New-onset diabetes after transplantation

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Actualités Jean Hamburger

Paris, 23-24 avril 2012

Table 2: Diagnostic criteria for posttransplant diabetes mellitus and impaired glucose metabolism

NODAT

Criteria for new-onset diabetes after transplantation mellitus
(Require one of three)

1 Symptoms of hyperglycaemia with a random plasma glucose ≥11.1 mmol/L (200 mg/dL) OR
2 FBG ≥7.0 mmol/L (126 mg/dL; minimum 8 h fast) OR
3 2 h post-75 g OGTT plasma glucose ≥11.1 mmol/L (200 mg/dL)

A confirmatory test must be done on another day in the absence of unequivocal hyperglycemia accompanied by acute metabolic decompensation

Criteria for posttransplant impaired fasting glucose (IFG) or impaired glucose tolerance (IGT)

IFG

IFG FBG ≥6.1 (110 mg/dL) and <7.0 mmol/L (126 mg/dL) (assess further with OGTT)

IGT

IGT 2 h post-75 g OGTT plasma glucose ≥7.8 (140 mg/dL) and <11.1 mmol/L (200 mg/dL)

Recommended diabetes screening intervals after transplantation: weekly for first 4 weeks; months 3, 6 and 12; annually after the first year.

CJ Yates et al, Am J Transplant 2011

NODAT: incidence
(Various definitions)

Table 1: Studies using treatment based definitions of NODAT or registry data

Study	N	Definition	NODAT incidence (%)							Population	Primary maintenance immunosuppressive regimen
			Months post		Years post						
			1	6	1	3	5	10	15		
Cosio et al. (2001) (Ref. 5)	2078	Treatment past day 30			7	10	13	21	30	White/African American	Pred, CsA, Aza/MMF
Kasiske et al. (2003) (Ref. 4)	11 659	Medicare claim	9		16	24				US Medicare beneficiaries	Pred, CsA, MMF
Vincenti et al. (2008) (Ref. 6)	567	Treatment past day 30		13						59 centers, 16 countries	Pred, CsA/Tac, MMF
Luan et al. (2011) (Ref. 7)	25 837	Registry				16				White/African American	Pred, Tac, MMF/MFA (27% steroid free)

Pred = prednisone/prednisolone; CsA = cyclosporine A; Tac = tacrolimus; Aza = azathioprine; MMF = mycophenolate mofetil; MFA = mycophenolic acid; US = United States.

CJ Yates et al, Am J Transplant 2011

NODAT: incidence
(ADA/WHO definitions)

Table 3: Studies using ADA/WHO approved definitions of NODAT

Study	N	Definition	NODAT incidence (%)								Population	Primary maintenance immunosuppressive regimen
			Months post				Years post					
			1	2	3	6	1	4	6	7		
Hagen et al. (2003) (Ref. 9)	63	OGTT		19				22			White Norwegian	Pred, CsA, Aza
David-Neto et al. (2007) (Ref. 10)	84	OGTT	14	18		19	9				Nonobese Brazilian	Pred, Tac, MMF
Hur et al. (2007) (Ref. 11)	77	OGTT					39			35	Korean	Pred, CsA, MMF
Porrini et al. (2008) (Ref. 12)	154	OGTT			31		20				Spanish	Pred, Tac, MMF
Valderhaug et al. (2009) (Ref. 13)	1637	OGTT		17[2]							White Norwegian	Pred, CsA, Aza/MMF
Luan et al. (2010) (Ref. 14)	591	FBG						15[1]			White/African American	Pred, CsA, MMF/ Sirolimus

15 – 20% **25 – 30%**

Pred = prednisone/prednisolone; CsA = cyclosporine A; Tac = tacrolimus; Aza = azathioprine; MMF = mycophenolate mofetil.
[1]Median follow-up.
[2]Ten weeks posttransplant.

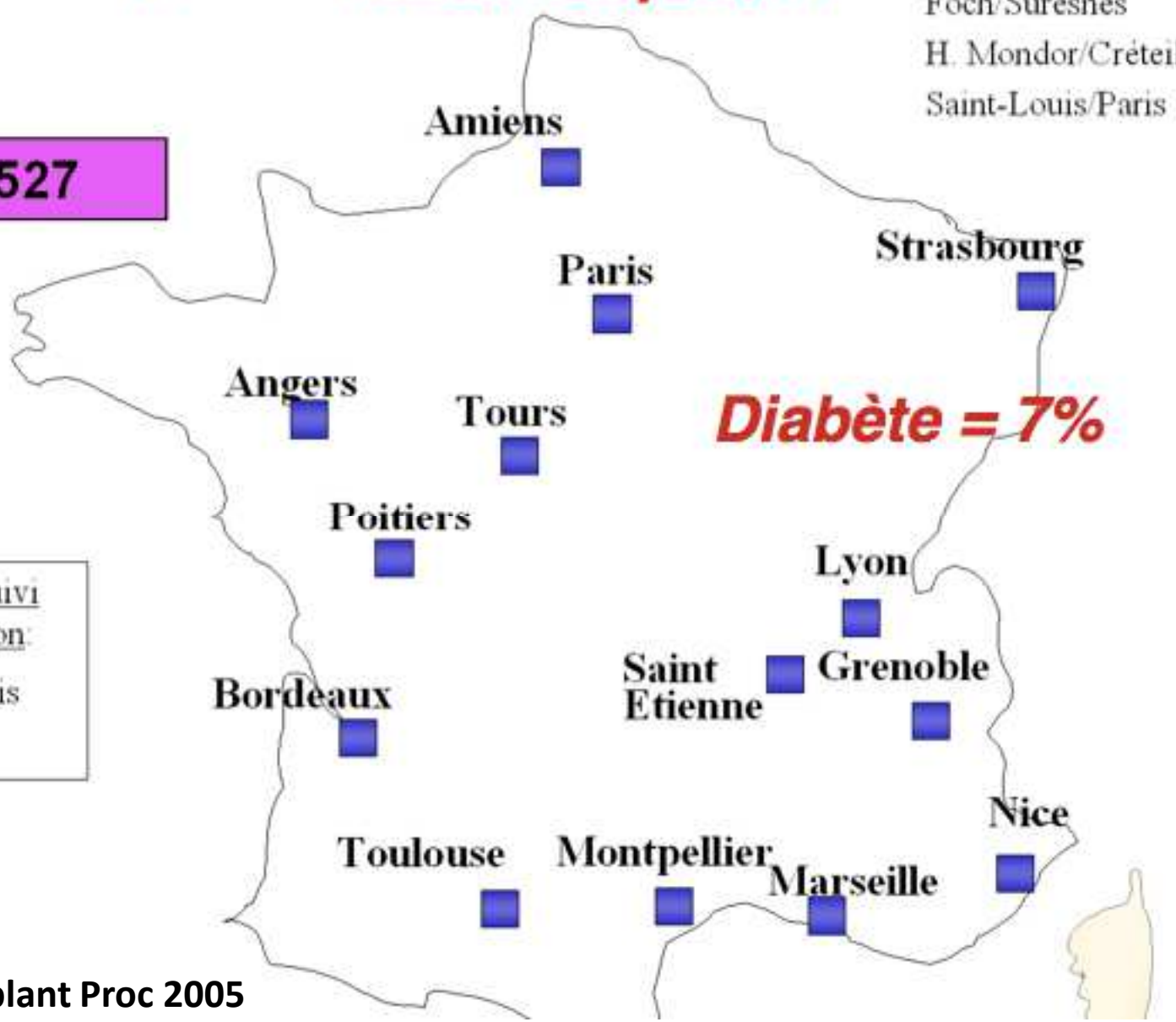
CJ Yates et al, Am J Transplant 2011

Centres participants

Etude Diapason

Paris:
Foch/Suresnes
H. Mondor/Créteil
Saint-Louis/Paris

N = 527



Diabète = 7%

Délai moyen de suivi post-transplantation:
13,6 (6 – 24) mois

M Marin et al, Transplant Proc 2005
F Trempé et al, Nephrol Thér 2005 (IC 11% à 3 ans)
N Kamar et al, Nephrol Dial Transplant 2007

NODAT: diagnostic criteria

- Fasting blood glucose = poor sensitivity
  - Pre-RT OGTT = 8.1% underdiagnosed diabetes
  - 78% would have been ignored using FBG!
- Post-RT OGTT in case of IFG detected only 47% of those with NODAT!
- Pre-evening meal glucose level is probably the most consistent marker.

HA Bergrem et al, Clin J Am Soc Nephrol 2010
TG Valderhaug et al, Transplantation 2009

NODAT: new diagnostic criteria?

- Afternoon capillary blood glucose
- HbA_{1C}:
  - **Pro**:
    - less biologic variability;
    - greater preanalytic stability,
  - **Con**:
    - Lack of universal availability,
    - Discordances with OGTT,
    - Confounding factors (Hb, EP, hemolysis etc.).

JN Clore et al, Endocr Pract 2009
DM Nathan et al, Diabetes Care 2009

Who needs an OGTT?

TABLE 4. Various combined cutoff values of fPG combined with HbA1c as selection criteria for an oral glucose tolerance test 10 wk after renal transplantation

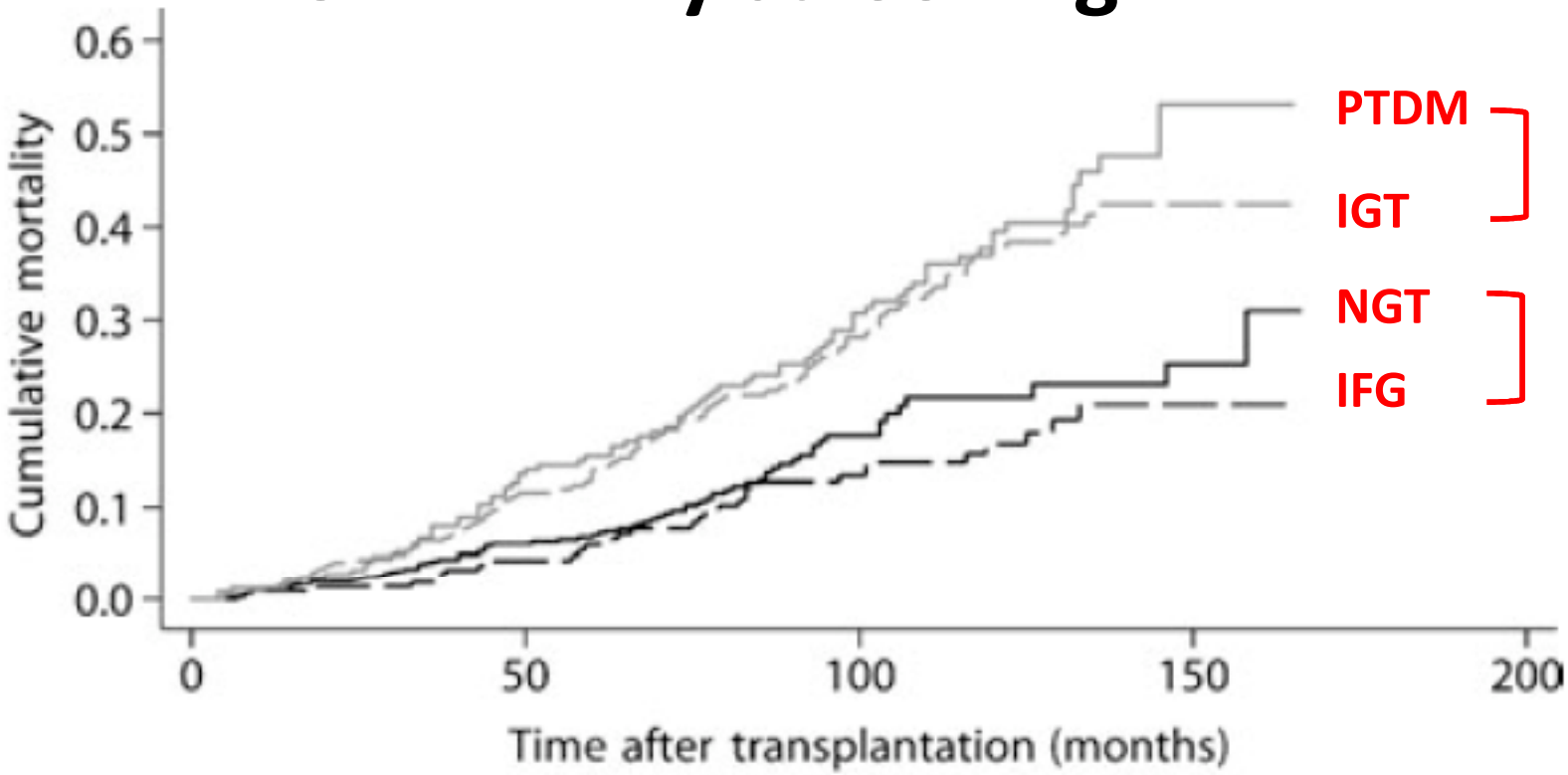
HbA1C > 5.7%, 91% NODAT but 50% of patients tested

	n (%)	
Combined cutoff value	OGTT needed (n=929)	PTDM identified (sensitivity) (n=47)
fPG ≥5.0 and HbA1c ≥5.7	270 (29)	37 (79)
fPG ≥5.0 and HbA1c ≥5.8	226 (24)	33 (70)
fPG ≥5.3 and HbA1c ≥5.7	189 (20)	32 (68)
fPG ≥5.3 and HbA1c ≥5.8	161 (17)	29 (62)

fPG, fasting plasma glucose; OGTT, oral glucose tolerance test; PTDM, post transplant diabetes mellitus.

TG Valderhaug et al, Transplantation 2009

NODAT: why screening?



Number at risk					
NGT	638	466	117	35	0
IFG	217	183	127	15	0
IGT	313	237	125	27	0
PTDM	242	183	111	13	0

1410 patients
OGTT at 10 weeks

TG Valderhaug et al, Diabetologia 2011

NODAT: risk factors

Nonmodifiable risk factors	
▪ Age	**Incidence and complications increase with age**
▪ Ethnicity	**Afro-american et hispanic**
▪ Family history of diabetes mellitus?	
▪ Cause of end-stage renal failure*	**APKD and glomerulonephritis**
▪ Gender?	**Male > female**
▪ HLA mismatch?*	
▪ Genetic susceptibility	**IL-6 gene promoter, TranscriptionCF7L2, HNF1beta,**
▪ Innate immunity*	**Mannose Binding Lectin level**
▪ Donor characteristics?*	
▪ Education	

*** Transplantation specific risk factor**

A Sharif et al, Nature Rev Nephrol 2010

NODAT: genetic susceptibility (IL6p)

Table 3. Cox model: HR of NODAT and 95% CI (retrospective cohort)[a]

Variable		HR	95% CI	*P*
Age (yr)				
<45		1	—	—
≥45		4.54	1.53 to 13.45	0.006
BMI (kg/m^2)				
<25		1	—	—
≥25		8.79	3.58 to 21.61	<0.0001
IL-6 −174 genotype				
GG	**43,8%**	1	—	—
GC	**42,4%**	0.15	0.02 to 1.17	0.074
CC	**13,8%**	0.08	0.01 to 0.71	0.023

J Bamoulid et al, J Am Soc Nephrol 2006

NODAT: genetic susceptibility (TSF7L2)

Table 3—*Characteristics of patients according to rs7903146 genotype*

	CC	CT	*P*
n	482	29	
Number of PTDM patients (%)	107 (22.2)	12 (41.4)	0.024*
Age (years) at transplantation	36.92 ± 10.73	36.72 ± 10.74	0.925
Family history of diabetes (%)	272 (58.5)	20 (71.4)	0.235*
Follow-up duration (months)	108.22 ± 59.78	111.34 ± 73.74	0.825
Body weight (kg)			
At transplantation	57.53 ± 10.64	55.06 ± 10.91	0.243
At 3 months after transplantation	57.82 ± 9.71	56.62 ± 9.73	0.526
At 6 months after transplantation	60.45 ± 9.81	59.06 ± 9.34	0.443
ΔBody weight (kg)			
At 3 months after transplantation	0.28 ± 4.61	1.57 ± 4.63	0.157
At 6 months after transplantation	2.92 ± 5.81	4.01 ± 5.63	0.321
FPG (mg/dl)			
At transplantation	92.94 ± 25.68	88.86 ± 20.62	0.381
At 3 months after transplantation	100.58 ± 32.30	101.55 ± 38.14	0.913
At 6 months after transplantation	98.10 ± 17.47	93.07 ± 26.73	0.454
At 12 months after transplantation	102.52 ± 32.14	103.51 ± 31.74	0.868
Duration of dialysis (months)	19.32 ± 31.02	18.43 ± 46.12	0.910
Patients with acute rejection (%)	123 (25.31)	3 (10.34)	0.069*
Patients with tacrolimus use (%)	110 (22.8)	10 (34.5)	0.175*
Creatinine (mg/dl)			
At 3 months after transplantation	1.39 ± 0.70	1.26 ± 0.36	0.104
At 6 months after transplantation	1.31 ± 0.35	1.23 ± 0.31	0.226
At 12 months after transplantation	1.31 ± 0.42	1.22 ± 0.31	0.172

ES Kang et al, Diabetes Care 2008

NODAT: genetic susceptibility (HNF1ß)

Kidney disease (especially bilateral)

- Glomerulocystic disease
- Renal cystic dysplasia
- Horseshoe kidney

Pancreatic abnormalities

- Partial or complete pancreas atrophy
- Early-onset diabetes
- Mild exocrine pancreatic insufficiency

Genital abnormalities

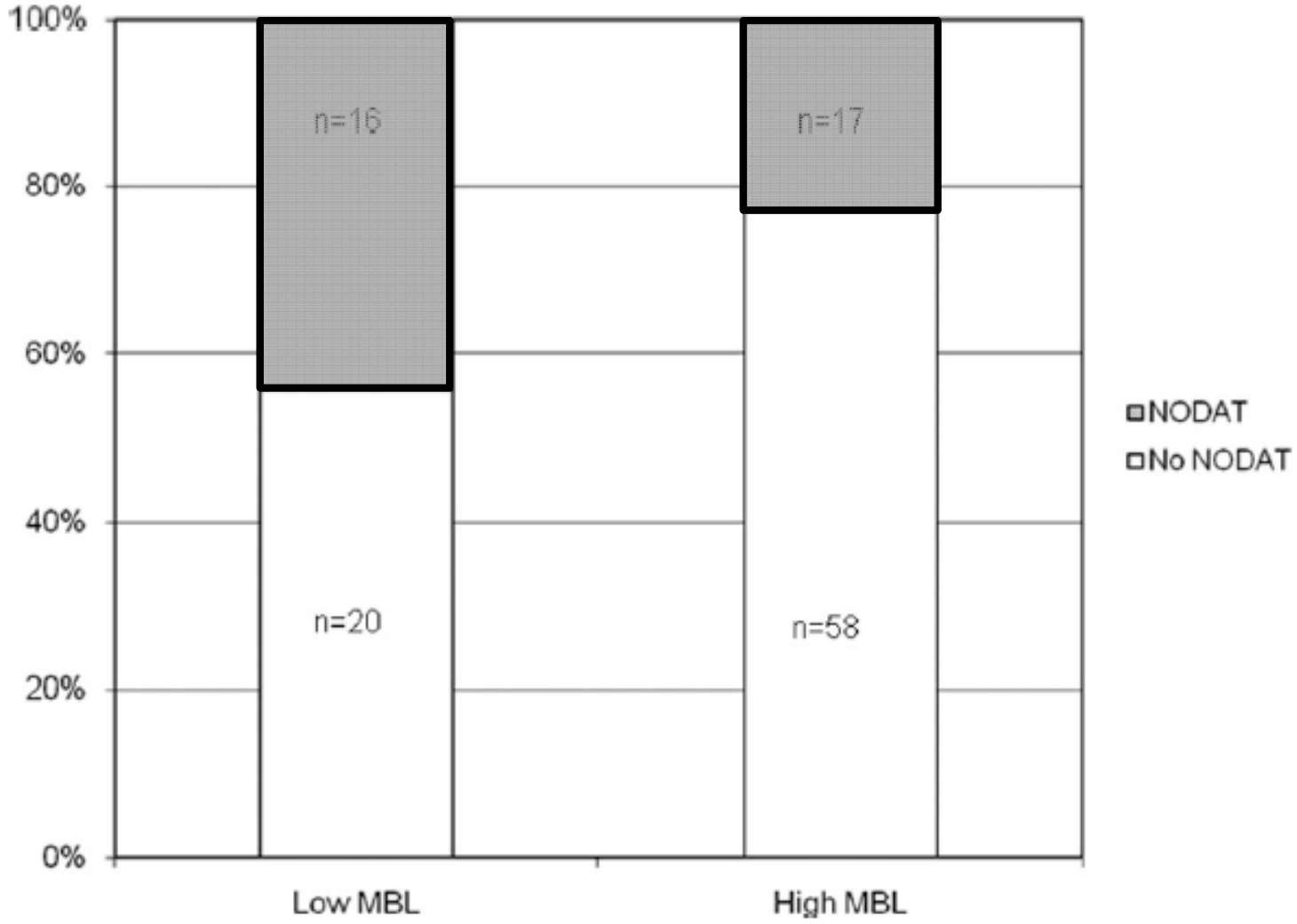
- Bicornuate or bicervical uterus
- Vaginal partition
- Cysts and atresia of male genital tract

Early-onset gout

Increased liver enzyme levels with normal liver histology

J Zuber et al, Nature Rev Nephrol 2009

NODAT: innate immunity
(serum mannose-binding lectin)



M Ibernon et al, Transplantation 2009

NODAT: risk factors

Modifiable risk factors

- Previous stress diabetes
- Obesity
- Metabolic syndrome
- High pretransplantation triglyceride level
- Cytomegalovirus infection*
- Hepatitis C virus infection*
- Immunosuppression* (tacrolimus, ciclosporin, sirolimus, corticosteroids)
- Rejection episodes?*
- Antihypertensive agents (β-blockers, thiazide diuretics)
- Biochemical abnormalities (low magnesium, high uric acid?)
- Impaired glomerular filtration rate?

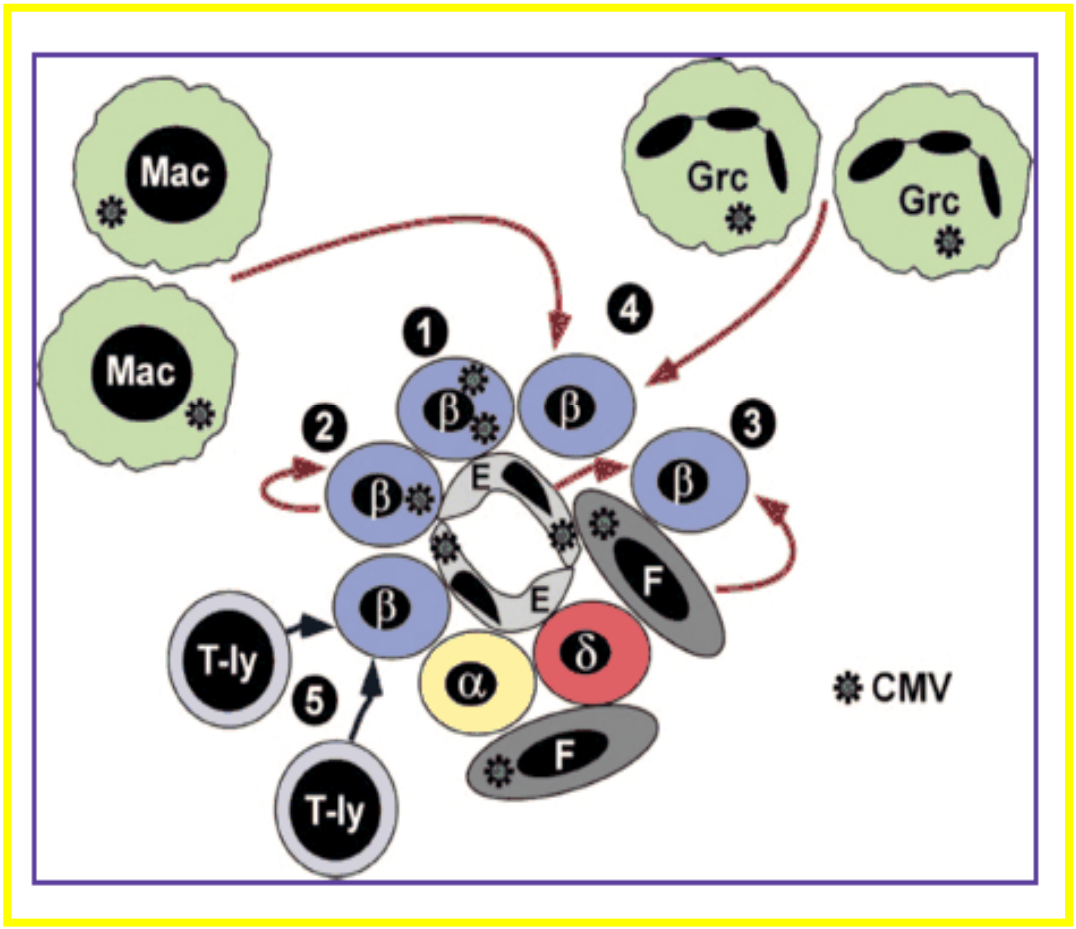
Any glucose abnormality, 1 week

Interaction with tacrolimus

*** Transplantation specific risk factor**

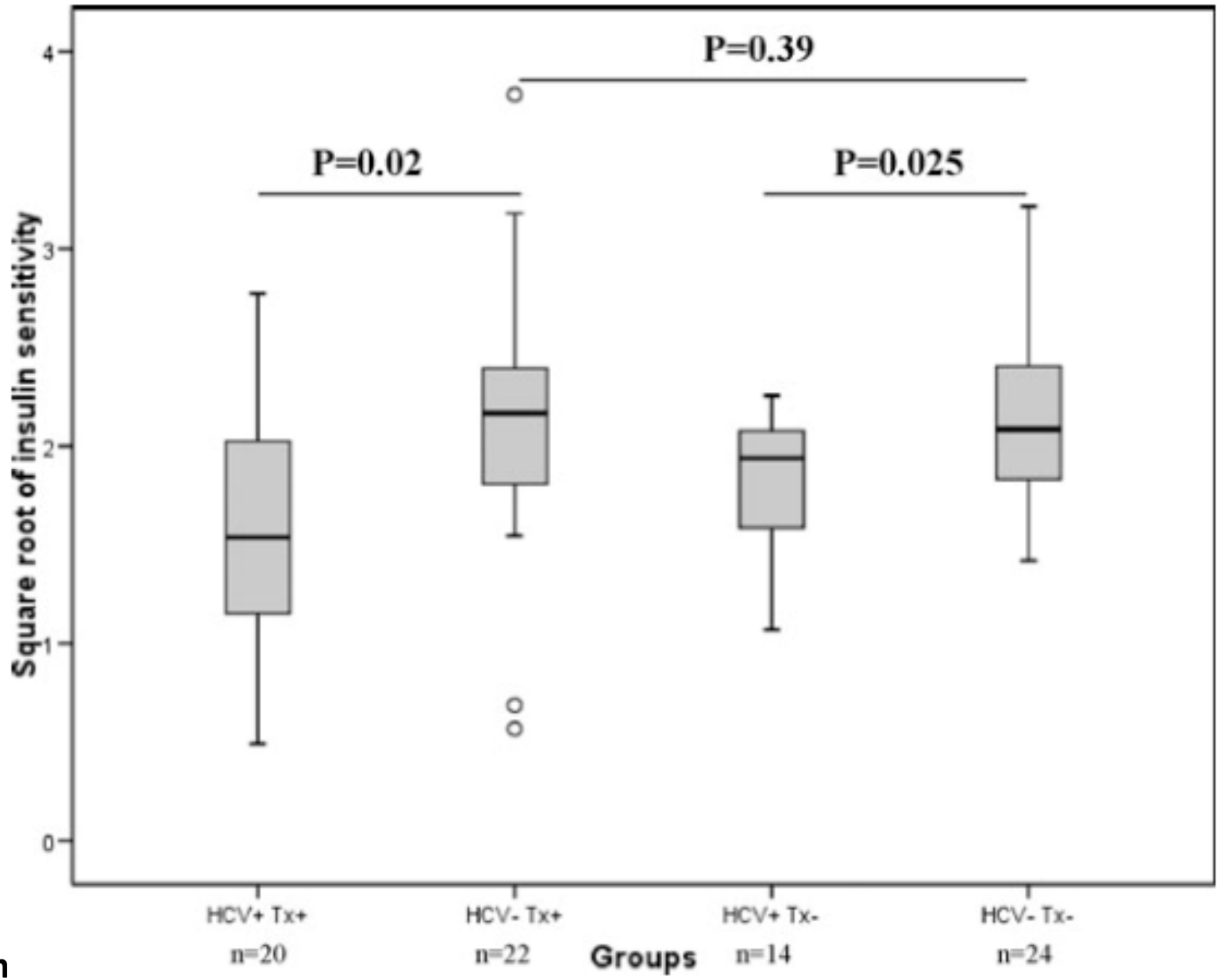
A Sharif et al, Nature Rev Nephrol 2010

NODAT: cytomegalovirus



1. CMV-induced cytopathic effects on ß cells,
2. Proinflammatory cytokines released by CMV-infected ß cells,
3. Proinflammatory cytokines released by other islet cells,
4. Proinflammatory cytokines released by other cells,
5. CMV-specific T cells.

J Hjelmeaeth et al, Nephrol Dial Transplant 2005



RD Bloom

S Baid-Agrawal et al, Am J Transplant 2009

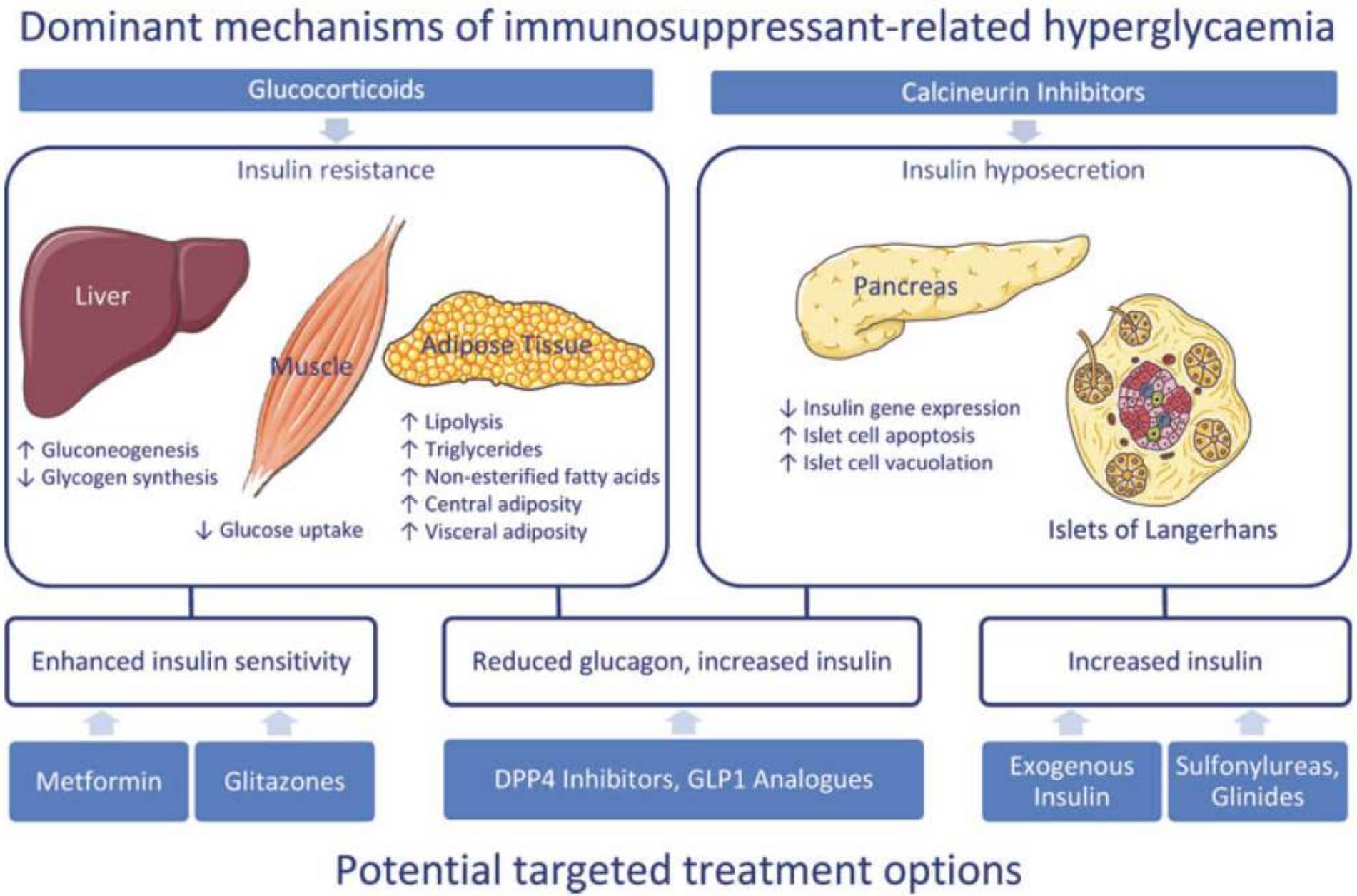
NODAT and immunosuppressive drugs

	Acute rejection	GFR	Blood pressure*	Lipid concentrations	NODAT
Corticosteroids	↓	..	↑↑	↑↑	↑↑
Ciclosporin A	↓↓	↓↓	↑↑↑	↑↑	↑
Tacrolimus	↓↓	↓↓	↑↑	↑	↑↑
mTORi/srl/evl	↓↓	↓/–	..	↑↑↑	..
MMF/MPA	↓	..	..	..	..
Azathioprine	↓	..	..	..	..
Belatacept	↓↓	..	..	..	..
Monoclonals†	↓↓	..	..	..	..

Direction of arrows shows increased or decreased effects. Number of arrows shows semiquantitative effect. GFR=glomerular filtration rate. NODAT=new-onset diabetes after transplantation. mTORi/srl/evl=inhibitors of mammalian target of rapamycin, sirolimus, and everolimus. MMF/MPA=mycophenolate mofetil, mycophenolic acid. *Hypertension. †Induction drugs (eg, basiliximab).

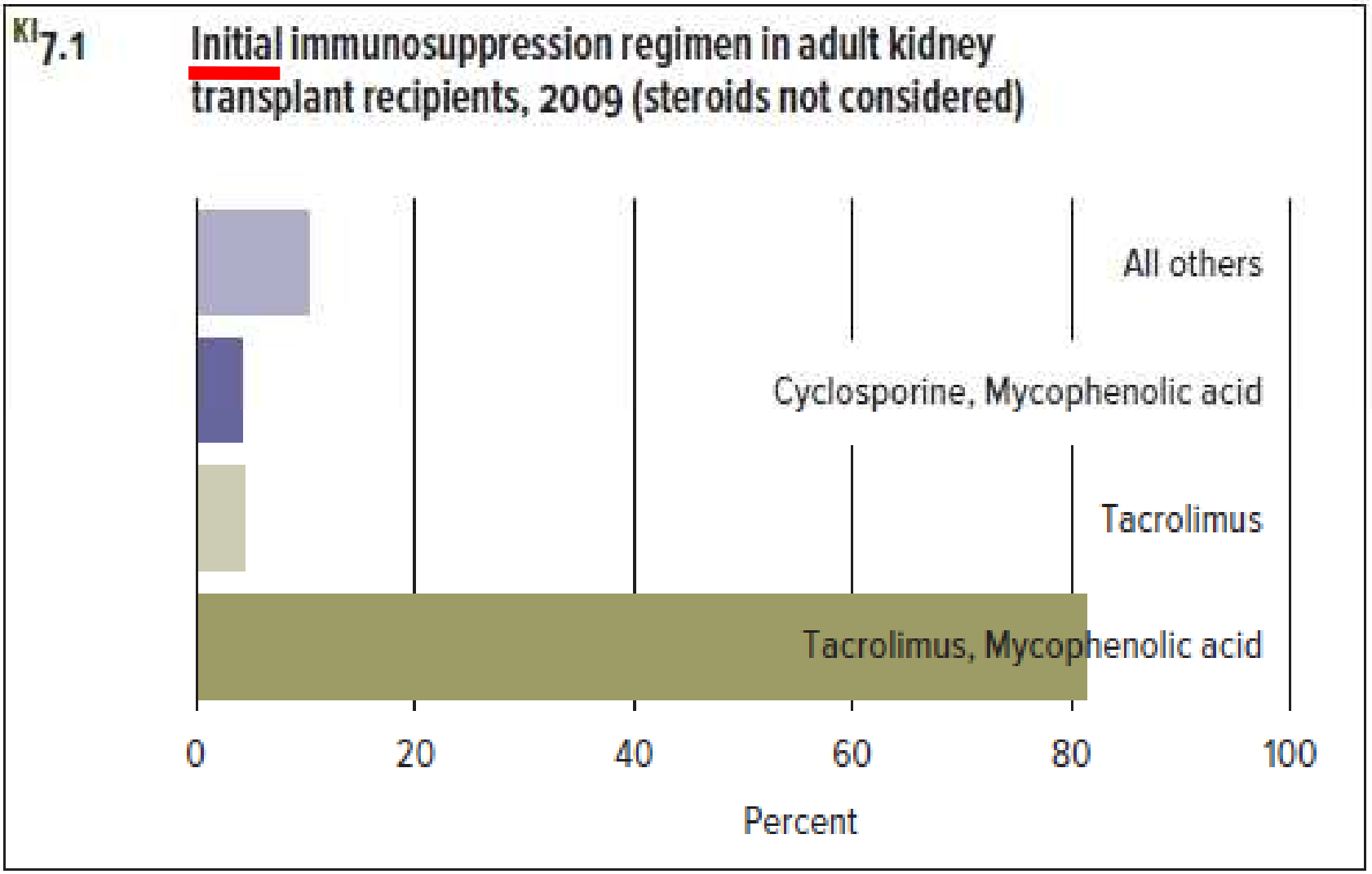
Table: **Effect of immunosuppressive drugs on cardiovascular risk factors**

AG Jardine et al, Lancet 2011



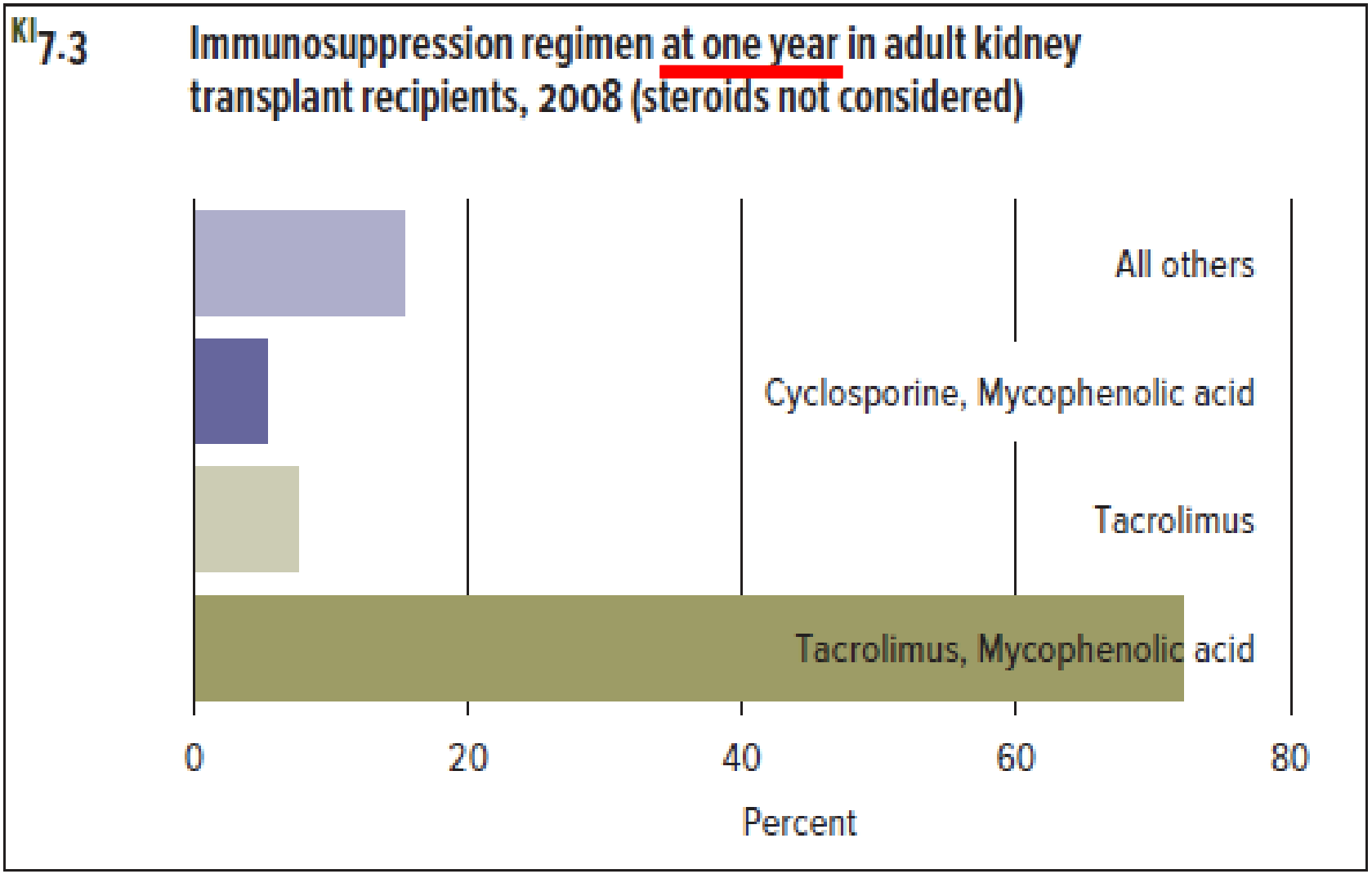
CJ Yates et al, Am J Transplant 2011

Immunosuppression: UNOS 2010



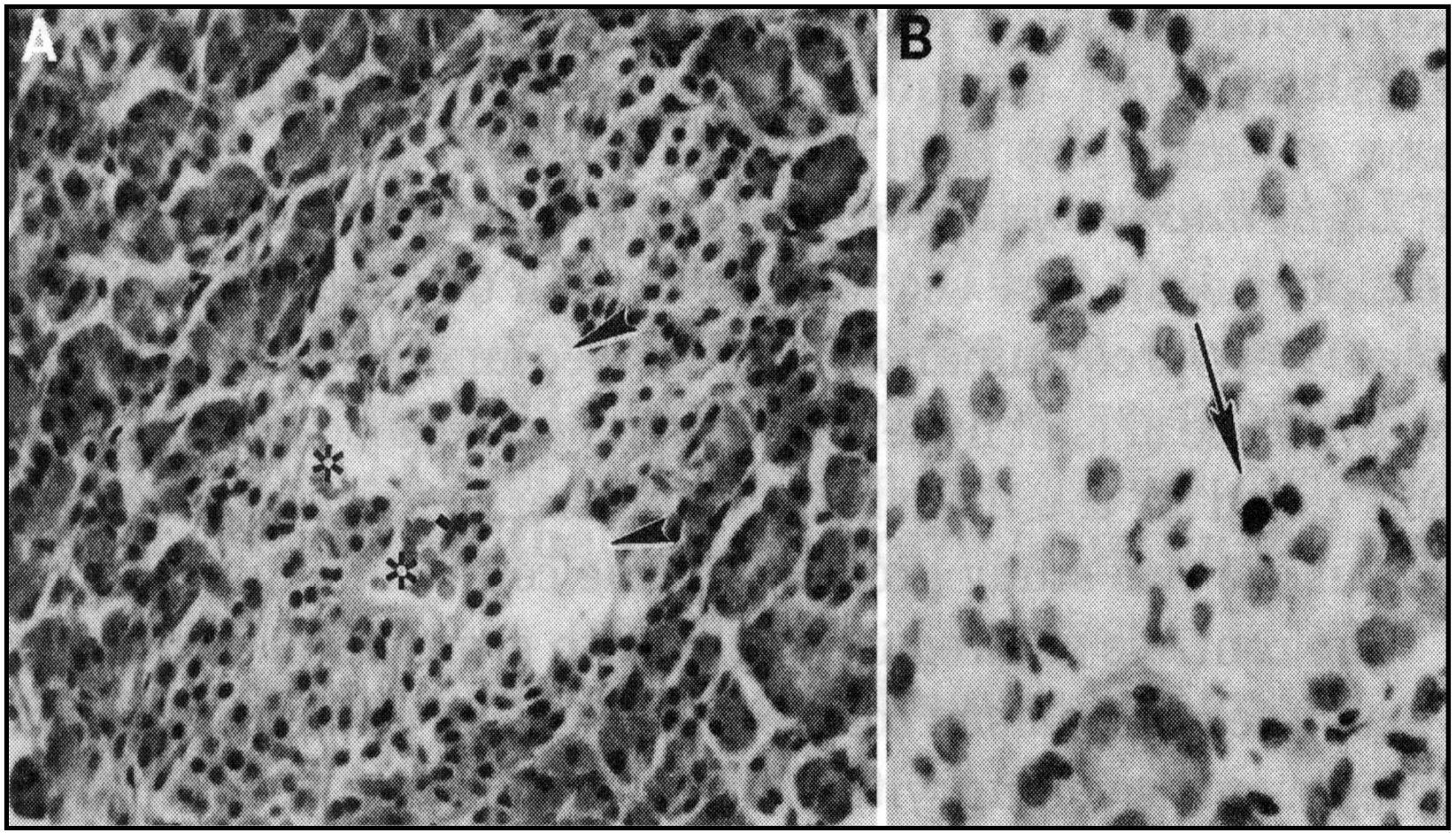
Am J Transplant 2012

Immunosuppression: UNOS 2010



Am J Transplant 2012

NODAT and CNIs



C Drachenberg et al, Transplantation 1999

NODAT: how to modify immunosuppression ?

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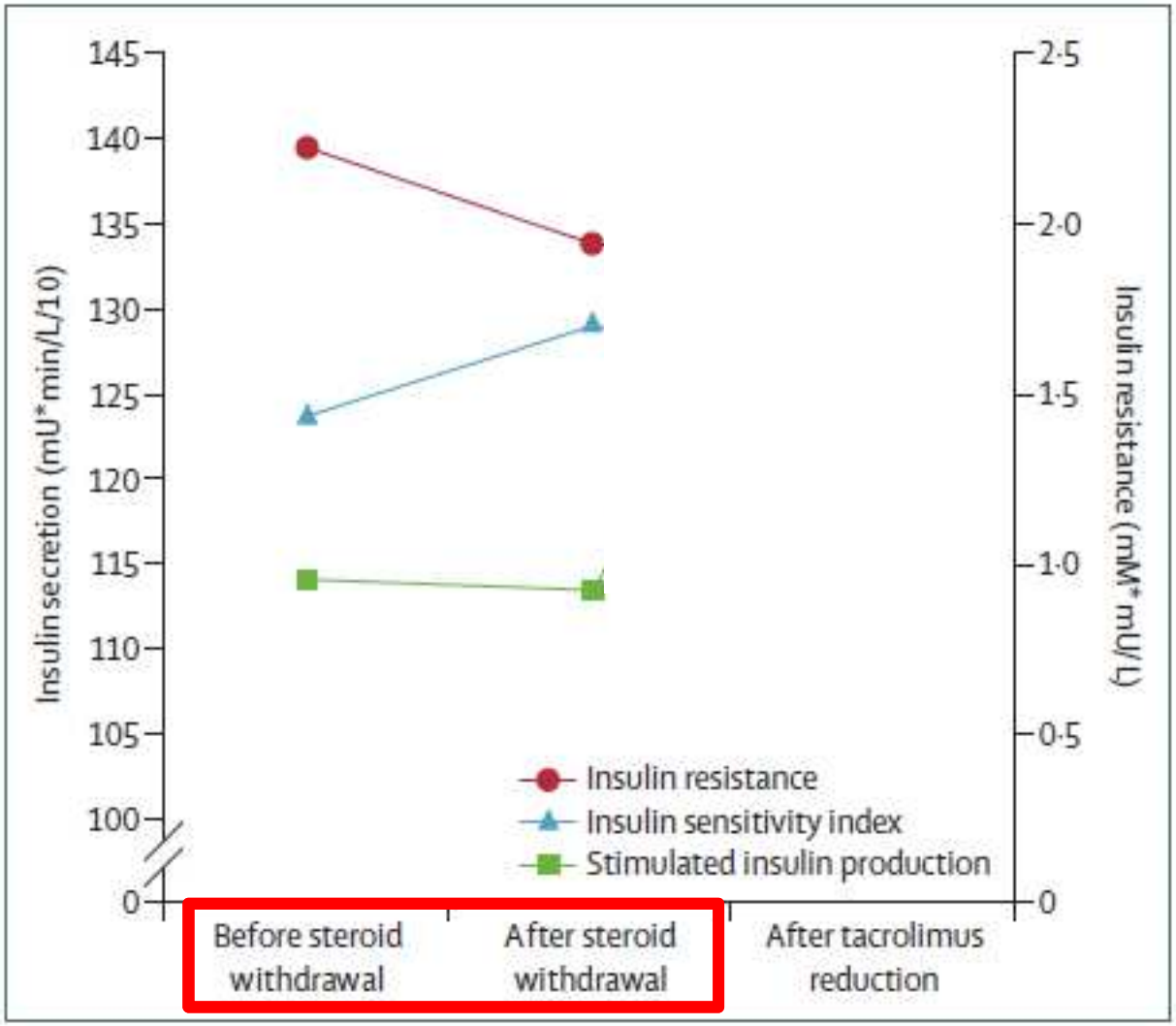
    - mTOR-inhs,
    - Betatacept,
- **To prevent NODAT:**
    - Avoid steroids or early withdrawal,
    - Lower tacrolimus or use CsA instead,
    - Avoid CNIs,
    - Early insulin therapy.

NODAT, steroids and tacrolimus



JP van Hooff et al, Transplantation 2005

NODAT and steroids: late withdrawal

SPECIAL FEATURE

A Systematic Review on Steroid Withdrawal Between 3 and 6 Months After Kidney Transplantation

Julio Pascual,[1,5] Cristina Galeano,[2] Ana Royuela,[3,4] and Javier Zamora[3,4]

J Pascual et al, Transplantation 2009

NODAT and steroids: late withdrawal

Table 1 Results obtained from dichotomous outcomes assessed in the meta-analysis of randomized controlled trials of late steroid withdrawal after kidney transplantation stratified by calcineurin inhibitor

	No. of trials	No. of participants	Effect size	
			Risk ratio (95% CI)*	*P* value
Death				
All	8	1779	0.96 (0.54–1.70)	0.89
Cyclosporine	6	1241	0.91 (0.41–2.02)	0.81
Tacrolimus	2	538	1.02 (0.45–2.30)	0.97
Graft loss excluding death				
All	8	1779	1.07 (0.76–1.52)	0.69
Cyclosporine	6	1241	0.90 (0.50–1.64)	0.74
Tacrolimus	2	538	1.17 (0.76–1.80)	0.47
ITT acute rejection (since the time of kidney transplantation)∞				
All	4	1180	1.20 (0.84–1.71)	0.31
Cyclosporine	2	642	1.42 (1.08–1.87)	0.013
Tacrolimus	2	538	1.05 (0.51–2.13)	0.90
ITT biopsy-proven acute rejection¤				
All	4	1237	1.27 (0.84–1.93)	0.26
Cyclosporine	3	791	1.61 (1.20–2.17)	0.0018
Tacrolimus	1	446	0.82 (0.57–1.18)	0.29
Patients on lipid-lowering therapy**				
All	3	687	0.86 (0.49–1.50)	0.60
Cyclosporine	1	149	1.49 (0.69–3.24)	0.31
Tacrolimus	2	538	0.66 (0.46–0.93)	0.017
NODAT				
All	3	656	0.58 (0.31–1.09)	0.089
Cyclosporine	1	118	0.50 (0.13–1.91)	0.31
Tacrolimus	2	538	0.61 (0.30–1.23)	0.17

J Pascual , Cur Op Organ Transplant 2011

NODAT: how to modify immunosuppression ?

- **In case of NODAT:**
  - **Stop steroids,**
  - **Convert from tacrolimus** to:
    - Cyclosporine, 
    - mTOR-inhs,
    - Betatacept,
- **To prevent NODAT:**
    - Avoid steroids or early withdrawal,
    - Lower tacrolimus or use CsA instead,
    - Avoid CNIs,
    - Early insulin therapy.

NODAT: conversion tacrolimus - CsA

	t_0	+3 months	+6 months	+12 months	*P*-value
Converted group (n = 34)					
FPG (mg/dl)	146 ± 64	111 ± 26	106 ± 19	104 ± 21[a]	<0.0001
HbA1c (%)	6.8 ± 0.8	6.6 ± 1.0	6.1 ± 0.6	6.0 ± 0.6[b]	<0.0001
Control group (n = 20)					
FPG (mg/dl)	154 ± 47	121 ± 25	121 ± 42	124 ± 30[a]	0.004
HbA1c (%)	5.9 ± 1.1	6.4 ± 1.4	6.7 ± 1.0	6.8 ± 1.5[b]	0.03

FPG, Fasting plasma glucose.

P-value corresponds to within-group comparisons. Between group comparisons: [a]$P = 0.007$ at t + 12 months, [b]$P = 0.06$ at t + 12 months.

L Ghisdal et al, Transplant Int 2008

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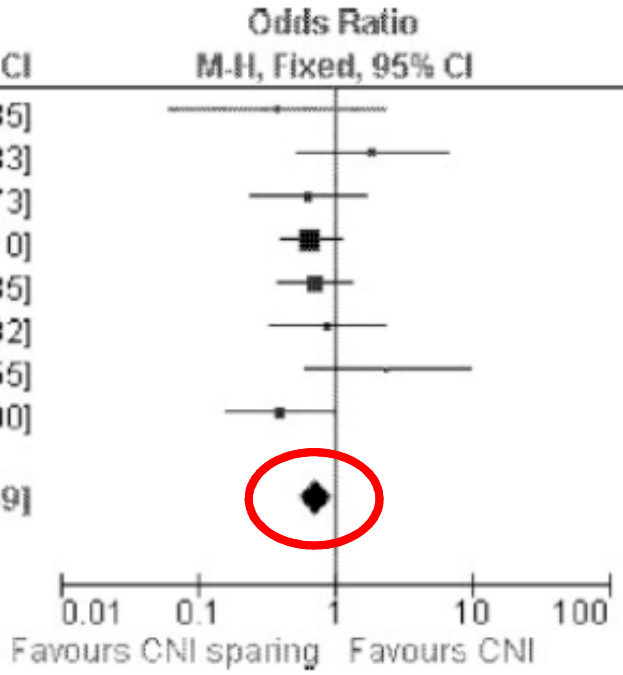
Influence of CNI-sparing IS on NODAT

Study or Subgroup	CNI sparing Events	Total	CNI Events	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)



A Sharif et al, J Am Soc Nephrol 2011

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    - Avoid CNIs,
    - Early insulin therapy.

NODAT: conversion CsA/belatacept

Switching from Calcineurin Inhibitor-based Regimens to a Belatacept-based Regimen in Renal Transplant Recipients: A Randomized Phase II Study

Lionel Rostaing,[*] Pablo Massari,[†] Valter Duro Garcia,[‡] Eduardo Mancilla-Urrea,[§] Georgy Nainan,[‖] Maria del Carmen Rial,[¶] Steven Steinberg,[**] Flavio Vincenti,[††] Rebecca Shi,[‡‡] Greg Di Russo,[‡‡] Dolca Thomas,[‡‡] and Josep Grinyó[§§]

Cardiovascular and Metabolic Changes

NODAT occurred in two patients receiving CNIs (2.9%; 95% CI 0.4, 10.2) and one receiving belatacept (1.7%; 95% CI 0.0, 9.1). Use of antidiabetic medication, whether in the whole study population or in the subgroups with and without diabetes at baseline, did not differ between treatment groups.

L. Rostaing et al,Clin J Am Soc Nephrol 2012

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    - Early insulin therapy.

NODAT and steroids: early withdrawal or maintenance?

ORIGINAL ARTICLES

A Prospective, Randomized, Double-Blind, Placebo-Controlled Multicenter Trial Comparing Early (7 Day) Corticosteroid Cessation Versus Long-Term, Low-Dose Corticosteroid Therapy

E. Steve Woodle, MD, M. Roy First, MD,† John Pirsch, MD,‡ Fuad Shihab, MD,§ A. Osama Gaber, MD,¶ and Paul Van Veldhuisen, PhD,‖ for the Astellas Corticosteroid Withdrawal Study Group*

New onset diabetes after transplant (NODAT) was similar with respect to proportions who required treatment (23/107 (21.5%); 18/86 (20.9%); however, fewer CSWD patients required insulin for NODAT at 5 years (4/107 (3.7%); 10/86 (11.6%), $P = 0.049$). Changes in HgA1c values (from baseline) were lower in CSWD patients at all time points except 4 years.

NODAT and steroids: early withdrawal or avoidance?

Table 3 Results obtained in the meta-analysis of randomized controlled trials of very early steroid withdrawal and steroid avoidance in kidney transplantation stratified by calcineurin inhibitor

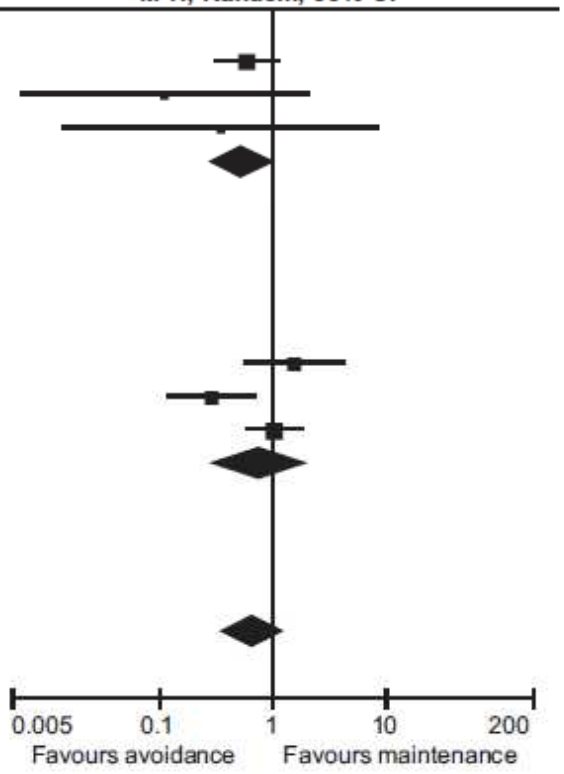
Outcome, by calcineurin inhibitor	No. of trials	No. of participants		Effect size	
		Avoidance therapy	Maintenance therapy	Risk ratio (95% CI)[a]	*P* value
Death					
All	6	24/936	19/831	1.10 (0.60–2.02)	0.75
Cyclosporine	3	7/334	3/211	1.27 (0.31–5.15)	0.73
Tacrolimus	3	17/602	16/620	1.09 (0.50–2.37)	0.83
Graft loss excluding death					
All	6	43/936	32/831	1.23 (0.73–2.07)	0.44
Cyclosporine	3	10/334	10/211	0.72 (0.28–1.84)	0.49
Tacrolimus	3	33/602	22/620	1.50 (0.78–2.88)	0.23
ITT acute rejection					
All	3	106/458	78/392	1.26 (0.85–1.87)	0.25
Cyclosporine	2	43/198	14/114	1.73 (0.99–3.05)	0.06
Tacrolimus	1	63/260	64/278	1.05 (0.78–1.43)	0.74
ITT biopsy-proven acute rejection					
All	5	209/891	106/799	1.84 (1.18–2.87)	0.007
Cyclosporine	2	86/289	27/179	2.01 (1.35–2.98)	0.0005
Tacrolimus	3	123/602	79/620	1.78 (0.85–3.73)	0.12
NODAT requiring any treatment					
All	6	57/798	66/678	0.65 (0.38–1.14)	0.13
Cyclosporine	3	19/319	20/202	0.54 (0.30–0.98)	0.043
Tacrolimus	3	38/479	46/476	0.75 (0.32–1.77)	0.52

J Pascual , Cur Op Organ Transplant 2011

NODAT and steroids: avoidance or maintenance?

Forest plot for NODAT requiring any treatment

Study or Subgroup	Steroid avoidance Events	Total	Steroid maintenance Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
CsA + MMF/Myf/mTOR						
Vincenti 2008 (15)	19	224	16	111	26.5%	0.59 [0.32, 1.10]
Kumar 2005 (12)	0	30	3	23	3.6%	0.11 [0.01, 2.04]
Montagnino 2005 (14)	0	65	1	68	3.1%	0.35 [0.01, 8.40]
Subtotal (95% CI)		**319**		**202**	**33.2%**	**0.54 [0.30, 0.98]**
Total events	19		20			
Heterogeneity: Tau² = 0.00; Chi² = 1.32, df = 2 (P = 0.52); I² = 0%						
Test for overall effect: Z = 2.02 (P = 0.04)						
TAC + MMF/Myf/mTOR						
Vitko 2003 (18)	9	127	6	131	17.9%	1.55 [0.57, 4.22]
Rostaing 2005 (17)	6	245	22	259	20.3%	0.29 [0.12, 0.70]
Woodle 2008 (19)	23	107	18	86	28.5%	1.03 [0.59, 1.78]
Subtotal (95% CI)		**479**		**476**	**66.8%**	**0.75 [0.32, 1.77]**
Total events	38		46			
Heterogeneity: Tau² = 0.47; Chi² = 7.70, df = 2 (P = 0.02); I² = 73%						
Test for overall effect: Z = 0.55 (P = 0.52)						
Total (95% CI)		**798**		**678**	**100.0%**	**0.65 [0.38, 1.14]**
Total events	57		66			
Heterogeneity: Tau² = 0.23; Chi² = 10.31, df = 5 (P = 0.07); I² = 50%						
Test for overall effect: Z = 1.41 (P = 0.13)						

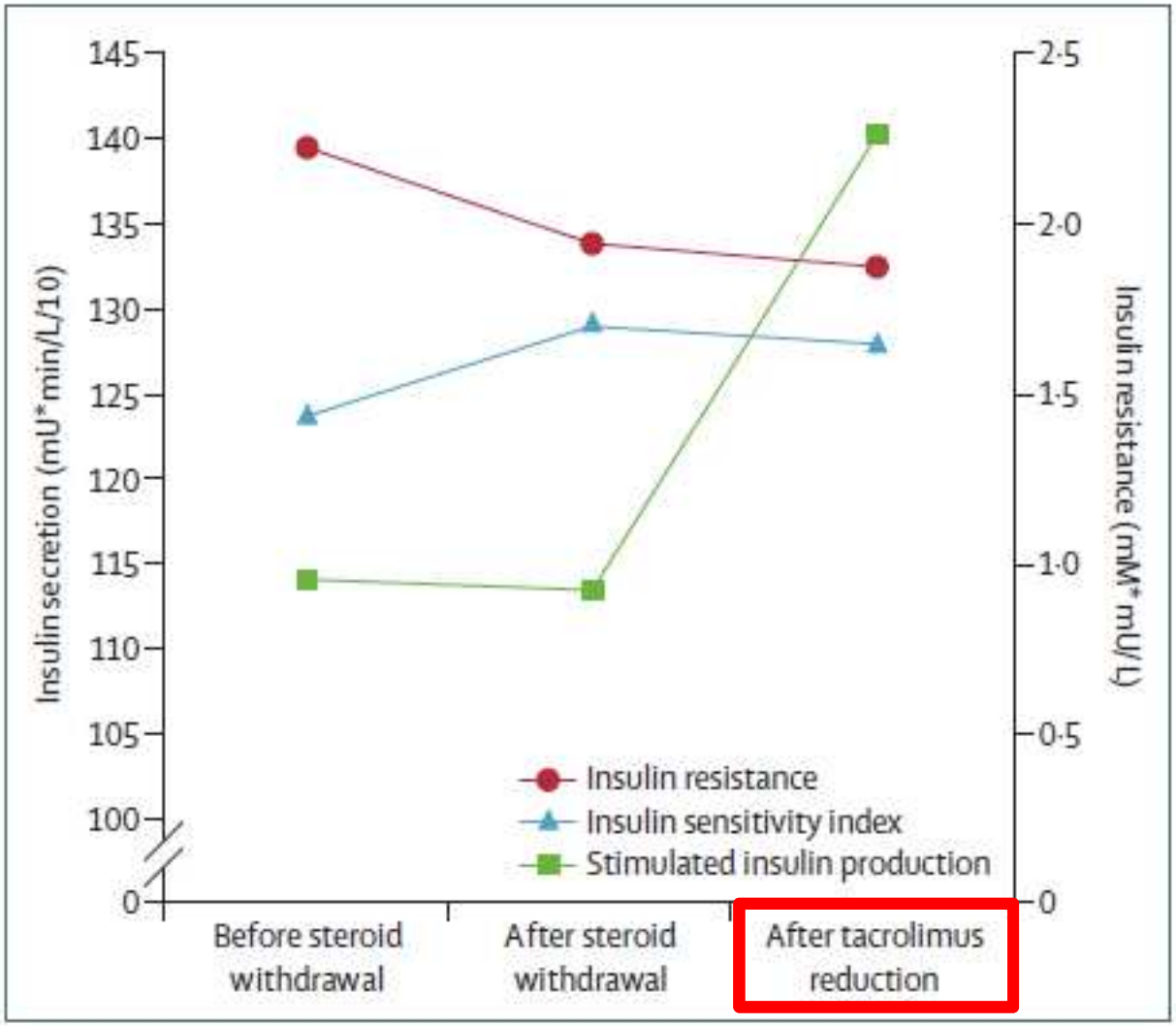


J Pascual et al, Nephrol Dial Transplant 2011

NODAT: how to modify immunosuppression ?

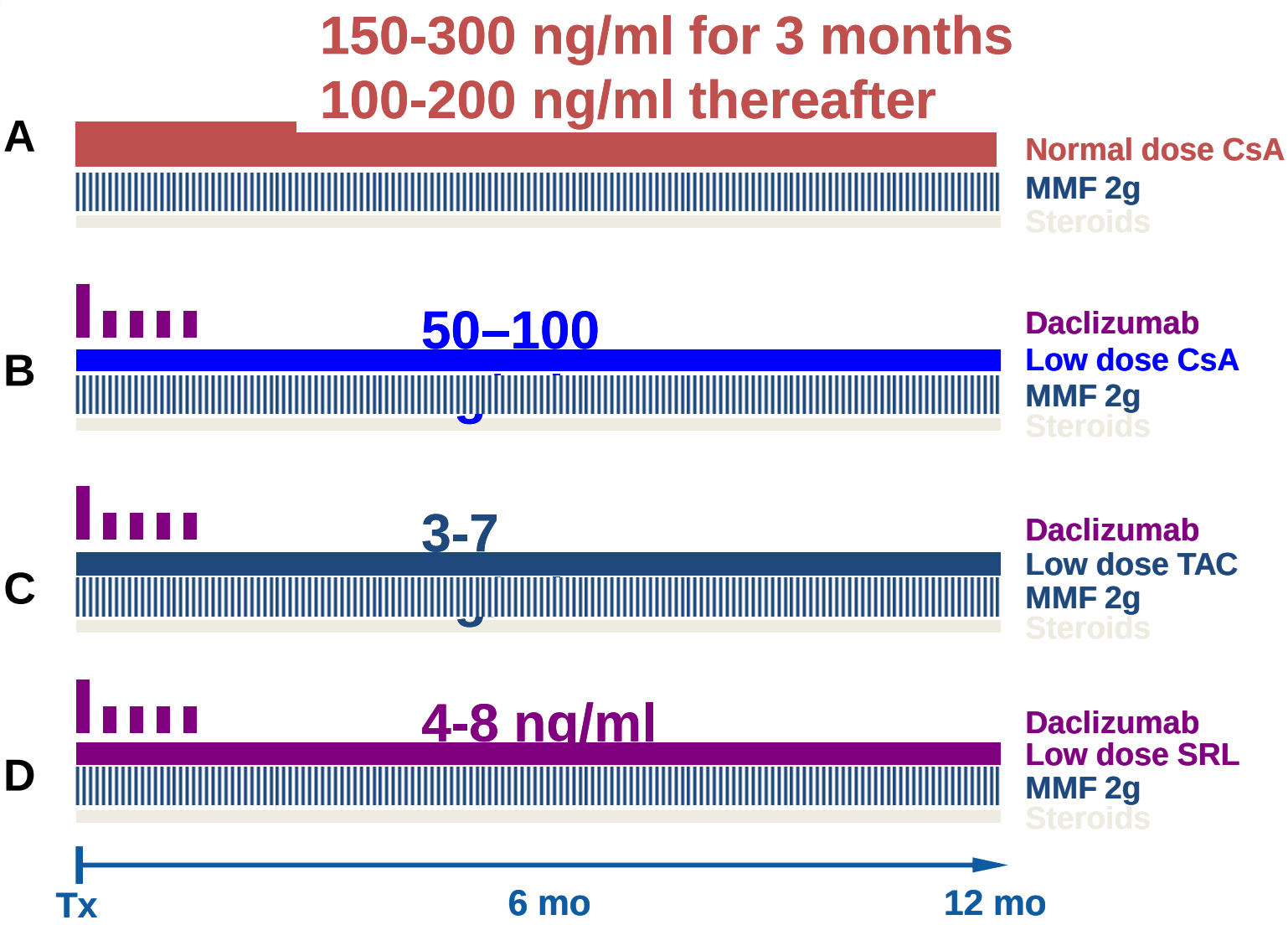
- **In case of NODAT:**
  - **Stop steroids,**
  - **Convert from tacrolimus** to:
    - Cyclosporine,
    - mTOR-inhs,
    - Betatacept,
- **To prevent NODAT:**
    - Avoid steroids or early withdrawal,
    - Lower tacrolimus or use CsA instead,
    - Avoid CNIs,
    - Early insulin therapy.

NODAT, steroids and tacrolimus



JP van Hooff et al, Transplantation 2005

Symphony study : design



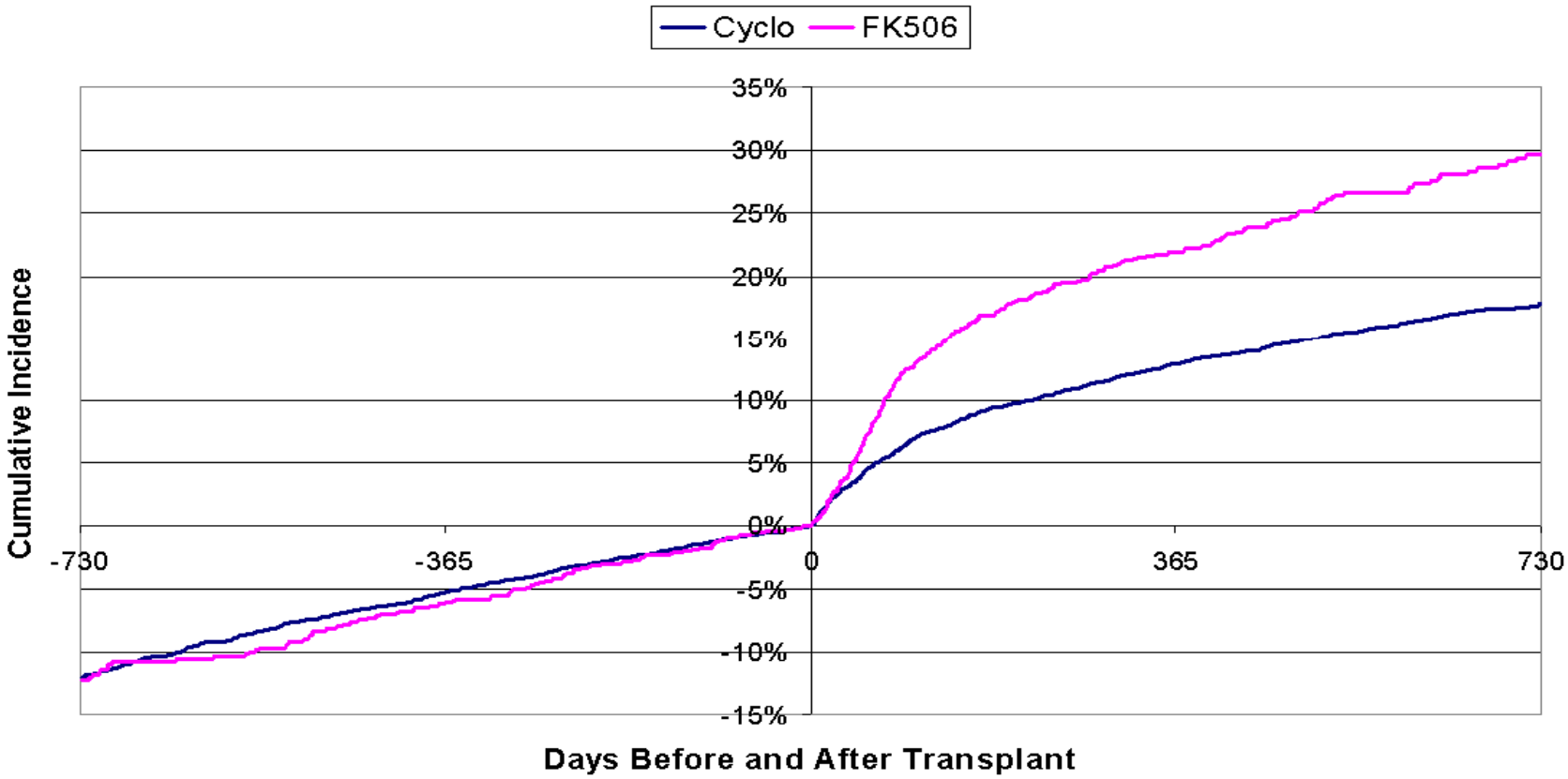
H Ekberg et al, N Engl J Med 2007

Symphony study: side effects

Event	Standard-Dose Cyclosporine (N = 384)	Low-Dose Cyclosporine (N = 408)	Low-Dose Tacrolimus (N = 403)	Low-Dose Sirolimus (N = 380)
		percent		
Kaplan–Meier estimate of selected events¶				
New-onset diabetes after transplantation (P = 0.02)	6.4	4.7	10.6	7.8
Use of antidiabetes medication (P = 0.37)‖	1.3	1.5	2.7	1.0
Diarrhea (P<0.001)	17.9	14.4	27.4	24.0
Lymphocele formation (P<0.001)**	7.0	6.8	4.0	15.8
Opportunistic infection (P = 0.03)	33.0	28.1	26.3	26.6
Cytomegalovirus (P = 0.003)	15.3	11.5	10.2	6.5

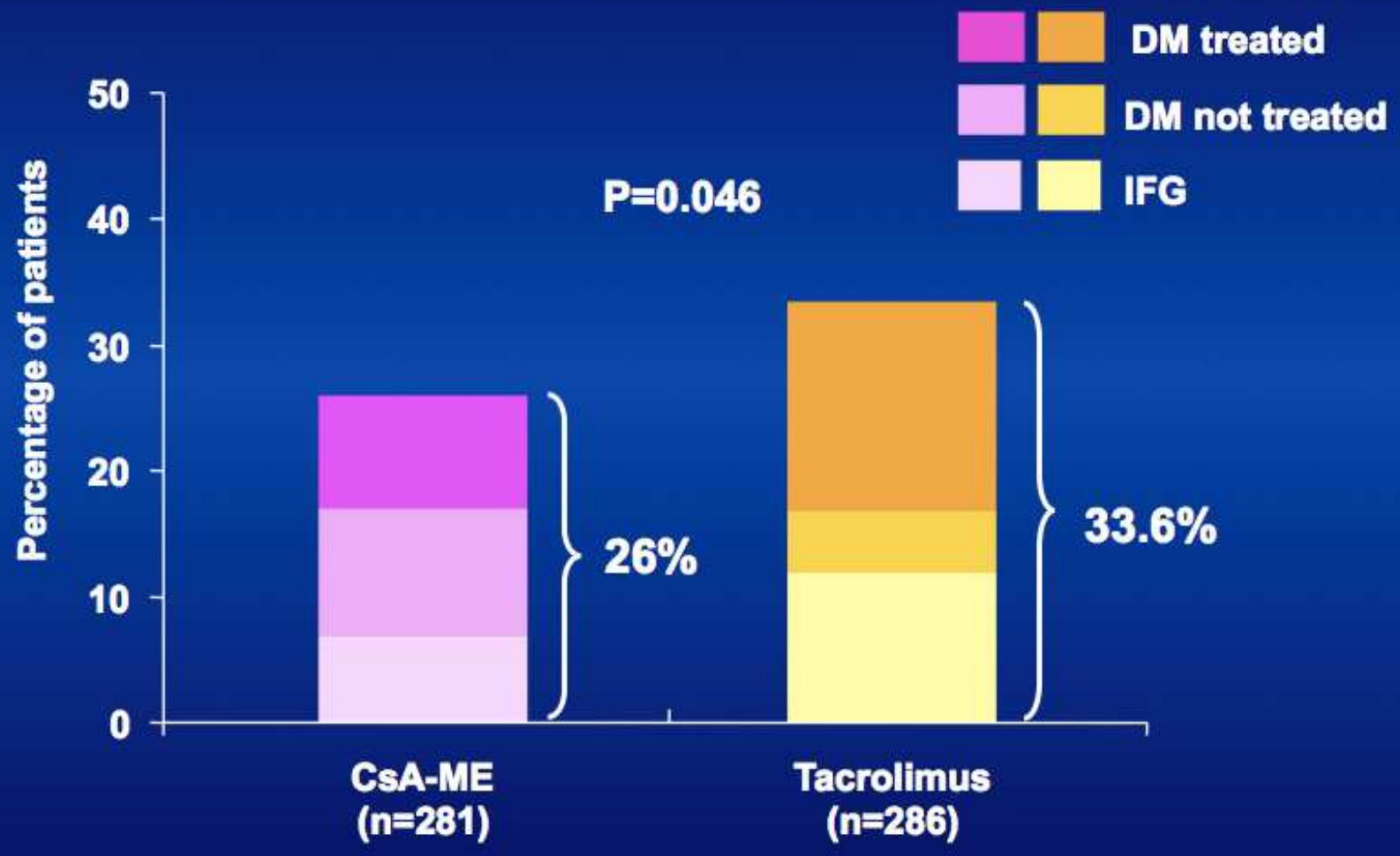
H Ekberg et al, N Engl J Med 2007

NODAT and tacrolimus



RS Woodward et al, Am J Transplant 2003

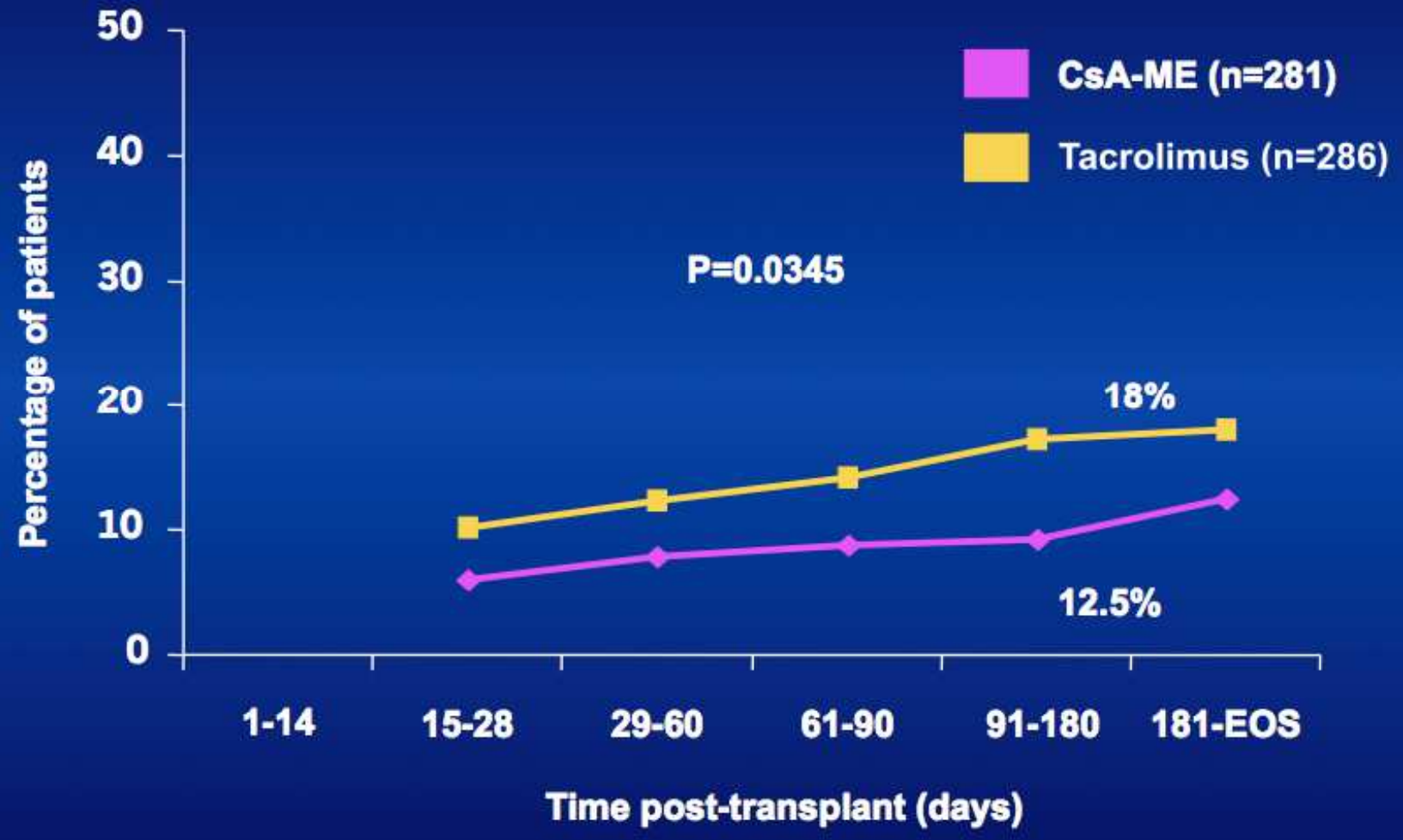
Primary safety endpoint: NODM or IFG by 6 months (OGTT)



Population of patients who were not diabetic at baseline

F Vincenti et al, Am J Transplant 2007

Treated diabetes by 6 months



KM estimate for time to first onset of hypoglycemic treatment (first 14 days post-transplant excluded). EOS, end of study

F Vincenti et al, Am J Transplant 2007

NODAT: how to modify immunosuppression ?

- **In case of NODAT:**
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- **To prevent NODAT:**
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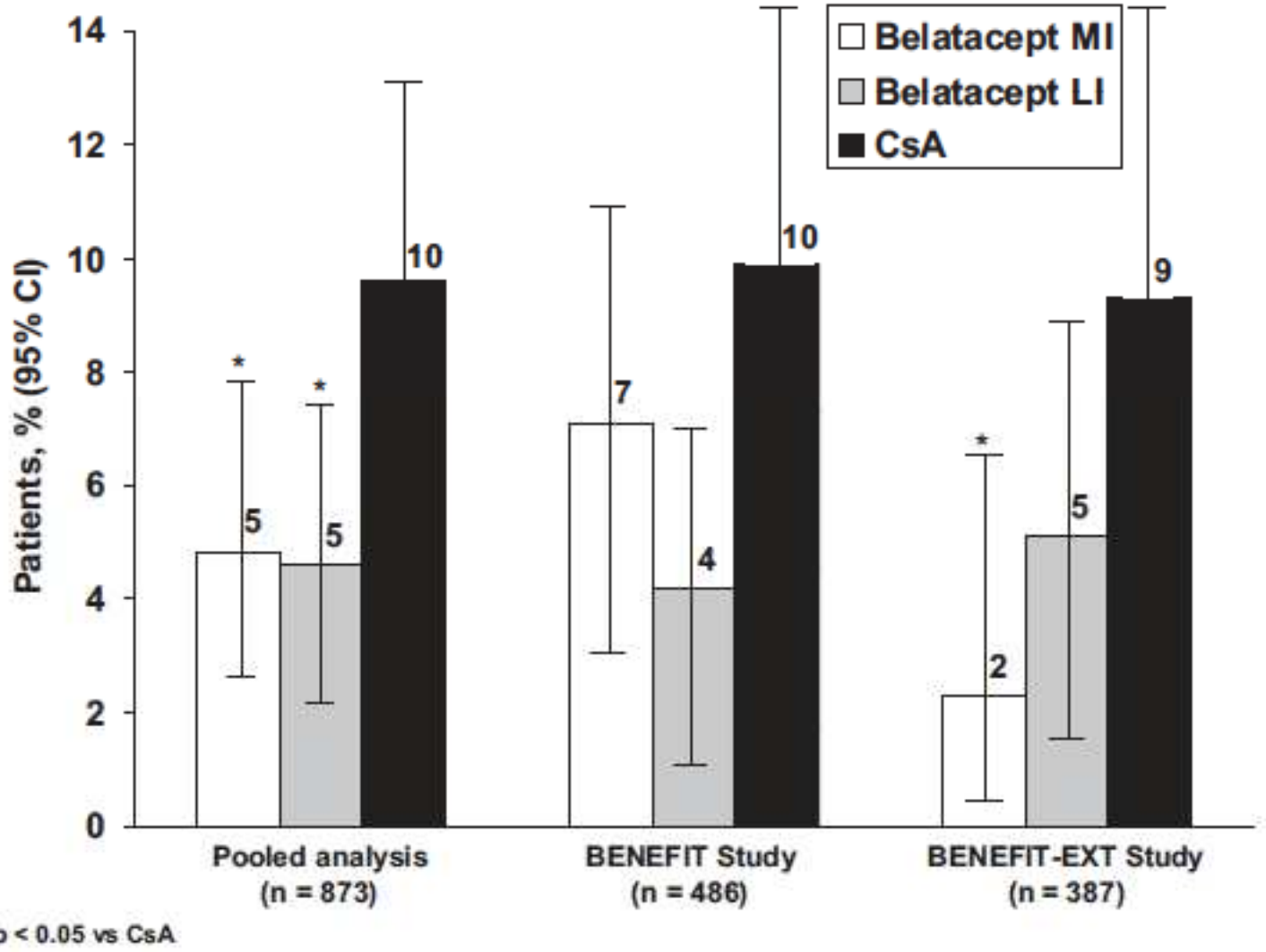
    - Lower tacrolimus or use CsA instead,
    - Avoid CNIs,
    - Early insulin therapy.

Belatacept and NODAT



Y Vanrenterghem et al, Transplantation 2011

NODAT: how to modify immunosuppression ?

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    - Avoid steroids or early withdrawal,
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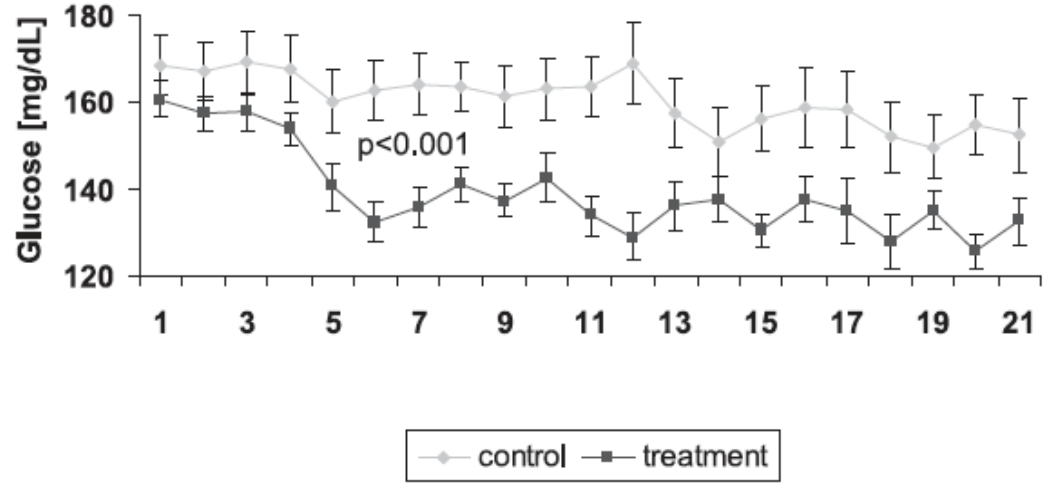
    - Avoid CNIs,
    - Early insulin therapy.

NODAT: early insulin therapy



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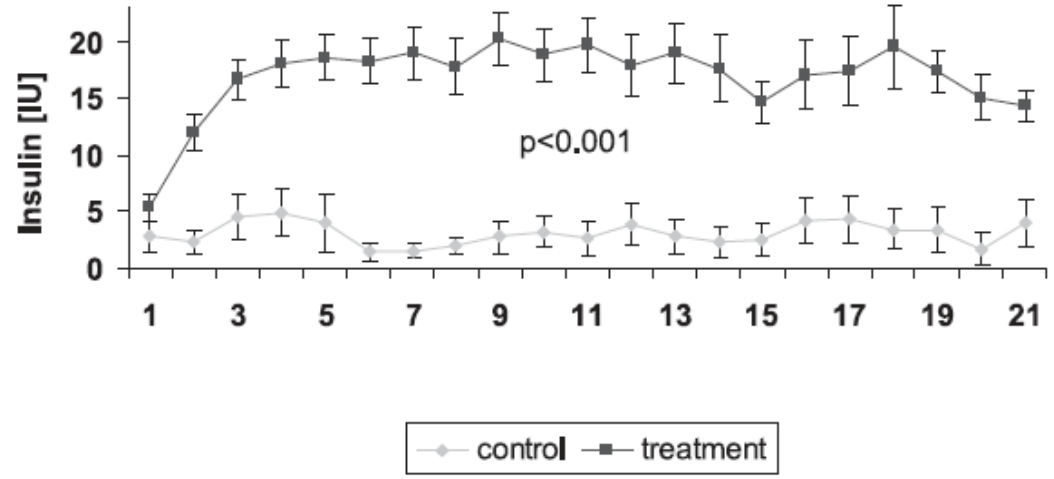
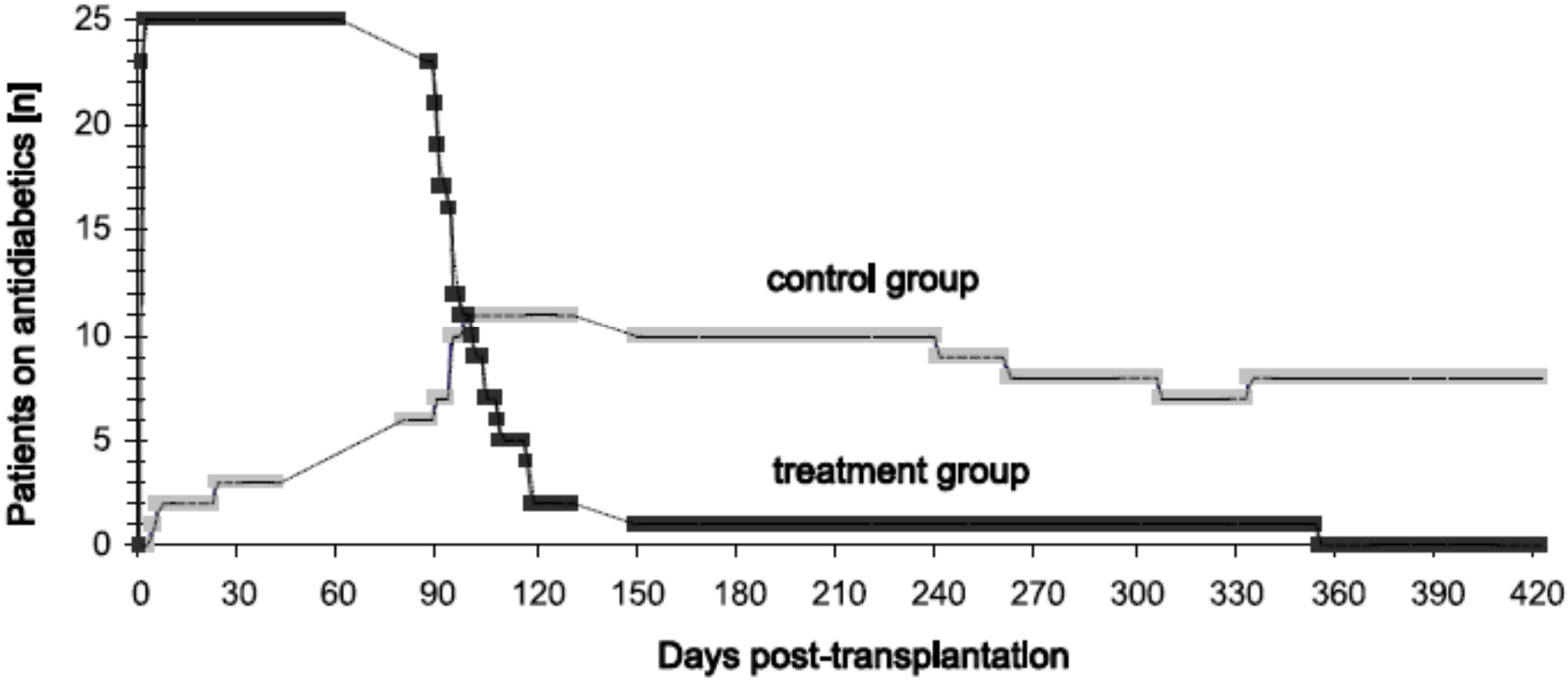
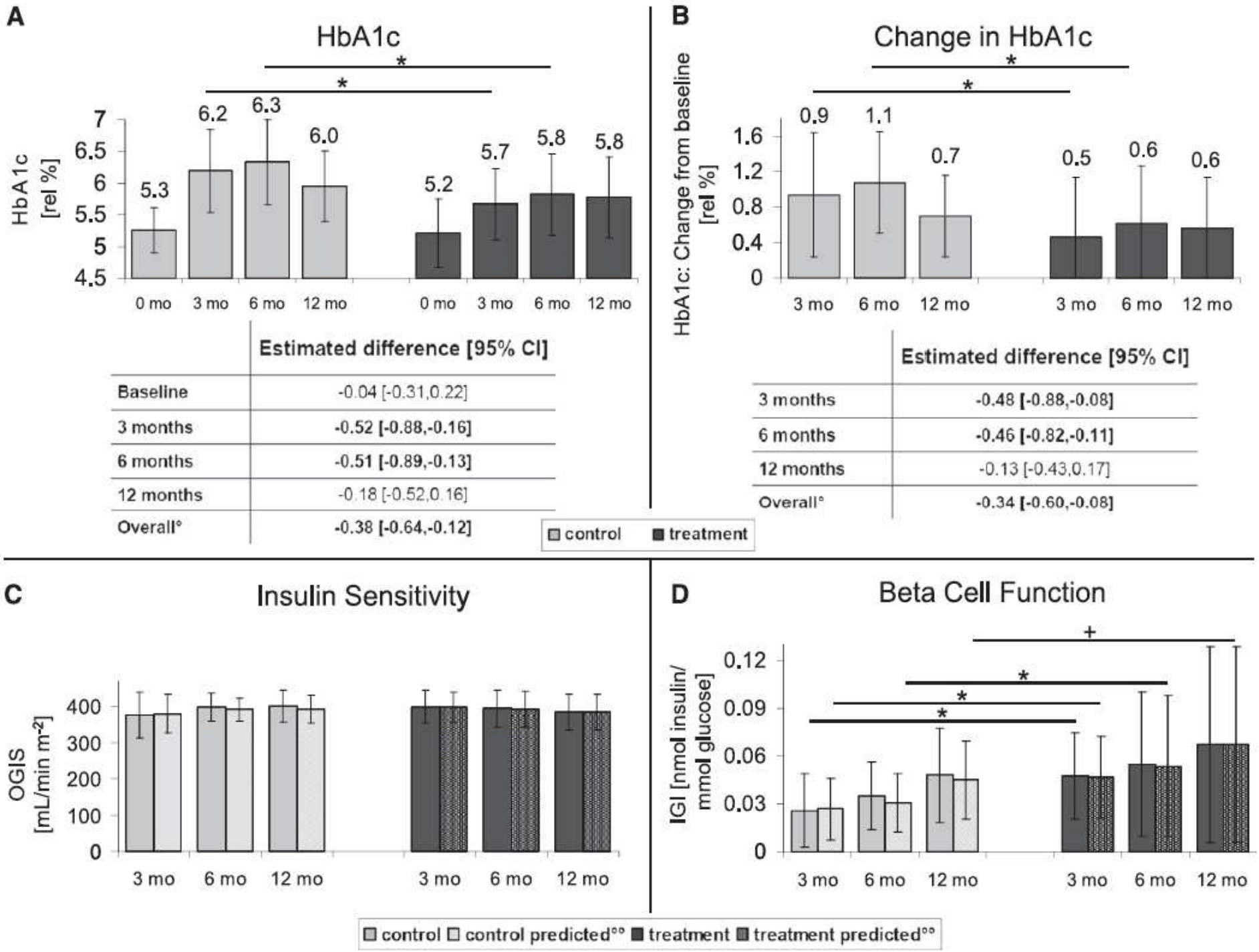


M Hecking et al, J Am Soc Nephrol 2012

NODAT: early insulin therapy

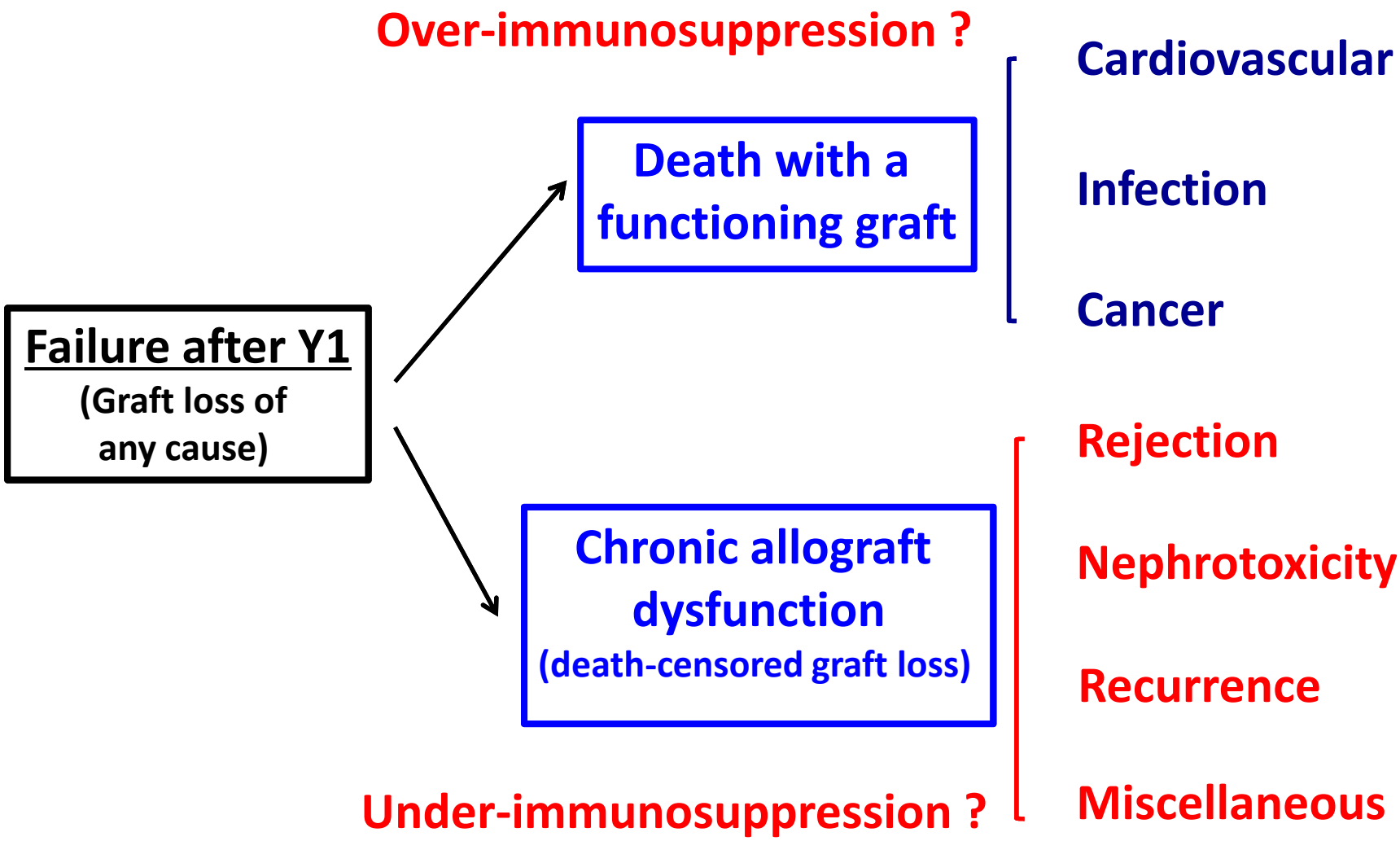


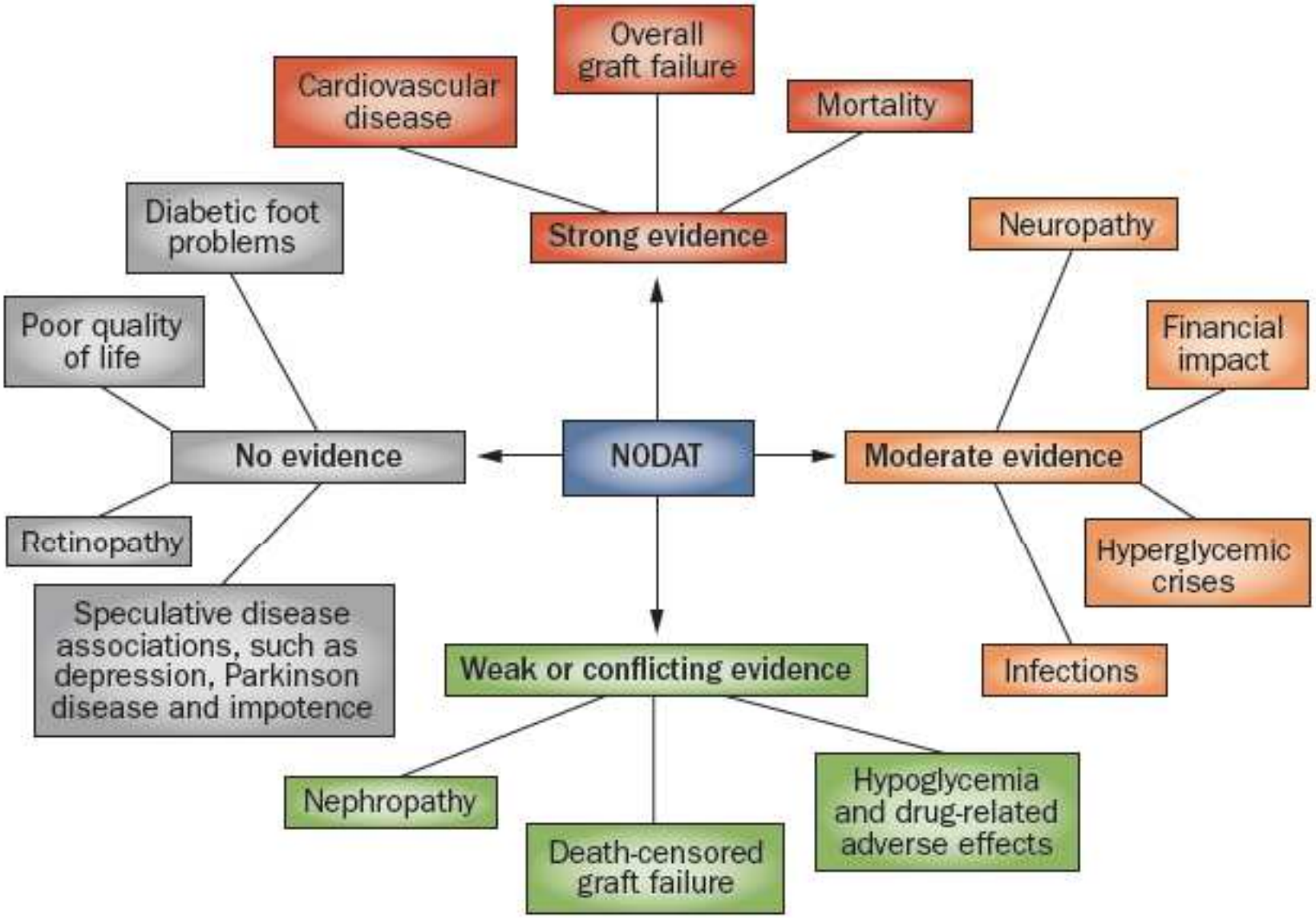
M Hecking et al, J Am Soc Nephrol 2012



	Estimated difference [95% CI]
Baseline	-0.04 [-0.31,0.22]
3 months	**-0.52 [-0.88,-0.16]**
6 months	**-0.51 [-0.89,-0.13]**
12 months	-0.18 [-0.52,0.16]
Overall°	**-0.38 [-0.64,-0.12]**

	Estimated difference [95% CI]
3 months	**-0.48 [-0.88,-0.08]**
6 months	**-0.46 [-0.82,-0.11]**
12 months	-0.13 [-0.43,0.17]
Overall°	**-0.34 [-0.60,-0.08]**


Over-immunosuppression ?
Death with a functioning graft
Cardiovascular
Infection
Cancer
Failure after Y1
(Graft loss of any cause)
Chronic allograft dysfunction
(death-censored graft loss)
Rejection
Nephrotoxicity
Recurrence
Miscellaneous
Under-immunosuppression ?



Are NODAT-induced complications equivalent to that of diabetes in non-transplanted patients?

A Sharif et al, Nature Rev Nephrol 2012

NODAT and mortality

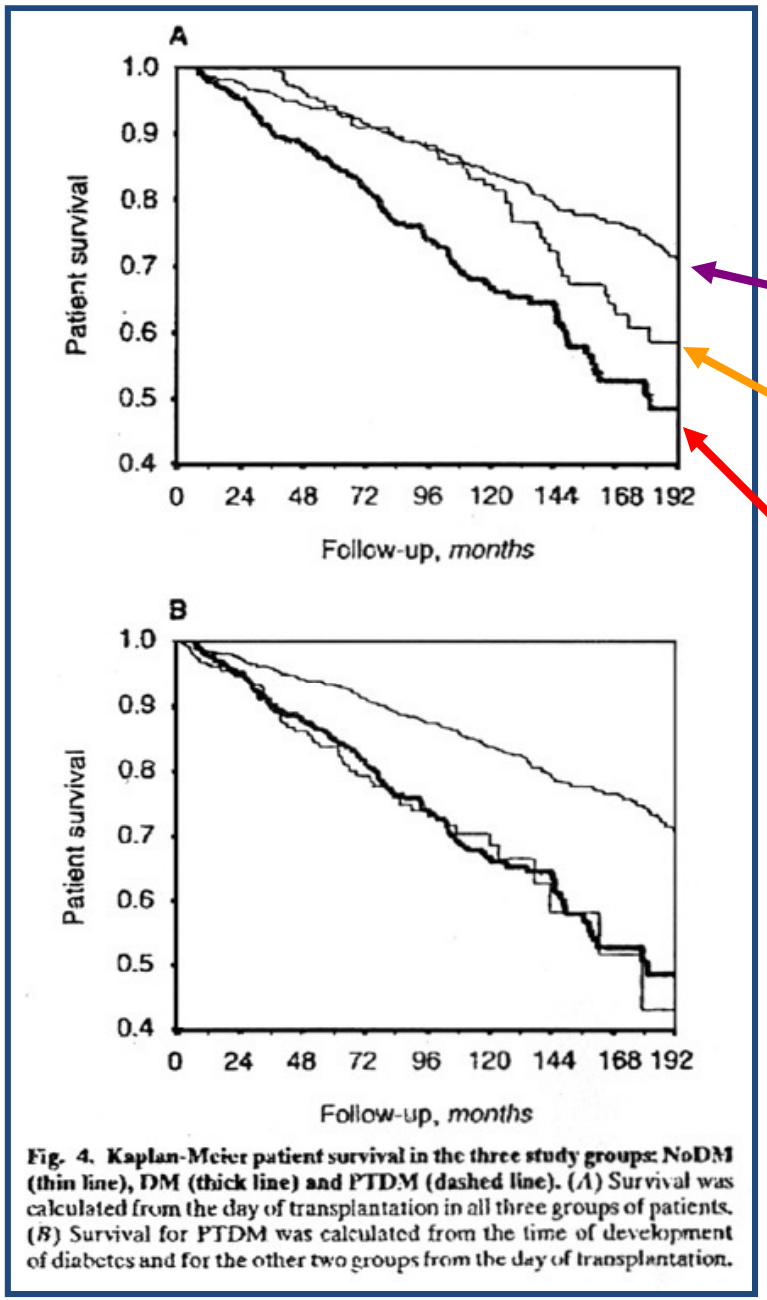


Fig. 4. Kaplan-Meier patient survival in the three study groups: NoDM (thin line), DM (thick line) and PTDM (dashed line). (A) Survival was calculated from the day of transplantation in all three groups of patients. (B) Survival for PTDM was calculated from the time of development of diabetes and for the other two groups from the day of transplantation.

No diabetes (n = 1186)

NODAT (n = 293)

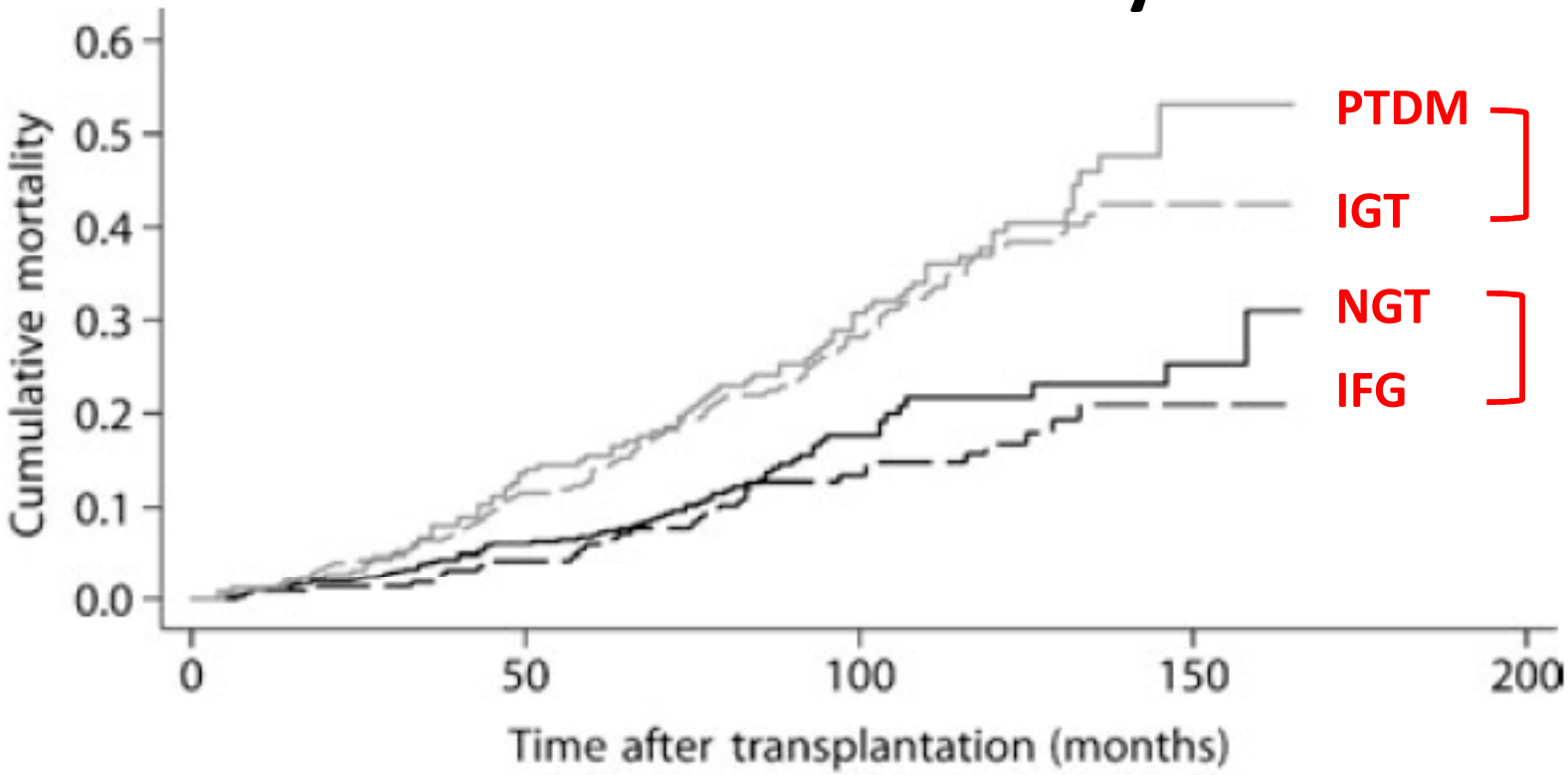
Pre-RT diabetes (n = 332)

A: Day 0 = RT date

B: Day 0 = NODAT diagnosis date

FG Cosio et al, Kidney Int 2002

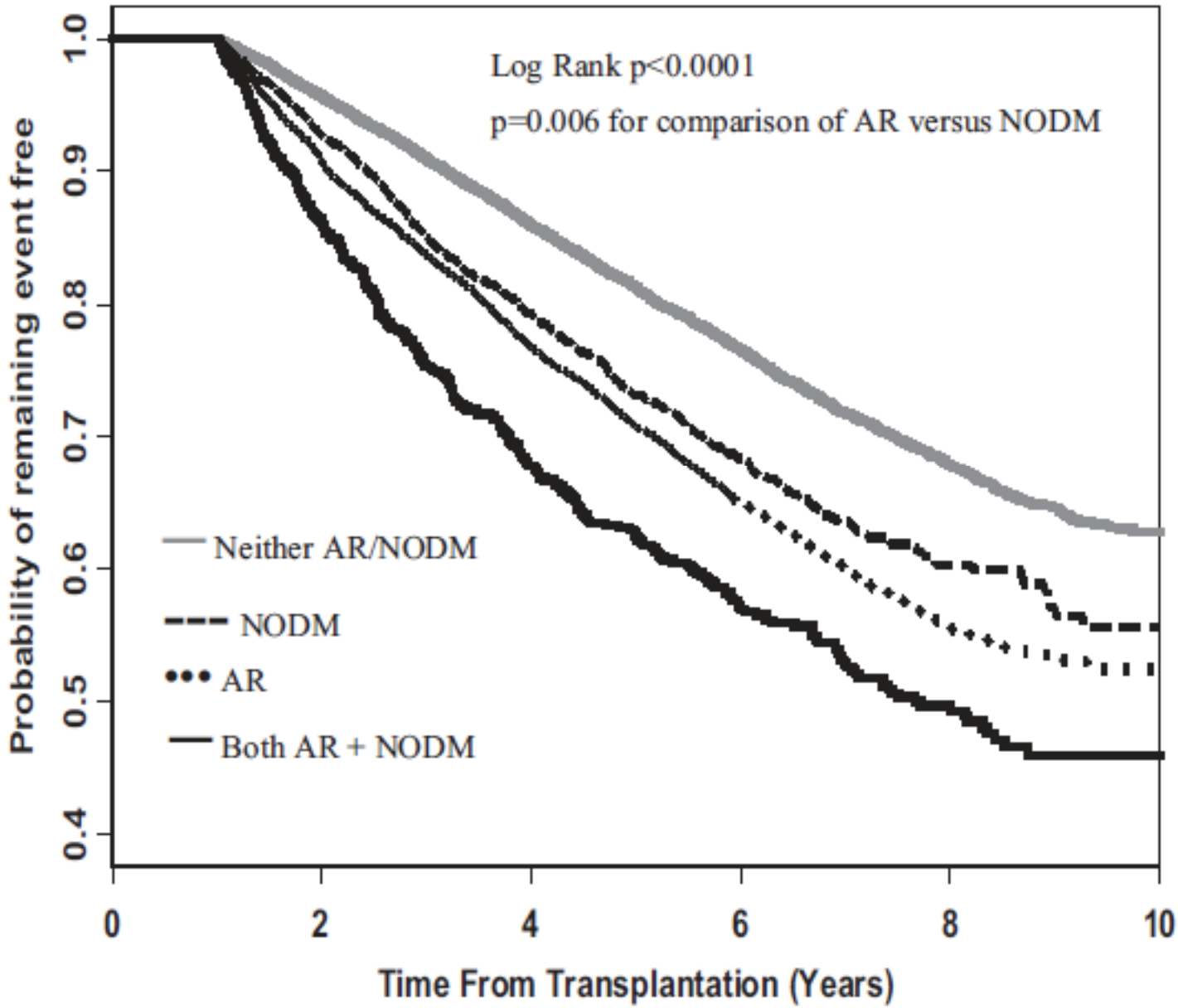
NODAT and mortality



Number at risk					
NGT	638	466	117	35	0
IFG	217	183	127	15	0
IGT	313	237	125	27	0
PTDM	242	183	111	13	0

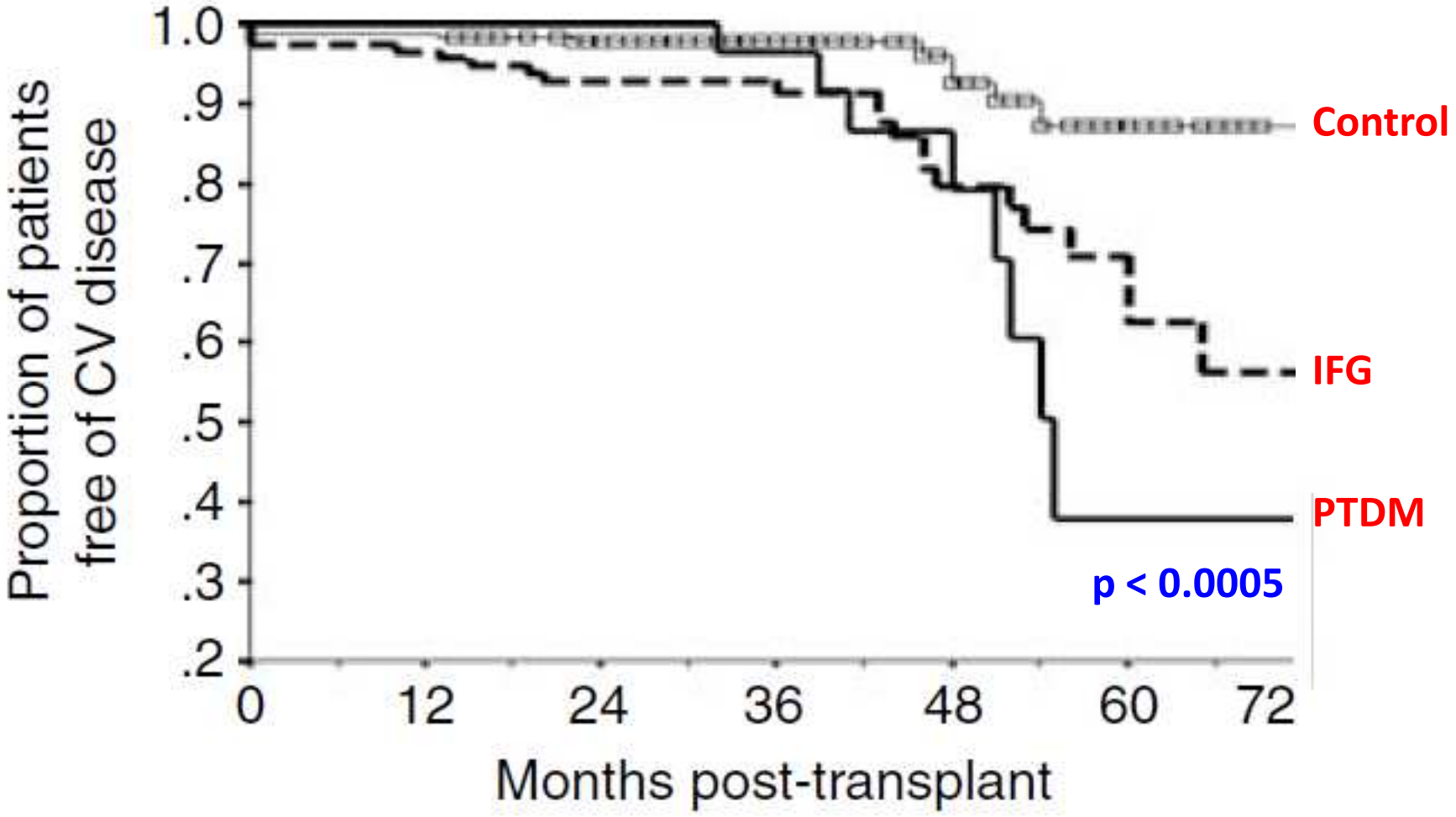
TG Valderhaug et al, Diabetologia 2011

NODAT and overall graft failure

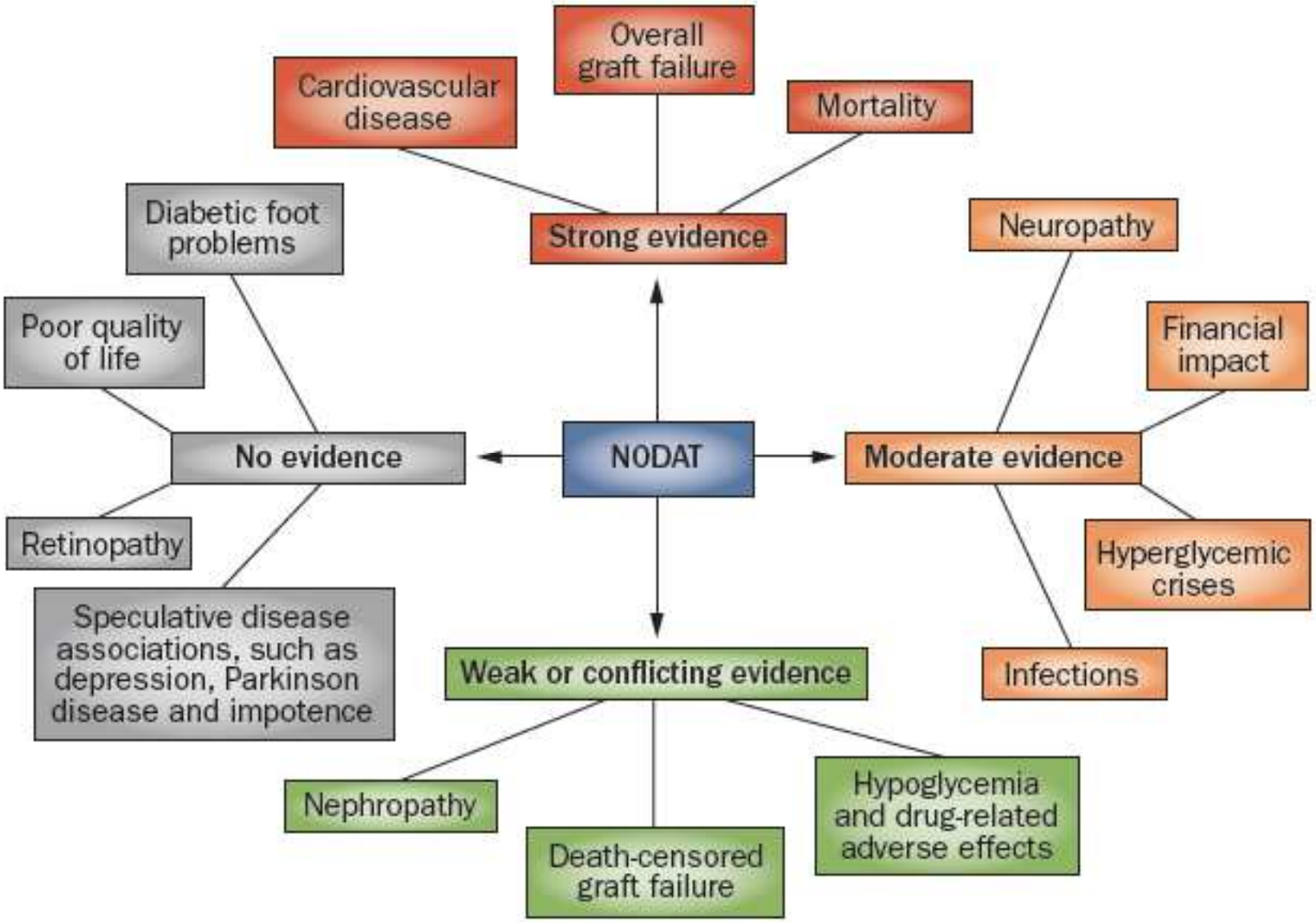


EH Cole et al, Clin J Am Soc Nephrol 2008

NODAT and cardiovascular disease



FG Cosio et al, Kidney Int 2005



A Sharif et al, Nature Rev Nephrol 2012

Drug	Avoid/dose adjustment	Drug-drug interaction
	Avoid	Increase sirolimus
zide, Gliclazide	—	Increase CsA levels
iidone	—	—
enclamide (Glyburide)	Avoid if GFR <50 mL/min/1.73 m^2	Increase CsA levels
epiride	Start with 1 mg/d	Increase CsA levels
ntide	Avoid if advanced CKD	—
ormin	Avoid if GFR <60 mL/min/1.73 m^2	—
formin	Avoid	—
bose, Miglitol	Avoid if GFR <30 mL/min/1.73 m^2	—
glinide	Cautious titration (start 0.5 mg if GFR <40 mL/min/1.73 m^2)	Increased levels of repaglinide with CsA
glinide	Cautious use if GFR <60 mL/min/1.73 m^2	Increased levels of nateglinide with CsA
itazone,	Avoid if heart failure	—
glitazone	Avoid if heart failure	—
atide	Avoid if GFR <30 mL/min/1.73 m^2	—
lintide	Avoid if GFR <20 mL/min/1.73 m^2	—
liptin	Reduce dose to 50 mg/d (GFR 50–30 mL/min/1.73 m^2), 25 mg (GFR <30 mL/min/1.73 m^2)	Metabolized by CYP3A4/5*
gliptin	Avoid if dialyzed, caution if GFR <60 mL/min/1.73 m^2 (need more data)	No interaction with CYP3A4/5 substrates
gliptin	2.5 mg daily if GFR <50 mL/min/1.73 m^2	Metabolized by CYP3A4/5*

NODAT: treatment.

L Ghisdal et al, Diabetes Care 2012

NODAT: conclusions

- NODAT is associated with **adverse** patient and graft **outcomes**.
- The **pathophysiology** of NODAT is similar to that of type 2 diabetes mellitus but is complicated by both transplantation-sepcific and nontransplantation-related risk factors.
- An understanding of **nonmodifiable risk factors** for NODAT can enable preemptive risk stratification of patients to prevent development of NODAT.
- The attenuation of **modifiable risk factors** for NODAT may inhibit the evolution of transplant-associated hyperglycemia and/or NODAT.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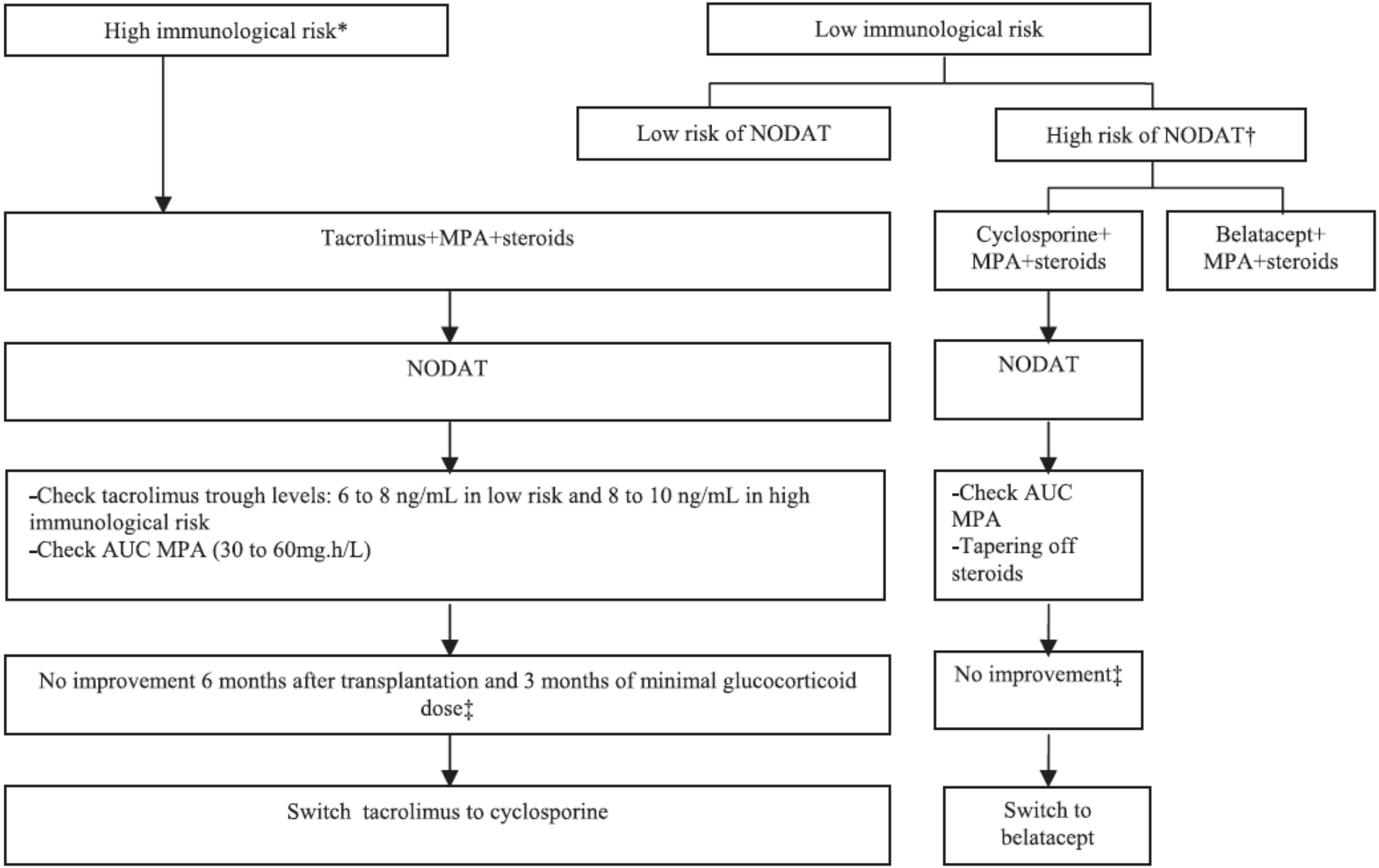
Thanks for your attention!



L Ghisdal et al, Diabetes Care 2012