Superior Long-Term Outcome of Pancreas Transplantation Alone with Portal Venous Drainage vs. Systemic Venous Drainage

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Joseph Scalea, Eric Siskind, Niket Todi, Lauren Pettinato, Amanda Bartosic, Blythe Fiscella, Margaret Coakley, Allison Piedmonte, Jastine Paran, Jonathan Bromberg, Eugene Schweitzer, Cinthia Drachenberg
Stephen T. Bartlett

University of Maryland, Department of Surgery

Pancreas Transplantation

- Indicated for patients with Insulin Dependent Diabetes Mellitus and end stage renal disease (ESRD) often accompanied by retinopathy, neuropathy, accelerated atherosclerosis with or without hypoglycemic unawareness, seizures, coma.

Diabetes: Best Medical Therapy is Suboptimal

67 centers reporting to the US type 1 diabetes exchange:
Average HbA1c for treated patients in US: 8.3%

Life expectancy 11.1 years and 12.9 years less for men and women, respectively.

Under auspices of a clinical trial Hb1Ac 7.0% best achieve

Sudden cardiac death leading cause mortality young diabetics:
Hypoglycemia lengthens QT interval

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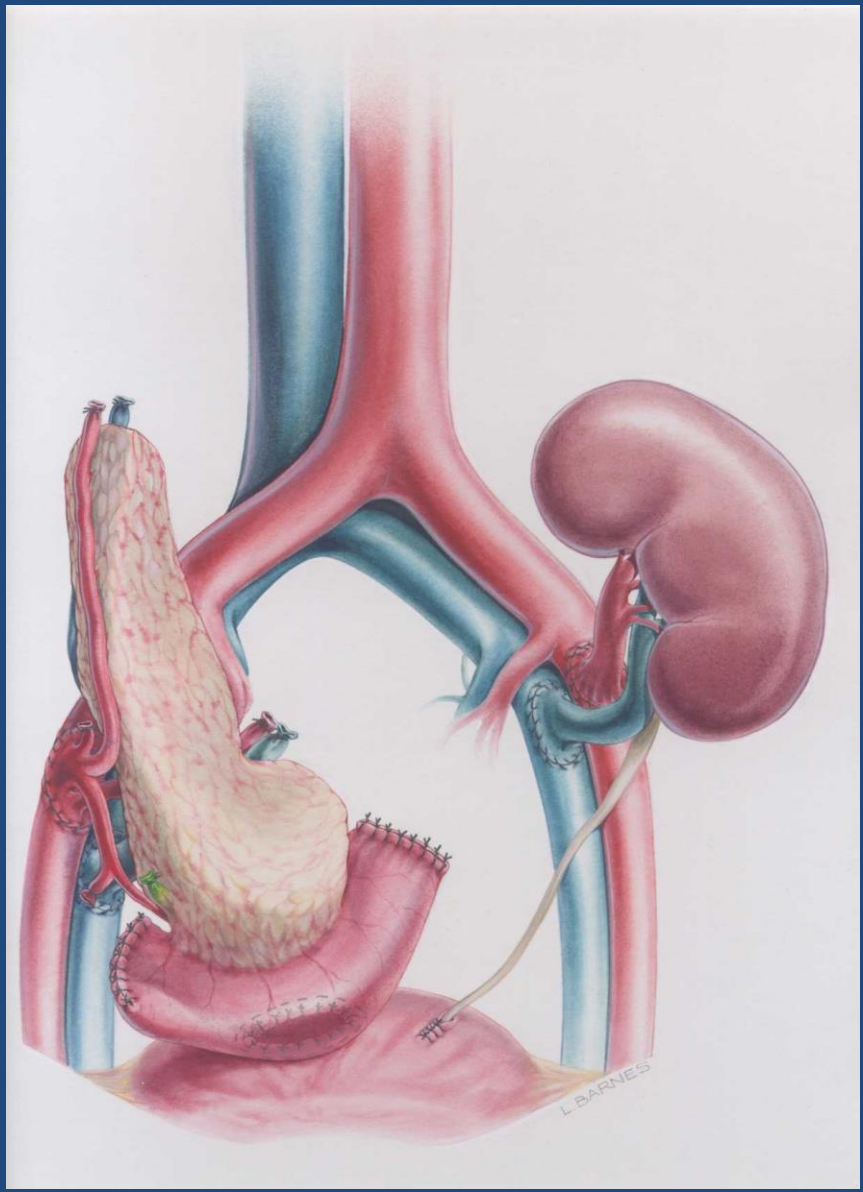
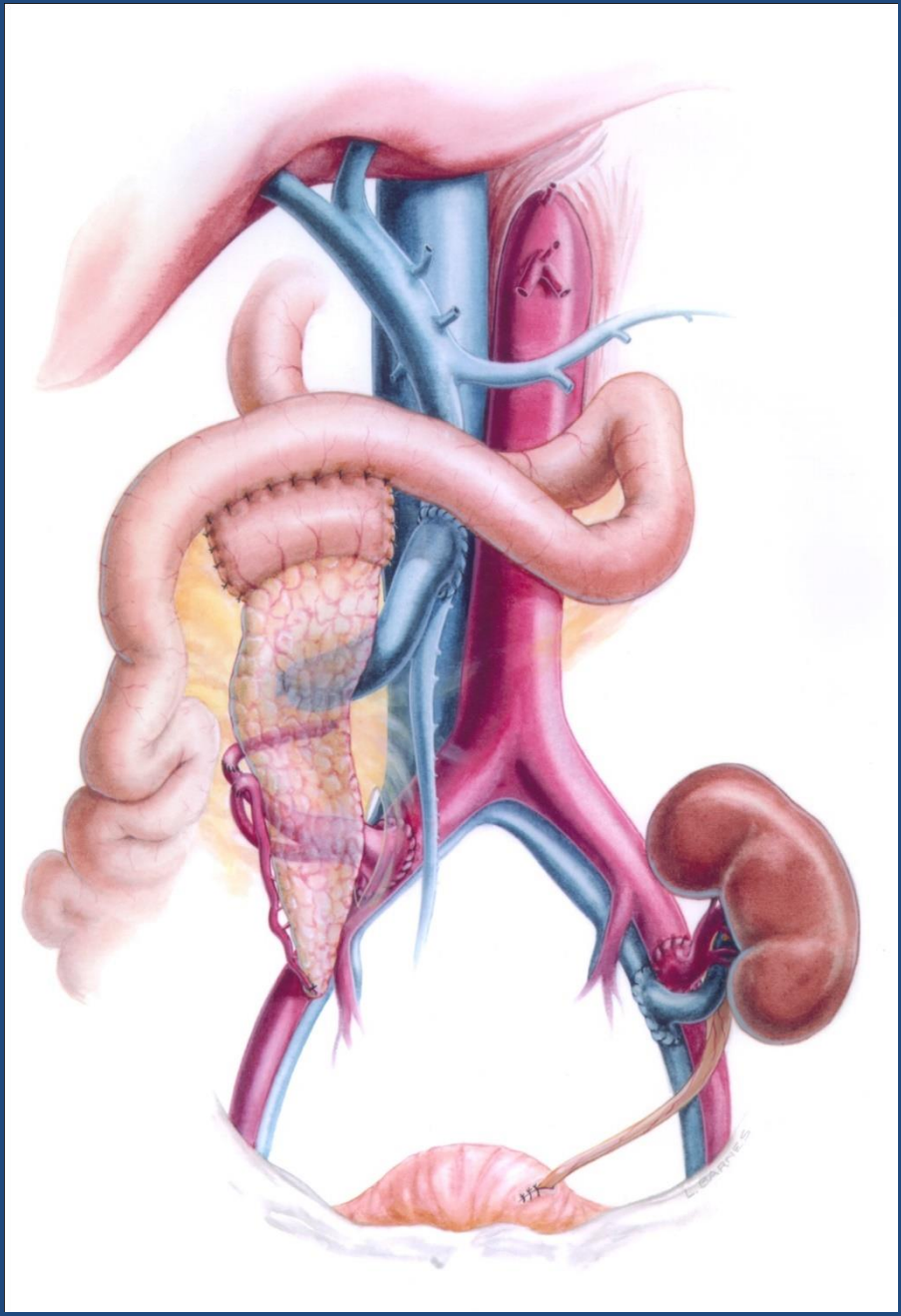
Pancreas Transplantation Alone (PTA)

- Limited indications: reserved for patients with medically refractory Type 1 diabetes without ESRD, unresponsive to best medical therapy whether physiologic, psychosocial or both resulting in:
  - Hypoglycemic unawareness
  - Seizures
  - Coma
  - Events frequently requiring second (relative) or third party (emergency services) to intervene

SPK/SVD



SPK/PVD



PTA-advantages of Portal Venous Drainage (PVD)

- Physiologic drainage of insulin through portal system avoids systemic hyperinsulinemia.
- Hyperinsulinemia has theoretical association with insulin resistance, accelerated atherosclerosis, and weight gain.
- Theoretical advantage of antigen delivery by portal drainage through liver, leading to lower incidence of rejection.

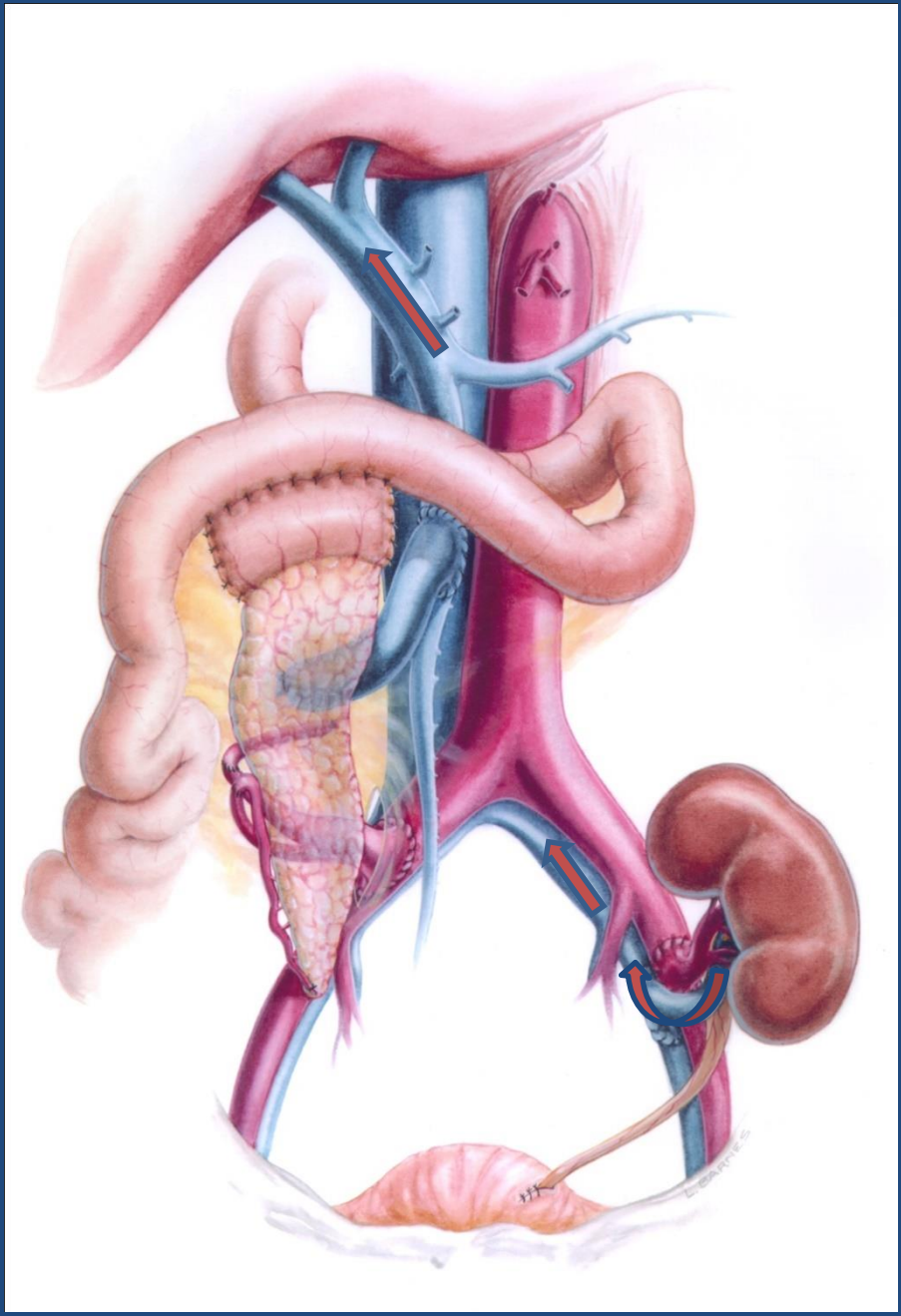
PTA-advantages of System Venous Drainage (SVD)

- Technically easier
- No need for longer Y-graft to tunnel through mesentery.
- More options for placement of organ (EIV, CIV, IVC) particularly in cases of re-transplantation.

Studies of PVD vs. SVD - graft survival

SPK	Year	PVD (%)	SVD (%)	Comment
Petruzzo (Lyon)	2008	78.4 (5y)	56.7	Randomized N=80 Cox regression not significant
McGillivray (Toronto)	2002	86 (3y)	86	Non-randomized 10% vs 31% rejection incidence
Buzerbachi (Toronto)	2011	75.5 (5y)	81.8	No difference BMI, insulin levels, lipid profile
Stratta (Memphis)	2001	85 (17m)	74	Morbidity, no difference
Stratta (Wake Forest)	2004	92 (6m)	87	Short-term study, no difference
Troppmann (U.C., Davis)	2004	__	__	No difference kidney survival or rate rejection
Philosophe (Baltimore)	2001	76 (3y)	76 (3y)	
PTA	**Year**	**PVD (%)**	**SVD(%)**	**Comment**
Philosophe (Baltimore)	2001	84 (3y)	50 (3y)	SPK, no difference PTA: PVD superior

Dual portal and systemic alloantigen delivery



Superior Long-Term Graft Survival of Pancreas Transplantation Alone Using PVD versus SVD: Two Decades of Experience at a High-Volume Center in the United States

- For more than 2 decades, our center has used a combination of venous drainage techniques, inclusive of portal venous drainage (PVD).
- In this 20 year follow up, we hypothesized that choice of pancreatic venous outflow technique would not predict rejection-free (RF) graft survival.

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Methods

- From 1992 to present, 143 PTAs were performed at the University of Maryland. Patients were divided into two groups: PVD (n=95) or SVD (n=48).

Methods

- Retrospective chart review
  - All PTAs from 1992 to May 2015 in UNOS database analyzed for graft survival (n = 147)
  - Graft failure determined by clinic notes
  - 5 patients excluded due to no operative note or immunosuppression record (n = 142)

Table 1

Parameters for PTAs: SVD vs PVD				
	All PTA (n=147)	PVD (n= 97)	SVD (n= 50)	*p*
Recipient age, years, mean	40.3	40.8	39.4	0.20 ^
Donor age, years, mean	24.0	24.0	24.0	0.49 ^
Recipient weight, pounds, at PTA	156.7	155.7	158.7	0.31 ^
Recipient race, African American, n (%)	4 (3)	1 (1)	3 (6)	0.08 ^^
Induction Immunsuppression*				
Thymoglobulin, n (%)	60 (46)	52 (63)	8 (16)	<0.01 ^^
Alemtuzumab, n (%)	17 (13)	5 (6)	12 (25)	<0.01 ^^
OKT3, n (%)	45 (34)	21 (26)	24 (49)	<0.01 ^^
ATGAM, n (%)	5 (4)	1 (1)	4 (8)	0.04 ^^
Steroids Alone, n (%)	5 (4)	1 (1)	4 (8)	0.04 ^^
Maintenance Immunosuppression**				
Cyclosporine	9 (6)	1 (1)	8 (17)	<0.01 ^^
Tacrolimus	119 (85)	87 (94)	32 (68)	<0.01 ^^
Mycophenolic Acid	131 (94)	91 (98)	40 (85)	<0.01 ^^
Steroids	68 (49)	49 (53)	19 (28)	0.17 ^^
Time period transplanted***				
1993-1999, n, (%) – era 1	68 (46)	36 (38)	30 (60)	0.01 ^^
2000-2004, n, (%) – era 2	54 (37)	49 (52)	5 (10)	<0.01 ^^
2005-2009, n, (%) – era 3	13 (9)	8 (8)	5 (10)	0.75 ^^
2010-2015, n, (%) – era 4	12 (8)	2 (2)	10 (20)	0.37 ^^
PRA at transplantation, mean (%)#	13.7	10.1	15.4	0.18 ^
PRA = 0% at transplantation, n (%)	46 (53)	30 (50)	16 (59)	0.95 ^^

*Induction records were complete for n=131 (89.1%) of cases, n=82 PVD, n=49 SVD; **Maintenance immunosuppression records were complete for n=140 (95.2% of cases); n=93 PVD, n=47 SVD; ***in 2 patients technique was unclear; #PRA was available and calculated for n=87 (59.2%) of cases; n=27 SVD, n=60 PVD; ^determined using student's test; ^^determined using z-test of proportions; ATGAM = anti-lymphocyte globulin, equine; Thymoglobulin = Anti-thymocyte antibody, rabbit; OKT3 = Anti-CD3 monoclonal antibody, murine

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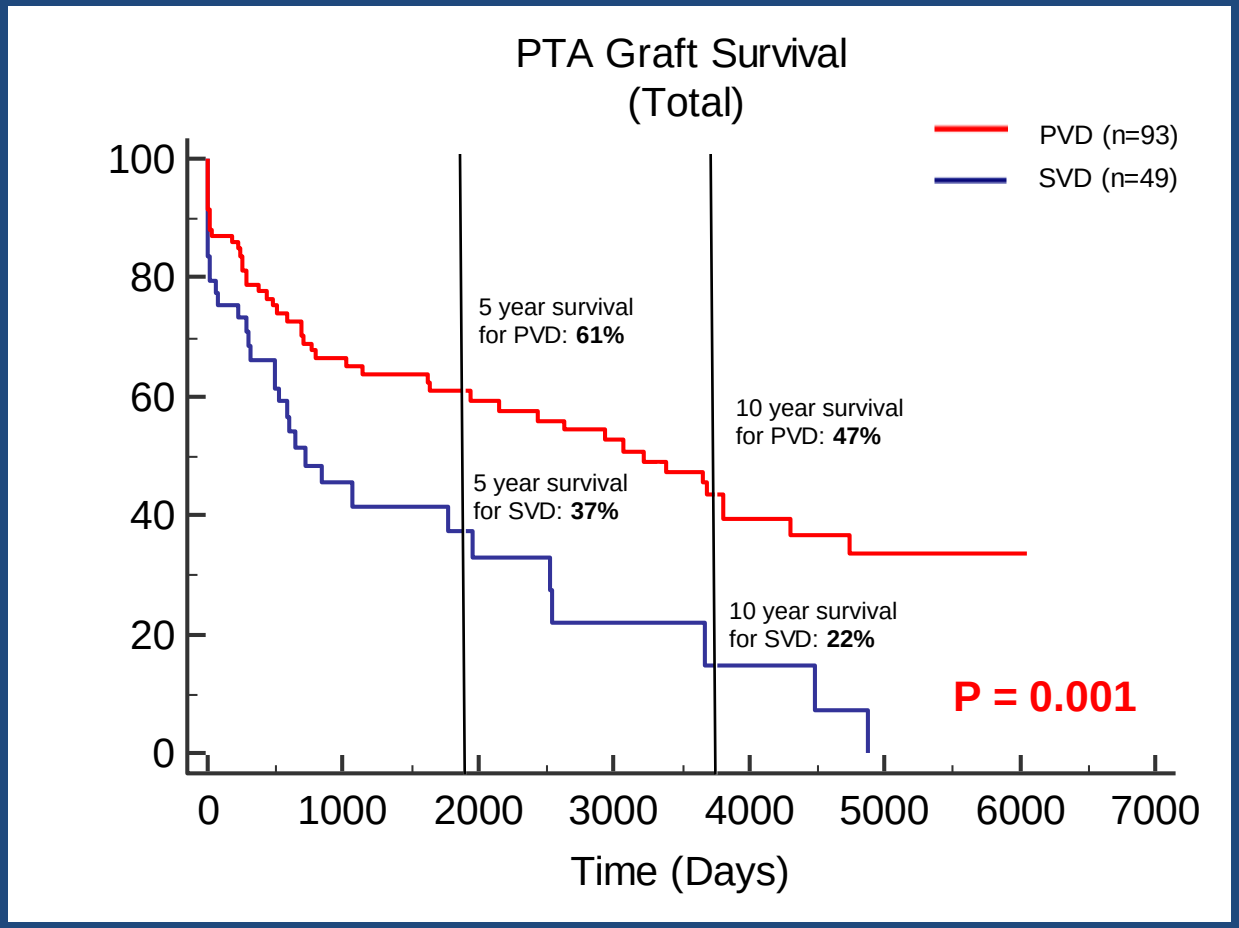
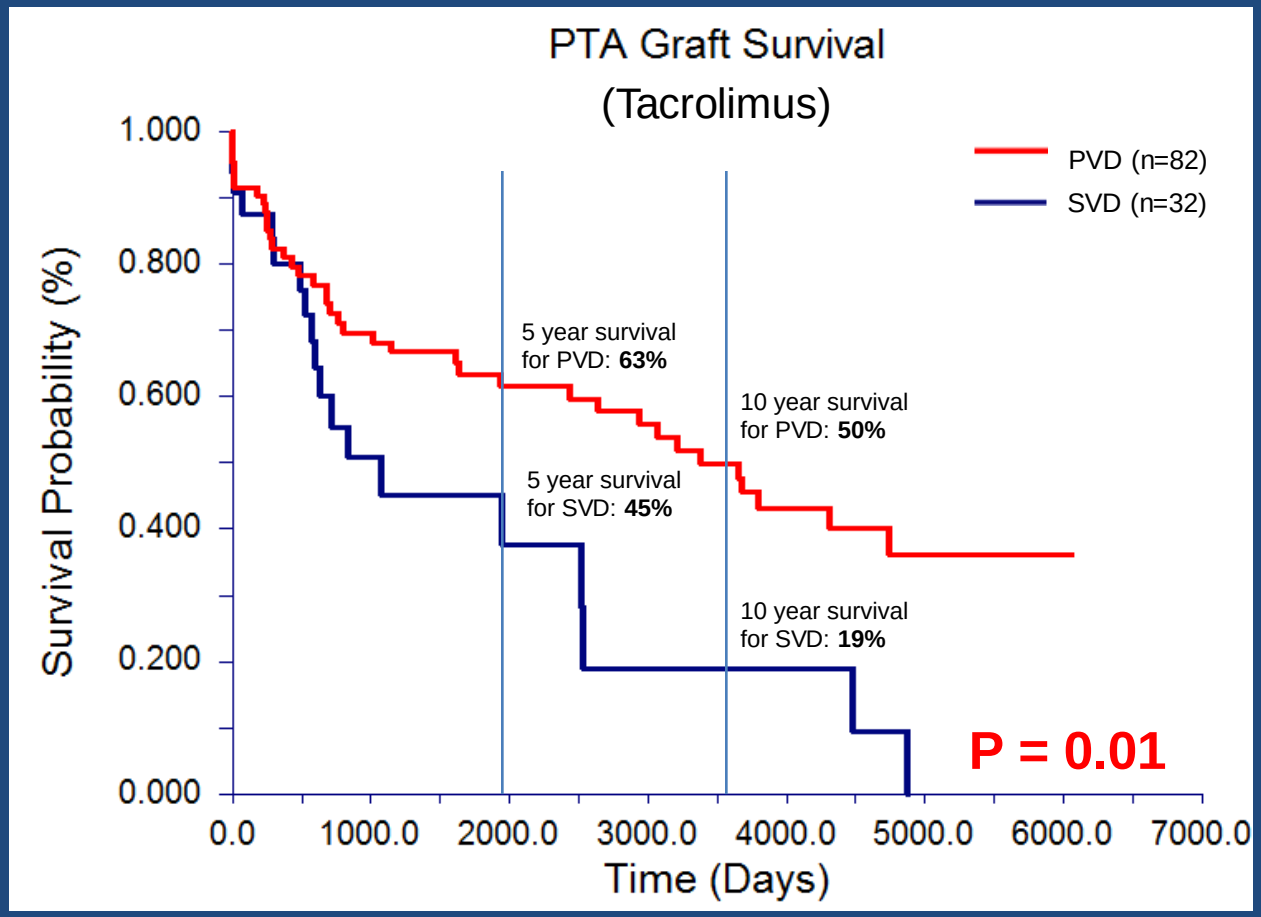

PTA Graft Survival
(Total)
PVD (n=93)
SVD (n=49)
100
80
60
40
20
0
5 year survival
for PVD: 61%
10 year survival
for PVD: 47%
5 year survival
for SVD: 37%
10 year survival
for SVD: 22%
P = 0.001
0
1000
2000
3000
4000
5000
6000
7000
Time (Days)

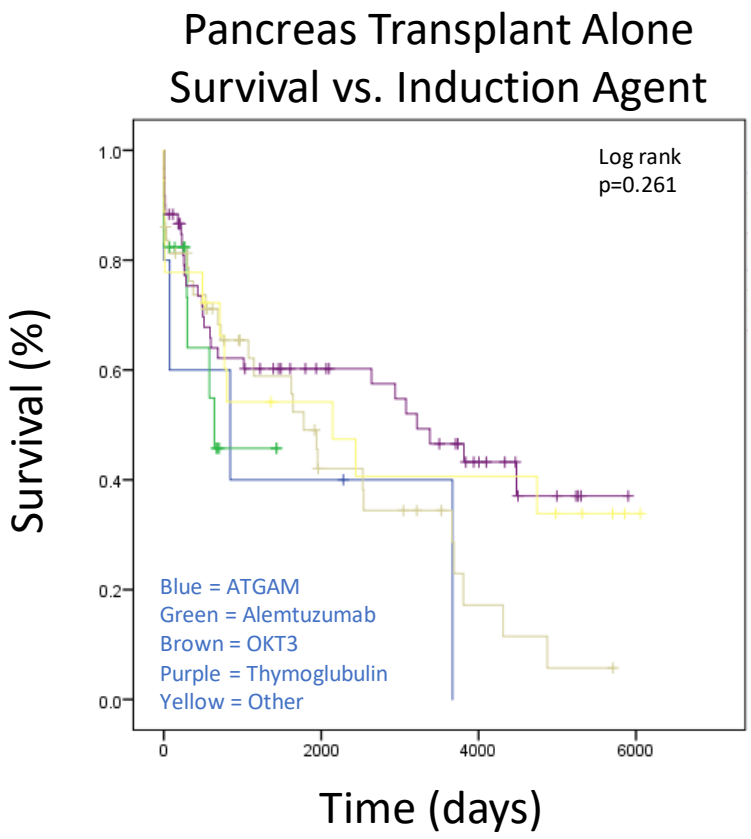
Methods

- 27 excluded for non-Tacrolimus immunosuppression regimen (n = 115)

	Patients with PVD (N=83)	Patients with SVD (N=32)	
Female	50 60%)	16 (50%)	
Average Age	41.4	38.8	


PTA Graft Survival
(Tacrolimus)
PVD (n=82)
SVD (n=32)
5 year survival
for PVD: 63%
10 year survival
for PVD: 50%
5 year survival
for SVD: 45%
10 year survival
for SVD: 19%
P = 0.01
Survival Probability (%)
1.000
0.800
0.600
0.400
0.200
0.000
0.0
1000.0
2000.0
3000.0
4000.0
5000.0
6000.0
7000.0
Time (Days)

Two Decades of PVD vs SVD: Methods



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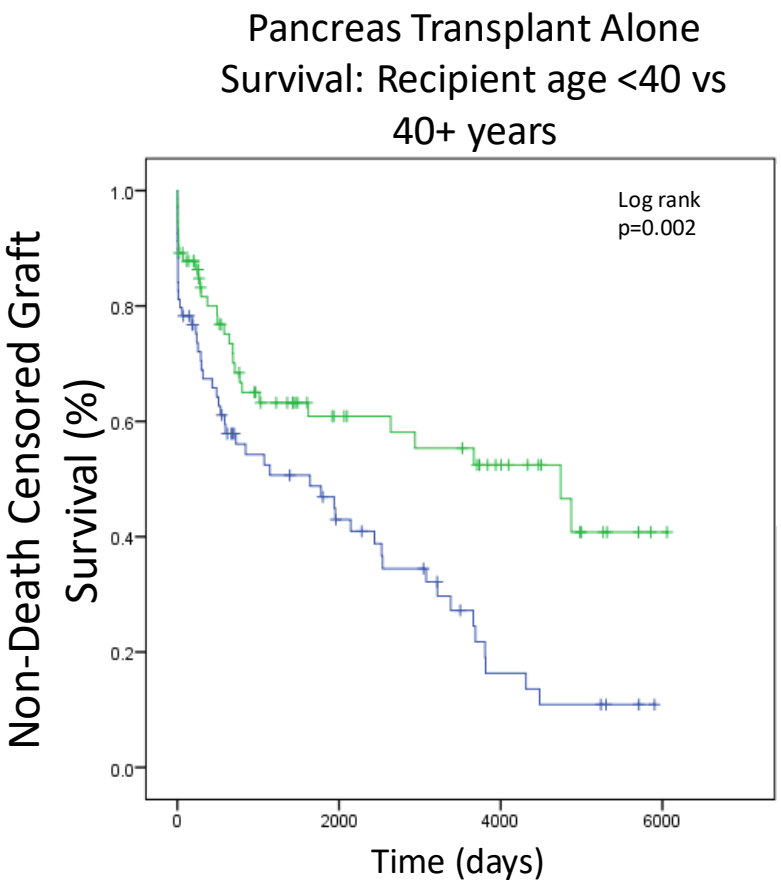
Two Decades of PVD vs SVD: Methods

RegPatients over aged 40 had better outcomes, than did younger patients

This may be due to the senility of the immunologic antidonor response, or perhaps non-compliance in the younger recipient population



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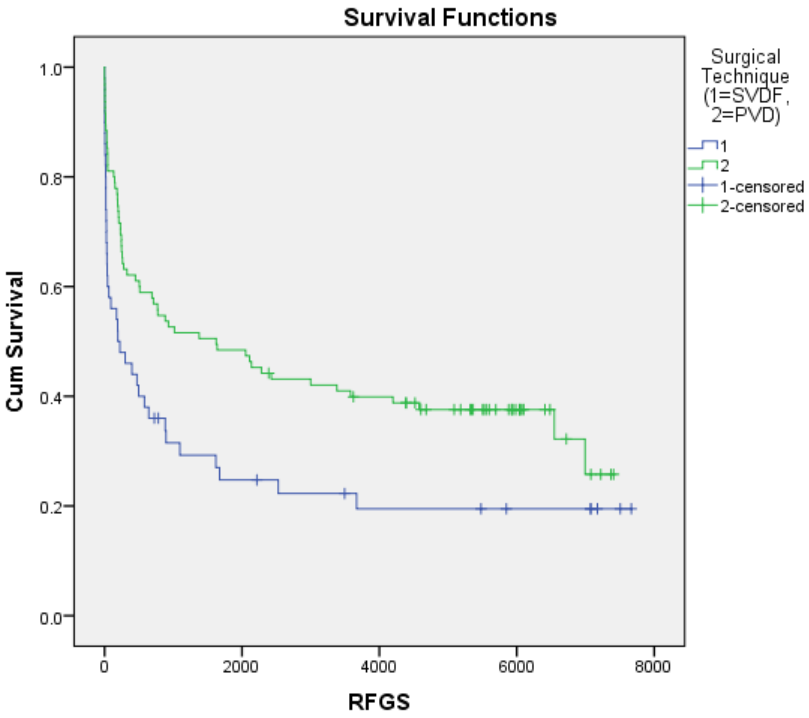
Rejection free graft survival:

- 1 year:
  - SVD: 46%
  - PVD: 62%

- This includes all rejection events
- Very rigid criteria
- Updated 3/2017



Two Decades of PVD vs SVD: Methods

Parameter	HR	*p*
Recipient age		
21-29 (REF)	1	0.024
30-39	0.924	0.835
40-49	0.387	0.031
50-58	0.456	0.089
Donor age	0.772	0.772
Gender (Female = REF)	0.972	0.913
Surgical technique (SVD = REF)	0.427	0.006
Induction agent		
ATGAM (REF)	1	0.455
Alemtuzumab	0.450	0.484
OKT3	0.718	0.561
Thymoglobulin	0.494	0.374
Steroids alone	1.224	0.765
Era		
Era 1 (REF)	1	0.003
Era 2	1.478	0.475
Era 3	7.447	0.007
Era 4	0.568	0.686

Multivariate analysis of parameters contributing to graft failure after pancreas transplant alone using the Cox proportional hazards analysis. Surgical technique, recipient age, and era were all contributory to graft loss, whereas gender, donor age, and immunosuppressive protocols were not. For Cox proportional hazards analysis, independent categorical variables delineated by "REF" were used as the reference comparators.

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Conclusions

- Patients who undergo portal venous drained PTAs have significantly longer graft survival than patients with systemic venous drained pancreas transplants .

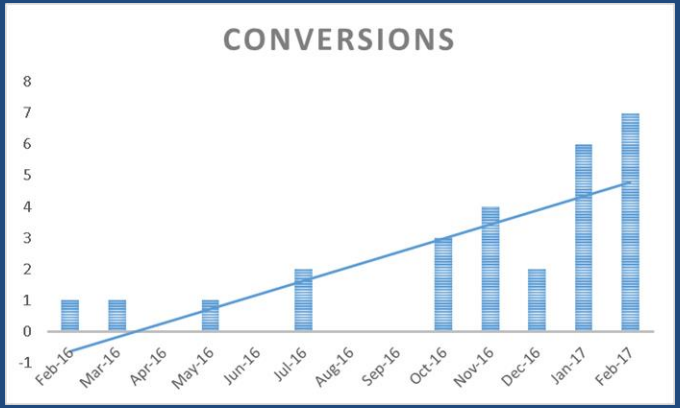
- The 63% 5-year and 50% 10-year PVD graft survival is superior to 50% 5-year graft survival for U.S. PTA (SRTR 2013 annual report) and current rates of insulin independence at selected islet transplant centers.

- The bar for “equivalency” of five year insulin independence of ITA and PTA has been raised from 50% to >60%.

Future Directions

- Collecting all biopsy specimens, re-analyzing for incidence of rejection
- Clinical research unit to compare physiologic capability for glucose disposal
- Contacting every patient for:
  - Exact functional status
  - Insulin requirement, if any
  - QOL
  - Weight gain (hyperinsulinemia theoretically associated with weight gain)

Improvement in Transplant Volume at UMMC



A Prospective Survey of Consecutive PTAs

- Background and Hypothesis:
  - Patients derive a significant benefit from PTA, however this benefit is difficult to quantify
  - We hypothesized that patients with a functional vs. failed PTA would have a higher quality of life
  - This is the first study to use (failed, prior PTA) as a control group, and thus, this is an important contribution to the surgical literature

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A Prospective Survey of Consecutive PTAs

- We identified 137 patients (excluding retransplants, PAK, and SPK)
- Each was called
- 4 domain, 15 question survey was administered

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A Prospective Survey of Consecutive PTAs

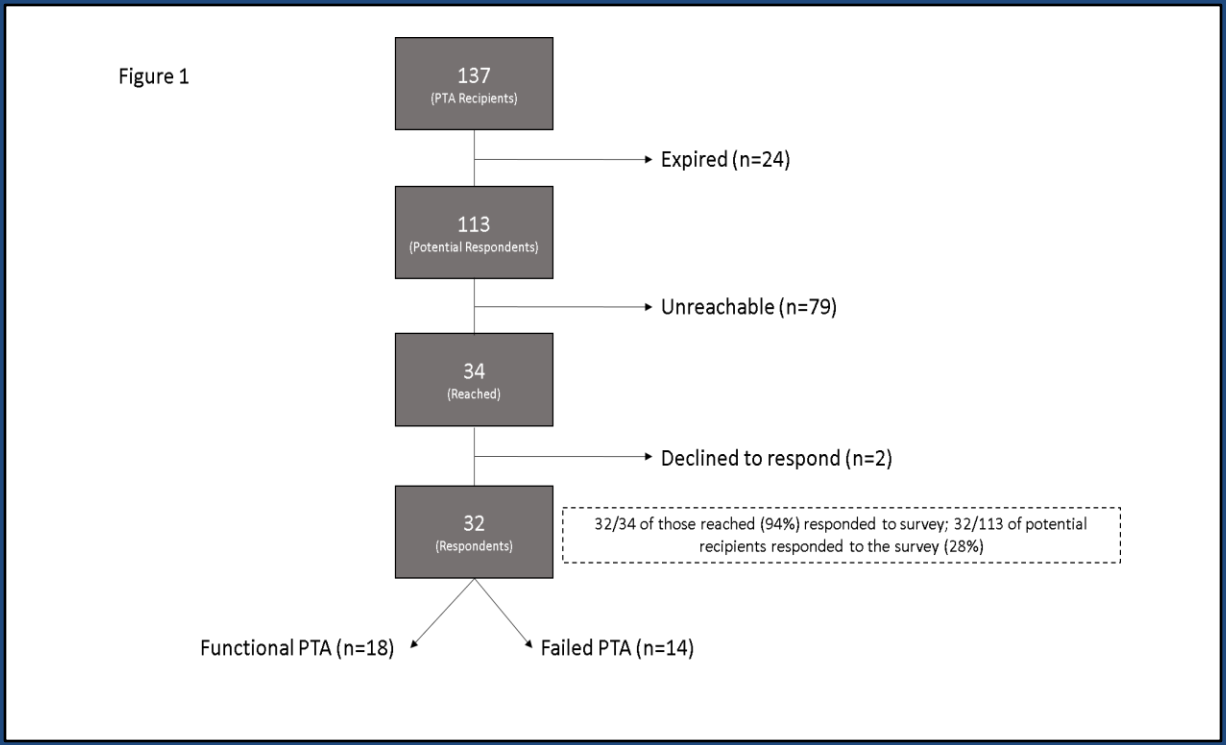

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Table 3

	Parametric comments from those with a functional pancreas transplant	Parametric comments from those with a failed pancreas transplant
Indifferent	• Patient updated staff on recent infection	• "I have severe gastroparesis" • Asked question about immunosuppression • Dr. [Endocrinologist] is my endocrinologist
Positive	• "The pancreas transplant saved my life" • "In 1997, he was given 2 years to live. Now he's lived 19 years later" • "excellent life since transplant" • Dr. [Txp Surgeon] was fantastic! • "I think what you have done for me is great. Dr. [Txp Surgeon] is a wonderful person and surgeon and I wouldn't be here without him!“	• "How old is too old for a pancreas if I am 70?" • "Pancreas [transplantation] was the best thing I ever did. I had 12 years without DM and my doctors said it saved my eyesight from retinopathy. Dr. [TxpSurgeon] is the best!"
Negative	• "My health was much worse after transplant due to multiple complications"; Would not do it again	• "I had a complicated course"; Would not do it again.

Brackets “[]” used to anonymize comments. Txp = Transplant; No patients’ comments were removed.

A Prospective Survey of Consecutive PTAs

- Conclusions:
  - These data demonstrate the value of PTA, even in 2017
  - There is enormous patients satisfaction
  - Surgeons need to take a more active role in the care of the severely diabetic

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