Actualización en donación a corazón parado en trasplante hepático

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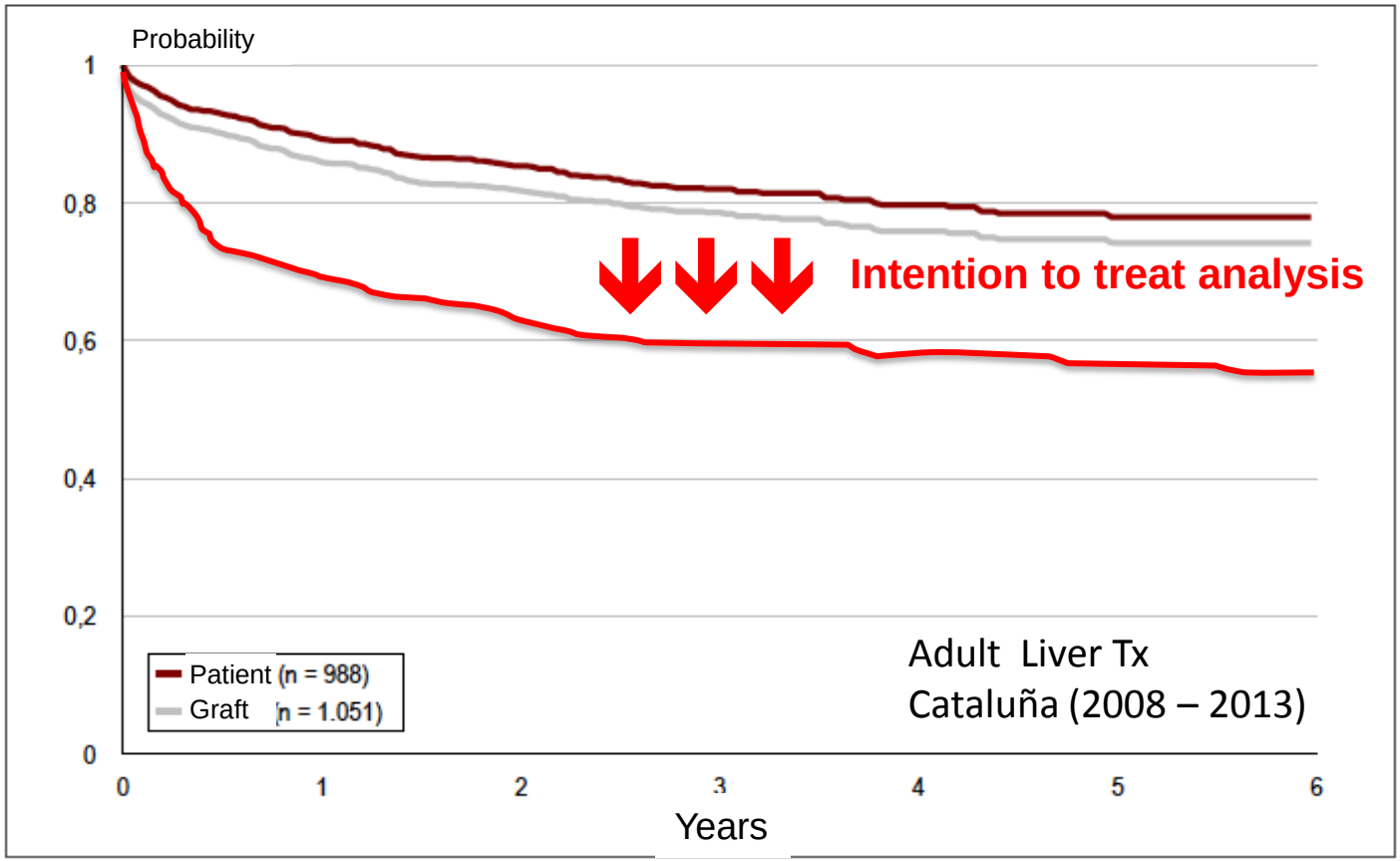
Patient & Graft Survival



OCATT
Organització Catalana de Trasplantaments

	1r mes	3r mes	6è mes	1r any	2n any	3r any	4rt any	5è any
Patient	0,97	0,95	0,93	0,89	0,85	0,82	0,80	0,78
Graft	0,95	0,92	0,90	0,86	0,82	0,79	0,76	0,74

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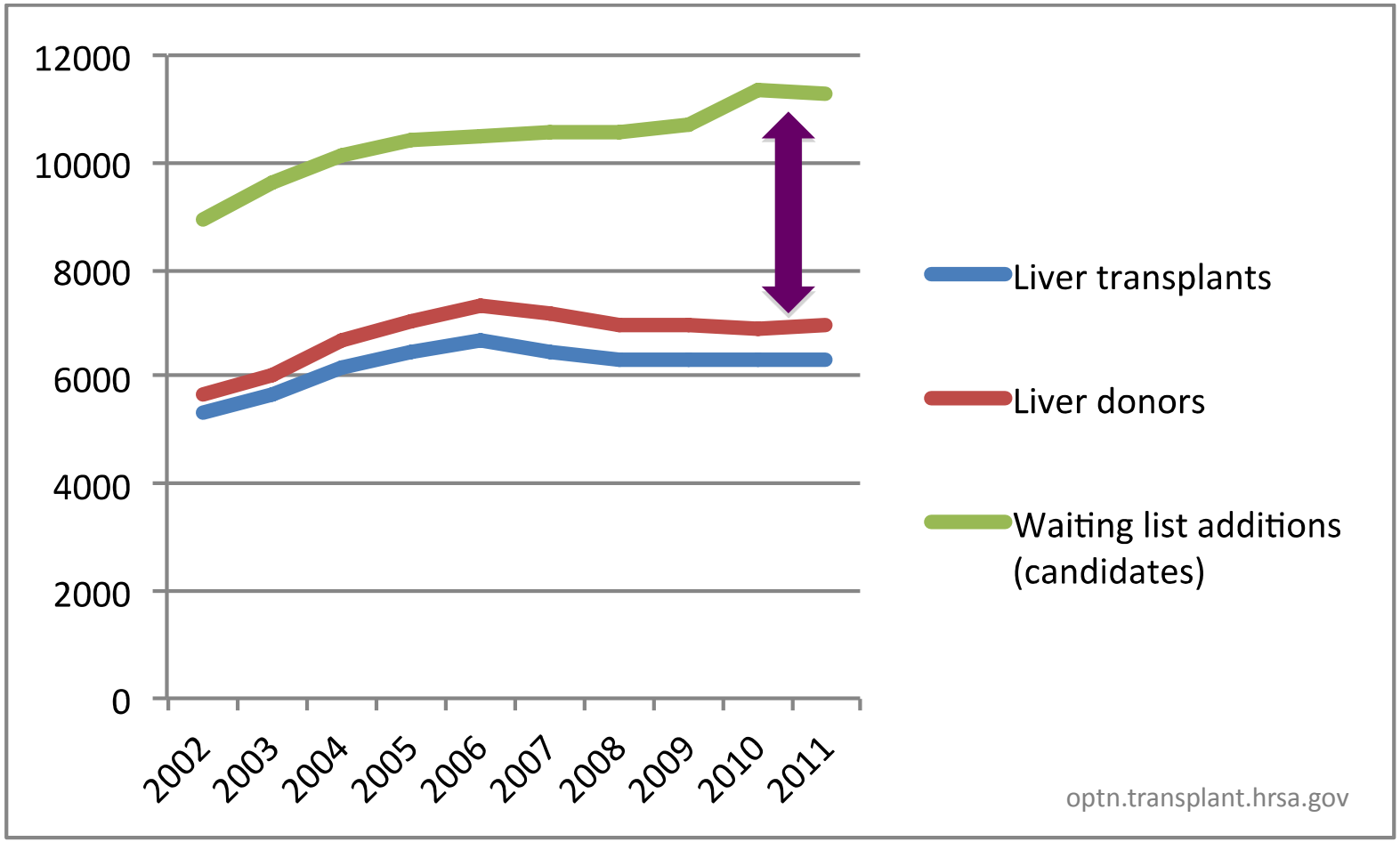
Liver Transplant Waiting List UK / Spain 2013

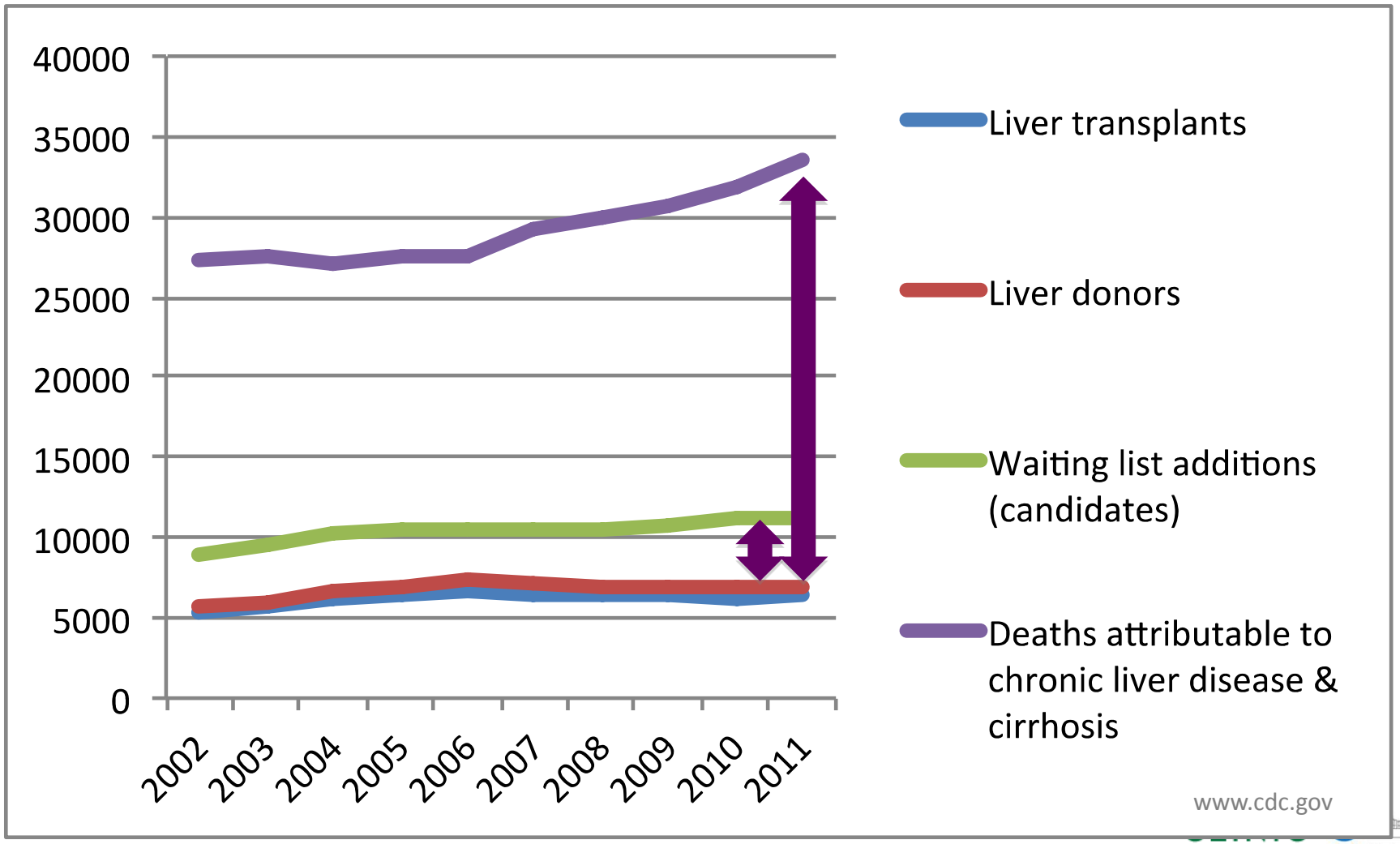
	UK	SPAIN
Population (millions):	63.1	46.9
Total number of patients ever active on the WL	1631	2095
Patients awaiting for a transplant (only active candidates) on 31/12/2013	525	667
Patients who died while on the WL during 2013	77	117

(Transplant Newsletter Vol. 19, Nº 1, September, 2014)

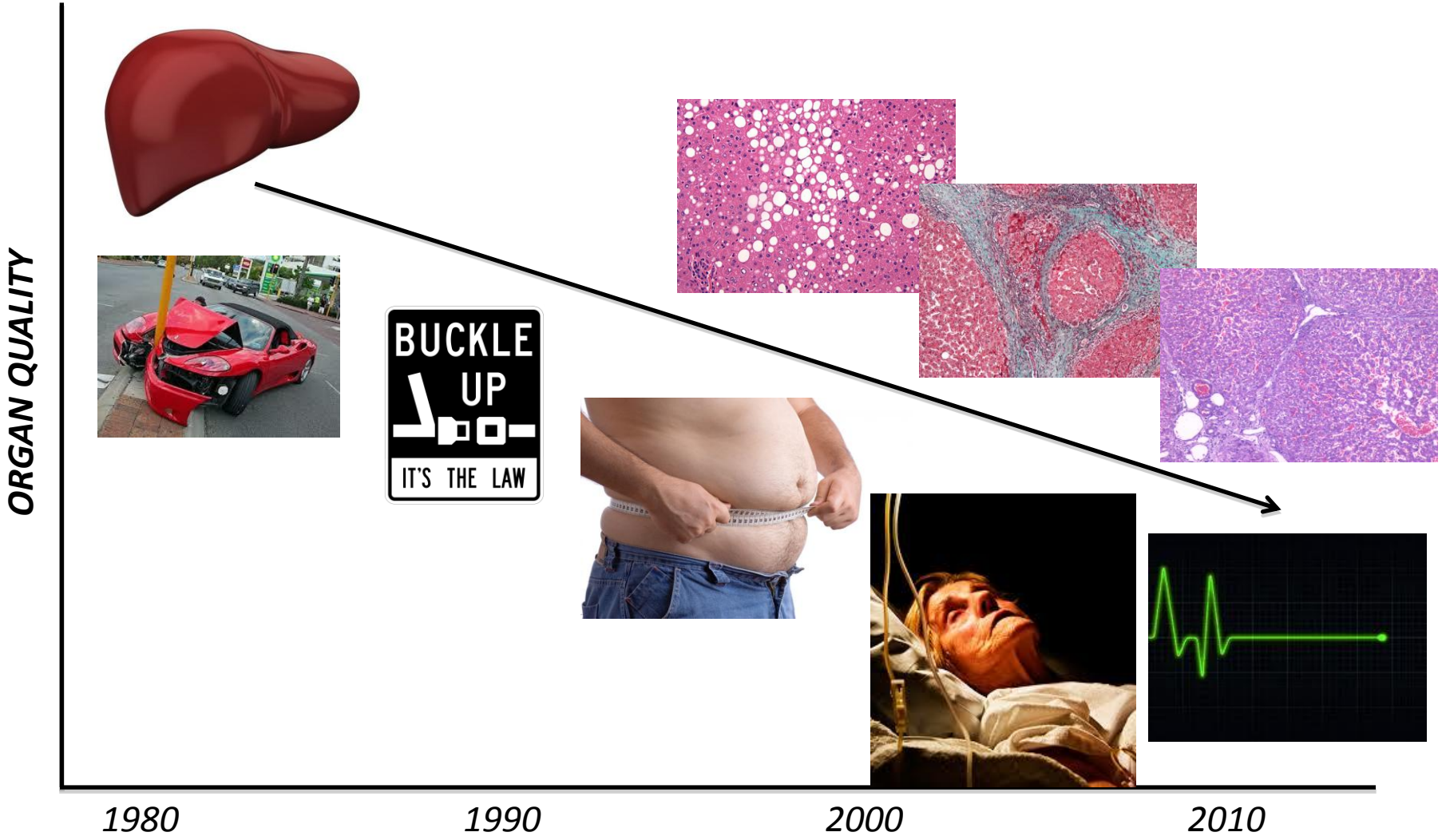
Transplant-Waiting List Disparity…



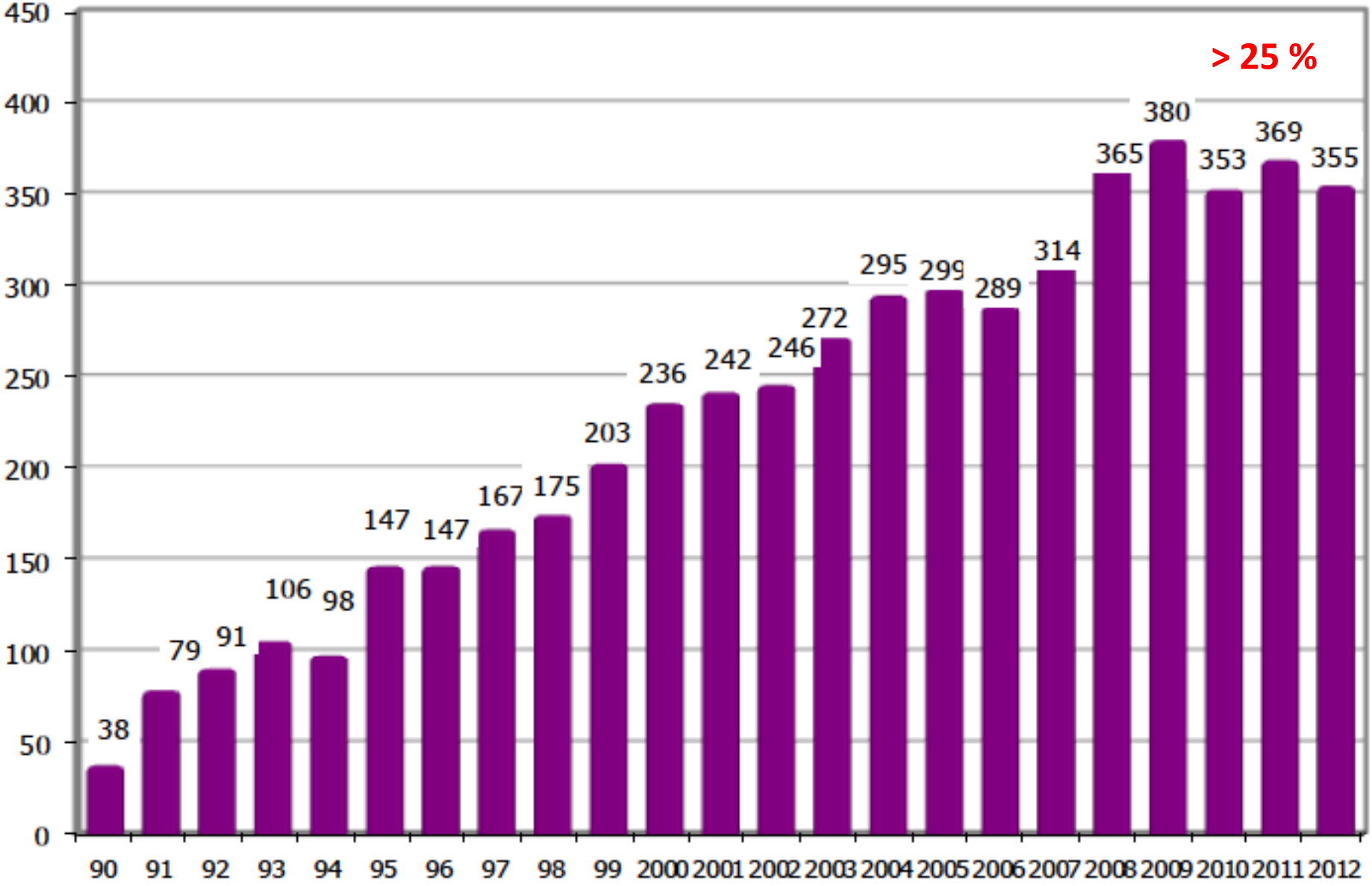
The *Real* Disparity…



Fewer and fewer “ideal” organs…



LIVERS DISCARDED IN SPAIN

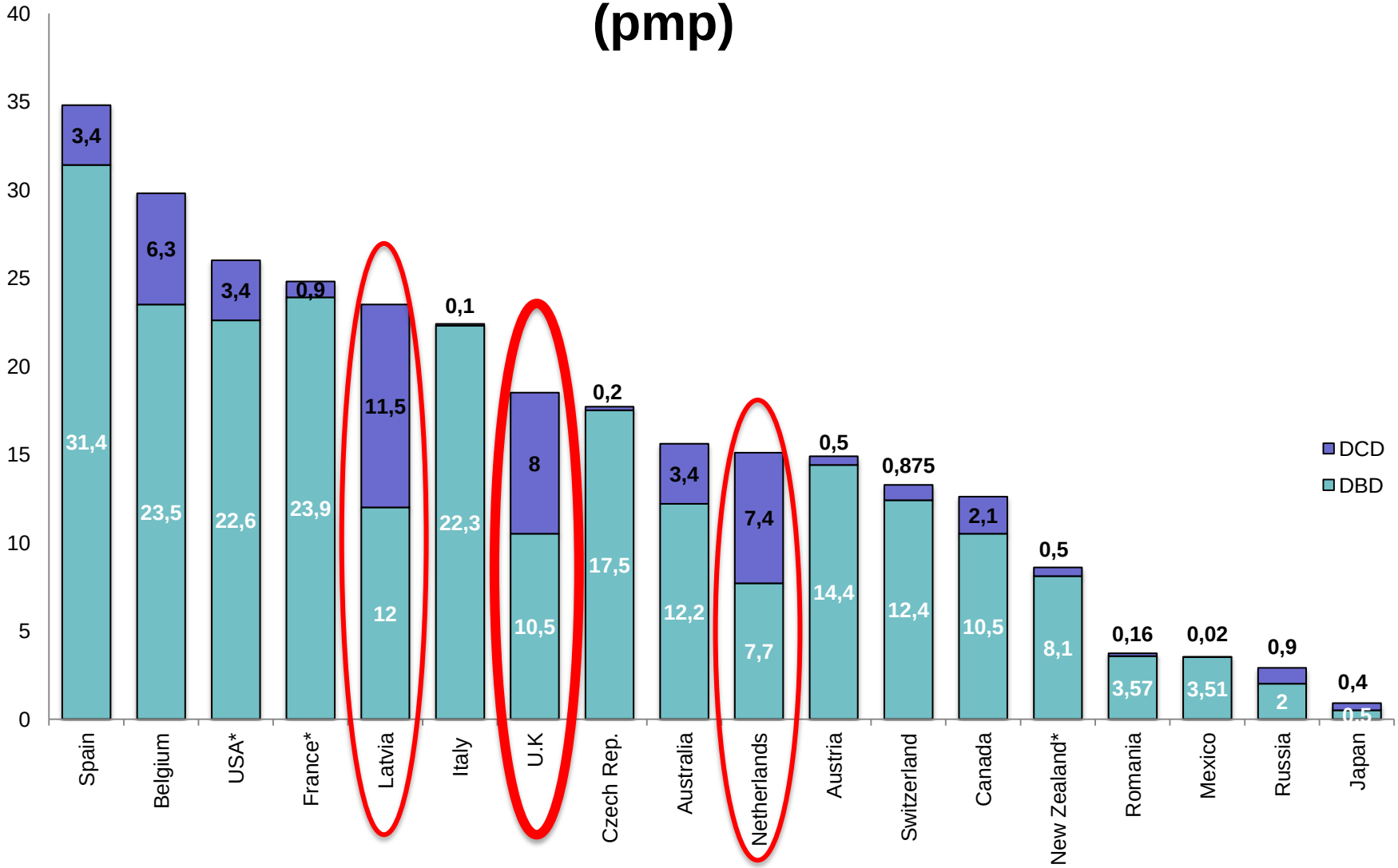


Organ Donation and Transplantation Activity UK / Spain 2013

	UK	SPAIN
Population (millions):	63.1	46.9
Deceased organ donors (all types)	1323 (21 pmp)	1655 (35.3 pmp)
Donors after circulatory death	**544 (8.6 pmp)**	**159 (3.4 pmp)**
Liver transplants (total)	904(14.3 pmp)	1093(23.3 pmp)
LT from living donors	30 (0.5 pmp)	23 (0.5 pmp)
LT from DCD	**146 (2.3 pmp)**	**29 (0.6 pmp)**

(Transplant Newsletter Vol. 19, Nº 1, September, 2014)

Worldwide Actual DBD and DCD donors 2012 (pmp)



www.irodat.org

Organ Donors in Canada

- 2001: Deceased donor rate: 13.1 pmp
- 2010: Deceased donor rate: 13.6 pmp

(Spain 32 pmp, US 25 pmp)

Wait list deaths:

16% of kidney-pancreas
19% of lung
22% of liver
24% of heart

} Transplant Candidates

*(Squires JE et al., Implementation Science 2014, **9**:80)*

DCD in Canada

- Started in 2006
- In 2011: (% of all deceased organ donors)
  - 20% in Ontario (3.1 DCD pmp)
  - 9.5% in Quebec (1.6 DCD pmp)
  - 8.7% in BC (1.5 DCD pmp)
  - 8% in Alberta (0.8 pmp)
  - 8% in Nova Scotia (2.1 pmp)

"Canada would see a dramatic increase in the number of available organ donations if DCD donation rates were to increase to international standards."

*(Squires JE et al., Implementation Science 2014, **9**:80)*

Can non-heart-beating donors replace cadaveric heart-beating liver donors?

Prerequisites for establishing a NHBD liver transplant program

Controlled NHBD

(1) Ensure appropriate legal framework
(2) Establish protocols for NHBD retrieval and train donor coordinators and other teams
(3) Identify Inten cols for withdrawal of treatment
(4) Develop a suc followed by liver program, concentrating experience initially within a small team
(5) Address consent and allocation issues for NHBD liver transplantation
(6) Concentrate on busiest units first with extensive experience of use of marginal grafts and then expand the program

Donor ↑ 20%

Uncontrolled NHBD

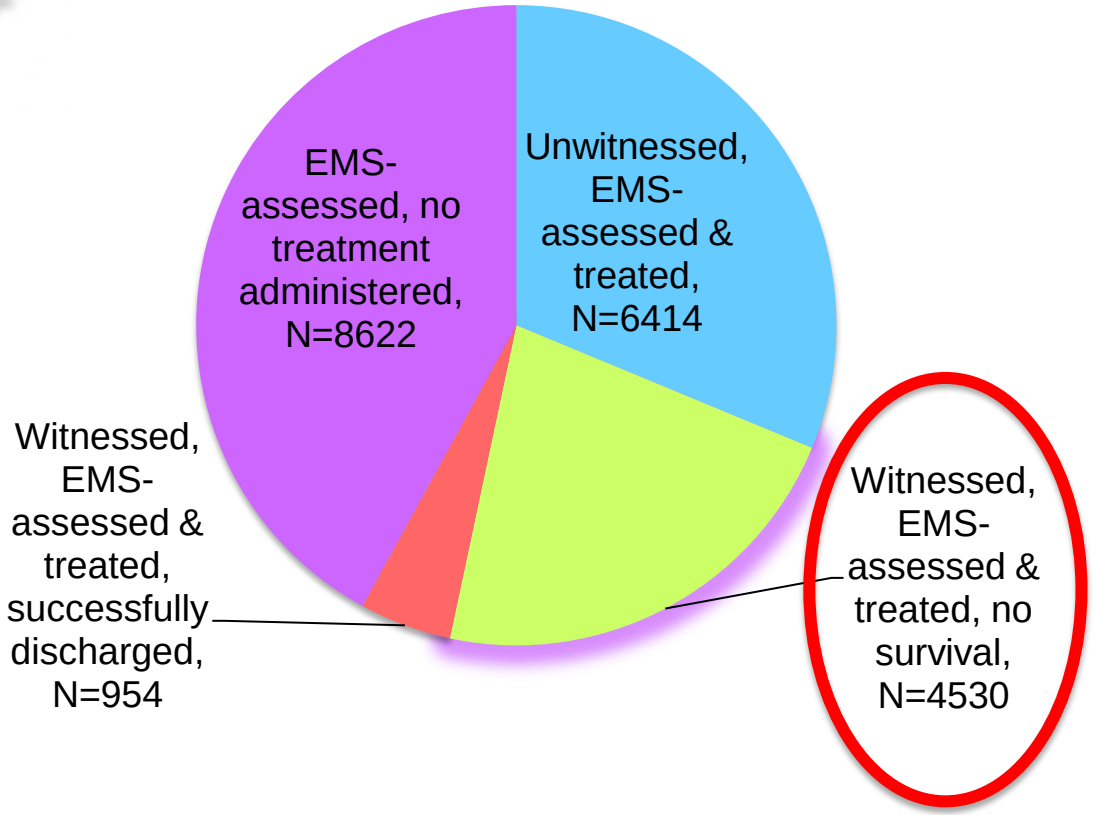
(1) Establish legal and ethical framework acceptable to the public
(2) Carry out public and political consultation with consideration towards 'presumed consent' (opt out) policy for organ donation
(3) Develop a regic y of dedicated resuscitation ambulances deployed within defined territories to identify and resuscitate pot
(4) Establish a robust protocol for cessation of resuscitation, consent issues, donor maintenance and subsequent retrieval
(5) Twenty-four-hour availability of a dedicated retrieval team of surgeons, nurses and donor coordinators trained for uncontrolled NHBD
(6) Develop cooperation and involvement of the hospital emergence department to establish the program (if possible, develop uncontrolled NHBD after a successful controlled NHBD program)

Donor ↑↑↑ 300%

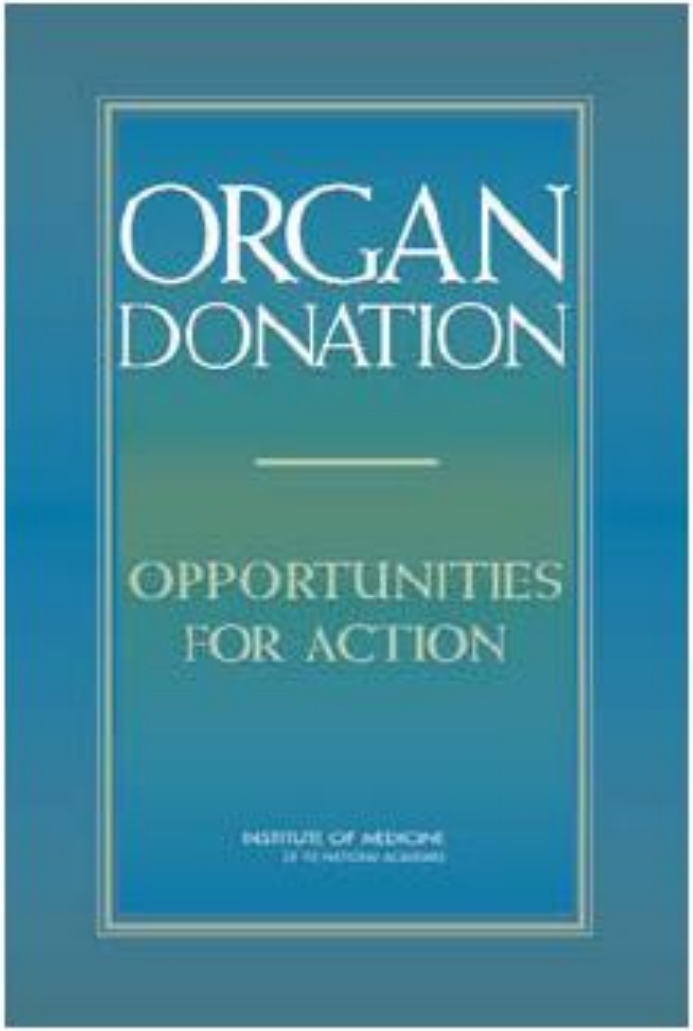
"The greatest potential lies with uncontrolled NHBD, but changes are needed from Governments to provide a clear legal framework, funding and training for the infrastructure and acceptance by the public."

Deshpande R & Heaton N, J Hepathol 2006.

Out-of-hospital cardiac arrest



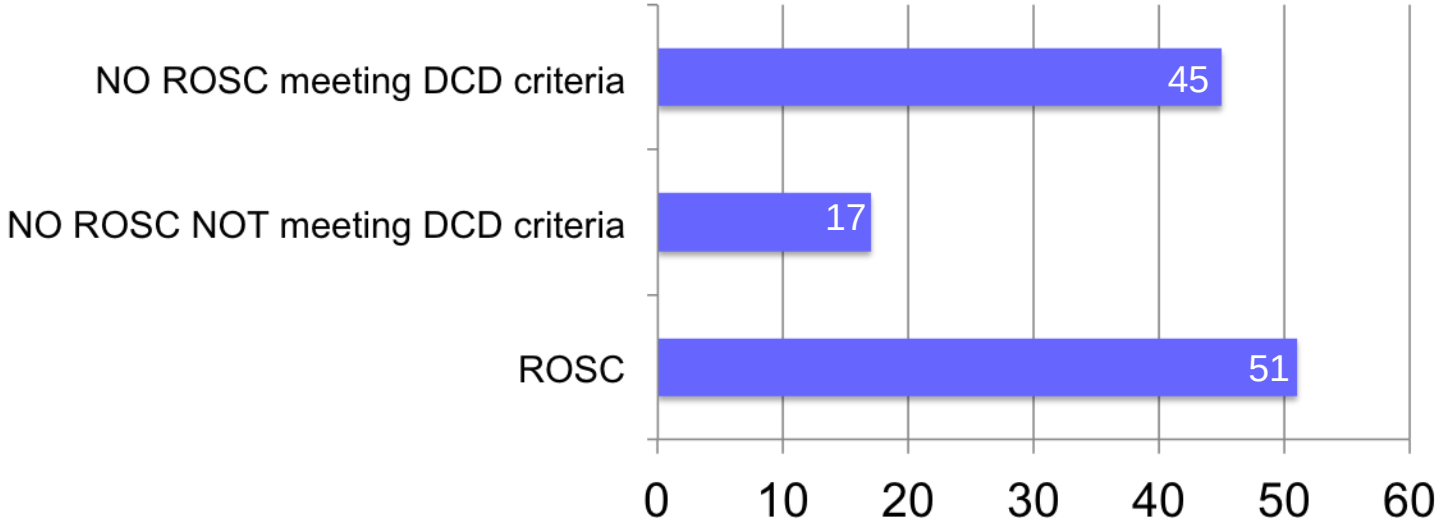
Nichol G, JAMA 2008.



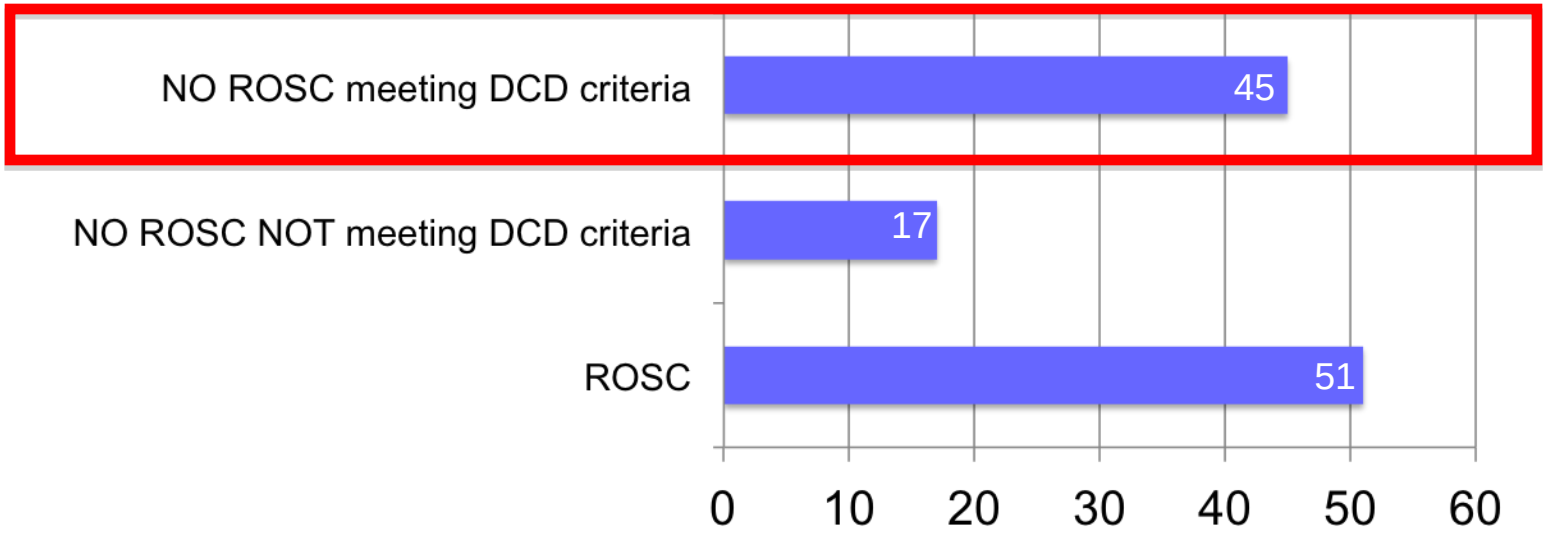
*"[A]t least **22,000 people each year** who die of cardiac arrest outside of a hospital could be potential organ donors."*

-U.S. Institute of Medicine, 2006

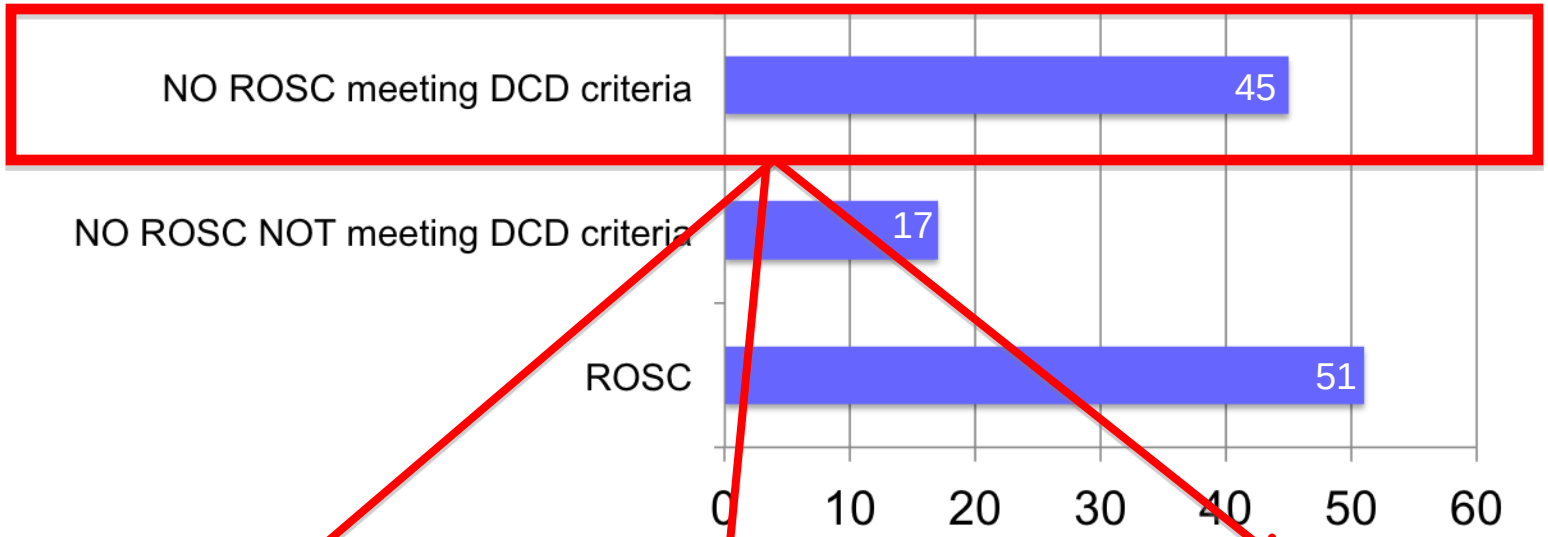
OHCA Transferred to H. Clínic (year 2012)

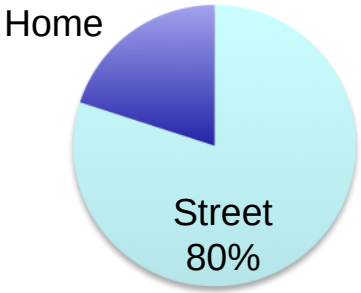


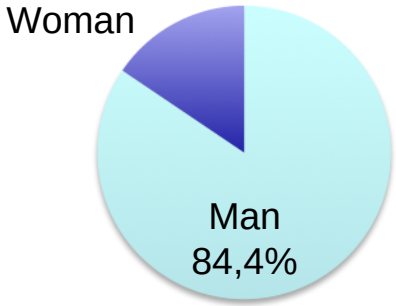
OHCA Transferred to H. Clínic (year 2012)



OHCA Transferred to H. Clínic (year 2012)







Age (n , %)		
< 20	2	(4,4%)
20 - 29	3	(6,7 %)
30 - 39	10	(22,2 %)
40 - 49	11	(24,4 %)
50 - 59	11	(24,4 %)
60 - 69	8	(17,8 %)
Total	45	

Uncontrolled DCD in the UK

- Although a number of transplant units have in the past supported uncontrolled DCD organ retrieval from nearby Emergency Departments, these programmes are currently inactive. However, plans to introduce uncontrolled DCD in Scotland are well advanced, with the programme due to commence in 2013. Further details of this programme will become provided as they become available.

http://www.odt.nhs.uk/donation/deceased-donation/donation-after-circulatory-death/

Accessed January 2014

DCD Preservation Injury

Pre-preservation warm ischemic injury

Cold ischemic injury

Re-warming injury

Reperfusion injury

Minutes → ***Hours***

Intraoperative management

Cardiac arrest

Organ procurement

Warm ischemia

Liver transplant

Postoperative care

Post-transplant Follow-up

Hemodynamics

- DCD grafts are more likely to develop post-reperfusion syndrome.

	DCD (17)	DBD(17)	p value
Post-reperfusion syndrome (min)	45 (30-64)	0	<0.001

Broomhead et al, Liver Transplantation 2012

Hemodynamics

- ↑ Vasopressor support

	DCD (17)	DBD (17)	p value
Norepinephrine (hours)	20.5 (12-37)	9.5(5-16)	<0.02

Broomhead et al, Liver Transplantation 2012

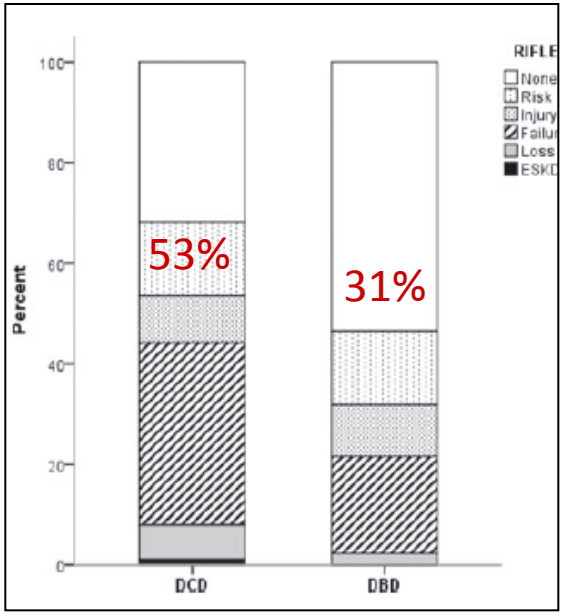
- ↓ End-organ blood flow: intestinal & renal ischemia, etc.

19% renal replacement

Renal

Donation After Cardiac Death Liver Transplant Recipients Have an Increased Frequency of Acute Kidney Injury

Leithead, AJT, 2012.



Renal

- Hemodynamic disturbances: hypoperfusion
- Vasopressors
- Transfusion
- Remote IRI

Table 4: Logistic regression analysis of variables associated with perioperative acute kidney injury following donation after cardiac death liver transplantation

	Univariate analysis		Multivariate model	
	OR (95% CI)	p-Value	OR (95% CI)	p-Value
Age (years)	1.03 (0.98–1.08)	0.319	1.04 (0.97–1.12)	0.266
Female gender	1.40 (0.59–3.30)	0.442	1.19 (0.38–3.73)	0.760
Pretransplant				
MELD score	1.00 (0.92–1.08)	0.956	1.01 (0.91–1.13)	0.825
eGFR (mL/min/1.73 $m^{2)}$	1.00 (0.99–1.02)	0.744	1.01 (0.99–1.03)	0.384
Refractory ascites	3.00 (0.75–11.95)	0.119	3.81 (0.78–18.52)	0.097
Insulin-dependent diabetes	1.35 (0.35–5.18)	0.658	0.94 (0.18–5.00)	0.940
Hypertension	0.72 (0.24–2.20)	0.566	0.66 (0.15–2.95)	0.587
Perioperative				
Log intraoperative RCC transfusion (units)	6.35 (1.09–37.03)	0.040	8.88 (0.91–86.26)	0.060
Log peak AST (u/L)	6.14 (2.62–14.40)	<0.001	7.44 (2.78–19.88)	<0.001

Reference group (relative risk 1.00): male gender, no refractory ascites, no insulin-dependent diabetes mellitus, no hypertension.
AST = aspartate aminotransferase; CI = confidence interval; eGFR = estimated glomerular filtration rate; MELD = model for end-stage liver disease; OR = odds ratio; RCC = red cell concentrate.

Leithead, AJT, 2012.

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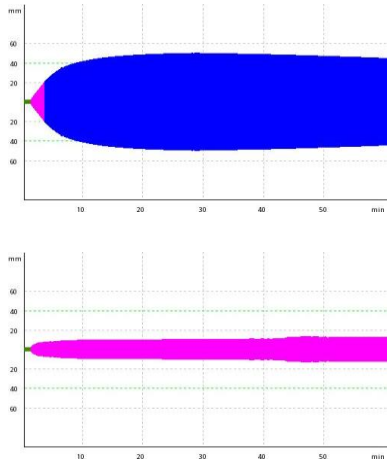
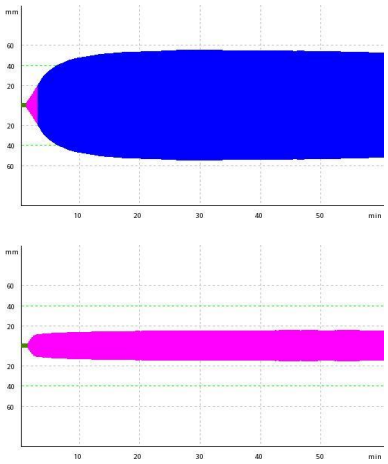
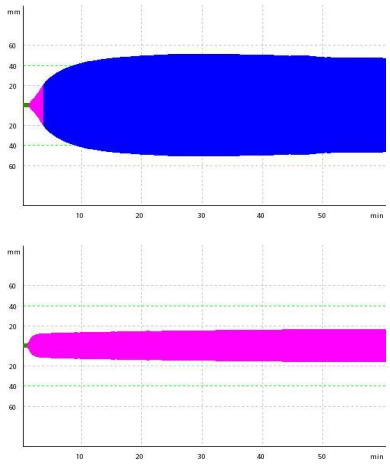
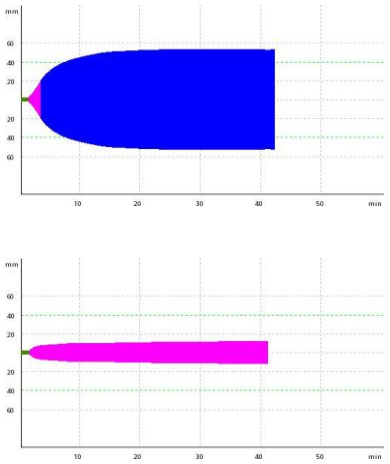
Case scenario

LT 1397: DBD

Start	Hepatectomy	Reperfusion	Biliary anast
			

TP%	62	56	45	39
PTratio	1.3	1.38	1.79	1.83
PLQ	75.000	117000	104000	111000
FIB	2	2.4	2, 0	2, 10

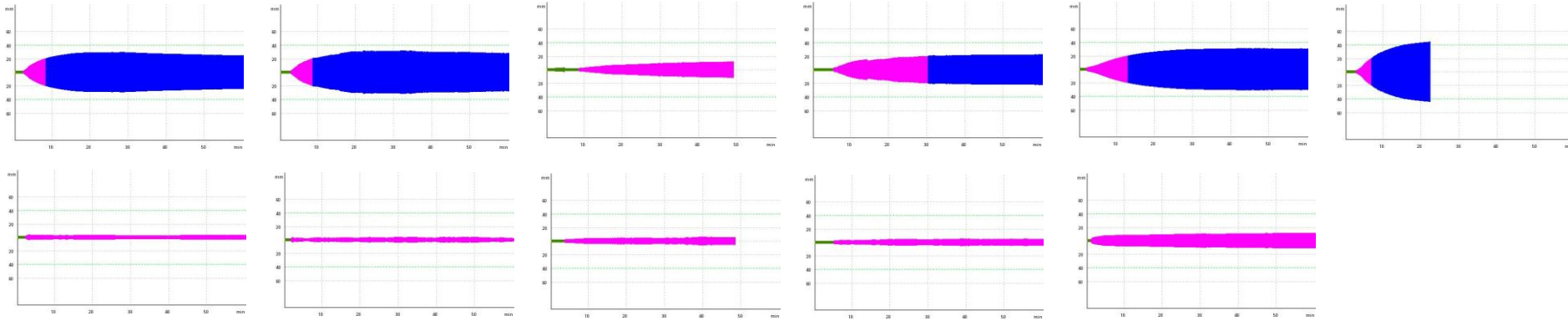
PFC
PLQ
CRIOP

Case scenario

LT 1567: uDCD

Tranexámic a

Start	Hepatectomy	Reperfusion	Biliary anast	60min post-b.a	120 min post-b.a



bleeding **packing**

TP%	21	29	11	30	40
PTratio	3, 21	2, 46	5, 68	2, 20	1.8
PLQ	60.000	67.000	27.000	40.000	50.000
FIB	1, 21	2, 20	1, 20	1, 80	2, 20

PFC		482	970
PLQ		1	1
CRIOP	18	15	15

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Coagulation

Tabla 2: Consumo de hemoderivados intra y postoperatorio en un grupo de receptores de injertos hepáticos procedentes de donantes en asistolia no controlada comparados con receptores de donantes en muerte encefálica en el periodo comprendido entre los años 2002 y 2013. Análisis pareado 1:2 por edad, sexo, índice de masa corporal, puntuación Child e indicación de trasplante.

	DONANTES EN ASISTOLIA (n=39)	DONANTES EN MUERTE ENCEFÁLICA (n=80)	p
INTRAOPERATORIO			
Concentrados de Hematíes			
Pacientes transfundidos, n (%)	30 (77)	56 (70)	0,51
Unidades	6 (4-9)	5 (2-7)	0,09
Plasma Fresco Congelado			
Pacientes transfundidos, n (%)	36 (92)	53 (66)	**<0,01**
Unidades	8 (4-14)	6 (4-10)	0,09
Plaquetas			
Pacientes transfundidos, n (%)	27(69)	34 (43)	**<0,01**
Crioprecipitados/fibrinógeno			
Pacientes transfundidos, n (%)	23 (59)	22 (28)	**<0,01**
Pacientes no transfundidos, n (%)	1 (2,5)	15 (19)	**0,01**
POSTOPERATORIO (0-4 DÍAS)			
Concentrados de Hematíes			
Pacientes transfundidos, n (%)	30 (77)	47 (59)	0,09
Unidades	7 (4-14)	2 (2-4)	**<0,01**
Plasma Fresco Congelado			
Pacientes transfundidos, n (%)	30 (77)	36 (45)	**<0,01**
Unidades	11 (4-22)	3 (2-4)	**<0,01**
Plaquetas			
Pacientes transfundidos, n (%)	23 (59)	16 (20)	**<0,01**
Crioprecipitados/fibrinógeno			
Pacientes transfundidos, n (%)	9 (23)	3 (4)	**0,01**
Pacientes no transfundidos, n (%)	5 (13)	19 (24)	0,09
Pacientes no transfundidos globalmente (intra y postoperatorio), n (%)	0 (0)	7 (9)	**0,04**

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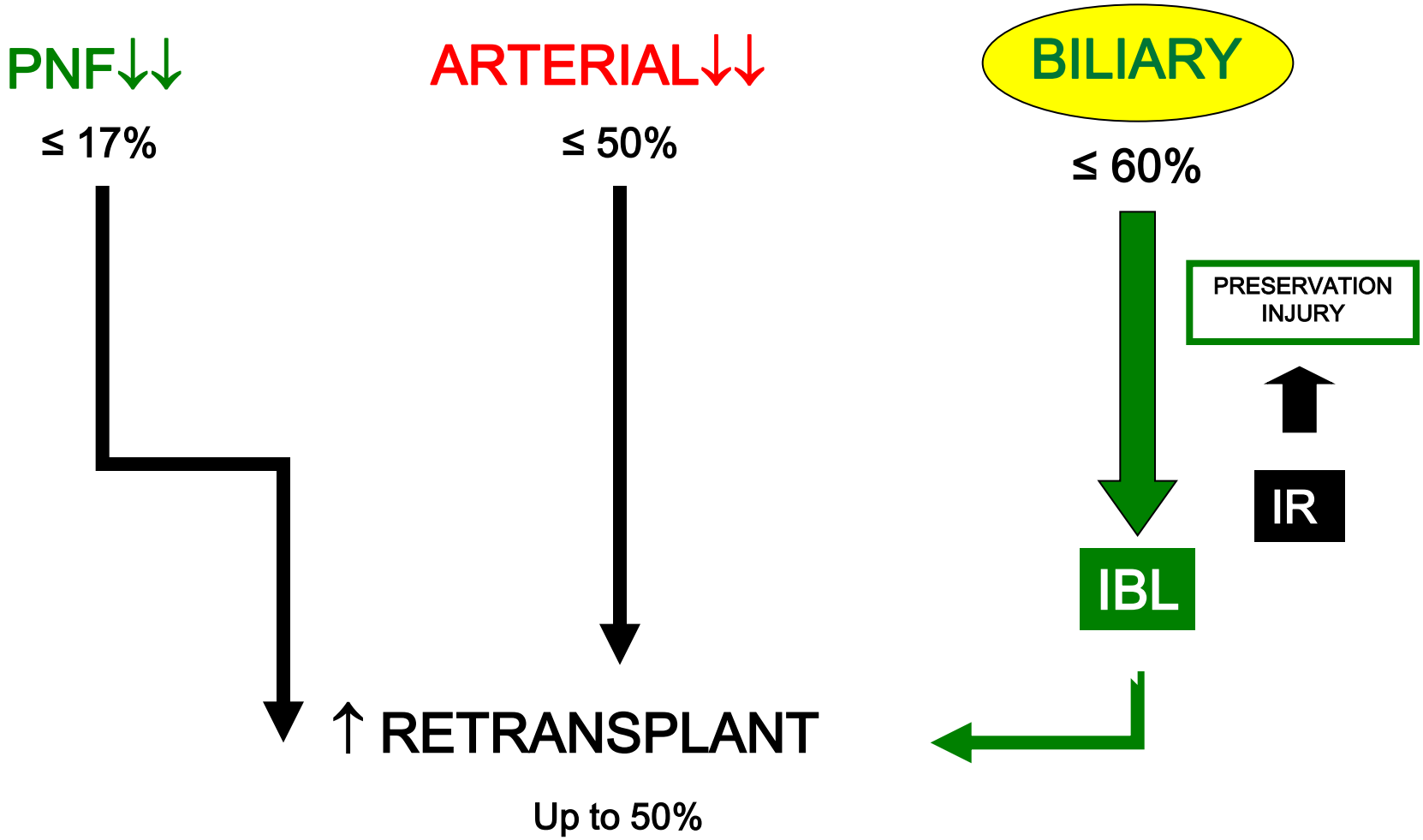
DCD transplant protocol (intraop. and ICU)

- Hemodynamic
  - Accurate fluid monitorization: PVC / PCP around 5 mmHg
  - Early vasoconstrictor support: start before reperfusion
  - Protection of renal function: MAP > 70 mmHg and urine ouput > 0.5 ml/Kg/h

DCD transplant protocol (intraop. and ICU)

- Coagulation:
  - Hb 8 gr/L or Hct 24%
  - Tranexamic acid 10 mg/Kg post-induction, and 10 mg/Kg/h until biliary anastomosis
  - Platelets > 50.000 x 10^9 and fibrinogen > 2 gr/L before reperfusion / at skin closure
  - FFP 15 ml/Kg, if INR >1.7 / PT < 40%
  - fVIIr, only if uncontrolled bleeding
  - PCC, DDAVP: no indication
  - If there is still microvascular bleeding, packing for 48h
  - In ICU, blood product transfusion only if actively bleeding

Liver transplant from DCD: complications



Single center experiences with DCD-LT

	University of Wisconsin, Wisconsin (n = 36)*	Albert Einstein Medical Center, Pennsylvania (n = 19)†	University of Pennsylvania, Pennsylvania (n = 30)‡	Kings College, London, United Kingdom (n = 32)§	Johns Hopkins University, Maryland (n = 20)
Demographics					
Donor age (years)		34	30	36	35
Recipient age (years)				38	53
WIT (minutes)	17	20	20	14	33
CIT (hours)	8.2	9.5	6.1	8.6	8.7
MELD score at orthotopic LT					19.6
Peak ALT (IU/mL)		141			1757
Results					
Follow-up time (months)‖	36 (1–80)	16 (1.5–37)	27 (1–46)	15 (1–40)	14 (1–73)
Patient survival	68% at 3 years	74%	79% at 3 years	89% at 1 year	78% at 1 year
Graft survival	50%		72% at 3 years	86% at 1 year	62% at 1 year
Retransplantation	19%	11%	6%	3%	20%
Biliary complications	37%	11%	33%	9%	55%
Hepatic artery complications	22%	16%	0	6%	30%
Primary nonfunction	5%	5%	6%	3%	5%

(Maheshwari A., Liver Transplantation 13,2007)

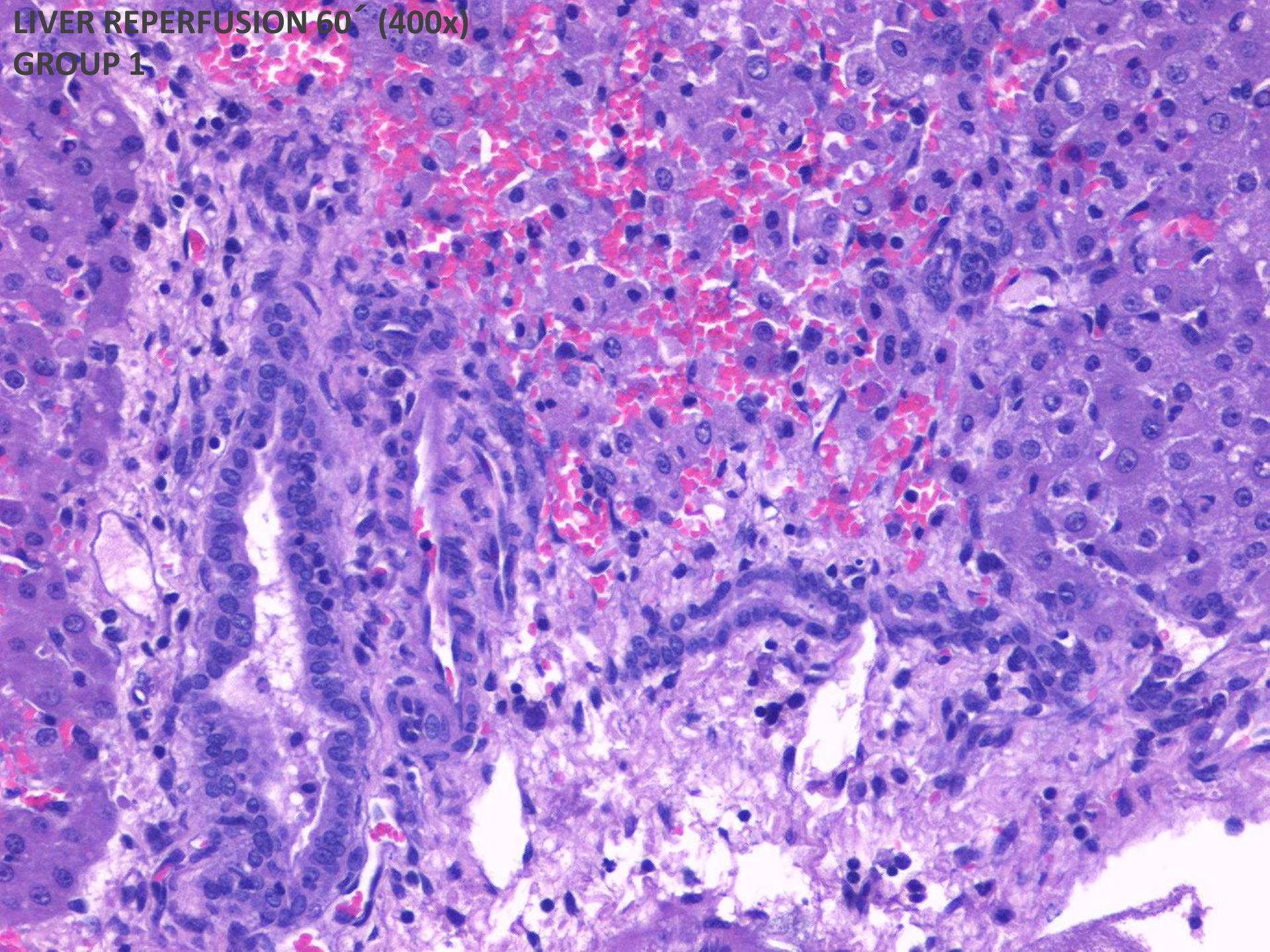
DCD morbidity

	DCD		DBD		*P*
Number	51		334		
Recipient age (years)	54.8 ± 6.8		53.3 ± 9.4		NS
Recipient gender	M38/F13		M236/F98		NS
MELD	19.6 ± 6.9		18.8 ± 8.2		NS
Status 1	0		6		NS
Donor age (years)	37.7 ± 14.5		40 ± 16.4		NS
Donor gender	M37/F14		M206/F128		NS
Total ischemia time (minutes)	473 ± 130		463 ± 160		NS
Anastomosis time (minutes)	36.1 ± 11		34.8 ± 8.1		NS
Primary nonfunction	0		11		NS
Hepatic artery thrombosis	0		16		NS
Biliary anastomotic strictures	5		26		NS
Ischemic cholangiopathy	7	**(14 %)**	4	**(1 %)**	0.0001

(University of Washington, Seattle)

Excluding donors that weighed >100 kg or those older than 50 years of age with >9h of total ischemia time, 6 out of 7 livers that did develop IC could have been avoided.

(Chan E Y., Liver Transplantation 14 2008)


LIVER REPERFUSION 60´ (400x)
GROUP 1

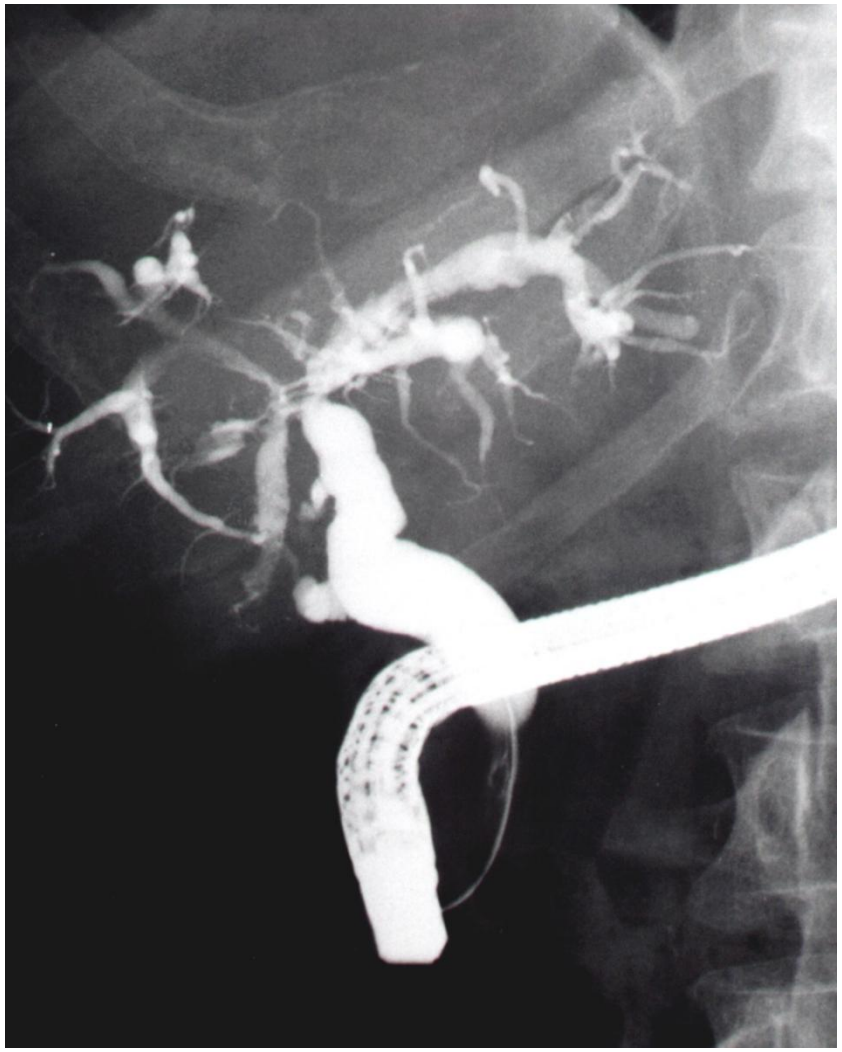
Isch. Cholangiopathy after LT

10 days

1 month

3 months

Isch. Cholangiopathy after LT



Ischemic cholangiopathy in LT from DCD

Isch. Chol.: Cost, When ReOLT?

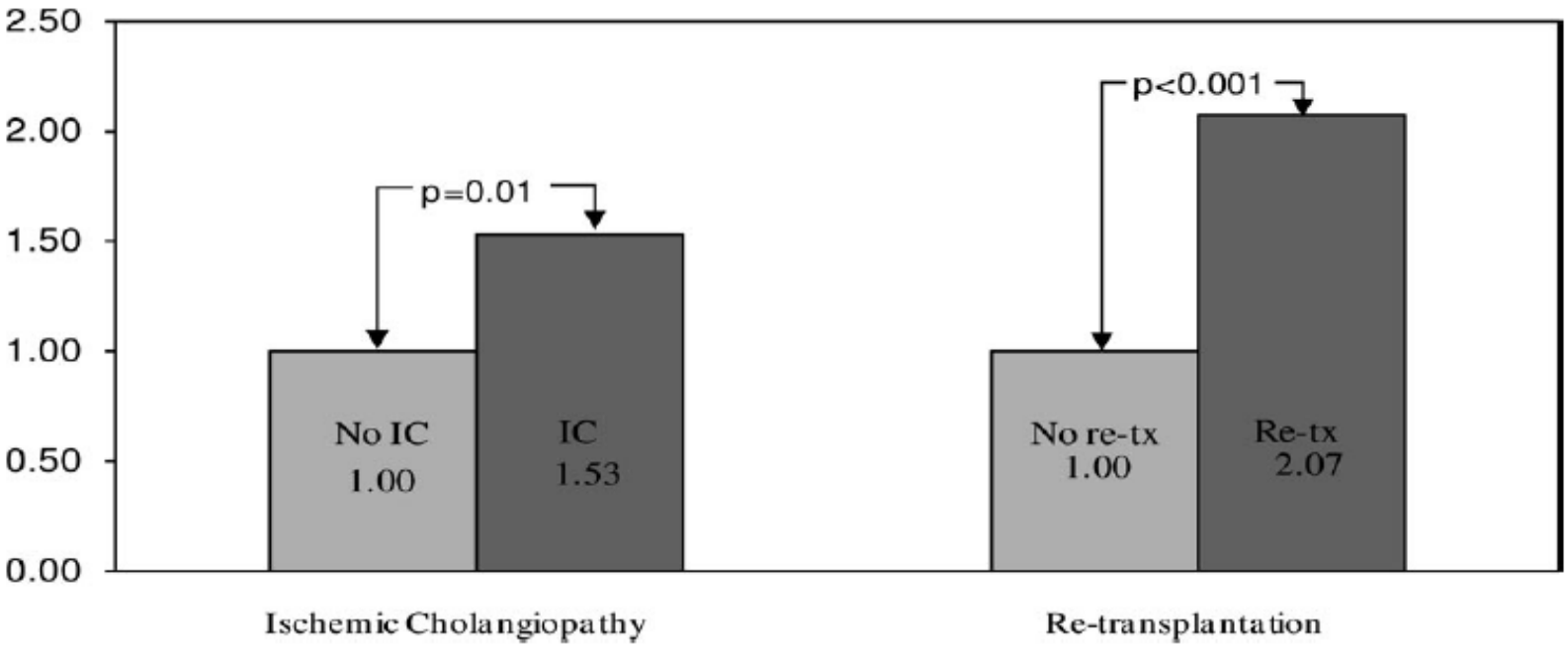
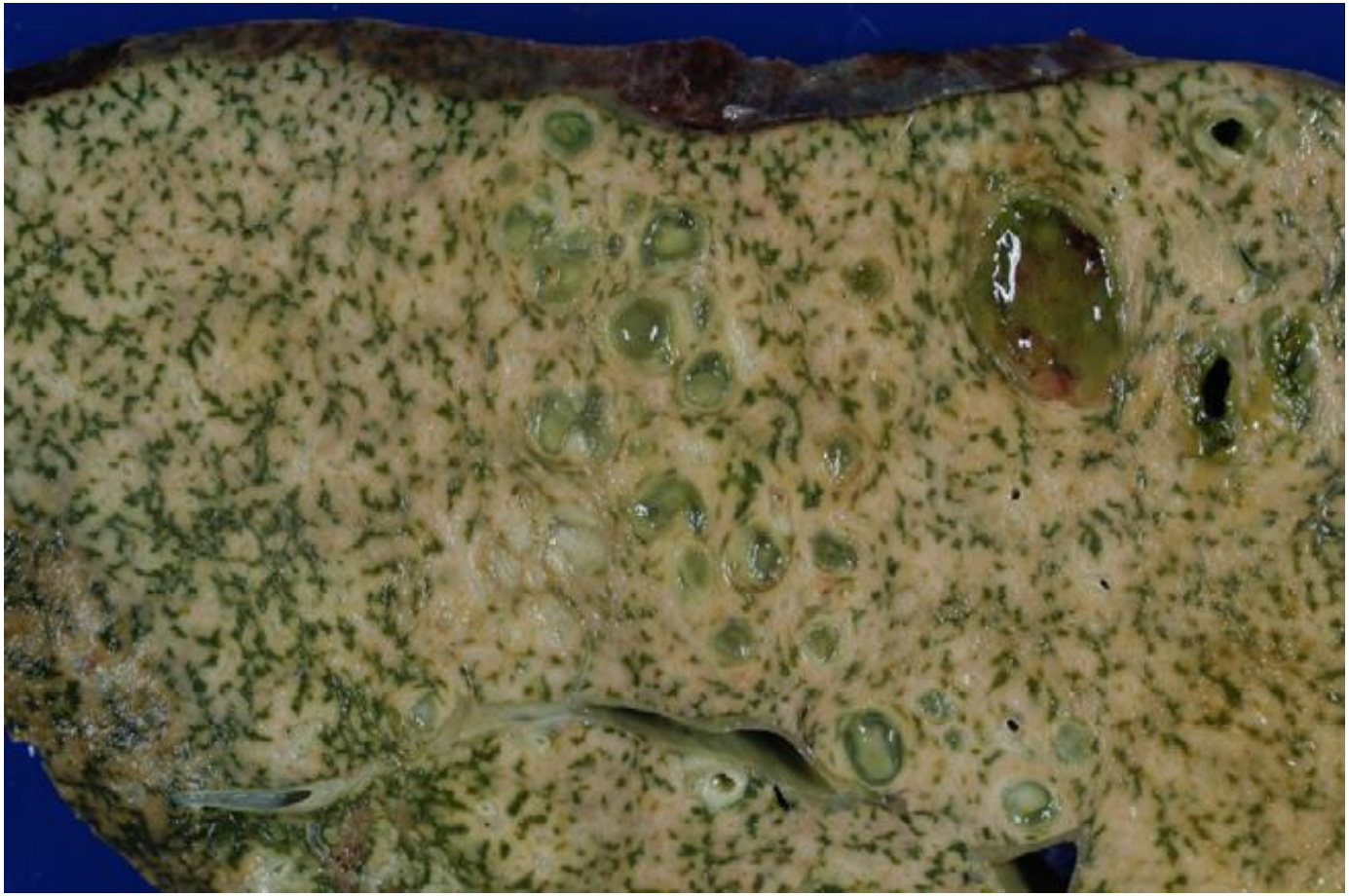


FIGURE 4. One year post-transplantation costs according to development of ischemic cholangiopathy or need for retransplantation.

(Jay CJ., Annals of Surgery (251), April 2010)

We want to use more DCD livers but … we have to avoid this! :



Lens S, Med Clin (Barc). 2012 .

Organ maintenance

Cardiac arrest

Organ procurement

Intraoperative management

Warm ischemia

Liver transplant

Postoperative care

Post-transplant Follow-up

Organ Maintenance

Technique	Results
Perfusion *in situ*	Quick and easy. Inferior results (kidney).
Thoraco-abdominal compressions	Simultaneous chest (mechanical) and abdominal (manual) compressions with the aim of maintaining MAP ≥70 mmHg and PaO2 ≥100 mmHg.[1,2]
Hypothermic recirculation	Primarily used to maintain Maastricht type III donors. Variable results, with high rates of DGF in some series (kidney). Little experience in Maastricht type II donors.[1,2]
Normothermic recirculation	Better immediate function, technique of choice for the preservation of abdominal organs. [3,4]

[1]Otero A. Transplantation 2003.
[2]Suárez F. Transplantation 2008.
[3]Fondevila C. Am J Transplant 2007.
[4]Fondevila C. Am J Transplant 2012.

DCD Maintenance

CPR & death diagnosis

Organ preservation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4 Ondas
13:21
Adulto
** SpO2 BAJA
ELECTR. ECG
FC
ST-I
ST-II
ST-aVR
EV
SpO2
87
Pulso
89
FR
Monitor En Espera
Config. Principl
Pantalla Principl
PHILIPS


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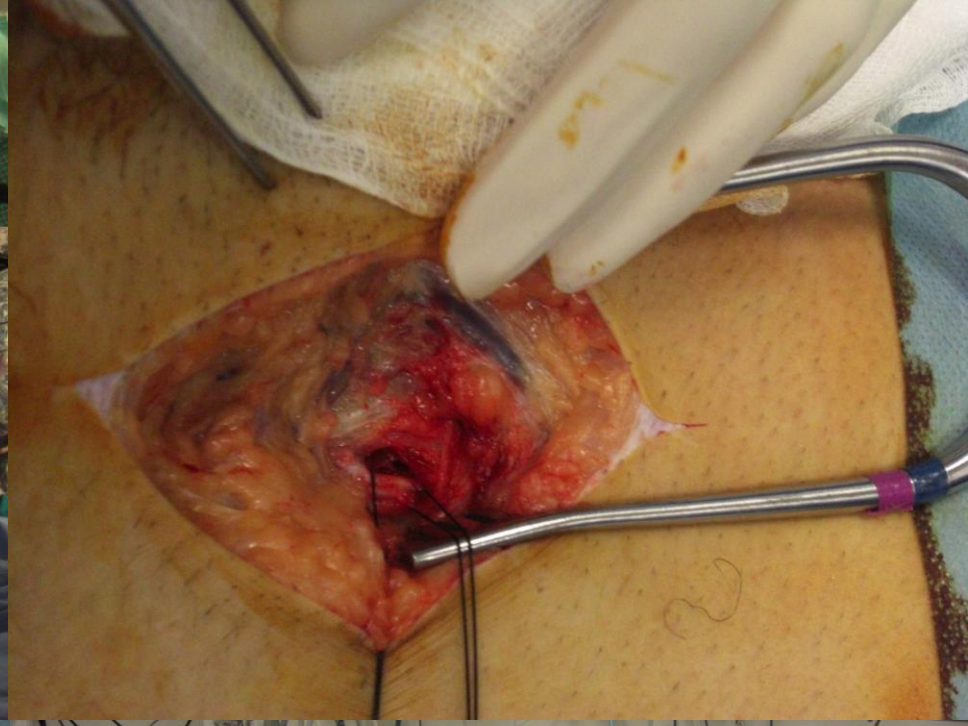
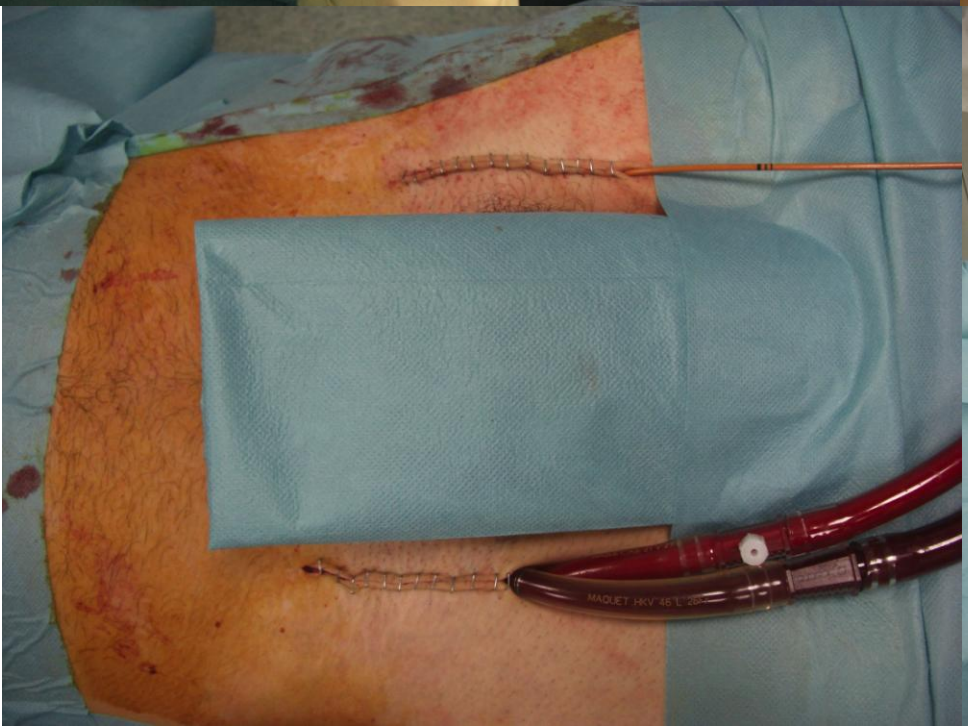
HOSPITAL CLÍNIC DE BARCELONA
PHILIPS




MAQUET HKV 45 L

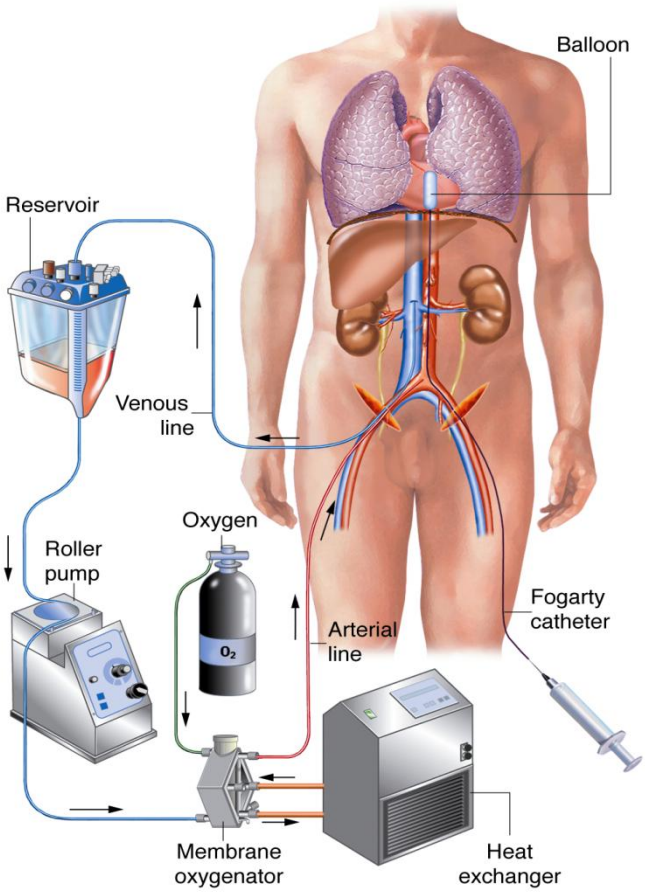
Organ Maintenance
(controlled DCD)

NRP

DCD OLT Hospital Clínic Protocol

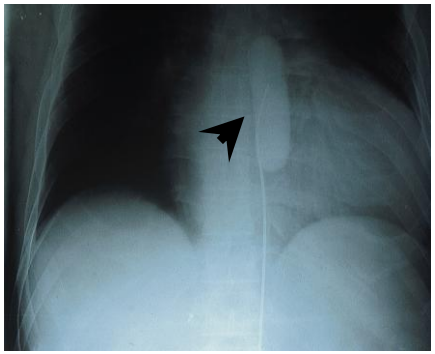
uDCD

- CARDIAC ARREST
- TRANSPORT
- HOSPITAL ARRIVAL
- DEATH DECLARATION
- CANNULATION
- NRP



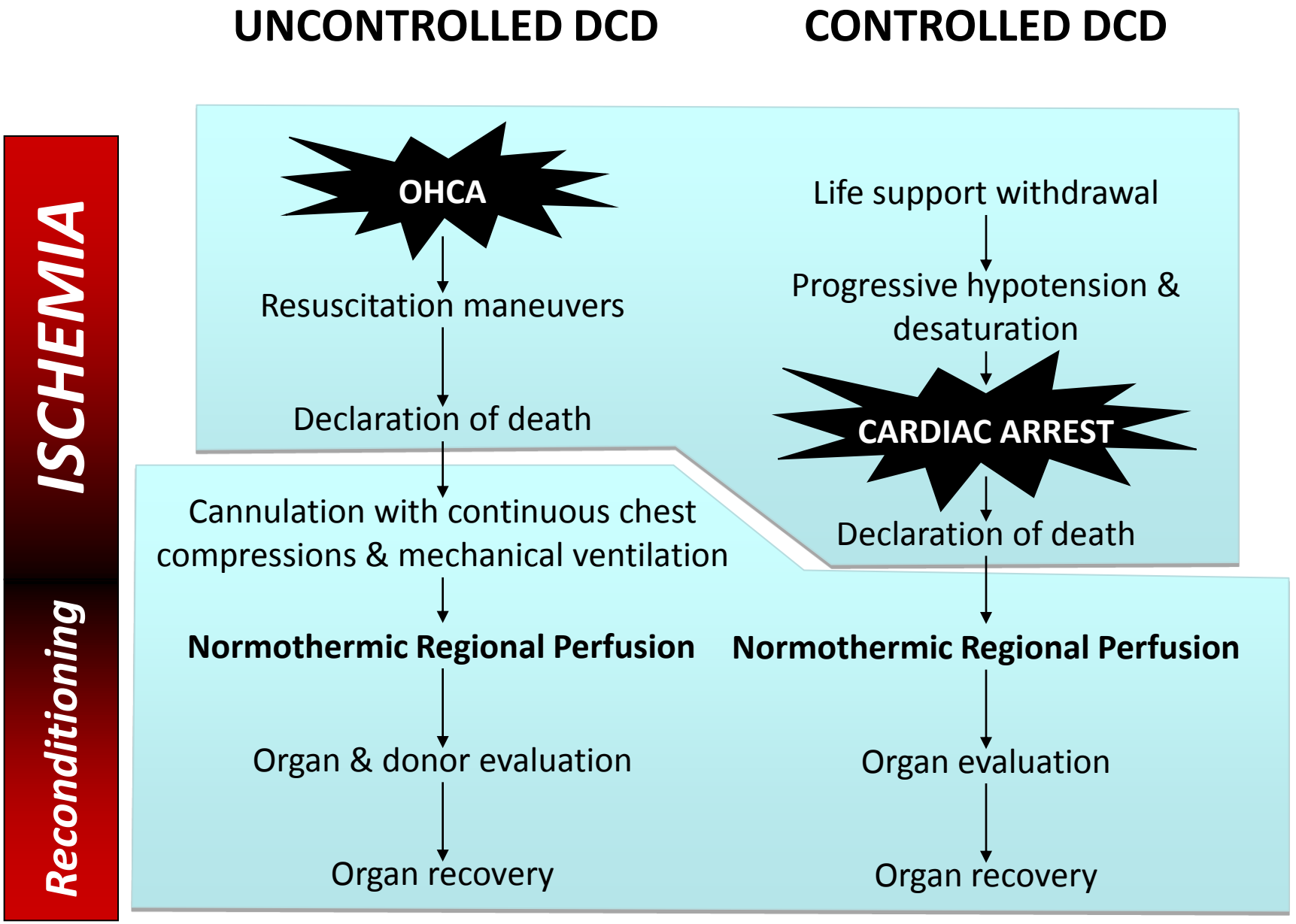
cDCD

- CANNULATION
- LIFE SUPPROT WITHDRAWAL
- CARDIAC ARREST
- DEATH DECLARATION
- NRP



Fondevila C et al, Am J Transplant 2007.
Fondevila C et al, Am J Transplant 2012.

CLÍNIC BARCELONA Hospital Universitari
Universitat de Barcelona

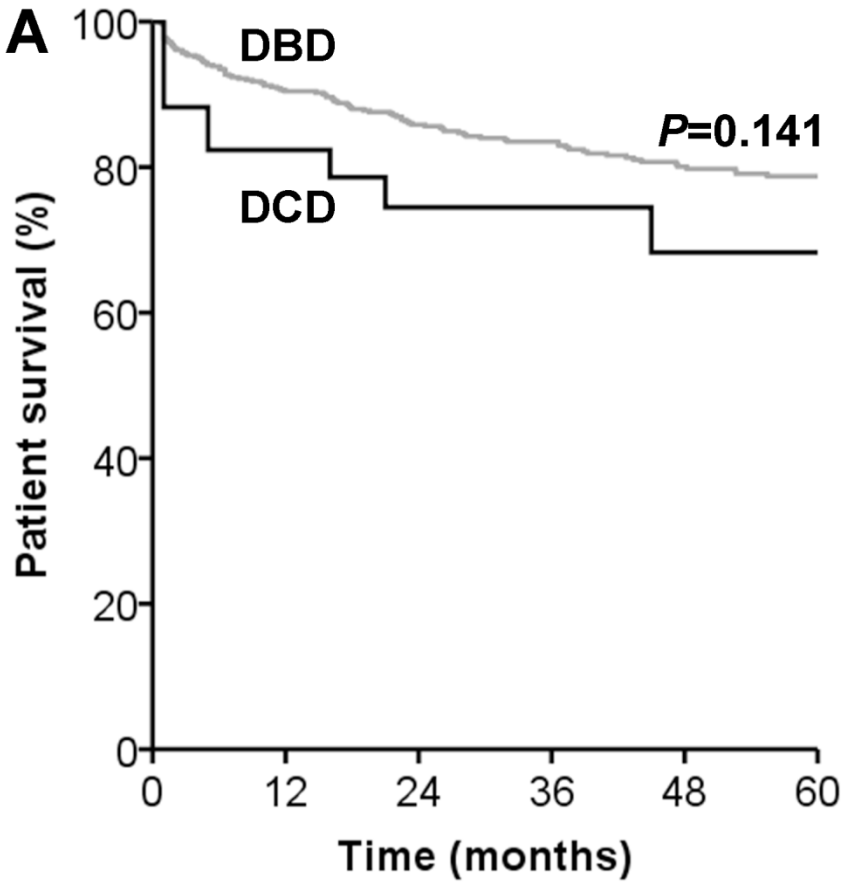

UNCONTROLLED DCD
CONTROLLED DCD
ISCHEMIA
Reconditioning
OHCA
Resuscitation maneuvers
Declaration of death
Life support withdrawal
Progressive hypotension & desaturation
CARDIAC ARREST
Declaration of death
Cannulation with continuous chest compressions & mechanical ventilation
Normothermic Regional Perfusion
Organ & donor evaluation
Organ recovery
Normothermic Regional Perfusion
Organ evaluation
Organ recovery

DCD Selection Criteria

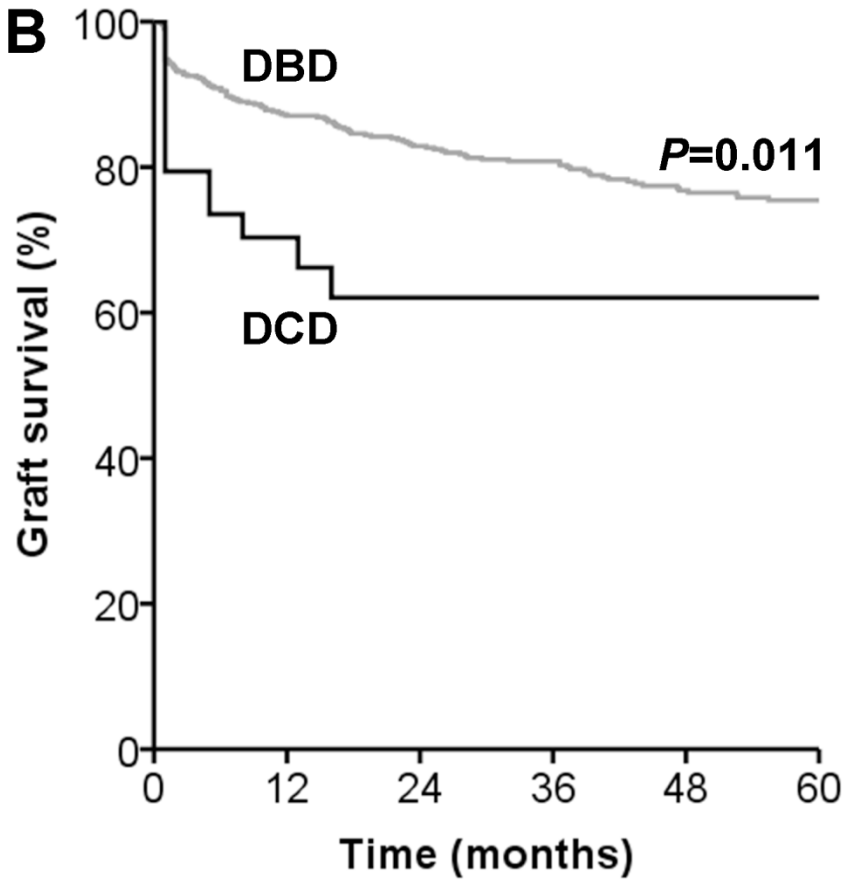
		Hospital Clínic Barcelona[1,2]
Normothermic regional perfusion	Tº	37 ºC
	pH	7.35-7.45
	PaO_2	100-150 mmHg
	Hct	>20%
	Initial AST, ALT	<3 x ULN
	Final AST, ALT	<4 x ULN
	Pump flow	>1.7 L/min with Fogarty in supraceliac aorta
	Heparinization	1.5 mg/kg every 90 min.
	Time	<4 hours

Fondevila C, Am J Transplant 2007. Fondevila C, Dig Liver Dis Suppl 2009.

Liver Survival Outcomes



DCD	34	24	17	14	9	6
DBD	538	463	390	315	254	207



DCD	34	19	12	10	6	4
DBD	538	444	375	304	242	193

Fondevila C, Am J Transplant 2011.

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Clinical Outcomes with NRP in DCD Organ Transplantation

Group	Period	DCD category	N	DGF (%)	PNF (%)	One-year survival (%)
KIDNEY						
Michigan	2000-2013	3	48	31*	3*	NR
Barcelona	2002-2014	2	158	65	9	88
La Pitié Salpêtrière	2007-2013	2	43	56	0	91
St. Petersburg	2009-2011	2	44	52	0	96
Suwon, Korea	2012	2	2	0	0	NR
LIVER						
La Coruña	1994-2005	2	10	-	NR	NR
Michigan	2000-2013	3	13	-	0	86
Barcelona	2002-2014	2	42	-	10	73
Madrid	2006-2007	2	20	-	10	86

*Rates are for 29 kidneys transplanted at the University of Michigan.

Hessheimer AJ, Transplant Int 2014.

Single-Center Experiences with Controlled DCD Liver Transplant

	N	Source	1-yr graft survival	1-yr patient survival	IC	All biliary complications
Abt 2003	15	UPenn	72%	79%	27%	33%
Chan 2008	52	UWash	~80%	~84%	14%	--
de Vera 2007	141	Pitt	69%	79%	16%	25%
Dezza 2007	13	Ghent	54%	62%	23%	--
Foley 2011	87	Wisconsin	69%	84%	34%	47%
Fujita 2007	24	Florida	69%	87%	13%	--
Grewal 2009	108	Mayo (FL)	79%	92%	8%*	--
Kaczmarek 2007	11	Newcastle	73%	82%	27%	45%
Maheshwari 2007	20	Hopkins	55%	75%	50%	60%
Manzarbeitia 2004	19	Albert Einstein	--	90%	--	11%
Pine 2009	39	St. James (UK)	80%	80%	21%	33%
Skaro 2009	32	Northwestern	61%	74%	38%	53%
DeOliveira 2011	167	King's College	90%	90%	2.5%	15%

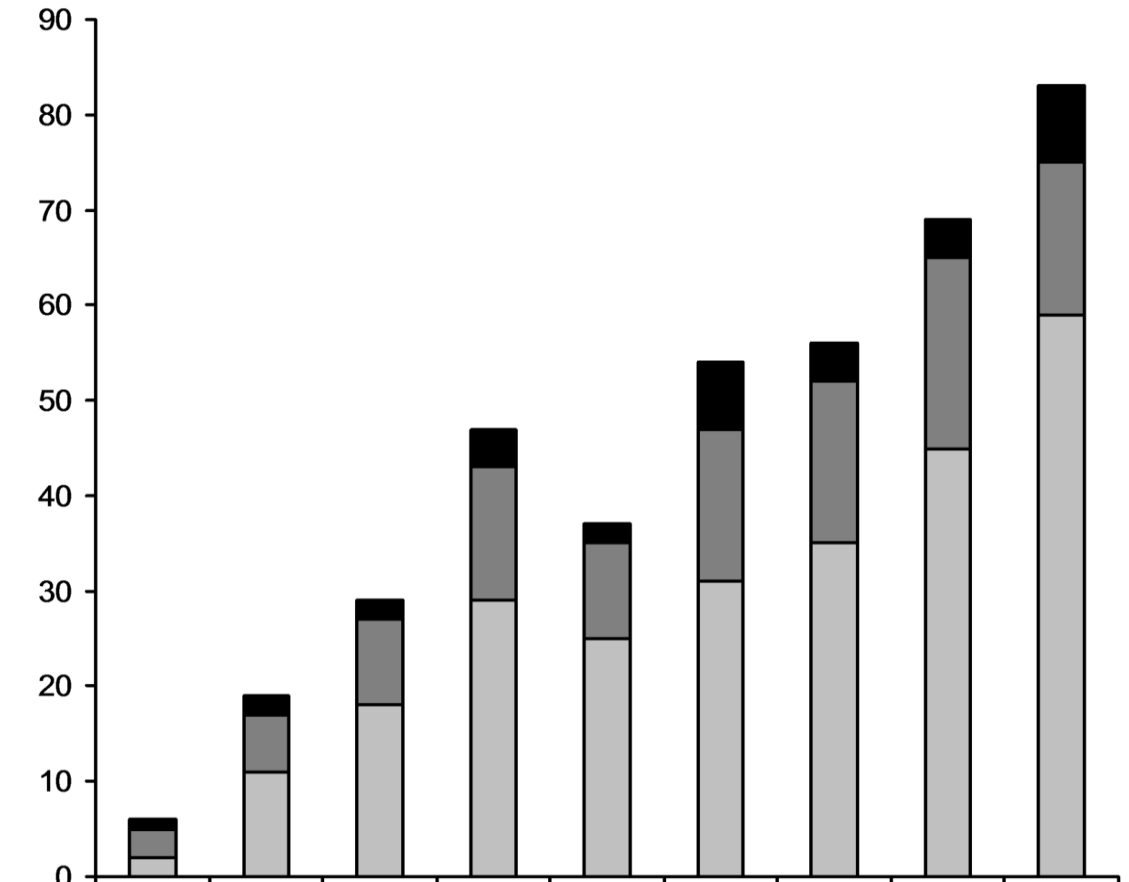
*Only cases leading to graft loss.

Fondevila 2011 ★	34	Barcelona	70%	82%	8%	12%

★ Uncontrolled

Year-to-year evolution of uncontrolled DCD activity:

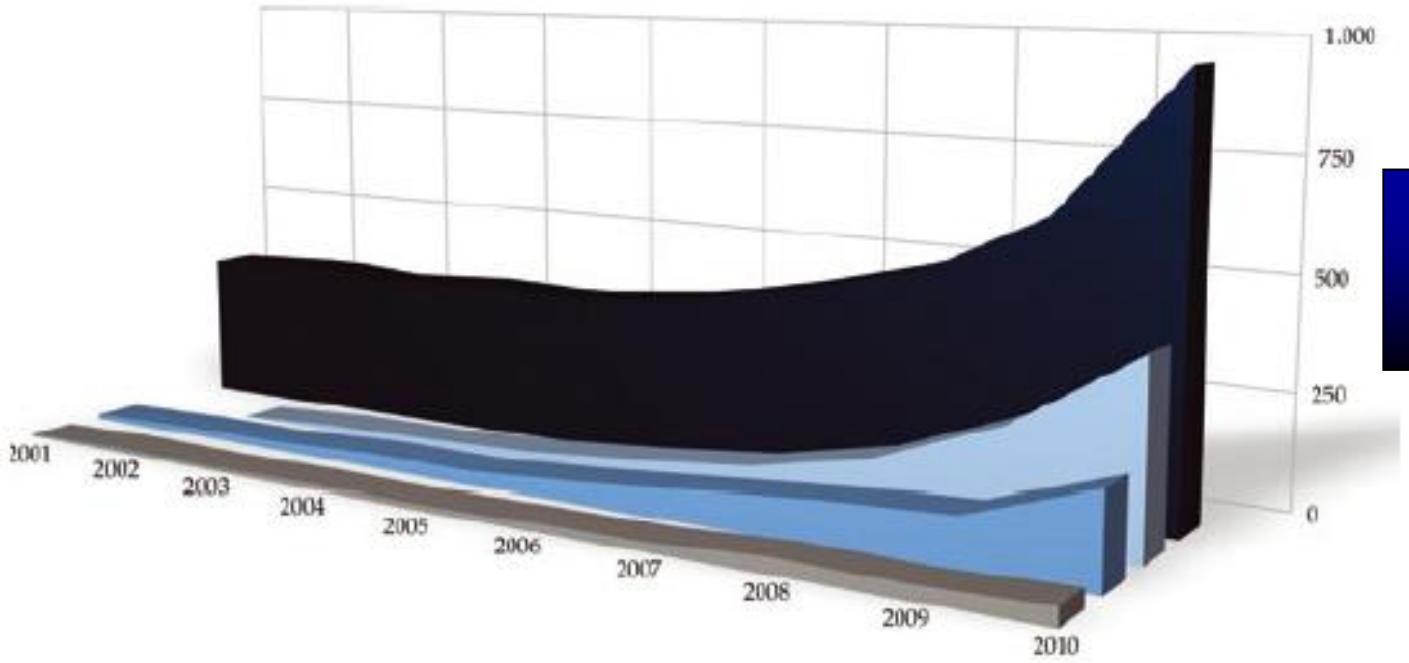
Stringent criteria



	2002*	2003	2004	2005	2006	2007	2008	2009	2010
Transplants (N=34)	1	2	2	4	2	7	4	4	8
Organ Donors (N=111)	3	6	9	14	10	16	17	20	16
Potential Donors (N=255)	2	11	18	29	25	31	35	45	59

Fondevila C, Am J Transplant 2011.

Year-to-year evolution of controlled DCD activity:



	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
DCDD USED GRAFTS	5	10	8	13	12	18	21	36	32	41
DCDD ACCEPTED OFFERS	11	18	19	30	31	49	72	95	110	201
DCDD DECLINED OFFERS	0	0	14	18	27	48	75	130	235	412
TOTAL DONATION OFFERS	347	358	342	357	349	375	429	494	631	951

Stringent criteria

Figure 3: King's College Hospital annual evolution since the start of the DCDD programme (2001–2010) of total donation offers and DCDD accepted, declined offers and used grafts.

Davila D. Am J Transplant 2012.

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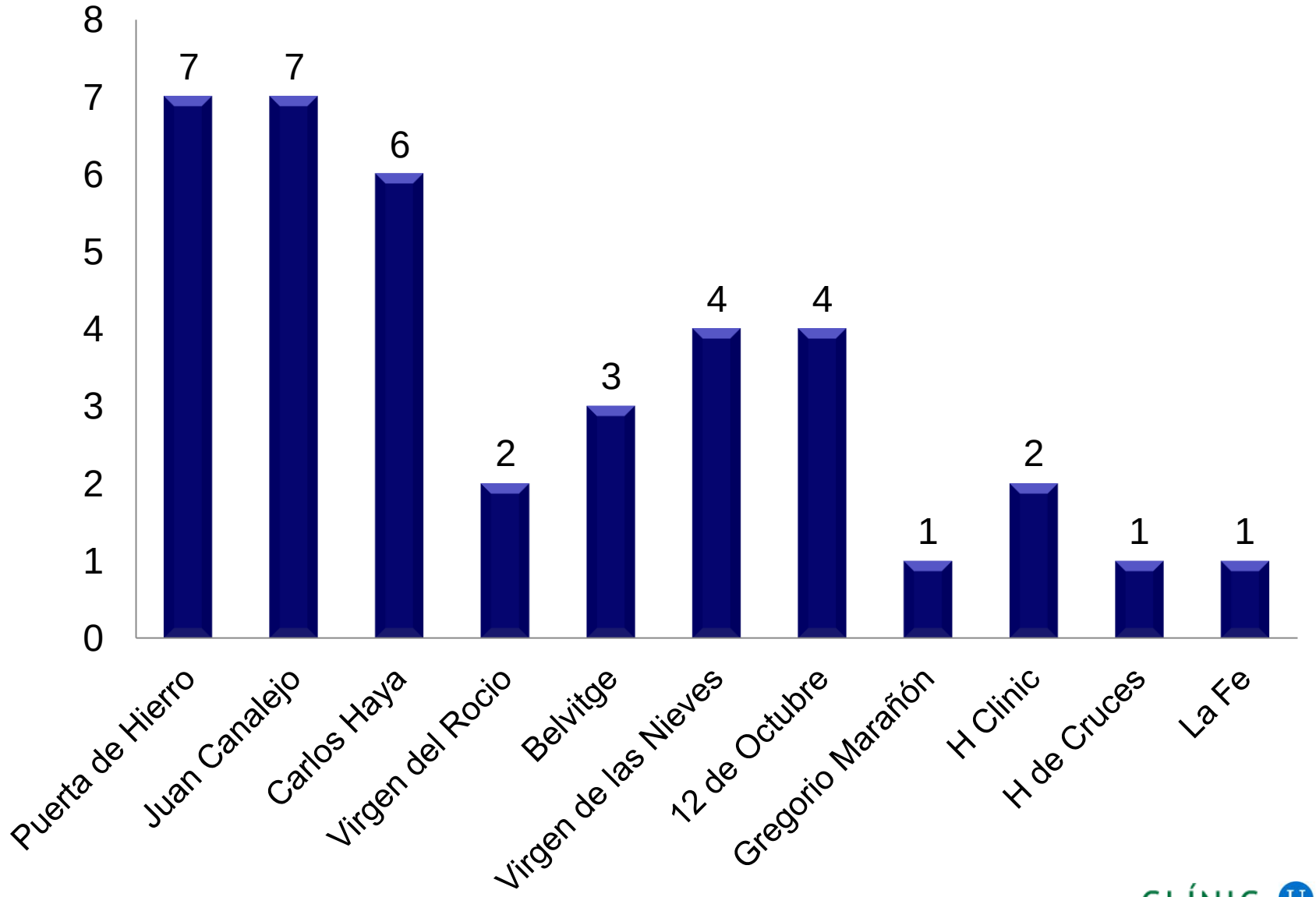
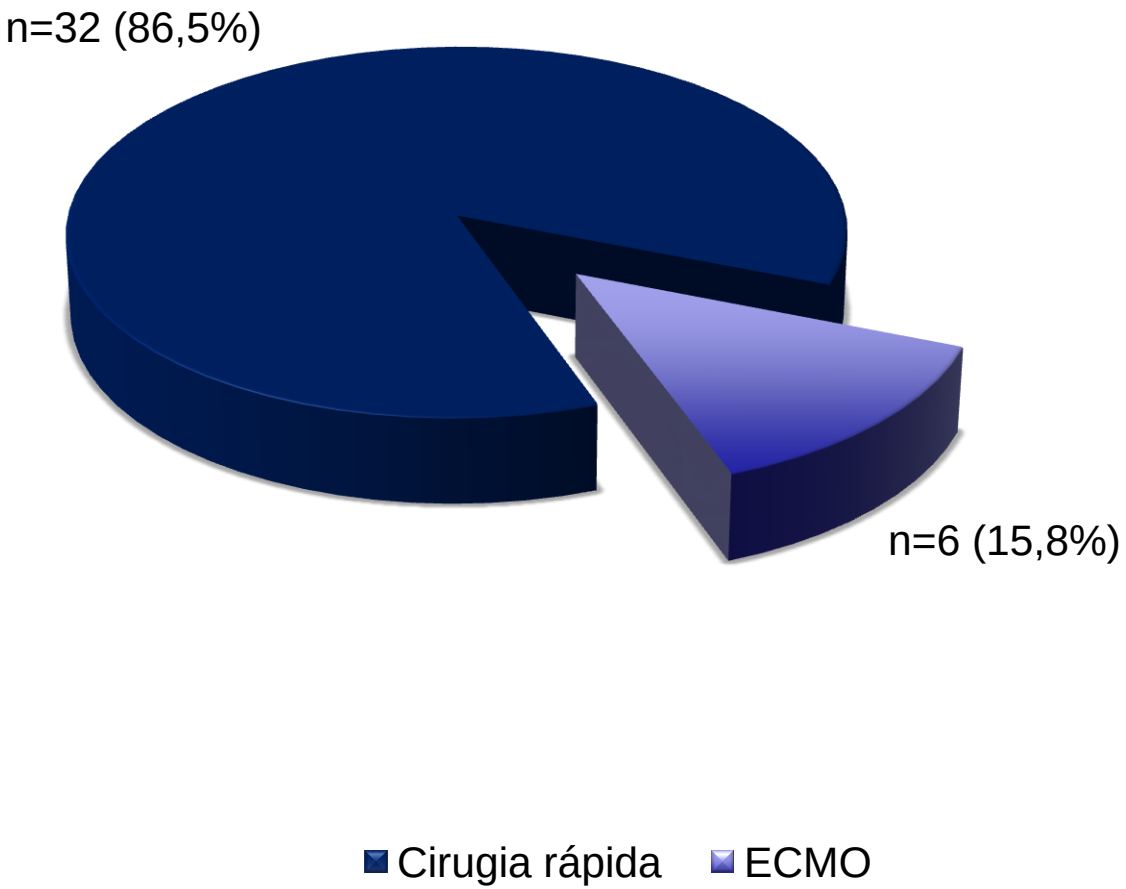
Hospitales (N=11)



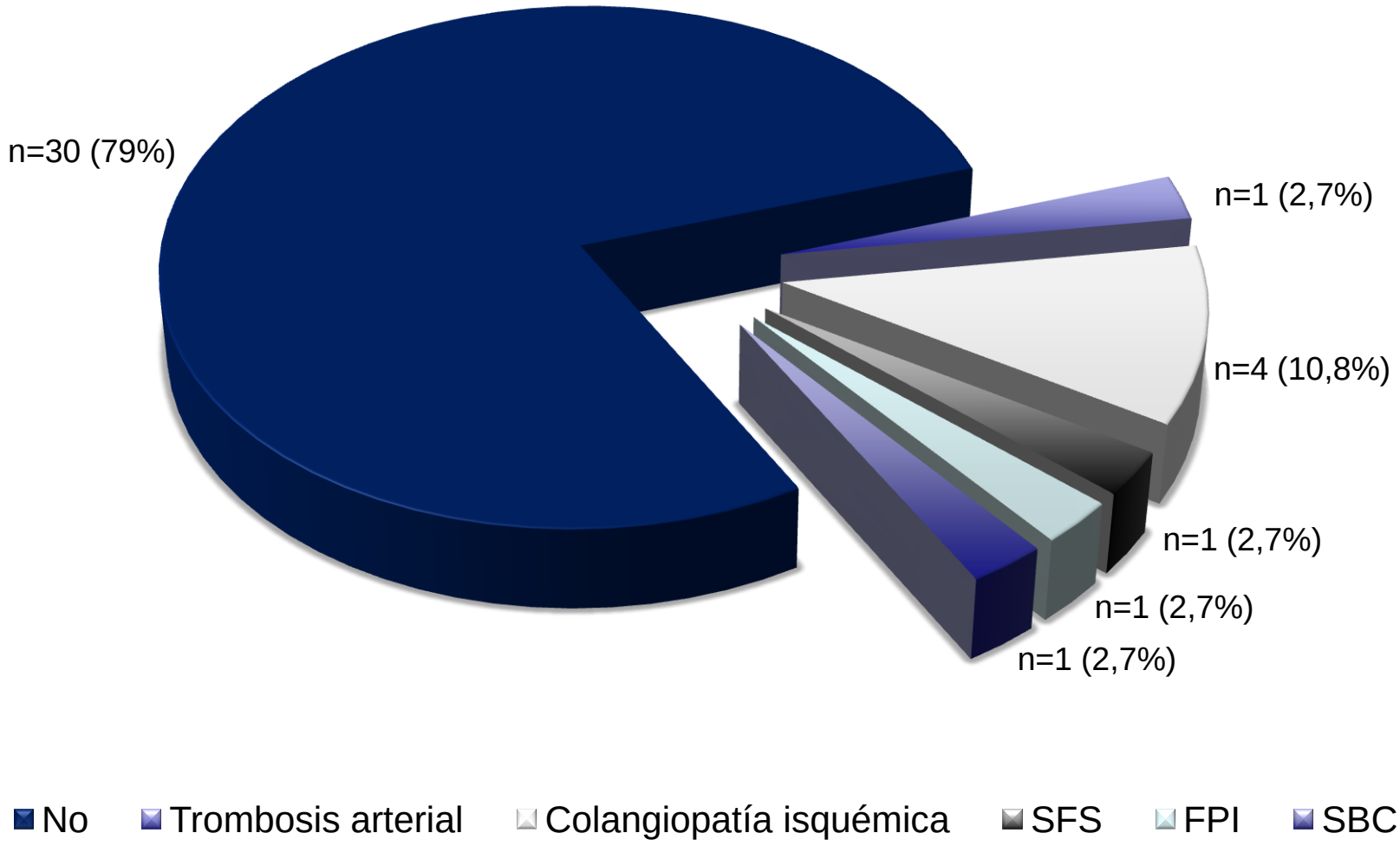
Cortesía Dr. V. Sánchez-Turrión

Tipo de extracción



Cortesía Dr. V. Sánchez-Turrión

Complicaciones



Cortesía Dr. V. Sánchez-Turrión

Causas de pérdida del injerto

✓ Colangiopatía isquémica	4 (3Rtx)
✓ Trombosis arterial	1 (Rtx)
✓ Síndrome de small for size	1 (Rtx)
✓ Fallo primario del injerto	1 (Rtx)
✓ Síndrome de Bud-Chiari	1 (Éxitus)

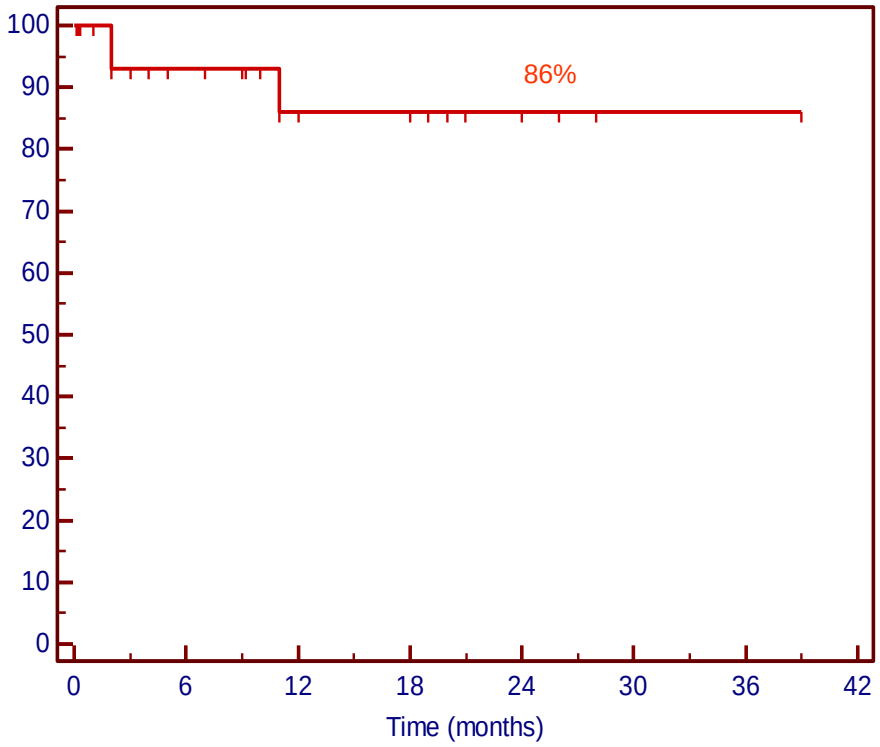
Causas de éxitus del receptor

✓ Colangiopatía isquémica	1 (Rtx)
✓ Colangiopatía isquémica	1 (en espera Rtx)
✓ Síndrome de Bud-Chiari	1

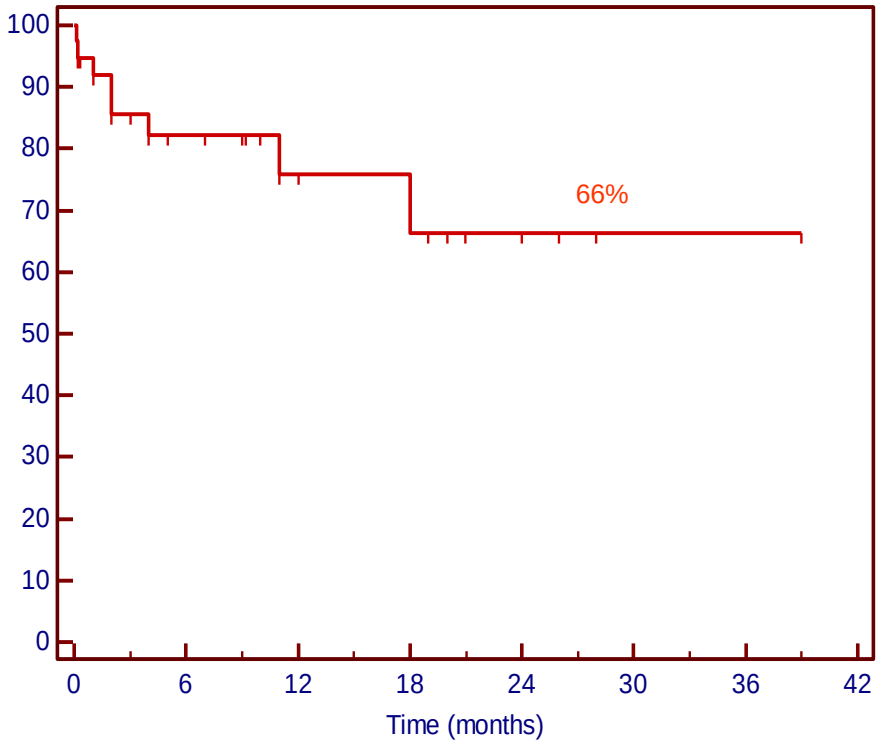
Cortesía Dr. V. Sánchez-Turrión

Supervivencia

Paciente



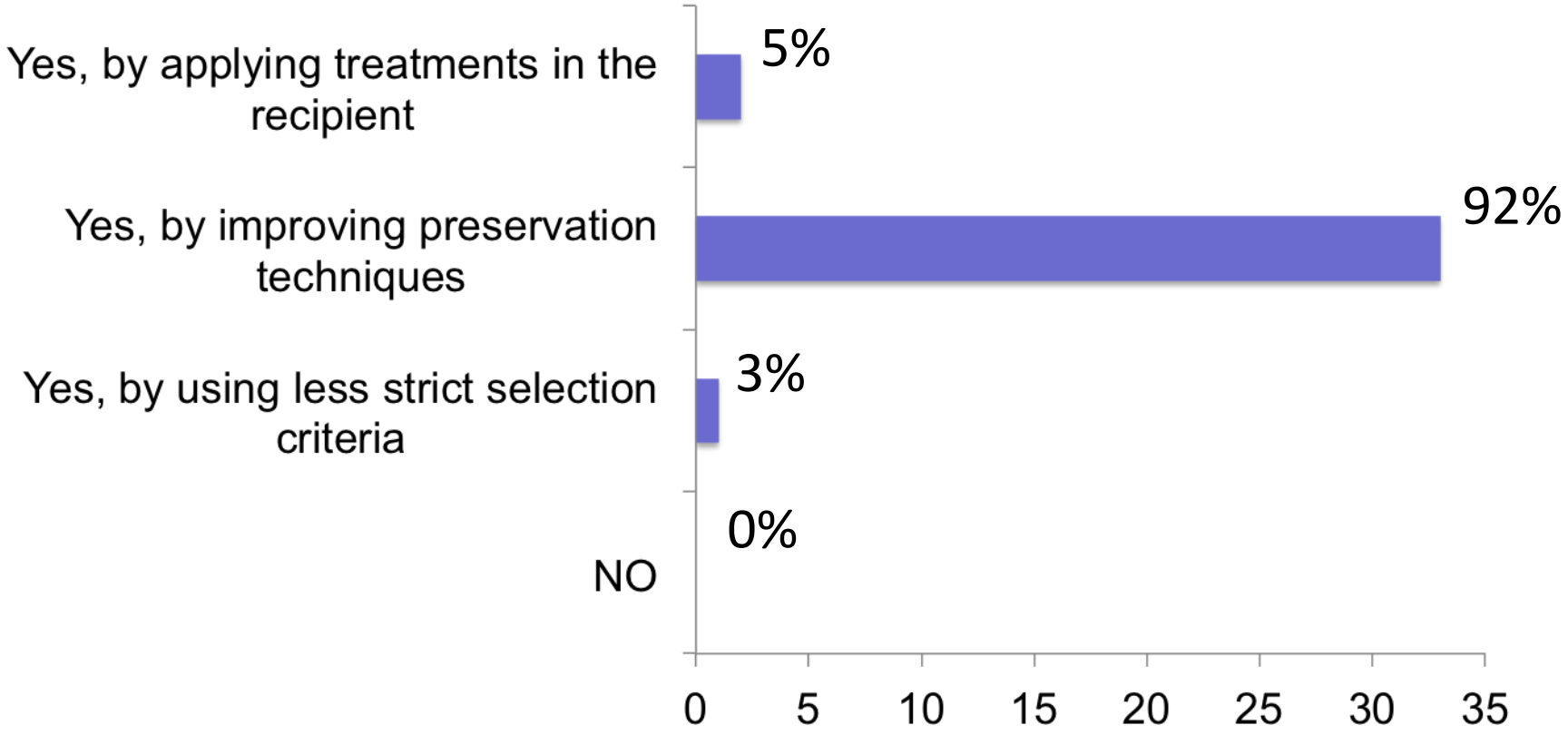
Injerto



Cortesía Dr. V. Sánchez-Turrión

II INTERNATIONAL WORKSHOP ON UNCONTROLLED DCD DONORS, Barcelona, June 27-28, 2013

Q: Do you think the applicability of uncontrolled DCD organ transplantation can be improved?



Strategies to improve outcomes

- Donor treatment:
  - Use of different substances / treatments during NRP

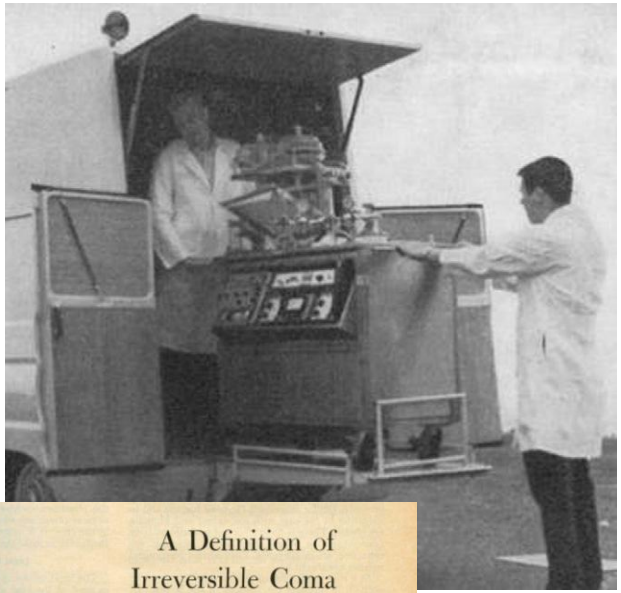
- Recipient treatment

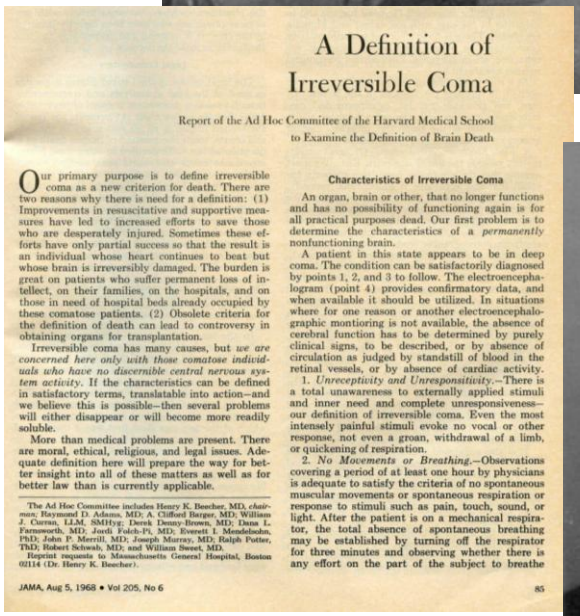
Strategies to improve outcomes

- Donor treatment:
  - Use of different substances / treatments during NRP
- Recipient treatment
- *Ex-vivo* preservation:
  - Cold storage
  - Hypothermic / Normothermic machine perfusion

Machine Perfusion in LTx

- Not new:
  - Dates back to the early- to mid-1900s (first NMP, later HMP)
  - Fell out of favor when:
    - Brain death defined (organs recovered with heart still beating)
    - Modern static cold storage solutions developed





A Definition of Irreversible Coma

Report of the Ad Hoc Committee of the Harvard Medical School to Examine the Definition of Brain Death

Our primary purpose is to define irreversible coma as a new criterion for death. There are two reasons why there is need for a definition: (1) Improvements in resuscitative and supportive measures have led to increased efforts to save those who are desperately injured. Sometimes these efforts have only partial success so that the result is an individual whose heart continues to beat but whose brain is irreversibly damaged. The burden is great on patients who suffer permanent loss of intellect, on their families, on the hospitals, and on those in need of hospital beds already occupied by these comatose patients. (2) Obsolete criteria for the definition of death can lead to controversy in obtaining organs for transplantation.

Irreversible coma has many causes, but *we are concerned here only with those comatose individuals who have no discernible central nervous system activity*. If the characteristics can be defined in satisfactory terms, translatable into action—and we believe this is possible—then several problems will either disappear or will become more readily soluble.

More than medical problems are present. There are moral, ethical, religious, and legal issues. Adequate definition here will prepare the way for better insight into all of these matters as well as for better law than is currently applicable.

The Ad Hoc Committee includes Henry K. Beecher, MD, *chairman*; Raymond D. Adams, MD; A. Clifford Barger, MD; William J. Curran, LLM, SMHyg; Derek Denny-Brown, MD; Dana L. Farnsworth, MD; Jordi Folch-Pi, MD; Everett I. Mendelsohn, PhD; John P. Merrill, MD; Joseph Murray, MD; Ralph Potter, ThD; Robert Schwab, MD; and William Sweet, MD.

Reprint requests to Massachusetts General Hospital, Boston 02114 (Dr. Henry K. Beecher).

JAMA, Aug 5, 1968 • Vol 205, No 6

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Characteristics of Irreversible Coma

An organ, brain or other, that no longer functions and has no possibility of functioning again is for all practical purposes dead. Our first problem is to determine the characteristics of a *permanently* nonfunctioning brain.

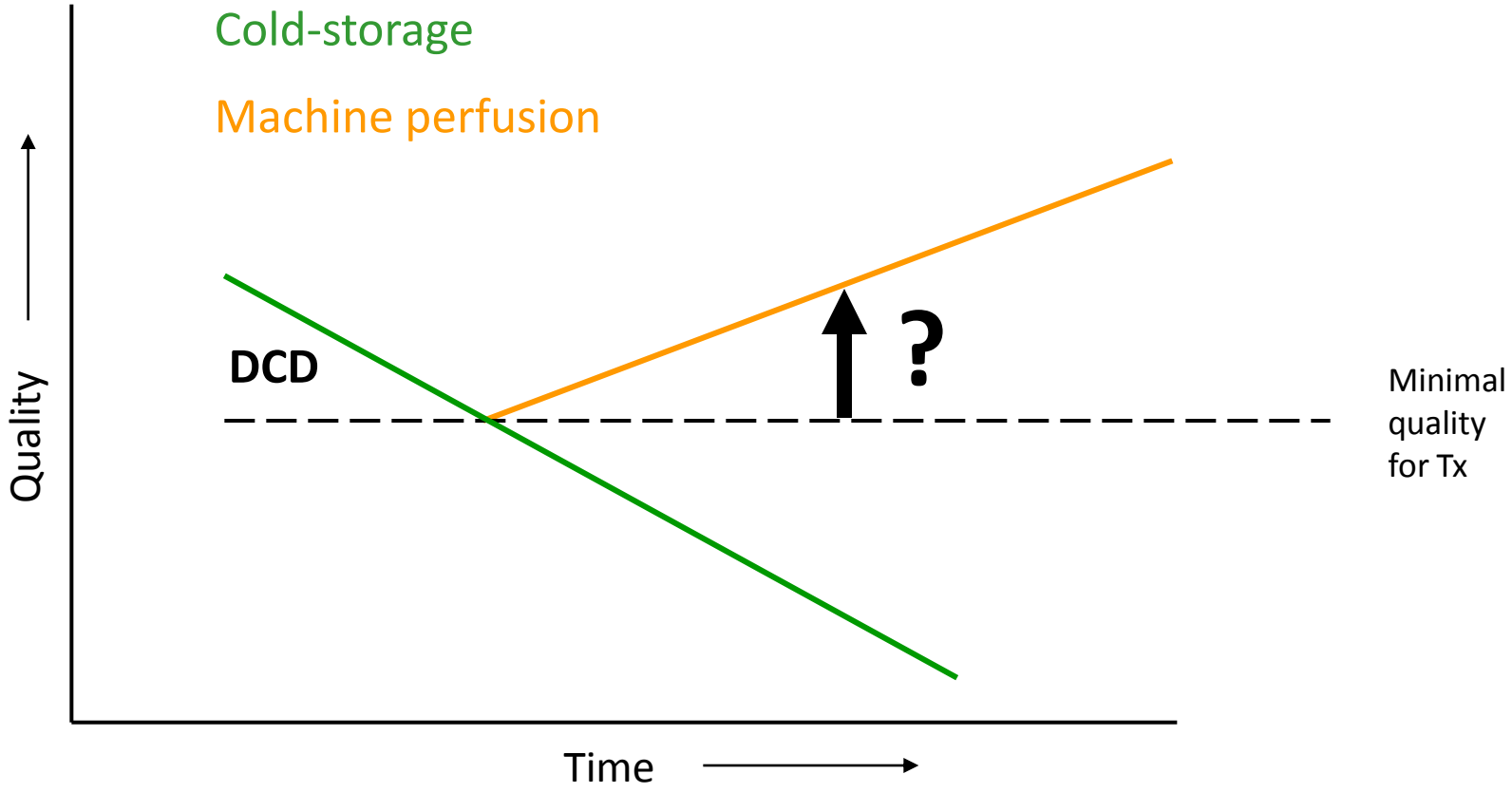
A patient in this state appears to be in deep coma. The condition can be satisfactorily diagnosed by points 1, 2, and 3 to follow. The electroencephalogram (point 4) provides confirmatory data, and when available it should be utilized. In situations where for one reason or another electroencephalographic monitoring is not available, the absence of cerebral function has to be determined by purely clinical signs, to be described, or by absence of circulation as judged by standstill of blood in the retinal vessels, or by absence of cardiac activity.

1. *Unreceptivity and Unresponsitivity.*—There is a total unawareness to externally applied stimuli and inner need and complete unresponsiveness—our definition of irreversible coma. Even the most intensely painful stimuli evoke no vocal or other response, not even a groan, withdrawal of a limb, or quickening of respiration.

2. *No Movements or Breathing.*—Observations covering a period of at least one hour by physicians is adequate to satisfy the criteria of no spontaneous muscular movements or spontaneous respiration or response to stimuli such as pain, touch, sound, or light. After the patient is on a mechanical respirator, the total absence of spontaneous breathing may be established by turning off the respirator for three minutes and observing whether there is any effort on the part of the subject to breathe

Fuller BJ, Cryobiology 2007.

Machine Perfusion in LTx



Future of liver MP

- Well-designed clinical trials:
  - Marginal grafts that *undoubtedly* wouldn't be used otherwise
  - RCTs with *clinically relevant* endpoints (e.g., EAD, PNF, survival)
- Ongoing investigation:
  - Cellular/molecular alterations in DCD
  - Pathways implicated in regeneration
  - How to supplement all that is needed *in vivo* *in vitro*…