

Impact of Preservation Solution on Abdominal Transplant Outcomes

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- **Financial disclosures**
 - None

- **Conflict of interest disclosures:**
 - PI for Novartis *Transform* Trial
 - Co-PI for Shire Viro-Pharma SHP616-302
 - Invited speaker for Waters Medical Systems

Goals of Organ Preservation

- **Maximize organ function post-transplant**
- **Allow for organ transport and increased geographic access**
- **Allow time for recipient preparation**
- **Allow time for cross-match to be performed**

Static Cold Storage

- Organs flushed with cold preservation solution and packaged in additional solution on ice until transplant

“Gold Standard” for abdominal and thoracic transplantation



ACCS06
UNOS ID
A1
DONOR ABO 04/01/15
CROSS CLAMP DATE 1357 EST
CROSS CLAMP TIME (Military Time) Time Zone

CONTENTS OF BOX:
CHECK ALL THAT APPLY:
 SPLEEN BLOOD
 NODES
 DOCUMENTATION
 OTHER:

Ice 1:	Date	Time	Initial
Ice 2:			

NYAP
ORIGIN: TING, OPO
001 003 6667


LEFT KIDNEY **KEEP UPRIGHT**

DONATED
HUMAN ORGAN/TISSUE
for TRANSPLANT

TO (INSTITUTION):
CITY: STATE: TEL: ()
If available, PRIMARY FLIGHT #: If available, CONNECTING FLIGHT #:

In case of delays or problems call UNOS Organ Center at 1-800-292-9537 a 24 hour number.

This shipment is made possible by an exchange of information through United Network for Organ Sharing, a charitable, non-profit organization which has no proprietary interest in this container or its contents. UNOS ORGAN LIFE
UNITED NETWORK FOR ORGAN SHARING

HANDLE WITH CARE 
CONTENTS—NOT RESTRICTED, PACKED IN COMPLIANCE WITH IATA PACKAGING INSTRUCTION 650 (NET ICE)

Ischemia Reperfusion Injury

↓ O₂ leads to mitochondrial damage ↓ ATP



↓ ATP leads to ↓ Na⁺/K⁺-ATPase function
Na⁺ influx and cellular swelling



↓ ATP leads to Ca²⁺ channel dysregulation
Ca²⁺ influx and ROS generation



Lipid, DNA, and protein damage
Cell Death

Organ Preservation Solutions

The “IDEAL” Solution:

- Prevents cell swelling and tissue edema

Hydroxyethyl starch, lactobionate, raffinose, mannitol, tryptophan

- Maintains intracellular pH

Histidine

- Provides substrates for generation of ATP, etc.

Adenosine, ketoglutarate, L-arginine

- Prevents injury from oxygen free radicals

Glutathione, allopurinol, N-acetylcysteine

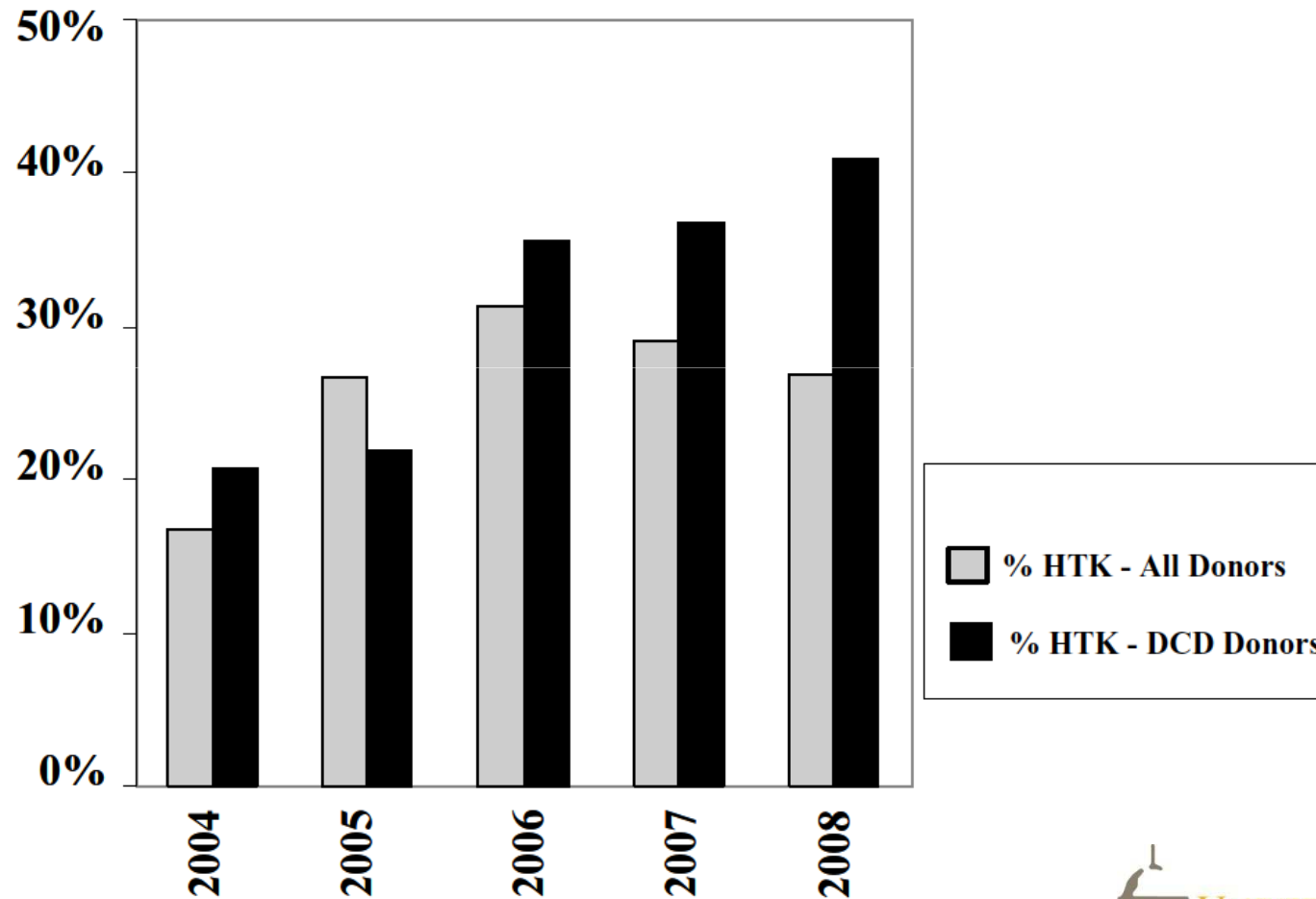
Abdominal Organ Preservation Solutions

- **University of Wisconsin (UW) solution has been the “gold standard” for abdominal organ procurement and preservation since 1988**
- **Reports of equivalent graft outcomes with UW and Histidine-Tryptophan-Ketoglutarate (HTK) led to increased HTK use in the US**

***** UW or HTK used for > 98% abdominal organ procurements in the US***

Increased HTK Use for Abdominal Organ Recovery

Especially Donation after Cardiac Death Transplants



UW versus HTK - Composition

Table 1. Comparison of Constituents of UW vs HTK Solution

Component	UW (mmol/L)	HTK (mmol/L)
Na	30	15
K	120	9
pH	7.4	7.1
Lactobionate	100	
Glutathione	3	
Raffinose	30	
Hydroxyethyl starch	5 gm%	
Adenosine	5	
Histidine		180
Tryptophan		2
Ketoglutarate		1
Mannitol		30

Potential Benefits of HTK

Reduced potassium levels = safer reperfusion

**Reduced viscosity = better penetration of
microvasculature**

Reduced cost = despite increased volume

Does preservation solution impact liver allograft survival?

Early Studies in Liver Transplant

Pokorny, et al (2004) *Transplant Int* 17: 256-60 (Austria/Germany)

4 European transplant centers followed 214 patients receiving HTK-preserved liver transplants

****1 year graft survival 80% HTK (equivalent to historical UW)**

Rayya et al (2008) *Transplant Proc* 40: 891-4 (Germany)

69 HTK-preserved compared to 68 UW-preserved liver transplants

****HTK 1 year graft survival (71%) versus UW (78%) (p=NS)**

****HTK much higher re-transplantation (13%) versus UW (7%)**

Early Studies in Liver Transplant

Mangus, et al (2008) *Liver Transplant* 14: 365-73

371 HTK compared to 327 UW preserved liver transplants

- * No difference in 1 year graft survival (85%)**
- * Donation after cardiac death and CIT > 12h had reduced 1 year graft survival with HTK preservation**

Histidine–Tryptophan–Ketoglutarate (HTK) Is Associated with Reduced Graft Survival in Deceased Donor Livers, Especially Those Donated After Cardiac Death

American Journal of Transplantation 2009; 9: 286–293

Reviewed UNOS database of liver transplants from July 1, 2004 to February 28, 2008 (N=17,428)

- Exclusion criteria:**
- 1. Recipient age < 18 years**
 - 2. Multi-organ transplant**
 - 3. Split graft**
 - 4. Living donor**
 - 5. Alternative solution**

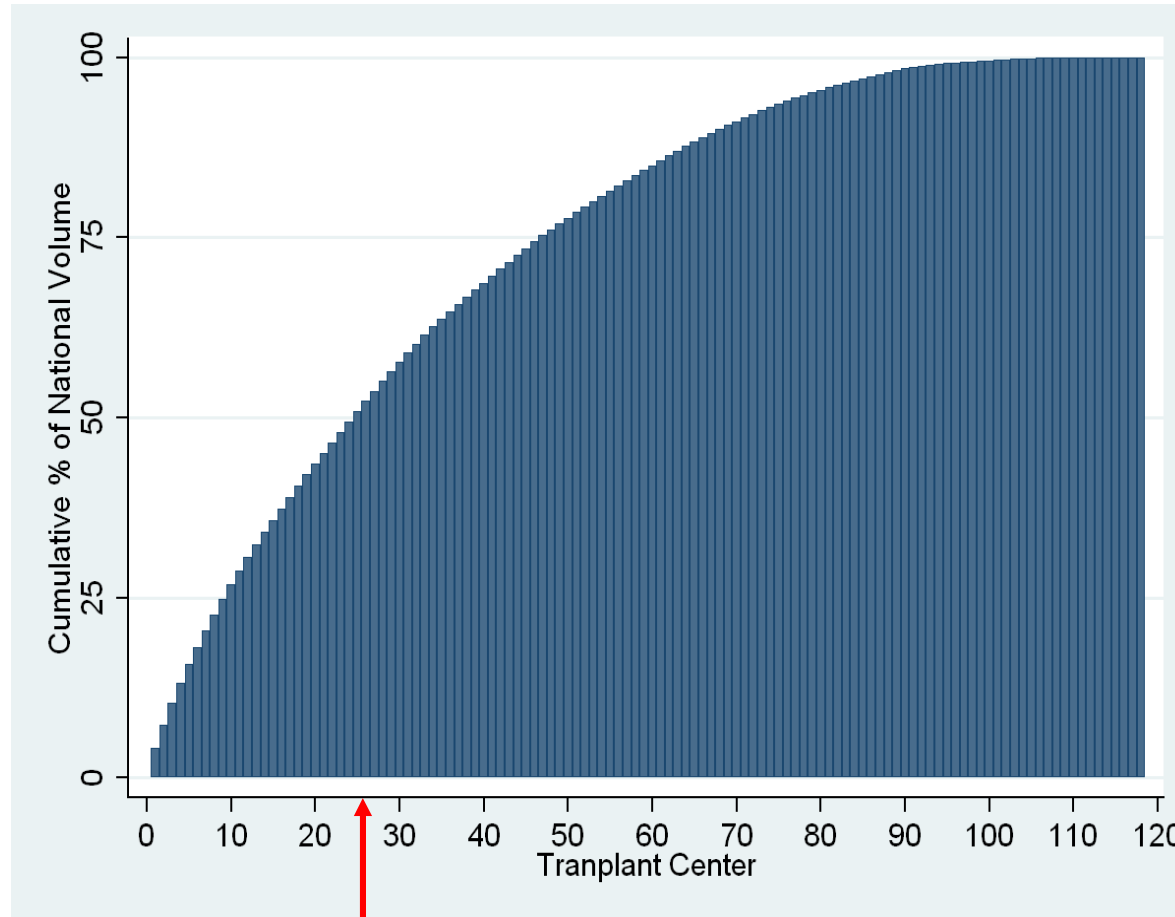
Study Hypotheses

- 1. Single center studies underpowered to detect differences in graft survival or generate stable multivariate models**
- 2. Single center studies confounded by era effects between HTK cohort and historical UW controls**
- 3. Single center studies may not be generalizable due to center-specific effects**

Liver Transplant Demographics

	UW (n=12,673)	HTK (n=4,755)
Transplant Characteristics		
Cold ischemia time (h)	7.6	7.3
Share type - Local (%)	68.4	75.5
Recipient Characteristics		
Age (y)	52.6	52.9
Female (%)	31.8	31.8
Ethnicity - Caucasian (%)	71.6	77.0
Hospitalized (%)	29.7	25.5
On life support (%)	6.6	5.4
Prior transplant (%)	8.0	7.5
Status 1	6.7	4.7
Donor Characteristics		
Age (y)	41.9	41.6
Female (%)	40.4	40.7
Ethnicity - Caucasian (%)	65.1	75.1
Cause of death - ICH (%)	45.3	43.6
Donor after cardiac death (%)	4.5	5.3

Distribution of Liver Transplants by Center

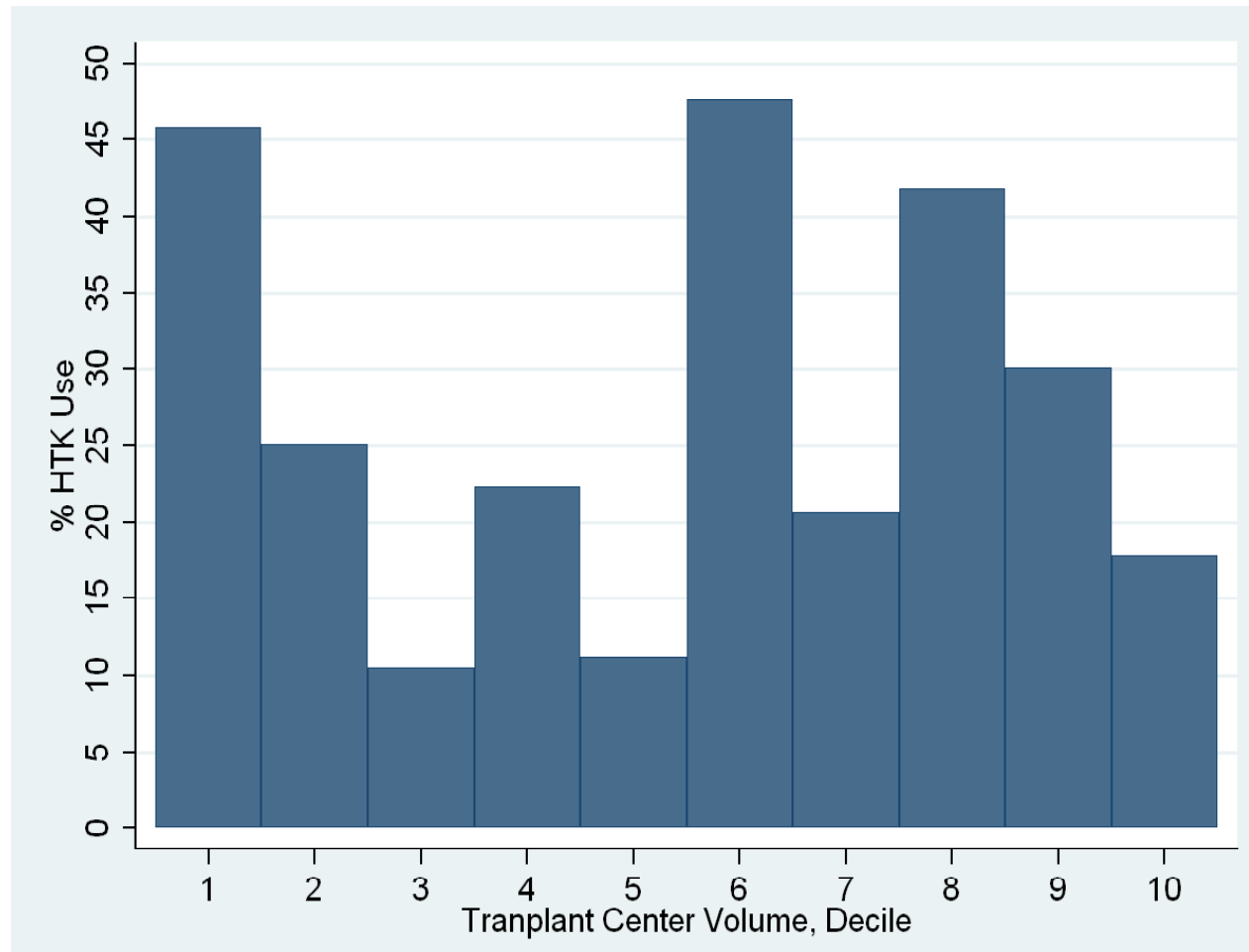


****50% of liver transplants performed by 25 transplant centers**

Evaluation of Center-Specific Effects

- 1. Evaluated distribution of transplants among transplant centers**
- 2. Evaluated the % HTK use as function of transplant center volume**
- 3. Included transplant center volume in multivariate regression models**
- 4. Performed clustered variance estimates to account for correlation of practice patterns by transplant center**

HTK Use in Liver Transplant is Not Impacted by Center Volume



Multivariate Model for Graft Loss

Risk factors for graft loss determined with Cox proportional hazards models adjusted for:

Recipient: age, gender, ethnicity, primary diagnosis, BMI, albumin, diabetes, encephalopathy, hypertension, hospitalized, on life support, prior transplant, prior abdominal surgery, Status 1

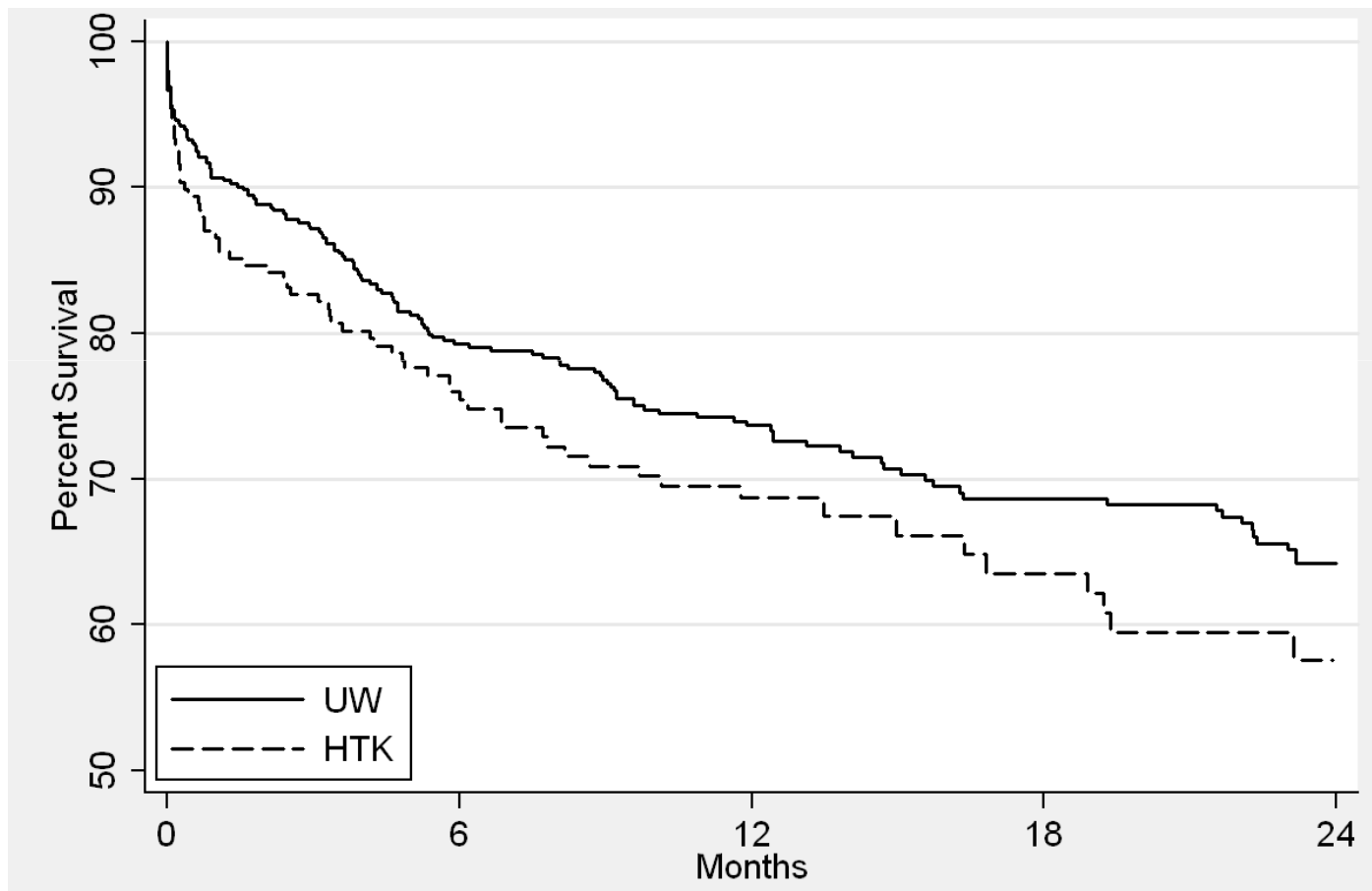
Donor: age, gender, ethnicity, BMI, creatinine, diabetes, hypertension, cause of death

Graft: cold ischemia time, donation after cardiac death

HTK Preservation is a Risk Factor for Graft Loss after Liver Transplantation

	Multivariate - Patient and Center Level*	
	HR (95% CI)	p-value
All deceased donor transplants (n=4,755 HTK and 12,673 UW)	1.13 (1.03-1.24)	0.007
Donor after cardiac death (n=254 HTK and 575 UW)	1.39 (1.07-1.81)	0.013

Kaplan-Meier Graft Survival Curves for DCD Liver Transplants



HTK Increases Risk of Early (< 30 days) Graft Loss after Liver Transplantation

	Multivariate - Patient and Center Level**	
	OR (95% CI)	p-value
All deceased donor transplants (n=4,755 HTK and 12,673, UW)	1.19 (1.02-1.40)	0.031
Cold ischemia time \geq 8 h (n=1,491 HTK and 4,345 UW)	1.31 (1.08-1.60)	0.007
Cold ischemia time < 8 h (n=2,540 HTK and 6,428 UW)	1.13 (0.91-1.33)	0.3
Donor after cardiac death (n=254 HTK and 575 UW)	1.63 (0.93-2.91)	0.09
Donors Age \geq 70 years (n=225 for HTK and 739 for UW)	1.67 (0.94-2.96)	0.081

**Does preservation solution impact
liver allograft survival?**

YES!

Does preservation solution impact liver allograft survival?

- HTK use associated with significant reduction in graft survival
- Effect more pronounced for “less ideal” grafts: DCD, CIT > 8 hours, age > 70 years
- HTK use results in increased risk of early graft loss

Does preservation solution impact pancreas allograft survival?

Key Previous Studies - Pancreas

Englesbe, et al (2006) *Transplantation* 82: 136-9 (Mich)

Multicenter (4) analysis 36 HTK-preserved compared to 41 historical UW-preserved pancreas transplants

****90 day graft survival 86% HTK versus 90% UW**

****HTK >> UW acute rejection (30.5% vs. 12.2%)**

Key Previous Studies - Pancreas

Alonso, et al (2008) *Am J Transplant* 8: 1942-5

81 historical UW-preserved and 16 HTK-preserved pancreas transplants

- * 3 yr graft survival 70% HTK versus 90% UW
- * HTK >> UW graft thrombosis (19% vs. 4%)
- * HTK >> UW graft pancreatitis (56% vs. 23%)
- * UW for 25 subsequent pancreas transplants resulted in no further graft thromboses and 100% graft survival at 1 year

Does preservation solution impact pancreas allograft survival?

- HTK use associated with significant reduction in graft survival for pancreas grafts (N=4392; HR 1.30, p=0.014)
- Effect more pronounced for “less ideal” grafts: CIT > 12 hours (HR 1.42, p=0.017)
- HTK use results in increased risk of early graft loss (OR 1.54, p=0.008)

Does preservation solution impact kidney allograft survival?

Key Previous Studies - Kidney

Roels, et al (1998) *Transplantation* 66: 1660-4 (Belgium)

82 HTK-preserved and 241 UW-preserved kidney transplants

*** CIT > 24h HTK 50% delayed graft function versus UW 23.9%**

*** 1 year graft survival: CIT > 24h = 77% HTK vs. 91% UW
CIT < 24h = 88% HTK vs. 93% UW**

Opelz and Döhler (2007) *Transplantation* 83: 247-53 (Germany)

**9,677 HTK-preserved and 53,560 UW-preserved kidney transplants
from Collaborative Transplant Study project 1990-2005**

*** Relative Risk graft loss 1.42 HTK vs. 1.21 UW**

Key Previous Studies - Kidney

Lynch, et al (2008) *Am J Transplant* 8: 567-73

317 HTK-preserved compared to 317 historical controls of UW-preserved deceased donor kidney transplants

- * No significant difference in graft survival through 4 yrs
- * Increased DGF with HTK

Table 4: Delayed graft function and technical graft failure in renal allografts

Effect	Preservative		p-Value
	UW (n = 317)	HTK (n = 317)	
Deceased donors			
Delayed graft function	17.4%	26.2%	0.005*
Technical graft failure	0%	0.9%	0.249

Does preservation solution impact kidney allograft survival?

- HTK use associated with significant reduction in death-censored graft survival for kidneys (N=21,626; HR 1.20, p=0.008)
- No impact on delayed graft function (OR 0.99, p=0.7)

Potential Mechanisms

- **HTK contains fewer antioxidants**
- **HTK lacks strong oncotic agent which may play a critical role in preventing tissue edema**

****May be particularly critical for liver and pancreas***

Conclusions

**Preservation solution matters in
abdominal transplantation**

**Impact more pronounced with
less “ideal” donor grafts**

