Erasmus MC
University Medical Center Rotterdam

Use of tacrolimus to optimize long term outcomes after kidney transplantation

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Iran, Feb 18, 2021

Disclosures

Name:

Teun van Gelder, MD, Erasmus Medical Center Rotterdam, Netherlands

Commercial Interests & Nature of Relationships:

- Roche, Novartis, Astellas, Chiesi, Roche Diagnostics, Thermo Fisher: Consultant/Speaker received honoraria
- Chiesi and Astellas: Research Grant Support, study on transplant related diseases

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N ENGL J MED 351;26 WWW.NEJM.ORG DECEMBER 23, 2004

MEDICAL HISTORY

Transplantation — A Medical Miracle of the 20th Century

Peter J. Morris, F.R.S.

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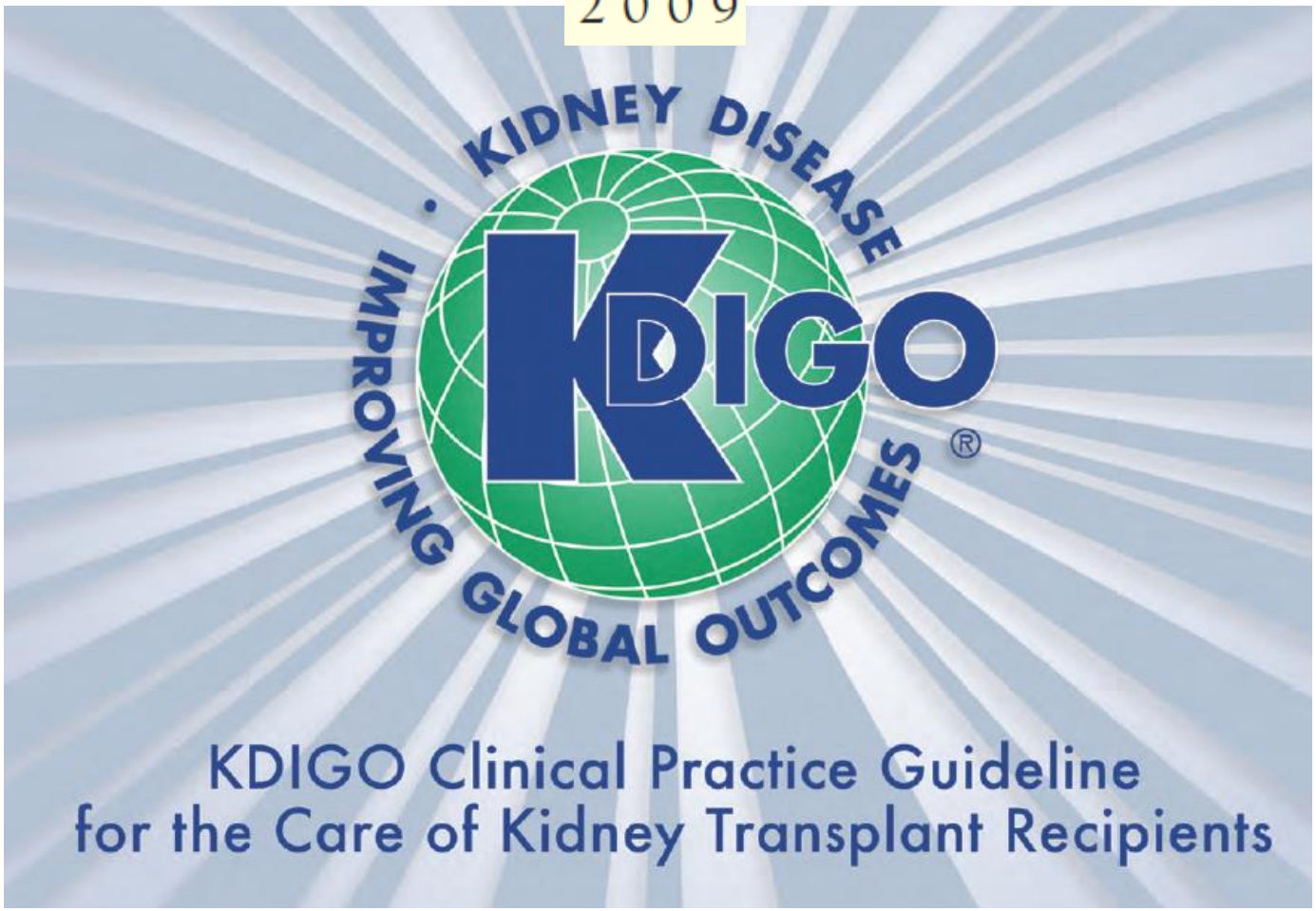
American Journal of Transplantation

2009



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Chapter 2: Initial Maintenance Immunosuppressive Medications

2.1: We recommend using a combination of immunosuppressive medications as maintenance therapy including a CNI and an antiproliferative agent, with or without corticosteroids. *(1B)*

2.2: We suggest that tacrolimus be the first-line CNI used. *(2A)*

2.2.1: We suggest that tacrolimus *or* CsA be started before or at the time of transplantation, rather than delayed until the onset of graft function. *(2D tacrolimus; 2B CsA)*

2.3: We suggest that mycophenolate be the first-line antiproliferative agent. *(2B)*

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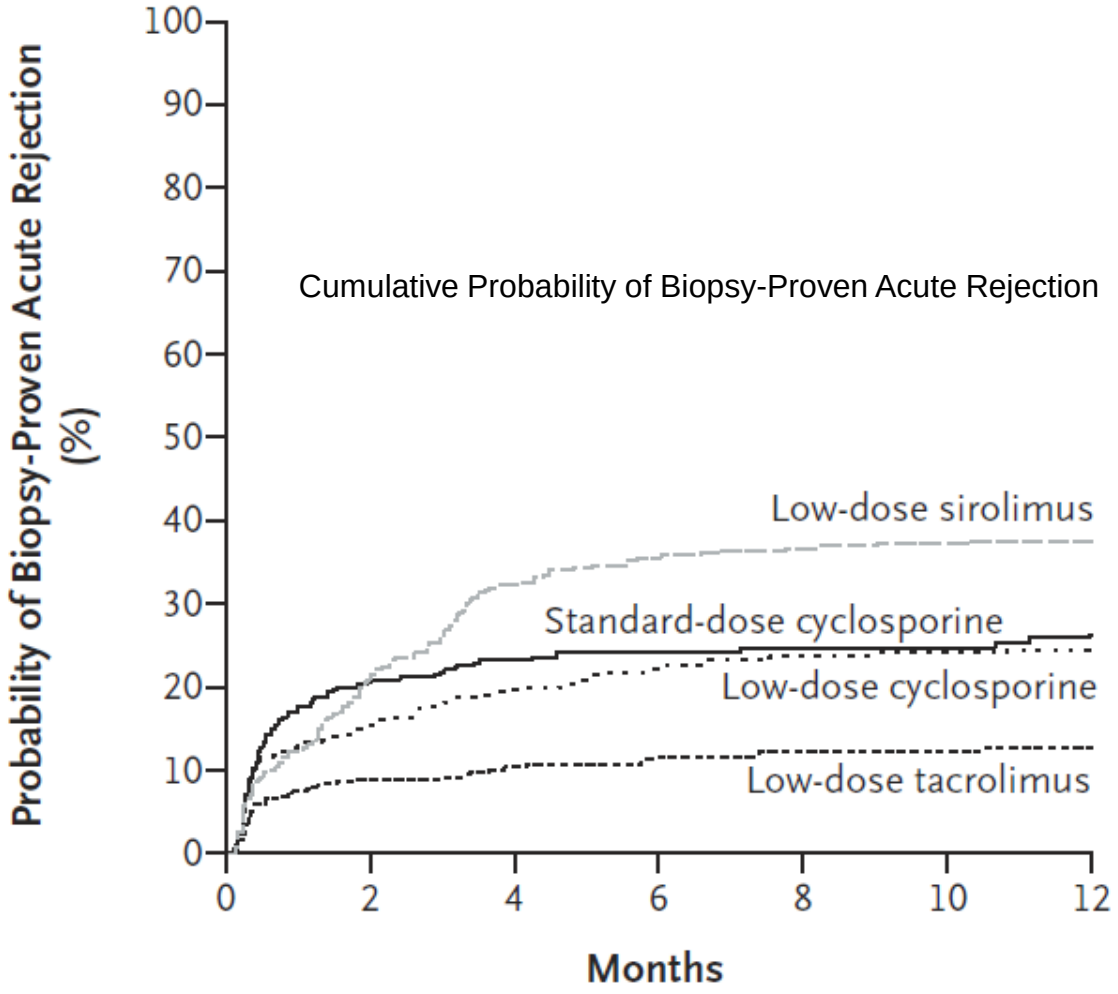
Reduced Exposure to Calcineurin Inhibitors in Renal Transplantation

N Engl J Med 2007;357:2562-75.



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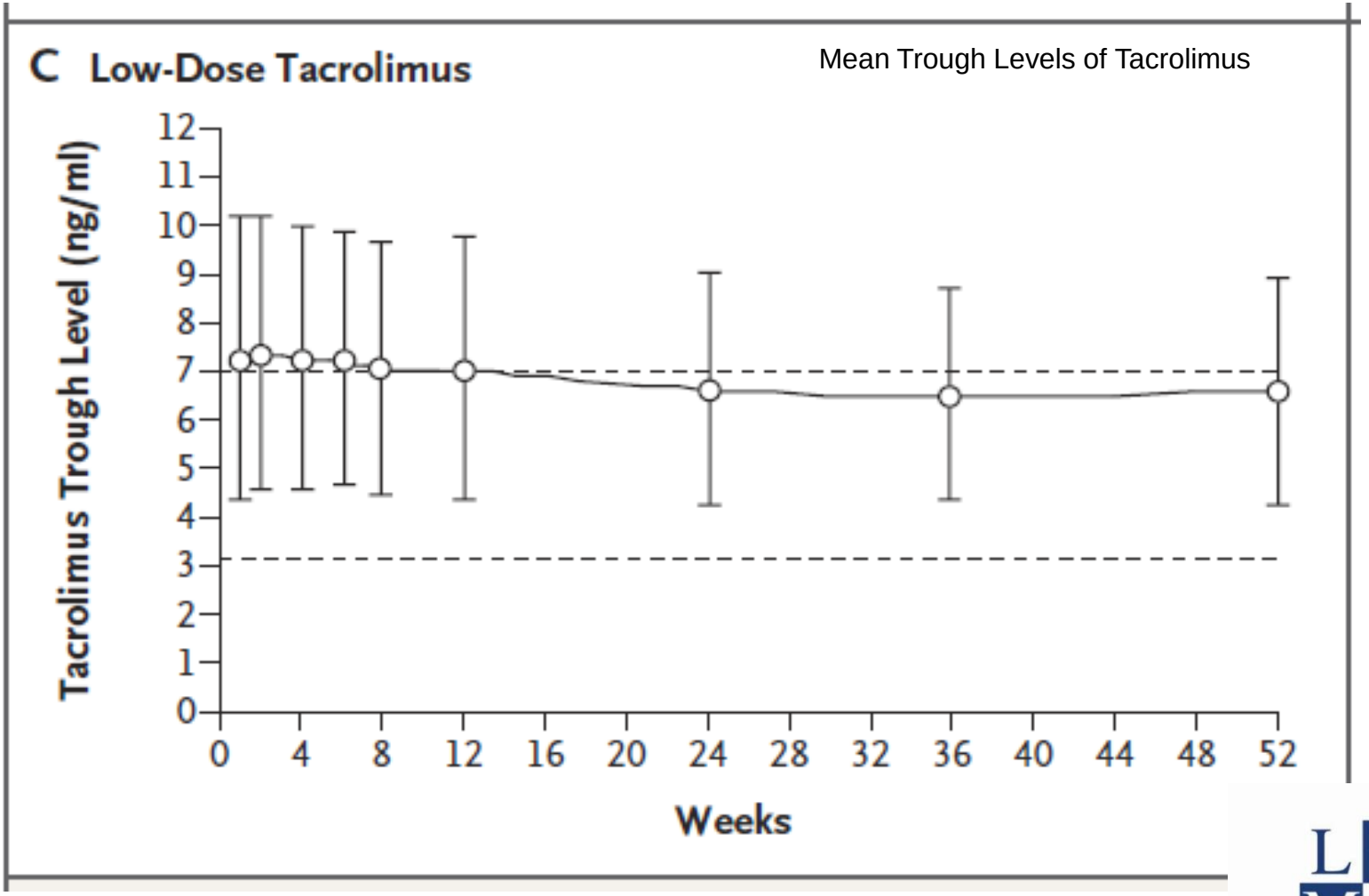
Not really a “low-dose tacrolimus” study..



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Current immunosuppressive strategies in our center:

Low risk:

- Tac + MMF + prednisone (3 m)

(target Tac trough from 10 to 4-6 ng/mL)

Intermediate risk:

- anti IL2R induction + Tac + MMF + prednisone (6 m)

(target Tac trough from 10-12 to 5-7 ng/mL)

High risk:

- T-cell depletion + Tac + MMF + prednisone (6 m)

(target Tac trough from 10-14 to 5-8 ng/mL)

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TAC:Tacrolimus, MMF: Mycophenolate Mofetil, IL2R: Interleukin-2 Receptor

(*Transplantation* 2017;101: S1–S56)

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]

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Broad perspective:

Non-adherence

Intra-patient variability

Under-immunosuppression

Adverse effects related to immunosuppression

Donor Specific Antibodies and antibody mediated rejection

Cardiovascular complications

Delayed Graft Function and ischemia-reperfusion injury

(*Transplantation* 2017;101: S1–S56)

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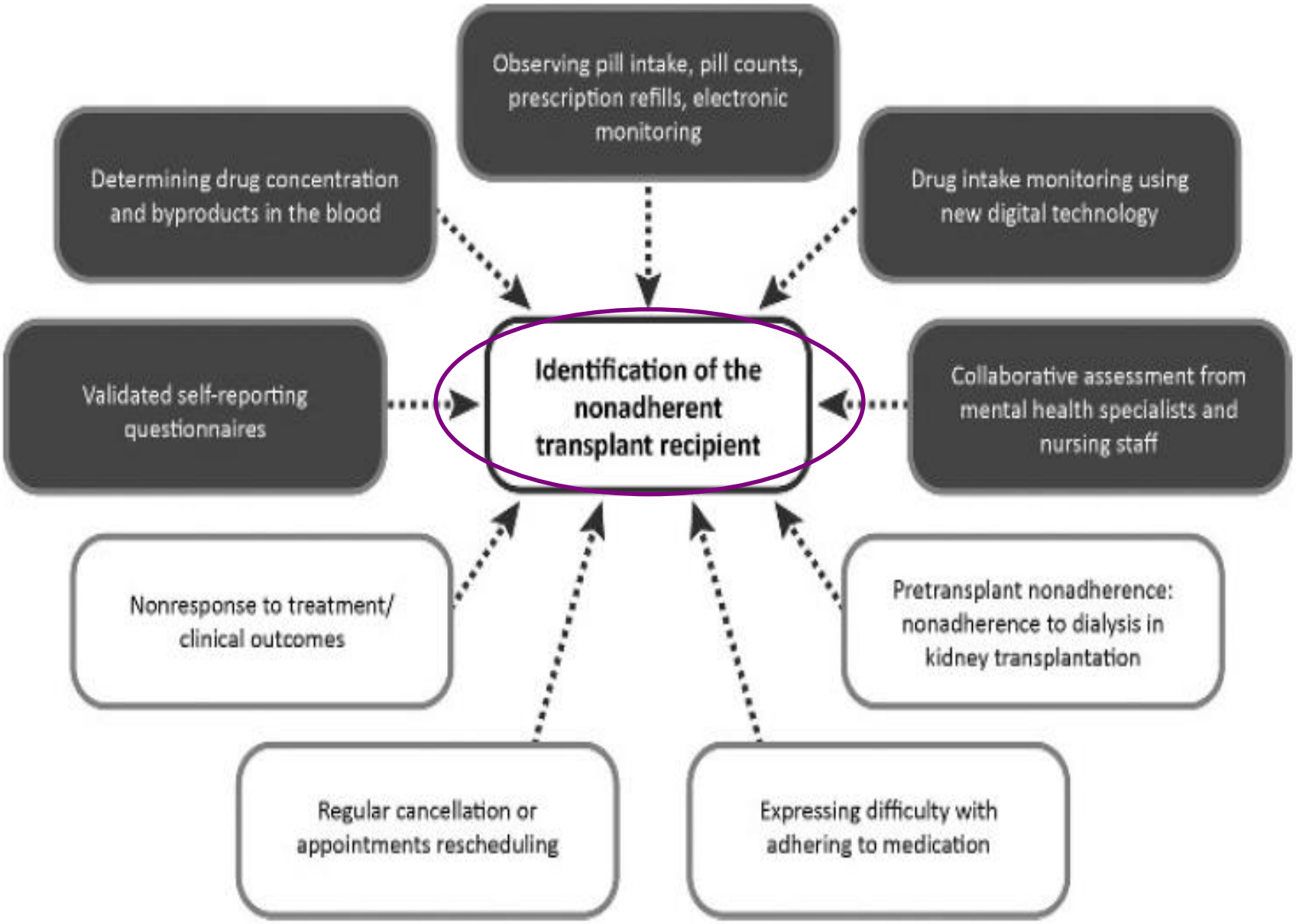
(*Transplantation* 2017;101: S1–S56)



Intra-patient variability

CV% calculation

High variability

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
Tacrolimus daily dose (mg/day)	5	5	5	5	5
Target trough (ng/mL)	6.2	7.9	5.2	8.5	4.9

SD	1.60
MEAN	6.54
CV	25%

Low variability

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
Tacrolimus daily dose (mg/day)	5	5	5	5	5
Target trough (ng/mL)	6	6.8	5.5	5.8	5.3

SD	0.58
MEAN	5.88
CV	10%

CV, coefficient of variation; SD, standard deviation

Neuberger J, et al. Transplantation 2017;101(4S): S1–S56.

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High intra-patient tacrolimus variability

- Concentrations will often be outside the therapeutic range
- Below target: increased risk of rejection
- Above target: increased risk of toxicity
- High IPV leads to poor transplant outcomes in transplant patients

1. Shuker N et al. Transpl Int. May 2016; 2. van Gelder T. Kidney Int. 2014;85(6):1267–1268. 3. Neuberger J et al. Transplantation 2017;101(4S): S1–S56

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Transplant International 2016; 29: 1158–1167

Transplant International

ORIGINAL ARTICLE

A high intrapatient variability in tacrolimus exposure is associated with poor long-term outcome of kidney transplantation

Nauras Shuker[1,2], Lamis Shuker[1], Joost van Rosmalen[3], Joke I. Roodnat[1], Lennaert C. P. Borra[2], Willem Weimar[1], Dennis A. Hesselink[1] & Teun van Gelder[1,2]

	Hazard ratio (95% CI)	*P*-value
Recipient age at transplantation (year)	0.980 (0.970–0.991)	<0.001
eGFR at 6 months (ml/min)	0.985 (0.976–0.995)	0.002
Tac IPV% (high)	1.420 (1.059–1.903)	0.019
Transplant number (>1)	1.505 (1.066–2.125)	0.020
Mean Tac concentration (ng/ml)	0.913 (0.839–0.994)	0.036
HLA mismatch (none)	1.087 (0.989–1.194)	0.084
DGF	0.736 (0.473–1.146)	0.175
Donor type (deceased)	0.791 (0.555–1.127)	0.194

Results of the multivariable Cox regression analysis. Impact of Tac intrapatient variability on the composite end point (graft failure, late biopsy-proven acute rejection, transplant glomerulopathy, or doubling of serum creatinine concentration) censored for death

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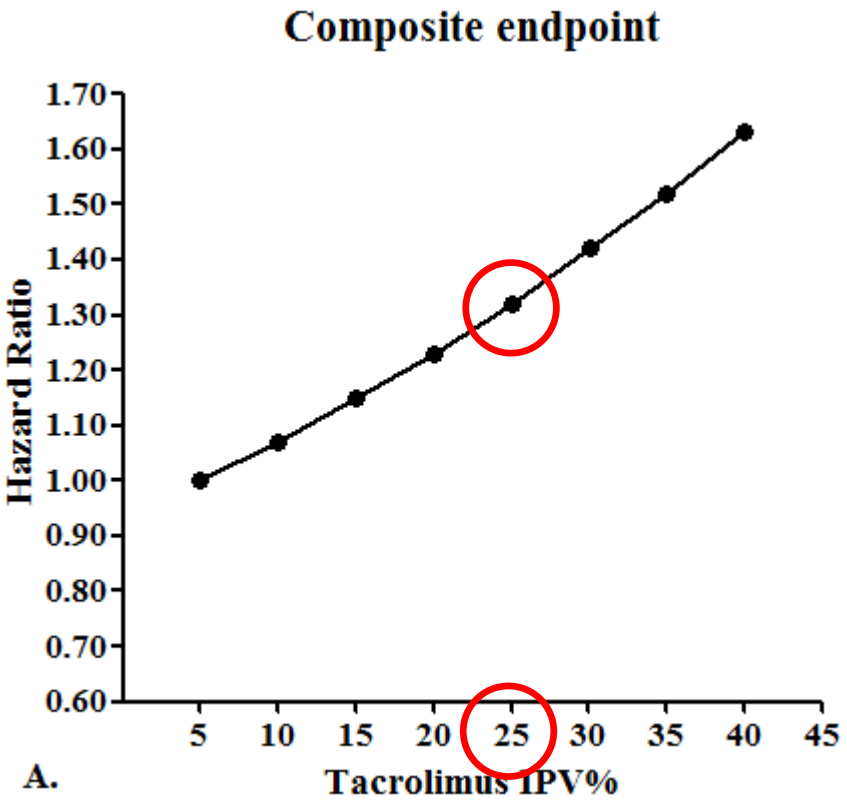
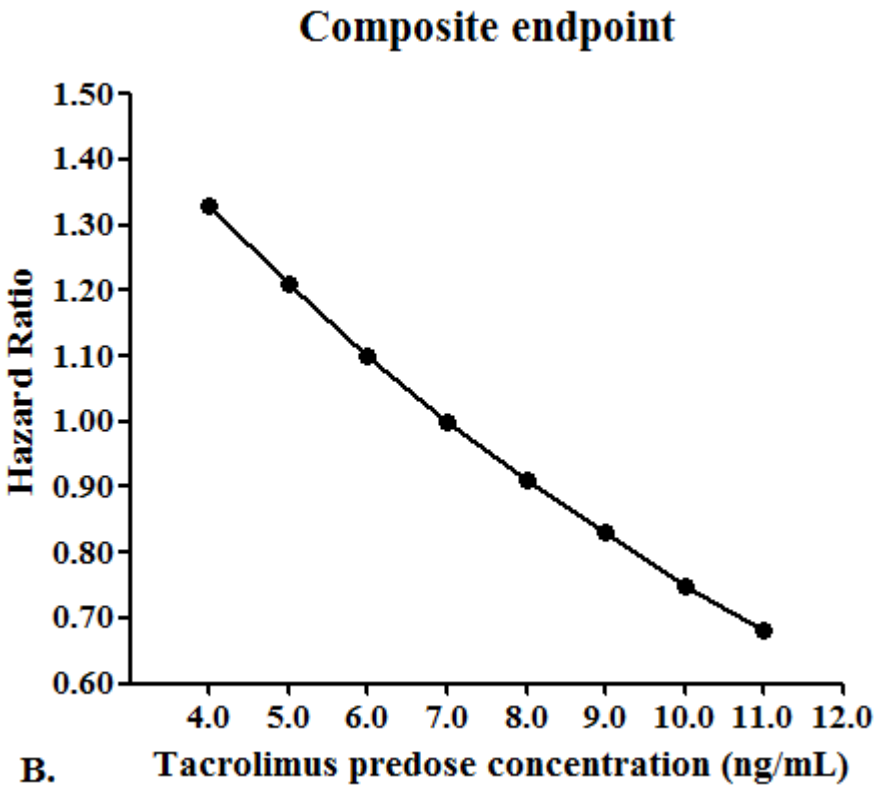
Estimated hazard ratios

Transplant International 2016; 29: 1158–1167





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

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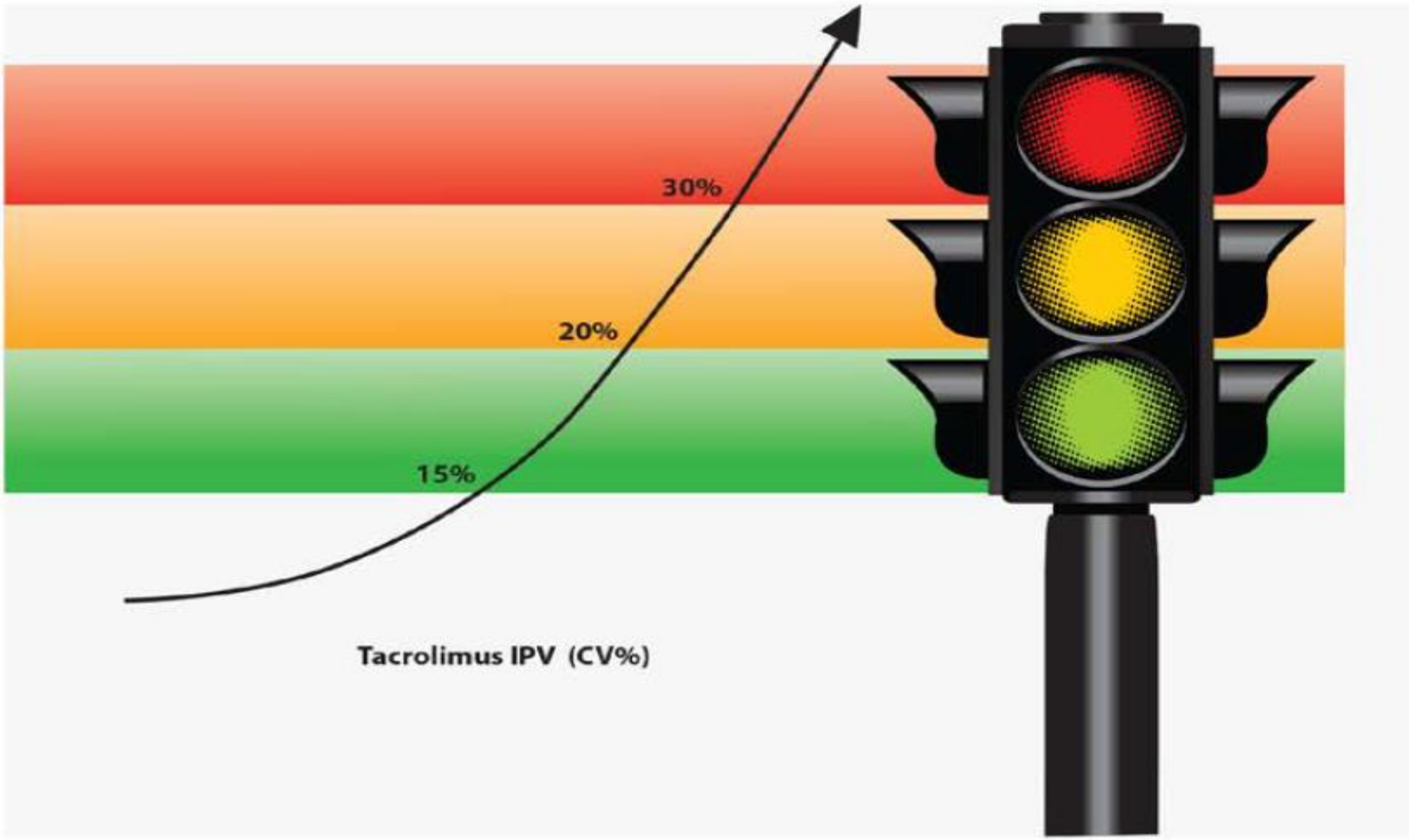
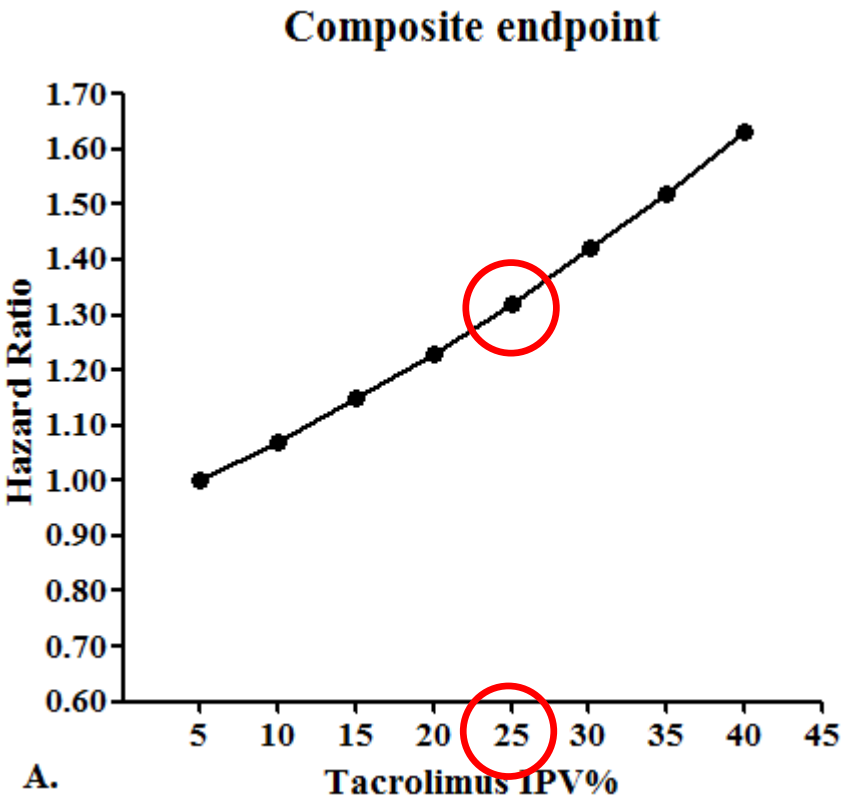
(*Transplantation* 2020;104: 1330–1340).

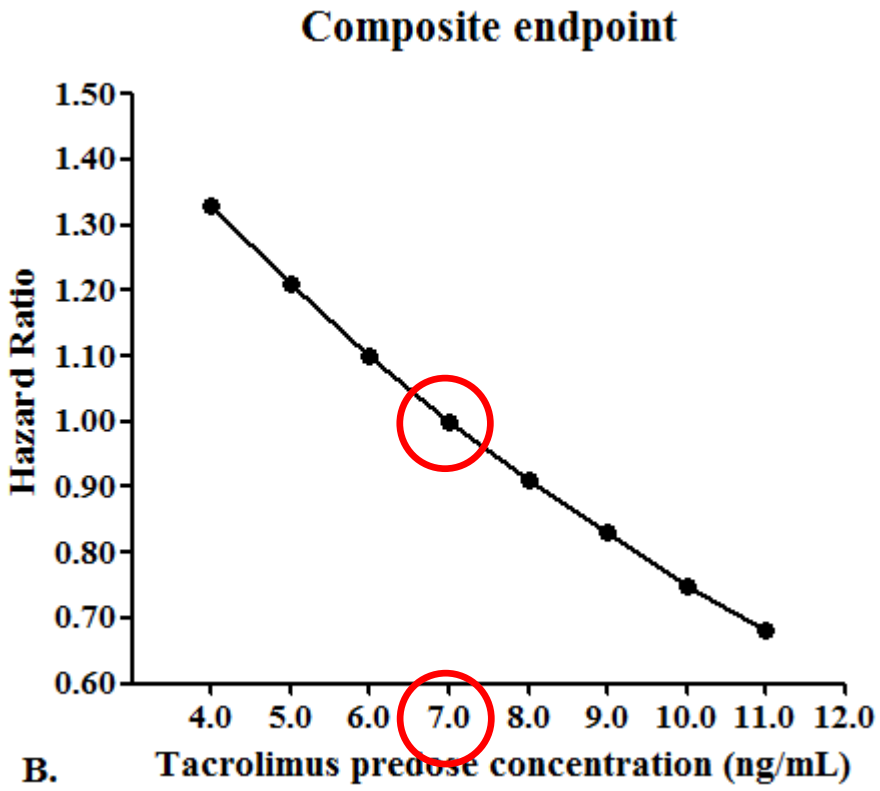
Intrapatient variability : suggested thresholds for clinical diagnostic work-up



Estimated hazard ratios

Transplant International 2016; 29: 1158–1167





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

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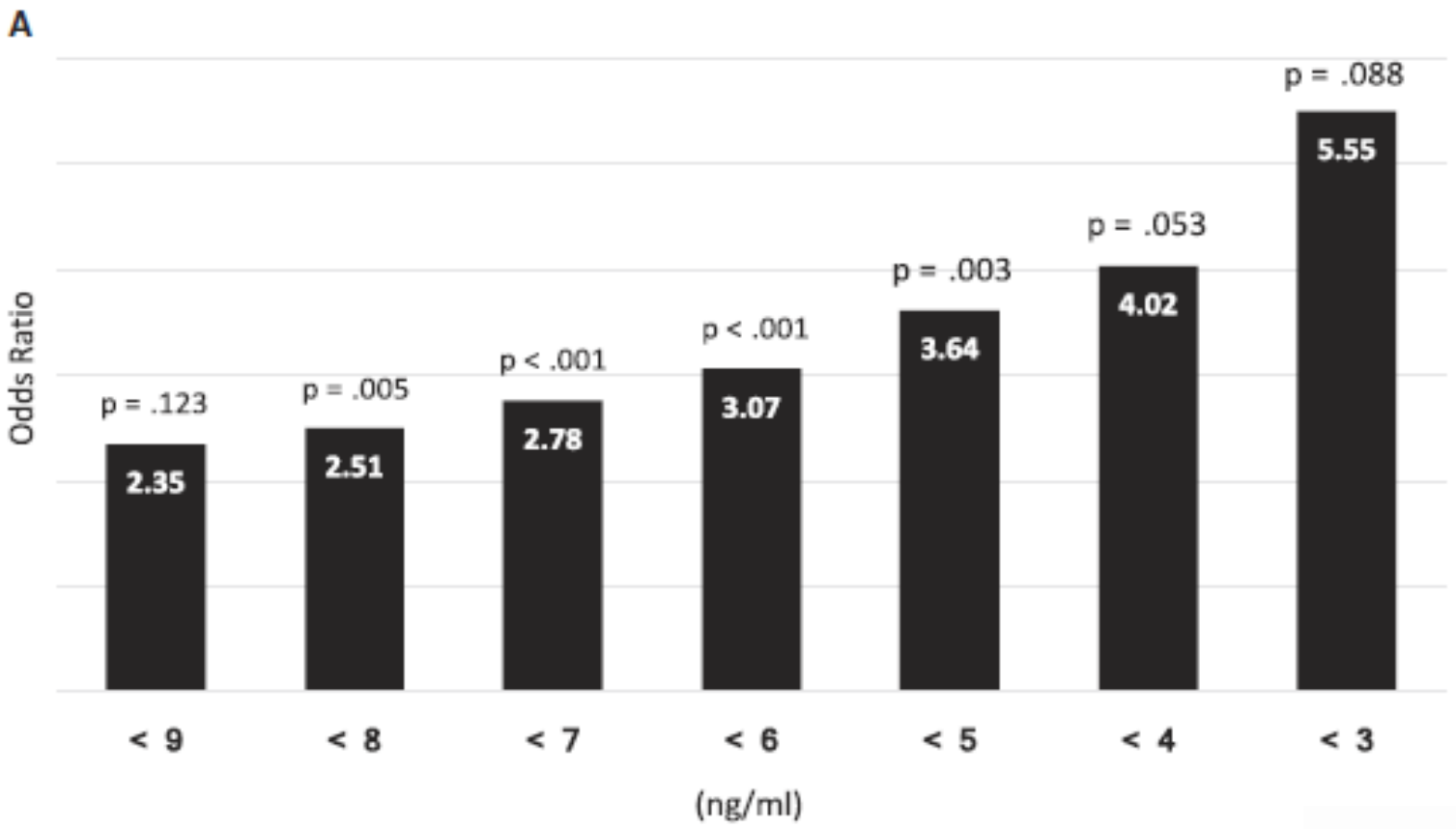
Odds ratio for dnDSA for mean TAC C0 by 6 months and dnDSA by 6 months

Am J Transplant. 2018;18:907–915.



TAC: Tacrolimus, dnDSA: de novo Donor-Specific Antibodies

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High Intrapatient Variability of Tacrolimus Concentrations Predicts Accelerated Progression of Chronic Histologic Lesions in Renal Recipients

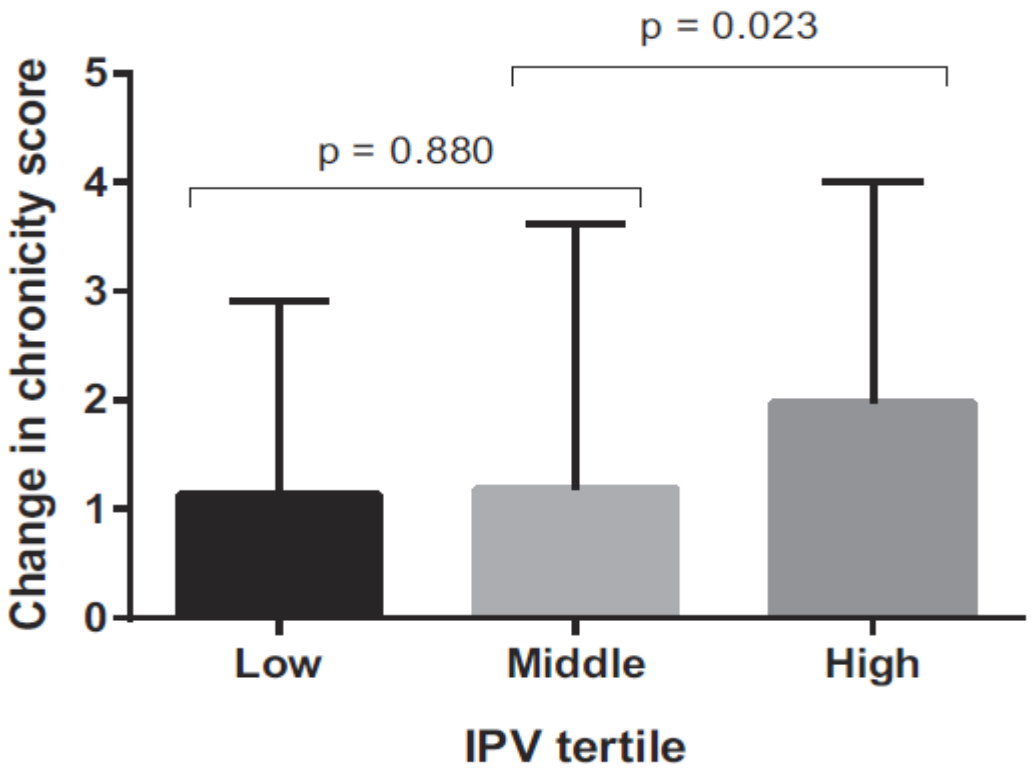

Figure 2: Change in chronicity score between month 3 and year 2, by intrapatient variability (IPV) tertile.

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TABLE 3. (*Transplantation* 2017;101: S1–S56)

Patient-level interventions for nonadherence to immunosuppressive regimens[55,82,83,86,93,95]

Patient-level interventions	Examples
Counseling/behavioral interventions	• Training patients during inpatient recovery on how to take medications • Providing adherence reminders during clinic visits • Medication schedules
Psychological/affective interventions	• Involving family • Providing support with educational and behavioral interventions • Establishing support groups directed at adherence
Educational/cognitive interventions	• Providing printed medication instructions/clear prescription instructions • Individual patient/family teaching
Medical interventions	• Simplified regimens, eg, monotherapy, once-daily dosing or long-acting parenteral administration • Medication reminder cues, prefilled/easy-to-use pill boxes, contingency plans for missed doses • Clinicians need to be aware of concomitant medications and focus on prescribing the most essential medication

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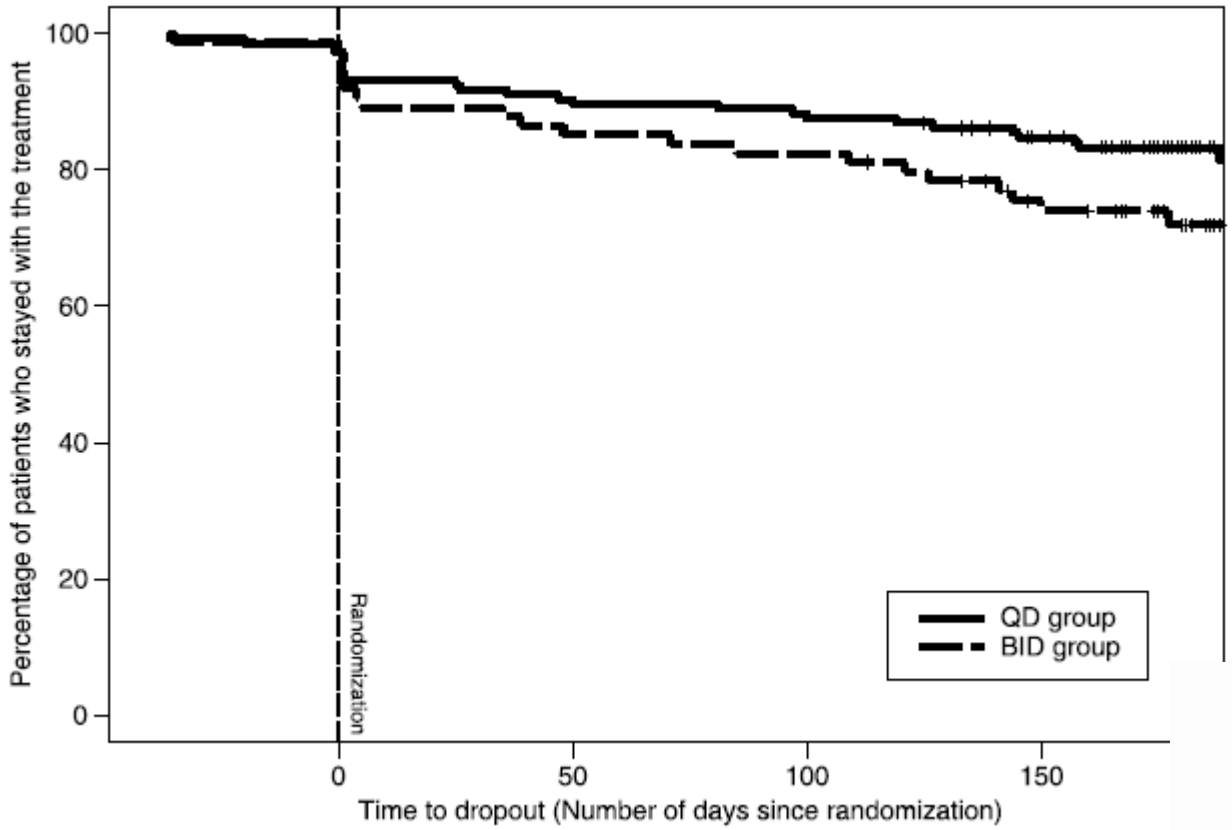
(*Transplantation* 2013;95: 333–340)

Improved Adherence to Tacrolimus Once-Daily Formulation in Renal Recipients: A Randomized Controlled Trial Using Electronic Monitoring

Dirk R.J. Kuypers,[1,9] Patrick C. Peeters,[2] Jacques J. Sennesael,[3] Mireille N. Kianda,[4] Bernard Vrijens,[5,6] Paulus Kristanto,[5] Fabienne Dobbels,[7] Yves Vanrenterghem,[1] Nada Kanaan,[8] on behalf of the ADMIRAD Study Team



Kaplan-Meier estimates of the percentage of patients continuing with the treatment over time. Each small vertical tick mark indicates that a patient was censored in the calculation as he/she completed the study.

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(*Transplantation* 2014;97: 775–780)

Lower Variability in 24-Hour Exposure During Once-Daily Compared to Twice-Daily Tacrolimus Formulation in Kidney Transplantation

Frank Stifft,[1] Leo M.L. Stolk,[2] Nasrullah Undre,[3] Johannes P. van Hooff,[1] and Maarten H.L. Christiaans[1,4]

TABLE 1. Mean pharmacokinetic parameters for Tac BID and Tac QD

Parameter	Tac BID, n=40	Tac QD, n=40	*P*
Daily dose (mg/kg)	0.05 (0.04; 0.02–0.12)[a]	0.05 (0.04; 0.02–0.13)[a]	0.09
AUC_{0-24} (µg·hr/L)	219.2 (208.1–230.9)	213.3 (202.6–224.5)	0.37
$DnAUC_{0-24}$ (µg·hr/L/mg/kg)	4944 (4358–5414)	4793 (4244–5414)	0.30
C_{min} (µg/L)	7.4 (7.0–7.7)	6.6 (6.2–7.0)	0.003
DnC_{min} (µg/L/mg/kg)	166.1 (144.9–190.4)	146.2 (127.7–167.3)	<0.001
Intraindividual variability AUC (%)	14.1 (12.3–16.0)	10.9 (9.4–12.4)	0.012
Intraindividual variability C_{min} (%)	15.3 (13.3–17.3)	13.7 (12.2–15.2)	0.21

Conclusions intra-patient variability

Intra-patient variability is a predictor for poor outcome after transplantation

True for kidney and other organs / children and adults

Intervention: improve adherence

Switch to once daily formulation to reduce variability.

Avoid too low tacrolimus concentrations: more rejection!

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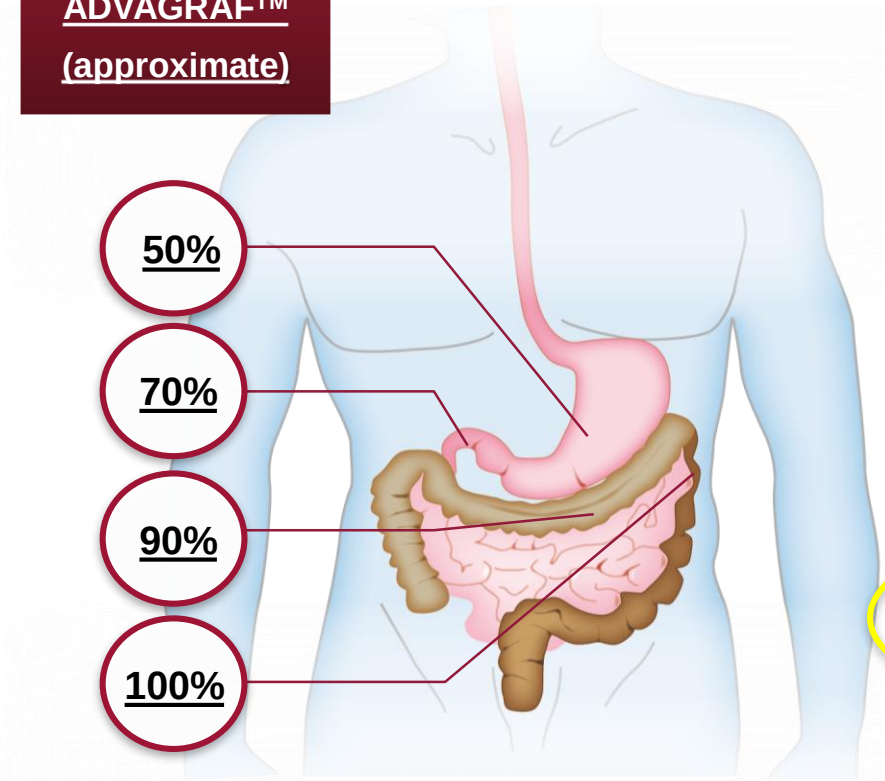
Tacrolimus extended release formulation

	Absorption of tac BID (approximate)	Absorption of ADVAGRAF™ (approximate)
1 hr	75%	50%
2 hr	100%	70%
3 hr		90%
4 hr		100%



- Tacrolimus is a substrate of cytochrome P450 3A (CYP3A) and P-glycoprotein (P-gp)
- With Advagraf ™ less tacrolimus is available for absorption in the proximal small intestine.
- Intra-patient variability is reduced.

Tacrolimus extended release formulation enables a greater proportion of tacrolimus to be absorbed in the lower GI tract than from immediate-release formulation

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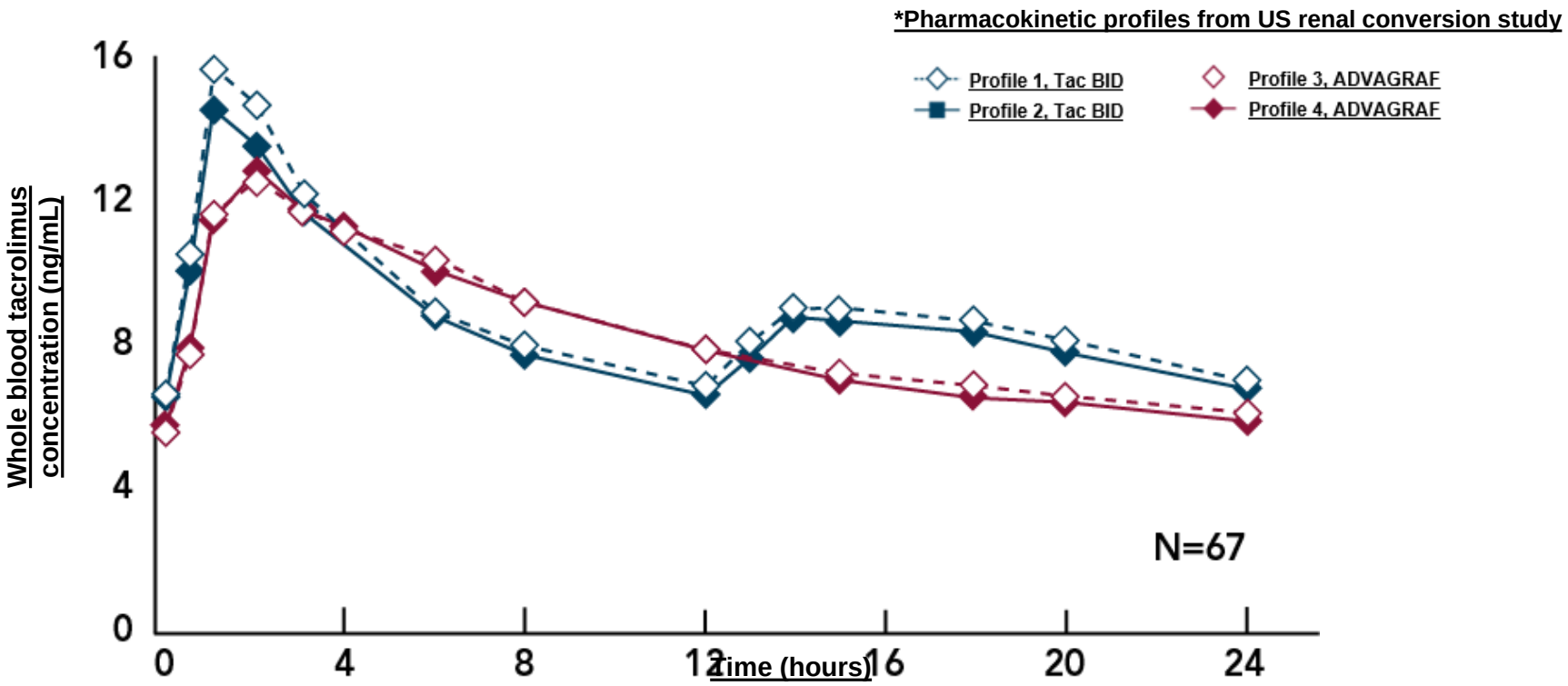
European Medicines Agency. European public assessment report (EPAR): ADVAGRAF : scientific discussion. EMA website. Published 2007

PK/PD Profile of Tacrolimus QD vs.BID



Potential effects of ADVAGRAF™ as a prolonged-release formulation in reduction of intra-patient variability

- Improved adherence[4]
- Less food & GI effects[5]
- No asymmetric dosing[5]
- More consistent AUC exposure[6]

1. DOF ADV11004 (Alloway Whole Blood Levels PK); 2. EMA. *European public assessment report (EPAR): ADVAGRAF: scientific discussion* 2007; 3. Kolonko A et al. *Transplant Proc* 2011;43:2950–2953; 4. Kuypers DRJ et al. *Transplantation* 2013;95:333−340; 6. Cervelli M, Russ G. *Aus J Pharmacy* 2012;93:83–86; 6. Stifft F et al. *Transplantation* 2013. Epub, ahead of print

Pharmacokinetic features, compared to Prograf™:

Tacrolimus prolonged-release (Advagraf™, XL, Astagraf) has:

- a lower maximum plasma concentration (C-max)
- a delay in time to C-max (t-max)
- a similar strong correlation between C-trough and AUC
- on average about 10% lower tacrolimus exposure
- similar C-trough target concentrations
- been reported to result in lower [Tac] in first days post-surgery
    - kidney versus liver
    - de novo versus switch at later point in time

American Journal of Transplantation 2009; 9: 2505–2513

LIVER TRANSPLANTATION 17:167-177, 2011

Clin Pharmacokinet (2015) 54:993–1025

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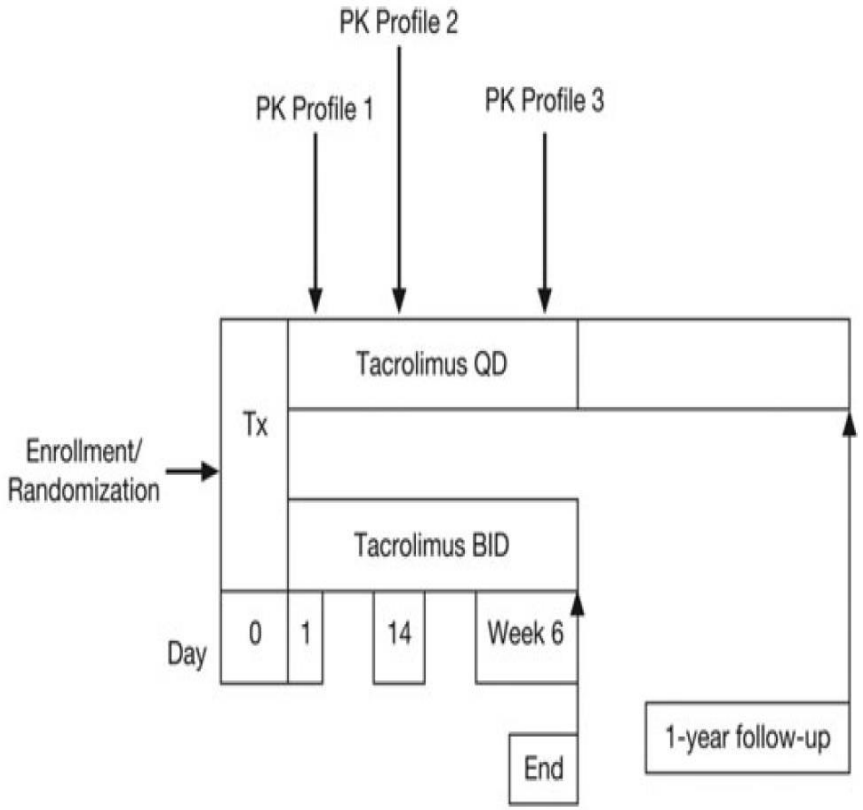
American Journal of Transplantation 2009; 9: 2505–2513

Pharmacokinetics for Once- Versus Twice-Daily Tacrolimus Formulations in *De Novo* Kidney Transplantation: A Randomized, Open-Label Trial



Study design and schedule of PK profiles

Table 1: Baseline demographics and disease characteristics

Full Analysis Set	Tacrolimus QD (n = 60) Patients (%)	Tacrolimus BID (n = 59) Patients (%)
Male	34 (56.7)	44 (74.6)[2]
Female	26 (43.3)	15 (25.4)
Age (years)[1]	44.0 (19–66)	43.6 (21–65)
Height (cm)[1]	169.3 (149–193)	168.9 (148–184)
Weight (kg)[1]	70.2 (41–115)	69.3 (40–100)
Caucasian	58 (96.7)	59 (100)
Black	0	0
Asian	0	0
Other	2 (3.3)	0

Table 1: Baseline demographics and disease characteristics

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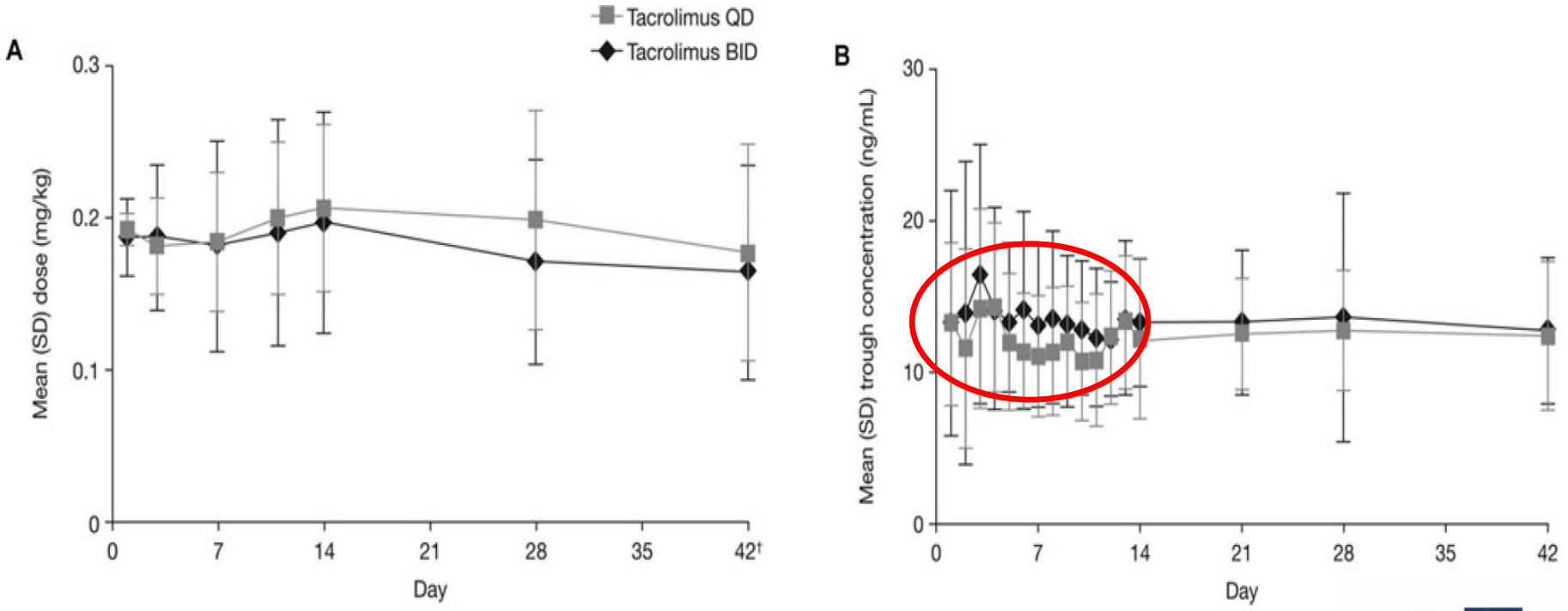
American Journal of Transplantation 2009; 9: 2505–2513

Pharmacokinetics for Once- Versus Twice-Daily Tacrolimus Formulations in *De Novo* Kidney Transplantation: A Randomized, Open-Label Trial



Summary of daily tacrolimus doses (A) and trough concentrations (B) (Full Analysis Set).
†Completers only at week 6

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Transplantation Proceedings, 42, 3034–3037 (2010)

Extended-Release Tacrolimus Therapy in De Novo Kidney Transplant Recipients: Single-Center Experience

A. Andrés, M. Delgado-Arranz, E. Morales, T. Dipalma, N. Polanco, E. Gutierrez-Solis, J.M. Morales, M. Praga, E. Gutierrez, and E. Gonzalez

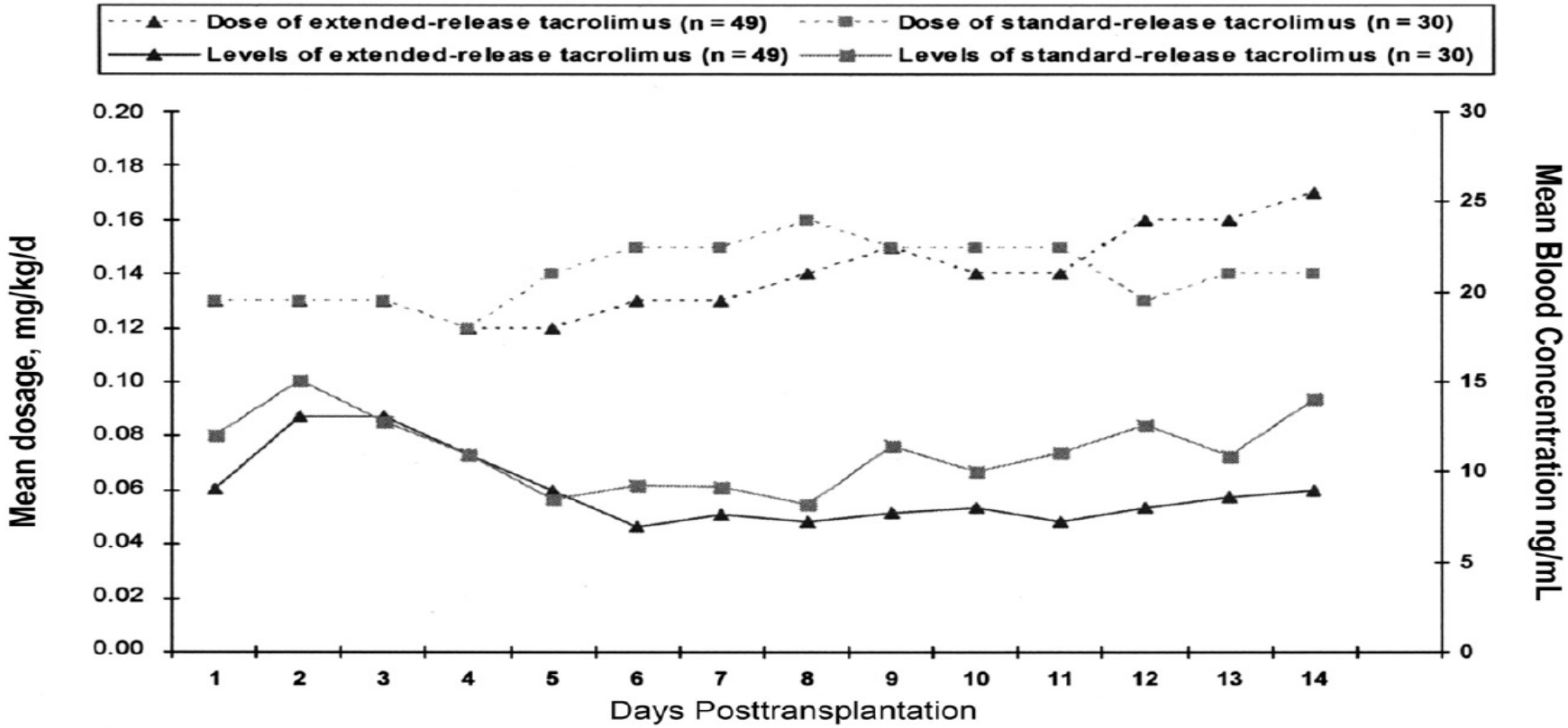
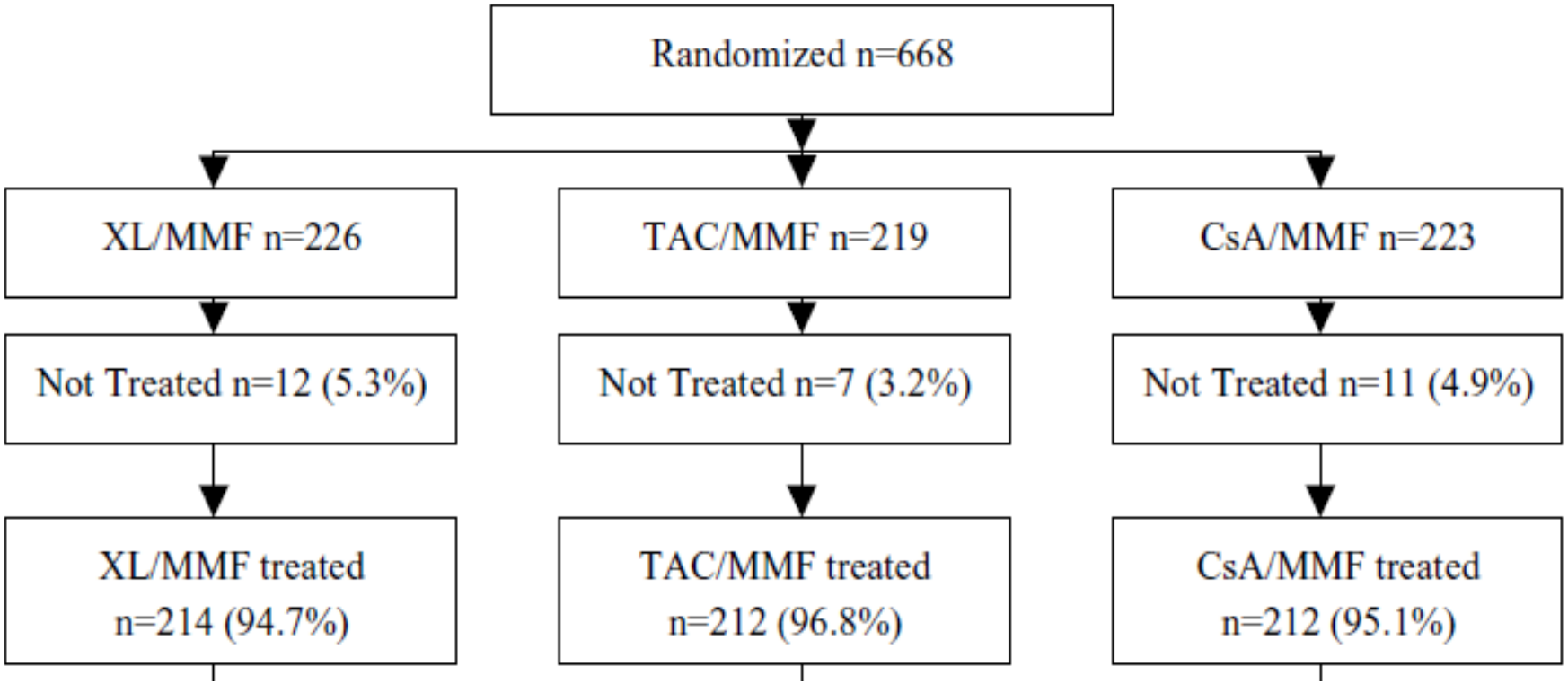


Fig 1. Evolution of tacrolimus dosage and blood trough concentration in the first 14 days posttransplantation in 2 study groups, extended-release and standard-release formulation, respectively.

Comparing tacrolimus once daily and twice daily

American Journal of Transplantation 2007; 7: 595–608

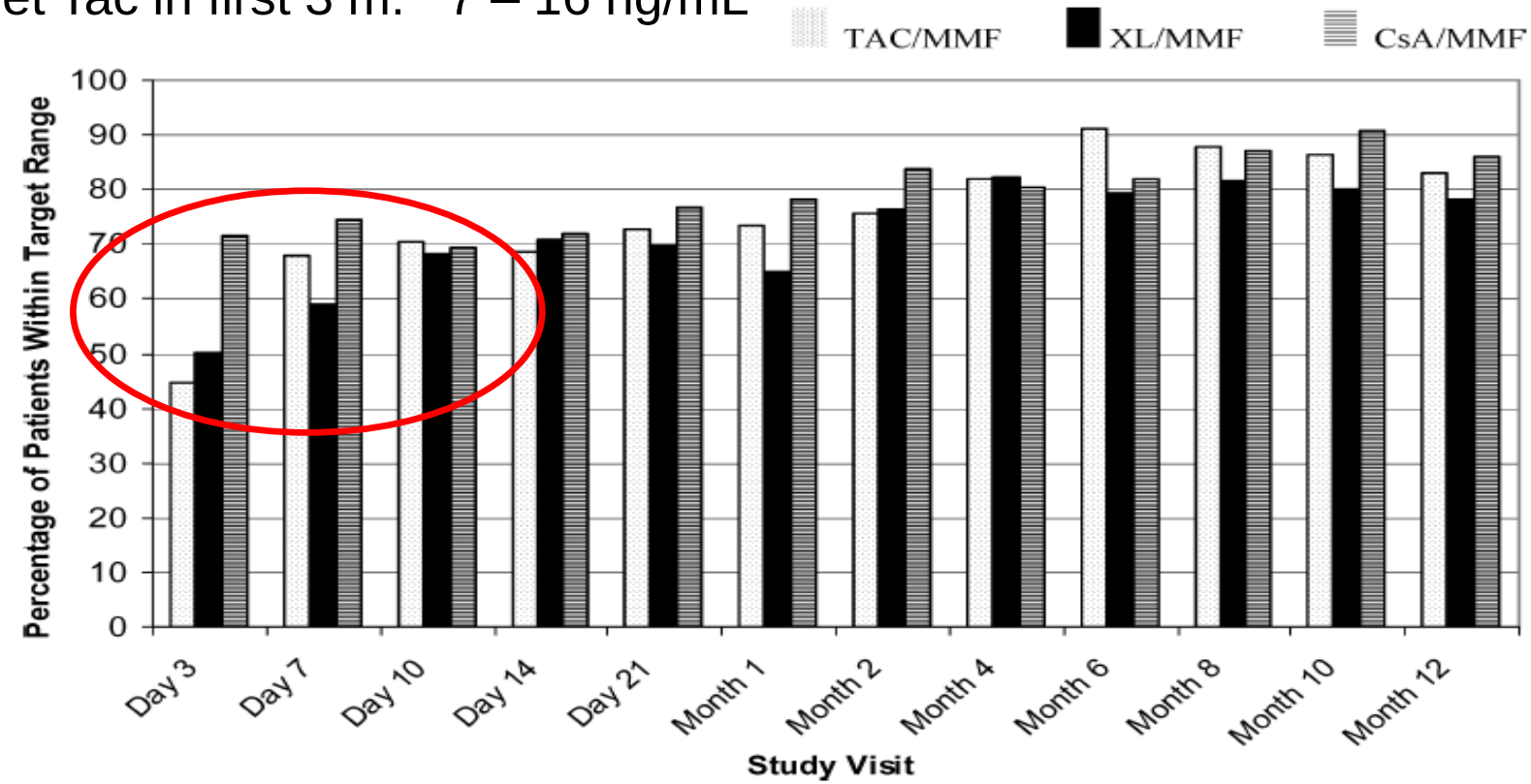
One-Year Results with Extended-Release Tacrolimus/ MMF, Tacrolimus/MMF and Cyclosporine/MMF in *De Novo* Kidney Transplant Recipients



American Journal of Transplantation 2007; 7: 595–608

One-Year Results with Extended-Release Tacrolimus/ MMF, Tacrolimus/MMF and Cyclosporine/MMF in *De Novo* Kidney Transplant Recipients

Tac bid start = 0,075 – 0,1 mg/kg bid
Tac XL start = 0,15 – 0,20 mg/kg qd
Target Tac in first 3 m: 7 – 16 ng/mL



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.

One-Year Results with Extended-Release Tacrolimus/MMF, Tacrolimus/MMF and Cyclosporine/MMF in *De Novo* Kidney Transplant Recipients

American Journal of Transplantation 2007; 7: 595–608

Table 3: Dose and tacrolimus whole blood trough concentrations by visit in white and black transplant recipients

	XL/MMF				TAC/MMF			
	White (n = 160)		Black (n = 41)		White (n = 152)		Black (n = 51)	
	Mean daily dose (mg/kg)	Mean trough concentration (ng/mL)	Mean daily dose (mg/kg)	Mean trough concentration (ng/mL)	Mean daily dose (mg/kg)	Mean trough concentration (ng/mL)	Mean daily dose (mg/kg)	Mean trough concentration (ng/mL)
Day 7	n = 159	n = 128	n = 41	n = 35	n = 150	n = 114	n = 49	n = 32
	0.14	10.79	0.14	7.85	0.12	11.24	0.12	8.60
Month 1	n = 153	n = 138	n = 37	n = 32	n = 148	n = 124	n = 47	n = 34
	0.14	11.11	0.18	10.83	0.11	11.28	0.15	10.79

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One-Year Results with Extended-Release Tacrolimus/MMF, Tacrolimus/MMF and Cyclosporine/MMF in *De Novo* Kidney Transplant Recipients

American Journal of Transplantation 2007; 7: 595–608

Table 4: Efficacy failure in *de novo* kidney transplant recipients at 1-year posttransplant

	XL/MMF (n = 214)	TAC/MMF (n = 212)	CsA/MMF (n = 212)
Efficacy failure[1]	30 (14.0%)	32 (15.1%)	36 (17.0%)
Death	3	9[2]	5[2]
Graft failure	5	9	4[3]
BCAR (local assessments)	22[4]	16	29
Lost to follow-up	3	4	1
Treatment difference[5]	−3.0%	−1.9%	
95.2% confidence interval[6]	−9.9%, 4.0%	−8.9%, 5.2%	

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One-Year Results with Extended-Release Tacrolimus/MMF, Tacrolimus/MMF and Cyclosporine/MMF in *De Novo* Kidney Transplant Recipients

American Journal of Transplantation 2007; 7: 595–608

Table 8: Trough concentrations (ng/mL) at days 3 and 30 in patients with and without BCAR during the first 30 days posttransplant

Treatment group	Visit (day)	Patients with BCAR		Patients without BCAR		p-value
		n	Mean ± SD	n	Mean ± SD	
XL/MMF	3	10	11.2 ± 9.10	179	11.3 ± 7.17	0.7457
	30	10	10.5 ± 4.11	172	11.2 ± 4.96	0.8434
TAC/MMF	3	4	10.8 ± 4.88	168	13.0 ± 8.86	0.8751
	30	8	10.3 ± 3.81	166	11.2 ± 4.65	0.6206
CsA/MMF	3	10	218.9 ± 95.84	162	275.7 ± 154.8	0.4382
	30	7	271.6 ± 108.3	159	311.7 ± 126.1	0.4167

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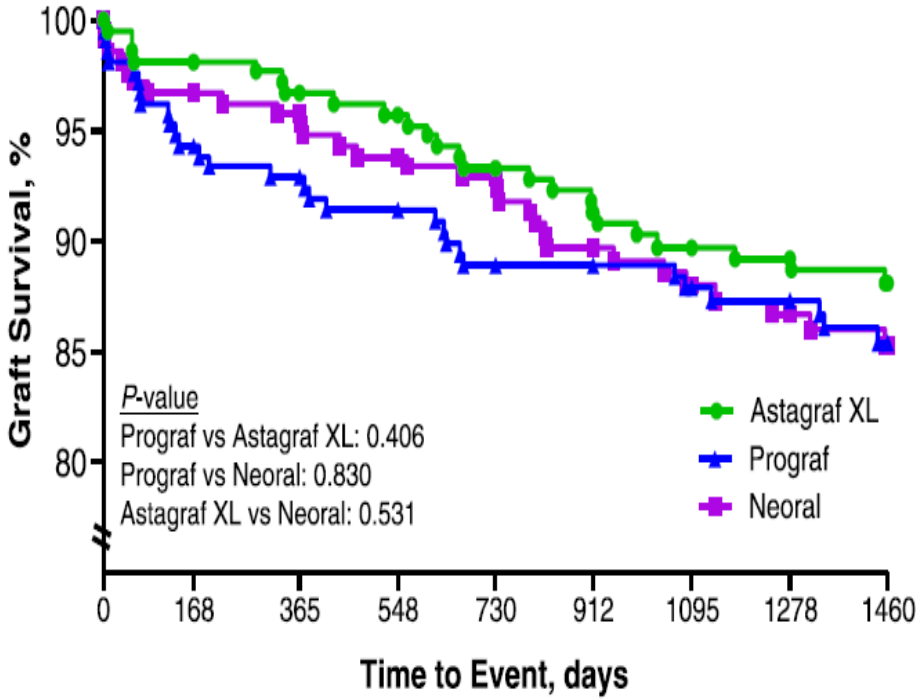
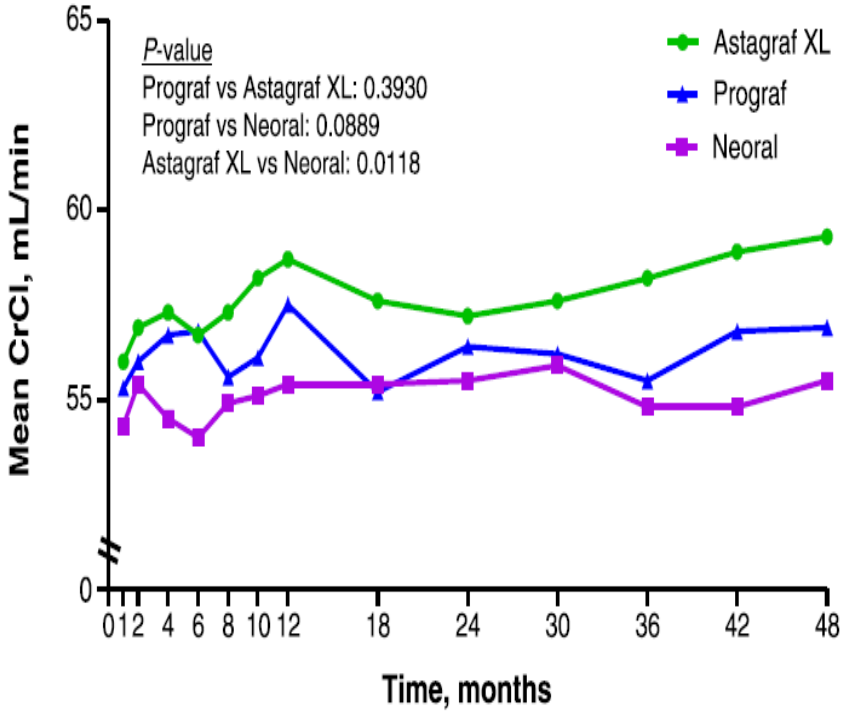
Long-Term Follow-Up of a Phase III Clinical Trial Comparing Tacrolimus Extended-Release/MMF, Tacrolimus/MMF, and Cyclosporine/MMF in De Novo Kidney Transplant Recipients



Patient survival over 4 years in the three treatment arms. Percent of survival over 4 years in three treatment groups, measured in days. Number at risk indicates the number of active patients at each time interval.



Renal function measured by Cockcroft-Gault equation over 4 years in the three treatment arms. Renal function measured by CrCl in milliliters per minute over 4 years in the three treatment arms. Number analyzed indicates the number of active patients who had a laboratory assessment.

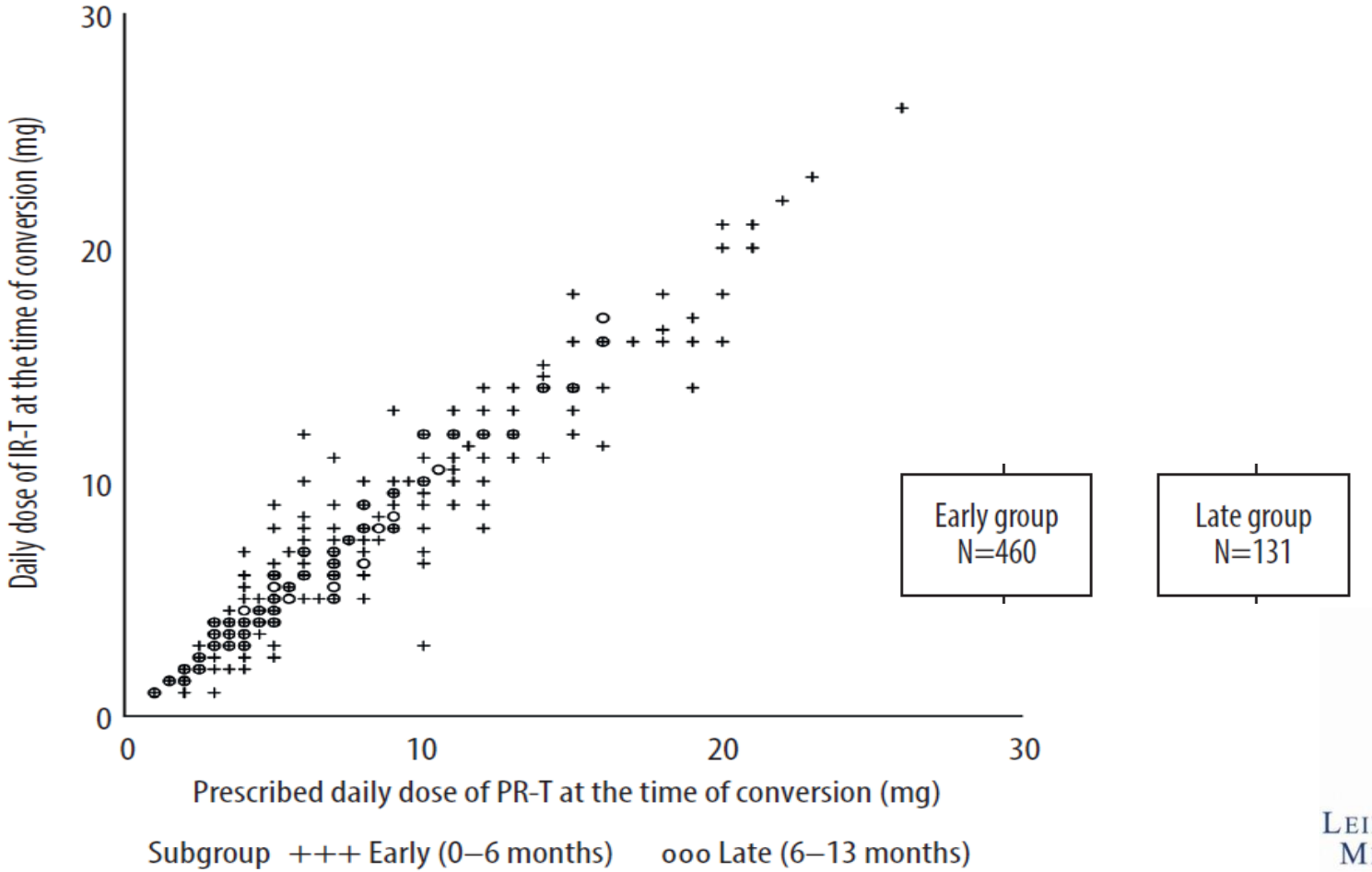
Erasmus MC

(*Transplantation* 2014;97: 636–641)

A Prospective, Observational Study of Conversion From Immediate- to Prolonged-Release Tacrolimus in Renal Transplant Recipients in France: The OPALE Study

Valérie Moal
Philippe Grimbert
Adrien Beauvais
Laurence Dubel
Yann Le Meur

Ann Transplant, 2019; 24: 517-526



Doses of immediate- and prolonged-release tacrolimus at time of conversion in the early and late groups (analysis population).

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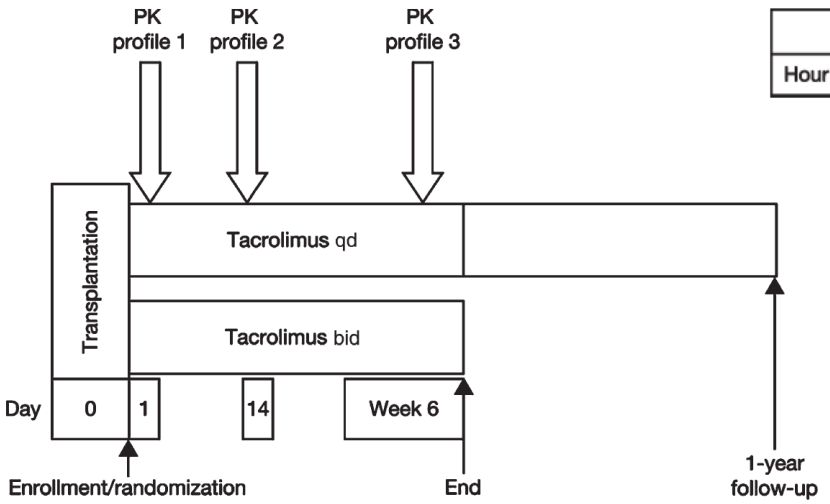
Pharmacokinetics for Once-Daily Versus Twice-Daily Tacrolimus Formulations in De Novo Liver Transplantation: A Randomized, Open-Label Trial



24-hour blood concentration–time profile																
Hour	0	0.5	1	2	3	4	6	8	12	12.5	13	14	15	16	18	20	24

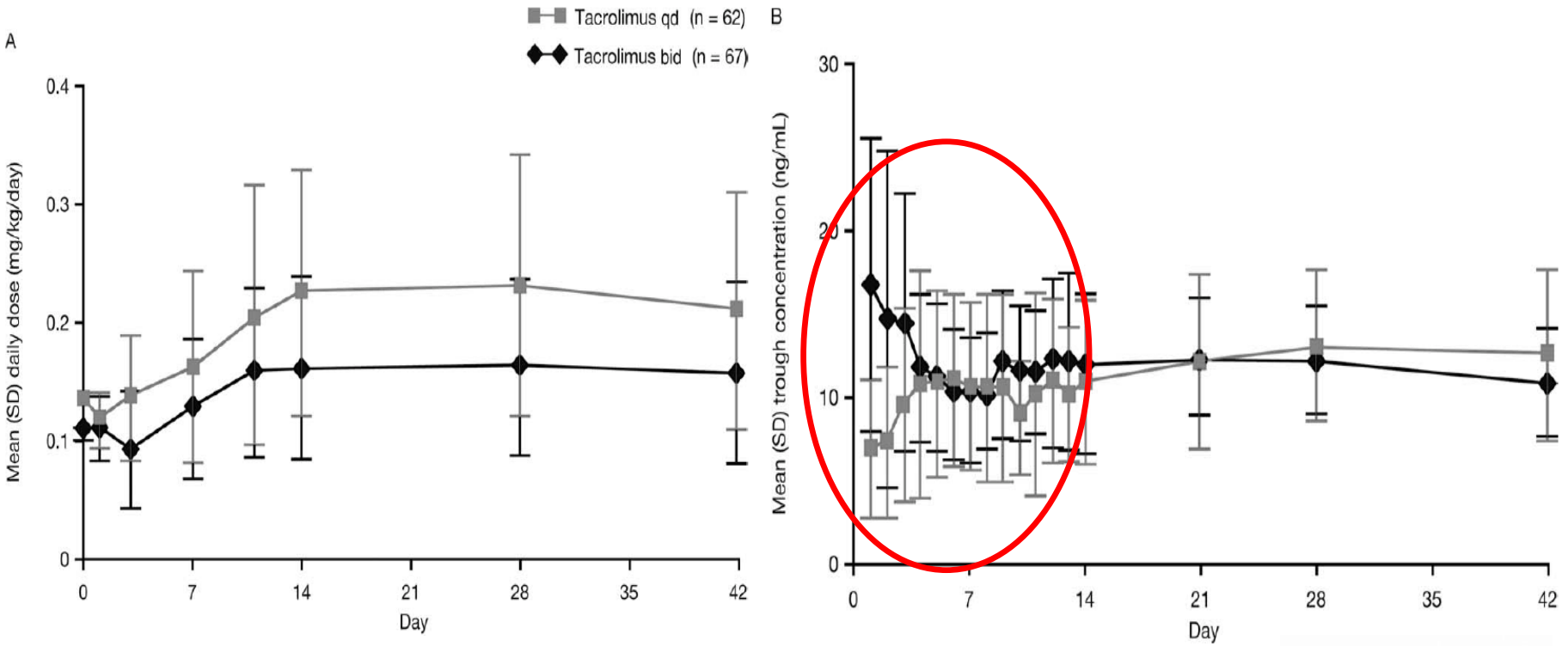
Study design and schedule of PK profiles

Baseline Demographics and Disease Characteristics

Characteristics	Tacrolimus qd (n = 67)	Tacrolimus bid (n = 62)
Full Analysis Set		
Male patients (n [%])	49 (73.1)	45 (72.6)
Age (years), mean (range)	49.4 (24-65)	52.4 (27-68)
Weight (kg), mean (range)	78.0 (40-127)	77.5 (48-142)
Race, n (%)		
Caucasian	65 (97.0)	61 (98.4)
Black	1 (1.5)	0
Asian	0	1 (1.6)
Other	1 (1.5)	0

LIVER TRANSPLANTATION 17:167-177, 2011

Pharmacokinetics for Once-Daily Versus Twice-Daily Tacrolimus Formulations in De Novo Liver Transplantation: A Randomized, Open-Label Trial



Summary of (A) daily tacrolimus doses and (B) trough concentrations (Full Analysis Set).

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Lower tacrolimus exposure after start Advagraf™:

My interpretation is:

- some studies do see it, others do not
- seems more prominent after liver than after kidney transplantation
- limited to first 3-4 days after surgery
- no association with increased rejection rate
- related to changes in GI motility??
- higher starting dose?

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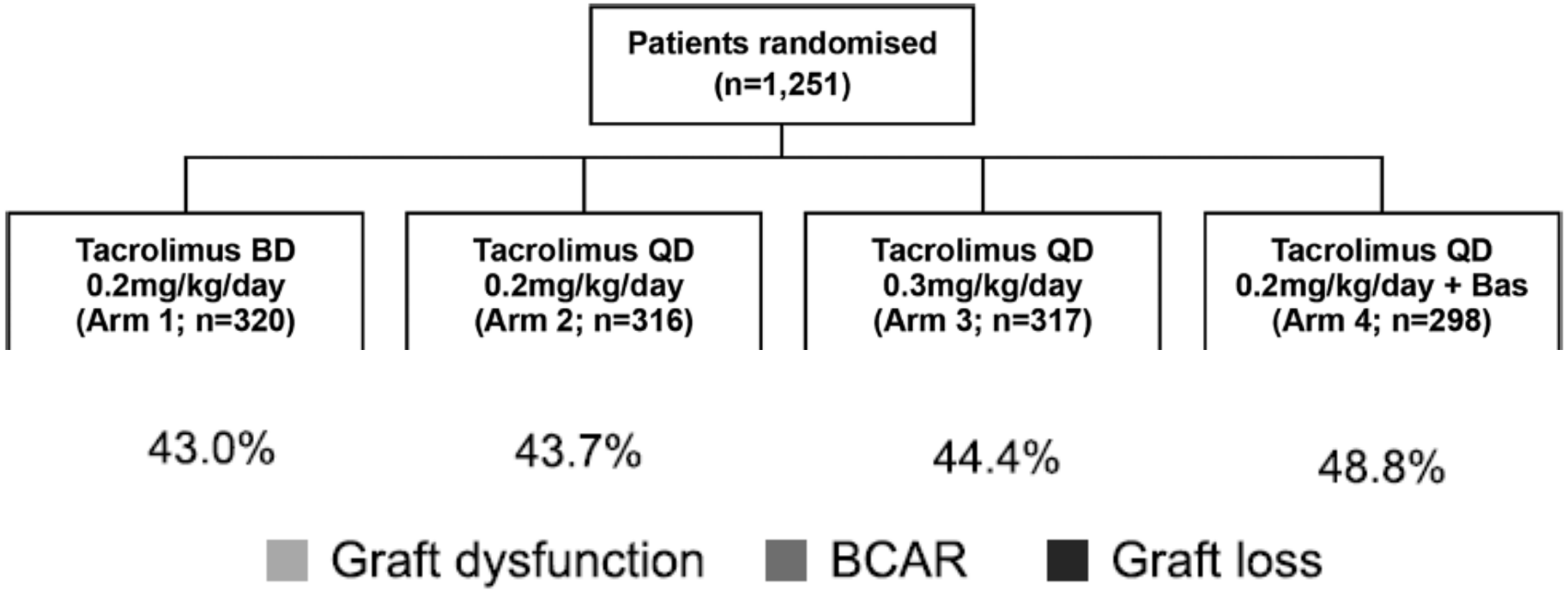
(*Transplantation* 2013;96: 897–903)

OSAKA Trial: A Randomized, Controlled Trial Comparing Tacrolimus QD and BD in Kidney Transplantation

Laetitia Albano,[1] Bernhard Banas,[2] Juergen L. Klempnauer,[3] Maciej Glyda,[4] Ondrej Viklicky,[5] and Nassim Kamar,[6,7] on behalf of the Optimising immunoSuppression After Kidney transplantation with ADVAGRAF (OSAKA) study group



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Experimental and Clinical Transplantation (2014) 4: 323-327

Conversion From Twice-Daily to Once-Daily Extended-Release Tacrolimus in Renal Transplant Recipients: 2-Year Results and Review of the Literature

Table 1. Baseline Characteristics

Characteristics	n=130
Age (y)	53
Sex (men)	73 (56%)
Graft function (creatinine [μmol/L])	118
Years posttransplant	5.4

Figure 2. Tacrolimus Blood Levels After Conversion Over Time

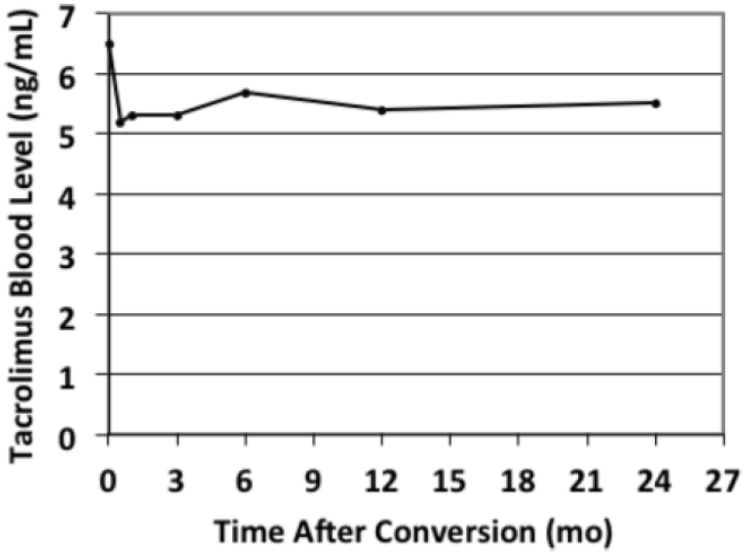

Figure 3. Proportion of Patients With Higher or Lower Dosage of Extended-Release Tacrolimus After Conversion Over Time (Compared to Baseline)

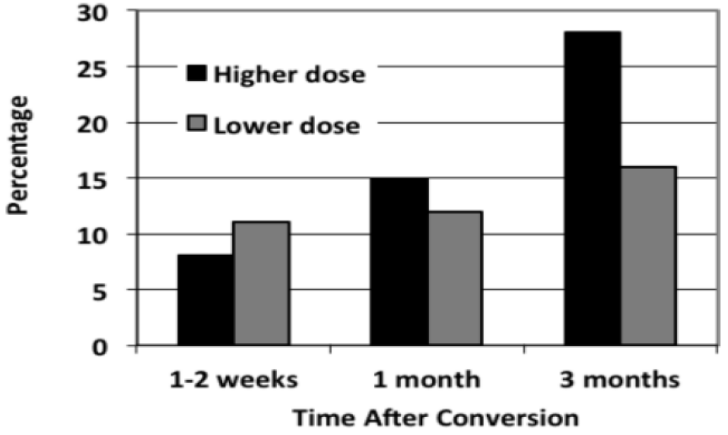

Table 3. Variation in the Doses of Extended-Release Tacrolimus (Compared With Baseline)

Change in Dosage (mg)	1-2 wk	1 mo	3 mo
>- 1.5	0	0	0
-1	1%	2%	2%
-0.5	10%	10%	14%
No change	81%	74%	56%
+0.5	8%	10%	16%
+1 0	5%	9%	
>+ 1.5	0	0	3%

Personal Experience - 1:

Patients start with tacrolimus bid at transplantation.

Switch to tacrolimus once daily at discharge.

Check tacrolimus levels weekly thereafter (in 1st month).

Patients > 1 yr post-transplant are often reluctant to change.

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Personal Experience - 2:

If IPV is high: search for reason, discuss adherence, switch if agreed.

Need to switch high if IPV above 30%

Careful if IPV is high and mean [Tacrolimus] is low.

Switch to Advagraf TM on 1:1 basis, unless patient is already close to lower threshold of target range.

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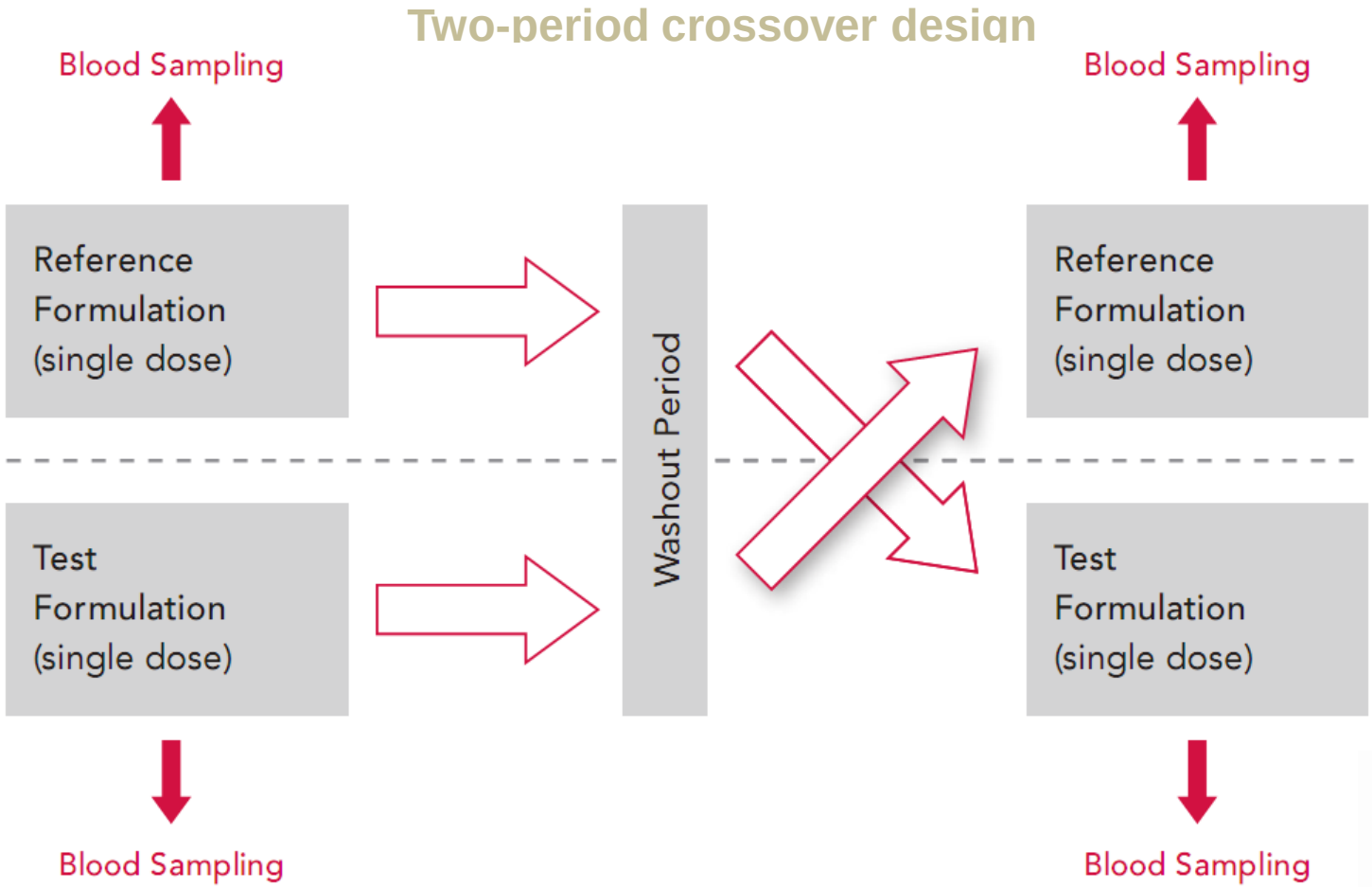
What is a generic drug?

…a drug that is comparable to brand/reference/innovator drug in dosage form, strength, route of administration and quality.

Two-period crossover design



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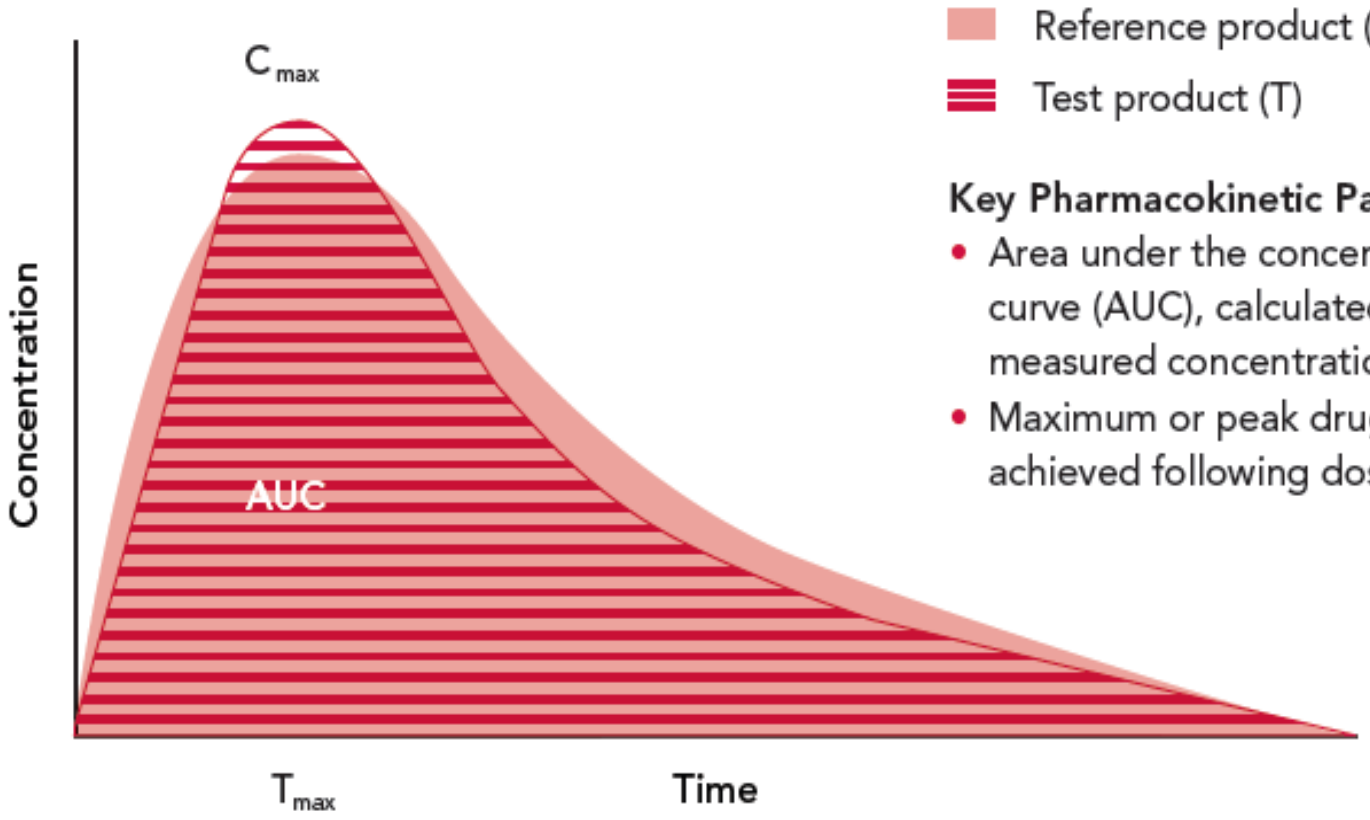
Bioequivalence Assessment Pharmacokinetic Parameters

Comparison of the key pharmacokinetic parameters, AUC and C_{max}



Reference product (R)

Test product (T)

Key Pharmacokinetic Parameters

- Area under the concentration-time curve (AUC), calculated to the last measured concentration (AUC_{∞})
- Maximum or peak drug concentration achieved following dosing (C_{max})

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Criteria for Demonstrating Bioequivalence

Two drug products are considered bioequivalent if 90% Confidence Intervals for both AUC and Cmax mean ratios fall entirely within the acceptance limits of 80–125%

Source: The European Agency for the Evaluation of Medicinal Products (CPMP). Note for guidance on the investigation of bioavailability and bioequivalence.

Available at http://www.emea.europa.eu/pdfs/human/qwp/140198enfin.pdf.

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Are drugs which are bioequivalent also interchangeable?

Perspective of health insurance companies.

Perspective of MDs.

Perspective of PharmDs.

Perspective of patients.

Transplant International

European Society for Organ Transplantation

Advisory Committee Recommendations on Generic Substitution of Immunosuppressive Drugs

Dr. Teun van Gelder

(on behalf of the ESOT Advisory Committee on Generic Substitution)

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Transplant International © 2011 European Society for Organ Transplantation 24 (2011) 1135–1141

Substitution: by whom and when?

If a patient is switched from innovator drug to generic drug then the treating physician may want to check drug concentrations in blood, and check if the patient is doing the right thing.

- crucial that MD takes the initiative to substitute, and not the PharmD

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Substitution: by whom and when?

If a patient is switched from innovator drug to generic drug then the treating physician may want to check drug concentrations in blood, and check if the patient is doing the right thing.

- crucial that MD takes the initiative to substitute, and not the PharmD

Health insurance companies should not force PharmDs to substitute.

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Concerns regarding substitution.

1. Who decides in whom and when substition takes place?
2. Following a first substitution there will be more substitutions to other generic formulations.

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Concerns regarding substitution.

1. Who decides in whom and when substition takes place?
2. Following a first substitution there will be more substitutions to other generic formulations (price driven)
3. (Repetitive) substitutions will lead to confusion and mistakes.

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Confusion and mistakes

Successively providing patients with different generic formulations will lead to confusion and errors and to reduced adherence.

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ORIGINAL RESEARCH | Annals of Internal Medicine

Burden of Changes in Pill Appearance for Patients Receiving Generic Cardiovascular Medications After Myocardial Infarction

Cohort and Nested Case–Control Studies

Aaron S. Kesselheim, MD, JD, MPH; Katsiaryna Bykov, PharmD, MS; Jerry Avorn, MD; Angela Tong, MS; Michael Doherty, MS; and Niteesh K. Choudhry, MD, PhD

Ann Intern Med. 2014;161:96-103.

Conclusion: Variation in the appearance of generic pills is associated with nonpersistent use of these essential drugs after MI among patients with cardiovascular disease.

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Conclusions:

1. In Europe : ESOT guideline has supported physicians in their discussions with payers.

2. In Netherlands: almost no generic substitution of tacrolimus

3. Special considerations for Iran:

- procedures for registration of generic products
- surveillance of drug producing companies (quality?)
- financial considerations (co-payment?
- prescriber vs payer (government and/or health insurance company)
- national or international guideline? Iranian Soc Tx?

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In Summary

Tacrolimus is still the cornerstone of immunosuppression after tx.

We have learned that tacrolimus levels should remain sufficiently high.

Intra-patient variability can identify patients at risk for poor outcome.

Once daily dosing can improve adherence and reduce variability.

Tacrolimus is classified as NTI: should only use formulations that fulfill bioequivalence criteria according to EMA guidelines

tvangelder@lumc.nl

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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: +98 21 8605 6520

Advagraf Caps all strength- SmPC- IR- en- Mar 2020

Prograf Caps all strength-SmPC-IR-en-Sep 2019

Erasmus MC

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