Immunosuppressive therapies in Diabetic kidney transplant recipients

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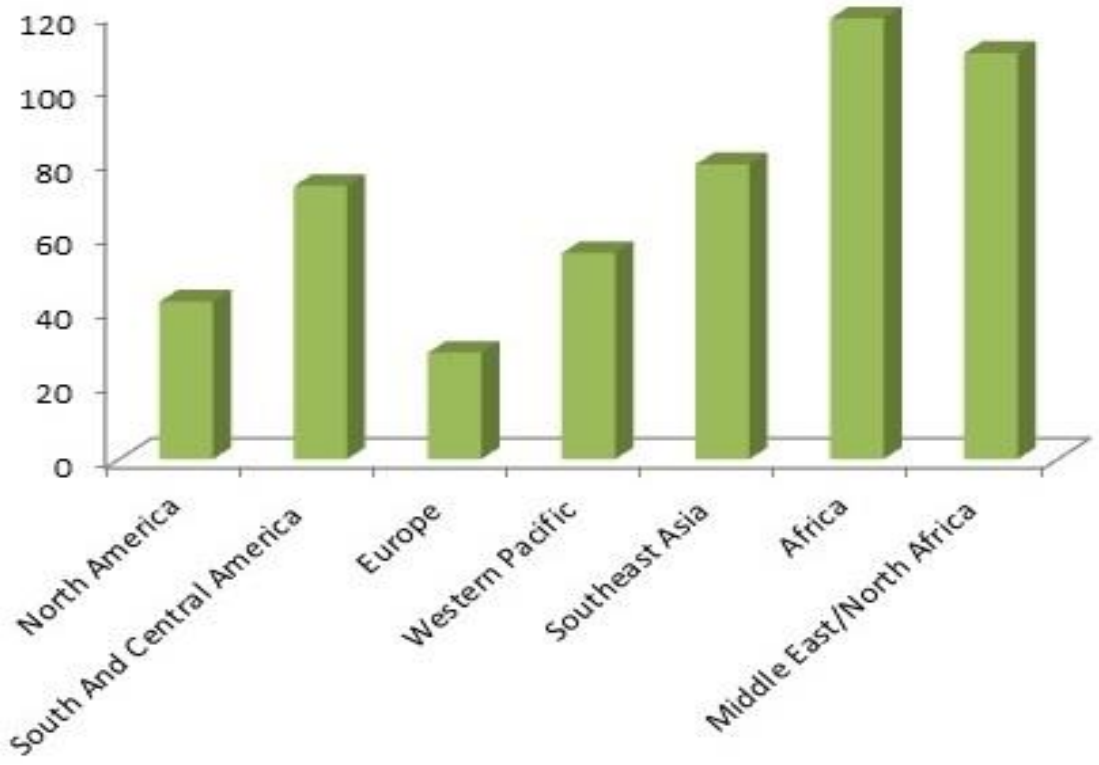
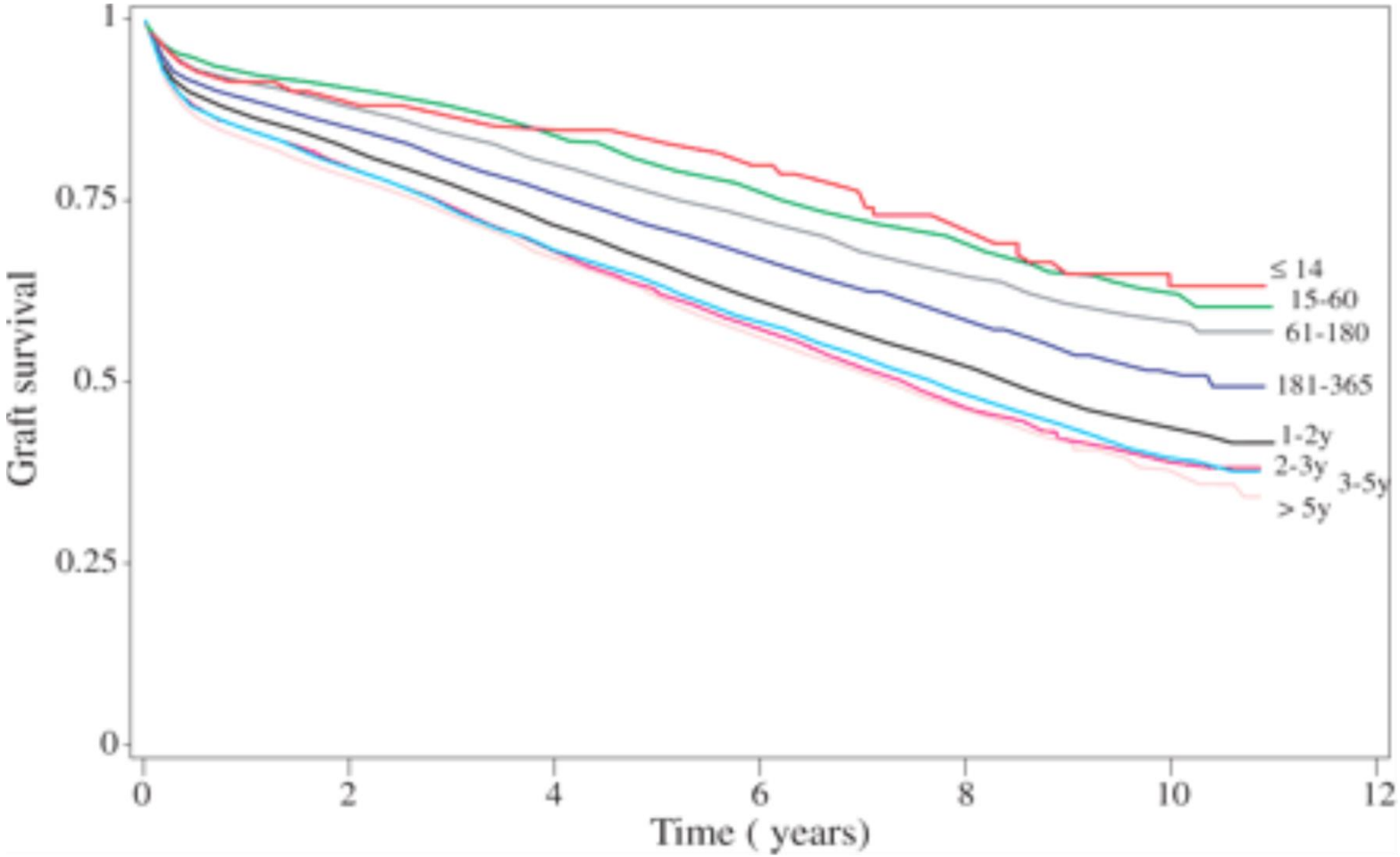
World diabetes cases expected to jump 55% by 2035





From: Duration of end-stage renal disease and kidney transplant outcome

Nephrol Dial Transplant. 2004;20(1):167-175. doi:10.1093/ndt/gfh541

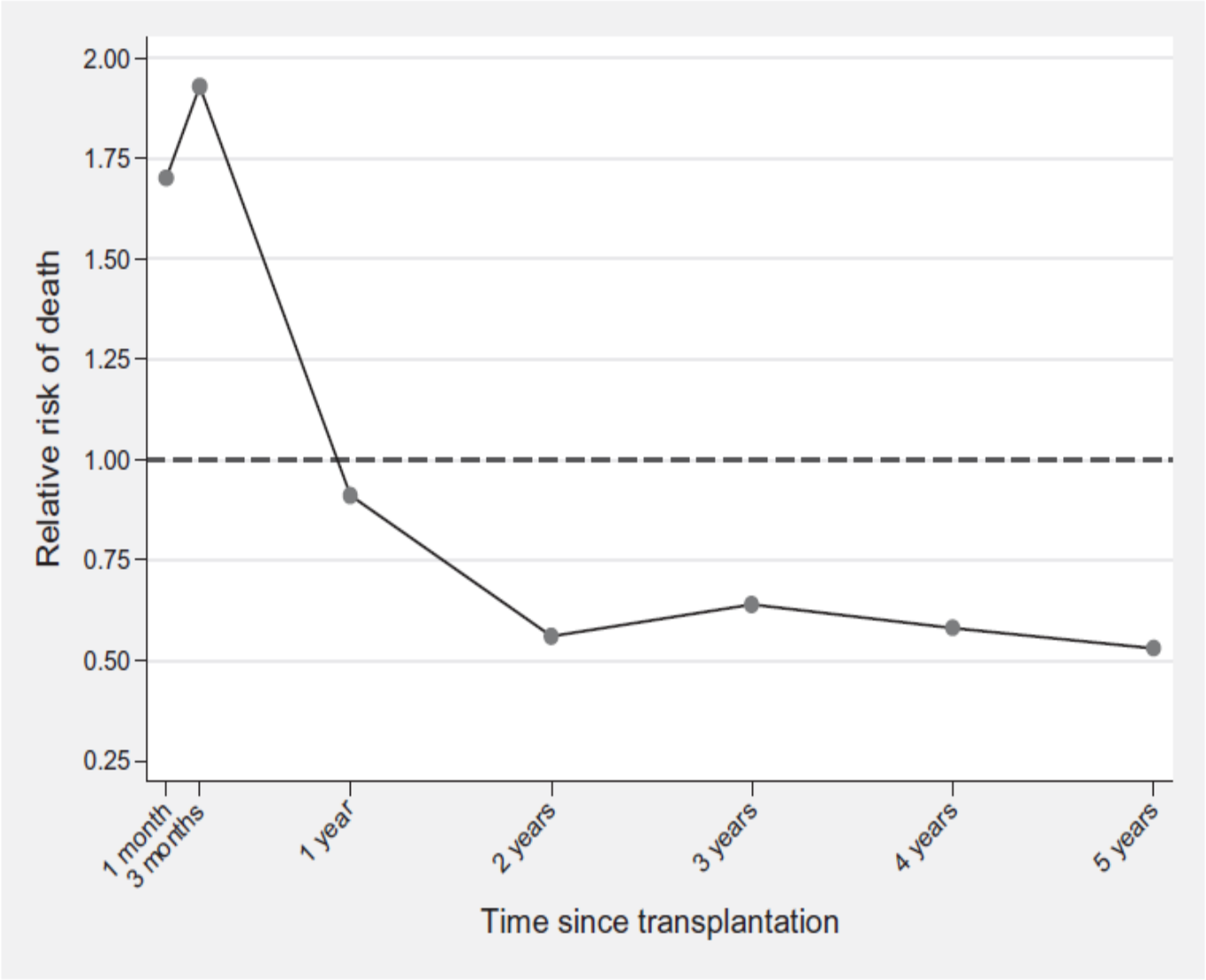


Fig. 2. Adjusted relative risk of death for transplant recipients compared with on-pool dialysis patients during the first 5 years post-transplant. The reference group was the 1157 patients on dialysis who were on the transplant waiting list (RR, 1.0). Values were adjusted for age, sex cause of ESKD, year of placement on the waiting list and time from first treatment for ESKD to placement on the waiting list.

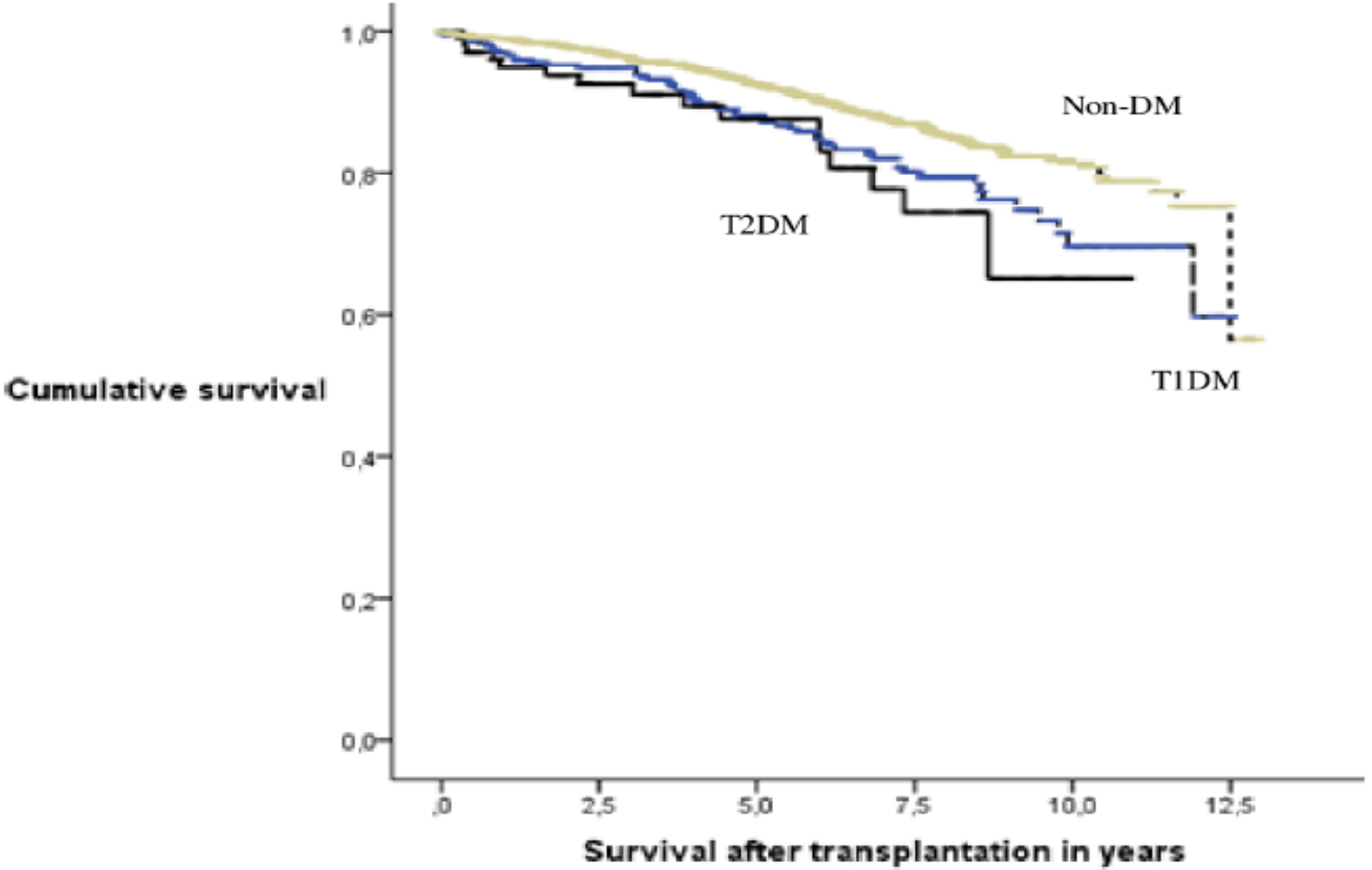
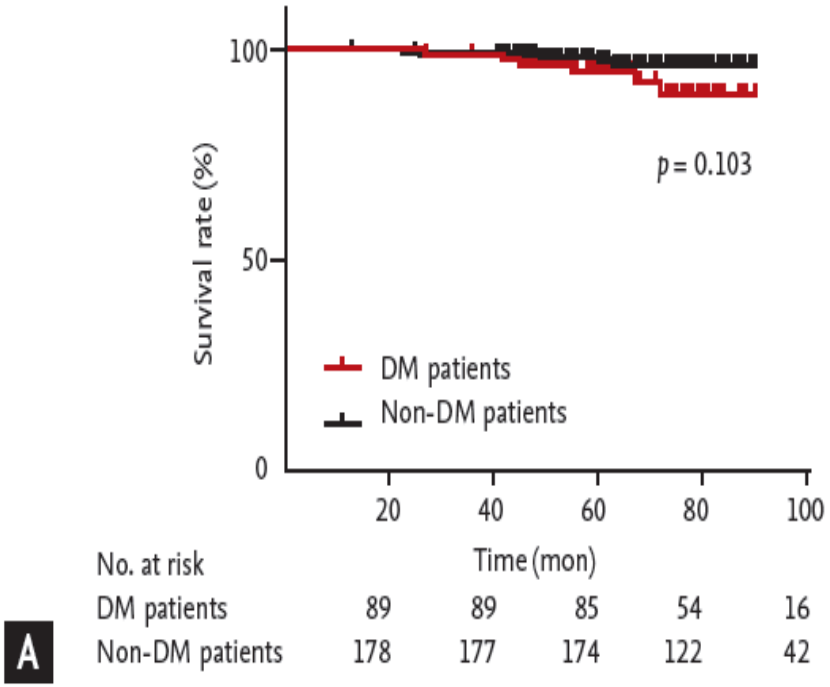


Fig 2. Cumulative survival probability after renal transplantation in type 1 and type 2 diabetes and non-diabetic patients. Cumulative survival probability in years after renal transplantation in type1 (--line), type 2 (—line) diabetic patients and in patients without diabetes (—line) in Finland in 2000–2010. T1DM = type 1 diabetic patients, T2DM = type 2 diabetic patients, Non-DM = non-diabetic patients.

https://doi.org/10.1371/journal.pone.0201478.g002

2017 Aug 21.
https://doi.org/10.3904/kjim.2016.067

Outcomes of living donor kidney transplantation in diabetic patients: age and sex matched comparison with non-diabetic patients



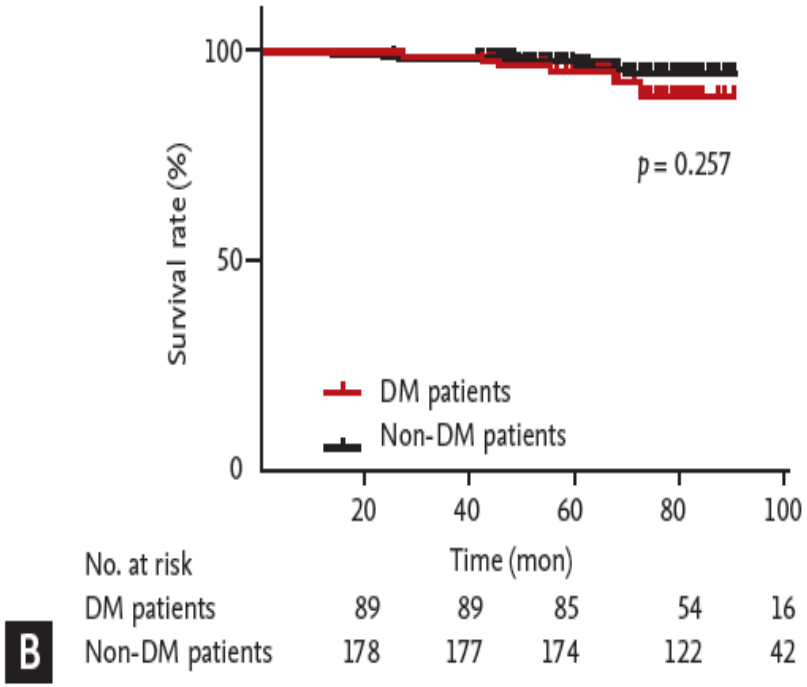


Figure 2. (A) Death-censored graft survival (B) non-death-censored graft survival. DM, diabetes mellitus.

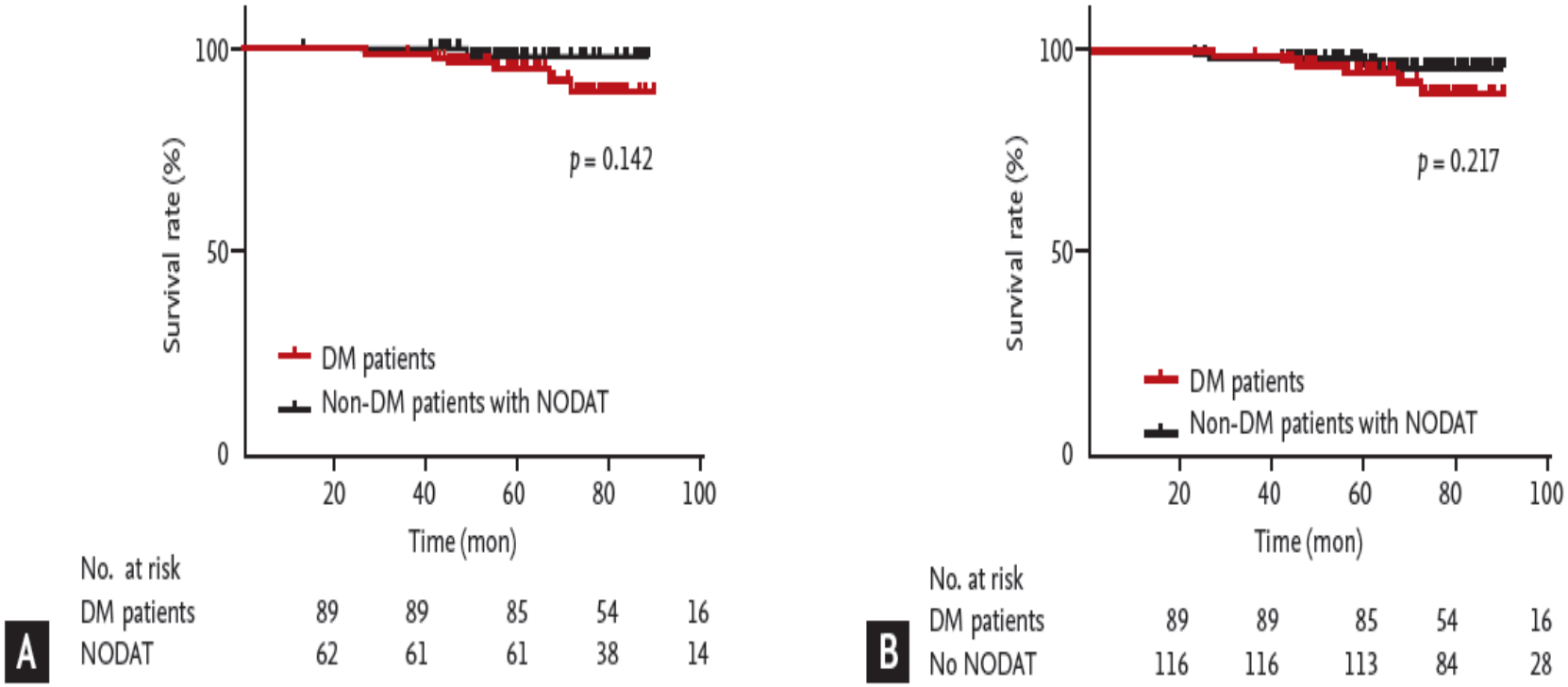
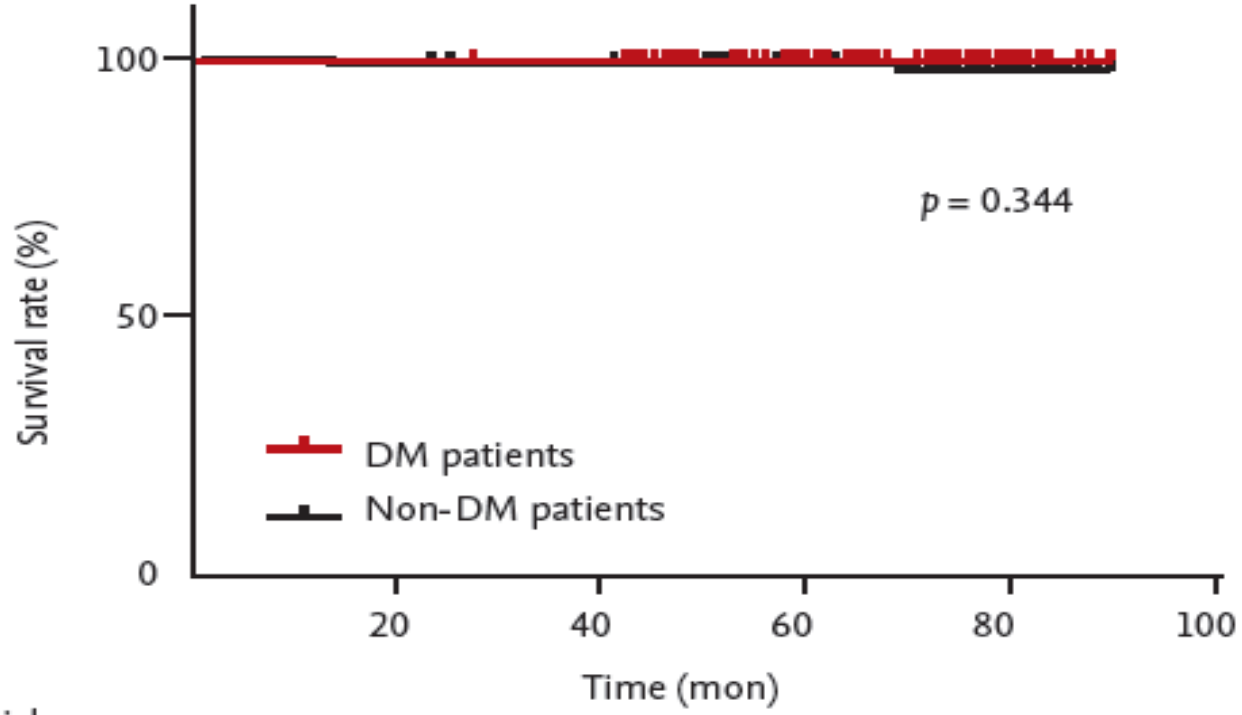


Figure 4. Graft survival of patients (A) with and (B) without new-onset diabetes after kidney transplantation. DM, diabetes mellitus; NODAT, new onset diabetes after transplantation.



No. at risk					
DM patients	89	89	86	56	17
Non-DM patients	178	177	175	123	42

Figure 3. Mortality. DM, diabetes mellitus.

Table 2. Incidence of acute rejection

Variable	DM patients (n = 89)	Non-DM patients (n = 178)	*p* value
Within 1 year of KT, %			
T cell mediated rejection	10.1	8.4	0.655
Antibody mediated rejection	0	0.6	1.000
After 1 year of KT, %			
T cell mediated rejection	15.7	12.4	0.452
Antibody-mediated rejection	4.5	5.6	0.780

DM, diabetes mellitus; KT, kidney transplantation.

Table 3. Incidence of infection

Variable	DM patients (n = 89)	Non-DM patients (n = 178)	*p* value
Within 1 year of KT, %	32.6	30.3	0.779
Cytomegalovirus	9.0	14.0	0.324
BK virus	10.1	10.1	1.000
Pneumocystis	1.1	0.6	1.000
Pneumonia	3.4	2.2	0.689
Urinary tract infection	12.4	7.9	0.267
Sepsis	9.0	2.8	0.036
Others	12.4	8.4	0.381
After 1 year of KT, %	23.6	12.9	0.035
Cytomegalovirus	2.2	1.1	0.603
BK virus	2.2	0.6	0.258
Pneumocystis	0	1.1	0.554
Pneumonia	4.5	5.1	1.000
Urinary tract infection	12.4	3.9	0.017
Sepsis	4.5	4.5	1.000
Others	14.6	2.8	0.001

DM, diabetes mellitus; KT, kidney transplantation.

DISCUSSION

In the present study, kidney transplantation outcomes (graft survival, mortality, acute rejection, and delayed graft function) in diabetic patients were comparable with those in non-diabetic patients. Urinary tract infection and other infections as well as cardiovascular events occurred more frequently in diabetic patients. However, DM, cardiovascular disease, and infection were not significant risk factors of graft failure. Late rejection (acute rejection after 1 year of transplantation) was the most important risk factor for graft failure after adjusting for DM, HLA mismatch, rejection and unrelated donor.

BENEFITS OF TRANSPLANTATION

KidneyTx is considered the best treatment of patients with ESRD and it has been associated with a 25%–65% patient survival benefit.

***Kidney Tx** is the preferred RRT for diabetic patients with ESRD, as well since it generally results in better survival and quality of life than dialysis.*

- We recommend that diabetic patients who are eligible receive a kidney transplant rather than continue dialysis.
- **Pre-emptive kidney transplantation** rather than initiation of dialysis followed by transplantation is preferred, and, if possible, a **living-donor kidney** is preferred to a deceased-donor kidney.
- We also suggest that all waitlisted diabetic patients register on both the standard-donor waitlist and the expanded-criteria-donor (ECD) waitlist. Although ECD kidneys do not meet the criteria for standard-donor kidneys, diabetic patients who receive them are likely to live longer than if they remained on dialysis.

TRANSPLANTATION (A PILEGGI, SECTION EDITOR)

Diabetes and Kidney Transplantation: Past, Present, and Future

- Patients with **type 2 diabetes** who receive a renal allograft have a higher survival rate compared with patients who are maintained on chronic hemodialysis therapy.
- **Pre-emptive transplantation** and the use of living donors have improved overall survival.
- Avoidance of dialysis-associated comorbidities, diminished immune response, and cardiovascular complications are the main benefits of **PKT**.

Outcomes Post Transplant on Diabetic Recipients

Barbosa et al. (JAMA 1994) reported prevention of the typical histological changes associated with diabetic nephropathy with tight glycemic control of these patients.

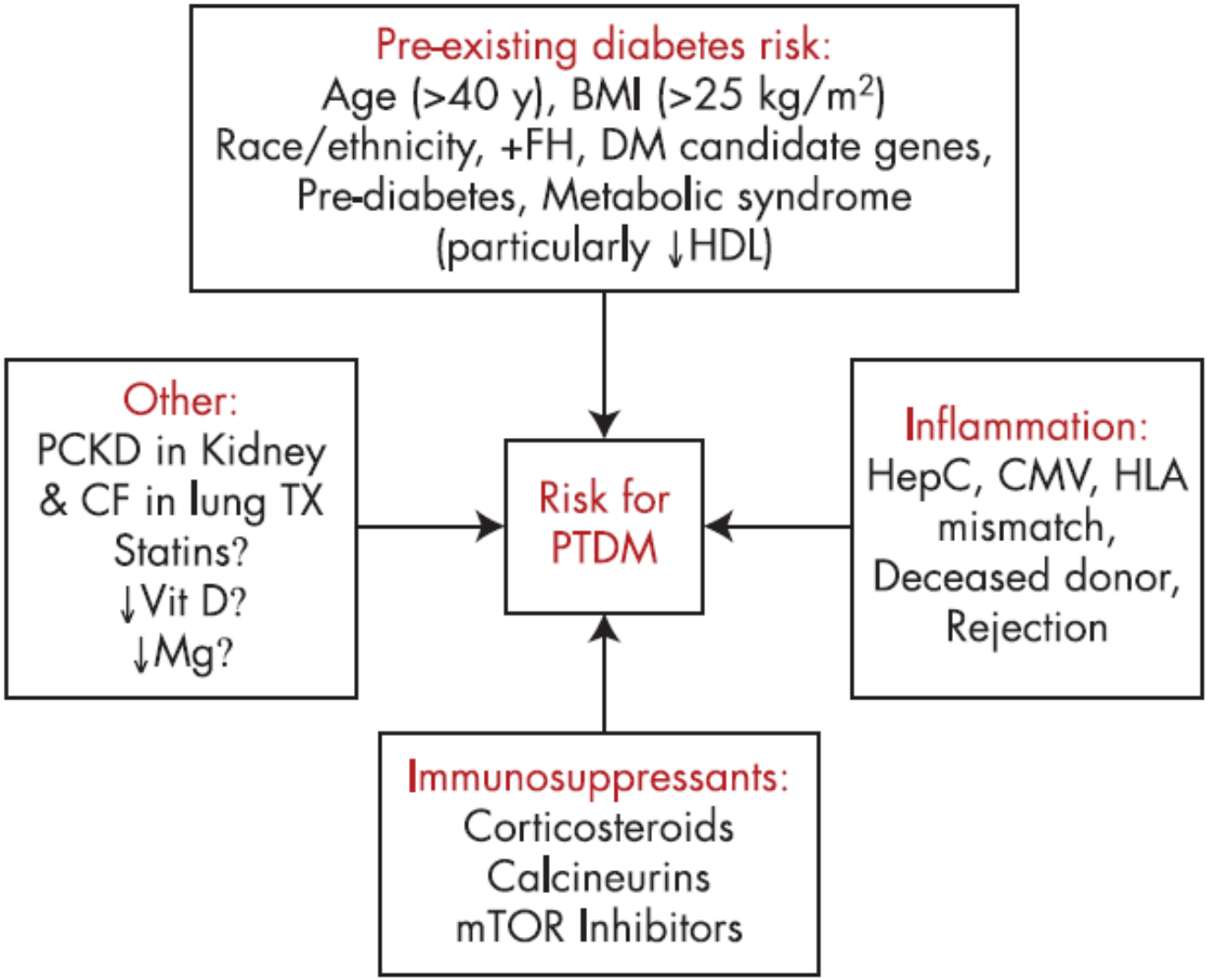
Glycemic control may become acutely worse in the immediate posttransplant period, in part due to increased insulin resistance and impaired insulin secretion associated with **steroids, calcineurin inhibitors in particular tacrolimus, and sirolimus.**

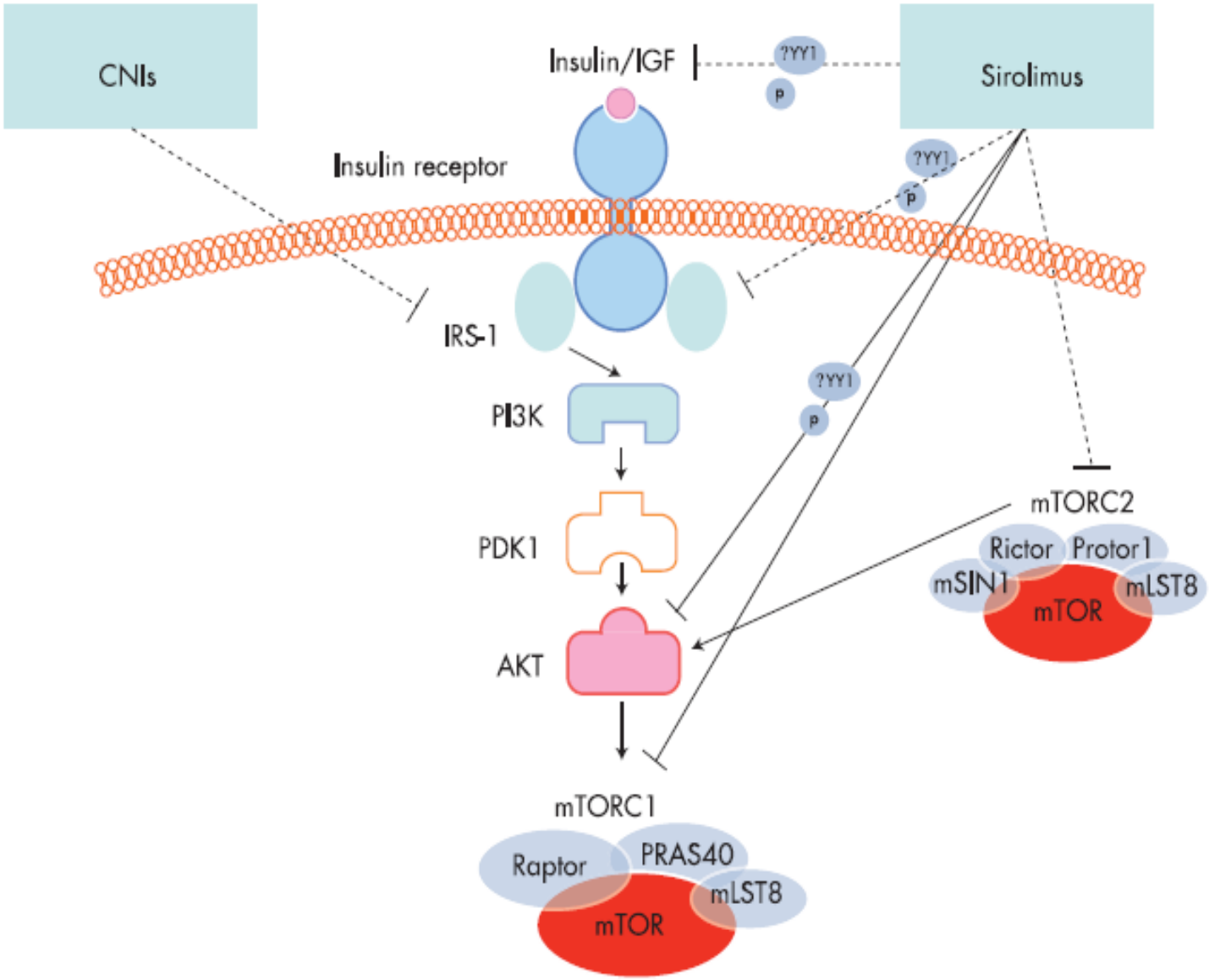
PLOS ONE | https://doi.org/10.1371/journal.pone.0195566 April 18, 2018

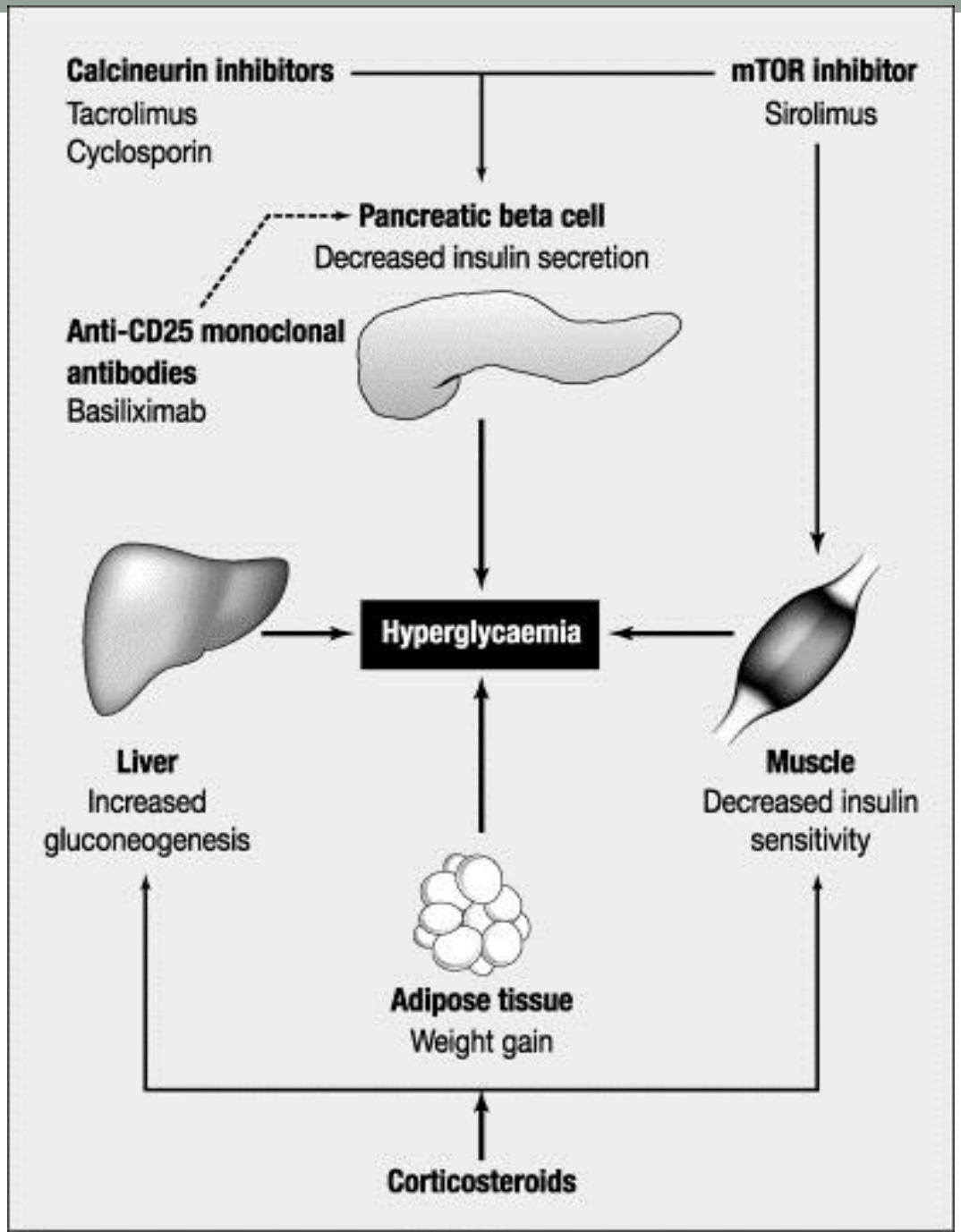
RESEARCH ARTICLE

Effect of post-transplant glycemic control on long-term clinical outcomes in kidney transplant recipients with diabetic nephropathy: A multicenter cohort study in Korea

RFs for PTDM


Pre-existing diabetes risk:
Age (>40 y), BMI (>25 kg/m²)
Race/ethnicity, +FH, DM candidate genes,
Pre-diabetes, Metabolic syndrome
(particularly ↓HDL)
Other:
PCKD in Kidney
& CF in lung TX
Statins?
↓Vit D?
↓Mg?
Risk for PTDM
Inflammation:
HepC, CMV, HLA
mismatch,
Deceased donor,
Rejection
Immunosuppressants:
Corticosteroids
Calcineurins
mTOR Inhibitors


CNIs
Insulin/IGF
?YY1
P
Sirolimus
Insulin receptor
?YY1
P
IRS-1
PI3K
?YY1
P
PDK1
mTORC2
Rictor
Protor1
mSIN1
mLST8
mTOR
AKT
mTORC1
Raptor
PRAS40
mLST8
mTOR


Calcineurin inhibitors
Tacrolimus
Cyclosporin
mTOR inhibitor
Sirolimus
Pancreatic beta cell
Decreased insulin secretion
Anti-CD25 monoclonal antibodies
Basiliximab
Hyperglycaemia
Liver
Increased gluconeogenesis
Muscle
Decreased insulin sensitivity
Adipose tissue
Weight gain
Corticosteroids

What will be the best immunosuppressive treatment for diabetic patients ???

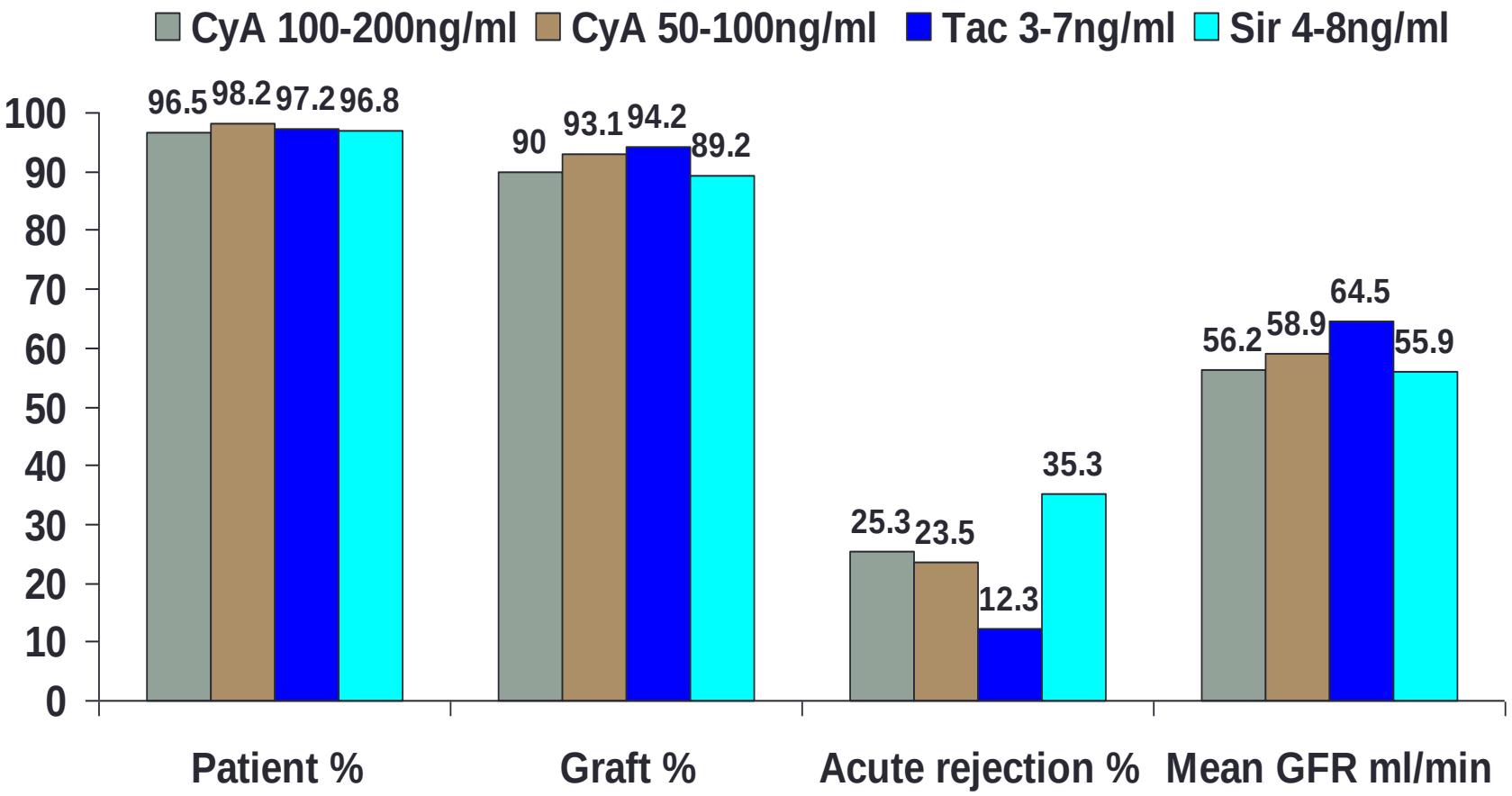
Expert Review of Clinical Pharmacology

EXPERT REVIEW OF CLINICAL PHARMACOLOGY
https://doi.org/10.1080/17512433.2018.1479638

Tailoring tacrolimus therapy in kidney transplantation

Tac is now the main immunosuppressive used in kidney Tx since 1990 and especially after **SYMPHONY** study in 2007.

Tac based therapy is superior to sandimmune with less early CNI nephrotoxicity but comparable chronic arteriolar toxicity.


CyA 100-200ng/ml
CyA 50-100ng/ml
Tac 3-7ng/ml
Sir 4-8ng/ml
100
90
80
70
60
50
40
30
20
10
0
96.5
98.2
97.2
96.8
90
93.1
94.2
89.2
25.3
23.5
12.3
35.3
56.2
58.9
64.5
55.9
Patient %
Graft %
Acute rejection %
Mean GFR ml/min

Tailoring tacrolimus in the setting of uncontrolled blood glucose

American Journal of Transplantation 2007; 7: 1506–151

DIRECT study

Results of an International, Randomized Trial Comparing Glucose Metabolism Disorders and Outcome with Cyclosporine Versus Tacrolimus

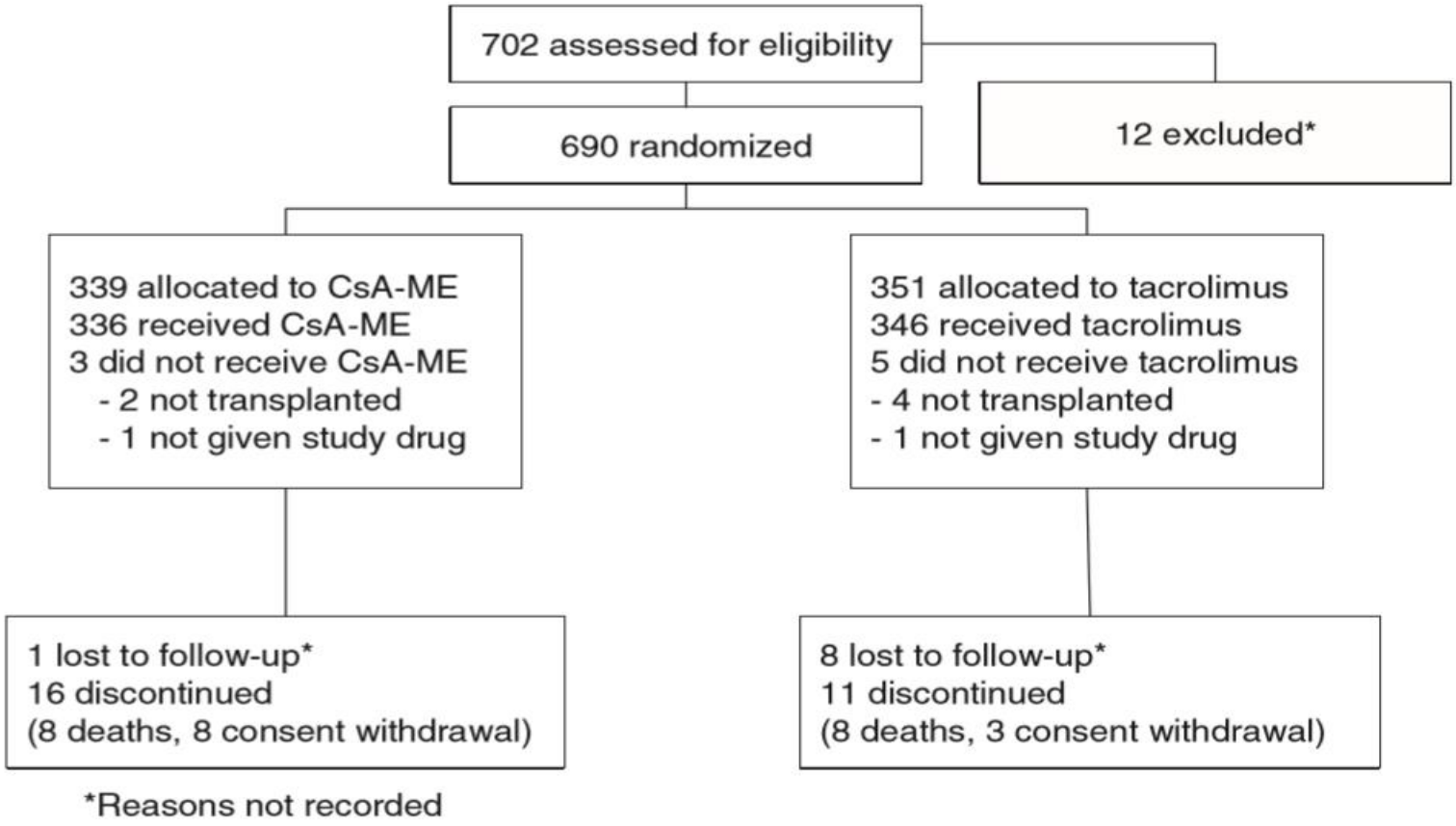


Figure 1: Patient disposition. CsA-ME = cyclosporine microemulsion; ITT = intent-to-treat.

Glucose Metabolism Disorders: CsA vs. Tacrolimus

Table 3: Insulin secretion, sensitivity and disposition index at 6 months among normoglycemic patients and patients with NODAT who were not receiving hypoglycemic medication

	Normoglycemic patients (n = 300)	Untreated NODAT: CsA-ME (n = 29)	Untreated NODAT: tacrolimus (n = 14)
Insulin secretion (pmol/L)			
Phase 1	1146 (899–1359)	625 (279–920)	314 (124–581)
Phase 2	304 (244–357)	187 (103–246)	116 (72–186)
Insulin sensitivity	0.076 (0.065–0.089)	0.043 (0.034–0.057)	0.049 (0.016–0.064)
Disposition index[1]	100 (82–127)	26 (8–45)	9 (–1, 22)

Values are shown as medians (interquartile range).

[1]Disposition index = (first and second phase insulin release) x insulin sensitivity.

DIRECT: Diabetes incidence after renal Tx

These results demonstrate that CsA-ME is associated with a significantly lower incidence of NODAT and IFG, and NODAT requiring treatment, than tacrolimus at 6 months posttransplant in renal transplant patients.

This advantage was achieved with no loss of efficacy for CsA-ME versus tacrolimus,as measured by a composite endpoint of BPAR, graft loss or death.

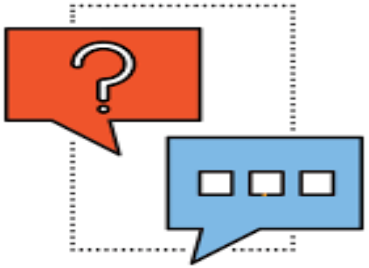
Ghisdal et al in 2008 reported that Tac induced NODAT was successfully reverted after conversion to cyclosporine.

Q:

When a patient presents with Tac induced NODAT, it is worth to convert to CsA.

OSAKA study

Extended release Formulations of Tac (Advagraf and Envarsus)



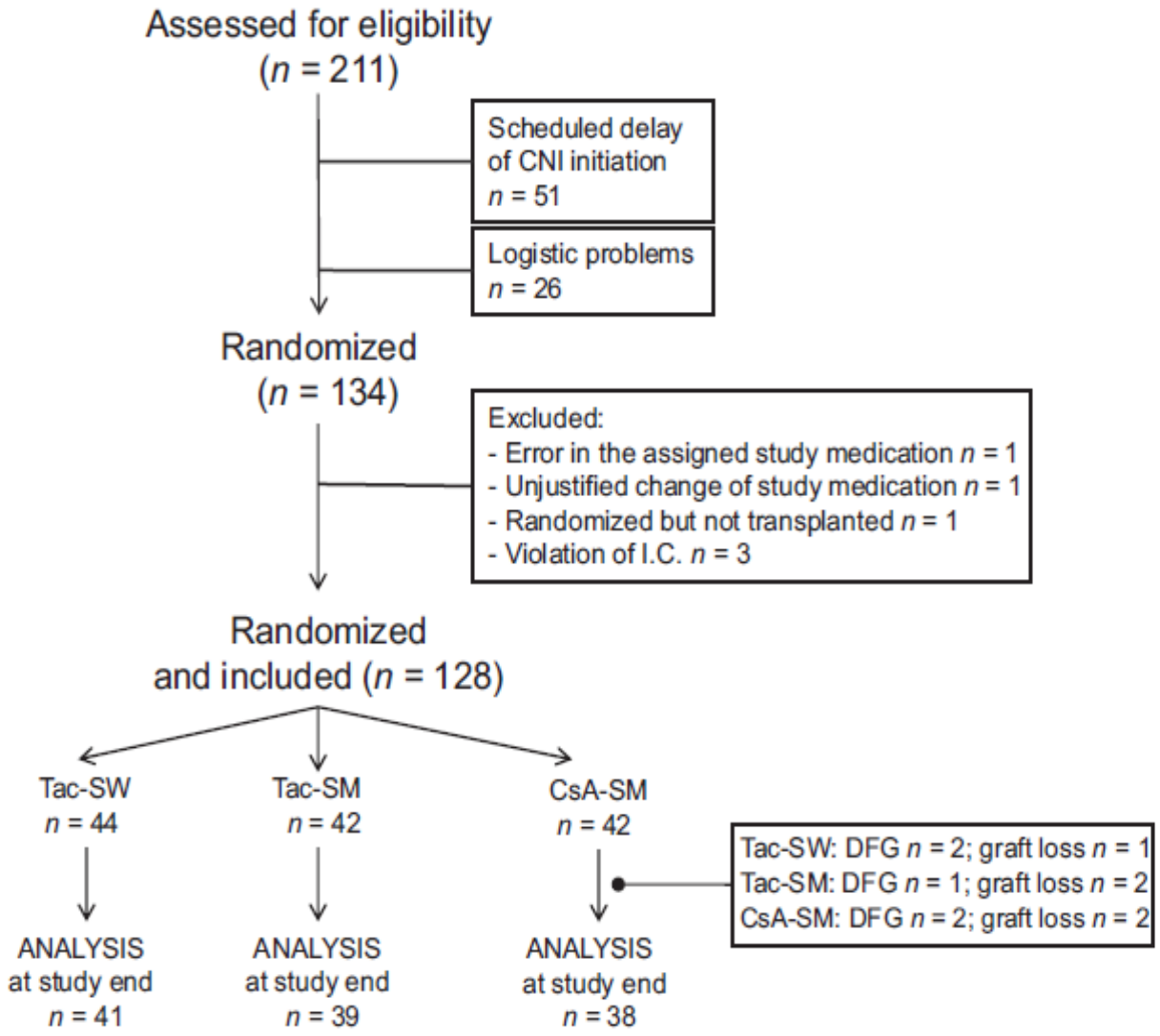
RESPONSE

KI REPORTS
KIReports.org

Kidney Int Rep (2018) ■, ■–■; https://doi.org/10.1016/j.ekir.2018.07.009

Randomized Controlled Trial Assessing the Impact of Tacrolimus Versus Cyclosporine on the Incidence of Posttransplant Diabetes Mellitus

Kidney Int Rep (2018) ■, ■–■; https://doi.org/10.1016/j.ekir.2018.07.009



Kidney Int Rep (2018) ■, ■–■; https://doi.org/10.1016/j.ekir.2018.07.009

Table 1. Baseline characteristics of the 3 study arms (original assigned groups)

Variable	Tac-SW (n = 44)	Tac-SM (n = 42)	CsA-SM (n = 42)	All (n = 128)	P
Age (yr)	61.2 ± 7.6	61.6 ± 7.3	60.2 ± 8.3	61 ± 7.7	0.7
Gender (% female)	11 (25)	12 (28.6)	12 (28.6)	35 (27.3)	0.9
Race	41W/1NA/2H	38W/1NA/3H	39W/1BR/1NA/1H	118W/1BR/3NA/6H	0.8
Dialysis duration (mo)	37.9 ± 30	28.6 ± 23.6	33 ± 26.3	33.2 ± 26.8	0.3
Donor age (yr)	62.1 ± 10.4	62.9 ± 8.9	61.6 ± 10	62.2 ± 9.8	0.8
Donor creatinine (mg/dl)	0.8 ± 0.3	0.9 ± 0.4	0.9 ± 0.3	0.9 ± 0.3	0.6
Expanded criteria donor (%)	25 (57)	26 (62)	26 (62)	77 (60)	0.9
Cold ischemia time (h)	16.8 ± 5.5	18.2 ± 5.4	17.3 ± 6.4	17.4 ± 5.8	0.6
HLA-A-B-DR mismatches	3.6 ± 1.2	4 ± 0.9	4.2 ± 1.1[a]	3.9 ± 1.1	0.01
PRA (>0 and <25%)	3	0	1	4	0.3
Delayed graft function (%)	17/44 (38.6)	24/42 (57.1)	25/42 (59.5)	66/128 (51.5)	0.09
Body mass index (kg/m^2)	26.9 ± 3.7	27.9 ± 3.7	27.9 ± 4.1	27.6 ± 3.8	0.4
Family history of diabetes (%)	3 (8) Unknown: 6	4 (12) Unknown: 9	9 (23) Unknown: 3	16 (14.5) Unknown: 18	0.2
Fasting glucose (mg/dl)	91.9 ± 13.2	97.7 ± 14.3	91.9 ± 13.9	93.9 ± 14	0.09
HbA1c (%)	5.3 ± 0.5	5.4 ± 0.3	5.3 ± 0.4	5.3 ± 0.4	0.8
Triglycerides (mg/dl)	184.3 ± 11.9	199.3 ± 92	209.7 ± 109	197.6 ± 105.8	0.5
Total cholesterol (mg/dl)	165.9 ± 48	162.8 ± 39.3	179.4 ± 42.5	169.4 ± 43.8	0.2
HDL cholesterol (mg/dl)	41 ± 14.4	42.5 ± 12.1	42.2 ± 15.3	41.9 ± 13.9	0.9
LDL cholesterol (mg/dl)	98.5 ± 36.6	90 ± 37.5	103.8 ± 36	97.6 ± 36.8	0.3

BR, Black race; W, White race; CsA-SM, cyclosporine A and steroid minimization; H, Hispanic; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NA, North African; PRA, panel-reactive antibodies; Tac-SM, tacrolimus and steroid minimization; Tac-SW, tacrolimus and rapid steroid withdrawal.

[a] $P < 0.05$ CsA-SM versus TAC-SW.

Kidney Int Rep (2018) ■, ■–■; https://doi.org/10.1016/j.ekir.2018.07.009

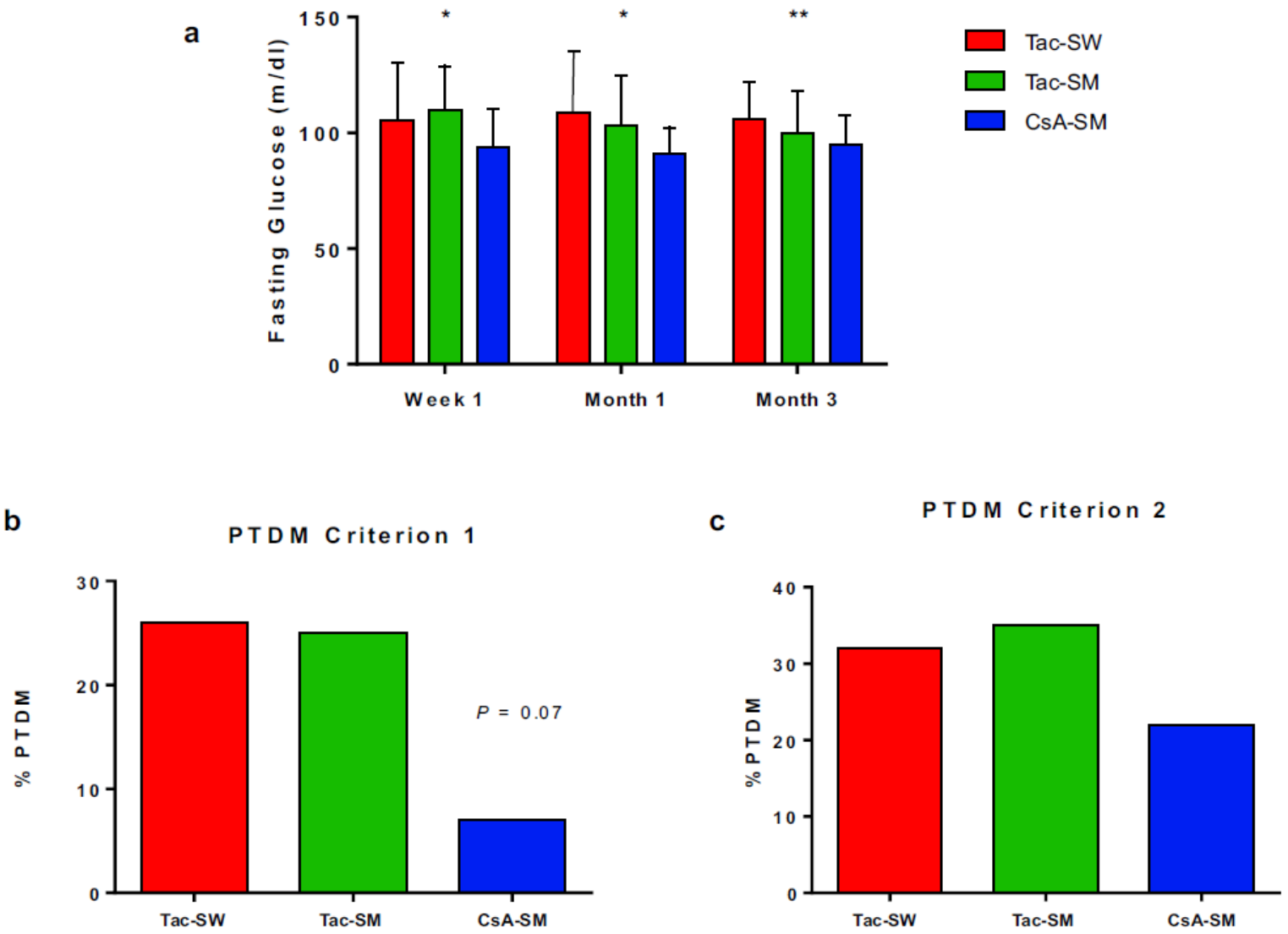


Figure 2. Glucose homeostasis alterations 3 months after transplantation in each study arm. (a) Fasting plasma glucose. (b) Proportion of patients with posttransplant diabetes (PTDM) according to criterion 1. (c) Proportion of patients with PTDM according to criterion 2. CsA-SM, cyclosporine A and steroid minimization; Tac-SM, tacrolimus and steroid minimization; Tac-SW, tacrolimus and rapid steroid withdrawal. $*P <$ 0.05 CsA-SM versus Tac-SW or Tac-SM; $**P < 0.05$ CsA-SM versus Tac-SW.

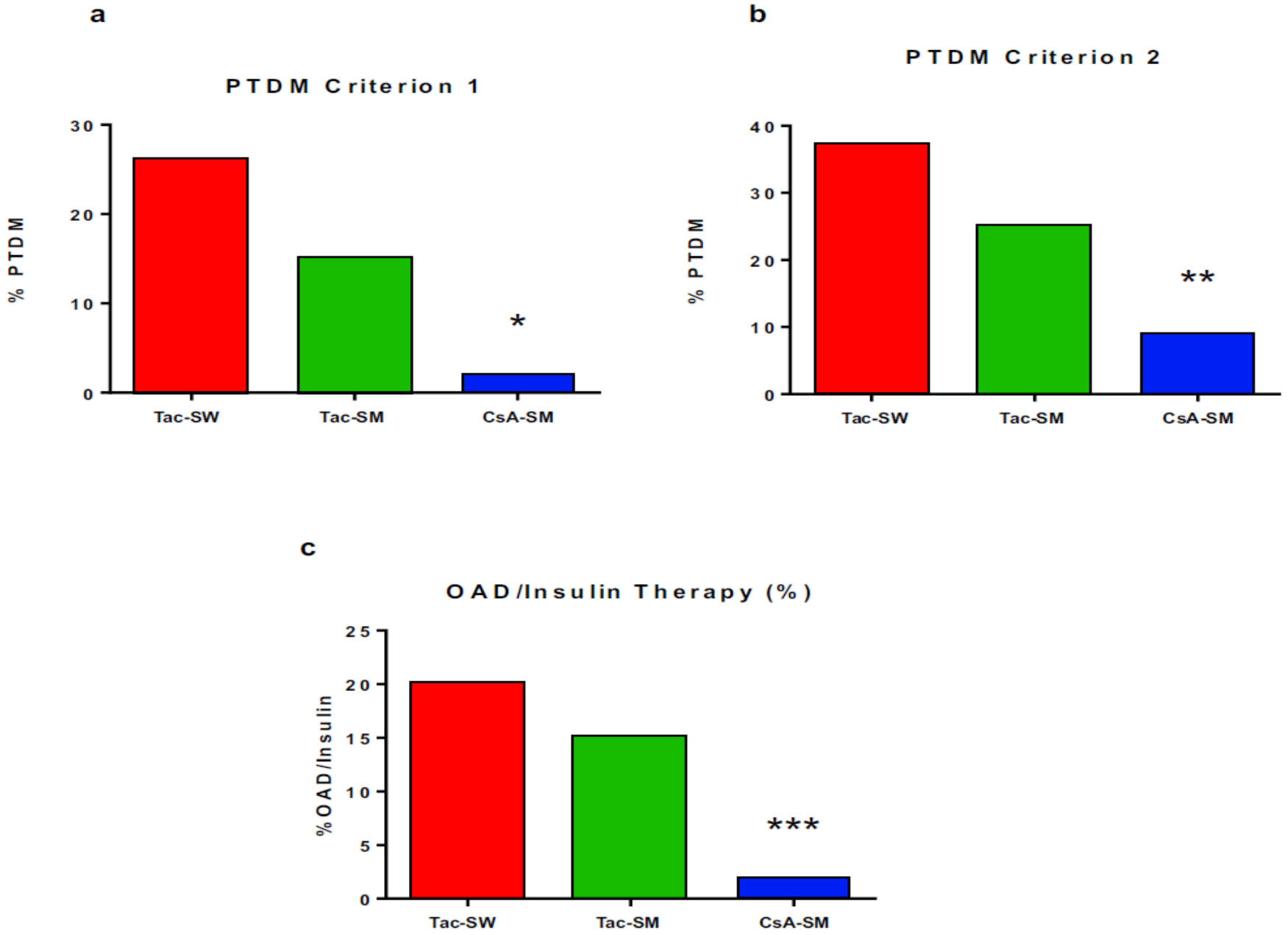


Figure 3. Glucose homeostasis alterations 12 months after transplantation (end of study) in each study arm. (a) Proportion of patients with posttransplant diabetes (PTDM) according to criterion 1. (b) Proportion of patients with PTDM according to criterion 2. (c) Proportion of patients requiring treatment with hypoglycemic drugs. CsA-SM, cyclosporine A and steroid minimization; Tac-SM, tacrolimus and steroid minimization; Tac-SW, tacrolimus and rapid steroid withdrawal. $^{*}P < 0.01$; $^{**}P < 0.05$; $^{***}P = 0.06$.

Kidney Int Rep (2018) ■, ■–■; https://doi.org/10.1016/j.ekir.2018.07.009

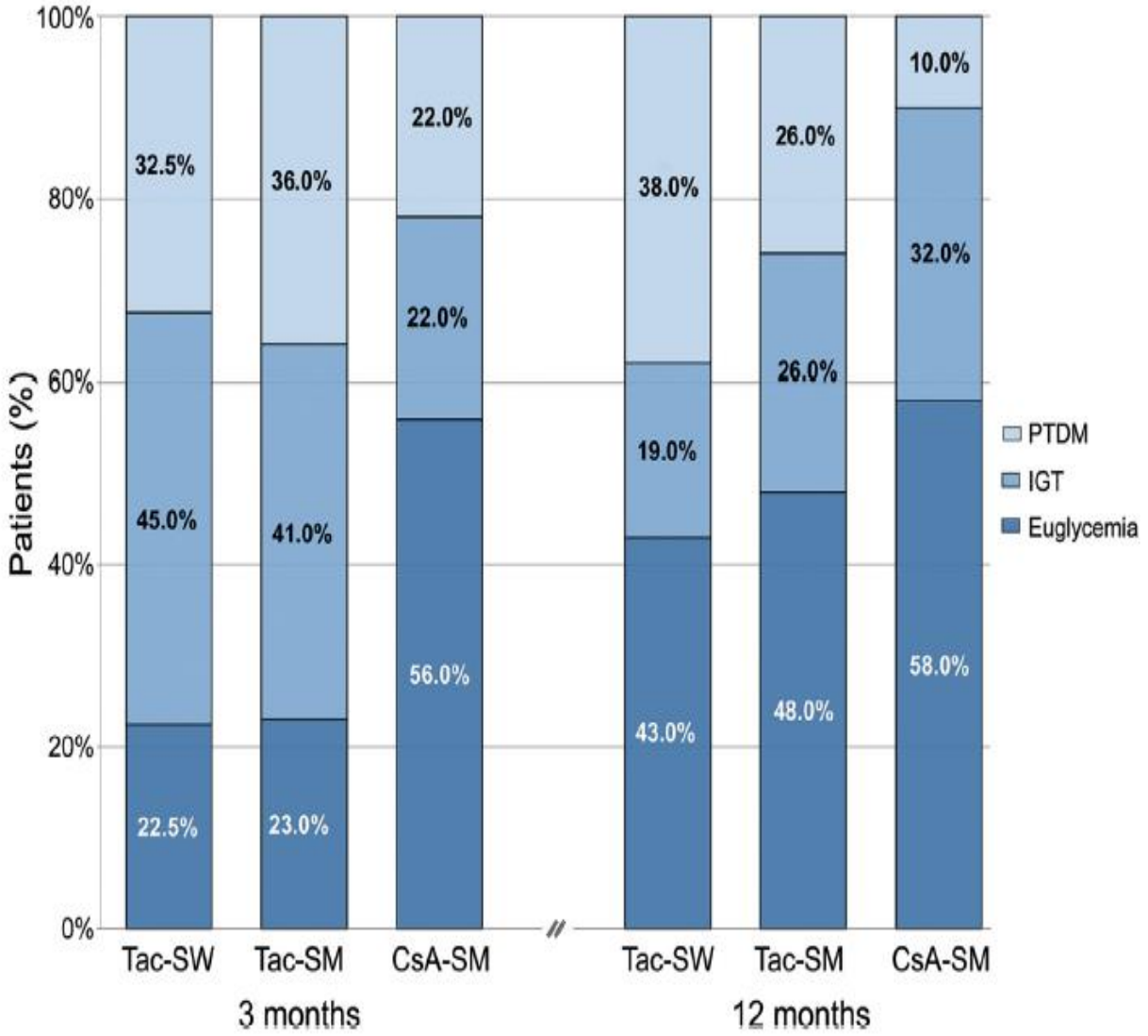


Figure 4. Evolution of glucose homeostasis alterations in each study arm from 3 to 12 months after transplantation. CsA-SM, cyclosporine A and steroid minimization; IGT, impaired glucose tolerance; PTDM, posttransplant diabetes; Tac-SM, tacrolimus and steroid minimization; Tac-SW, tacrolimus and rapid steroid withdrawal.

Kidney Int Rep (2018) ■, ■–■; https://doi.org/10.1016/j.ekir.2018.07.009

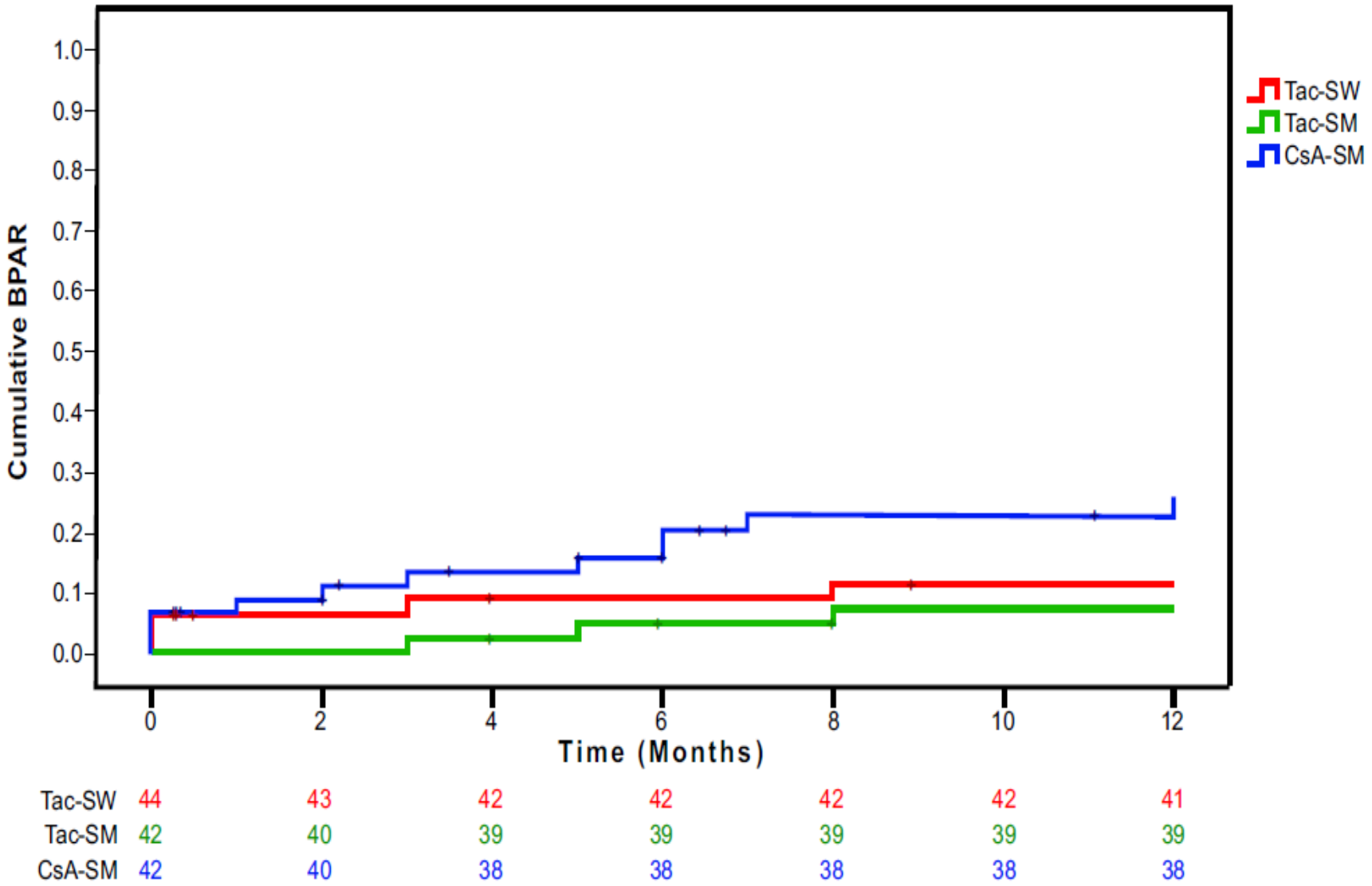
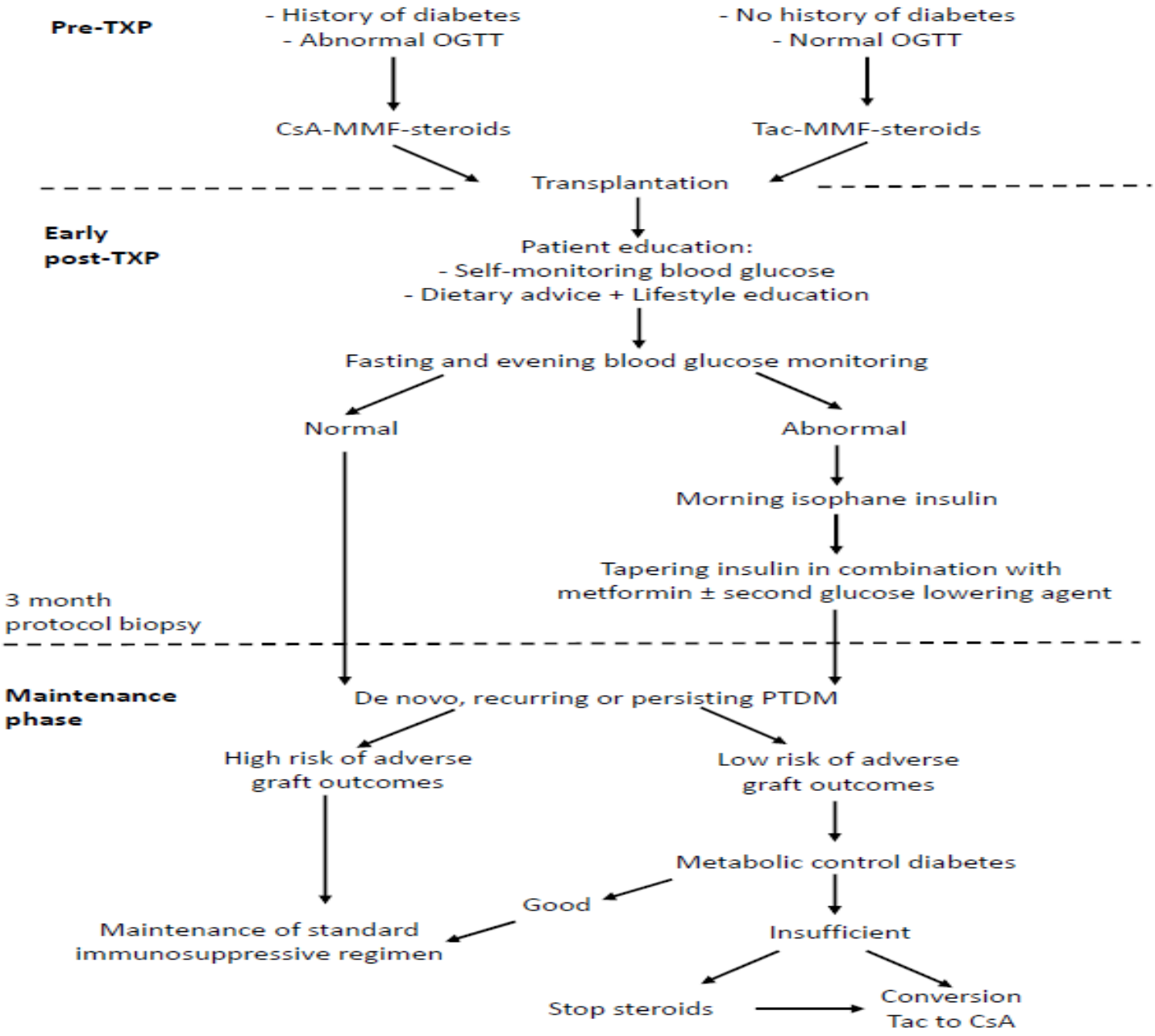


Figure 5. Cumulative incidence of biopsy-proven acute rejection (BPAR) in each study arm. Log-rank test $P = 0.04$. CsA-SM, cyclosporine A and steroid minimization; Tac-SM, tacrolimus and steroid minimization; Tac-SW, tacrolimus and rapid steroid withdrawal.

DISCUSSION

This study shows that in patients with a high risk for PTDM, tacrolimus-based immunosuppression, administered with basiliximab and MMF plus SM, provides the best balance between PTDM and acute rejection incidence. Under a similar regimen, rapid SW did not further reduce the incidence of PTDM and was associated with a slight increase in biopsy-proven acute rejection (BPAR).


Pre-TXP
- History of diabetes
- Abnormal OGTT
- No history of diabetes
- Normal OGTT
CsA-MMF-steroids
Tac-MMF-steroids
Transplantation
Early post-TXP
Patient education:
- Self-monitoring blood glucose
- Dietary advice + Lifestyle education
Fasting and evening blood glucose monitoring
Normal
Abnormal
Morning isophane insulin
Tapering insulin in combination with metformin ± second glucose lowering agent
3 month protocol biopsy
Maintenance phase
De novo, recurring or persisting PTDM
High risk of adverse graft outcomes
Low risk of adverse graft outcomes
Metabolic control diabetes
Good
Insufficient
Maintenance of standard immunosuppressive regimen
Stop steroids
Conversion Tac to CsA

Tailoring Tacrolimus treatment

Tac+ MMF+Steroid

PTDM
Uncontrolled BS

Continue treatment for 3- 6 months

BS controlled

Continue as before

BS uncontrolled

Conversion

Tacrolimus minimization under the Umbrella of using **mTOR inhibitors** instead of MPA

TRANSFORM study

ATHENA study

Meta-analysis by Mallat et al….


Thank
you