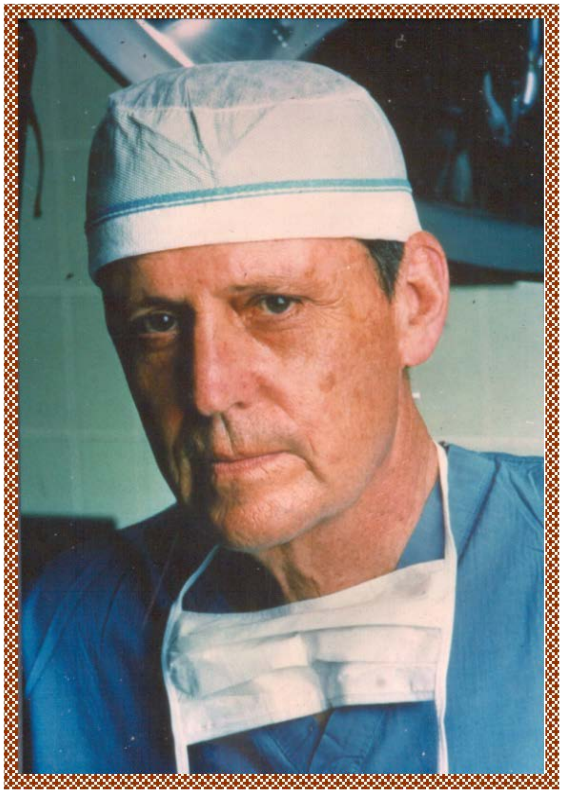
A CRITICAL ANALYSIS OF ORGAN PERFUSION SOLUTIONS IN LIVER TRANSPLANTATION

John J. Fung, MD
Director, Cleveland Clinic Health System Center for Transplantation

Disclosure: I have been a consultant for Dupont, Odyssey and Sangstat
I have been a collaborator with Breonics

Dr. Thomas Starzl (University of Colorado)

“The provision of a viable and minimally damaged homograft is undoubtedly the most important single factor in the determinant of success.”



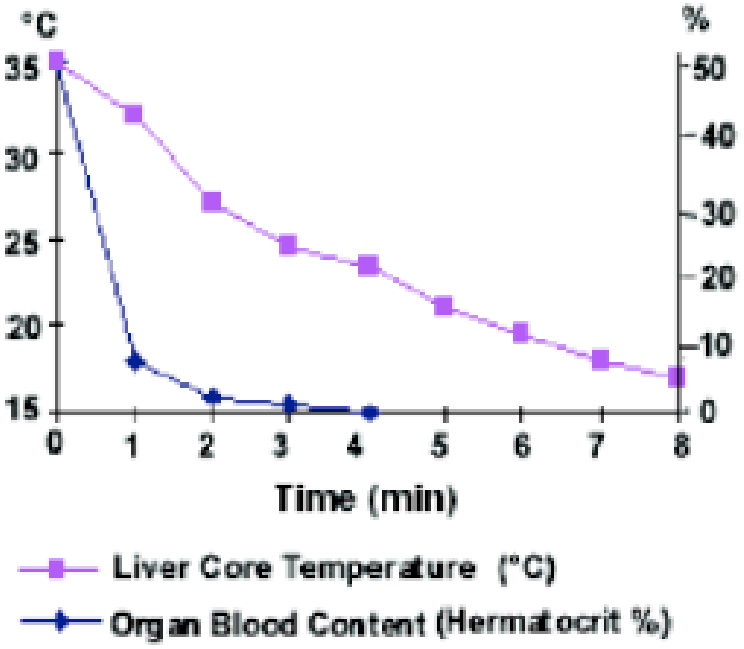
Ischemia-Reperfusion Injury

- Ischemia starts by interrupting blood supply to organs or tissues
- Anaerobic metabolism results in accumulation of end products of metabolism: e.g. protons, lactate, hypoxanthine
- Upon reperfusion, these by-products contribute to the generation of oxygen free radicals, which damage tissues termed ischemia-reperfusion injury (IRI)
- Metabolism is not arrested in cold conditions, but slowed by a factor of 1.5–2 for each 10° C fall in temperature

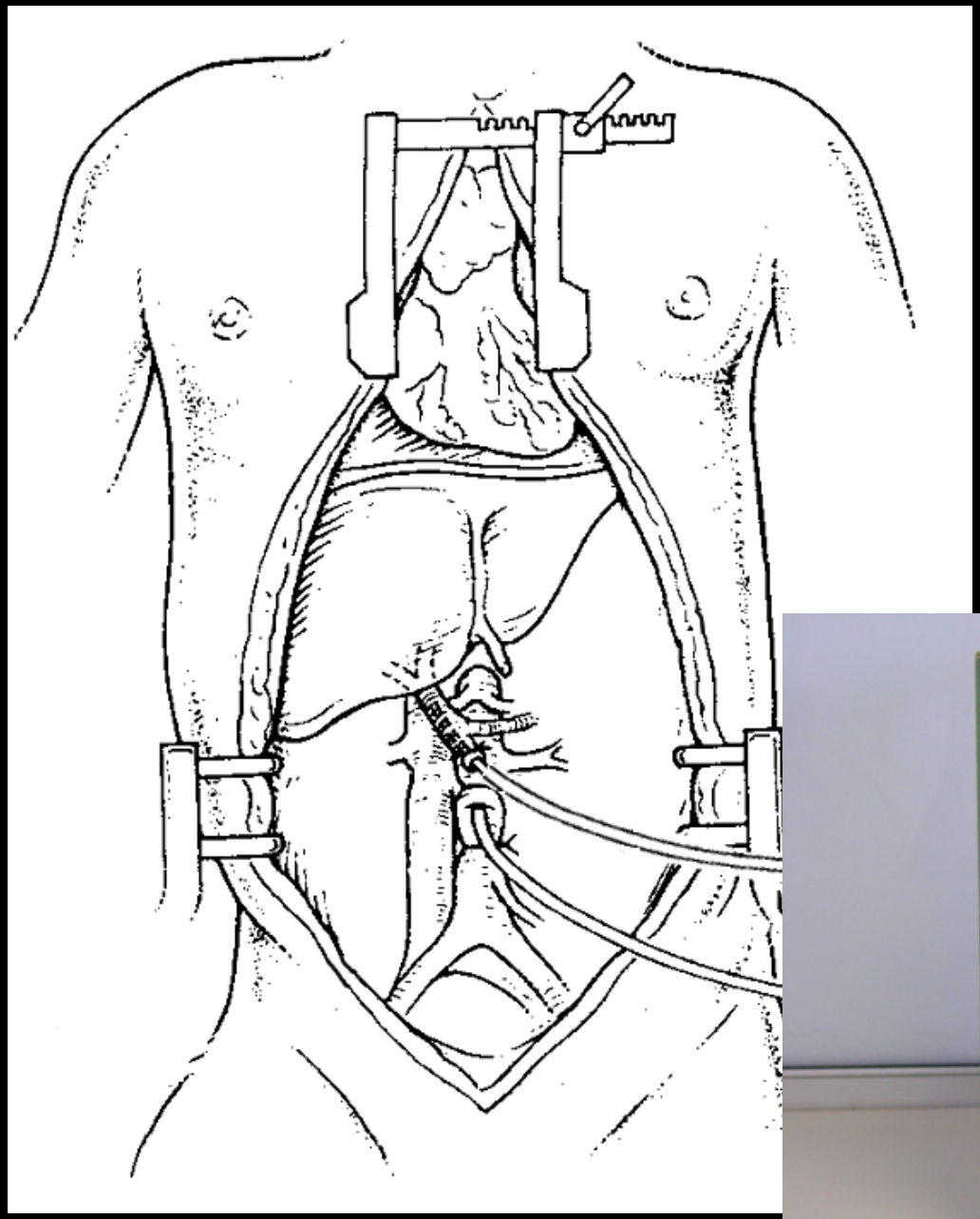
Clinical Impact of IRI

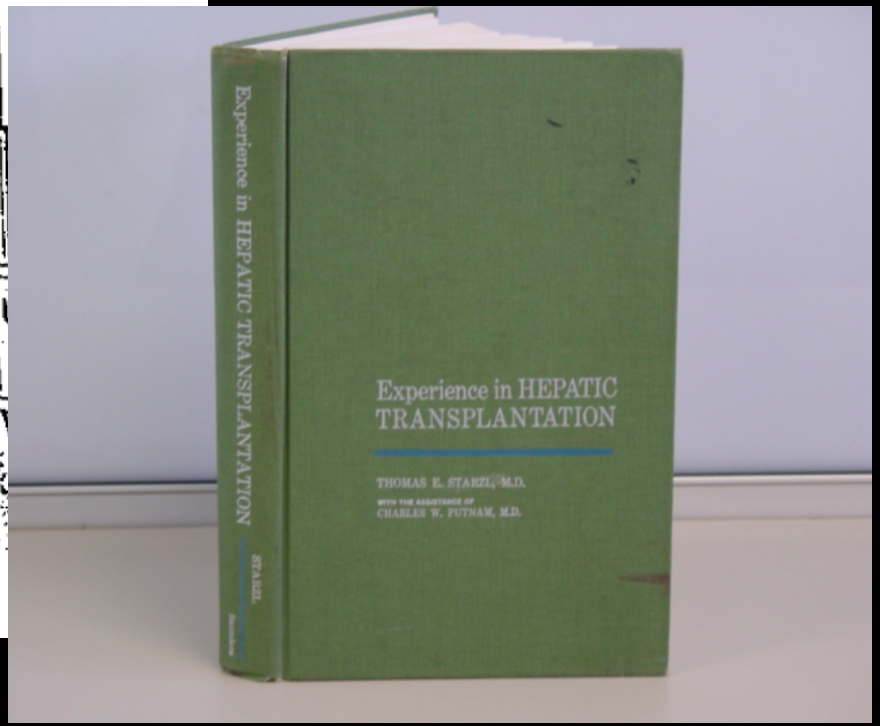
- Problems associated with IRI of allografts:
  - Contributes to morbidity
  - Leads to primary non-function or primary dysfunction
  - Associated with an increase in graft rejection
  - Increases discard of allografts due to outcome concerns

Principles of Current Organ Preservation

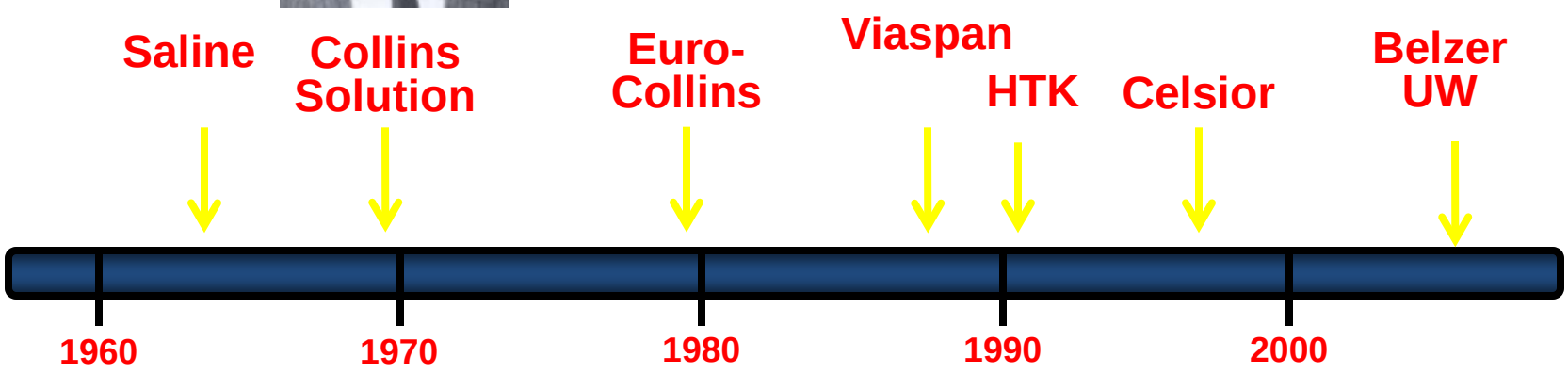


- Exsanguination to reduce intravascular thrombosis
- Hypothermia to reduce cellular metabolism
- Maintain cell membrane integrity to avoid cellular swelling
- Reduce ROS mediated damage after reperfusion
- Susceptibility to cold ischemic injury: vascular endothelium > parenchymal cells




Experience in HEPATIC TRANSPLANTATION
THOMAS E. STARZL, M.D.
WITH THE ASSISTANCE OF
CHARLES W. PUTNAM, M.D.
Experience in HEPATIC TRANSPLANTATION
STARZL

Timeline of Cold Static Organ Preservation



Component	Eurocollins	UW	HTK	Celsior
Sodium (mmol/L)	10	29	15	100
Potassium (mmol/L)	107	125	9	15
Magnesium(mmol/L)	-	5	4	13
Calcium (mmol/L)	-	-	0.015	0.25
Sulfate (mmol/L)	-	5	-	-
Lactobionate (mmol/L)	-	100	-	80
Phosphate (mmol/L)	57	25	-	-
Raffinose (mmol/L)	-	30	-	-
Adenosine (mmol/L)	-	5	-	-
Glutathione (mmol/L)	-	3	-	3
Allopurinol (mmol/L)	-	1	-	-
Ketoglutarate (mmol/L)	-	-	1	20
Histidine (mmol/L)	-	-	198	30
Starch (gm/L)	-	50	-	-
Mannitol (mmol/L)	-	-	30	60
Glucose (mmol/L)	194	-	-	-
Tryptophan (mmol/L)	-	-	2	-
Osmolalrity (mOsm/L)	355	320	310	320

Euro-Collins Solution

High potassium, glucose, and phosphate-based solution

Designed to mimic composition of intracellular fluid

Low cost

Poor preservation quality

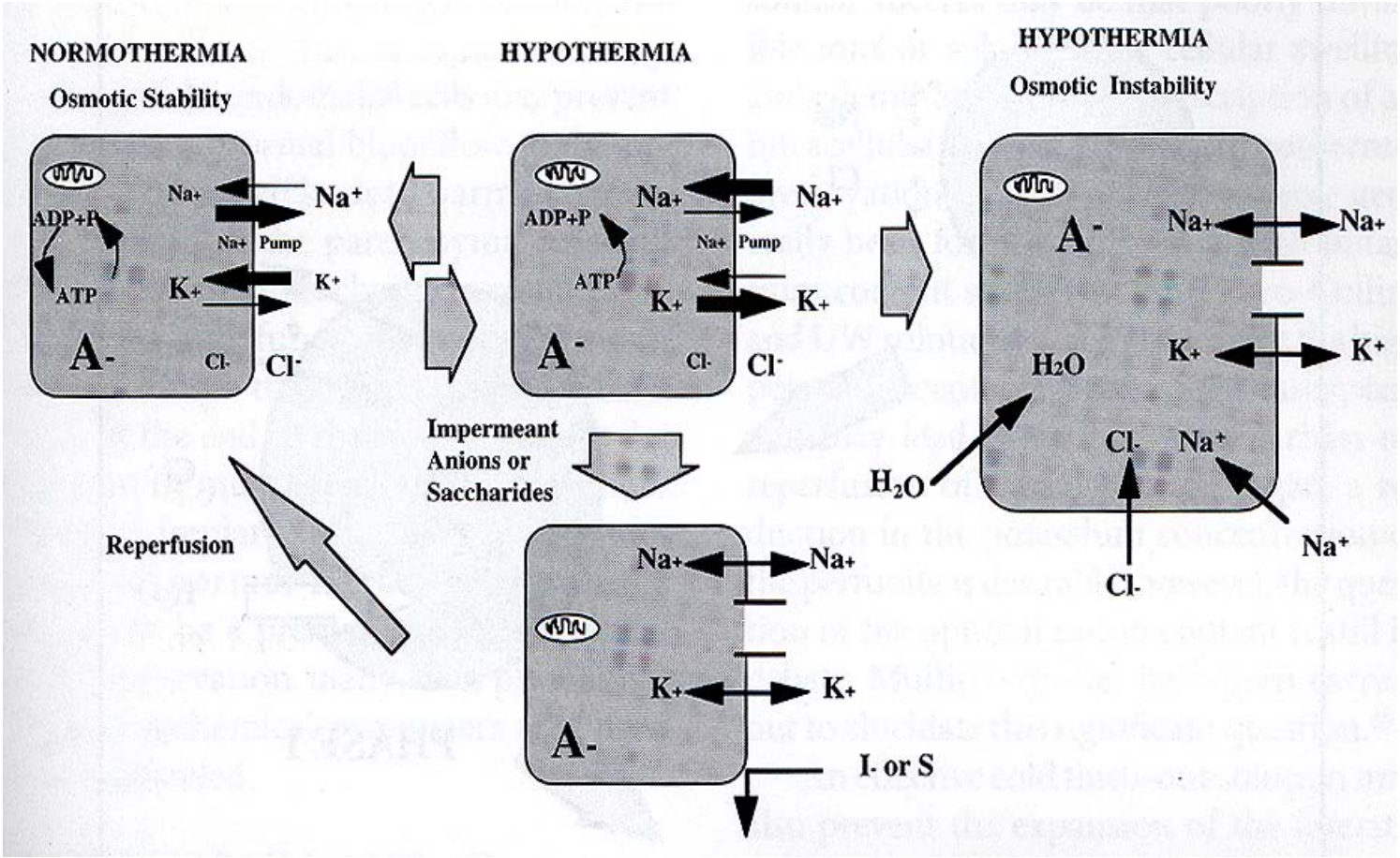
Short preservation times achievable

1987

Belzer develops a new preservation solution which revolutionizes organ storage and permits long distance shipping of organs for transplantation

UW Solution

- **Use of impermeant molecules, lactobionate and raffinose, in preventing cell swelling**
- **First developed for and applied in preservation of canine pancreas**
- **Hydroxyethyl starch to minimize interstitial edema during machine perfusion, not necessary during cold storage**
- **High [K^+], low [Na^+]**



Southard and Belzer

SUMMARY OF SAFETY AND EFFICACY SUBMITTED IN 1988 TO SUPPORT ORIGINAL 510(k) FILING

Introduction

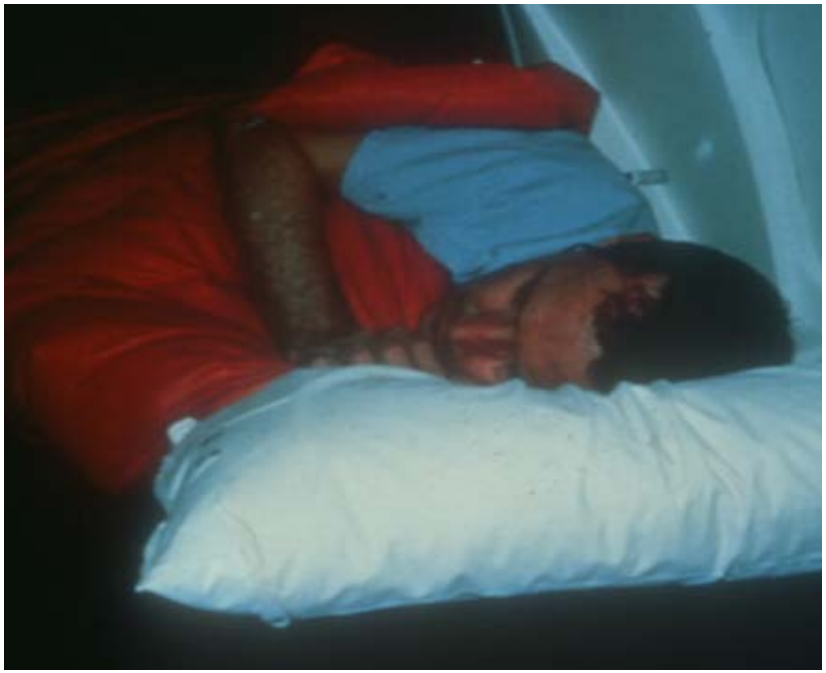
The Belzer UW Cold Storage Solution preserves organs, by cold storage, just as well as currently marketed media, such as Collins' solution. Belzer UW Cold Storage Solution, hereafter known as BELZER UW-CSS, can be used for cold storage of the liver, pancreas, and kidney. BELZER UW-CSS has the potential to be used as a general solution for most organs, both for initial cooling during in situ donor organ flushing and for subsequent cold storage. Use of BELZER UW-CSS could transform liver and pancreas transplantation from emergency operations to semi-elective procedures.

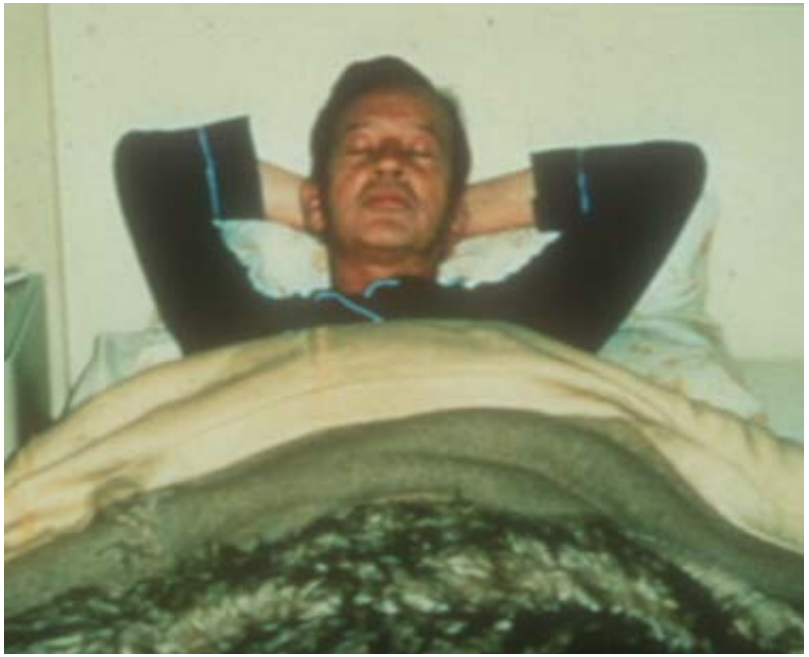
Summary

Results from clinical trials demonstrate the ability of this solution to safely preserve kidney, liver, and pancreas prior to transplantation. Furthermore, this solution extends the preservation time for all of these organs compared with the duration of organ preservation deemed safe and effective with Collins' solution. This should increase the supply of much needed and valuable donor organs by reducing organ wastage.

Thus, this solution is both safe and substantially equivalent to Collins' and EuroCollins solutions.

Beware of Claims





Starzl - Urgent

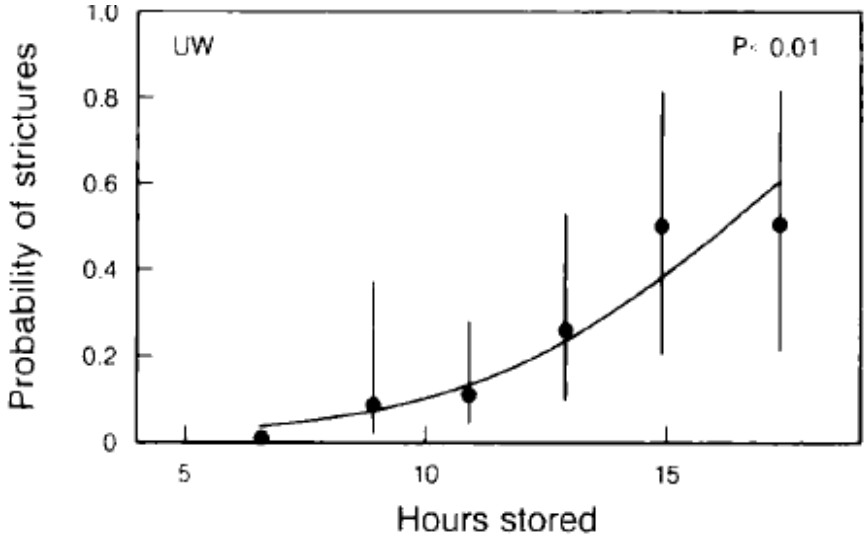
Belzer – Semi-Elective

Ischemic-type Biliary Complications after Orthotopic Liver Transplantation

(HEPATOLOGY 1992;16:49-53.)

LUIS SANCHEZ-URDAZPAL,[1] GREGORY J. GORES,[2] ELLEN M. WARD,[3] TIMOTHY P. MAUS,[3] H. ERIK WAHLSTROM,[1] S. BREANNDAN MOORE,[4] RUSSELL H. WIESNER[2] AND RUUD A.F. KROM[1]

Recently, a new type of biliary complication has been identified after OLT. These complications represent bile duct strictures and dilatations involving only the biliary tree of the graft; they are nonanastomotic, they can be multiple or single and they can occasionally cause intrahepatic bile leakage (Fig. 1). Unlike other types of biliary complications that are usually seen in the weeks immediately after OLT, strictures and dilatations of the biliary tree of the graft are most often diagnosed later in the postoperative course, usually between 1 and 3 mo after transplantation.

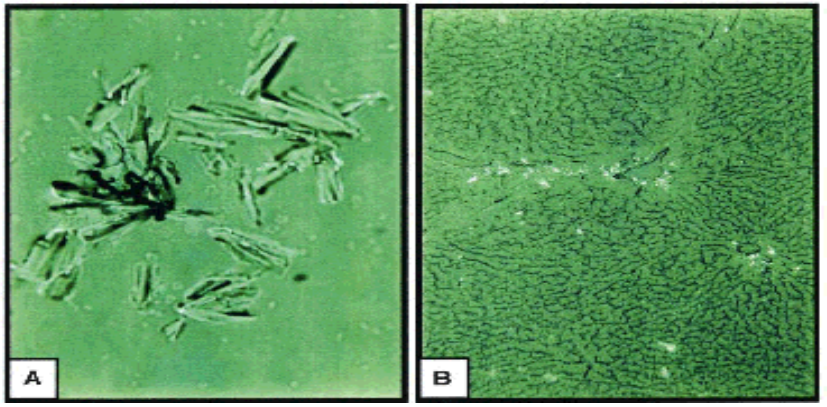


Because the use of UW solution has allowed liver grafts to be preserved twice as long as previously possible with Euro-Collins solution, OLT has become a semielective procedure.

However, later in the postoperative course, an alarmingly high incidence of ITBCs was observed.

UW Solution: Disadvantages

- **High viscosity**
- **Solution cannot be released into circulation (high K content)**
- **Particles ~ 100 µm in diameter contained in stored solution: must use in-line filtration with 40 µm pore size. Particles caught in capillary bed of perfused organ, resulting in vascular constriction, impeded reperfusion, and reduction of functional recovery**

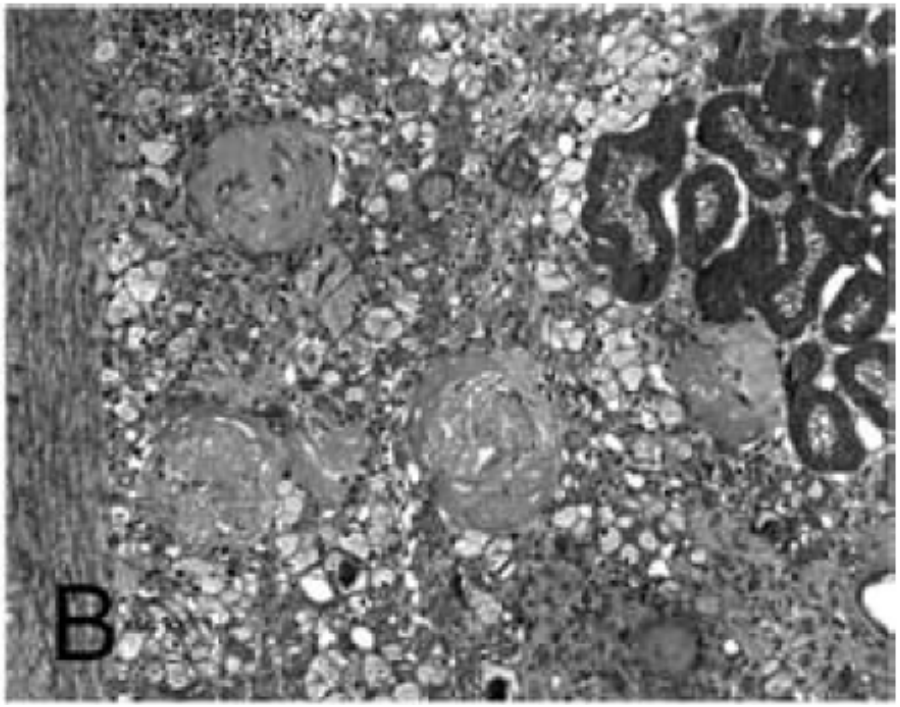


Tullius et al: *AJT* **2**:627

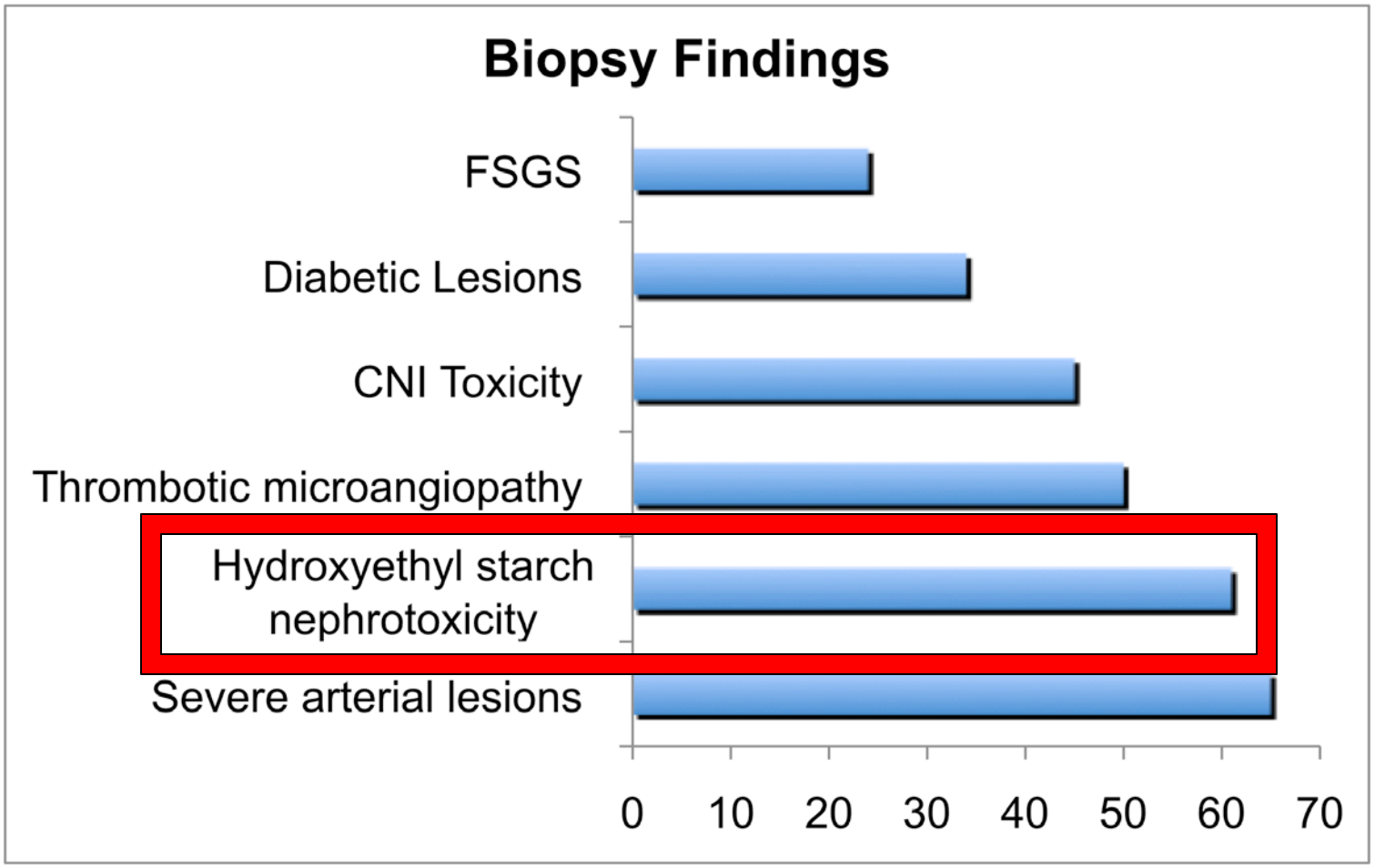
American Journal of Transplantation 2005; 5: 1120–1129
Blackwell Munksgaard

Evangeline Pillebout[a,*], Dominique Nochy[b], Gary Hill[b], Filomena Conti[c], Corinne Antoine[a], Yvon Calmus[a] and Denis Glotz[a]

Renal Histopathological Lesions After Orthotopic Liver Transplantation (OLT)



(B) Chronic hydroxyethylstarch nephotoxicity and focal cortical atrophy (FCA). Biopsy from a patient showing an area of focal cortical atrophy in the superficial cortex. This is associated with lesions related to the infusion of Elhoes®, with an infiltration of the tubules and interstitium by cells with micovacuolated cytoplasm and shrunken nuclei, and tubules with osmotic-nephrosis-like lesions. Masson trichrome, ×200. (C)


Biopsy Findings
FSGS
Diabetic Lesions
CNI Toxicity
Thrombotic microangiopathy
Hydroxyethyl starch nephrotoxicity
Severe arterial lesions
0
10
20
30
40
50
60
70

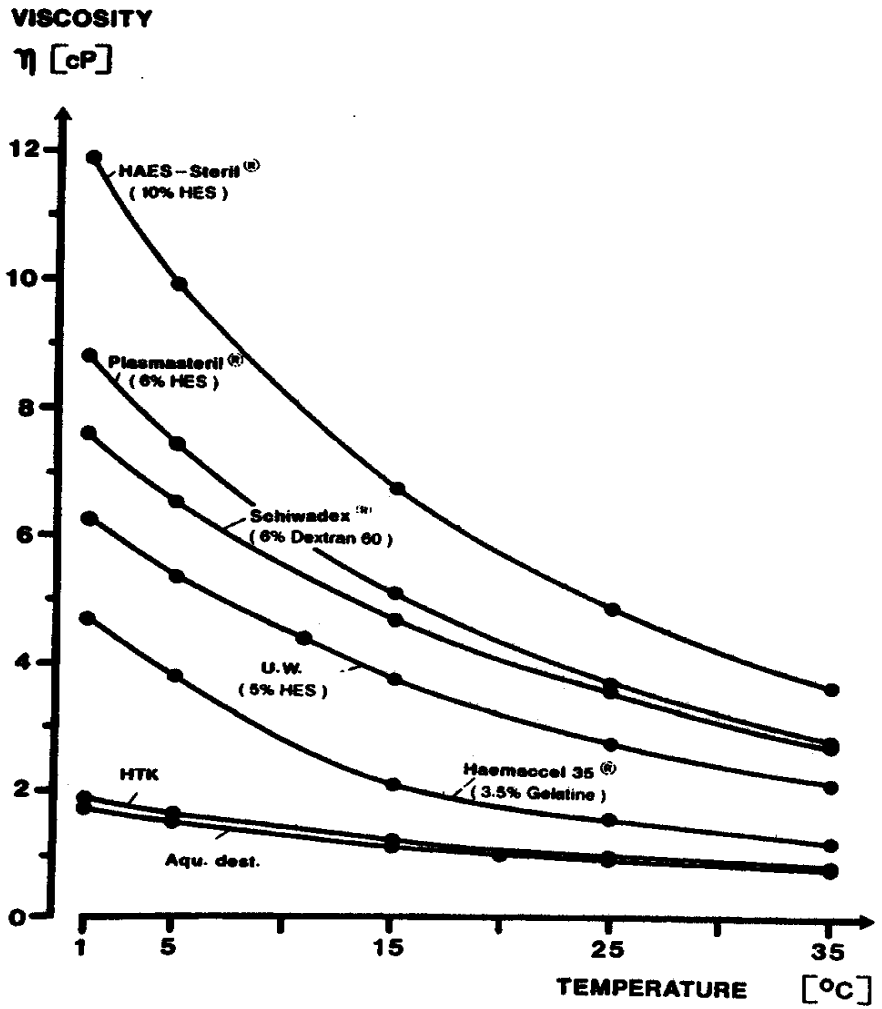


Fig. 7: Viscosity of solutions in medical use as compared to water depending on the respective solution temperature (10 cP ≡ I Pa - s)

M.M. Gebhard, H.J. Kirlum, C. Schlegel. Organ preservation with the solution HTK

HTK Solution (Custodiol)

- **Developed as cardioplegia**
- **Low potassium**
- **High buffering capacity of histidine**
- **No colloid - viscosity equal to that of pure water from 1 to 35^0C, with mean flow rate 3X that of UW solution at equal perfusion pressure - organs exsanguinate and cool down to lower temperatures more rapidly than with UW**

510(k) Summary

Custodiol® HTK Solution

Common/Classification Name: Isolated Kidney Perfusion and Transport System and Accessories, 21 CFR 876.5880

Dr. Franz Köhler Chemie GmbH
Postfach 1117
D-64659 Alsbach-Hähnlein
Germany

A. LEGALLY MARKETED PREDICATE DEVICES

For its indication for use, the **Custodiol HTK Solution** is substantially equivalent to the Belzer UW Cold Storage Solution, which was cleared by FDA as K944866 on 04 April 1996 for the multiple indication of kidney, liver, and pancreas preservation. For its specific formulation and other physical and chemical characteristics, it is substantially equivalent to the currently marketed **Custodiol** product as cleared under K992209 and K020924.

Celsior Solution

- **Crystalloid solution**
- **Low potassium**
- **Utilizes buffering capacity of histidine**
- **Use of impermeant molecules, lactobionate and raffinose, in preventing cell swelling**

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

AUG - 5 1999

Mark D. Tolpin, M.D
Senior Vice President
Worldwide Clinical Research
and Regulatory Affairs
SangStat Medical Corporation
1505 Adams Drive
Menlo Park, CA 94025

Re: K991594.
Celsior™ Cold Flush, Storage and
Transport Solution for Hearts
Dated: May 6, 1999
Received: May 7, 1999
Regulatory Class: II
21 CFR §876.5880/Procode: 78 MSB

Dear Dr. Tolpin:

We have reviewed your Section 510(k) notification of intent to market the device referenced above and we have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

Retrospective Database Reviews

Histidine-Tryptophan-Ketoglutarate (HTK) Is Associated with Reduced Graft Survival of Deceased Donor Kidney Transplants

American Journal of Transplantation 2009; 9: 1–7

Histidine-Tryptophan-Ketoglutarate (HTK) Is Associated with Reduced Graft Survival in Pancreas Transplantation

American Journal of Transplantation 2009; 9: 217–221

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

Table 2: Risk factors for graft loss after adult deceased donor liver transplantation—all donors

	HR (95% CI)	p-Value
A. Transplant characteristics		
HTK preservation	**1.14 (1.05–1.23)**	0.002
Cold ischemia time $\geq = 8$ h	1.20 (1.12–1.29)	<0.001
B. Recipient characteristics		
Age (year)		
18–34	1.14 (0.96–1.35)	*
35–49	Reference	
50–64	1.18 (1.09–1.29)	<0.001
>=65	1.49 (1.32–1.69)	<0.001
Gender (female)	1.01 (0.93–1.09)	*
Ethnicity		
Caucasian	Reference	
African American	1.26 (1.13–1.41)	<0.001
Hispanic	0.88 (0.79–0.99)	0.03
Asian	0.85 (0.70–1.04)	*
Other	1.39 (1.02–1.91)	0.039
Diagnosis		
Hepatitis C	1.22 (1.10–1.36)	<0.001
Alcoholic cirrhosis	0.88 (0.76–1.01)	*
PBC	0.90 (0.72–1.13)	*
PSC	0.85 (0.69–1.04)	*
HCC	1.32 (1.16–1.50)	<0.001
Autoimmune hepatitis	0.91 (0.71–1.15)	*
Idiopathic	1.00 (0.85–1.17)	*
BMI >35	1.16 (1.05–1.29)	0.004
MELD	1.02 (1.01–1.02)	<0.001
Hospitalized	1.24 (1.13–1.36)	<0.001
On life support	1.73 (1.51–1.98)	<0.001

Retrospective Database Reviews

American Journal of Transplantation 2015; 15: 395–406
Wiley Periodicals Inc.

doi: 10.1111/ajt.13060

Compared Efficacy of Preservation Solutions in Liver Transplantation: A Long-Term Graft Outcome Study From the European Liver Transplant Registry

R. Adam[1,*], V. Delvart[1], V. Karam[1], C. Ducerf[2], F. Navarro[3], C. Letoublon[4], J. Belghiti[5], D. Pezet[6], D. Castaing[1], Y. P. Le Treut[7], J. Gugenheim[8], P. Bachellier[9], J. Pirenne[10], P. Muiesan[11] and all the ELTR contributing centres, the European Liver, Intestine Transplant Association (ELITA)

Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

Table 4: Multivariate analysis of risk factors for graft loss in the global cohort. Center stratified Cox regression analysis

Risk factors	p	RR	CI 95%
1. Recipient HIV (+)	<0.0001	1.50	[1.29; 1.75]
2. Donor age ≥65 years	<0.0001	1.41	[1.32; 1.51]
3. Recipient anti HCV (+)	<0.0001	1.40	[1.34; 1.47]
4. Main disease: ACHF	<0.0001	1.34	[1.22; 1.47]
5. Partial liver graft	<0.0001	1.30	[1.16; 1.44]
6. Recipient age ≥60 years	<0.0001	1.29	[1.23; 1.37]
7. Non-ABO isogroup	<0.0001	1.24	[1.14; 1.34]
8. Recipient HBsAg (−)	<0.0001	1.24	[1.15; 1.33]
9. Ischemia time ≥12 h	<0.0001	1.19	[1.11; 1.27]
10. Recipient male	<0.0001	1.10	[1.05; 1.15]
11. HTK	0.02	1.10	[1.01; 1.20]
12. Main disease: not cirrhosis	0.01	1.09	[1.04; 1.15]

RR, risk ratio; CI, confidence interval; ACHF, acute hepatic failure. Cox model with 34 520 observations.

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2. Donor age ≥65 years	<0.0001	1.41	[1.32; 1.51]
3. Recipient anti HCV (+)	<0.0001	1.40	[1.34; 1.47]
4. Main disease: ACHF	<0.0001	1.34	[1.22; 1.47]
5. Partial liver graft	<0.0001	1.30	[1.16; 1.44]
6. Recipient age ≥60 years	<0.0001	1.29	[1.23; 1.37]
7. Non-ABO isogroup	<0.0001	1.24	[1.14; 1.34]
8. Recipient HBsAg (–)	<0.0001	1.24	[1.15; 1.33]
9. Ischemia time ≥12 h	<0.0001	1.19	[1.11; 1.27]
10. Recipient male	<0.0001	1.10	[1.05; 1.15]
11. HTK	0.02	1.10	[1.01; 1.20]
12. Main disease: not cirrhosis	0.01	1.09	[1.04; 1.15]

RR, risk ratio; CI, confidence interval; ACHF, acute hepatic failure. Cox model with 34 520 observations.

Table 2: Risk factors for graft loss after adult deceased donor liver transplantation—all donors

	HR (95% CI)	p-Value
A. Transplant characteristics		
HTK preservation	**1.14 (1.05–1.23)**	0.002
Cold ischemia time ≥ = 8 h	1.20 (1.12–1.29)	<0.001
B. Recipient characteristics		
Age (year)		
18–34	1.14 (0.96–1.35)	*
35–49	Reference	
50–64	1.18 (1.09–1.29)	<0.001
>=65	1.49 (1.32–1.69)	<0.001
Gender (female)	1.01 (0.93–1.09)	*
Ethnicity		
Caucasian	Reference	
African American	1.26 (1.13–1.41)	<0.001
Hispanic	0.88 (0.79–0.99)	0.03
Asian	0.85 (0.70–1.04)	*
Other	1.39 (1.02–1.91)	0.039
Diagnosis		
Hepatitis C	1.22 (1.10–1.36)	<0.001
Alcoholic cirrhosis	0.88 (0.76–1.01)	*
PBC	0.90 (0.72–1.13)	*
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HCC	1.32 (1.16–1.50)	<0.001
Autoimmune hepatitis	0.91 (0.71–1.15)	*
Idiopathic	1.00 (0.85–1.17)	*
BMI >35	1.16 (1.05–1.29)	0.004
MELD	1.02 (1.01–1.02)	<0.001
Hospitalized	1.24 (1.13–1.36)	<0.001
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Table 4: Multivariate analysis of risk factors for graft loss in the global cohort. Center stratified Cox regression analysis

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This study has some limitations. It is retrospective and nonexhaustive of all the data concerning particularly the early posttransplant course. The different groups presented some differences concerning donors, recipients, indications or details of the operative procedure. However, the large multicentric cohort of patients prospectively collected through the ELTR, allowed a multivariate as well as different subgroup analyses, converging in a robust evaluation of the influence of preservation solutions on graft outcome.

LIVER TRANSPLANTATION 18:113-120, 2012

ORIGINAL ARTICLE

Validation of the Donor Risk Index in Orthotopic Liver Transplantation Within the Eurotransplant Region

Joris J. Blok,[1*] Andries E. Braat,[1*] Rene Adam,[3] Andrew K. Burroughs,[4] Hein Putter,[2] Nigel G. Kooreman,[1] Axel O. Rahmel,[5] Robert J. Porte,[6] Xavier Rogiers,[7] and Jan Ringers[1] for the European Liver Intestine Transplant Association and the Eurotransplant Liver Intestine Advisory Committee

1) Preservation solution use is not random –
   a) UK (Marshall/UW)
   b) France (IGL-1)
   c) Germany (HTK)
2) Prioritization, allocation and transplant practices varied

Reichert *et al. Journal of Negative Results in BioMedicine* 2013, **12**:18
http://www.jnrbm.com/content/12/1/18

RESEARCH Open Access

Prognostic limitations of the Eurotransplant-donor risk index in liver transplantation

Benedikt Reichert[1,2†], Alexander Kaltenborn[1,3*†], Alon Goldis[4] and Harald Schrem[1]

Endpoint				ET-DRI cut off values			
	AUROC	95%-CI	Logistic regression p-value		Sensitivity	Specificity	Overall correctness
3-month mortality	0.477	0.390-0.564	p = 0.692	2.06	26.7%	81.4%	54%
1-year mortality	0.492	0.405-0.579	p = 0.573	2.06	26.7%	81.4%	54%
3-month graft survival	0.524	0.477-0.601	p = 0.475	1.95	38%	74.5%	56.3%
1-year graft survival	0.540	0.473-0.607	p = 0.475	1.84	47.4%	63.6%	55.5%

AUROC = area under the receiver operating characteristic curve; 95%-CI = 95%-Confidence Interval

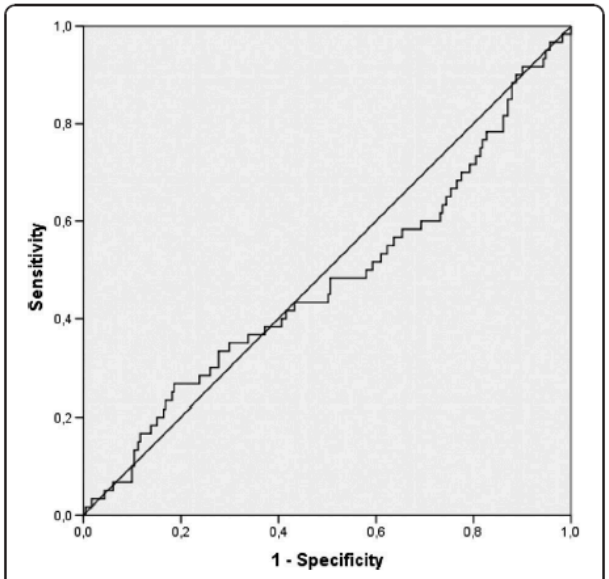
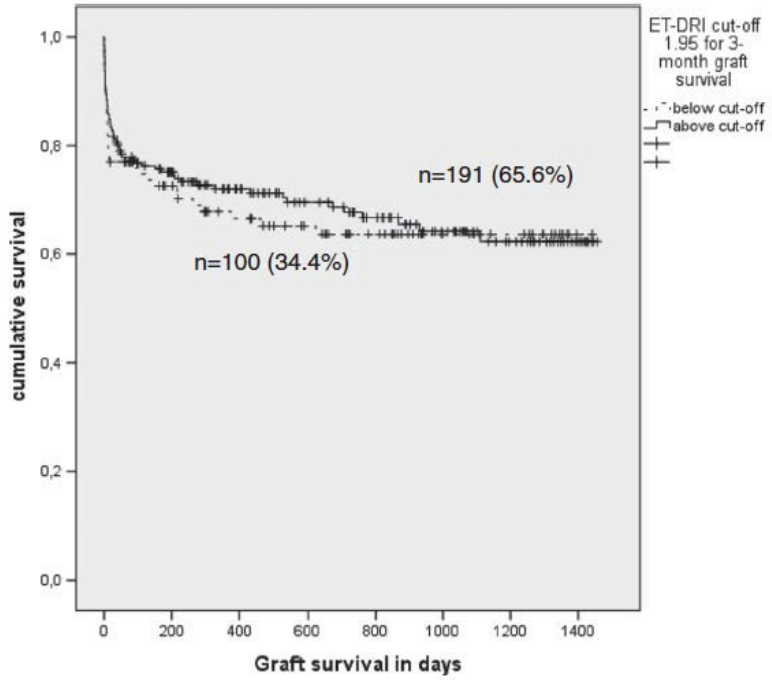


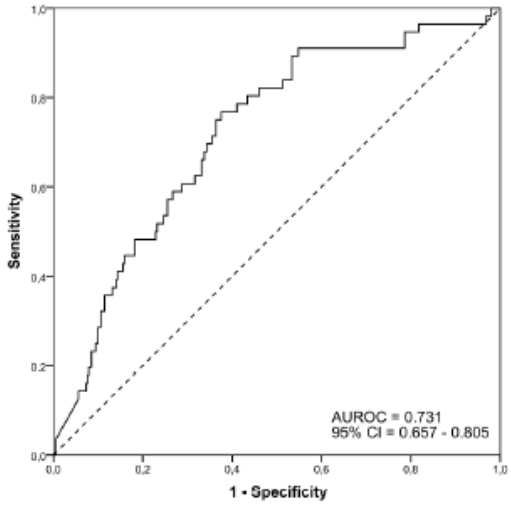
Figure 1 Shown is the ROC-Curve for the prediction of 3-month mortality after liver transplantation with the ET-DRI (AUROC = 0.477; 95%CI: 0.390-0.564).

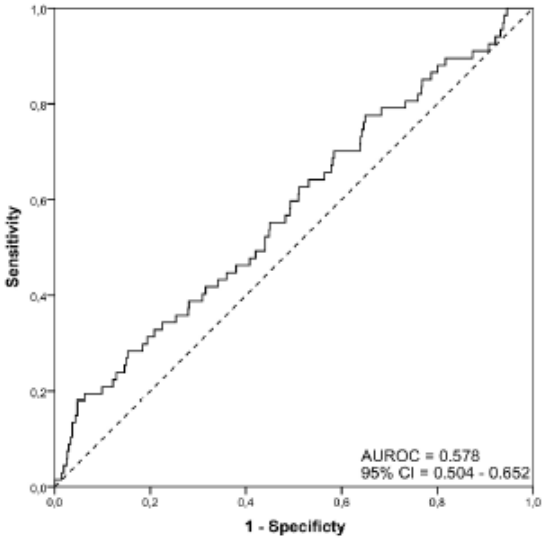


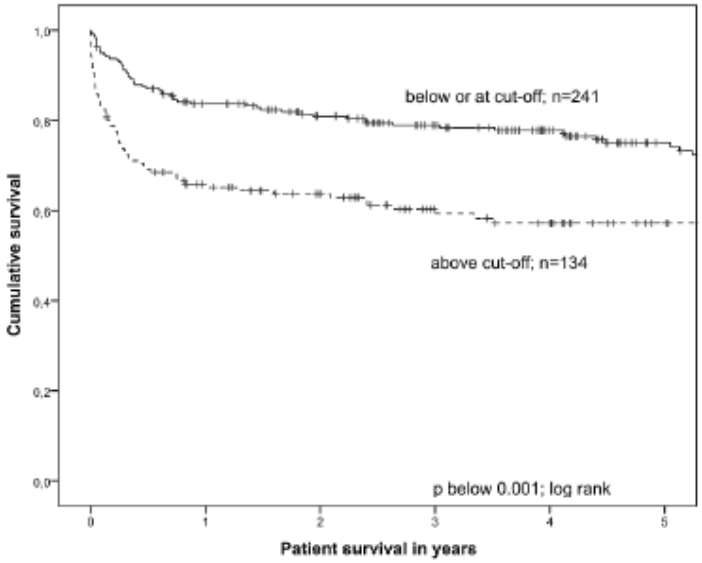
The New Liver Allocation Score (LivAS) for Transplantation is Validated in Germany but Not in the UK Due to Different Selection and Survival Benefits

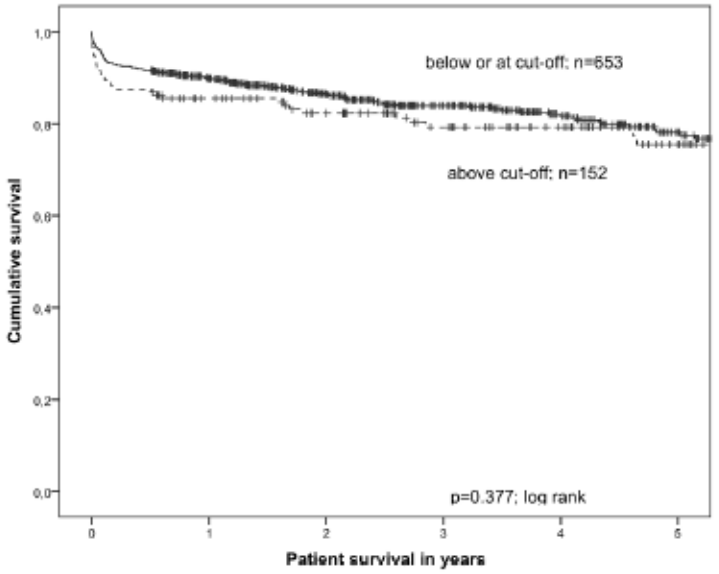
Harald Schrem [1, 2] *, Moritz Focken [1, *], Bridget Gunson [3, 4], Benedikt Reichert [5], Darius Mirza [3], Hans-Heinrich Kreipe [6], Desley Neil [7], Alexander Kaltenborn [1, 8], Alon Goldis [9], Christian Krauth [10], Keith Roberts [3], Thomas Becker [5], Jürgen Klempnauer [2], James Neuberger [3, 11]

	Variables	Germany (Kiel and Hannover)	England (Birmingham)
Donor data	Donor ICU stay in days	p=0.498	p=0.635
	Donor ICU stay > 11.5 days	p=0.031 OR: 1.564, 95%-CI: 1.042-2.348	p=0.233
	Donor sodium in mmol/l	p=0.669	p=0.908
	Donor Sodium > 160 mmol/l	p=0.009 OR: 1.564, 95%-CI: 1.042-2.348	p=0.227
	Donor liver biopsy prior to TX	p=0.029 OR: 1.654, 95%-CI: 1.052-2.601	p=0.091
	Donor liver macrosteatosis in % *	p<0.001 OR: 1.053, 95%-CI: 1.034-1.072	p=0.148
	DCD donor	n.a.	p=0.290
	Donor LivAS component	p<0.001 OR: 2.130, 95%-CI: 1.681-2.699	p=0.910
Recipient data	Age at transplant in years	p=0.004 OR: 1.023, 95%-CI: 1.007-1.039	p=0.407
	Creatinine in µmol/l	p<0.001 OR: 1.003, 95%-CI: 1.002-1.005	p=0.926
	Creatinine below 45 µmol/l	p=0.521	p=0.998
	Creatinine > 80 µmol/l	p<0.001 OR: 2.573, 95%-CI: 1.748-3.787	p=0.667
	Creatinine > 160 µmol/l	p<0.001 OR: 2.685, 95%-CI: 1.756-4.106	p=0.998
	Creatinine > 240 µmol/l	p=0.150	p=0.586
	Creatinine in normal range	p<0.001 OR: 0.485, 95%-CI: 0.335-0.701	p=0.271
	Platelets in tsd/µl	p<0.001 OR: 0.995, 95%-CI: 0.992-0.997	p=0.414
	Hemoglobin in g/dl	p<0.001 OR: 0.836, 95%-CI: 0.762-0.916	p=0.373
	Retransplantion due to PNF	p<0.001 OR: 3.915, 95%-CI: 2.096-7.313	p=0.292
	Artificial ventilation pre TX	p<0.001 OR: 2.951, 95%-CI: 1.922-4.532	p<0.001 OR: 3.381, 95%-CI: 1.852-6.175
	Portal vein thrombosis at Tx	p=0.032 OR: 1.726, 95%-CI: 1.049-2.841	p=0.032 OR: 3.047, 95%-CI: 1.101-8.430
	Recipient LivAS component	p<0.001 OR: 2.163, 95%-CI: 1.754-2.668	p=0.001 OR: 1.820, 95%-CI: 1.267-2.612
	LivAS	**p<0.001 OR: 2.435, 95%-CI: 1.994-2.974**	**p=0.004 OR: 1.655, 95%-CI: 1.174-2.334**


Sensitivity
1 - Specificity
AUROC = 0.731
95% CI = 0.657 - 0.805


Sensitivity
1 - Specificty
AUROC = 0.578
95% CI = 0.504 - 0.652


Cumulative survival
Patient survival in years
below or at cut-off; n=241
above cut-off; n=134
p below 0.001; log rank


Cumulative survival
Patient survival in years
below or at cut-off; n=653
above cut-off; n=152
p=0.377; log rank

American Journal of Transplantation 2009; 9: 286–293
Wiley Periodicals Inc.

doi: 10.1111/j.1600-6143.2008.02478.x

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

Z. A. Stewart, A. M. Cameron, A. L. Singer, R. A. Montgomery and D. L. Segev*

Evaluation of the effect of HTK preservation on allografts as a function of CIT found that allografts with CIT $>=$ 8 h (HR 1.16, $p = 0.009$) were impacted more than allografts with CIT $<$ 8 h (HR 1.11, $p = 0.46$) (Table 5). Adjusting for transplant center volume and clustered variance estimates by center made this effect more pronounced, as CIT $>=$ 8 h (HR 1.16, $p = 0.033$) still had statistically significant reduced graft survival versus CIT $<$ 8 h (HR 1.10, $p = 0.084$) (Table 5).

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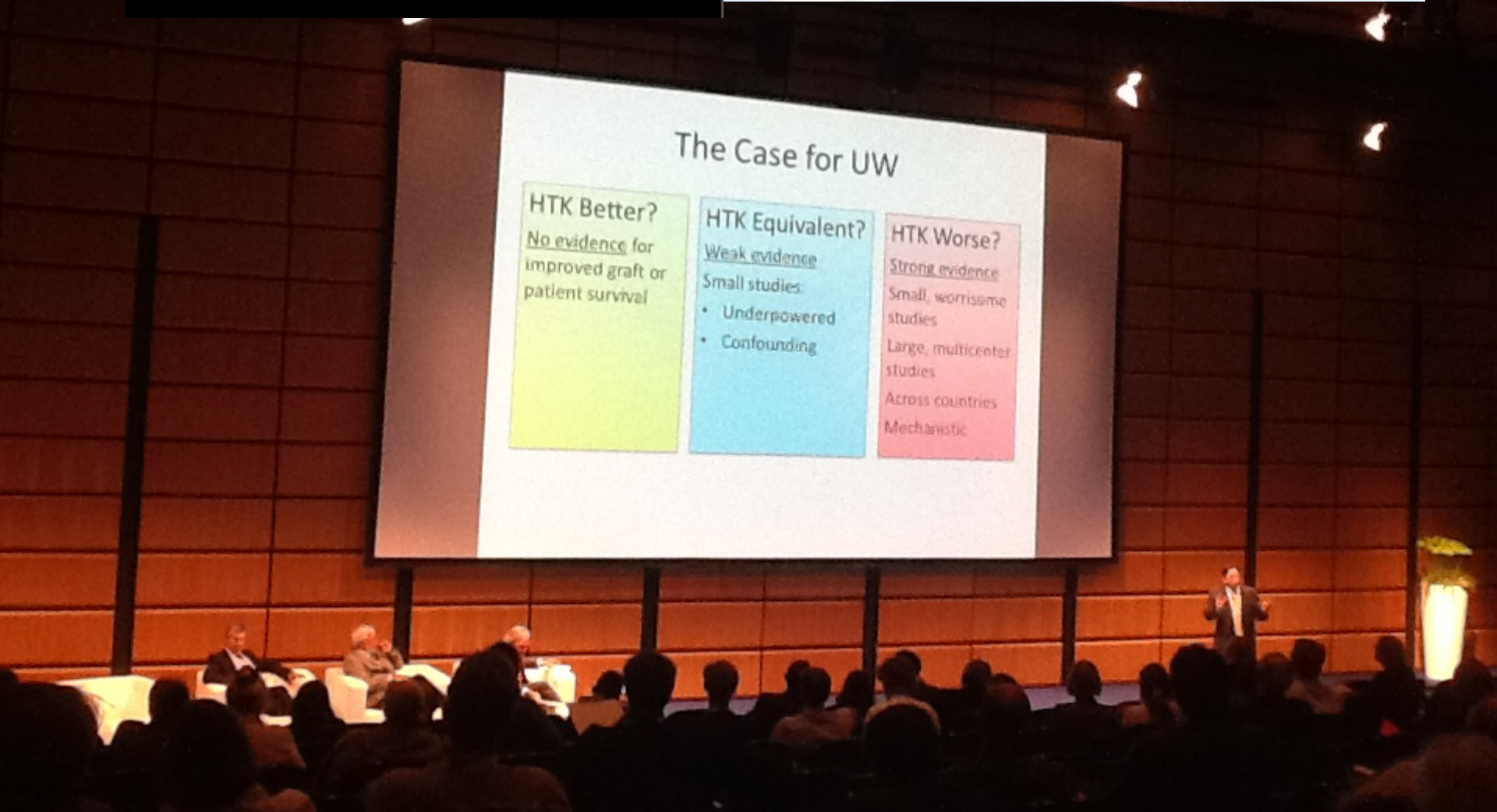
2013 :
A PRESERVATION ODYSSEY

RUTGER PLOEG
RENE ADAM
DORRY SEGEV
FERDINAND MÜHLBACHER

Tuesday 10 September, 13:00-14:00
Level O2, Room B (opposite Rising Stars Lounge)




2013 :
A PRESERVATION ODYSSEY
RUTGER
PLOEG
RENE
ADAM
DORRY
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MÜHLBACHER
Tuesday 10 September, 13:00-14:00
Level O2, Room B (opposite Rising Stars Lounge)
Bridge to Life
RENE
ADAM
DORRY
SEGEV

American Journal of Transplantation 2015; 15: 395–406
Wiley Periodicals Inc.

doi: 10.1111/ajt.13060

Compared Efficacy of Preservation Solutions in Liver Transplantation: A Long-Term Graft Outcome Study From the European Liver Transplant Registry

R. Adam[1,*], V. Delvart[1], V. Karam[1], C. Ducerf[2], F. Navarro[3], C. Letoublon[4], J. Belghiti[5], D. Pezet[6], D. Castaing[1], Y. P. Le Treut[7], J. Gugenheim[8], P. Bachellier[9], J. Pirenne[10], P. Muiesan[11] and all the ELTR contributing centres, the European Liver, Intestine Transplant Association (ELITA)

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Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

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Wiley Periodicals Inc.

doi: 10.1111/j.1600-6143.2010.03037.x

Special Feature

Liver Transplantation in the United States, 1999–2008

P. J. Thuluvath[a,b,*], M. K. Guidinger[c,d], J. J. Fung[e], L. B. Johnson[b], S. C. Rayhill[f] and S. J. Pelletier[c,g]

[a] *Mercy Medical Center, Baltimore, MD*
[b] *Georgetown University Hospital, Washington, D*
[c] *Scientific Registry of Transplant Recipients, Ann MI*
[d] *Arbor Research Collaborative for Health, Ann Arb*
[e] *Cleveland Clinic, Cleveland, OH*
[f] *Center for Health and Healing, Oregon Health an Science University, Portland, OR*
[g] *University of Michigan, Ann Arbor, MI*
[*] *Corresponding author: Paul J. Thuluvath, thuluvath@gmail.com*

Note on sources: The articles in this report are ba the reference tables in the 2009 OPTN/SRTR Ann Report. *Table numbers are noted in brackets and found online at: http://ustransplant.org.*

Recipient factors such as age, race, etiology of liver disease including HCC, BMI, presence of diabetes, previous liver transplantation and donor factors such as age and race had an effect on 1-year patient survival. Hospitalized patients and those on mechanical support had a lower survival *[Table 9.10a]*. Blood type and sex had no effect. Data were available for recipient serum sodium and organ preservation solution between 2005 and 2008; neither recipient serum sodium (<130 vs. ≥130 mmol/L) nor the type of preservation solution (University of Wisconsin [UW] solution Viaspan vs. Custodiol® histidine-tryptophan-ketogluterate [HTK]) had an impact on survival. Please note that over the past 4 years (2005–2008), approximately 27% of all liver allografts utilized Custodial® HTK preservation solution compared to 68% for UW solution (SRTR analysis 2009).

American Journal of Transplantation 2010; 10 (Part 2): 973–986
Wiley Periodicals Inc.

doi: 10.1111/j.1600-6143.2009.03008.x

Special Feature

Organ Donation and Utilization in the United States, 1999–2008

A. S. Klein[a,*], E. E. Messersmith[b,c], L. E. R. Kochik[e], P. K. Baliga[f] and A. O. Ojo[b]

[a] *Cedars-Sinai Medical Center, Los Angeles, CA*
[b] *Scientific Registry of Transplant Recipients, An MI*
[c] *Arbor Research Collaborative for Health, Ann A*
[d] *New York Presbyterian Hospital, Columbia, Nev*
[e] *Finger Lakes Donor Recovery Network, Roches*
[f] *Medical University of South Carolina, Charlesto*
**Corresponding author: Andrew S. Klein, kleinas@cshs.org*

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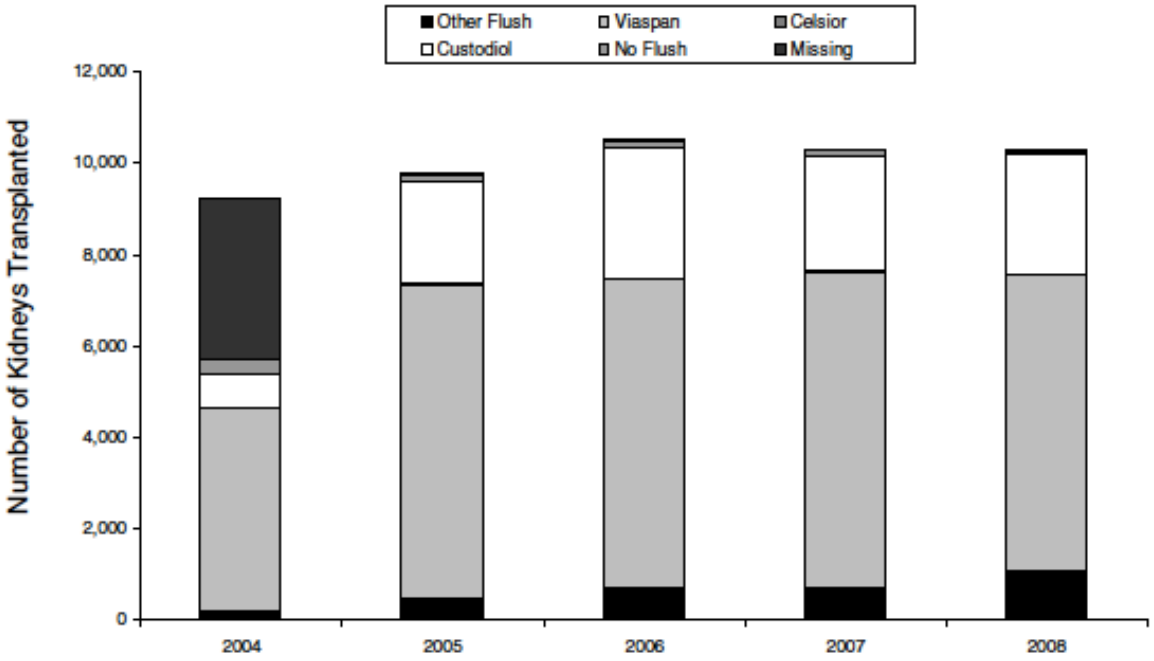

Source: SRTR analysis. Data as of May, 2009.

Using the SRTR Database

- Only adult first liver-only transplants from 2002-2008 were included and only for those whom flush and storage solutions were the same
- All patients had minimum one year follow up
- 25,616 patients, 20,901 (82%) with UW and 4,715 (18%) with HTK
- Analyzed >100 clinically relevant recipient, donor, and procedure variables

Adjusting for Multiple Tests

No. of independent tests	2	5	10	20	50	100
Probability of one or more $p < 0.05$ by chance	10%	23%	40%	64%	92%	98%
To keep alpha = 0.05 accept as significant only p less than	0.025	0.010	0.005	0.0025	0.0010	0.0005

Use p = 0.05 / no. of tests

Comparison of Peri-operative Donor and Recipient Variables Analyzed

Study	Variables	Adjusted p Value
Adam	27	0.00185
Stewart	26	0.00192
Cleveland Clinic	187	0.00027

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4. Main disease: ACHF	<0.0001	1.34	[1.22; 1.47]
5. Partial liver graft	<0.0001	1.30	[1.16; 1.44]
6. Recipient age ≥60 years	<0.0001	1.29	[1.23; 1.37]
7. Non-ABO isogroup	<0.0001	1.24	[1.14; 1.34]
8. Recipient HBsAg (−)	<0.0001	1.24	[1.15; 1.33]
9. Ischemia time ≥12 h	<0.0001	1.19	[1.11; 1.27]
10. Recipient male	<0.0001	1.10	[1.05; 1.15]
11. HTK	0.02	1.10	[1.01; 1.20]
12. Main disease: not cirrhosis	0.01	1.09	[1.04; 1.15]

RR, risk ratio; CI, confidence interval; ACHF, acute hepatic failure. Cox model with 34 520 observations.

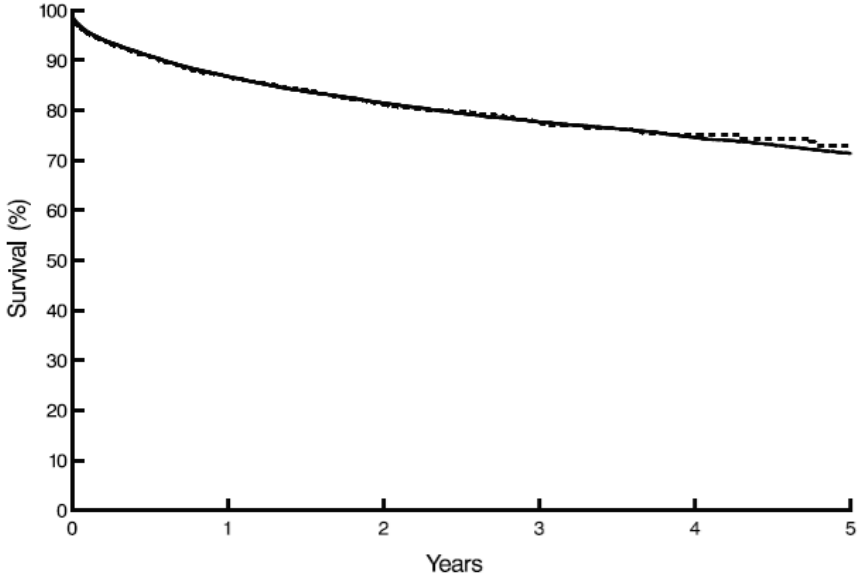
Statistical Analysis

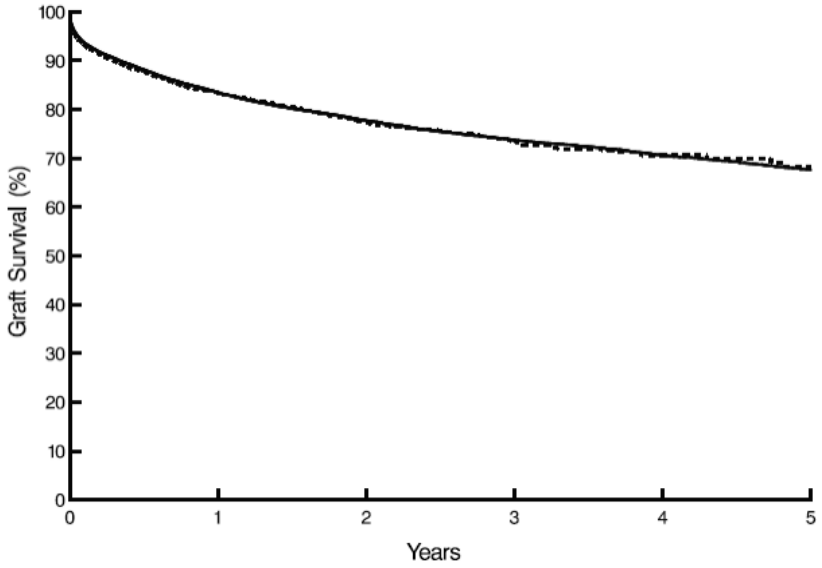
- Three comparisons:
  - Unadjusted graft survival
  - Bootstrapping hazard modeling using risk factors for graft survival determined using non-proportional, multiphase, multivariable hazard methodology
  - Propensity-matched comparison

Results

- Validation of reported significant recipient factors of graft failure in the early and later phases after DDLT
- **OPS did not appear as a statistically significant predictor of graft failure**
  - hospital death, re-transplant rates and relisting rates were not different

Unadjusted Patient and Graft Survival - HTK vs UW



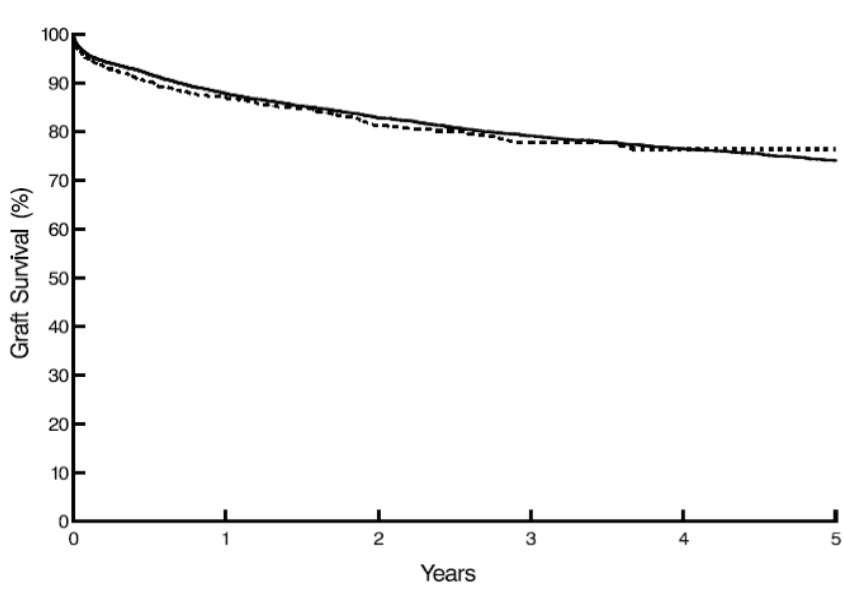


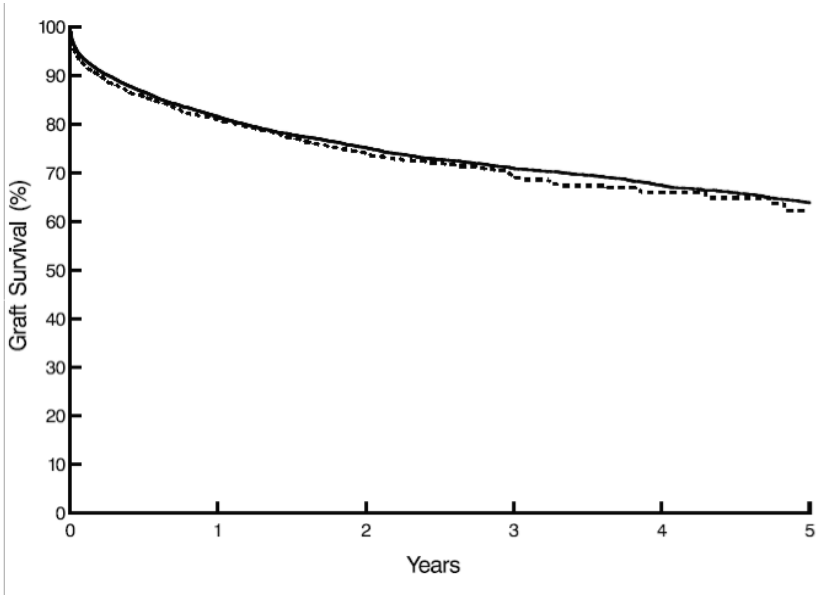
UW n=20,901 **HTK n=4,715** **Adult LTX from 2002-2008**

PS: p =0.90 **log rank test** **GS: p=0.60**

Unadjusted Patient and Graft Survival - HTK vs UW

Adult LTX from 2002-2008: By DRI - 2.5





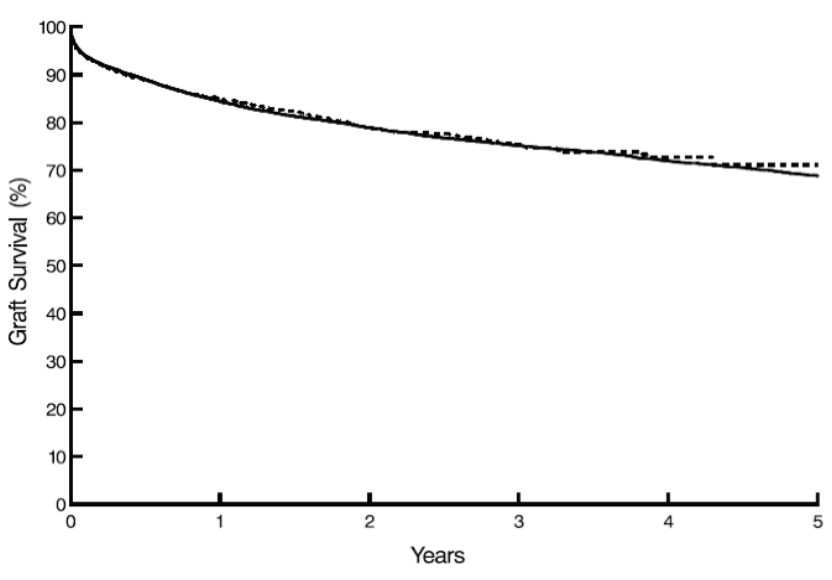
7,883 UW
1,826 HTK
DRI $\leq$ 2.5 p = 0.20

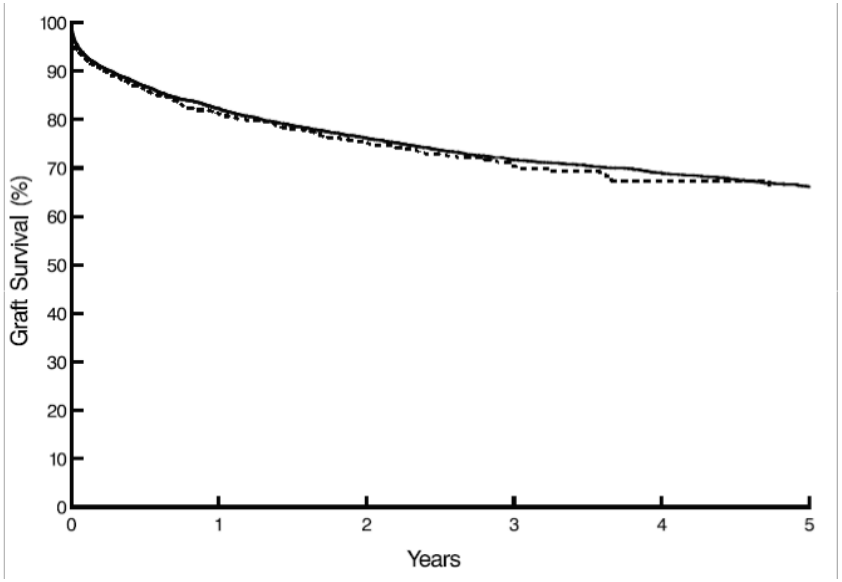
log rank test

10,484 UW
2,314 HTK
DRI >2.5: p = 0.20

Unadjusted Patient and Graft Survival - HTK vs UW

Adult LTX from 2002-2008: By CIT - 8 hrs (non-DCD)





14,053 UW

3,279 HTK

CIT ≤ 8 hr p = 0.70

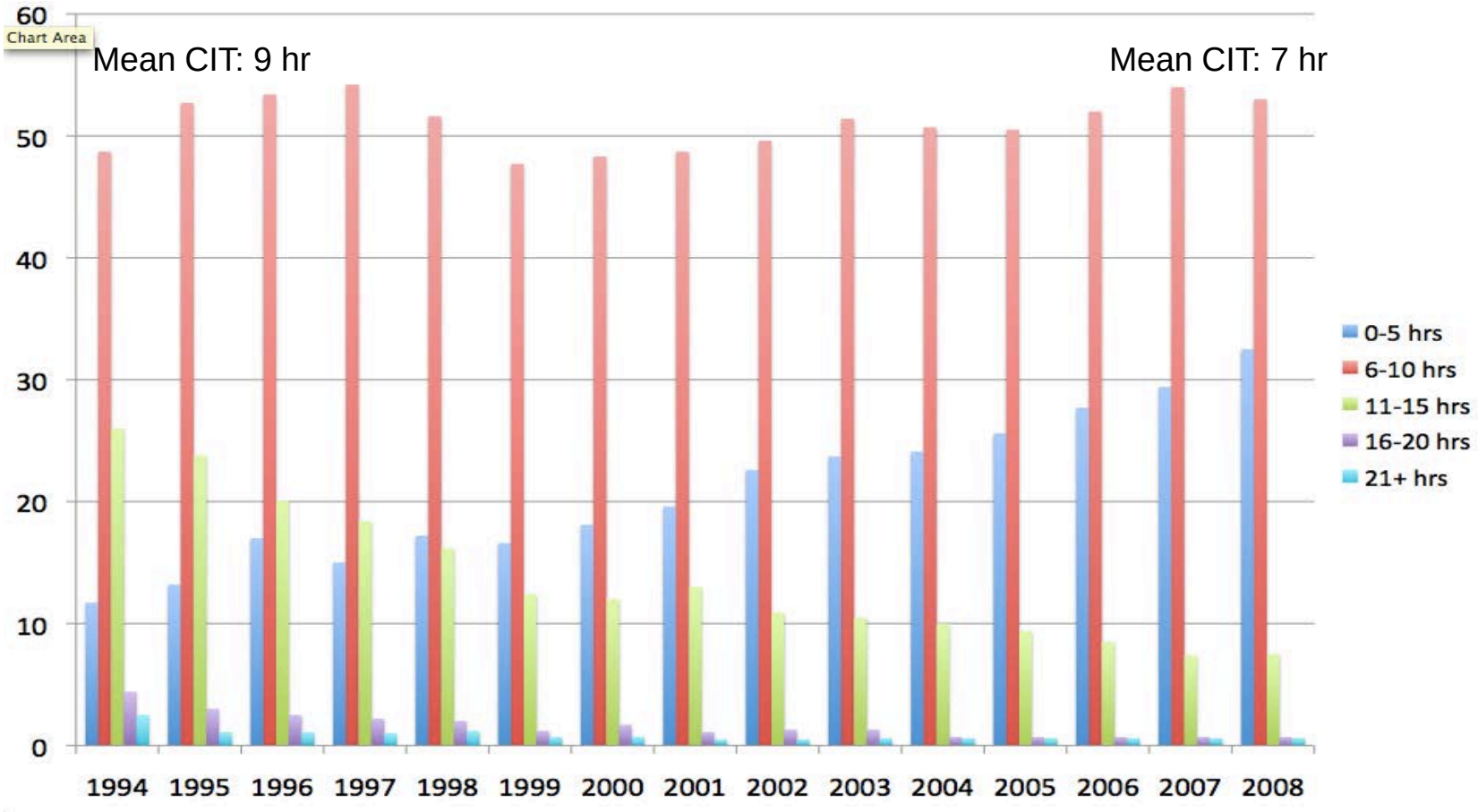
log rank test

6,119 UW

1,177 HTK

CIT >8 hr: p = 0.50

UNOS CIT in LTX 1994-2008



Risk Factors for Graft Failure - Early

Risk Factor	*P*	Bootstrap %
Early hazard phase		
Older recipient age (years)	<.0001	96
Recipient race White or Black	<.0001	69
Recipient portal vein thrombosis	<.0001	99
Recipient previous abdominal surgery	<.0001	67
Candidate last creatinine (used for MELD)	<.0001	96
Candidate last MELD	<.0001	76
Recipient on life support just prior to tx	<.0001	100
Recipient previous kidney transplant	<.0001	87
Donor race non-White	<.0001	89
Donor donation after cardiac death	<.0001	100
Donor risk index	<.0001	58

Risk Factors for Graft Failure - Late

Risk Factor	*P*	Bootstrap %
Late hazard phase		
African American recipient	<.0001	98
Recipient primary diagnosis for tumors	<.0001	94
Recipient hepatitis C virus	<.0001	100
Donor age (years)	<.0001	100

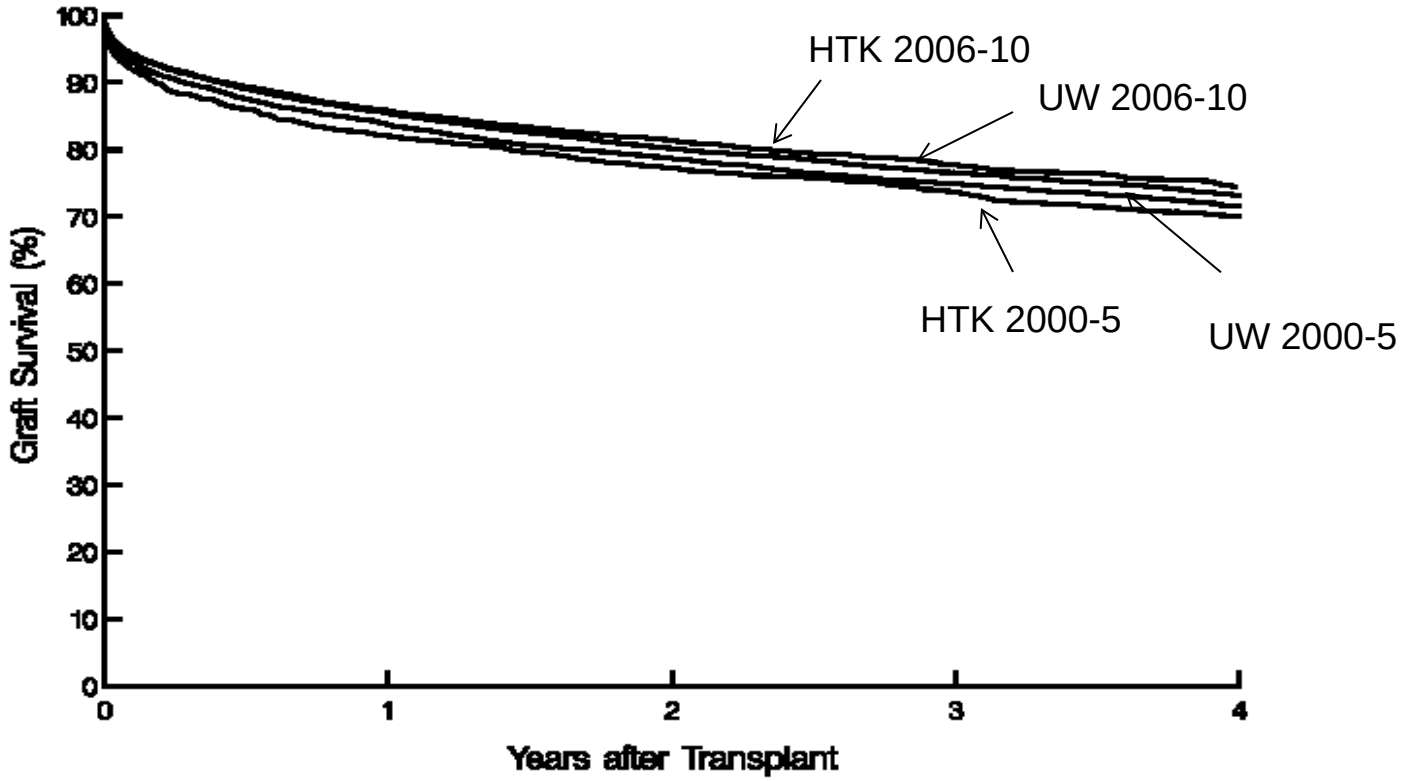
Unadjusted US 1-year Graft Survival Rates by Year of Transplant

Year	UW Survival Curve		HTK Survival Curve		
	N	1-yr survival	N	1-yr survival	p
2002	3684	83.5%	65	81.5%	.86
2003	3889	82.9%	183	78.1%	.083
2004	3687	83.6%	535	80.6%	.067
2005	3247	82.2%	1167	81.8%	.88
2006	3052	83.6%	1398	84.1%	.71
2007	3083	84.5%	1274	87.6%	.20

Liver Transplant Graft Survival

SRTR Data, 2000-2010, N=55110, Age 18+

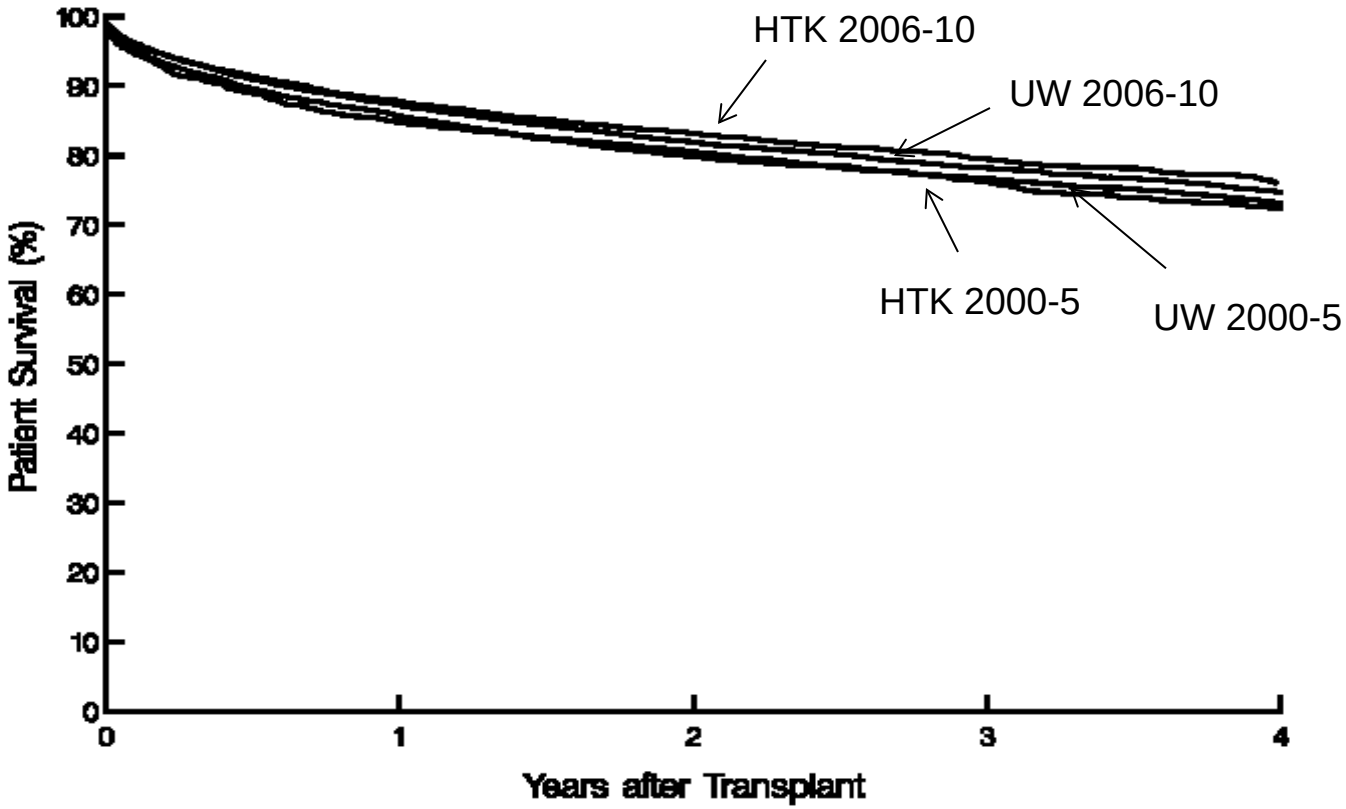
By Years and Preservation Solution: 2001-2005 vs 2006-2010 and UW vs HTK



Liver Transplant Patient Survival

SRTR Data, 2000-2010, N=55110, Age 18+

By Years and Preservation Solution: 2001-2005 vs 2006-2010 and UW vs HTK



Comparing HTK Users - 2010 UNOS Report - ADDLT

Center	Patient Survival	Graft Survival
United States	88.5	84.7
Methodist - Memphis	92.1 (+1.0)	87.4 (+0.5)
University of Indiana	90.0 (+0.7)	87.4 (+1.5)
Cleveland Clinic	91.6 (+1.7)	87.9 (+1.3)

Comparing UW Users – 2010 UNOS Report - ADDLT

Center	Patient Survival	Graft Survival
Johns Hopkins	75.6 (-13.9)	69.7 (-14.2)
MUSC	87.5 (-1.1)	85.0 (-2.4)
Univ. Pennsylvania	86.7 (-2.1)	84.8 (-1.1)
Univ. Wisconsin	90.0 (+4.4)	85.2 (+3.7)

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HTK preservative solution is associated with increased biliary complications among patients receiving DCD liver transplants: A single center experience

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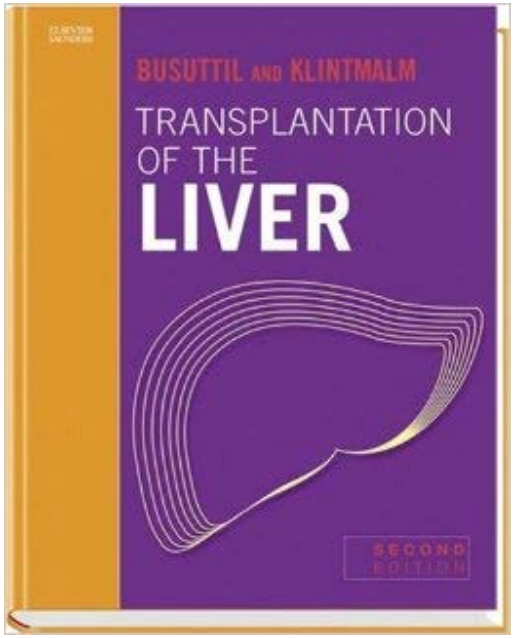
1997 – 2010: 40 DCD

	N	Age	WIT (min)	Death	HAT	ReTx
HTK	20	42	28.1±15.1	6	3	5*
UW	20	26	25.7±8.5	8	1	0

*2 ReTx for anastomotic bile leak only!!!

Table 3. Nature of the biliary complications.

	HTK (n=17)	UW (n=18)	p-value
Anastomotic strictures(AS)	4	2	
Nonanastomatic strictures(NAS)	2	2	
Bile leak(BL)	4	2	
AS with NAS	2	0	
AS with BL	0	1	
AS and NAS with BL	1	0	
Total	13 (76%)	7 (39%)	0.041



Technical Problems: Biliary

PETER NEUHAUS
ANDREAS PASCHER

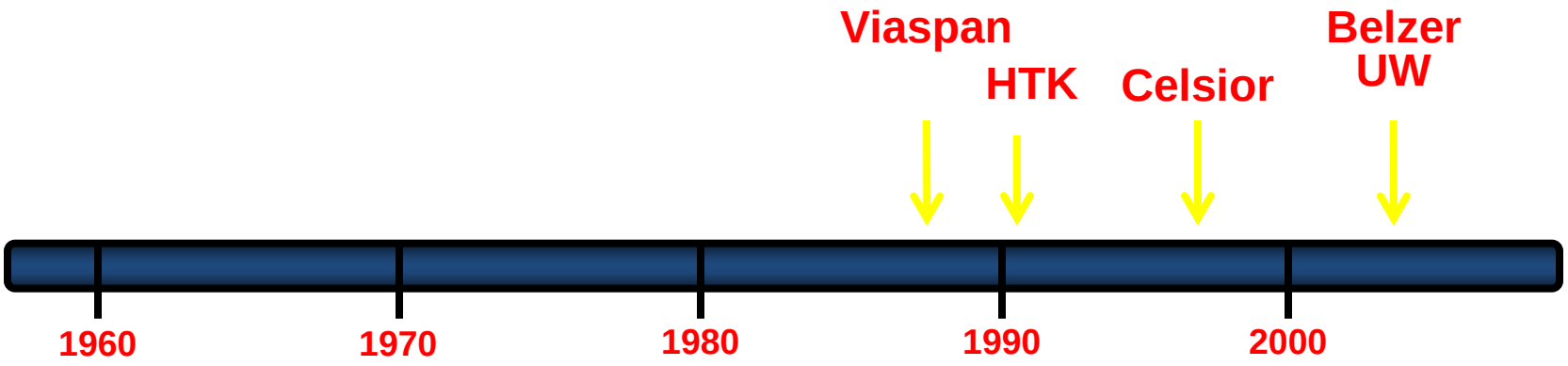
Early Bile Leaks

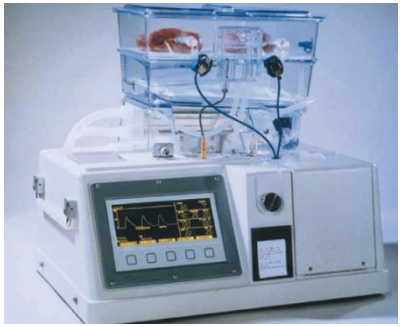
Leaks may originate from the anastomosis (Fig. 62–3); either the donor or recipient cystic duct stump; the cut surface in the case of a reduced-size graft, split graft, or a graft from a living donor; or the T-tube exit site if a T tube is used. After CC, bile leaks that are not related to T-tube removal usually present within the first 30 days after OLT.[3,8] Most leaks have technical causes.

Anastomotic Strictures

Early anastomotic strictures (Fig. 62–5) are predominantly caused by technical failure. A transient narrowing

Timeline of Machine Organ Preservation





Hypothermic Mechanical Perfusion

Normothermic Mechanical Perfusion

SUMMARY

- Current approaches to static cold storage of livers has shown no significant changes over the past 25 years. Under normal clinical practices, the most currently utilized cold storage solutions, UW and HTK are equivalent.
- Retrospective large database analysis are prone to design and data flaws, the complex risk factor interactions and practices not captured by databases, have profound impact on conclusions
- Improved surgical technique, consciously reducing CIT and expediting revascularization of liver allografts has critical in maintaining good outcomes
- Future improvements in allograft function, extending preservation times, extending use of expanded criteria donors including DCD, await the application of machine preservation technology