# Optimization of the use of Advagraf ™ in kidney transplants

Daniel Serón
Nephrology Department
Hospital Vall d'Hebron
Barcelona

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ADV vs PGF de novo

Therapeutic monitoring

TAC metabolism

Compliance

ADV:Advagraf;  PGF: Prograf ; TAC: Tacrolimus

# ADV vs PGF de novo

Therapeutic monitoring

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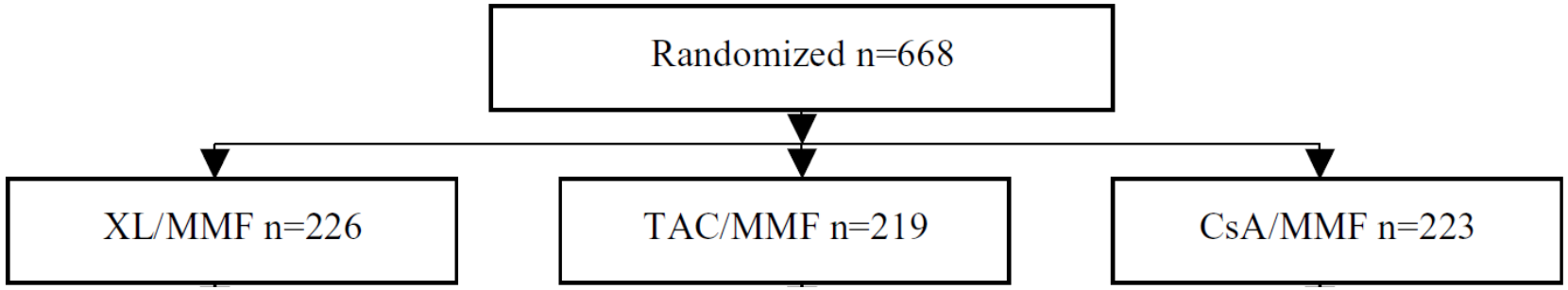
ADV: Advagraf;  PGF: Prograf ; TAC: Tacrolimus

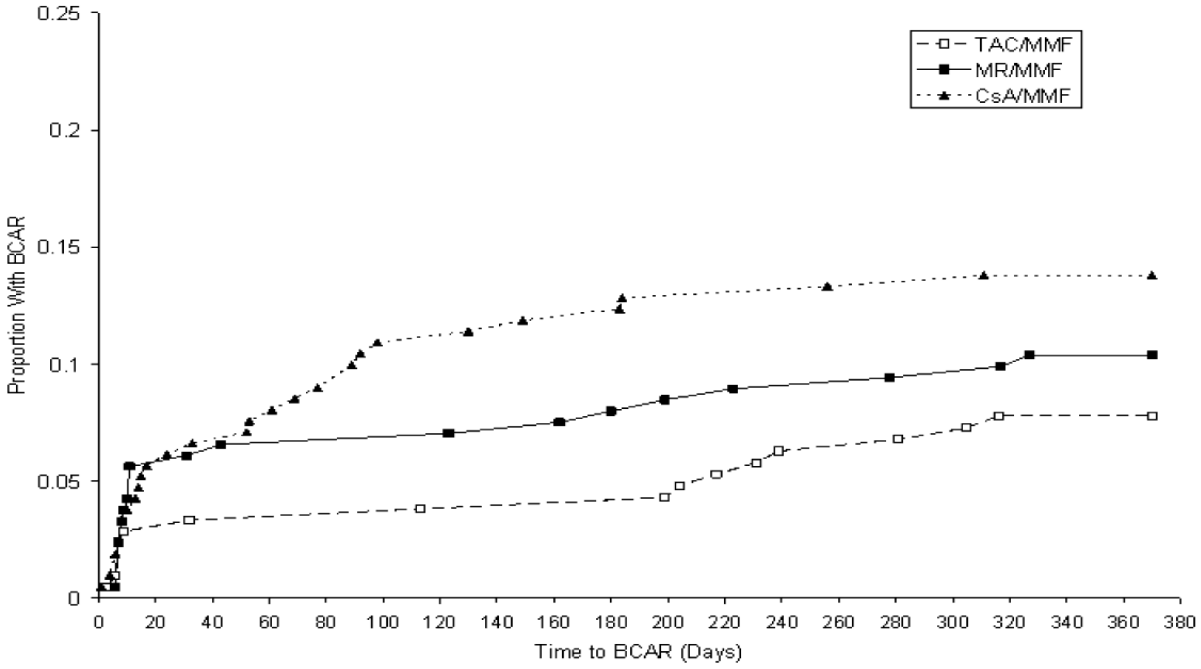
# ADV, PGF, CsA




| | XL/MMF (n = 214) | TAC/MMF (n = 212) | CsA/MMF (n = 212) |
|---|---|---|---|
| Patient survival[1] | 98.6% | 95.7% | 97.6% |
| Kaplan–Meier estimate difference[2] | 1.0% | −1.9% | |
| 95% confidence interval | −1.6%, 3.6% | −5.3%, 1.5% | |
| Graft survival | 96.7% | 92.9% | 95.7% |
| Death or graft failure | 7 | 15[1] | 9[1] |
| Kaplan–Meier estimate difference[2] | 1.0% | −2.9% | |
| 95%confidence interval | −2.7%, 4.6% | −7.3%, 1.6% | |

Treatment groups were compared for day 365 data using the log-rank test censoring patients at the time of the last follow-up. MMF = mycophenolate mofetil; XL = tacrolimus extended-release formulation; TAC = tacrolimus twice-a-day formulation; CsA = cyclosporine microemulsion.

ADV: Advagraf, PGF:Prograf, CsA: Cyclosporine



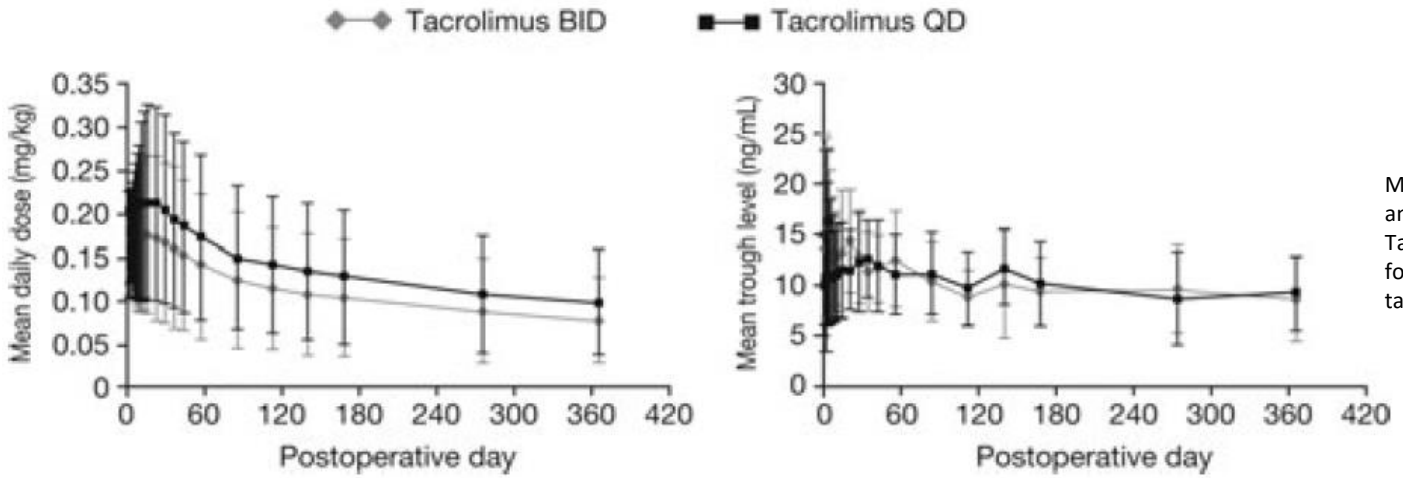

Kaplan–Meier estimate of time to occurrence of first biopsy-confirmed acute rejection. XL: tacrolimus extended-release formulation; TAC = tacrolimus twice-a-day formulation; CsA = cyclosporine microemulsion; MMF = mycophenolate mofetil; BCAR = biopsy confirmed acute rejection. Kaplan–Meier plot of BCAR censored at time of last follow-up.

Silva HT et al. Am J Transplant 2007; 7: 595

# TAC once daily vs twice daily in de novo KT without induction

## phase III double blind, double dummy, n=667

| | Overall population | |
|---|---|---|
| | Tacrolimus BID (n = 336) | Tacrolimus QD (n = 331) |
| Primary endpoint | | |
| Local BPAR over 24 weeks | | |
| Event rate for BPAR | 14.9% | 18.6% |
| p-Value† | 0.245 | |
| Treatment difference (Tacrolimus QD minus Tacrolimus BID) | 3.8% | |
| 95% CI | −2.1%, 9.6% | |
| Secondary BPAR endpoints | | |
| Central BPAR over 24 weeks# | | |
| Event rate for BPAR (signs & symptoms) | 14.5% | 18.5% |
| p-Value† | 0.197 | |




Mean daily tacrolimus dose and trough levels (per-protocol set). Tacrolimus BID = twice-daily tacrolimus formulation; Tacrolimus QD = once-daily tacrolimus formulation.

TAC:Tacrolimus; KT:Kidney Transplantation

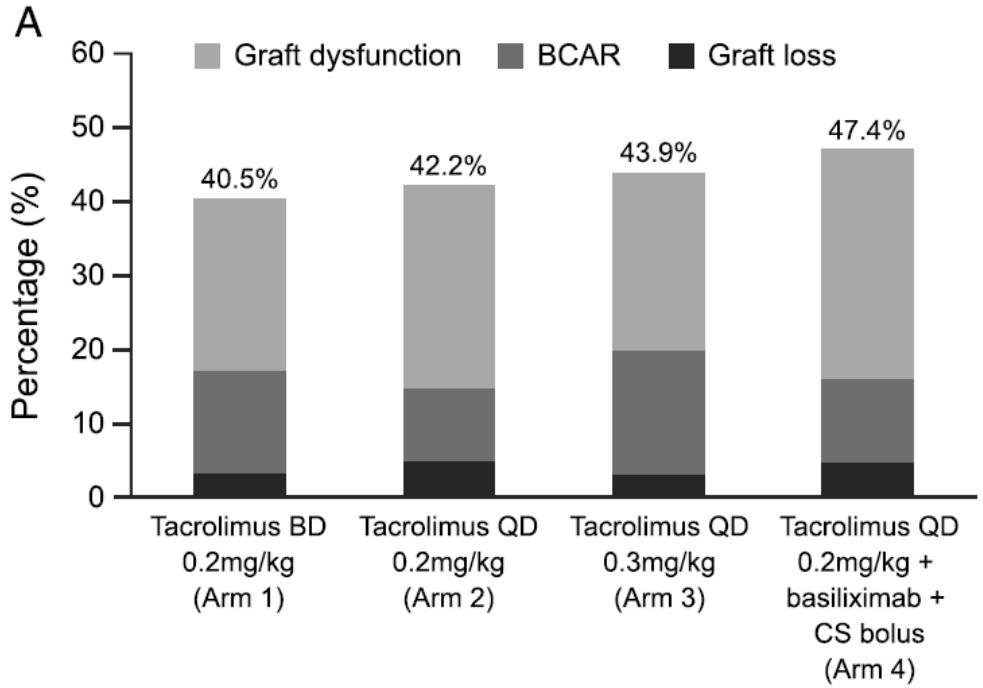
Krämer BK et al. Am J Transplant 2010; 10: 2632

# Osaka trial TAC BID vs QD

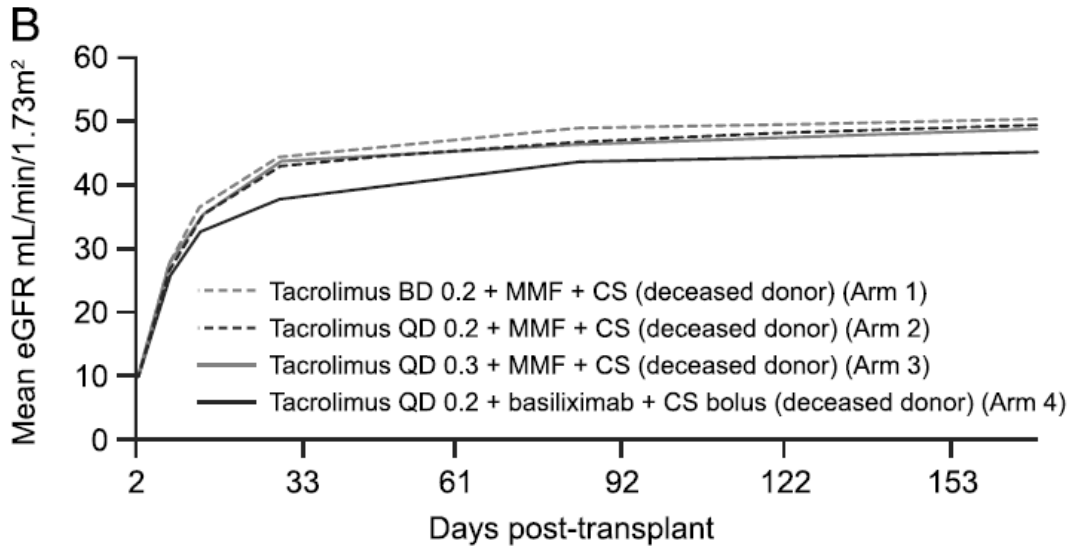
**TABLE 1.** Patient and donor demographics and transplantation information (FAS)

| Arm 1 | Arm 2 | Arm 3 | Arm 4 |
|---|---|---|---|
| Tac BD 0.2 mg/kg/day (n=309) | Tac QD 0.2 mg/kg/day (n=302) | Tac QD 0.3 mg/kg/day (n=304) | Tac QD 0.2 mg/kg/day+ Bas (n=283) |

Patient and donor demographics and transplantation information (FAS)




Primary endpoint: (A) efficacy failure rates (PPS).Data represent the first event for each patient. BCAR, biopsy-confirmed acute rejection; CS, corticosteroid; FAS, full analysis set; PPS, per protocol set.




(B) time course of eGFR in patients who received a kidney from a deceased donor (FAS).Bas, basiliximab; CS, corticosteroid; MMF, mycophenolate mofetil; Tac, tacrolimus.

TAC:Tacrolimus; BID: twice daily; QD:once daily, VS: Versos

Albano L et al. Transplantation 2013; 96: 897

# Comparison of ADV to PGR in the novo KT

| Study | Immunosuppression | Patient Survival | Graft Survival | BPAR (%) |
|---|---|---|---|---|
| | | 1 year | 1 year | 1 year |
| Silva HT Jr et al. *[7]* Phase III trial | Advagraf® | 98.6% | 96.7% | 22% |
| n = 638 | Prograf® | 95.7% | 92.9% | 16% |
| | Neoral® | 97.6% | 95.7% | 29% |
| | + MMF/steroids/basiliximab | | | |
| | | 24 weeks | 24 weeks | 24 weeks |
| Krämer et al. *[11]* Phase III trial | Advagraf® | 96.9% | 91.5% | 20.4% |
| n = 667 | Prograf® | 97.5% | 92.8 % | 15.8% |
| | + MMF/steroids/no induction | | | |
| | | 24 weeks | 24 weeks | 24 weeks |
| Albano et al. *[10]* Phase IV trial | Advagraf® 0.2 mg/kg/d | 97.3% | 90.4% | 10.3% |
| n = 1198 | Advagraf® 0.3 mg/kg/d | 98% | 94.1% | 16.1% |
| | Prograf® 0.2 mg/kg/d | 97.7% | 93.4% | 13.6% |
| | + MMF/steroids | | | |
| | Advagraf® 0.2 mg/kg/d | 98.9% | 91.8% | 12.7% |
| | + basiliximab/MMF | | | |

ADV:Advagraf; PGR:Prograf; KT: Kidney transplantation

Noble J et Al. Exp Rev Clin Immunol 2018; 14: 461

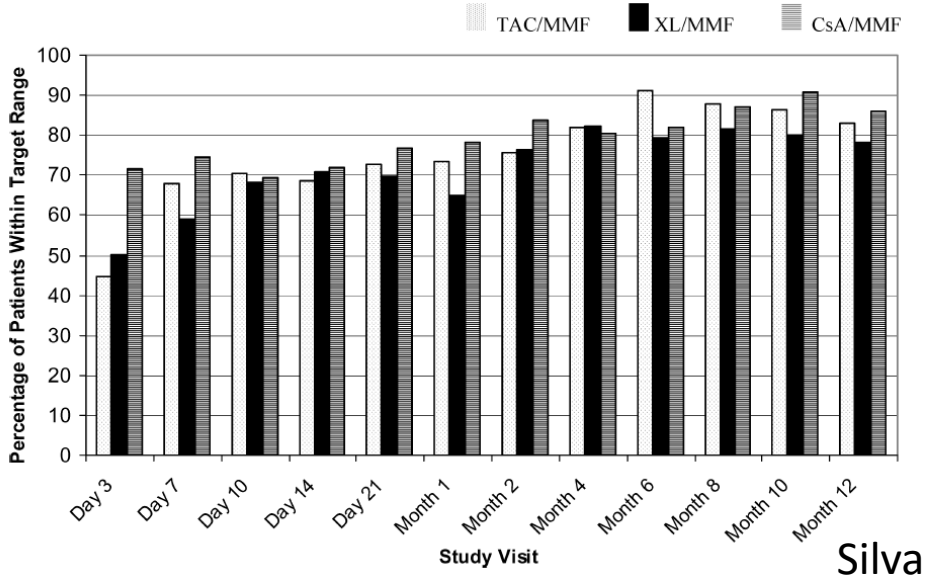
# Target TAC levels above and below target

7-16 ng/ml 0-3m

5-15 ng/ml >3m

| | Above target | | Below target | | Mean trough concentration (ng/mL) | |
|---|---|---|---|---|---|---|
| | XL/MMF | TAC/MMF | XL/MMF | TAC/MMF | XL/MMF | TAC/MMF |
| Day 3 | n = 36 | n = 47 | n = 58 | n = 48 | n = 189 | n = 172 |
| | 19.0% | 27.3% | 30.7% | 27.9% | 11.28 | 12.99 |
| Month 2 | n = 10 | n = 11 | n = 33 | n = 29 | n = 181 | n = 165 |
| | 5.5% | 6.7% | 18.2% | 17.6% | 10.15 | 10.06 |
| Month 4 | n = 13 | n = 7 | n = 18 | n = 20 | n = 174 | n = 151 |
| | 7.5% | 4.6% | 10.3% | 13.2% | 9.02 | 8.80 |

Tacrolimus whole blood trough concentrations by visit




Percentage of patients within the target study drug trough concentration range by visit. XL: tacrolimus extended-release formulation; TAC = tacrolimus twice-a-day formulation; CsA = cyclosporine microemulsion; MMF = mycophenolate mofetil

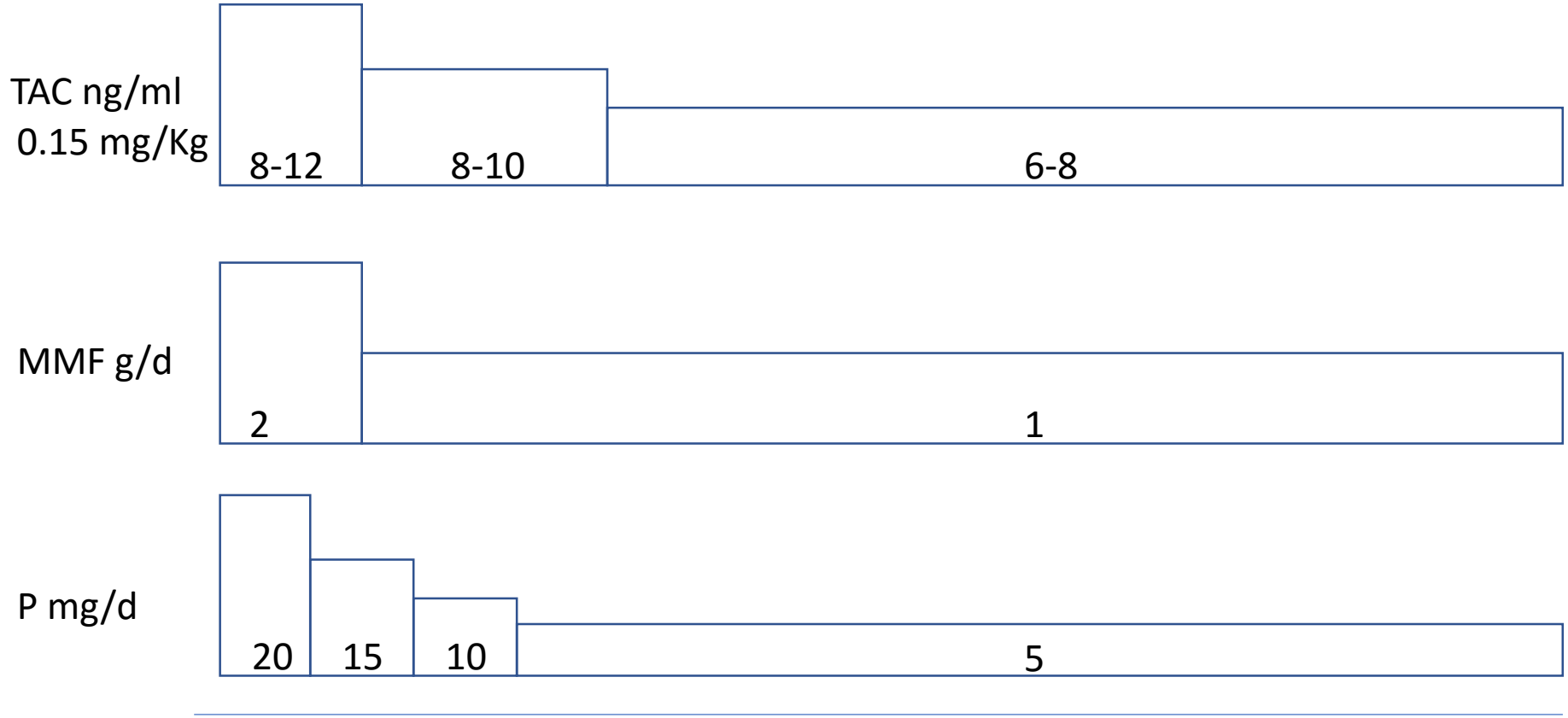
TAC:Tacrolimus

Silva HT et al. Am J Transplant 2007; 7: 595

# Immunosuppression at Vall d'Hebron

High risk : Thymoglobulin 1.25 mg/kg day 0 and 1 mg/kg days 1, 3, 5, 7

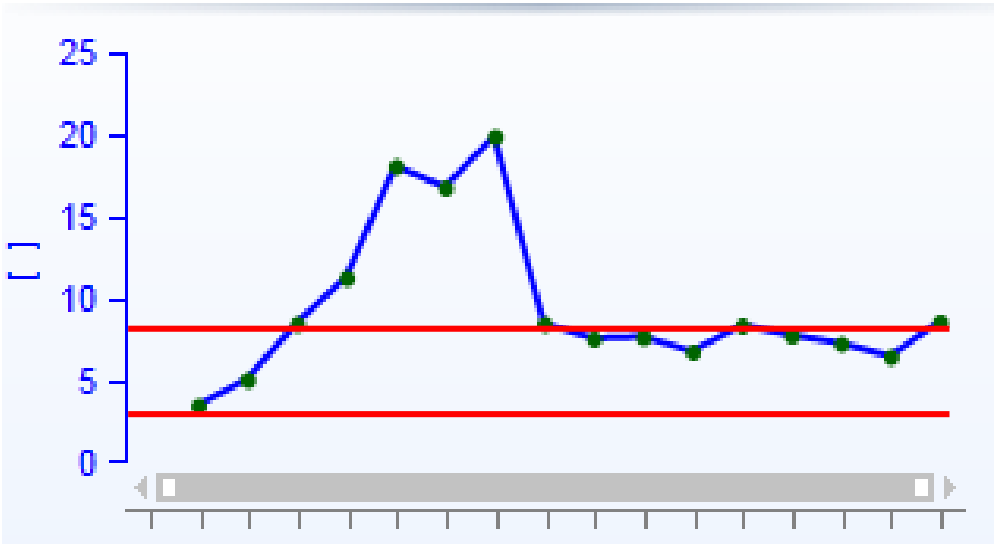
Low risk : Basiliximab 20 ng days 0



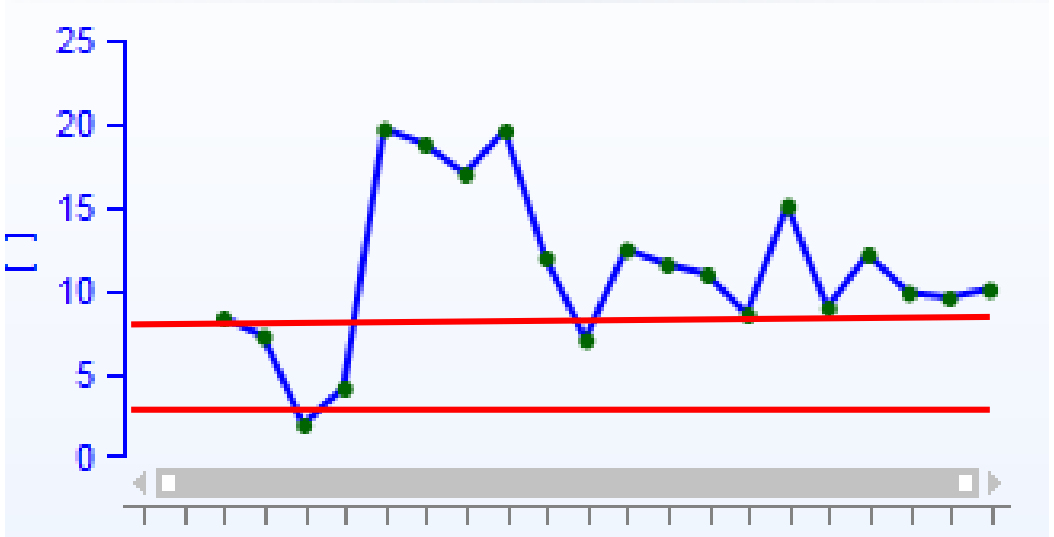

TAC: Tacrolimus; MMF: Mycophenolate mofetil ; P:prednisolone

Immunosuppressive schedule at Vall d'Hebron Hospital

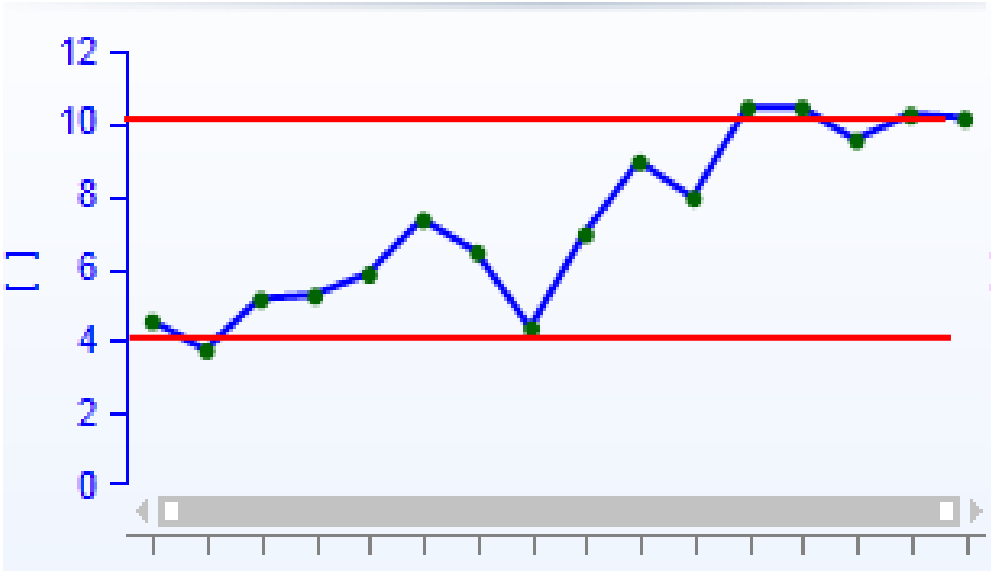
EMR 28/7/2016-15/1/2018



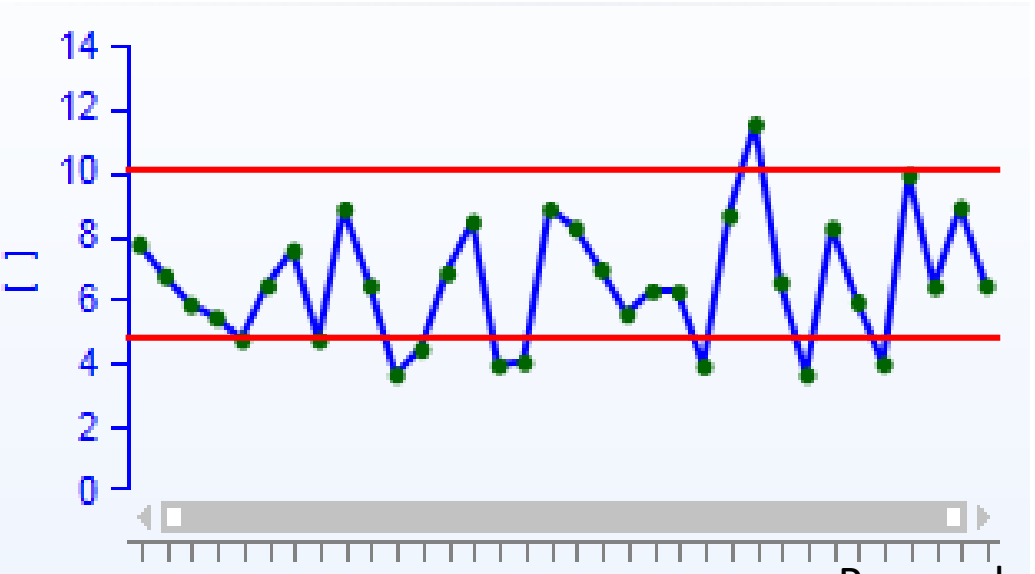

FO 23/3/2016-22/1/2018




DVN 28/9/2011-13/4/2018




MBG 27/6/2014-5/8/2020




Personal experience

4 Personal experience with TAC levels

# Time to reach the steady state

| | ADV (n=106) | PGF (n=95) | p |
|---|---|---|---|
| Time to steady State[1] (days) | 9.2±1.1 | 8.1±4.7 | 0.49 |
| Dose Adjustments to reach steady State | 1.2±1.7 (0-8) | 1.7±1.5 (0-7) | 0.03 |
| Dose to attain the steady State (mg/d) | 7.2±2.4 (1-17) | 7.0±2.7 (2-17) | 0.69 |

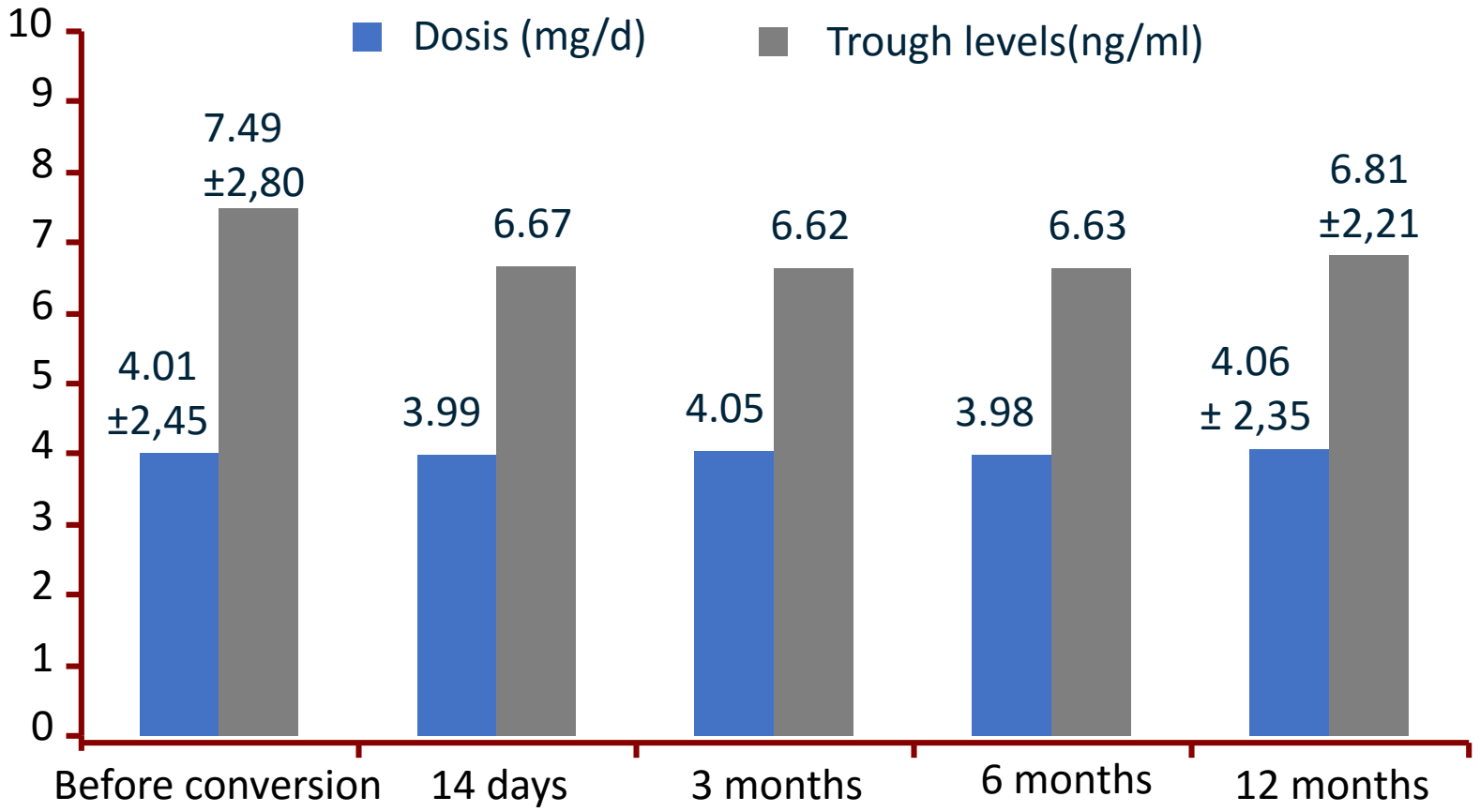
1:Time to steady State : 1st attainment of consecutive trough levels between 5-10 ng/ml

Fanous H et al. Clin Kidney J 2013; 45

# Evolution study (n=1832)

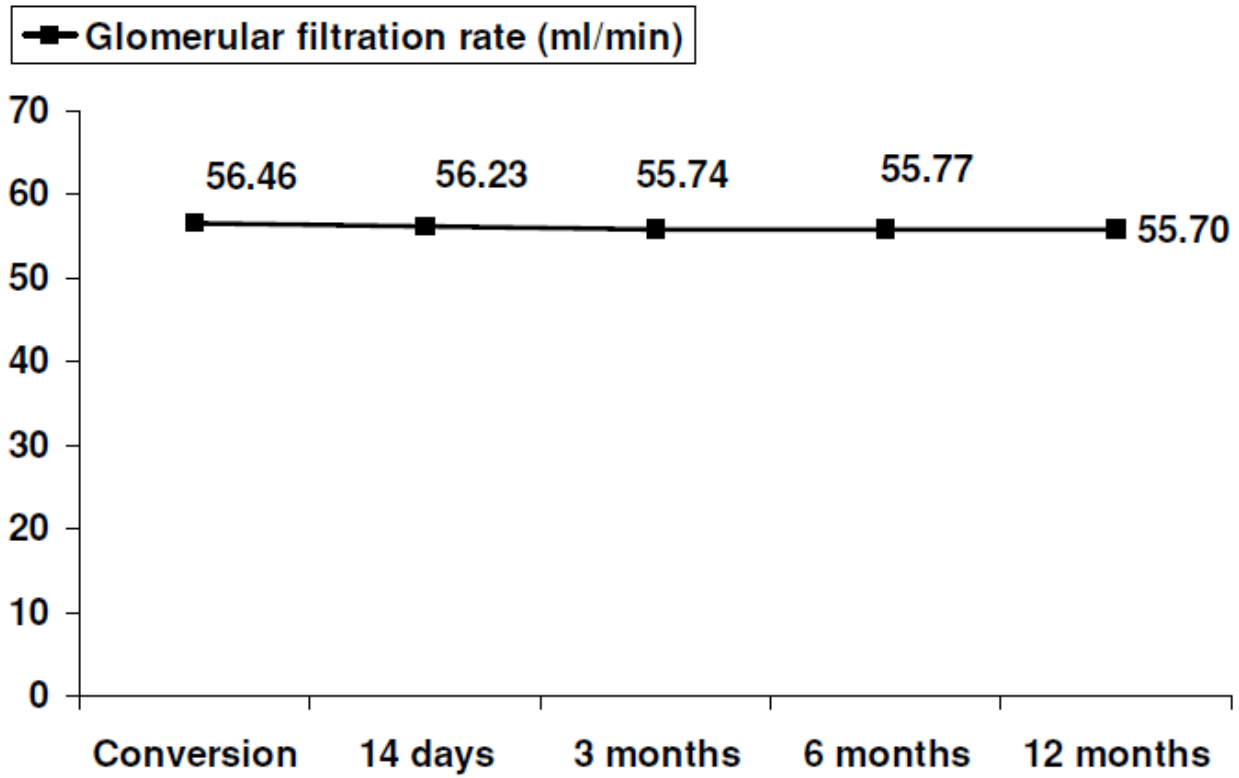
Conversion TAC twice to once daily: 1.0 to 1.0 or 1.1 to 1.1 if throug levels > 6 ng/ml at 4.9 ±4.0 years after transplant

| | | |
|---|---|---|
| Dose variability at 12 m : | +1,24% | p<0.001 |
| Levels variability at 12 m : | -9,1% | p<0.0001 |




Guirado L, et al. Am J Transplant 2011; 11: 1965

# Evolution of e-GFR after conversion




Guirado L, et al. Am J Transplant 2011; 11: 1965

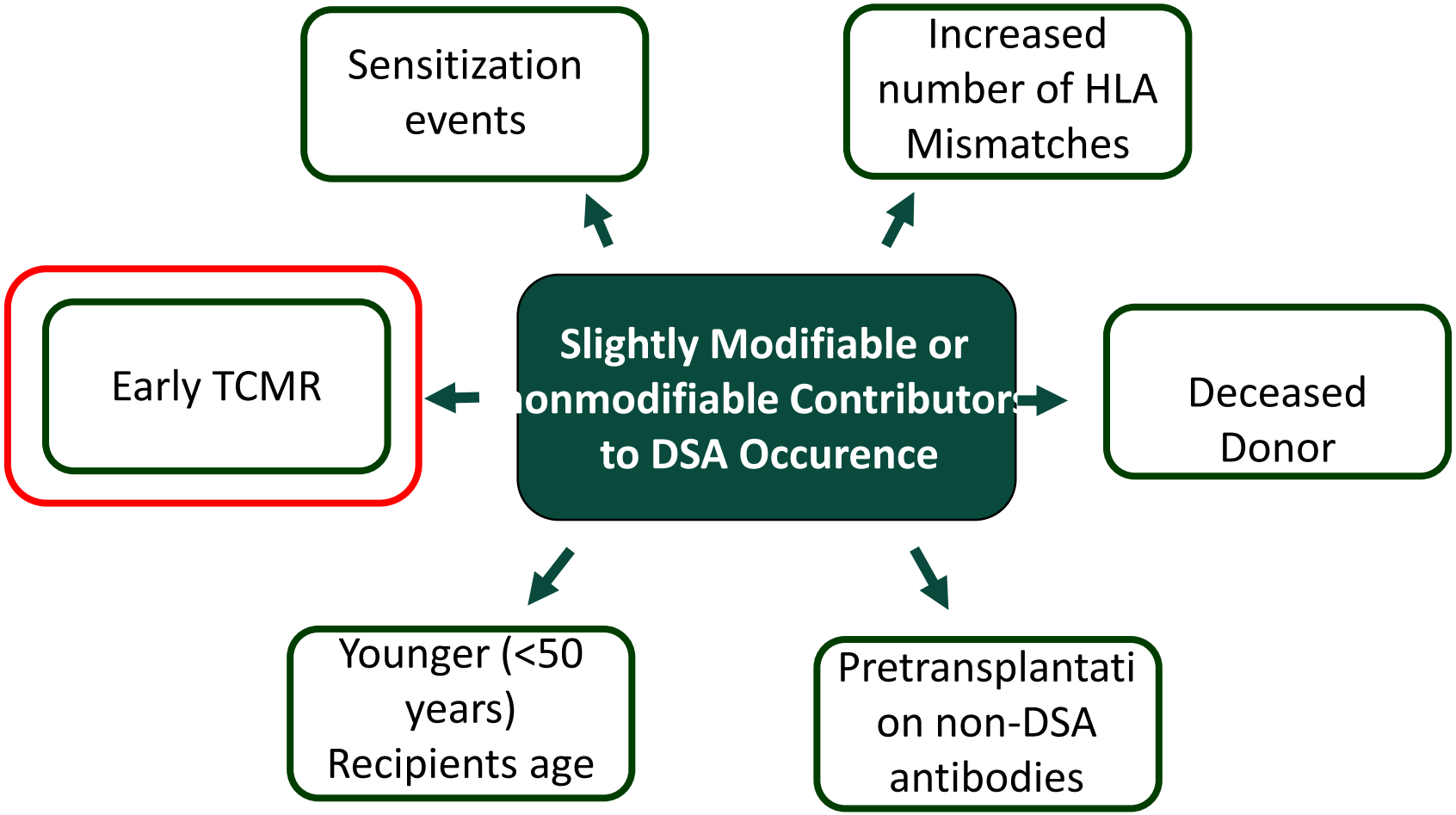
OPEN

# Practical Recommendations for Long-term Management of Modifiable Risks in Kidney and Liver Transplant Recipients: A Guidance Report and Clinical Checklist by the Consensus on Managing Modifiable Risk in Transplantation (COMMIT) Group

James M. Neuberger, MD, FRCP,[1] Wolf O. Bechstein, MD, PhD,[2] Dirk R.J. Kuypers, MD, PhD,[3] Patrizia Burra, MD, PhD,[4] Franco Citterio, MD, FEBS,[5] Sabina De Geest, PhD, RN,[6,7] Christophe Duvoux, MD, PhD,[8] Alan G. Jardine, MD, FRCP,[9] Nassim Kamar, MD, PhD,[10] Bernhard K. Krämer, MD,[11] Herold J. Metselaar, MD, PhD,[12] Frederik Nevens, MD, PhD,[13] Jacques Pirenne, MD, MSc, PhD,[14] Manuel L. Rodríguez-Perálvarez, MD, PhD,[15] Didier Samuel, MD, PhD,[16] Stefan Schneeberger, MD,[17] Daniel Serón, MD, PhD,[18] Pavel Trunečka, MD, PhD,[19] Giuseppe Tisone, MD,[20] and Teun van Gelder, MD, PhD[21]

Transplantation 2017; 101: S1-S56

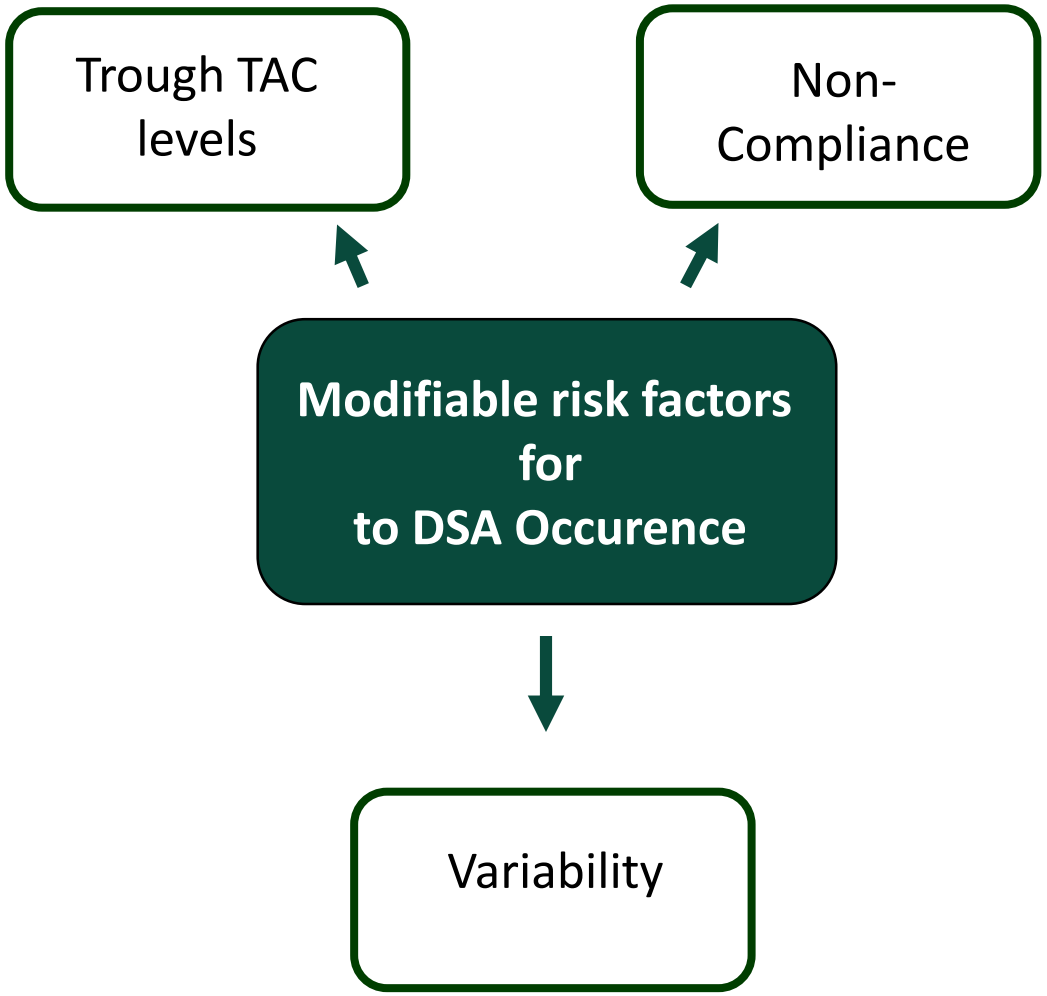
# Slightly Modifiable or nonmodifiable Contributors to DSA Occurence




DSA: Donor specific antibody; HLA :Human leukocyte Antigen; TCMR:T-Cell Mediated Rejection

Neuberger J et al. Transplantation 2017; 7: 518 (2)

# Modifiable risk factors for dnDSA




dnDSA: de novo donor specific antibody, TAC: Tacrolimus

Neuberger J et al. Transplantation 2017; 7: 518

ADV vs PGF de novo

Therapeutic monitoring

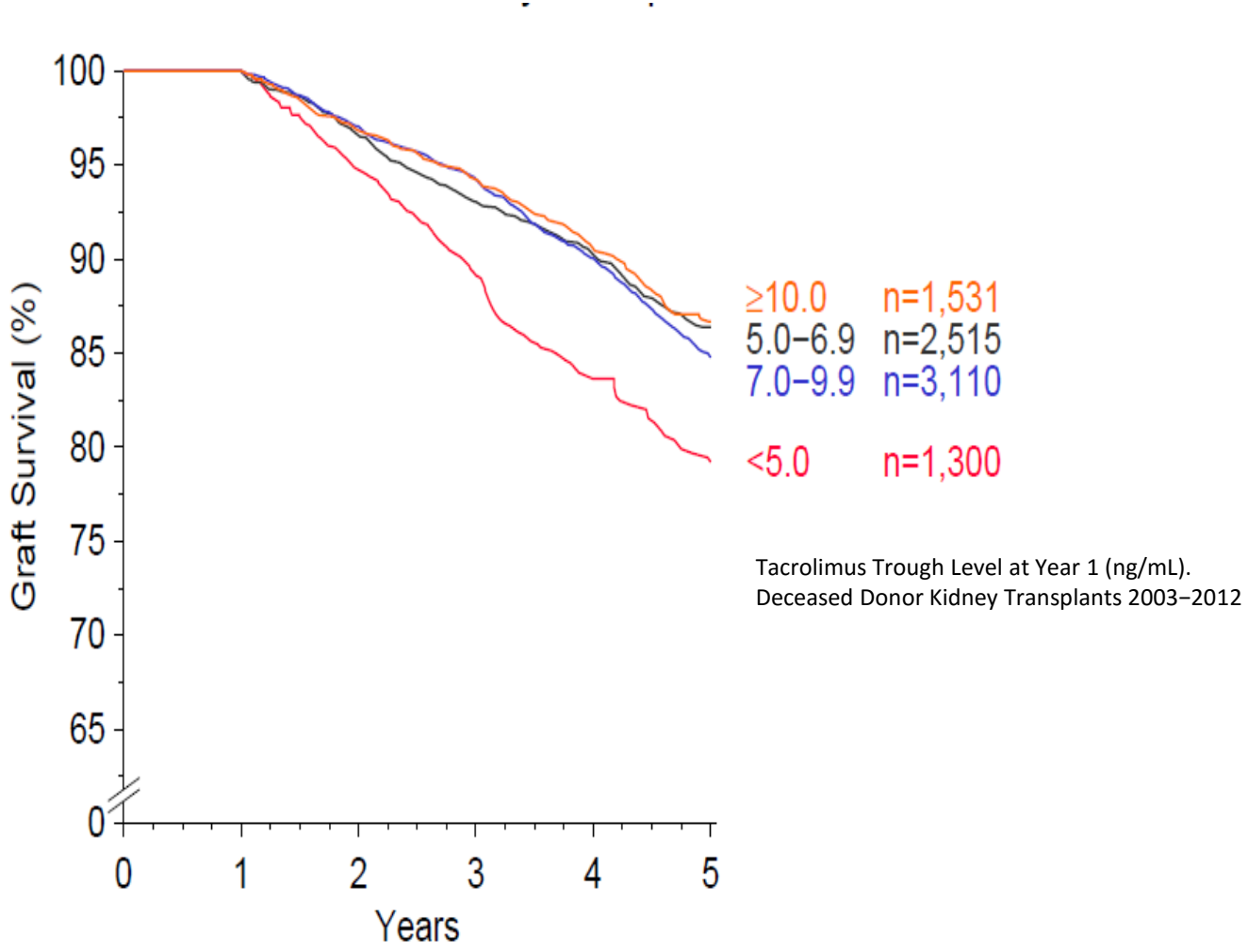
TAC metabolism

Compliance

ADV:Advagraf; PGF: Prograf ; TAC: Tacrolimus

# Low TAC trough levels and risk of graft failure

Kidney graft survival (serum creatinine <260µmol/L);

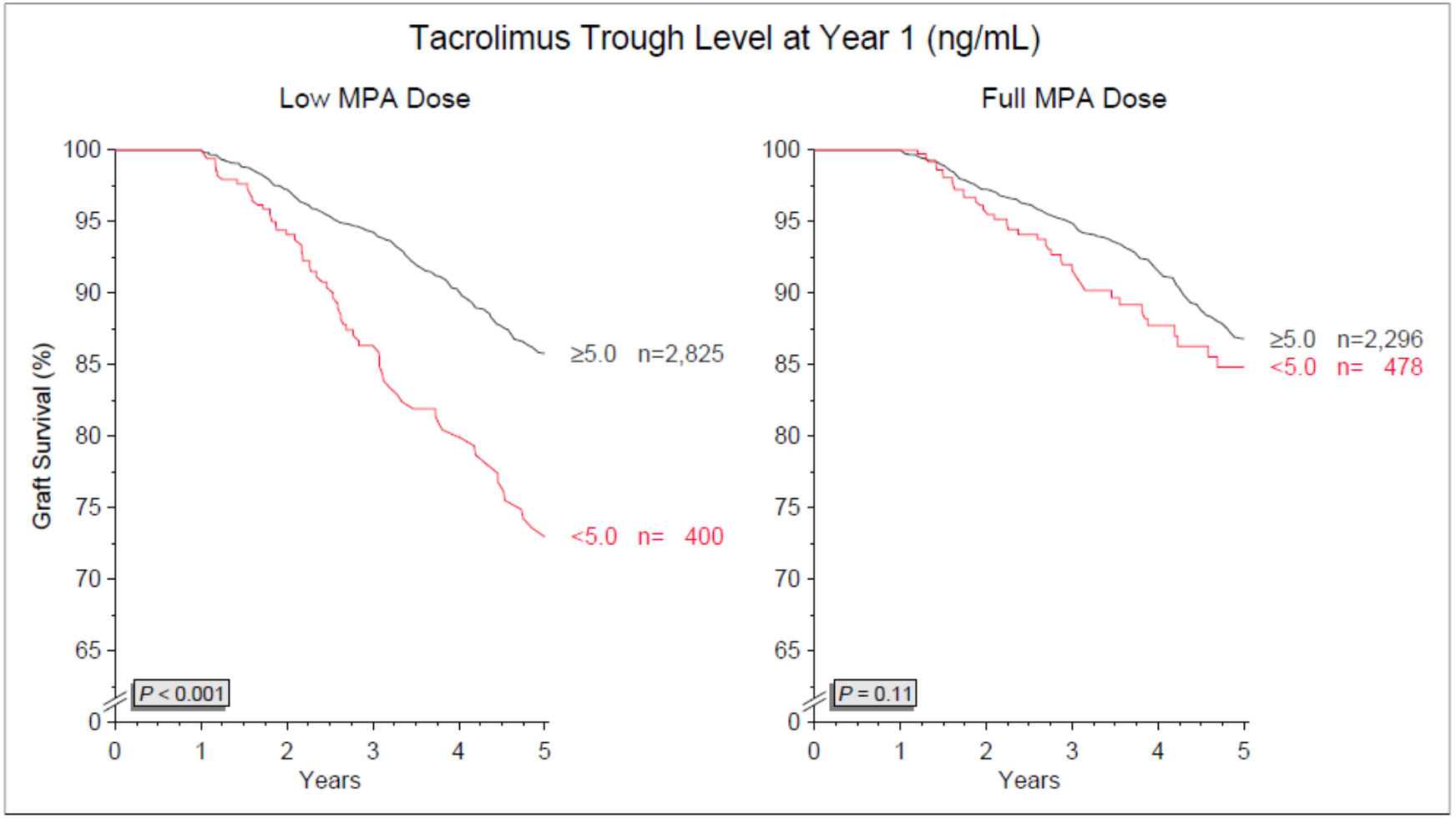



Tacrolimus Trough Level at Year 1 (ng/mL).
Deceased Donor Kidney Transplants 2003–2012

Opelz G. Collaborative Transplant Study Newsletter 2014;1:1–4.

TAC:Tacrolimus

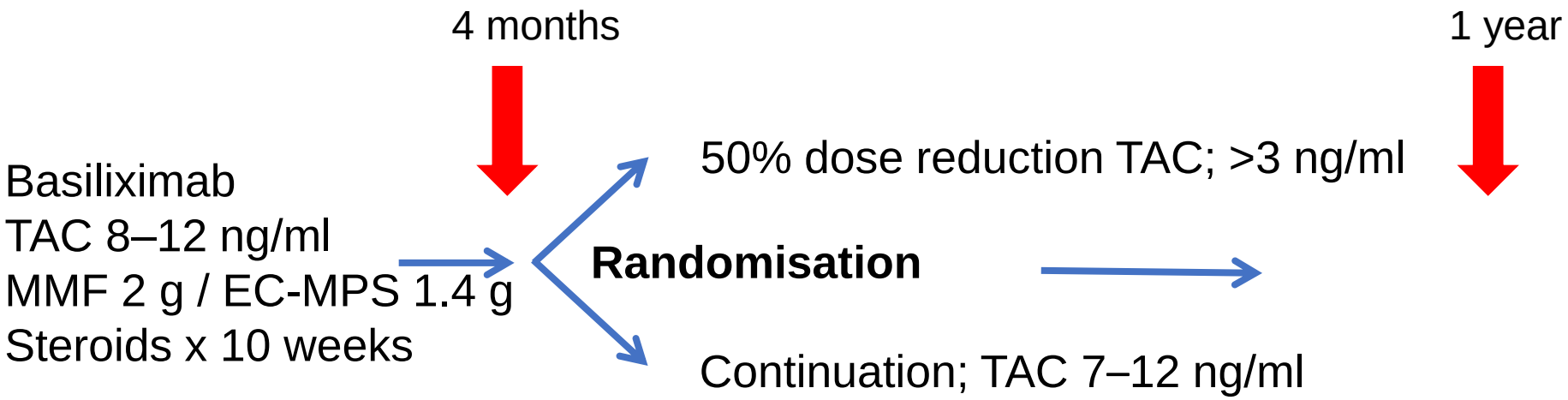
# Low exposure of TAC and survival in patients according to MMF dose≥1.5 g/d




TAC:Tacrolimus; MPA: Mycophenolic acid, MMF :Mycophenolate mofetil

Collaborative transplant study . Newsletter 1: 2014

# Reduced vs standard prolonged-release tacrolimus: Prospective randomised trial in low-risk steroid-free patients




**PS:** The initial doses of MMF and EC-MPS were 2000 and 1440 mg/day, respectively.

Gatault P et al. Am J Transplant 2017;17:1370–1379.

VS: Versus; TAC:Tacrolimus MMF :Mycophenolate mofetil; EC-MPS: Enteric-Coated Mycophenolate Sodium

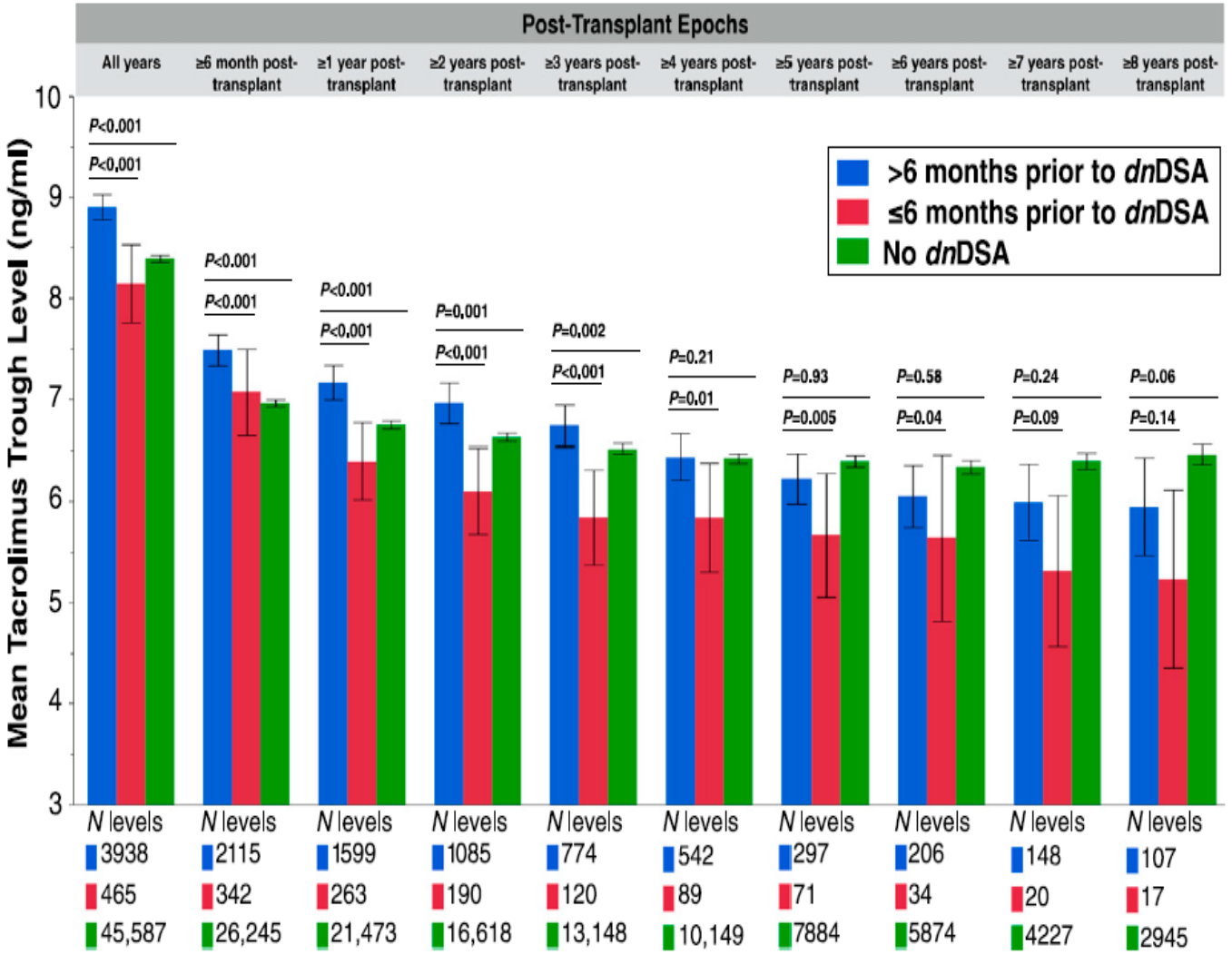
# Reduced vs standard QD TAC:increased risk of BPAR, inflammation and *de novo* DSAs

| | Low TAC (87) | Standard TAC (99) | p-value |
|---|---|---|---|
| TAC level at 6 m (ng/ml) | 5.3 ± 1.7 | 8.4 ± 2.1 | <0.0001 |
| TAC level at 12 m (ng/ml) | 5.6 ± 2.0 | 7.4 ± 2.0 | <0.0001 |
| BPAR | 10 | 3 | 0.016 |
| Protocol biopsy at 1 year | | | |
| i > 0 (%) | 21.4 | 8.8 | 0.047 |
| t > 0 (%) | 19.6 | 8.7 | 0.076 |
| i+t | 1.14 ± 1.21 | 0.72 ± 1.01 | 0.038 |
| dnDSAs | 6 | 0 | 0.008 |

Gatault P et al. Am J Transplant 2017;17:1370–1379.

VS : versus; QD:once daily; BPAR: biopsy proven acute rejection; DSAs:donor specific antibody; TAC:Tacrolimus

# Mean trough levels 6 months before dnDSA

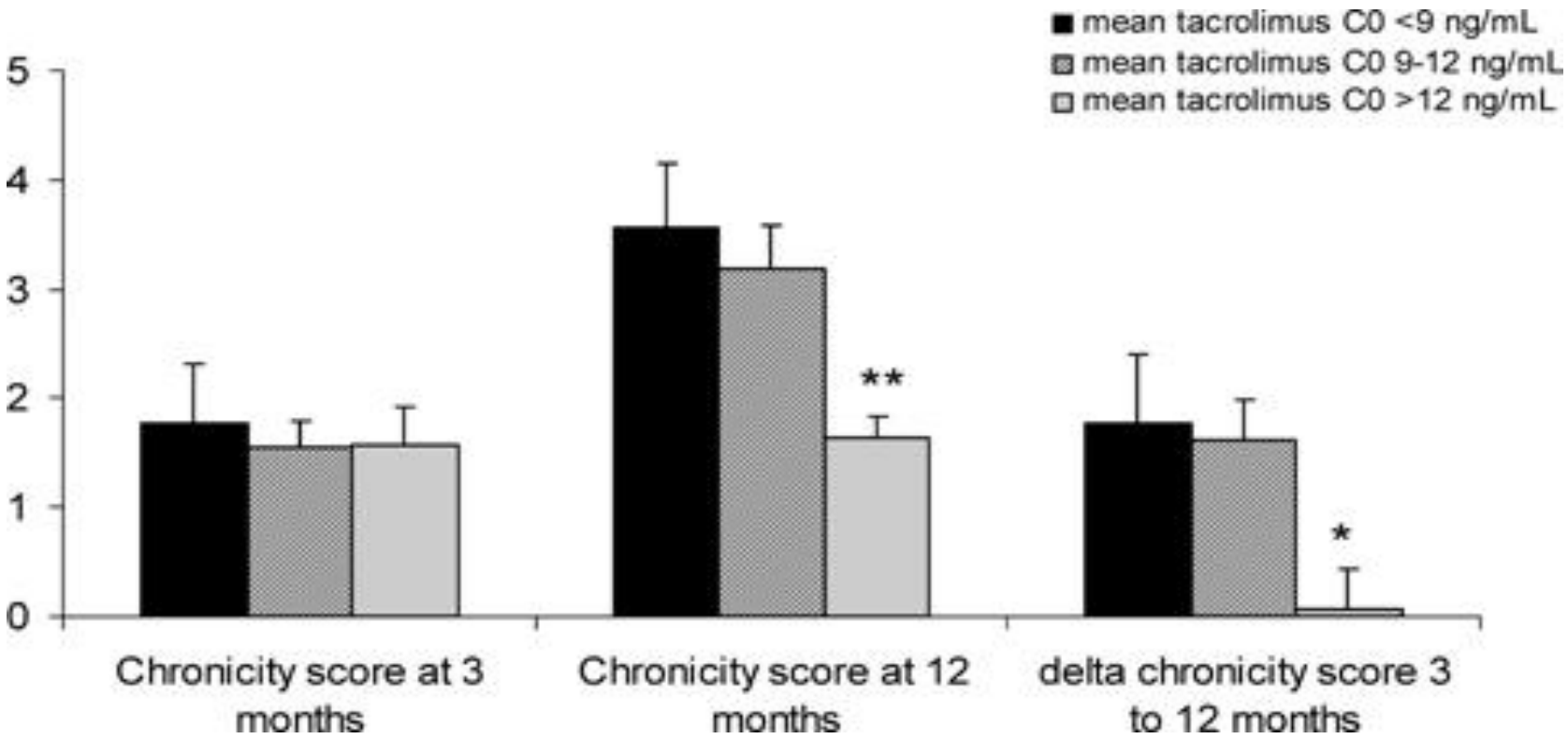



In recipients who developed dnDSA, mean tacrolimus trough levels dropped significantly in the 6 months prior to dnDSA onset compared with their earlier trough levels. Mean tacrolimus levels in the six months prior to dnDSA onset were compared to all previous levels within distinct time epochs to show the consistency of association irrespective of the timing of dnDSA onset. Tacrolimus levels within the No dnDSA group are included for reference. Values represent the mean tacrolimus trough levels and their 95% confidence intervals.

Wiebe C et al. J Am Soc Nephrol 2017 ; 28: 3353

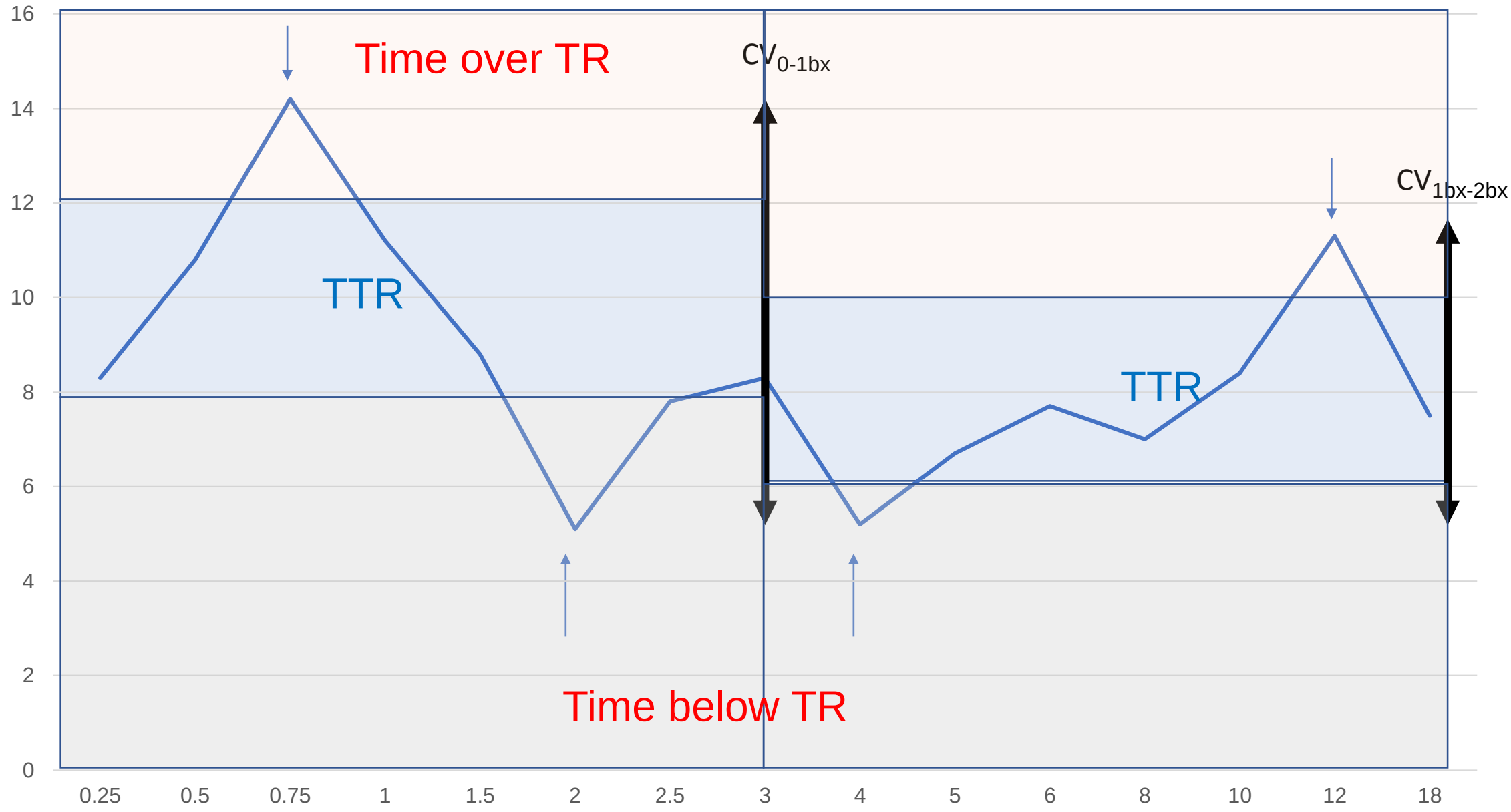
# Tac Exposure and Evolution of Histology in the First Year After Transplantation

(n=61 pairs of biopsies)




Tac:Tacrolimus

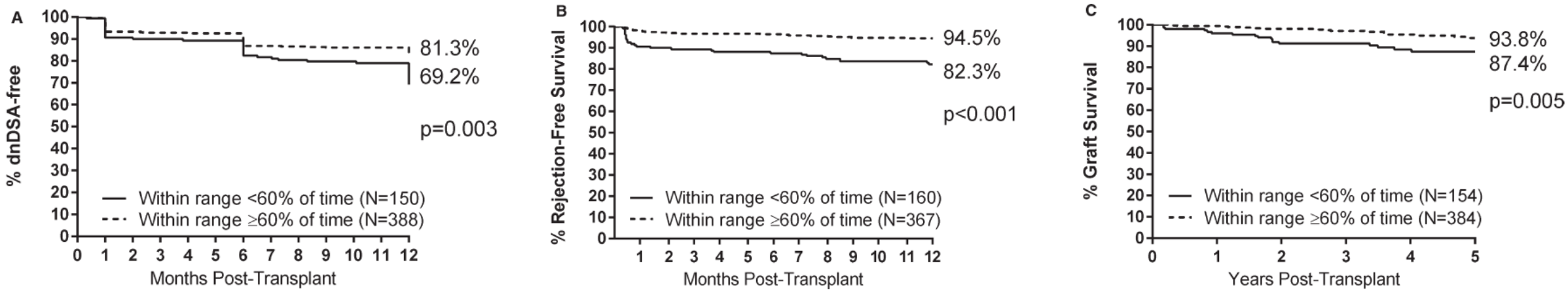
Naesens M et al. AJT 2007; 7: 2114




**TTR**: Time in Therapeutic Range

Chamoun B et al. J Clin Med 2020

# Mean TAC levels and time under the therapeutic range (5-10 ng/ml) < 60% during ther 1st year




Kaplan-Meier plot for TTR <60% compared to TTR ≥60% and (A) percent dnDSA-free survival by 12 months, (B) percent acute rejection-free survival by 12 months, and (C) percent death-censored graft loss by 5 years

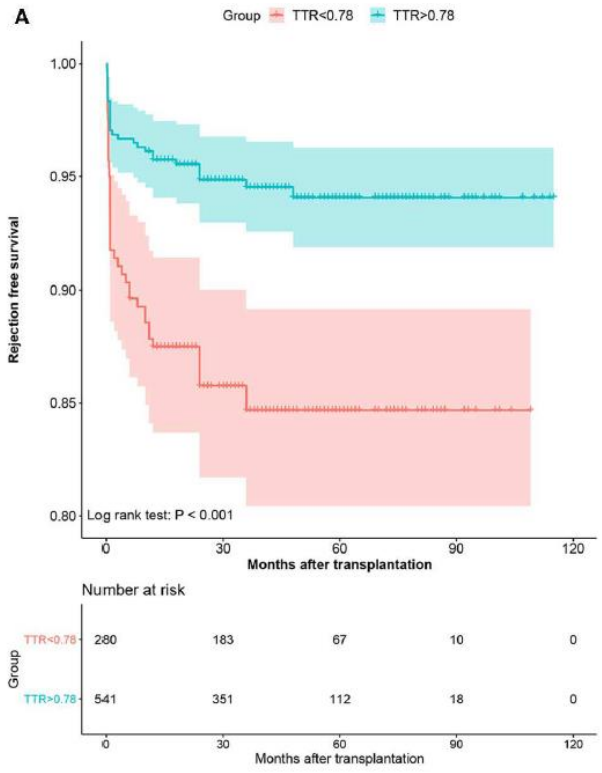
Tac:Tacrolimus

Davis S et al. Am J Transplant 2018; 18: 907

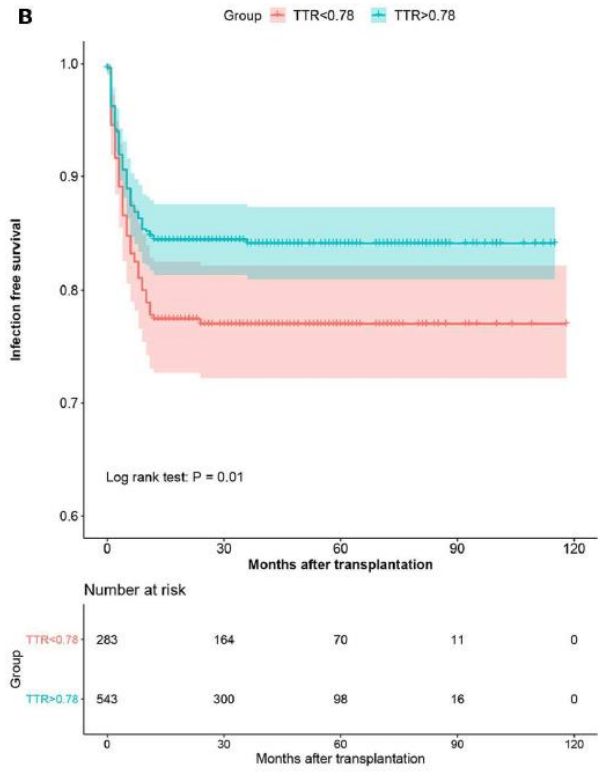
# ↑ TTR in the 1st year predicts better outcomes in líving donor KT

## TTR 5-10 ug/ml 0-3 m and 4-8 ug/ml 4-12 m, TTR < 78%

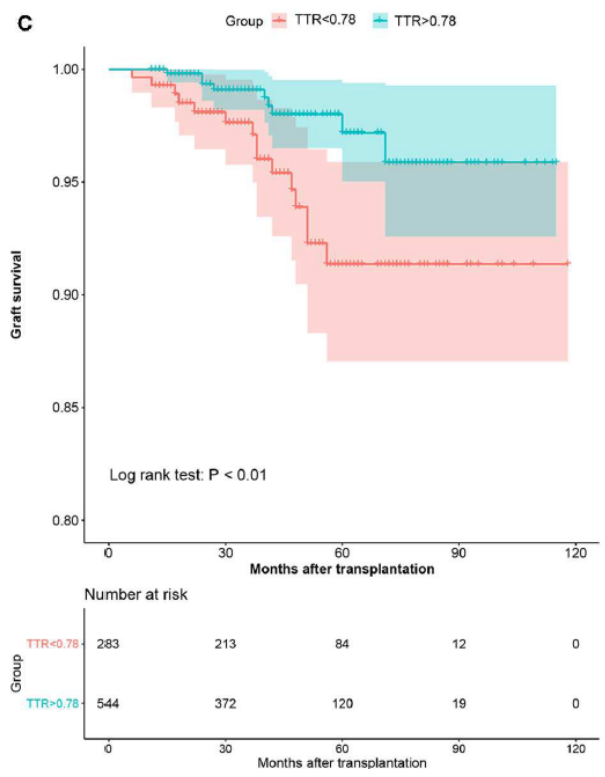
Rejection free



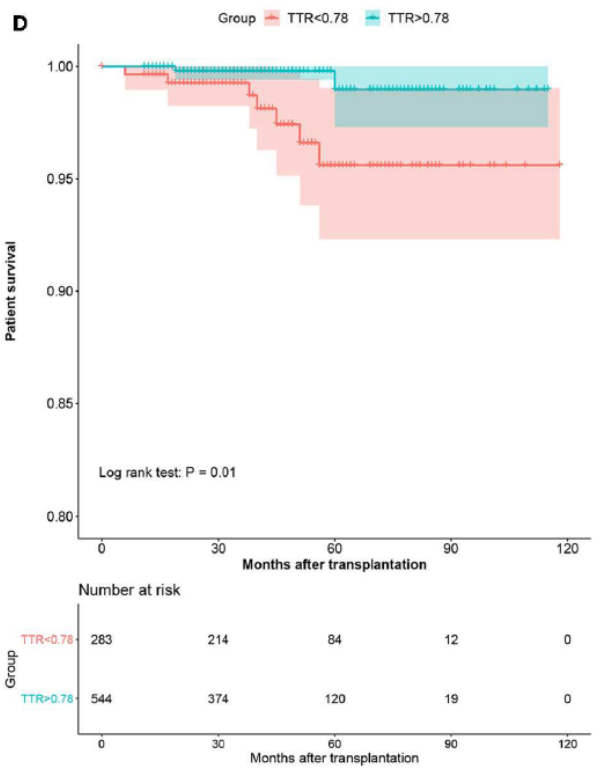

Infection free




Graft survival



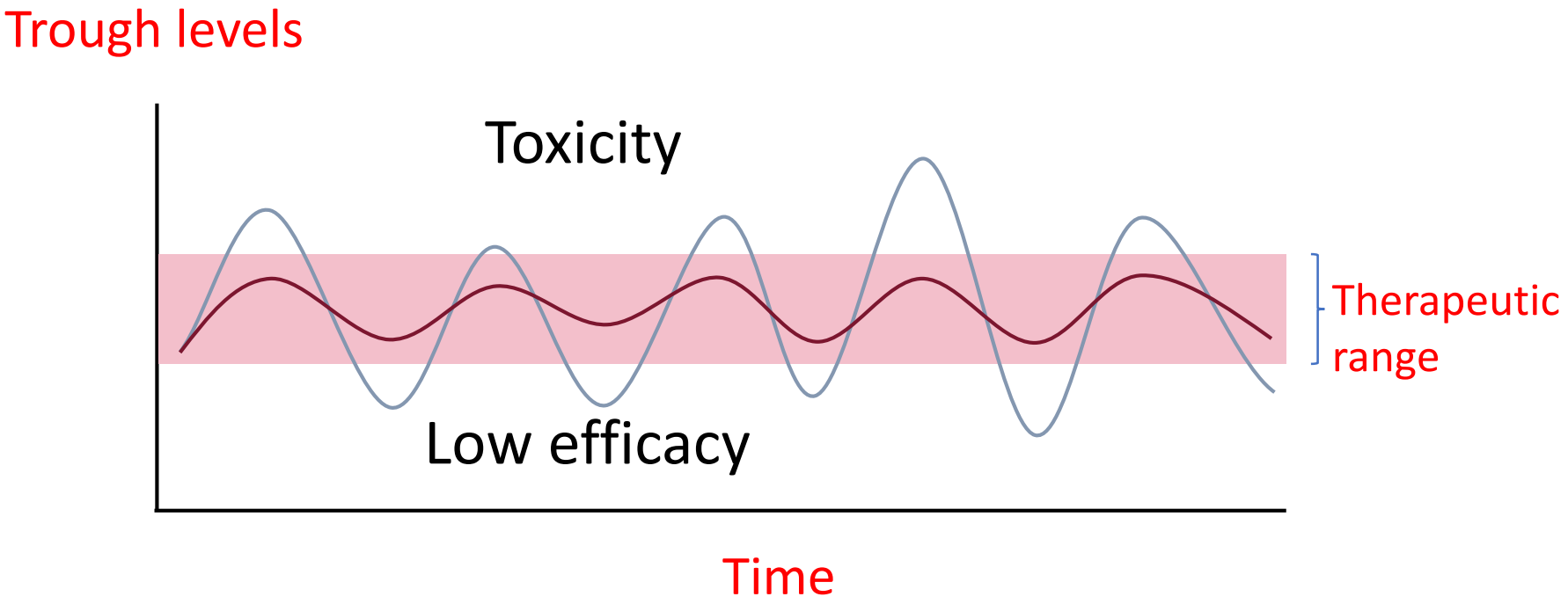

Patient survival




TTR: Time in Therapeutic Range ; KT: Kidney transplantation

Song T et al. Front Immunol 2019; 10: article 2912

# Variability of TAC trough levels between visits

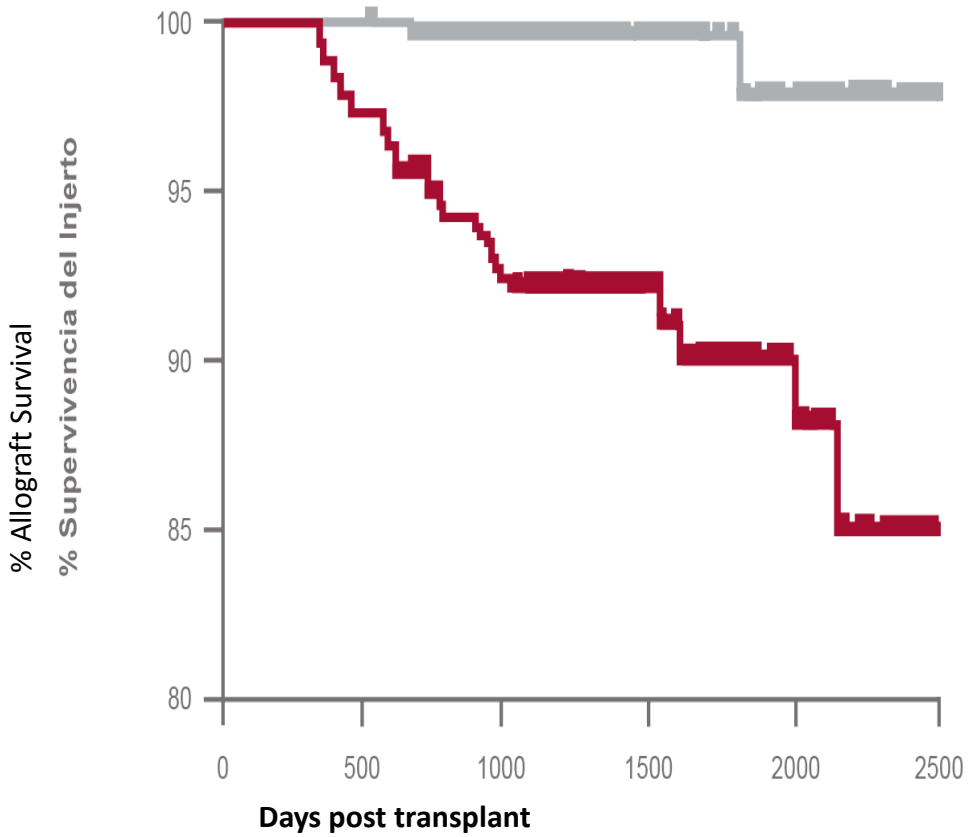



TAC: Tacrolimus

Figure made by the presenter

# Death censored graft survival & TAC var

## N=376




Low var=190

High var=186

HR = 4.928
95% CI = 2.050 - 11.85
p = 0.0004

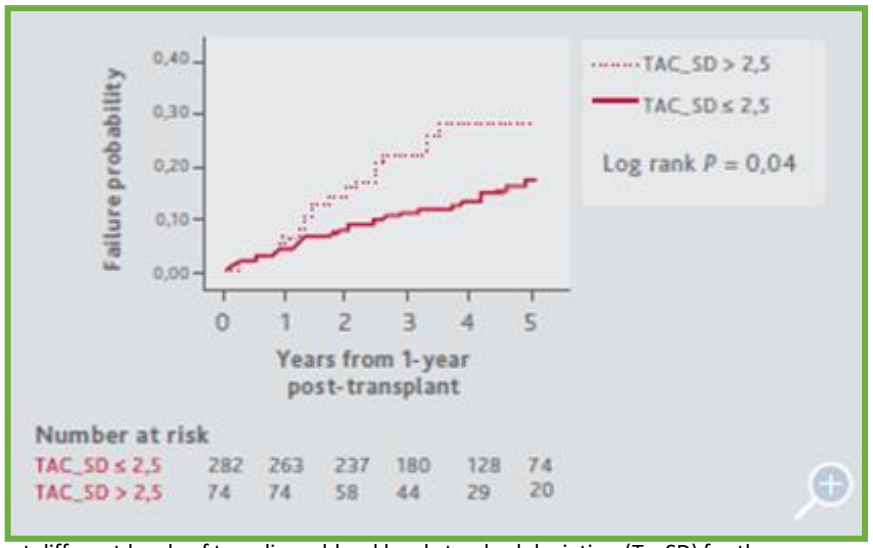
Allograft survival is significantly worse in the high variability group. HR, hazard ratio; CI, confidence interval.

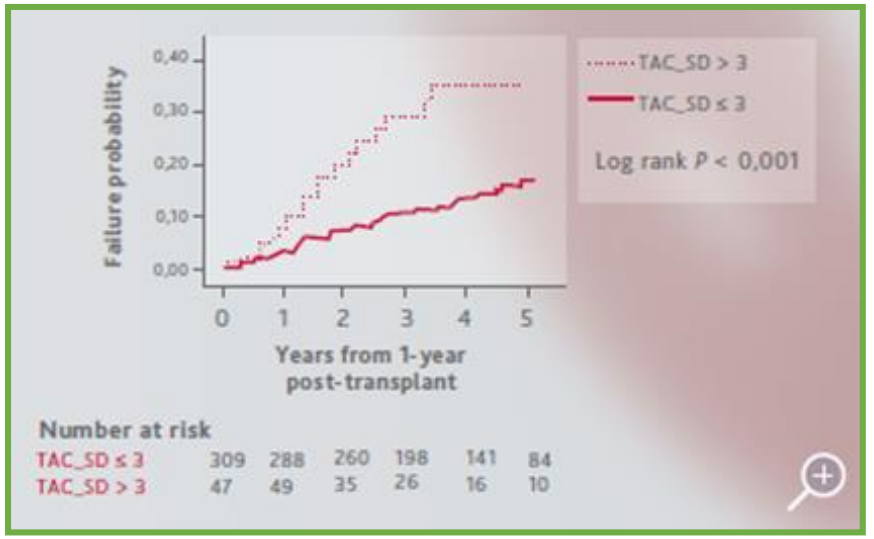
Whalen HR et al. Transplantation 2017; 101: 430

TAC:Tacrolimus

# TAC var and outcome: (late acute rejection, TG, graft failure and death with function (n=318)





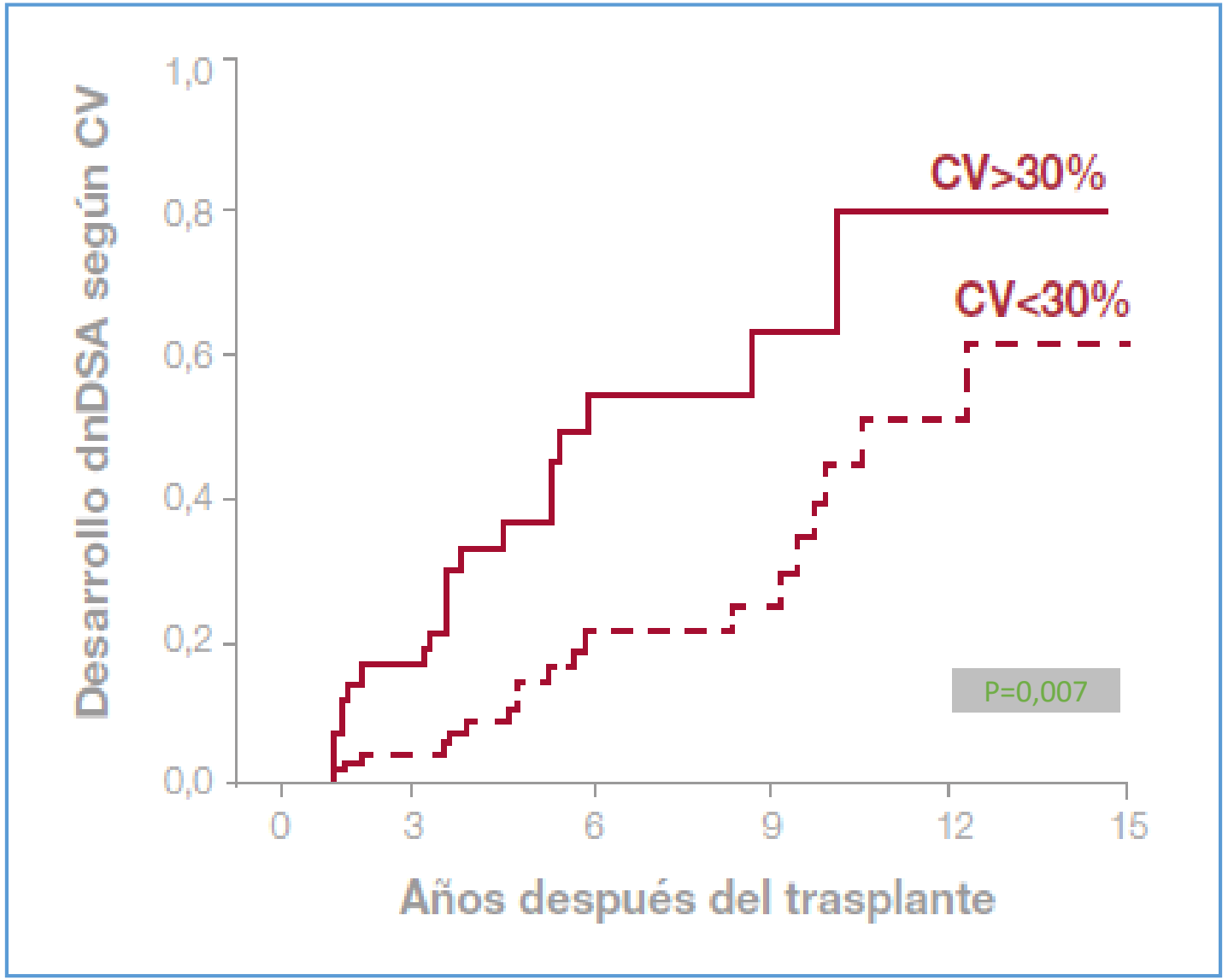

TAC: Tacrolimus;
TG: or transplant glomerulopathy

Extended Kaplan–Meier failure curves at different levels of tacrolimus blood level standard deviation (TacSD) for the composite end point (late acute rejection, or transplant glomerulopathy, and total graft loss) and secondary composite end point (death with function excluded).

Sapir-Pichhadze T et al. Kidney Int 2014; 85: 1404

# Variabilidad de tacrolimus y *de novo* DSA

N=310, CV 4-12m, renal allograft survival > 1y



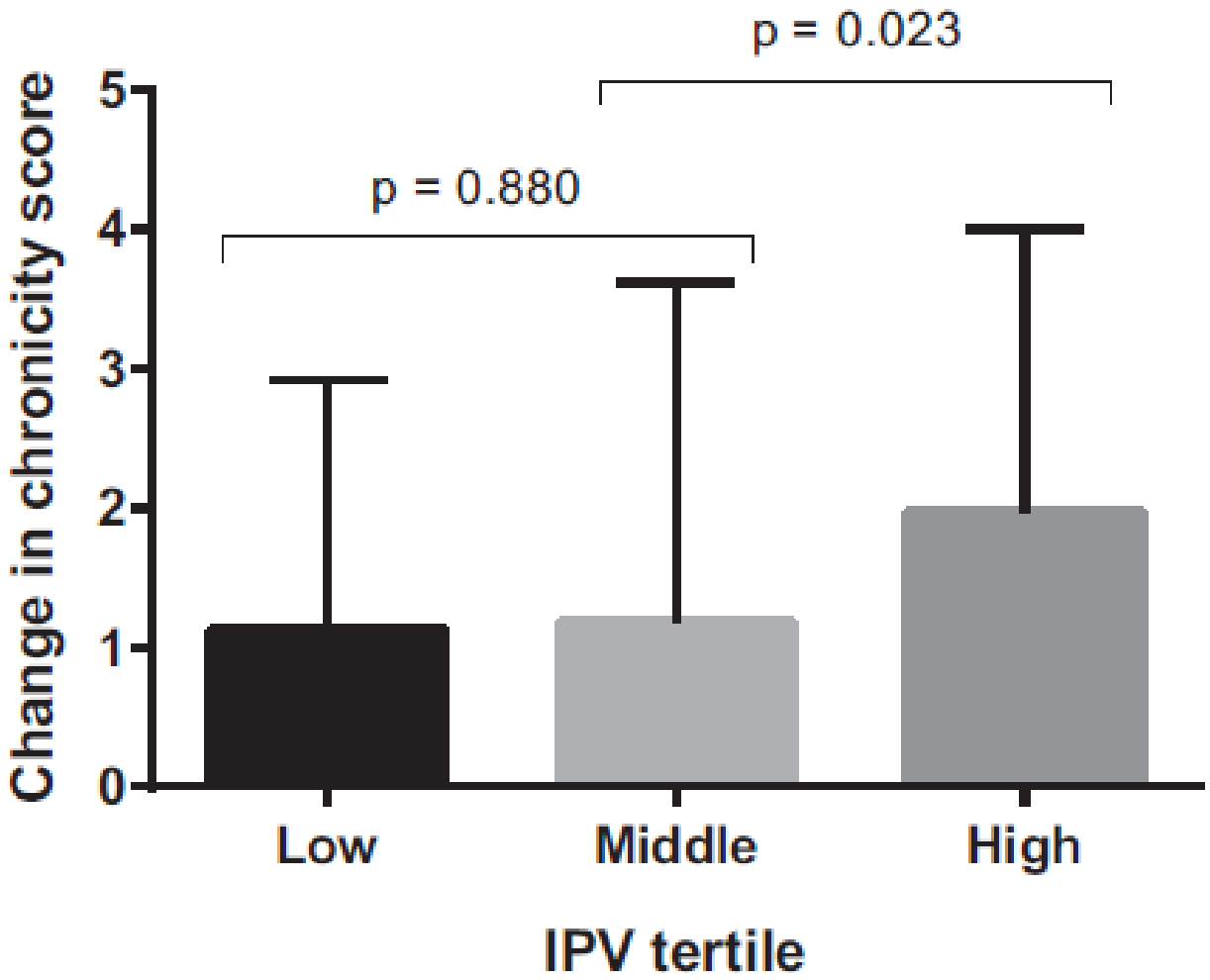

Rodrigo E et al. Transplantation 2016; 100: 2479

dnDSA detection according to CV (>30%, continuous line, <30% dashed line). Log-rank P = 0.007.

DSA: donor specific antibody

# Chronicity score between 3 and 24 months and variability between 6 and 12 m

Chronicity score : ci+ct+ah+cv+cg; n=220 patients

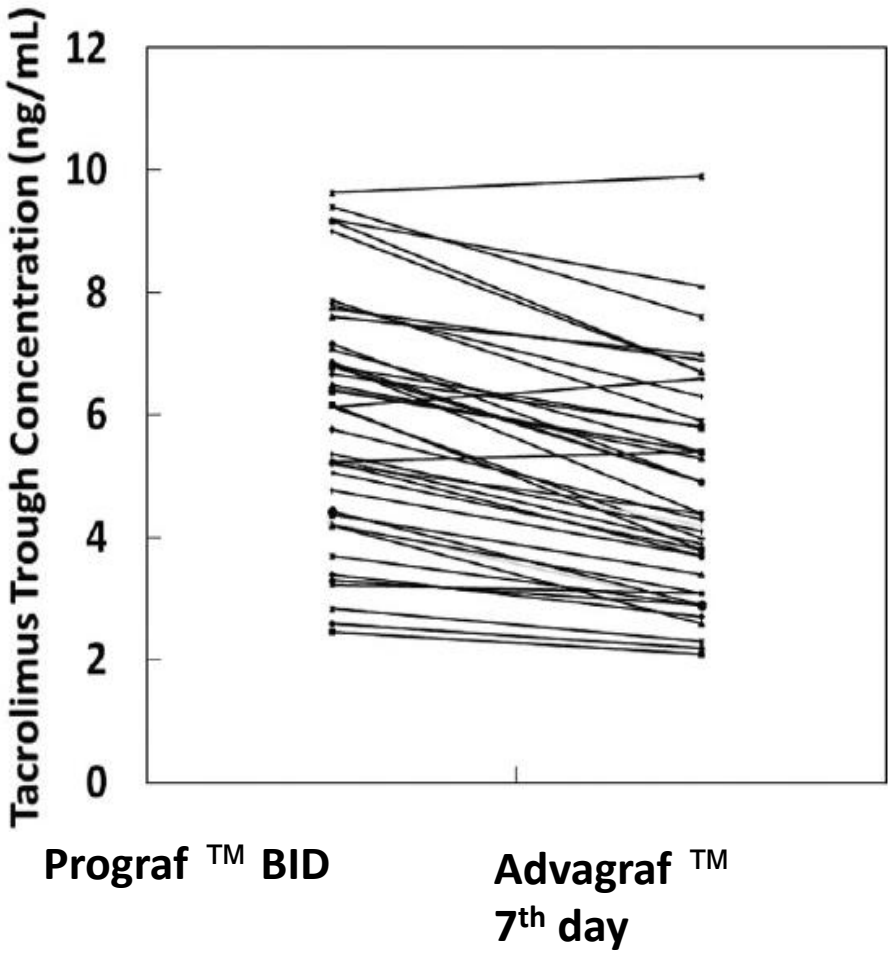


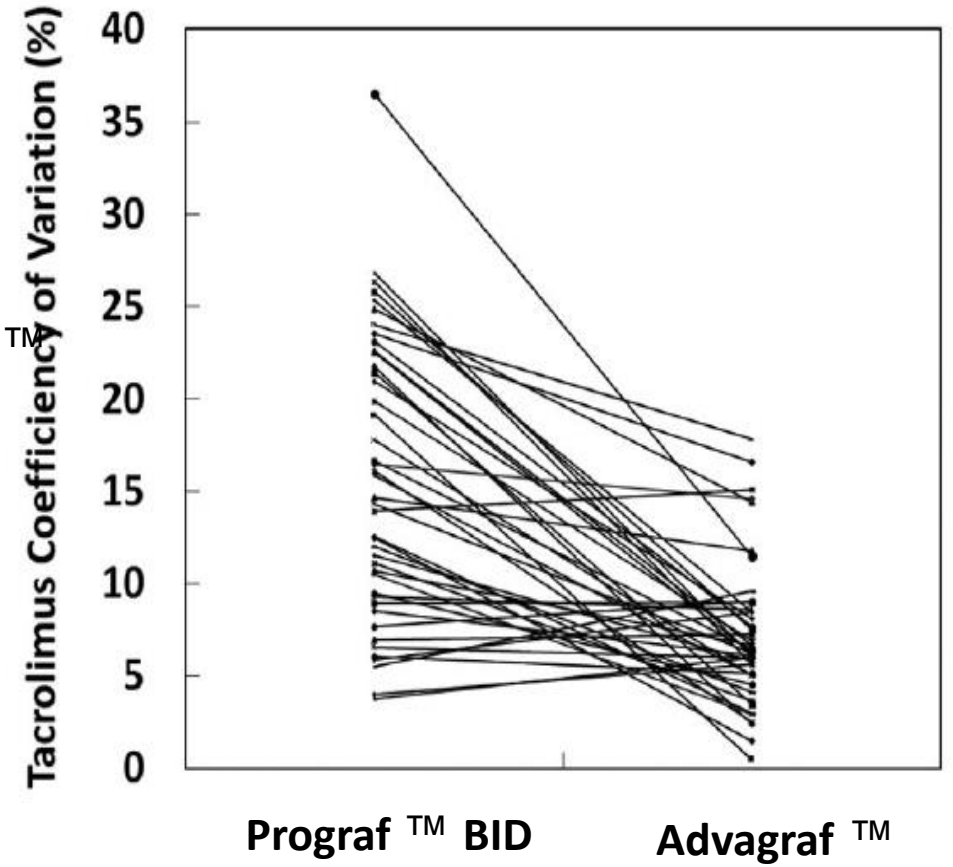

Ah: arteriolar hyaline thickening; cg: chronic transplant glomerulopathy; ci: interstitial fibrosis; ct: tubular atrophy; cv: fibrous intimal thickening

Vanhove T et al. Am J Transplant 2016; 16: 2954

# Converting from Prograf™ BID to Advagraf ™ reduces IPV

Follow up= 6.3 ± 4.8 years, (N=129)



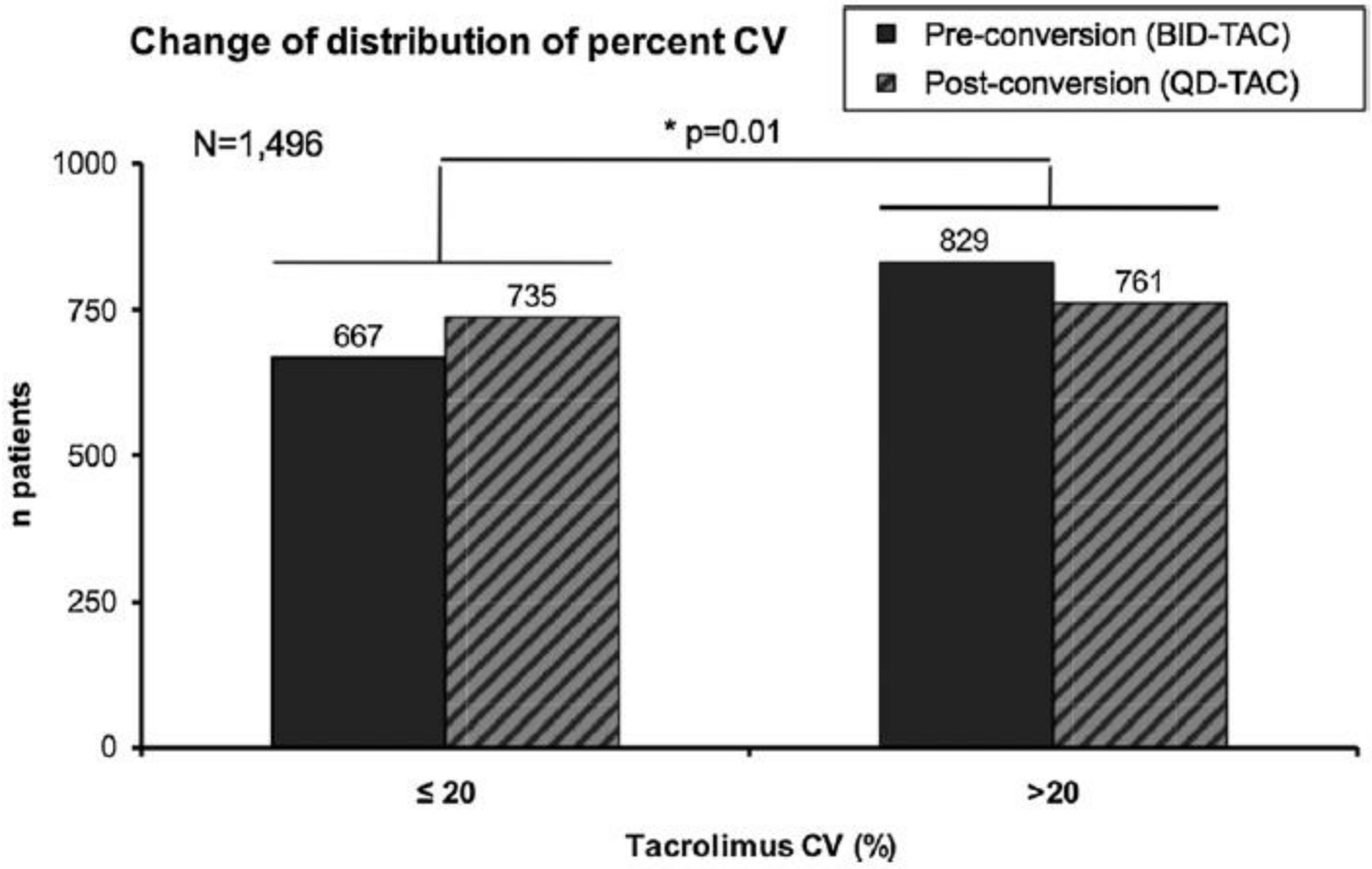

IPV: Intra – patients variability

Wu MJ et al. Transplantation 2011;92:648–652.

# CV before and after conversion from QD to BID-TAC

## % with CV > 20%

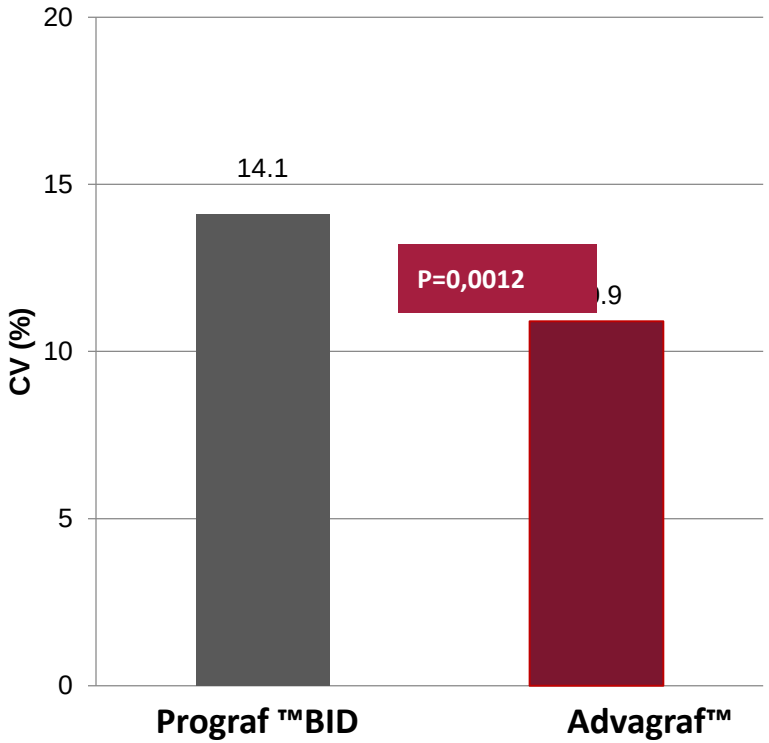
## n=1798

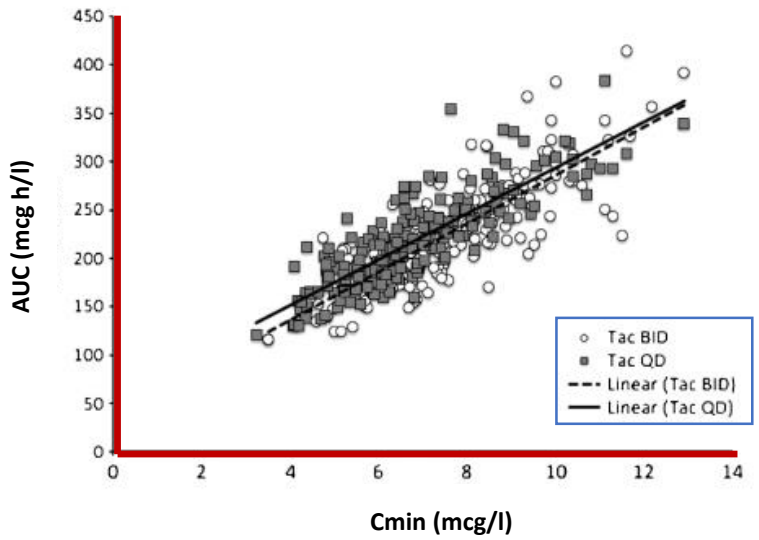



Guirado L, et al. Transplantation Direct 2015; 1(7): e24. DOI: 10.1097/TXD0000000000000536

# AUC var after Conversion  to prolonged TAC release

(n=40  patients, 5 AUC pre and 5 AUC post conversión)



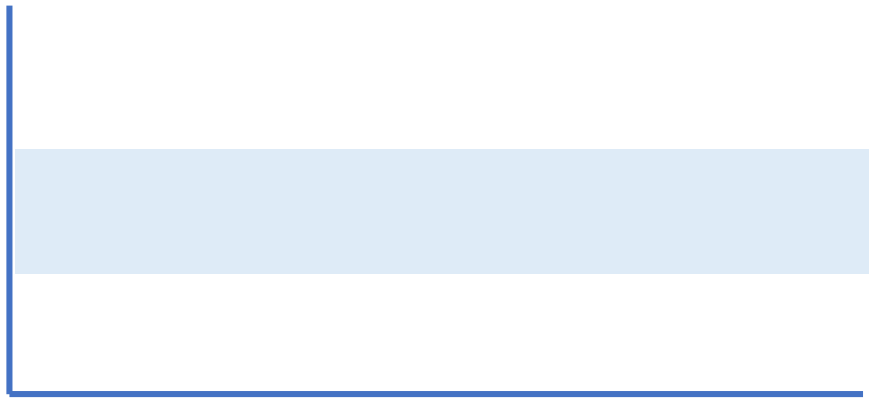




AUC: Area under curve, TAC:Tacrolimus

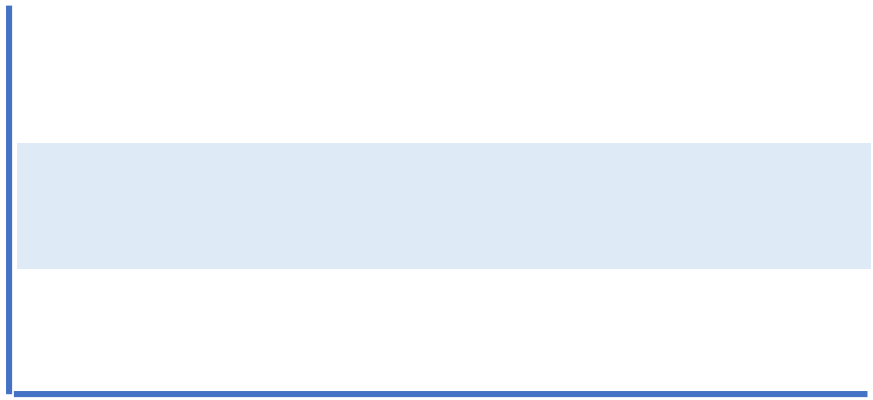
Stifft F et al.Transplantation  2014; 97: 775

# Same coefficient of variation differentTTR and mean

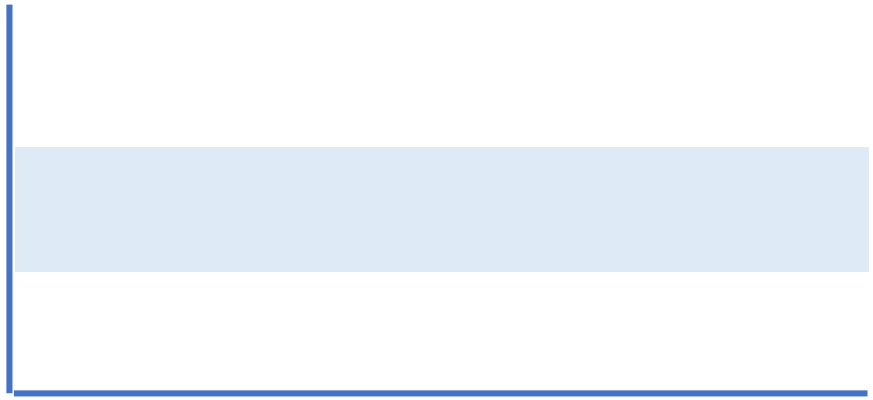
1



2



3



What is more determinant of outcome,

CV or TTR?

CV: Coefficient Of Variation, TTR: Time In Therapeutic Range

Figure made by the presenter

# Correlation between CV and TTR at 4 and 18 m

## 4m

| | CV-TAC |
|---|---|
| TTR | -0.476<br><0.001 |
| Above TR | 0.293<br>0.006 |
| Below TR | 0.338<br>0.002 |

## 18m

| | CV-TAC |
|---|---|
| TTR | -0.149<br>0.178 |
| Above TR | 0.111<br>0.318 |
| Below TR | 0.229<br>0.037 |

CV: Coefficient Of Variation, TTR: Time In Therapeutic Range

Chamoun B et alJ Clin Med 2021; 32(1):33

# Poor outcome in patients with high CV is due to low TTR

## n=538, follow up 4.1 y

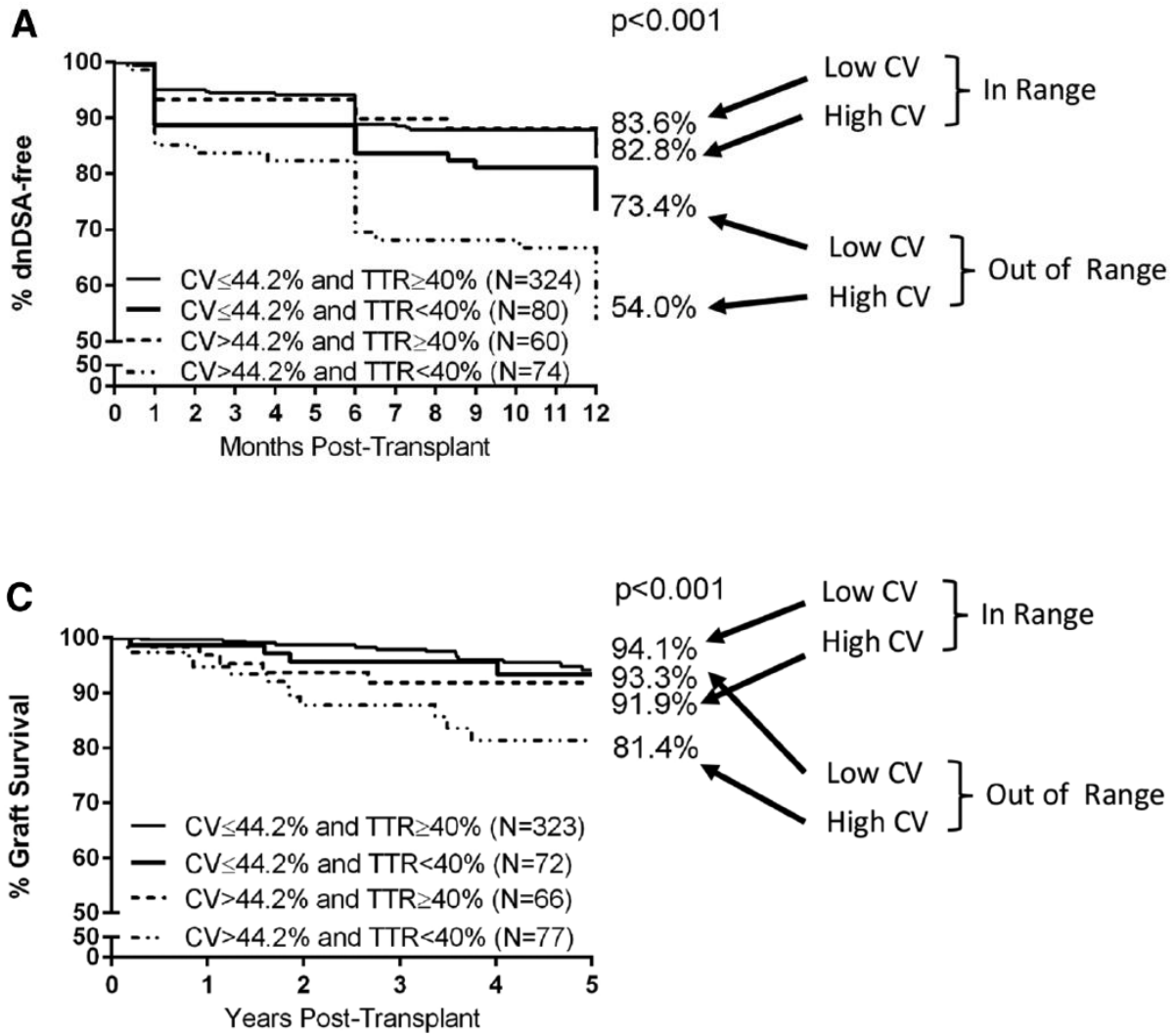
(CV and TTR calculated during the first y of follow up)

| | Covariate | Estimate (95% CI) | *P* |
|---|---|---|---|
| dnDSA | TTR | OR = 0.98 (0.97-0.99) | **0.002** |
| | CV | OR = 1.01 (0.99-1.02) | 0.268 |
| Acute rejection[b] | TTR | HR = 0.97 (0.96-0.98) | **<0.001** |
| | CV | HR = 1.00 (0.98-1.02) | 0.981 |
| Death-censored graft loss | TTR | HR = 0.99 (0.97-1.00) | 0.090 |
| | CV | HR = 1.03 (1.01-1.05) | **0.003** |

CV: Coefficient Of Variation, TTR: Time In Therapeutic Range

Davis S et al. Transplantation 2020; 104: 881

# High CV and Low TTR




CV: Coefficient Of Variation, TTR: Time In Therapeutic Range

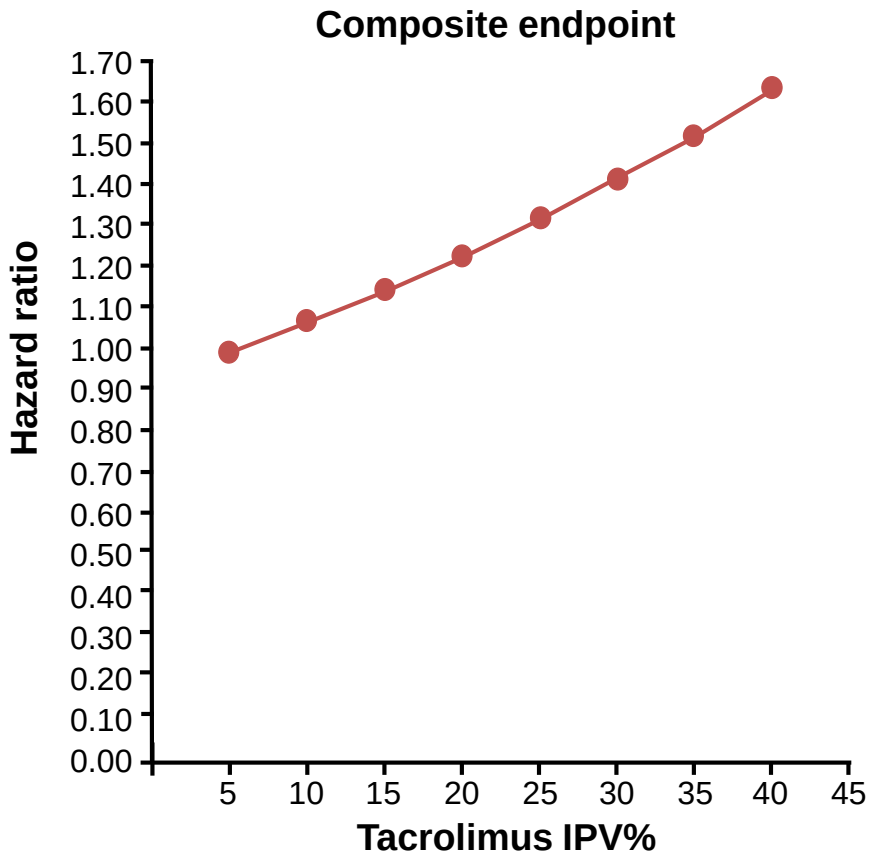
Davis S et al. Transplantation 2020; 104: 881

# High IPV is associated with worse long-term outcomes

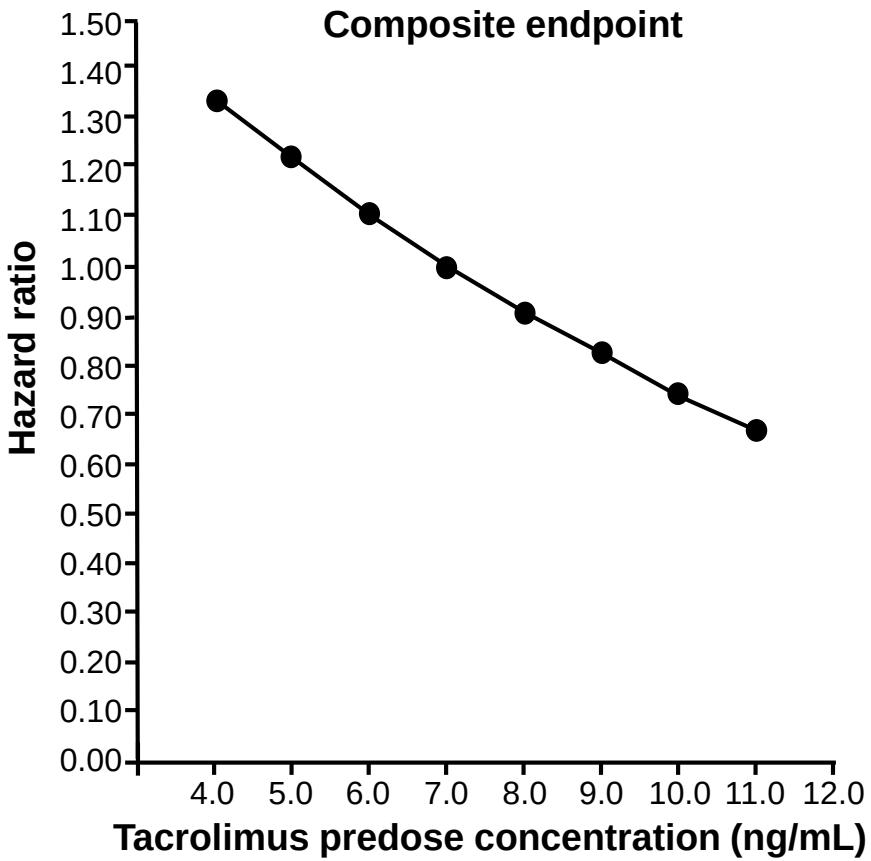
## Composite endpoint: Late biopsy-proven acute rejection, transplant glomerulopathy or doubling of serum creatinine, graft failure

808 renal transplant recipients transplanted between 2000 and 2010

(a)




(b)




IPV: intra patients variability

Calculated hazard ratios of the composite end point with increasing Tac IPV (a) and decreasing Tac predose concentrations (b).

Shuker N et al. Transpl Int 2016;29:1158–1167.

ADV vs PGF de novo

Therapeutic monitoring

TAC metabolism

Compliance

# TAC metabolism rate

## N=248 patients  Basiliximab+TAC+MMF+P

$$C/D\,ratio\,(ng/mL * 1/mg) = \frac{blood\,Tac\,trough\,level\,(ng/mL)}{daily\,Tac\,dose\,(mg)}$$

C/D ratio 1, 2, 3, 6, 12, 24 m

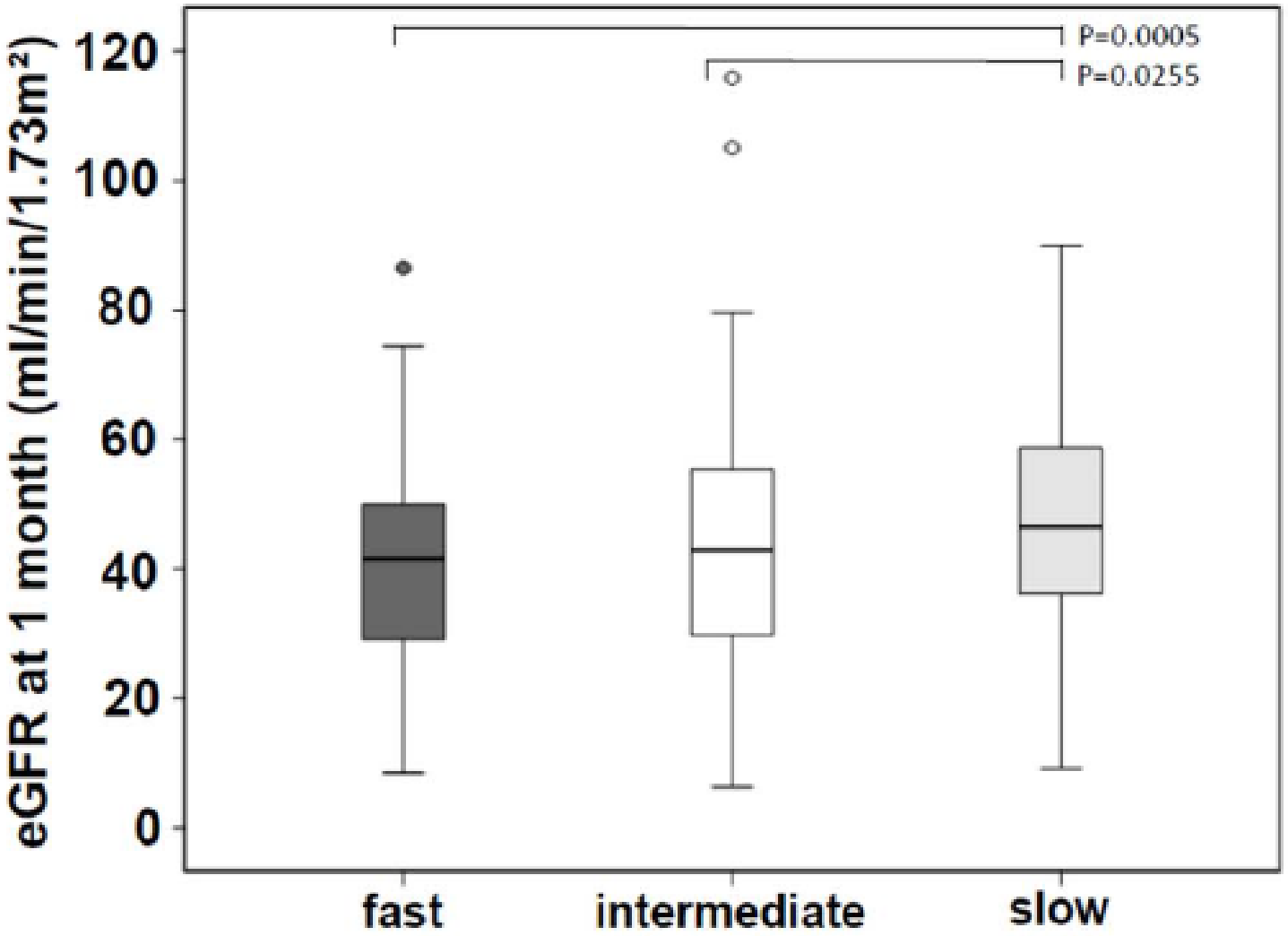
- Fast
- Intermediate
- Low

TAC:Tacrolimus ; MMF: Mycophenolate mofetil

Thölking G et al. Plos One )(10) e111128

# e GFR and C/D ratio

eGFR value comparison between the three metabolism groups




eGFR:estimated glomerular Filtration rate; C/D ratio: Concentration/Dose ratio

Thölking G et al. Plos One (10) e111128

# Out come and C/D ratio

Antibodies, HLA MM, DGF, infections and biopsy results

| | fast metabolizers (n = 122) | interm. metabolizers (n = 91) | slow metabolizers (n = 82) | P-value |
|---|---|---|---|---|
| PRA (>20%) | 2 (2%) | 3 (3%) | 2 (2%) | – |
| HLA MM | | | | |
| no HLA MM | 15 (12%) | 13 (14%) | 10 (12%) | |
| 1–3 HLA MM | 67 (55%) | 45 (50%) | 50 (61%) | 0.651 |
| 4–6 HLA MM | 40 (33%) | 33 (36%) | 22 (27%) | |
| DGF | 25 (21%) | 15 (17%) | 11 (13%) | 0.434 |
| CMV | | | | |
| CMV high risk | 30 (25%) | 16 (18%) | 20 (24%) | |
| CMV interm. risk | 77 (63%) | 61 (69%) | 51 (62%) | 0.784 |
| CMV low risk | 15 (12%) | 12 (13%) | 11 (13%) | |
| CMV infection | 15 (12%) | 11 (12%) | 5 (6%) | 0.292 |
| BK viremia | 8 (7%) | 7 (8%) | 1 (1%) | 0.11 |
| biopsy results | | | | |
| indication biopsies | 53 (43%) | 30 (33%) | 18 (22%) | 0.006 |
| TMR | 2 (2%) | 4 (4%) | 1 (1%) | – |
| AMR | 5 (4%) | 3 (3%) | 0 | – |
| CNI-nephrotoxicity | 13 (11%) | 2 (2%) | 2 (2%) | 0.015 |
| BK nephropathy | 5 (4%) | 0 | 0 | 0.024 |
| others | 28 (23%) | 21 (23%) | 15 (18%) | – |

C/D ratio: Concentration/Dose Ratio

Thölking G et al. Plos One (10) e111128

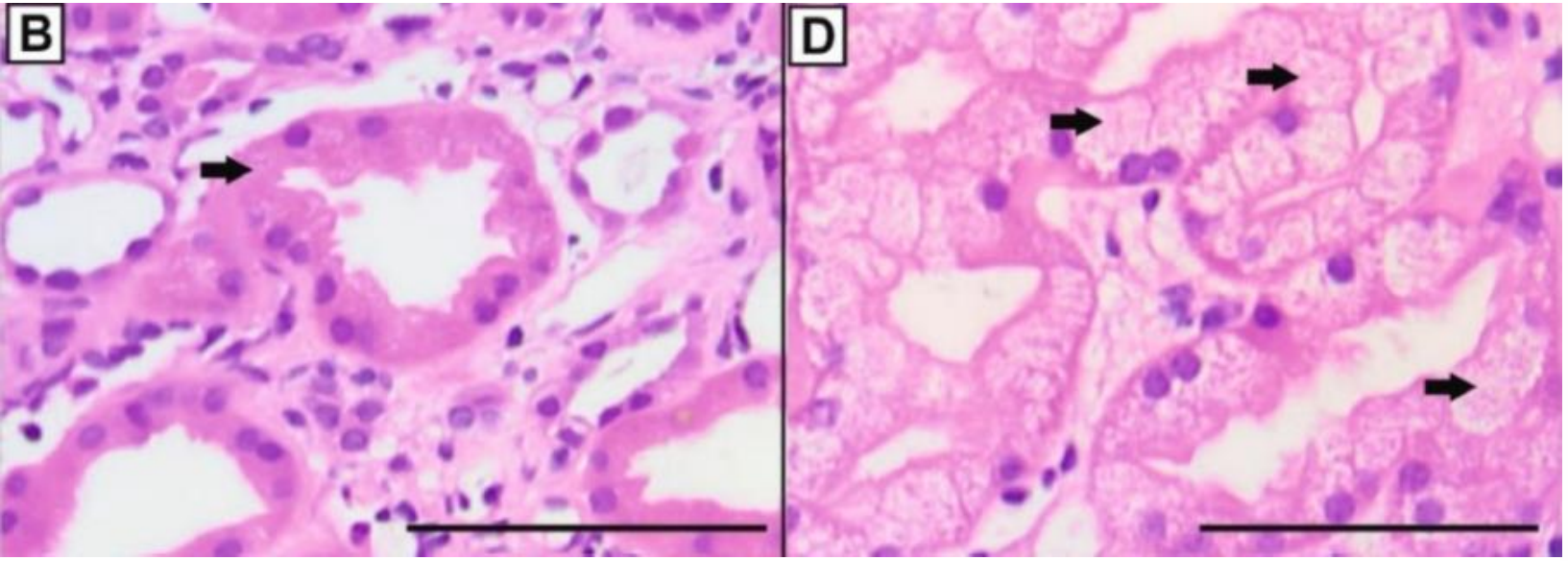
# Isometric vacuolization and C/D ratio

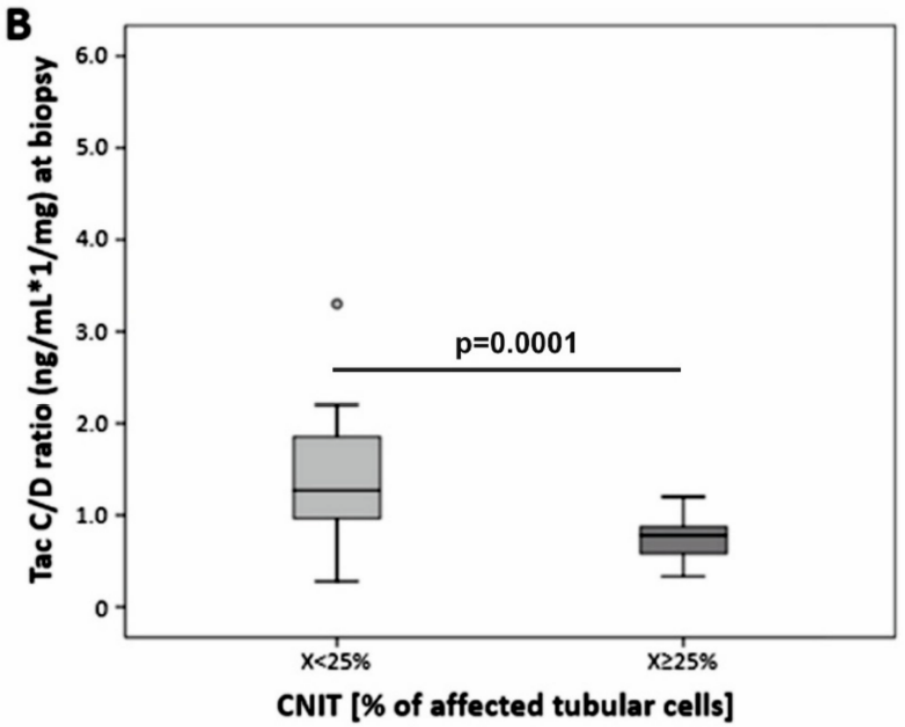
N= 55 consecutive biopsies

Isometric vacuolization

<25%

≥25%

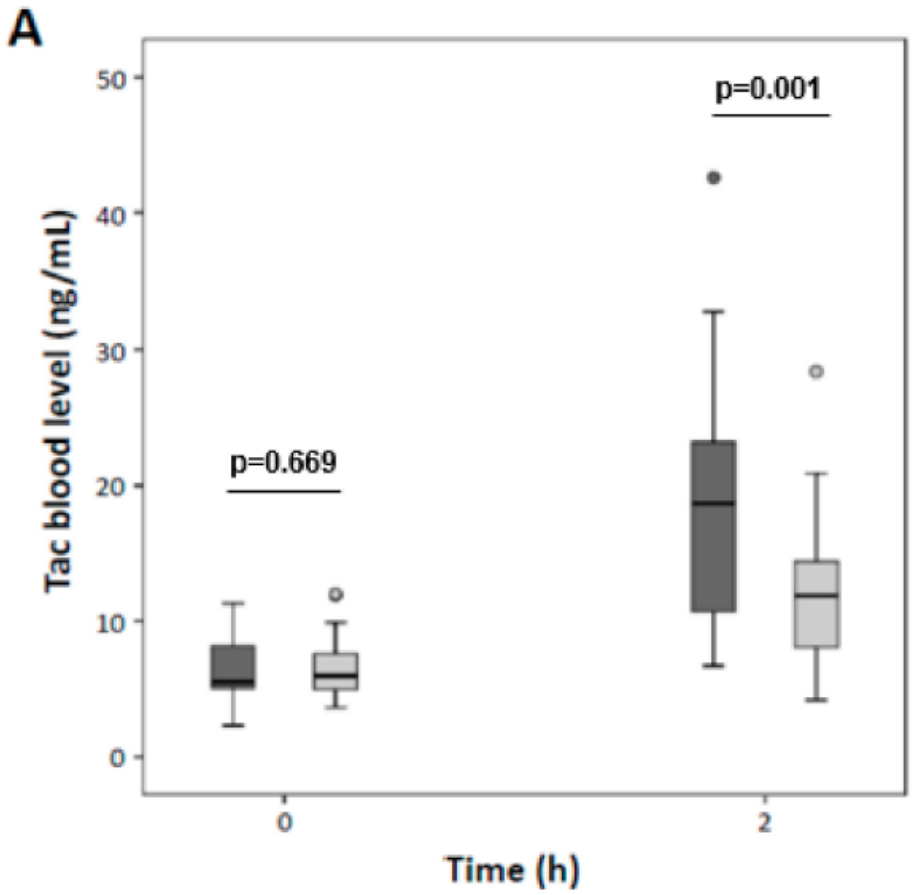


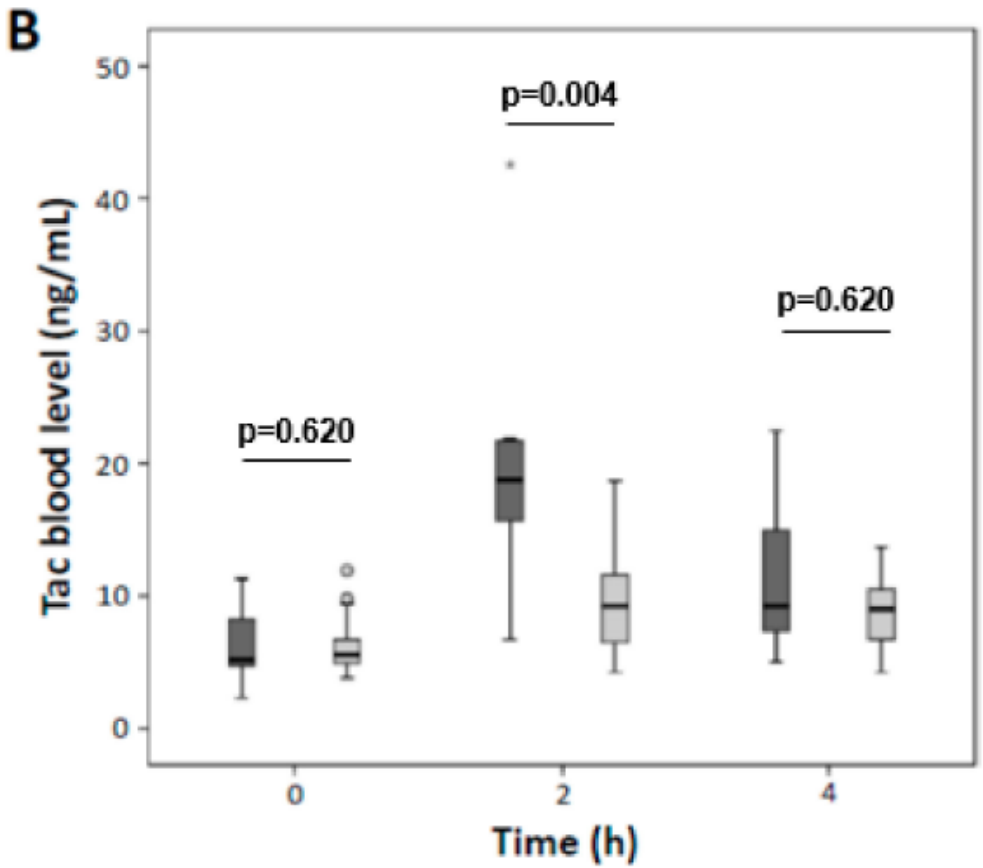

Thölking G et al. J Clin Med 2019; 8: 1586

# C2 in patients with high and low C/D ratio (< 1.05)
n=55

n=56




n=25




Thölking G et al. J Clin Med 2019; 8: 1586

# High TAC clearance and progression of IFTA

n= 504 pts

Basiliximab+TAC+MMF+P

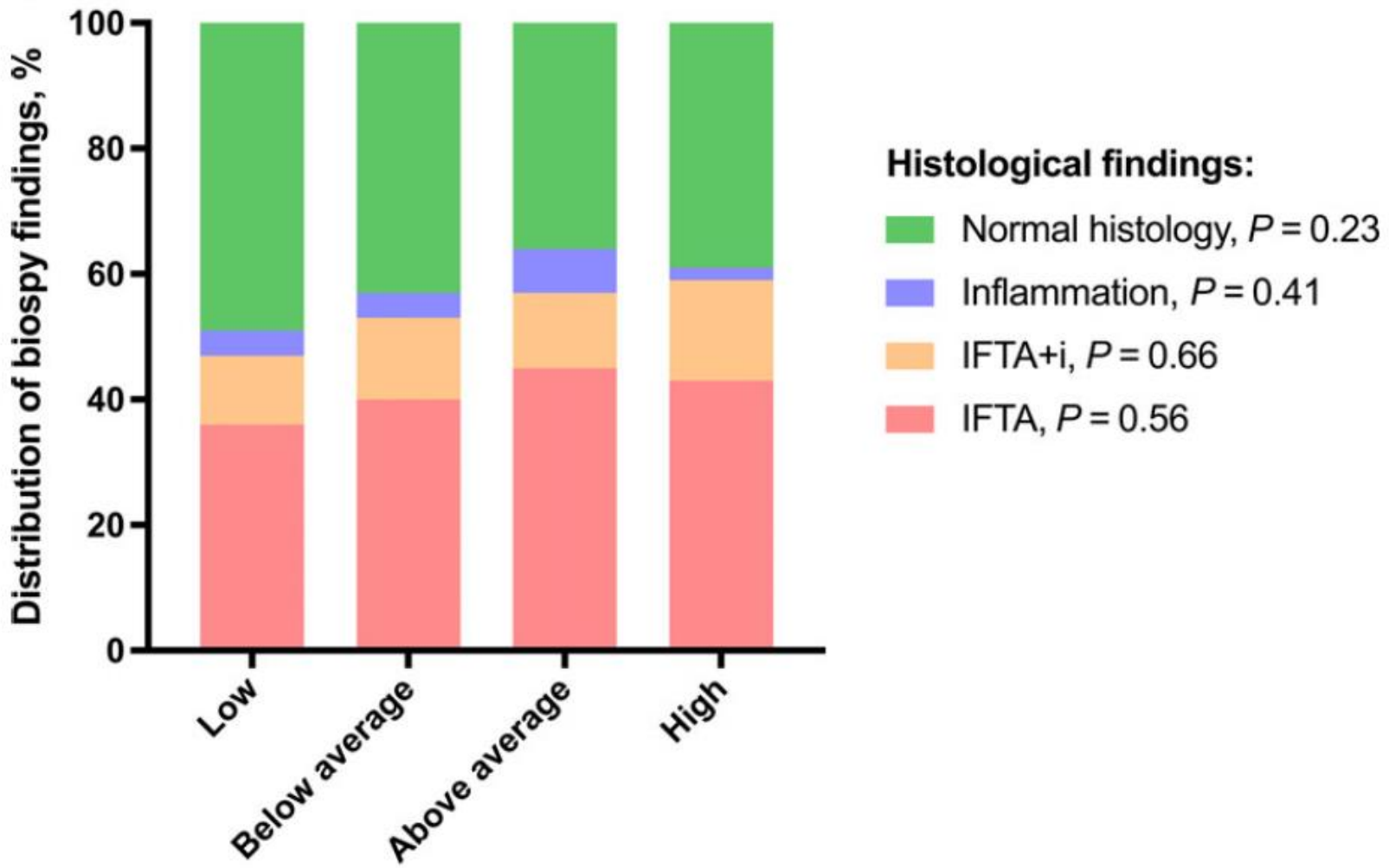
C/D ratio classified into quartiles


TAC:Tacrolimus, MMF: Mycophenolate mofetil, IFTA: renal interstitial fibrosis and tubular atrophy; C/D ratio: Concentration/ Dose ratio

Egeland RJ et al. Transplant Int 2019; 32: 357

# High TAC clearance and progression of IFTA

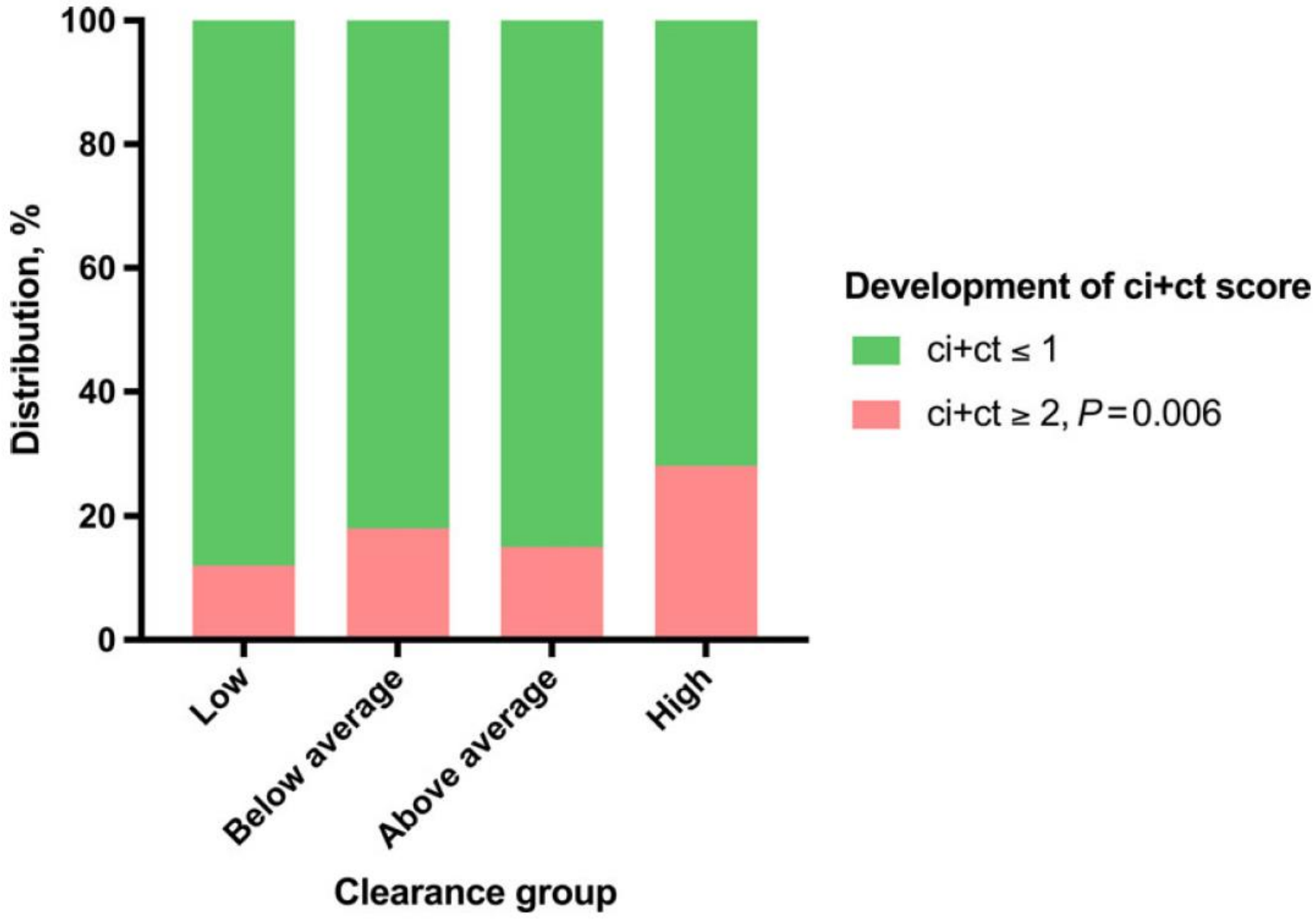
## Basal biopsy at 7 weeks




TAC:Tacrolimus, IFTA: renal interstitial fibrosis and tubular atrophy

Egeland RJ et al. Transplant Int 2019; 32: 357

# High TAC clearance and progression of IFTA




TAC:Tacrolimus, IFTA: renal interstitial fibrosis and tubular atrophy

Egeland RJ et al. Transplant Int 2019; 32: 357

# Therapeutic drug monitoring at 4 and 18 months N=85

| Variable | First biopsy | Second biopsy | p-value |
|---|---|---|---|
| Time of biopsy (months) | 4.2 ± 1.9 | 17.3 ± 3.6 | n.a. |
| Tacrolimus dose (mg/day) | 6.6 ± 3.9 | 4.9 ± 3.1 | **0.001** |
| TAC-$C_0$ (ng/mL) | 9.6 ± 2.4 | 8.5 ± 2.3 | **0.002** |
| CV of TAC-$C_0$ (%) | 31 ± 13 | 20 ± 14 | **0.001** |
| Time in TR (%) | 55 ± 24 | 70 ± 25 | **0.001** |
| Time above TR (%) | 35 ± 25 | 26 ± 29 | 0.066 |
| Time below TR (%) | 10 ± 13 | 4 ± 11 | **0.004** |
| C/D (ng/mL/mg) | 2.00 ± 1.42 | 2.19 ± 1.02 | 0.119 |

Clinical data at the time of the first and second surveillance biopsies of the studied cohort

Chamoun B et al. J Clin Med 2021; 10(1):141

# Inflammation at early and late BX

| Variable | No inflammation (n=66) | Inflammation (n=19) | p-value |
|---|---|---|---|
| **First biopsy** | | | |
| TAC-$C_0$ (ng/mL) | 10.0 ± 2.4 | 8.3 ± 2.2 | **0.007** |
| **Second Biopsy** | | | |
| Time below TR (%) | 3 ± 10 | 12 ± 15 | **0.005** |

Chamoun B et al. J Clin Med 2021; 10(1):141

# Progression of fibrosis

| Variable | No IFTA progression | IFTA progression | p |
|---|---|---|---|
| Mean C/D (ng/mL/mg) | 2.3 ± 1.3 | 1.7 ± 0.7 | **0.019** |

Chamoun B et al. J Clin Med 2021; 10(1):141

ADV vs PGF de novo

Therapeutic monitoring

TAC metabolism

Compliance

# Morisky scale yes (0) and no (1)

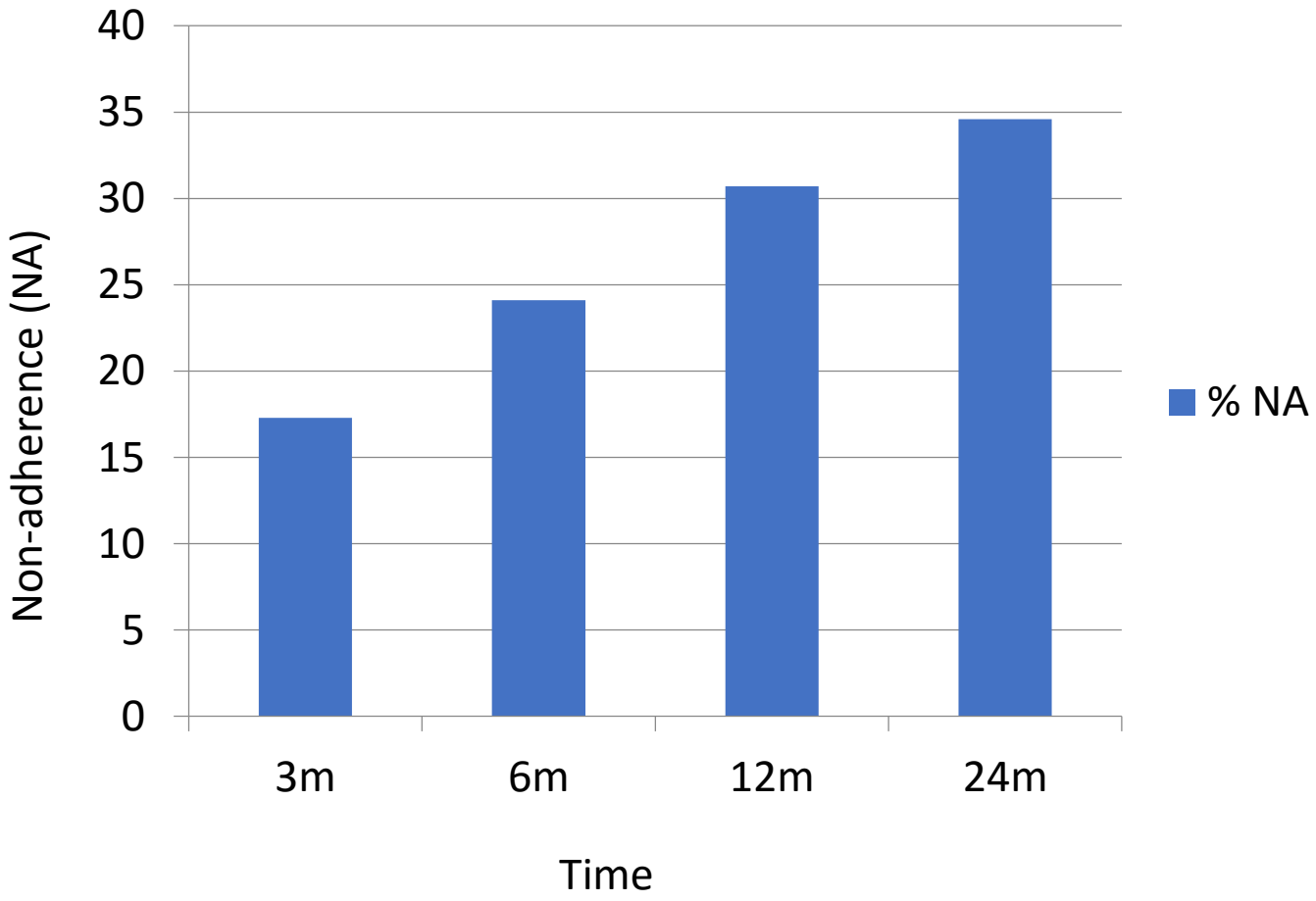
| MMAS-4 | Medication-taking Adherence Scale (MMAS, four-item scale) |
|---|---|
| Do you ever forget to take your medicine? | |
| Are you careless at times about taking your medicine? | |
| Sometimes when you feel worse when you take the medicine, do you stop taking it? | |
| When you feel better do you sometimes stop taking your medicine? | |

| Adherence | MMAS-4 Score |
|---|---|
| High Adherence | 0 |
| Medium Adherence | 1-2 |
| Low Adherence | 3-4 |

Couzi et al  et al. Transplantation 2013; 95: 326

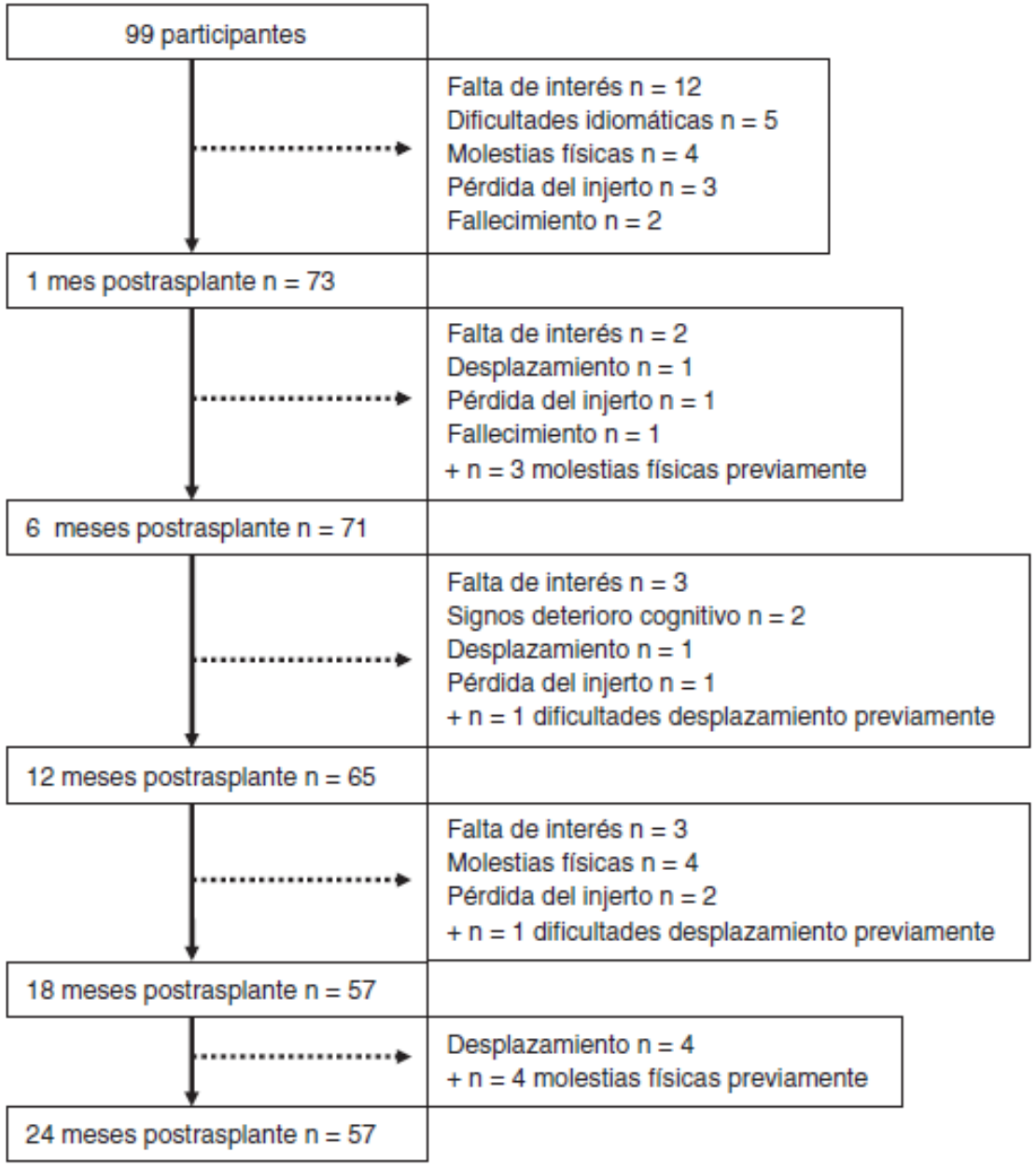
# Prevalence of non-adherence

N=312 pts. : Morisky scale > 0



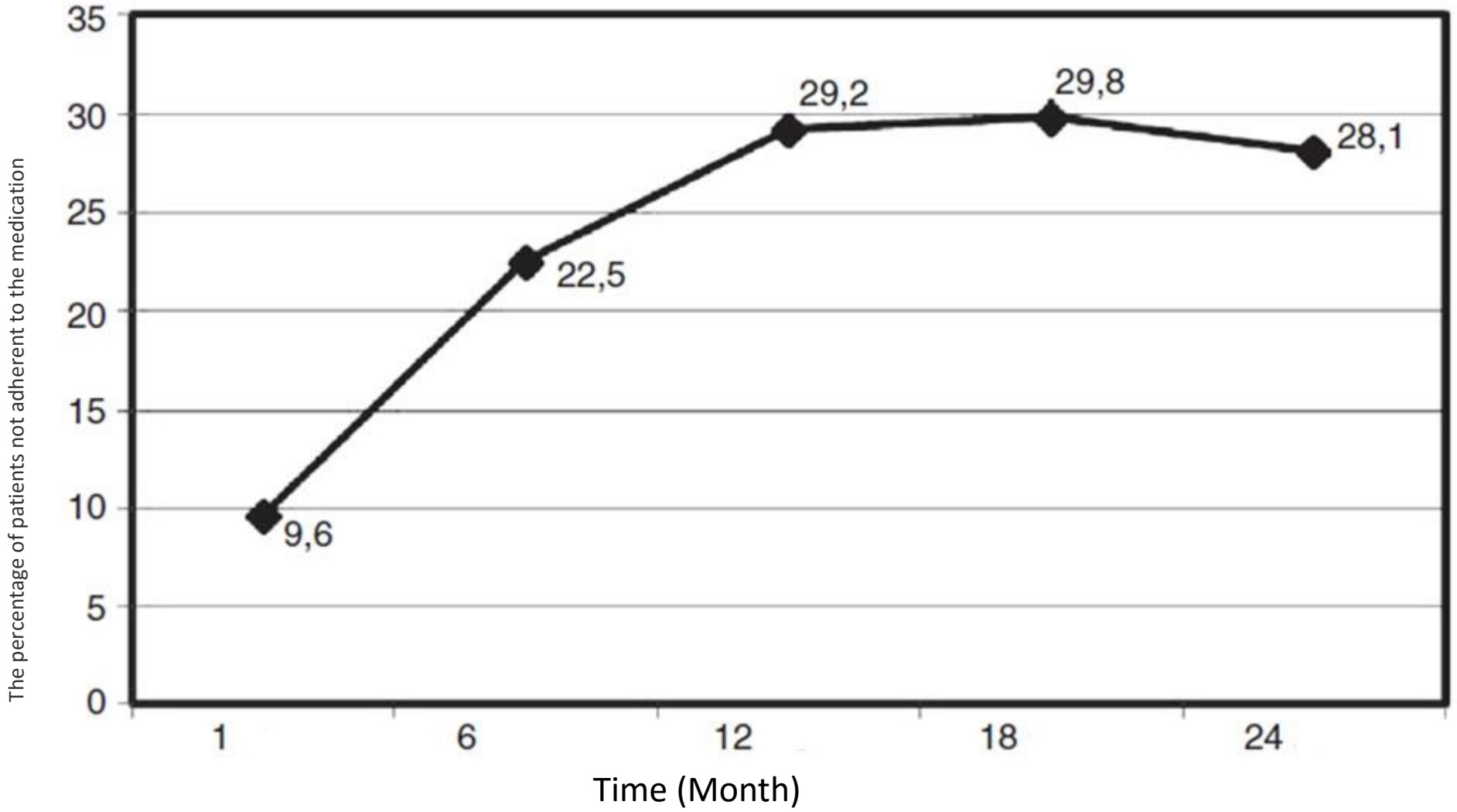

Couzi et al  et al. Transplantation 2013; 95: 326

# Adherence to treatment




Costa Requena G y cols . Rev Calidad Asisitencial 2017; 32(1):33

# Non compliance: SMAQ questionnare



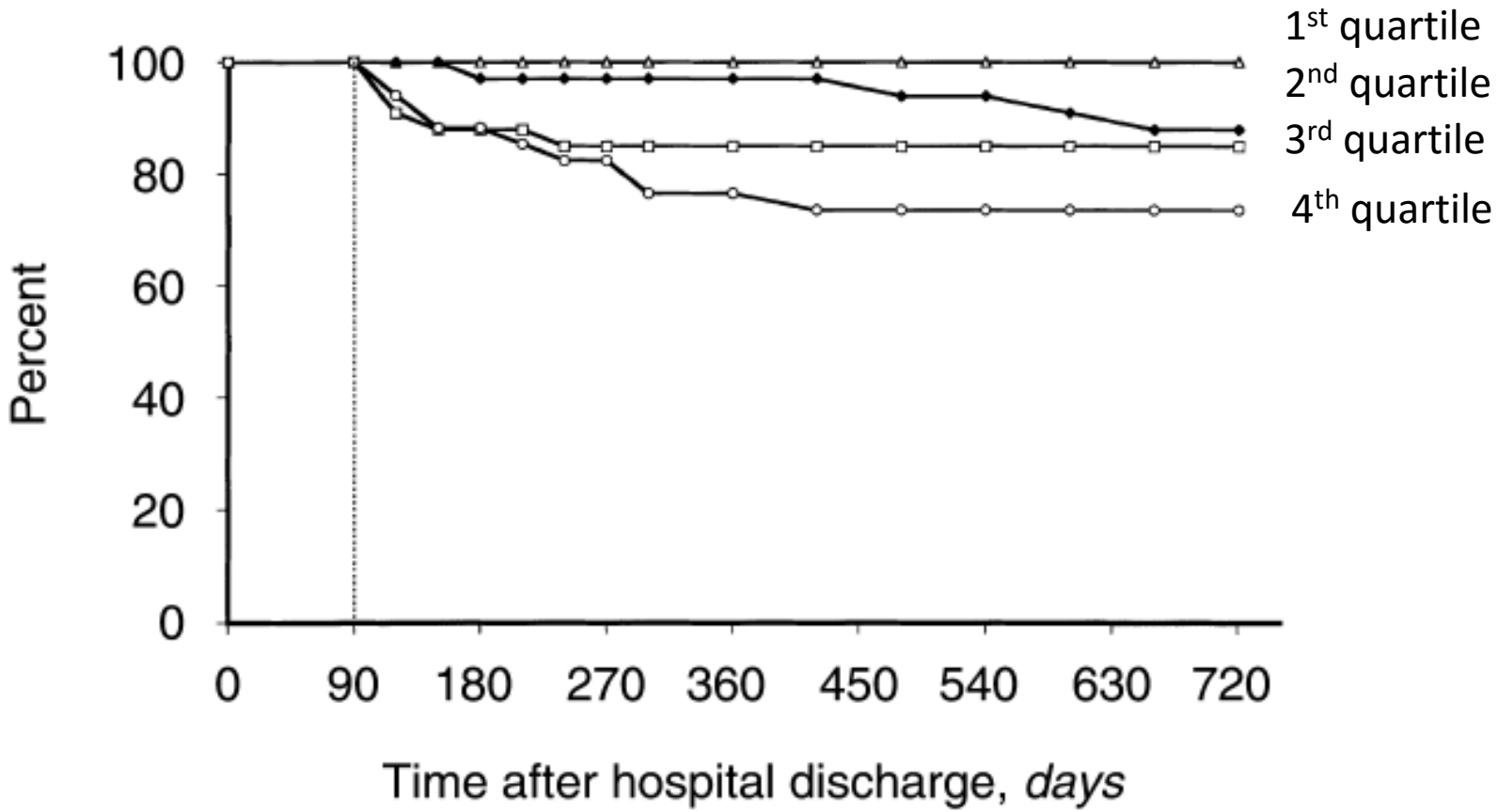

SMAQ: Simplified Medication Adherence Questionnaire

Costa Requena G y cols . Rev Calidad Asisitencial 2017; 32(1):33

# Electronic monitoring of no-compliance

180 AZA treated pts classified according to quartiles of compliance and AR

Rejection free survival after 90 days of TX

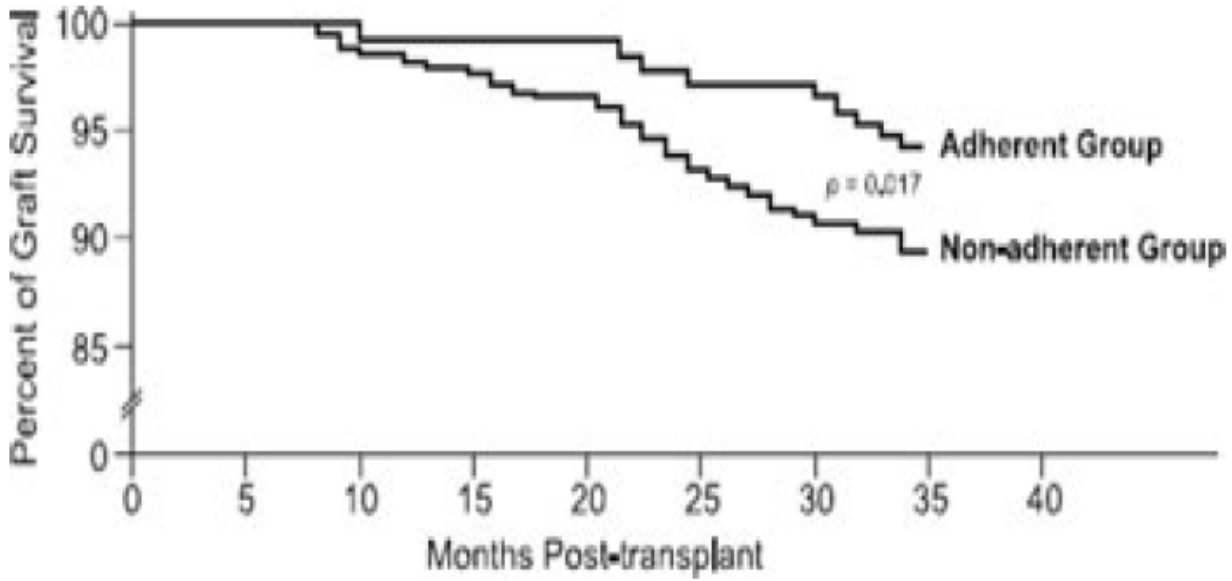



AZA: Azathioprine

Nevins TE et al. Kidney int 2001; 60: 1565

# Non adherence and graft survival

## n=877 (medication / possesion ratio)

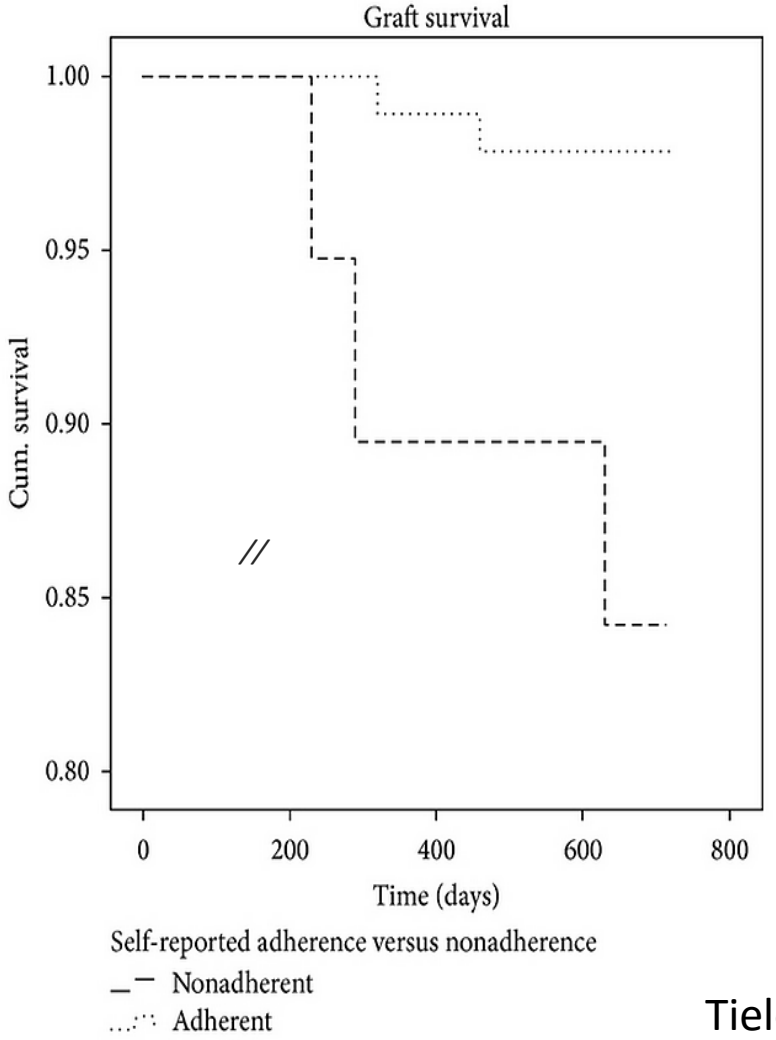



Kaplan–Meier estimates of graft survival in the adherent and nonadherent groups during the 36-month post transplant period.

Crisholm_Burns MA et al. Am J Transplant 2009; 9: 2497

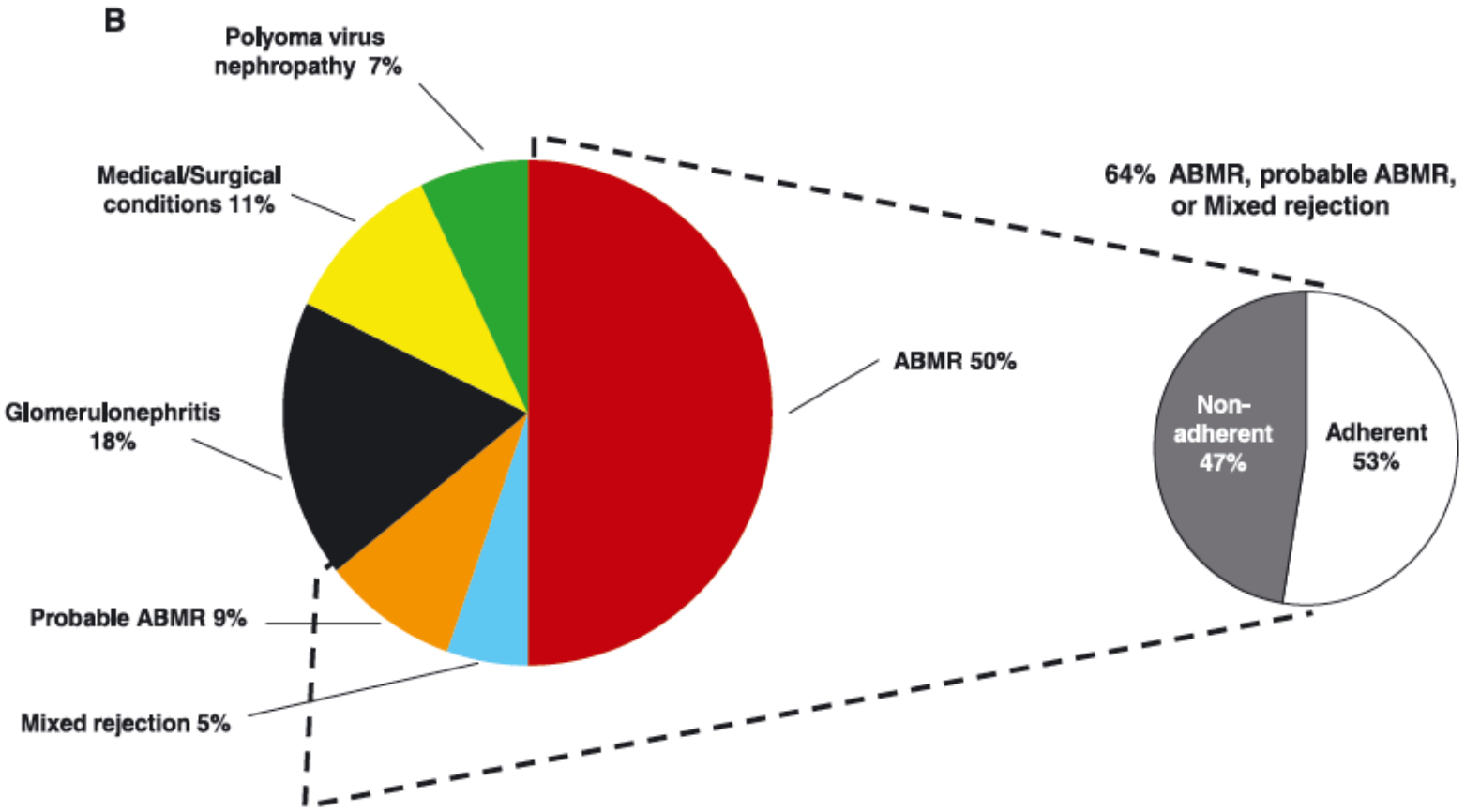
# Non-adherence is associated with poor graft survival in kidney transplantation

Kaplan-Meier graft survival. The non-adherent group consisted of 19 patients (3 graft failures) and the adherent group consisted of 94 patients (2 graft failures)




Tielen M et al. J Transplant 2014; Article 675301.

# Cause of graft failure and non adherence




Sellares J et al. Am J Transplant 2012; 12: 388-399.

# Factors associated with non-adherence

Socio-economic factors

financial difficulties / lack of transportation

Health organization barriers

limited amount of time/patient, staff rotation

Disease related factors

depression and anxiety

Therapy related factors

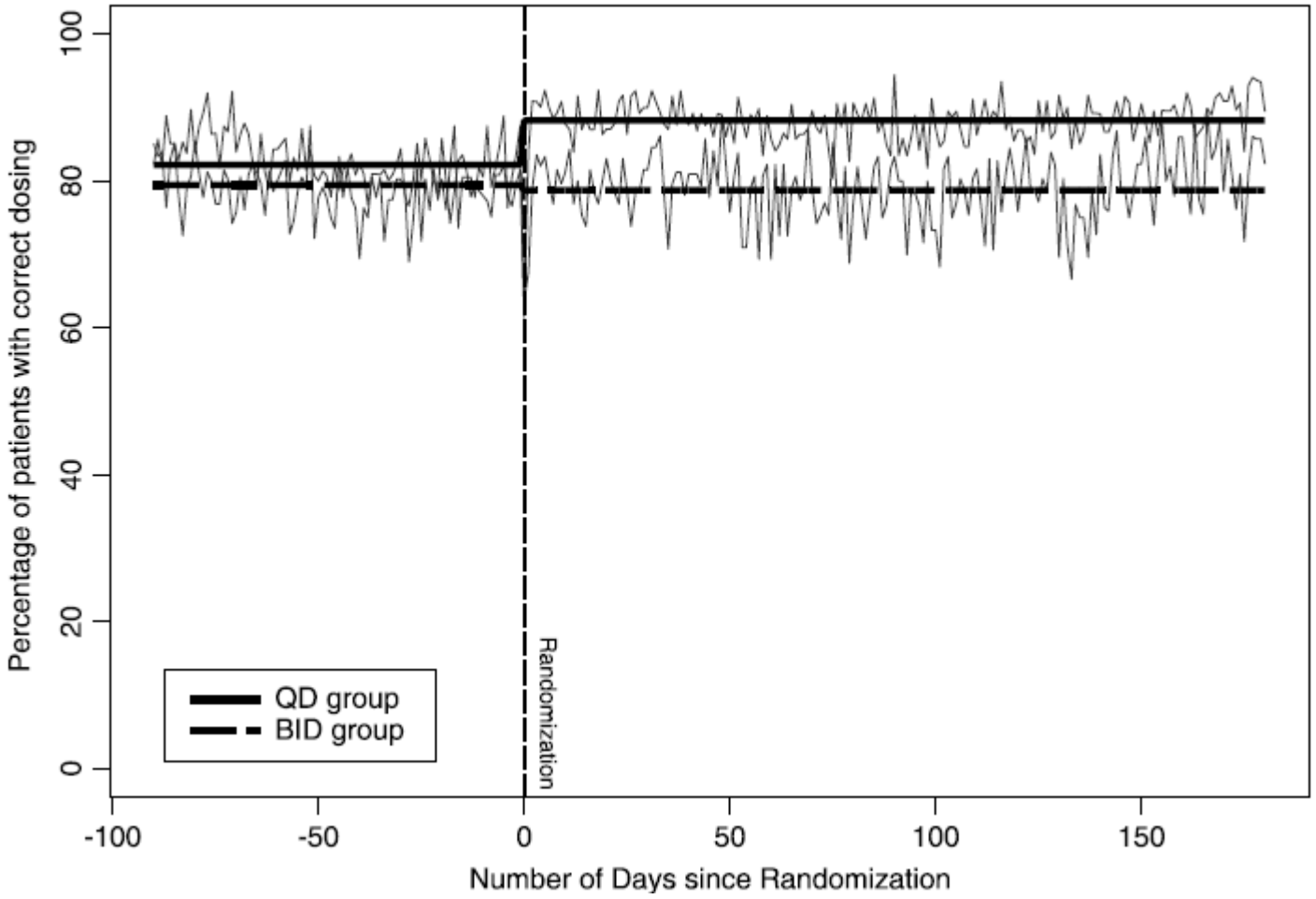
side effects of drugs, complex dose regimens

Patient related factors

communication barriers, health attitudes
health beliefs and literacy

Moreso F et al. Transplant Res  Risk Management 2015; 7: 27

# Improvements in correct dosing after conversion from TAC to ADV (n=219 pts) ADMIRAD study

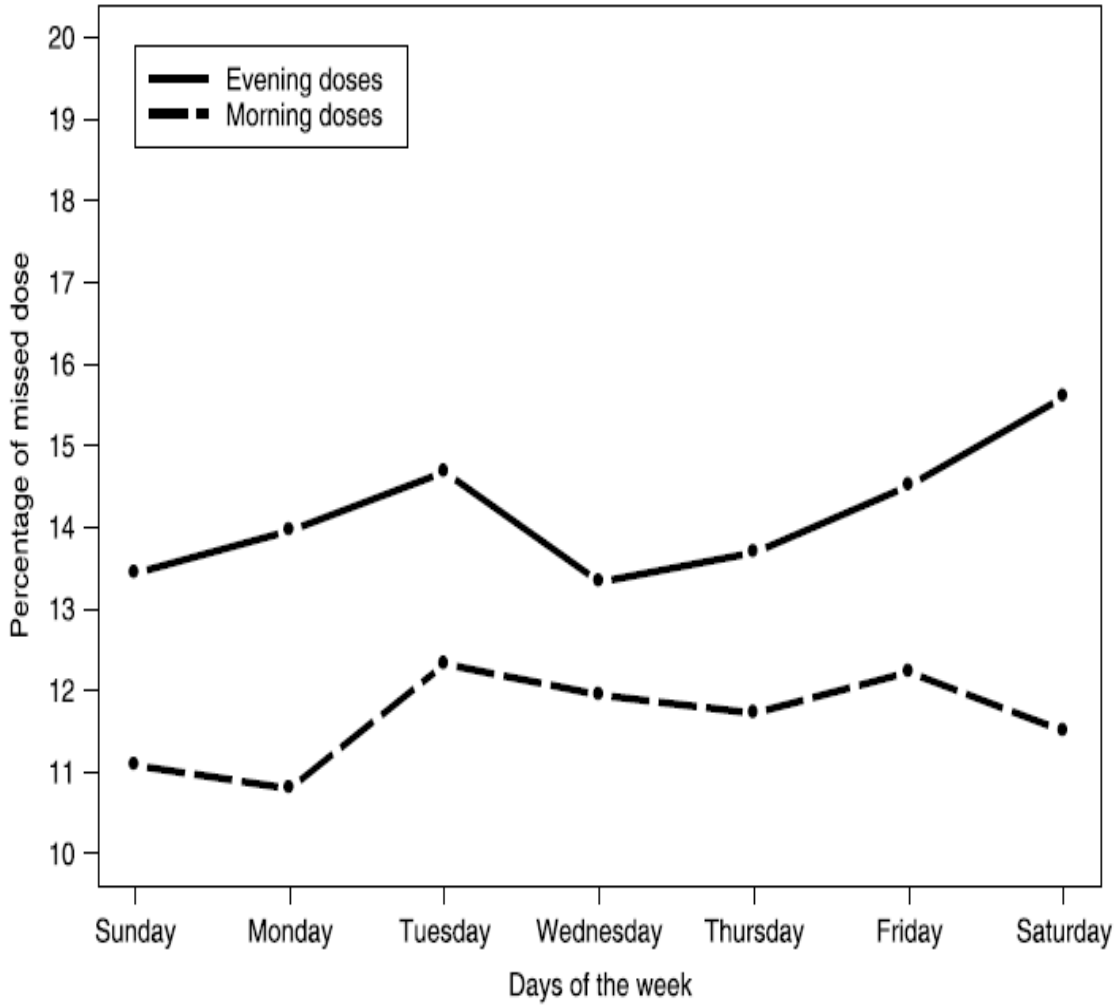



The implementation of each dosing regimen represented by the day-to-day

TAC: Tacrolimus, ADV: Advagraf

Kuypers et al. Transplantation 2013; 95: 333

# Percentage of missed doses by days of the week and morning/evening doses for tacrolimus BID

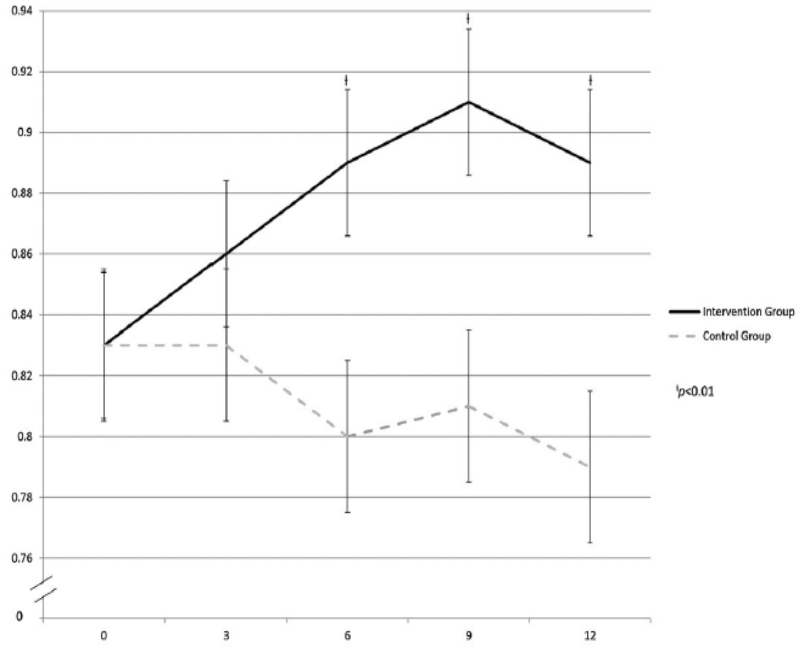



BID: Twice daily

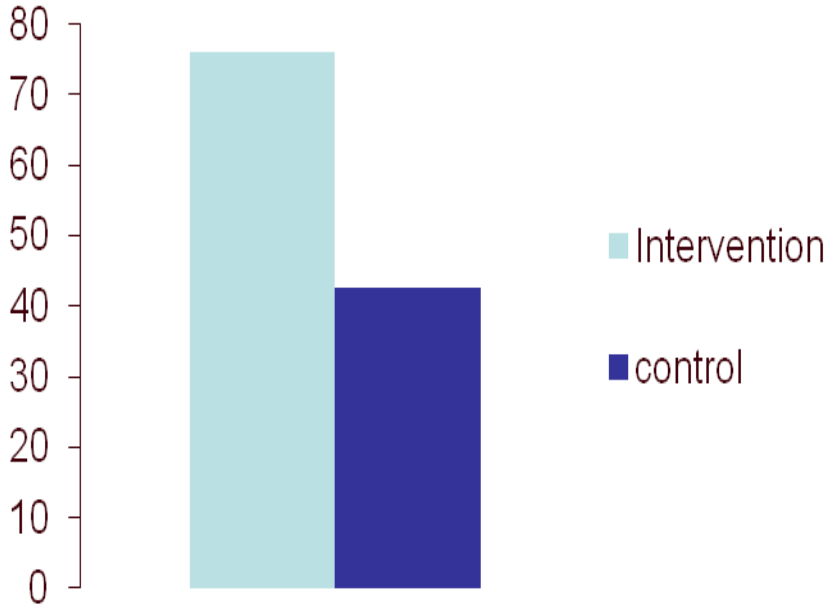
Kuypers DRJ et al. Transplantation 2013;95:333–340.

# Prospective randomized study: adherence contract vs conventional follow up

Adherence (pharmacy refill records)




Probability (%) NOT to be hospitalized



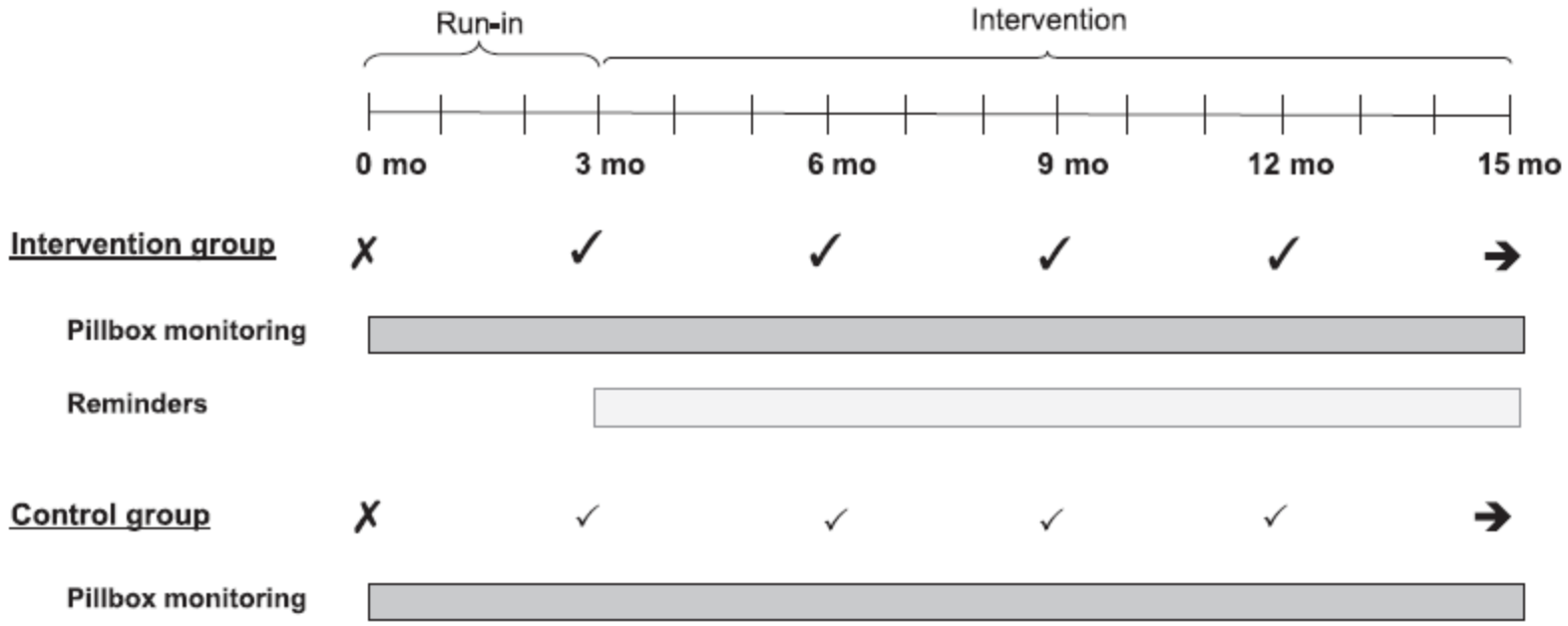

Immunosuppressant therapy (IST) adherence rates in the intervention group compared to the control group.

Chisholm-Burns MA et al. Am J Transplant 2013; 13: 2364.

# Randomized trial of a multicomponent intervention to promote medication adherence

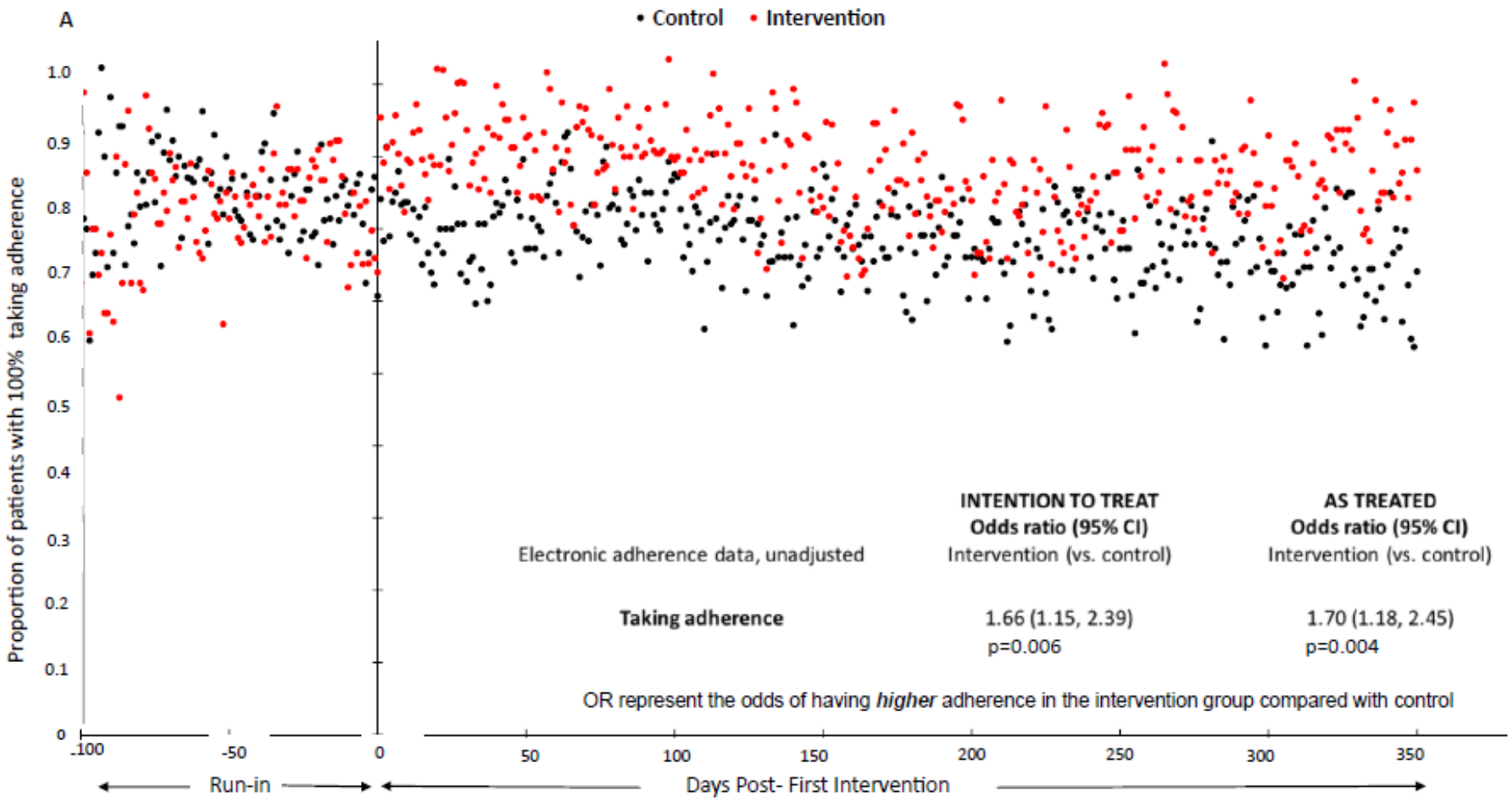
## The Teen Adherence in Kidney Transplant Effectiveness of intervention trial (TAKE IT)

## Intervention 81, control 88




Bethany J et al. Am J Kidney Dis 2018; 72: 30

# Taking adherence

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# Conclusions

ADV de novo same efficacy as PGF de novo

TAC levels should be > 5 ng/ml if the patient is taking MMF2g/d
TAC levels should be > 7 ng/ml if the patient is taking MMF 1g/d

High VAR and time below TR is associated with poorer outcome

High C/D is associated with nephrotoxiciy

Non-adherence decreases after slow-release TAC conversion and multicompetent intervention

ADV: Advagraf; PGF: Prograf, MMF: mycophenolate Mofetil; VAR: Variability; **TR**:Therapeutic Range; C/D: Concentration/Dose

- For full prescribing information of Prograf ™ and Advagraf ™ please refer to Astellas medical representative.
- Adverse events should be reported. Please report adverse events to
- pv@apint-ne.com or safety@behestan-mfg.com
- Phone number is: +982186056520

- Advagraf Caps all strength- SmPC- IR- en- Mar 2020
- Prograf Caps all strength-SmPC-IR-en-Sep 2019