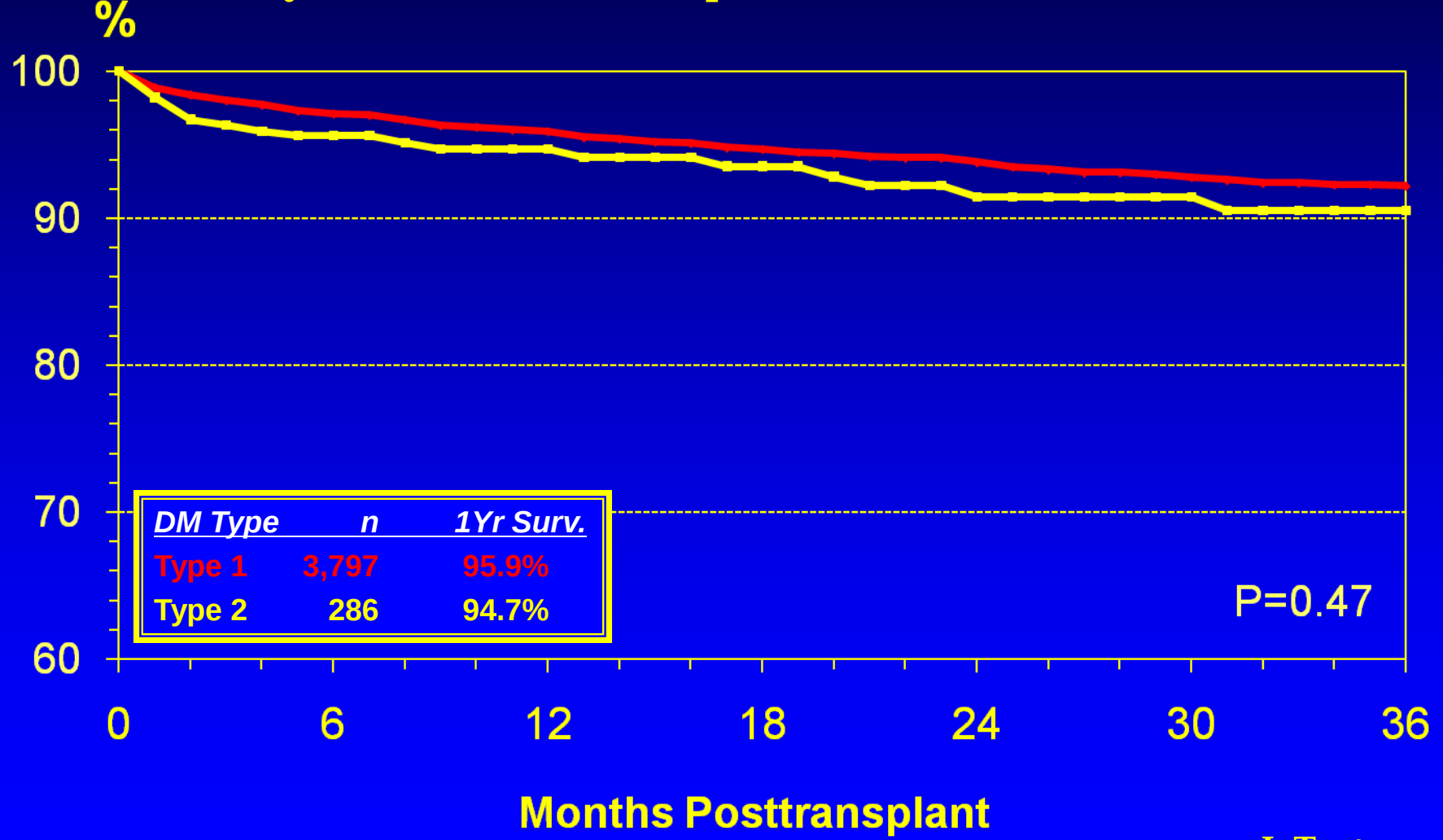
USA Primary DD Pancreas Transplants 1/1/1994 – 12/31/2010



IPTR/UNOS

SPKT Patient Survival by Diabetes Type

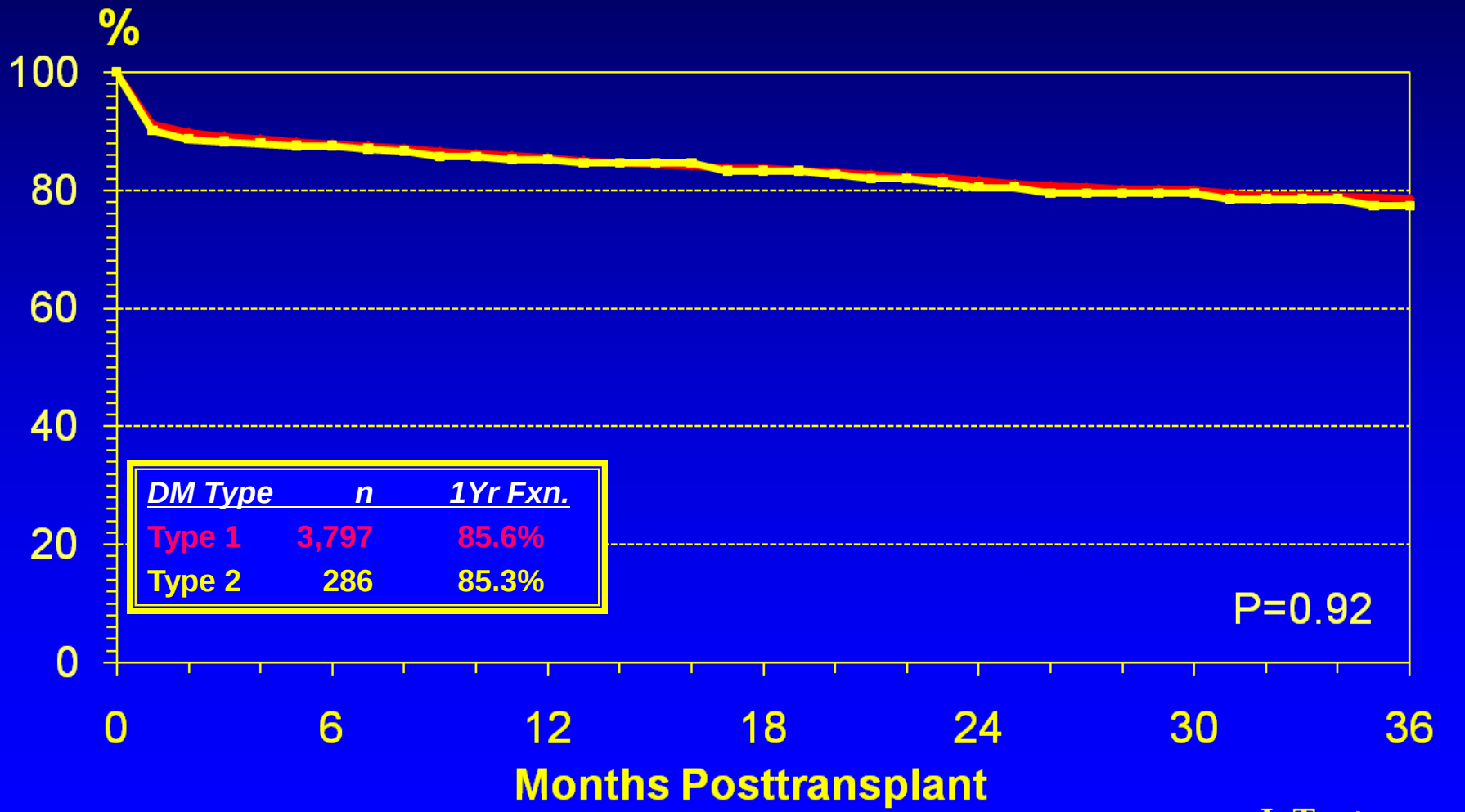
USA Primary DD Pancreas Transplants 1/1/2006 – 12/31/2010



IPTR/UNOS

SPKT Pancreas Graft Function by Diabetes Type

USA Primary DD Pancreas Transplants 1/1/2006 – 12/31/2010



IPTR/UNOS

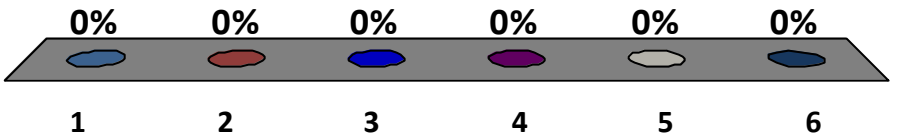
Optimal Type 2 DM Patient For Pancreas Transplant

- **Insulin-dependent**
- **Fasting C-peptide >2 ng/ml *and***
- **BMI ≤ 30 kg/m^2 *or***
- **Low insulin requirement (no evidence for severe insulin resistance)**
- **Avoid obese recipients with high insulin requirements and metabolic syndrome**
- **Primarily SPK candidates – uremic T2DM**
- **Mild to moderate co-morbidities (minimal cardiovascular disease)**
- **Potential obstacles – ASCVD, PVD, reduced kidney survival**

Courtesy of R. Stratta

Which T2DM are considered appropriate for pancreas transplantation?

1. Lean and no significant CVD
2. No insulin use and obese
3. Kidney disease and insulin requiring
4. All of the above
5. 1 & 3
6. None of the above



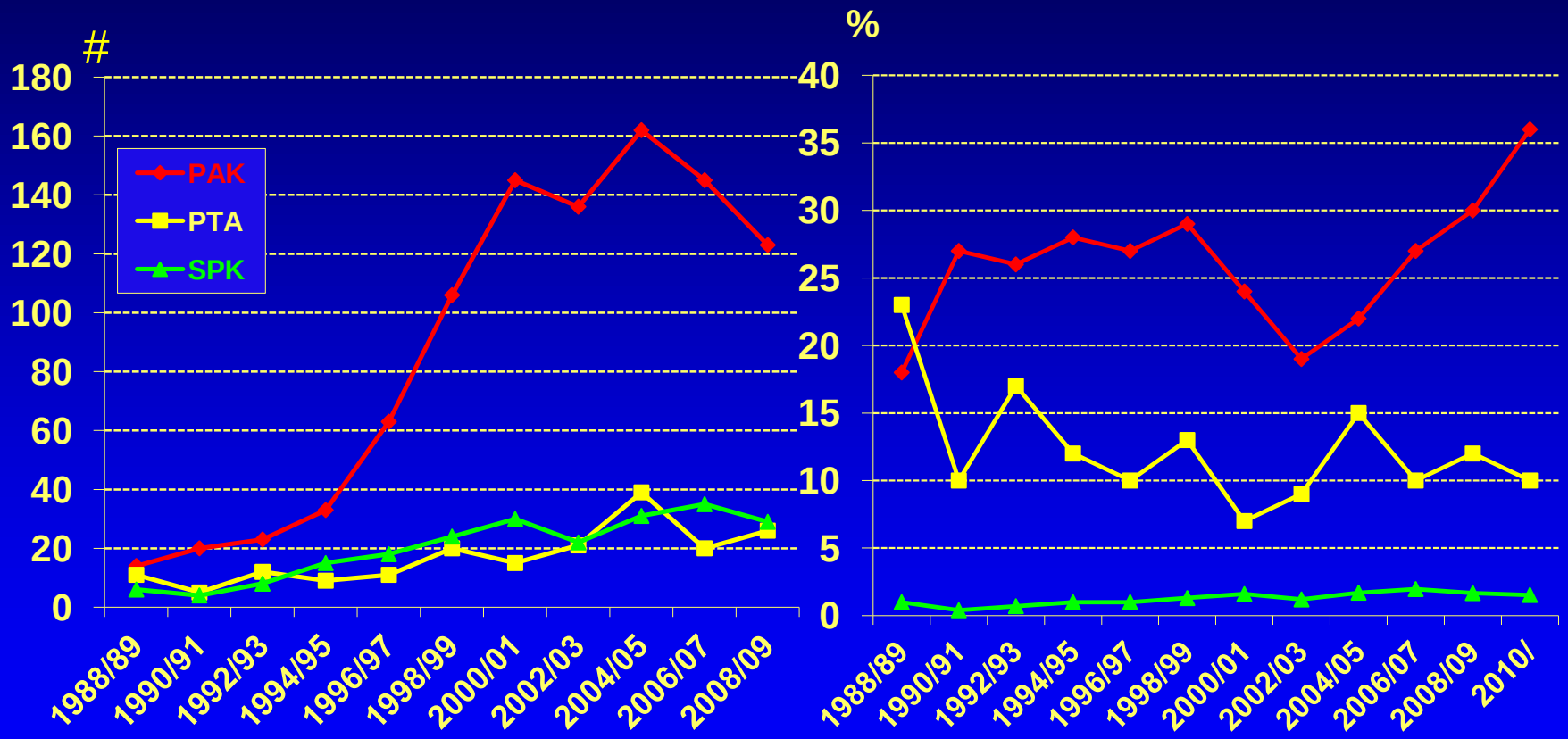
Re-Transplantation

Immunological and Surgical Risks

- Re-SPK vs. Kidney alone ?
- Vascular /Cardiac disease?
- Sensitized?
- Risk of losing pancreas function after KASPK

Pancreas Retransplants

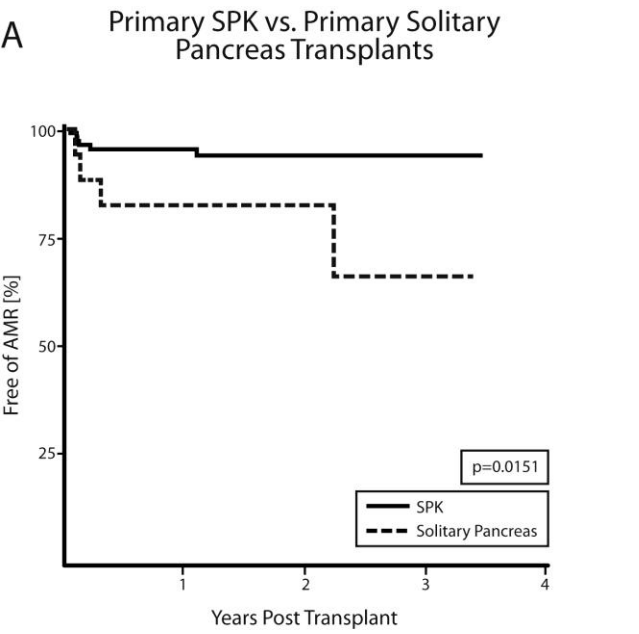
USA Pancreas Transplants 1/1/1988 – 12/31/2010



IPTR/UNOS

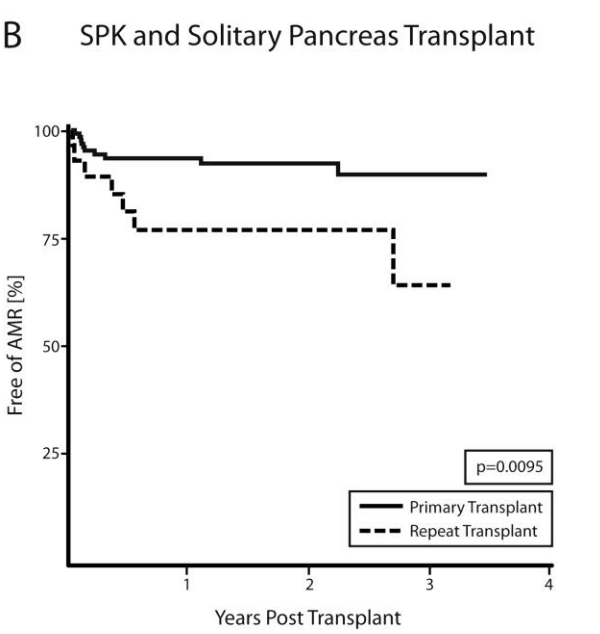
Repeat Transplant and Solitary Pancreas Transplant are Risk Factors for AMR

A



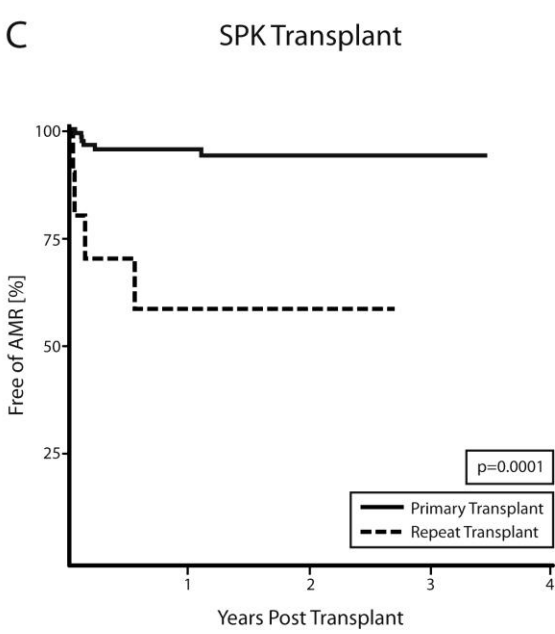
Primary SPK	10%
Primary Sol Panc	19%

B



Primary Panc	10%
Repeat Panc	26%

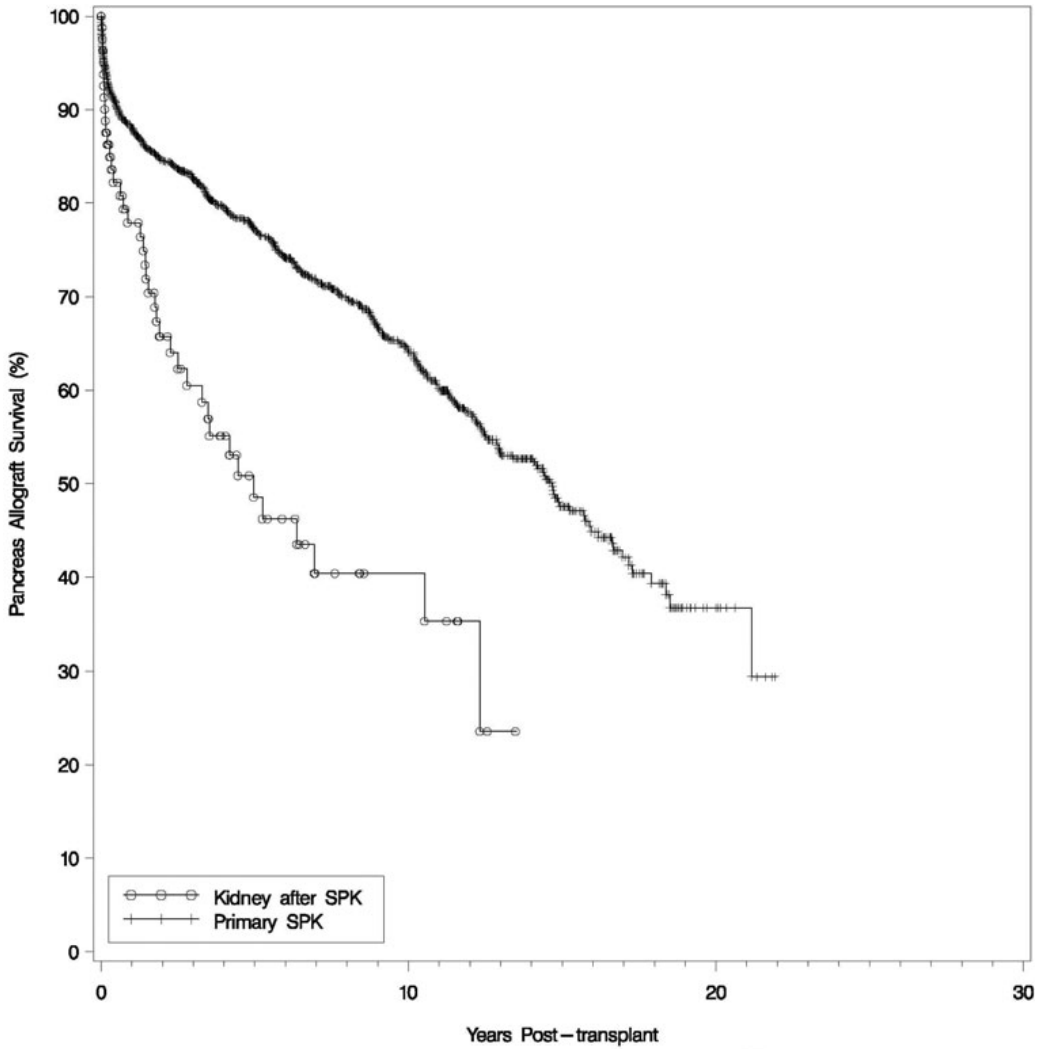
C



Primary SPK	10%
Repeat SPK	42%

Niederhaus et al. AJT, 2013

KASPK: Risk of Return to Insulin



LaMattina et al. AJT 2012


FEB 21 2004


HERSHEY'S