CNI – Wie niedrig geht noch?

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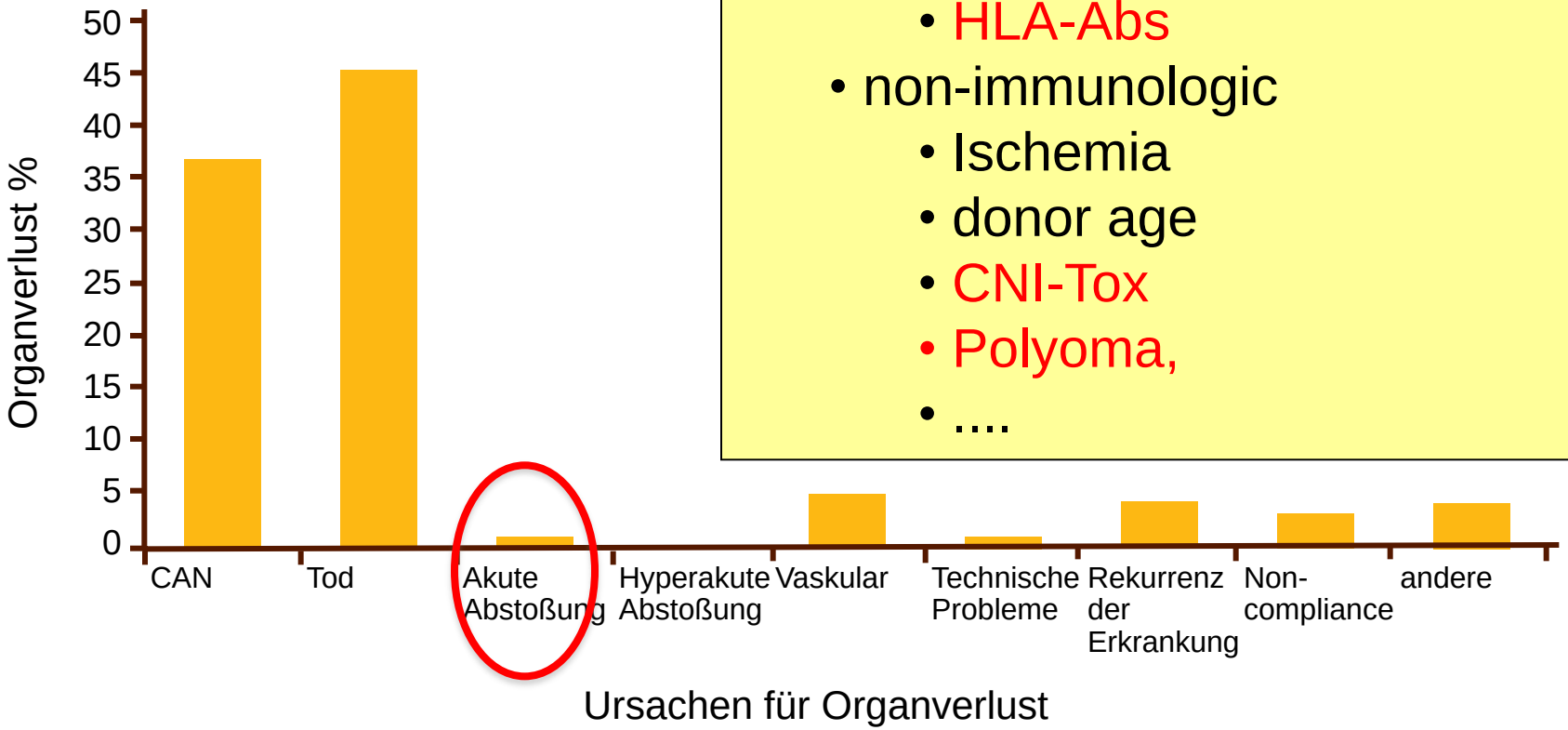
Warum verlieren wir die Transplantate?

Hauptgründe sind Tod und CAN, aber nicht akute Rejektion!!

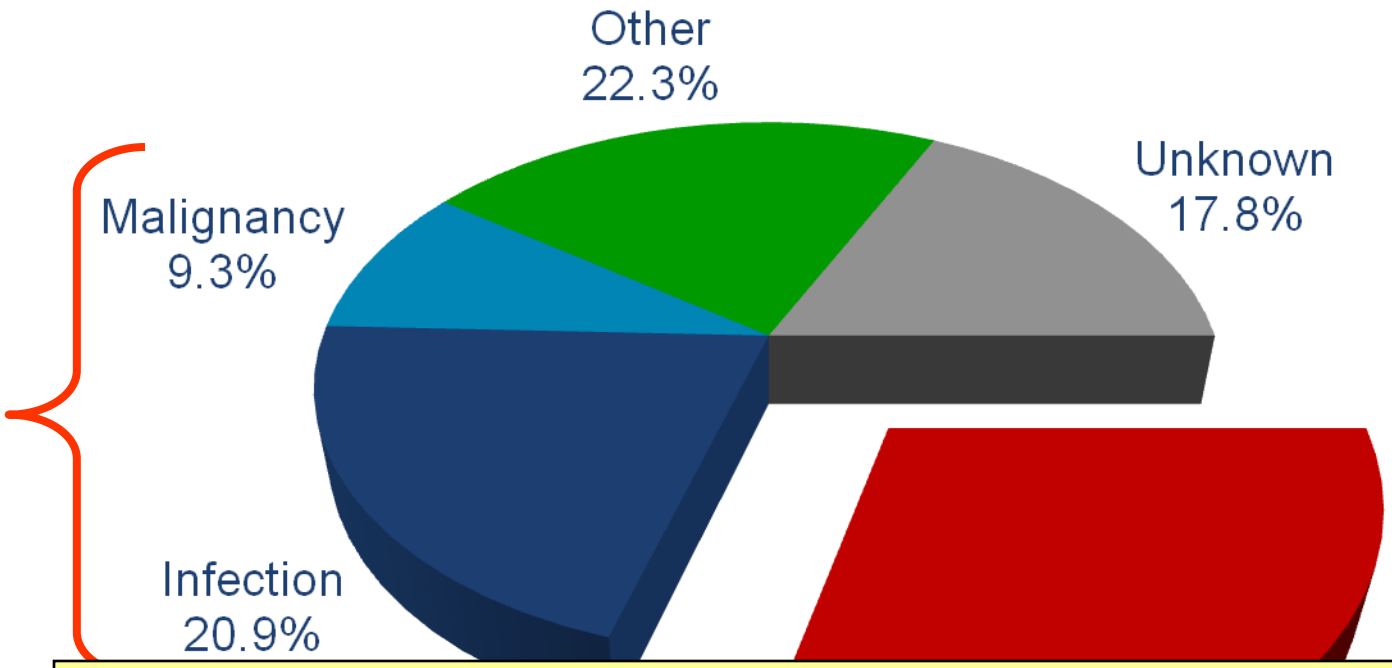
CAN = IFTA
- Immunologic & non-adherence
  - HLA-Abs
- non-immunologic
  - Ischemia
  - donor age
  - CNI-Tox
  - Polyoma,
  - ....



1. ANZDATA Registry Report 2004. Eds. Macdonald S, Excell L. Australia and New Zealand Dialysis and Transplantation Registry, Adelaide, Australia 2. Pascual M et al. New Eng J Med 2002; 346: 580–90 3. Sijpkens Y et al. Kidney Int 1999; 56: 1920–7. Die Abbildung zeigt die Ursachen für Organverlust in Australien in 2003. CAN = chronische allograft Nephropathie

Woran sterben die Transplantierten?

An Überimmunsuppression und kardiovasculär!!

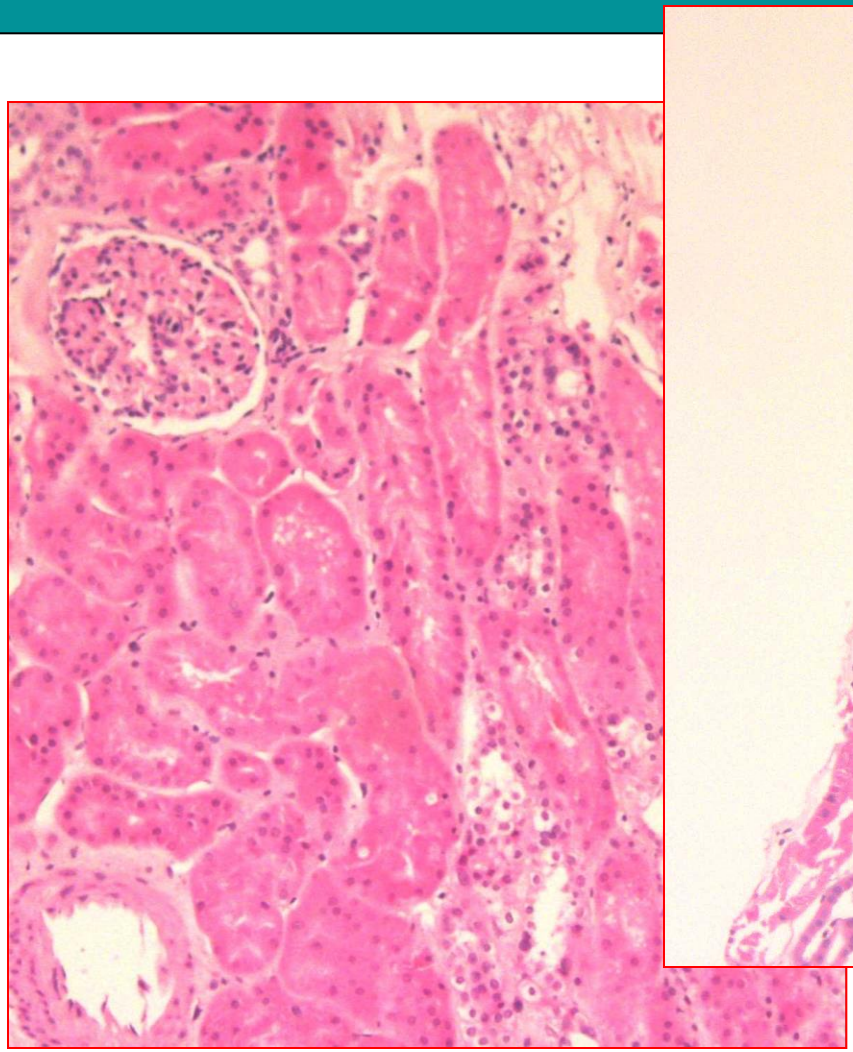


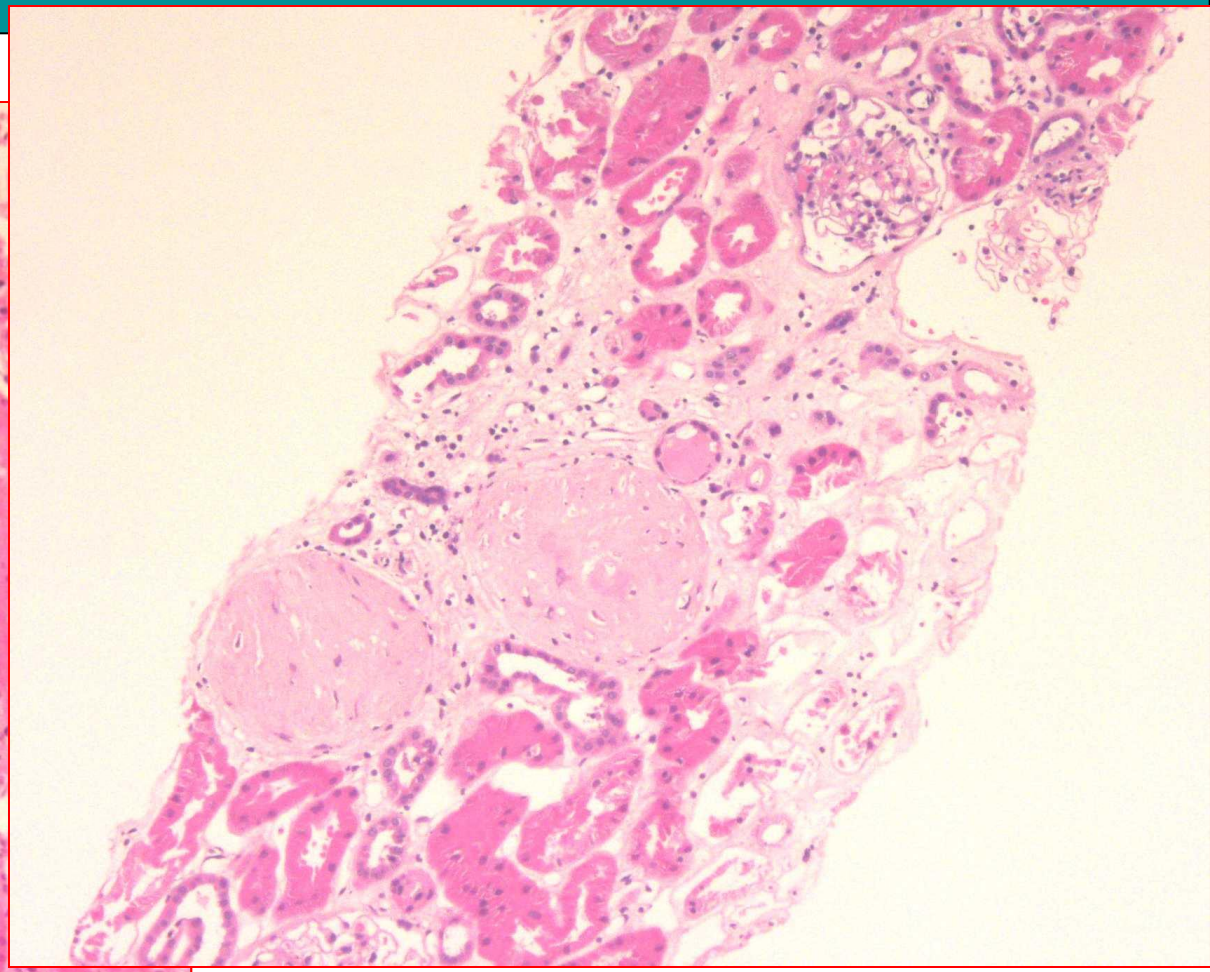
CNIs:

- direct effect on overimmunosuppression
- increased cardiovascular toxicity

Pie chart shows causes of death with a functioning graft between 2005 to 2009 in the USA. CV=cardiovascular.
United States Renal Data System (USRDS). Chapter 7: Transplantation. In: Atlas ESRD (Volume 2).
Available online at: http://www.usrds.org/atlas.aspx (accessed July 2012).

Chronic Nephron Loss Due to CNI Toxicity





Nankivell BJ, et al. *N Engl J Med* 2003; 349:2326-33.

Problems of CNIs

- good short-term results, but no real improvement of long-term-outcome
- insufficient rejection prophylaxis for humoral rejection
- overimmunosuppression
  - infections (Polyoma)
  - tumors
- poor side effect profile
  - nephrotoxicity
  - cardiovaskular side effects
  - cosmetic, GI…

Clear need for CNI sparing protocols

CNI-sparing protocols

I. Complete CNI avoidance

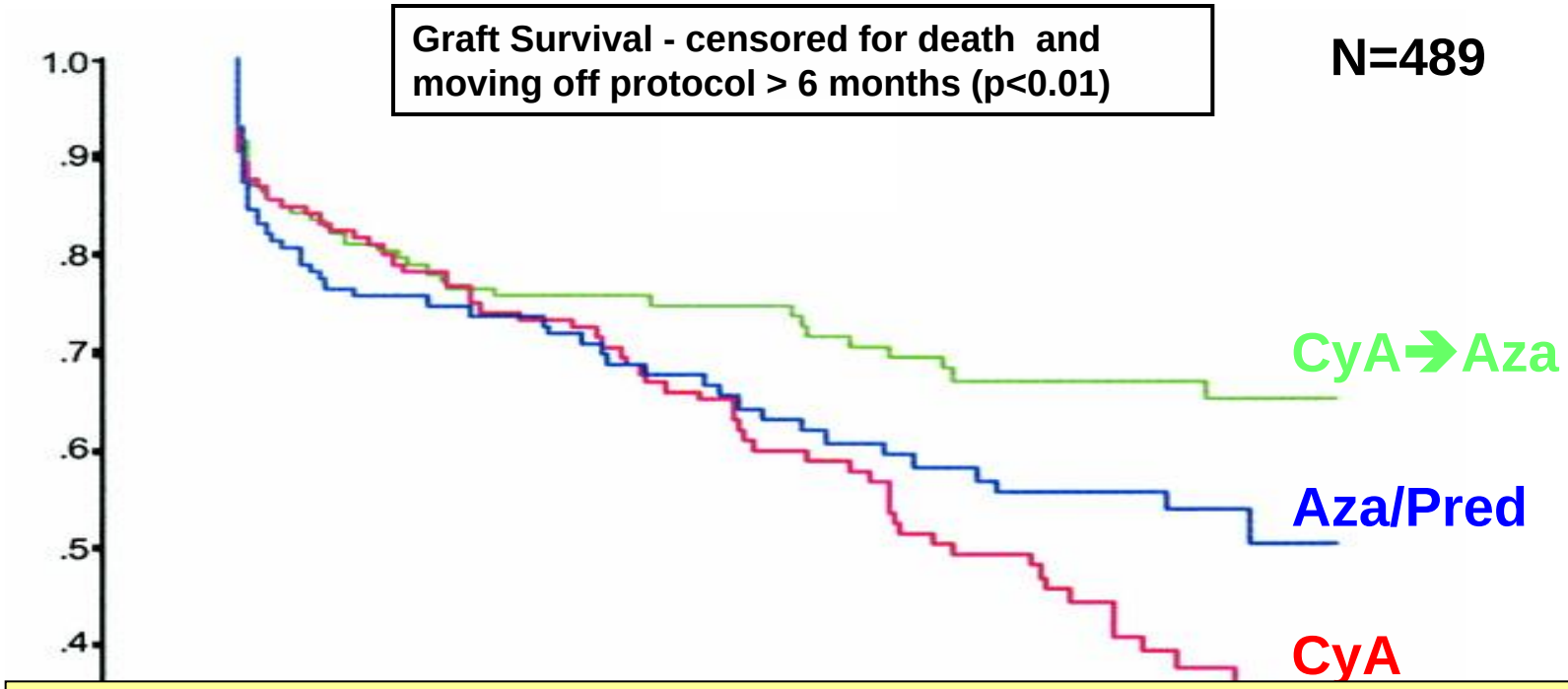
Or

II. CNI withdrawal

Or

III. CNI minimization

Prospective Australian Cyclosporine Withdrawal trial - 15 Year Follow Up



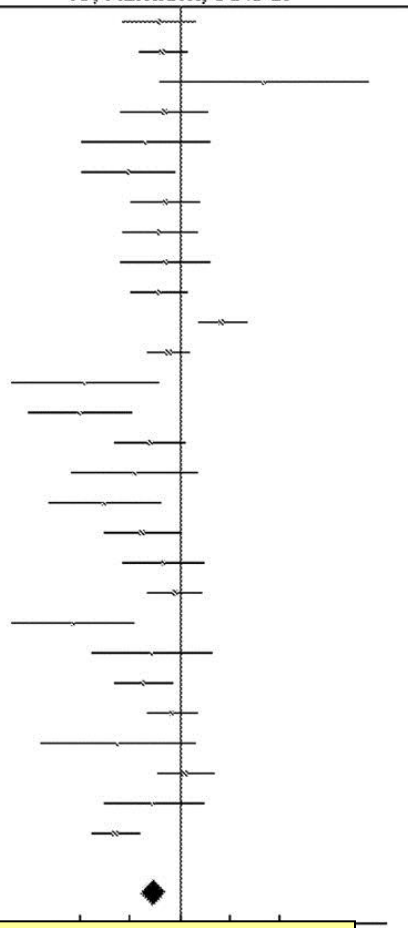
Continuous CNI: worse renal function worse long-term outcome

CyA n=165 short term CsA followed by Aza
AP n=158 Aza + Pred
Cy n=166 long term CsA

Gallagher et al. Transplantation 2004; 78; 1653.

III. CNI minimization strategies graft function: CNI sparing vs standard

Study or Subgroup	CNI Mean	CNI SD	CNI Total	CNI sparing Mean	CNI sparing SD	CNI sparing Total	Weight	Mean Difference IV, Random, 95% CI
Andres 2008	43.1	12	28	47.2	17	32	3.9%	-4.10 [-11.48, 3.28]
Andres 2009	41.6	16.8	94	44.9	16.2	88	4.9%	-3.30 [-8.09, 1.49]
Asberg 2006	69	29	9	52	20	19	1.1%	17.00 [-3.97, 37.97]
Buchler 2007	56.9	21	51	59.9	26.5	63	3.5%	-3.00 [-11.72, 5.72]
Budde 2010	53	24.5	42	60	39.4	53	2.3%	-7.00 [-19.94, 5.94]
Busque 2009	73.3	13.7	17	83.6	14.8	19	3.3%	-10.30 [-19.61, -0.99]
Chan 2008	72.5	15.2	44	75.3	16.6	39	4.1%	-2.80 [-9.68, 4.08]
De Sevaux 2001	65	28	124	69	31	121	3.9%	-4.00 [-11.40, 3.40]
Durrbach 2008	41.9	15.2	19	44.7	16.6	31	3.4%	-2.80 [-11.79, 6.19]
Durrbach 2010	45.2	21.1	130	49.5	25.4	134	4.6%	-4.30 [-9.93, 1.33]
Ekberg-2 2007	65.4	27	204	56.7	26.9	321	4.9%	8.70 [3.97, 13.43]
Ekberg-3 2007	57.1	25.1	289	59.4	25.1	274	5.2%	-2.30 [-6.45, 1.85]
European Multicentre 1982	54	48.7	60	73	27.2	44	1.9%	-19.00 [-33.71, -4.29]
Flechner 2002	61.1	14.6	30	81.1	23.9	27	2.9%	-20.00 [-30.42, -9.58]
Glotz 2010	62	15.9	38	68	20.5	63	4.0%	-6.00 [-13.15, 1.15]
Grimbert 2002	39	18	12	48	20	27	2.4%	-9.00 [-21.67, 3.67]
Hamdy 2005	79.6	25.5	55	94.9	28.9	39	2.7%	-15.30 [-26.60, -4.00]
Hernandez 2007	52	18	61	59.5	24	61	3.9%	-7.50 [-15.03, 0.03]
Kamar 2006	52.8	23.7	71	56	24.5	64	3.7%	-3.20 [-11.35, 4.95]
Larson 2006	56	14	51	57	17	71	4.6%	-1.00 [-6.51, 4.51]
Lo 2004	50.5	20.8	18	72	20	27	2.5%	-21.50 [-33.72, -9.28]
Martinez-Mier 2006	67.5	18.6	18	73.2	19.1	19	2.5%	-5.70 [-17.85, 6.45]
Nashan 2004	53.5	12.1	39	60.9	11.3	24	4.5%	-7.40 [-13.30, -1.50]
Noel 2009	49.3	17.9	93	50.9	17.2	96	4.8%	-1.60 [-6.61, 3.41]
Ponticelli 1988	54.7	19.3	18	67.2	35.7	30	1.8%	-12.50 [-28.08, 3.08]
Salvadori 2009	62.5	20.7	111	61.3	22	113	4.6%	1.20 [-4.39, 6.79]
Vincenti 2005	68	28.1	54	73.2	22.5	47	3.1%	-5.20 [-15.08, 4.68]
Vincenti 2010	50.4	17.7	181	63.4	27.7	179	4.9%	-13.00 [-17.81, -8.19]
Total (95% CI)			1961			2125	100.0%	-5.31 [-7.81, -2.82]



➔ Better graft function for minimization

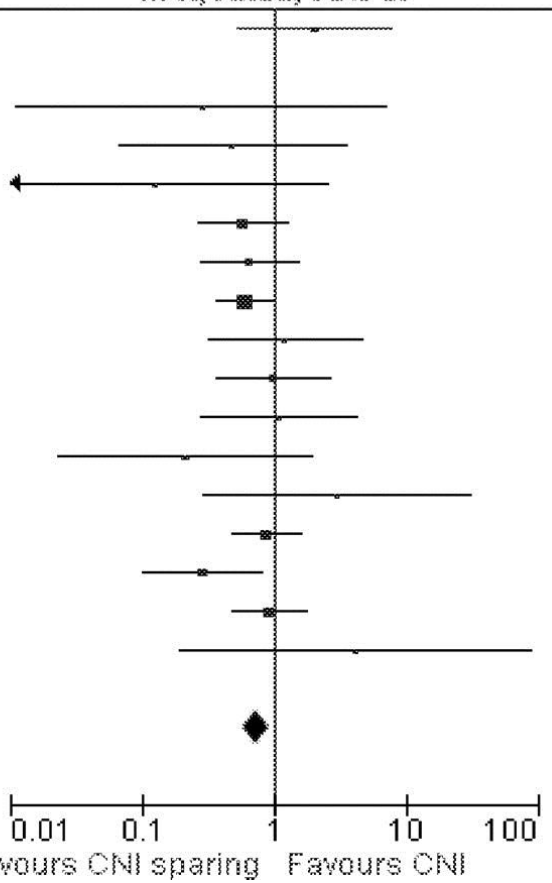
Adnan Sharif et al. JASN 2011;22:2107-2118

III. CNI minimization strategies
Forest plot of overall graft survival

Study or Subgroup	CNI sparing Events	CNI sparing Total	CNI Events	CNI Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Andres 2008	7	36	4	38	1.9%	2.05 [0.55, 7.72]
Budde 2010	0	66	0	76		Not estimable
Chan 2008	0	49	1	43	1.0%	0.29 [0.01, 7.21]
Chan 2009 (A)	2	82	2	41	1.6%	0.49 [0.07, 3.59]
Ciancio 2005	0	30	3	30	2.1%	0.13 [0.01, 2.61]
De Sevaux 2001	11	152	19	161	10.4%	0.58 [0.27, 1.27]
Ekberg 2007	10	183	14	173	8.3%	0.66 [0.28, 1.52]
Ekberg-3 2007	30	399	46	390	26.2%	0.61 [0.38, 0.99]
Gaston 2009	5	243	4	237	2.4%	1.22 [0.32, 4.61]
Hernandez 2007	9	80	9	80	4.9%	1.00 [0.38, 2.67]
Kandaswamy 2005	5	82	4	72	2.4%	1.10 [0.28, 4.28]
Nashan 2004	1	58	4	53	2.5%	0.21 [0.02, 1.99]
Russ 2003	3	33	1	31	0.6%	3.00 [0.30, 30.50]
Salvadori 2006	24	224	26	219	14.3%	0.89 [0.49, 1.61]
Salvadori 2009	5	142	16	143	9.4%	0.29 [0.10, 0.81]
Tedesco-Silva 2006	20	231	21	224	11.8%	0.92 [0.48, 1.74]
Vathsala 2005	3	20	0	10	0.3%	4.20 [0.20, 89.61]
Total (95% CI)		**2110**		**2021**	**100.0%**	**0.73 [0.58, 0.92]**
Total events	135		174			

Heterogeneity: $Chi^2 = 14.20$, $df = 15$ ($P = 0.51$); $I^2 = 0\%$

Test for overall effect: $Z = 2.62$ ($P = 0.009$)



➔ Better graft survival for minimization

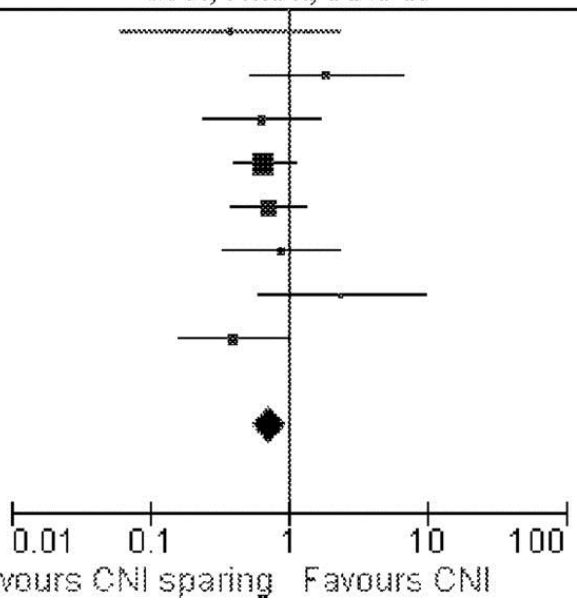
Adnan Sharif et al. JASN 2011;22:2107-2118

Less new onset diabetes after transplantation for CNI sparing

Study or Subgroup	CNI sparing Events	CNI sparing Total	CNI Events	CNI Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Asberg 2006	2	23	4	20	3.6%	0.38 [0.06, 2.35]
Chan 2008	8	49	4	43	3.3%	1.90 [0.53, 6.83]
Durrbach 2010	7	175	11	184	9.4%	0.66 [0.25, 1.73]
Ekberg-2 2007	30	399	43	401	36.4%	0.68 [0.42, 1.10]
Ekberg-3 2007	19	399	25	390	22.1%	0.73 [0.40, 1.35]
Hernandez 2007	9	80	10	80	8.1%	0.89 [0.34, 2.32]
Salvadori 2009	7	142	3	143	2.6%	2.42 [0.61, 9.55]
Vincenti 2010	7	211	16	204	14.4%	0.40 [0.16, 1.00]
Total (95% CI)		**1478**		**1465**	**100.0%**	**0.74 [0.55, 0.99]**
Total events	89		116			

Heterogeneity: Chi² = 7.51, df = 7 (P = 0.38); I² = 7%

Test for overall effect: Z = 2.06 (P = 0.04)



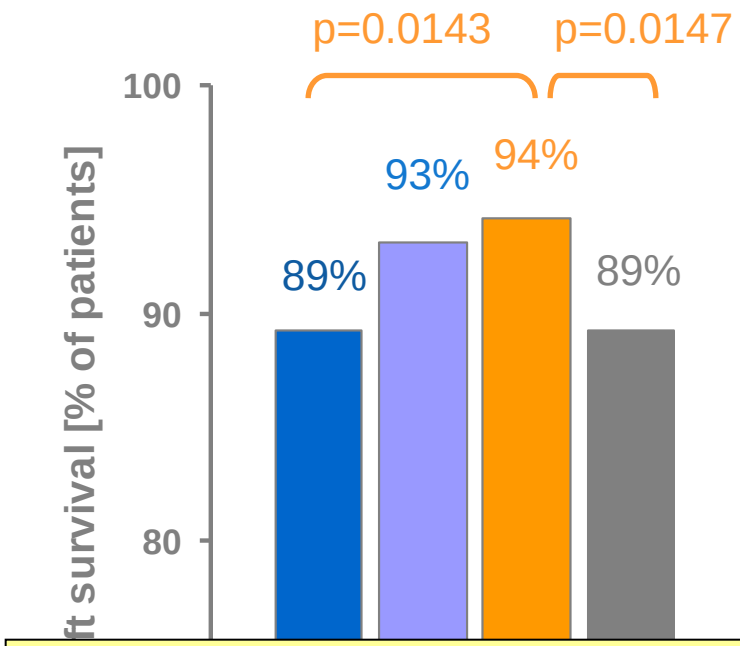
CNI minimization:
similar rejection risk but better renal function, less side effects and better graft survival

Adnan Sharif et al. JASN 2011;22:2107-2118

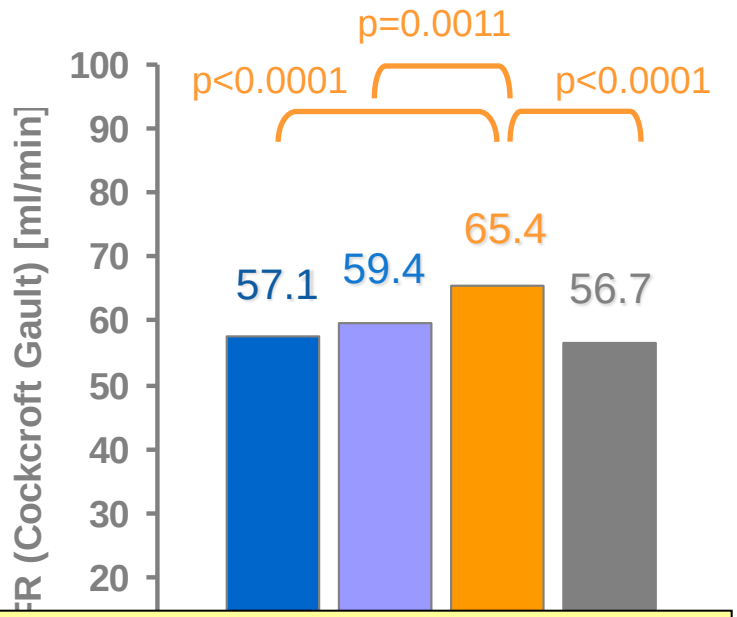
CNI minimization: SYMPHONY study

low Tac + MMF better rejection prophylaxis and better GFR

Better graft survival



Better GFR



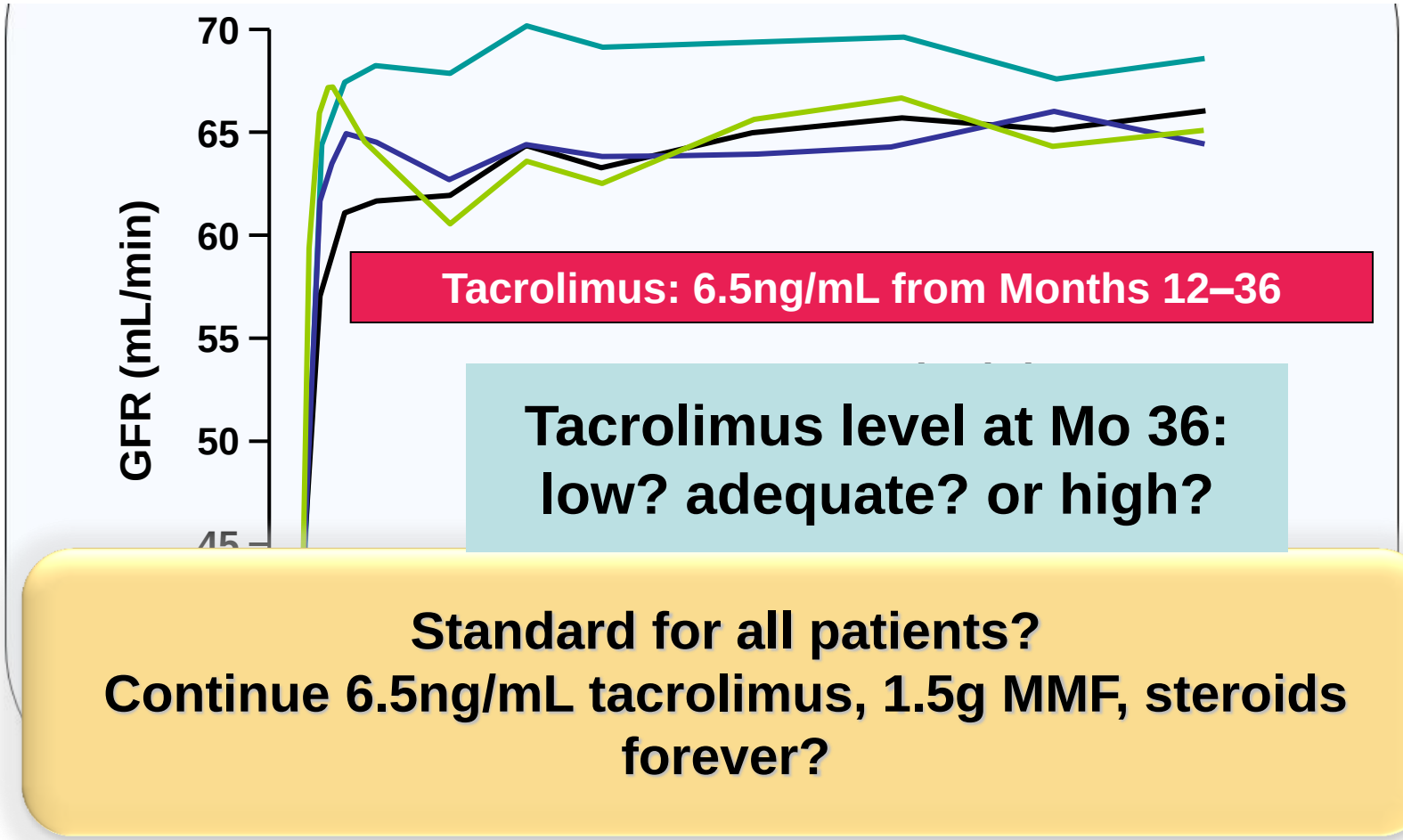
But:

what is „low“?

how to improve long-term results?

ITT population

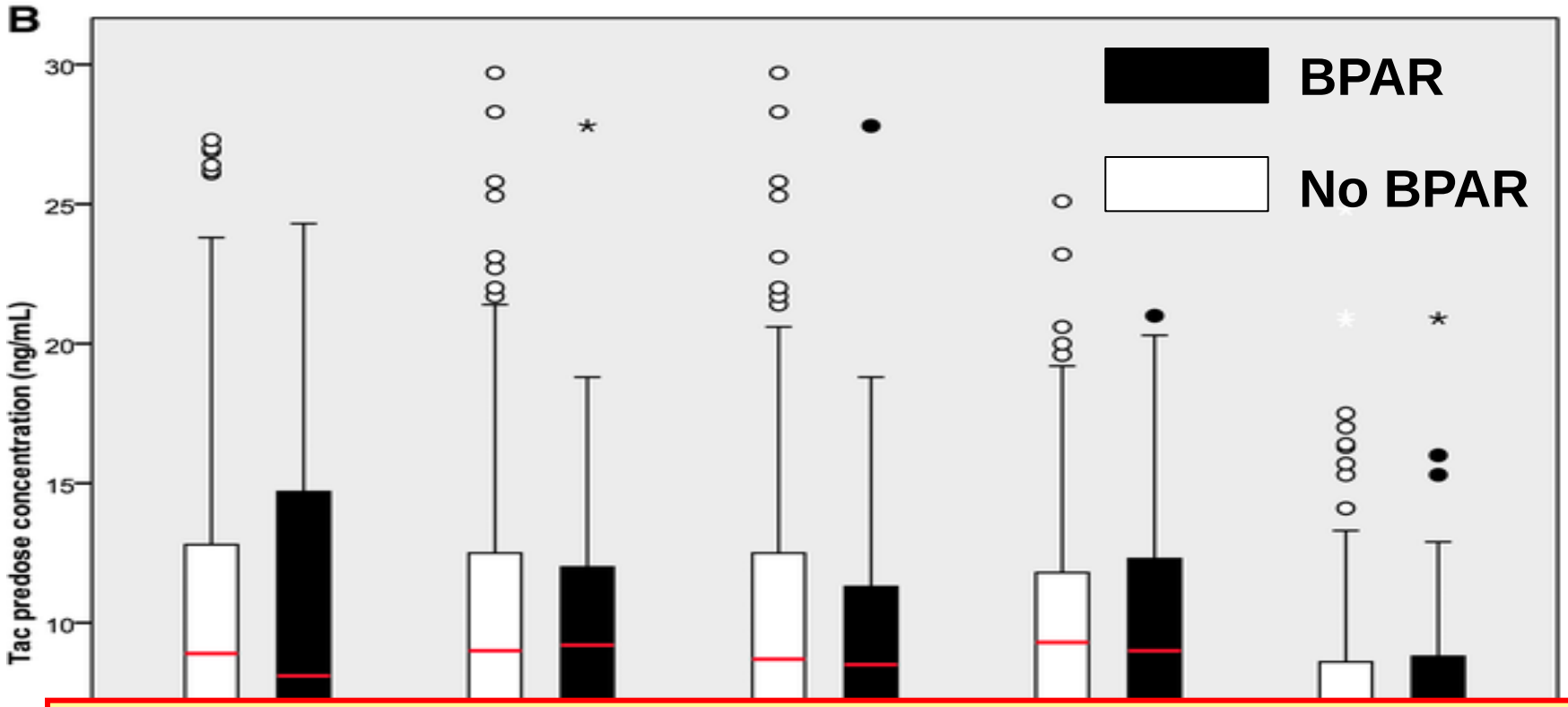
SYMPHONY trial: renal function at 3 years



Standard for all patients?
Continue 6.5ng/mL tacrolimus, 1.5g MMF, steroids forever?

Ekberg H, et al. Am J Transplant 2009:9:1876–1885

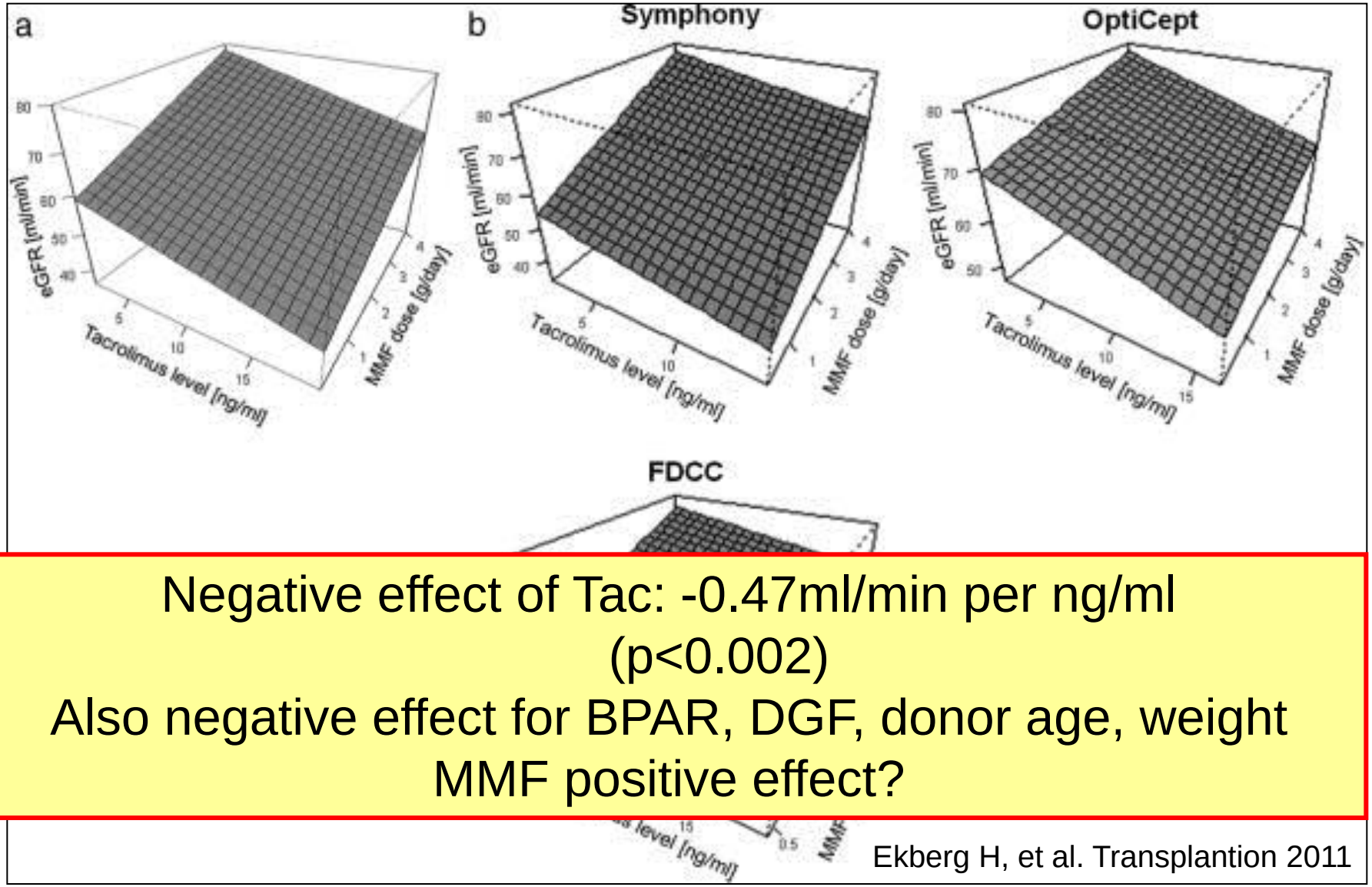
Tac C0 Does Not Predict the Risk of Acute Rejection After Renal Tx: A Pooled Analysis From Three RCTs (n=1304)



91/136 rejections occured in 1st Mo
No difference in patients with Tac above/below 5 or 10ng/ml
No difference in high risk patients
Multivariate only DGF and induction correlated with BPAR

Bouamar R, et al. AJT 2013

eGFR at 1 year as a function of Tac exposure and MMF dose in previous 6 months in 998 patients



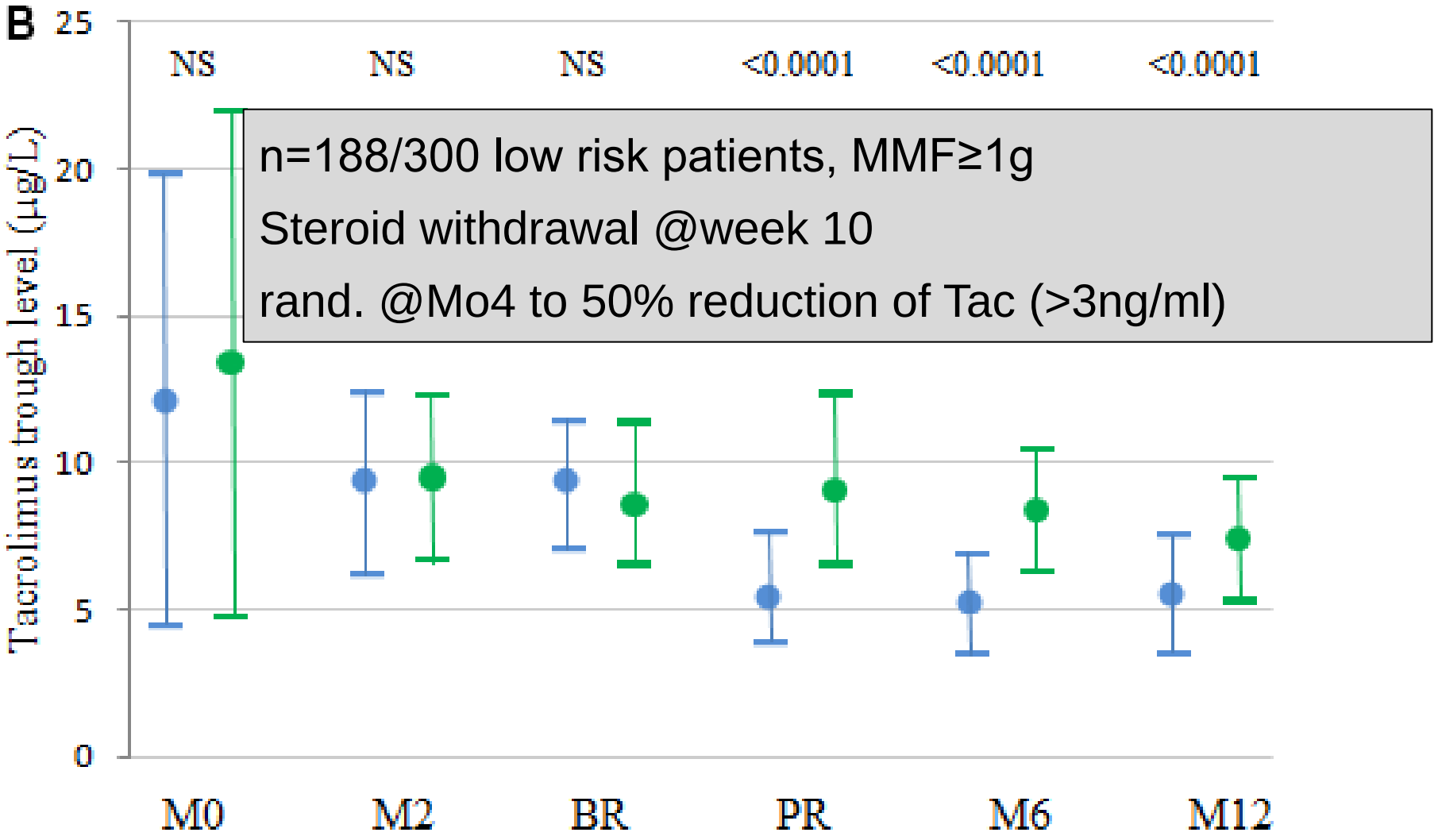
Negative effect of Tac: -0.47ml/min per ng/ml ($p<0.002$)

Also negative effect for BPAR, DGF, donor age, weight

MMF positive effect?

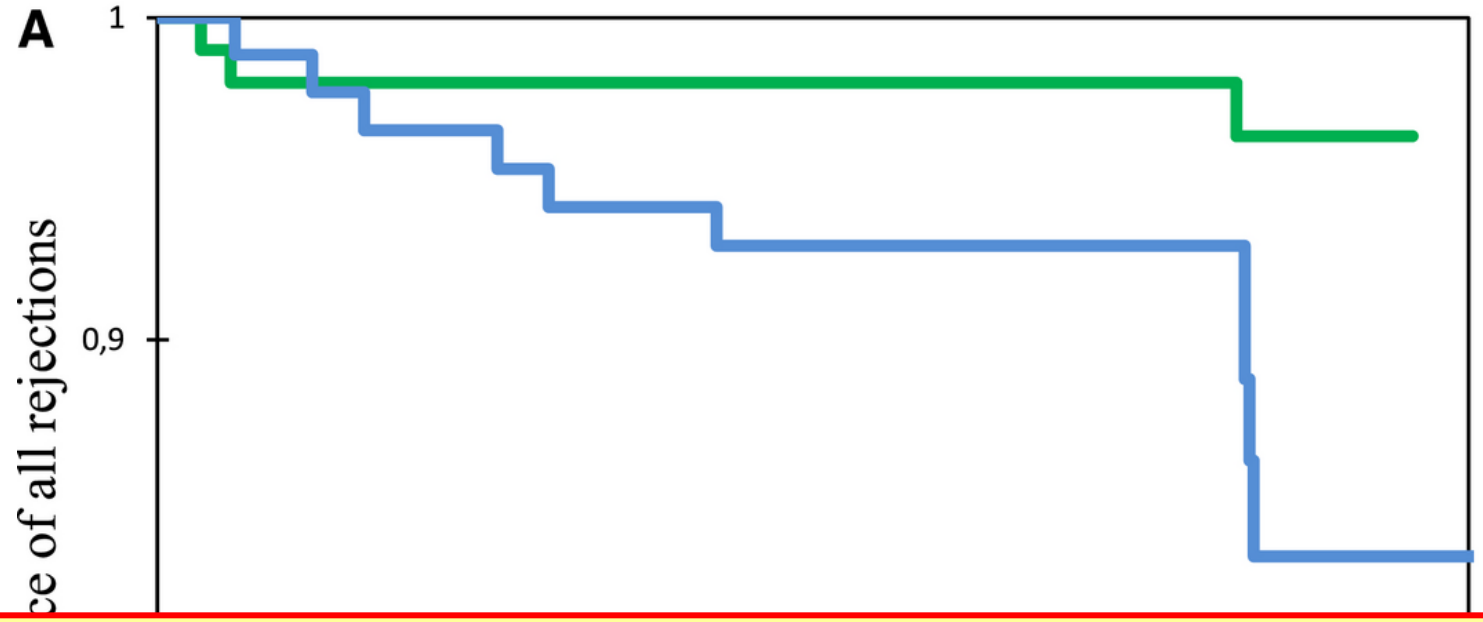
Ekberg H, et al. Transplantion 2011

Tac Reduction @Mo4 in Low-Risk Kidney Transplant Recipients



Gatault P et al. AJT 2017

50% Reduction of Tac Dose @Mo4 Increases Risk of Rejection and DSA in steroid free pts.

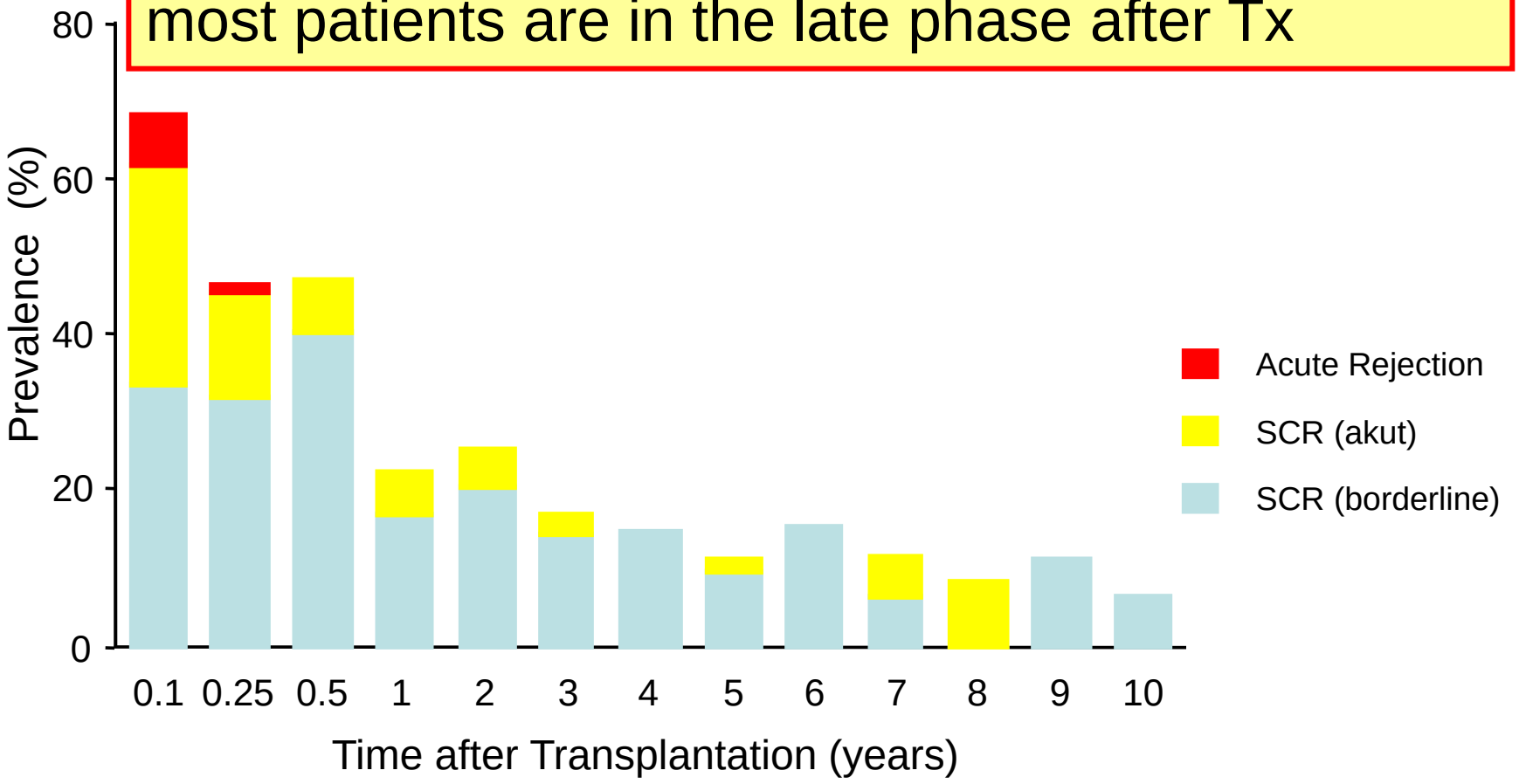


1. Steroid withdrawal @week 10 in Tac/MMF patients is safe
2. Tac reduction @Mo 4 in steroid free patients on 1,2gMMF resulted in more rejections + more DSA (n=6 vs 0), without a benefit in GFR

Gatault P et al. AJT 2017

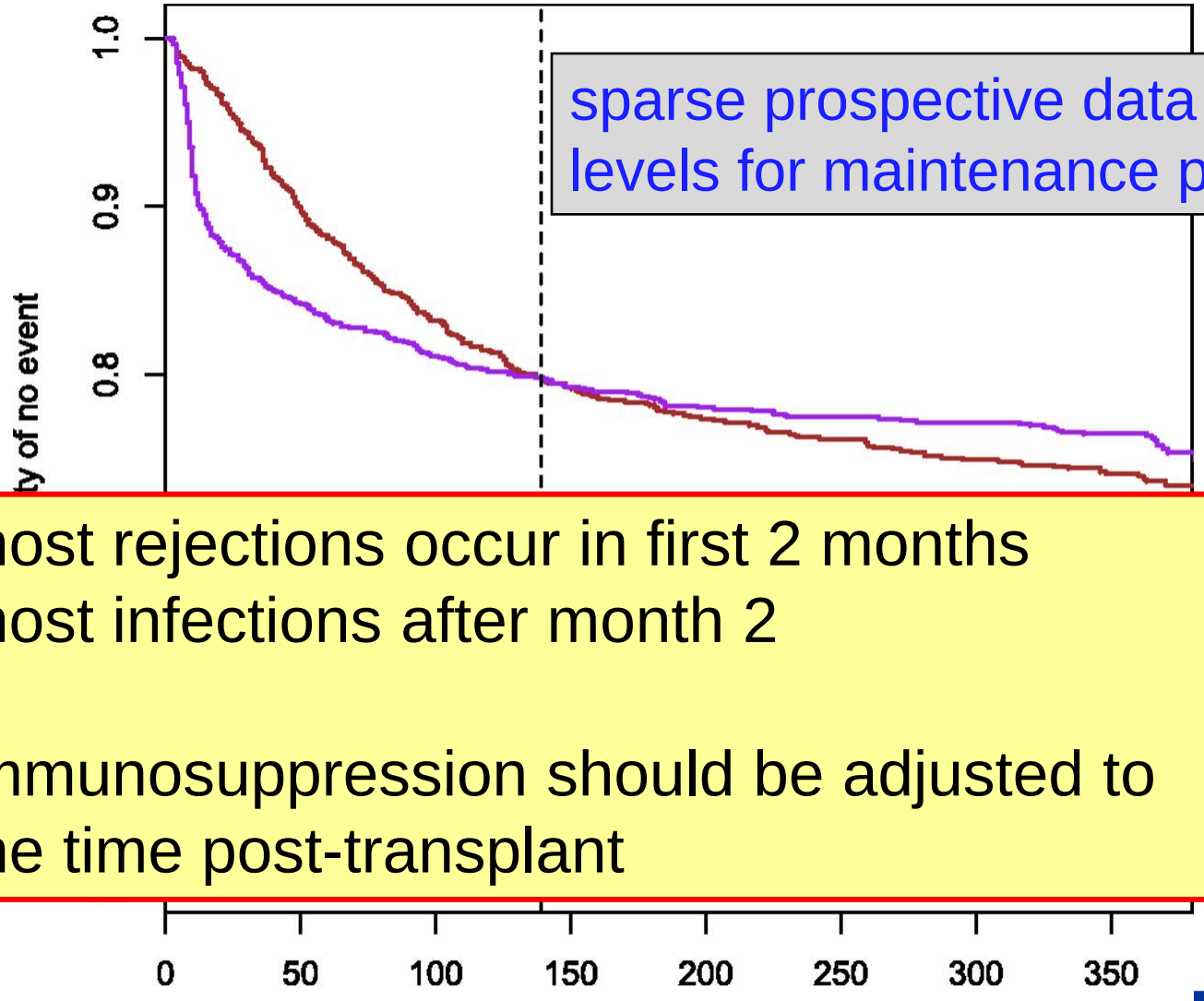
Time dependent risk of rejection

most rejections occur early
most patients are in the late phase after Tx



Nankivell BJ et al. *N Engl J Med* 2003; 349:2326-33.

More severe infections than rejections in the first year after transplantation



sparse prospective data on Tac levels for maintenance pts.

most rejections occur in first 2 months
most infections after month 2

immunosuppression should be adjusted to the time post-transplant

Pietro E. Cippà et al. CJASN 2015;10:2213-2220

CJASN

KDIGO-Richtlinien für die Nachsorge

- long-term maintenance immunosuppression
  - lowest doses, continue CNIs and steroids
- monitoring immunosuppression
  - check blood levels

Eher Allgemeinplätze, wenig konkret.
Was sind denn jetzt die Zielspiegel??

The OPTIMA study: optimizing tacrolimus maintenance levels

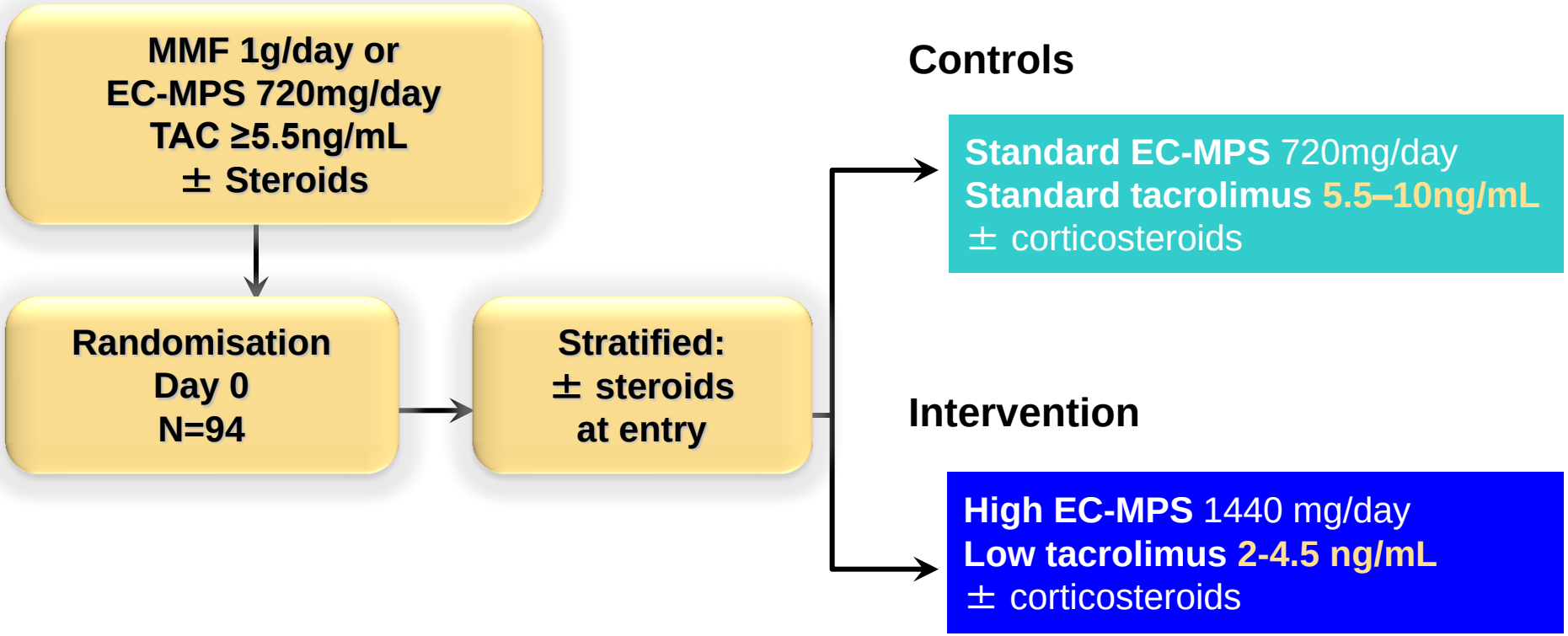
- **Prospective, 12-month, multicentre, randomised, open-label study**
- **323 CsA-treated patients (>12mo post Tx) in the US**
  - N=111 continue CsA (50-250: 128ng/mL)
  - N=112 Standard Tac (6-9: 6.9ng/mL)
  - N=100 Low Tac (3-6: 4.9ng/mL)
- **at 12 Mo no difference in patient, graft survival, BPAR**
- **better Cystatin C, creatinine and eGFR in low Tac group**
- **Better lipids for Tac, safety and NODAT identical**

• Conversion to low Tac (4.9ng/ml) in maintenance patients is safe and results in better renal function
• Tac maintenance levels of ≈5ng/ml could be sufficient

Bolin P et al. Transplantion 2008:86:88-95

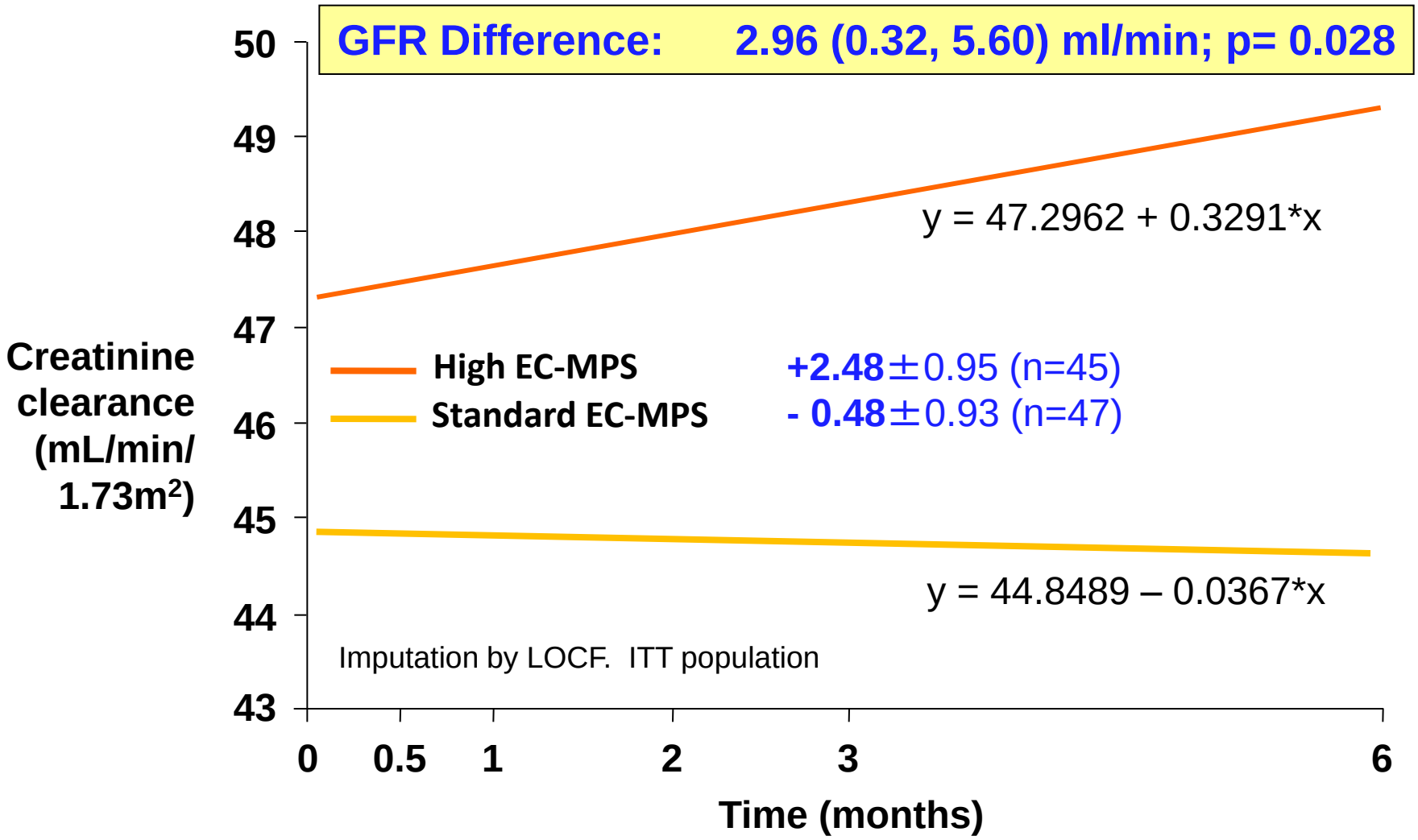
Olympe: study design

- Stable patients (eGFR 30–60mL/min) >12 months post-transplant
- Primary endpoint: Change in eGFR (eMDRD) from baseline to Month 6



Kamar N et al. Clin Nephrol 2012;77:126–136

Change in creatinine clearance (aMDRD) from baseline to Month 6



Kamar N et al Clin Nephrol 2012

Efficacy failures at Month 6 : None

	Standard EC-MPS (N=47)	High EC-MPS (N=45)
Efficacy failure (BPAR, graft loss, death or lost to follow-up)	0 (0.0%)	0 (0.0%)
BPAR	0 (0.0%)	0 (0.0%)
Graft loss	0 (0.0%)	0 (0.0%)
Death	0 (0.0%)	0 (0.0%)
Lost to follow-up	0 (0.0%)	0 (0.0%)

Tac level of 4-5ng/ml in combination with full dose MPA might be sufficient in maintenance patients

Kamar N et al Clin Nephrol 2012

Zusammenfassung

- **CNI Toxizität ist eine wichtige Ursache der chron. Transplantatdysfunktion und CNIs erhöhen das Risiko für Infektionen, Tumore und kardiovaskuläre Erignisse im Langzeitverlauf**
- **CNI Reduktion ist mit einem besseren Transplantat-überleben, einer besseren Nierenfunktion und weniger Nebenwirkungen (z.B. Diabetes, Tumore) assoziiert.**
- **Der Tacrolimus Talspiegel ist bei Verwendung von Induktion und MPA nicht mit der Rejektionsrate, jedoch mit der Nierenfunktion assoziiert.**

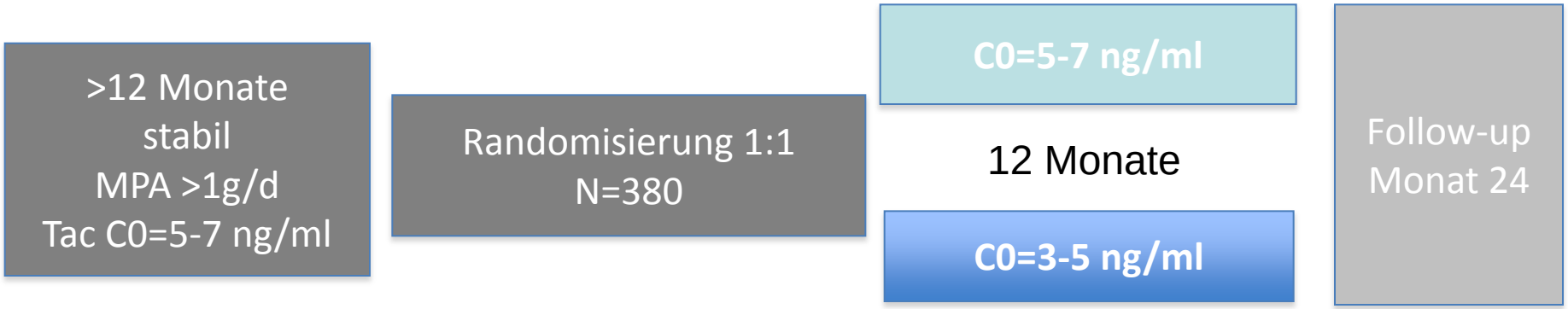
Zusammenfassung

- **Ein 50%-ige Tacrolimus Reduktion nach 4 Monaten geht bei steroidfreien Patienten mit vermehrten Rejektionen und DSA einher.**
- **Es gibt keine guten Daten zum Tacrolimus-Spiegel im Langzeitverlauf, eine Reduktion unter 5ng/ml könnte sicher sein.**

Wir benötigen mehr Daten!!!

Evidenz schaffen durch Protect Studie

Frage: reicht ein Tac Spiegel von 3-5ng/ml in Kombination mit MPA im Langzeitverlauf (>1 Jahr nach Tx)??



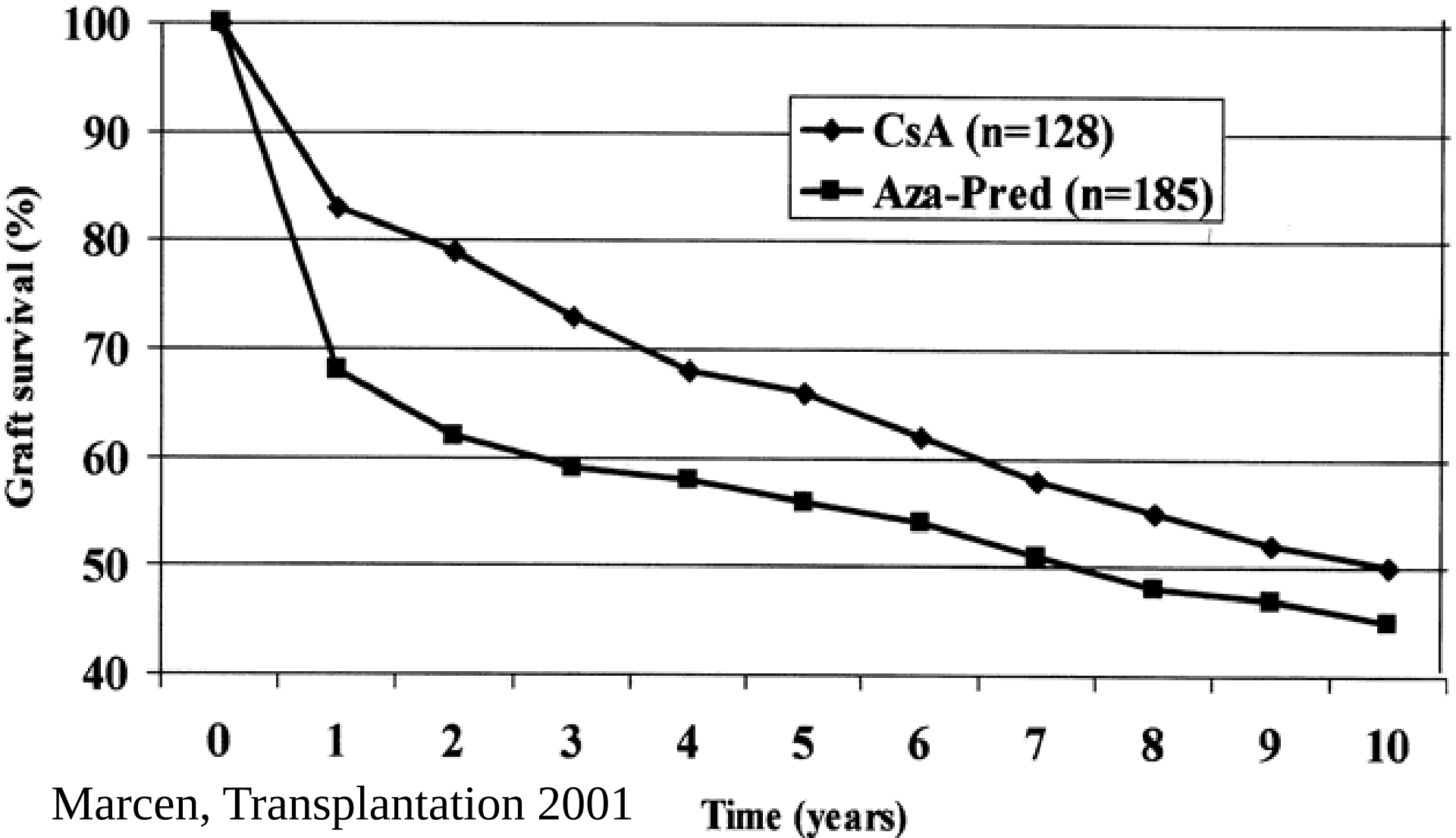
Primärer (kombinierter) Endpunkt:
Tod, Tx-Verlust, BPAR (Banff grade ≥IA) nach 12 Monaten

Hoffnung, daß durch eine vorsichtige weitere CNI-Reduktion im Langzeitverlauf die Ergebnisse verbessert werden

Vielen Dank für Ihre Aufmerksamkeit!!

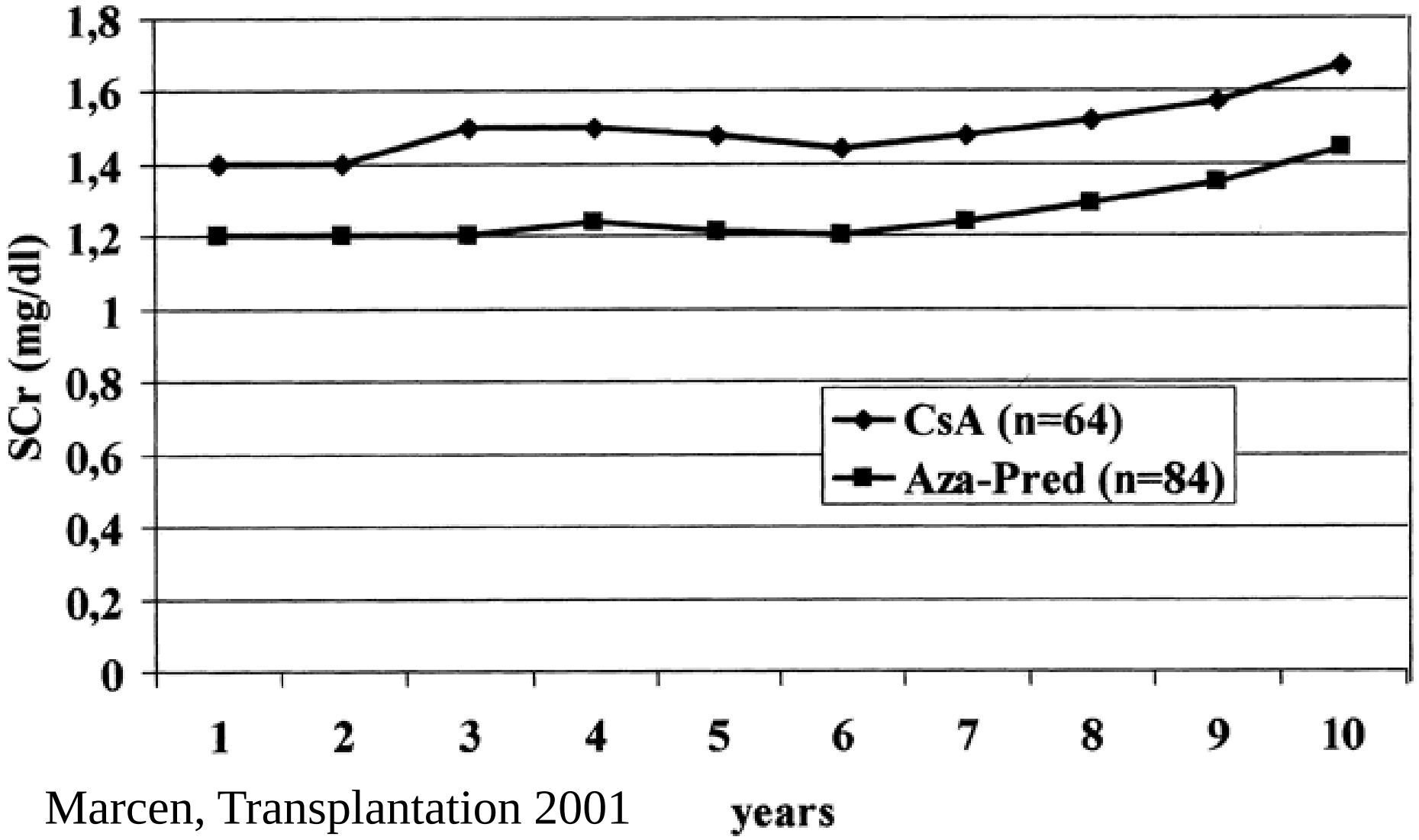
CHARITÉ

Better graft survival after NTx with Cyclosporine



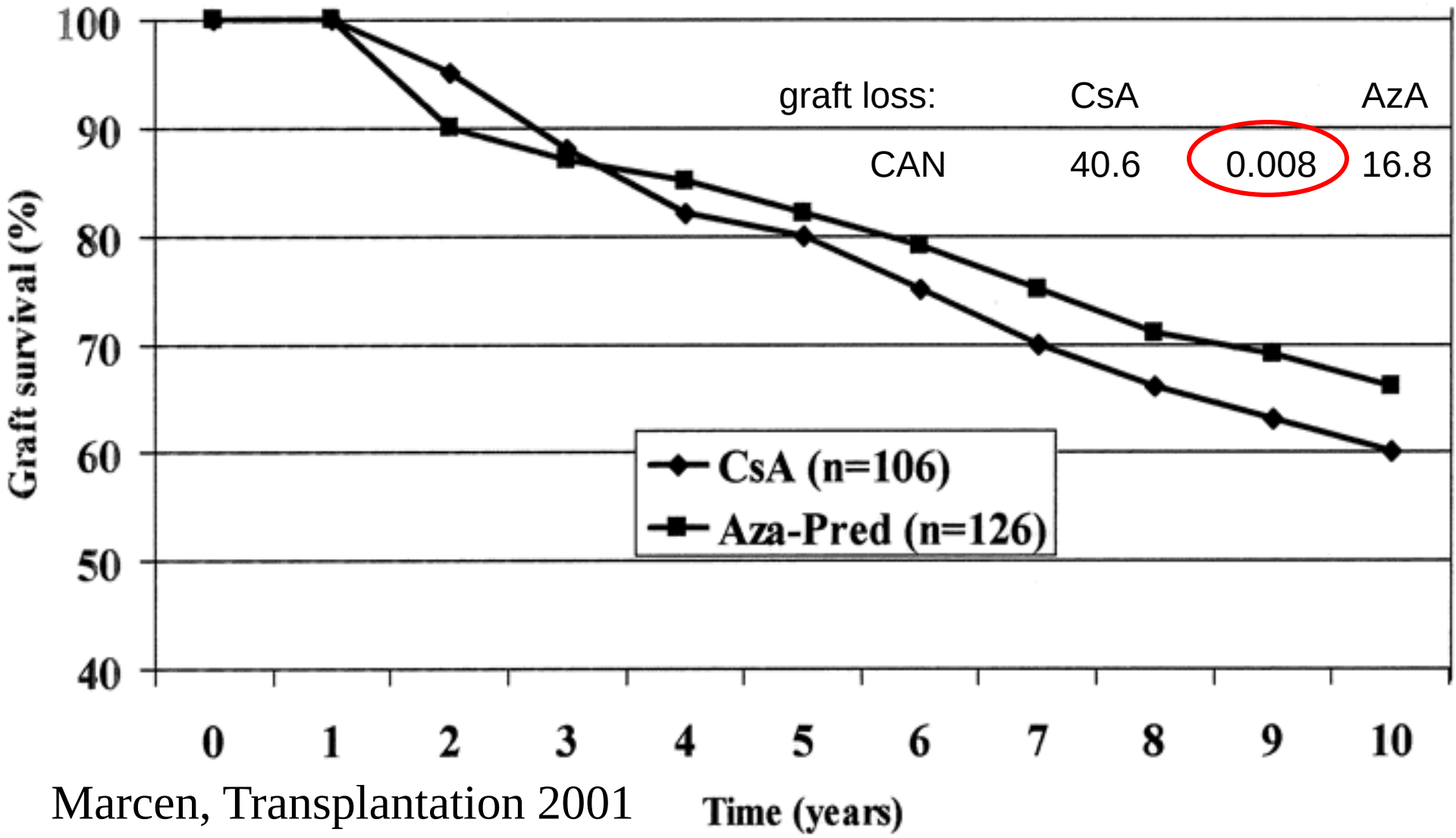
Marcen, Transplantation 2001

But better kidney function with Azathioprin due to acute CNI-toxicity (vasoconstriktion)



Marcen, Transplantation 2001

Detrimental effect of CsA on long-term graft survival

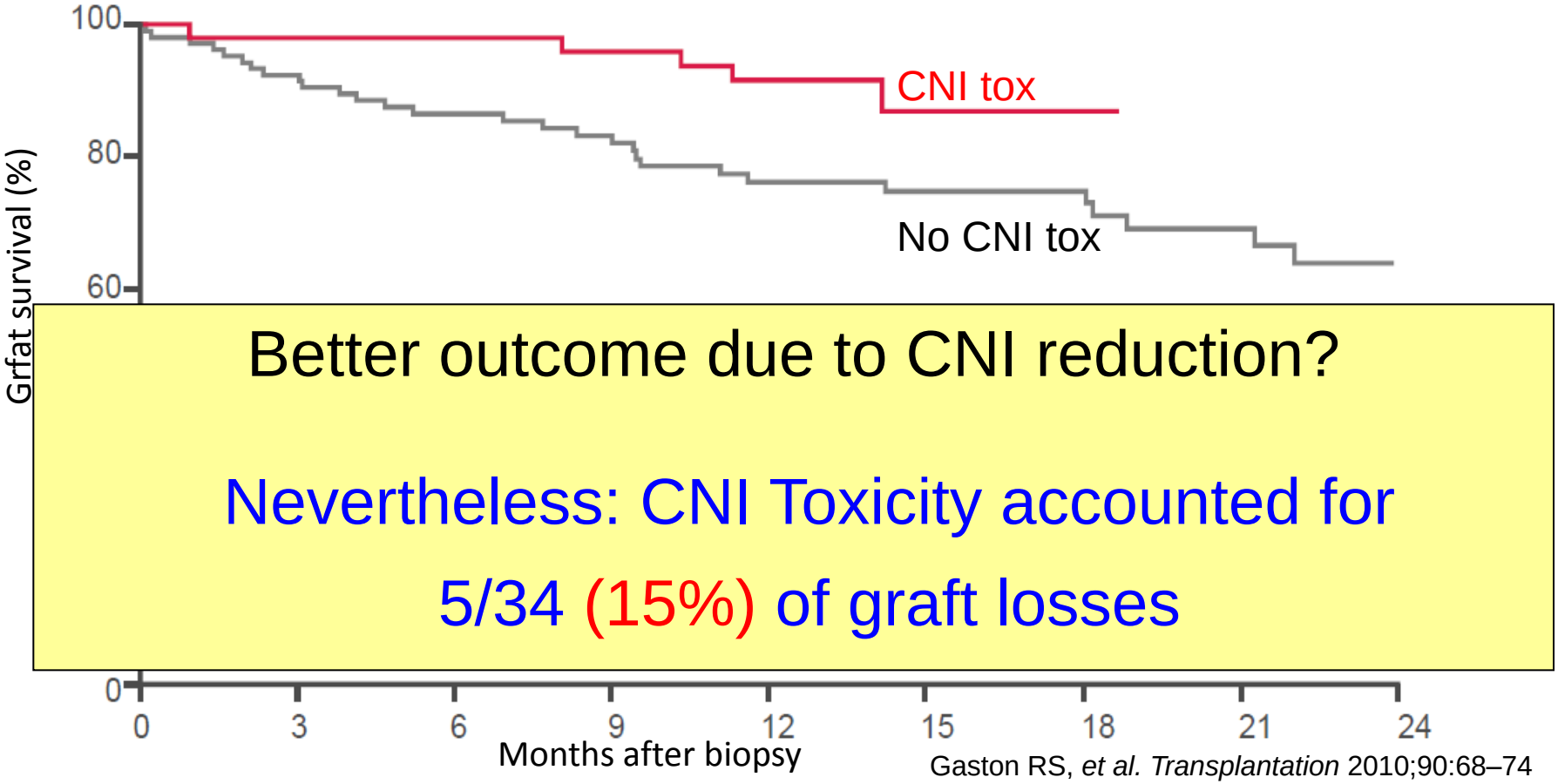


Marcen, Transplantation 2001

Lower rate of graft loss with CNI-Toxicity

DeKAF study: n=173 patients with late-onset graft dysfunction taken 7.3 ±6.0 years after Tx:

35% had locally diagnosed CNI-Toxicity



Better outcome due to CNI reduction?

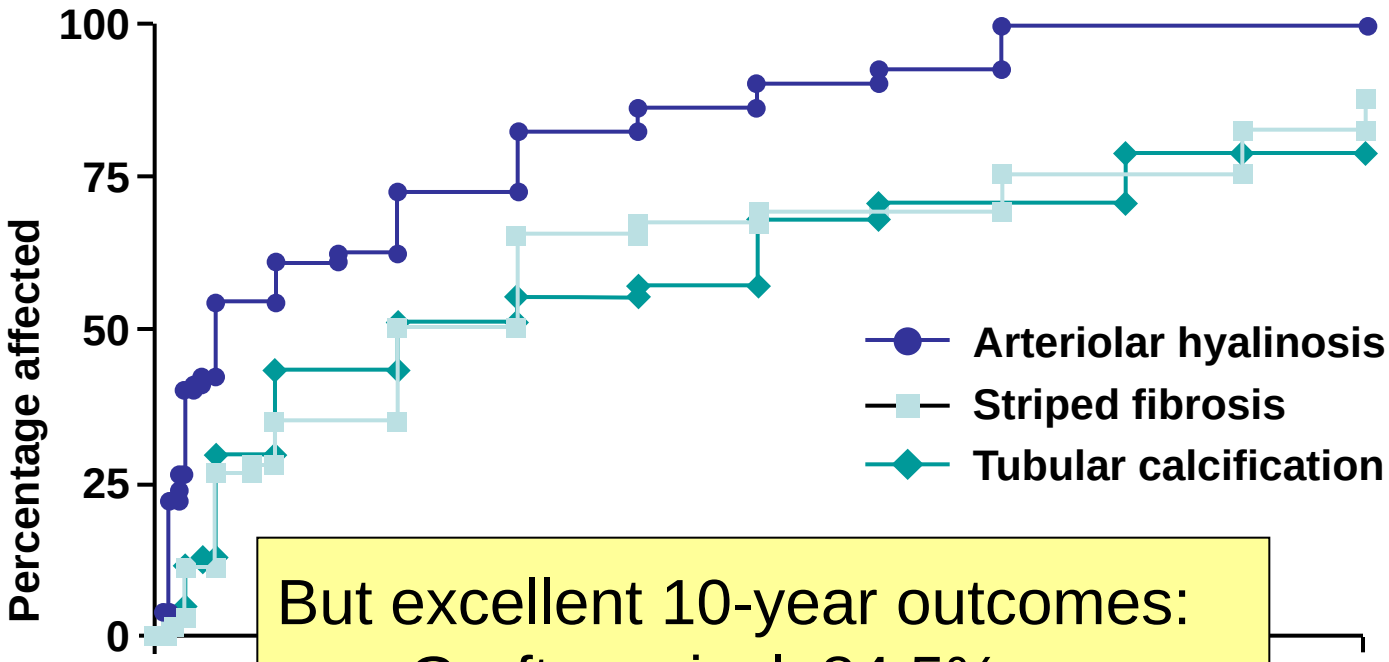
Nevertheless: CNI Toxicity accounted for 5/34 (15%) of graft losses

Gaston RS, *et al. Transplantation* 2010;90:68–74

100% CNI nephrotoxicity after 10 years

N=99 kidney–pancreas transplants; donor age: 25.5 years

CsA: on average 204ng/mL over 10 years!



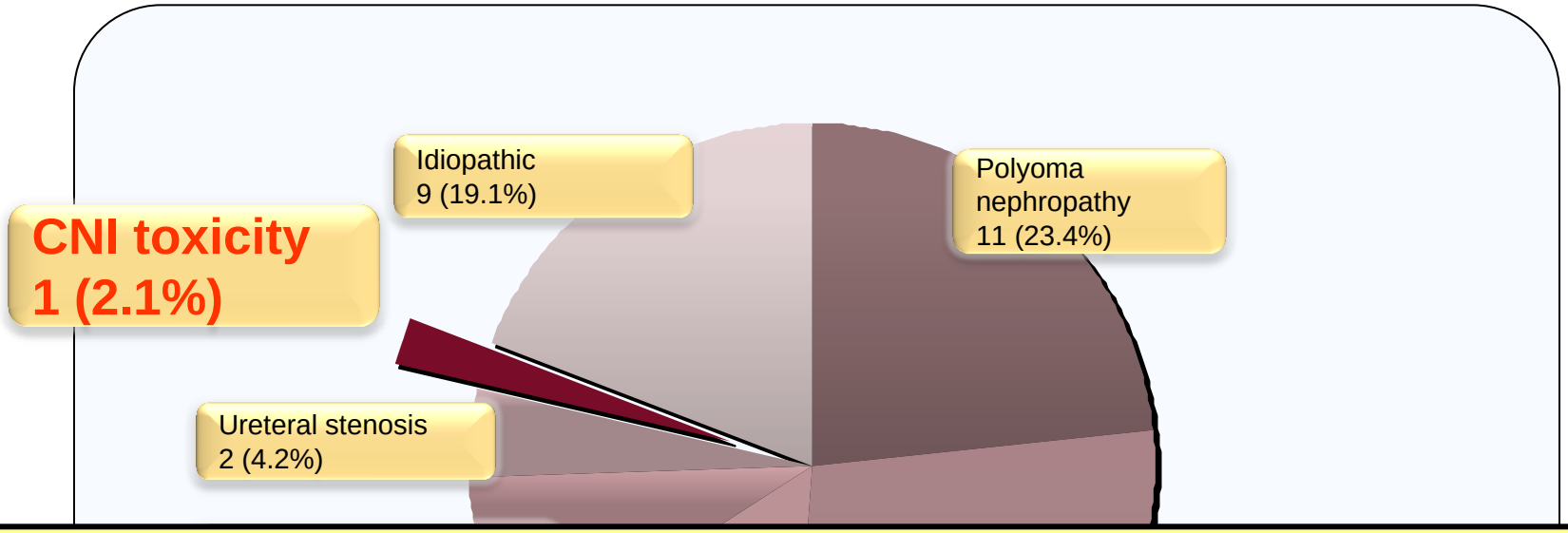
But excellent 10-year outcomes:

- Graft survival: 84.5%
- Creatinine: 1.62mg/dL

1. Nankivell BJ et al. N Engl J Med 2003;349:2326–2333
2. Nankivell BJ et al. Transplantation 2004;78:557–565

Mayo Clinic 1996–2006; causes of IF/TA

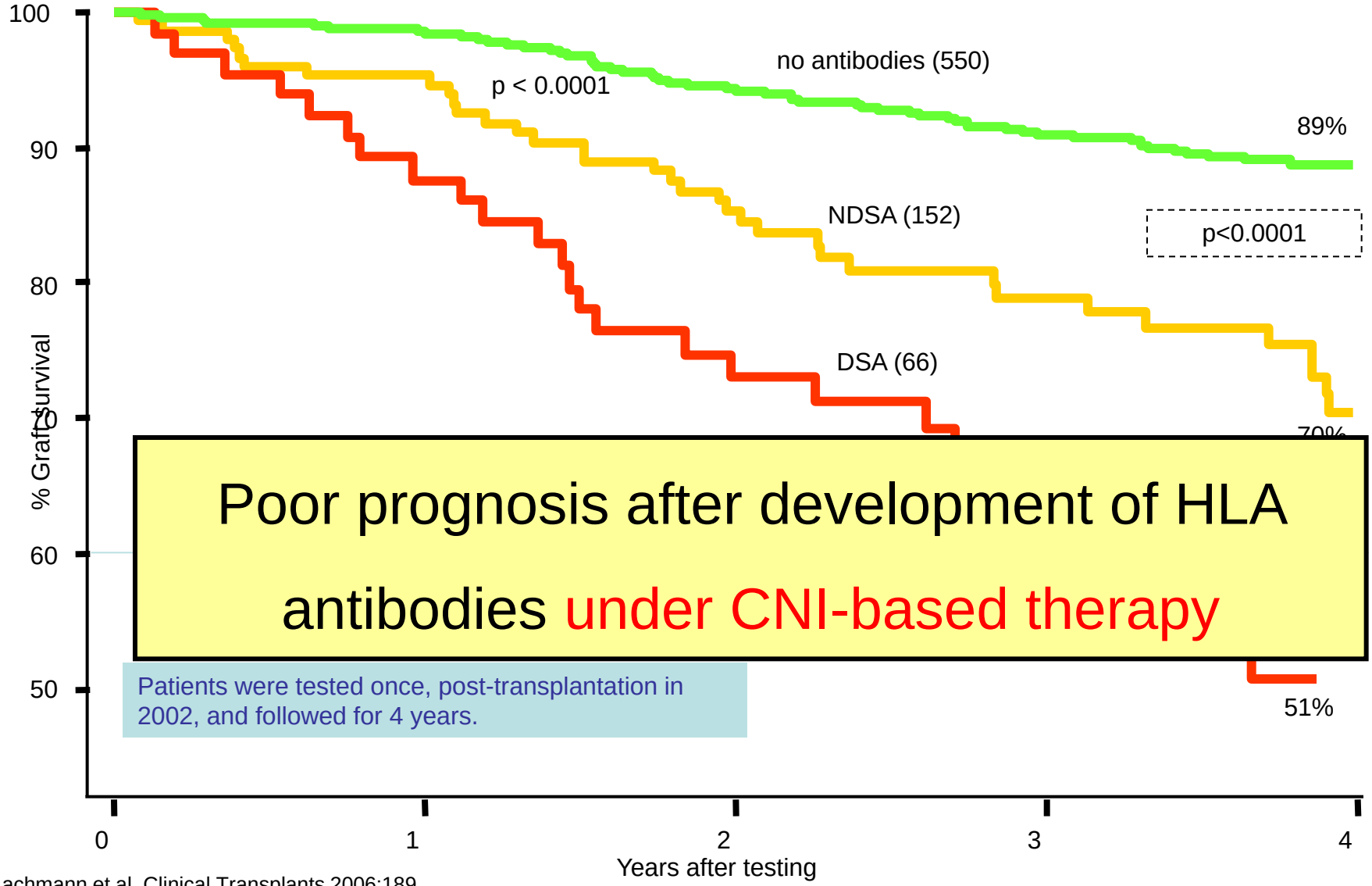
(n=47; 50±33 months after NTx)



1% or 100%??

It is obviously difficult to assess prevalence of CNI nephrotoxicity after renal transplantation, which also depends on time after transplantation

Impact of donor specific antibodies (DSA) on graft survival



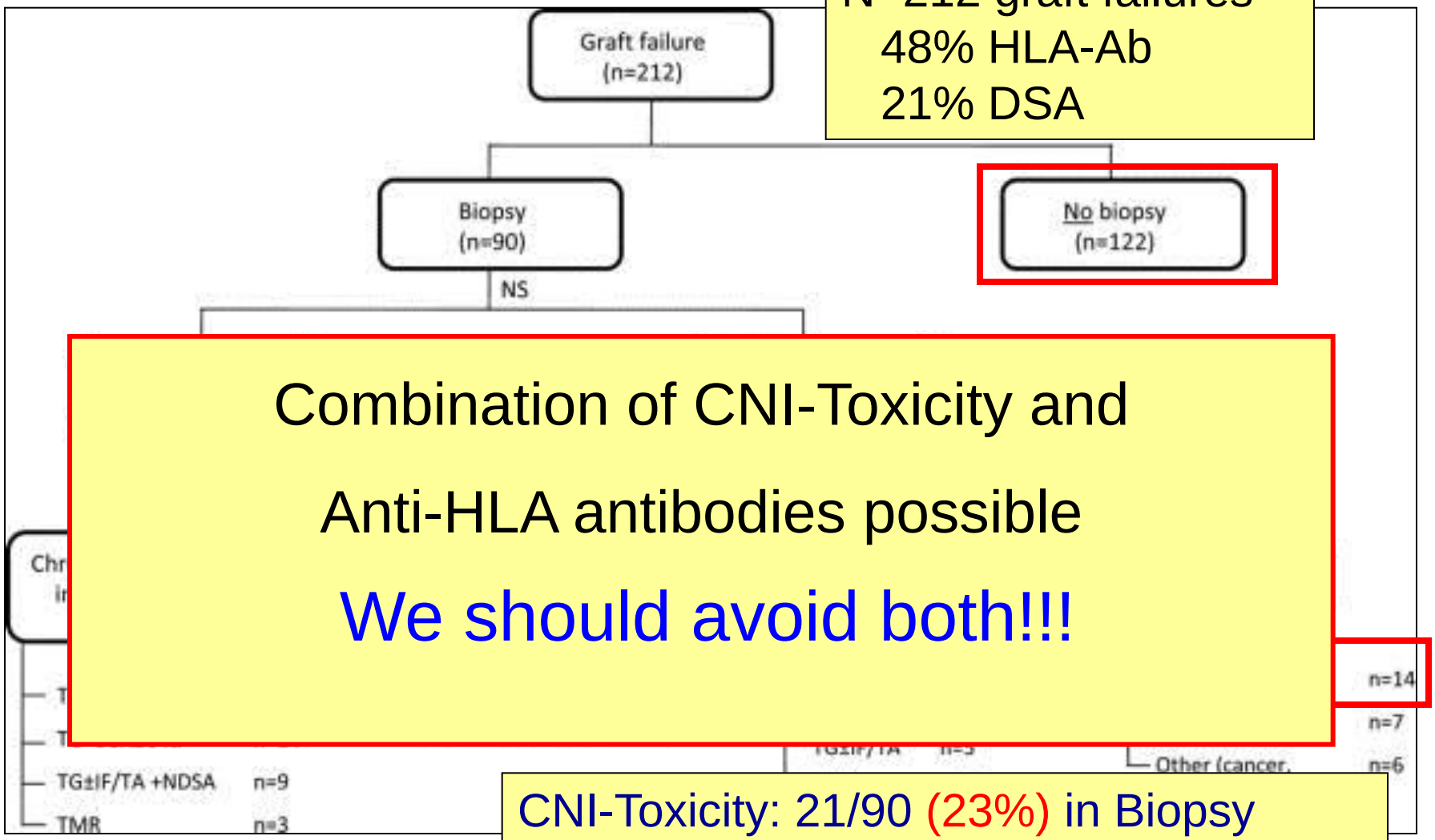
Poor prognosis after development of HLA antibodies under CNI-based therapy

Patients were tested once, post-transplantation in 2002, and followed for 4 years.

Lachmann et al. Clinical Transplants 2006:189

CNI-Toxicity or HLA Antibodies?

N=212 graft failures
48% HLA-Ab
21% DSA



Combination of CNI-Toxicity and

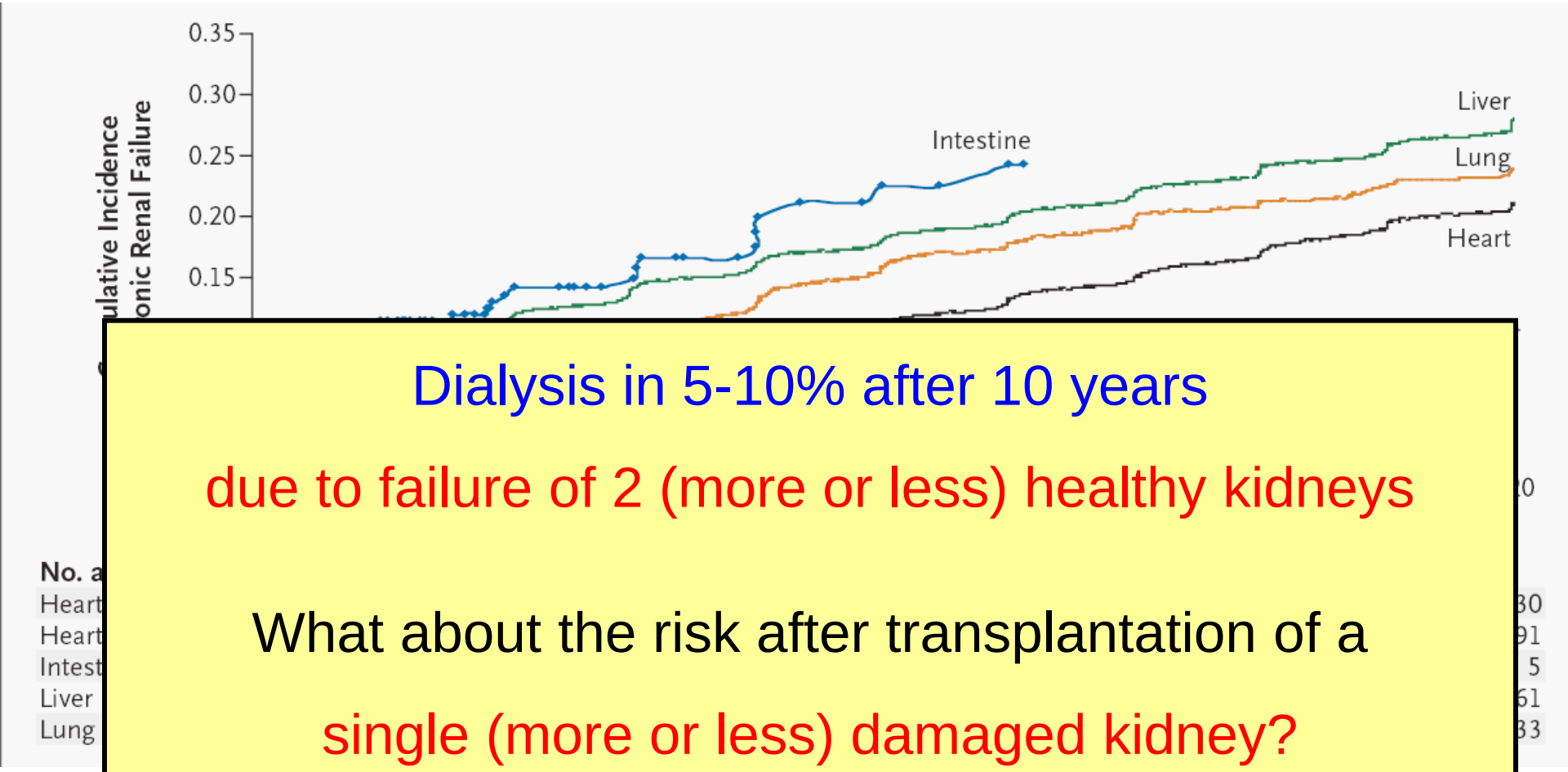
Anti-HLA antibodies possible

We should avoid both!!!

CNI-Toxicity: 21/90 (23%) in Biopsy

Lachmann et al. Transplantation 2009;87:1505–1513.

Chronic renal insufficiency (GFR <29ml/min) after organ transplantation



Dialysis in 5-10% after 10 years

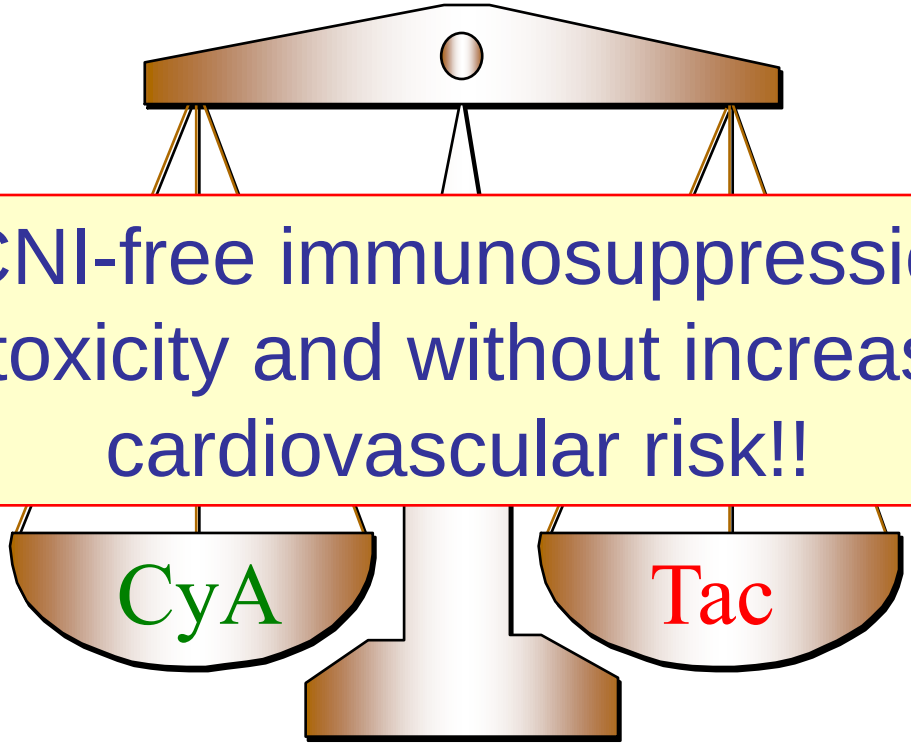
due to failure of 2 (more or less) healthy kidneys

What about the risk after transplantation of a

single (more or less) damaged kidney?

Ojo, NEJM 2002

It´s not only nephrotoxicity:
Which side effect would you prefer?



Aim is a CNI-free immunosuppression without nephrotoxicity and without increasing the cardiovascular risk!!

hirsutism	or	Hair loss
Gingival hyperplasia		Tremor
Lipidemia		Diabetes
Rejection		Polyoma

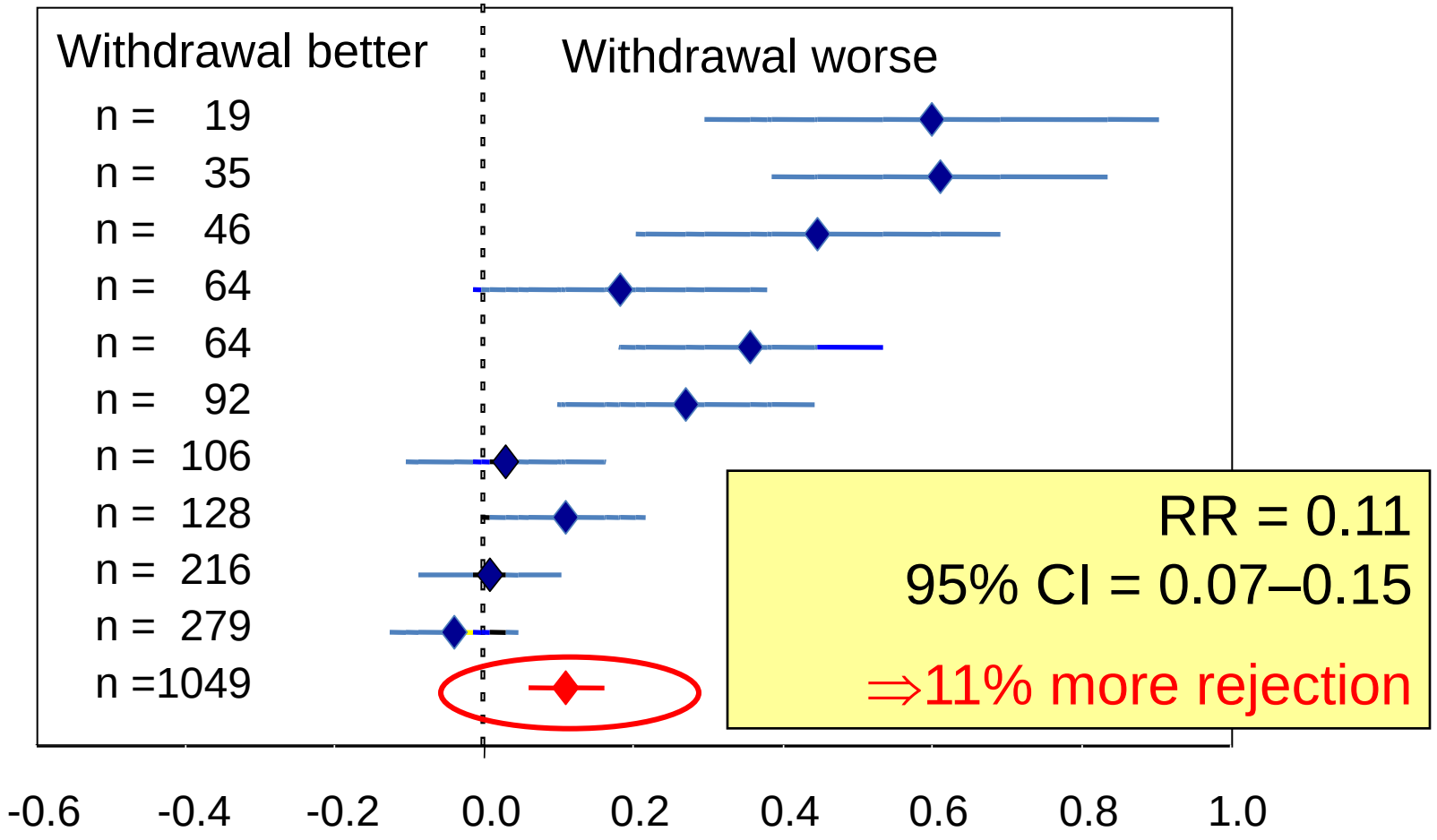
So why didn't we do anything about it?

- Good tolerability of CNIs
- Good short term results
- Inadequate short term results for Aza & Pred

  $\Rightarrow$ no good alternatives
- Didn't believe the studies
- Uncertainty about the benefits
- Inertia/human nature
- Marketing pressure for CNI's
- **Fear of acute rejection episodes**
- **Fear of subclinical rejection***

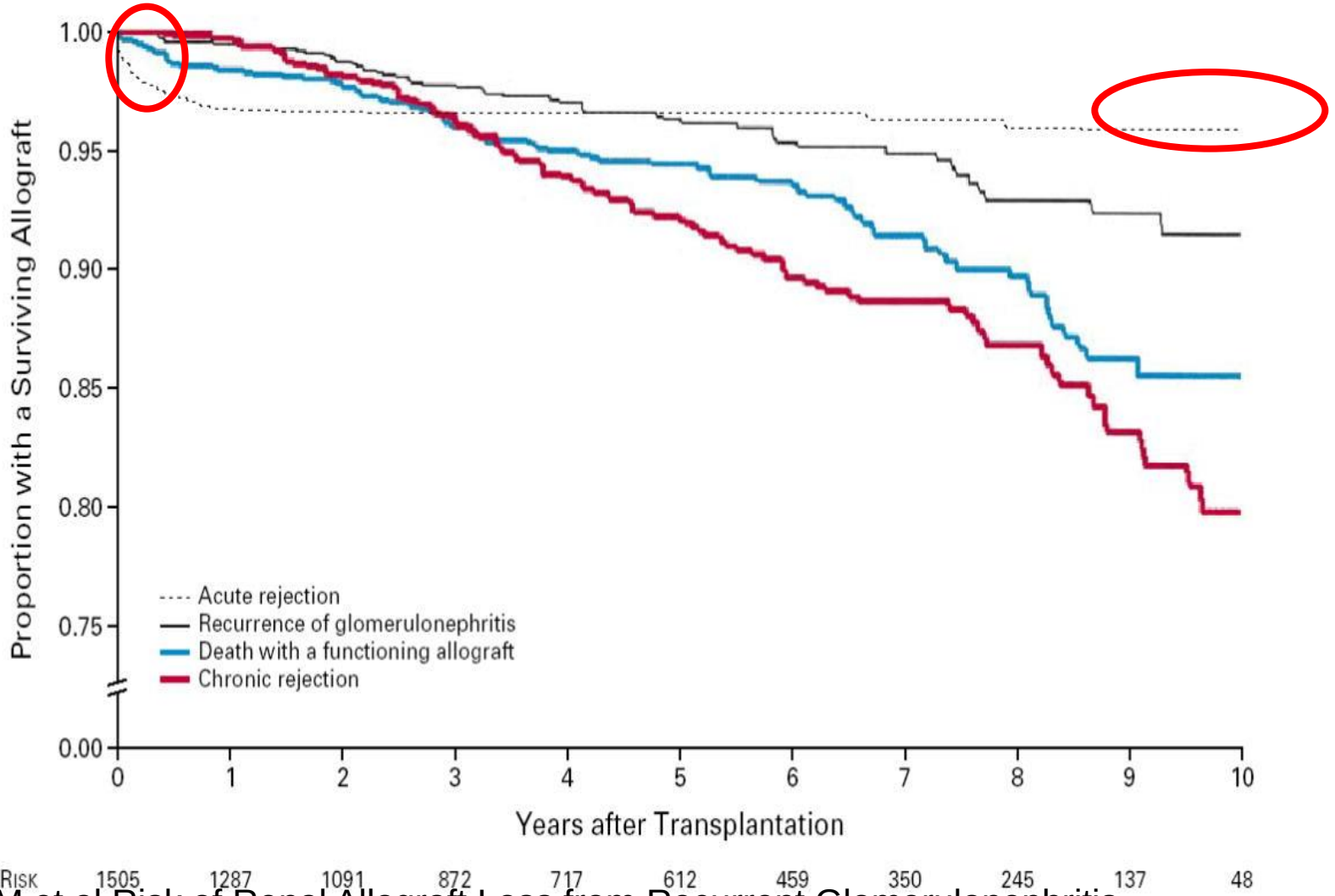
According to J. Chapman and *K. Budde.

CsA withdrawal and acute rejection: early studies (before 2000)



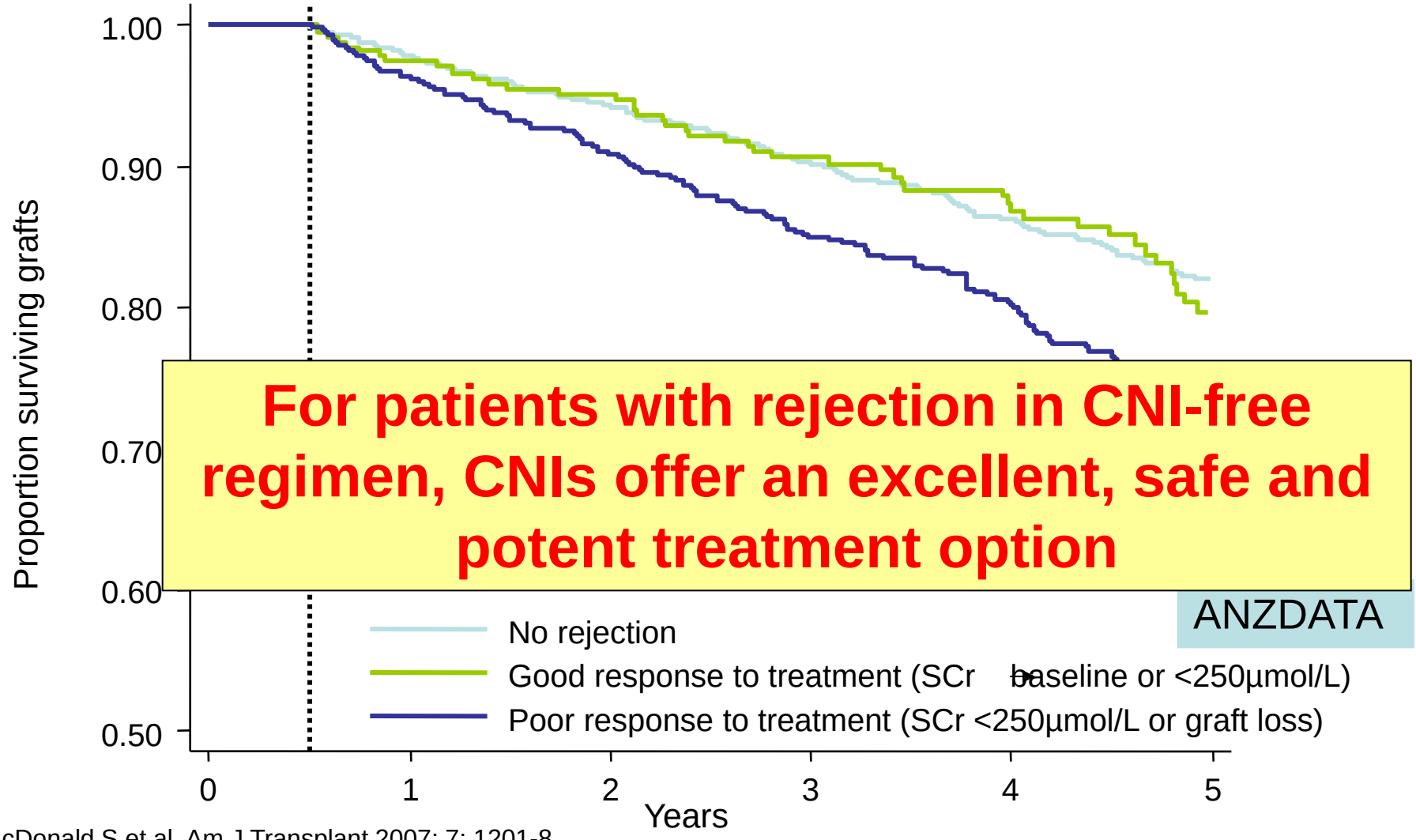
Kasiske B JASN 2000

acute rejection is not the main reason for graft loss anymore



Briganti EM et al Risk of Renal Allograft Loss from Recurrent Glomerulonephritis, N Engl J Med, 347: 103-109, 2002

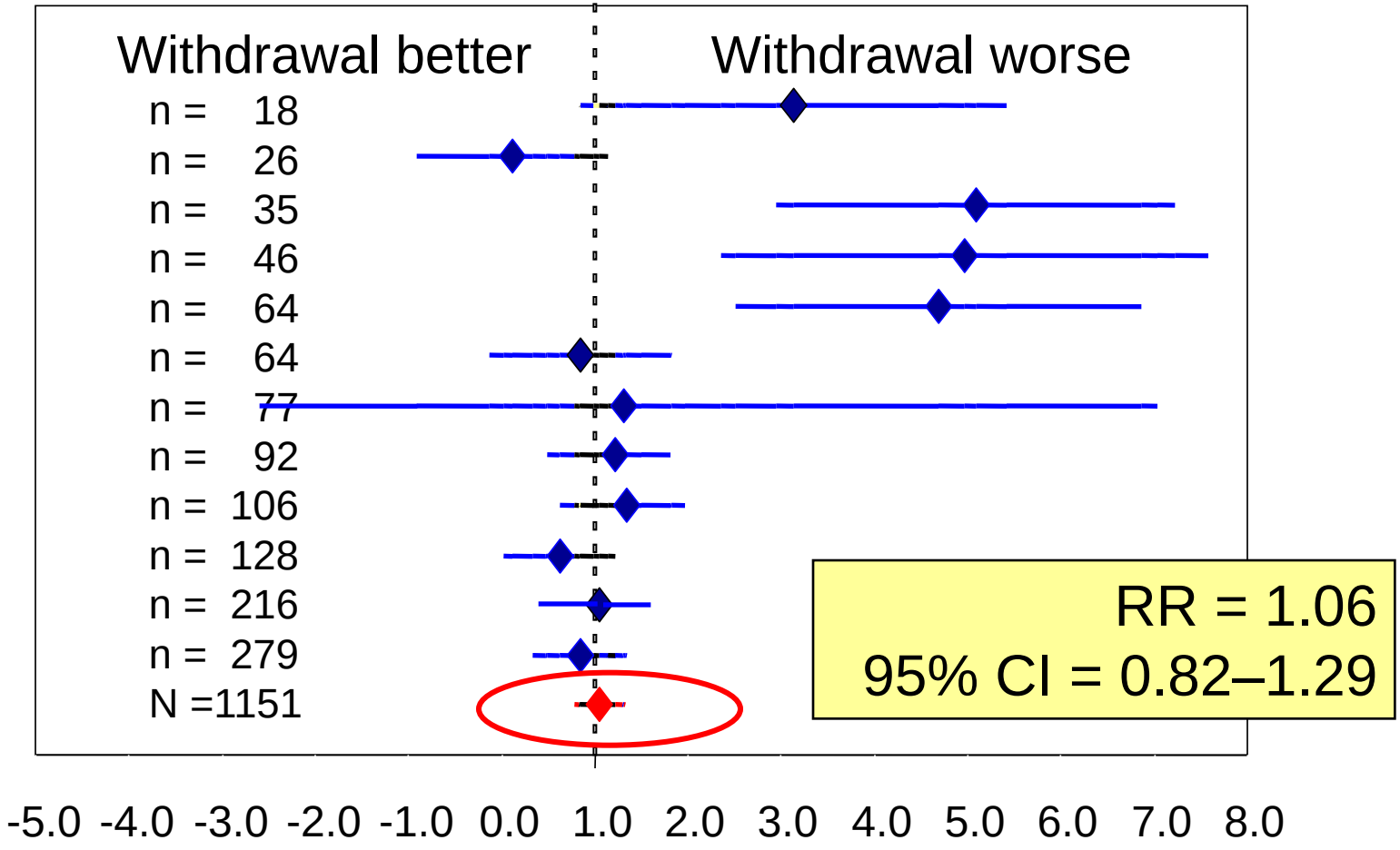
Graft survival by response to 1st rejection episode



For patients with rejection in CNI-free regimen, CNIs offer an excellent, safe and potent treatment option

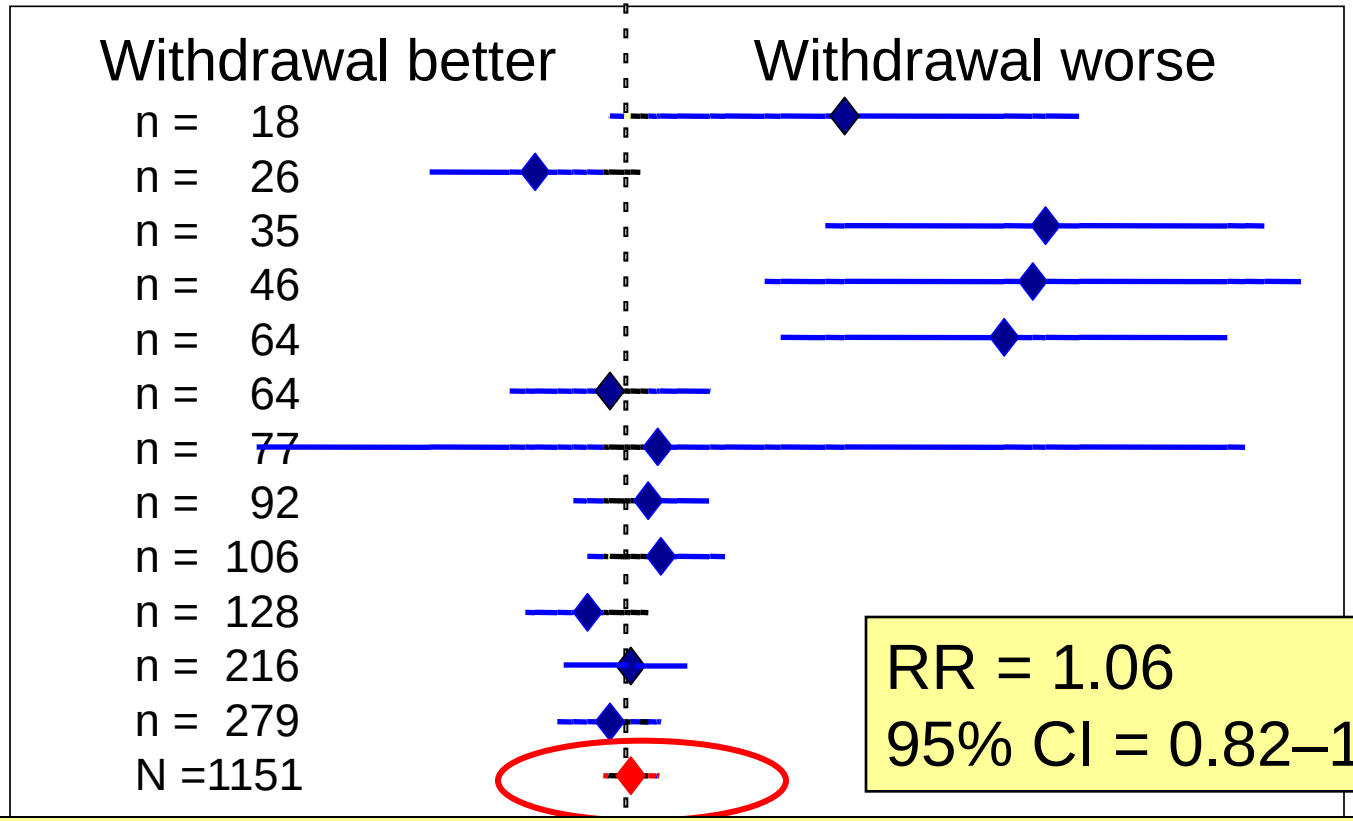
McDonald S et al. Am J Transplant 2007; 7: 1201-8

CsA withdrawal and graft survival: early studies (before 2000)



Kasiske B JASN 2000

CsA withdrawal and graft survival: early studies (before 2000)



RR = 1.06
95% CI = 0.82–1.29

Higher rejection frequency counterbalanced by CNI toxicity

Kasiske B JASN 2000

Long Search for optimal CNI doses: CsA level associated with Malignancy

n=231 low risk patients randomized at 1 year posttransplant

50% reduction of CsA level (75-125 vs. 150-250 ng/ml)

differences maintained for > 5years

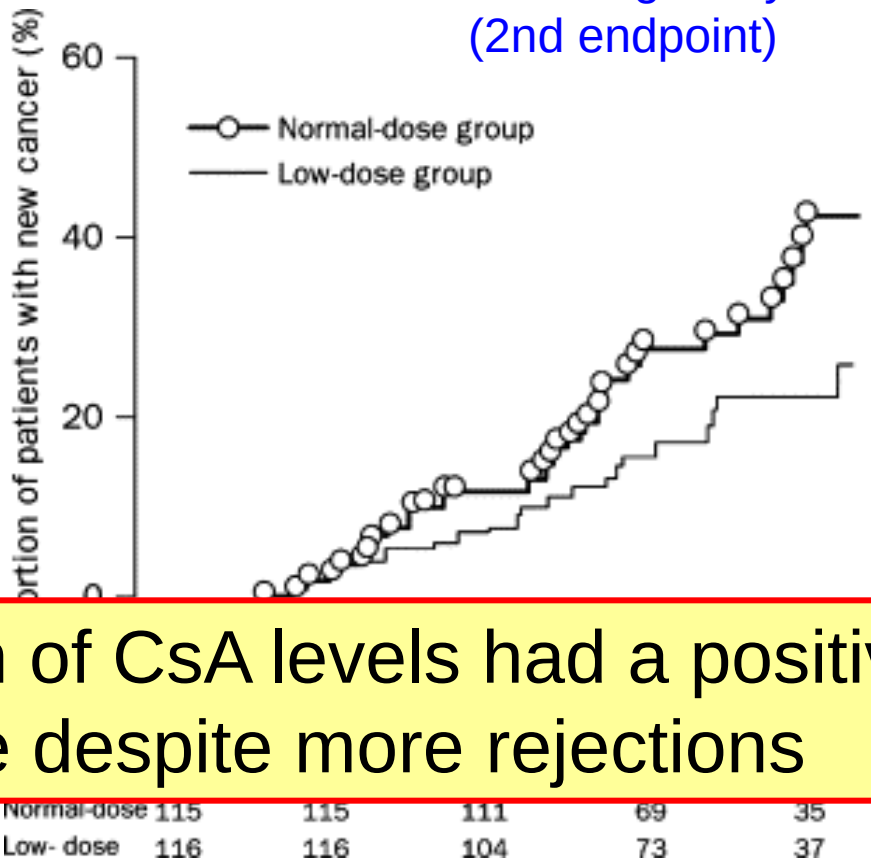
90% ATG induction

77% Azathioprine

low CsA:

- less virus infections (14 vs 8%)
- more rejections (8 vs 1%)
- similar GFR
- similar graft (89 vs 82%)

Low CsA: less malignancy (2nd endpoint)

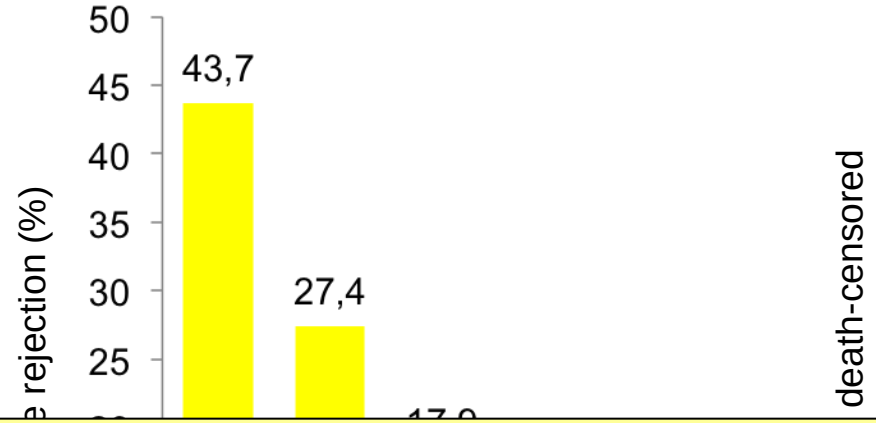


Substantial Reduction of CsA levels had a positive effect on outcome despite more rejections

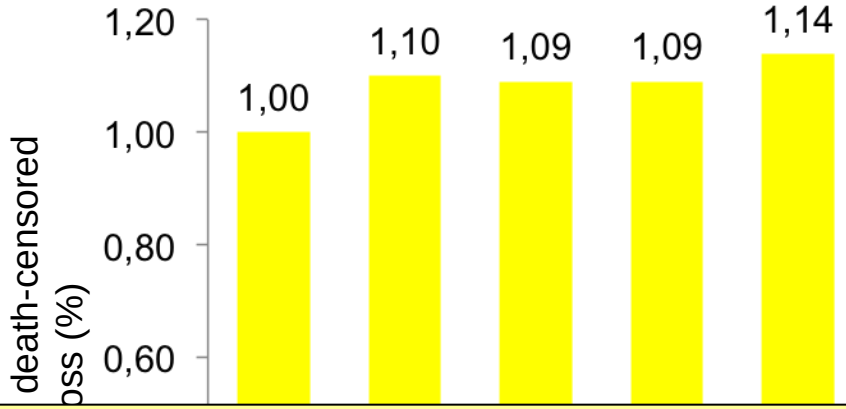
Dantal et al. Lancet 1998

No improvement in overall graft survival despite reduction in acute rejection

Incidence of early acute rejection episodes (within 6 months) by era



Relative risk for death-censored graft loss (deceased donor)

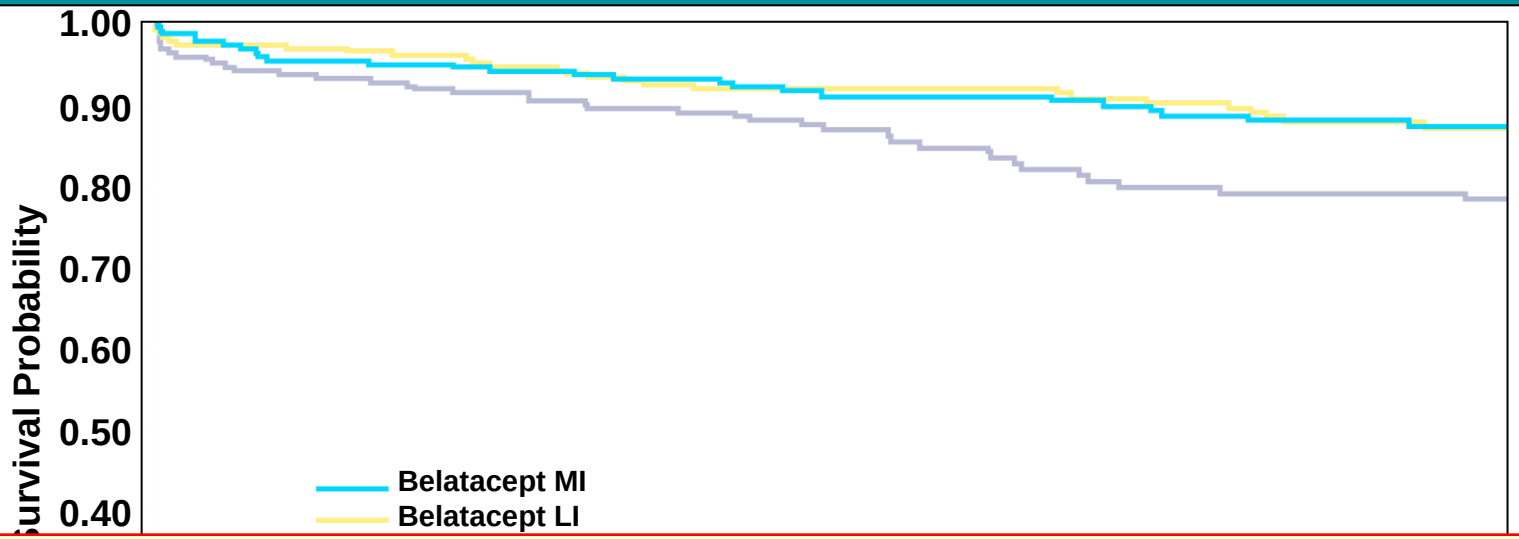


It is more than rejection prophylaxis!

Is any further progress possible
with nephrotoxic CNIs, which increase cardiovascular burden and allow
the development of HLA-Abs?

Meier-Kriesche H-U, *et al. Am J Transplant* 2004;4:378–383.

Belatacept vs CsA: less Death or Graft Loss From Randomization to Month 84



43% RR in death/graft loss,
despite more & more severe rejections
and better
renal function, histology, blood pressure, lipids, glucose and less DSA

Bela LI vs. CsA	0.0045	0.477 (0.277, 0.819)	Bela LI vs. CsA	0.0210	0.570 (0.348, 0.935)

CI=confidence interval; CsA=cyclosporine A; HR=hazard ratio; LI=less intensive; MI=more intensive.

Vincenti F, *et al. NEJM 2016*