

Use of suboptimal donors – do we miss an opportunity?

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Factors influencing Kidney transplant Outcome

Before Tx

Donor

- * Age
- * **Clinical condition**
- * Type (living; cadaveric)
- * HLA match

Recipient

- * Age
- * Sensitisation
- * Immune reactivity
- * Viral status
- * Dialysis vintage

Transplant center – experience, organisation, skills...

After Tx

- Chronic rejection
- Tx glomerulopathy
- Calcineurin inhibitors
- *Metabolic complications*

American Journal of Transplantation



THE OFFICIAL JOURNAL OF THE AMERICAN SOCIETY OF TRANSPLANTATION
AND THE AMERICAN SOCIETY OF TRANSPLANT SURGEONS

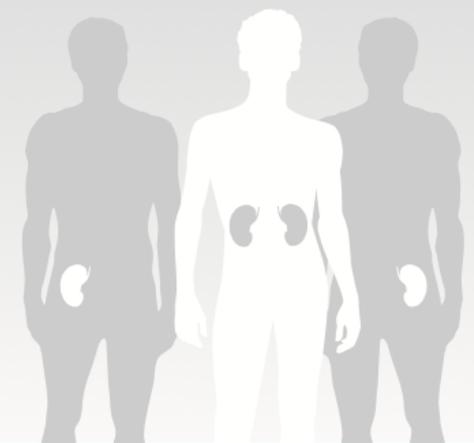


KDIGO Clinical Practice Guideline
for the Care of Kidney Transplant Recipients

WILEY-BLACKWELL

SUPPLEMENT 3 • VOL 9 • 2009

Smjernice ERBP o evaluaciji darivatelja i primatelja bubrežnog transplantata i perioperativnoj skrbi



nacionalne smjernice za
obradu i odabir primatelja
i darivatelja bubrega

usklađene sa smjericama
2013. ERBP GUIDELINE ON THE MANAGEMENT AND EVALUATION
OF THE KIDNEY DONOR AND RECIPIENT

2014 / 2. izdanje



Donor evaluation

- ✿ “European Best Practice Guidelines for Kidney Transplantation” – NDT, 2000 (15) Suppl.7:39-51
- ✿ Section II: Evaluation and selection of donors
- ✿ Guideline II 1.1. Selection of donors

Organ evaluation

Assessment of criteria:

1. clinical
 - * 2. morphologic
 - * 3. functional
- * With adequate evaluation, explantation, organ procurement and transplantation, we can avoid transmission infective and tumor disease to recipient.

Ideal donor

- ✿ Generally healthy person
- ✿ Between 10 and 55 yrs
- ✿ With brain death
- ✿ Without signs of infection
- ✿ With good organ function

- ✿ Most of potential donors do not fulfill this criteria

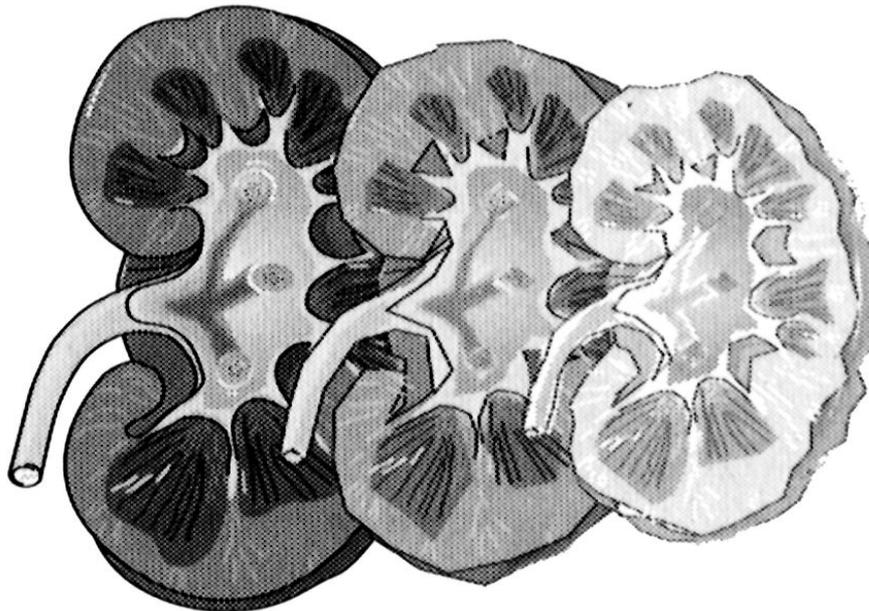
- ✿ It is necessary to establish limits regarding donor choice according to
 - ✿ Age
 - ✿ Clinical condition
 - ✿ Organ function

Exclusion criteria for organ donation

- ❁ malignancy (except benign tumors of CNS, nonmelanotic skin tumors and «in situ» tumors of cervix uteri)
- ❁ multiorgan failure and sepsis
- ❁ acute hepatitis
- ❁ active TBC

Exclusion criteria for kidney donation

- * Exclusion criteria for all organs
- * + chronic kidney disease (ClCr < 60 ml/min, proteinuria > 0,5 g/24 h)



Relative exclusion criteria for kidney donation

- ❁ Age
- ❁ Arterial hypertension
- ❁ Diabetes
- ❁ Acute renal failure
- ❁ Prolonged cold ischemia >24 h
- ❁ Nephropathies
- ❁ Viral carriers – hepatitis B and C (except similar recipients, hepatitis C should be treated)

“Expanded Donor Criteria” – EDC

- ✿ Guideline II 1.1. D: ...relative contraindications are based on the quality of potential graft and include suboptimal to non-acceptable renal function or presence of risk-factors...
(Evidence level C)
- ✿ Guideline II 1.1. E: ...the aim of the procurement team should be to increase the acceptance rate of potential donors without risking unacceptably poor graft function and survival... *(Evidence level C)*

Expanded Donor Criteria – EDC

- ❁ Guideline II 1.1. F: ...in the absence of “gold standard” it is recommended that donors should be evaluated on the basis of renal function – ClCr, age and vascular disease...
- ❁ limits may be ClCr < 60 ml/min or 50-60 ml/min for marginal and
- ❁ < 50 ml/min for unacceptable – dual Tx.
- ❁ Age >70, vascular risk factors, glomerular sclerosis on biopsy may add negatively to the evaluation (*Evidence level B*)

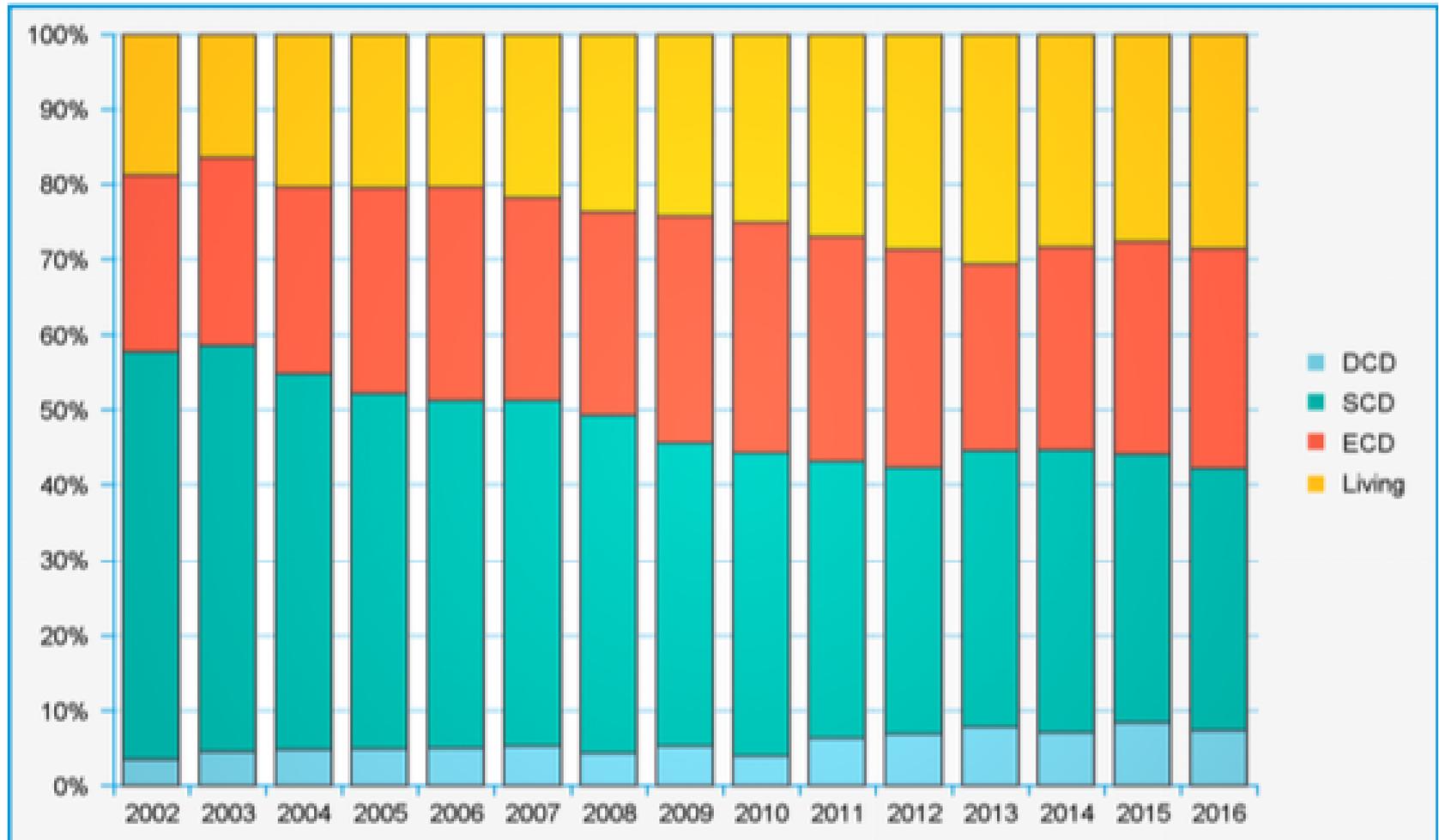
Expanded Donor Criteria – EDC

- ✿ Donor > 70 yrs without risk factors
- ✿ Donor > 60 yrs with minimal risk factors and border criteria for KBB, proteinuria, vascular changes, hypertension and diabetes
- ✿ Signs of kidney disorder regardless of age
- ✿ eGFR – 50-60 ml/min – suboptimal but acceptable, < 50 – “dual kidney Tx” or unacceptable
- ✿ Biopsy – “Remuzzi criteria”

Expanded Donor Criteria – EDC

- ✿ Guideline II 1.1. G: ...recipients of suboptimal kidneys or dual kidneys should have given their informed consent prior to transplantation. (*Evidence level C*)

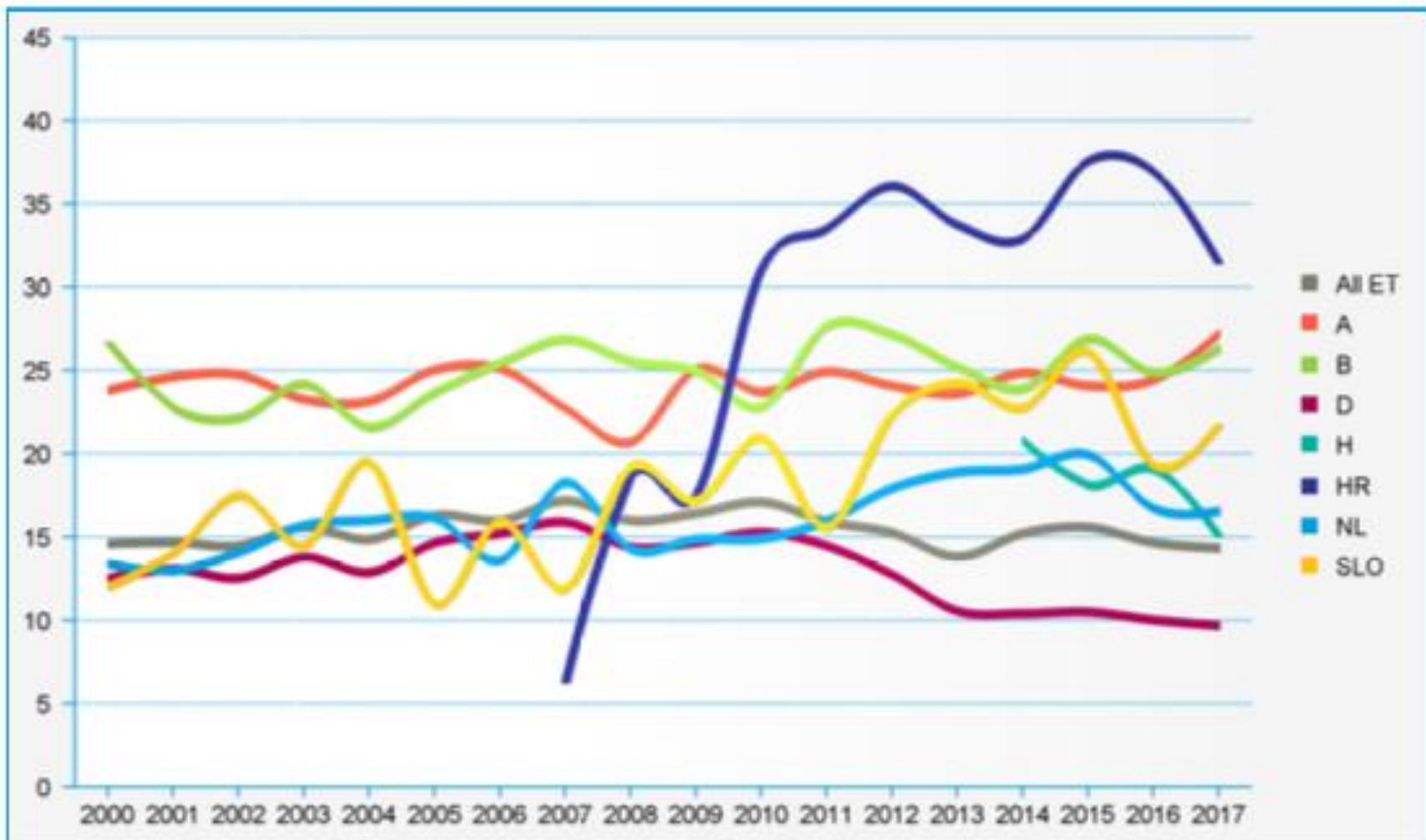
Kidneys donated in All ET, by year, by donor type %



statistics.eurotransplant.org : 1235E_All ET_kidney : 15.09.2017



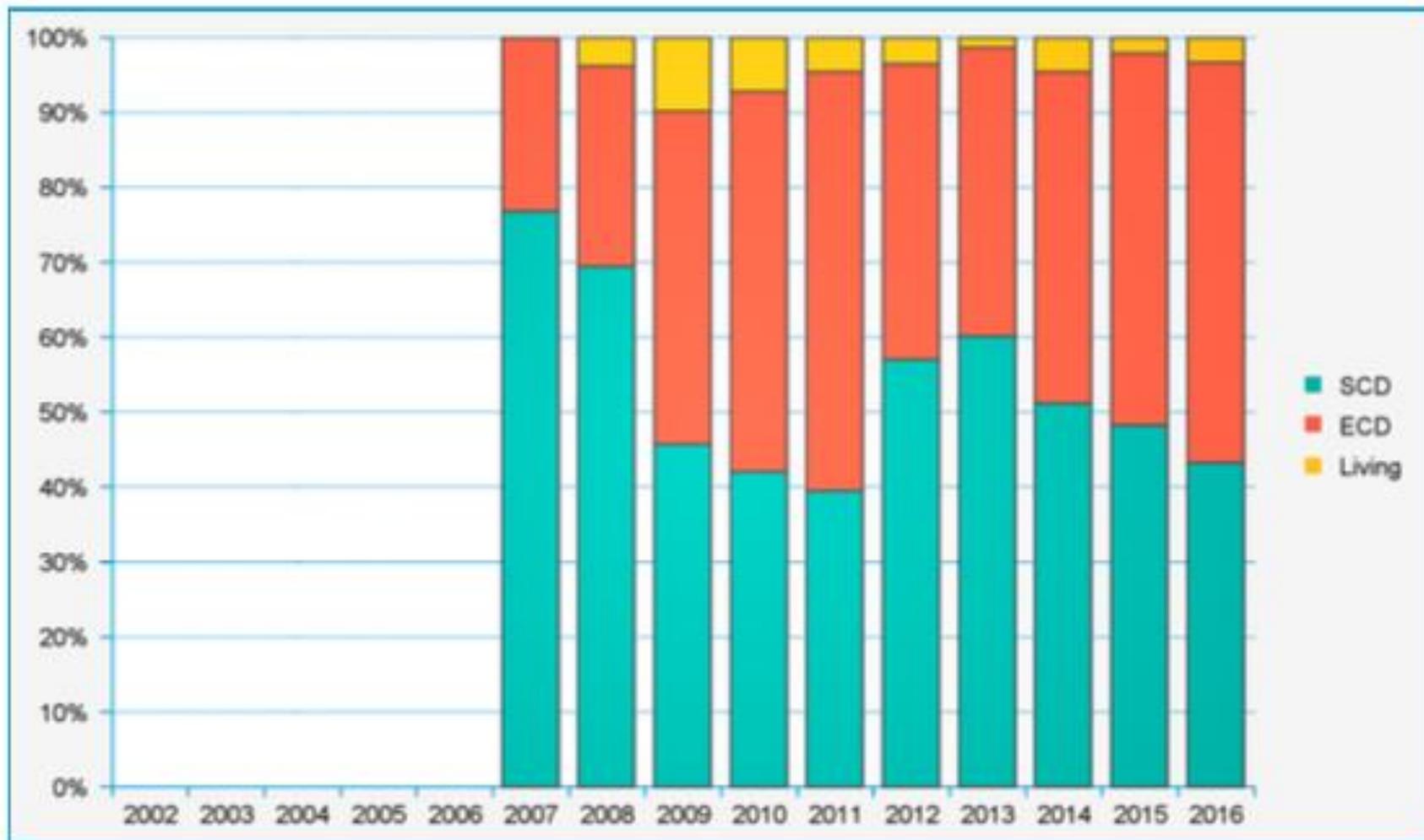
Deceased kidney donors reported, per million population, by year, by donor country



statistics.eurotransplant.org : 1248P_kidney : 07.09.2017 : 2017 estimated



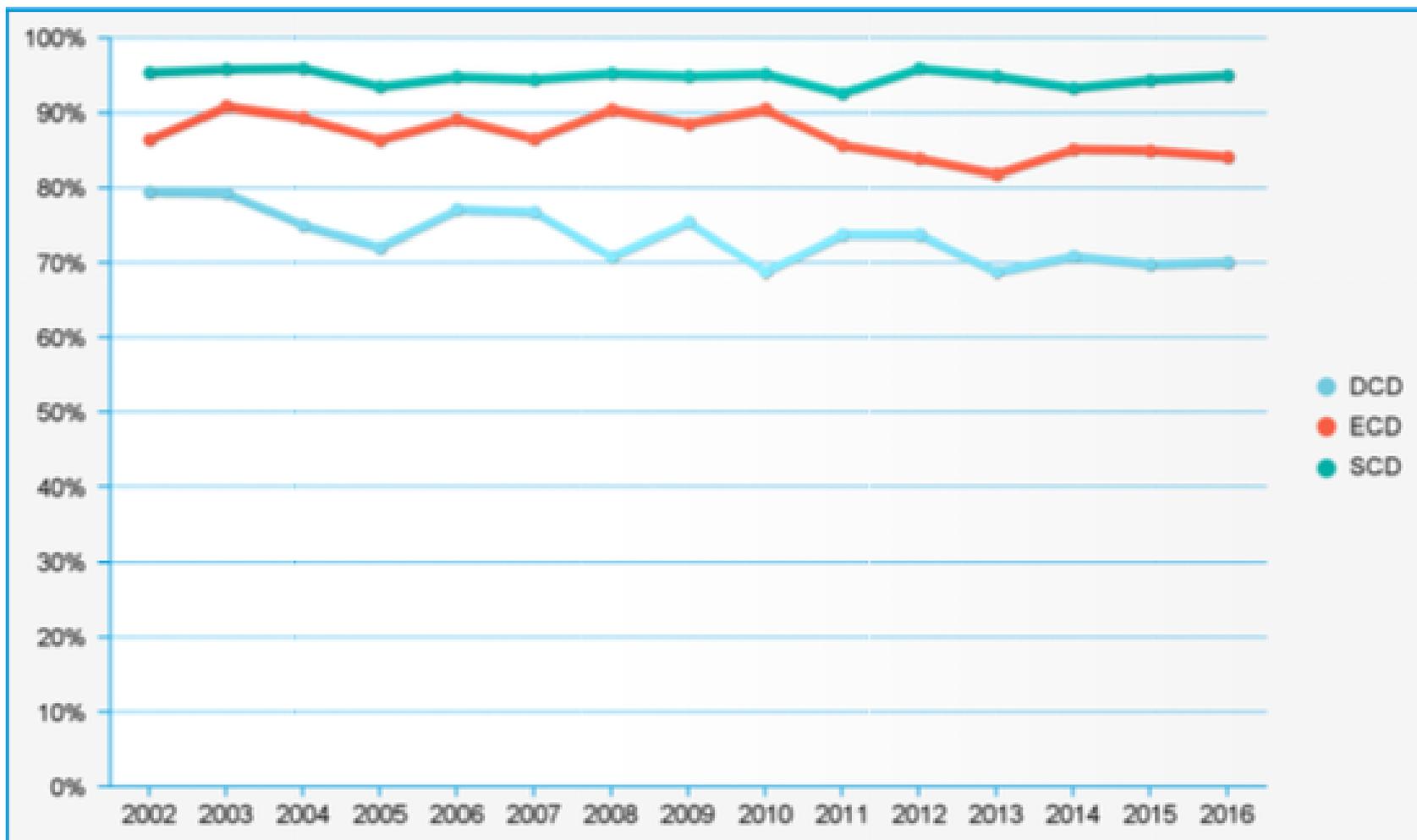
Kidneys donated in Croatia, by year, by donor type %



statistics.eurotransplant.org : 1235E_Croatia_kidney : 15.09.2017



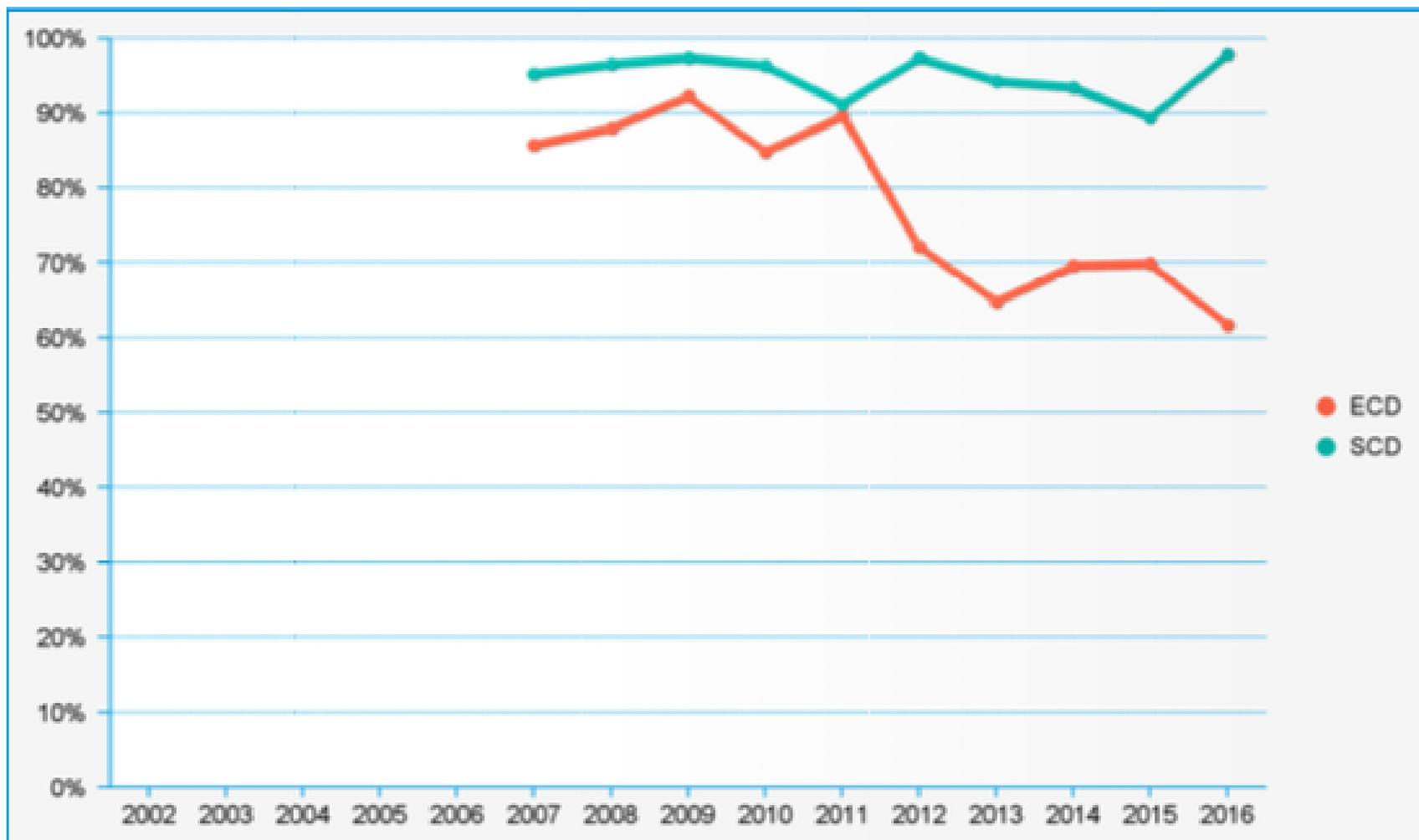
Deceased kidney donors in All ET, usage rate, by year, by donor type ECD/SCD/DCD



statistics.eurotransplant.org : 1231E_All ET_kidney : 15.09.2017 : % reported donors used for transplant



Deceased kidney donors in Croatia, usage rate, by year, by donor type ECD/SCD/DCD



statistics.eurotransplant.org : 1231E_Croatia_kidney : 15.09.2017 : % reported donors used for transplant



Acute renal failure

- ✿ **Expanding the criteria of renal kidneys for transplantation: use of donors with acute renal failure (Benjamin Derouere i sur. Department of Nephrology, Dialysis and Transplantation, Le Kremlin Bicetre, University Paris XI, APHP, France; **NDT Advance Access published online on February 17, 2010**)**
- ✿ ... outcome of transplanted kidneys procured in the presence of acute renal failure (ARF).
- ✿ Transplant patients ($n = 52$) with a kidney procured **with ARF** were studied.
- ✿ Mean donor age was 45.7 ± 12.7 years, and the mean SCr at the time of harvesting was 276.3 ± 104.2 $\mu\text{mol/l}$. There were no significant differences between the two groups regarding age of recipient, gender of the donor or recipient, cold ischaemia time, occurrence of cardiac arrest, collapse or acute rejection.
- ✿ **Conclusions.** ARF before organ procurement does not have a negative effect on subsequent renal function. However, old age, CVD risk factors, and late renal function recovery after transplantation are correlated with subsequent lower renal function. **Thus, renal grafts with ARF can be used for renal transplantations.**

Immunological risk

- ❁ **Immunological risk in recipients of kidney transplants from extended criteria donors** (Carine Diet i sur. Nephrology and Renal Transplantation Department, Henri Mondor Hospital, Créteil, France; **NDT Advance Access published online on March 10, 2010**)
- ❁ ... a kidney from a marginal **donor** is likely to elicit a strong and specific immune response...
- ❁ ... the effect of extended **criteria donor** (ECD) on the incidence of biopsy-proven acute rejection (BPAR) and the effect of immunological risk factors on graft outcome in a large cohort of kidney transplant recipients ($n = 2121$ patients) grafted with ECD ($n = 656$ patients) or optimal **donor** (OD) ($n = 1465$ patients).
- ❁ ... The incidence of BPAR was not statistically different between the ECD group recipients (105/656, 16%) and the OD group recipients (251/1465, 17%) ($P = 0.52$). The death-censored graft survival data for OD and ECD groups, as a function of immunological status did not affect graft survival in ECD transplant recipients ($P = 0.64$).
- ❁ **Conclusion.** Although our groups were not homogenous, our study did not reveal an increased risk of acute rejection in recipients of ECD allograft.

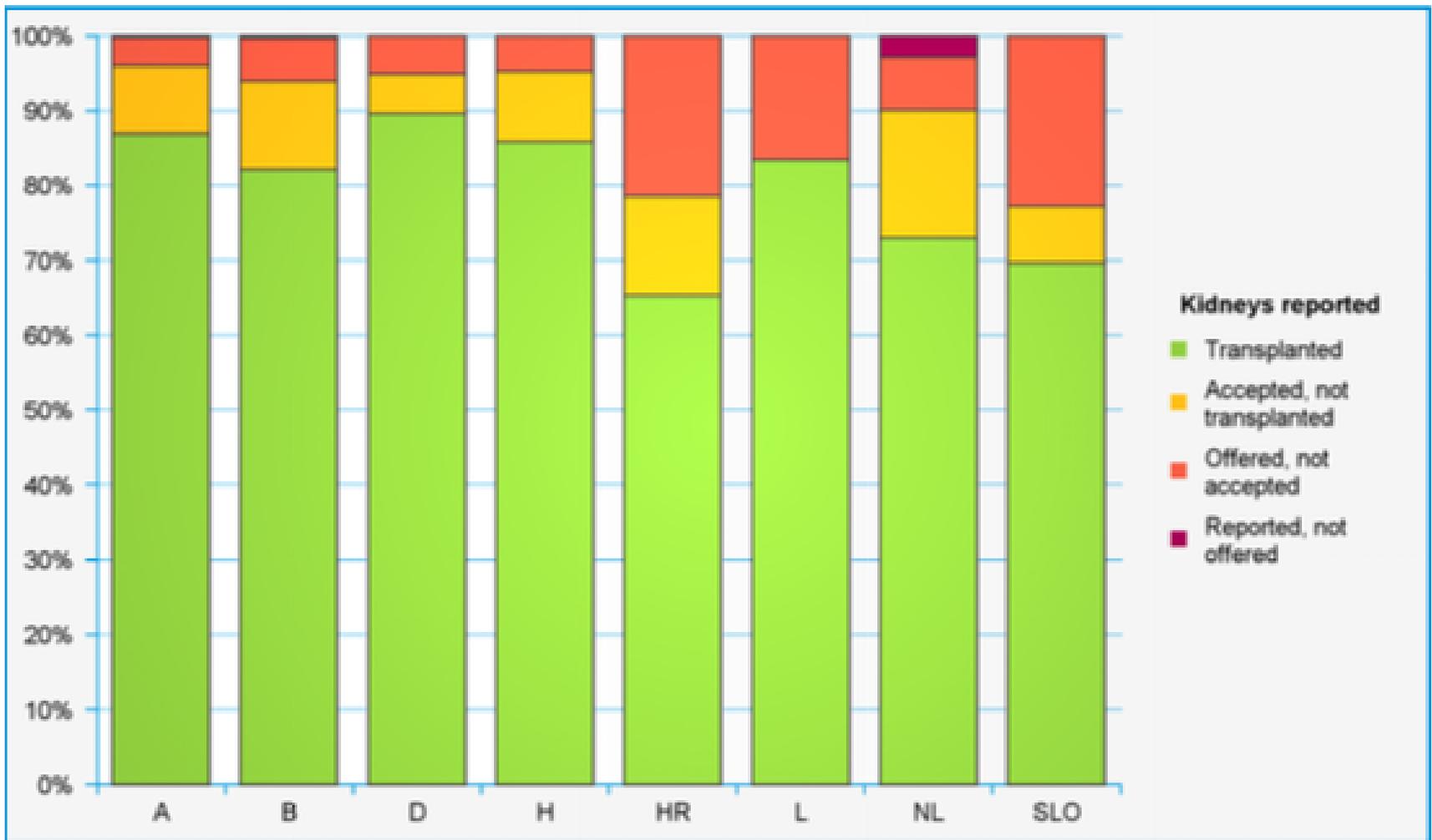
Retransplantation

- ✿ **Should Extended-Criteria Donor Kidneys Be Used in Patients Undergoing Retransplantation?** (Ron Shapiro, MD, Medscape 2007)
- ✿ The authors studied 9641 adult renal transplant recipients who had experienced graft failure of their first kidney transplant between 1995 and 2004. The outcomes were compared with those of patients who remained on the transplant waiting list, those who received standard-criteria donor (SCD) kidneys, and those who received expanded-criteria donor (ECD) kidneys.
- ✿ SCD kidney transplantation was associated with a 56% decrease in mortality (covariate-adjusted hazard ratio of 0.44) compared with waiting on dialysis, but ECD kidney transplantation was not associated with any reduction in mortality when compared with remaining on the waiting list (HR 0.98).
- ✿ This suggests that patients undergoing retransplantation should wait for an SCD kidney. These data suggest that ECD kidneys should be used selectively, preferably in patients undergoing their first transplant.

EDC and mortality

- ❁ **Deceased-Donor Characteristics and the Survival Benefit of Kidney Transplantation (Merion JM i sur; JAMA. 2005;294(21):2726-2733)**
- ❁ Retrospective cohort study using data from a US national registry of mortality and graft outcomes among kidney transplant candidates and recipients. The cohort included 109127 patients receiving dialysis and added to the kidney waiting list between January 1, 1995, and December 31, 2002, and followed up through July 31, 2004.
- ❁ ECD kidney transplants should be offered principally to candidates older than 40 years in OPOs with long waiting times. In OPOs with shorter waiting times, in which non-ECD kidney transplant availability is higher, candidates should be counseled that ECD survival benefit is observed only for patients with diabetes.

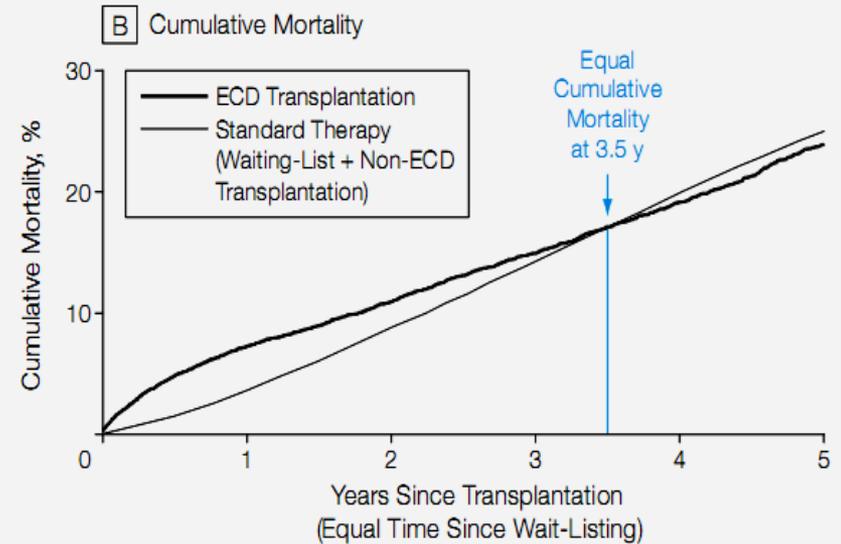
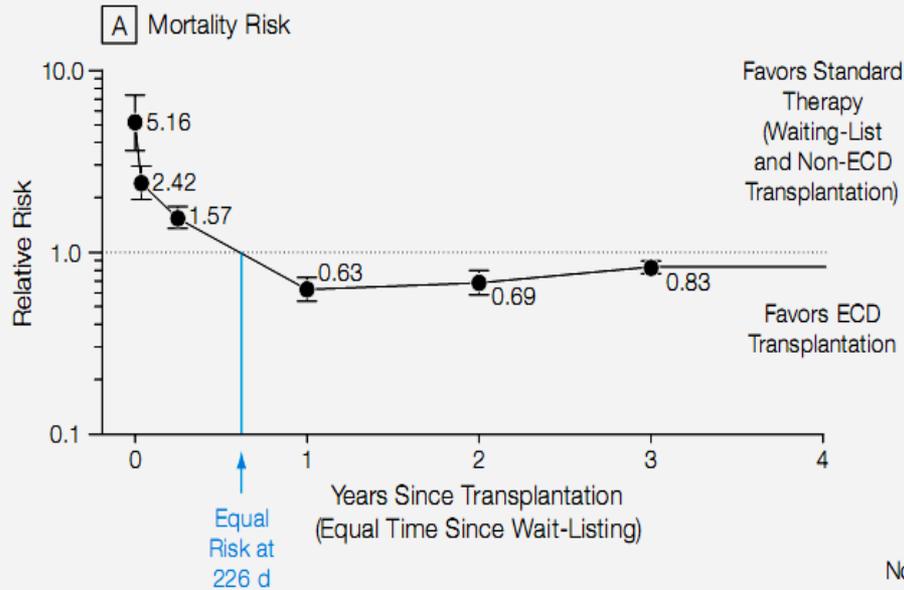
Kidney donation, deceased donors in 2016, by country, by allocation phase %



statistics.eurotransplant.org : 1256P_2016_kidney : 15.09.2017 : counting each individual reported kidney



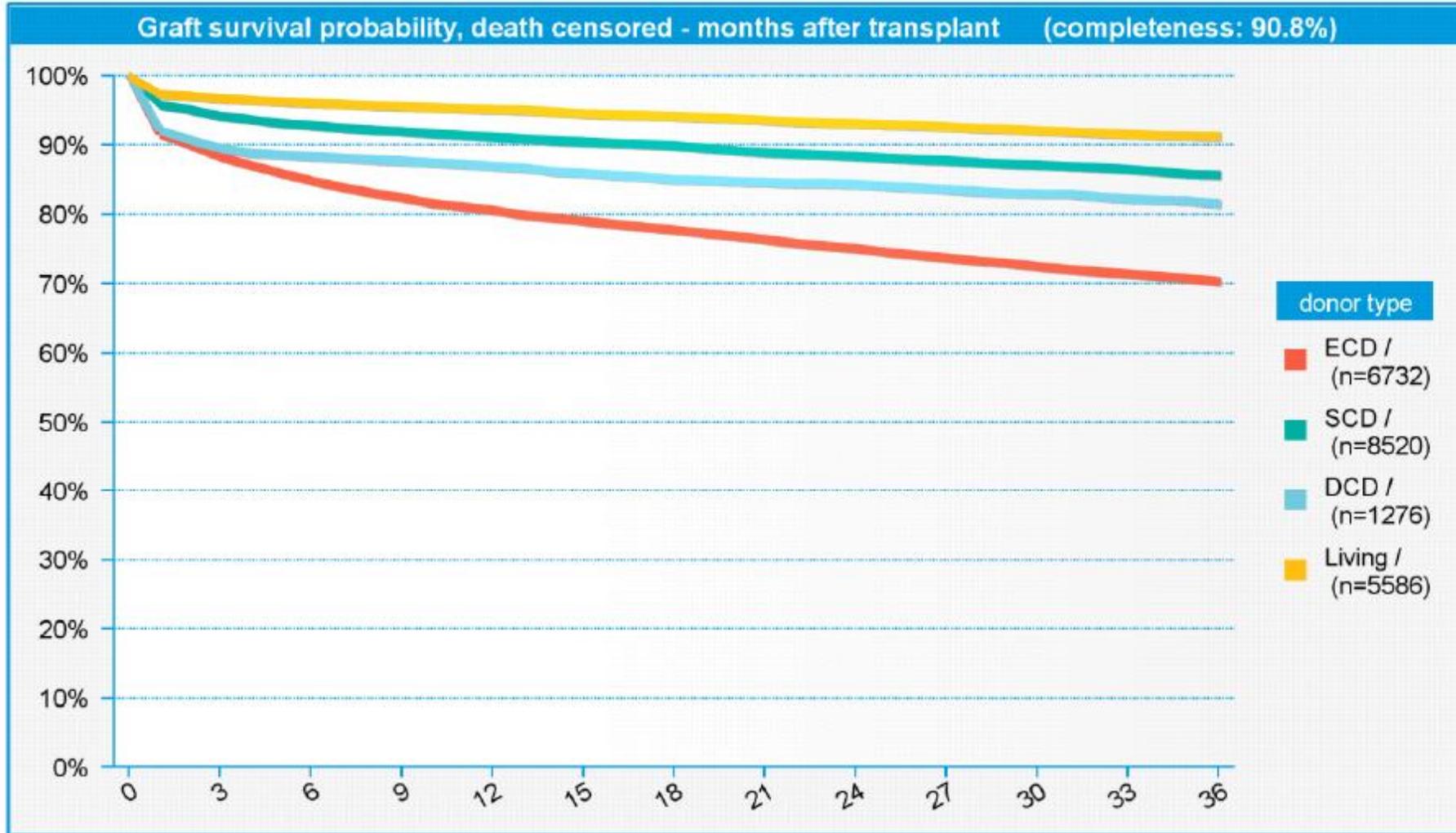
EDC and mortality



No. at Risk

EDC Transplantation	7790	6250	5014	3403	2900	2053
Standard Therapy	109127	90046	73392	55407	41092	29711

Kidney-only transplants (all donors) 2004-2010, in All ET, 3-year survival probability, by donor type



Who can benefit from ECD?

- ✧ Patients older than 40 yr
- ✧ Long median waiting time (> 4 yr)
- ✧ Patients with diabetes or hypertension
- ✧ Patients of low immunological risk
- ✧ Dialysis patients with vascular access problems
- ✧ Dialysis patients whose life expectancy in dialysis is lower than the estimated waiting time for kidney transplantation

Special programs- ET

- ✿ Sensitized patients
- ✿ “Senior program”
- ✿ Urgent list



ET Kidney Allocation System

**Highly immunized
Acceptable Mismatch (AM) - Program**

Zero Mismatch (“full house”)

**Pediatric Donor (< 10 a) to Pediatric Recipient (< 6 a)
when HLA-DR-identical**

Eurotransplant Senior Program (ESP)

**ETKAS
Point Score System (including HU)**

A

B/L

D

HR

NL

SLO

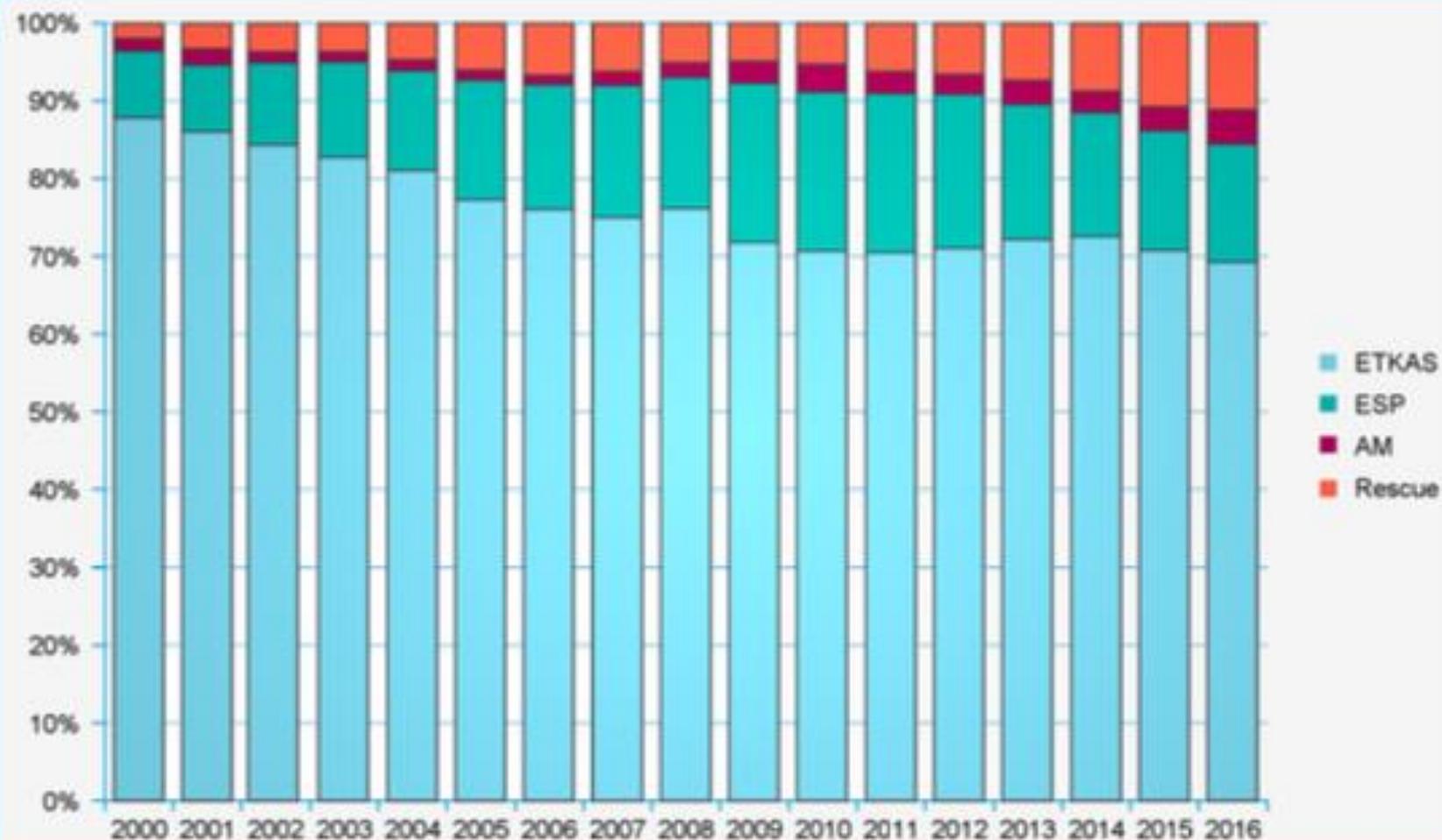
HUN

Eurotransplant Senior Program (ESP)

Practical implementation

- * Priority allocation for kidneys from donors over age 65 years to recipients over age 65 years
-> “old for old” program
- * First transplant
- * No HLA-matching
- * Regional allocation
 - * Short ischemic time

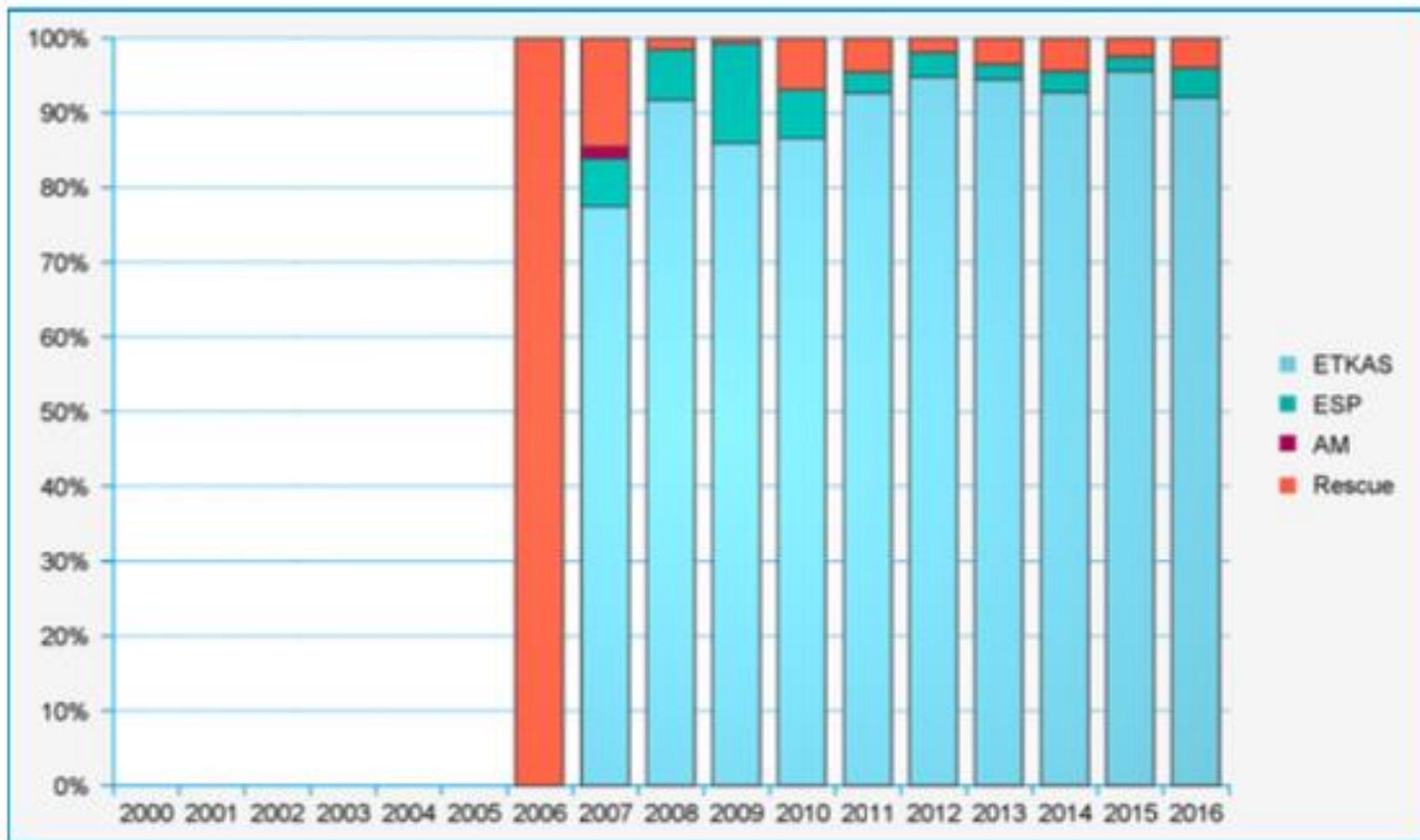
Kidney-only transplants (deceased donor) in All ET, by year, by allocation program %



statistics.eurotransplant.org : 2362P_All ET_kidney : 15.09.2017



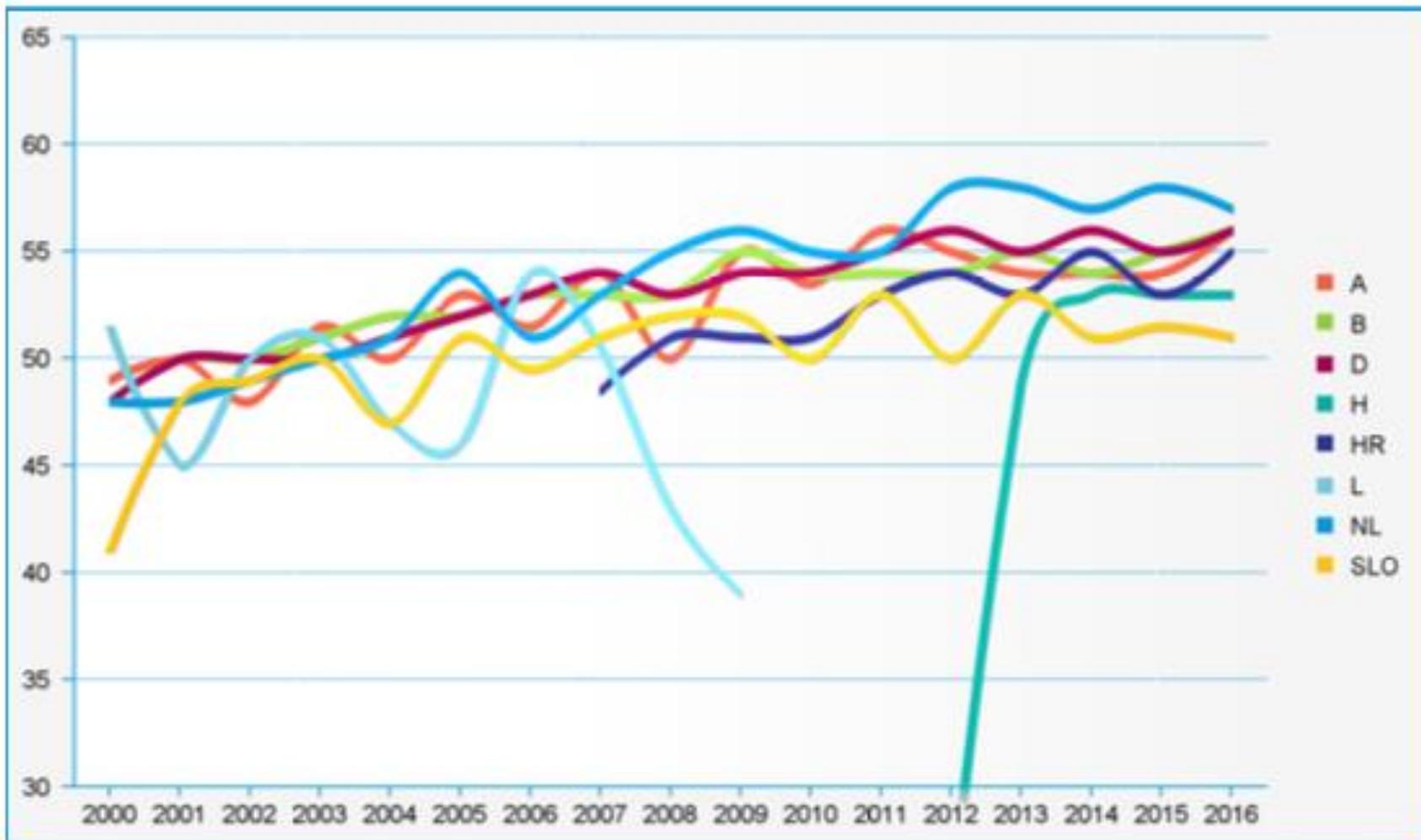
Kidney-only transplants (deceased donor) in Croatia, by year, by allocation program %



statistics.eurotransplant.org : 2362P_Croatia_kidney : 15.09.2017



Kidney transplants (deceased donor), median recipient age, by year, by country



statistics.eurotransplant.org : 2106P_kidney : 15.09.2017



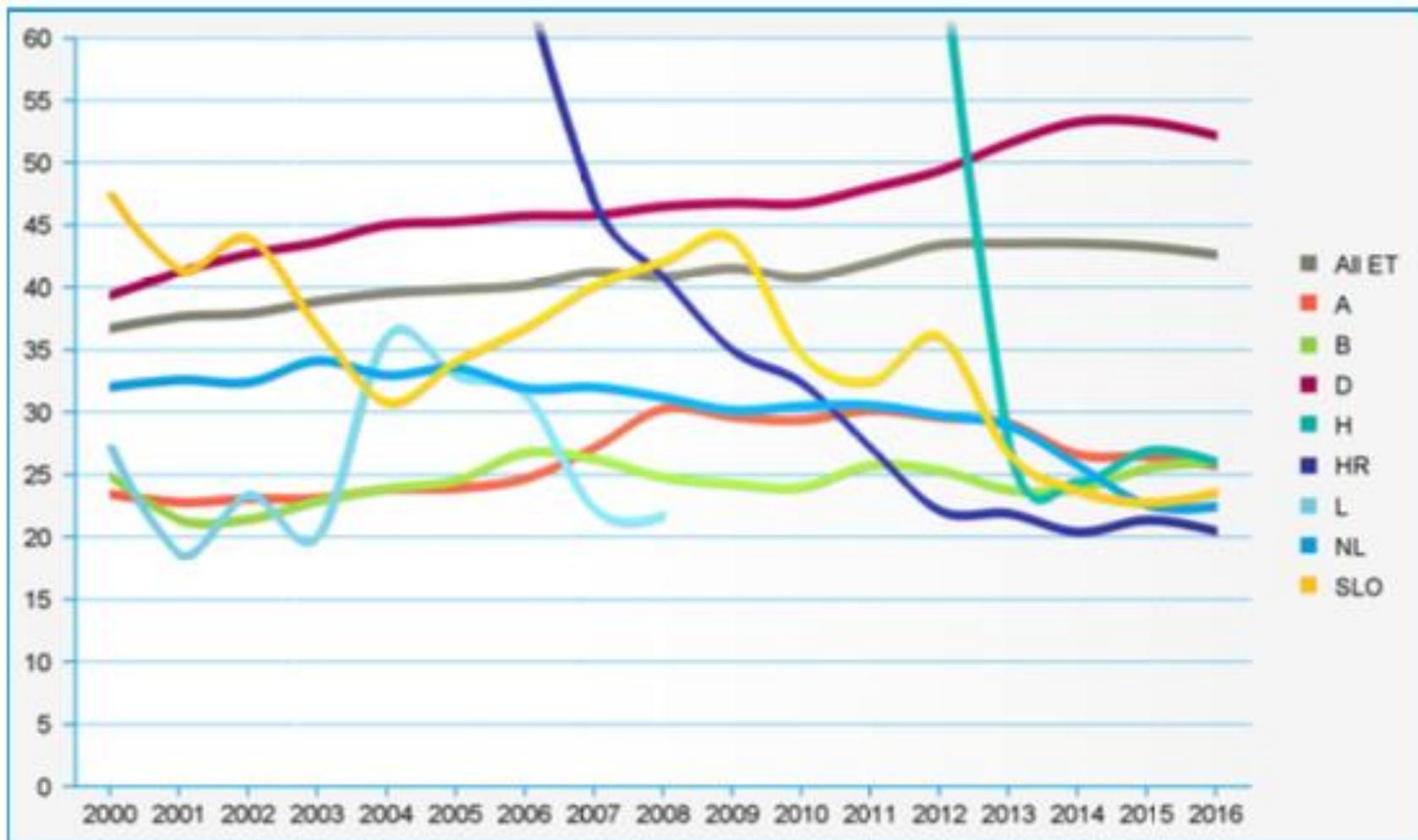
HR - ET

- ✧ Better organisation
- ✧ Better coordination
- ✧ Transplantation of high dialysis vintage patients
- ✧ Lower HLA match
- ✧ More EDC
- ✧ More complications
 - ✧ Surgical
 - ✧ Non-surgical

Use of EDC – benefits and harms

- ✿ Higher number of kidney transplants, reducing of waiting list
- ✿ Lower graft survival
- ✿ Should not influence patient mortality, especially in the “senior programme”

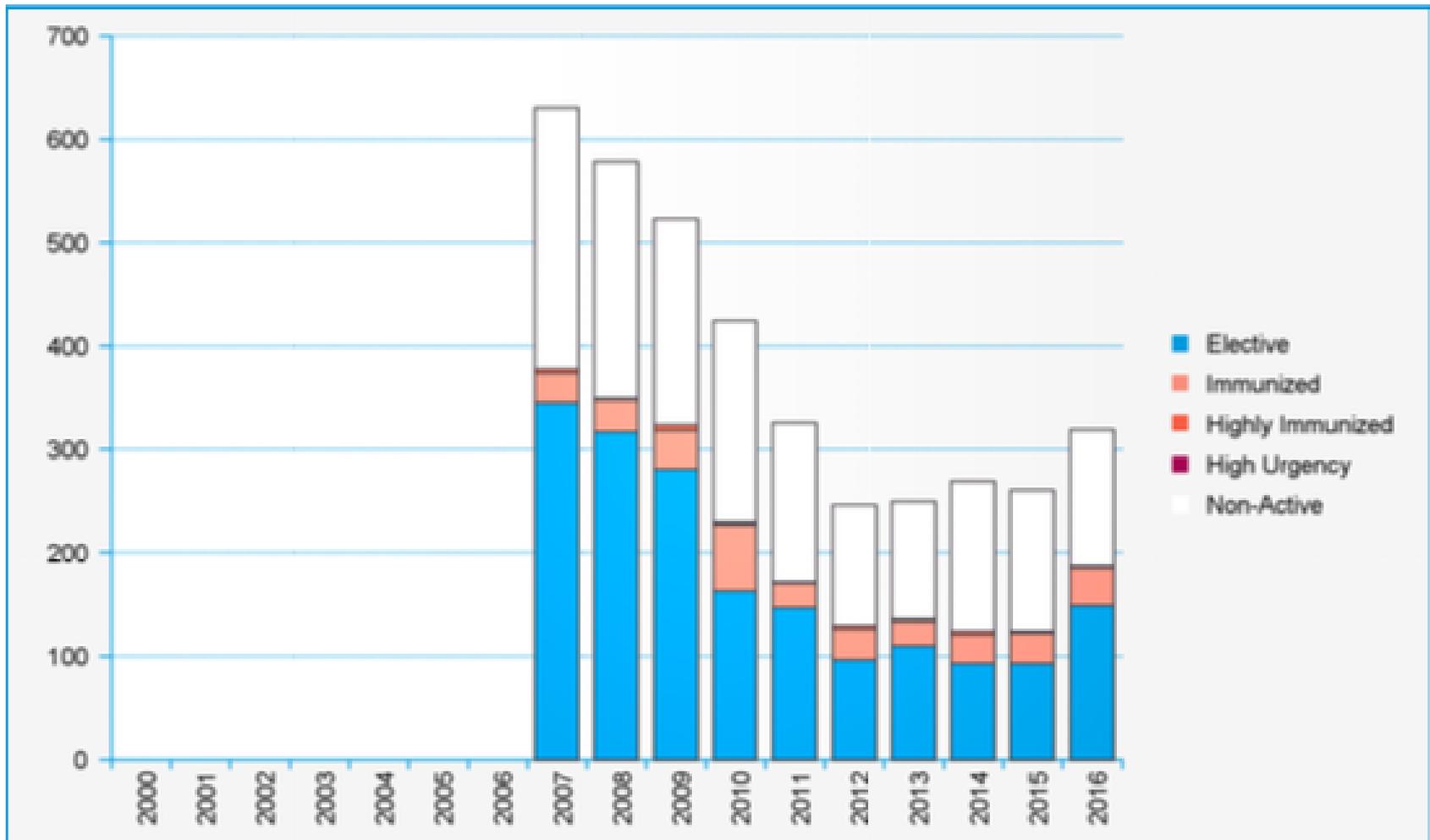
Active kidney waiting list (at year-end), median time waiting, by year, by country



statistics.eurotransplant.org : 3087P_kidney : 15.09.2017 : months since first dialysis, otherwise months on WL



Kidney waiting list (at year-end) in Croatia, by year, by urgency



statistics.eurotransplant.org : 3063P_Croatia_kidney : 15.09.2017 : including recipients also waiting for other organs



Use of EDC – benefits and harms

- ✿ Higher number of kidney transplants, reducing of waiting list
- ✿ Lower graft survival
- ✿ Should not influence patient mortality, especially in the “senior programme”

Selected efficacy and safety results

ESP vs Control (ETKAS, recipients 60-64 yrs)

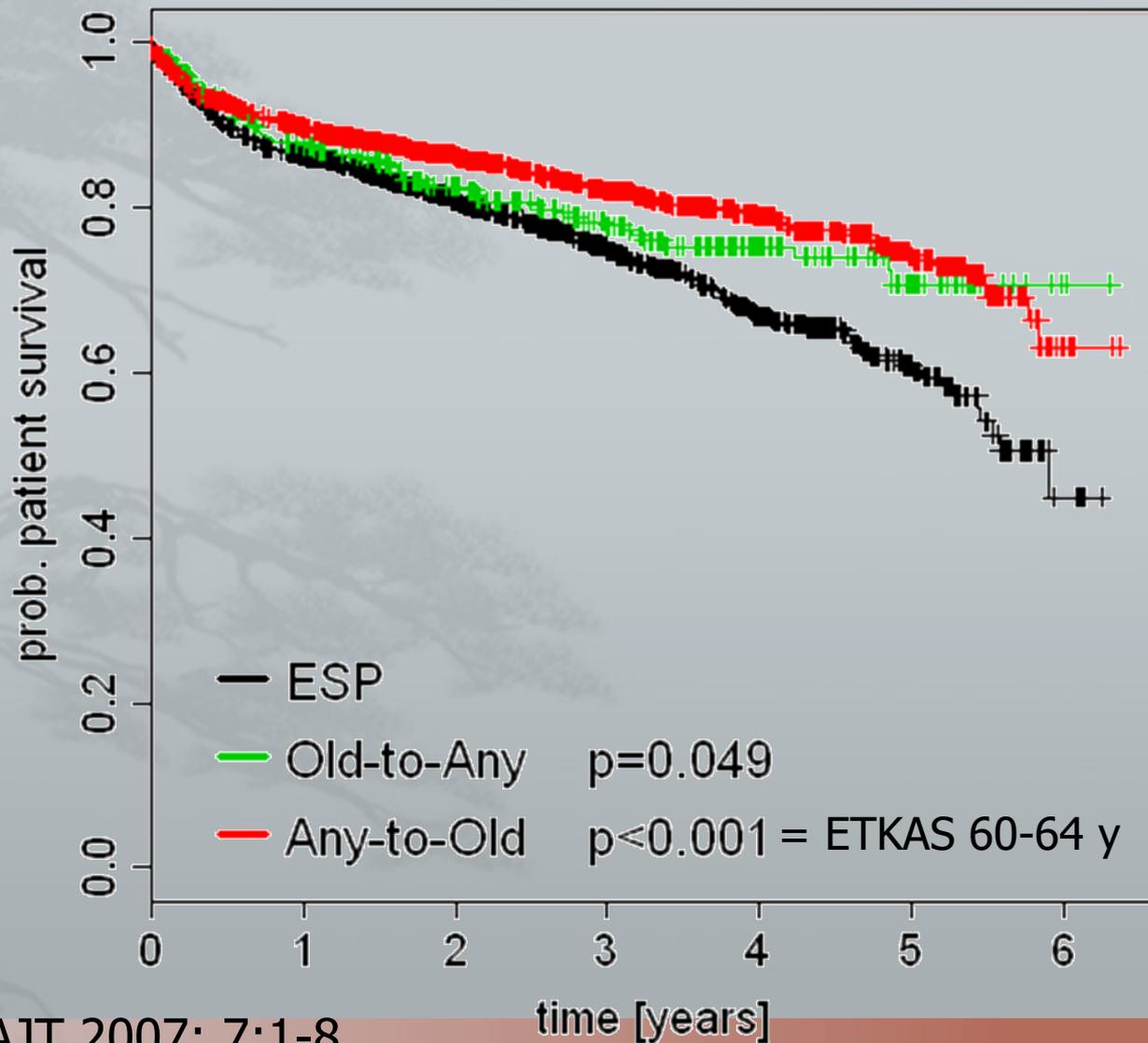
Eurotransplant 2009-2014

	ESP	ETKAS (recip. 60-64 a)	p-value
Median waiting time (yrs)	3.55	4.64	< 0.001
Cold ischemia time (hrs)	11.9 +/- 5.2	17.5 +/- 6.4	< 0.001
CIT < 8 hours (%)	25.7	5.0	< 0.001
CIT > 12 hours (%)	43.1	81.2	< 0.001
Delayed graft function (%)	29.7	30.9	n.s.
Never functioning graft (%)	7.3	5.0	n.s.
SCr at 2 weeks ($\mu\text{mol/L}$)	186 +/- 166	153 +/- 181	< 0.007
SCr at 6 months ($\mu\text{mol/L}$)	159 +/- 84	127 +/- 71	< 0.001
Acute rejection at any time (%)	29.1	20.1	< 0.001

Use of EDC – benefits and harms

- ✿ Higher number of kidney transplants, reducing of waiting list
- ✿ Lower graft survival
- ✿ Should not influence patient mortality, especially in the “senior programme”

Patient survival for ESP patients vs. control Eurotransplant, 1999-2004



EDC – “pro et contra”

- ✿ Annual mortality rate in dialysis patients exceeds 20%
- ✿ Rapidly growing transplant waiting lists
- ✿ Survival advantage of ECD kidney transplant recipients over dialysis patients remaining on transplant waiting list
- ✿ 70% increased risk for graft failure vs SCD kidneys
- ✿ 17% primary graft non-function vs SCD kidneys
- ✿ Increased treatment cost and resource use
- ✿ Higher perioperative mortality, DGF, acute rejections and long-term graft survival

Immunosuppression?

- ❁ ...recipients of ECD kidneys generally have improved survival compared with wait-listed dialysis patients
- ❁ ...benefits of transplantation using kidneys from ECDs are dependent on patient characteristics and the waiting time on dialysis.
- ❁ Because of the increased risk of poor graft function, calcineurin inhibitor (CNI)-induced nephrotoxicity, increased incidence of infections, cardiovascular risk, and malignancies, elderly recipients of an ECD kidney transplant are a special population that requires a tailored immunosuppressive regimen.
- ❁ CNI-free regimens are not universally accepted due to occasionally high rejection rates.
- ❁ However, reduced CNI exposure regimens based on mTOR inhibitors have shown acceptable outcomes in appropriately selected ECD transplant recipients (tacrolimus+MMF vs sirolimus MMF – doubled AR).
- ❁ Best results obtained with anti-IL-2 receptors, MMF, steroids, and moderate exposure to tacrolimus might constitute an advisable strategy.

Conclusions – maximising benefits from ECD

- ✿ Modifying allocation rules for ECD kidneys in an effort to match the appropriate kidney to the appropriate recipient
- ✿ Preimplantation renal biopsy for ECD kidney recipients
- ✿ Simultaneous dual ECD kidney transplantation
- ✿ Restricting the use of ECD kidneys to patients of low immunological risk
- ✿ Applying individualized immunosuppressive regimens

Conclusions – individualised immunosuppression regimens for ECD

- ✿ Reduce overall immunosuppression burden, especially in elderly recipients of ECD kidney transplants
- ✿ Reduced CNI exposure regimens (target CNI blood levels 25%-50% lower)
- ✿ Delayed CNI introduction regimens
- ✿ Reduced CNI exposure and mTOR-inhibitors-based regimens



Opatija, Croatia, October 11-14, 2018



DiaTransplant 2018

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