STEROID FREE PROTOCOLS, CURRENT USE & FUTURE TRENDS

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Urology & Nephrology Center
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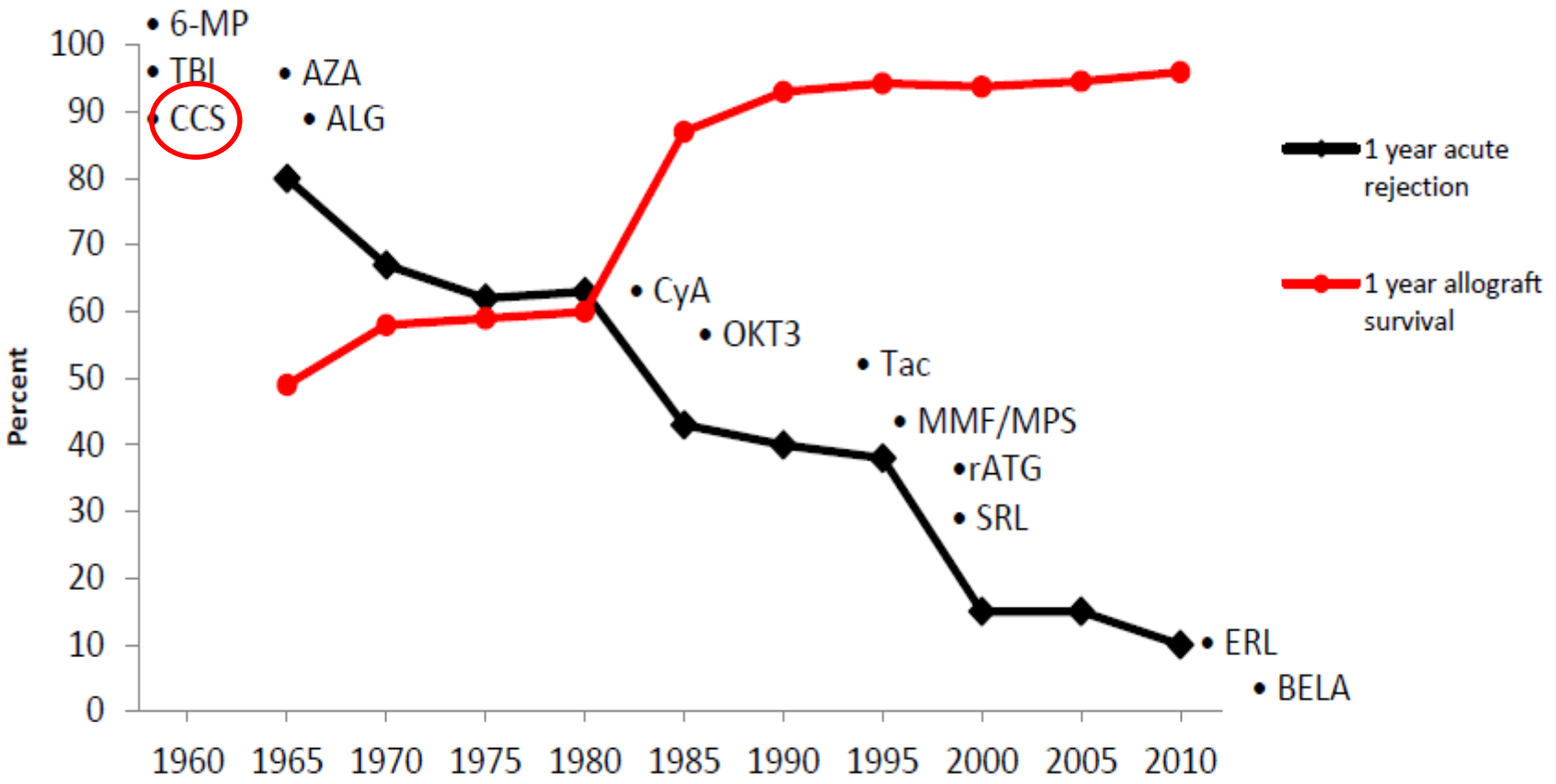
Evolution in immunosuppression and correlations to 1 y allograft survival and rejection



Zand MS Semin Dial 2005; 18: 511-9

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Steroids in renal transplantation: Background

- Corticosteroids had been a mainstay of immunosuppressive protocols in kidney transplantation.

- Steroids are associated with debilitating side effects, including hypertension, hyperlipidemia, cataracts, avascular necrosis, osteoporosis, mood and appearance changes, and, in children, growth retardation.

- Treatment of these steroid-related side effects adds to the cost of transplants.

- Steroid-induced co-morbidities increases noncompliance which is associated with an increased incidence of ARE, chronic rejection, and graft loss.

Steroid- free protocols: Rationale

The negative impact of CS on CV risk factors:

- Hypertension
- Diabetes mellitus
- Dyslipidemia

Non-cardiovascular adverse events:

- Growth retardation
- Bone problems (osteoporosis, fractures, avascular necrosis)
- Impaired wound healing
- Subcapsular cataract
- Cosmetic effects leading to patient non-compliance

Steroid- free protocols: Rationale

The negative impact of CS on CV risk factors:

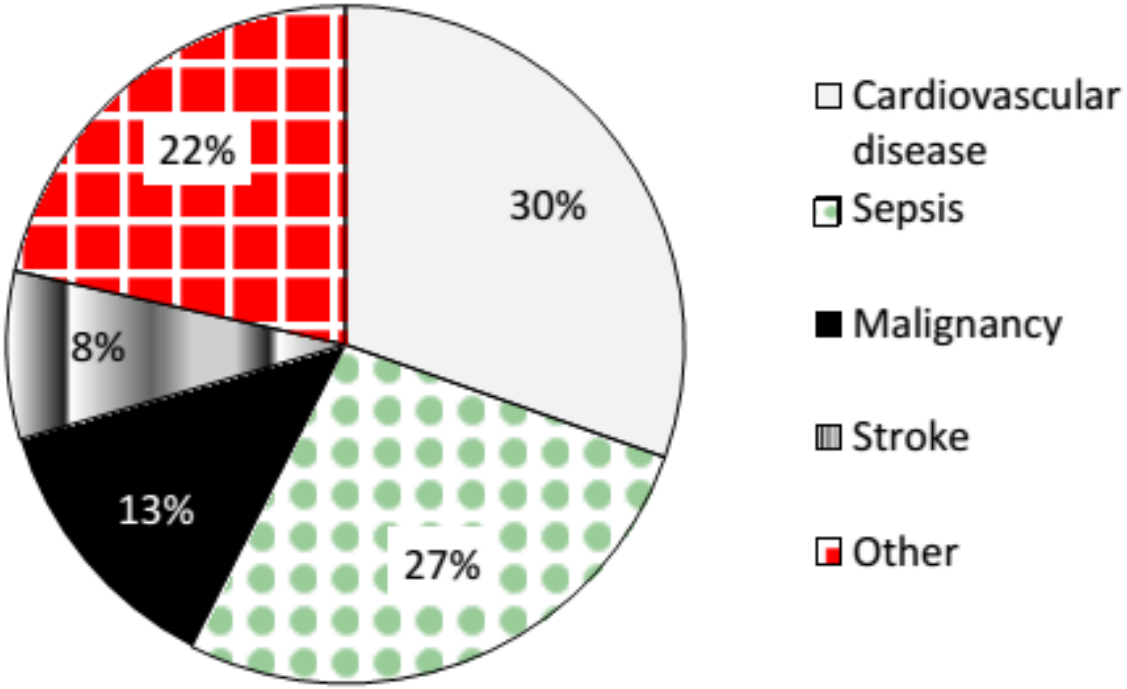
- Hypertension
- Diabetes mellitus
- Dyslipidemia

Non-immune triggers of CAI

Non-cardiovascular adverse events:

- Growth retardation
- Bone problems (osteoporosis, fractures, avascular necrosis)
- Impaired wound healing
- Subcapsular cataract
- Cosmetic effects leading to patient non-compliance

Long-term causes of death in renal transplants



Sood et al, Int Urol Nephrol 2010; 42(4): 929-34.

Steroid- free protocols: Questions to be answered

- Despite the progress made over the past three decades with steroid-free immunosuppression in kidney transplantation, there are still lingering questions and concerns about the long-term effects of steroid-free immunosuppression.

- Are there real long-term metabolic benefits?
- Is there an increased risk of acute rejection or chronic allograft dysfunction?
- What is the impact on graft survival?

http://www.kidney-international.org

mini review

Steroid-free maintenance immunosuppression in kidney transplantation: is it time to consider it as a standard therapy?

Fu L. Luan[1], Diane E. Steffick[2] and Akinlolu O. Ojo[1,2]

[1]Department of Internal Medicine, Division of Nephrology, University of Michigan, Ann Arbor, Michigan, USA and [2]Arbor Research Collaborative for Health, Ann Arbor, Michigan, USA

Steroid- free protocols: Dilemma

Data from studies on CS minimization have produced conflicting results regarding benefit vs harm.

- Clinical heterogeneity across the steroid avoidance studies .
- Wide spectrum of induction and maintenance immunosuppression agents used.

Steroid- free protocols: Terminology

CS avoidance:

- Either no CS use at all
- CS use only until day 7 after transplantation (Tx)

CS withdrawal:

- **Early withdrawal** (weeks or months after Tx, usually 3-6 months)
- **Late withdrawal** (at least 6 months after Tx)

Steroid- free protocols: Induction therapy

- Steroid-free regimens require the use of potent induction immunosuppression and the selection of low immunological risk recipients.

- Attempts to use CS avoidance regimens in the absence of induction immunosuppression resulted in unacceptably high acute rejection rates.

http://www.kidney-international.org review

KDIGO clinical practice guideline for the care of kidney transplant recipients: a summary

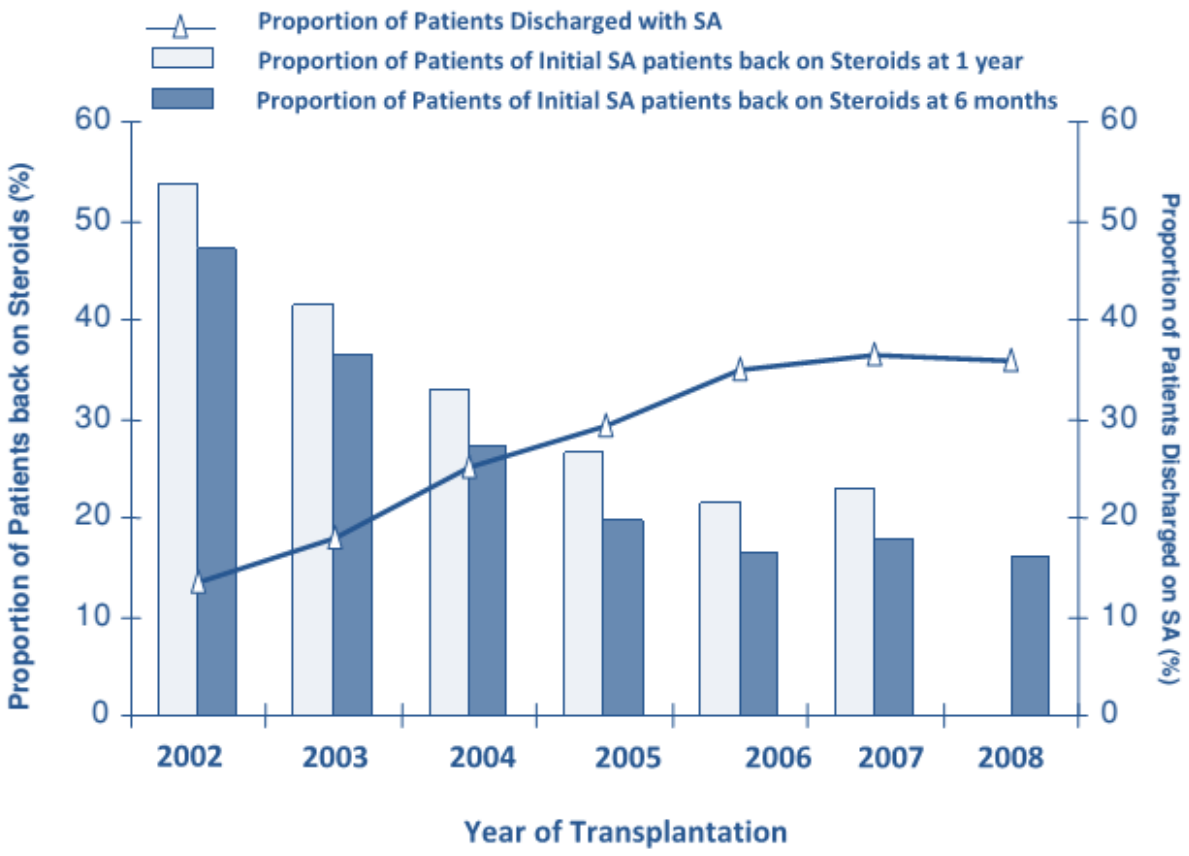
2.4: We suggest that, in patients who are at low immunological risk and who receive induction therapy, corticosteroids could be discontinued during the first week after transplantation. (*2B*)

American Journal of Transplantation 2009; 9: 2768–2776
Wiley Periodicals Inc.

doi: 10.1111/j.1600-6143.2009.02838.x

The Success of Continued Steroid Avoidance After Kidney Transplantation in the US

J. D. Schold[a,c], A. Santos[a], S. Rehman[a], J. Magliocca[b] and H.-U. Meier-Kriesche[a,*]



Approximately 90% of United States renal transplant recipients with a steroid-free regimen have received induction with a lymphocyte-depleting agent.

Anti- IL-2 receptor antagonists have been used in the remaining 10%

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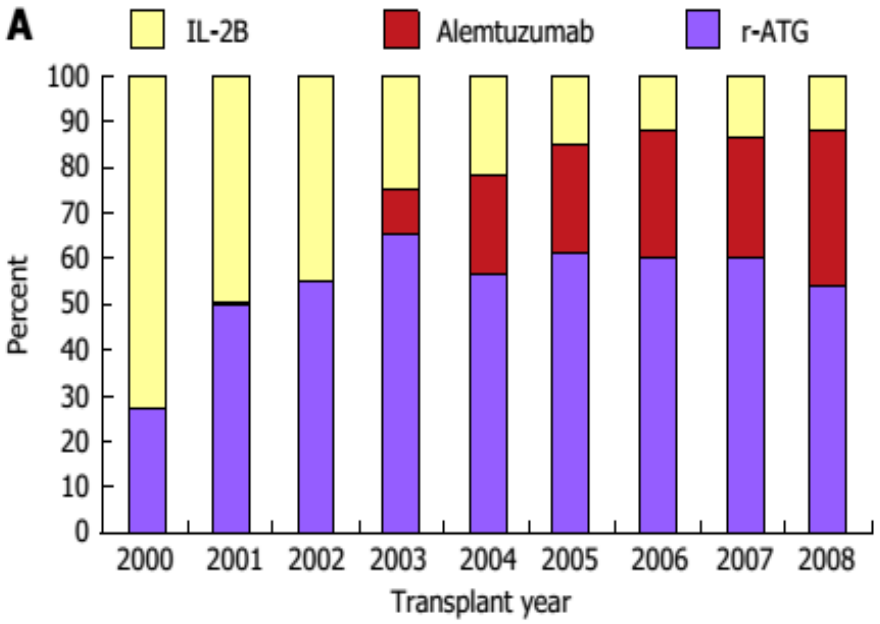
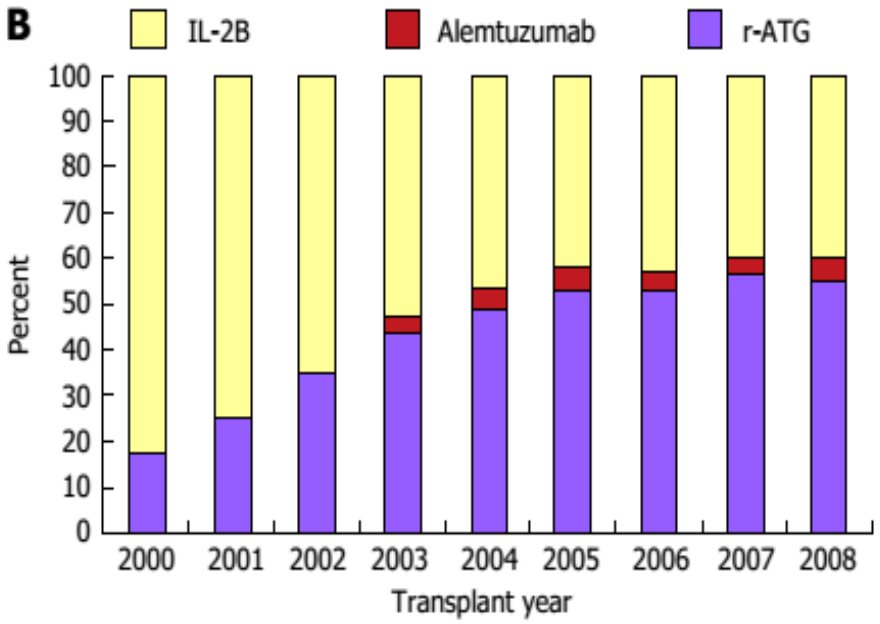
Impact of steroid maintenance on the outcomes in first-time deceased donor kidney transplant recipients: Analysis by induction type





Steroid-free

Steroid-based

Sureshkumar KK et al, World J Transplant 2014 September 24; 4(3): 188-195

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NEFROLOGIA 2016;36(5):469–480

Sociedad Española de Nefrología

nefrología

Revista de la Sociedad Española de Nefrología

www.revistanefrologia.com

Brief review

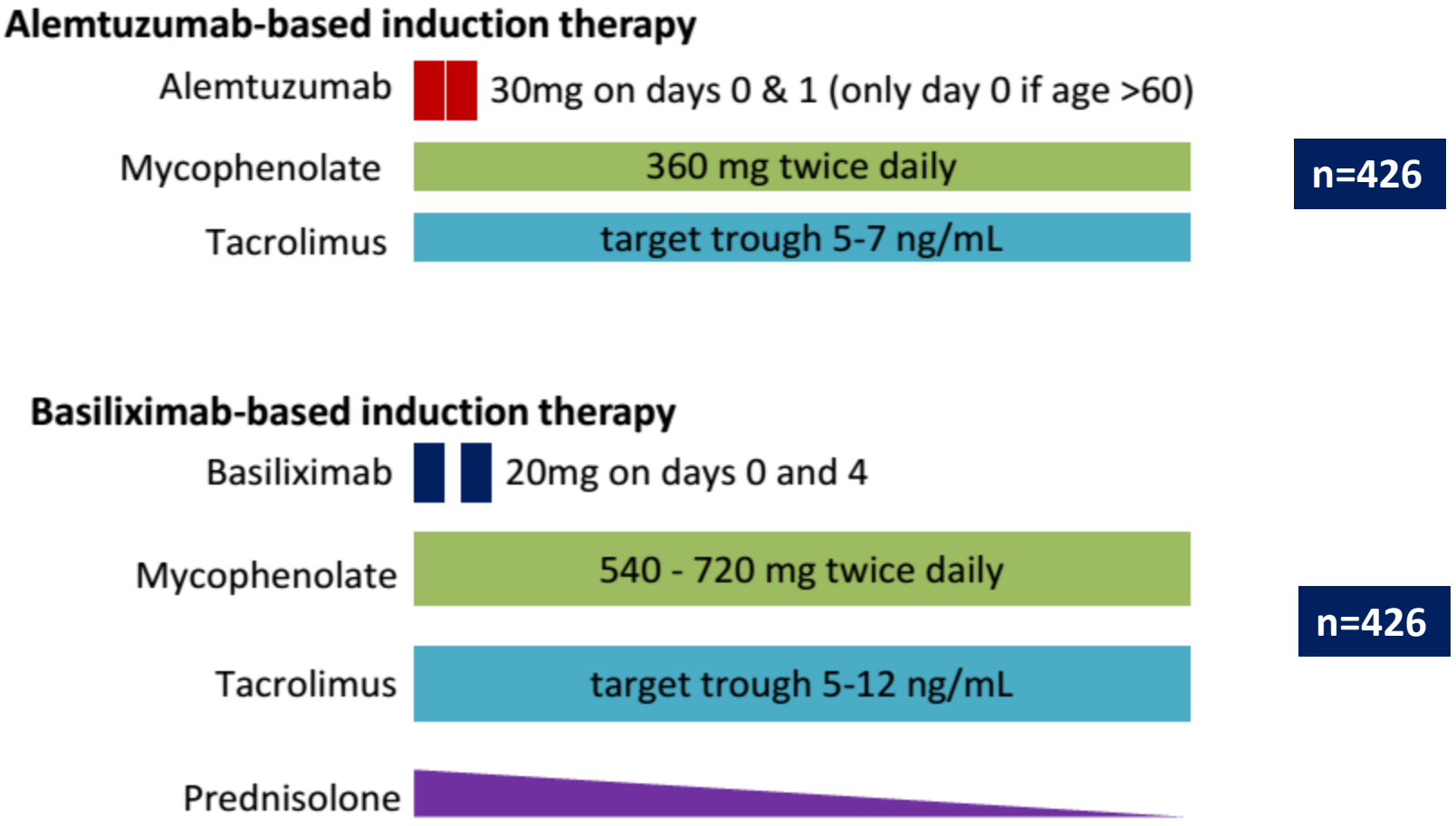
Lymphocyte-depleting induction and steroid minimization after kidney transplantation: A review

Maarten Naesens[a,b], *Stefan Berger*[c], *Luigi Biancone*[d], *Marta Crespo*[e,f], *Arjang Djamali*[g], *Alexandre Hertig*[h], *Robert Öllinger*[i], *José Portolés*[j], *Andreas Zuckermann*[k], *Julio Pascual*[e,f,*]

Table 1 – Randomized trials of rATG or alemtuzumab induction with steroid avoidance in kidney transplantation.

Study	Risk status, N	Study duration	rATG	Steroids	Maintenance	BPAR (%)	Graft/ patient survival (%)[a]
rATG induction							
Kandaswamy[31] Single center	Unselected N = 239	2Y	1.25–1.5 mg/kg × 5	i.v. + oral to day 5	CsA, MMF	6	95/98
					High TAC Low SRL	4	94/97
					Low TAC High SRL	5	96/97
Laftavi[32] Single center	Moderate/low N = 60	12M	1 mg/kg × 3–5	i.v. + oral to day 7	TAC, MMF	13	–
				i.v. + oral ongoing		11	–
Stevens[33] Single center	Moderate/low N = 180	6M	6 mg/kg × 1	i.v. only (<7 days)	TAC/SRL or MMF/SRL	8	100/100
			1.5 mg × 4			12	98.6/96
Ciancio[34] Single center	Unselected N = 150	12M	1 mg/kg × 3 + daclizumab 1 mg/kg × 2	i.v. + oral (<7 days)	TAC, MMF	3	97/100
					TAC, EC-MPS	9	96/99
Woodle[5] Multicenter	Living donor Moderate/low N = 151	12M	1.25–1.5 mg/kg × 4	i.v. + oral (<7 days)	TAC, MMF	13.9	98.1/100
			No rATG	i.v. + oral ≥ 3M		19.4	97.9/100
Grafals[35] Single center	Low N = 45	12M	0.75 mg/kg × 3	i.v. + oral (<7 days)	TAC, MMF	10	85/85
			1.24 mg/kg × 3			17	100/100
Alemtuzumab induction							
Vathsala[36] Multicenter	Moderate/low N = 30	6M	ALEM 20 mg × 2	i.v. × 1	Reduced CSA	25	85/95
			None	Standard	CSA, AZA	20	100/100
Margreiter[37] Multicenter	Moderate/low N = 131	12M	ALEM 20 mg × 2	i.v. × 2	Delayed TAC	20	96/98
			None	Standard	TAC, MMF	32	90/98
Chan[38] Single center	Unselected N = 123	24M	ALEM 30 mg × 1	i.v. + oral to day 7	TAC	11.1	97.6/100
			DAC 2 mg/kg × 3		TAC, MMF	17.7	95.1/97.5
Welberry Smith[39] Single center	Moderate/low N = 116	12M	ALEM 30 mg × 1	i.v. × 1	TAC	10.3	94.9/96.6
			BAS 20 mg × 2		TAC, MMF	24.1[b]	94.8/96.6
3C Study Group Multicenter[40]	Unselected (4% sensitized) N = 852	6M	ALEM 30 mg × 2	None	Reduced TAC Reduced MMF	7	96/97
			BAS 20 mg × 2	Oral (ongoing)	TAC, MMF	16[c]	97/99

Alemtuzumab-based induction treatment versus basiliximab-based induction treatment in kidney transplantation (the 3C Study): a randomized trial



3C Study Collaborative Group, Haynes Ret al, *Lancet* 2014; **384**: 1684-1690

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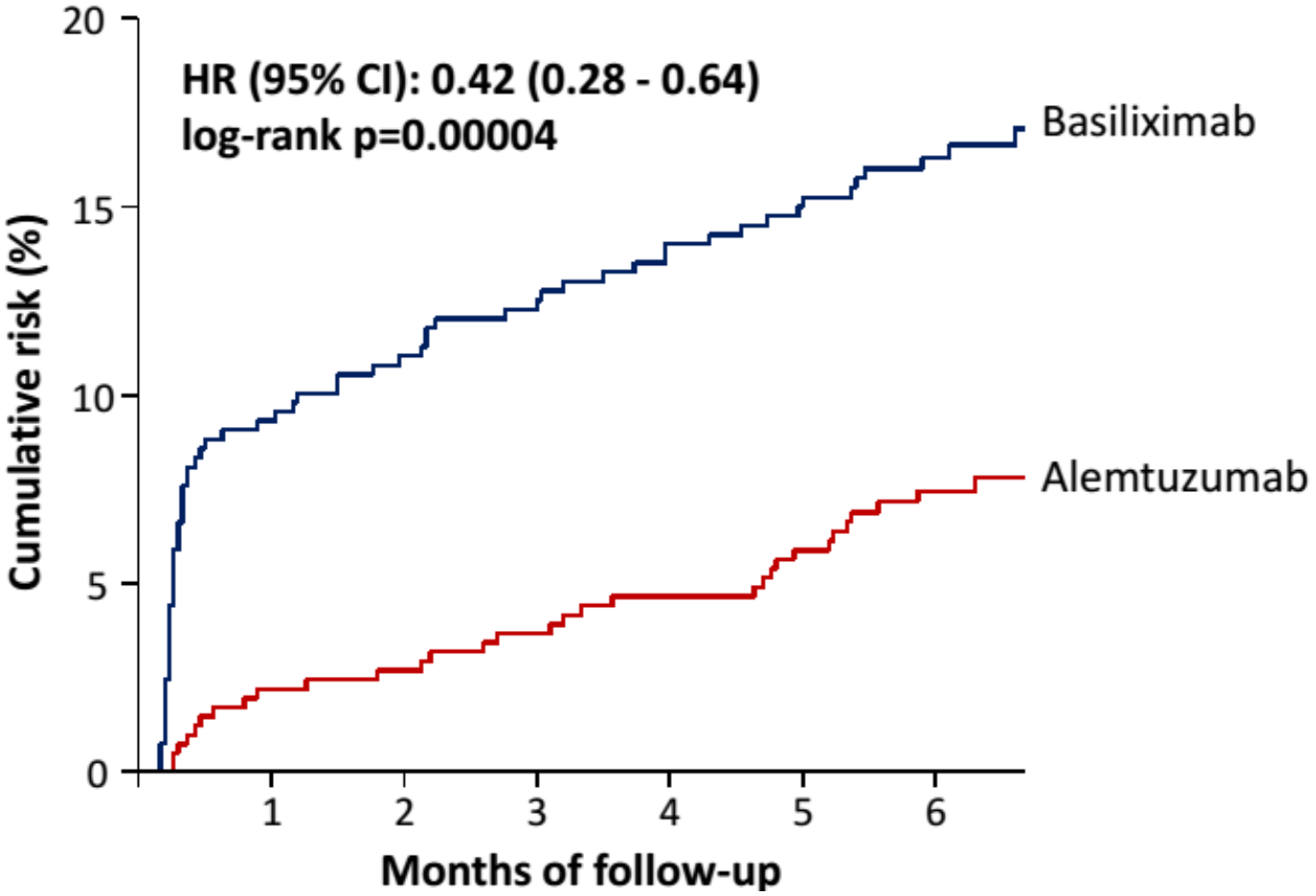

3C Study Collaborative Group, Haynes Ret al, *Lancet* 2014; **384**: 1684-1690

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Nephrol Dial Transplant (2012) 27: 825–832
doi: 10.1093/ndt/gfr374
Advance Access publication 22 July 2011

Very early steroid withdrawal or complete avoidance for kidney transplant recipients: a systematic review*

Julio Pascual[1], Ana Royuela[2,3], Cristina Galeano[4], Marta Crespo[1] and Javier Zamora[2,3]

Table 1. RCTs comparing steroid avoidance or very early withdrawal and steroid conventional use and maintenance included in this review[a]

Trials	*n*	Multicentre trial	CNI	Anti-metabolite	Antibody induction treatment	Conventional therapy	Follow-up period (months)	Completeness of follow-up (%)
Kim *et al.* [11]	24	Yes	CsA	MMF	IL-2 receptor blocker (basiliximab)	The same but with steroids	24	Not available
Kumar *et al.* [12]	77	No	CsA	MMF/SRL	IL-2 receptor blocker (basiliximab)	The same but with steroids	24	100
Vincenti *et al.* [13]	83	Yes	CsA	MMF	IL-2 receptor blocker (basiliximab)	The same but with steroids	12	100
Montagnino *et al.* [14]	133	No	CsA	Everolimus	IL-2 receptor blocker (basiliximab)	The same but with steroids	24	Not available
Vincenti *et al.* [15]	224	Yes	CsA	Myf	IL-2 receptor blocker (basiliximab)	The same but with steroids	12	Not available
Laftavi *et al.* [16]	60	No	Tac	MMF	Anti-lymphocytic depletive antibodies	The same but with steroids	12	Not available
Rostaing *et al.* [17]	538	Yes	Tac	MMF	IL-2 receptor blocker (daclizumab)	Tac + MMF and steroids	6	82
Vitko *et al.* [18]	298	Yes	Tac	MMF	No	The same but with steroids	6	93
Woodle *et al.* [19]	386	Yes	Tac	MMF	Anti-lymphocytic depletive antibodies or IL-2 receptor blocker	The same but with steroids	60	100

Pascual et al, Neprol Dial Transplant 2012: 27: 825-832.

Vincenti et al. A Randomized, Multicenter Study of Steroid Avoidance, Early Steroid Withdrawal or Standard Steroid Therapy in Kidney Transplant Recipients. *American Journal of Transplantation* 8:307-316, 2008

American Journal of Transplantation 2008; 8: 307–316
Blackwell Munksgaard

doi: 10.1111/j.1600-6143.2007.02057.x

A Randomized, Multicenter Study of Steroid Avoidance, Early Steroid Withdrawal or Standard Steroid Therapy in Kidney Transplant Recipients

F. Vincenti[a,*], F. P. Schena[b], S. Paraskevas[c], I. A. Hauser[d], R. G. Walker[e] and J. Grinyo[f], on behalf of the FREEDOM Study Group[†]

A three-am, prospective, randomized, open-label, multi-center, study in 40 international centers

- 336 renal transplant recipients with PRA ≤ 20%
- Basiliximab as an induction therapy
- No CS at all *vs* CS withdrawal at day 7 *vs* standard CS
- Maintenance immunosuppression consisted of cyclosporine and MMF

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American Journal of Transplantation 2008; 8: 307–316
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Table 8: Parameters associated with steroid exposure at month 12. Continuous variables are shown as median values unless otherwise stated

	Steroid free (n = 112)	Steroid withdrawal (n = 115)	Standard steroids (n = 109)
De novo use of antihyperglycemic medication	5 (4.5%)[1]	14 (12.2%)	16 (14.7%)
Change in body mass index (kg/m^2)	1.03	0.88[2]	1.88
Total cholesterol (mmol/L) [range]	4.9 [2.5–7.5]	4.9 [3.0–6.8]	5.0 [3.0–9.7]
Triglyceride level (mmol/L) [range]	1.6 [0.4–8.1]	1.6[3] [0.4–7.3]	1.9 [0.6–11.0]
Use of lipid-lowering medication	59 (53.2%)	42 (36.5%)[4]	57 (52.3%)
Use of antihypertensive medication	83/104 (79.8%)	86/106 (81.1%)	89/101 (88.1%)
Mean change in spine bone mass density (% change)	−1.80 ± 6.72	−1.77 ± 6.03	−1.53 ± 9.93
Mean change in hip bone mass density (% change)	1.21 ± 8.25 (n = 38)	0.64 ± 8.36 (n = 39)	−0.23 ± 8.10 (n = 36)

[1]p = 0.010; [2]p = 0.008; [3]p = 0.030; [4]p = 0.018 (all vs. standard-steroids group).

American Journal of Transplantation 2008; 8: 307–316
Blackwell Munksgaard

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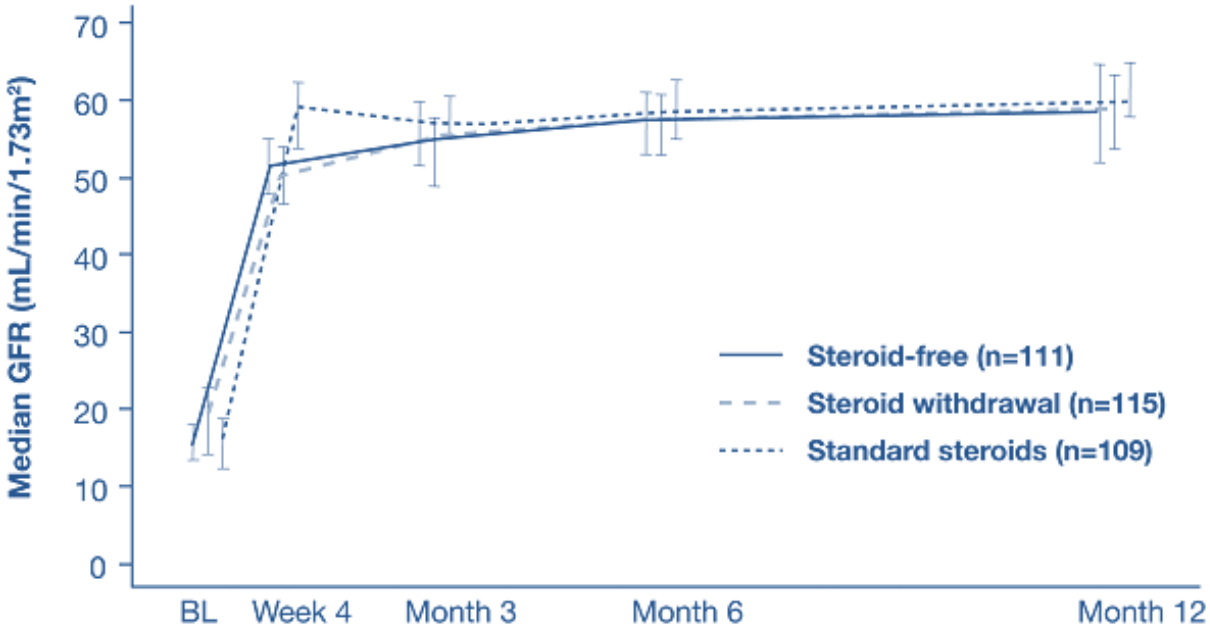

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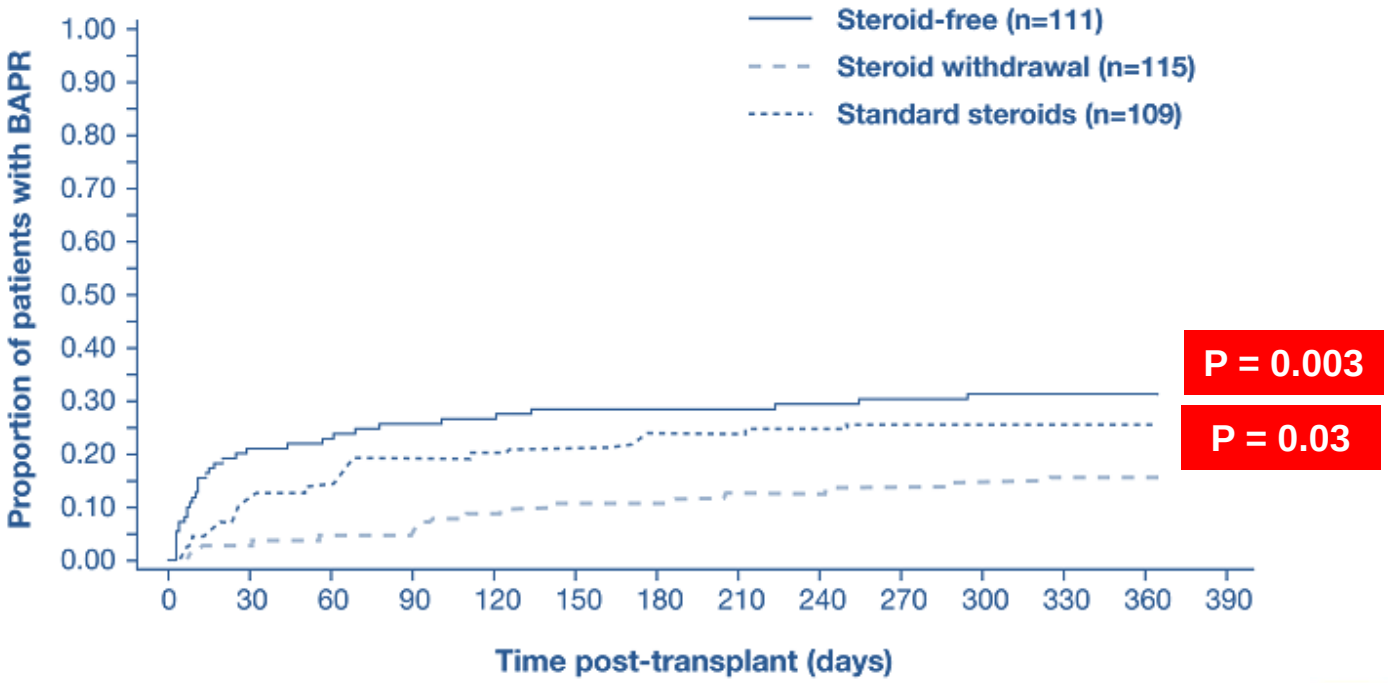

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In a standard-risk renal transplant population receiving CsA & MPS and basiliximab, withdrawal of steroids by the end of the first week posttransplant may offer a favorable risk–benefit balance, with comparable 1-year renal graft function to a standard steroids regimen.

Longer follow-up is required, however, to characterize the safety and the benefit of steroid sparing beyond 1 year.

Steroid- free protocols: RCTs

- Steroid avoidance

VS

- Late steroid withdrawal

Steroid avoidance VS Steroid withdrawal

- It appears that late CS withdrawal (more than 6 mo and possibly years after Tx) represents the least favorable method of the CS minimization strategies.

- By that time, certain CS-related complications would already have been established.

- Acute rejection risk is clearly increased upon late withdrawal of immunosuppressants as dictated by cases of non-compliant patients.

http://www.kidney-international.org review

KDIGO clinical practice guideline for the care of kidney transplant recipients: a summary

3.3: If prednisone is being used beyond the first week after transplantation, we suggest prednisone be continued rather than withdrawn. (*2C*)

Steroid- free protocols:
Impact on graft histopathology

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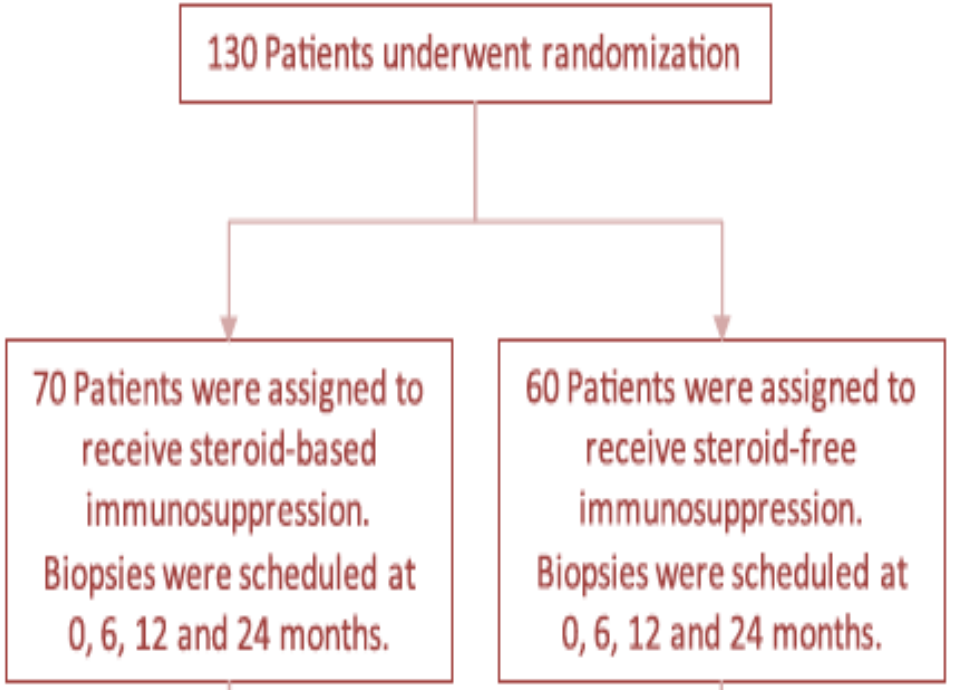
American Journal of Transplantation 2012; 12: 2730–2743
Wiley Periodicals Inc.

doi: 10.1111/j.1600-6143.2012.04144.x

Subclinical Inflammation and Chronic Renal Allograft Injury in a Randomized Trial on Steroid Avoidance in Pediatric Kidney Transplantation

M. Naesens[a,b,c], O. Salvatierra[c], M. Benfield[d], R. B. Ettenger[e], V. Dharnidharka[f], W. Harmon[g], R. Mathias[h] and M. M. Sarwal[b,h,*], for the SNS01-NIH-CCTPT Multicenter Trial



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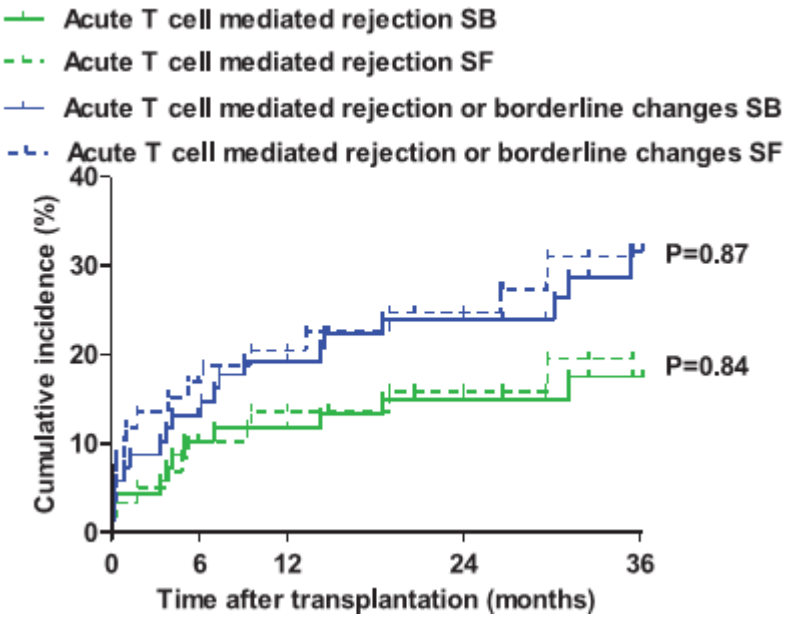
Acute rejection and borderline changes



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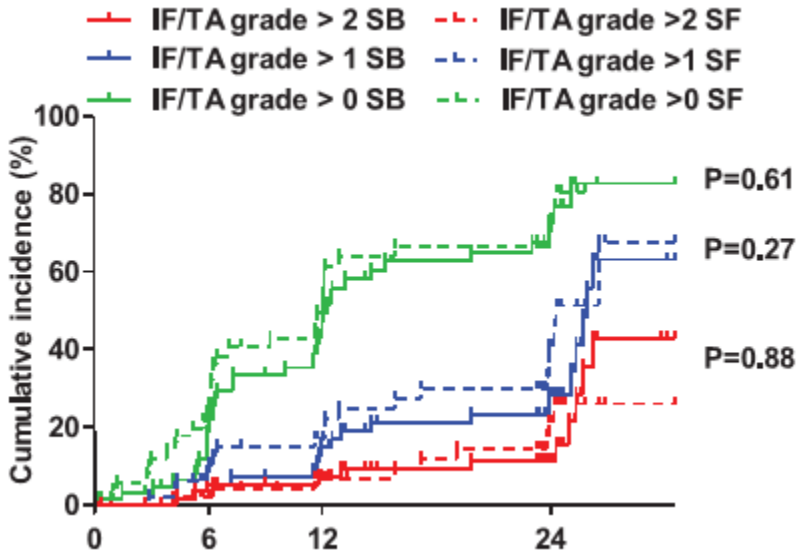
Chronic histological damage

IF / TA grades



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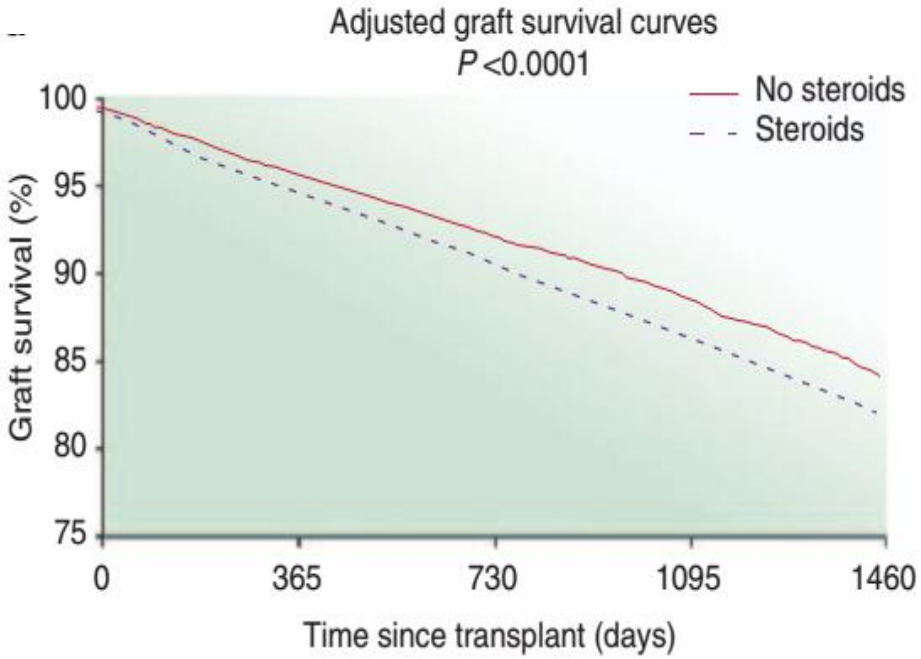
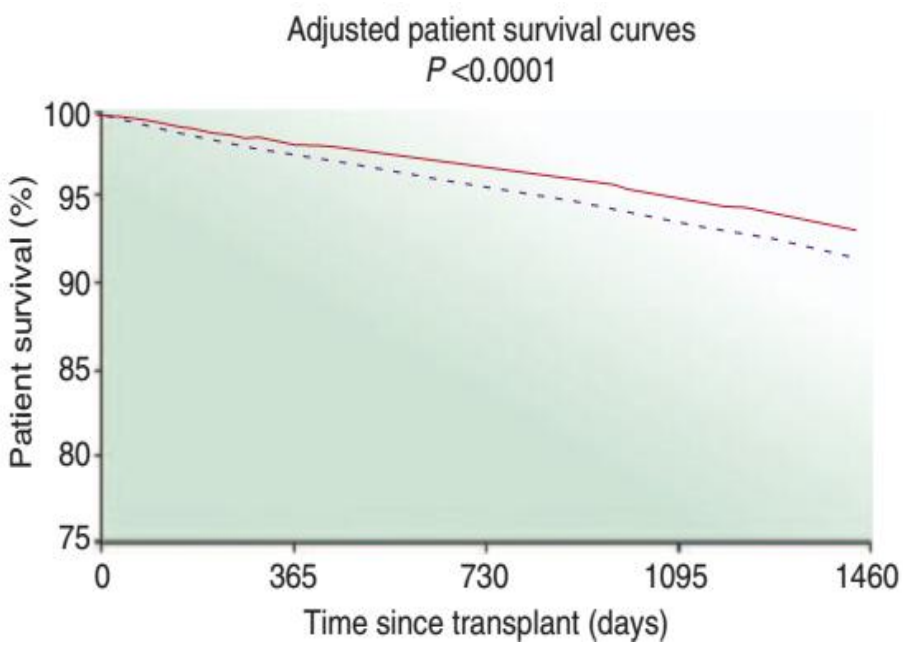
Steroid- free protocols:
Impact on graft & patient survival

Outcome of kidney transplant patients discharged with and without steroids during 2000 and 2006





Luan et al. Kidney Interna tional (2009) 7 6, 825–830

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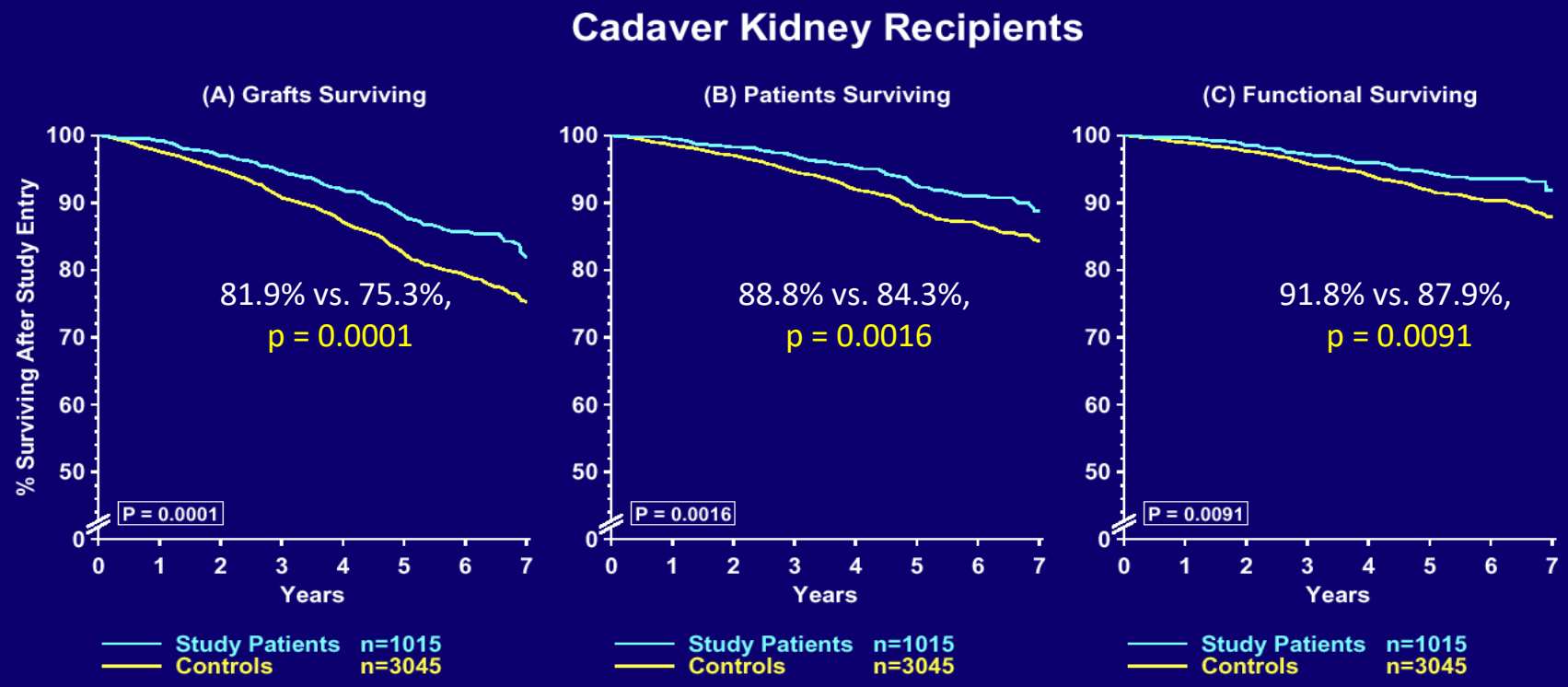
Opelz et al. Long term prospective study of steroid withdrawal in Kidney and Heart Transplantation. *American Journal of Transplantation* 5:720-728, 2006

Long-Term Prospective Study of Steroid Withdrawal in Kidney and Heart Transplant Recipients



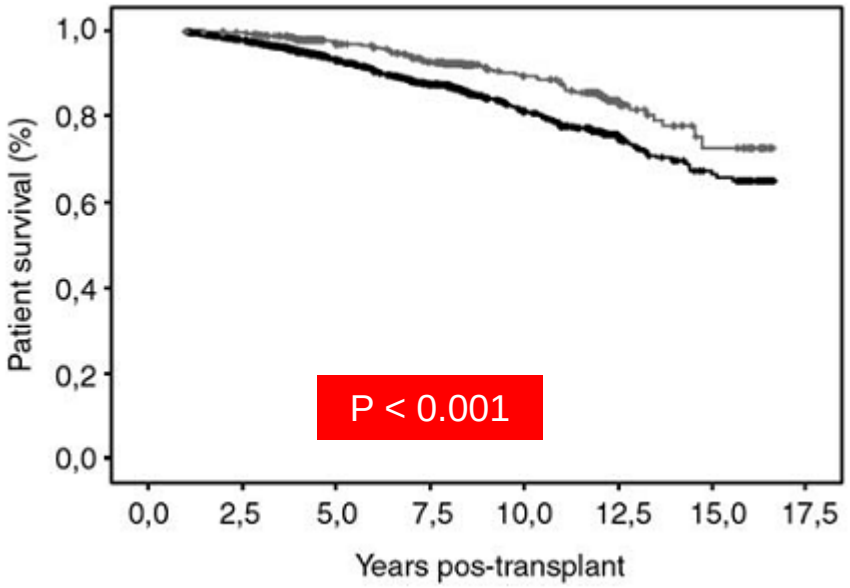
Opelz G et al, Am J Transpl 5: 720, 2006

NDT Plus (2010) 3 [Suppl 2]: ii32–ii36
doi: 10.1093/ndtplus/sfq064

NDT PLUS
Nephrology Dialysis Transplantation

Effect of long-term steroid withdrawal in renal transplant recipients: a retrospective cohort study

Miguel Gonzalez-Molina[1], Miguel Angel Gentil[2], Dolores Burgos[1], Mercedes Cabello[1], Carmen Cobelo[1], Jesús Bustamante[3], Pedro Errasti[4], Antonio Franco[5] and Domingo Hernández[1]



Steroid withdrawal in selected patients had no negative effect over time on renal function and graft survival, and it was associated with reduced mortality.

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Steroid- free protocols: Benefits

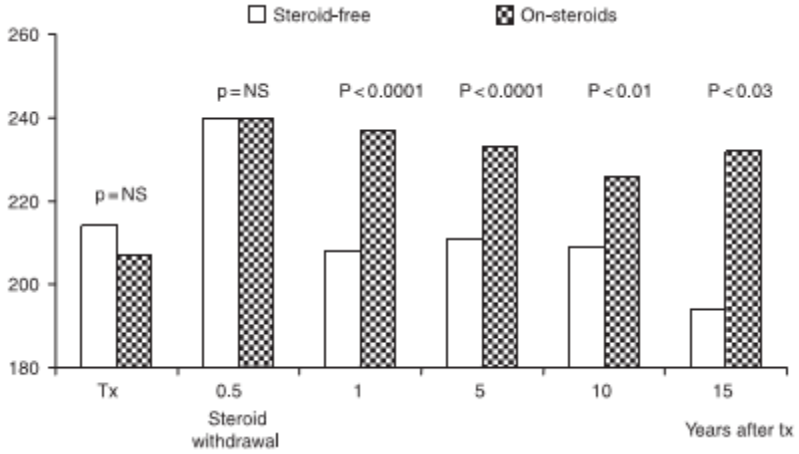
- Cardiovascular risk
- Stroke & CVA
- Bone diseases
- Overall mortality (death with function grafts)
- NODAT

Clin Transplant 2006: 20: 571–581 DOI: 10.1111/j.1399-0012.2006.00579.x

Clinical Transplantation

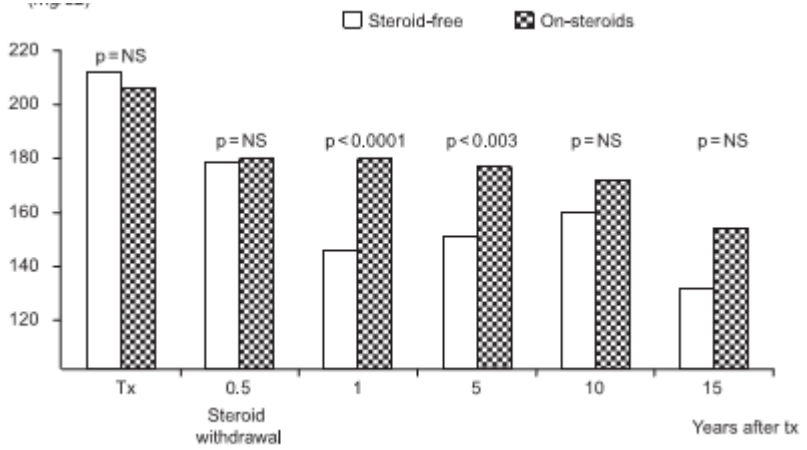
Steroid-free immunosuppression regime reduces both long-term cardiovascular morbidity and patient mortality in renal transplant recipients

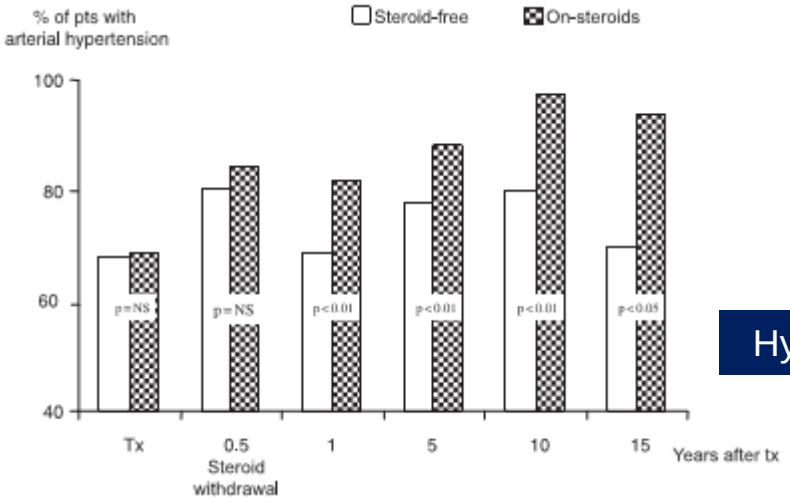
Sandrini S, Maffeis R, Setti G, Bossini N, Maiorca P, Maffei C, Guerini S, Zubani R, Portolani N, Bonardelli S, Nodari F, Giulini SM, Cancarini G.



Serum Cholesterol

Serum Triglycerides





Hypertension

Sandrini et al, Clin Transplant 2006: 20: 571–581.

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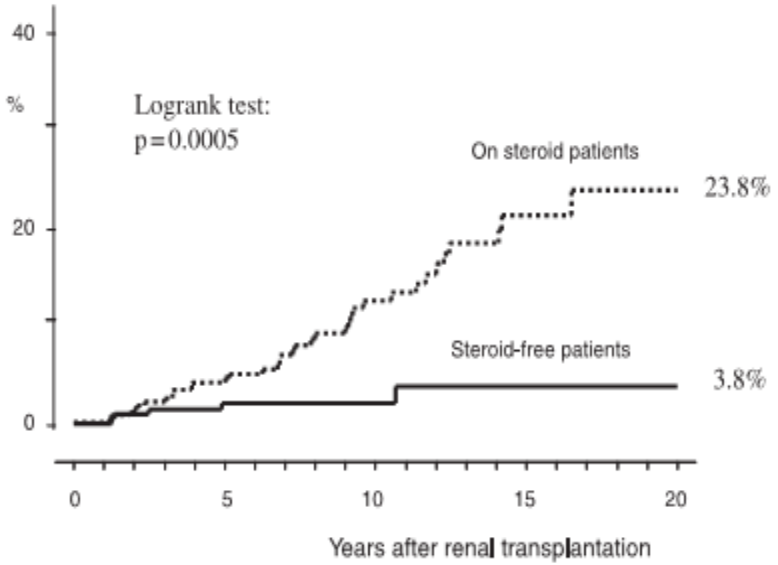
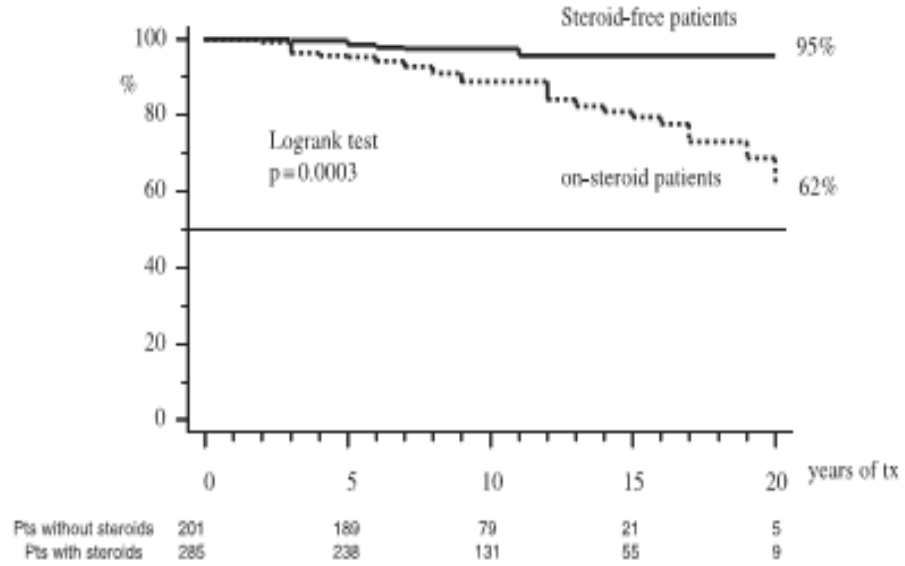


Estimated cumulative probability of developing CVD



Estimated cumulative probability of patient survival

Sandrini et al, Clin Transplant 2006: 20: 571–581.

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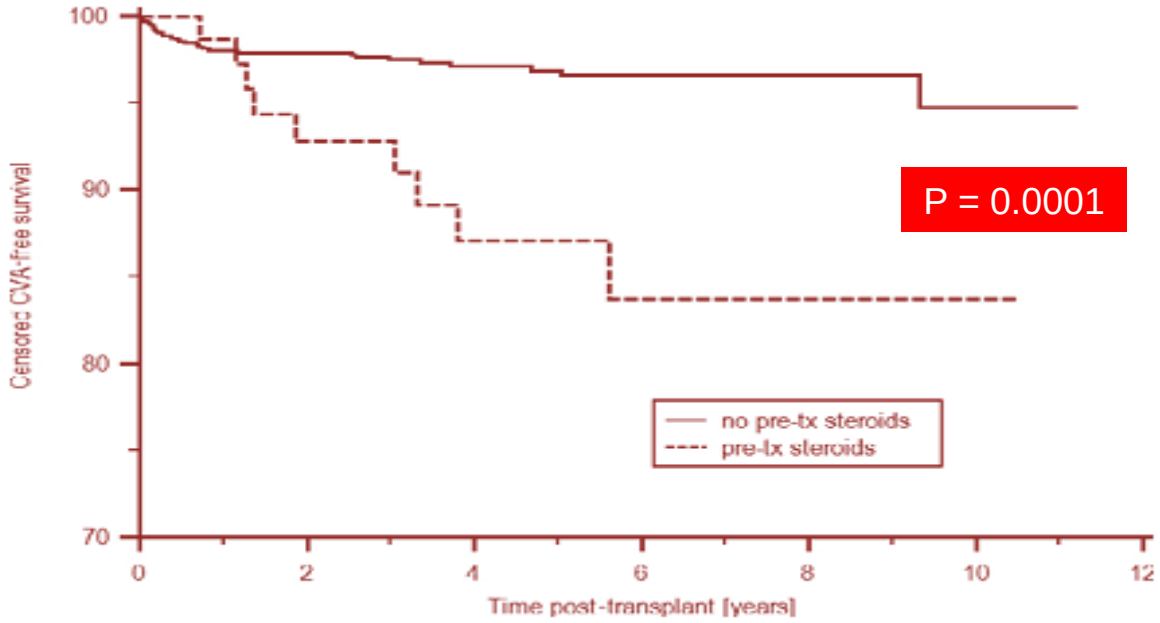
Clin Transplant 2015: 29: 18–25 DOI: 10.1111/ctr.12476

Clinical Transplantation

Incidence, risk factors, and outcomes of stroke post-transplantation in patients receiving a steroid sparing immunosuppression protocol

Willicombe M, Kumar N, Goodall D, Clarke C, McLean AG, Power A, Taube D. Incidence, risk factors, and outcomes of stroke



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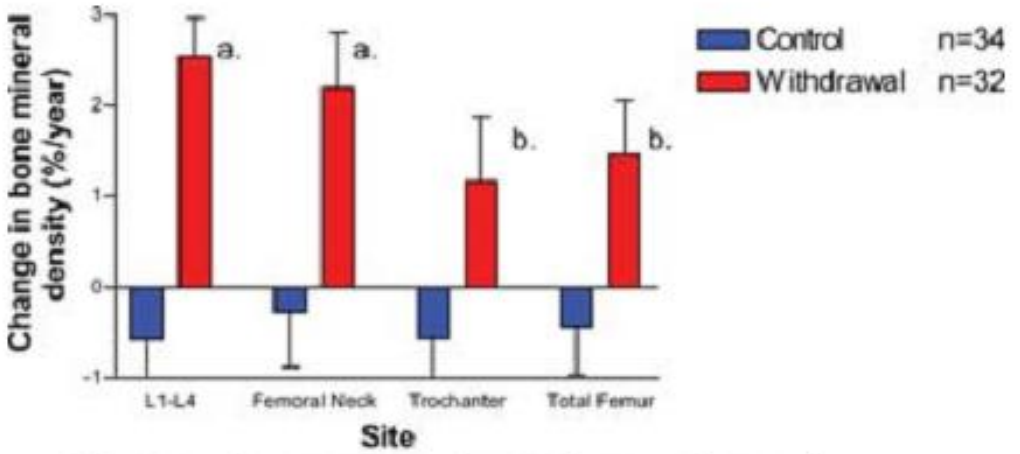
American Journal of Transplantation 2006; 6: 2929–2936
Blackwell Munksgaard

doi: 10.1111/j.1600-6143.2006.01557.x

Late Low-Dose Steroid Withdrawal in Renal Transplant Recipients Increases Bone Formation and Bone Mineral Density

C.K.T. Farmer[a,*], G. Hampson[b], I.C. Abbs[a], R.M. Hilton[a], C.G. Koffman[a], I. Fogelman[c] and S.H. Sacks[a]

Changes in bone mineral density



a. p<0.01 compared to control b. p<0.05 compared to control

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American Journal of Transplantation 2006; 6: 2929–2936
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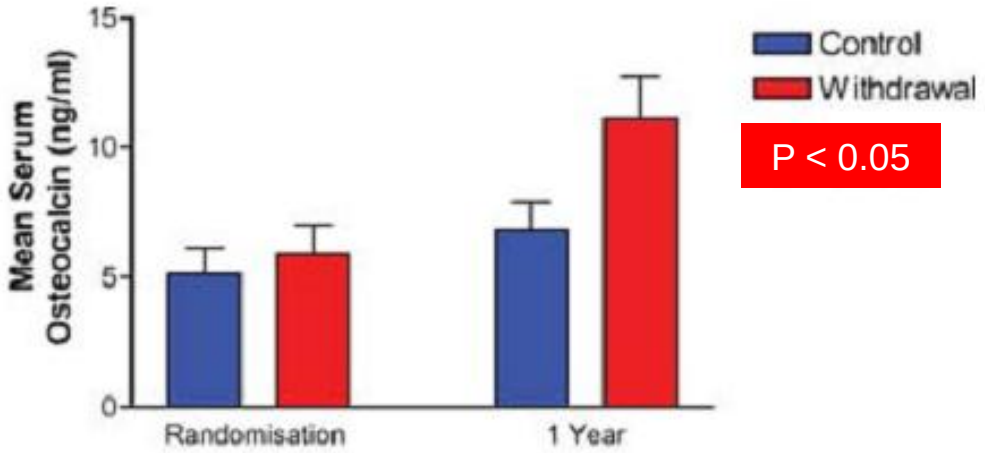
Serum Osteocalcin



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American Journal of Transplantation 2006; 6: 2929–2936
Blackwell Munksgaard

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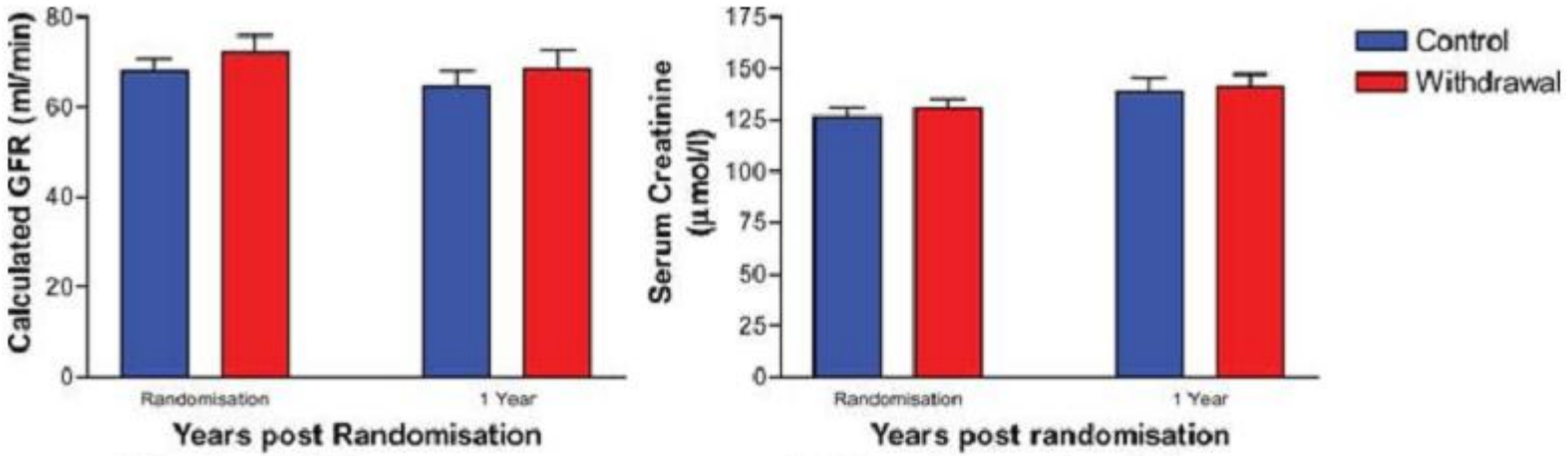

a. Calculated GFR

b. Mean Serum Creatinine

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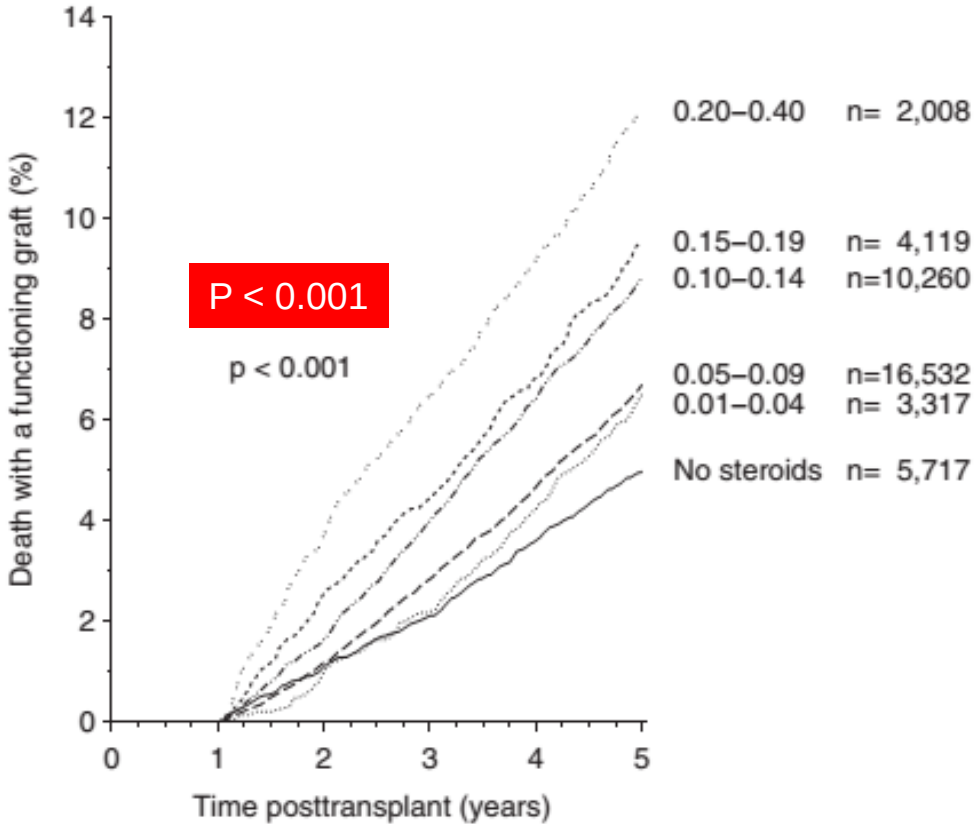
American Journal of Transplantation 2013; 13: 2096–2105
Wiley Periodicals Inc.

doi: 10.1111/ajt.12313

Association Between Steroid Dosage and Death With a Functioning Graft After Kidney Transplantation

G. Opelz* and B. Döhler



Steroid dose mg/kg/day

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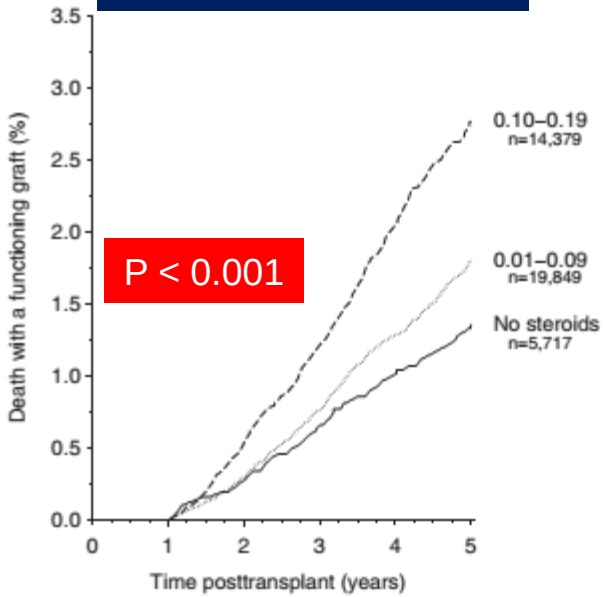
American Journal of Transplantation 2013; 13: 2096–2105
Wiley Periodicals Inc.

doi: 10.1111/ajt.12313

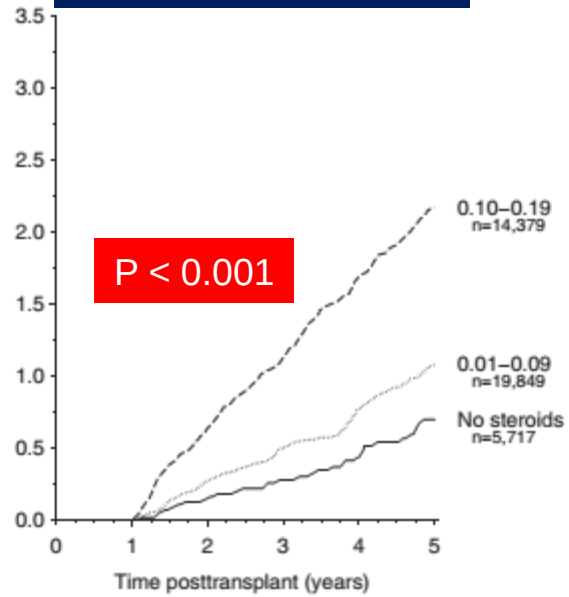
Association Between Steroid Dosage and Death With a Functioning Graft After Kidney Transplantation

G. Opelz* and B. Döhler

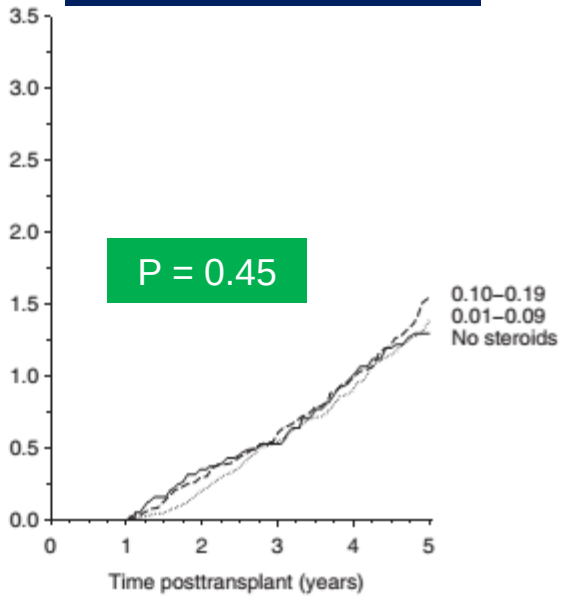
Death due to CVD



Death due to infection



Death due to malignancy



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American Journal of Transplantation 2015; 15: 1982–1990
Wiley Periodicals Inc.

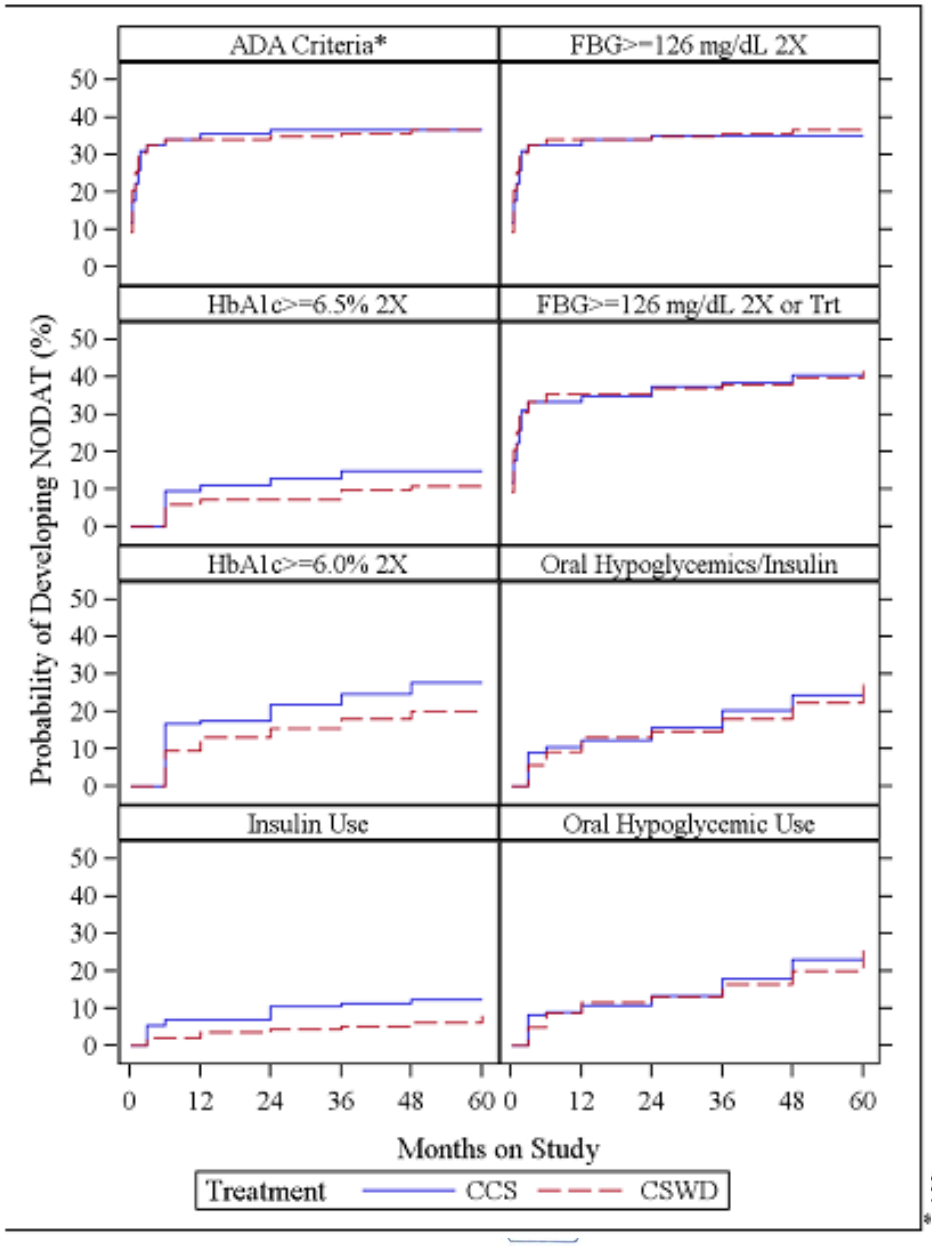
doi: 10.1111/ajt.13247

Brief Communication

New-Onset Diabetes After Transplantation: Results From a Double-Blind Early Corticosteroid Withdrawal Trial

J. D. Pirsch[1], A. K. Henning[2], M. R. First[3,*], W. Fitzsimmons[3], A. O. Gaber[4,5], R. Reisfield[3], F. Shihab[6] and E. S. Woodle[7]

Steroid withdrawal has a limited impact in reducing NODAT when compared to low-dose prednisone (5 mg/day from month 6 to 5 years)



Pirsch et al. A JT 2015; 15: 1982–1990

Steroid - free protocols: Pediatric recipients

American Journal of Transplantation 2015; 15: 2203–2210
Wiley Periodicals Inc.

doi: 10.1111/ajt.13270

Brief Communication

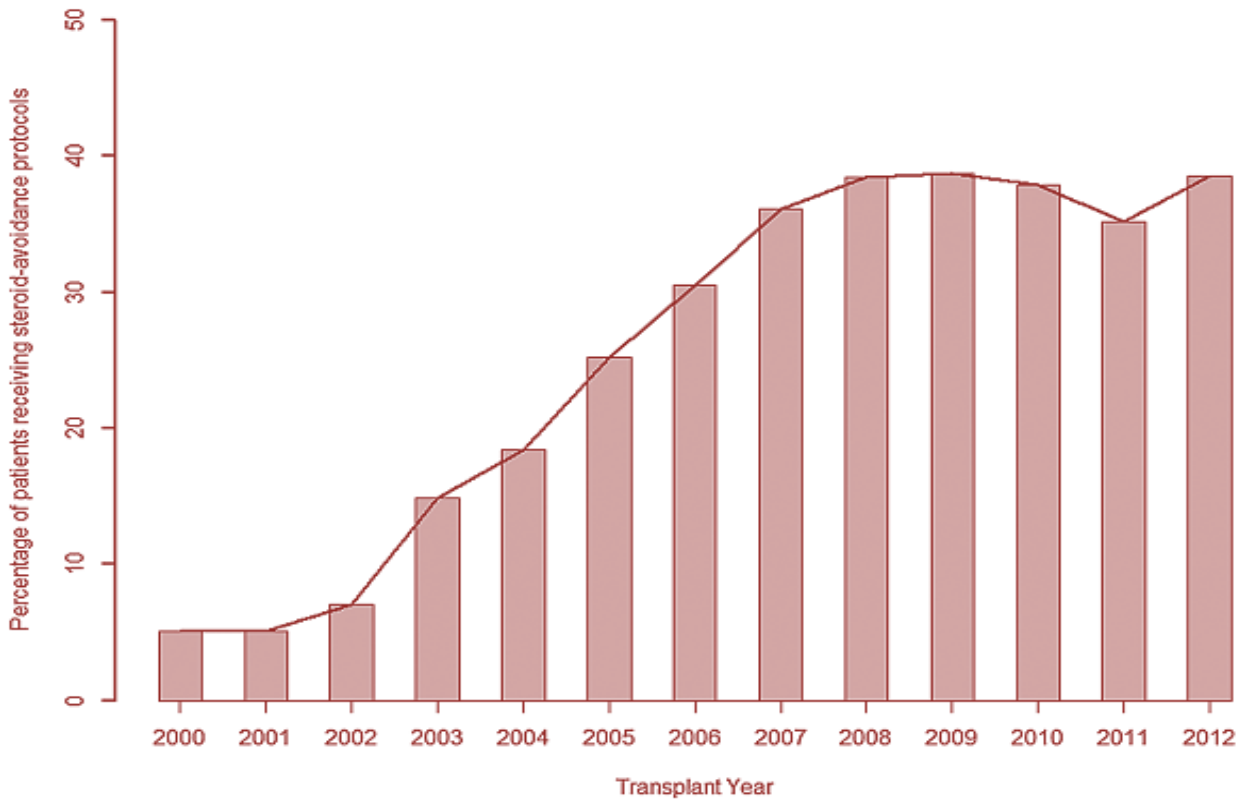
Clinical Practice of Steroid Avoidance in Pediatric Kidney Transplantation

E. Nehus[1,2,*], C. Liu[3], D. K. Hooper[1,2,4], M. Macaluso[2,3] and M.-O. Kim[2,3]

reactive antibody; UNOS, United Network of Organ Sharing

Percentage of patients treated with steroid avoidance by transplant year.

UNOS



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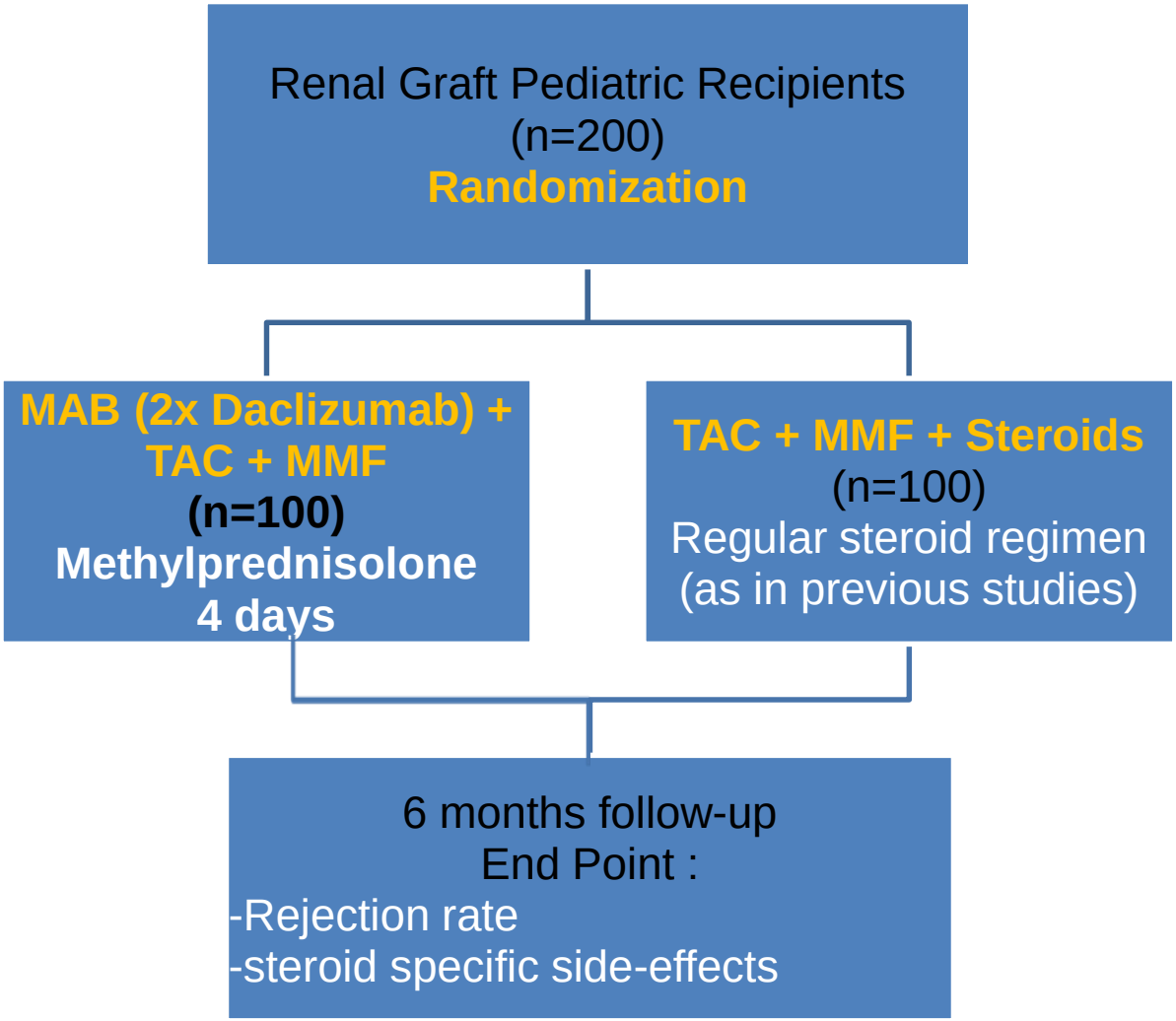
European TWIST Study: Design



Grenda et al. A JT 2010; 10: 828–836

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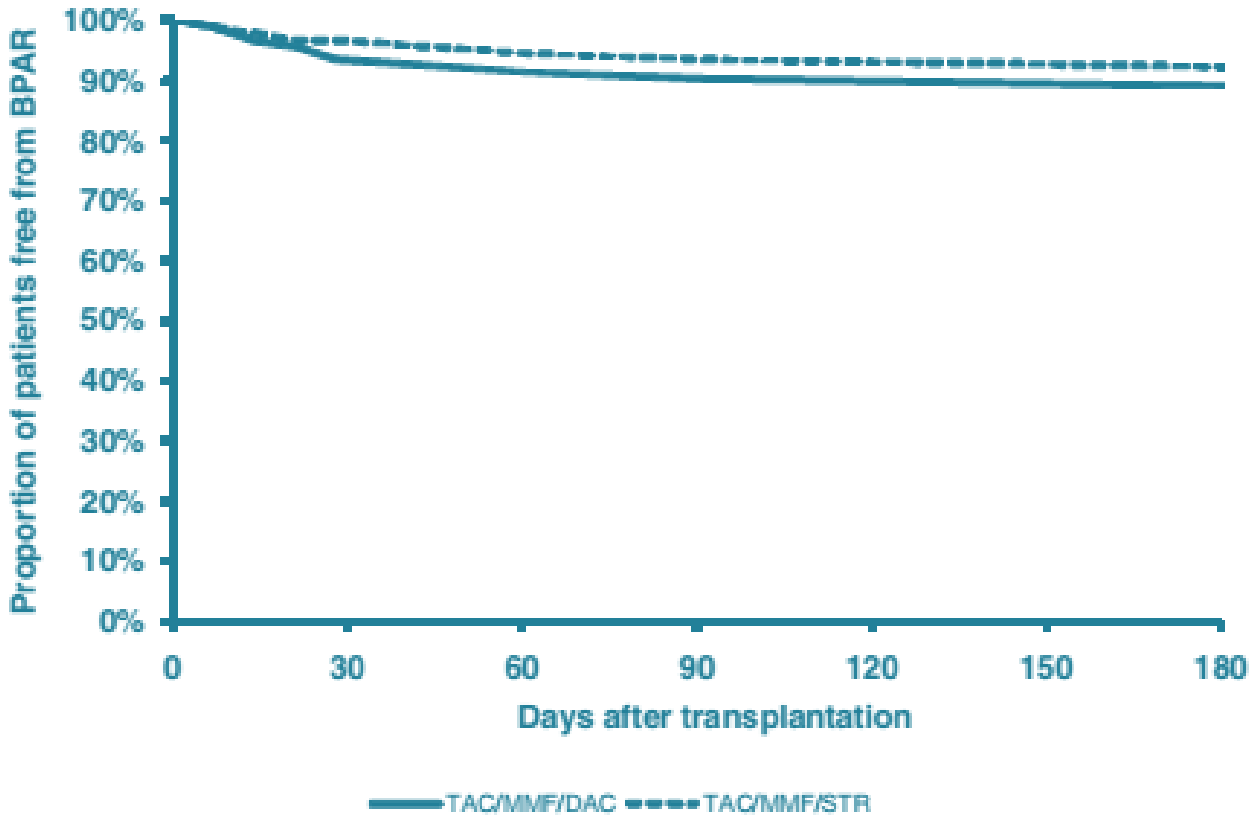
European TWIST Study: impact BPAR



Grenda et al. A JT 2010; 10: 828–836

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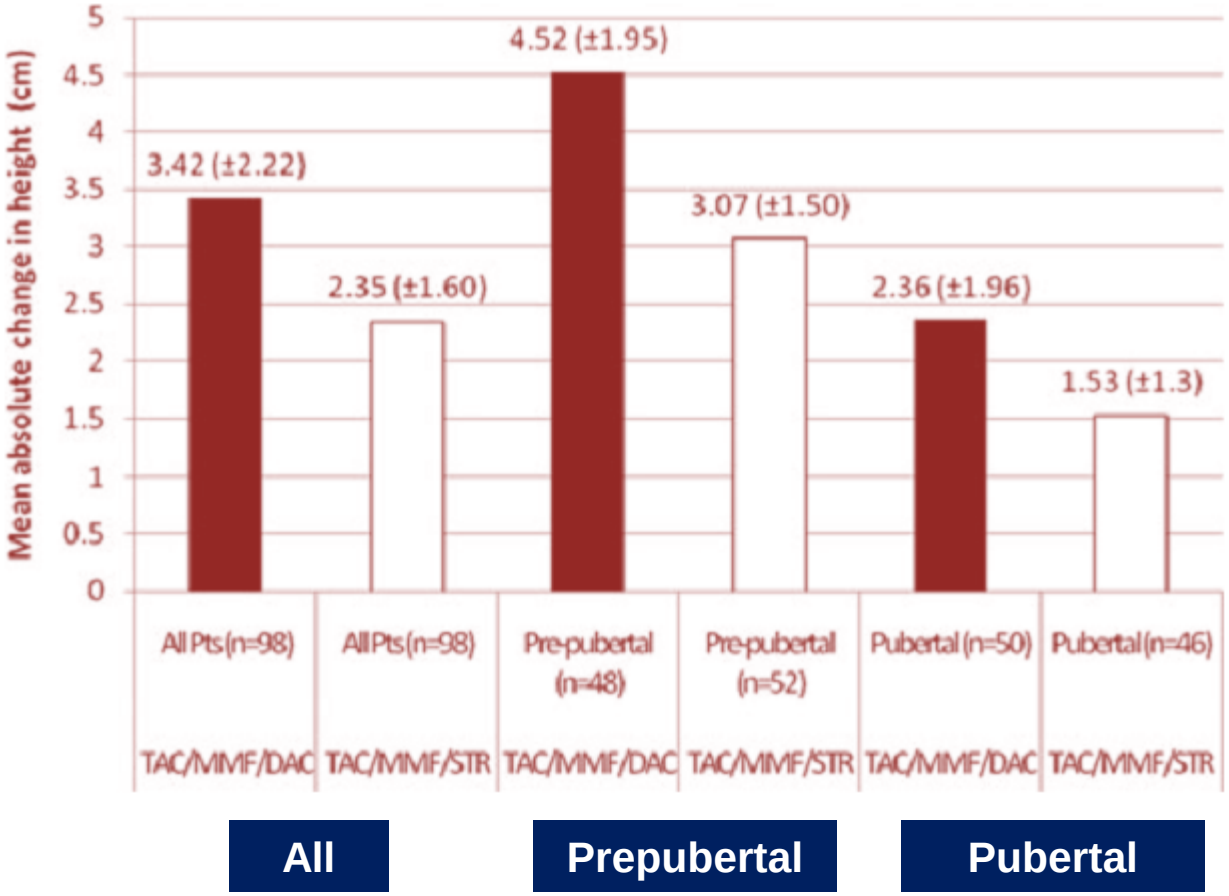
European TWIST Study: impact on growth



All **Prepubertal** **Pubertal**

Absolute change in mean height at 6 months.

- *Greater in patients treated with TAC/MMF/DAC than in those treated with TAC/MMF/STR*
- *Greater in prepubertal than in pubertal children in both treatment groups*

Grenda et al. A JT 2010; 10: 828–836

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PLOS ONE | DOI:10.1371/journal.pone.0146523 March 18, 2016

RESEARCH ARTICLE

Steroid Avoidance or Withdrawal Regimens in Paediatric Kidney Transplantation: A Meta-Analysis of Randomised Controlled Trials

Huanxi Zhang[1☯], Yitao Zheng[1☯], Longshan Liu[1], Qian Fu[1], Jun Li[1], Qingshan Huang[2], Huijiao Liu[3], Ronghai Deng[1*], Changxi Wang[1*]

1 Organ Transplant Center, the First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China, **2** Medical Information Institute, Sun Yat-Sen University, Guangzhou, China, **3** Department of Neurology, the First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China

☯ These authors contributed equally to this work.
* wangchx@mail.sysu.edu.cn (CW); mddrh81@163.com (RD)

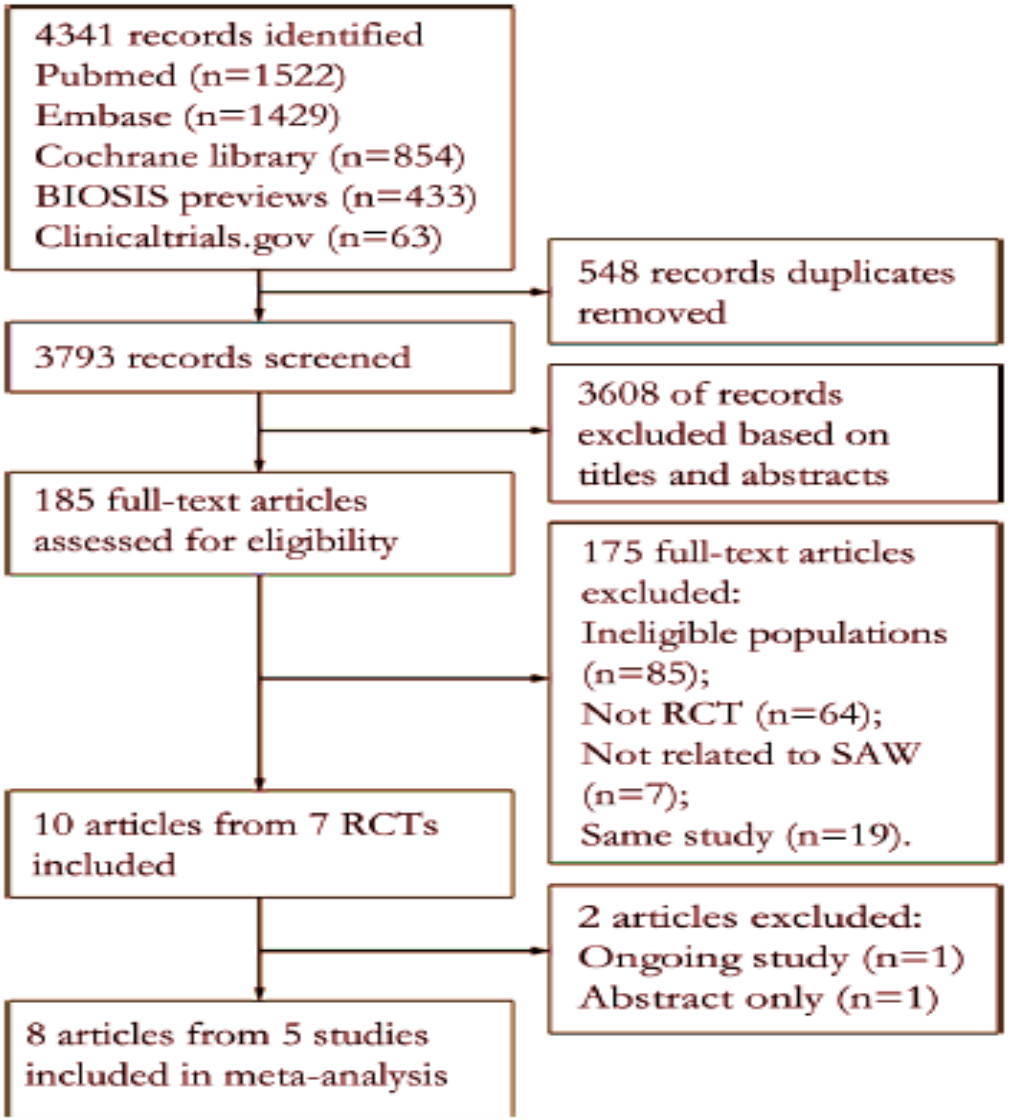


Fig 1. Flow chart showing the sources and identification of the included studies. Abbreviations: RCT, randomised controlled trial; SAW, steroid avoidance or withdrawal.

PLOS ONE | DOI:10.1371/journal.pone.0146523 March 18, 2016

RESEARCH ARTICLE

Steroid Avoidance or Withdrawal Regimens in Paediatric Kidney Transplantation: A Meta-Analysis of Randomised Controlled Trials

Characteristics of the included studies.

Source	Follow-up (years post-withdrawal)[c]	Sample size (SAW/SB)	Age range (years)	Country	Race (white/black/Asian/others)(%)	PRA	Time of starting withdrawal post-transplant	Concomitant IST	Primary outcome
Webb et al., 2015	2	98/98	2~18	EU, Israel, South Africa	86.2/5.1/6.9/1.5	≤50%	Day 5	DcL/TAC/MMF	growth
Mericq et al., 2013	1	14/16	1~16	Chile	All Chileans	no limits	Day 6	BsL/TAC/MMF	growth
Sarwal et al., 2012	3	60/70	0~21	USA	52.3/26.1/6.1/15.4	≤20%	CA	DcL/TAC/MMF	growth, AR
Hocker et al., 2010	2.25	23/17	0~18	Germany	97.6/-/2.4/-	≤80%	Year 1–2[a]	CsA/MMF	growth
Benfield et al., 2010	2.5	73/59	0~20	USA	75.0/15.2/3.8/6.1	no limits	Month 6[b]	BsL/TAC/SRL BsL/CsA/SRL	growth

Steroid Avoidance or Withdrawal in Pediatric Kidney Transplantation: Meta Analysis of Randomized Controlled Trials

Steroid –free regimens are justified in selected pediatric renal allograft recipients because it provides significant benefits in post-transplant growth within the first year post-withdrawal with minimal effects on the risk of AR, graft function, and graft and patient survival within 3 years post-withdrawal.

The selected pediatric recipients should have the following characteristics:

- Prepubertal
- Caucasian
- Primary disease not related to immunological factors
- De novo kidney transplant recipient
- Low PRA

Steroid- free protocols: High risk patients

- Risk for recurrence of Glomerulonephritis
  - African Americans

Transplantation. 2011 June 27; 91(12): 1386–1391. doi:10.1097/TP.0b013e31821bf157.

Recurrent Glomerulonephritis Under Rapid Discontinuation of Steroids

Aleksandra Kukla[1], **Eric Chen**[1], **Richard Spong**[1], **Marc Weber**[1], **Yasser El-Shahawi**[1], **Kristen Gillingham**[2], **Arthur J. Matas**[2], and **Hassan N. Ibrahim**[1,3]

[1]Division of Renal Diseases and Hypertension, University of Minnesota, Minneapolis, MN.

[2]Department of Surgery, University of Minnesota, Minneapolis, MN.

Rate of histologic recurrence (%)

	GN: no steroids				GN: steroids				
	N	1 yr	5 yr	7 yr	n	1 yr	5 yr	7 yr	*P*
Focal segmental GN	61	17	28.8	28.8	49	6.4	9.2	12.3	0.02
Membranous nephropathy	12	8	31	31	12	0	0	10[a]	0.04
Membranoproliferative[a]	18	5.5	11.2	31	31	6.7	11	16	0.5
IgA nephropathy	65	1.6	8.8	22	66	1.6	3.3	5.2	0.02
Chronic GN	27	0	0	0	49	0	0	0	
SLE	15	0	0	0	22	0	0	0	
Rapidly progressive GN	8	0	0	0	8	0	0	0	
Anti-GBM	3	0	0	0	11	0	0	0	
Henoch-Schonlein purpura	4	0	0	0	7	0	0	0	
Wegener's granulomatosis	2	0	0	0	5	0	0	0	
Overall recurrence rate (%)		6.7	13.7	19.2		2.4	3.8	5.3	<0.0001

Kukla et al. Transplantation 2011 27; 91(12): 1386–1391

American Journal of Transplantation 2008; 8: 1759–1760
Wiley Periodicals Inc.

doi: 10.1111/j.1600-6143.2008.02292.x

Letter to the Editor

Steroid Avoidance in African Americans: Does Inadequate Induction Lead to Increased Early Rejection and Long-Term Graft Injury?

Attempting steroid avoidance in AA renal allograft recipients with great caution, including use of potent induction therapy, TCL/MMF, surveillance biopsy and close monitoring.

Doshi et al. AJT 2008; 8: 1759–1760

International Journal of Clinical Medicine, 2016, 7, 204-216
Published Online March 2016 in SciRes. http://www.scirp.org/journal/ijcm
http://dx.doi.org/10.4236/ijcm.2016.73021

Scientific Research Publishing

Impact of Maintenance Steroids versus Rapid Steroid Withdrawal in African-American Kidney Transplant Recipients: Comparison of Two Urban Centers

W. James Chon[1*], Amishi Desai[2*], Coady Wing[3], Divya Arwindekar[4], Ignatius Y. S. Tang[4,5], Michelle A. Josephson[1], Sanjeev Akkina[2]

[1]Department of Medicine, Division of Nephrology, University of Chicago Medicine, Chicago, IL, USA
[2]Department of Medicine, Division of Nephrology, Loyola University Medical Center, Maywood, IL, USA
[3]School of Public and Environmental Affairs, Indiana University, Bloomington, IN, USA
[4]Department of Medicine, Division of Nephrology, University of Illinois Hospital & Health Sciences System, Chicago, IL, USA
[5]Department of Medicine, Division of Nephrology, Jesse Brown VA Medical Center, Chicago, IL, USA

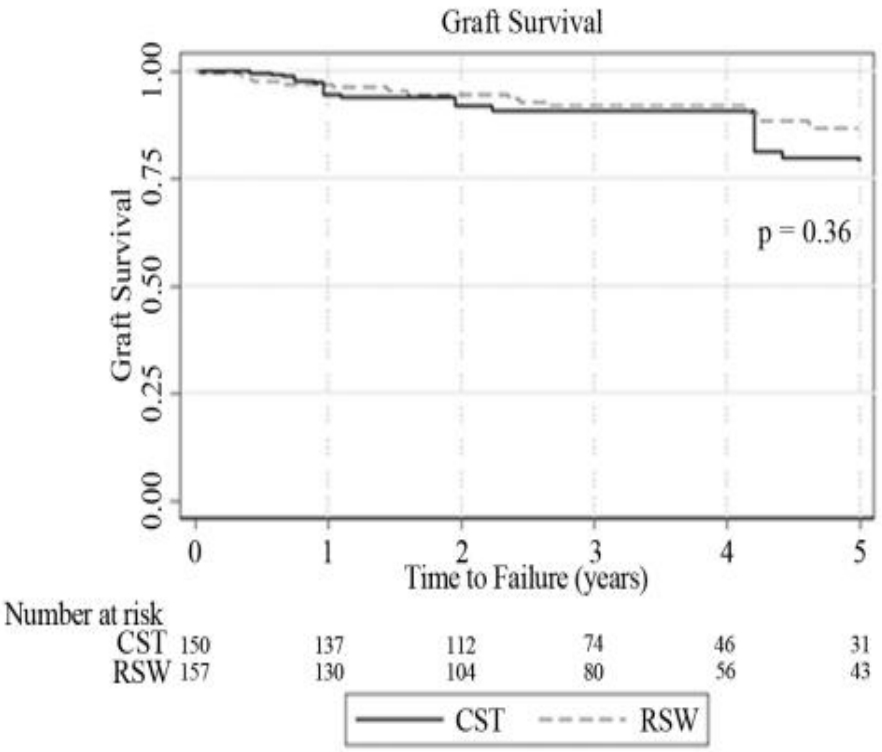
Urology and Nephrology Center
Mansoura University

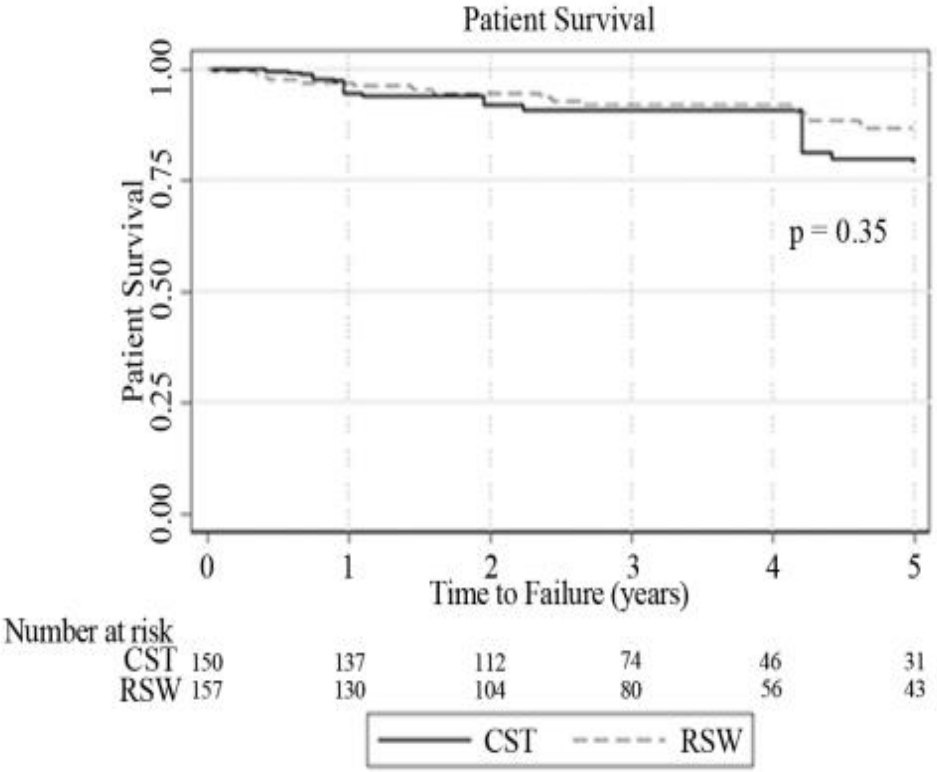
Impact of Maintenance Steroids versus Rapid Steroid Withdrawal in African-American Kidney Transplant Recipients

	CST	RSW
Induction Therapy	Anti-thymocyte globulin 1.5 mg/kg × 4 doses (maximum 100 mg/day) Methylprednisolone	Anti-thymocyte globulin 1.5 mg/kg (ideal body weight) × 5 doses (no maximum dose) Methylprednisolone
Maintenance immunosuppression	Tacrolimus (trough level) • 0 - 6 months - 6 - 9 ng/mL • >6 months - 4 - 7 ng/mL Mycophenolate mofetil 1000 mg bid or mycophenolate sodium 720 mg bid Prednisone taper to 5 mg daily by 1 month	Tacrolimus (trough level) • 0 - 2 months - 8 - 12 ng/mL • >2 months - 5 - 10 ng/mL Mycophenolate mofetil 1000 mg bid or mycophenolate sodium 720 mg bid Prednisone tapered off by day 6

Chon et al. Int J Clin Med, 2016, 7, 204-216

Impact of Maintenance Steroids versus Rapid Steroid Withdrawal in African-American Kidney Transplant Recipients





Chon et al. Int J Clin Med, 2016, 7, 204-216

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Mansoura Experience

Experimental and Clinical Transplantation (2007) 2: 673-679

Steroid-Avoidance Immunosuppression Regimen in Live-Donor Renal Allotransplant Recipients: a Prospective, Randomized, Controlled Study

Ahmed H Nematalla, Mohmed A Bakr, Osama A Gheith, Amgad E ELAgroudy, EL-Metwally ELShahawy, Mohamed AGhoneim

(June 2004 – July 2005)

100 recipients randomized into 2 groups

Group I: St (3 days) Tac + MMF (50 patients)

Group II: St + Tac + MMF (50 patients)

Both groups: Basiliximab induction.

Table 2. Histopathologic examination of graft biopsies (event biopsy)

	Experimental group (n=50)	Control group (n=50)	*P* value
Acute rejection episodes			
Total number	8 (16%)	8 (16%)	
Banff grade			
Borderline	6	5	
Grade Ia	–	1	
Grade IIa	2	2	.479
Early/late	6/2	6/2	
Steroid sensitive/resistant	6/2	6/2	
Acute tubular necrosis	6	1	.041
Acute tacrolimus nephrotoxicity	1	1	
Normal	5	1	
Time to 1st rejection episode			
Range (days)	3-29	2-214	
Mean±SD (days)	1.88±5.85	15±51.57	.009

Table 3. Laboratory evaluation of patients in both groups at different time intervals

	Experimental group (n=50)	Control group (n=50)	*P* value
Graft function follow-up	Mean±SD	Mean±SD	
Creatinine level (μmol/L) at the			
1st week	132±107	99.6±116	.12
1st month	132±66	91.3±24.3	.01
6th month	107.9±24.3	99.6±24.3	.51
12th month	107.9±45	107.9±0.44	.90
	Mean±SD	Mean±SD	
Creatinine clearance (mL/min) at the end of the			
1st week	77.3±18.1	80.9±13.7	.23
1st month	68.7±20.0	79.3±21.3	.38
6th month	76.4±18.1	73.4±14.4	.89
12th month	74.9±23.1	71.3±10.9	.86
Lipid profile	Mean±SD	Mean±SD	
High-density lipoprotein (mmol/L)			
Baseline	204±0.97	2.44±35	.71
At 12 months	3.36±0.77	4.07±0.56	.04
Cholesterol (mmol/L)			
Baseline	3.7±0.59	4.18±0.93	.72
At 12 months	4.1±0.81	5.76±1.35	.001
Triglyceride level (mmol/L)			
Baseline	1±0.41	098±0.17	.15
At 12 months	1.01±0.23	1.35±0.31	.001

Table 4. Posttransplant complications in both groups

	Experimental group (n=50)			Control group (n=50)			*P* value
Antihypertensive medications	1 drug	2 drugs	3 drugs	1 drug	2 drugs	3 drugs	
Baseline	24%	0%	0%	32%	0%	0%	.528
6 months	4%	0%	0%	12%	20%	0%	.0020
12 months	4%	0%	0%	12%	8%	24%	.0009
Mean body weight in kilograms							
At 2 weeks	61.72±14.30			59.04±11.32			
At 12 months	67.80±16.20			70.52± 14.51			< .0001
Diabetes mellitus	2			8			.037
Gastritis	9			12			.390
Bone and joint pain	2			8			.042
Acne	1			10			.001
Infections - bacterial							
Urinary tact infections	8			16			.029
Chest infections	6			16			.02
Infections - viral							
Cytomegalovirus	1			3			.297
Herpes zoster	–			4			.040
Infections - fungal	2			4			.395
Admissions	5/50			12/50			.03
Surgical complications	0			9			.001

Experimental and Clinical Transplantation (2007) 2: 673-679

Steroid-Avoidance Immunosuppression Regimen in Live-Donor Renal Allotransplant Recipients: a Prospective, Randomized, Controlled Study

Ahmed H Nematalla, Mohmed A Bakr, Osama A Gheith, Amgad E ELAgroudy, EL-Metwally ELShahawy, Mohamed AGhoneim

Conclusions: **In living-donor renal transplant recipients with low immunologic risk, steroid avoidance (using basiliximab induction, tacrolimus, mycophenolate mofetil maintenance, and 3 days' steroid treatment) is feasible, safe, and carries with it fewer morbidities compared with the same immunosuppressive protocol with steroid maintenance. Longer follow-ups are required to prove the safety of this regimen.**

Transplantation Proceedings, 47, 1099–1104 (2015)

Long-Term Study of Steroid Avoidance in Renal Transplant Patients: A Single-Center Experience

A.M. Nagib*, M.H. Abbas, M.M. Abu-Elmagd, A.A.E.F. Denewar, A.H. Neamatalla, A.F. Refaie, and M.A. Bakr

Department of Dialysis and Transplantation, the Urology and Nephrology Center, Mansoura University, Mansoura, Egypt

Urology and Nephrology Center
Mansoura University

Transplantation Proceedings, 47, 1099–1104 (2015)

Long-Term Study of Steroid Avoidance in Renal Transplant Patients: A Single-Center Experience

A.M. Nagib*, M.H. Abbas, M.M. Abu-Elmagd, A.A.E.F. Denewar, A.H. Neamatalla, A.F. Refaie, and M.A. Bakr

Department of Dialysis and Transplantation, the Urology and Nephrology Center, Mansoura University, Mansoura, Egypt

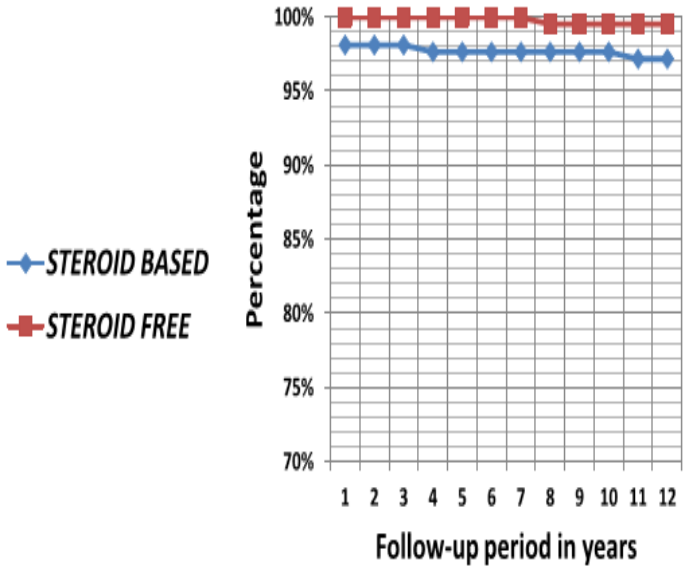

Fig 1. Patient survival.

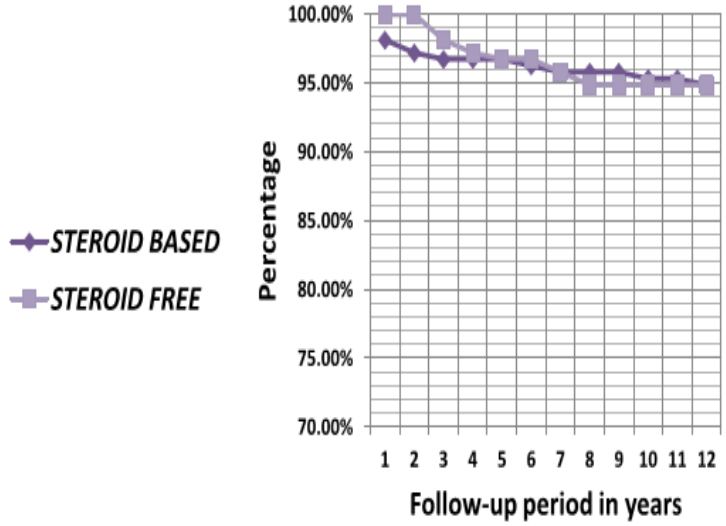

Fig 2. Graft survival.

Transplantation Proceedings, 47, 1099–1104 (2015)

Long-Term Study of Steroid Avoidance in Renal Transplant Patients:

Table 3. Posttransplantation Complications

Variable	Steroid-Free (Tac + MPA) (n = 214)	Steroid Maintenance (Steroid + Tac + MPA) (n = 214)	*P* Value
NODAT	12 (5%)	29 (15%)	.03
Early, first 1.5 y	5 (2%)	14 (7%)	
Late, after 1.5 y	7 (3%)	15 (8%)	
Hypertension	89 (40%)	151 (80%)	.05
Early, first 1.5 y	51 (23%)	81 (43%)	
Late, after 1.5 y	38 (17%)	70 (37%)	
Malignancy	0 (0%)	9 (4%)	<.001
Infection			<.001
Bacterial	37 (20%)	49 (1%)	
Viral	15 (7.5%)	20 (9%)	
Cytomegalovirus	10 (5%)	9 (4%)	
Hepatitis C virus	1 (0.5%)	3 (1.5%)	
Herpes zoster	3 (1.5%)	4 (2%)	
Hepatitis B Virus	1 (0.5%)	3 (1.5%)	

Experimental and Clinical Transplantation (2011) 2: 121-127

ARTICLE

Steroid Avoidance Reduce the Cost of Morbidities After Live-donor Renal Allotransplants: A Prospective, Randomized, Controlled Study

Osama A. Gheith, Ahmed H. Nematalla, Mohamed A. Bakr, Ayman Refaie, Ahmed A. Shokeir, Mohamed A. Ghoneim

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Table 4. Posttransplant complications and their costs in both groups.

Complications	Group A (n=50) (steroid free)			Group B (n=50) (control)			*P* value
Antihypertensives	1 Drug	2 Drugs	3 Drugs	1 Drug	2 Drugs	3 Drugs	
Basal	24%	0%	0%	32%	0%	0%	.528
6 Months	4%	0%	0%	12%	20%	0%	.0020
2 Months	4%	0%	0%	12%	8%	24%	.0009
Total cost							
1 Drug	USD $500.00			USD $1243.60			.04
≥ 2 Drugs	USD $0.00			USD $5349.00			.02
Diabetes mellitus	2			8			.037
Cost of therapy	USD $75.00			USD $272.70			.04
Gastritis	9			12			.390
Cost of therapy	USD $200.00			USD $261.00			.23
Infections - Bacterial							
UTI	8			16			.029
Chest infections	6			16			.02
Cost of therapy	USD $109.00			USD $272.00			.045
Infections - Viral							
CMV infection:	1			3			.297
Herpes zoster	–			4			.040
Cost of therapy	USD $1000.00			USD $3018.00			.35
Infections - fungal	2			4			.395
Cost of therapy	USD $36.30			USD $72.7			.05
-Admission (d)	94			213			.03
Cost of hospitalization	USD $8545.00			USD $19,363.00			.04
†-Total cost of nonimmunologic morbidities	USD $10,495.30			USD $29,952.00			.025

Experimental and Clinical Transplantation (2011) 5: 295-301

Alemtuzumab Preconditioning Allows Steroid-calcineurin Inhibitor-free Regimen in Live-donor Kidney Transplant

Ayman F. Refaie,[1] Khaled M. Mahmoud,[1] Amani M. Ismail,[2] Hussein A. Sheashaa,[1] Ahmed I. Kamal,[1] Mohamed A. Ghoneim[3]

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Phase I:

21 recipients randomized into 2 groups

Group I: Tacrolimus (11 patients)

Group II: Sirolimus (10 patients)

Both groups: Alemtuzumab, single dose, 30 mg, preoperative.

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Alemtuzumab Preconditioning Allows Steroid-calcineurin Inhibitor-free Regimen in Live-donor Kidney Transplant

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Phase II:

20 recipients

- Tacrolimus + MMF (3 months)
- Switch to sirolimus + MMF If - rejection-free
  - no subclinical rejection
  - no proteinuria

Both groups: Alemtuzumab, single dose, 30 mg, preoperative.

Current immunosuppression (Phase 1)

Sirolimus-based	
Sirolimus monotherapy	4
Sirolimus + Aza	2
Tacrolimus-based	Steroid-free=14/18
Tacrolimus monotherapy	4
Tac + Aza	3
Tac + MMF	1
Tac + MMF + St	4

Abbreviations: Aza, azathioprine; MMF, mycophenolate mofetil; St, steroid

Current immunosuppression (Phase 2)

Sirolimus-based	
Sirolimus monotherapy	3
Sirolimus + MMF	10
Sirolimus + Aza	2
	Steroid-free=17/20
Tacrolimus-based	CNI-free = 15/20
Tac + MMF +St	3
Tac+ Aza	2

Abbreviations: Aza, azathioprine; MMF, mycophenolate mofetil; St, steroid

Conclusion: antibody preconditioning with alemtuzumab in kidney transplant could allow use of a steroid-calcineurin inhibitor-free regimen. Meanwhile, this regimen appears to be a reasonably effective and attractive one, with good patient acceptance, excellent patient and graft survival rates.

http://www.kidney-international.org

mini review

Steroid-free maintenance immunosuppression in kidney transplantation: is it time to consider it as a standard therapy?

Fu L. Luan[1], Diane E. Steffick[2] and Akinlolu O. Ojo[1,2]

[1]Department of Internal Medicine, Division of Nephrology, University of Michigan, Ann Arbor, Michigan, USA and [2]Arbor Research Collaborative for Health, Ann Arbor, Michigan, USA

Steroid- free protocols: Conclusions

- Steroid-free protocols are safe and could be considered as a standard of care only for a selected group of patients:

I. Low-immunologic risk

II. Pediatric transplants

III. Diabetics, cardiac or obese patients

- The safety of steroid-free immunosuppression has improved with the use of tacrolimus, mycophenolate mofetil and especially with the regular use of induction antibody therapy.

Steroid- free protocols: Conclusions

- The metabolic benefits of steroid-free regimens are confirmed (CVD, bone mineral density, CVA, diabetes, gastritis, cosmetic appearance, adherence, etc …… better patient survival .
- Steroid avoidance is better than late withdrawal.
- Surveillance and screening for de novo DSA are recommended to detect any sign of long-term under-immunosuppression.

Steroid- free protocols: Conclusions

- Long term RCTs that has adequate statistical power to detect differences in acute rejection and major adverse events is needed to determine whether the benefit of steroid avoidance outweigh the harm.


Thank You