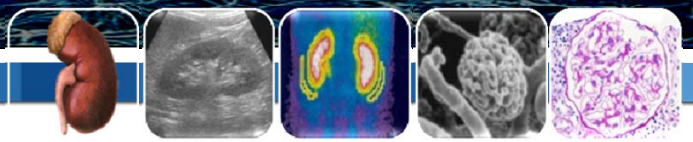
2017.5.3 KSN 2017 KDIGO-KSN Joint Symposium

Kidney Transplantation in Korea



Byung Ha Chung[a,b], Chul Woo Yang[a,b]

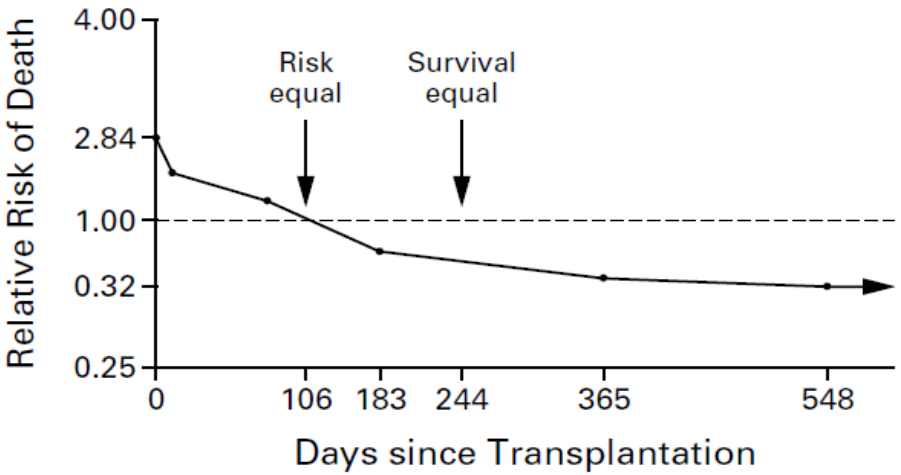
[a]Transplant Research Center

[b]Division of Nephrology, Department of Internal Medicine,

The Catholic University of Korea, Seoul, Korea.

Why Kidney transplantation ??

COMPARISON OF MORTALITY IN ALL PATIENTS ON DIALYSIS, PATIENTS ON DIALYSIS AWAITING TRANSPLANTATION, AND RECIPIENTS OF A FIRST CADAVERIC TRANSPLANT



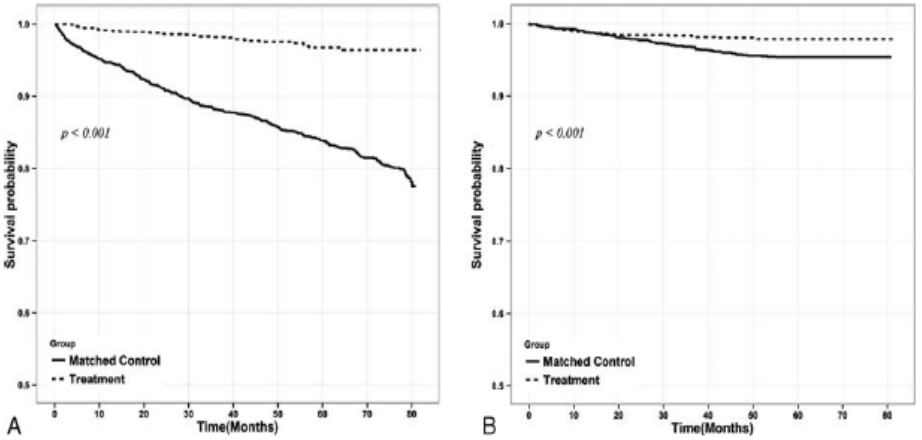
"Long-term survival is better among those on the waiting list who eventually undergo transplantation"

Wolfe L et al, N Eng J Med 1999; 341:1725

Superior outcomes of kidney transplantation compared with dialysis

An optimal matched analysis of a national population-based cohort study between 2005 and 2008 in Korea

All cause mortality **Mace free survvial**



"Korean dialysis patients had significantly more cardiovascular events and higher all-cause mortality than KT patients"

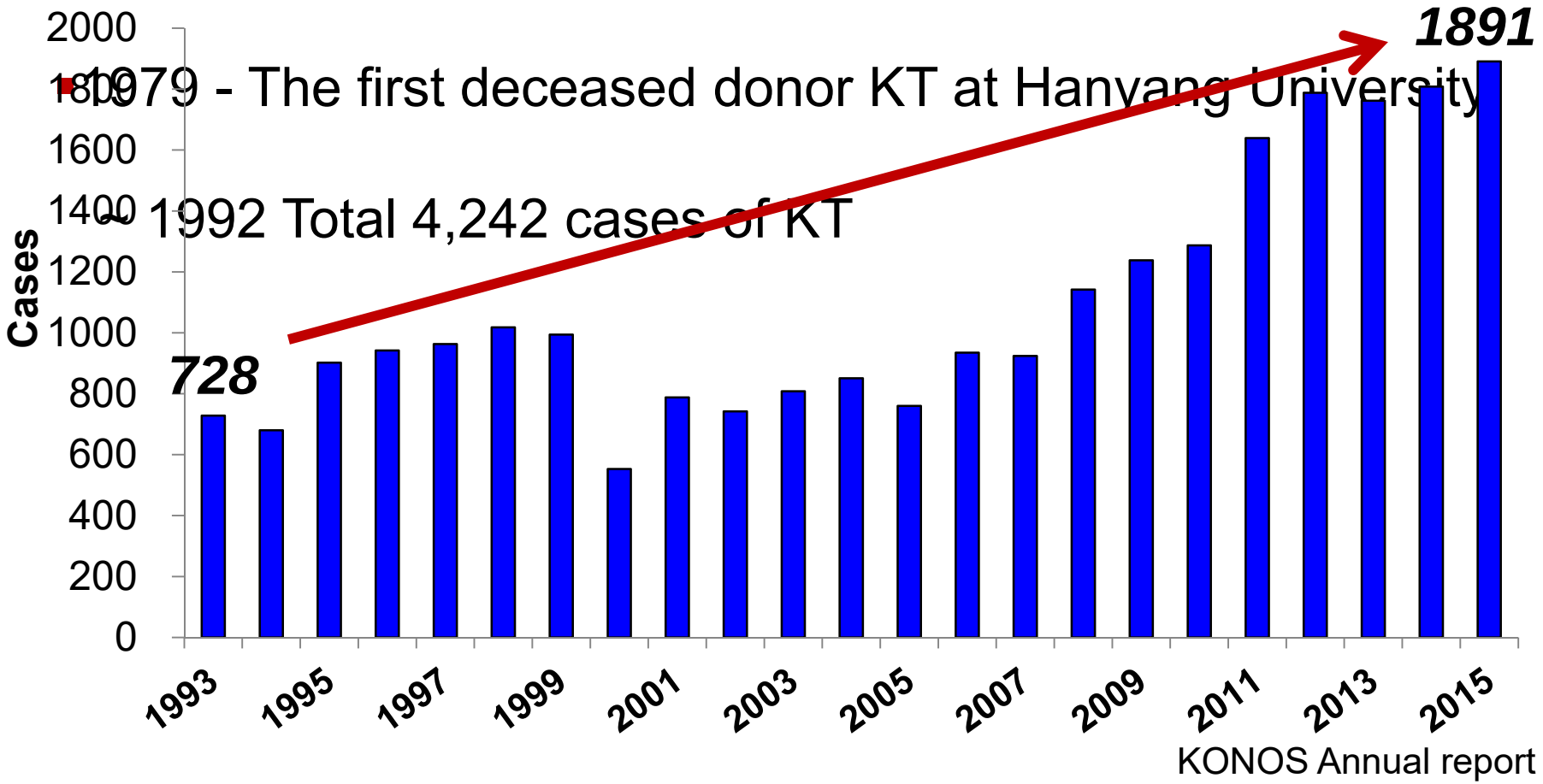
Yoo KD et al, Medicine 2016; 95: 33

The first successful kidney transplantation in Korea, 1969. 3.25

Increase of Kidney transplantation in Korea

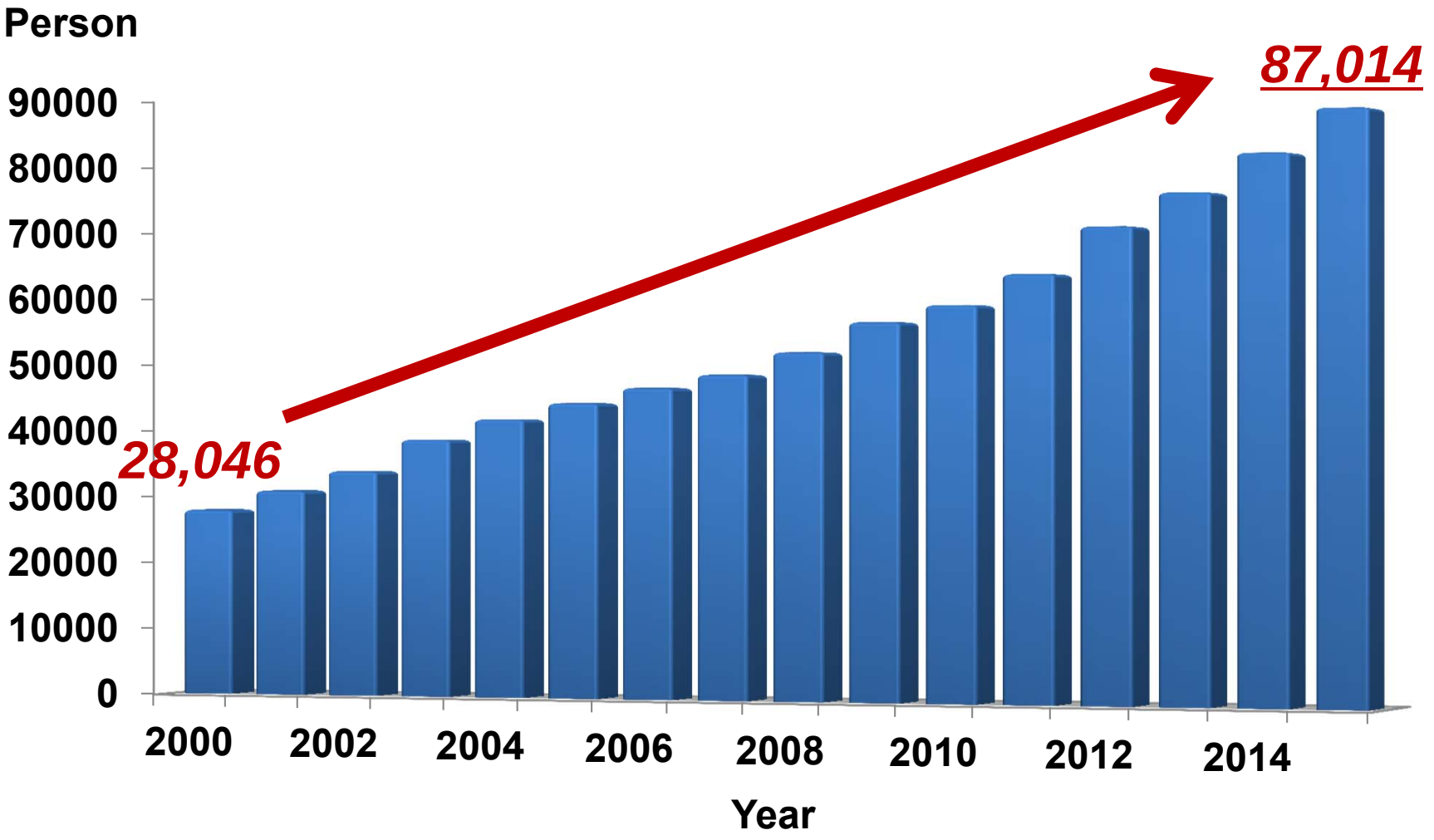
1969 ~2015 - 29,385 cases of KT

- 1969 - The first living donor KT, 6 cases in this year
- 1979 - The first deceased donor KT at Hanyang University
- 1992 Total 4,242 cases of KT



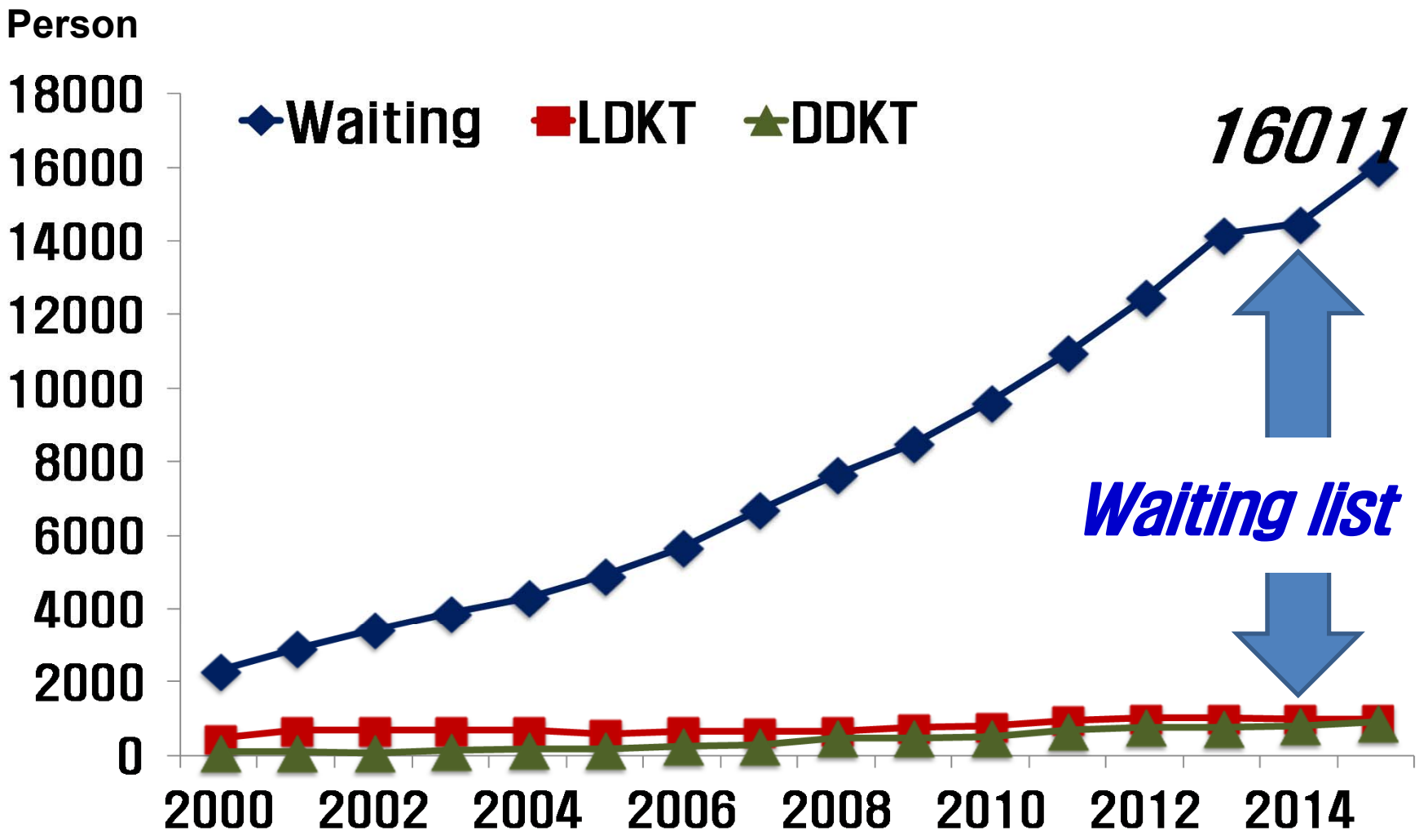
KONOS Annual report

Increase of ESRD Patients in Korea

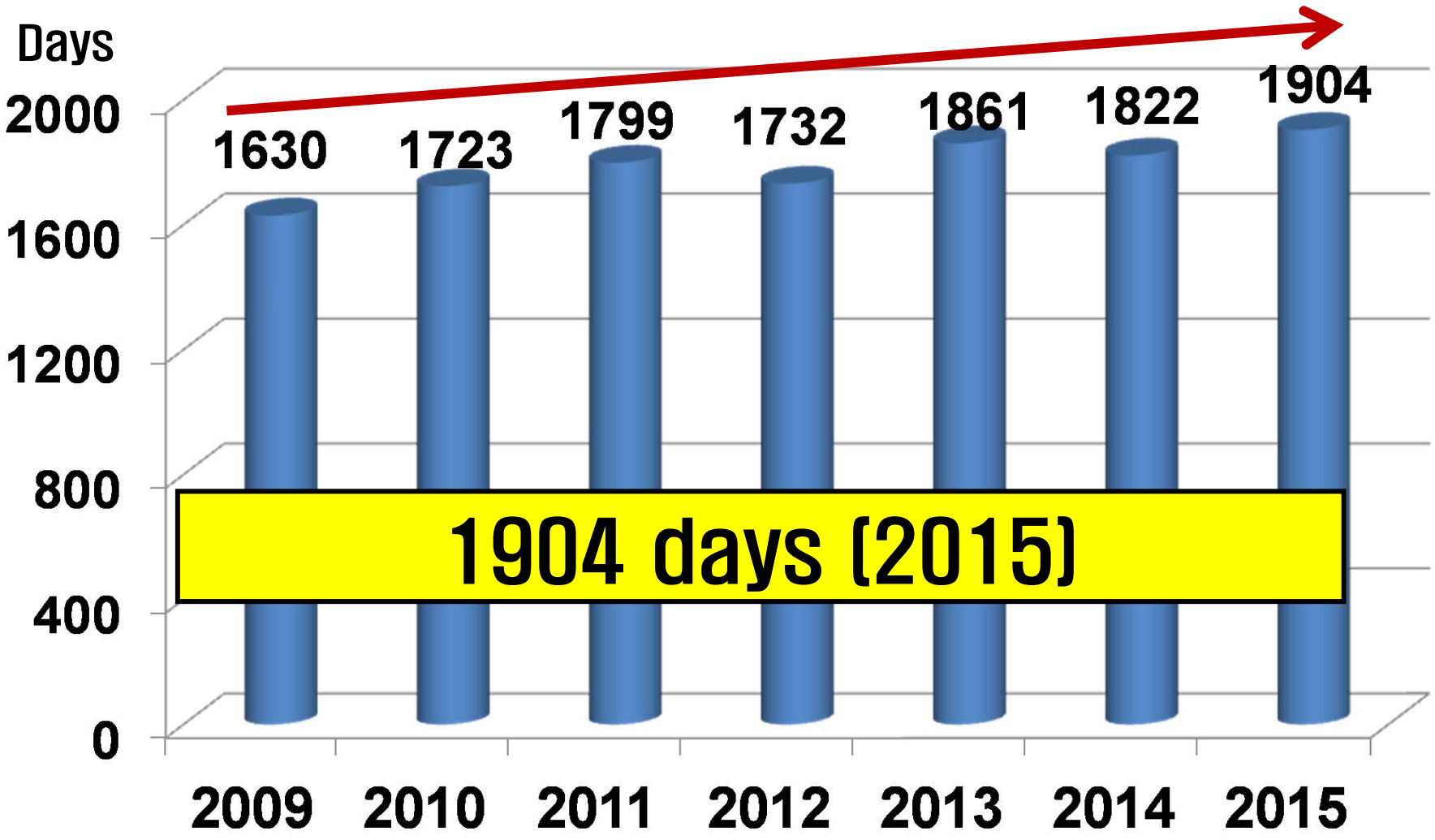


Current Renal Replacement Therapy in Korea

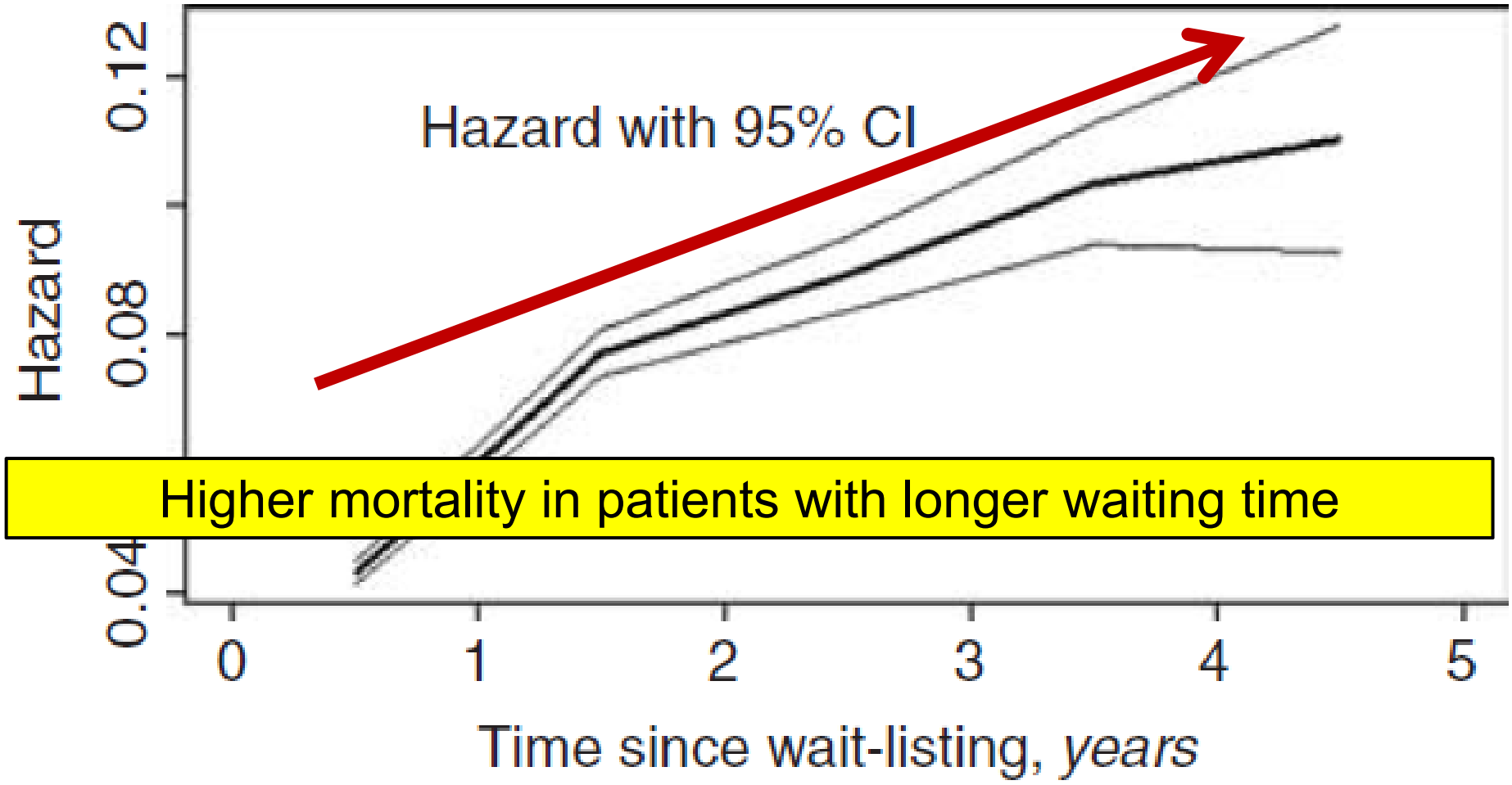
Increase of patient number on waiting list



Waiting time of DDKT



The impact of waiting time and comorbid conditions on the survival benefit of kidney transplantation

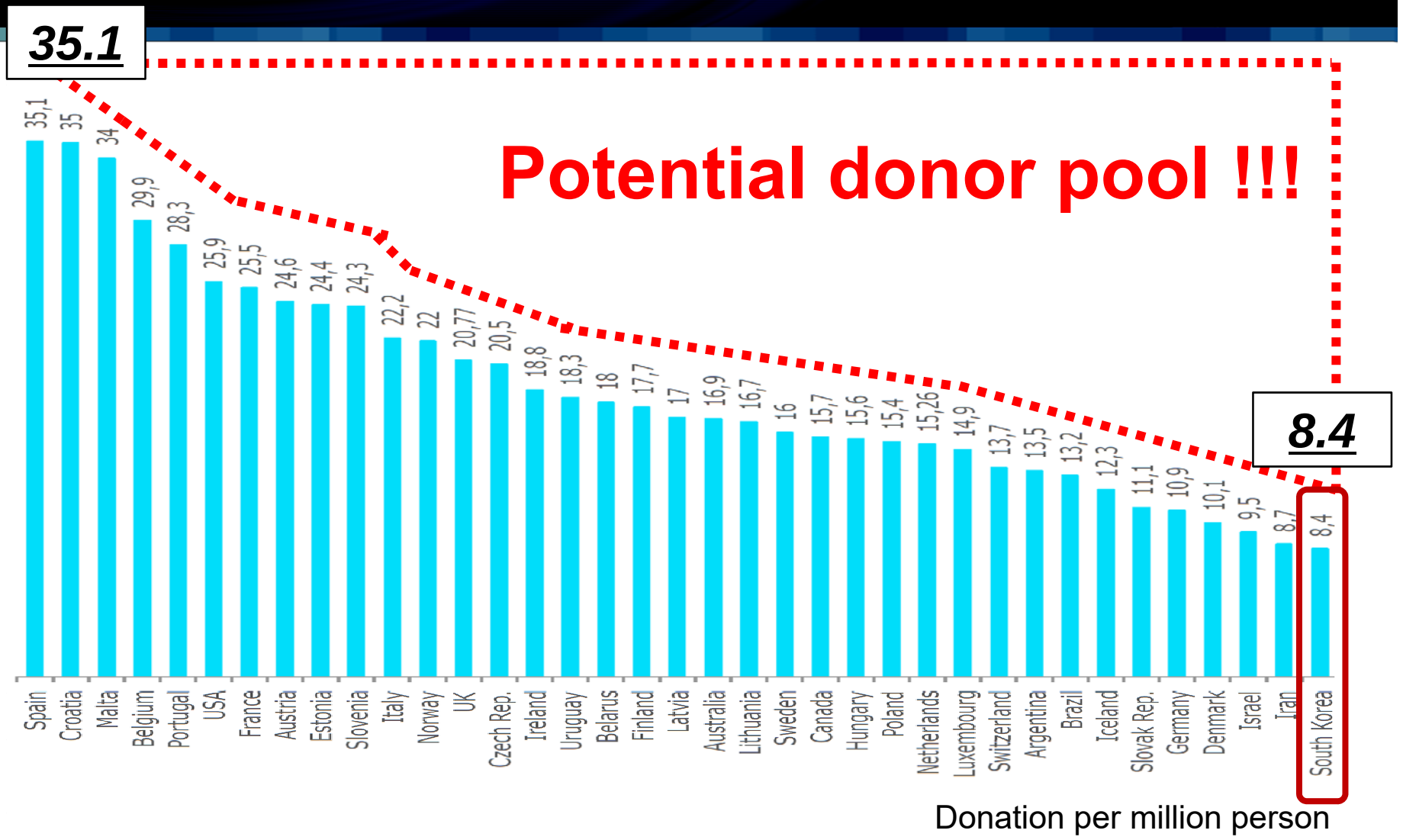


Grill L et al, Kidney Int 2005; 68: 2345

Two strategy to increase DDKT

- Increase of potential donor pool
- Use of expanded criteria donor

Worldwide deceased organ donors



Int Registry in Organ Donation and Transplantation, Dec 2014

Importance of Social Consensus

chosun.com 사회

검색

뉴스 오피니언 경제 스포츠 연예 라이프

사회 종합

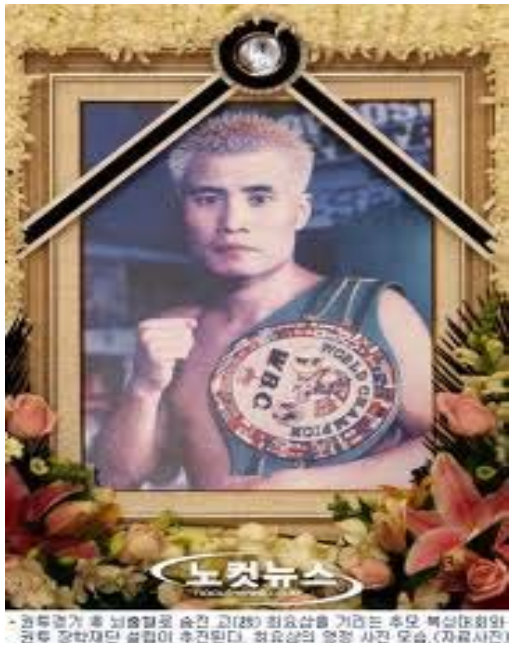
고(故) 김수환 추기경 각막 기증 참뜻 기리려… 범국민 장기 기증 운동 펼친다

정지섭 기자

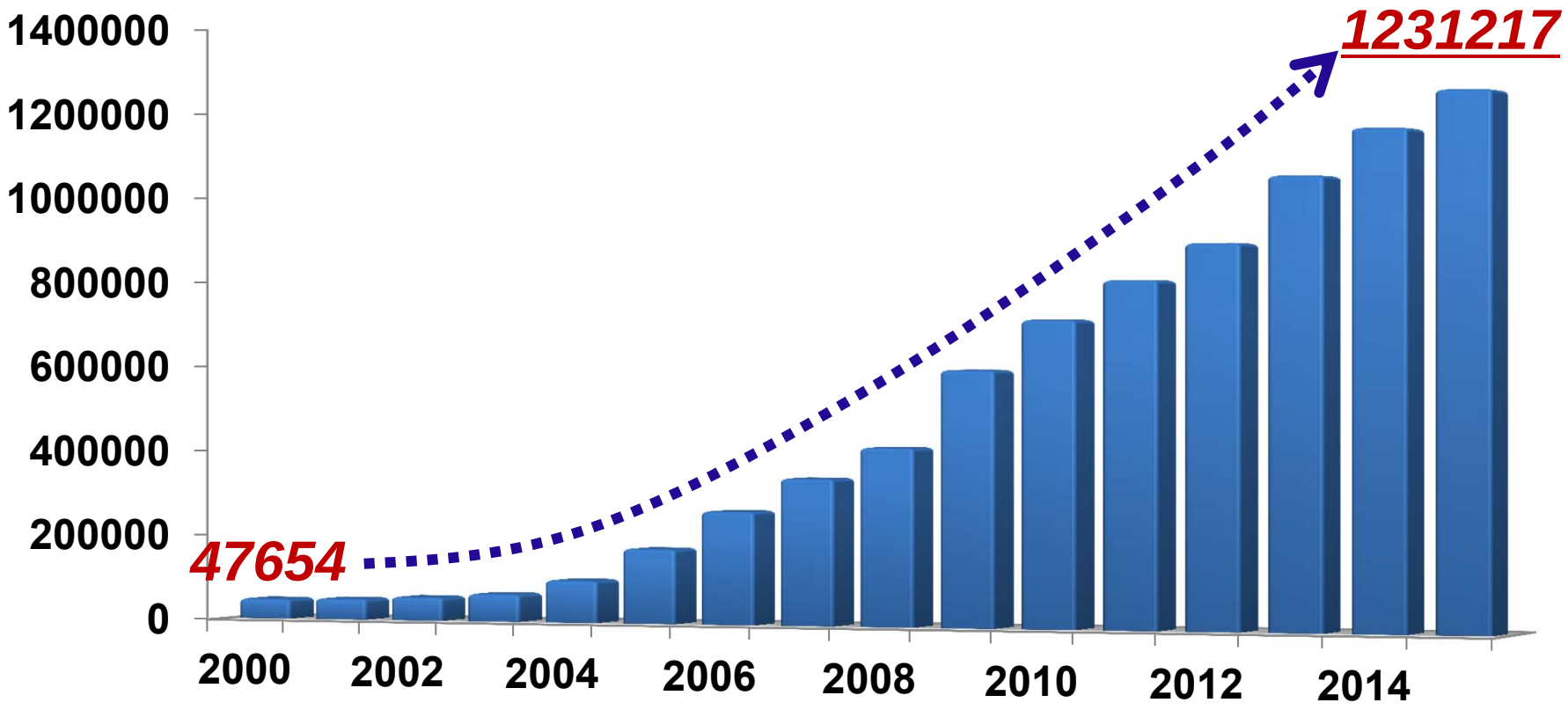
hankooki.com 한국일보

[한국일보 2008.1.3 기사]

최요삼, 6명에게 장기 기증



Cumulative numbers of organ donation volunteer



Increasing number of deceased donor pool may give a more chance to ESRD patients on the wait list in Korea.

Expanded criteria donor

UNOS criteria

Donor condition	Age (years)	
	50-59	≥60
CVA + HTN + Creatinine > 1.5mg/dL	X	X
CVA + HTN	X	X
CVA + Creatinine > 1.5mg/dL	X	X
HTN + Creatinine > 1.5mg/dL	X	X
CVA		X
HTN		X
Creatinine > 1.5mg/dL		X

KONOS criteria

Variables
Age ≥ 60
GFR ≤ 60 mL/min
or serum creatinine ≥ 3.0 mg/dL
Hypotensive episode ≥ 3
Proteinuria (++) ≥ 2
Non-heart beating donor

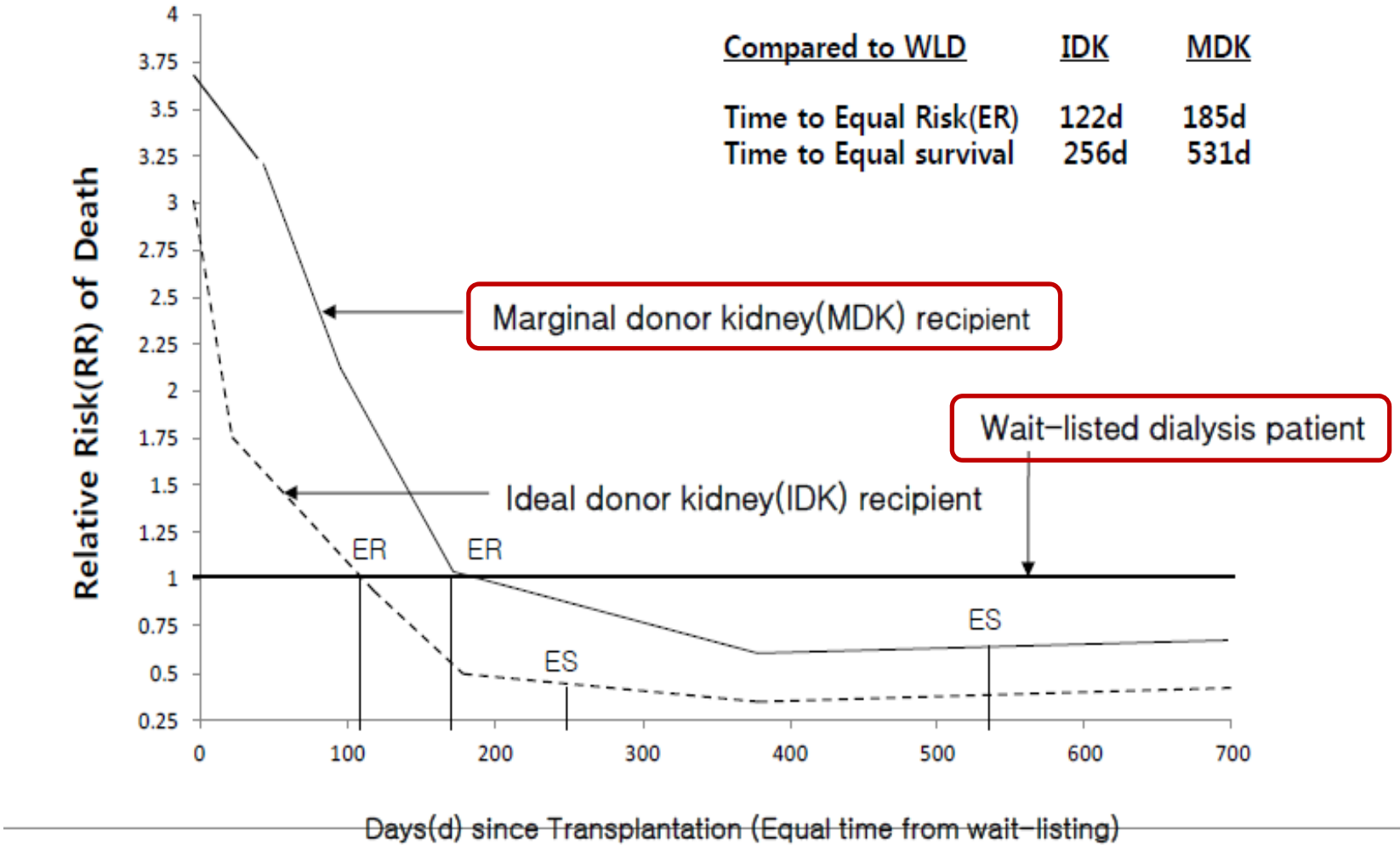
More than one of above

Suspicious of pre-existing chronic kidney disease

Metzger et al. Am J Transplant2003; 3 (Suppl. 4): 114–125

plant2003; 3 (Suppl. 4): 114–125

Survival benefits of ECD KT over Dialysis

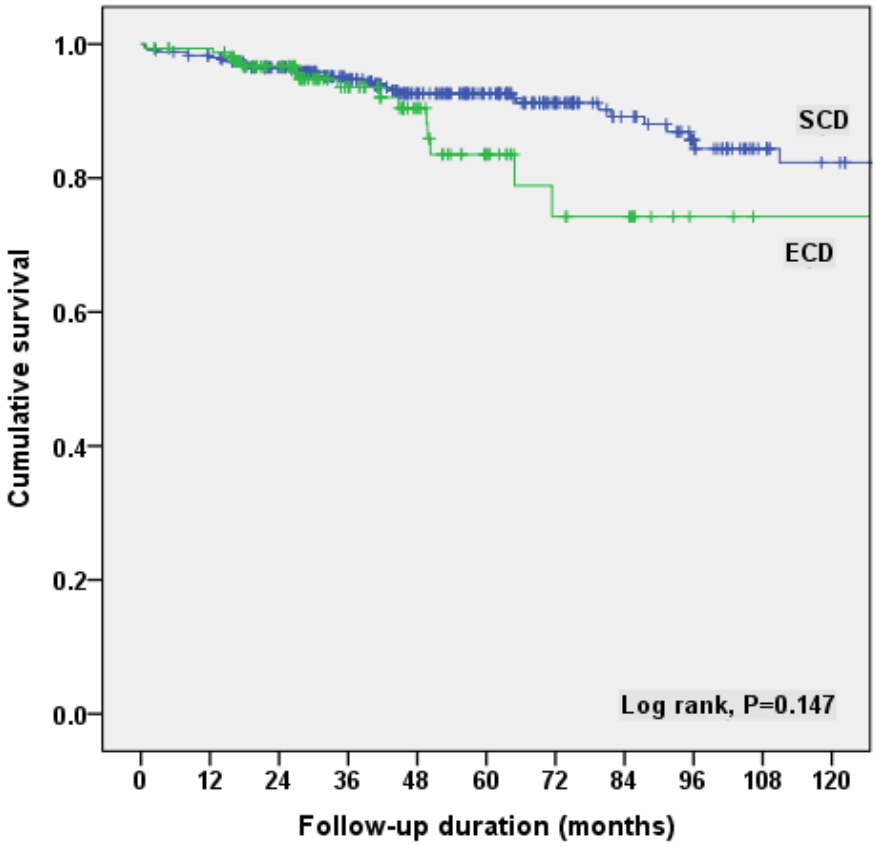


Ojo AO et al. J Am Soc Nephrol 2001;12:589

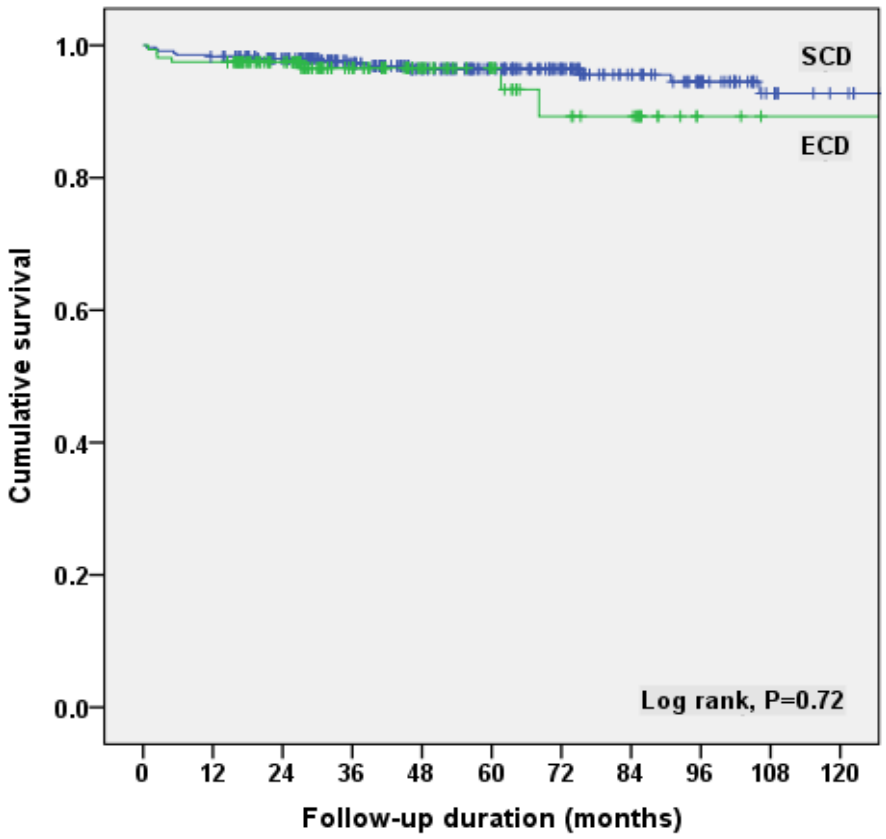
Comparison of allograft and patient survival between SCD and ECD group

509 cases of DDKT from 3 transplant centers

Allograft survival

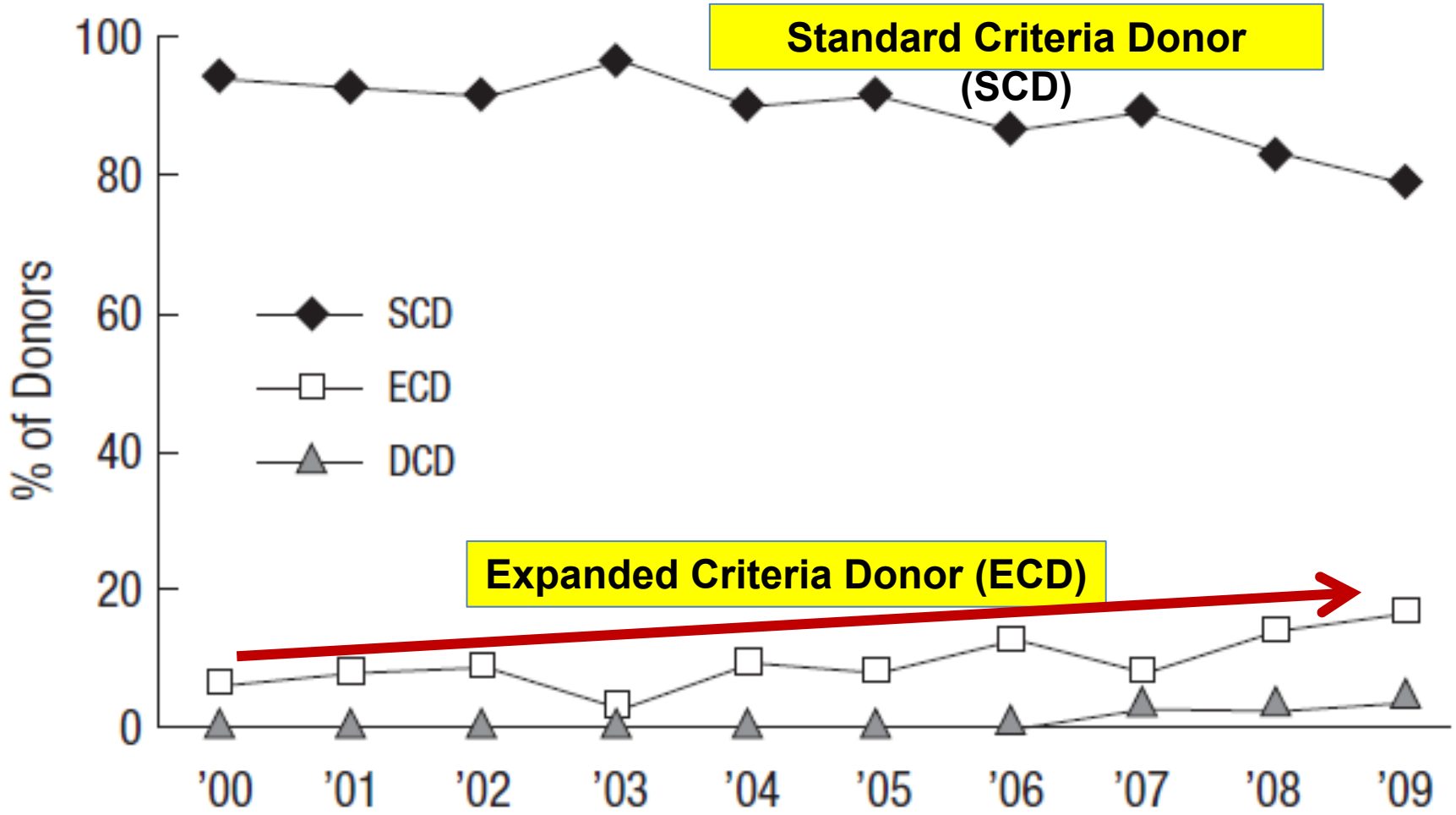


Patient survival



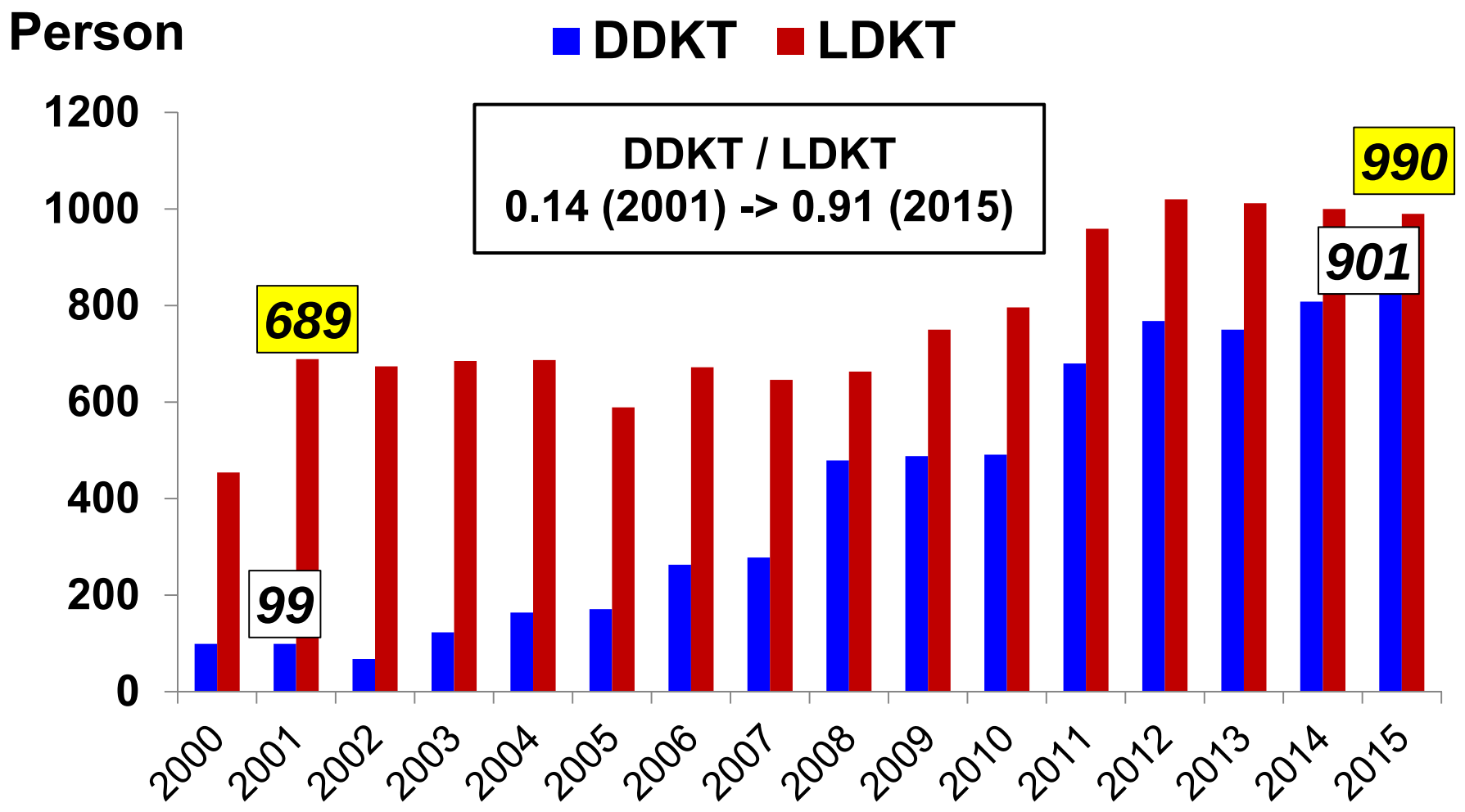
Park WY et al, Abstract number KSN-17-C005

Increase of DDKT from ECD in Korea



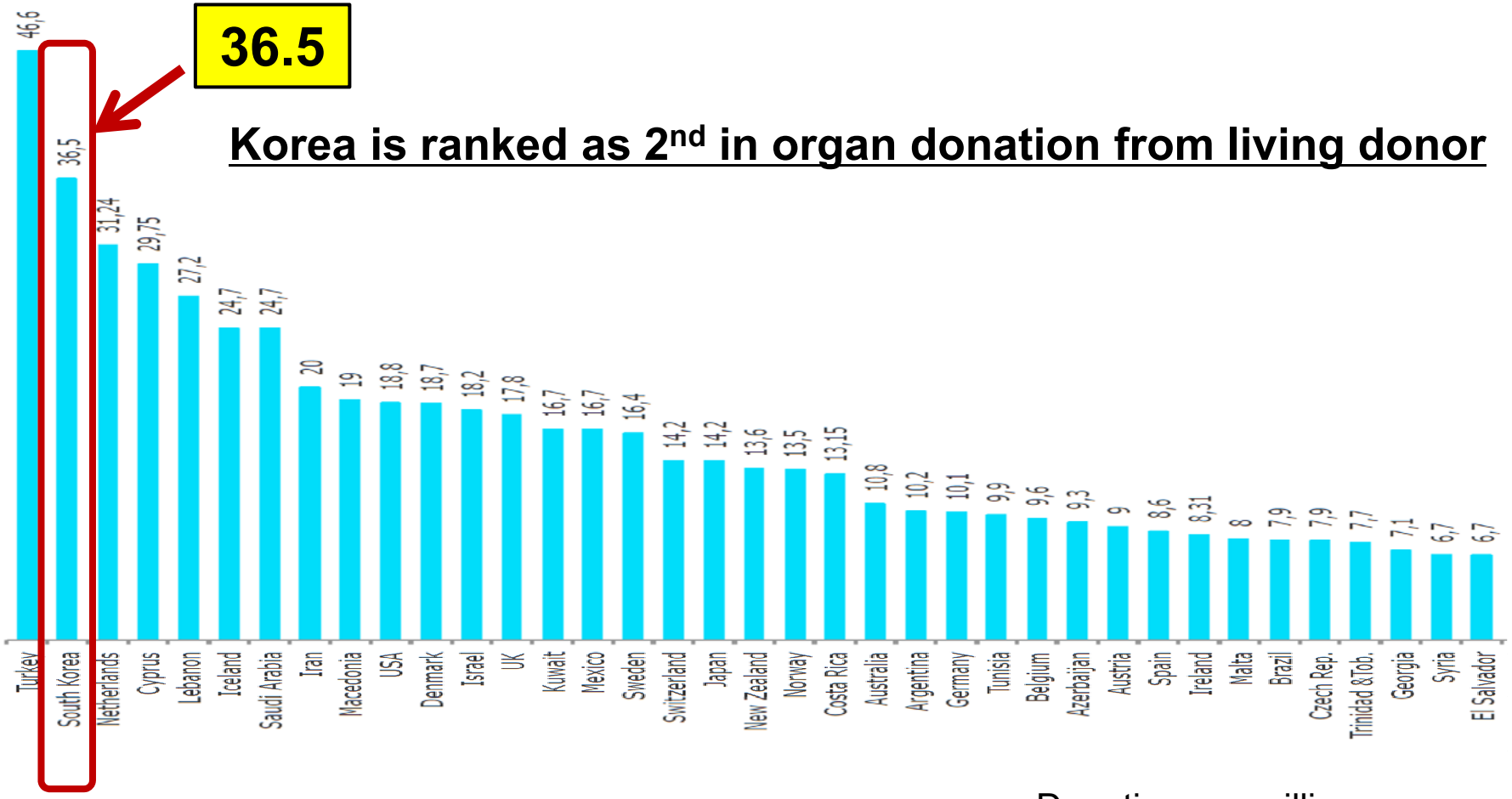
Min SI et al. *J Korean Med Sci* 25:1122-7, 2010

Increase of deceased donor KT



KONOS Annual report

Worldwide living organ donors



Korea is ranked as 2nd in organ donation from living donor

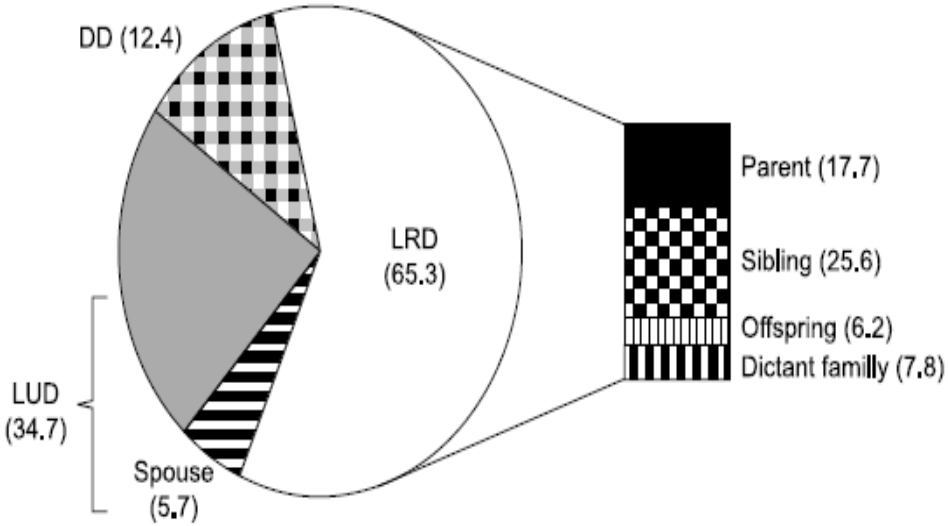
Donation per million person

Int Registry in Organ Donation and Transplantation, Dec 2014

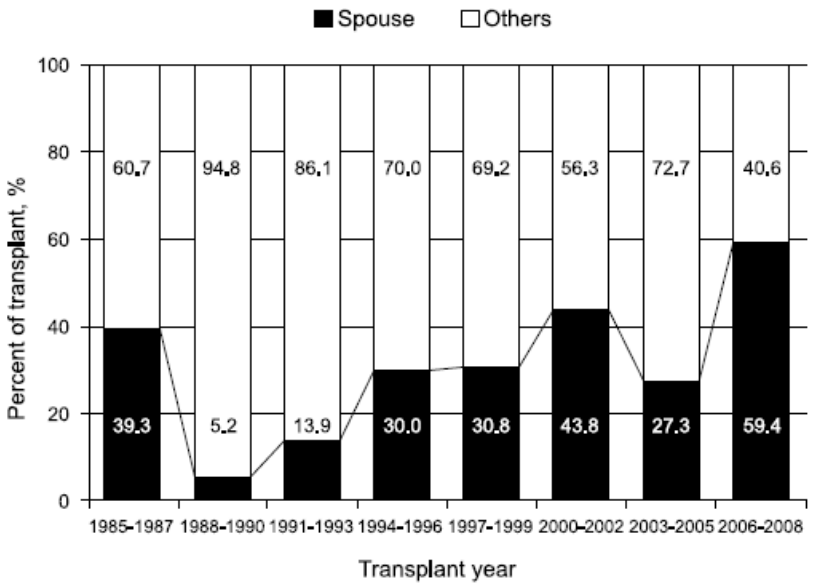
Changing pattern of donor source

- Seoul St. Mary's Hospital
- 1969 – 2008 ; 1969 cases

Living donor subtype



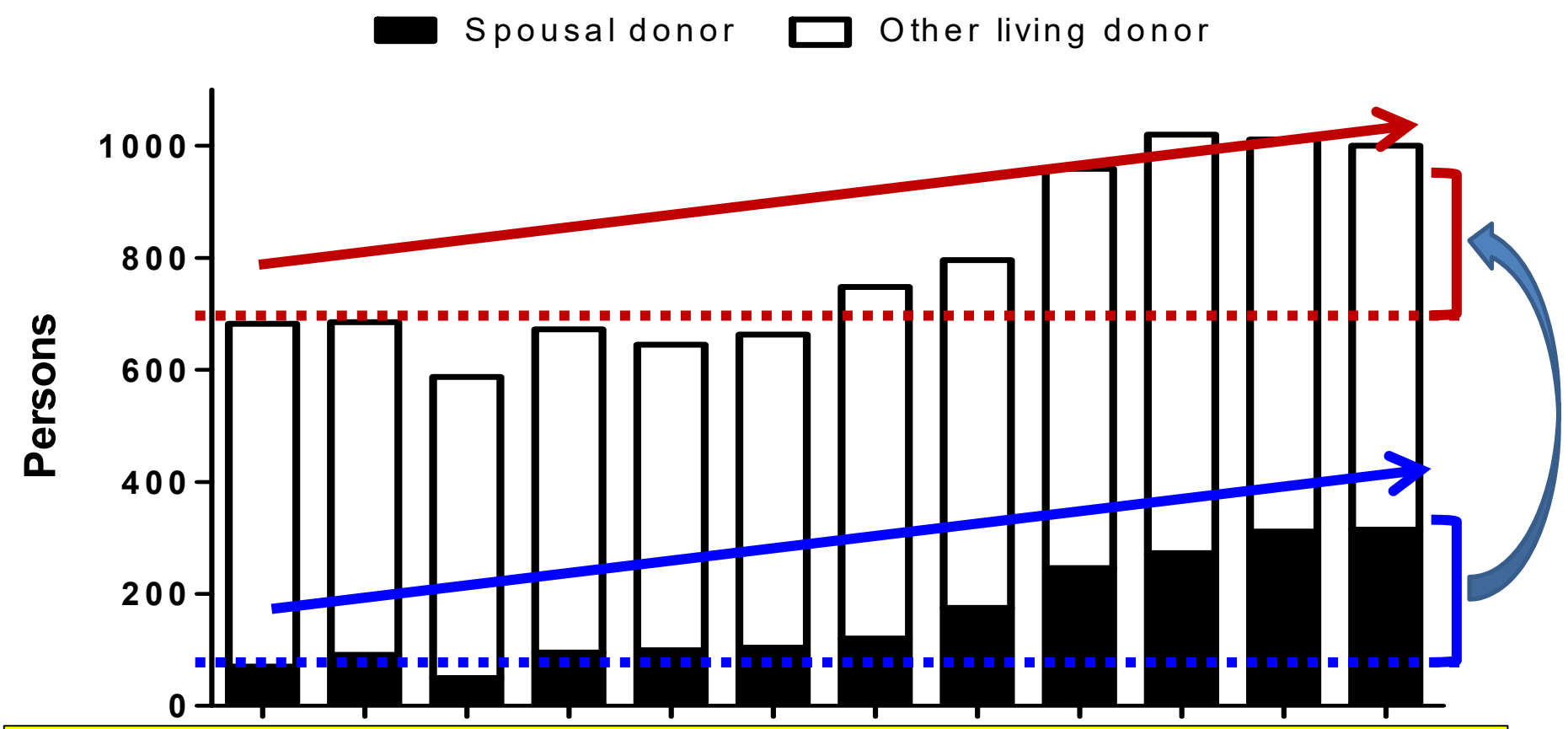
Within Living unrelated donor



Increasing pattern of spousal donor kidney transplantation

Chung BH et al KJIM 2010;:670

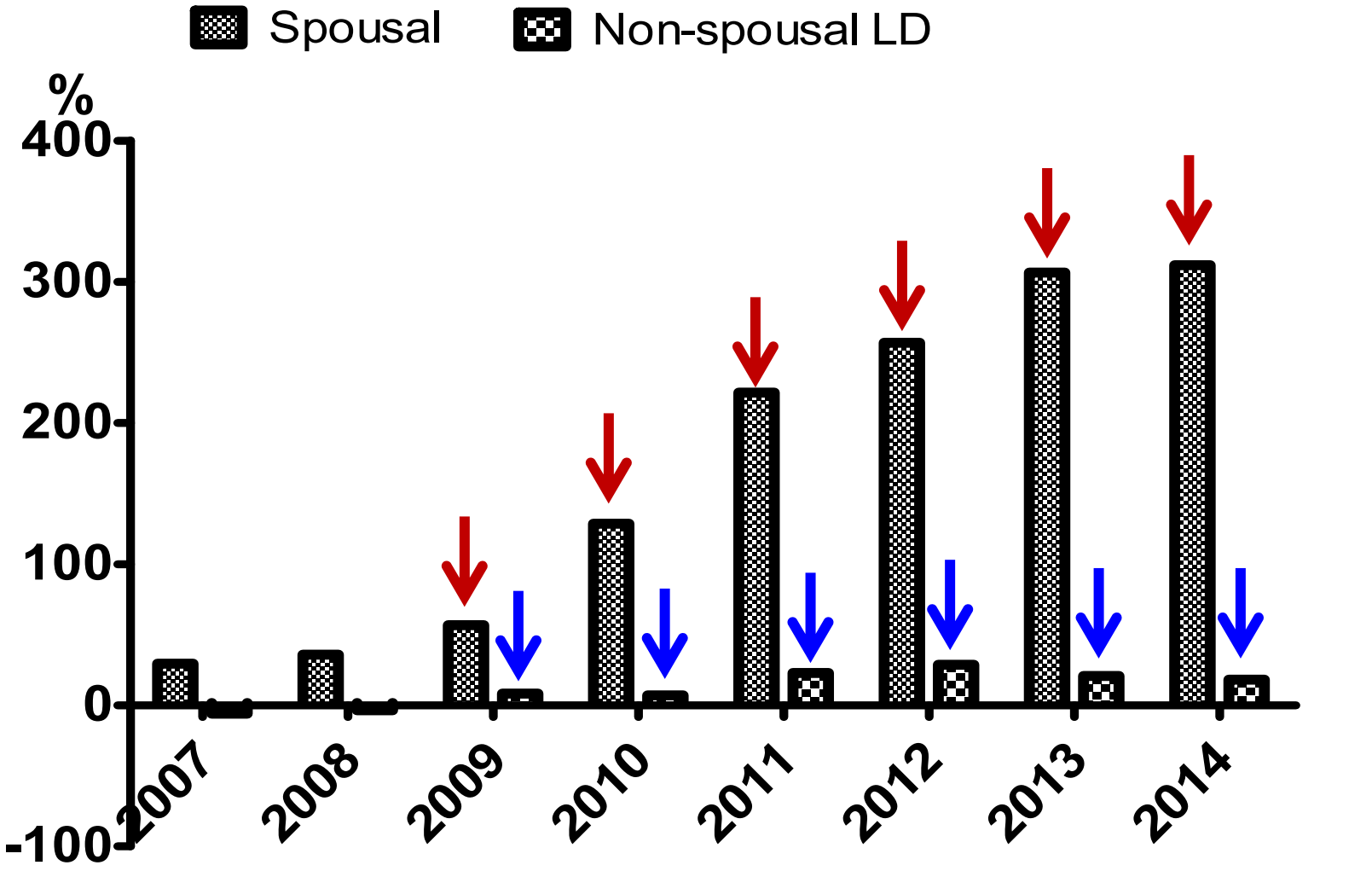
Increase of spousal donor KT



Increase of Spousal donor accounts for nearly 90 % of the increase of total living donor during the past 10 years

Annual report of KONOS

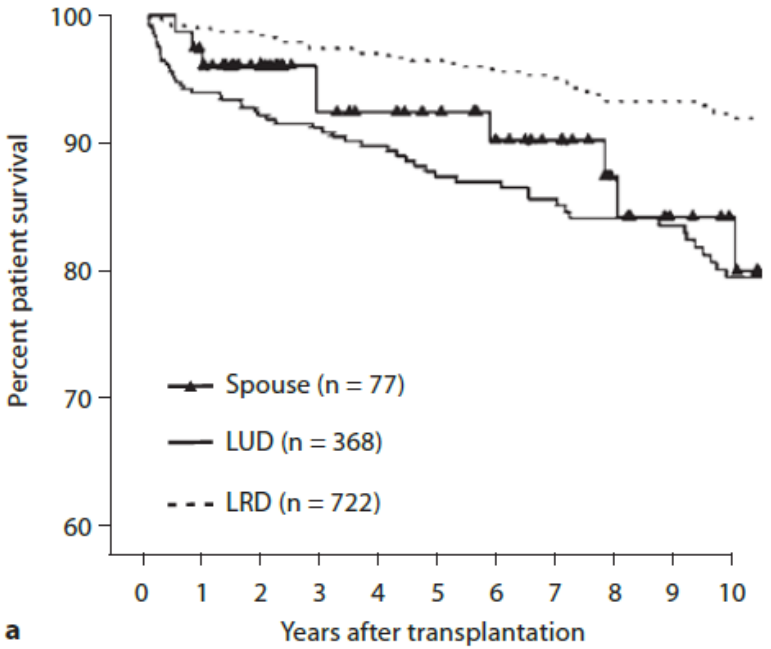
Comparison of the increased portion of SDKT and non-spousal LDKT



Annual report of KONOS

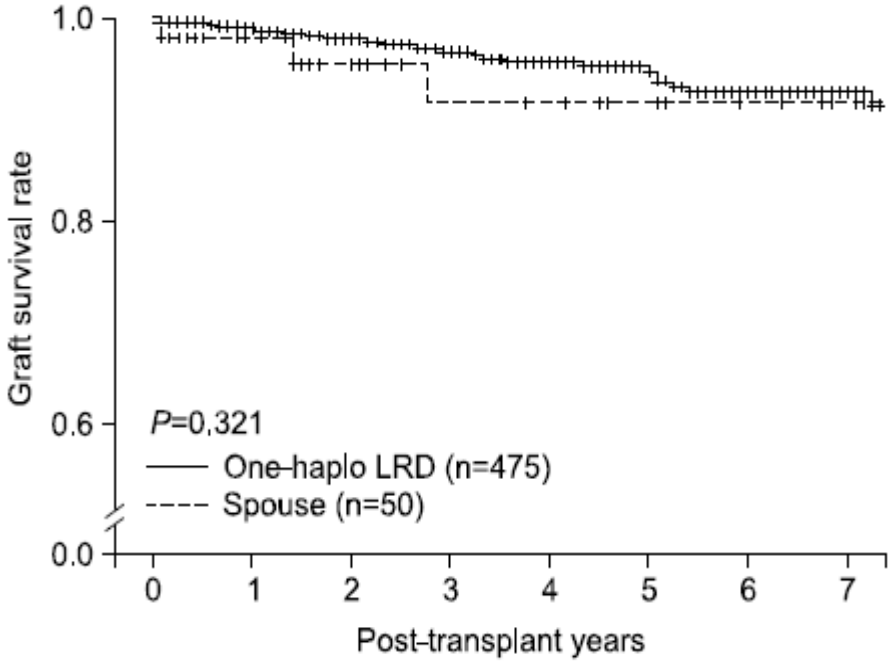
Allograft outcome of Spousal donor KT

Seoul St. Mary's Hospital



Yoon et al. Nephron Clin Pract 2009; 113: c241

Severance Hospital



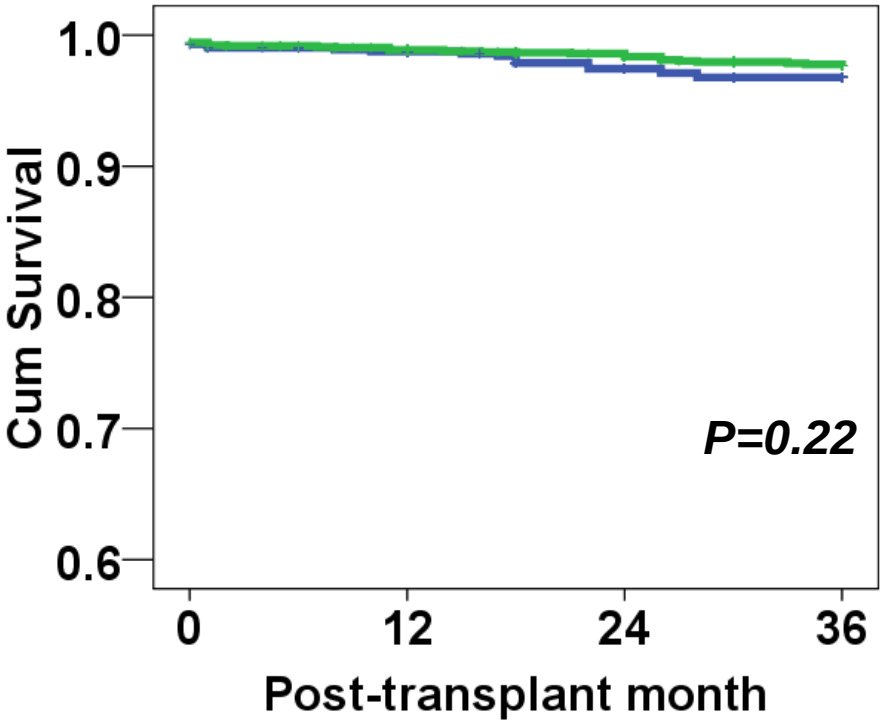
Lee et al. J Korean Soc Transplant 2008; 22: 232

Clinical outcome of Spousal donor KT

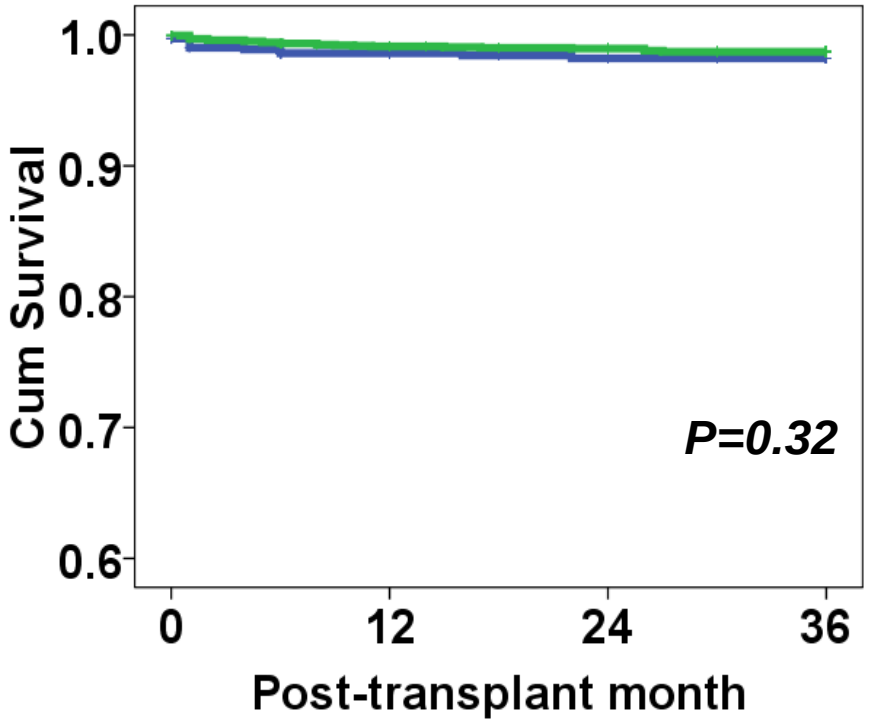
Korean **O**rgan **T**ransplantation **R**egistr**Y** (**KOTRY**) - 2009 ~ 2012

Spousal donor LDKT (n=724) vs. Living related donor (n=2112)

Allograft survival



Patient survival



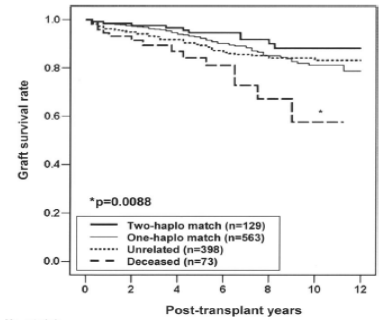
Donor exchange program

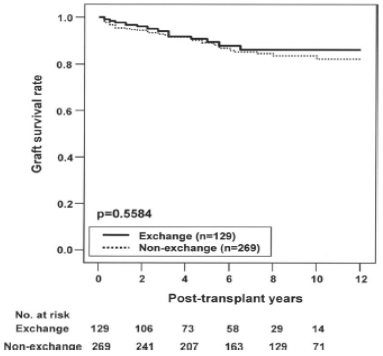
Patients who do not have ABO or HLA compatible donors

Exchange Living-Donor Kidney Transplantation: Merits and Limitations

TABLE 3. Transplantation outcomes by allocation methods for unrelated donors

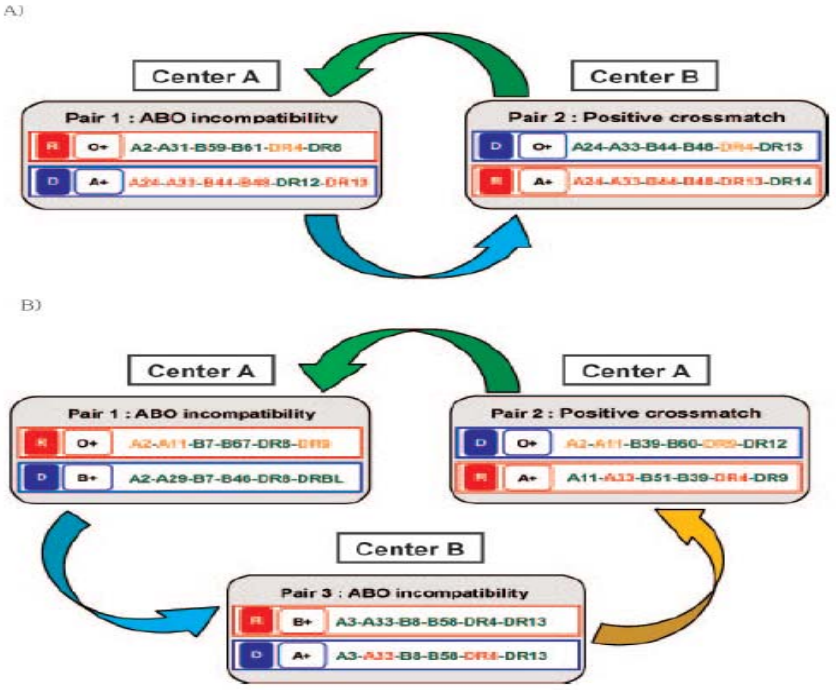
Transplant outcomes	Exchange donor	Nonexchange donor	*P*
N	129	269	
Mean follow-up duration (mo)	64.3±38.1	84.0±41.6	<0.001
Delayed graft function	0/129	2/269 (0.7%)	0.326
Acute rejection within 1 yr	40/129 (31.0%)	80/269 (29.7%)	0.796
Serum creatinine level at discharge (mg/dL)	1.62±1.34	1.46±1.09	0.196
Causes of graft failure	13 (10.1%)	39 (14.5%)	0.454
Patient death	8 (61.5%)	18 (46.2%)	
Acute rejection	3 (23.1%)	6 (15.4%)	
Chronic rejection	1 (7.7%)	5 (12.8%)	
Graft thrombosis	1 (7.7%)	0 (0.0%)	
Infection	0 (0.0%)	3 (7.7%)	
Recurrent disease	0 (0.0%)	3 (7.7%)	
Poor compliance	0 (0.0%)	3 (7.7%)	
Primary non-function	0 (0.0%)	1 (2.6%)	





Huh KH et al. Transplantation 2008; 86: 430

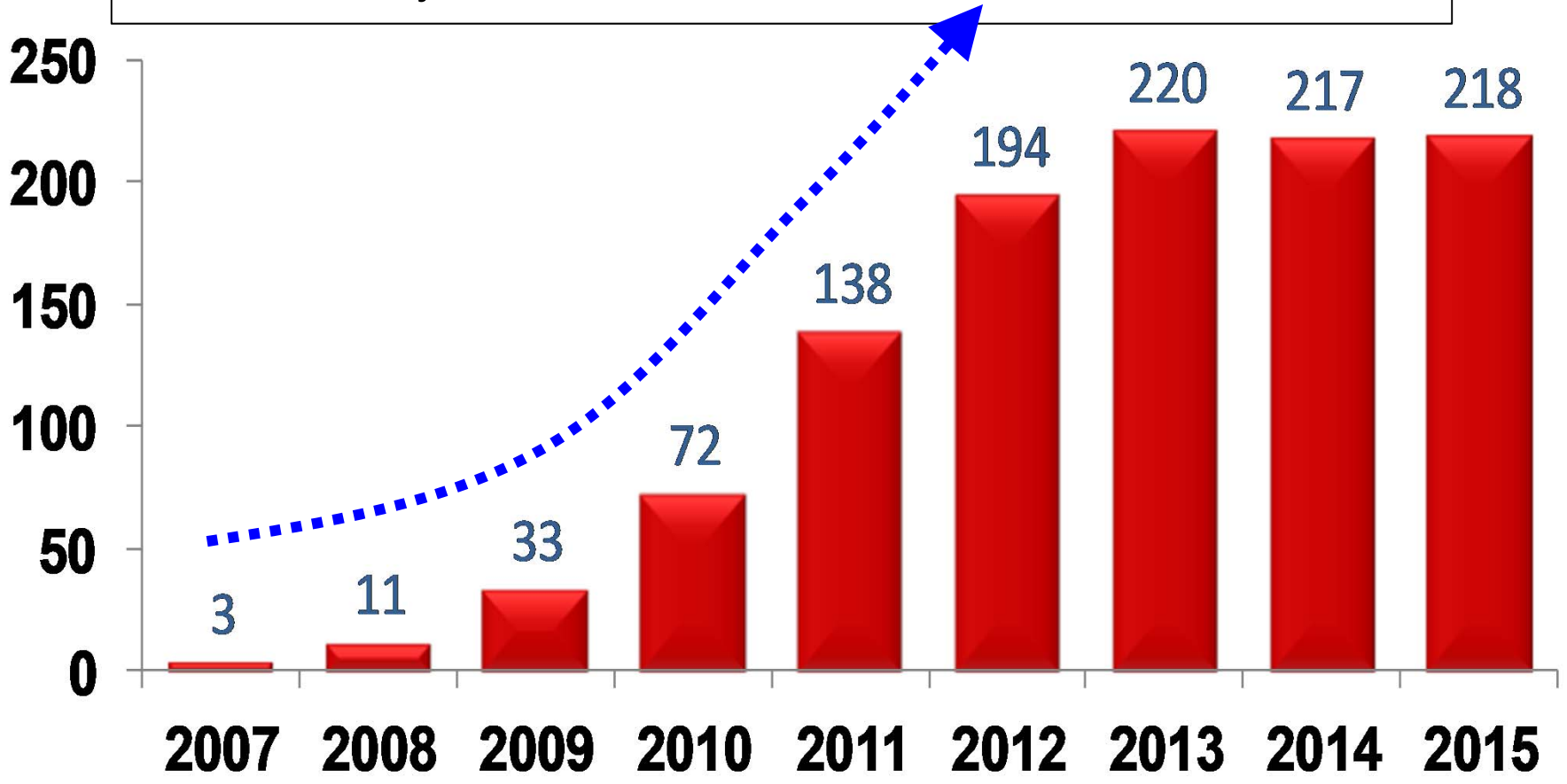
Outcome of Multipair Donor Kidney Exchange by a Web-Based Algorithm



Kim BS et al. J Am Soc Nephrol 2007; 18: 1000

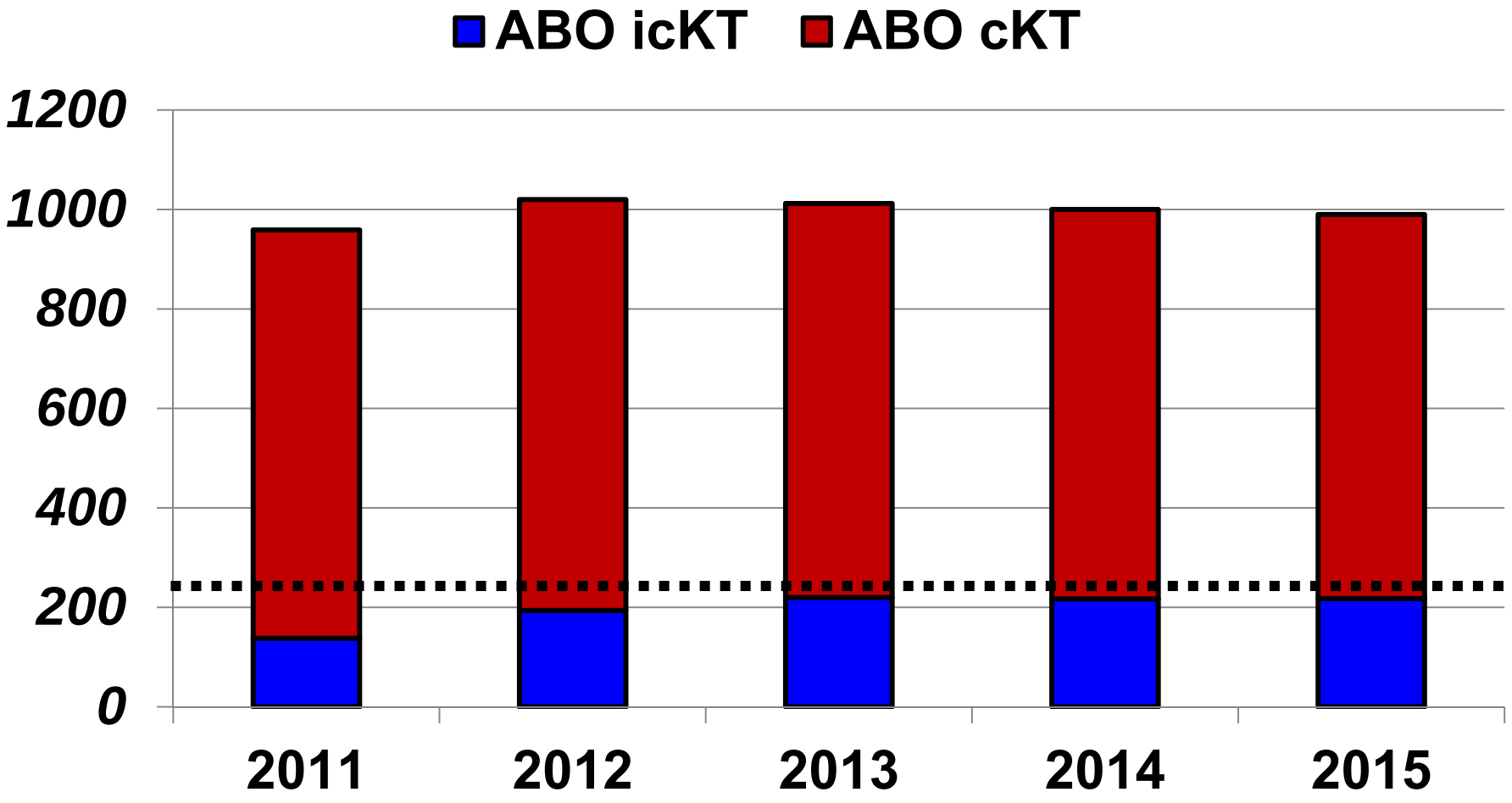
Increase of ABOic KT in Korea

- 1st ABO incompatible (ic) KT in Korea
- 2007. 2 Maryknoll Medical Center, Busan, Korea



KONOS Annual report

Proportion of ABO ickT



20 % of total living donor kidney transplantation

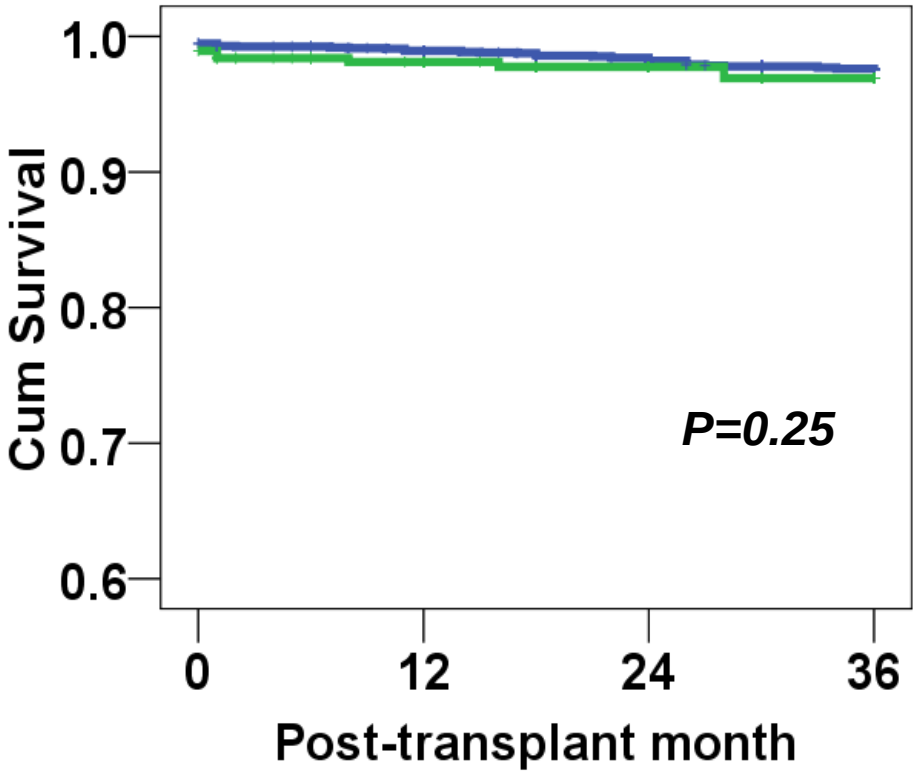
KONOS Annual report

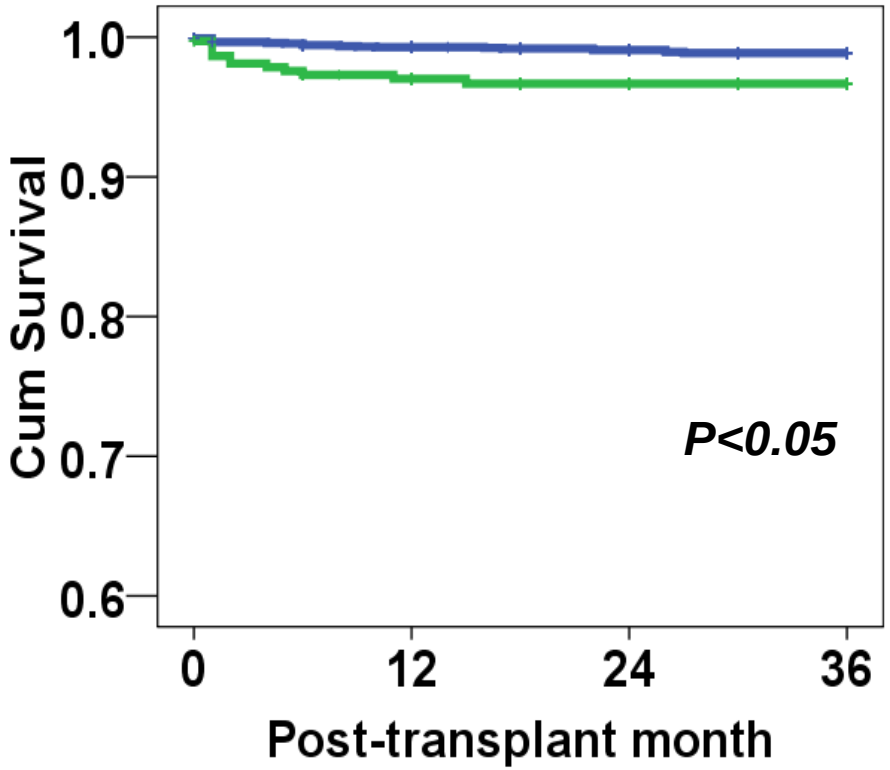
Clinical outcome of ABO icKT

Korean **O**rgan **T**ransplantation **R**egistr**Y** (**KOTRY**) - 2009 ~ 2012

3043 cases of Living donor kidney transplantation

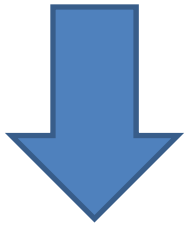
ABOic KT (n=375) vs. ABO cKT (n=2668)





KT in highly sensitized patients

- HLA antibody monitoring method
- Desensitization for HLA antibody



Successful kidney transplantation
in highly sensitized patients

Advance of anti-HLA Ab screening method

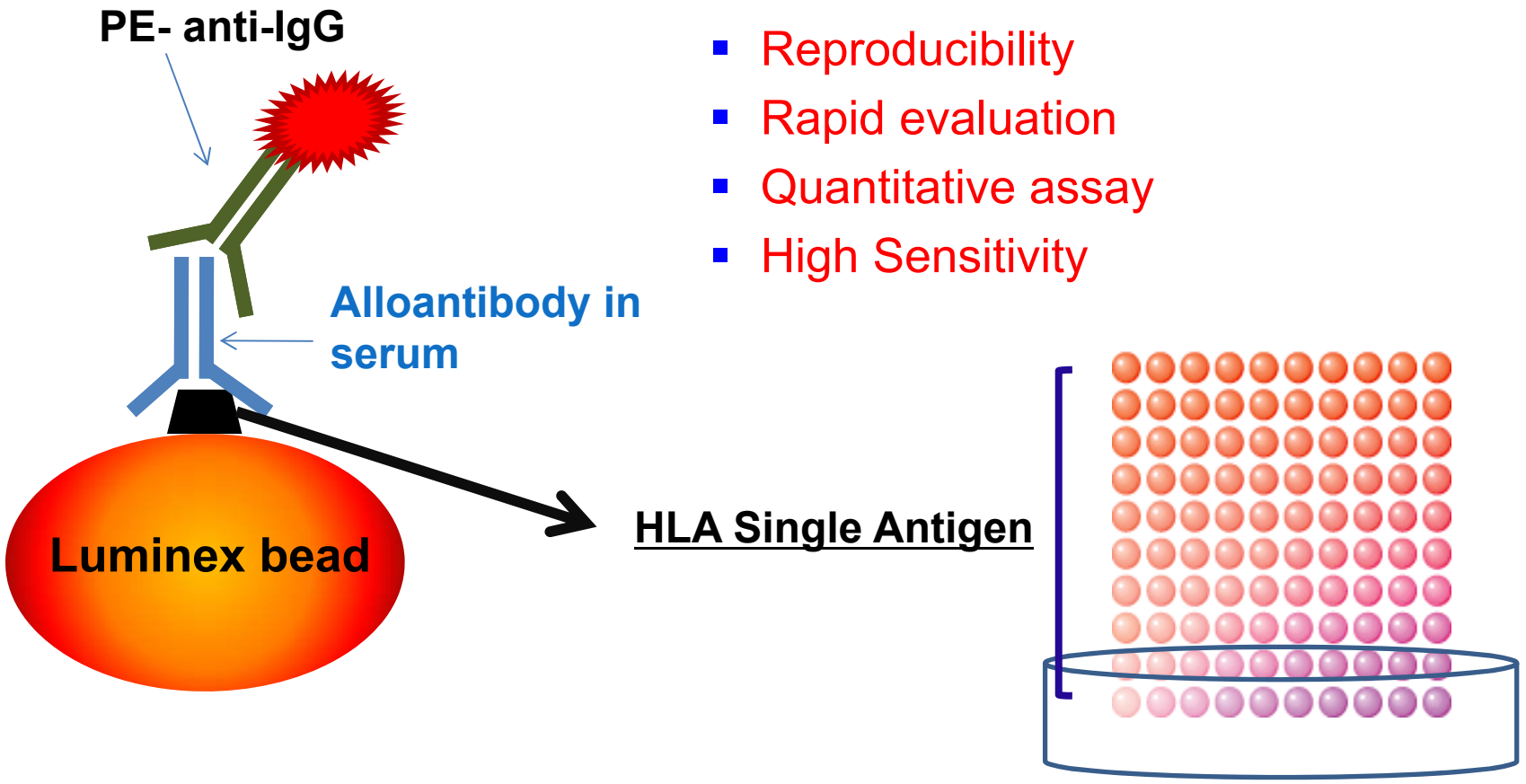
Cell-based assays		Solid-phase methods		
CDC (Complement-dependent)	Flow-cytometry (Complement-independent)	**ELISA**	**Flow-cytometry beads**	**Multiplex platform Luminex**

Better sensitivity and specificity for the prediction of ABMR !!

Girnita et al. Pediatr Transplantation 2006

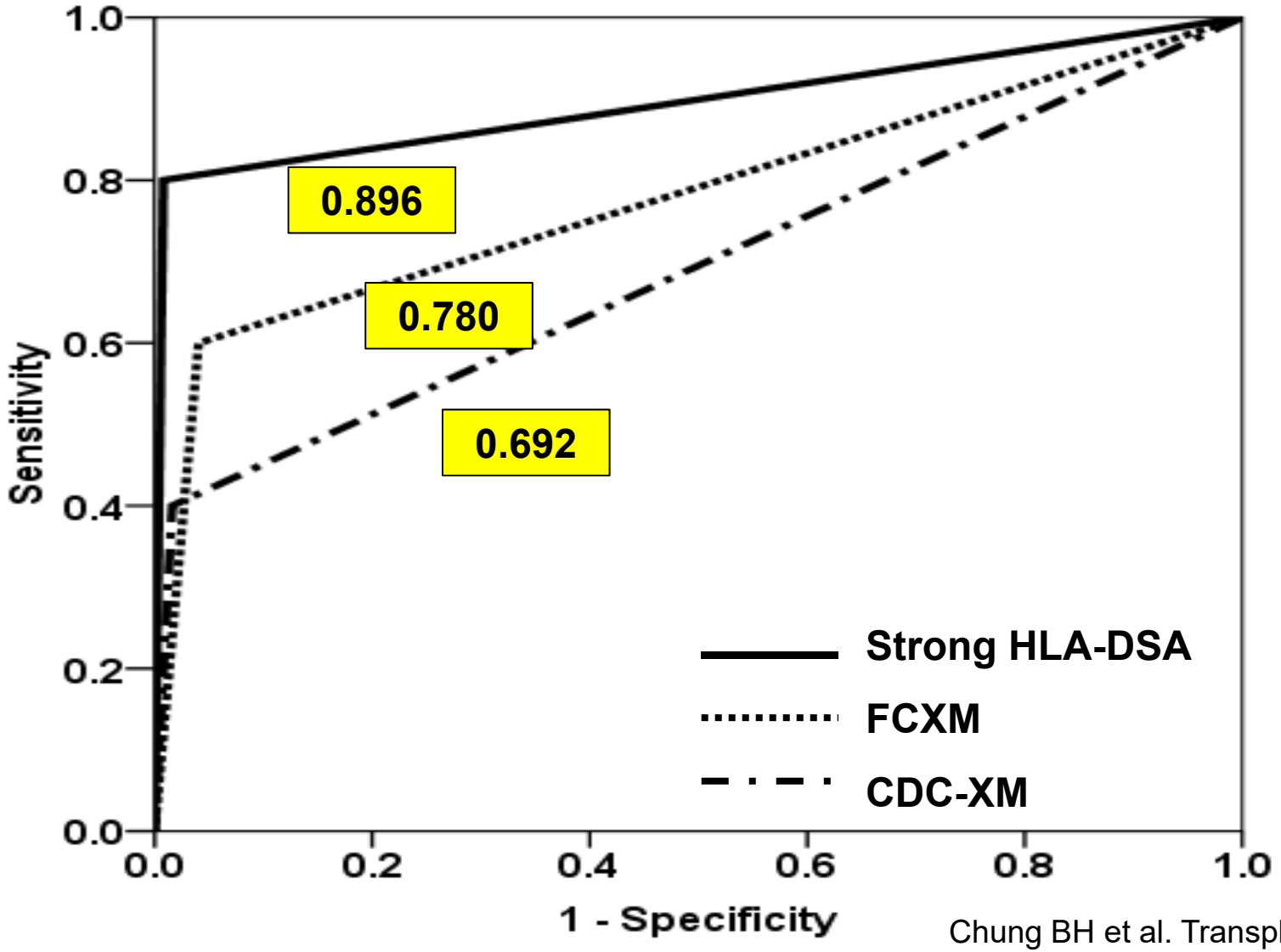
Luminex Single Antigen Bead

- Detection of anti-HLA antibody at Single Antigen level
- Match with Donor HLA typing → Determine Donor Specificity



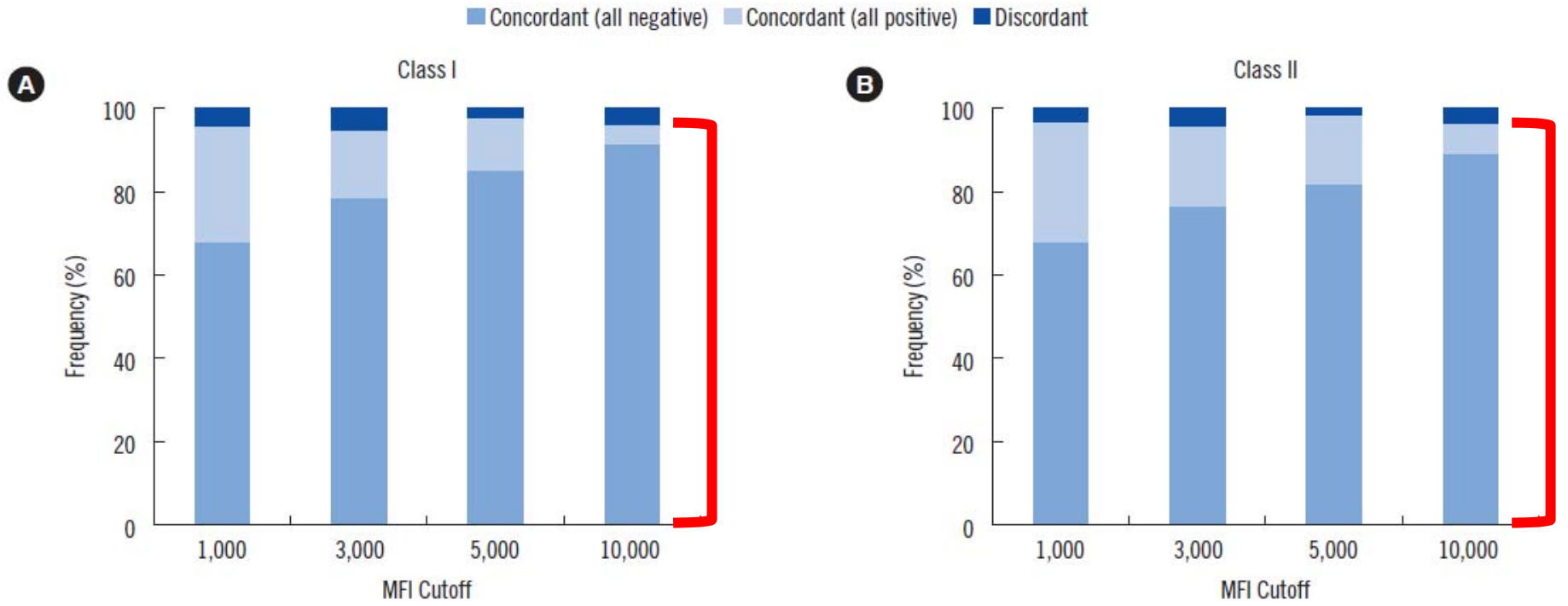
- Reproducibility
- Rapid evaluation
- Quantitative assay
- High Sensitivity

Prediction of ABMR



Chung BH et al. Transpl Int 2013

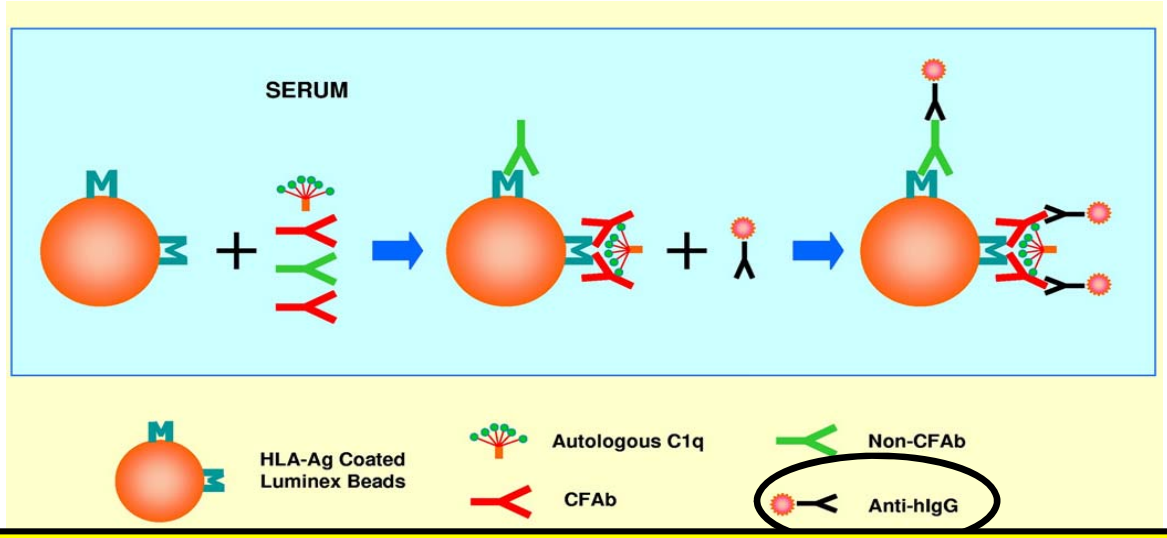
Interlaboratory Comparison of the Results of Lifecodes LSA Class I and Class II Single Antigen Kits for Human Leukocyte Antigen Antibody Detection



Analysis of SAB performed in five laboratories using identical protocol and reagents resulted in high levels of concordance and strong correlation

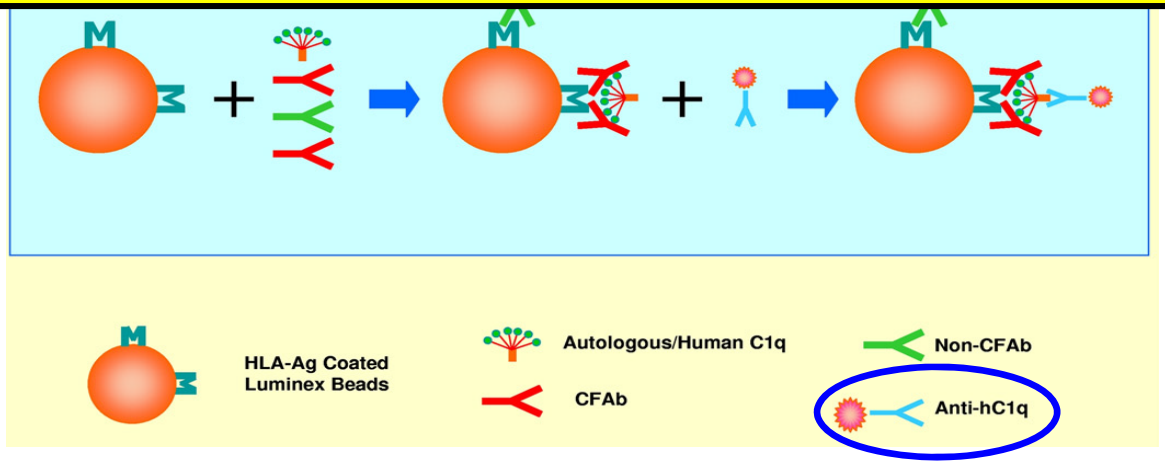
Oh EJ et al, Ann Lab Med 2015;35:321

Complement binding assay



IgG-SAB

Complement-fixing capability of HLA antibodies can be determined using **C1q or C3d solid phase assays**



C1q-SAB

Human Immunology 72 (2011) 849-858

Desensitization Strategy

B-cell targeting therapies

Plasma cells

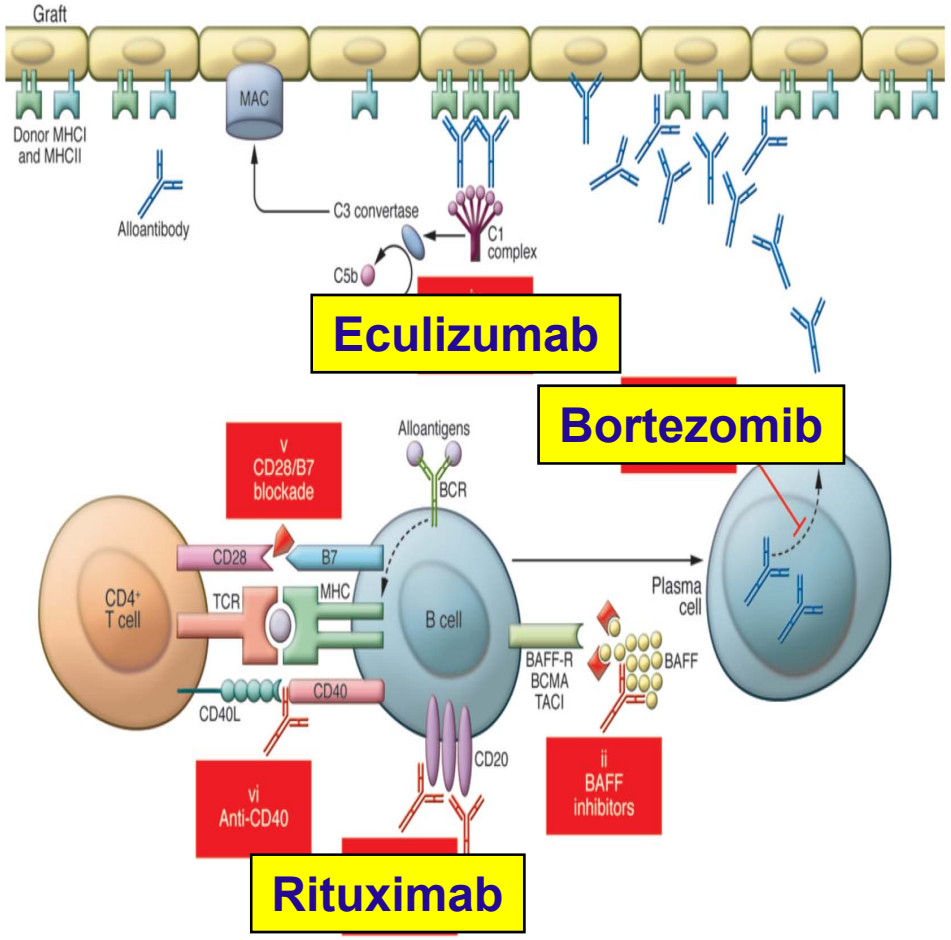
Clonal expansion

Pre B cells & B cells

PP/ IVIG

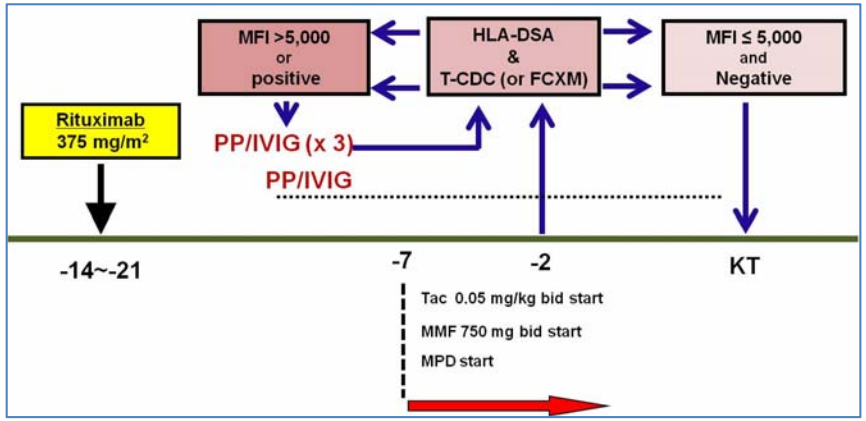
Splenectomy

Rituximab

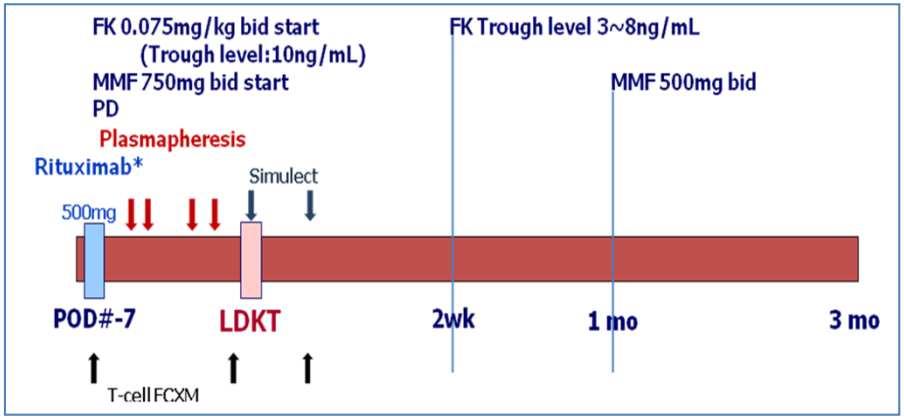


Desensitization for LDKT

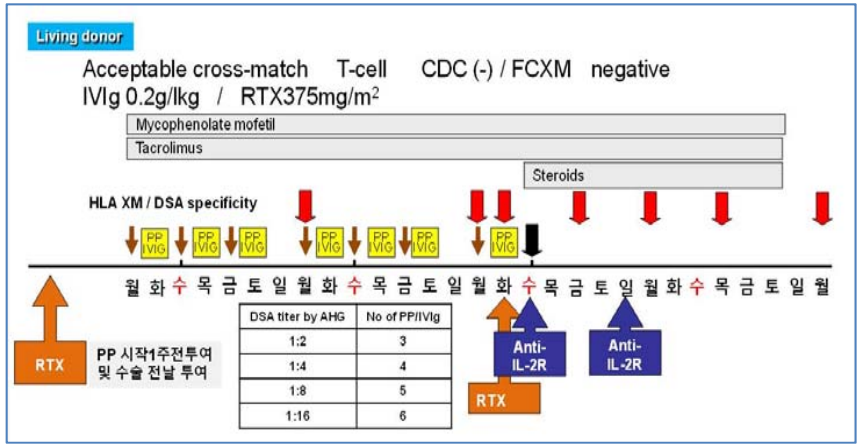
Protocols in most centers are based on RTX/PP/low dose IVIg in Korea



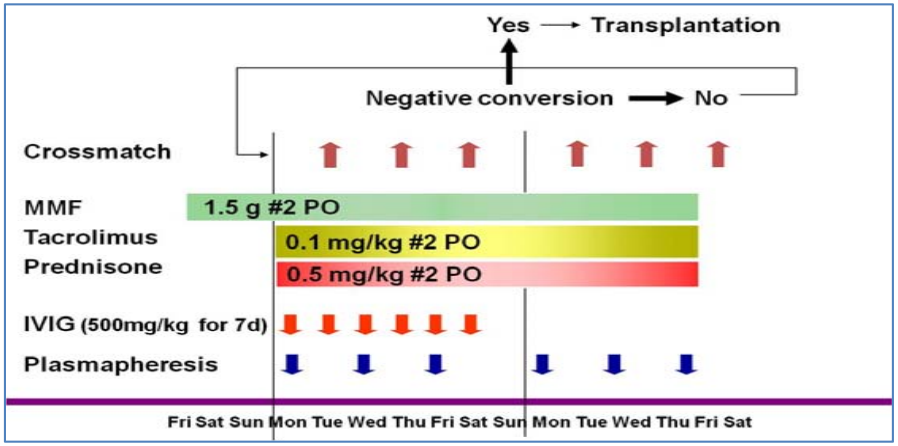
Seoul St. Mary's Hospital



Asan Medical Center



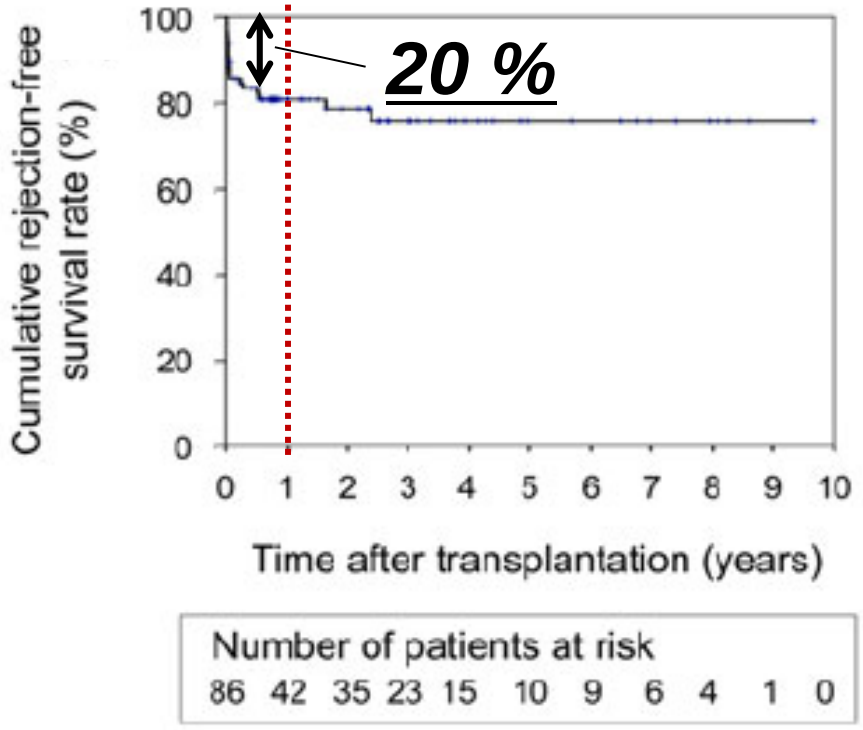
Seoul National University Hospital

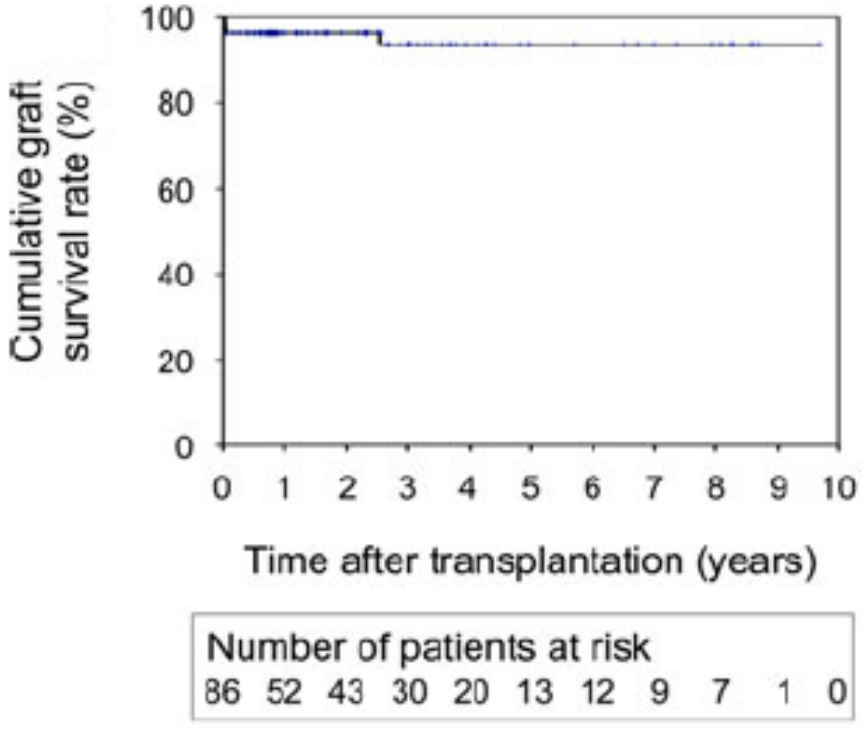


Severance Hospital

Clinical outcomes of Highly Sensitized Patients in Korea

- 86 highly sensitized patients from six transplant center in Korea
- Between 2002 and 2010



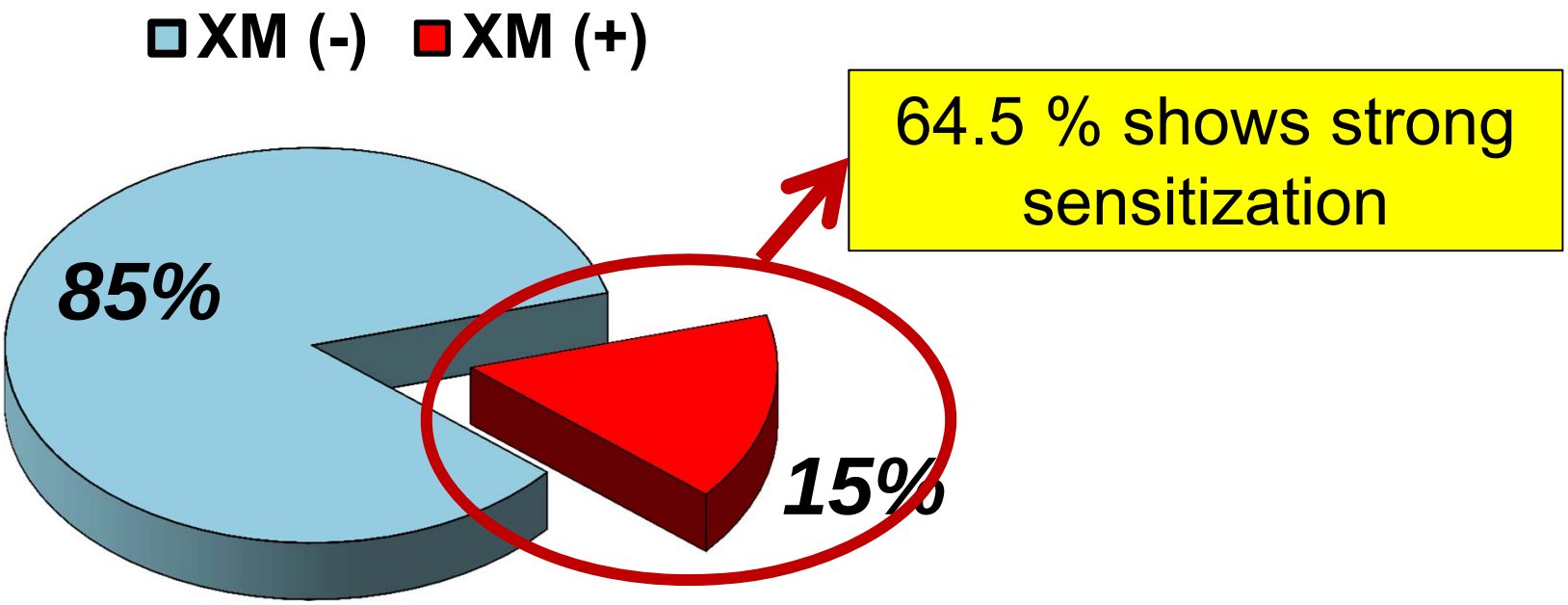


3 year allograft survival rate ; 93.8 %

Huh KH et al. Int Urol Nephrol 2012;44:1549

Sensitization rate in patients in waiting list

Out of 3145 ESRD patients on waiting list



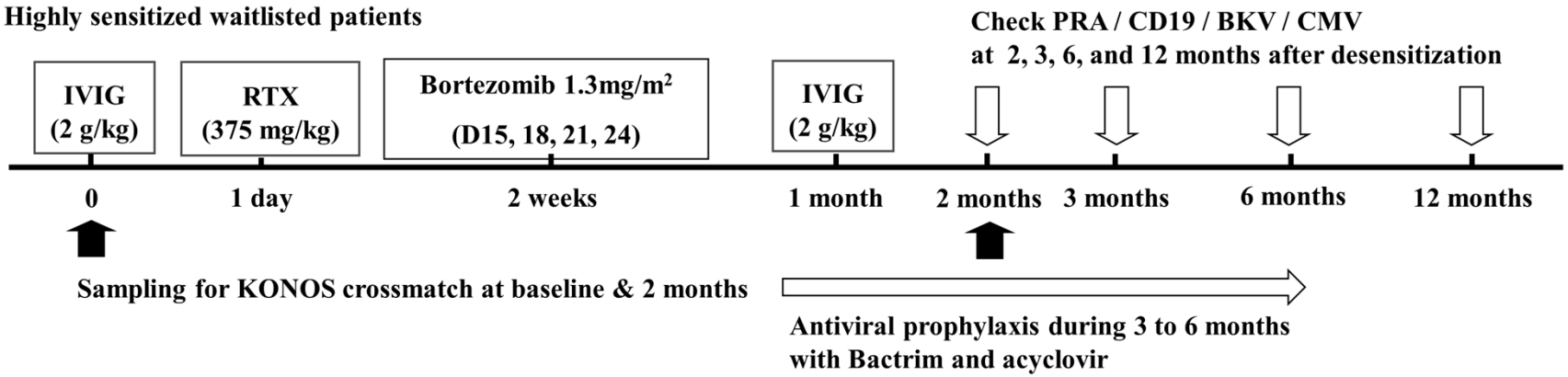
Park et al. Transplant Proc 2016; 48: 2464

Medicine®
CLINICAL TRIAL/EXPERIMENTAL STUDY

OPEN

Desensitization Using Bortezomib and High-dose Immunoglobulin Increases Rate of Deceased Donor Kidney Transplantation

- 2 doses of High dose IVIg (2g / kg)
- Single dose of rituximab (375 mg/m2)
- 4 doses of bortezomib (1.3 mg/m2)



Desensitization decreased MFI of class I PRA
Success rate of DDKT higher in study group (42.1 % vs. 23.5 %)

Jeong JC et al, Medicine 2016; 95: 5

Advancement of immune suppression

Azathioprine Era

Calcineurin inhibitors Era

Drug Minimization

Costimulation blockade ???

Corticosteroid

Azathioprine

OKT3

CsA (1984)

Tacrolimus (1998)

MMF (1997)

Thymoglobulin

Basiliximab

Sirolimus

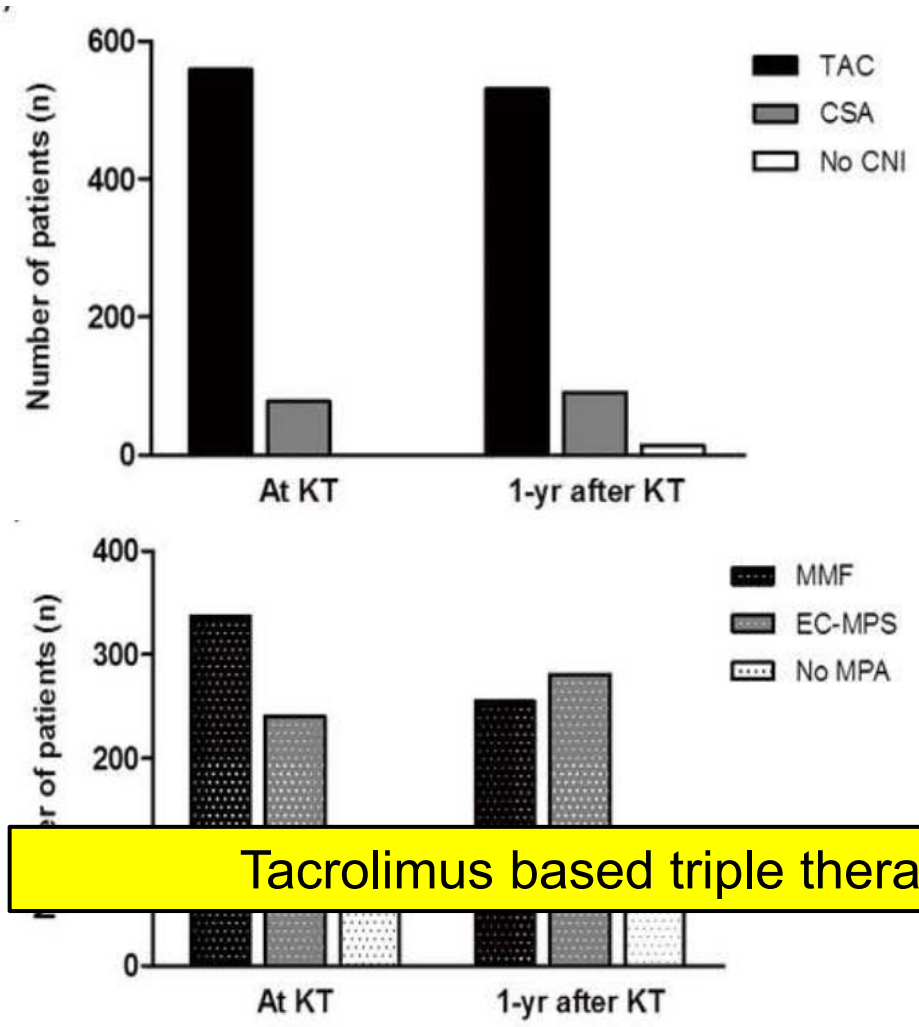
EC-MMF

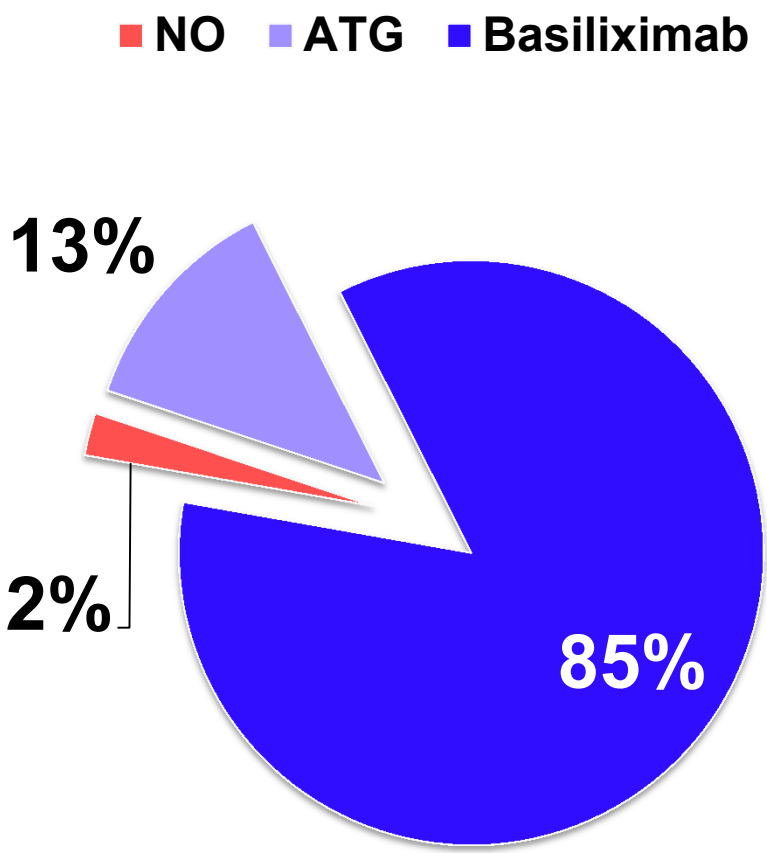
1969.3 1980 1990 2000 2010

- Prograf 1998년,
- Advagraf 2010 년
- Cipol-N 1997년
- Neoral 1984년
- Myrept 2009년
- Tacrobell 2005년
- Cellcept 1997년
- Myfortic 2003년

Immune Suppression pattern

636 KTRs from 9 transplant center



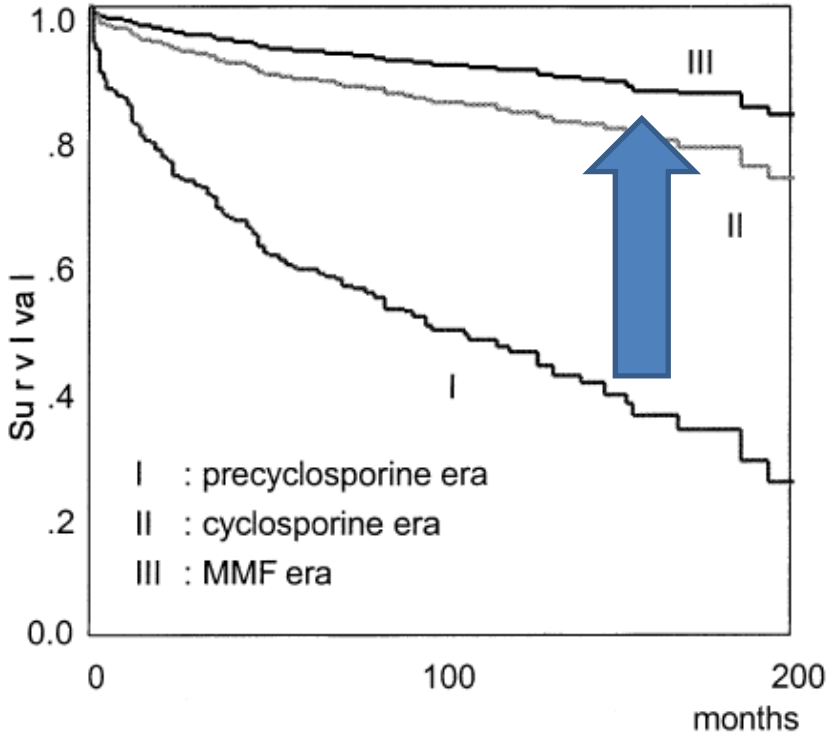


Tacrolimus based triple therapy with basiliximab induction

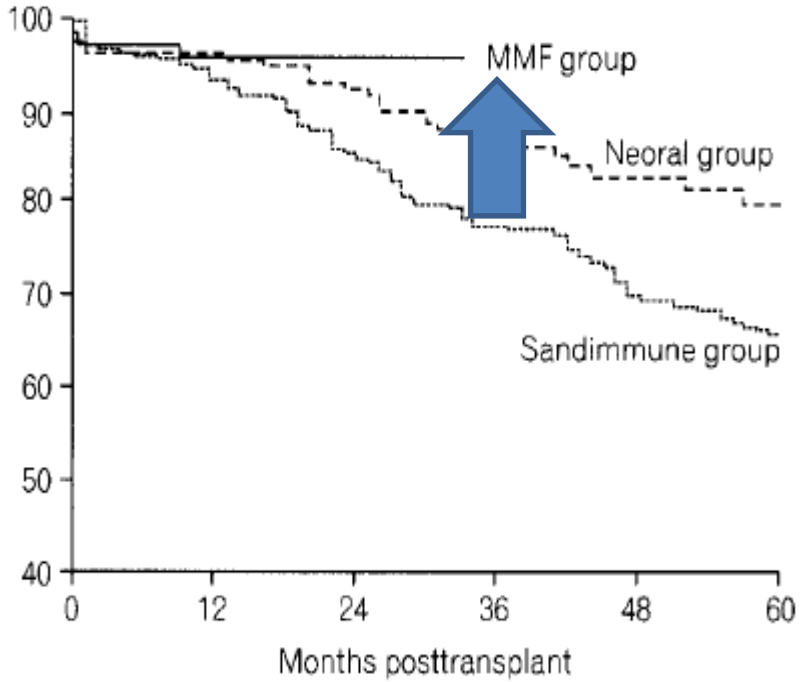
Chang JY et al, PLoS One on revision

Improvement allograft survival

Pre-CNI era → CNI era → CNI+MMF era



Kwon et al. Transplant Proc 2005; 37: 690



Kim et al. J Korean Soc Transplant 2001; 15: 8

Two sides of Strong Immune suppression

Rejection ↓

Complication ↑

Complications of Immune suppressant

Metabolic complication

Post-transplant malignancy

Opportunistic Infection

KT across ABO or HLA barrier

Korean **O**rgan **T**ransplantation **R**egistr**Y** (**KOTRY**) - 2009 ~ 2012

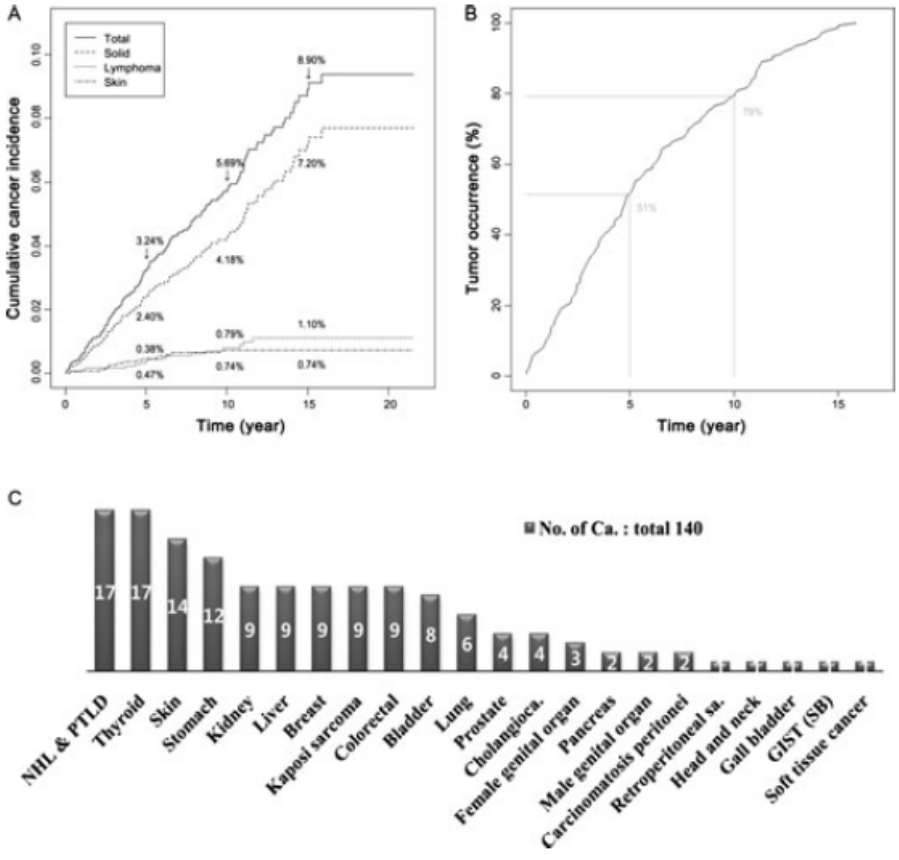
	ABOi+HLAi (n=1)	HLAi (n=2)	ABOi (n=6)	CONT (n=11)
Infection, n (%)	1 (100)	2 (100)	5 (82.3)	3(27.3)
Cardiovascular disease, n (%)	0 (0)	0 (0)	0 (0)	2 (18.2)
Malignancy, n (%)	0 (0)	0 (0)	0 (0)	1 (9.1)
Suicide, n (%)	0 (0)	0 (0)	0 (0)	1 (9.1)
Other, n (%)	0 (0)	0 (0)	1 (16.7)	4 (36.4)

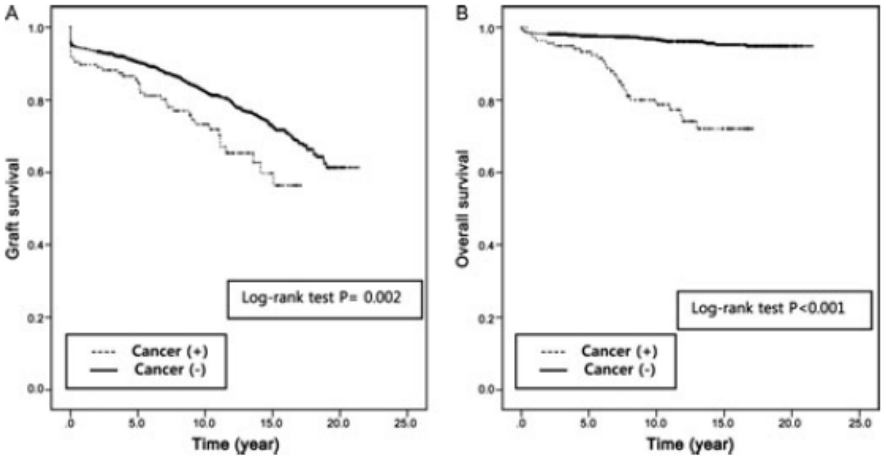
	Crude Models			Adjusted Model		
	HR	**95% CI**	***P***	**HR**	**95% CI**	***P***
ABOi	3.65	1.45 - 9.19	0.006	1.36	0.28 - 6.60	0.70
HLAi	1.89	0.55 - 6.44	0.31	0.96	0.15 - 6.22	0.96
DSZ	3.79	1.57 - 9.18	0.001	3.40	1.41 - 8.25	0.002

Ko et al, Transpl Int 2017 Epub ahead of print

Post-transplant malignancy

- Total 2365 KTRs between 1989 and 2009 in Asan Medical Center
- 140 cases of malignancy in 136 KTRs.





Kim JH et al, Clin Transplant 2014;28:434

Advancement of Kidney Transplantation

Aza, Steroid

1955 1st KT in the world

1969 1st KT in Korea

Calcineurin inhibitor

DM, Cardiovascular, infection complication, Malignancy

↓

Drug minimization

↓

Immune Tolerance

???

1950 **Corticosteroid**

1960 **Azathioprine**

1970

1980 **Cyclosporin**

1990 **Tacrolimus**
MMF

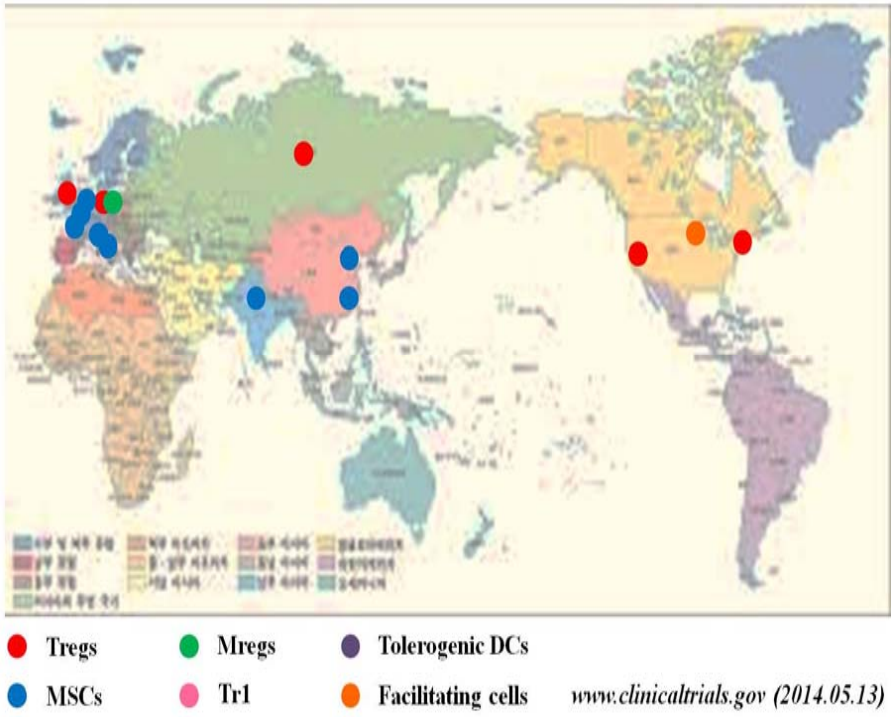
2000 **Sirolimus**
Everolimus

2010 **CTLA4Ig – Not available in Korea**

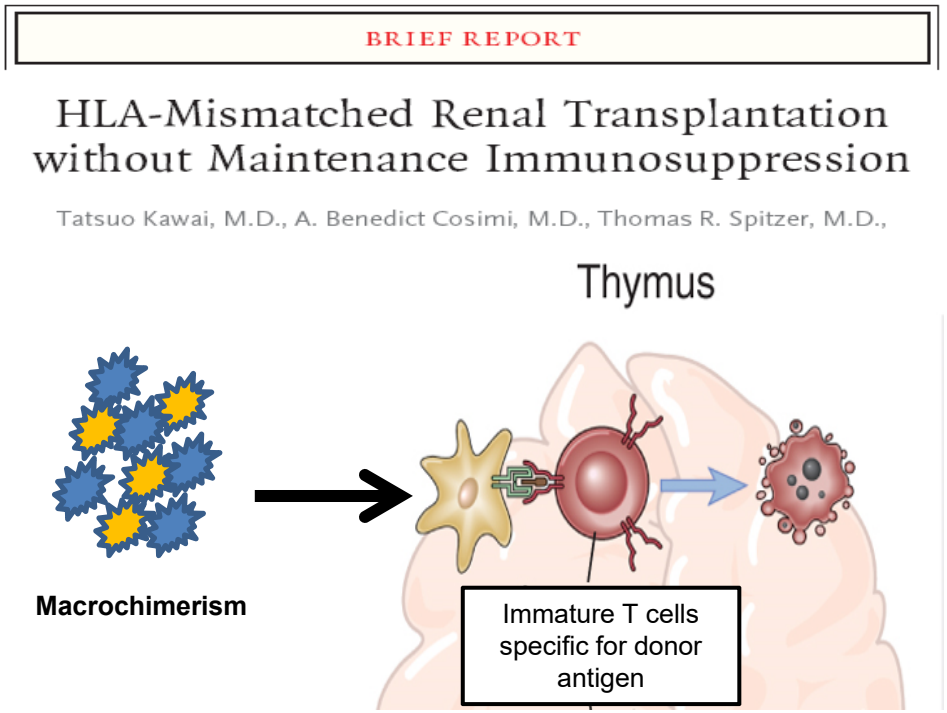
Mixed chimerism
Cell therapy
….

In the Future…

Cell therapy in kidney transplantation



Induction of Mixed chemirism



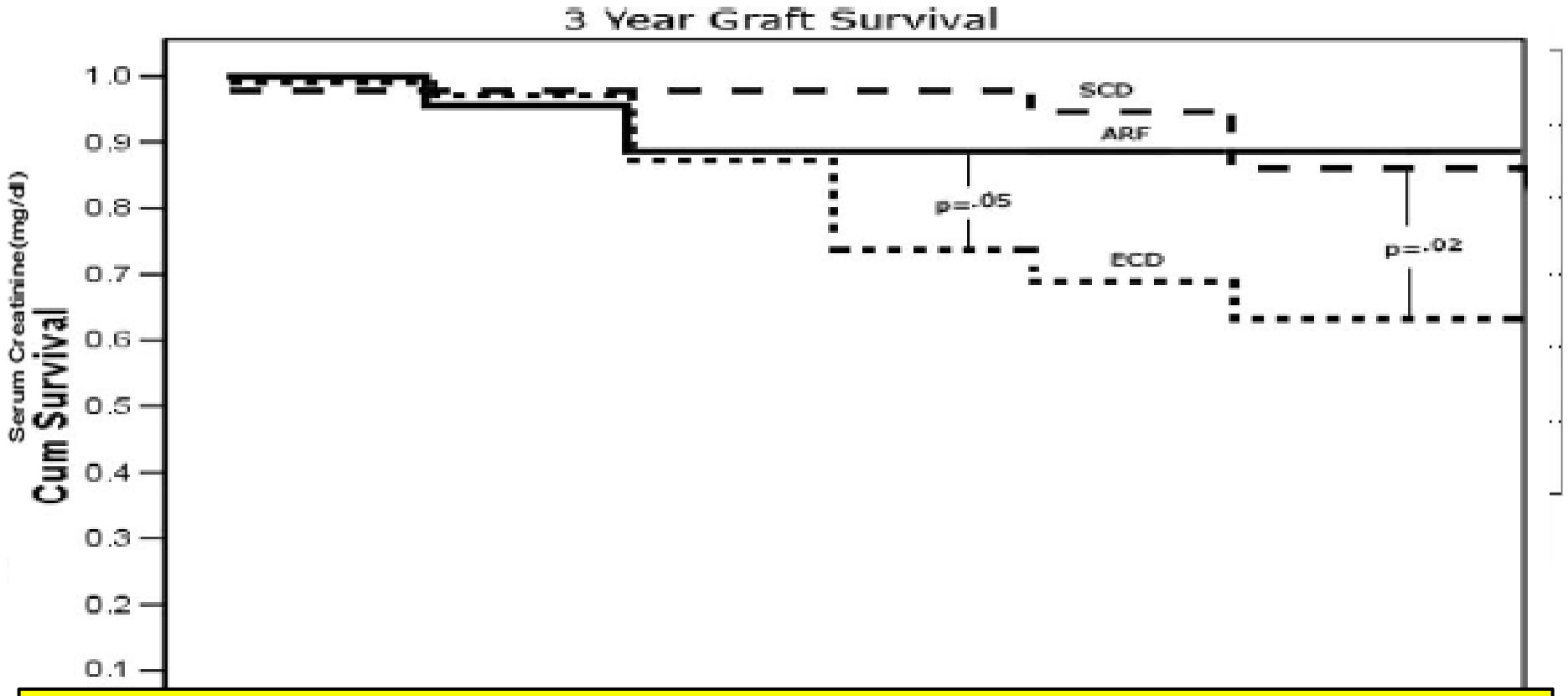
Pilat et al Nat Rev Nephrol 2010;6:594

Summary

- Kidney transplantation shows increasing pattern not only in quantity but also in quality
- Increase of donor pool and also use of expanded criteria donor contribute to the increase of DDKT
- In LDKT, use of spousal donor and ABOi KT may contribute to the increase of LDKT
- Advances of immune suppression and also effective desensitization technique, immune monitoring methods all together enables KT in immunologically high risk patients.
- Future innovative strategy for immune tolerance…


CATHOLIC
UNIVERSITY OF KOREA
Thank you for your attention

Successful Transplantation of Kidneys from Deceased Donors with Acute Renal Failure: Three-Year Results

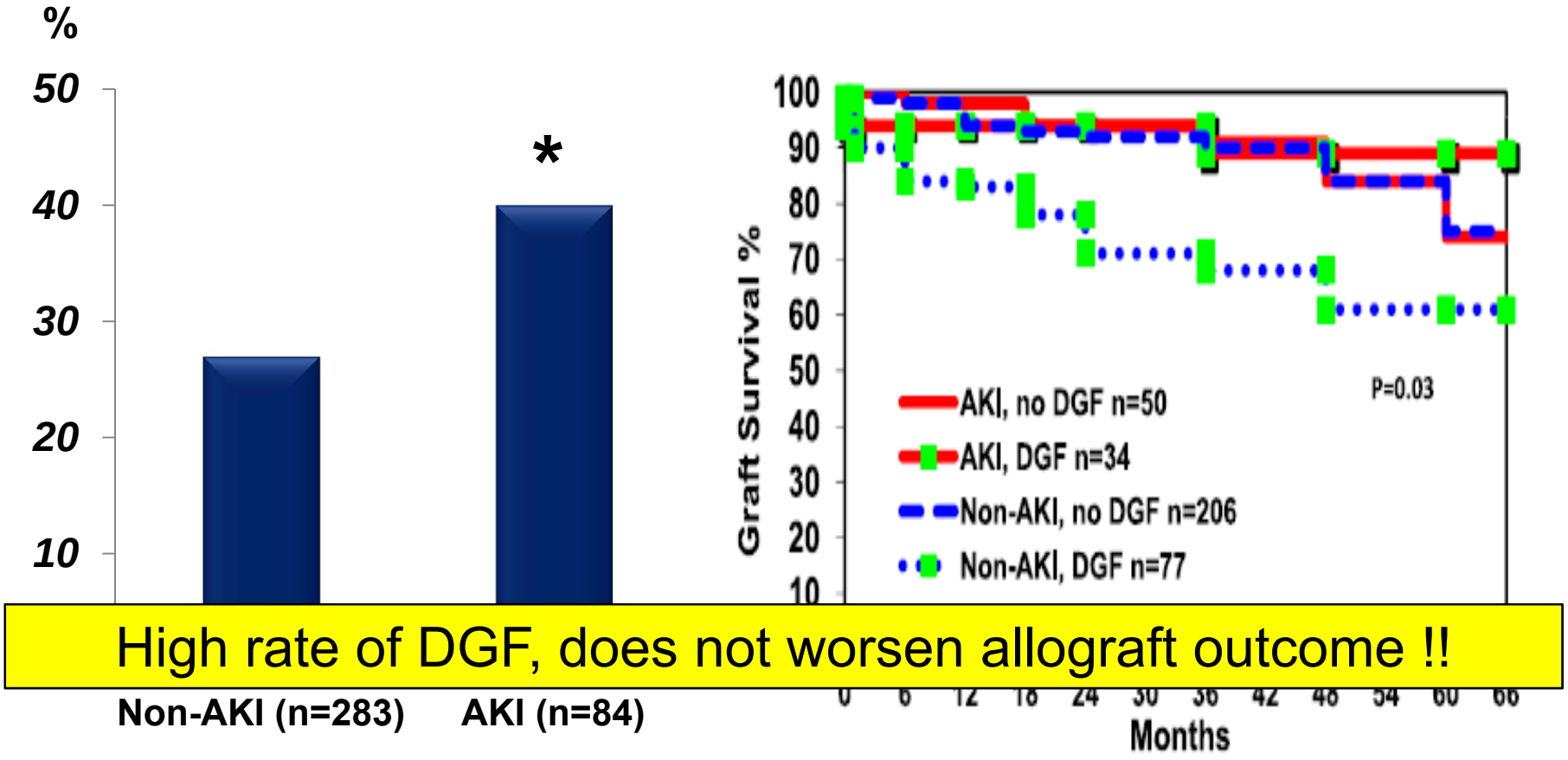


- KT of kidneys from deceased donors with ARF provides comparable survival and function compared to kidneys from non-ARF donors.

Kumar et al. Trasplantation. 2006; 82: 1640

Evolving Experience Using Kidneys from Deceased Donors with Terminal Acute Kidney Injury

- Definition of AKI ; Doubling of the admission Scr level & terminal Scr level > 2.0 mg/dL



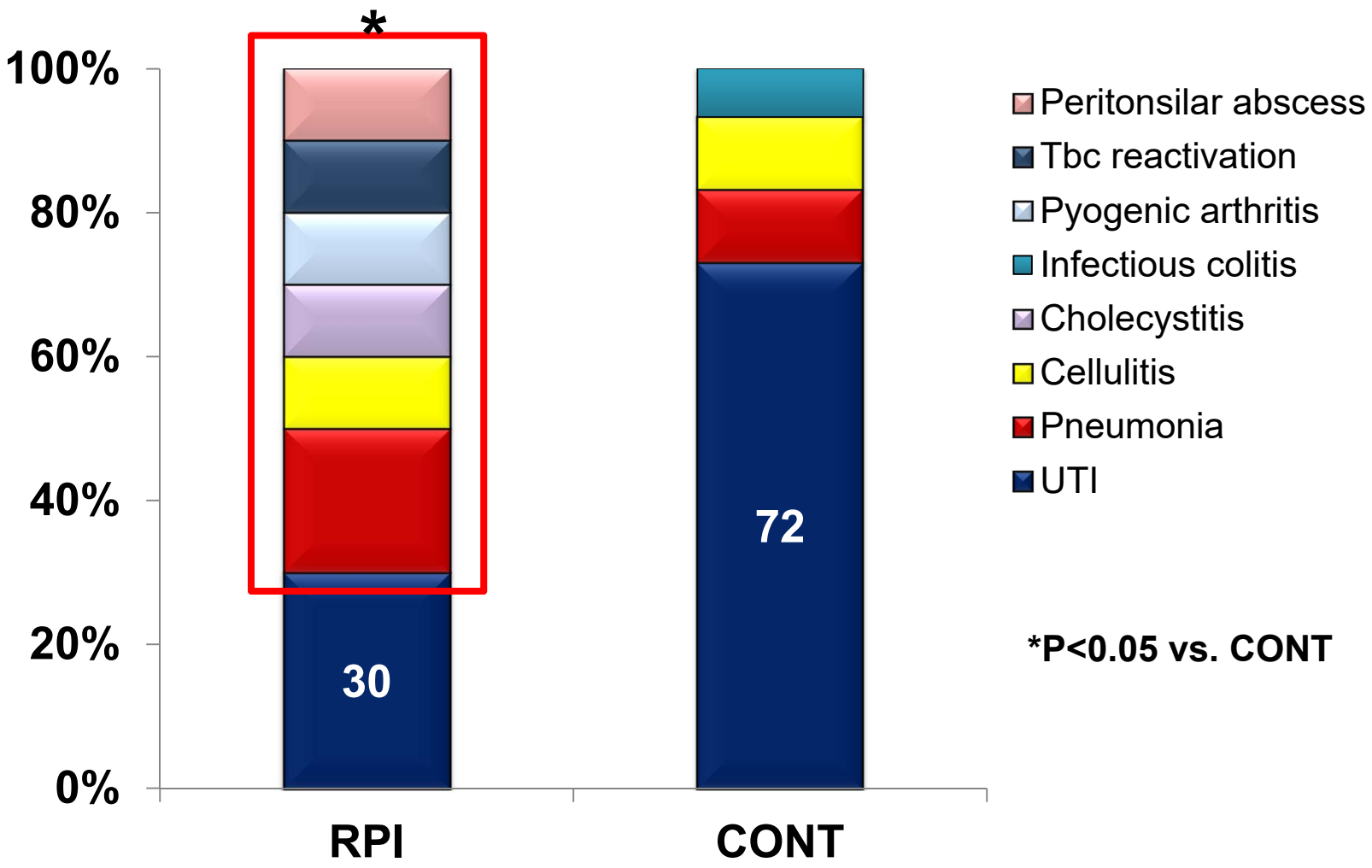
High rate of DGF, does not worsen allograft outcome !!

Farney et al. J Am Coll Surg. 2013; 216: 645

Contents

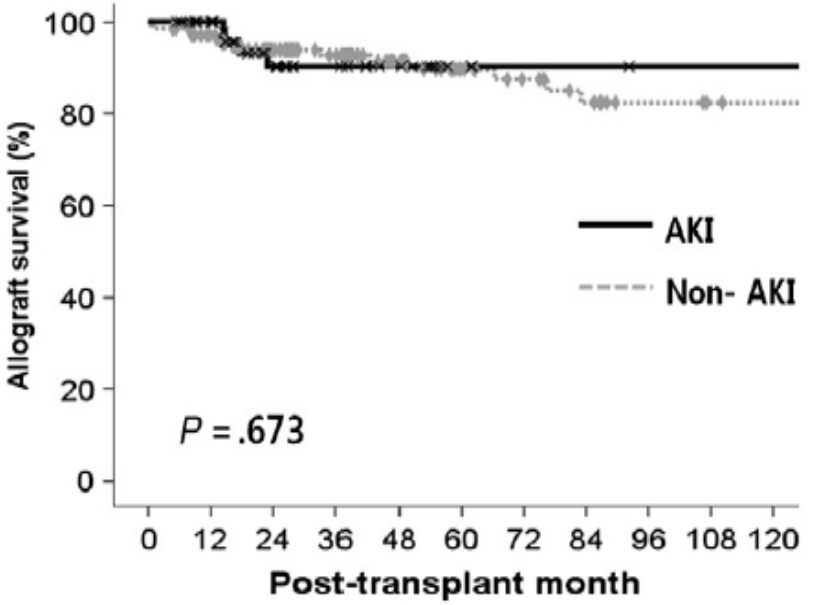
- History of kidney transplantation in Korea
- Efforts to increase DDKT
- Efforts to increase LDKT
- Advancement of Immune suppression
- Advancement of Immune monitoring
- Future perspectives

More severe form of infection

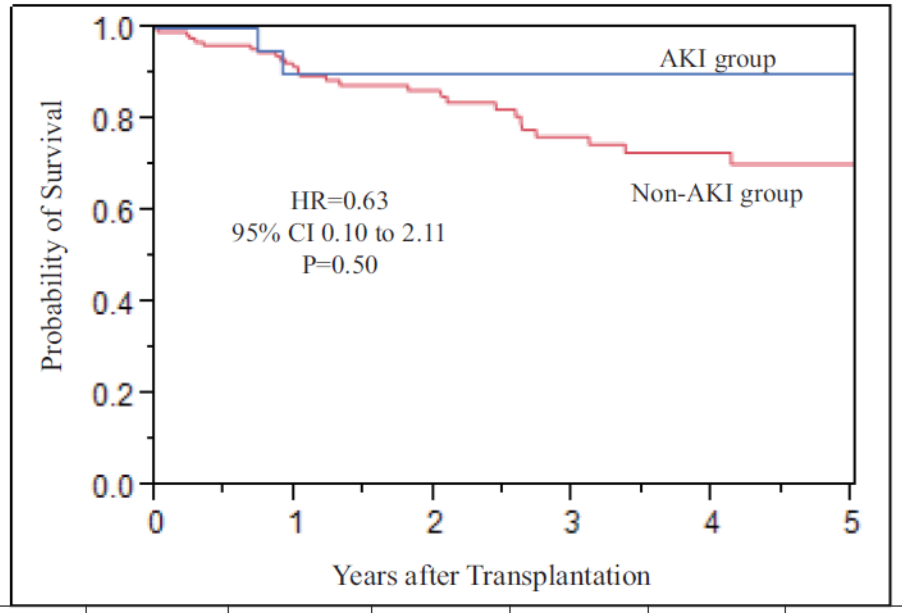


Chung BH et al, Transpl Inf Dis 2013

Clinical outcome of KT from deceased donor with AKI



AKI	57	54	34	25	20	11	8	5	4	4	4
Non-AKI	147	122	95	78	59	41	35	32	26	24	23



AKI	23	18	6	5	4	2
Non-AKI	137	111	71	50	33	22

Death-censored graft survival of deceased donor with AKI is not inferior than non-AKI.

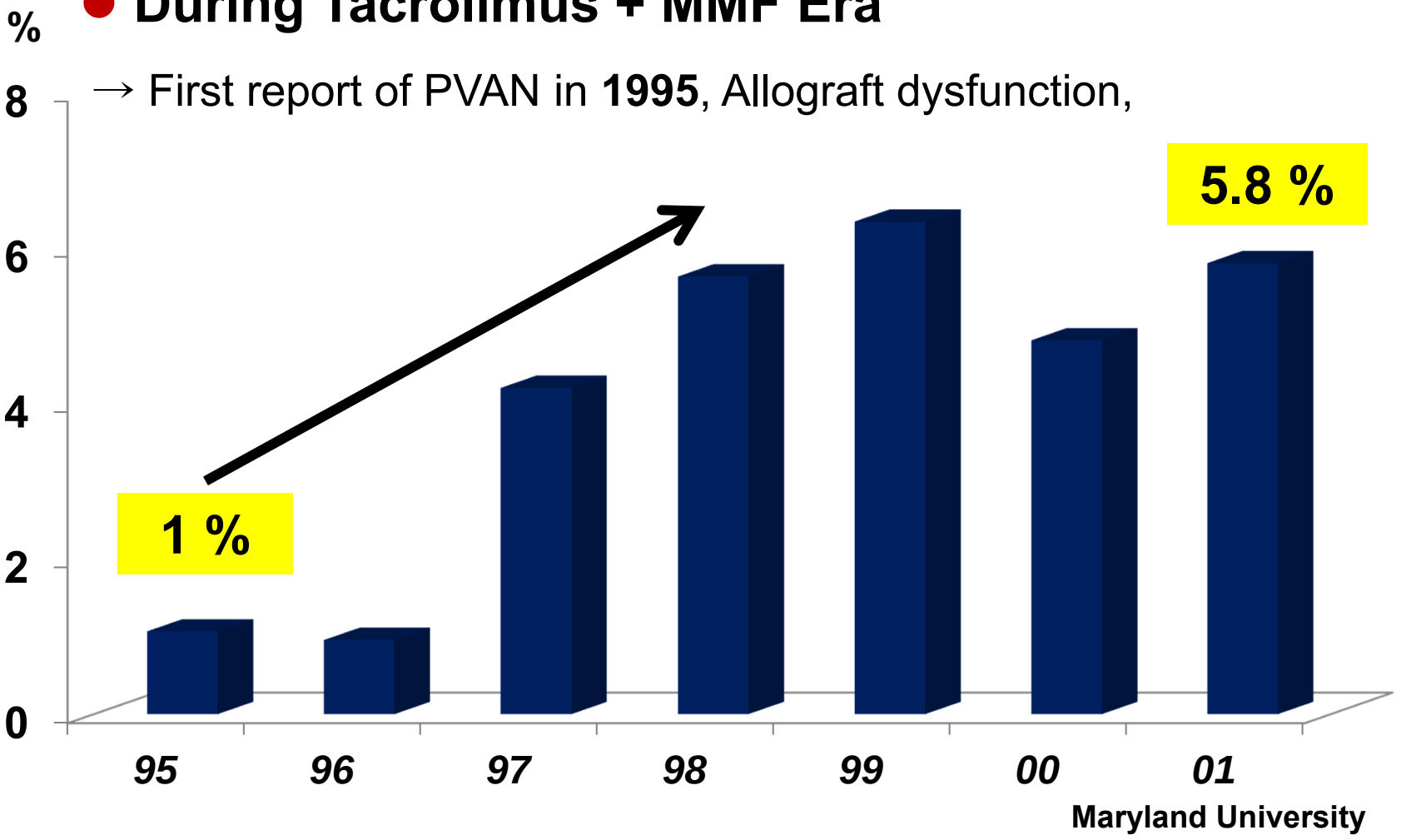
Lee MH et al. *J Crit Care* 29(3):432-7, 2014

Heilman RL et al. *Am J Transplant* 15(8):2143-51, 2015

Incidence of BKVAN (PVAN)

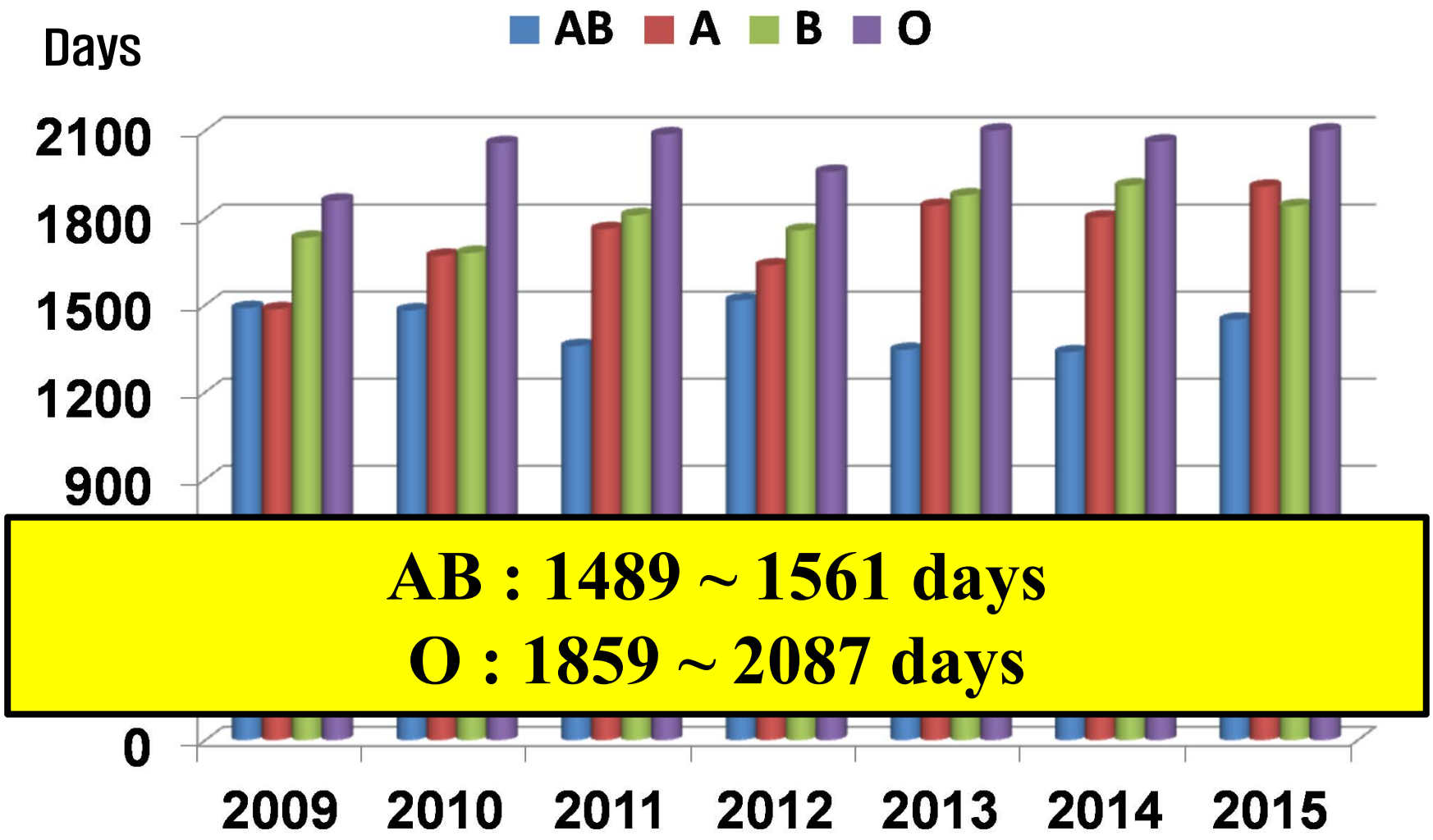
- **During Tacrolimus + MMF Era**

→ First report of PVAN in **1995**, Allograft dysfunction,



Ramos et al, Clin Transpl 2003;143

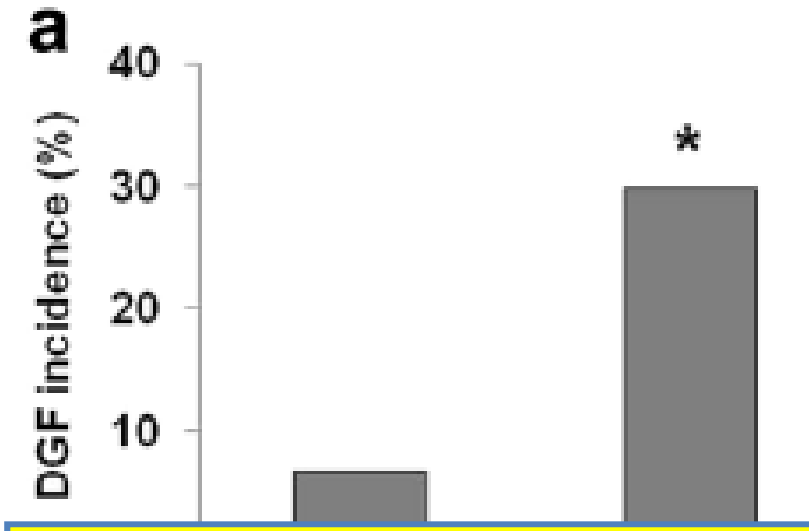
Waiting time according to blood type

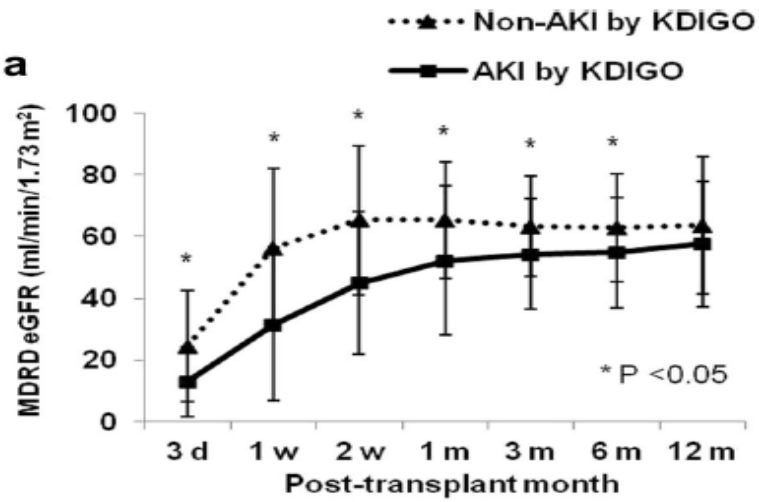


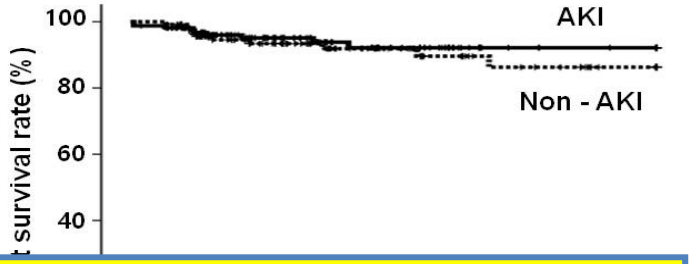
RESEARCH ARTICLE Open Access

Prediction of clinical outcomes after kidney transplantation from deceased donors with acute kidney injury: a comparison of the KDIGO and AKIN criteria

285 cases of DDKT from 3 transplant centers



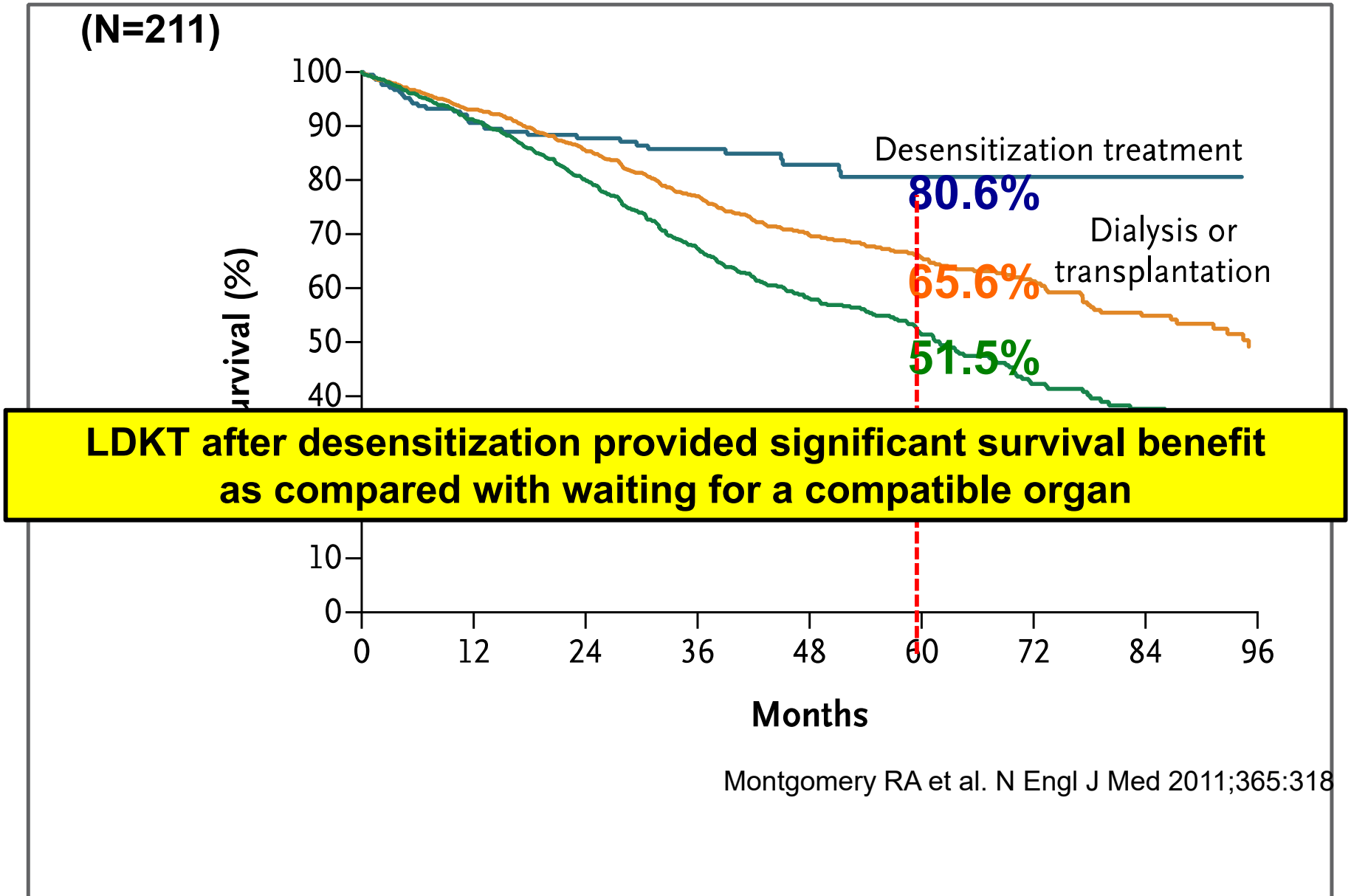




Death-censored graft survival of deceased donor with AKI is not inferior than non-AKI.

Kim et al BMC Nephrol 2017:18;39

Why KT after desensitization?



LDKT after desensitization provided significant survival benefit as compared with waiting for a compatible organ

Montgomery RA et al. N Engl J Med 2011;365:318