
بسم الله الرحمن الرحيم

The Living donors are better than the Deceased Donors: A fact or Fiction?

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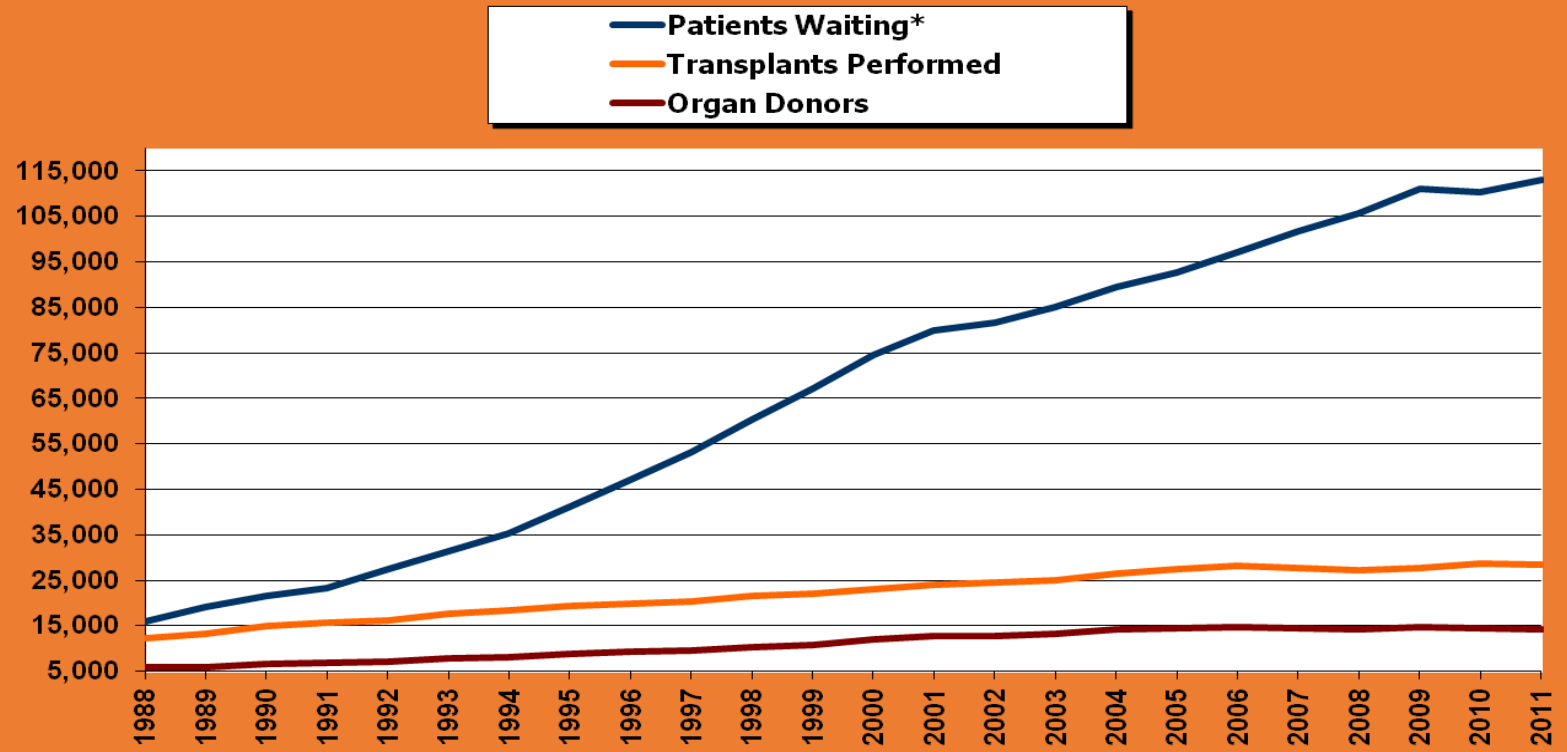
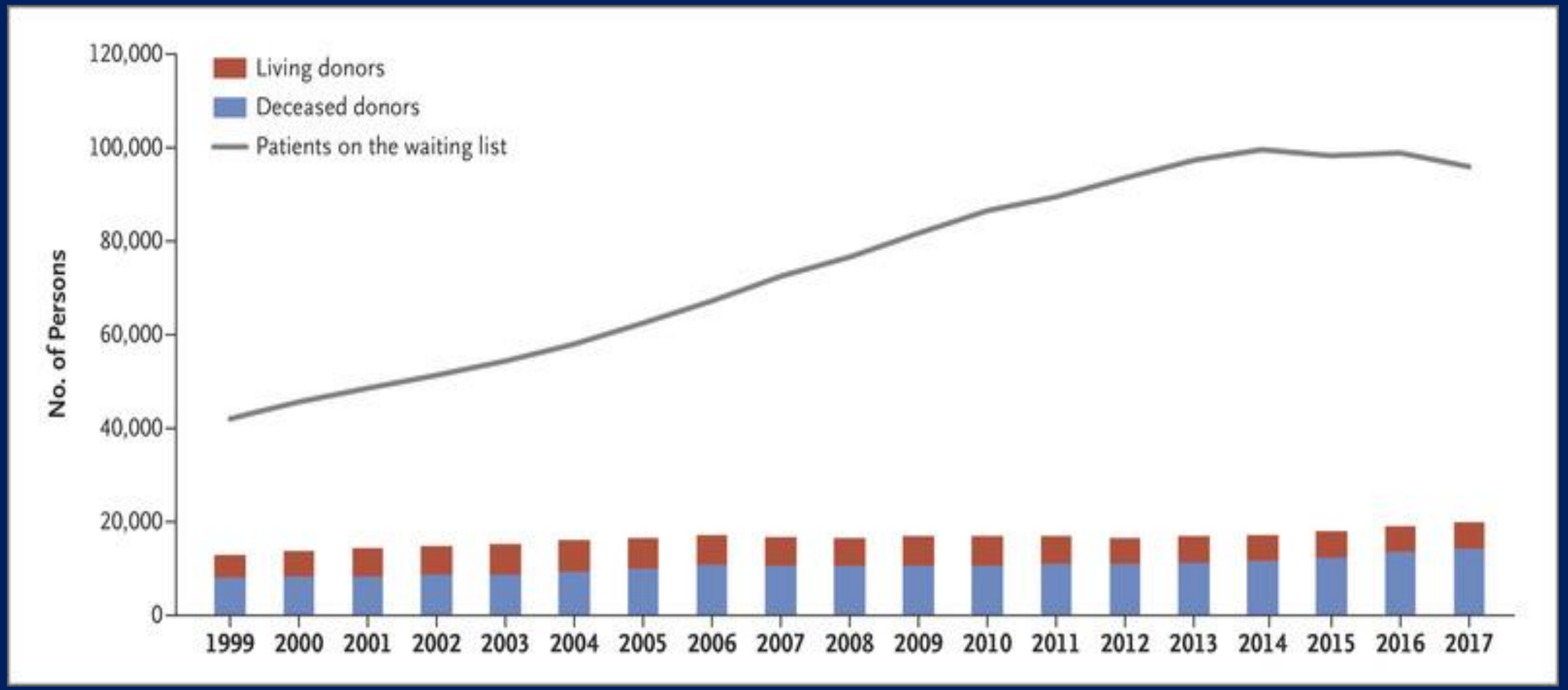
Outline

1. Patient and Graft survivals
2. Economical burden of deceased and living transplantation on the community and recipients
3. Pre-emptive renal Transplantation: Deceased or Living?
4. Influences of the living and deceased donors on the recipient Immunology

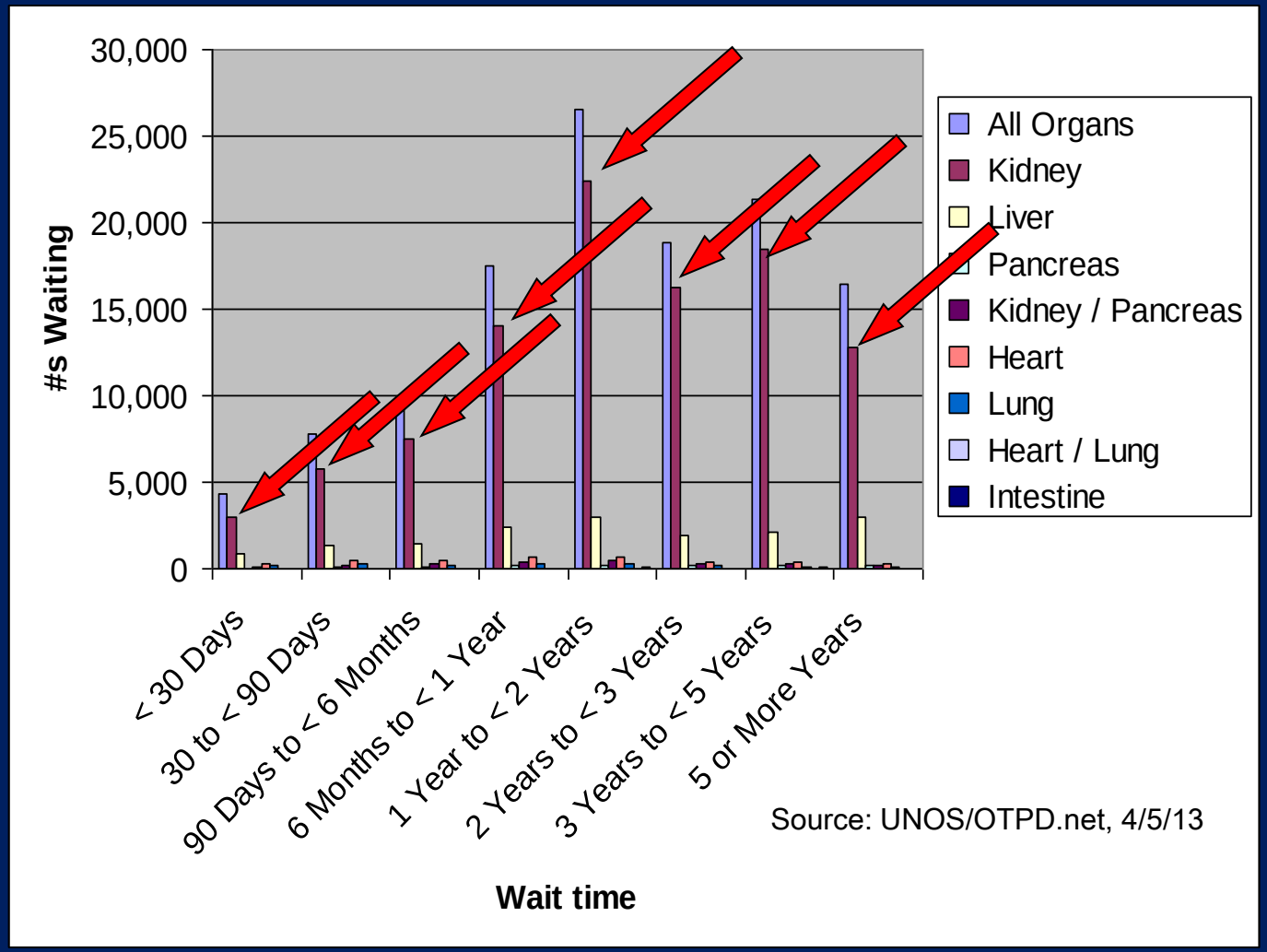
"The Gap"



*Data based on snapshot of the UNOS, OPTN waiting list and transplants on the last day of each year.


120,000
100,000
80,000
60,000
40,000
20,000
0
No. of Persons
Living donors
Deceased donors
Patients on the waiting list
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017

How long does the typical waitlisted patient wait for a transplant?



UW Average Waiting Times

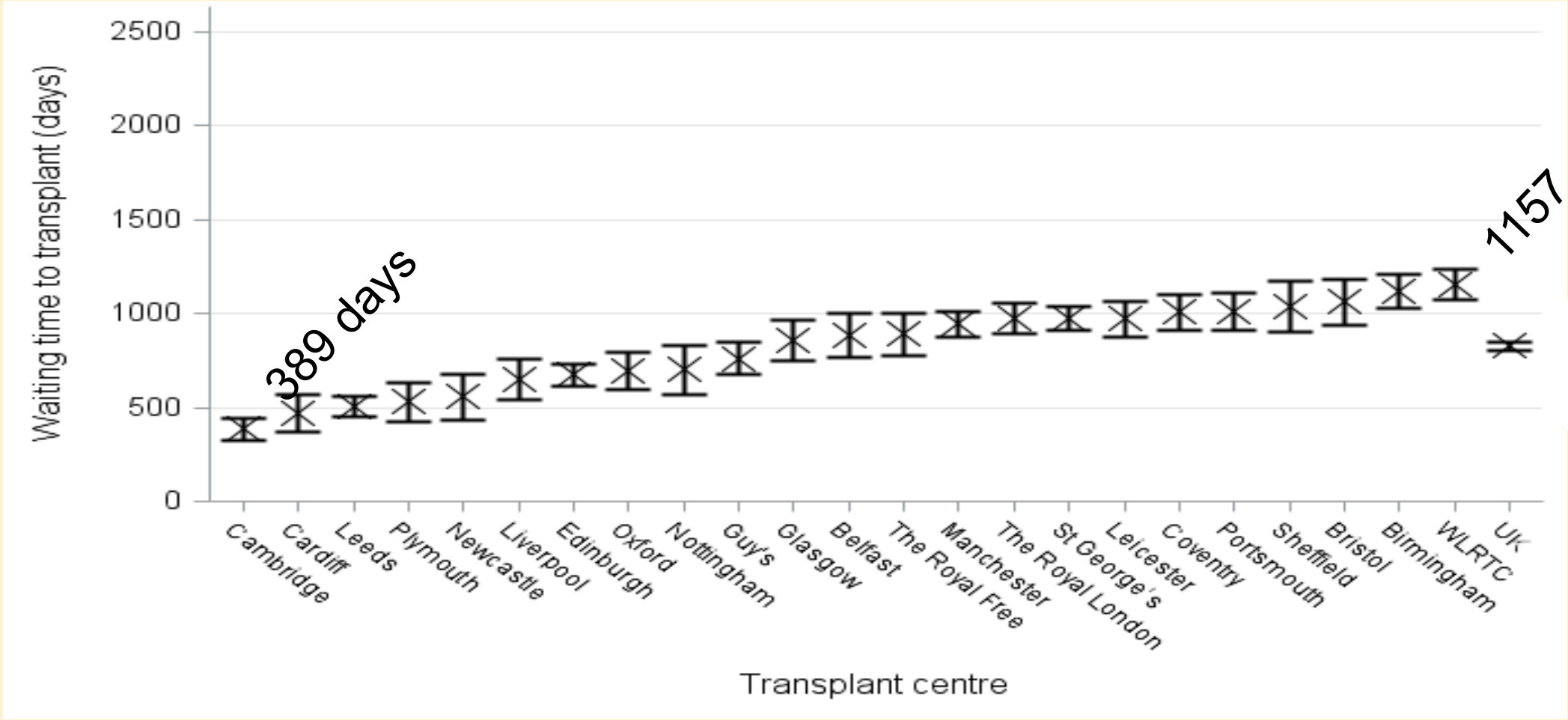
Deceased Donor Kidney Transplants

- Wait Time by Blood Type

(Includes patients transplanted between 7/1/2010 - 6/30/2012)

ABO	Average days
A	315
AB	286
B	684
O	811

Median waiting time to deceased donor kidney transplant for adult patients, 1 April 2011 – 31 March 2014



829 days
2.3 years


*Each day, 10 European citizens die whilst waiting for a suitable organ transplant, that's almost 4,000 people on a yearly basis**

**3820 deaths on the waiting list in 2009, Council of Europe data 2010*

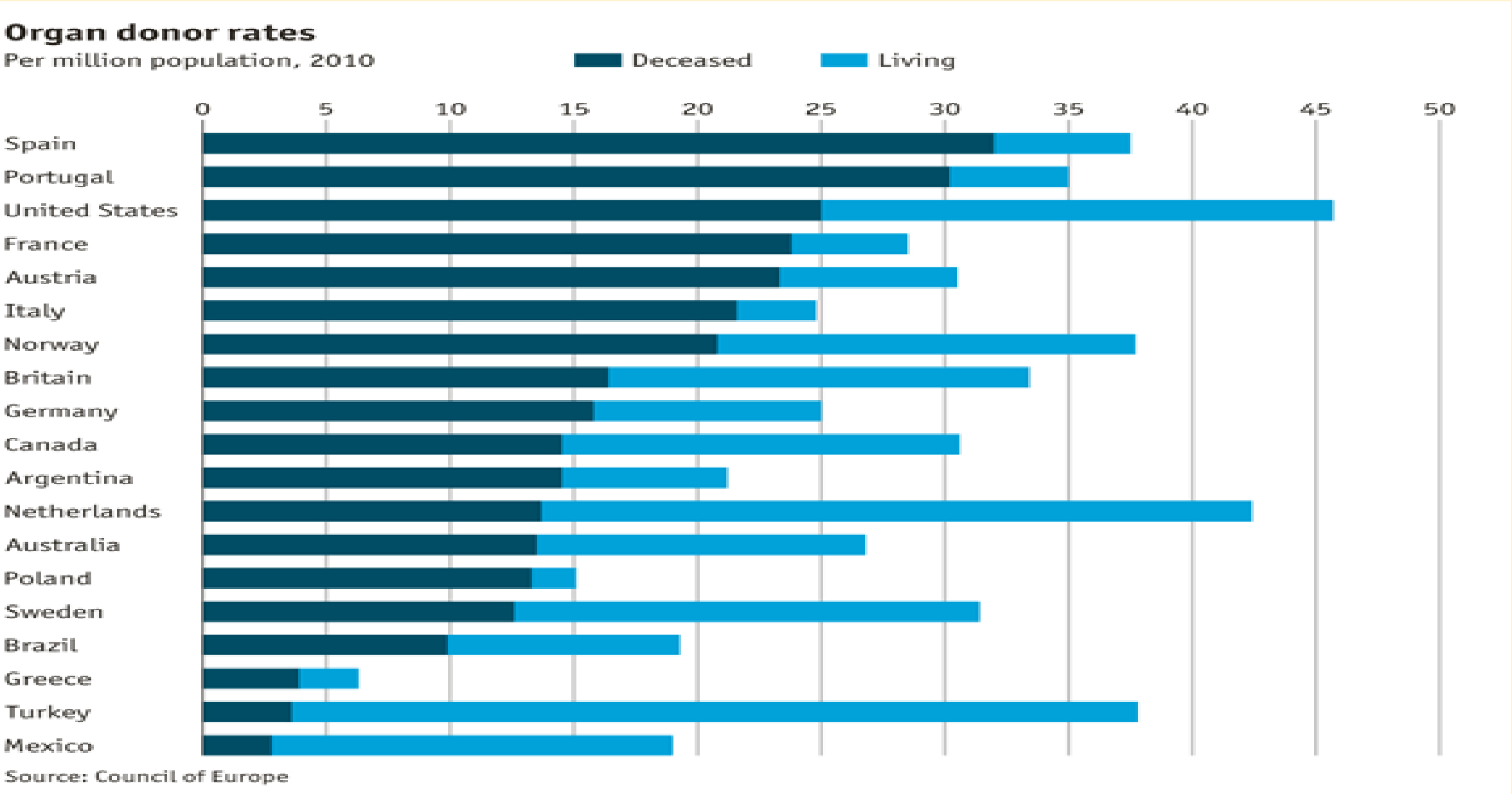
Shortage of Donor Kidneys

- >35,000 new patients added to kidney waiting list each year (96 additions per day, one every 15 min)
- Only 19,310 kidney transplants were performed in 2016 (53 per day, one every 27 min)
- >4000 deaths on kidney waiting list each year (11 per day, one every 133 min)
- **Annual mortality on waiting list is 6-7% (10% if diabetic)**
- Almost half (46%) of kidney transplant candidates ≥60 years of age placed on waiting list will die before receiving a deceased donor kidney transplant

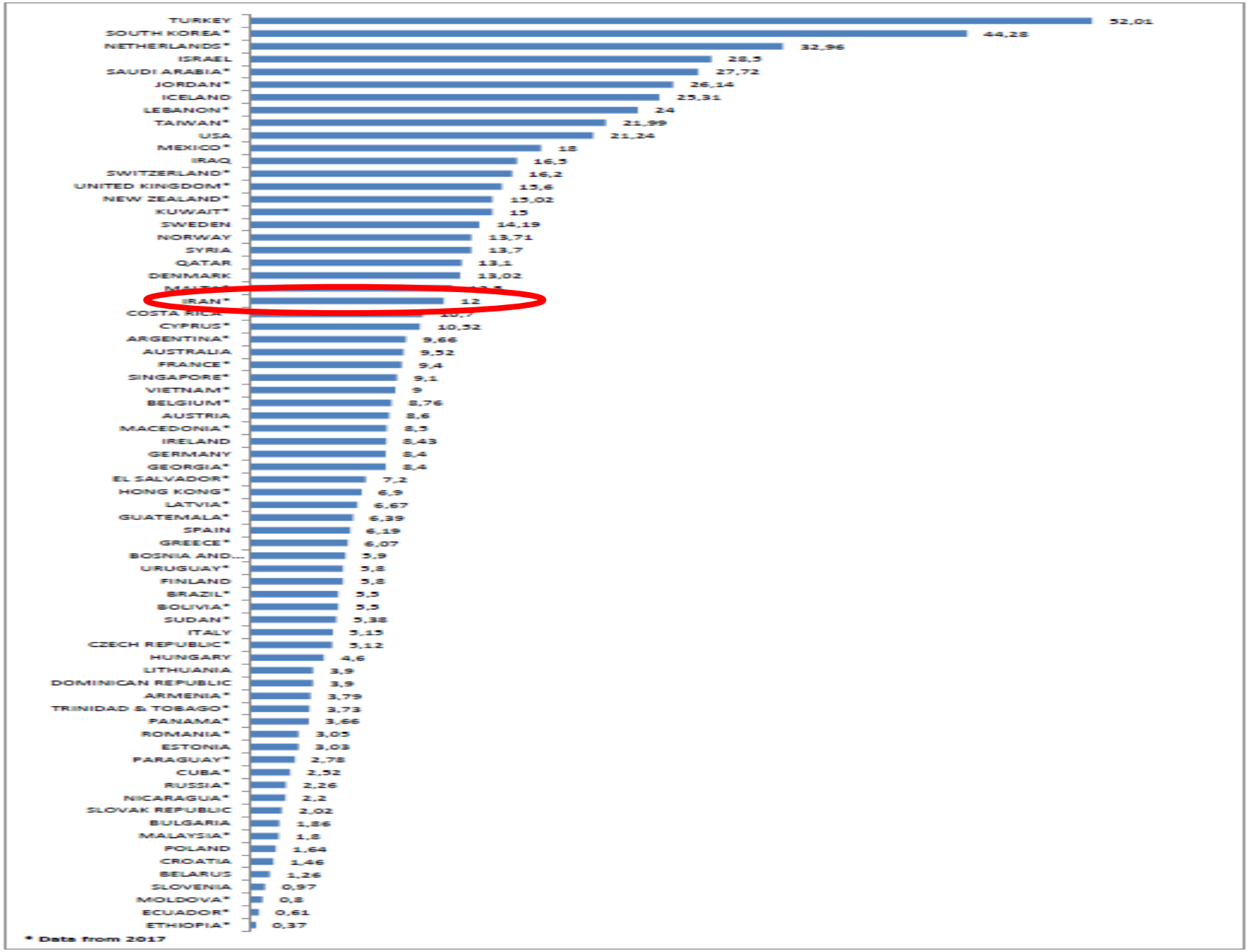
Shortage of Donor Kidneys

- Only 25% of active wait-list candidates are transplanted in a given year; chance of receiving a deceased donor kidney transplant within one year of listing is <10%
- <20% of kidney waiting list transplanted each year (median waiting time of 5 years)
- Median waiting times and kidney discard rates have doubled in the new millennium
- **Loss of quality and quantity of life by those on the waiting list** remains a staggering and sobering reality

International Living Donor Rates

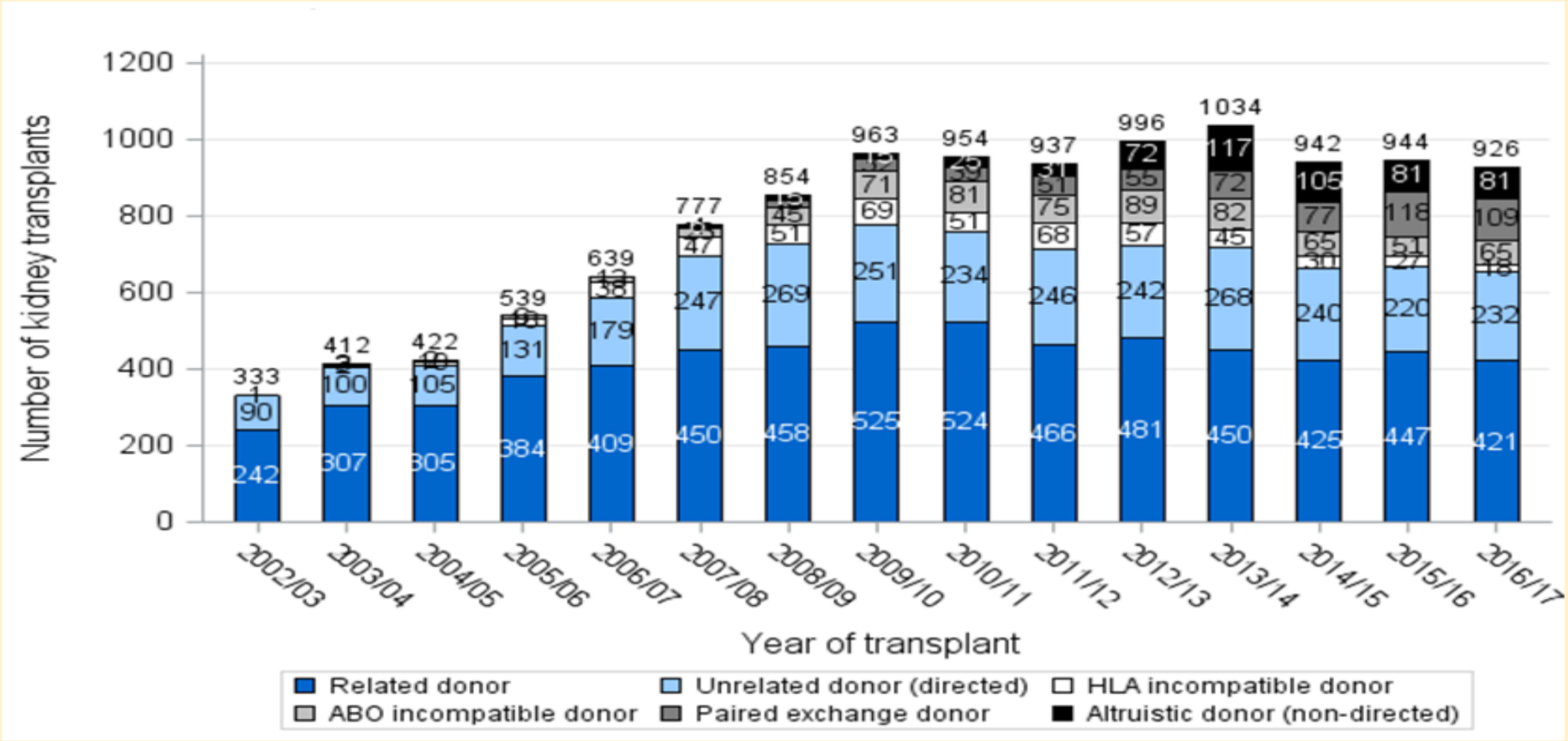


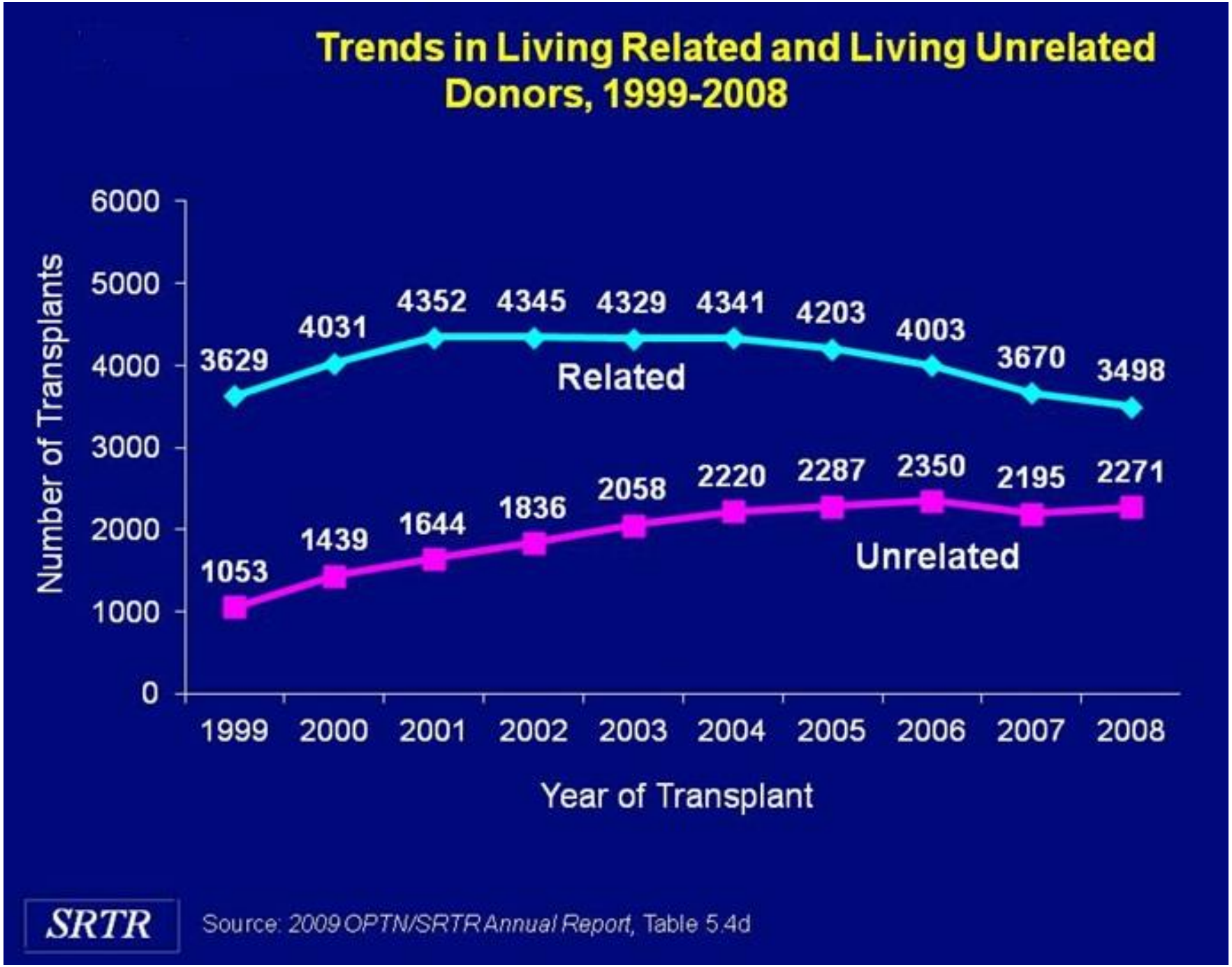
WORLDWIDE LIVING ORGAN DONORS 2018 (pmp)



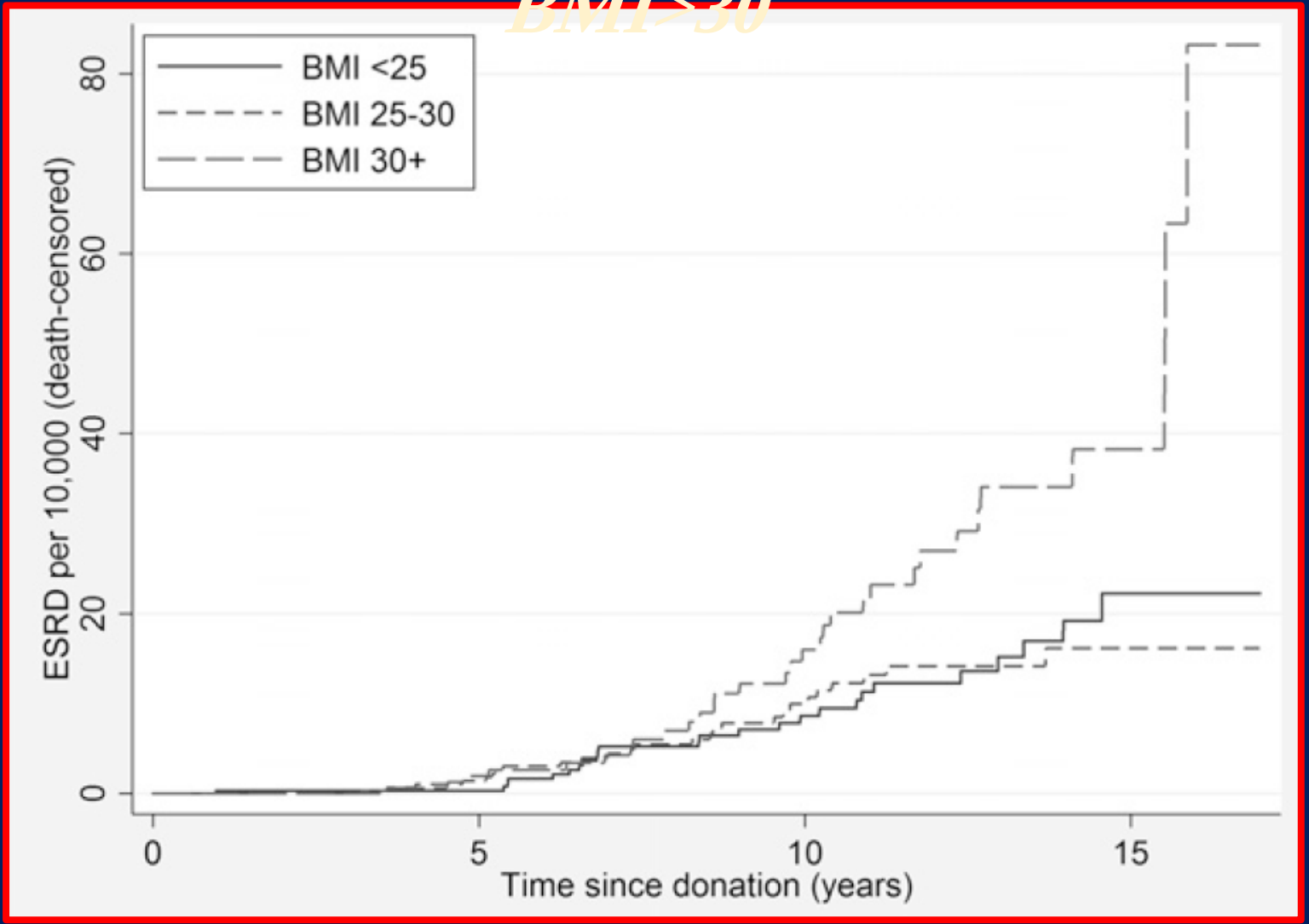
* Data from 2017

Living donor kidney transplants, 2002-2017



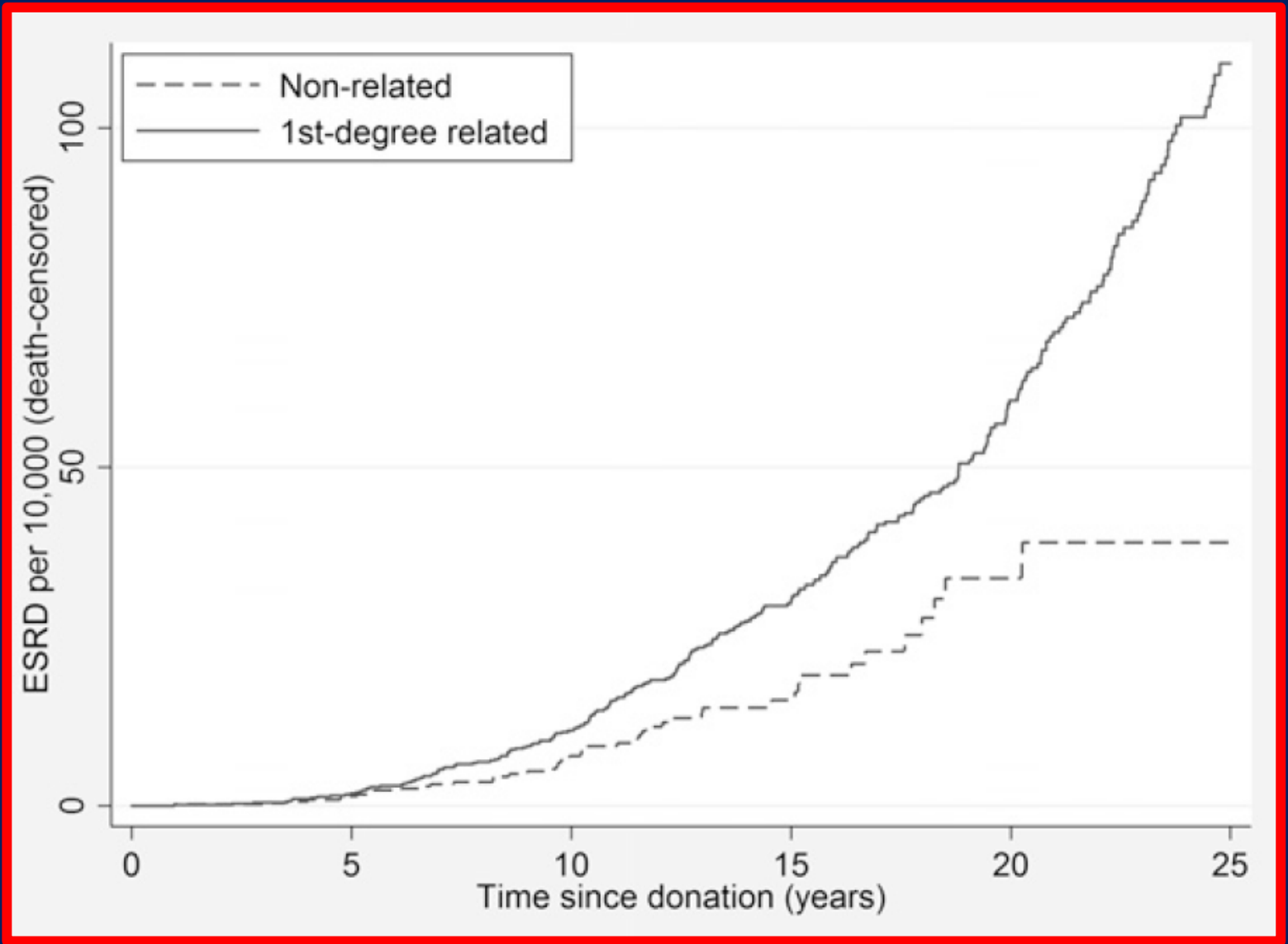

Trends in Living Related and Living Unrelated Donors, 1999-2008
Number of Transplants
6000
5000
4000
3000
2000
1000
0
3629
4031
4352
4345
4329
4341
4203
4003
3670
3498
Related
1053
1439
1644
1836
2058
2220
2287
2350
2195
2271
Unrelated
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
Year of Transplant
SRTR
Source: 2009 OPTN/SRTR Annual Report, Table 5.4d

Cumulative incidence of ESRD was lowest among living donors with BMI <25 and highest among donors with BMI>30



Allan B. Massie et al. JASN 2017;28:2749-2755

Cumulative incidence of ESRD was higher among donors who were first-degree biologically related to their recipient.



Allan B. Massie et al. JASN 2017;28:2749-2755

Quantifying Postdonation Risk of ESRD in Living Kidney Donors

Low Risk of ESRD
in the *average* donor

20-year risk of ESRD
34 Cases / 10,000 Donors

Up to *8x higher risk* of
ESRD in some donor groups

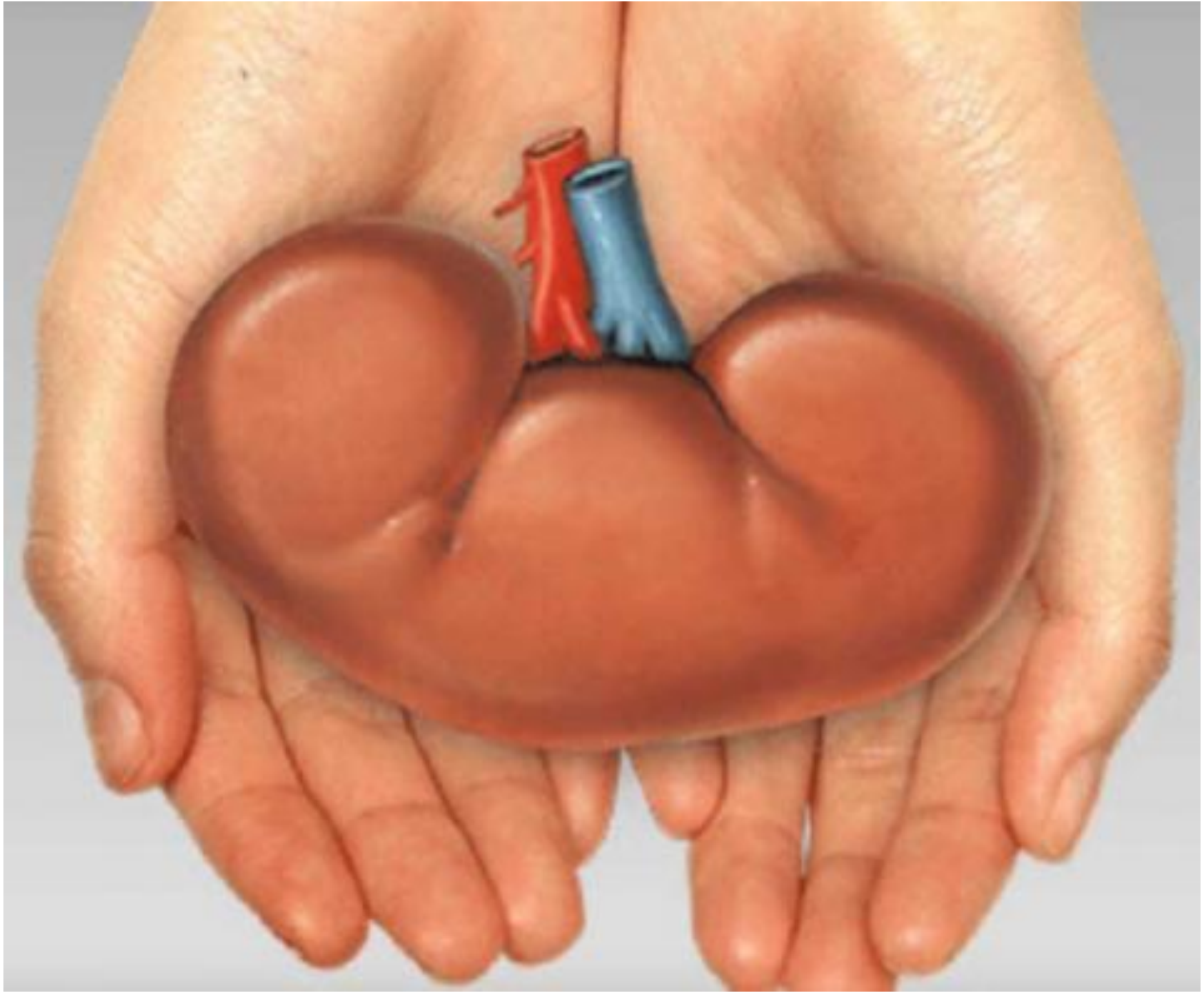
20-year risk of ESRD
256 Cases / 10,000 Donors

Calculate *personalized ESRD* risk using free calculator

Tool available for clinicians at:
transplantmodels.com/donorsrd/

dot: https://doi.org/10.1681/ASN.2016101084

JASN



Patient and Graft Survivals

Survival Benefit of Transplantation

- JAMA Surgery, 1/28/2015
- Retrospective analysis of UNOS data during a 25-year period (9/1/87 – 12/31/2012)
- 669,000 kidney wait-list patients studied
- **Median survival: 5.4 years for kidney wait-list, 12.4 years for transplanted patients**
- 1.37 million life-years saved by kidney transplant; mean of 4.4 life-years saved per recipient
- **Only 47% of patients ever received a kidney**

Inferior Survival Of Deceased Donor Kidneys After Tx

	1-year survival		5-year survival	
	2001-2002	2002-2003	1997-2002	1998-2003
Living Donor	94.3%	94.6%	78.6%	79.2%
Deceased Donor	88.7%	89.0%	65.7%	66.2%

Source: UNOS/OPTN

Inferior Survival Of Deceased Donor Kidneys After Tx…

- In 1995, Terasaki et al. showed that graft survival for LURD is superior compared to deceased donation, even though the average HLA matching is worse in LURD.
- In 2005, Futagawa et al. showed that long-term outcome after LURD is similar to that of parental or offspring donors.

Transplant Data 1994-2005, 2005.

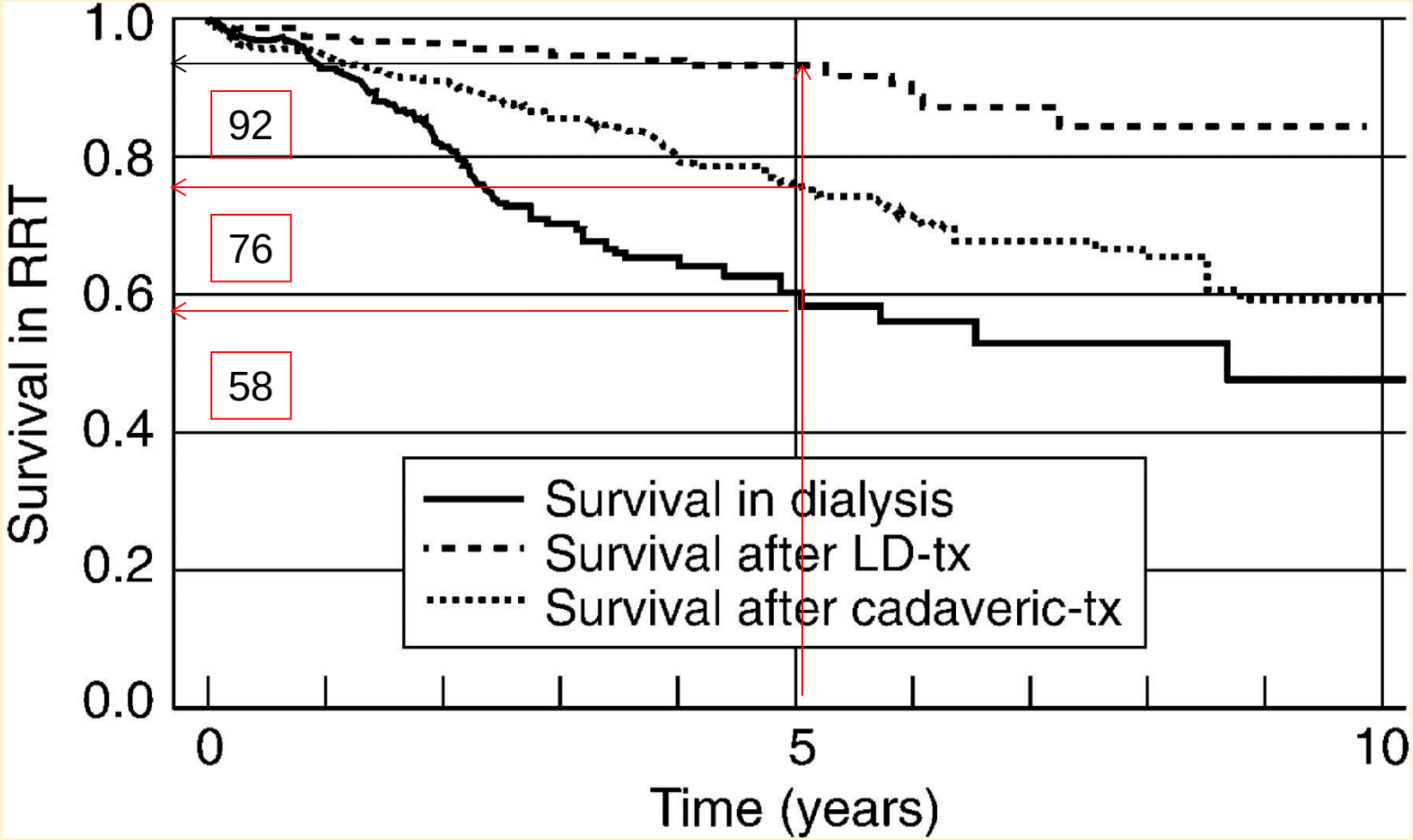
Inferior Survival Of Deceased Donor Kidneys After Tx…

- Twenty years ago, the typical donor was under the age of 30 years, fairly healthy and died of traumatic cerebral injury.
- Today, the average donor is over 50 years old and main cause of death is intracranial hemorrhage.

Inferior Survival Of Deceased Donor Kidneys After Tx…

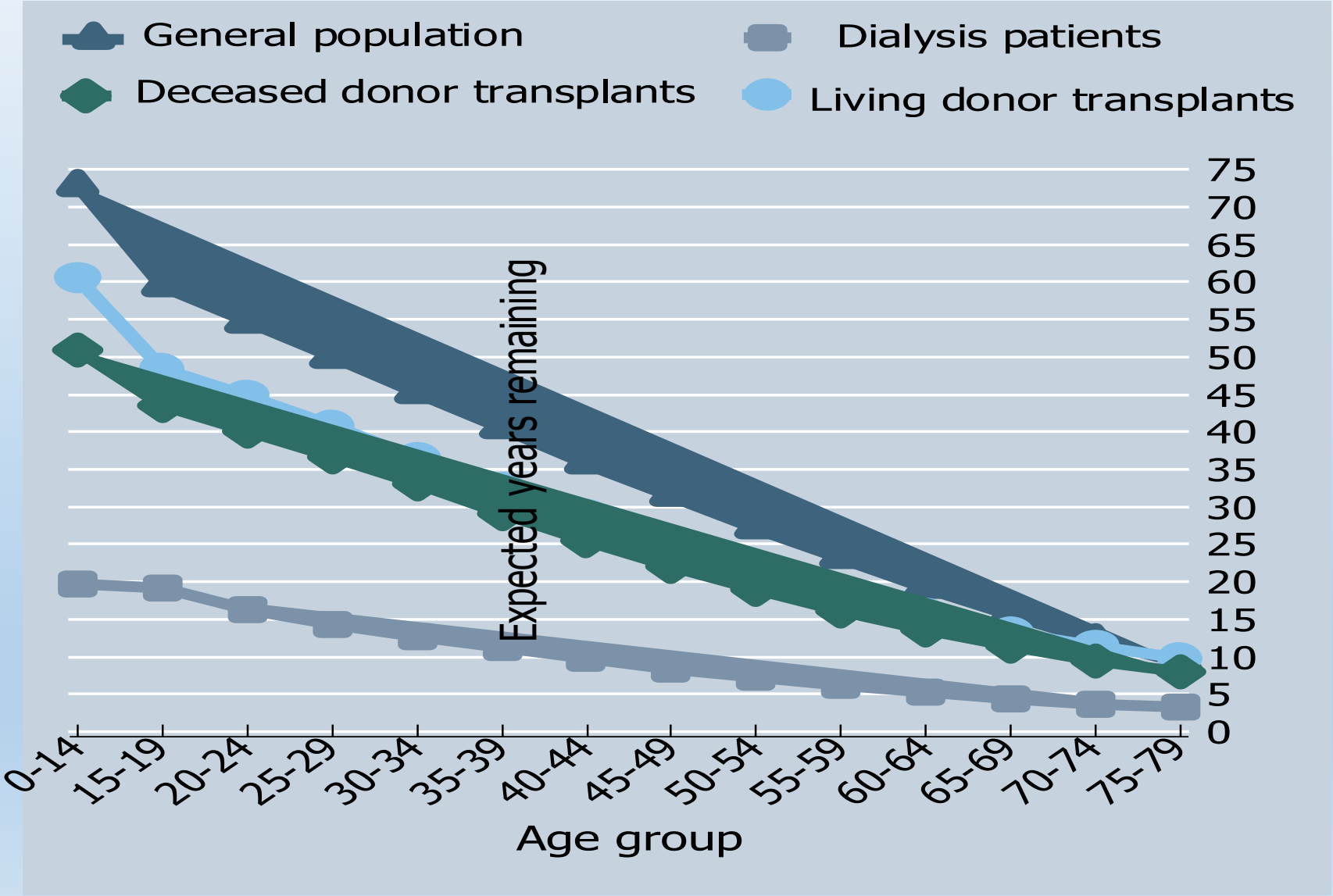
- Deceased donors tend to be older than living donors; however, within each age category, survival rates of living donor grafts are significantly higher than those of deceased donor grafts.

Kaplan–Meier survival curves for three groups of RRT patients: those transplanted with a living-related kidney donor (LD), those transplanted with a cadaveric kidney, and those remaining on dialysis.



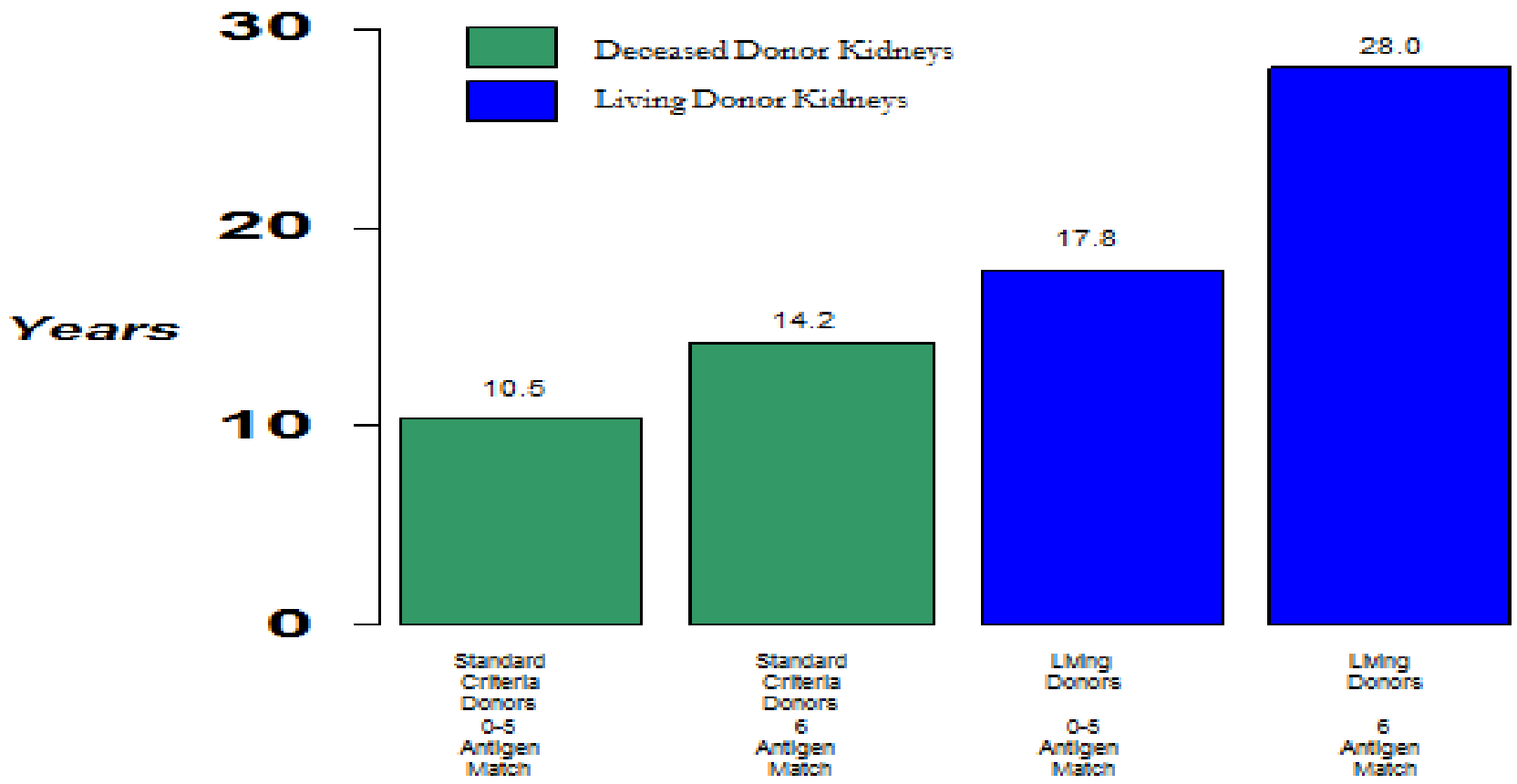
Medin C et al. Nephrol. Dial. Transplant. 2000;15:701-704

Years of life remaining the benefit of Living donor



Living Donor Kidneys Last Longer

Well matched living donor kidneys last even longer

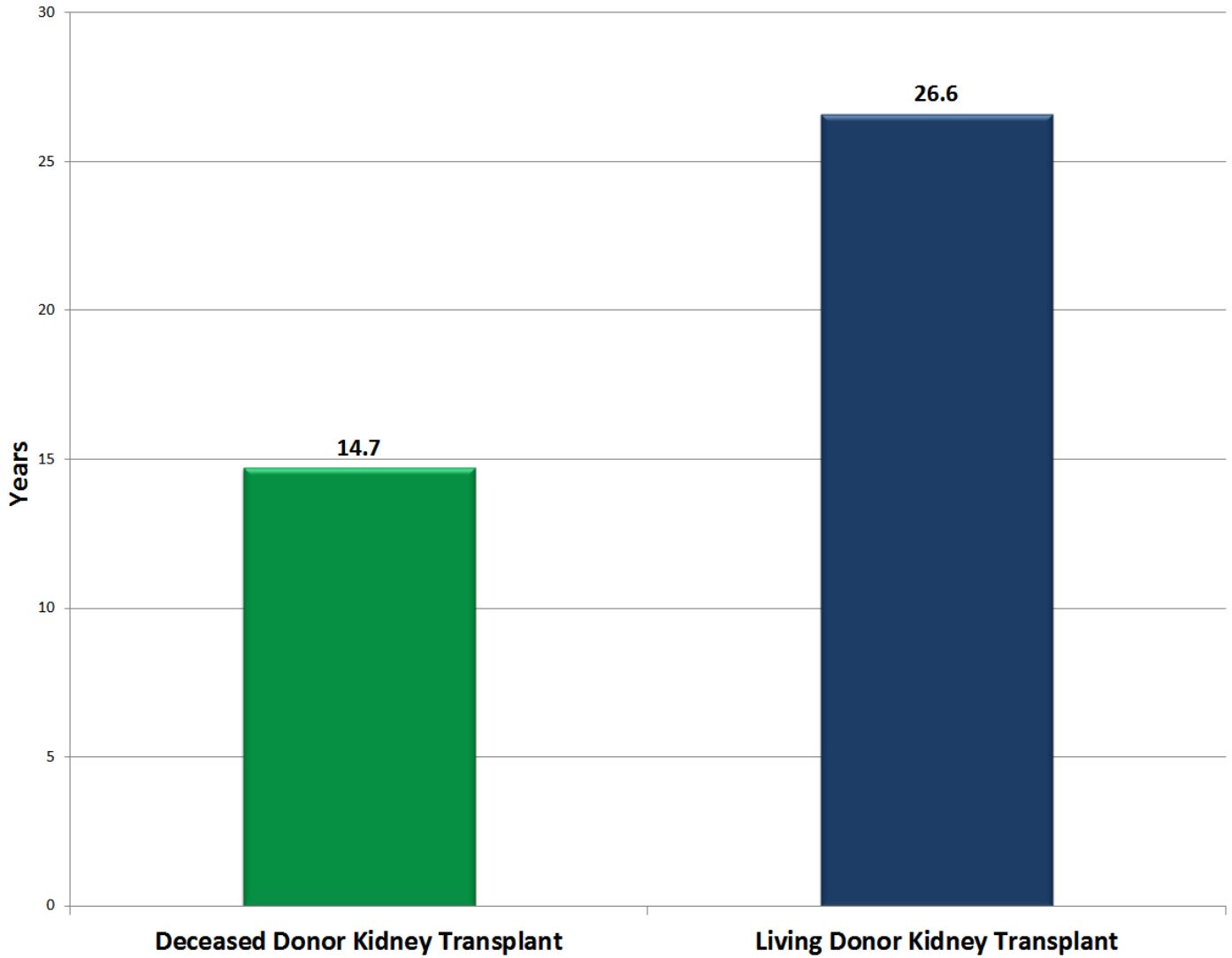


Graft half life. The point in time when exactly 50% of kidneys are still functioning

Source: Clinical Transplants 2005

Living Donor Kidneys Last Longer

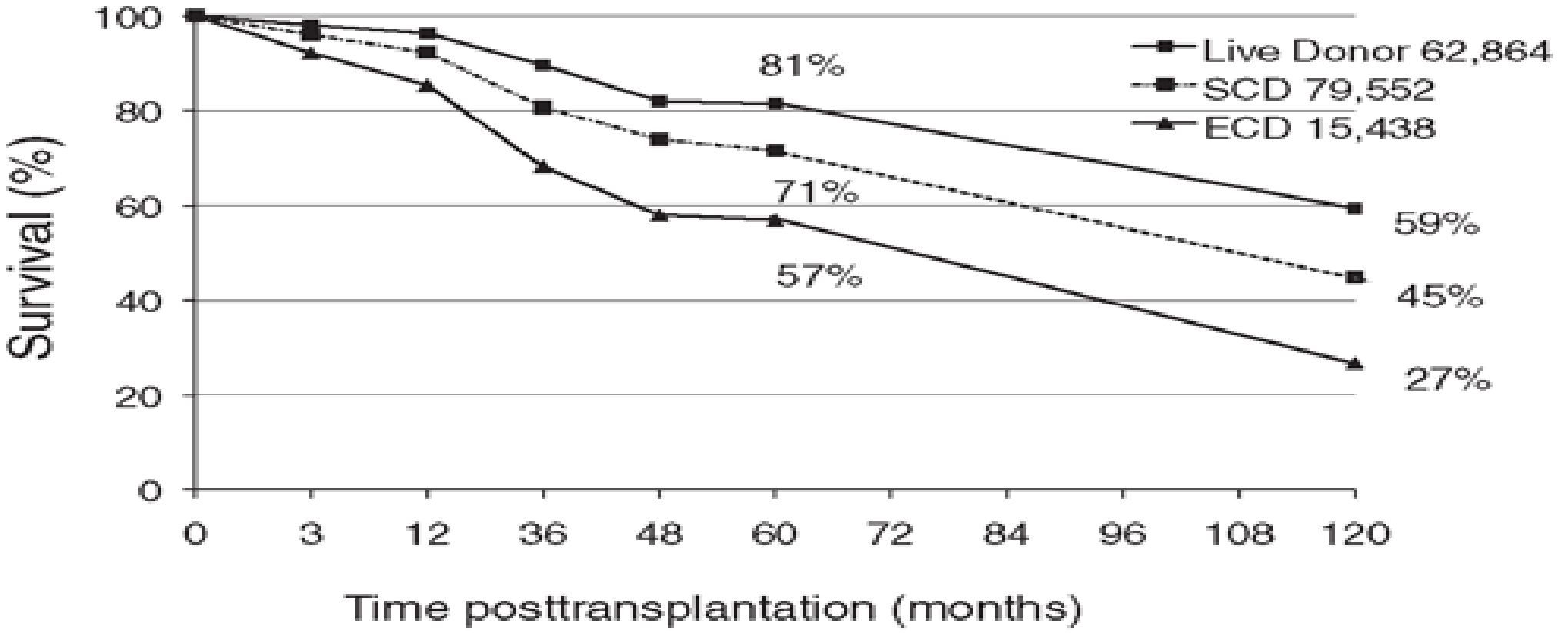
Well matched living donor kidneys last even longer



Graft half life. The point in time when exactly 50% of kidneys are still functioning.

**Source: 2010 OPTN/SRTR Annual Data Report, Published in American Journal of Transplantation 2012 12 (Suppl 1)*

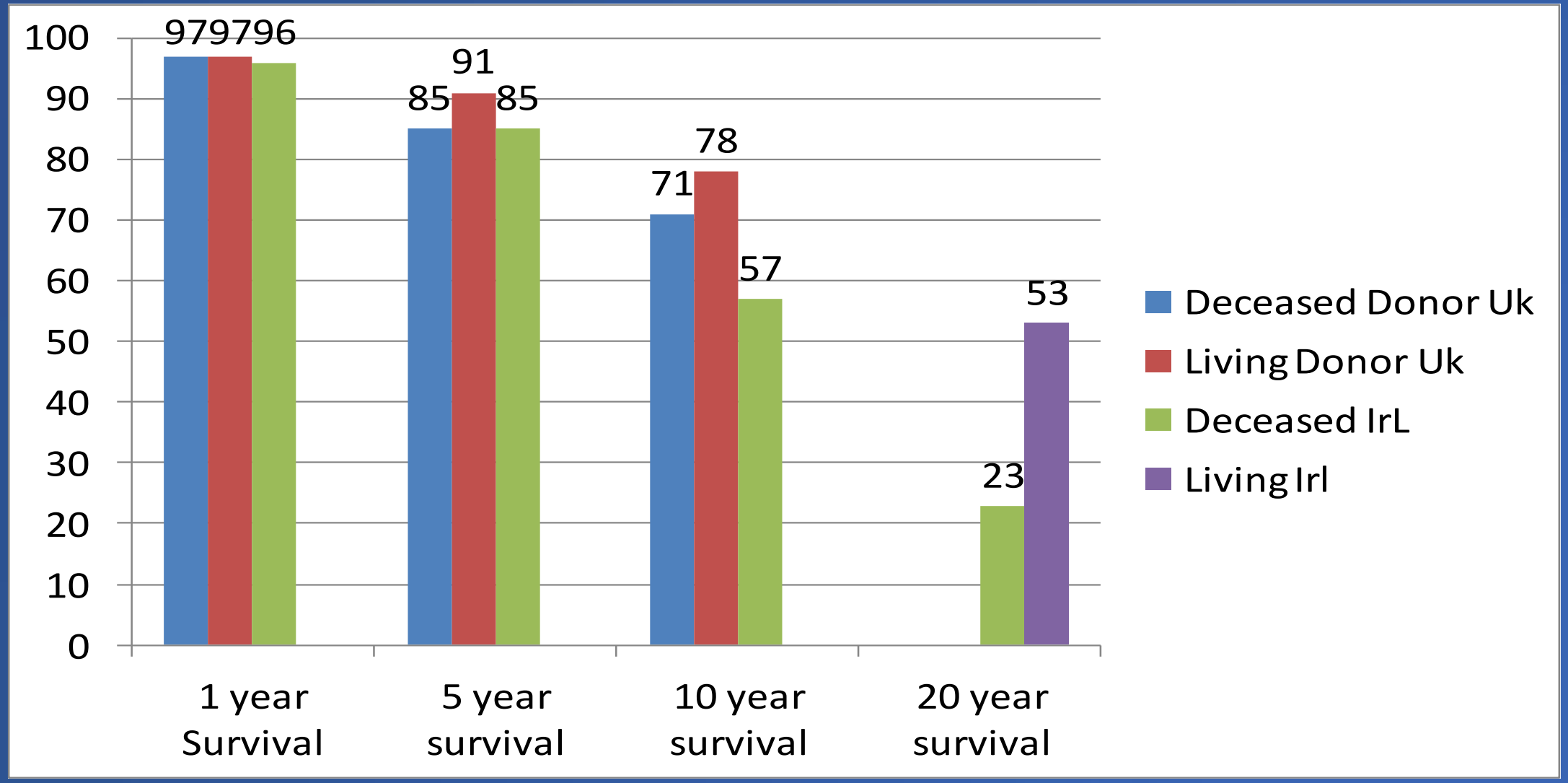
Kidney-only Graft Survival- according to donor source



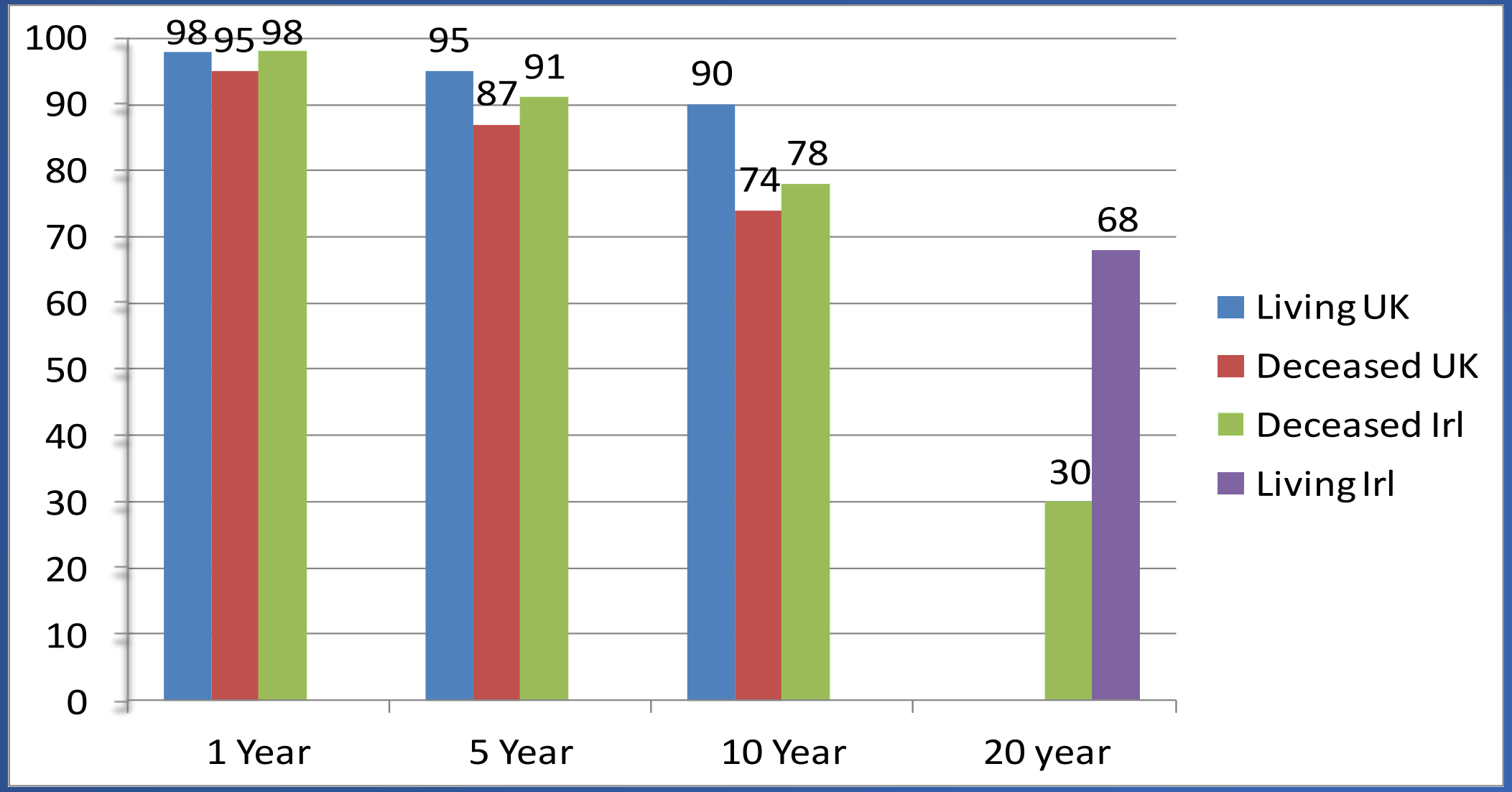
OPTN/SRTR Annual Report 2009

Source: McAninch JW, Lue TF: *Smith & Tanagho's General Urology*, 18th Edition: www.accessmedicine.com

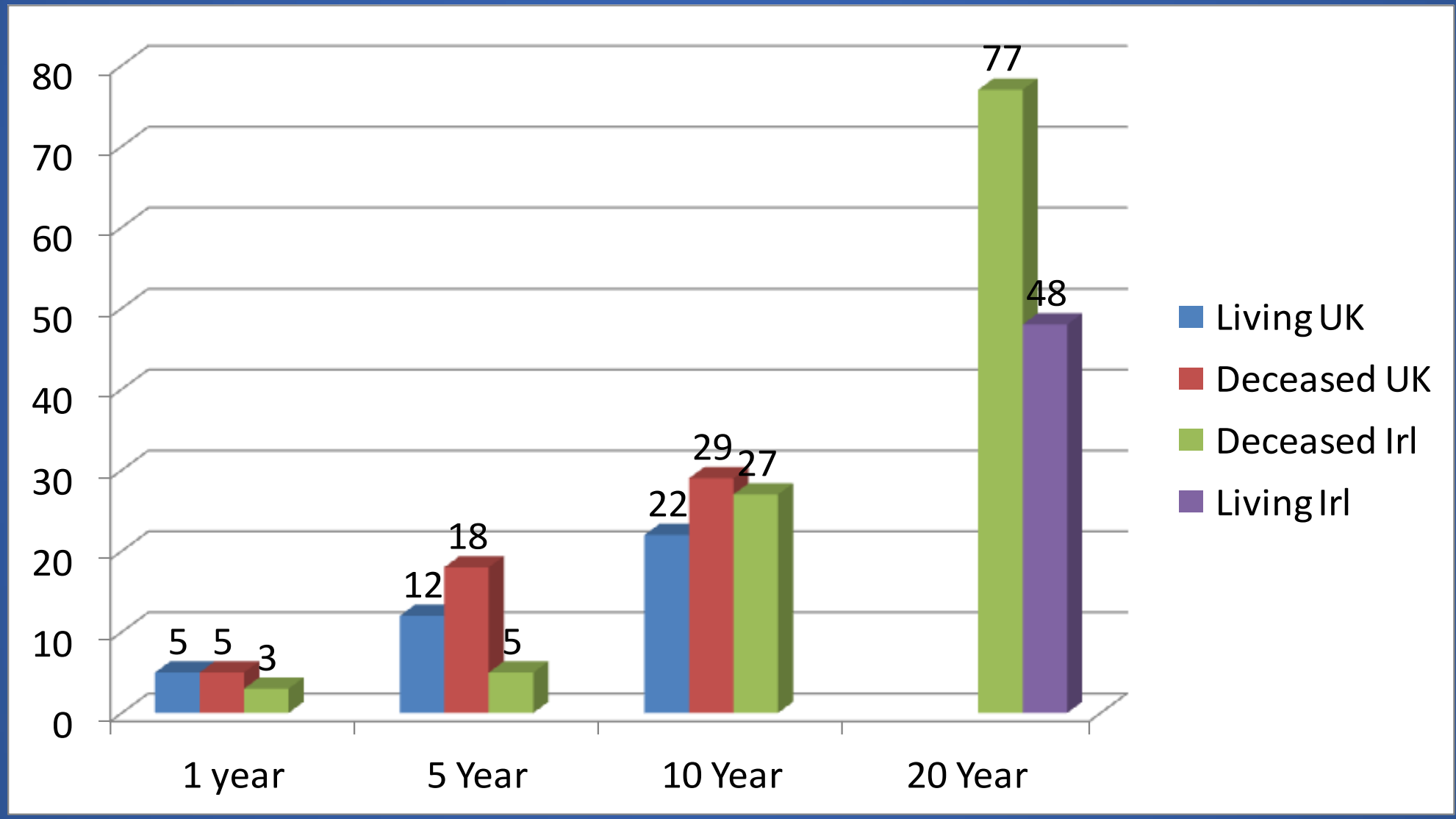
Deceased Vs Living Donor Outcome Graft



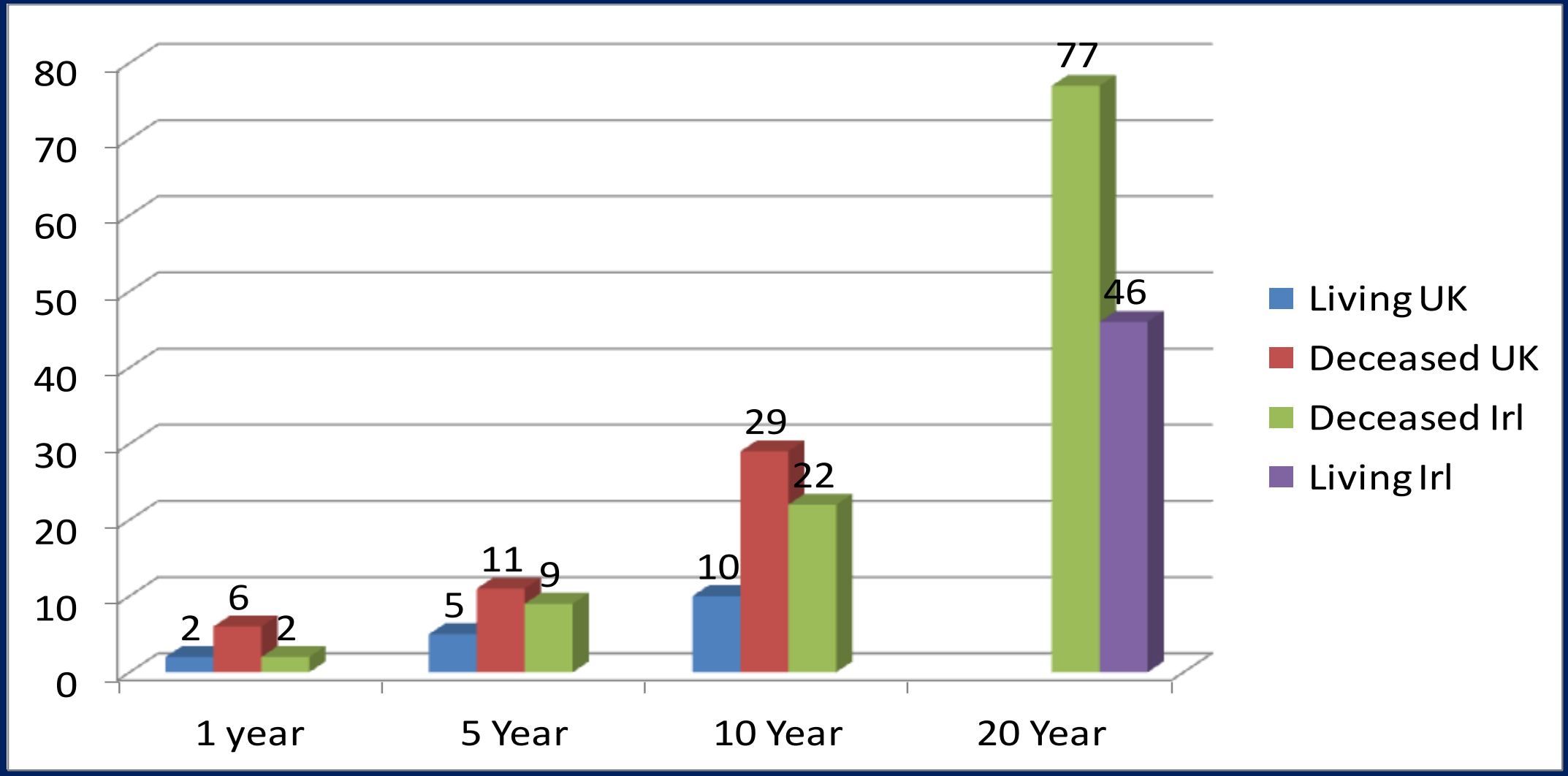
Deceased Vs Living Donor Patient Survival



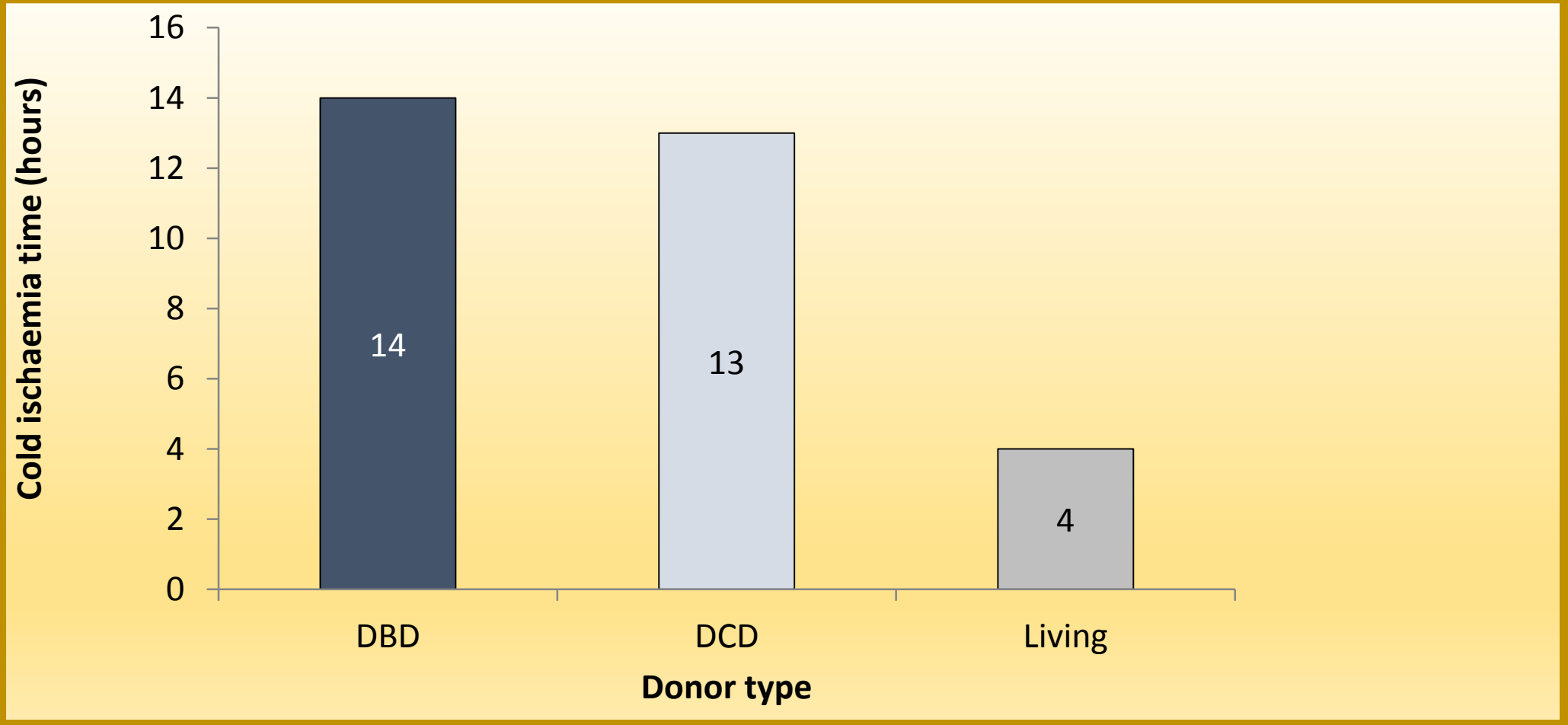
Graft Failure Deceased V living Donor

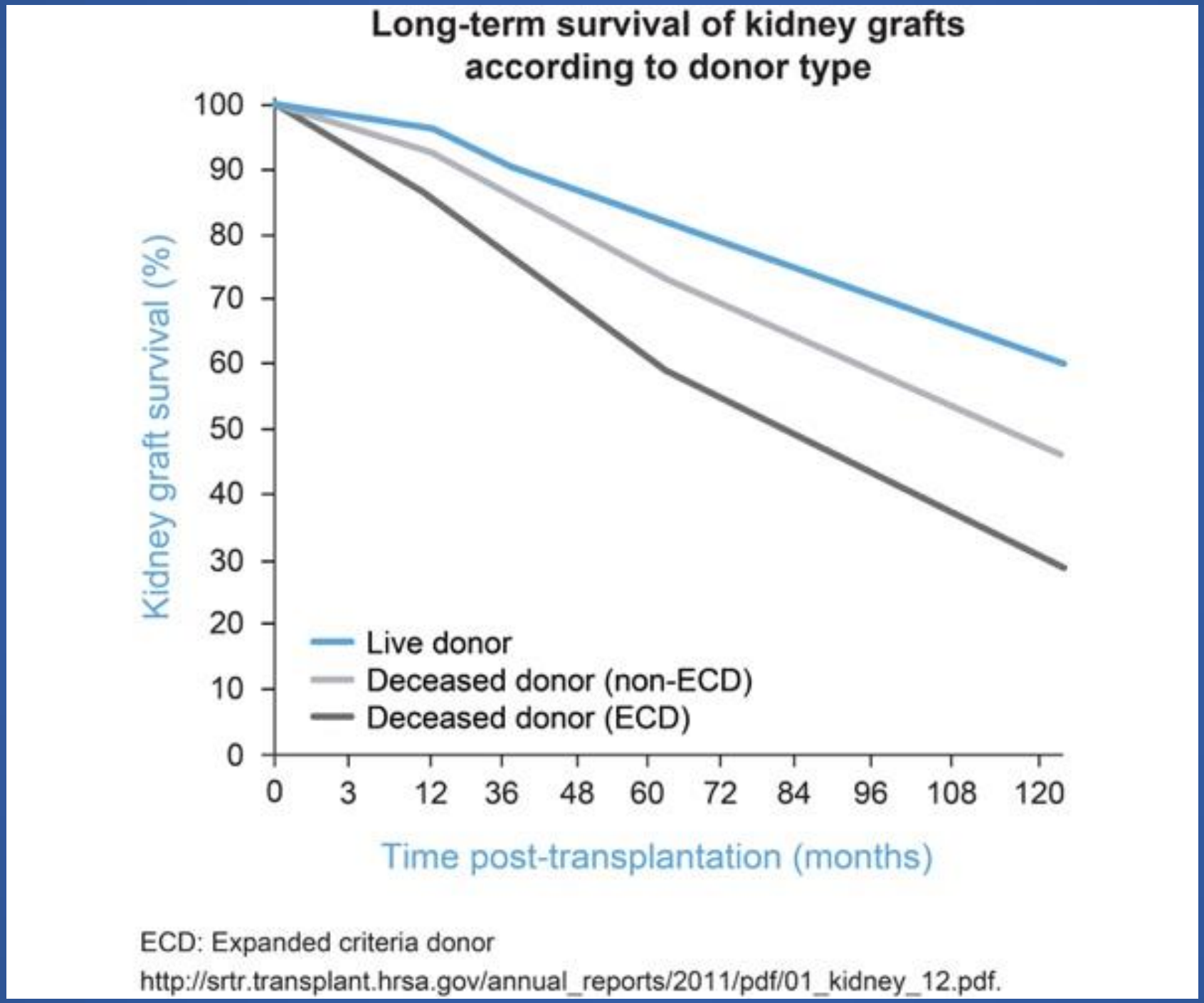


Long term Patient Mortality Deceased Vs living Donor



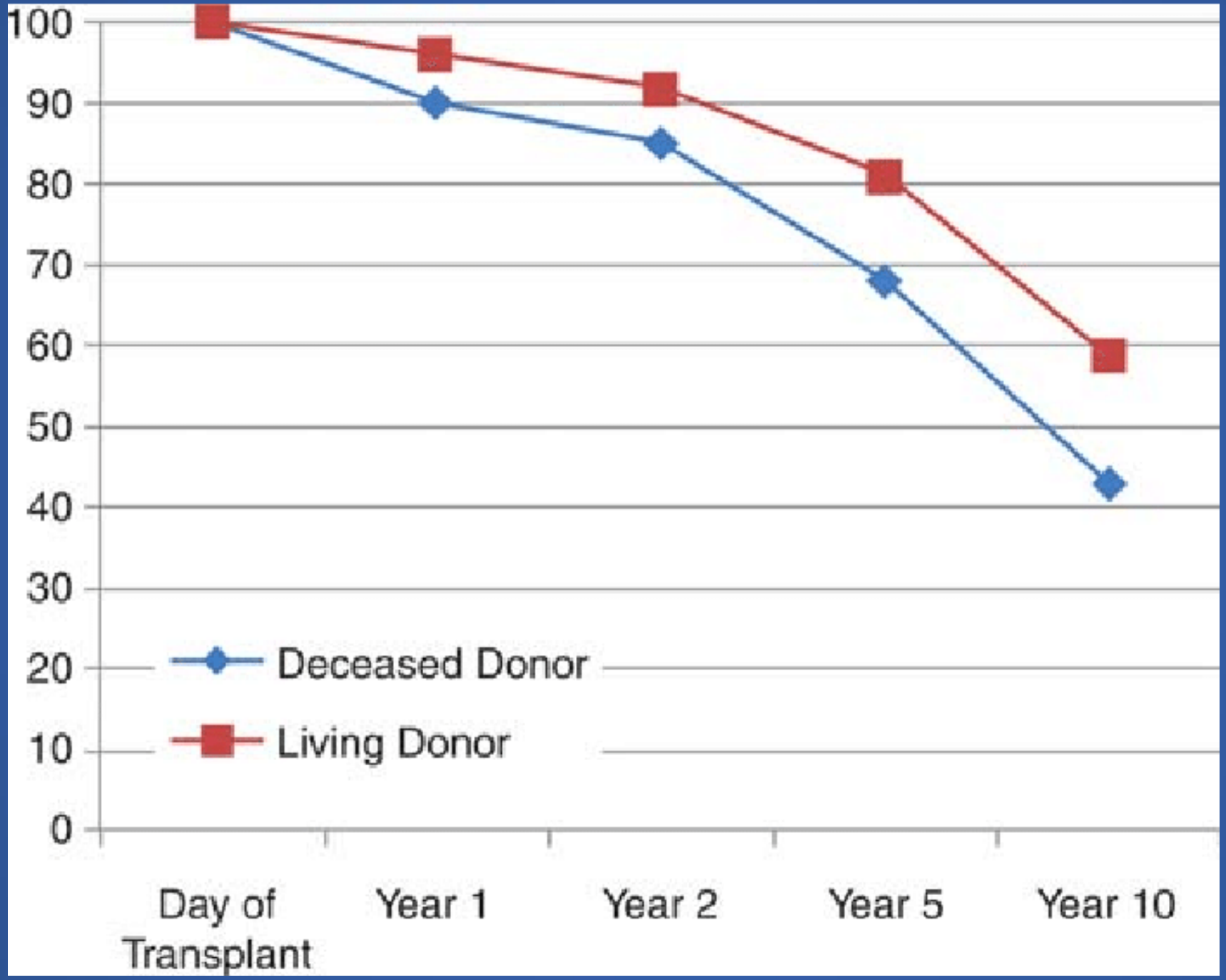
Cold ischaemia time for kidney transplants, 1 April 2016 – 31 March 2017



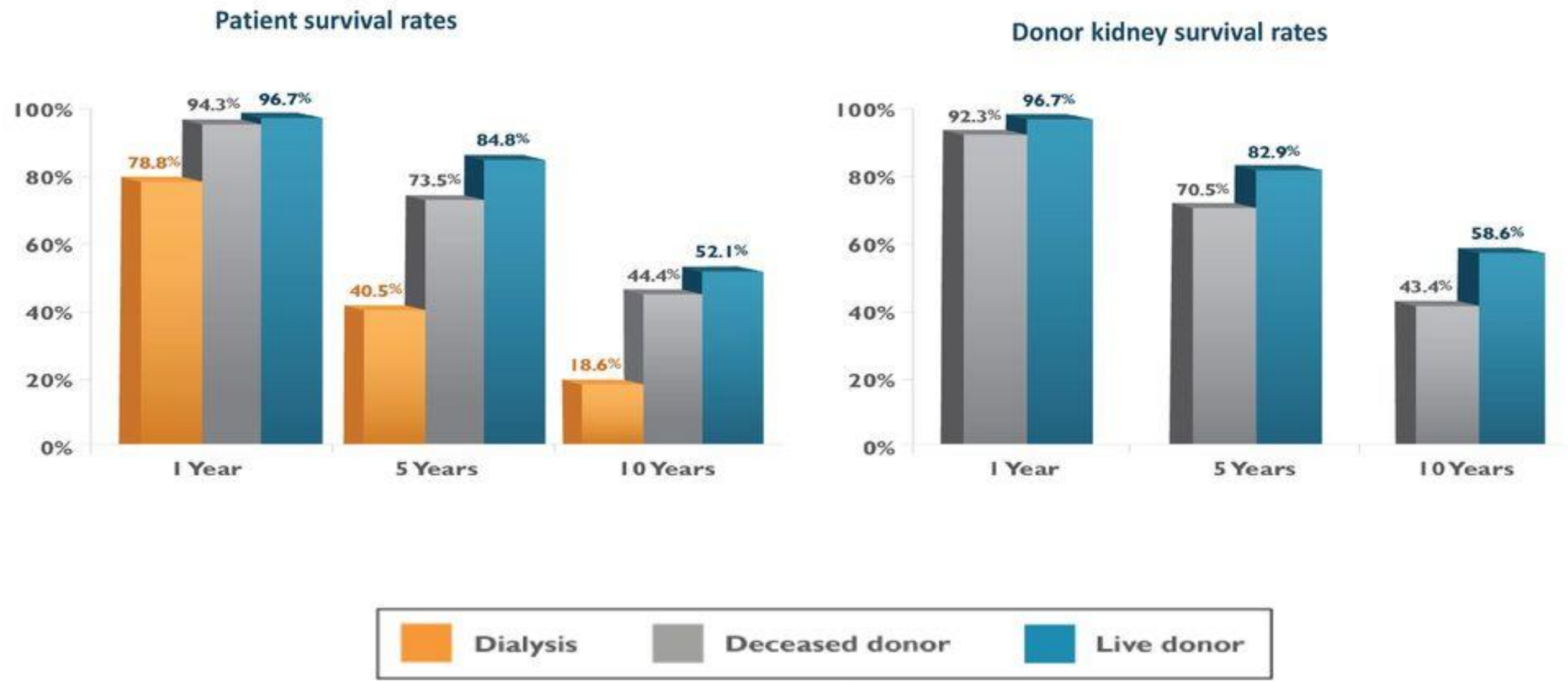


ECD: Expanded criteria donor

http://srtr.transplant.hrsa.gov/annual_reports/2011/pdf/01_kidney_12.pdf.


100
90
80
70
60
50
40
30
20
10
0
Deceased Donor
Living Donor
Day of Transplant
Year 1
Year 2
Year 5
Year 10

A Kidney Transplant From a Living Donor Results in Better Long-term Outcomes Than a Transplant From a Deceased Donor or Dialysis



[a] Data are from the USRDS *2014 Annual Data Report*; 1-year data are from 2011, 5-year data are from 2007, and 10-year data are from 2002.
USRDS. 2014 ADR chapters. http://www.usrds.org/2014/view/default.aspx. Accessed February 11, 2016.

Highly Sensitized Patients?

The Living donors are better than the Deceased Donors: Patient and graft survivals

Answer: Absolutely yes

- Higher patient and graft survivals
- Help to organ shortage
- Shorter waiting time
- Help to find a proper donor for highly sensitized patients
- Better selection and evaluation of donors and higher quality kidney (healthy donor, short ischemia time), which results in higher success rates and improved graft longevity
- Lower ischemic time result in lower DGF
- Scheduled event, can plan accordingly, can be performed during normal work day by rested team and fully prepared donor and recipient

Economical burden of deceased and living transplantation on the community and recipients


COST
COST

Economical burden of living transplantation

1.Pre-Transplant Costs

2.Post-Transplant Costs

Pre-Transplant Costs

1. Compensations
2. Medical Costs (Medicine prices, Laboratory investigation prices, Imaging investigation prices, Consultants, Procedures and Surgery prices, Clinic visits, Referrals, General ward, and ICU stay prices, etc)
    + For Recipients
    + For Donors

Post-Transplant costs

1. Immunosuppressive protocols
2. Rate of Rejections
3. Kidney Biopsy
4. Medicine prices
5. Costs of dialysis
6. Clinic visits, referrals, general ward, and ICU stay prices
7. LOS (length of stay in hospital)
8. The doses of maintenance immunosuppressant
9. The complications of Immunosuppressive agents and their costs
10. The rate of anti rejection therapy
11. Plasmapheresis
12. The re-admission rates and its costs
13. The outcomes and its costs

MEDICATION COSTS

Medication Cost at a Glance

Approximate prices 8/2016

Prograf:

- $1,715.00/month with No insurance
- $50/month with Medicare (B) only Life Long

Cellcept:

- $1,145.25/month with No insurance
- $70/month with Medicare (B) only
- Life Long

Valcyte:

- $1,741.00/month with No insurance
- OOP cost ranges with each insurance company
- 3 months - 1 year

Medications Post Transplant

New prescriptions

- Multiple new prescriptions post transplant

Pharmacy

- Local vs mail order

Cost

- Ranges with Insurance coverage

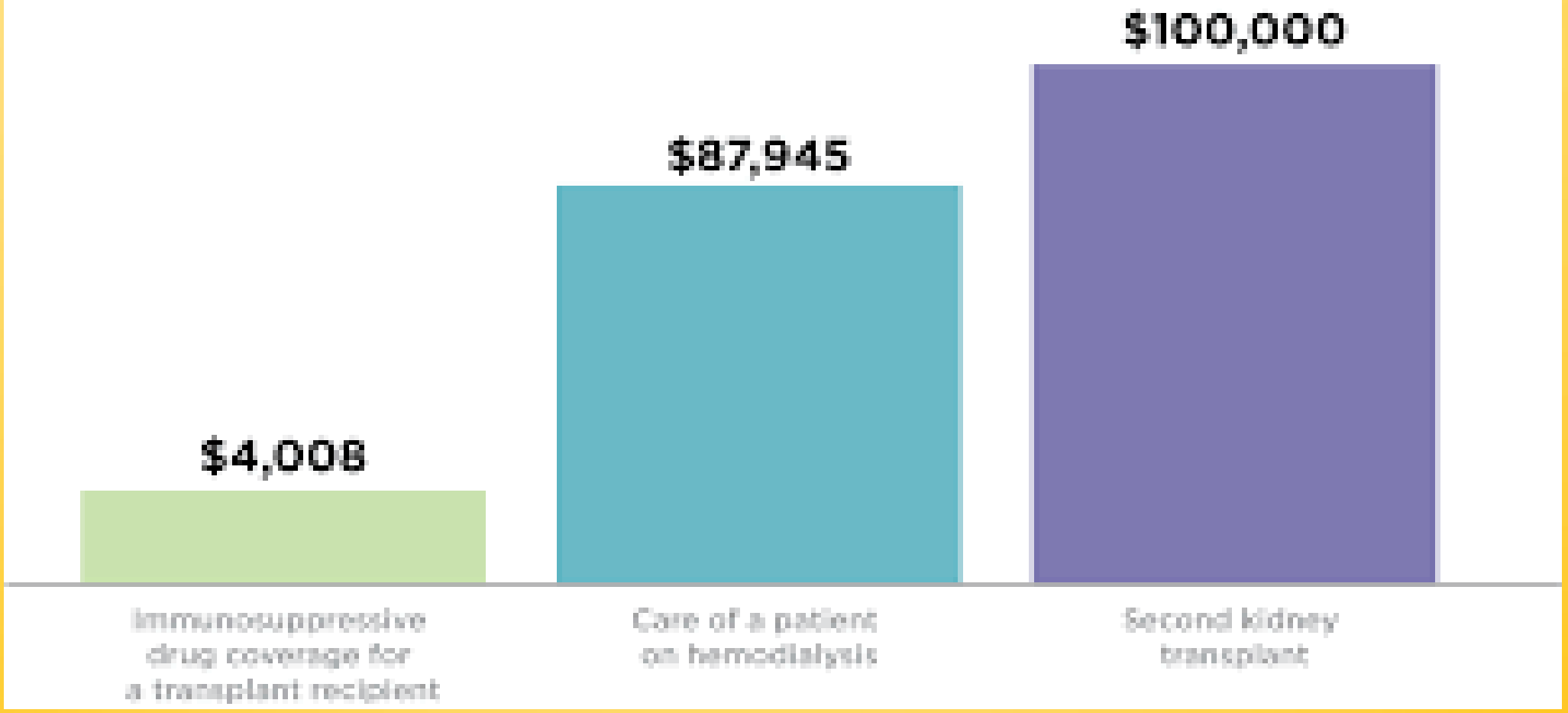
Table 1. Direct and Indirect Cost in the Model

Type of Treatment	Direct Costs (dollar)	Indirect Costs (dollar)	Total Costs (dollar)	Weighted Average Costs with a Discount Rate of 0.03 (dollar)	Effectiveness (DALY)	Cost-Effectiveness Ratio (dollar/DALY)	Incremental cost-effectiveness ratio (dollar /DALY)
Kidney Trans-plant from a Cadaveric	60848.3	85236.5	146084.8	13295.3	5.12	2528.5	0
Kidney Trans-plant from a Living Person	107096.2	77487.7	184584.01	19657.4	6.18	3181.07	5954.3
Chronic dialysis	1174306.7	39151.7	1213539.9	104649.3	6.52	15986.9	256525.3

Cost-effectiveness analysis of dialysis and kidney transplant; *Med J Islam Repub Iran* 2016, 30:390.

Annual Per Patient Cost:

Immunosuppressive Drugs vs. Dialysis or Second Transplant



Event generating the cost	Value	Deterministic sensitivity analysis	
		Range	
Transplant	$17,798	$15,820	$19,776
Hemodialysis (months)	$1,321	$1,174	$1,468
Peritoneal dialysis (months)	$1,307	$1,162	$1,452
Acute rejection	$809	$234	$1,132
Biopsy	$499	$444	$555
Medical consultation	$9	$8	$10
Day of hospitalization	$95	$84	$105
Plasmapheresis session	$842	$748	$936

Note: All distributions are uniform, except the cost of acute rejection, which has a gamma distribution. For this, interquartile ranges are shown

	Transplant	Dialysis	Incremental	Incremental cost-effectiveness ratio
Cost	USD $76,718	USD $76,891	USD $173	Dominated
Months of dialysis averted	8.69	43.76	35.07	Dominated
Gained months	47.8	40.9	6.9	Dominated
QALY	2.9832	2.1037	0.8795	Dominated
Deaths × 1,000	270	474	204	Dominated

QALY: Quality-adjusted life years

Financial Assistance for Living Kidney Donors Reduces Federal Dialysis Spending

Question:
Is support for donor out-of-pocket expenses cost-effective?

METHODS

National Living Donor Assistance Center 2012-2015

2425 applicants → 1330
= $6.8 M granted to low-income donors

RESULTS

Median costs per patient year

$81K vs. $30K

Estimated savings & ROI

1-Year:	$48.2 M	5x
3-Years:	$173.6 M	19x
5-Years:	$265.4 M	28x

RESULTS

Higher estimated savings & ROI in states with:

- ↑ Transplant wait time
- ↑ Dialysis & transplant costs
- \+ NLDAC donors

CONCLUSION: Financial support for living donors results in dramatic federal savings. True cost savings and improved quality of life likely exceed these estimates.

Mathur AK, Xing J, Dickinson DM, Warren PH, Gifford KA, Hong BA, Ojo A, Merion RM. Return on Investment for Financial Assistance for Living Kidney Donors in the US. Clinical transplantation. 2018 May:e13277.

Graphic created by
ARBOR RESEARCH COLLABORATIVE FOR HEALTH

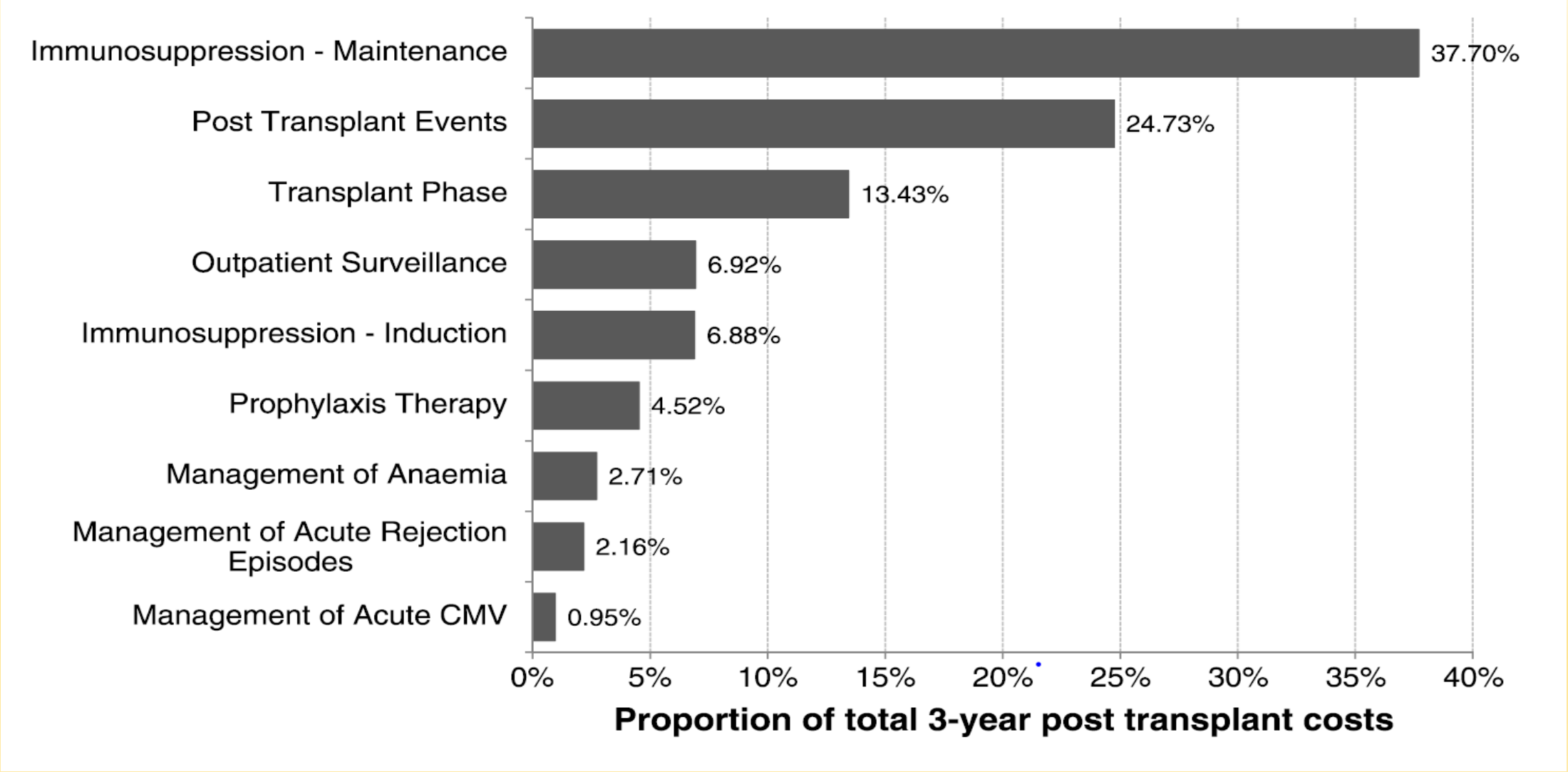
Costs, Outcomes, and Cost-Effectiveness

	Adult LKT	Adult DKT	Pediatric LKT	Pediatric DKT
Undiscounted costs and outcomes				
Total lifetime cost				
US $	151 336.88	171 517.83	197 119.03	178 102.17
RM	518 253.13	587 362.81	675 034.13	609 910.88
LYs	18.26	13.76	19.80	12.99
QALYs	17.67	13.29	N/A	N/A
Discounted costs and outcomes (3%)				
Total lifetime cost				
US $	119 702.30	147 152.10	154 840.78	159 312.54
RM	409 920.53	503 922.38	530 252.25	545 565.81
LYs	13.90	11.14	14.77	10.63
QALY	13.56	10.83	N/A	N/A
Cost-effectiveness				
Cost per LY				
US $	8609.11	13 208.85	10 484.60	14 985.33
RM	29 481.90	45 233.71	35 904.50	51 317.27
Cost-utility				
Cost per QALY				
US $	8825.85	13 592.28	N/A	N/A
RM	30 224.13	46 546.75		

N/A, not applicable.

Bavanandan et al. The Cost and Utility of Renal Transplantation in Malaysia. Transplantation 2015;1: e45

Average cost category as a proportion of total 3-year costs derived from the questionnaire analyses



Cost-effectiveness of kidney transplantation

- There are over 37,800 patients with end-stage renal failure in the UK.
- The average cost of dialysis is £30,800 per patient per year.
- The indicative cost of a kidney transplant (including induction therapy but excluding NHSBT costs) is £17,000 per patient per transplant.
- The immuno-suppression required by a patient with a transplant costs £5,000 per patient per year.
- **The cost benefit of kidney transplantation compared to dialysis over a period of ten years (the median transplant survival time) is £241,000 or £24,100 per year for each year that the patient has a functioning transplanted kidney.**

Cost-effectiveness of kidney transplantation

- In 2008-09, 2,497 people received a kidney transplant. These transplants are now saving the NHS £50.3m in dialysis costs each year for every year that the kidney functions.
- In 2008-09, 215 more kidney transplants were provided than in the previous year. These transplants are now saving the NHS £4.5m every year until graft failure.
- At the end of March 2009, the UK Transplant Registry had records of over 23,000 people in the United Kingdom with a functioning kidney transplant. In this year, these patients will save the NHS over £512m in the dialysis costs that they would need if they did not have a functioning kidney transplant.
- On 1 April 2009 there were 6,920 patients waiting for a transplant of which the majority will be on dialysis, costing around £193m per year. If all of these patients received a transplant, the approximate cost would be £41m per year, which represents a saving to the NHS of £152m per year.

UK Renal Registry

TABLE 3 Survival, cost, and cost-effectiveness results for discrete event simulation analysis of kidney transplantation

	KDPI ≤85 DDKT	KDPI >85 DDKT	PHS increased risk DDKT	Dialysis	HLA 0-3 mismatch LDKT	HLA 4-6 mismatch LDKT	ABOi LDKT	ILDKT
Cost over 10 y								
Mean	$292 286	$330 576	$307 052	$292 117	$253 119	$259 771	$364 755	$440 234
10%	$220 641	$211 611	$231 365	$131 037	$196 129	$200 125	$288 000	$289 993
Median	$273 835	$314 843	$290 808	$324 534	$234 935	$238 051	$356 059	$445 569
90%	$407 856	$476 886	$420 533	$407 548	$354 417	$366 870	$480 380	$569 605
Average QALY over 10 years								
Mean	6.07	5.20	5.91	4.03	6.34	6.33	6.12	5.47
10%	2.68	1.49	2.41	1.10	3.40	3.44	2.59	1.76
Median	6.95	6.15	6.91	4.45	7.07	7.06	7.05	6.53
90%	7.56	7.47	7.57	6.16	7.59	7.60	7.59	7.52
Cost per QALY over 10 years								
Mean	$49 017	$63 531	$51 922	$72 476	$39 939	$41 016	$59 564	$80 486
Median	$39 437	$51 206	$42 103	$72 926	$33 226	$33 704	$50 534	$68 219

ABOi, ABO-incompatible; ILDKT, incompatible living donor kidney transplantation; KPDI, Kidney Donor Profile Index; PHS, US Public Health Service; QALY, quality-adjusted life-year.

Am J Transplant. 2018;18:1168–1176.

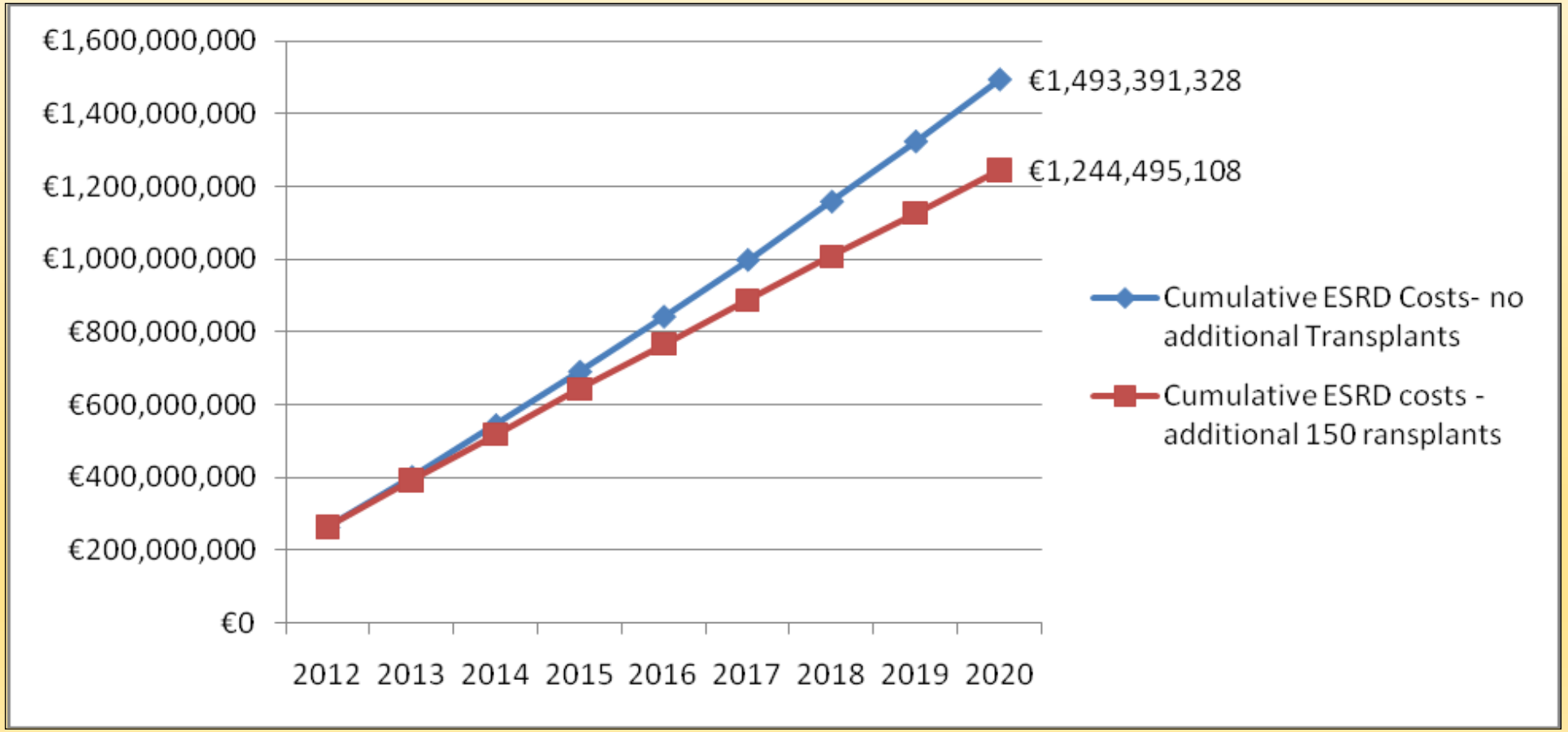
Cost-effectiveness

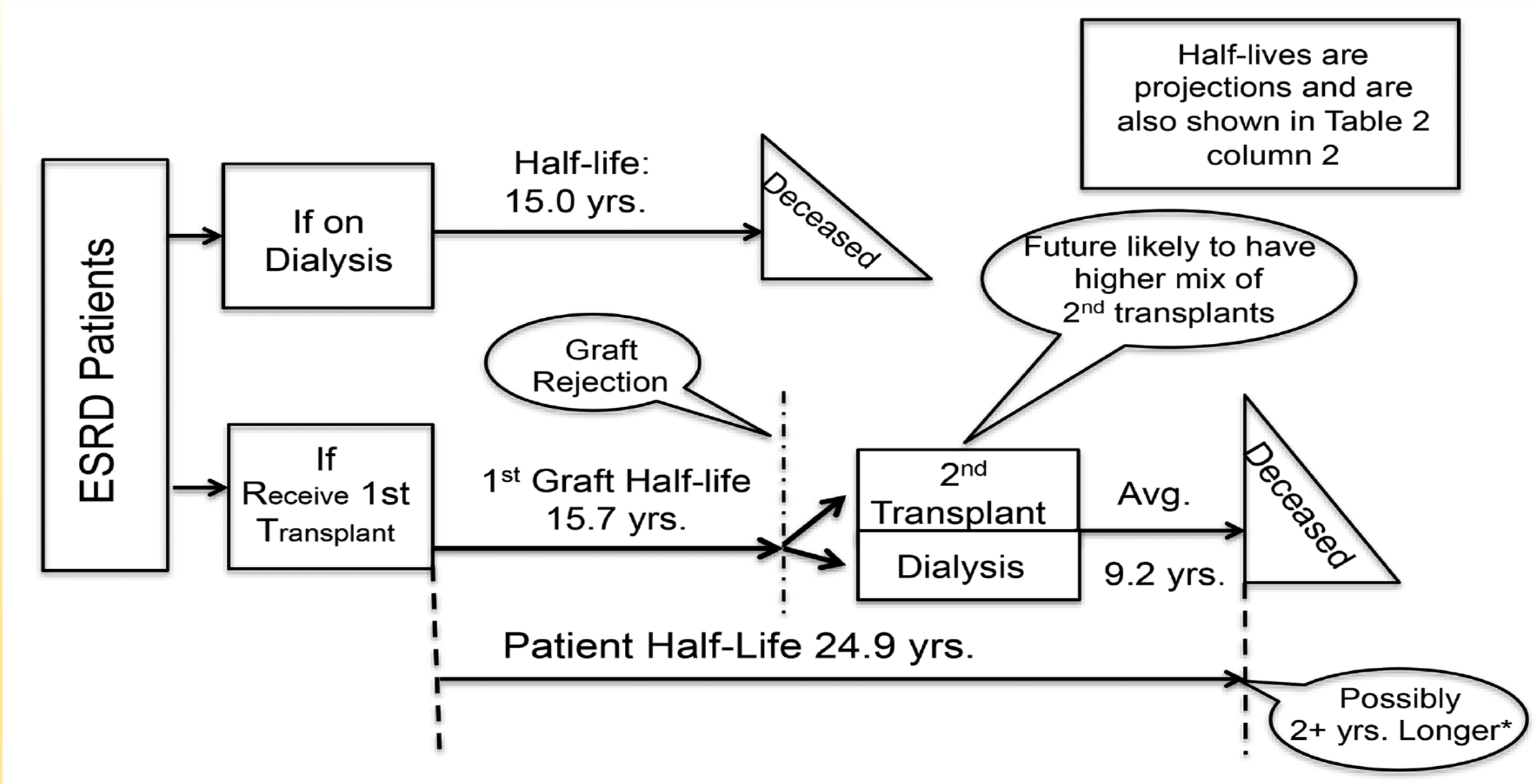
- the cost of a QALY obtained through dialysis is $186 000, while the cost of a QALY obtained through transplantation is only $49 000, less than a third as much.
- **Transplantation is clearly the more cost-effective treatment for ESRD**.

American Journal of Transplantation 2016; 16: 877–885

Financial impact of expanded transplant activity

Net savings of €248 million over 10 years





American Journal of Transplantation 2016; 16: 877–885

Conclusion: Cost-effectiveness of Living Vs Deceased Kidney Transplantation

- Pre-transplant period: Living donor kidney Tx is more expensive as compared to Deceased donor kidney Tx due to better evaluation of donor and its compensations
- Post-transplant period: Living donor kidney Tx is more be cost-effectiveness as compared to Deceased donor kidney Tx due to better outcomes, lower immunosuppression needs, reduced re-hospitalization, etc.

Pre-emptive renal Transplantation: Deceased or Living?

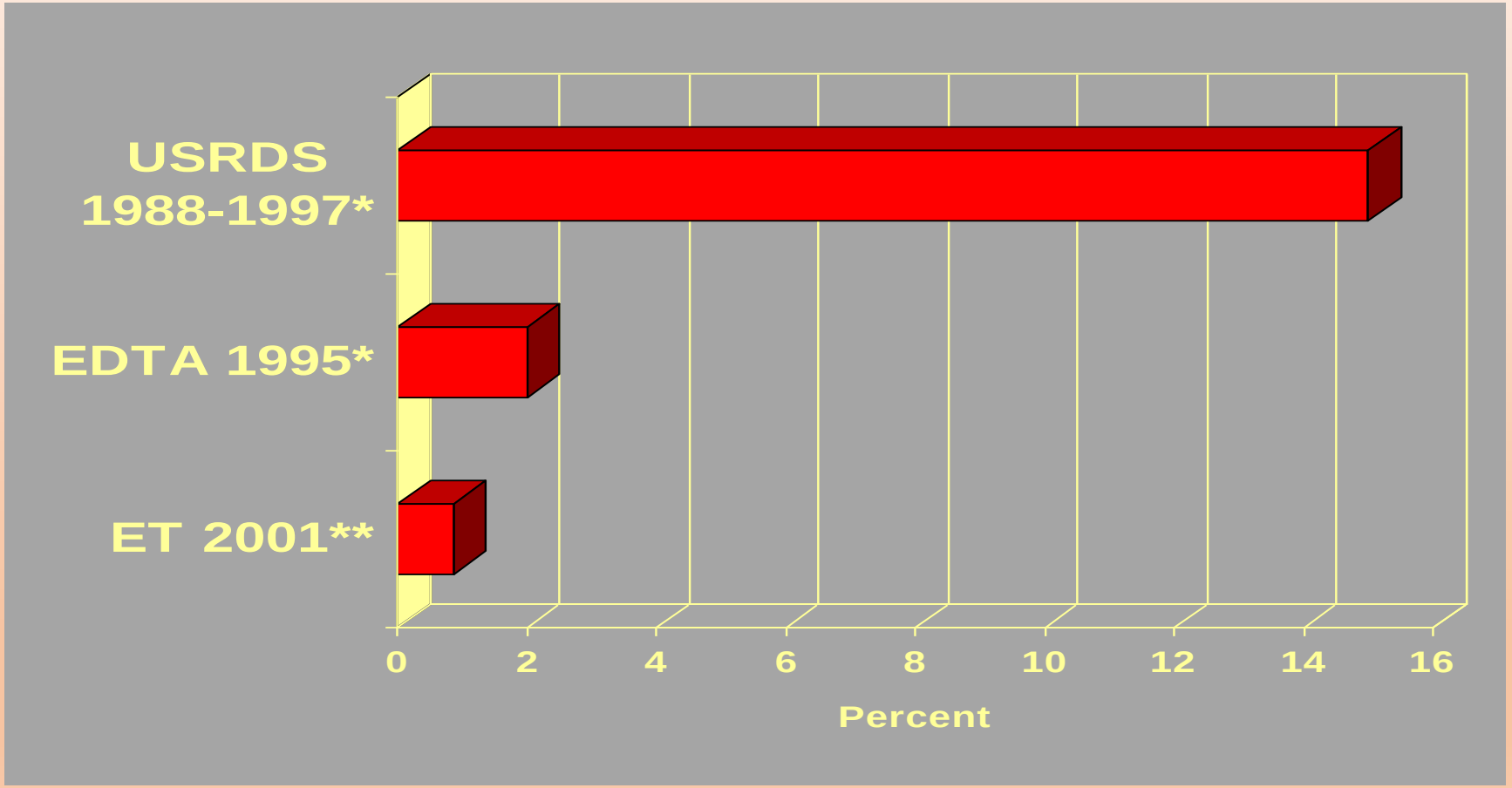
Preemptive kidney transplantation

- The preferred form of RRT and should be encouraged where feasible (Grade A).
- Not proceed unless GFR < 20 mL/minute and evidence of progressive and irreversible deterioration in renal function over previous 6–12 months.
- Exceptions may be made for patients receiving combined organ transplants where a kidney transplant is combined with a non-renal organ

Preemptive kidney transplantation

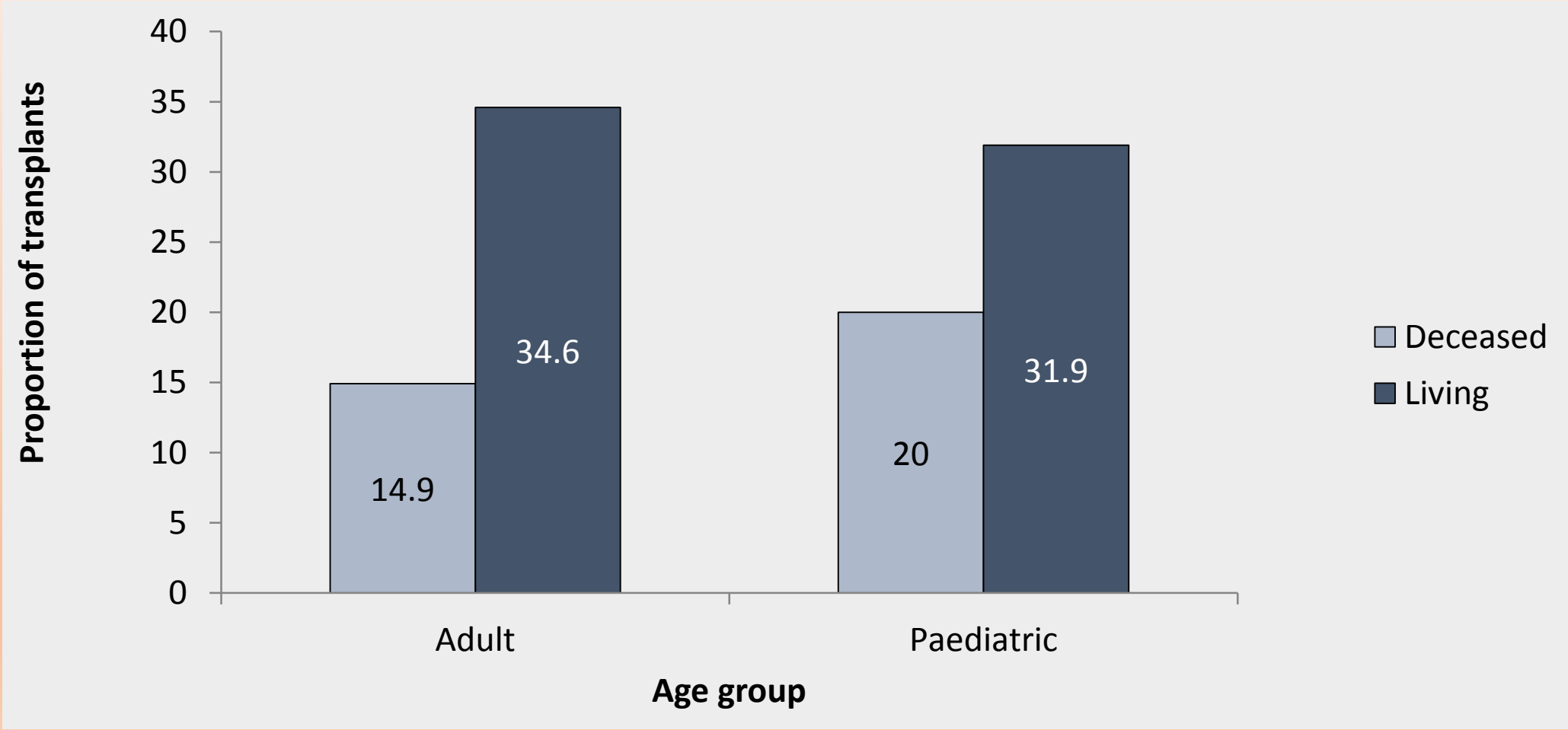
- Positive impact on patient and graft survival
- The rate of preemptive kidney tx in USA
  - Living: %25
  - Deceased: %7-8
- In Turkey: % 20

Preemptive Transplantation US *vs.* Europe Adult Patients



* Living + Cadaveric ** Cadaveric only

Pre-emptive transplants, 1 April 2016 – 31 March 2017



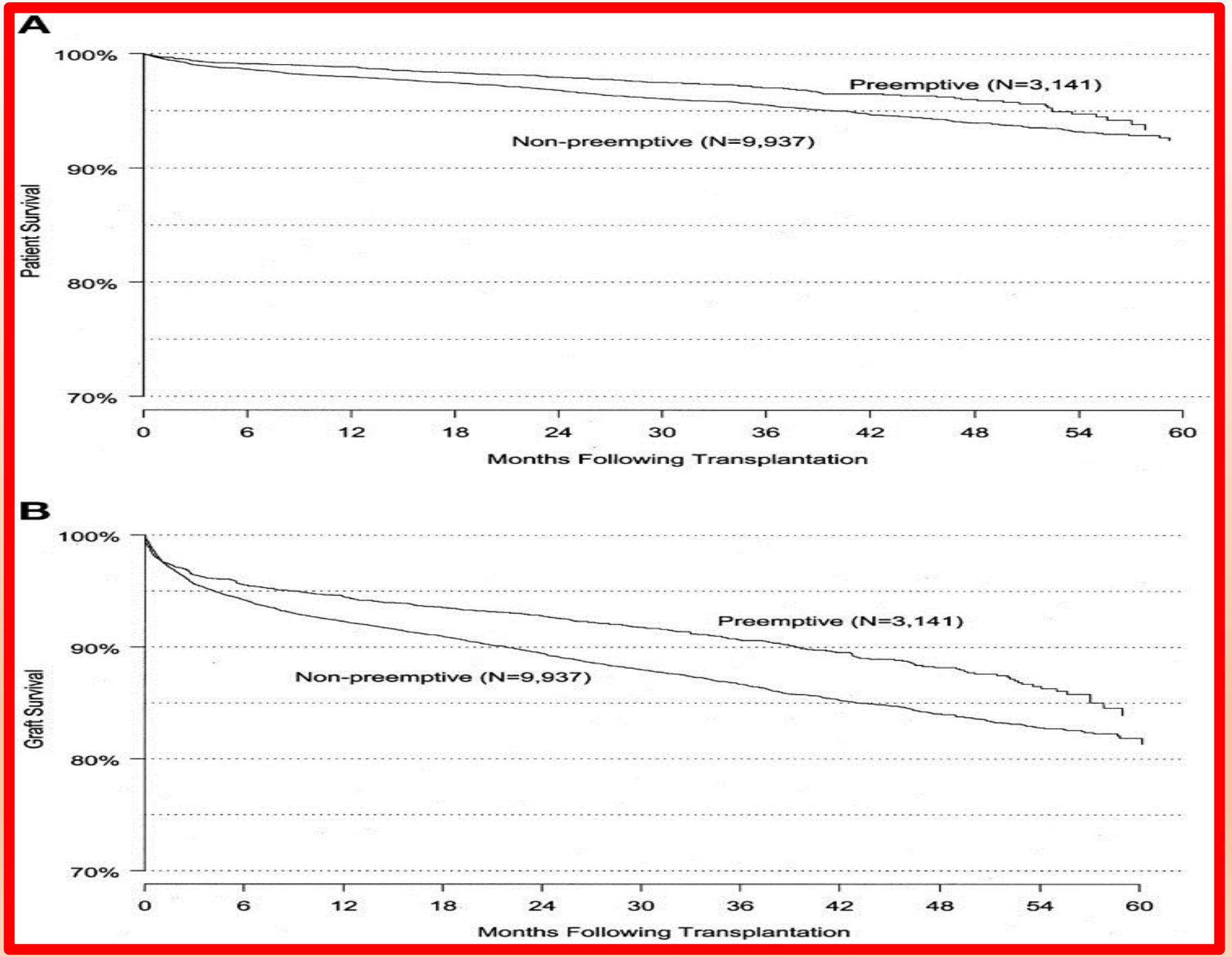
Preemptive transplant (transplant before dialysis started)

- MANY benefits including (Davis, Curr Opin Nephrol Hypertens, 2010):

- Decreased rejection rates by 25%
- Improved graft survival long-term
- Improved patient survival
- Less delayed graft function
- Decreased overall hospitalizations

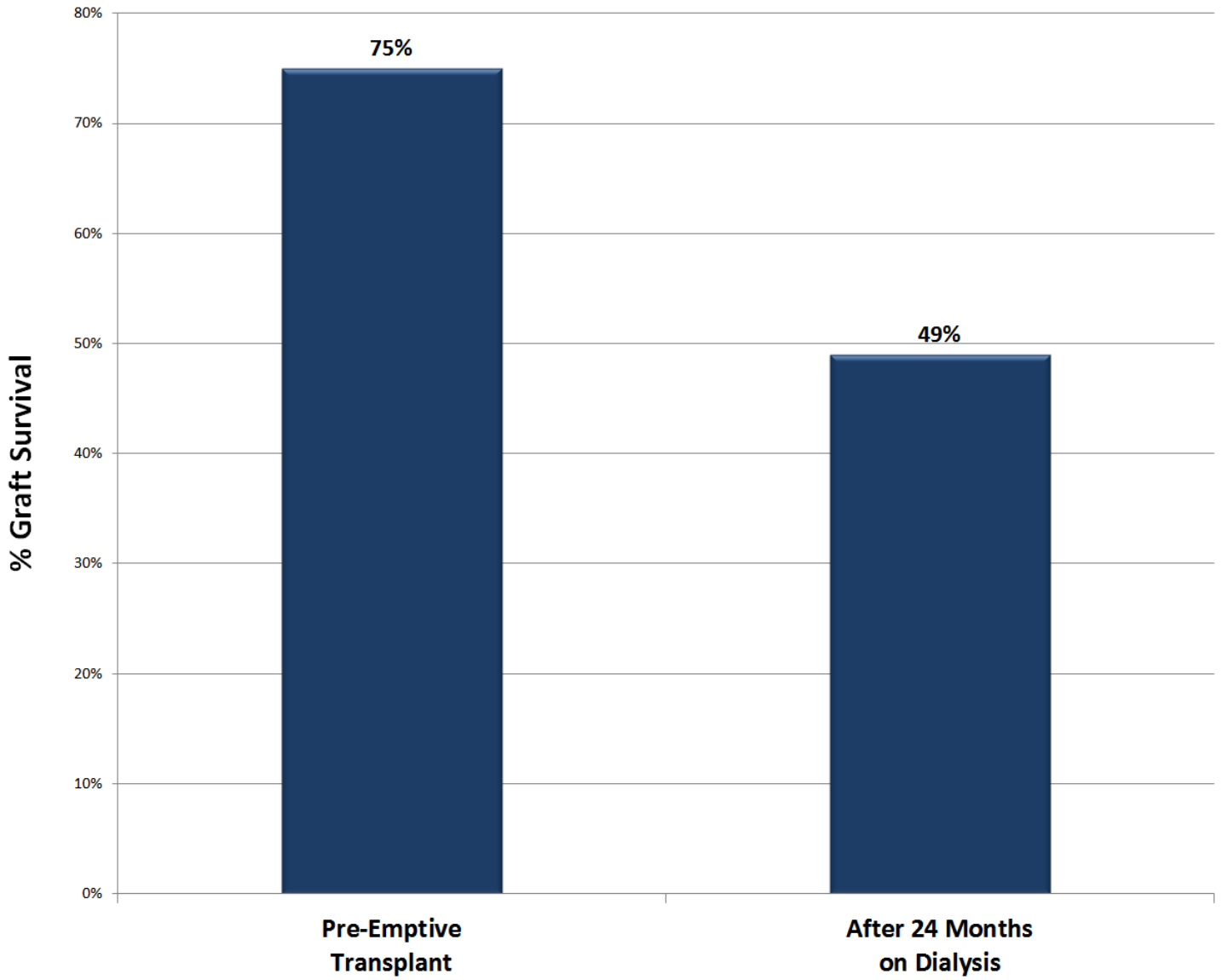
Benefits of Preemptive Transplantation

- The potential benefits of PKT include:
  - Decreased graft rejection rate, improved survival of the recipient and the graft as well. (see Fig.2).
  - Improved graft function and patient survival rate found in all age groups (Figure 3).
  - Improved quality of life and growth of the young.
  - Diabetic patients better in long-term survival with PKT.
  - Other benefits such as cost cuttings through avoidance of dialysis, decreased sensitization rates, fewer catheter-induced infections from dialysis, fewer events of hepatitis, less cardiac systolic disorders and hypertension, decreased rate of hospitalization etc.

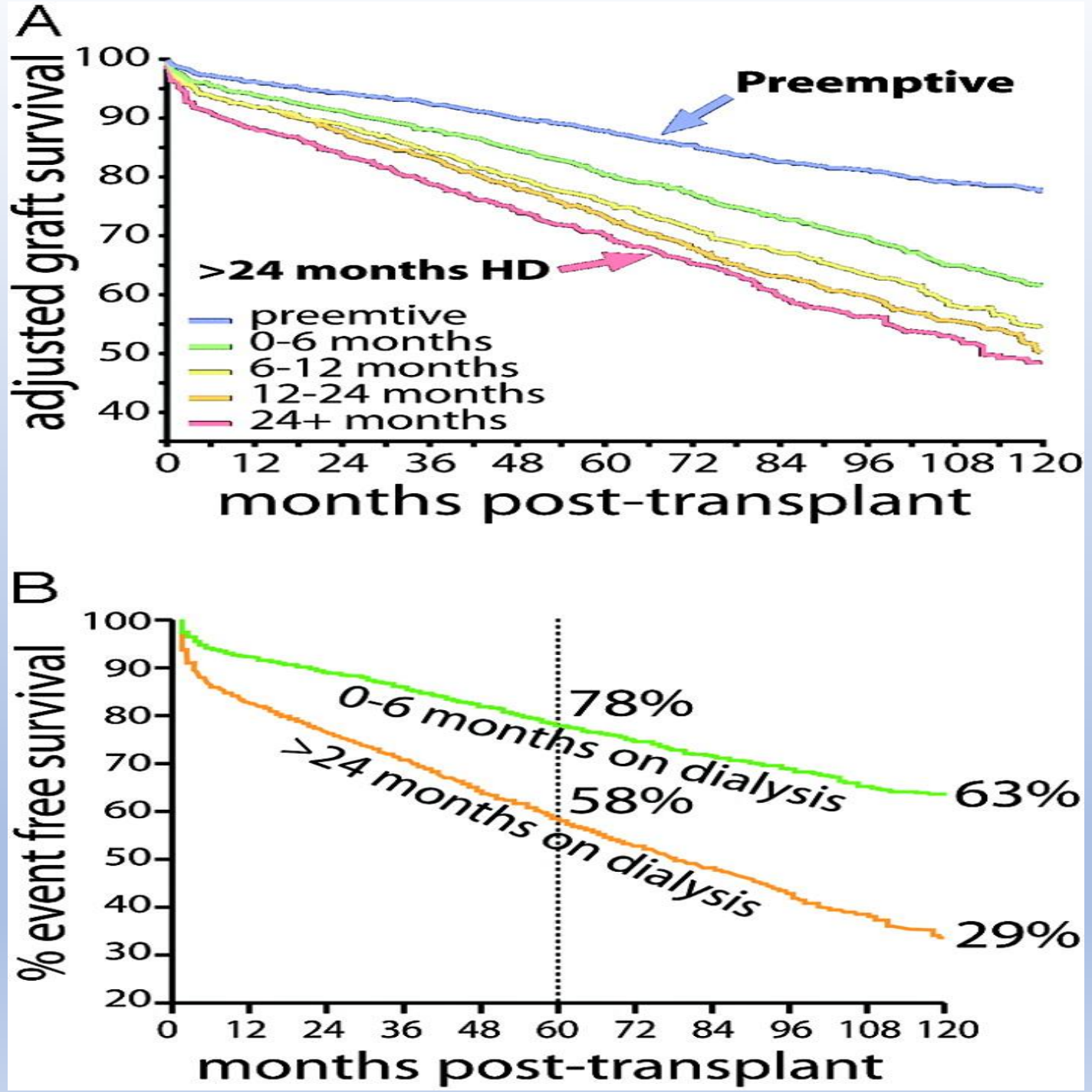

A
100%
90%
80%
70%
Patient Survival
Preemptive (N=3,141)
Non-preemptive (N=9,937)
0
6
12
18
24
30
36
42
48
54
60
Months Following Transplantation
B
100%
90%
80%
70%
Graft Survival
Preemptive (N=3,141)
Non-preemptive (N=9,937)
0
6
12
18
24
30
36
42
48
54
60
Months Following Transplantation

Ten Year Overall Adjusted Graft Survival

Pre-emptive Living Donor Transplant vs. Dialysis



*Source: Meier-Kriesch HU, Kaplan B., Transplantation, 2002 Nov 27; 74 (10): 1377-81


A
adjusted graft survival
100
90
80
70
60
50
40
Preemptive
>24 months HD
preemtive
0-6 months
6-12 months
12-24 months
24+ months
0 12 24 36 48 60 72 84 96 108 120
months post-transplant
B
% event free survival
100
90
80
70
60
50
40
30
20
0-6 months on dialysis
78%
63%
>24 months on dialysis
58%
29%
0 12 24 36 48 60 72 84 96 108 120
months post-transplant

DGF	PKTx	NPKTx
	2.5%	5.1%

(Mange KC, et al. New Engl J Med ,344:726-731; 2001)

DGF

- *Preemptive transplantation was associated with a lower rate of delayed graft function compared with nonpreemptive transplantation, for both cadaver donor* ***(8.4 versus 25.6%; P < 0.001)*** *and living donor transplants* ***(2.6 versus 6.1%; P < 0.001).***

- *(Kasiske BL, et al.J Am Soc Nephrol 13:1358-1364, 2002)*

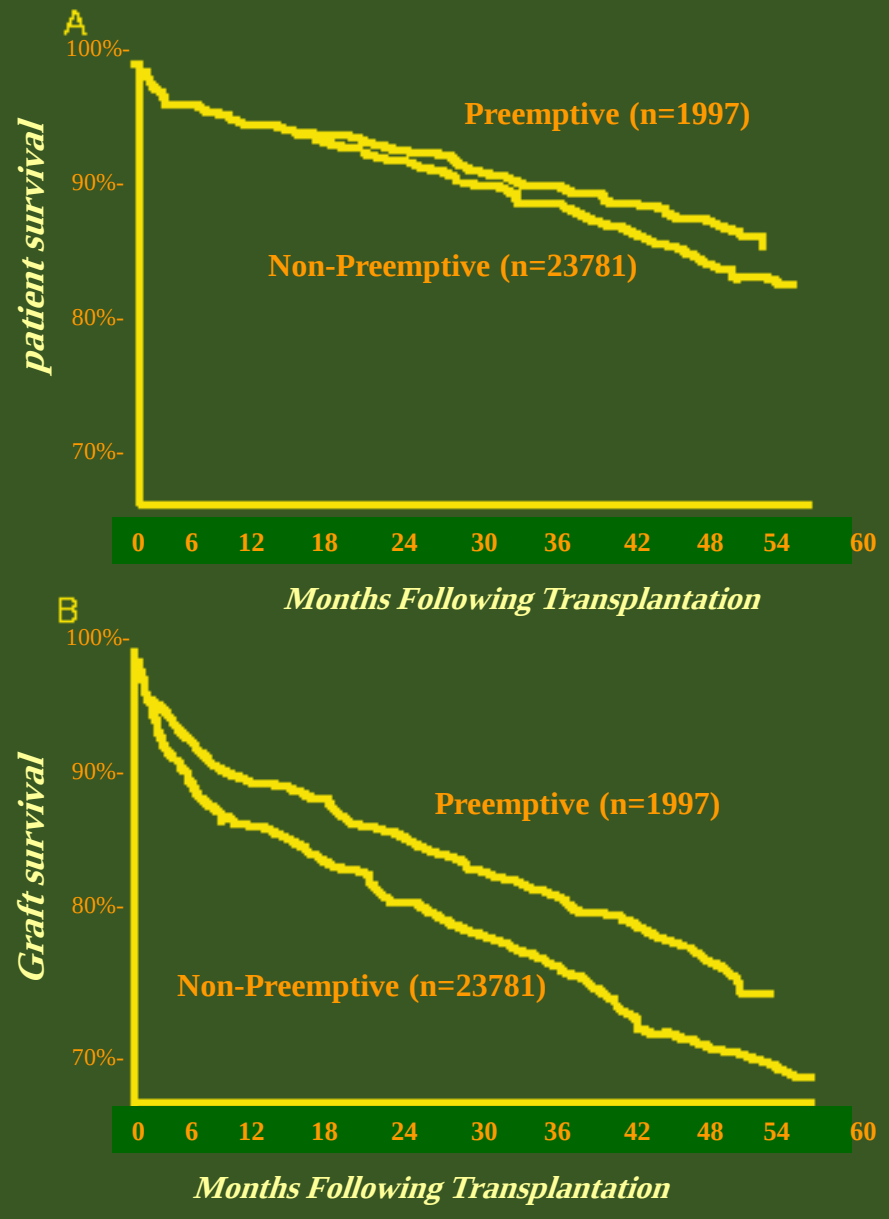
D G F

- ***Delayed graft function occurred more frequently in the dialysis group (24.5% vs 16%) .***

- *(Asderakis A, et al. NDT 13(7) 1799-1803, 1998)*

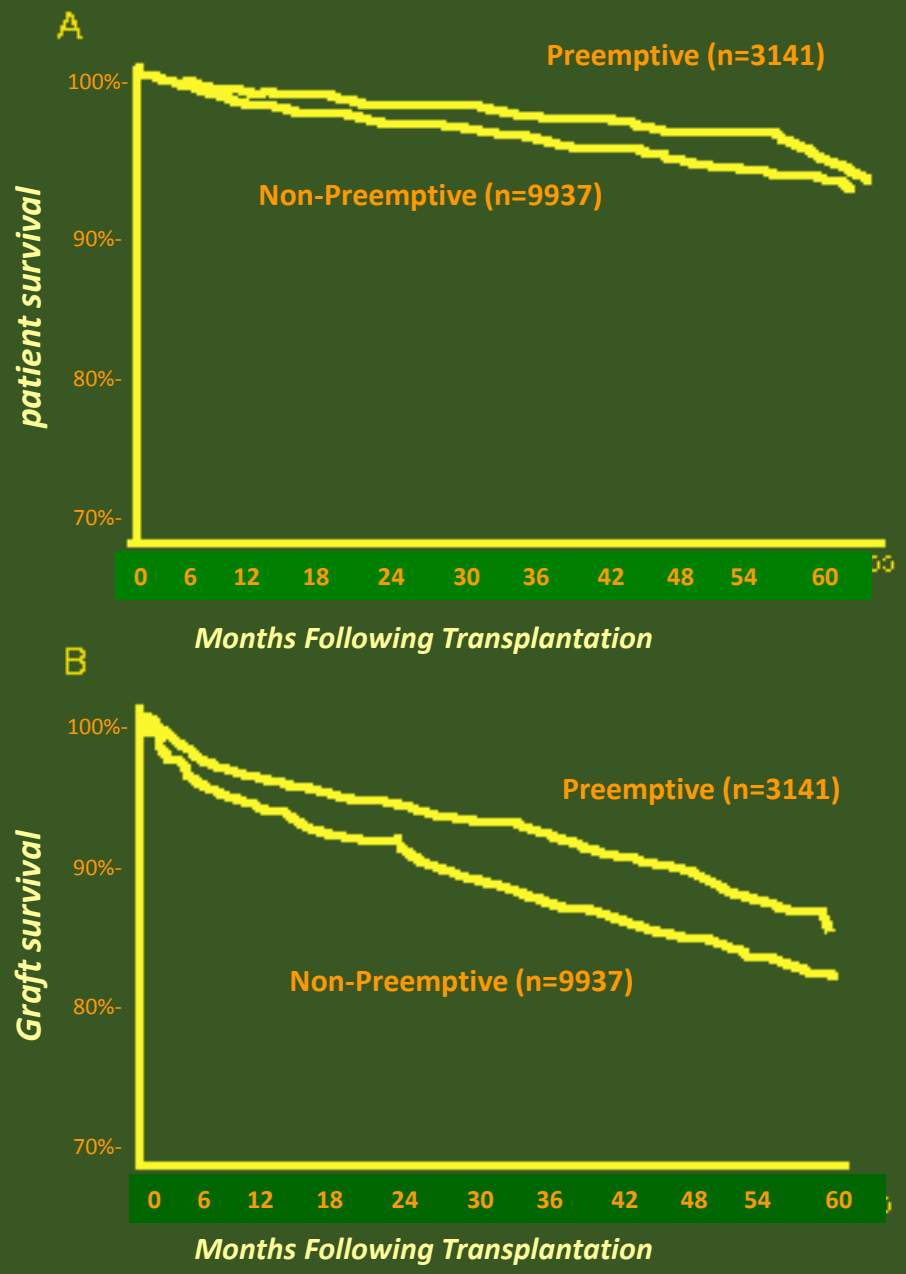
PKTx is associated with decreased Acute Rejection

- *Kevin C. Mange et al. New Engl J Med ,344:726-731; 2001*
- *Cacciarelli et al.Transplant Proc 25:2474-6;1993*



Relationship between preemptive transplantation and outcomes among recipients of cadaver donor kidney transplants. Shown are unadjusted, Kaplan-Meier patient survival (upper panel) and graft survival (lower panel).

Kasiske et.al. J Am Soc Nephrol 2002;13: 1358-64



Relationship between preemptive transplantation and outcomes among recipients of living donor kidney transplants. Shown are unadjusted, Kaplan-Meier patient survival (upper panel) and graft survival (lower panel).

Kasiske et.al. J Am Soc Nephrol 2002;13: 1358-64

The best option for RRT in children is preemptive Tx

Dialysis should be limited to those children who cannot benefit from preemptive Tx

Advantages

- **Avoids dialysis** (school attendance, social and family life)
- **Avoids vascular/peritoneal access**
- **Better results than non-preemptive Tx**
- **Cost effectiveness**

Drawbacks

- **Timing for putting the patient on the waiting list?**
- **Increased risk of non-adherence?**

Arguments in favour of PKTx

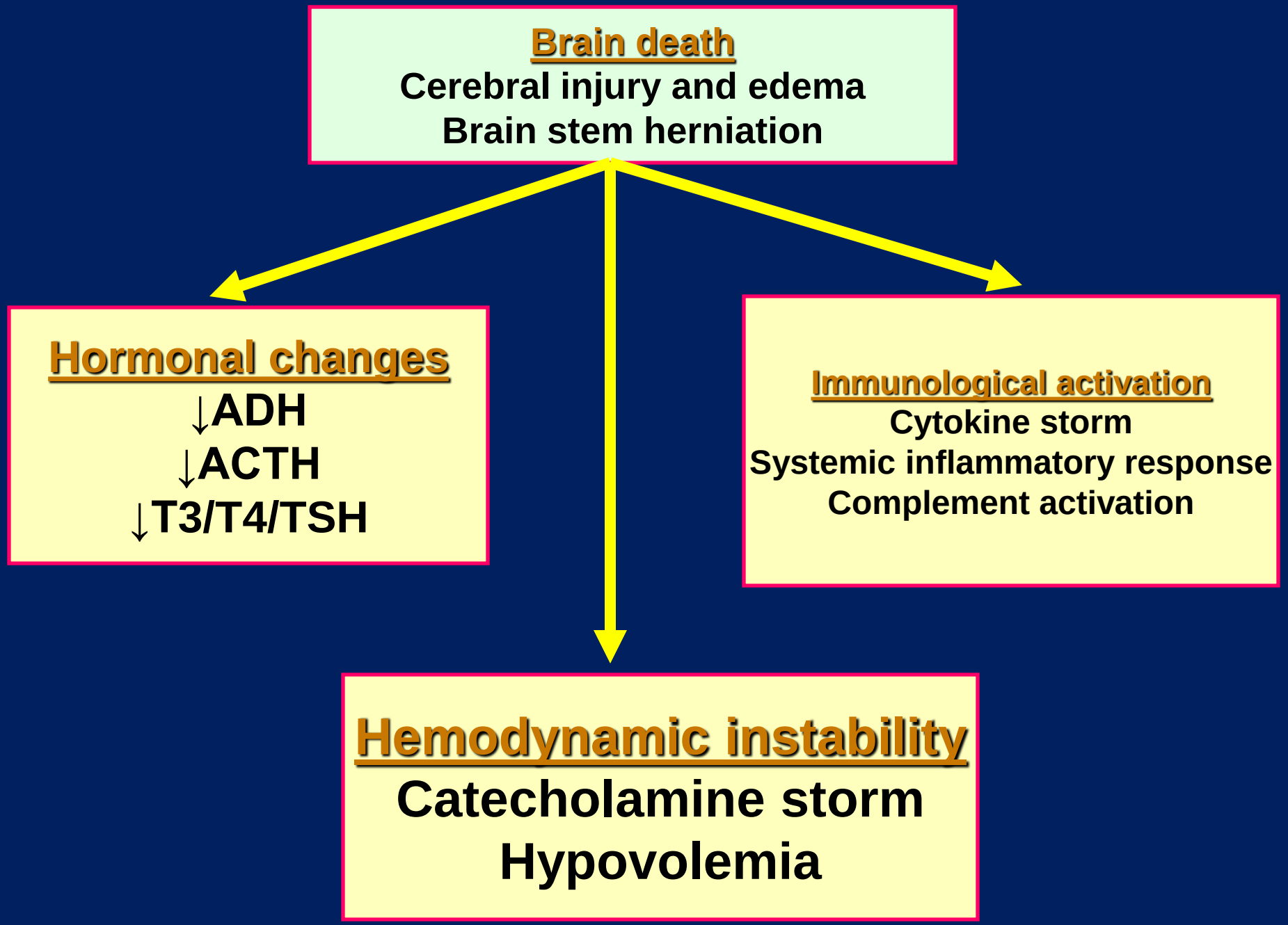
- *Better overall survival rates*
- *Less DGF*
- *Decreased Acute Rejection*
- *No need for vascular access or PD-catheter surgery*
- *Lower morbidity*
- *Avoidance of the costs & inconvenience of hemo- or peritoneal dialysis*

Arguments in favour of PKTx…

- ***Better rehabilitation and more frequent return to full-time employment after Tx***
- ***High quality of life***
- ***Improved growth***
- ***Decreased transfusion requirements***
- ***Preserved residual renal function***
- ***Early referral of patients***
- ***Socioeconomic benefits***

In conclusion:

- *Shorter waiting time (usually 1-2 months); permits preemptive transplantation to avoid dialysis*
- *Preemptive transplantation rate is higher in LKDT*
- *Better overall outcomes*
- *Less DGF*
- *No need for vascular access or PD-catheter surgery*
- *Avoidance of the costs & inconvenience of hemo- or peritoneal dialysis*


Brain death
Cerebral injury and edema
Brain stem herniation
Hormonal changes
↓ADH
↓ACTH
↓T3/T4/TSH
Immunological activation
Cytokine storm
Systemic inflammatory response
Complement activation
Hemodynamic instability
Catecholamine storm
Hypovolemia

Hemodynamic Changes

- Hemodynamic instability
- Catecholamine storm
- Hypovolemia

Hemodynamic Instability

- Among patients with brain death, intracranial pressure rises due to cerebral edema, which results in compression of brain tissue and subsequent venous congestion and increasing brain turgor.
- It triggers parasympathetic activity and results in a decreased systemic blood pressure.

Catecholamine Storm

- When the entire brain stem has become ischemic, the vagal cardiomotor nucleus is affected and solitary sympathetic stimulation will occur.
- As a result, massive release of catecholamines then ensues, which causes profound vasoconstriction with increased vascular resistance and endothelial injury.
- This process is referred to as the sympathetic or catecholamine storm.

The rise in serum epinephrine levels has been reported to be as high as 100-1000 fold higher compared to normal values in animal models of brain death.

- *The magnitude of catecholamine release is related to the severity of brain damage.*
- *The faster the rise in intracranial pressure, the higher the peak in catecholamine levels.*
- *Also, serum norepinephrine and dopamine concentrations are vastly increased after onset of brain death.*

Circulation 1993; 87: 230-9.

The catecholamine- induced increase in vascular resistance can be severe, reaching 4 times higher levels than basal values in the rat kidney.

- ***This causes renal blood flow to decrease by a factor of 2.4 and supports the hypothesis that the rigorous decline in organ perfusion leads to ischemic damage of potential grafts.***

Transplantation 1996; 62: 330-5.

Hormonal Changes

↓ ADH

↓ ACTH

↓ T3/T4/TSH

Hormonal Changes

Endocrine aberrations resulting from brain death include the initial release of anterior pituitary hormones which leads to a subsequent ***reduction*** in the levels of circulating ***thyroid hormone***, ***cortisol***, ***insulin*** and ***antidiuretic hormone*** (***vasopressin***).

Hormonal Changes

- Diabetes insipidus rapidly occurs, and cardiac arrhythmias and rapid fluctuations in blood pressure are common.
- Such factors may obviously adversely affect the function and integrity of the kidney.

Any acute stress will enhance the condition known as 'diabetes of injury', consisting mainly of hyperglycemia caused by increased gluconeogenesis and insulin resistance.

- ***The use of intensive insulin therapy in brain dead patients could attenuate renal damage, reduce inflammation, and enhance donor organ viability resulting in a better transplantation outcome.***

J Clin Endocrinol Metab 2003; 88: 1082-8.
J Clin Invest 2005; 115: 2277-86.

Experimental Brain Death Models

- *In recent years, the use of animal models with brain death has made it clear that organ quality is significantly diminished in brain dead animal.*

Pathophysiological effects of brain death on renal function and structures

Human studies (Japan)

- U/Na during the first 14 days
- Above normal of U/Osm on the first day but decreased gradually
- ↑Urine volume during the first 14 days as a consequence of DI
- Degenerative changes: Vacuolization, atrophy and necrosis of renal proximal and distal tubules
- Advancing glomerulitis and progressive periglomerulitis expressed inflammatory changes
- Periglomerular fibrosis
- Proliferation of the arterial intima and glomerular endothelium

Pathophysiological effects of brain death on renal function and structures

Animal Studies

Renal tubular damage as a consequence of brain death can be observed in urine:

- **Brush border enzymes: ↑Alk.Ph., Alanine amino peptidase, N-acetyle-β-D-glucosaminidase in urine**
- **Kidney injury molecule-1**

Immunological Activation

- Cytokine Storm
- Systemic Inflammatory Response
- Complement activation

American Journal of Transplantation 2011; 11: 1064–1070
Wiley Periodicals Inc.

doi: 10.1111/j.1600-6143.2011.03466.x

Brief Communication

Donor Brain Death Predisposes Human Kidney Grafts to a Proinflammatory Reaction after Transplantation

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[b] *Department of Nephrology, Leiden University Medical Center, Leiden, The Netherlands*
[*] *Corresponding author: D. K. de Vries, d.k.de_vries@lumc.nl*

Donor brain death has profound effects on post-transplantation graft function and survival. We hypothesized that changes initiated in the donor influence the graft's response to ischemia and reperfusion. In this study, human brain dead donor kidney grafts were compared to living and cardiac dead donor kidney grafts. Pretransplant biopsies of brain dead donor kidneys contained notably more infiltrating T lymphocytes and macrophages. To assess whether the different donor conditions result in a different response to reperfusion, local cytokine release from the reperfused kidney was studied by measurement of paired arterial and renal venous blood samples. Reperfusion of kidneys from brain dead donors was associated with the instantaneous release of inflammatory cytokines, such as G-CSF, IL-6, IL-9, IL-16 and MCP-1. In contrast, kidneys from living and cardiac dead donors showed a more modest cytokine response with release of IL-6 and small amounts of MCP-1. In conclusion, this study shows that donor brain death initiates an inflammatory state of the graft with T lymphocyte and macrophage infiltration and massive inflammatory cytokine release upon reperfusion. These observations suggest that brain dead donors require a novel approach for donor pretreatment aimed at preventing this inflammatory response to increase graft survival.

Key words: Brain death, cytokines, inflammation, ischemia, kidney transplantation, reperfusion

Abbreviations: HTK, histidine–tryptophan–ketoglutarate; LD, living donor; BDD, brain dead donor; CDD, cardiac dead donor; WIT, warm ischemia time; CIT, cold ischemia time; ICU, intensive care unit; UW, University of Wisconsin solution; LDH, lactate dehydrogenase; PMN, polymorphonuclear neutrophils; MPO, myeloperoxidase; bFGF, basic fibroblast growth factor; G-CSF, granulocyte colony stimulating factor; GM-GSF, granulocyte-macrophage colony-stimulating factor; IFN, interferon; IP, interferon-inducible protein; MCP, monocyte chemoattractant protein; MIP, macrophage inflammatory protein; PDGF, platelet-derived growth factor; TNF, tumor necrosis factor; DGF, delayed graft function; AUC, area under the curve; SEM, standard error of the mean.

Received 21 September 2010, revised 23 January 2011 and accepted for publication 23 January 2011

Introduction

Despite better immunological matching, kidney allografts of deceased donors demonstrate inferior graft function and survival in comparison with living unrelated donor grafts. This can only partially be explained by their longer cold ischemia duration (1). Therefore, it is likely that donor-specific characteristics influence post-transplantation graft function and explain differences in clinical success rate.

Donor brain death has a significant influence on graft function and survival (2). The unphysiological state of brain death is associated with systemic proinflammatory changes, as illustrated by increased levels of circulating cytokines which reflect an inflammatory state in peripheral organs. The expression of inflammatory factors in the kidney at time of donation is indeed increased in brain dead donors (3–5).

Previously we have shown that the graft reperfusion phase is dominated by an inflammatory response and that kidney grafts of living donors release cytokines immediately after reperfusion (6). It was thus hypothesized that the inflammatory changes associated with brain death influence the kidney graft and result in a different response to ischemia and reperfusion. In this explorative study we first assessed whether there are differences in inflammatory cell content between brain dead and living as well as cardiac dead donor kidney grafts before transplantation. We subsequently evaluated the inflammatory response to reperfusion of the donor kidney through measurement of arteriovenous concentration differences over the transplanted organ. Cardiac dead donor grafts were included in this study in order to evaluate a potential effect of longer cold ischemia duration of the deceased donor kidneys.

In ischemic/reperfusion injury, a clear-cut correlation was found between endothelial injury and acute rejection.

It is of importance that an increased immunogenicity is also observed in the brain dead donor organ as well.

Immunological Activation…

- Injury-induced inflammation also causes upregulation of adhesion molecules and class II MHC on renal allograft endothelium.
- In addition, a procoagulant state results from endothelial activation coupled with release of cytokines, complement activation, and depletion of tissue plasminogen activator.

Immunological Activation…

The expression of the major histocompatibilty complex class II is increased.

Transplantation 1998; 65: 1533-42.

Endothelial activation is present with the upregulation of adhesion molecules:

- E-selectin
- P-selectin
- Intracellular adhesion molecule-1
- Vascular cellular adhesion molecule-1

- Promote the rolling, adhesion, diapedesis, and subsequent leukocyte migration into the interstitium of the kidney.

Upregulation :

IL-1

IL-2

IL-6

VEGF

TNF-alfa

TGF-beta

MIP-1beta

Osteopontin

Interferon-gama

Membrane cofactor protein-1

Immunological Activation…

- Amplication of cytokines, chemokines, and adhesion molecules causes a chemotactic gradient that promotes the influx of leukocytes to the kidney.
- T cells, macrophages, and PMN leukocytes are all found in higher quantities in donor kidneys during brain death.

Transplantation 2004; 78: 978-86.

Immunological Activation…

- After reperfusion, a large difference in neutrophil infiltration and P-selectin expression can be observed between living & deceased donor grafts.
- Koo et al. showed that 53% of deceased donor renal allografts had increased neutrophil infiltration, against 0% of living related grafts.
- P-selectin expression was increased in 44% of deceased donor grafts, and 9% of living related grafts.

Koo et al.Am J Pathol 1998; 153: 557-66.

Immunological Activation…

In syngeneic animal model of renal Tx, short-term inflammatory changes to the kidneys:

- ✓The extent of leukocyte infiltration reaches its peak at 24 h after Tx in this syngeneic transplant model and corresponds with the levels of E- &P-selectin.
- ✓Allotransplant experiments have shown that after experimental brain death, recipients of brain dead kidneys sufferred from a greatly increased acute rejection rate.

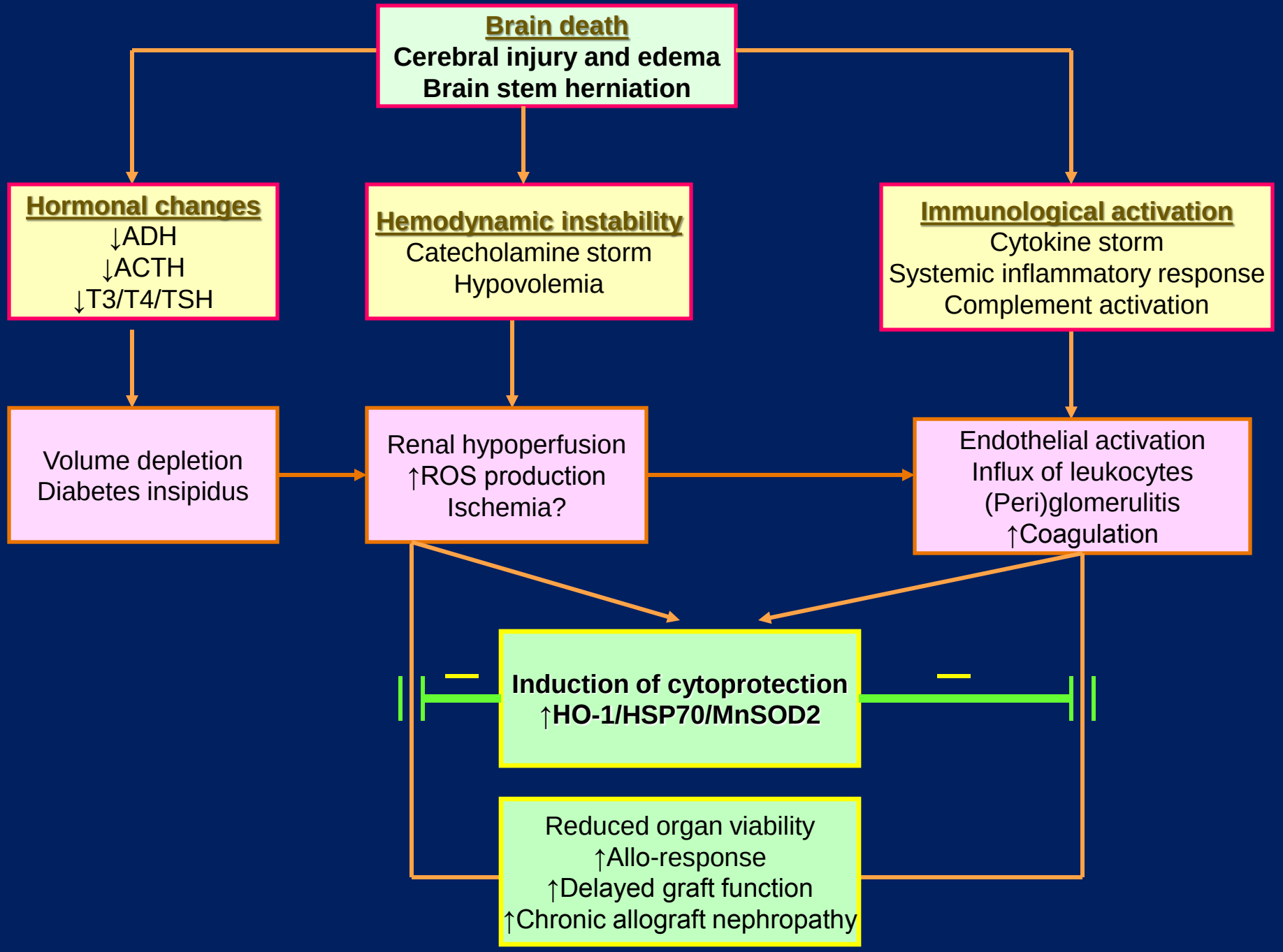
Ann Surg 2000; 232: 263-71.
Transplantation 2000; 69: 405-10.

Immunological Activation…

- When kidney allografts are treated with cyclosporine to prevent acute rejection, long-term renal function is adversely affected by brain death compared to syngeneic transplants.

- Thus, **the state of brain death can also enhance the develoment of chronic renal transplant dysfunction**.

J Am Soc Nephrol 2001; 12: 2474-81.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Hemodynamic instability
Catecholamine storm
Hypovolemia
Immunological activation
Cytokine storm
Systemic inflammatory response
Complement activation
Volume depletion
Diabetes insipidus
Renal hypoperfusion
↑ROS production
Ischemia?
Endothelial activation
Influx of leukocytes
(Peri)glomerulitis
↑Coagulation
Induction of cytoprotection
↑HO-1/HSP70/MnSOD2
Reduced organ viability
↑Allo-response
↑Delayed graft function
↑Chronic allograft nephropathy

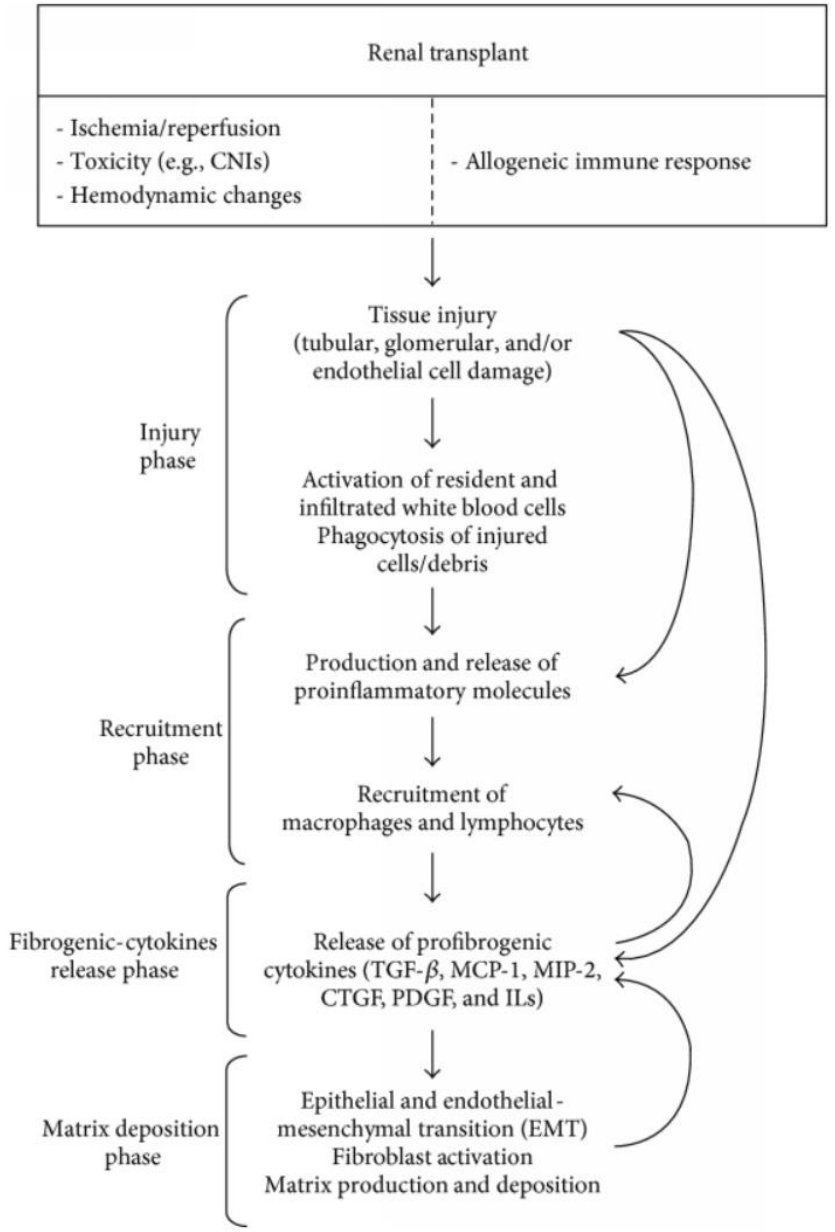

Figure 1: Renal transplant-induced fibrosis involves a complex multifactorial inflammatory process with the participation and interaction of infiltrated cells with different cell types in the kidney and is orchestrated by a network of cytokines/chemokines, growth factors, adhesion molecules, and signalling processes. These events include several phases in a dynamic process in which many of these events occur simultaneously, often in a mutually stimulating fashion.

Overview of studies that investigated the effects of specific interventions on brain death related damage

Human Studies		
Study	**Treatment**	**Main renal outcome**
Kuecuek (2005)	Steroids	Reduced expression of proinflammatory cytokines
Schnuelle (1999)	Dopamine	Improved graft survival, less acute rejection
	Norepinephrine	Improved graft survival, less acute rejection
Schnuelle (2001)	Catecholamine	Improved graft survival
Schnuelle (2004)	Dospamine	Improved graft survival, Improved short-term renal function

Overview of studies that investigated the effects of specific interventions on brain death related damage…

Animal Studies

Study	Treatment	Main renal outcome
Coleman (2006)	CEPO	Reduced expression of proinflammatory factors
Gasser (2002)	rPSGL-Ig	Improved graft survival, reduced chronic rejection
Kotsch (2006)	CoPP (HO-1induction)	Improved graft survival, reduced leukocyte infiltration
Pratschke (2001)	rPSGL-Ig Steroid	Improved graft survival, reduced chronic rejection Improved graft survival, reduced chronic rejection
Schaub (2004)	Dospamine	Reduced expression of proinflammatory factors

Carbamylated recombinant human Erythropoietin (CEPO), Recombinant P-selectin Glycoprotein Ligand-Ig (rPSGL-Ig), Cobalt Protoporphyrin (Copp)

Interventions that counteract the negative effects of brain death on the kidney, or could be used for this purpose in the future

❖ *Hemodynamic:*

- ✓ Catechoamines (Dopamine, epinephrine, Norepinephrine)
- ✓ Anti duretic hormone (ADH)

Interventions that counteract the negative effects of brain death on the kidney, or could be used for this purpose in the future…

❖ ***Anti-inflammatory***

- ✓ Immunosuppressants (glucocorticoids, Calcineurine inhibitors)
- ✓ Monoclonal antibodies against cytokines(TNF-α,IFN-γ,IL-2,IL-6)
- ✓ Inhibitors of chemokines (MCP-1, MIP-1$^{\alpha}$, MIP-1β)
- ✓ Carbamylated recombinant human Erythropoietin (CEPO)
- ✓ Recombinant P-selectin Glycoprotein Ligand-Ig (rPSGL-Ig)

Interventions that counteract the negative effects of brain death on the kidney, or could be used for this purpose in the future…

❖ *Induction of cytoprotection*

- HO-1 induction (Cobalt Protoporphyrin [Copp])
- HSP induction (Pyrrolidine Dithicarbamate [PDTC], Geranylgeranylacetone [GGA])

❖ *Signal transduction*

- Selective inhibitors of kinases (JNK, p38, ERK, RhoA)

Interventions that counteract the negative effects of brain death on the kidney, or could be used for this purpose in the future…

❖ *Gaseous substances*

- ✓ Carbon Monoxide (CO)
- ✓ Nitrous Oxide (NO)

❖ *Hormonal*

- ✓ Intensive insulin therapy

Increasing the Rate of Living Donor Kidney Transplantation in Ontario: Donor- and Recipient-Identified Barriers and Solutions

- Four main areas were identified as obstacles: lack of education for patients and families, lack of public awareness about LDKT, financial costs incurred by donors, and health care system–level inefficiencies.
- Several novel solutions were suggested, including peer mentorship, education through private sector partnership, youth education, consistent reimbursement policies to cover donors' out-of-pocket expenses, partnering with the paramedical/insurance industry to hasten the donor and recipient evaluation process, capturing the popular rise in the sharing economy to better connect potential donors with recipients, and the creation of a centralized source for information and support for LDKT in Ontario.

Getchell et al. 2017; Canadian Journal of Kidney Health and Disease

The reasons why living-donor kidney transplantation is increasing in Spain

- 1) **Better outcomes** than with cadaveric donor transplantation.
- This improved graft and patient survival can be explained by the fact that living donor transplantation involves younger recipients with better HLA matching, healthy donors, the absence of possible kidney damage secondary to brain death, reduced ischemic time and the possibility of pre-emptive transplantation.

Beatriz Domínguez-Gil et al. Present situat ion of kidney t ransplant at ion

The reasons why living-donor kidney transplantation is increasing in Spain

- 2) **The shortage of donors**: the relaxation of waiting list entry criteria makes meeting the transplant demand without living-donor kidney transplant at ion more difficult , especially in young recipients, where the chances of obtaining an age-appropriate donor are lower, due to the change in the age profile of deceased donors (increasingly older).

Beatriz Domínguez-Gil et al. Present situat ion of kidney t ransplant at ion

The reasons why living-donor kidney transplantation is increasing in Spain

- *3)* **Improvement in donor safety**: the excellent evaluation and monitoring of donors (based on international standards), in addit ion to the use of less invasive surgical techniques, have led to low complication rates and make the life expectancy of living donors similar to that of the general population.

Beatriz Domínguez-Gil et al. Present situat ion of kidney t ransplant at ion

The reasons why living-donor kidney transplantation is increasing in Spain

- *4)* **Barriers overcome**: the training effort by transplant teams, hospital and regional transplant coordination teams, and the Spanish National Transplant Organization is producing excellent results, which are visible in the gradual increase in the number of hospitals with a living- donor kidney transplantation programme and the effectiveness of such programmes.
- In addition, desensitized ion programmes and the nat ional crossover kidney transplant at ion programme have removed barriers to transplantation in cases of ABO incompatibility or positive crossmatch.

Beatriz Domínguez-Gil et al. Present situat ion of kidney t ransplant at ion

Benefits of Living Donation

- Shorter waiting time (usually 1-2 months); permits preemptive transplantation to avoid dialysis
- Higher quality kidney (healthy donor, short ischemia time), which results in higher success rates and improved graft longevity
- Scheduled event, can plan accordingly, can be performed during normal work day by rested team and fully prepared donor and recipient
- Psychological benefits to donor and recipient
- A living donor kidney transplant allows the deceased donor kidney that would be needed for this recipient to be given to another individual in need of a transplant, so in essence two people are removed from the kidney waiting list

Pros and Cons of Living Donor and Deceased Donor Kidney Transplantation

Living Donor Kidney Transplantation	Deceased Donor Kidney Transplantation
Pros: • Living donor kidneys last longer than deceased donor kidneys. • Living donor kidneys work better because they are outside the recipient's body for less time than are deceased donor kidneys. • The patient waits a couple of weeks or months for a living donor kidney transplant based on the speed of donor evaluation. • Surgery can be scheduled in advance. • Patients can get a living donor kidney transplant before starting dialysis. • Patients spend less time on dialysis, which means better health. • Doctors know more about the donor's health and possible risks for the recipient.	**Pros:** • Deceased donation does not harm the donor. • Deceased donation is an option for patients without a living donor.
Cons: • The donor needs to get major surgery. • Donation poses risks to the donor like any other surgery. • Patients may not have a living donor.	**Cons:** • The deceased donor kidney does not last as long as the living donor kidney. • The deceased donor kidney may not work as well as a living donor kidney because the deceased donor kidney is outside the donor's body for a longer time. • The patient waits on average 5 years for a deceased donor kidney transplant. • The deceased donor kidney can be offered at any time without knowing ahead of time. • Doctors know less about the donor's health and possible risks for the recipient.


Thank you all for
your attention