
The New Era of Steroid Sparing
The FREEDOM Trial
Flavio Vincenti

Flavio Vincenti, MD

Moffitt Hospital, UCSF

I have received research grants/contracts from BMS, Pfizer, Novartis, Astellas, Genzyme, Genentech, and Roche

This study was sponsored by Novartis Pharmaceuticals

Why Are Steroids Important

- Steroids inhibit transcription of cytokine genes
- Steroids inhibit post transcriptional levels of cytokines
- Steroid play a role as anti-inflammatory

Why Are Steroids Bad

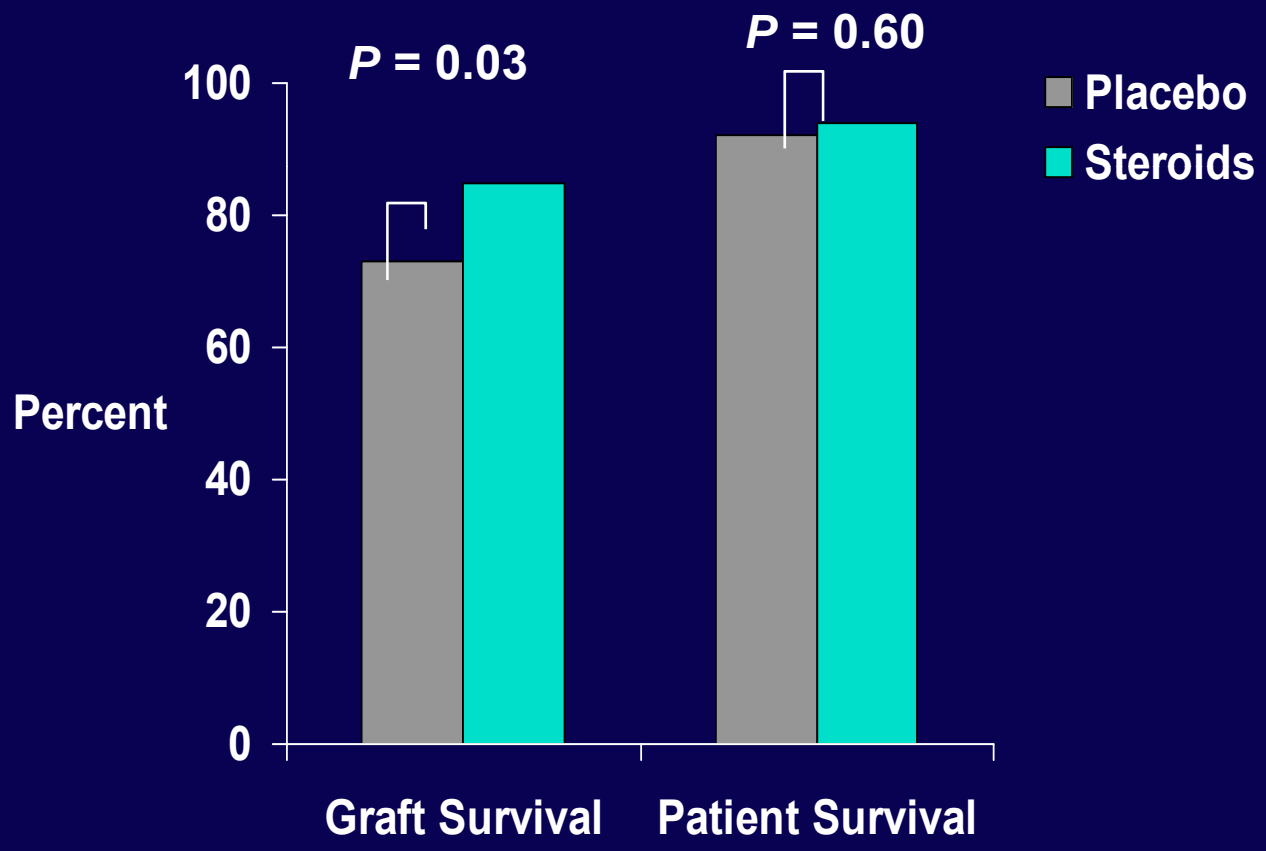
- Cosmetic side effects (increase non-compliance)
- Skeletal complications (osteopenia, fractures, aseptic necrosis)
- Eye complications (cataract, central serous retinopathy)
- Metabolic and CV complications
- Growth retardation

Dark Side of Steroid Sparing

- Greater incidence of acute rejection
- More leukopenia
- Potentiation of fibrogenic effects of CNI (?)
- Longer outcome unclear

Canadian Multicenter Trial

Results at Five Years



Sinclair NR. *CMAJ.* 1992;147:645-657.

Prednisone Withdrawal in Kidney Transplant Rejections on Cyclosporine and Mycophenolate Mofetil—A Prospective Randomized Study

Steroid Withdrawal Study Group

Transplantation 68:1865-1874, 1999

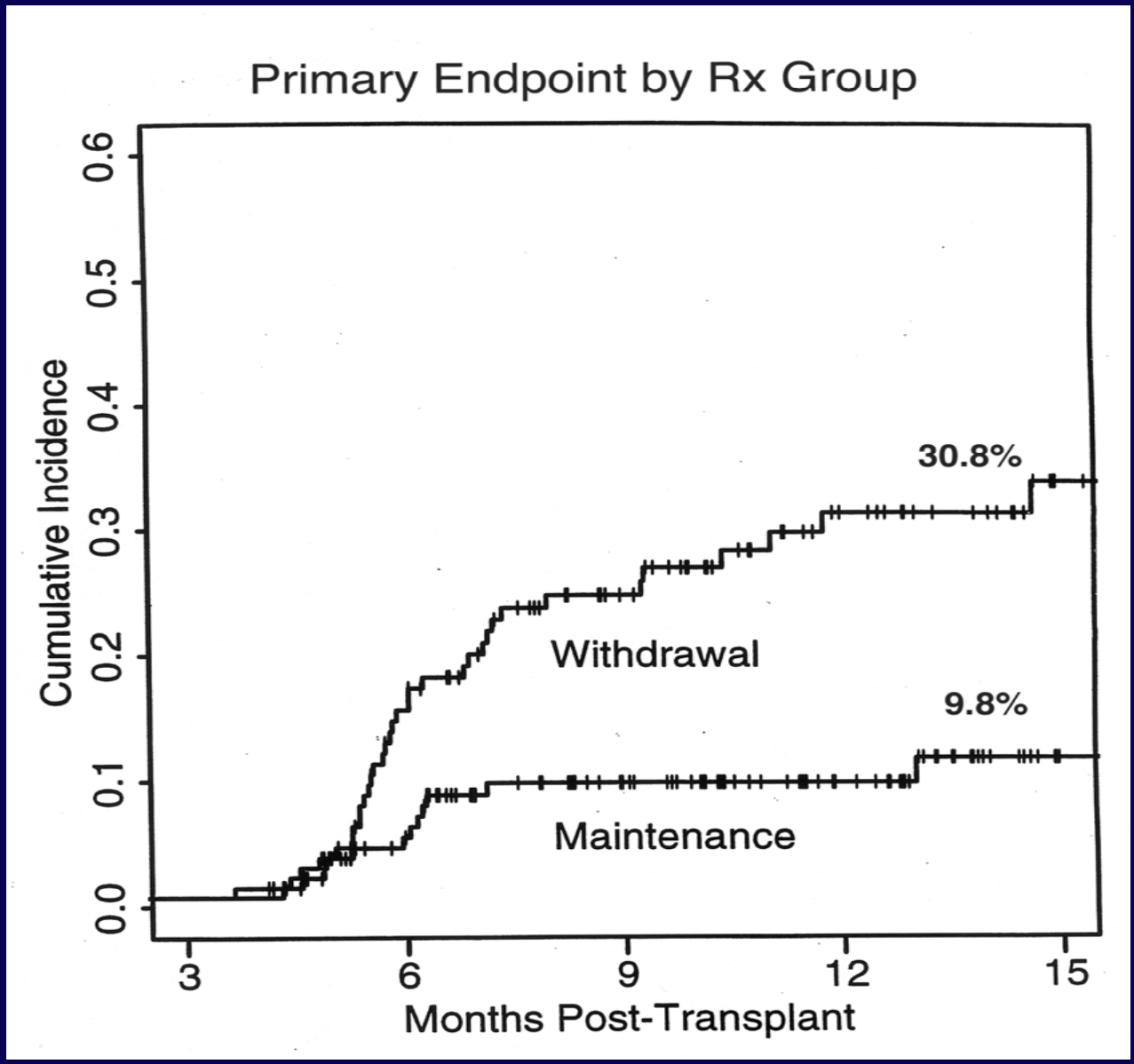
METHODS

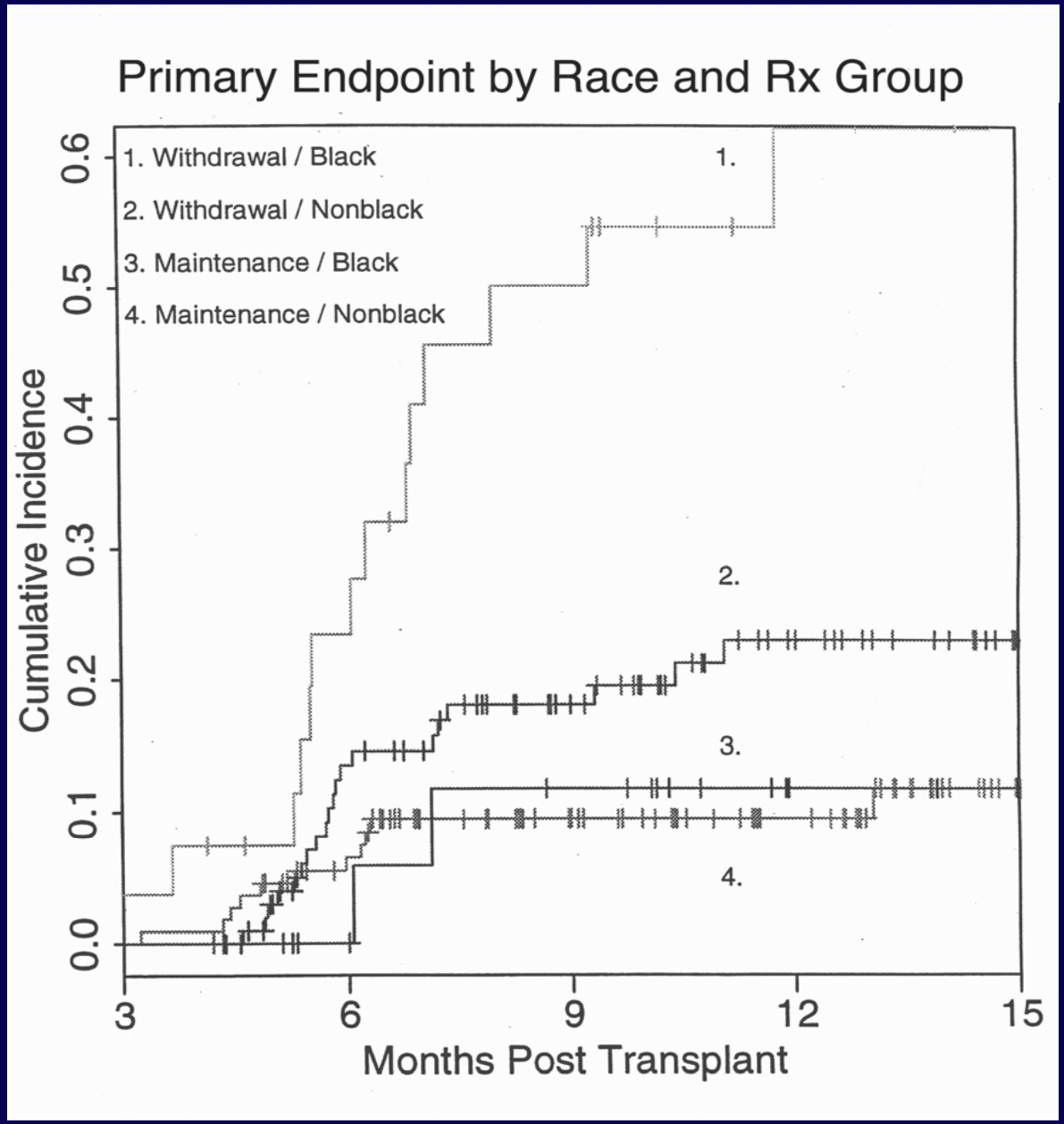
- Inclusion:
  First transplant recipients on CsA-MMF (dose ≥ 2 grams/day)-prednisone, no previous rejection and a serum creatinine < 2.4 mg%

- Design:
  Multicenter (21 sites) double blind trial with patients at 3 months post transplant randomized to continue on prednisone or withdraw from prednisone after 2 months

RESULTS

266 patients were enrolled when study stopped because of excess rejection in the prednisone withdrawal group. Kaplan Meier estimate of cumulative incidence of rejection or treatment failure are shown in the next slide.


Primary Endpoint by Rx Group
Cumulative Incidence
0.0
0.1
0.2
0.3
0.4
0.5
0.6
30.8%
Withdrawal
9.8%
Maintenance
3
6
9
12
15
Months Post-Transplant


Primary Endpoint by Race and Rx Group
1. Withdrawal / Black
2. Withdrawal / Nonblack
3. Maintenance / Black
4. Maintenance / Nonblack
1.
2.
3.
4.
Cumulative Incidence
0.0
0.1
0.2
0.3
0.4
0.5
0.6
3
6
9
12
15
Months Post Transplant

The Recent Trend in Steroid Sparing

- Very early steroid withdrawal (within 7 days of transplantation) may be safer and more desirable than late withdrawal
- These steroid sparing regimens include induction therapy (anti-IL2R mAb or Thymoglobulin)
- Benefits may be modest in the era of low dose prednisone maintenance therapy

Advantages of Very Early Withdrawal or Complete Avoidance of Corticosteroids in Renal Transplantation

- Steroid withdrawal while under the cover of induction therapy
- Acute rejection may occur early and be readily diagnosed and treated
- The host's immune response remains unmodified by the effect of chronic steroid therapy
  - No interference by steroids of tolerogenic pathway
  - Lack of steroid dependency
  - Prevention of heightened immune response after discontinuation of steroids
- More effective prevention of steroid side effects*

*Cremer et al. *Ann Thorac Surg*. 1999;67:130-133
Shane et al. *J Clin Endocrinol Metab*. 1997;82:1497-1506.

Design and Outcome of Newer and More Aggressive Corticosteroids

Design	Immunosuppression	Corticosteroid Regimen	Outcome
Canadian Open Label Multicenter Trial (n=57)	Daclizumab Induction MMF-CsA	None	AR at 1 year 25%
Open Label Randomized Multicenter Trial (n=83)	Basiliximab Induction MMF-CsA in both arms	Standard steroids 5 days of steroids	AR at 1 year 19% AR at 1 year 20%
Open Label Single Center in Living Donor Kidney Transplantation (n=51)	Thymoglobulin induction MMF-CsA	6 days of steroids	AR at 1 year 13%
Open Label Multicenter Trial (n=83)	Basiliximab Induction SRL-TAC	5 days of steroids	AR at 12 months 23%
Carmen Study European multicenter randomized trial (n=551)	Daclizumab induction-Tac-MMF vs. TAC-MMF-Pred	500 mg Standard steroids	AR 16.5 at 6 months AR 16.5 at 6 months

CsA=cyclosporine; MMF=mycophenolate mofetil; SRL=sirolimus; TAC=tacrolimus; DAC=daclizumab; Pred=prednisone

Is complete steroid avoidance as safe as rapid steroid withdrawal?

American Journal of Transplantation 2008; 8: 307-316

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

Flavio Vincenti
on behalf of the
FREEDOM Study Group

FREEDOM Study
12 Month Results

A 12-month, randomised, multicenter, open-label study to investigate the clinical outcomes of two immunosuppressive regimens of enteric coated MPS (*myfortic*®) with short-term steroid use or free of steroids compared with a regimen of enteric coated MPS with standard steroids in *de novo* kidney recipients receiving basiliximab and cyclosporine

FREEDOM: **Participating countries**

Argentina:	L. Toselli, P. Novoa
Australia:	R. Walker, G. Russ, S. Campbell, M. Jose
Brazil:	M. Mazalli, H. Tedesco
Canada:	A. Salazar, J. Zaltman, J. Lawen, P. Campbell, A. Shoker, S. Paraskevas
Germany:	I. Hauser, W. Arns
Italy:	F. Schena
Malaysia:	Z. Morad
New Zealand:	H. Pilmore
Singapore:	V. Anantharamar
Spain:	A. Fructuoso, J. Grinyo, J. Baltar
Taiwan:	P. Lee, S. Chu W. Yang
United Kingdom:	R. Moore, A. Ready, M. Shehata, S. Kashi
United States:	L. Leone, K. Bodziak, F. Vincenti, H. Sollinger, M. Peskovitz, W. Bennett, D. Holt, F. Ferguson

FREEDOM: Study objective

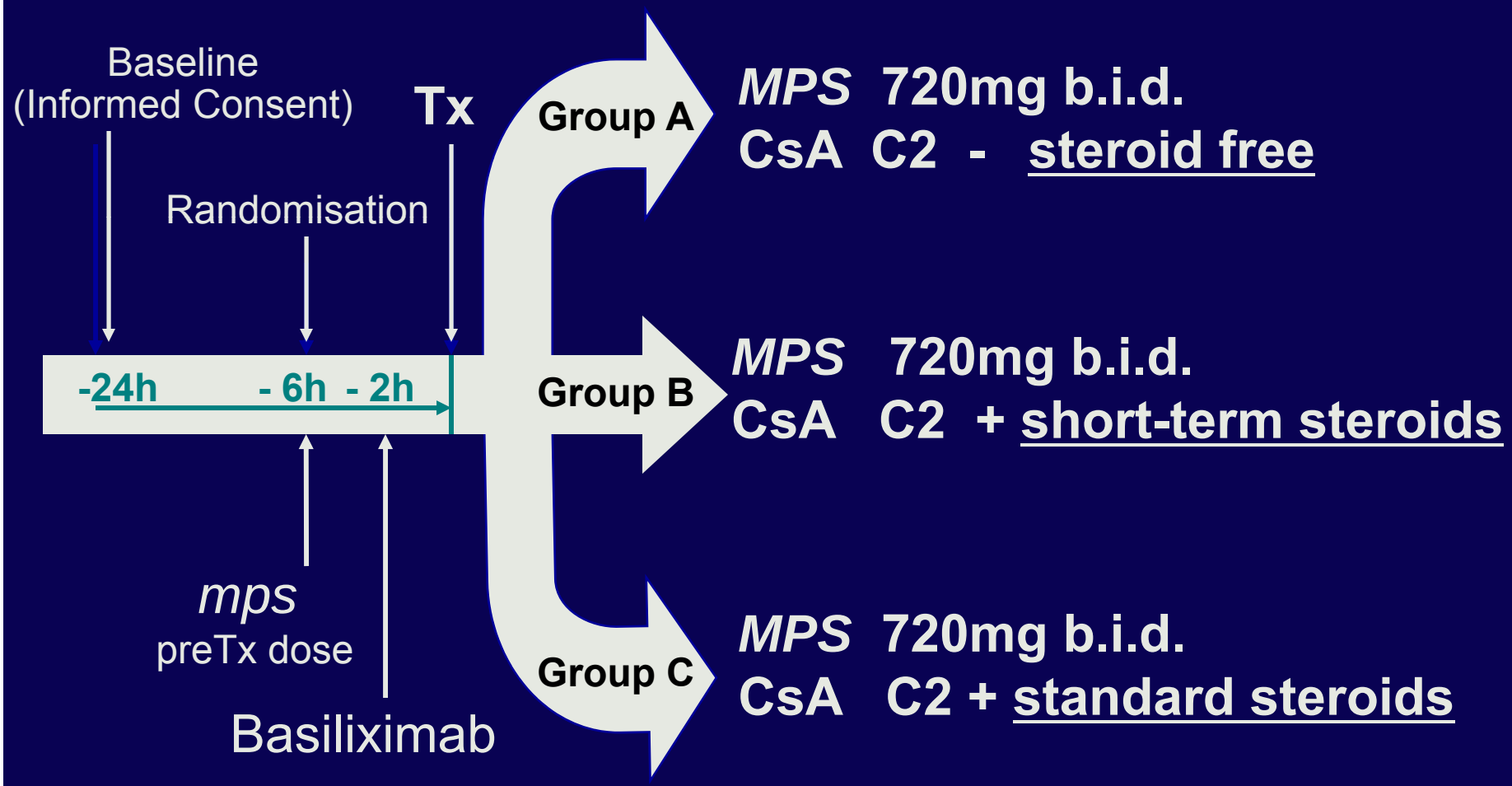
Primary efficacy endpoint

- To assess Kidney function as measured by GFR (calculated by using the Nankivell formula) at 12 months

Secondary efficacy endpoints

- Cumulative incidence of biopsy-proven acute rejection (BPAR) reported after 3 and 12 months
- Cumulative incidence of the composite variable BPAR, death or graft loss after 3 and 12 months
- Cumulative incidence of AEs and SAEs
- To evaluate the percentage of patients free of steroids at 12 months between the two investigational groups
- To evaluate other safety variables in de novo renal transplant recipients such as incidences of malignancies and infections
- To compare the blood pressure, lipids and glucose profiles after 3 and 12 months

FREEDOM: Study design



Sample size and power consideration

- The clinically tolerated value of the difference for considering non-inferiority was 7mL/min per 1.73m2.
- Based on values at 12 months from previous studies, the standard deviation for the standard regimens has been computed to be 15mL/min per 1.73m2.
- Based on this assumption and on a power of 80%, 89 patients per treatment arm are needed to show non-interiority.
- In order to take into account early withdrawals from the study, 110 patients per treatment arm have to be enrolled into the study.

Indication and main criteria

- Main inclusion criteria:
  - Male or female patients aged 18 to 75 years, who were first recipients of, heart-beating
  - Cadaveric, living unrelated or living related non-HLA identical donor kidney transplants
  - Treated with Simulect® and Neoral® as primary immunosuppression
- Main exclusion criteria:
  - Second or subsequent kidney transplant or multi-organ recipients (e.g. kidney and pancreas) or previous transplant with any other organ, kidneys from non-heart beating
  - Donors or HLA identical living related donors, ABO incompatibility
  - Panel reactive antibodies of >20%, cold ischemia time >24 hours
  - Cadaveric donor age >60 years
  - Thrombocytopenia, neutropenia and leukocytopenia

Patient demographics: no significant differences

	Steroid-free (n=111)	Steroid withdrawal (n=115)	Standard steroids (n=109)
Mean age (years)	43±13	46±12	47±13
Male gender	72 (65%)	84 (73%)	70 (64%)
Caucasian	91 (82%)	86 (75%)	78 (72%)
Black	0	0	4 (4%)
Other	20 (18%)	29 (25%)	27 (25%)

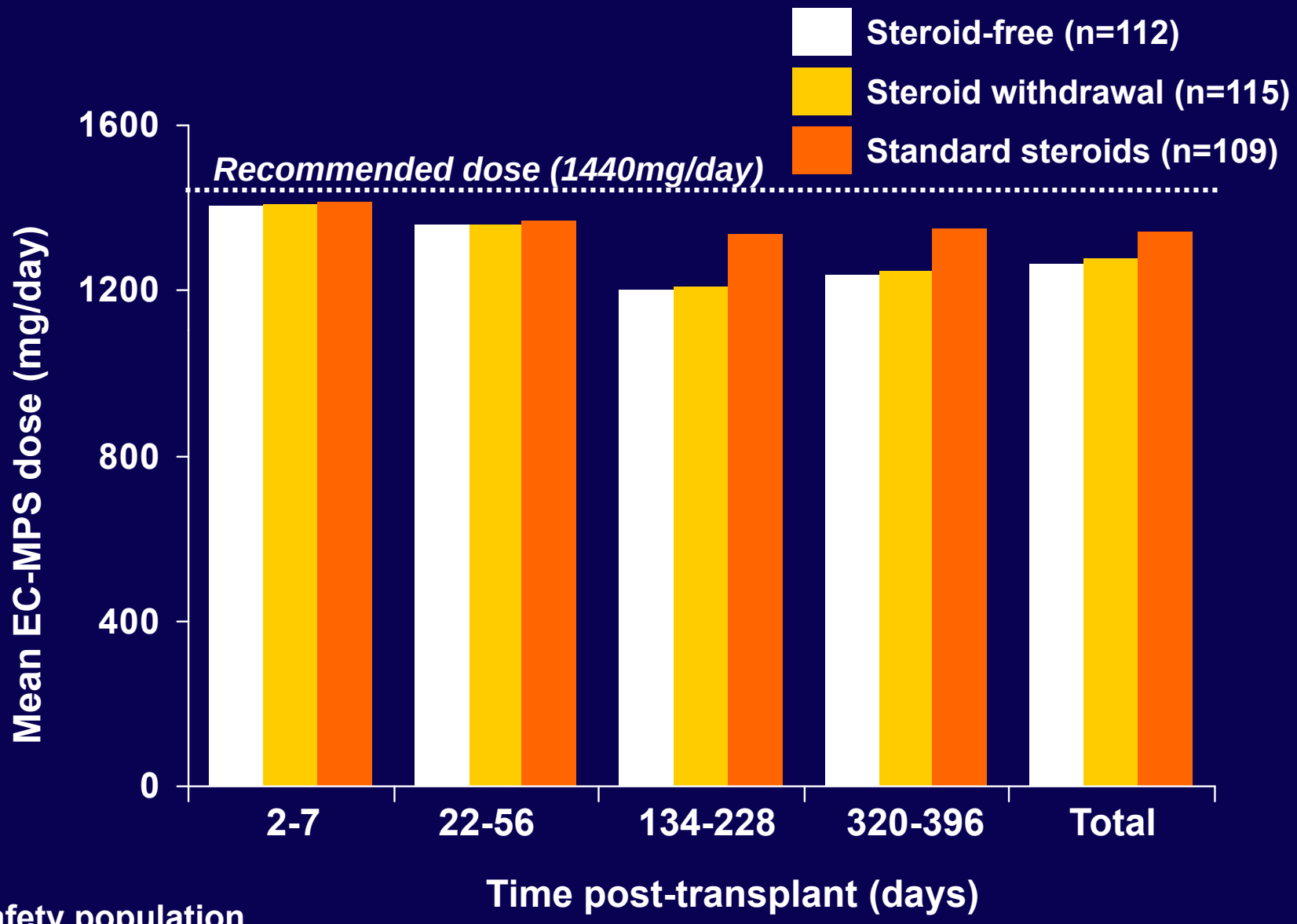
ITT population

Transplant characteristics

	Steroid-free (n=111)	Steroid withdrawal (n=115)	Standard steroids (n=109)
Deceased (heart-beating)	57 (51%)*	81 (70%)	64 (59%)
Living related	40 (36%)	24 (21%)	30 (28%)
Living unrelated	14 (13%)	10 (9%)	15 (13%)
PRA >20%	0	3 (3%)	0
Cold ischemia >24 hours	2 (2%)	8 (7%)	1 (1%)
First transplant	111 (100%)	115 (100%)	108 (99%)
Donor CMV+ Recipient–	19 (17%)	17 (15%)	12 (11%)
Mean donor age (years)	40±14	42±13	41±12
Donor age >60 years	5 (5%)	8 (7%)	5 (5%)
HLA mismatches 4-6	44 (40%)	43 (37%)	44 (40%)

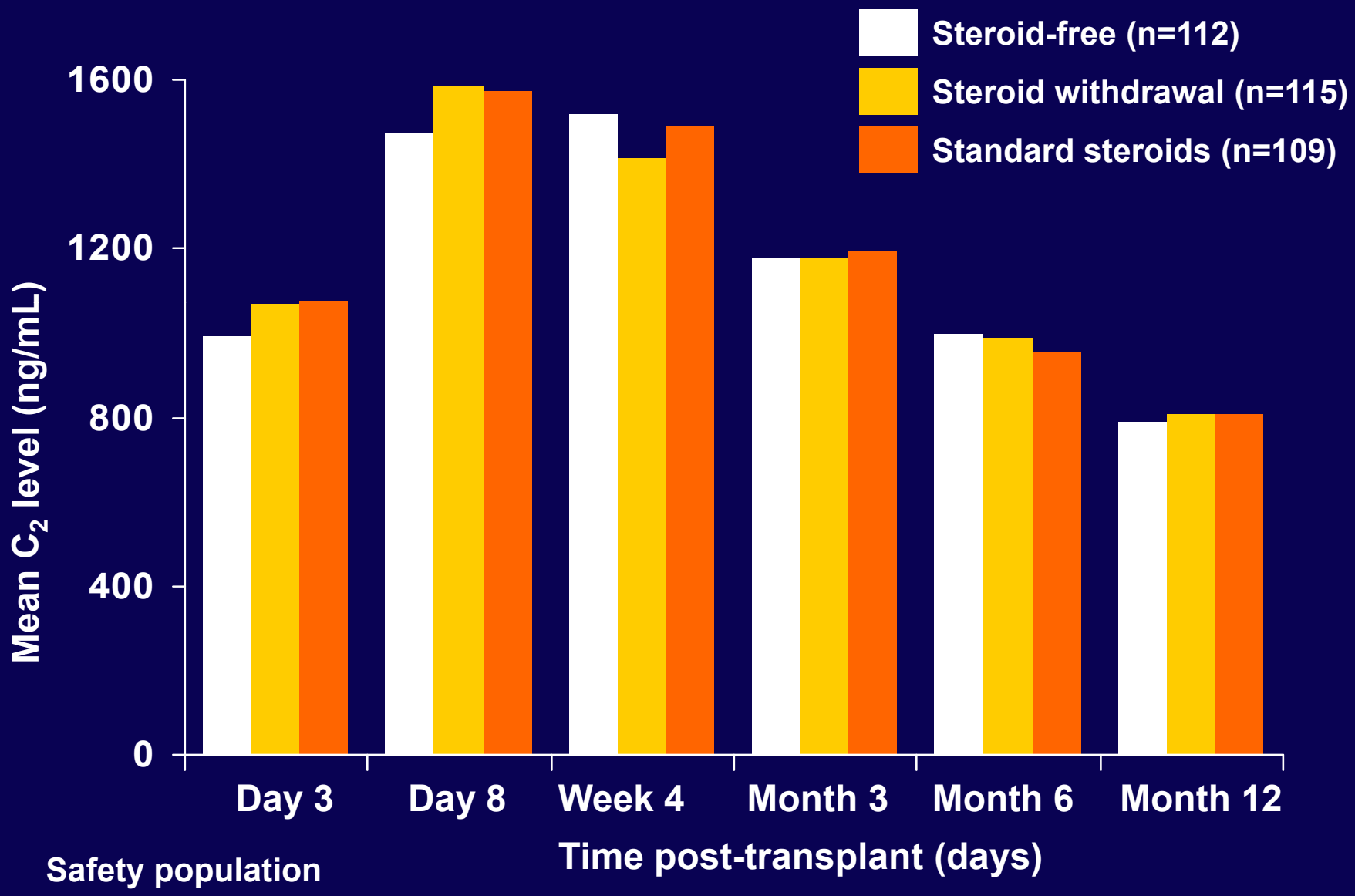
* p=0.014 versus steroid-withdrawal group. ITT population

EC-MPS average daily dose



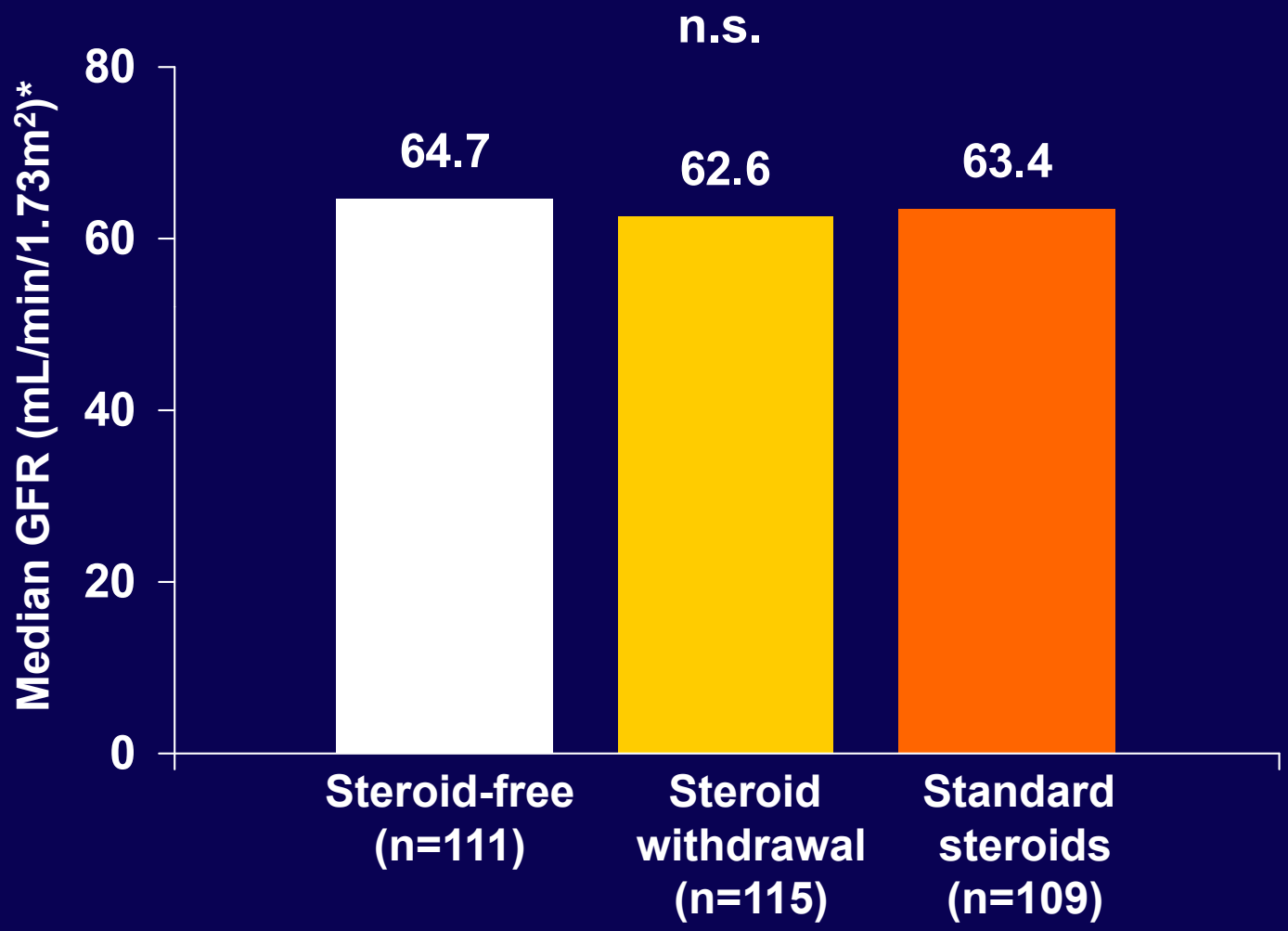
Safety population

CsA C_2 level



Safety population

No difference in renal function at month 12 (GFR)



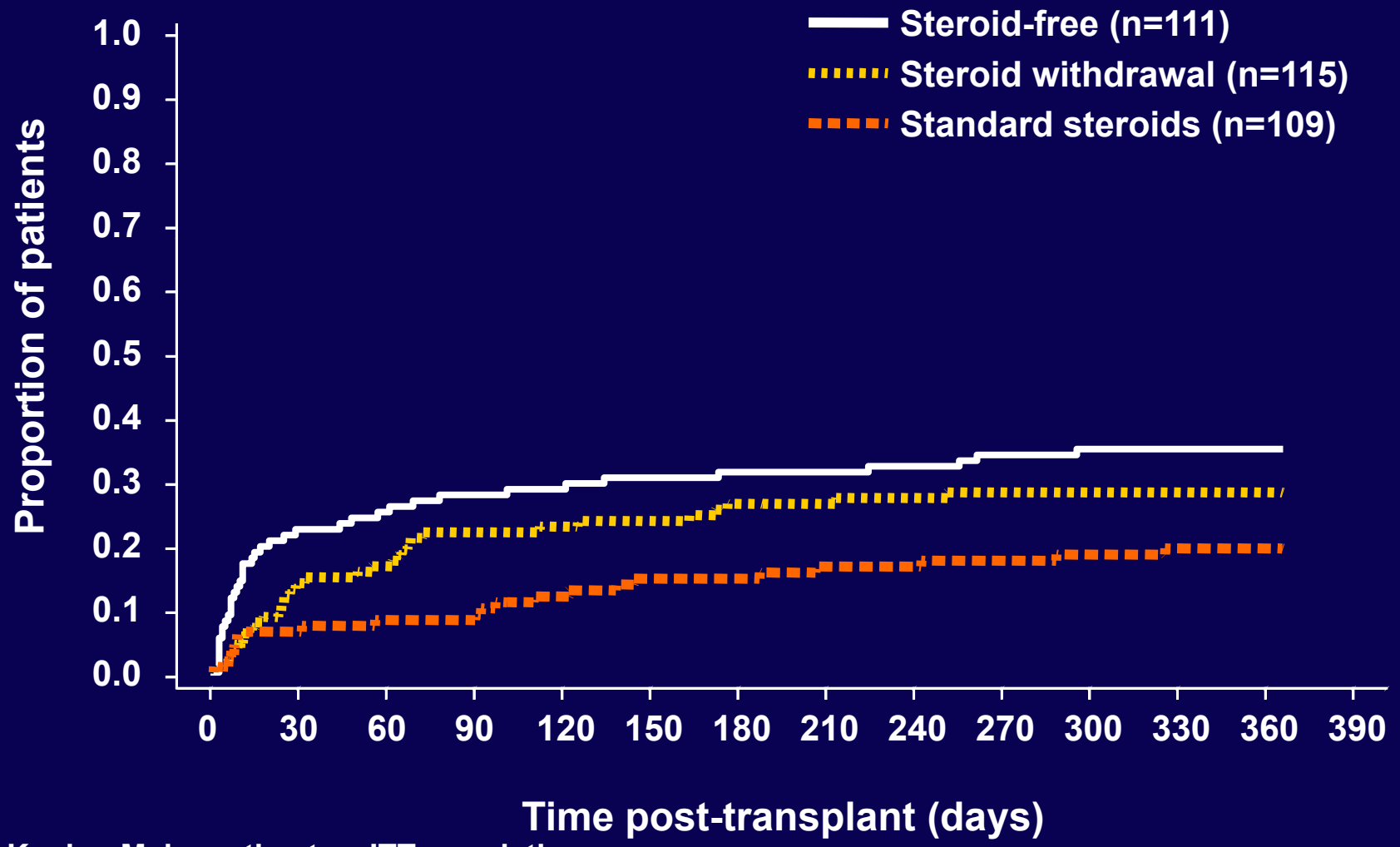
* Excludes patients who died or lost their grafts. ITT population

Renal Function at 12 Months. GFR calculated using Nankivell Formula

Observed case analysis[1]	Steroid-free (n=84)	Short term steroids (n=78)	Standard Steroids (n=85)
GFR (mL/min/1.73 m^2) Mean ± SD Median (range) 95% CI versus standard steroids	 64.7 ± 17.2 64.7 (25.6-127.3) -3.8-6.4	 61.6 ± 18.5 62.6 (2.1-112.4) -6.5-4.9	 62.1 ± 17.6 63.4 (1.7-92.0)

[1]Excluding patients who died or lost their graft.

Time to treatment failure within 12 months



Kaplan-Meier estimates. ITT population

Efficacy at 12 months

	Steroid-free (n=111)	Steroid withdrawal (n=115)	Standard steroids (n=109)
BPAR, GL or Death	40 (36.0%)[a]	34 (29.6%)	21 (19.3%)
BPAR	35 (31.5%)[c]	30 (26.1%)[b]	16 (14.7%)
Median time to first BPAR	14 days	52 days	104 days
Graft loss	4 (3.6%)	2 (1.7%)	2 (2.8%)
Death	5 (4.5%)	2 (1.7%)	2 (1.8%)

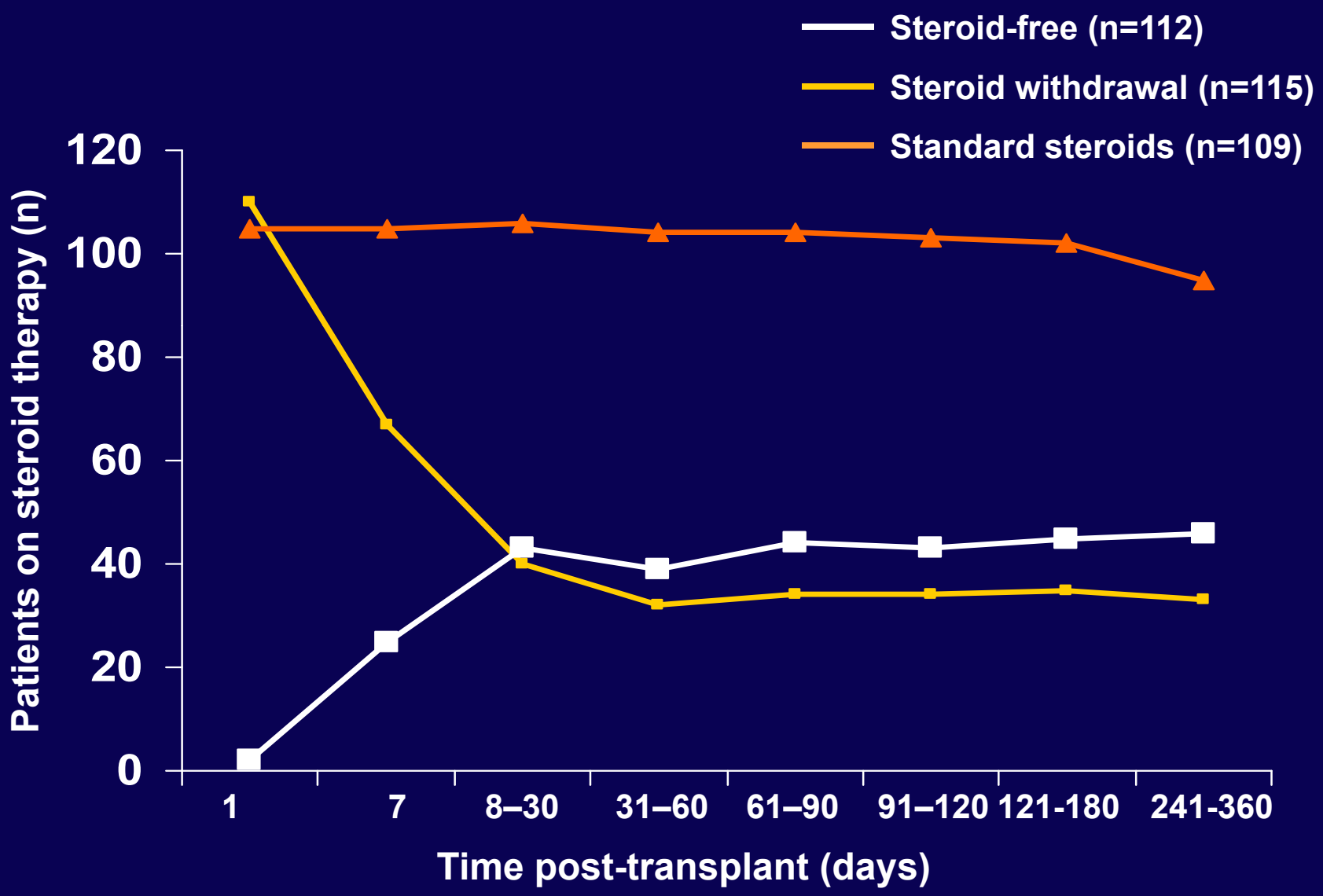
[a] P=0.007 vs standard steroids
[b] P=0.046 vs standard steroids
[c] P=0.004 vs standard steroids
ITT population

Frequency of biopsy & BPAR severity at 12 months

	Steroid-free (n=111)	Steroid withdrawal (n=115)	Standard steroids (n=109)
Mean number of biopsies per patient	1.7[a]	1.8[b]	1.2
Severity of BPAR:			
Mild (Grade IA)	20 (18.0%)[c]	16 (13.9%)	9 (8.3%)
Mild (Grade IB)	10 (9.0%)	6 (5.2%)	4 (3.7%)
Moderate (Grade IIA or IIB)	3 (2.7%)	5 (4.3%)	2 (1.8%)
Severe (Grade III)	0	1 (0.9%)	1 (0.9%)

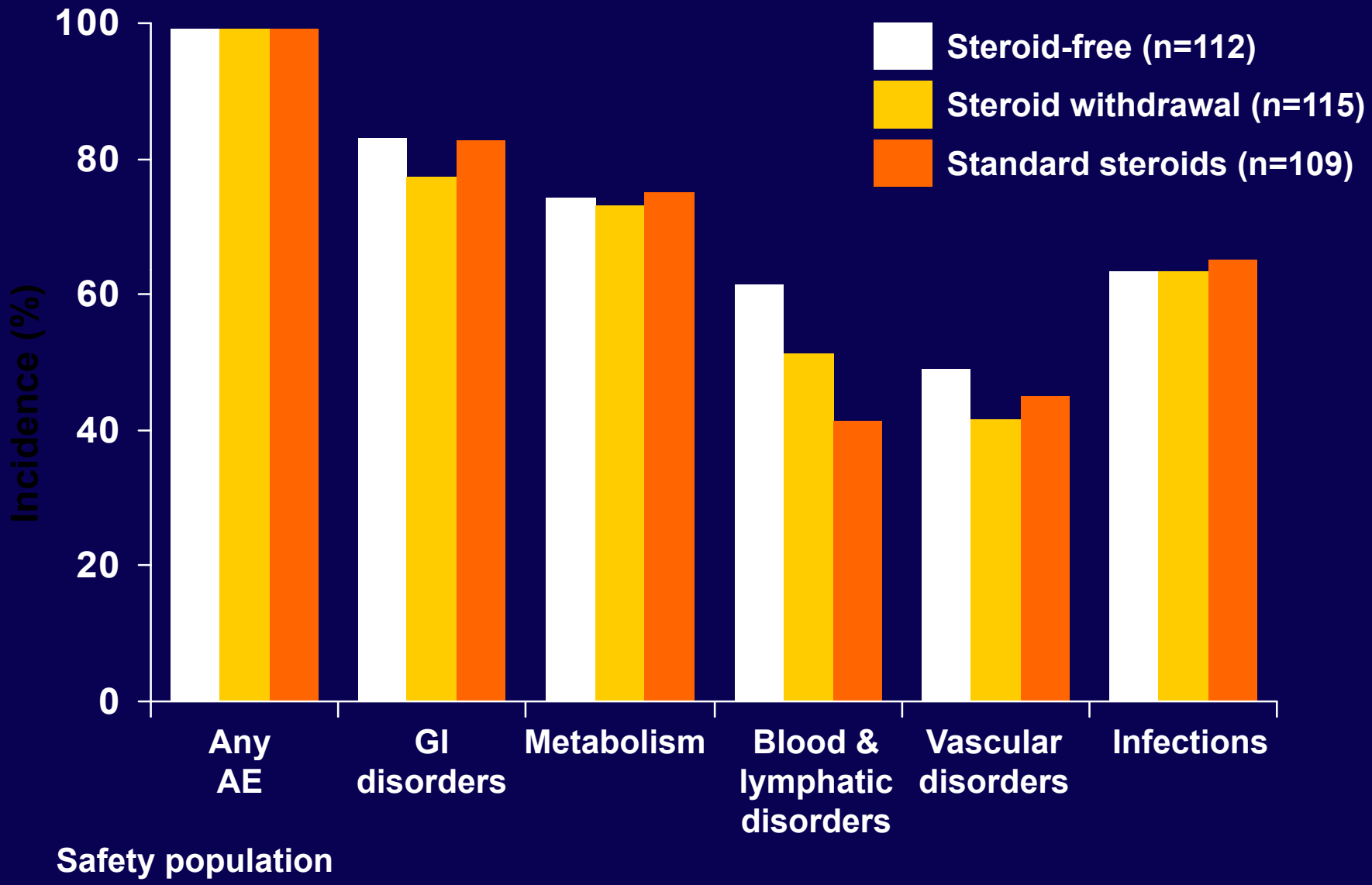
[a] P<0.05 vs standard steroids
[b] P=0.001 vs standard steroids
[C] p=0.032 vs standard steroids
ITT population

Patients on steroid therapy



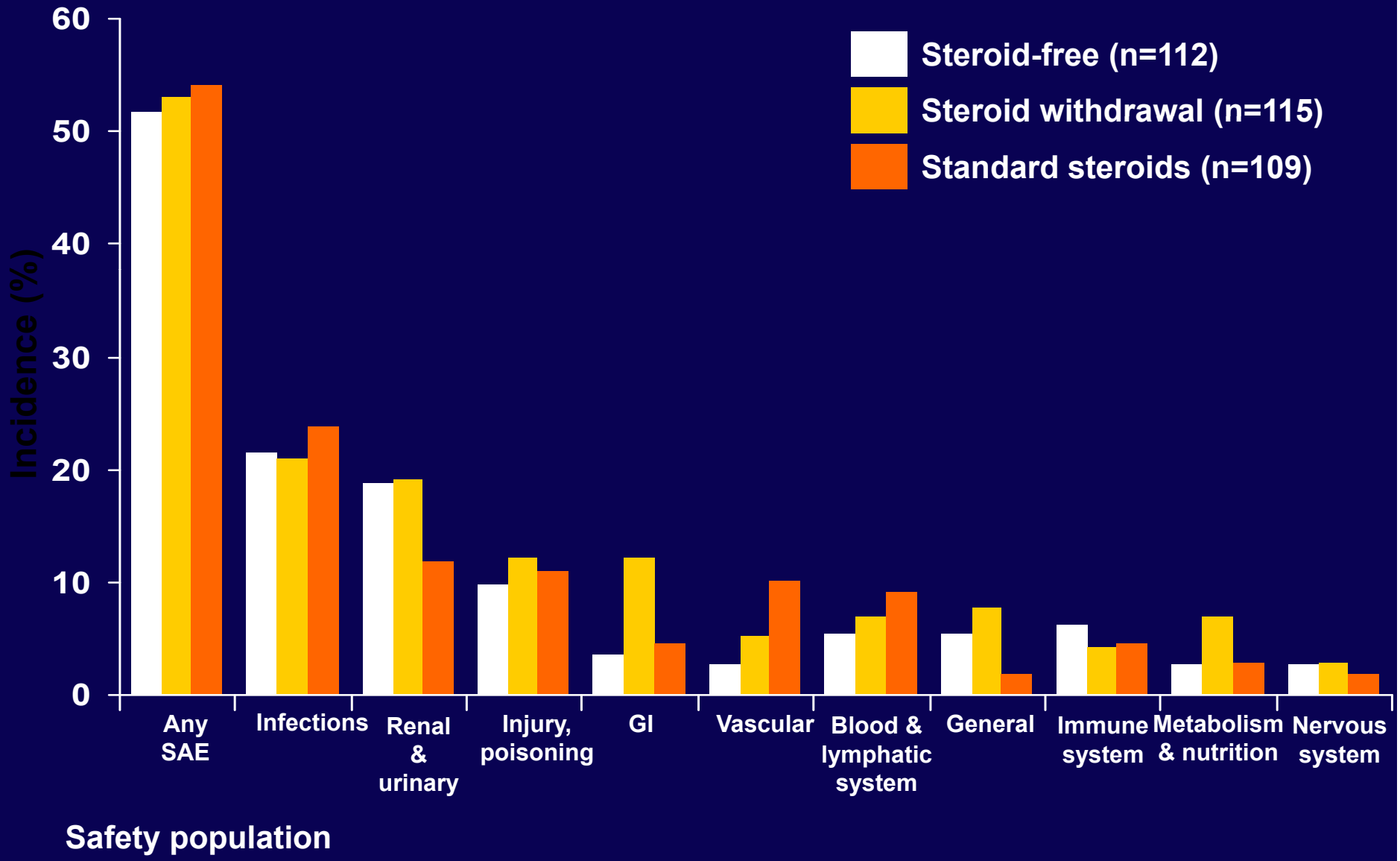
Safety population

Incidence of frequent (≥10%) adverse events



Safety population

Incidence of serious adverse events



Safety population

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/m2)	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%)	86/100 (81.1%)	89/101 (88.1%)
Mean change in spine bone mass density (1% 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-steroid group).

Summary

- In renal transplant patients receiving CsA-ME, EC-MPS + basiliximab, steroid withdrawal by day 7:
  - Achieves similar 12-month renal function versus standard steroids
  - Is not associated with a significant increase in risk of treatment failure versus standard steroids
- Rejection rates are higher and median time to first BPAR is shorter in steroid sparing regimen
- A higher number of biopsies (with more rejections classified as Grade IA) may have contributed to the higher incidence of BPAR in the steroid-sparing arms

Conclusions

- Steroid withdrawal by day 7 appears preferable to complete steroid avoidance
- However, more data will be obtained from long-term follow-up and may provide additional considerations regarding these three steroid regimens

Do Steroids Protect Against Calcineurin Inhibitor Nephrotoxicity?

- University of Wisconsin
  - 133 HLA-identical kidney transplant recipients
  - 58% returned to steroids, most often because of CNI toxicity
- University of Buffalo
  - 35 early SW vs 34 steroid-treated controls (RATG, TAC, MMF)
  - Protocol biopsies 1, 6 and 12 months
  - CNI toxicity 10% SW vs 3% steroid-treated

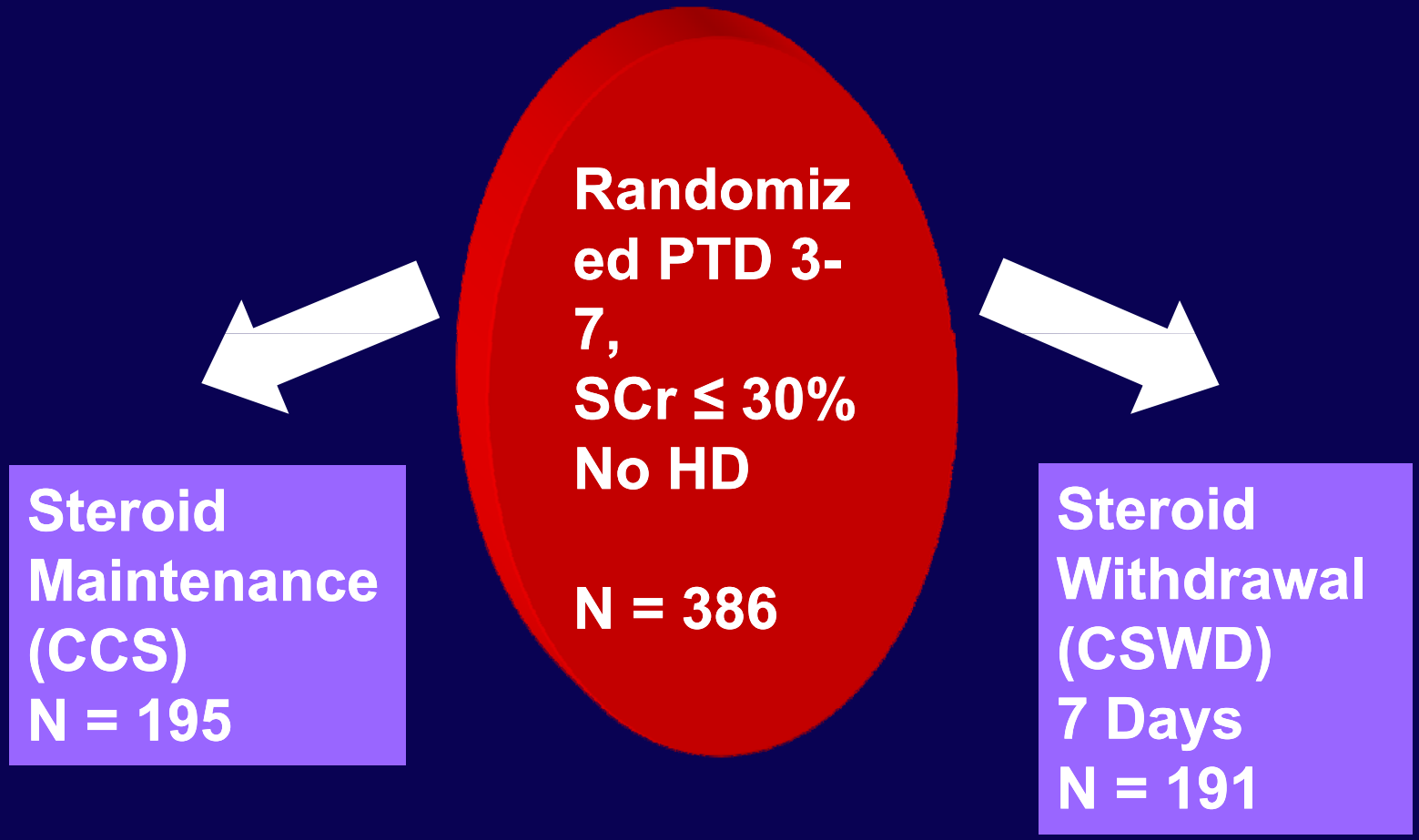
CI=Calcineurin inhibitor
SW=Steroid withdrawal

A Double-Blind, Multicenter, Prospective, Randomized Trial Comparing Early Corticosteroid Withdrawal and Long-Term Maintenance Corticosteroid Therapy in Renal Transplantation

E. Steve Woodle MD, William Fitzsimmons PharmD, M. Roy First MD, John Pirsch MD, Fuad Shihab MD, A. Osama Gaber MD, Paul Van Veldhuisen PhD

for the Astellas Corticosteroid Withdrawal Study Group

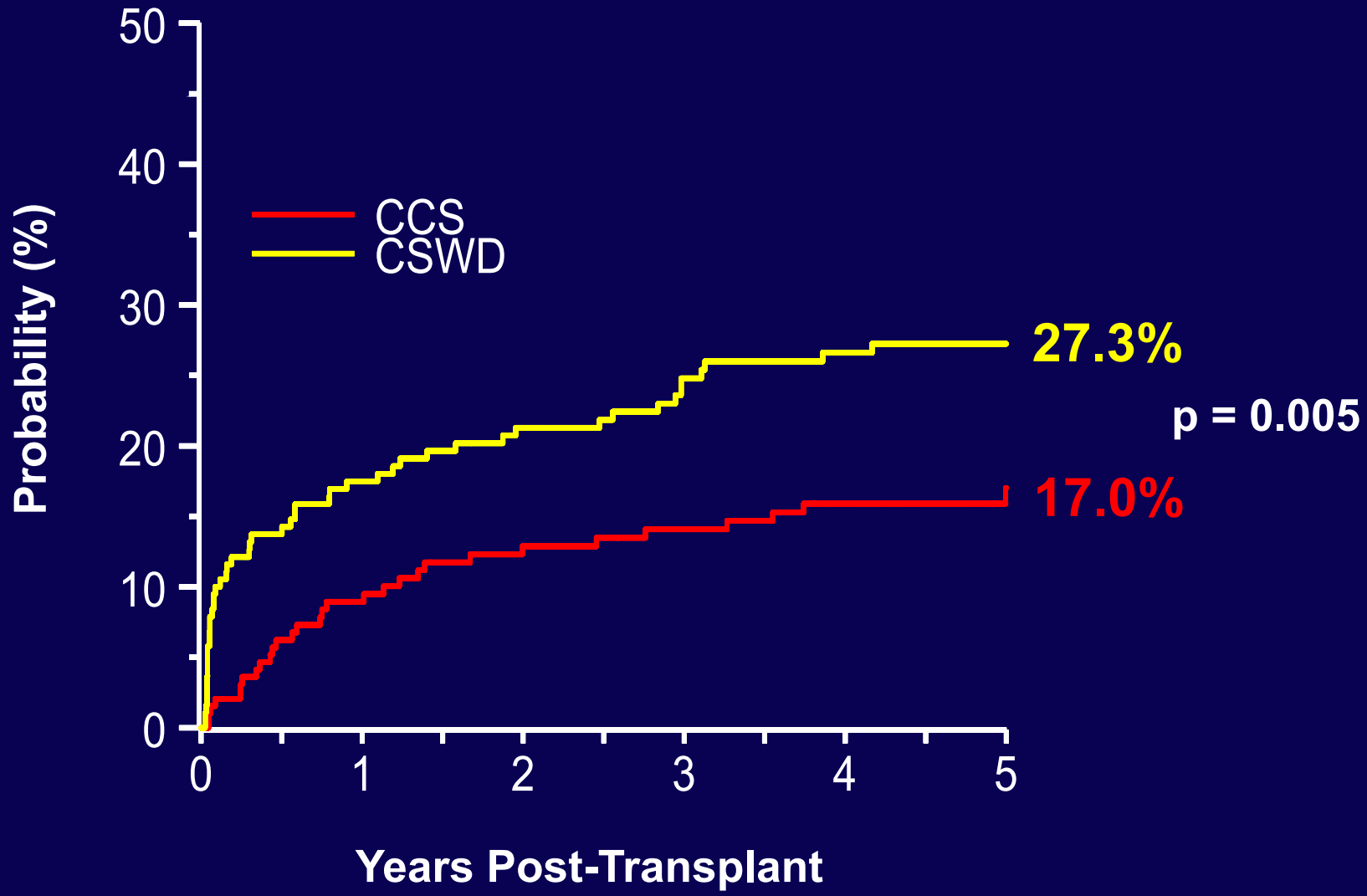
Design: Prospective, Double Blind, Stratified



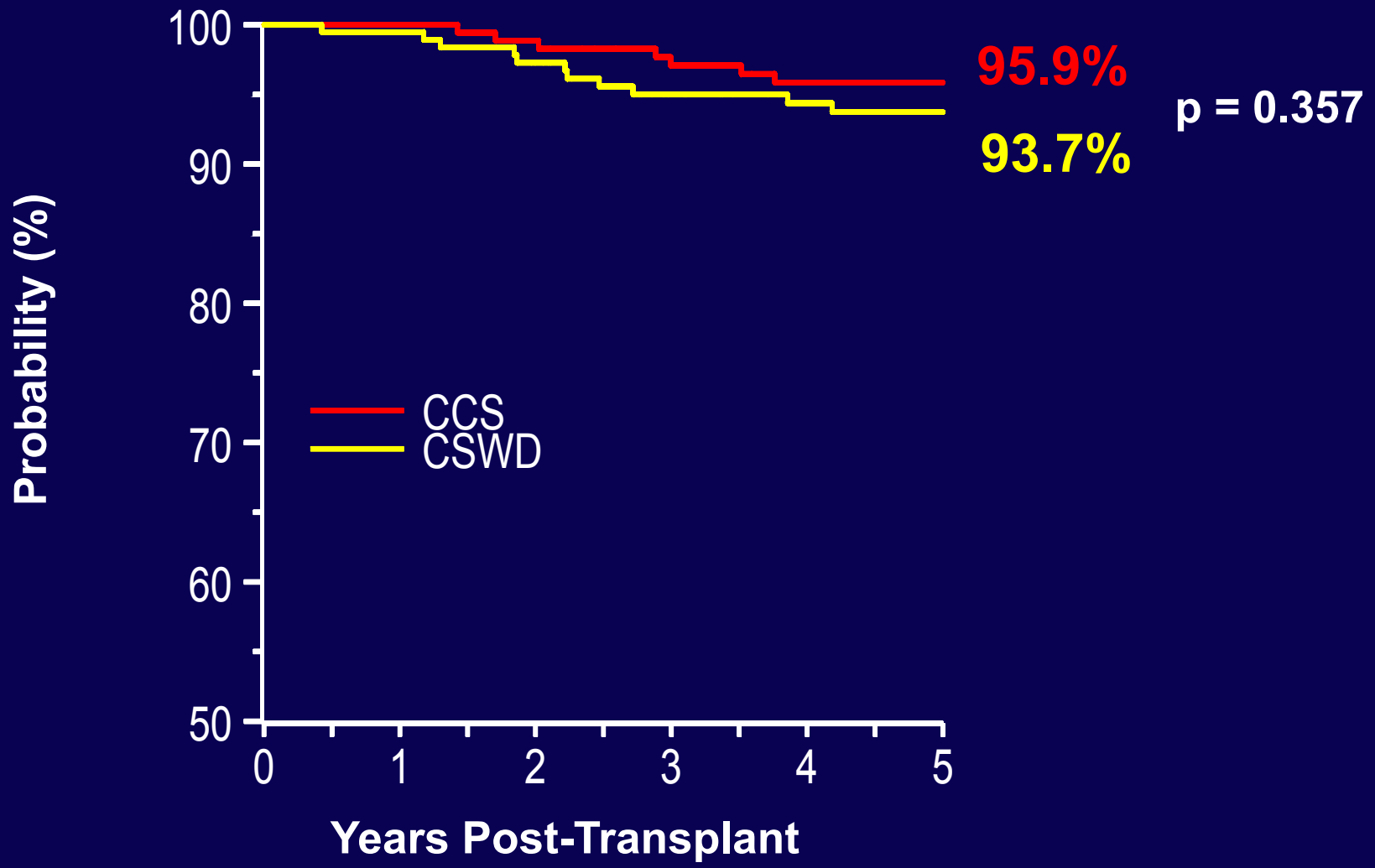
Stratification:

1. Live vs. deceased donor
2. AA vs. non-AA

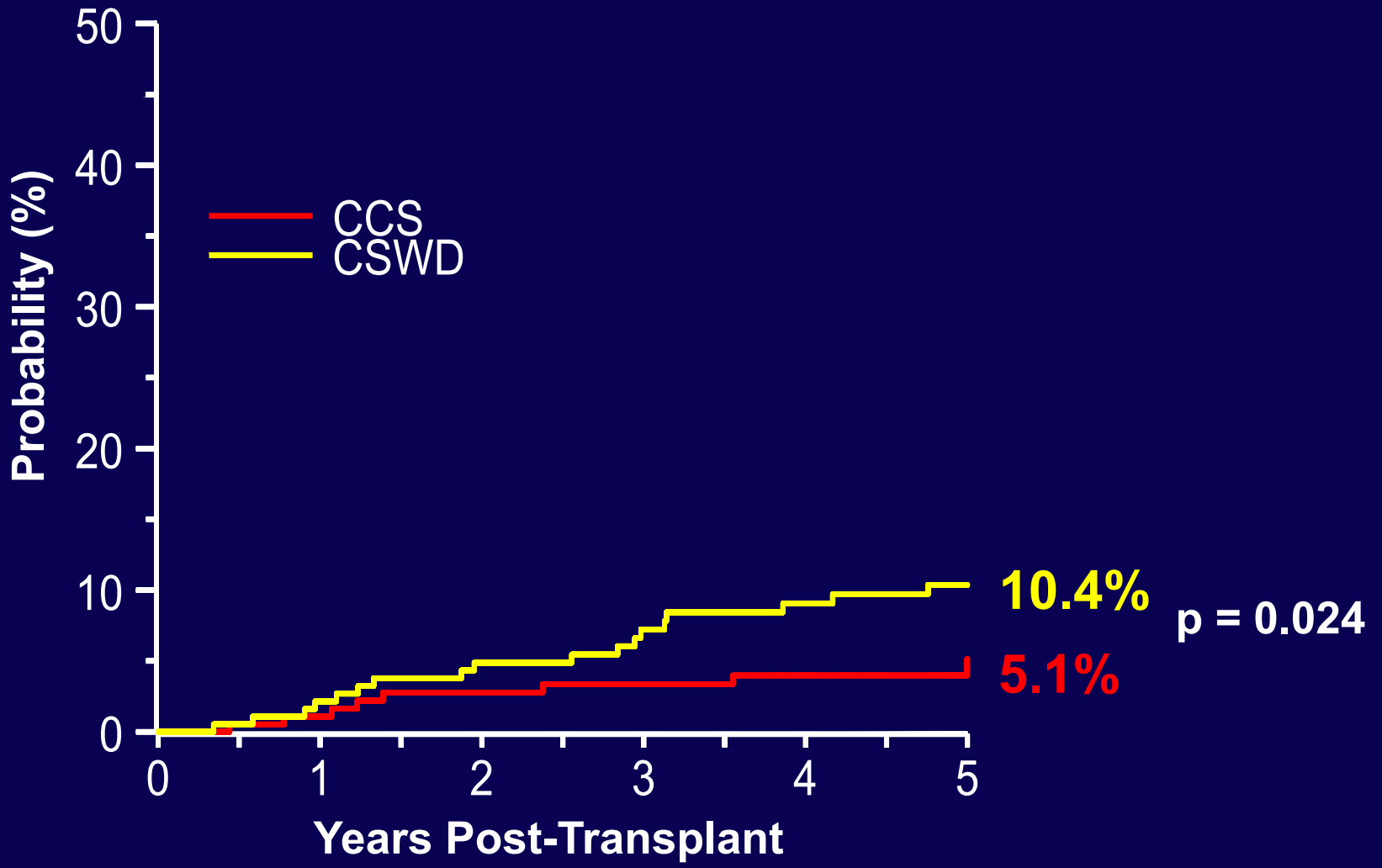
Biopsy Confirmed Acute Rejection



Death-censored Graft Survival During 5 Years



Biopsy Confirmed Chronic Allograft Nephropathy



Bone Complications During 5 Years

	CCS N=195	CSWD N=191	p-value*
Fractures and/or Avascular Necrosis	22 (11.3%)	10 (5.2%)	0.041

*Based on Fisher's Exact test

Risk Factors for Re-starting Steroids after Steroid Avoidance (SA) Among Kidney Transplant Patients in the US

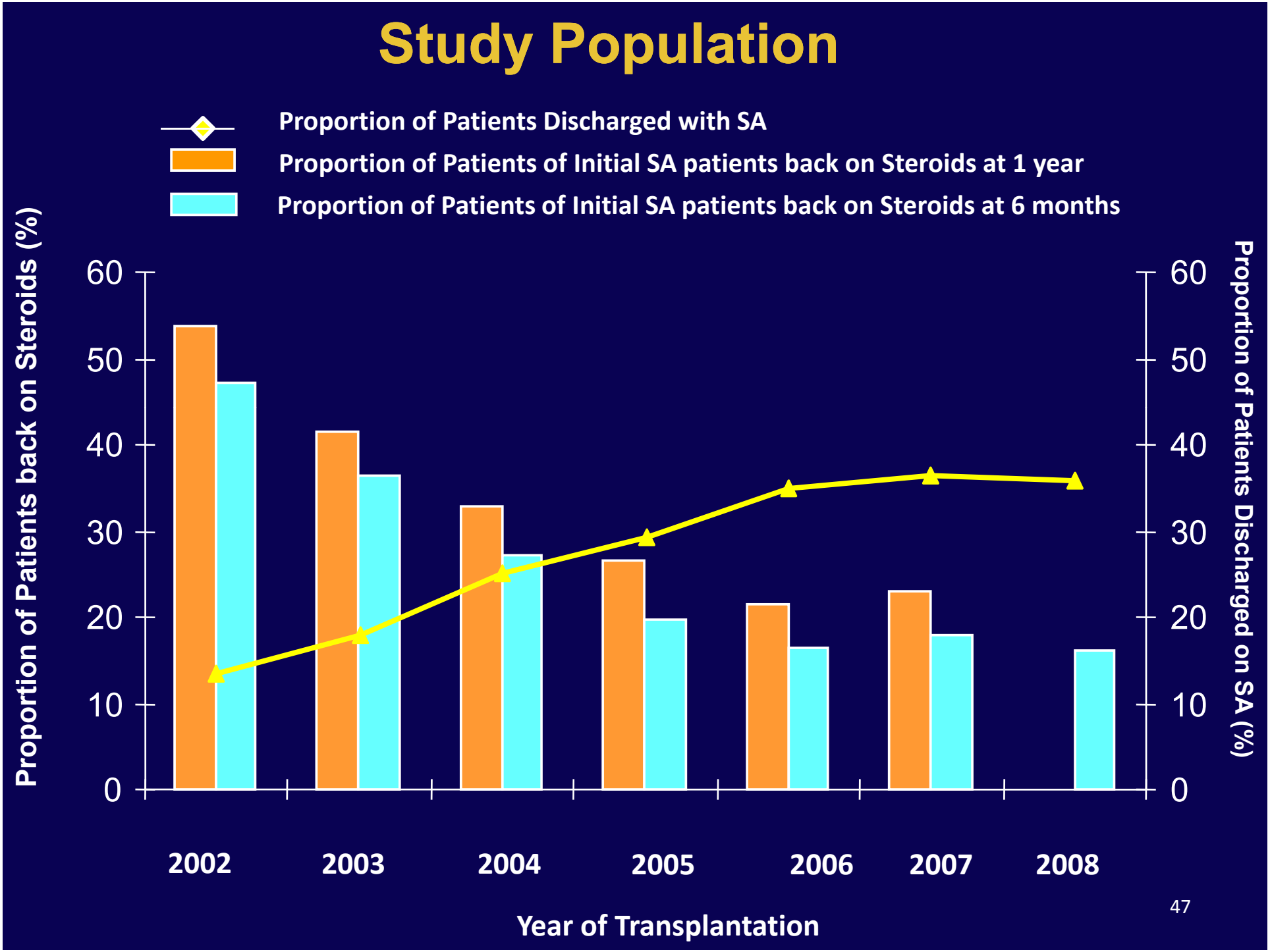
Alfonso Santos[1], Jesse D Schold[1], Shehzad Rehman[1], Joseph Magliocca[2], and Herwig-Ulf Meier-Kriesche[1].

Departments of Medicine [1] and Surgery[2], College of Medicine, University of Florida, Gainesville, FL, USA

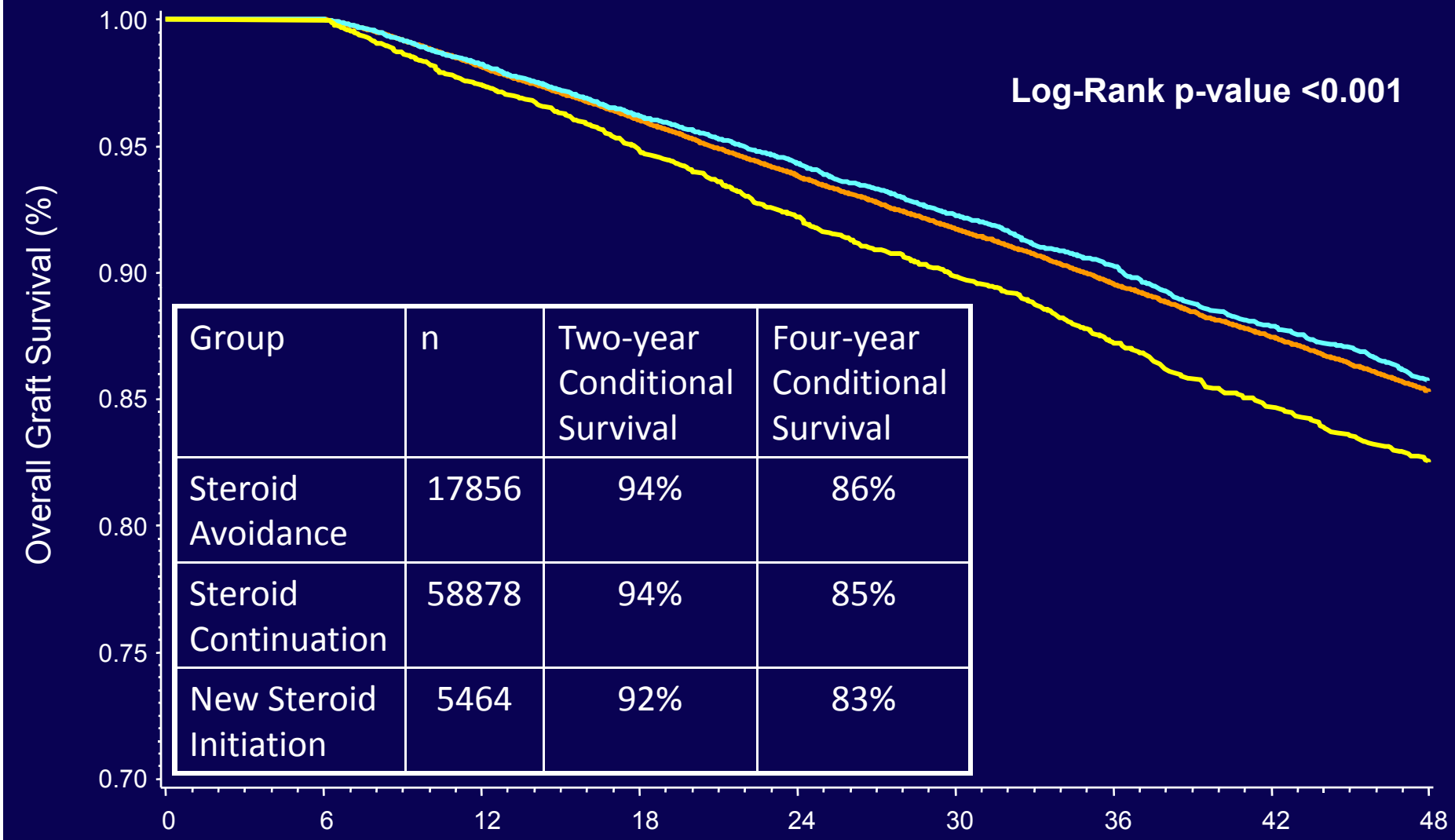
Methods

- Examined all solitary kidney transplants between 2002 – 2008 from the national SRTR database
- Patient categorized as: SA (steroid avoidance) or maintenance steroid based on discharge regimen after kidney transplantation
- Primary outcome analyzed: Risk factors for starting steroids among patients on SA regimen either within 6 or 12 months after transplantation using multivariate logistic models
- Additional analysis: Over-all graft loss after 6 months for patients initiated on steroids vs. patients maintained on steroids or patients remaining on SA using Kaplan-Meier and Cox models

Study Population



Conditional Overall Graft Survival of Patients on SA, Steroid Continuation, and New Steroid at 6 Months



Group	n	Two-year Conditional Survival	Four-year Conditional Survival
Steroid Avoidance	17856	94%	86%
Steroid Continuation	58878	94%	85%
New Steroid Initiation	5464	92%	83%

Summary

- 23,320 (28%) Kidney transplant recipients discharged without steroids
- 23% required steroid institution by 6 months
- 34% required steroids institution by 12 months
- 20% increased risk for Graft Loss after 6 months (compared with patients always on steroids)

Conclusions

- Rapid steroid withdrawal is associated with comparable graft survival but increased acute rejection as compared to maintenance steroid therapy
- The long term impact of steroid withdrawal on CAN remains unclear
- It is best to select patients who would likely benefit from steroid withdrawal