Pharmacokinetic of tacrolimus QD (Advagraf) in kidney transplantation

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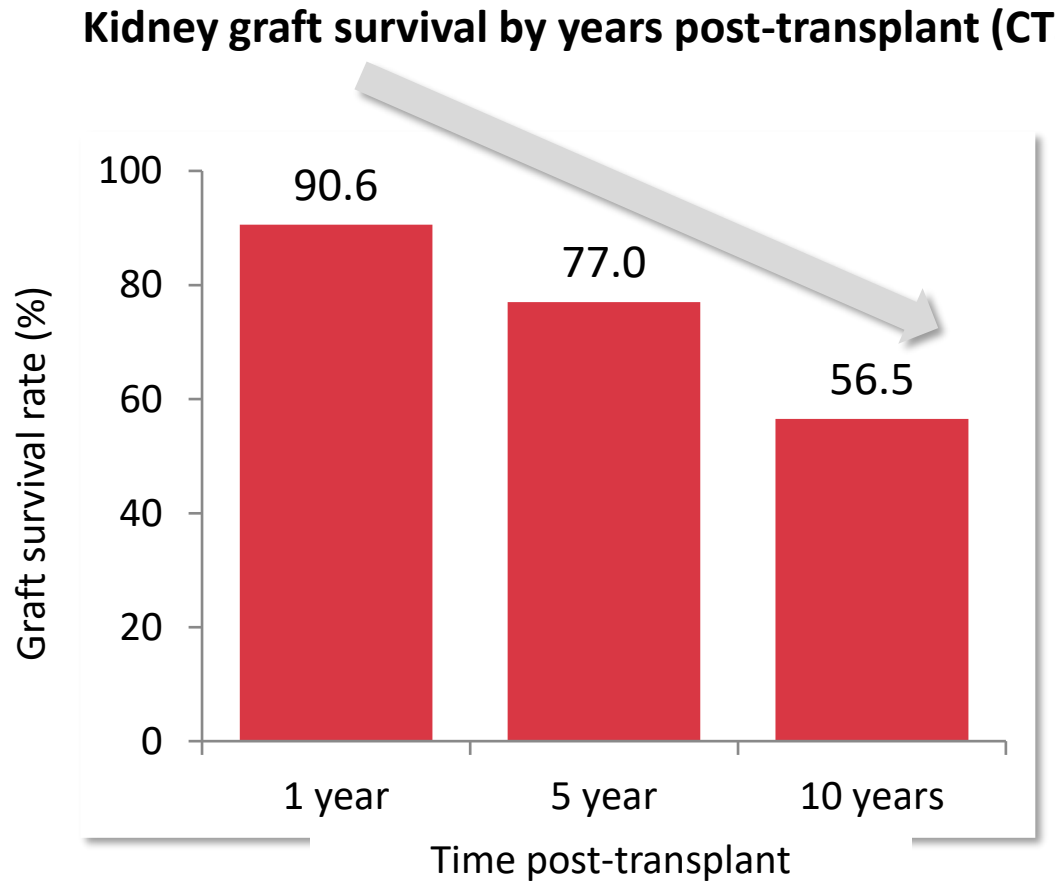
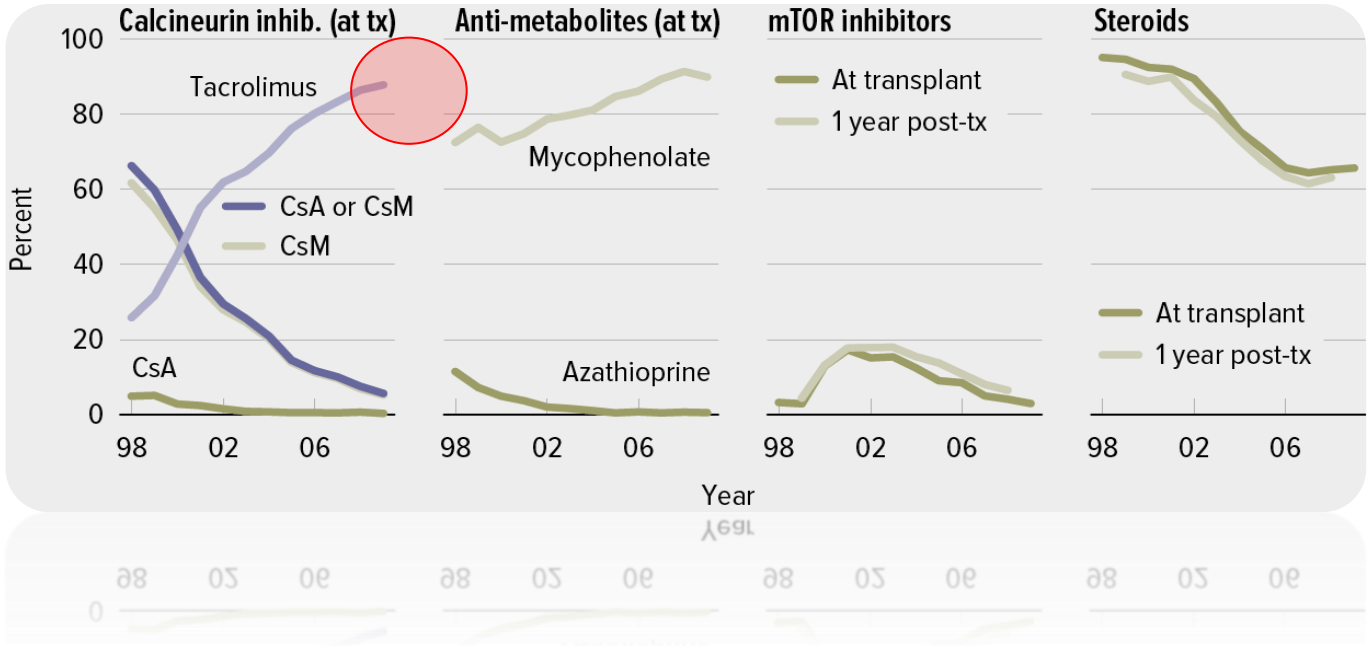
Maintaining long-term graft survival remains a challenge in kidney transplantation



10-year kidney graft survival rate is low (<60%)

CTS, Collaborative Transplant Study, Gondos A, et al. Transplantation 2013;95(2):267–74

Immunosuppression use in adult Kidney Transplant Recipients

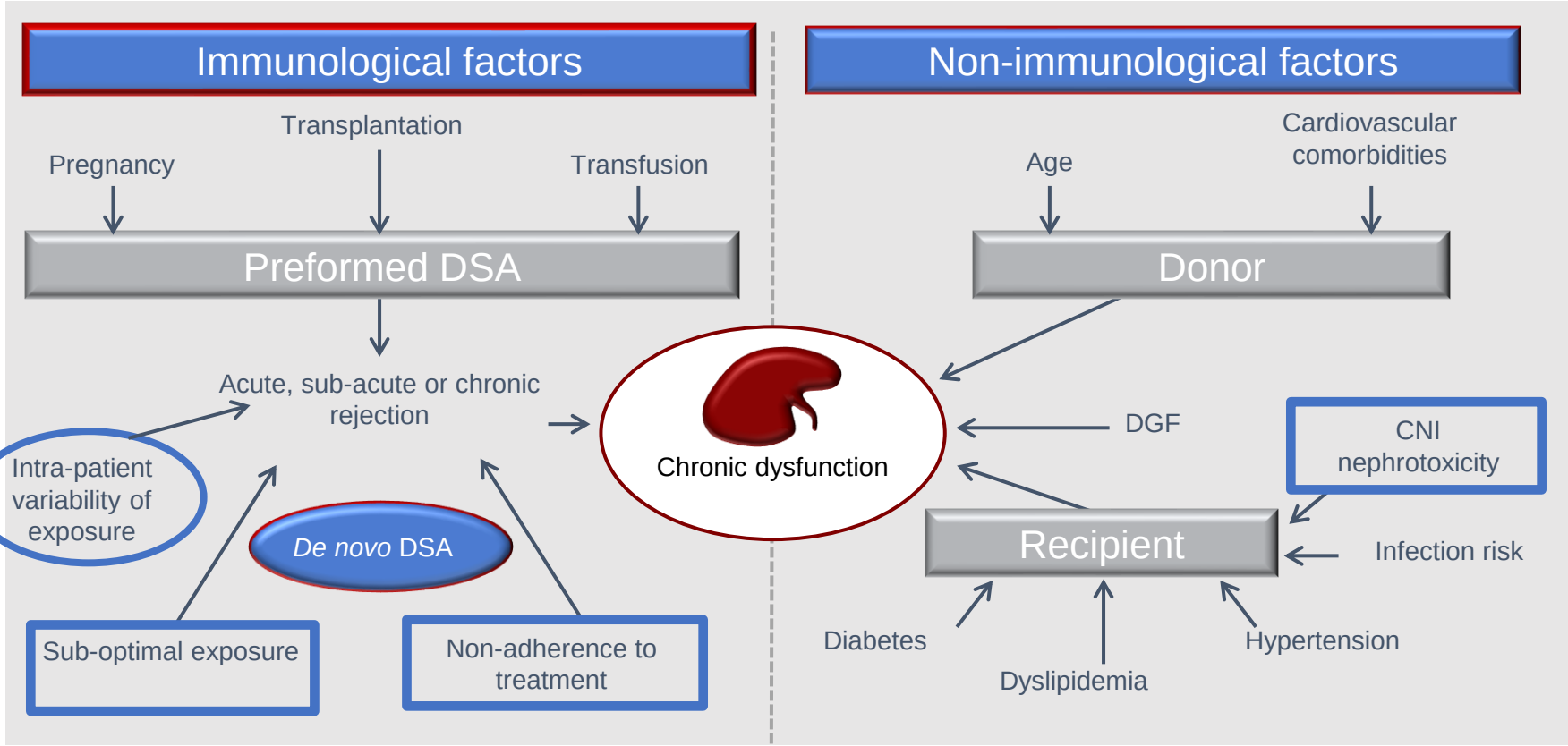


Similar trends observed on OPTN & SRTR Annual Data Report, 2016

United States Organ Transplantation - OPTN & SRTR Annual Data Report, 2010

Tacrolimus is now the cornerstone of IS therapy

Different factors impact on the life of the transplanted kidney



Lefaucheur C et al. *J Am Soc Nephrol* 2010;21:1398–1406; Sellares J et al. *Am J Transplant* 2012;12:388–399; Pascual M et al. *N Engl J Med* 2002;346:580–590; Legendre C et al. *Transpl Int* 2014;27:19–27; Sapir-Pichhadze R et al. *Kidney Int*. 2014;85(6):1404-11

Intra-patient Variability (IPV) of tacrolimus exposure

What is IPV?

Many factors can influence inter and intra-patient variability of tacrolimus exposure – examples

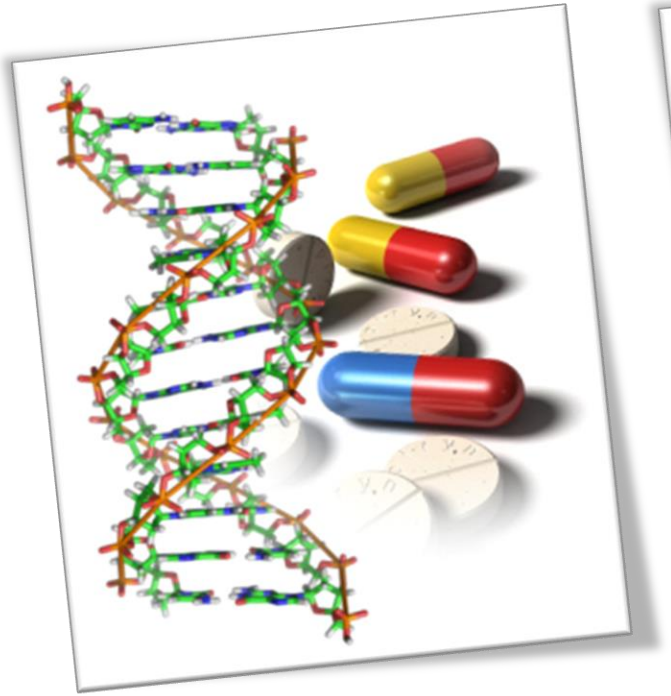
Factors	Inter-patient variability	Intra-patient variability
Genetic polymorphisms (e.g., CYP3A5)[3]	√	√
Food and Drug-drug interactions[1]	√	√
Race[2]	√	√
Pathophysiology e.g., liver dysfunction[2]	√	√
Non-adherence[4]		√
GI motility[1]/Diarrhoea[1]		√
Haematocrit[5]		√
Plasma protein levels[5]		√
Time post-transplant[1]		√
Drug formulation[6]		√

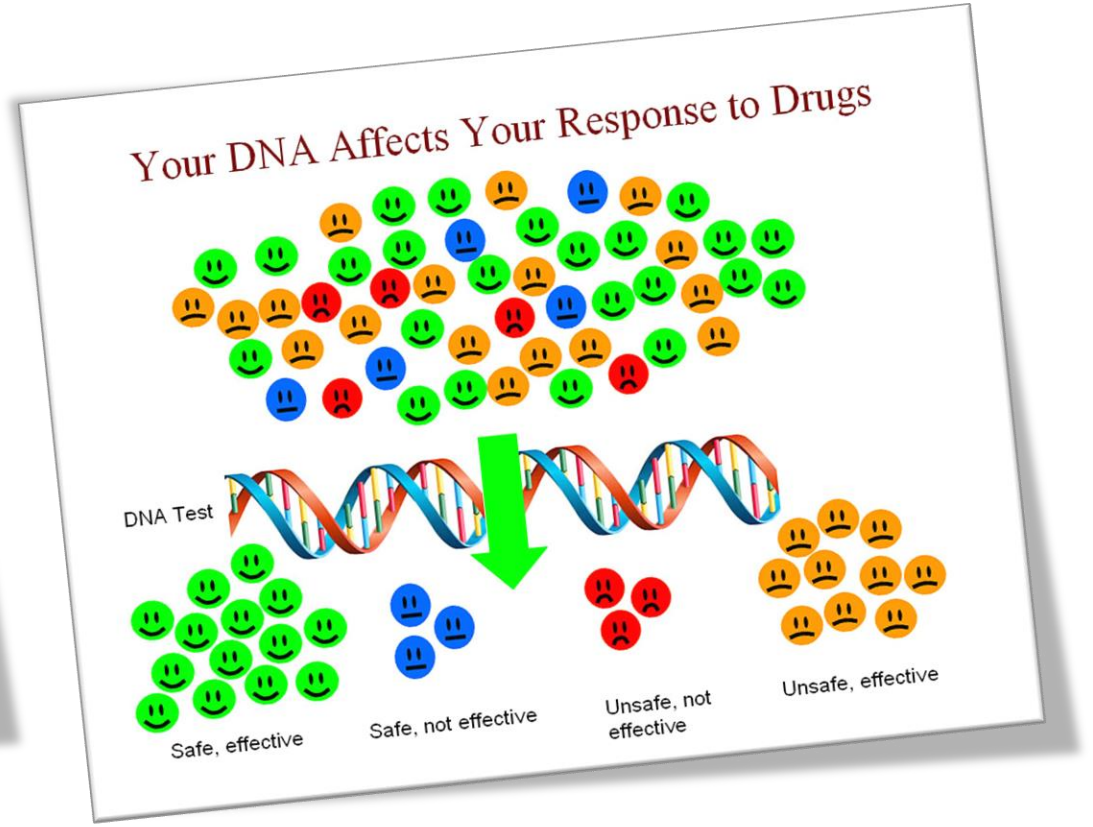
Modifying such factors can help to reduce variability in tacrolimus exposure – but this is not possible for all examples listed

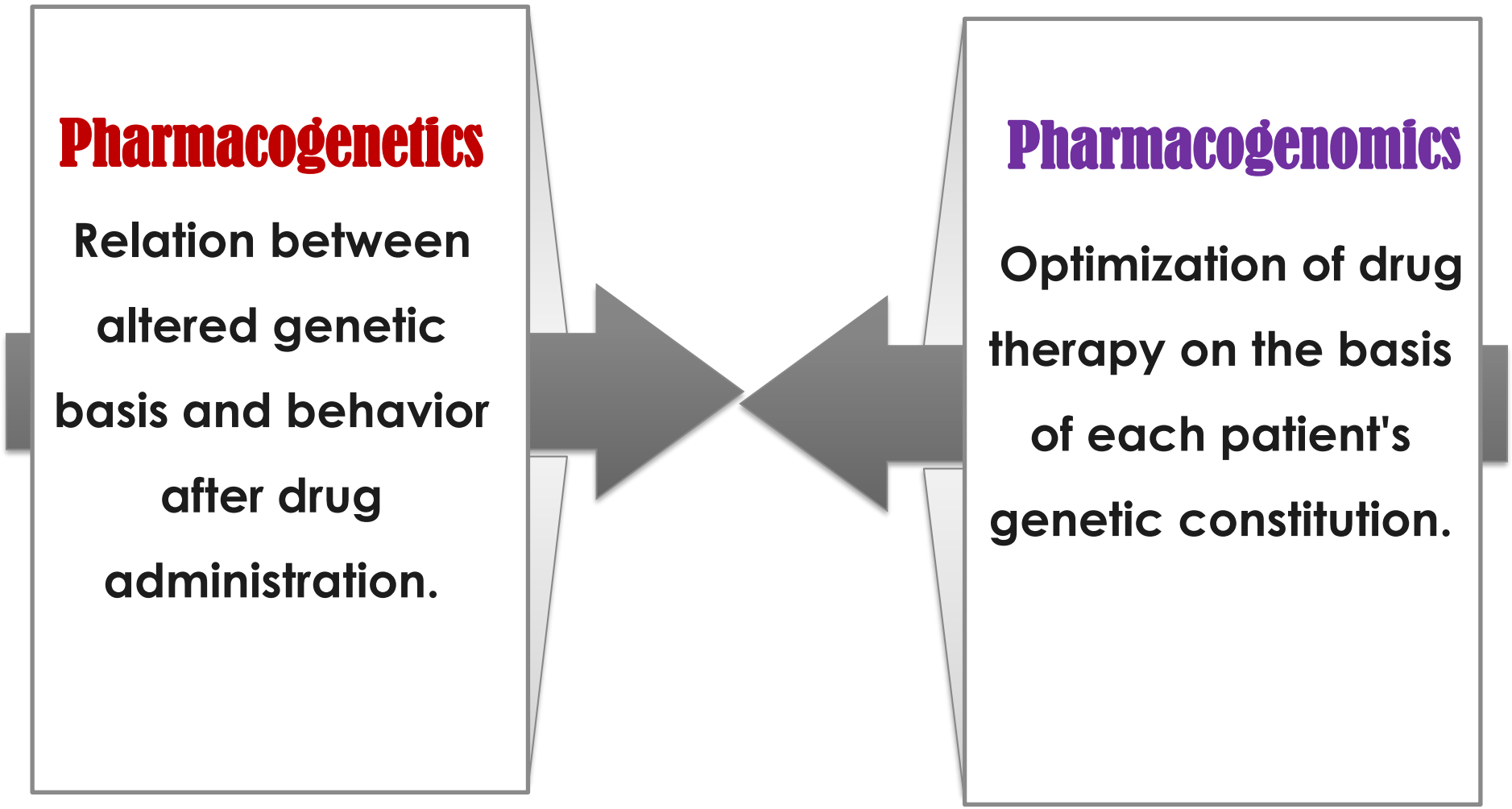
1. Shuker N, et al. Transplant Rev 2015;29(2):78–84. 2. Venkataramanan R, et al. Clin Pharmacokinet 1995;29:404–30.
3. Pashaee N, et al. Ther Drug Monit 2011;33(3):369–71. 4. Cervelli M, Russ G. Aus J Pharmacy 2012;93:83–6.
5. Undre NA. Nephrol Dial Transplant 2003;18(Suppl1):i12–i15. 6. Stifft F, et al. Transplantation 2014;97(7):775–80

Genetic polmorphisms

- Rapid advancement in genomics and transcriptomics assays has helped our understanding of the role of gene polymorphisms and changes in the transcription level of genes and its regulation.






Pharmacogenetics
Relation between altered genetic basis and behavior after drug administration.
Pharmacogenomics
Optimization of drug therapy on the basis of each patient's genetic constitution.

- **Single nucleotide polymorphisms (SNPs):** individual base positions in the genome that show natural variation in a population.
- SNPs represent the most abundant form of genetic variation in humans (> 90% differences between unrelated individuals).

Genes affecting TAC metabolism

- Genes encoding:
  - (CYP) 3A family enzymes
  - P-glycoprotein.
- CYP3A and P-gp are largely responsible for the poor oral bioavailability of TAC.

Cytochrome P450

- It is the generic name given to a large family of heme-containing enzymes.
- These enzymes are involved in the metabolism of xenobiotics, steroidogenesis and fatty acid metabolism.

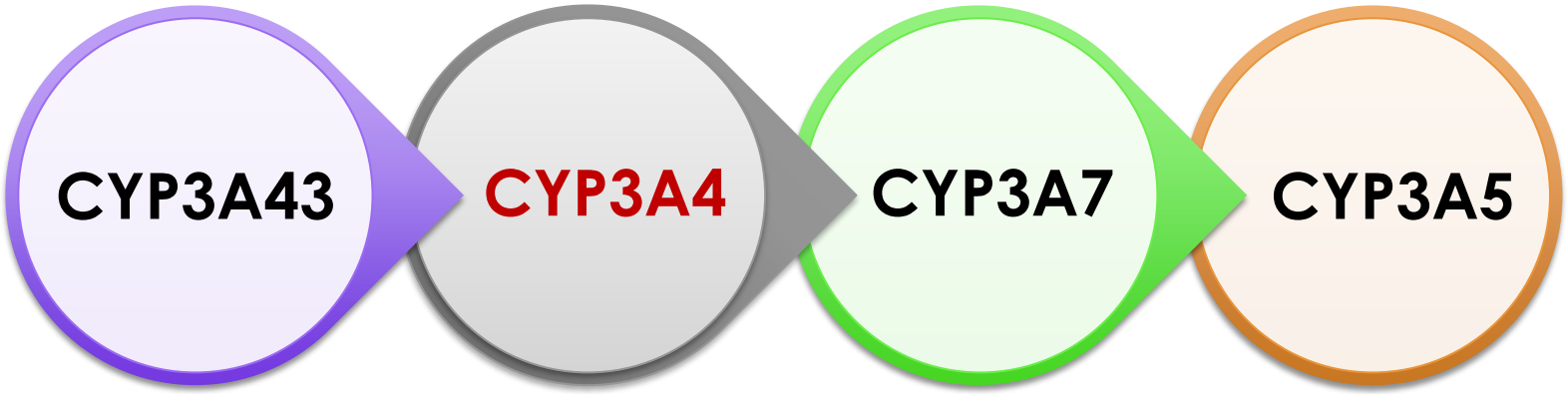
The human genome project identified 57 human CYP450 enzymes, ordered in 18 families and 43 subfamilies by sequence similarities.

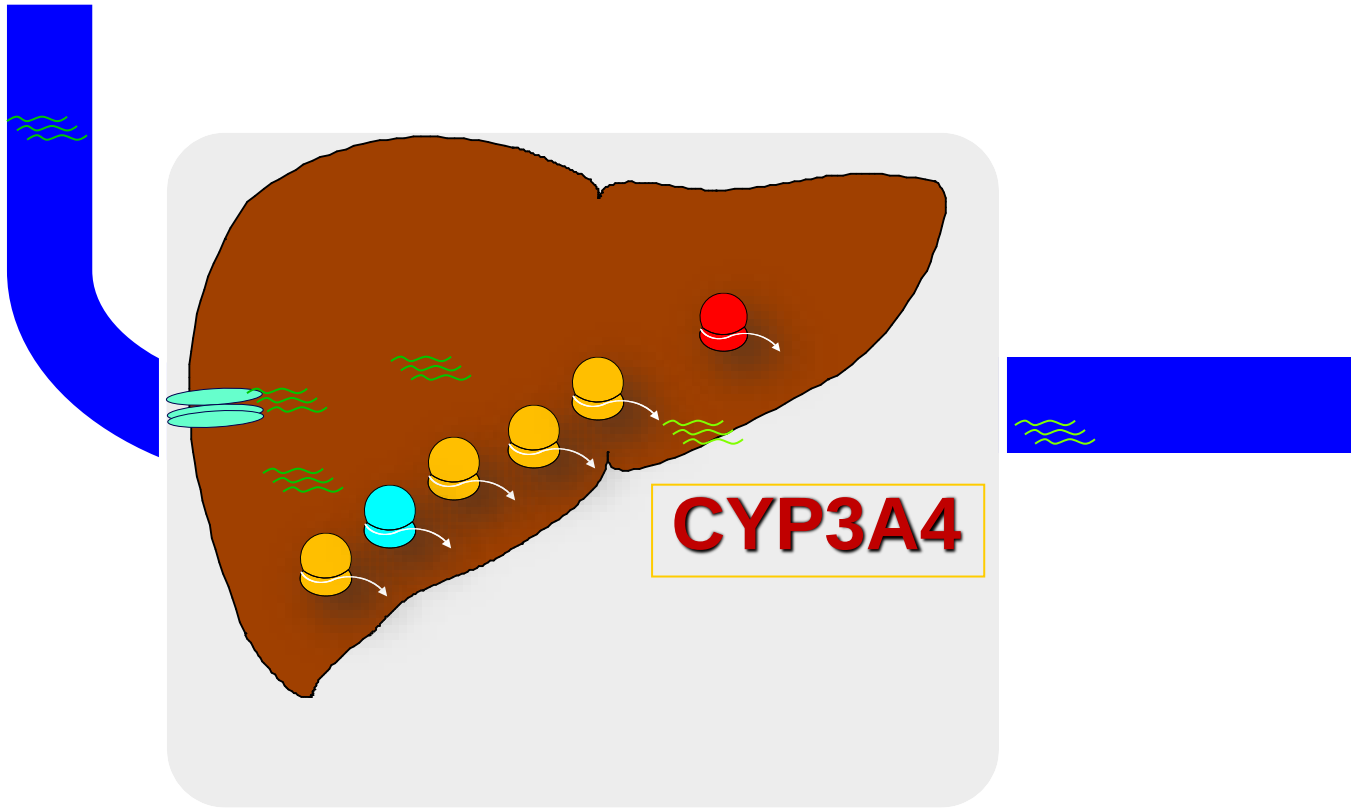
Human cytochrome P450 genes

Human P450 families	Functional members	Main functions
CYP1 (3 subfamilies)	1A1, 1A2, 1B1	Drug/xenobiotic metabolism
CYP2 (13 subfamilies)	2A6, 2A7, 2A13, 2B6, 2C8, 2C9, 2C18, 2C19, 2D6, 2E1, 2F1, 2J2, 2R1, 2S1, 2U1, 2W1	Drug/xenobiotic and steroid metabolism
CYP3 (1 subfamily)	3A4, 3A5, 3A7, 3A43	Drug/xenobiotic metabolism
CYP4 (6 subfamilies)	4A11, 4A22, 4B1, 4F2, 4F3, 4F8, 4F11, 4F12, 4F22, 4V2, 4X1, 4Z1	Arachadonic acid and fatty acid metabolism
CYP5 (1 subfamily)	5A1	Thromboxane A_2 synthesis
CYP7 (2 subfamilies)	7A1, 7B1	Rate-limiting step of bile acid biosynthesis (cholesterol elimination)
CYP8 (2 subfamilies)	8A1, 8B1	Prostacyclin and bile acid biosynthesis
CYP11 (2 subfamilies)	11A1, 11B1, 11B2	Key steps in steroid biosynthesis
CYP17 (1 subfamily)	17A1	Testosterone and oestrogen biosynthesis
CYP19 (1 subfamily)	19A1	Oestrogen biosynthesis (aromatase)
CYP20 (1 subfamily)	20A1	Unknown
CYP21 (1 subfamily)	21A2	Steroid biosynthesis
CYP24 (1 subfamily)	24A1	Vitamin D metabolism/inactivation
CYP26 (3 subfamilies)	26A1, 26B1, 26C1	Retinoic acid metabolism/inactivation
CYP27 (3 subfamilies)	27A1, 27B1, 27C1	Bile acid biosynthesis, vitamin D activation
CYP39 (1 subfamily)	39A1	Cholesterol metabolism
CYP46 (1 subfamily)	46A1	Cholesterol metabolism
CYP51 (1 subfamily)	51A1	Cholesterol biosynthesis

The enzymes transforming drugs in humans belong to the CYP families 1–4.

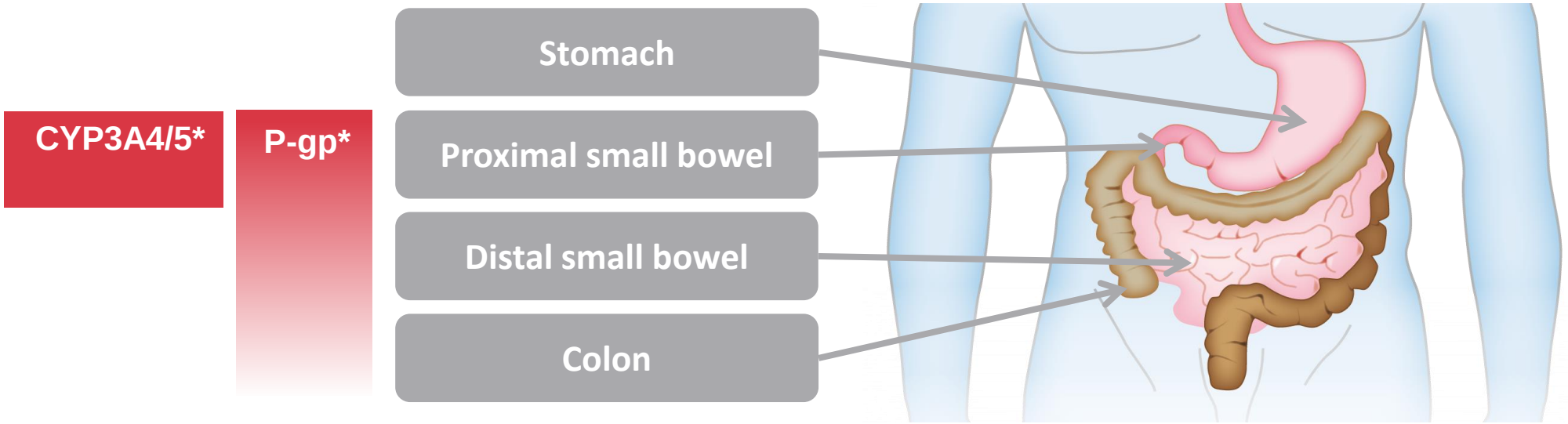
- **Cytochrome 3A subfamily** is the most abundant subfamily of the CYP450, localized in the kidney, intestine and the liver.
- This **family** has **4** isoforms located on **chromosome 7q21** in the order of:





30% of CYP3A4 expression is in the liver

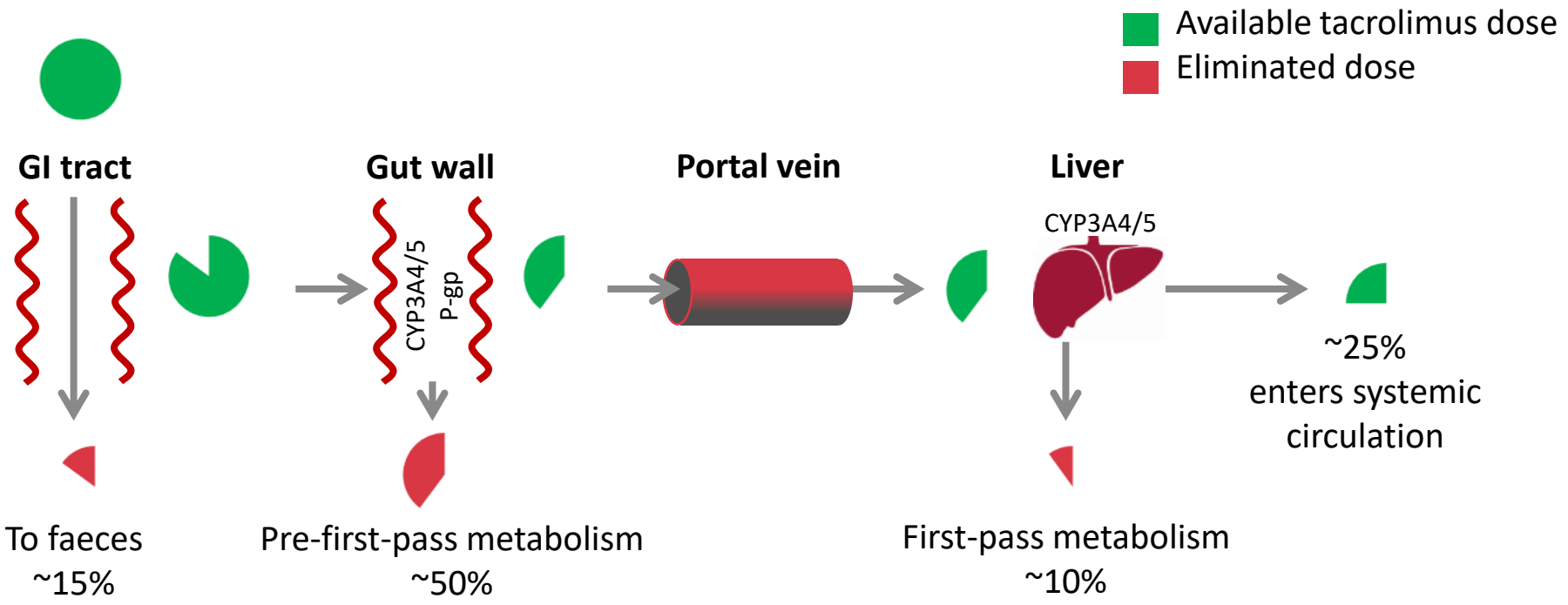
Oral tacrolimus is able to be absorbed throughout the GI tract and is influenced by CYP3A4/5 and P-gp



Tacrolimus absorption is rapid but bioavailability is low and variable[1,2]

1. Mekki Q, et al. Clin Pharmacol Ther 1993;53:238. 2. Prograf summary of product characteristics.
3. Jeong H, Chiou WL. Xenobiotica 2006;36(1):1–13. 4. Tuteja S, et al. Transplantation 2001;71(9):1303–7.
5. Cervelli M, Russ G. Aus J Pharmacy 2012;93:83–6

Oral tacrolimus is a substrate of CYP3A and P-gp in the GI tract[1,2]

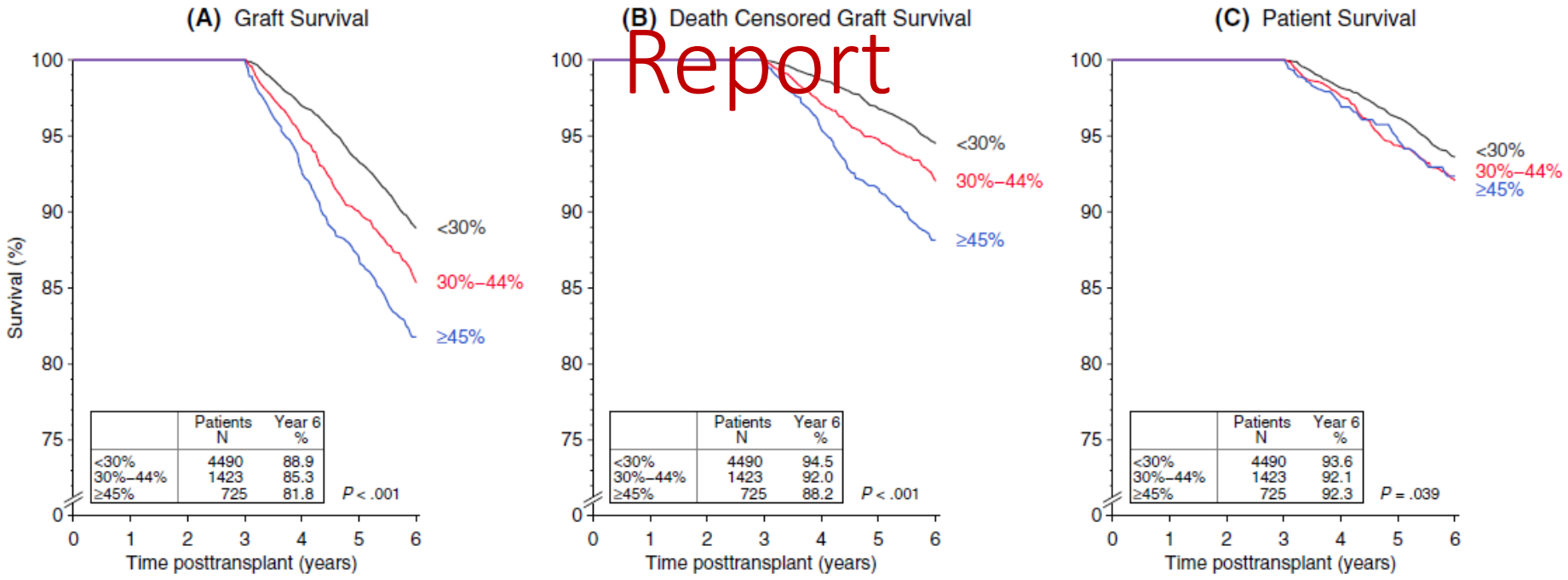


Mean oral bioavailability of tacrolimus is 20–25% (individual range in adult 6–43%)[3]

Modifying delivery by formulation change could affect IPV

1. Undre NA. Nephrol Dial Transplant 2003;18(Suppl1):i12–i15. 2. Cervelli M, Russ G. Aus J Pharmacy 2012;93:83–6.
3. Advagraf summary of product characteristics

Late IPV is a major problem in kidney transplantation: A CTS Report



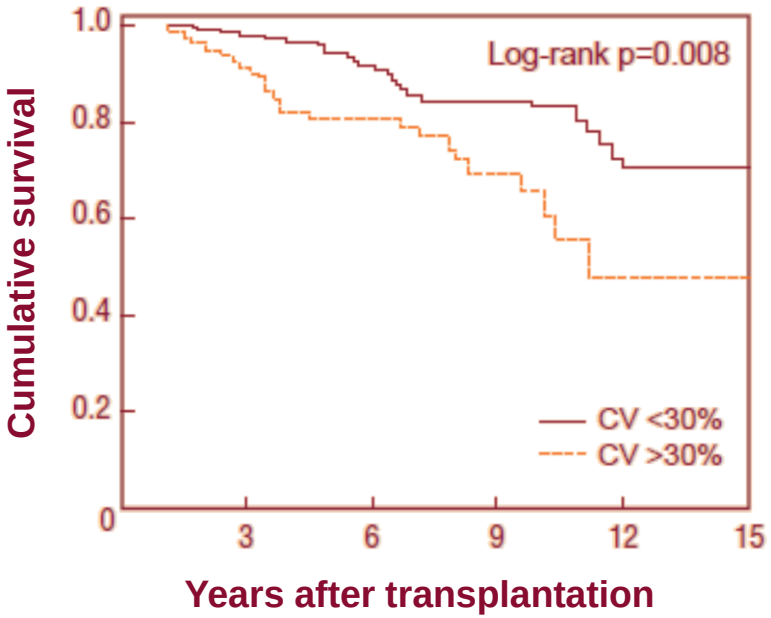
Influence of IPV of tacrolimus trough levels at years 1, 2, and 3 on post-transplant outcomes years 4-6 (P value of log rank test with trend)

Adapted from Susal et al

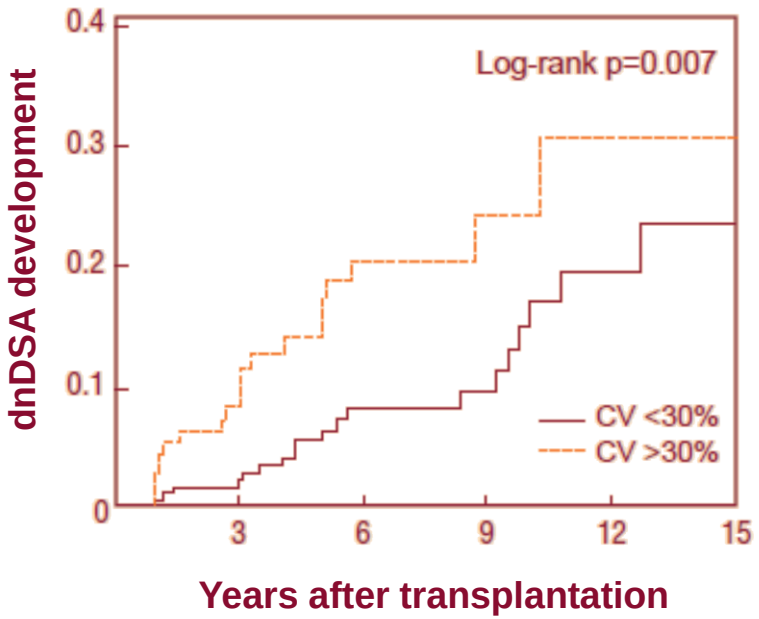
Caner Süsal, Am J Transplant. 2019;1–9.

High intra-patient variability is a predictor of graft loss and dnDSA development

Death-censored graft survival



dnDSA detection according to coefficient of variation



Adapted from reference 1.

dnDSA, *de novo* donor-specific HLA antibodies; CV, coefficient of variation
Rodrigo E, et al. Transplantation 2016;100:2479-2485.

Genetic polymorphisms in the CYP3A5 gene cause variability in systemic exposure to tacrolimus

Carriers of the CYP3A5*1 allele produce functional CYP3A5 protein[1]

– **Higher prevalence of CYP3A5*1 allele in black and Asian patients** than in Caucasian patients[1]

Homozygous carriers of the CYP3A5*3 allele produce low/undetectable levels of CYP3A5 protein[1]

Tacrolimus dose requirements are ~50% greater in patients with CYP3A5*1 allele (CYP3A5 expressors) than in CYP3A5*3 homozygotes (CYP3A5 non-expressors)[2]

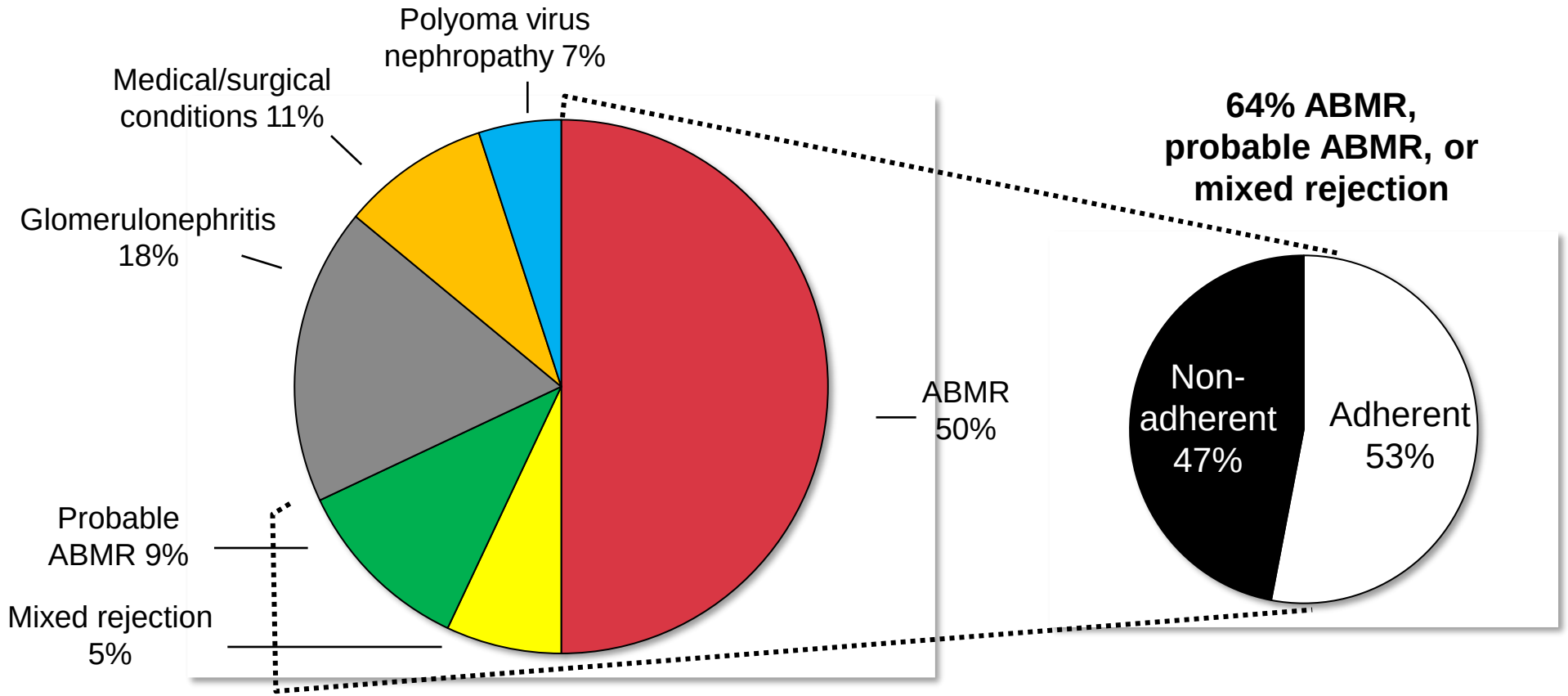
CYP3A5,[1] and to a lesser extent CYP3A4,[3] genetic polymorphisms are non-modifiable factors affecting inter-and intra-patient variability

CYP3A, cytochrome P450-3A

1. Staatz CE, et al. Clin Pharmacokinet 2010;49:141-175;
2 Hesselink DA, et al. Clin Pharmacokinet 2014;53:123-139;
3 Elens L, et al. Clin Chem 2011;57:1574-1583

Non-Adherence

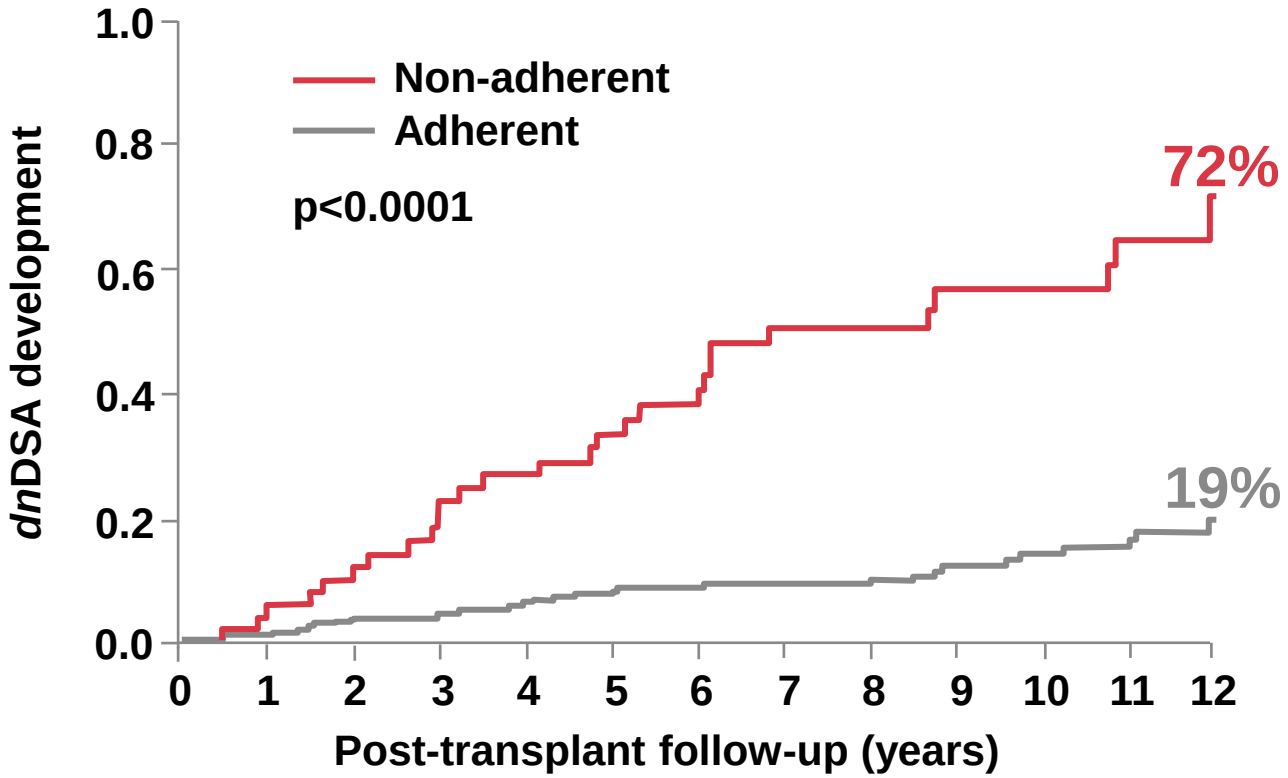
A high proportion of patients with kidney graft loss due to ABMR are non-adherent



A higher proportion of non-adherent patients were DSA+ than adherent patients (81% vs. 43%, p<0.001)

Sellarés J et al. *Am J Transplant* 2012;12;388–399.

Non-adherence is a predictor of *dn*DSA development in kidney transplantation



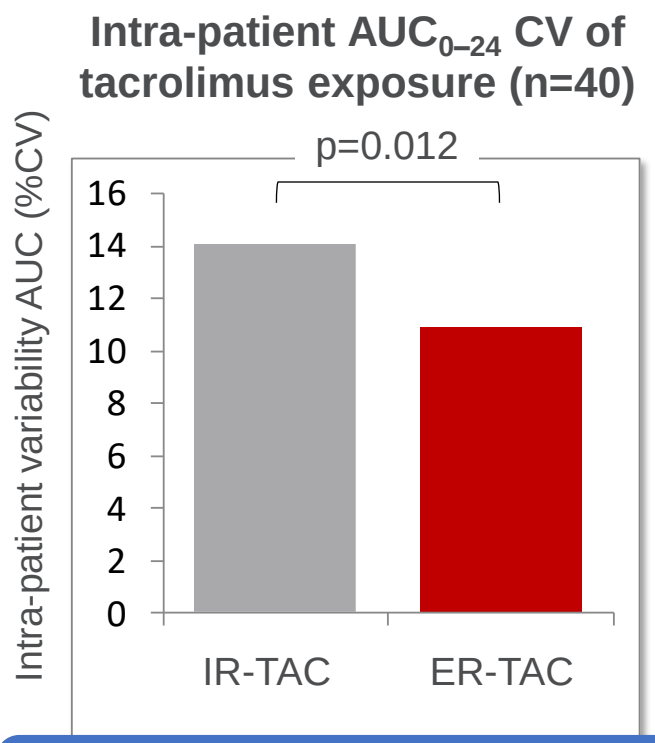
Non-adherence was an independent predictor of allograft failure following identification of *dn*DSA (HR 5.51, p<0.0001)

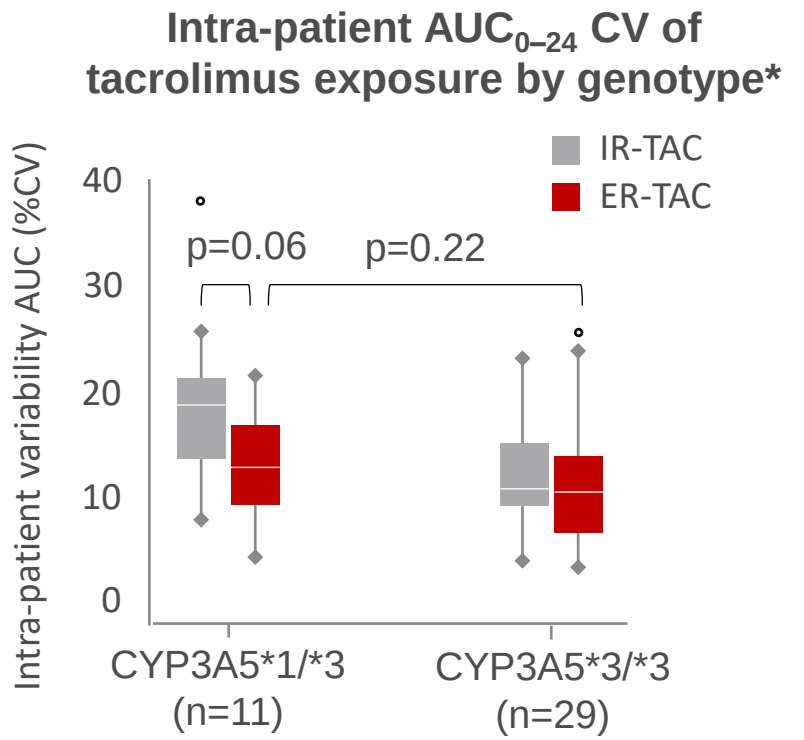
Wiebe C, et al. Am J Transplant 2015;15(11):2921–30

Pharmacokinetics Comparison

Does prolonged release tacrolimus have lower IPV?

Conversion from Prograf to Advagraf reduces IPV in tacrolimus $AUC_{0–24}$ in stable kidney transplant recipients





C_{min} intra-patient variability did not significantly change; however, tacrolimus $AUC_{0–24}$ CV reduced from 14.1% to 10.9% (p=0.012) following conversion from IR-TAC to ER-TAC

*On the graph, “o” denotes outlying value; horizontal black lines give the median, and the whiskers give the highest and lowest values with 1.5 times the inter-quartile range Right graph adapted from Stifft F, et al. (2014)

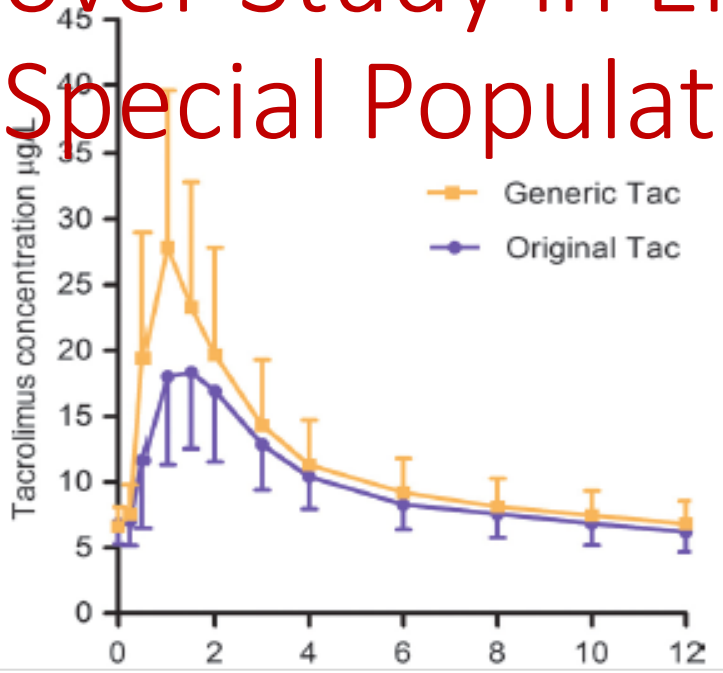
AUC, area under the curve; C_{min}, minimum concentration; CV, coefficient of variation; CYP3A, cytochrome P450 3A; IR-TAC: Immediate release tacrolimus; ER-TAC: Extended release tacrolimus

Stifft F, et al. Transplantation 2014;97(7):775–80

IR-TAC: Prograf
ER-TAC: Advagraf

Another source of variability
Brand vs Generic Formulations

between Original Tacrolimus and Generic Tacrolimus in a Randomised prospective Cross-over Study in Elderly Patients as Special Population



Mean (SD) whole blood concentration-time profiles of original and generic tacrolimus.

TABLE 2. Pharmacokinetic variables for original and generic tacrolimus

	Original Tac	Generic Tac	Ratio	90% CI	*P*
AUC_{0-12}, µg h/L	115±27	136±38	1.17	1.10–1.24	< 0.01
C_{max}, µg/L	19.6±6.3	30.2±11.6	1.49	1.35–1.65	< 0.01
C_0, µg/L	6.6±1.4	6.6±1.5	0.99	0.92–1.06	0.80
T_{max}, hr	1.4±0.7	1.1±0.5	0.71	0.55–0.91	0.04

All variables except T_{max} were ln-transformed before statistical analysis with an ANOVA model with fixed factors for treatment, period, sequence and a random factor for subject effect. T_{max} was analyzed using Wilcoxon signed rank test. Data are presented as mean±SD.

Robertsen I. et al, Transplantation. 2015;99(3):528-32

Percentage Change in Tacrolimus Trough Levels

The Impact of Conversion From Prograf to Generic Tacrolimus in Liver and Kidney Transplant Recipients With Stable Graft Function

J. D. Momper[a], T. A. Ridenour[b], K. S. Schonder[c], R. Shapiro[d], A. Humar[d] and R. Venkataramanan[a,e*]

Received 22 December 2010, revised 04 April 2011 and accepted for publication 07 April 2011

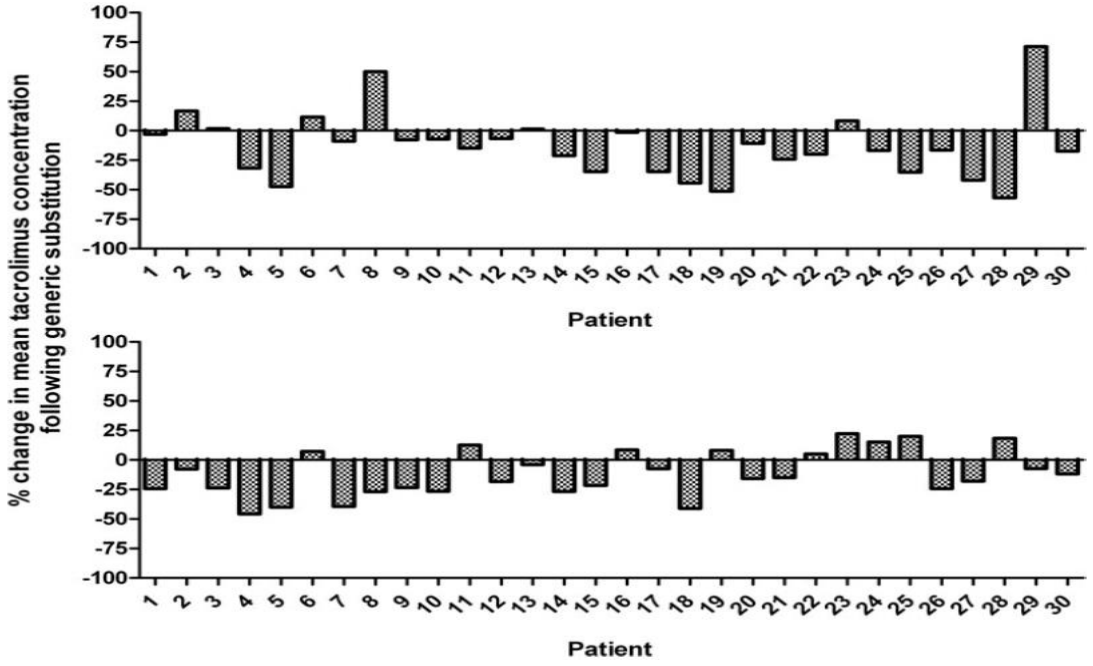


Figure 2: Percent change in the mean whole blood tacrolimus trough concentrations following generic substitution in liver (top) and kidney (bottom) transplant recipients when the dosing regimen remained constant.

Following switching between formulations patients should be monitored to ensure systemic exposure is maintained

Am J Transplant. 2011;11(9):1861-7

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THE Association of Tacrolimus Formulation Switching with Trough Concentration Variability

A Retrospective Cohort Study of Tacrolimus Use Post-Kidney Transplantation Based on National Drug Code (NDC) Numbers

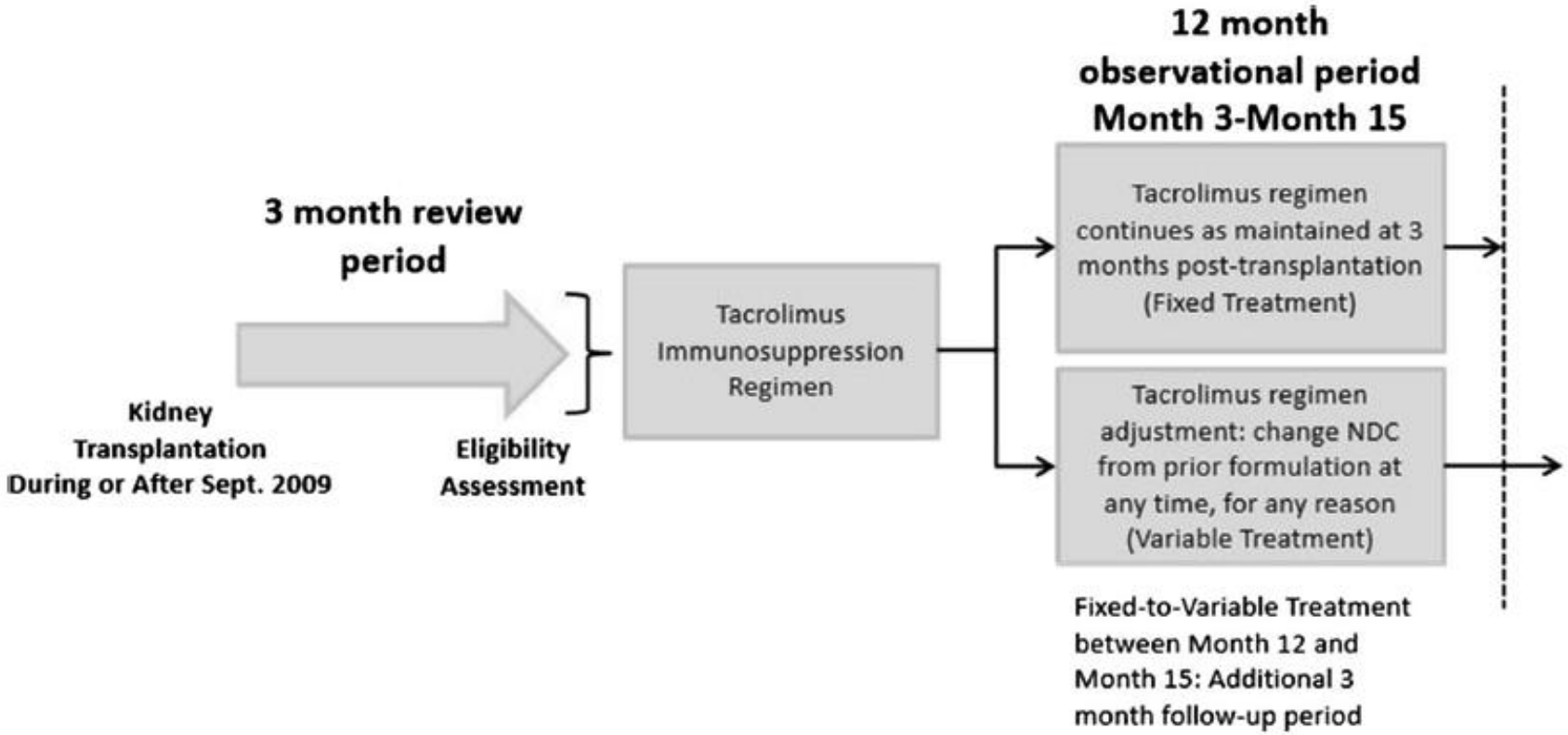
Hypothesis: Patients switching between tacrolimus formulations may have more variable levels than those remaining on 1 formulation.

Patients: Stable adult kidney transplant. Patients were categorized into two groups (fixed or variable formulation) using the US National Drug Code (NDC) on the basis of tacrolimus formulation usage over the 12-month period.

Schwartz et al, Adv Ther (2019) 36:1358–1369https://doi.org/10.1007/s12325-019-00950-5

THE Association of Tacrolimus Formulation Switching with Trough Concentration Variability

Study Design



305 patients enrolled from 4 US transplant centres; 44 (14.4%) multiple and 261 (85.6%) single formulation.

Schwartz et al, Adv Ther (2019) 36:1358–1369https://doi.org/10.1007/s12325-019-00950-5

THE Association of Tacrolimus Formulation Switching with Trough Concentration Variability

Table 3 Summary of tacrolimus use from month 3 through month 15 post-transplant

Tacrolimus use from month 3 through month 15 post-transplant	Fixed tacrolimus regimen (n = 261)	Variable tacrolimus regimen (n = 44)	p value
Tacrolimus dose adjustments, mean (SD)	2.4 (2.0)	2.8 (1.9)	0.237
Cumulative milligram dose change, mean (SD)	3.4 (3.4)	3.7 (2.8)	0.506
Tacrolimus trough to dose ratio, mean (SD)	2.02 (1.7)	2.22 (1.7)	< 0.001
Number of trough level measurements, mean (SD)	22.6 (9.5)	29.2 (12.7)	< 0.001
Tacrolimus trough level excursions from month 3 to 18, mean (SD)	10.5 (6.1)	13.9 (7.9)	< 0.001

p value: general linear model for continuous variables and Fisher's exact test for categorical variables
SD standard deviation

Tacrolimus trough level excursions above ±20% of the patient's mean trough concentration.

Schwartz et al, Adv Ther (2019) 36:1358–1369https://doi.org/10.1007/s12325-019-00950-5

- He concluded that a variable Tacrolimus formula regimen was associated with a higher frequency of trough level measurements and a greater number of excursions in trough levels compared with continuing on a fixed formulation in this retrospective chart review study

Conversion to single generic Renal Transplant Unit

- Retrospective study:
- Study group (n=39): generic post-transplantation – 2013.
- Control group (n=159): Patients who had been receiving brand tacrolimus since transplantation during 2011 and 2012.
- Data analysed for first year post transplantation: both groups.
- The immunosuppression regimen was standardised for both groups, as alemtuzumab induction, 3 doses of steroid, tacrolimus (0.1 mg/kg/day) and mycophenolic acid (720 mg twice a day)
- Target trough for all patients was 10-12 ng/ml for the first 3 months, 8-10ng/ml in the second 3 months and 6-8ng/ml for the remainder of the study period.
- Significant variability of trough was defined as an increase or decrease of >20% on a stable dose requiring dose alteration

Hauch A et al, Surgery. 2015;158(4):1049-54

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Conversion to single Generic tacrolimus

Table II. First year posttransplantation tacrolimus dose adjustments and mean levels for the generic and branded tacrolimus group

	Generic	*Brand*	P *value*
Number of patients, %	39	159	
Tacrolimus changes, %	5.4 (±4.4)	3.6 (±3.6)	**.038**
Tacrolimus level, ng/mL			
Week 1	9.6 (±4.4)	8.8 (±4.3)	.35
Month 1	8.7 (±3.7)	9.9 (±4.2)	.13
Month 3	10.9 (±8.3)	9.2 (±3.3)	.085
Month 6	11.4 (±4.9)	8.8 (±4.5)	**.009**
Mg infusions, *n*	5.0 (±7.5)	1.7 (±2.1)	**.001**
CSA conversions, %	11.3 (±3.2)	10.3 (±3.2)	.85
Follow-up, y	1.2 (±2.1)	2.4 (±7.7)	**.001**

Data are presented as mean (±SD). Values in bold indicate statistical significance.
CSA, Cyclosporine; *Mg*, magnesium.

Table III. Posttransplantation incidence of rejection, type, and grade of rejections during the first year after transplantation for the generic and branded tacrolimus group

Number of patients, n	*Generic* 39	*Brand* 159	P *value*
Rejection episodes, *n*			
6 months	7 (17.9%)	10 (6.2%)	.062
1 y	9 (23.1%)	16 (10.2%)	**.024**
Acute rejection episodes, *n*	4 (10.3%)	11 (6.9%)	.48
Banff 1	3 (7.7%)	9 (5.6%)	.63
Banff 2	1 (2.5%)	2 (1.3%)	.55
Antibody mediated rejection episodes, *n*	5 (12.8%)	5 (3.1%)	**.013**
And Banff 1	4 (10.3%)	2 (1.3%)	**.003**
And Banff 2	1 (2.5%)	3 (1.9%)	.79
Chronic rejection, *n*	2 (5.1%)	5 (3.1%)	.98
Annualized rejections, *n*/y	19*	8	**<.001**

Hauch A et al, Surgery. 2015;158(4):1049-54

Conversion to single Generic Renal Transplant Unit

- Generic group had greater drug variability (20% change)
- Generic group had more dose adjustments (5.42 vs 3.59, P= 0.038
- Yearly institutional cost: $18,000/yearly pharmacy saving but hospital cost was $652,862/year to treat rejection episodes.
- Greater incidence of rejection 23.1% Vs 10.2% ; P= .024 and concluded that this government – driven attempt at cost saving may be applicable to noncritical medications but this policy should be reconsidered for narrow therapeutic index medications such as Tacrolimus and other immunosuppressive medications.

Hauch A et al, Surgery. 2015;158(4):1049-54

Actions from Regulatory Agencies

European Medicines Agency

Originally asked for amendments to SmPC (Section 4.2)

- New update: October 2019
- Different oral formulations of tacrolimus should not be substituted without clinical supervision.
- Inadvertent, unintentional or unsupervised switching between different oral formulations of tacrolimus with different release characteristics is unsafe. This can lead to graft rejection or increased incidence of adverse reactions, including under- or over-immunosuppression, due to clinically relevant differences in systemic exposure to tacrolimus. Patients should be maintained on a single formulation of tacrolimus with the corresponding daily dosing regimen; alterations in formulation or regimen should only take place under the close supervision of a transplant specialist (see sections 4.4 and 4.8). Following conversion to any alternative formulation, therapeutic drug monitoring must be performed and dose adjustments made to ensure that systemic exposure to tacrolimus is maintained

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Clinical Data
Immediate Release vs Prolonged Release

- The once – daily (QD) , prolonged – release formulation of tacrolimus has been shown to improve adherence versus twice daily (BD) Tacrolimus.

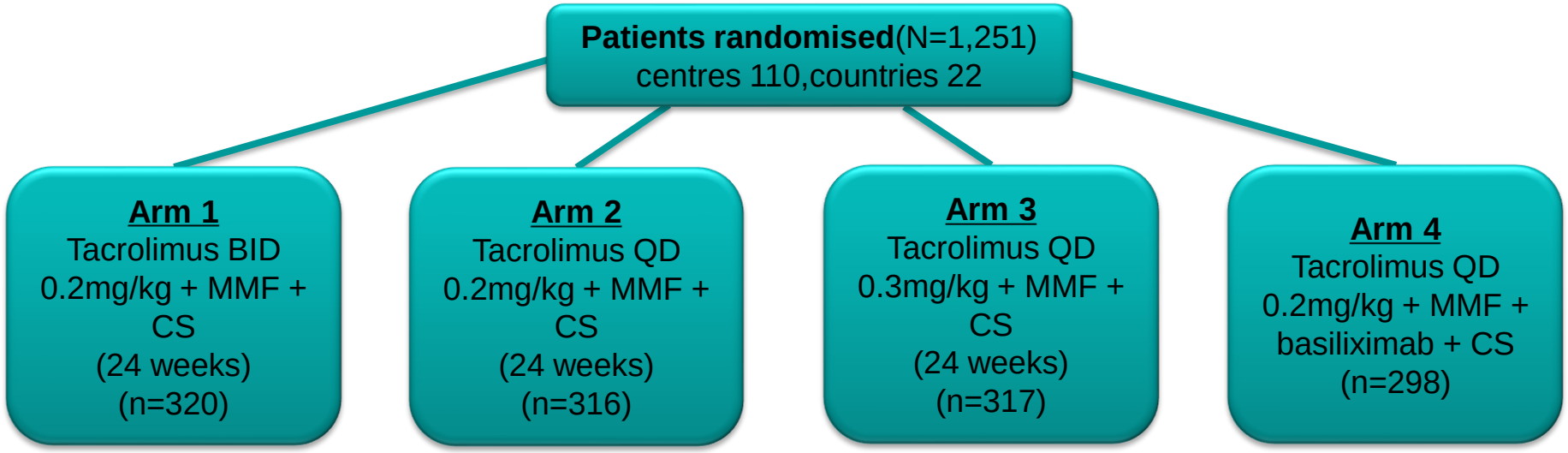
Non adherence in transplant recipients has been associated with poor graft outcomes.

Optimizing ImmunoSuppression After Kidney Transplantation with Advagraf™ (OSAKA study)

A multicenter, four-arm, randomized, open-label clinical study investigating optimized dosing in a PROGRAF™-/Advagraf-based immunosuppressive regimen in kidney transplant patients

Albano et al, Transplantation & Volume 00, Number 00, Month 00, 2013

Study design and analysis populations



Safety analysis set (SAF): patients who received ≥1 dose study medication

n=311 | n=309 | n=307 | n=287

Full analysis set (FAS): all patients from the SAF who were transplanted

n=309 | n=302 | n=304 | n=283

Per protocol set (PPS): all patients from the FAS who did not have major protocol deviations

n=237 | n=263 | n=246 | n=230

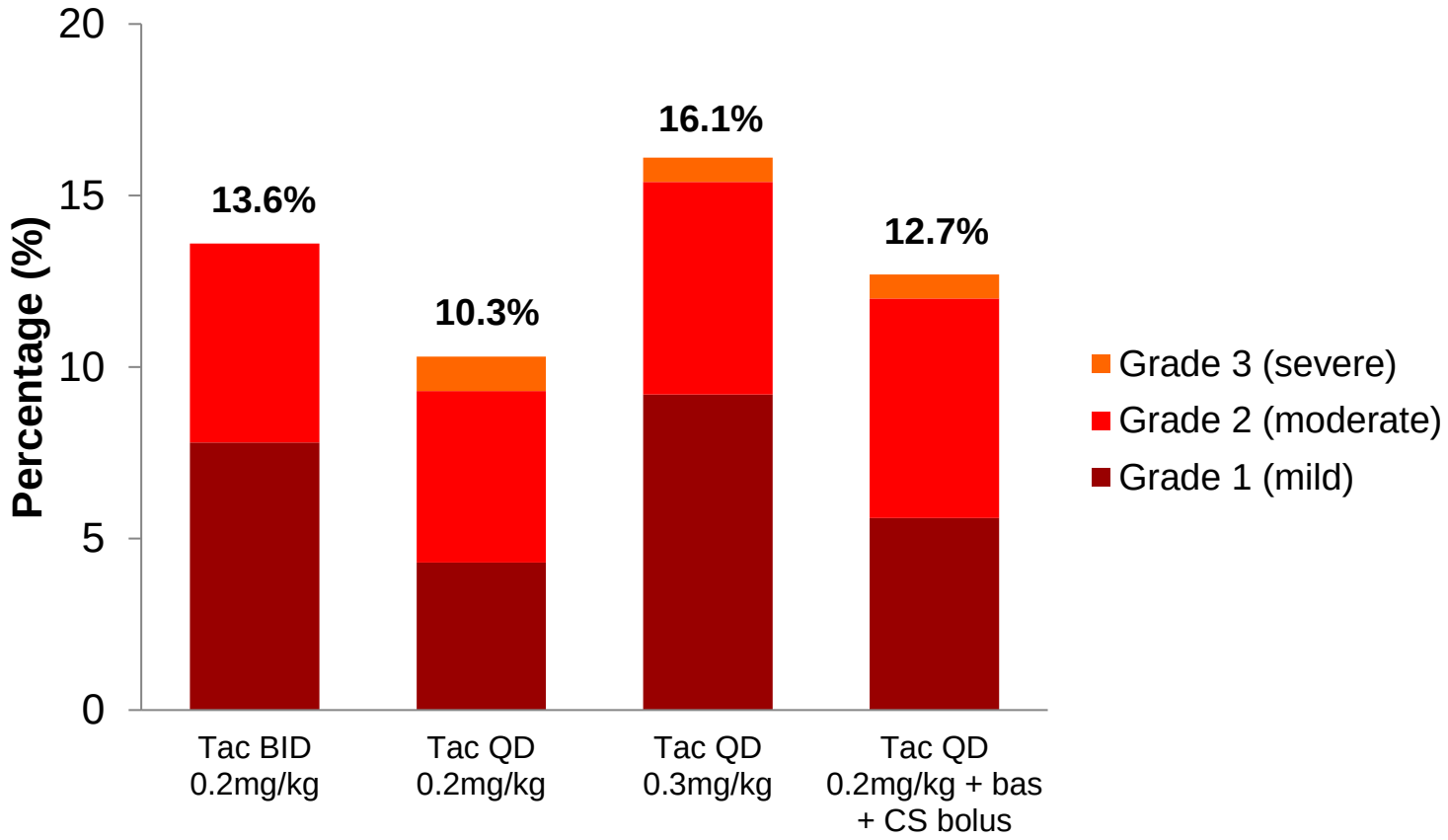
Target trough levels (ng/mL) :
10-15 (days 0-14); 5 12 (Days 15–42); 5–10 (Days 43 – 168)

Albano et al, Transplantation & Volume 00, Number 00, Month 00, 2013

- The primary composite end point efficacy failure was defined as graft loss, biopsy-confirmed acute rejection, or graft dysfunction at week 24 defined as eGFR < 40 ml/min/1.73 m^2 .

Results – BCAR

Incidence of BCAR was low, and time to first incidence of BCAR and severity of BCAR were comparable across treatment arms



(FAS)

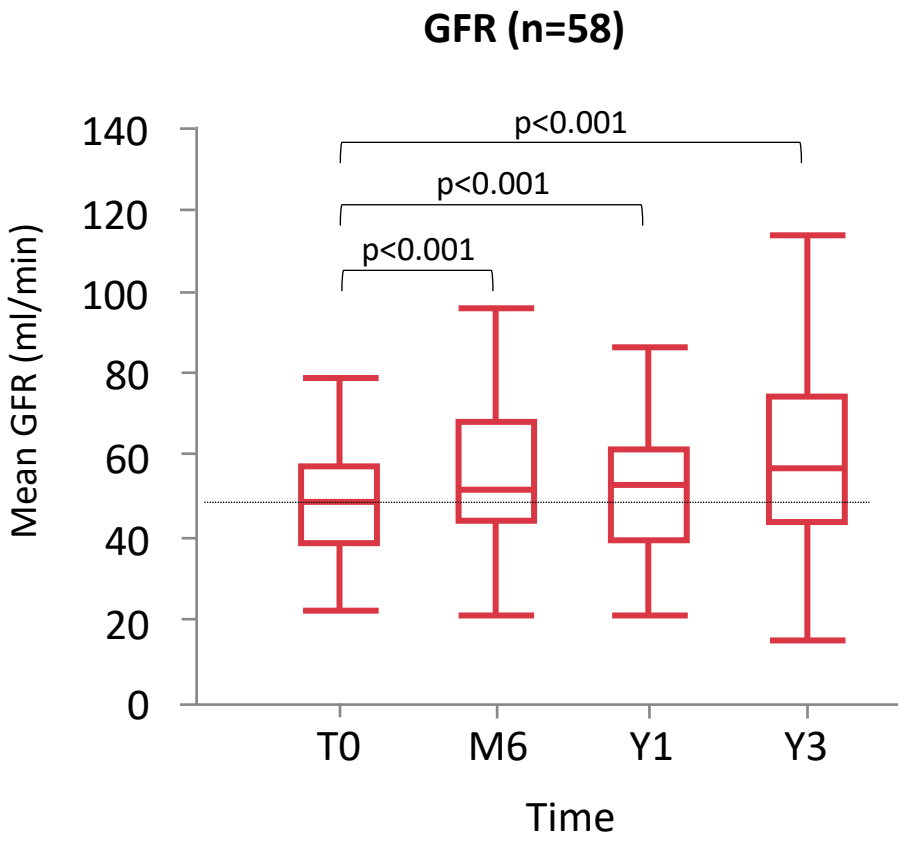
Albano et al, Transplantation & Volume 00, Number 00, Month 00, 2013

Summary: efficacy and safety OSAKA study

- At an initial daily dose of 0.2 mg/kg, Advagraf-based therapy without induction was non-inferior to Prograf-based therapy for efficacy and safety
- An increased starting dose of Advagraf (0.3mg/kg/day) offered no efficacy advantage
- BCAR was not increased in steroid avoidance arm (Basiliximab+Advagraf +MMF)
- Overall, renal function was similar on tacrolimus QD- and BID-based therapy

Albano et al, Transplantation & Volume 00, Number 00, Month 00, 2013

Conversion from Prograf to Advagraf is associated with beneficial renal effects over 3 years in stable kidney transplant patients



At 3 years, PR-TAC was associated with lower serum creatinine levels (1.47 vs. 1.67 mg/dl, p<0.05) and higher GFR (59.3 vs. 48.9 ml/min, p<0.001) than IR-TAC at baseline

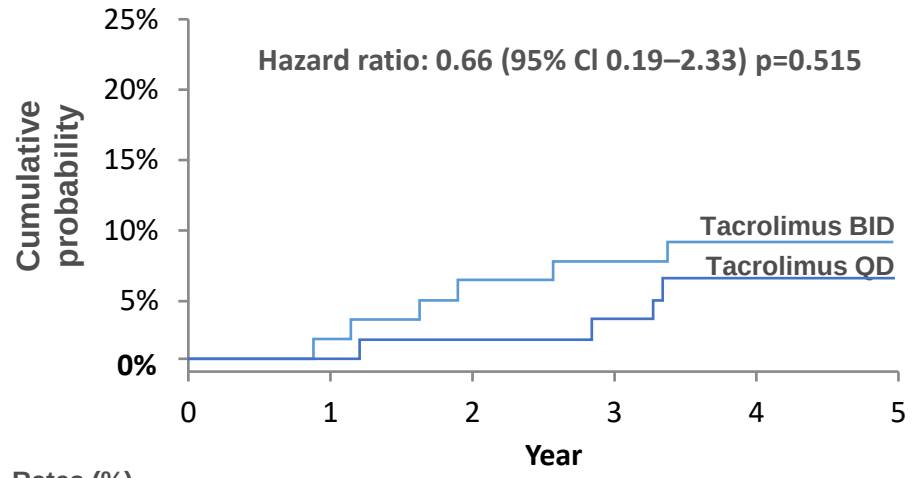
Adapted from Spagnoletti G, et al. Transplant Proc 2014;46(7):2224–7

- And suggested that improvement in renal function after conversion to ADV is related to the reduction of the 24- hour Tacrolimus area under the curve exposure.

Tacrolimus prolonged-release: 5-year graft-SURVIVAL in de novo living kidney transplant recipients

In a RCT once daily vs twice daily Tacrolimus for de novo living kidney transplantation.

Kaplan–Meier estimates for time to graft failure (non-censored for death)



Rates (%)						
Tacrolimus BID	0	1.6	6.3	7.9	9.5	9.5
Tacrolimus QD	0	0	1.6	3.2	6.5	6.5
No. at risk						
Tacrolimus BID	63	62	59	58	57	57
Tacrolimus QD	62	62	61	60	58	58

Adapted from **Okumi M, et al. 2018**[1]

In *de novo* living kidney transplant recipients, five-year cumulative graft failure rates were 6.5% and 9.5% for the tacrolimus QD (n=62) and tacrolimus BID (n=63) groups (noninferiority, p=0.009)

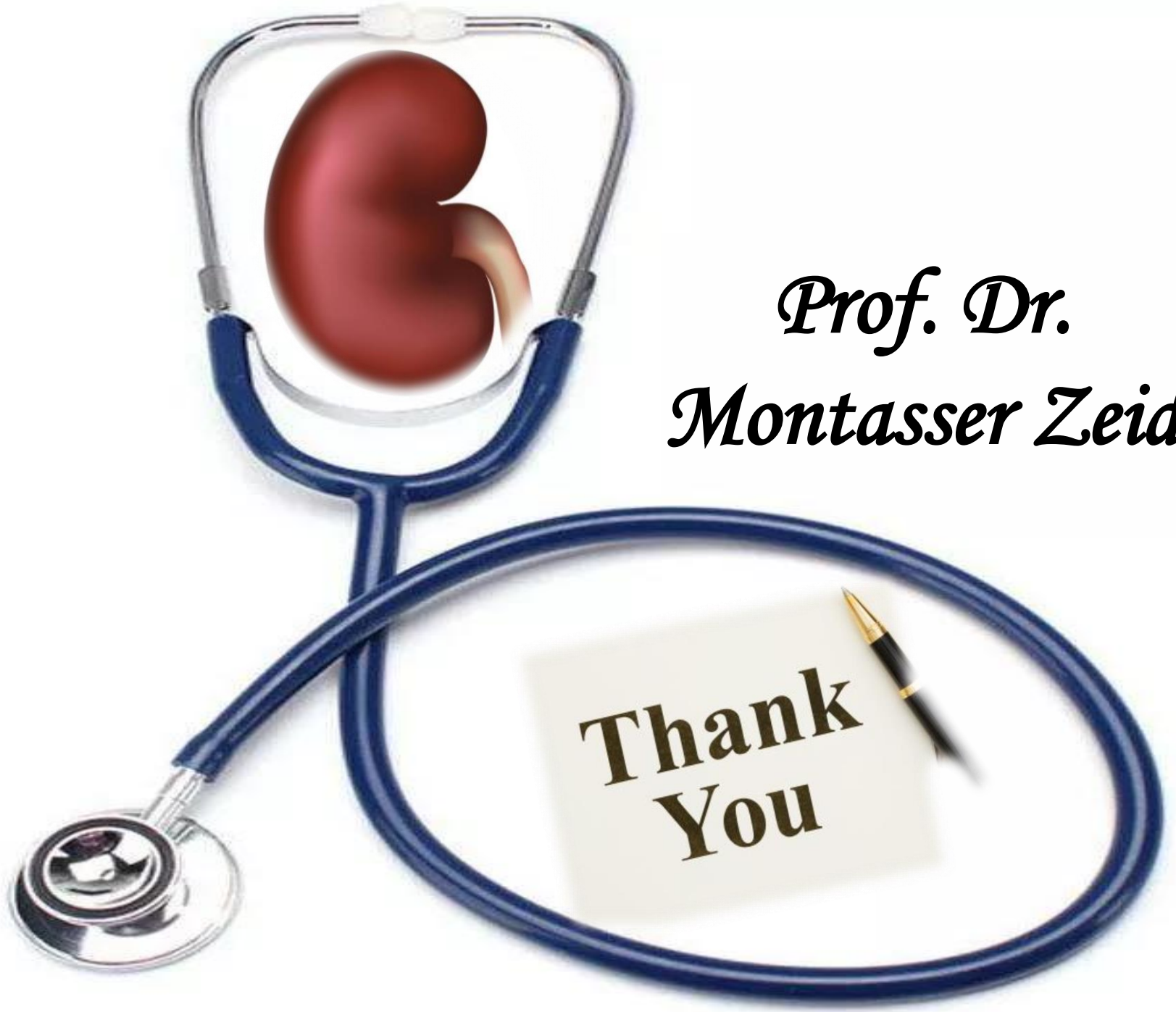
This study included patients with ABO/HLA incompatibilities

Okumi M, et al. Clin Transplant 2018;14:e13423

astellas

Overall Summary

- Maintaining long-term graft and patient survival is a challenge in kidney transplantation.
- Improving IPV may reduce the risk of sub-optimal immunosuppression and improve long-term outcomes.
- Sources of IPV:
  - Pharmacogenetics
  - Adherence
  - Switching between Branded and Generic Formulations
- Advagraf is the only formulation to demonstrate lower IPV compared to Prograf.
- In long term follow up Advagraf shows tendency for better renal function.



Prof. Dr.
Montasser Zeid