
**2017 BANFF-SCT**
**Joint Scientific Meeting**

**BARCELONA**
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**SCT Plenary 4**
**Thursday March 30, 2017**

# Pharmacogenetics to tailor Drug Exposure and Outcomes in Kidney Transplantation

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**The Netherlands**

# Disclosures

Consulting fees

Astellas Pharma, Glaxo Smith Kline, Novartis Pharma

Grant support

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Lecture fees

Astellas Pharma, Chiesi Pharma, Fresenius Medical Care, MSD, Roche

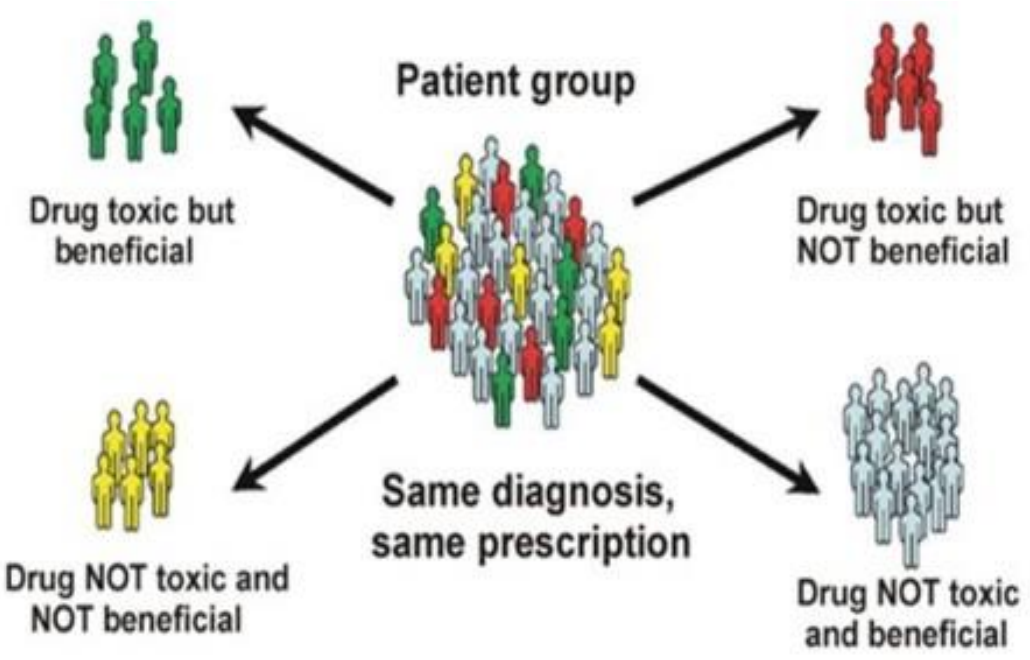







# “Personalized medicine”

- Choose the most appropriate drug for each individual
- Select an optimal dose
- Identify those at risk from (atypical) adverse drug reactions

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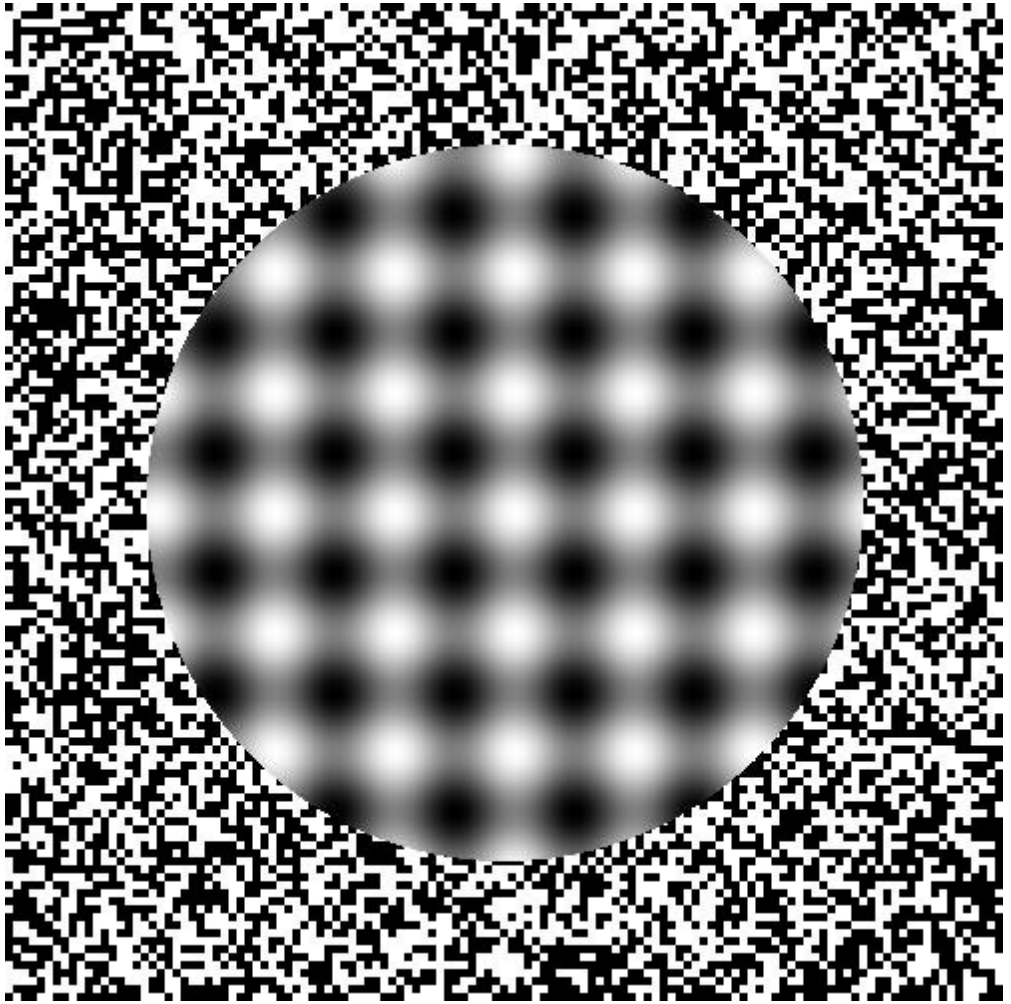
# Focus on tacrolimus



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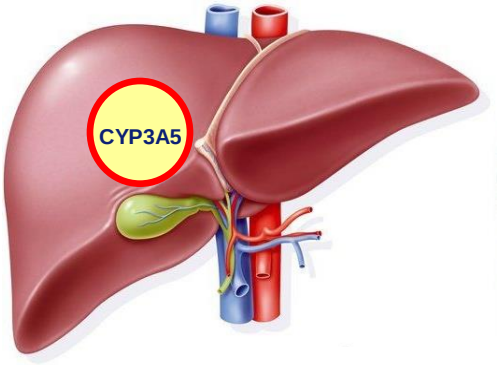
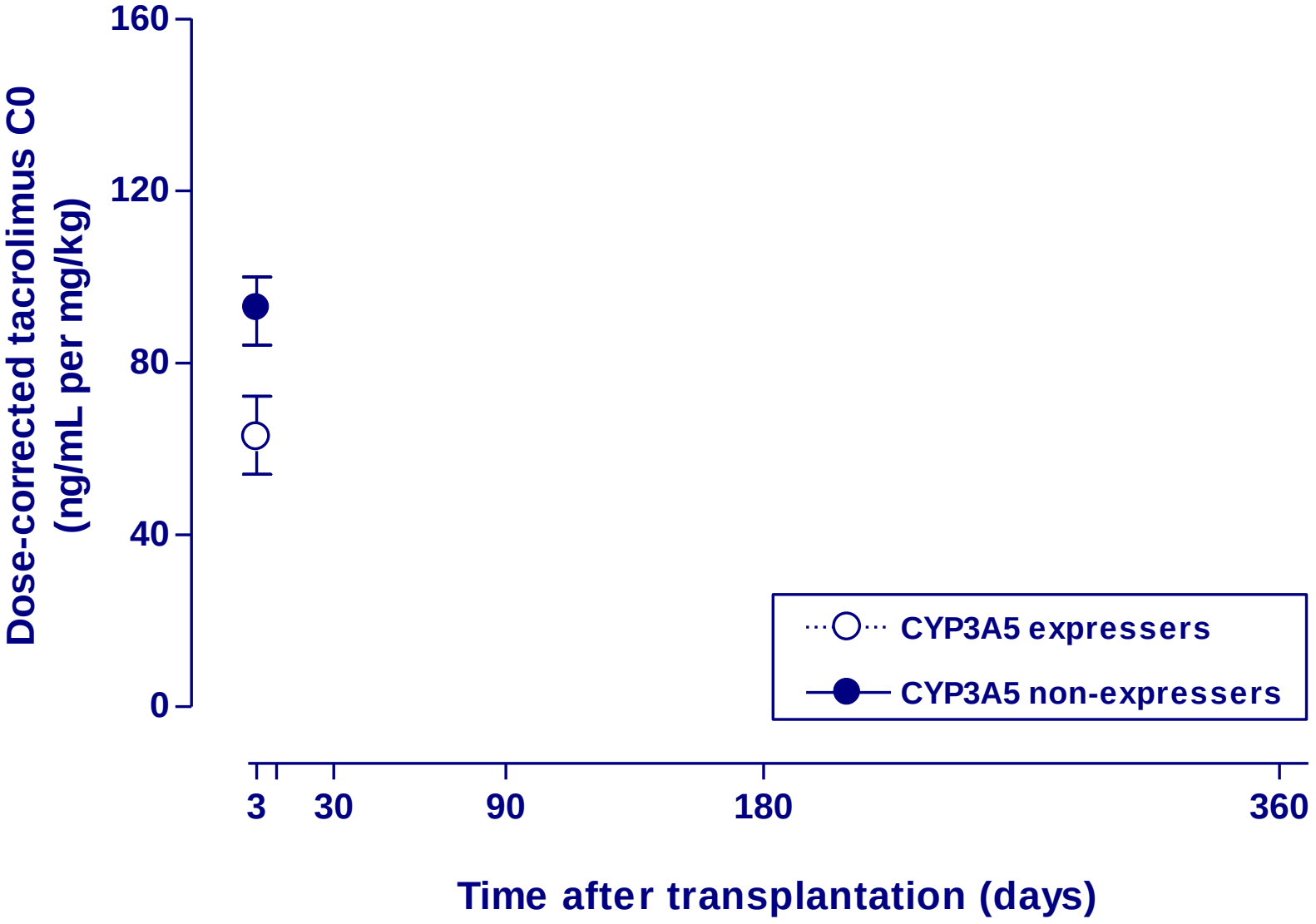
Matas, Am J Transplant 2014;14 (Suppl 1):11-44

# Tacrolimus

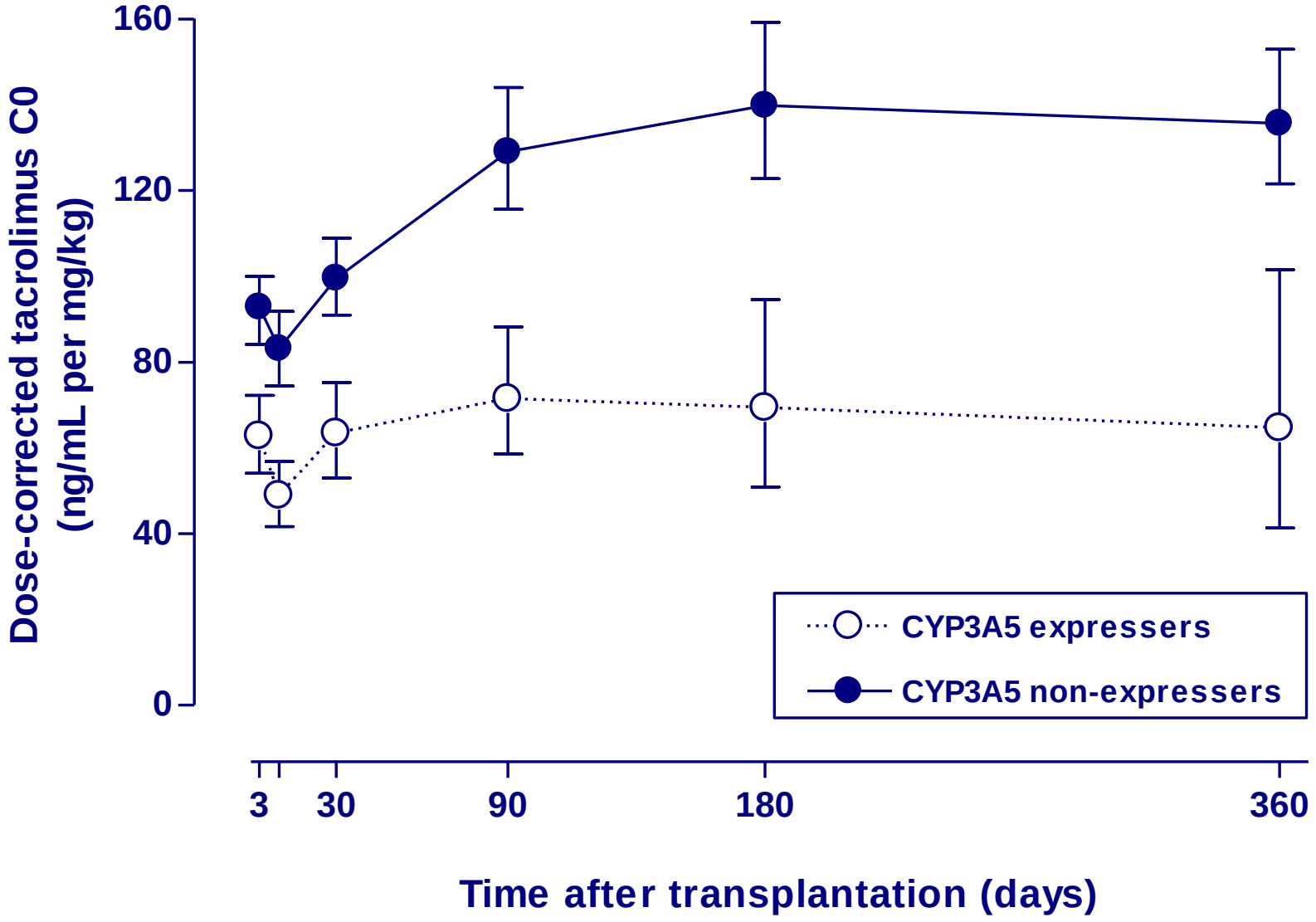
- Dosed by means of therapeutic drug monitoring (TDM)
- Metabolized by Cytochrome P450 3A5 (CYP3A5)
- Several single-nucleotide polymorphisms (SNP) in *CYP3A5* gene
- Best characterized is the *CYP3A5*3* SNP
- Causes alternative splicing and results in the absence of protein




Kuehl, Nat Genet 2001;27:83-91; Hustert, Pharmacogenet 2001;11:773-9




Hesselink, Pharmacogenet Genom 2008;18:339-48




Hesselink, Pharmacogenet Genom 2008;18:339-48

# Tacrolimus and *CYP3A5*

- *CYP3A5* expressors need a ~50% higher Tac dose to reach target concentrations after kidney transplantation

- This has been observed among heart, lung and liver transplant recipients, both adults and children


Thervet, Transplantation 2003;76:1233-5;

Anglicheau, Clin Pharmacol Ther 2004;75:422-33

Haufroid, Pharmacogenetics 2004;14:147-54;

MacPhee, Transplantation 2005;79:499-502;

MacPhee, Am J Transplant 2004;4:914-9;

Zheng, Am J Transplant 2003;3:477-83;

Zheng, J Clin Pharmacol 2004;44:135-40;

Tsuchiya, Transplantation 2004;78:1182-7

Zhao, Clin Pharmacol Ther 2009,86:609-18

Birdwell, Pharmacogenet Genom 2011;22:32-42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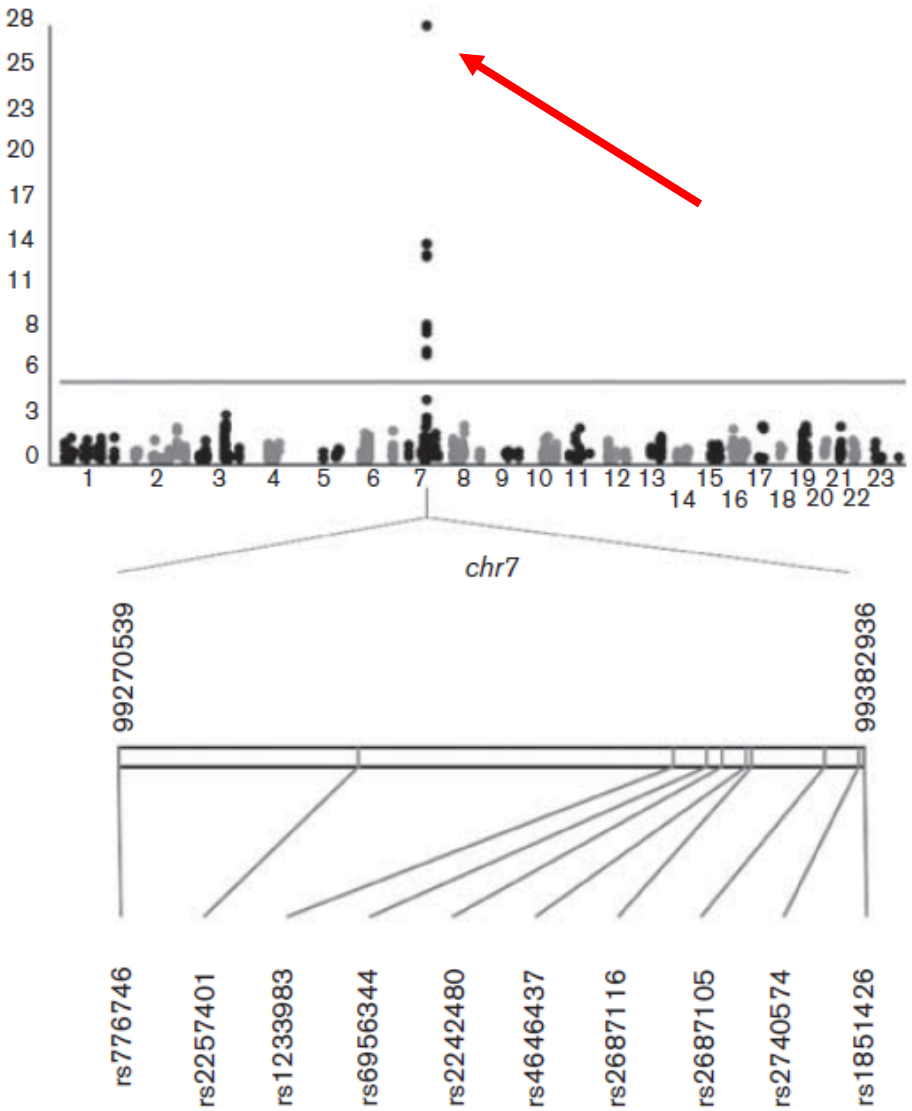
# *CYP3A5*3* is the top SNPP




Birdwell, Pharmacogenet & Genom 2011;22:32-42

# Residual variability

The P450 oxidoreductase *28 SNP is associated with

PPARA: A Novel Genetic Determinant of CYP3A4

Clin Pharm
DOI 10.10

ORIGI

atthias Schwab[1,4]

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Tacrolimus
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Ken Oga
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transplant recipient

Ingrid Lunde • Sara Bremer • Ka
Beata Mohebi • Miriam Dahl • St
Anders Åsberg • Hege Christensen

CYP3A4 G
With Seve

AN Werk[1], S Lefeldt[2], H Bruckmueller[1], G Hemmrich-Stanisak[3], A Franke[3], M Roos[2], C Küchle[2], D Steubl[2], C Schmaderer[2], JH Bräsen[4,5], U Heemann[2], I Cascorbi[1] and L Renders[2]

American Journal of Transplantation 2016; 16: 574–582
Wiley Periodicals Inc.



doi: 10.1111/ajt.13495

## Genomewide Association Study of Tacrolimus Concentrations in African American Kidney Transplant Recipients Identifies Multiple *CYP3A5* Alleles

W. S. Oetting[1,*], D. P. Schladt[2], W. Guan[3], M. B. Miller[1], R. P. Remmel[1], C. Dorr[2], K. Sanghavi[1], R. B. Mannon[4], B. Herrera[5], A. J. Matas[6], D. R. Salomon[7], P.-Y. Kwok[5], B. J. Keating[8] and A. K. Israni[2,9,10,†] and P. A. Jacobson[1,†] for the DeKAF Investigators

*The Pharmacogenomics Journal* **15**, 288-292 (June 2015) | doi:10.1038/tpj.2014.67

High frequency and founder effect of the CYP3A4*20 loss-of-function allele in the Spanish population classifies CYP3A4 as a polymorphic enzyme

M Apellániz-Ruiz, L Inglada-Pérez, M E G Naranjo, L Sánchez, V Mancikova, M Currás-Freixes, A A de Cubas, I Comino-Méndez, S Triki, A Rebai, M Rasool, G Moya, M Grazina, G Opocher, A Cascón, P Taboada-Echalar, M Ingelman-Sundberg, A Carracedo, M Robledo, A Llerena and C Rodríguez-Antona

# Novel *CYP3A4* intron 6 polymorphism

- *CYP3A4* intron 6 SNP (rs35599367 C>T), *CYP3A4*22* allele
- T variant associated with decreased hepatic mRNA expression and decreased CYP3A4 enzymatic activity
- T variant associated with lower statin doses required for lipid control
- Minor allele frequency ~5%

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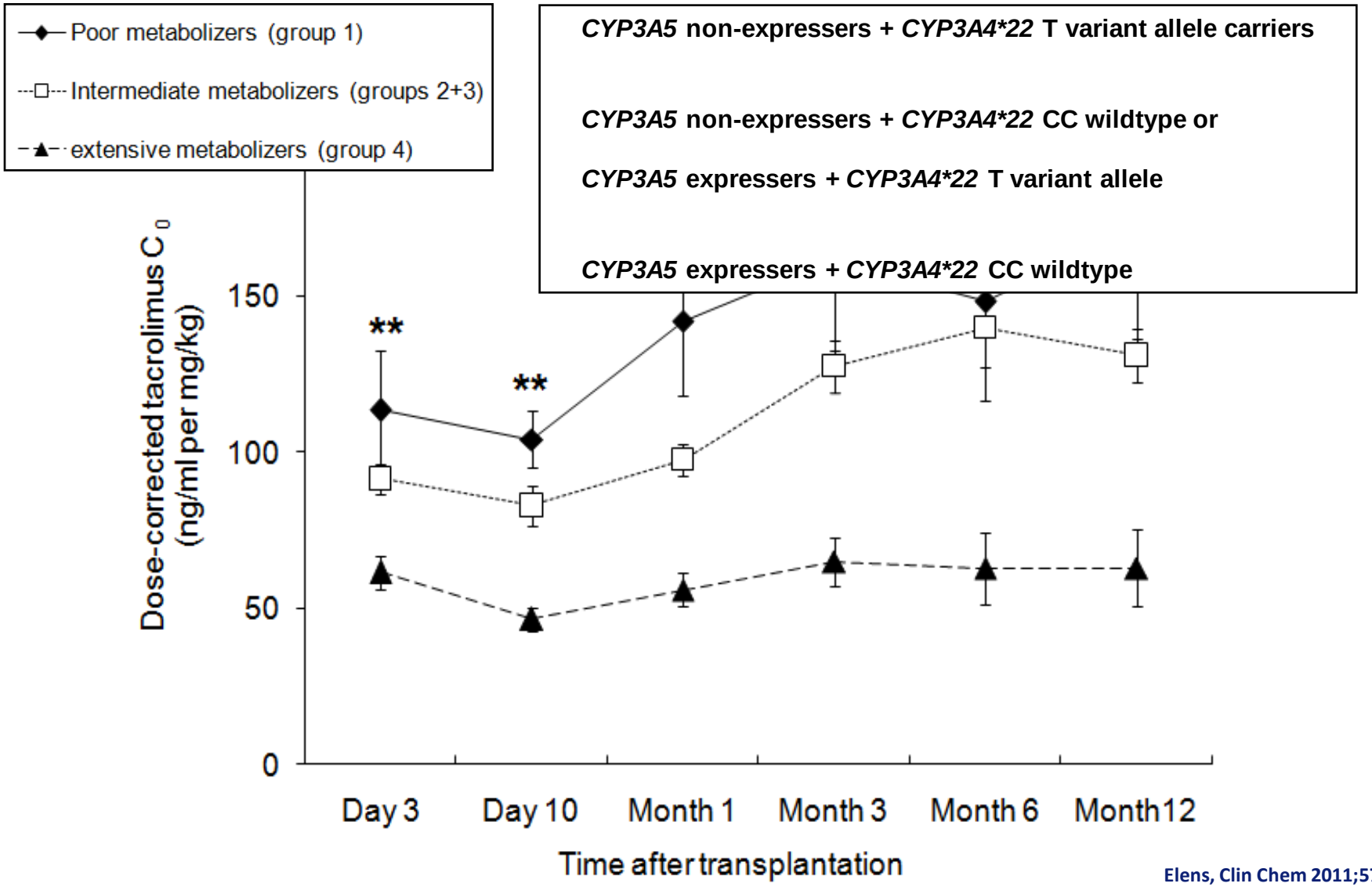
Wang, Pharmacogenomics J 2010;11:274-86

# *CYP3A5* + *CYP3A4* genotype affects Tac dose requirement




Elens, Clin Chem 2011;57:1574-83

# Poor metabolizers are at risk of early Tac overexposure

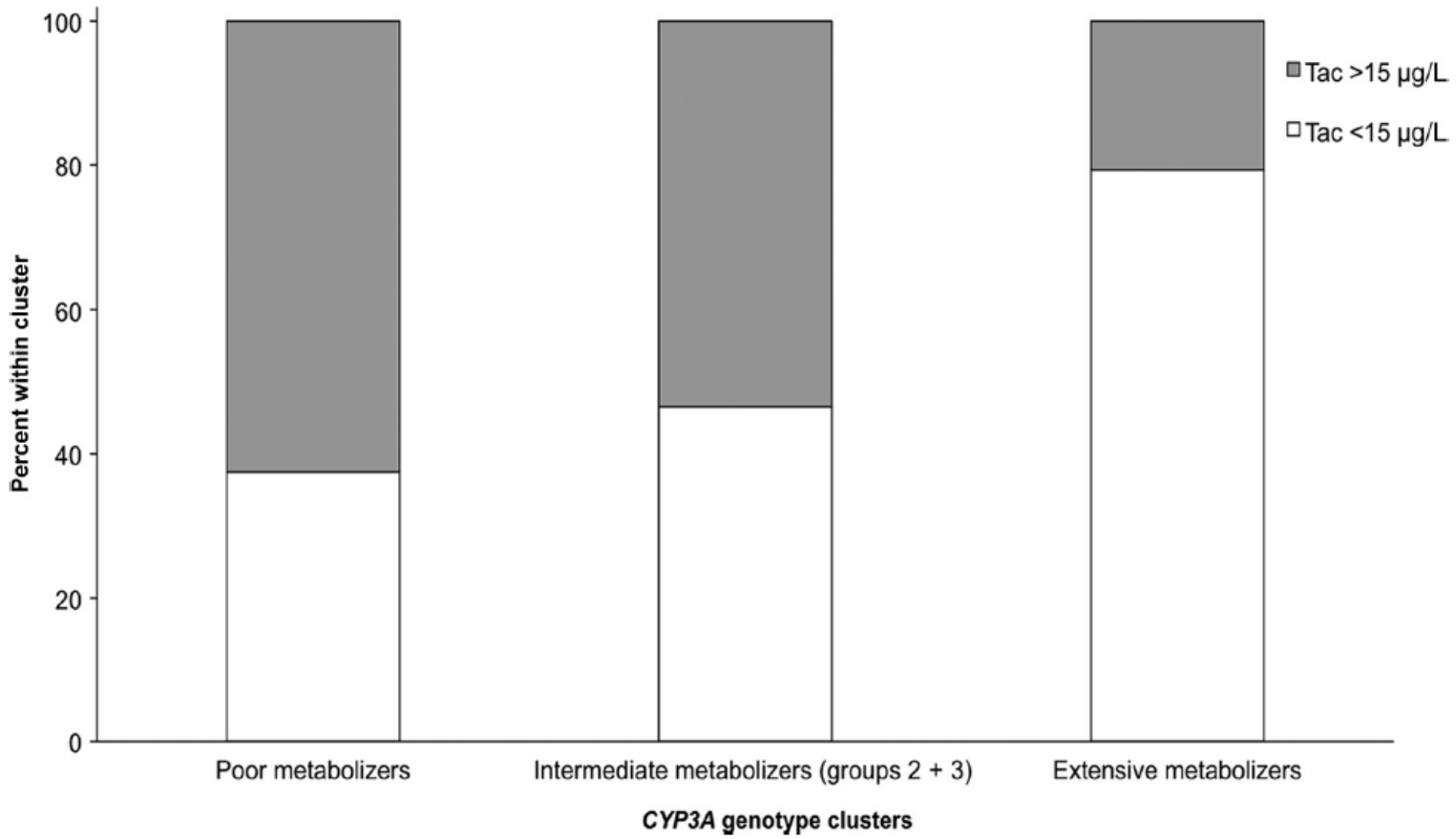
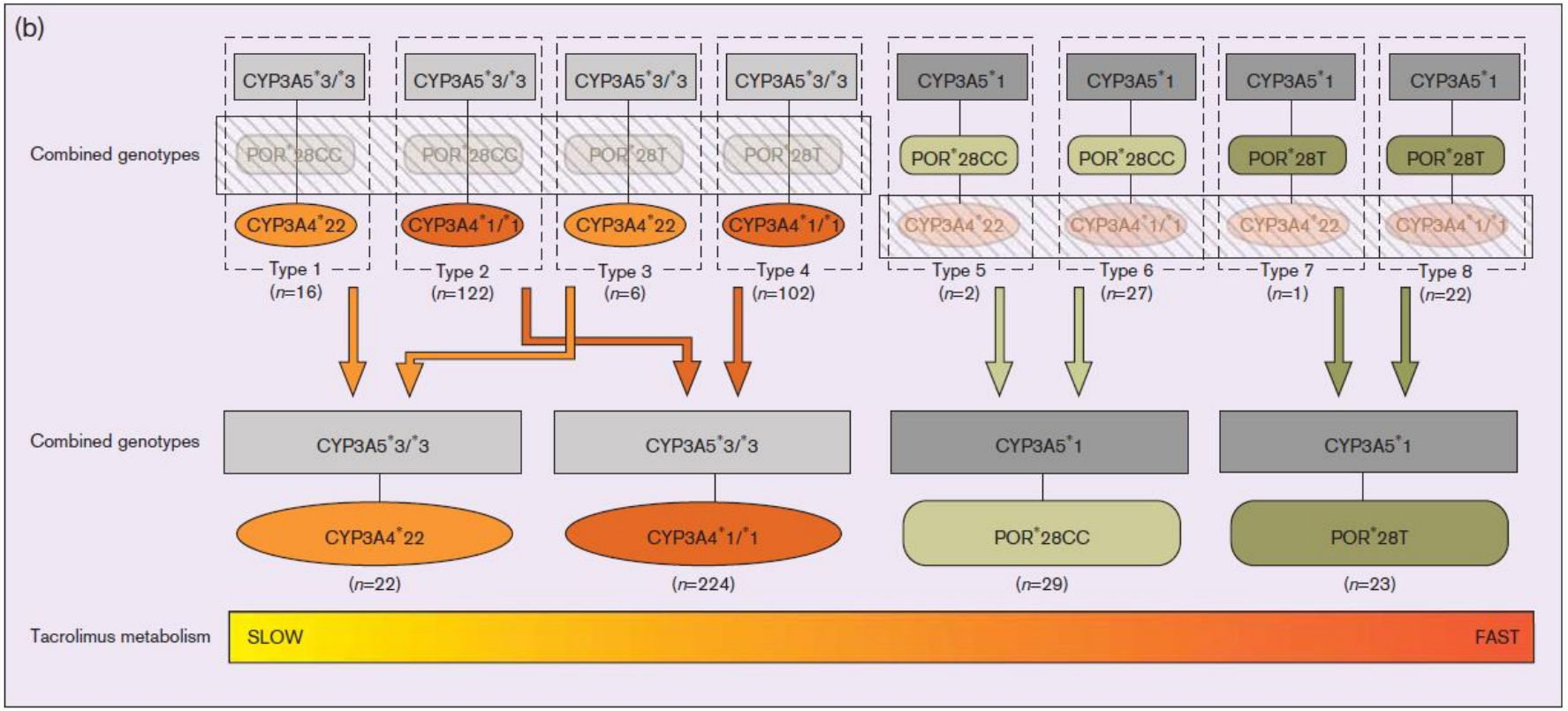



**Fig. 1.** Percentage of patients within each *CYP3A* metabolizer cluster stratified by day 3 values of $C_0$ below or above the 15-$\mu$g/L supratherapeutic threshold.

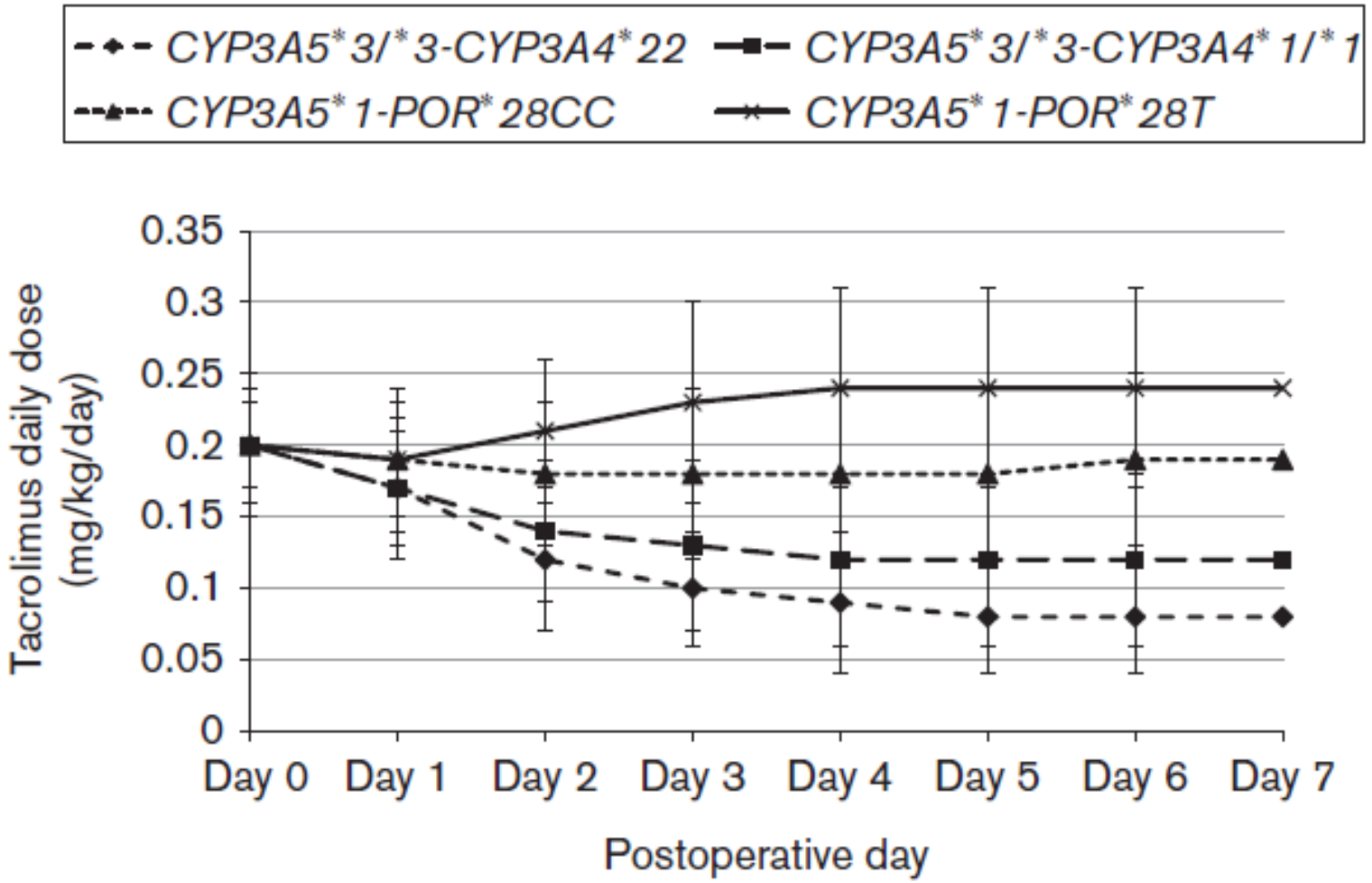
Elens, Clin Chem 2011;57:1574-83

# *CYP3A5 + CYP3A4 + POR* genotype and tacrolimus



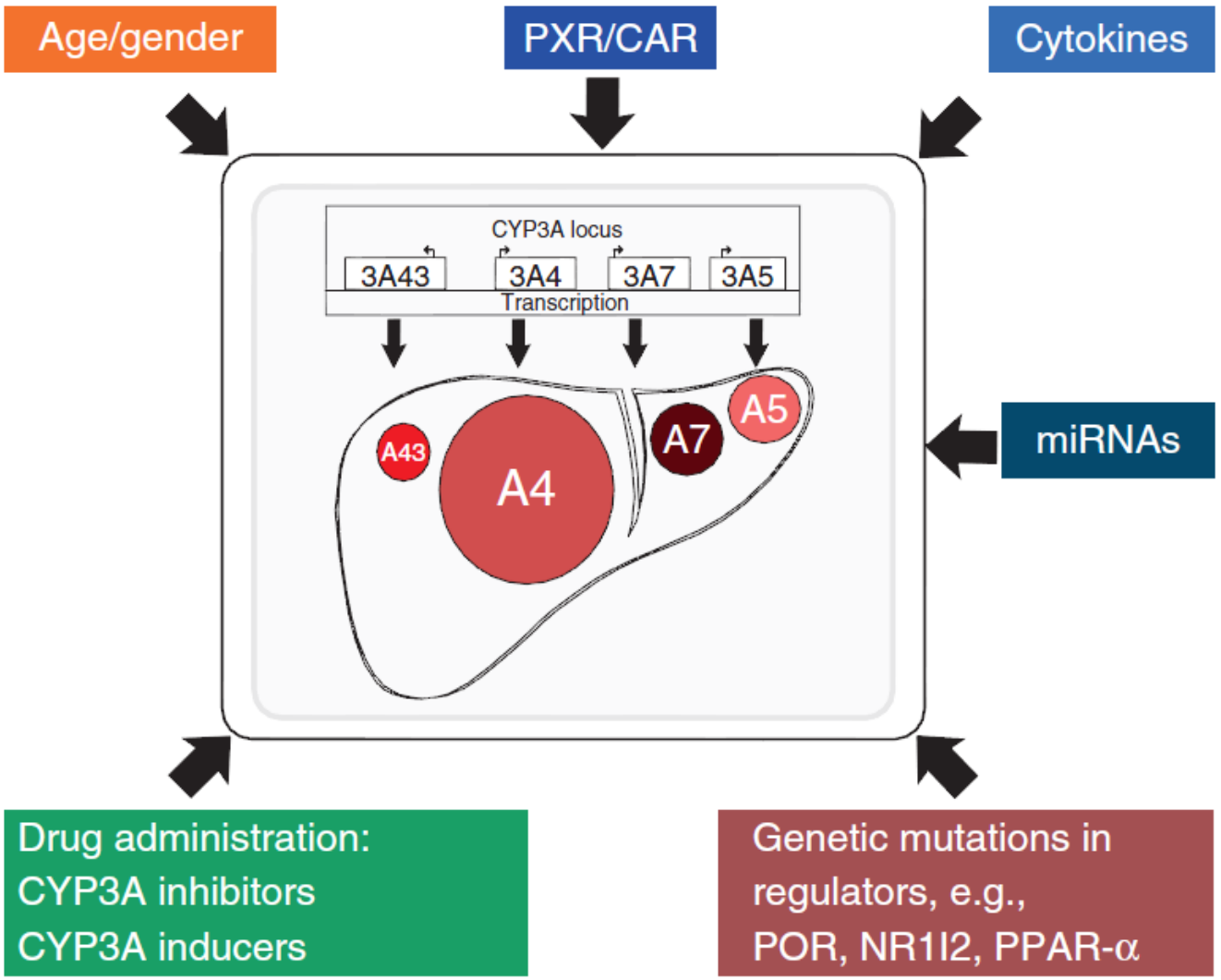

Kuypers, Pharmacogenetics Genom 2014;24:597-606

# *CYP3A5 + CYP3A4 + POR* genotype and tacrolimus




Kuypers, Pharmacogenetics Genom 2014;24:597-606

# Model




Werk, Clin Pharmacol Ther 2014;96:340-8

# DEMAND EVIDENCE AND THINK CRITICALLY

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# Hypothesis

- A *CYP3A5*-based tacrolimus (starting)dose is more effective and safe compared to coventional bodyweight-based Tac dosing

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# TACTIC trial -Study design

**Transplantation**

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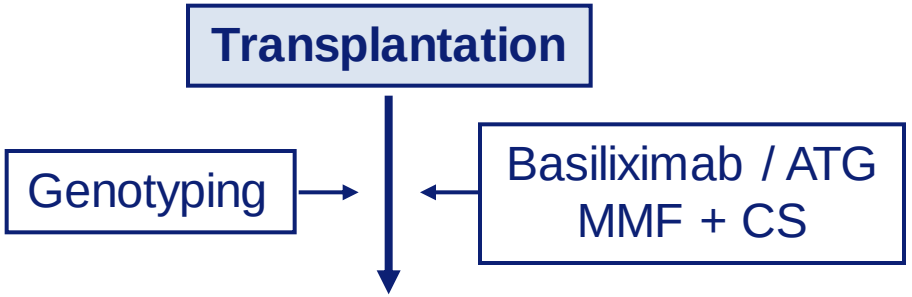
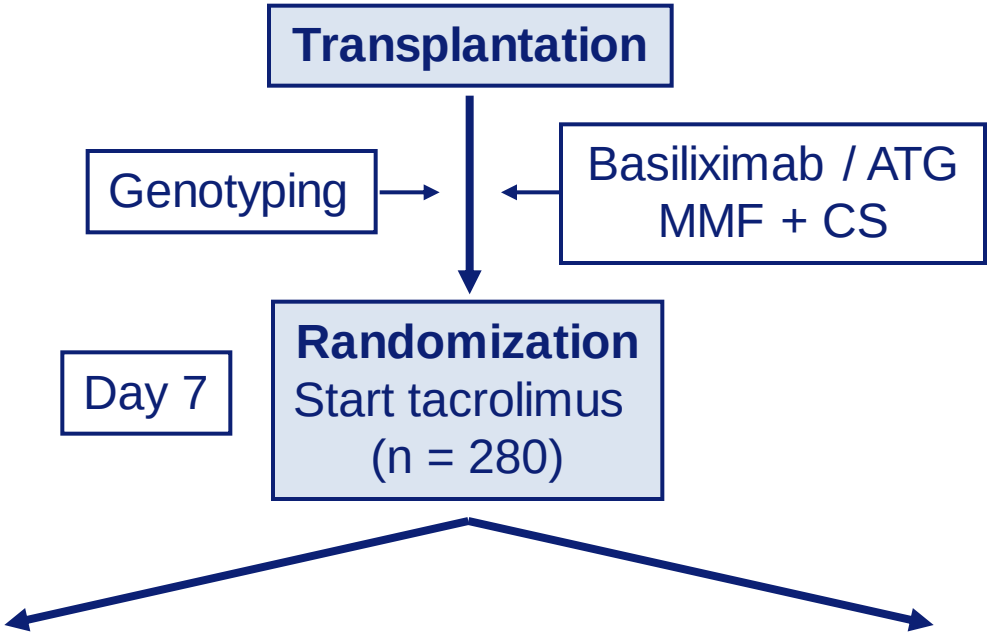
Courtesy of dr. Eric Thervet

# TACTIC trial -Study design




Courtesy of dr. Eric Thervet

# TACTIC trial -Study design

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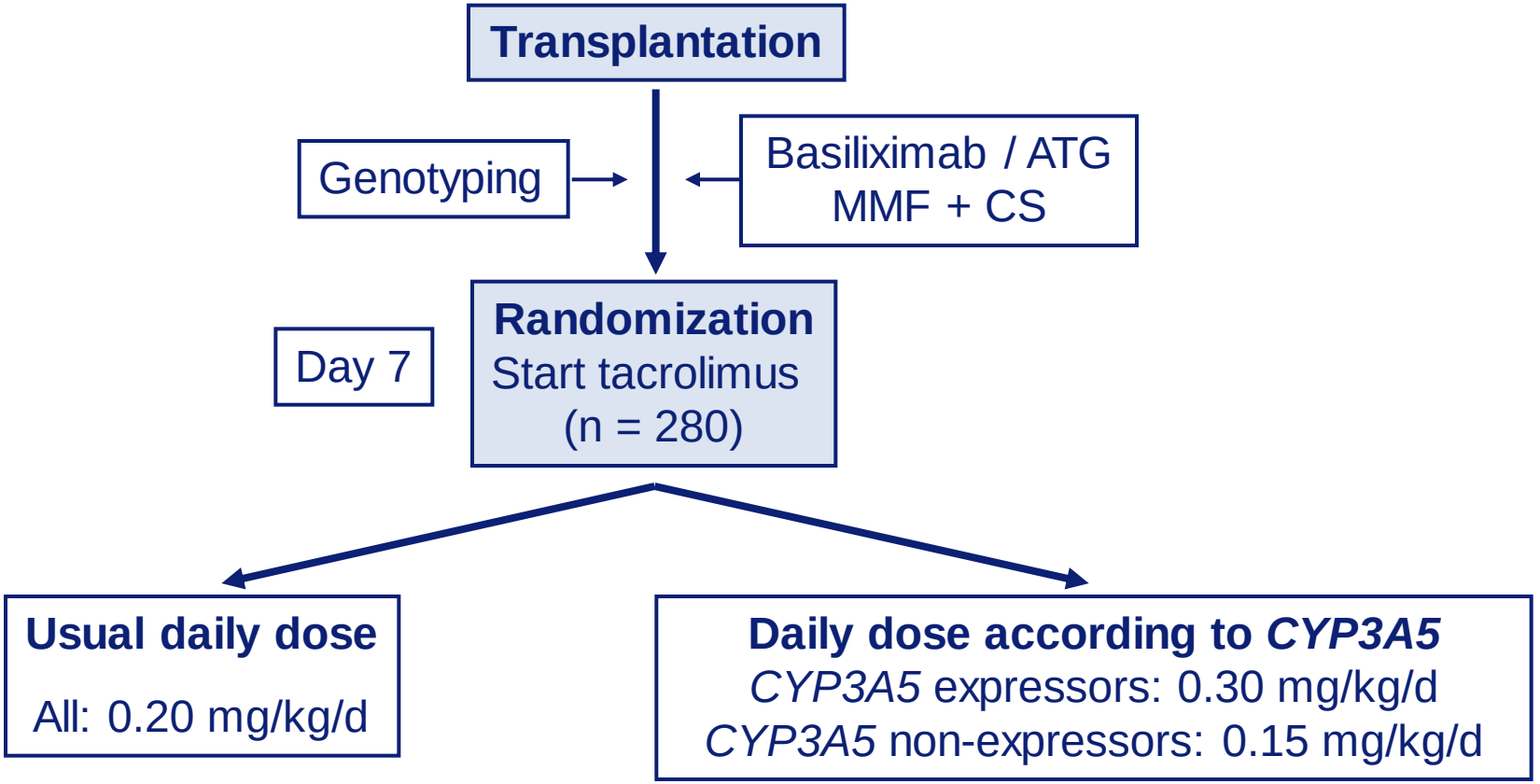
Courtesy of dr. Eric Thervet

# TACTIC trial -Study design

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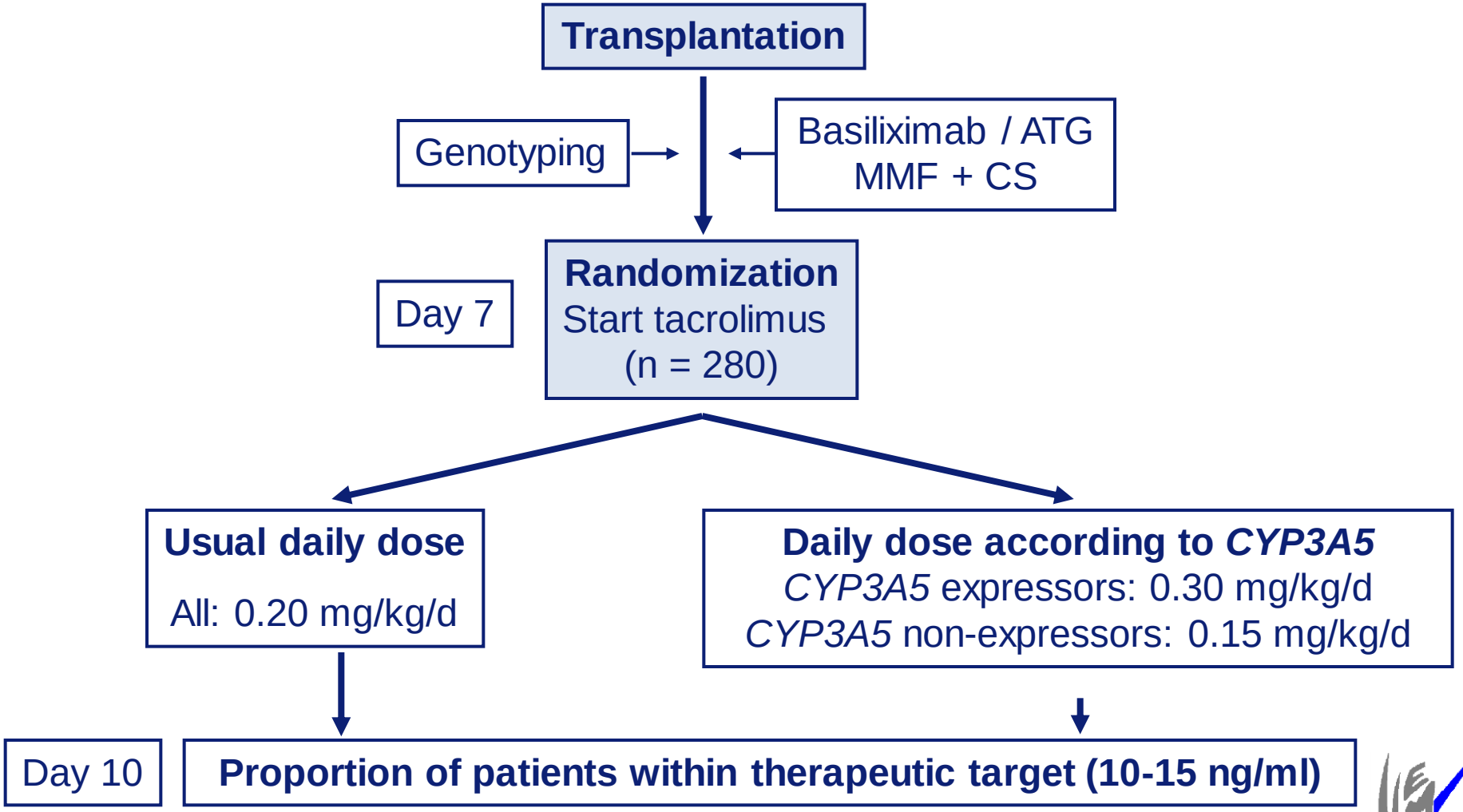
Courtesy of dr. Eric Thervet

# TACTIC trial -Study design




PARIS DESCARTES

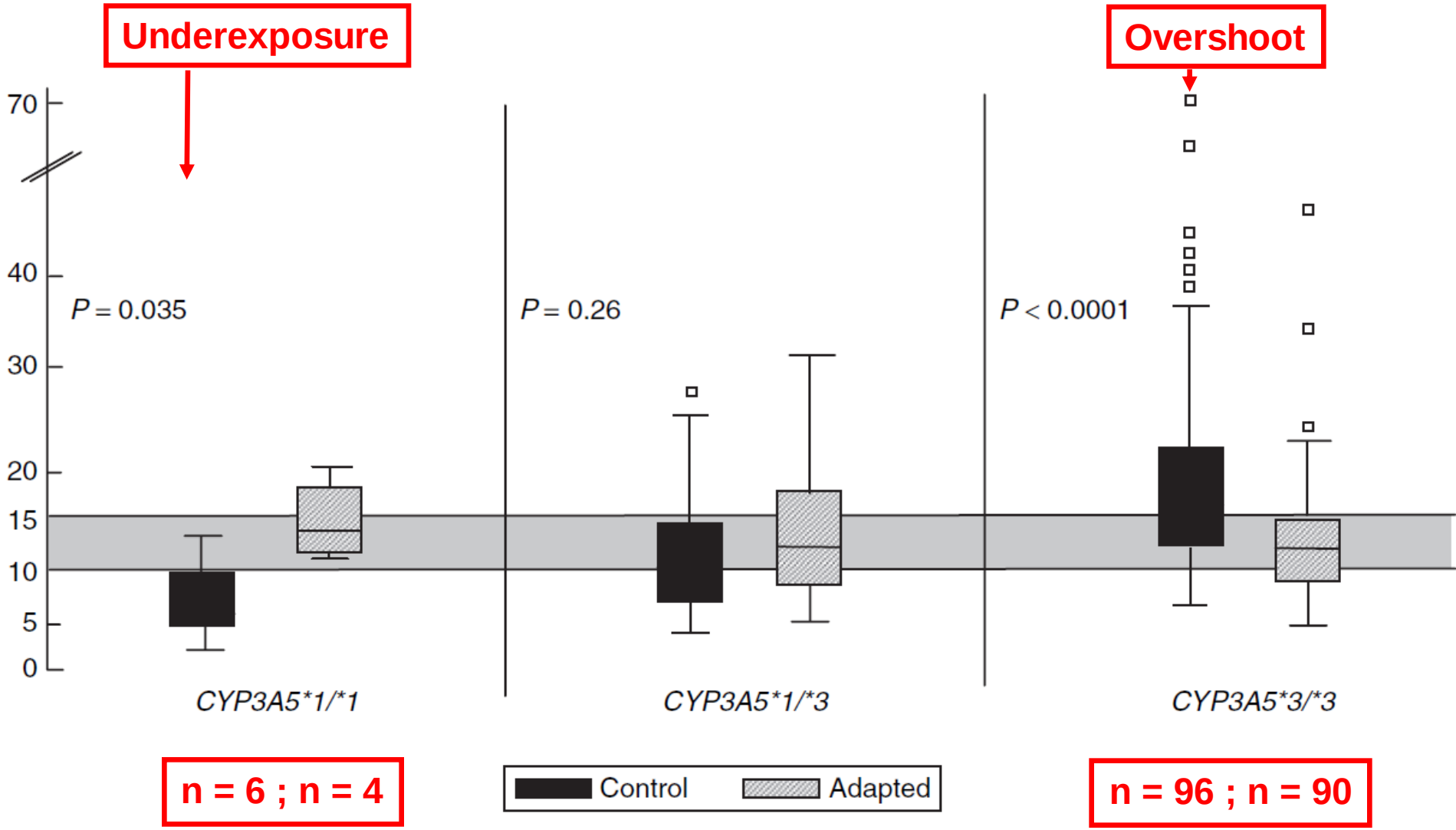
Courtesy of dr. Eric Thervet

# Higher proportion within target range through genotyping

| End point | Control group (*n*=120) | Adapted-dose group (*n*=116) | *P* value |
|---|---|---|---|
| *Primary end point* | | | |
| Proportion of patients with TAC $C_0$ in target range after six oral doses, % (95% CI) | 29.1 % (22.8-35.5) | 43.2% (36.0-51.2) | 0.030 |

Thervet, Clin Pharmacol Ther 2010;87:721-6

# Higher proportion within target range through genotyping




Thervet, Clin Pharmacol Ther 2010;87:721-6

# TACTIC Clinical endpoints

# Extrapolation of TACTIC?

- Delayed introduction of Tac (after day 6)
- Heavy immunosuppression (rATG induction; high dose MMF)
- Immunologically low-risk population

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# Relevance of TACTIC?

- More relevant when Tac introduced on day of transplant?
- More relevant for immunologically high-risk population?
- Or when giving no rATG induction therapy or “normal” dose MMF?

  - “Mozaiek study” (NTR 2226; www.trialregister.nl)

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van Gelder, Clin Pharmacol Ther 2010;87:640-1

# Hypothesis of the trial (NTR2226)

Pharmacogenetic (*CYP3A5*) adaptation of the Tac starting dose

- is more effective in reaching the Tac target concentration range

and

- leads to superior clinical outcomes

compared with conventional, bodyweight-based Tac dosing

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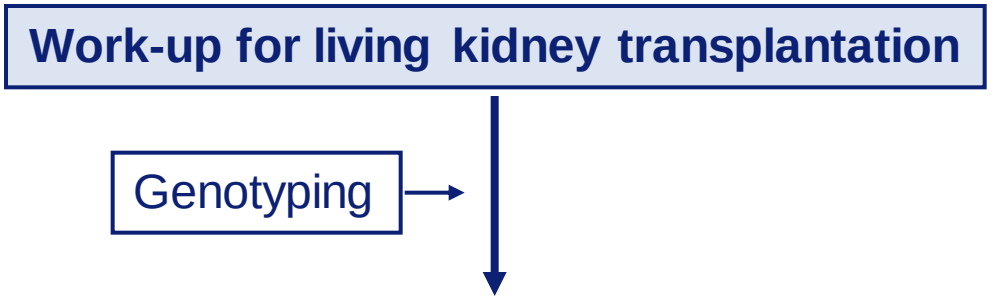
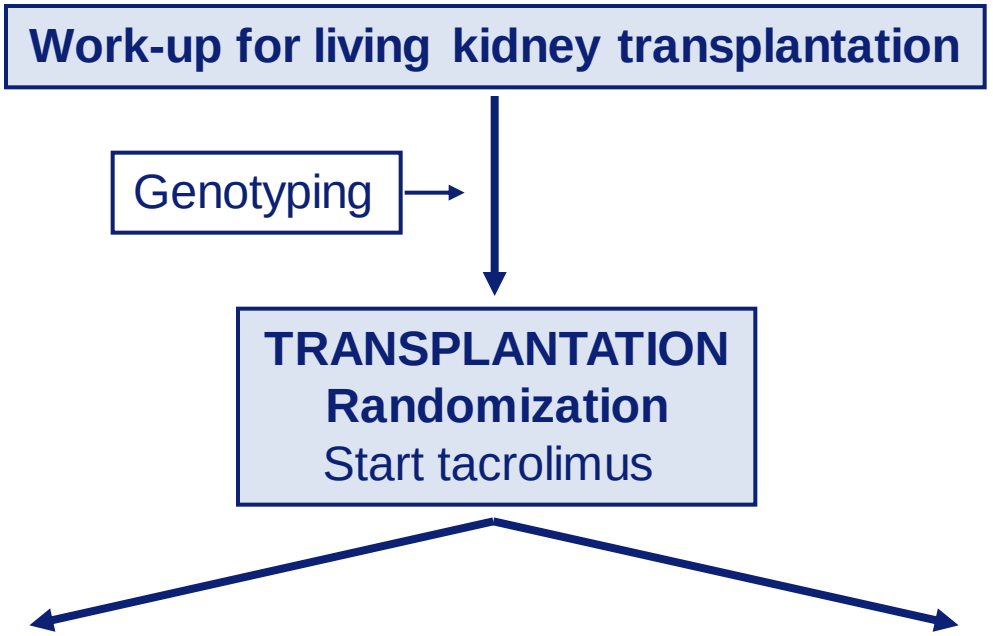
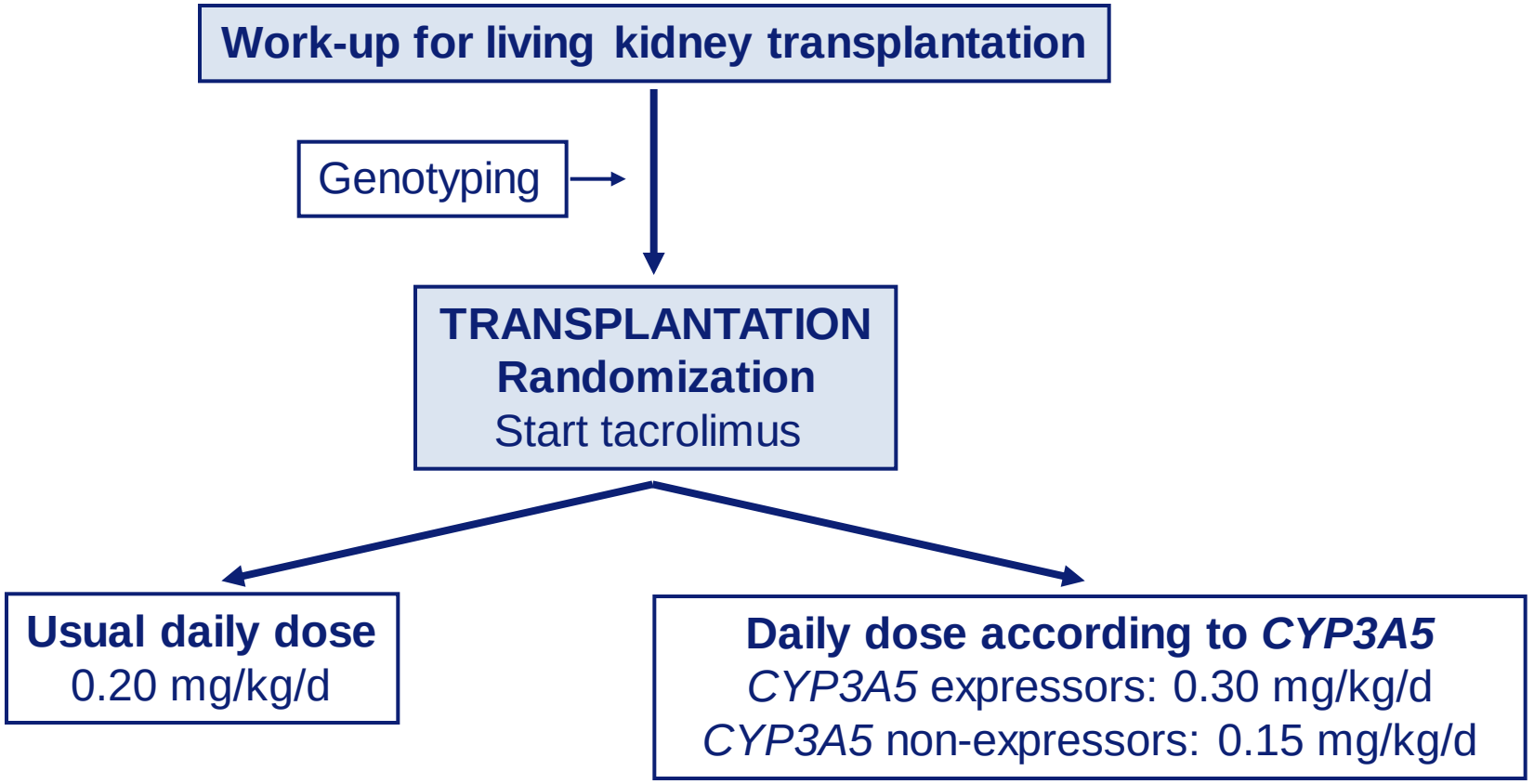
# Trial Design



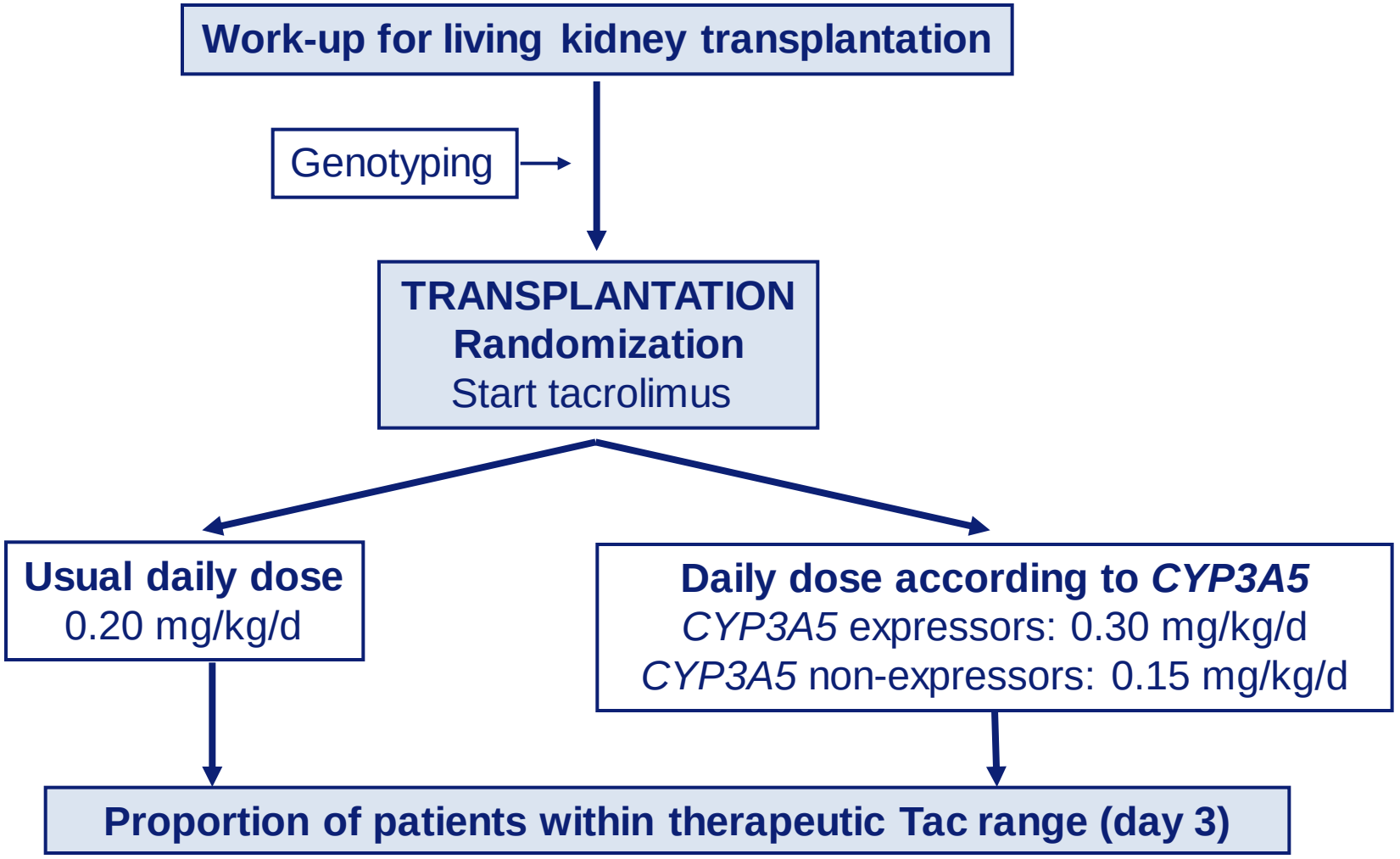
# Trial Design



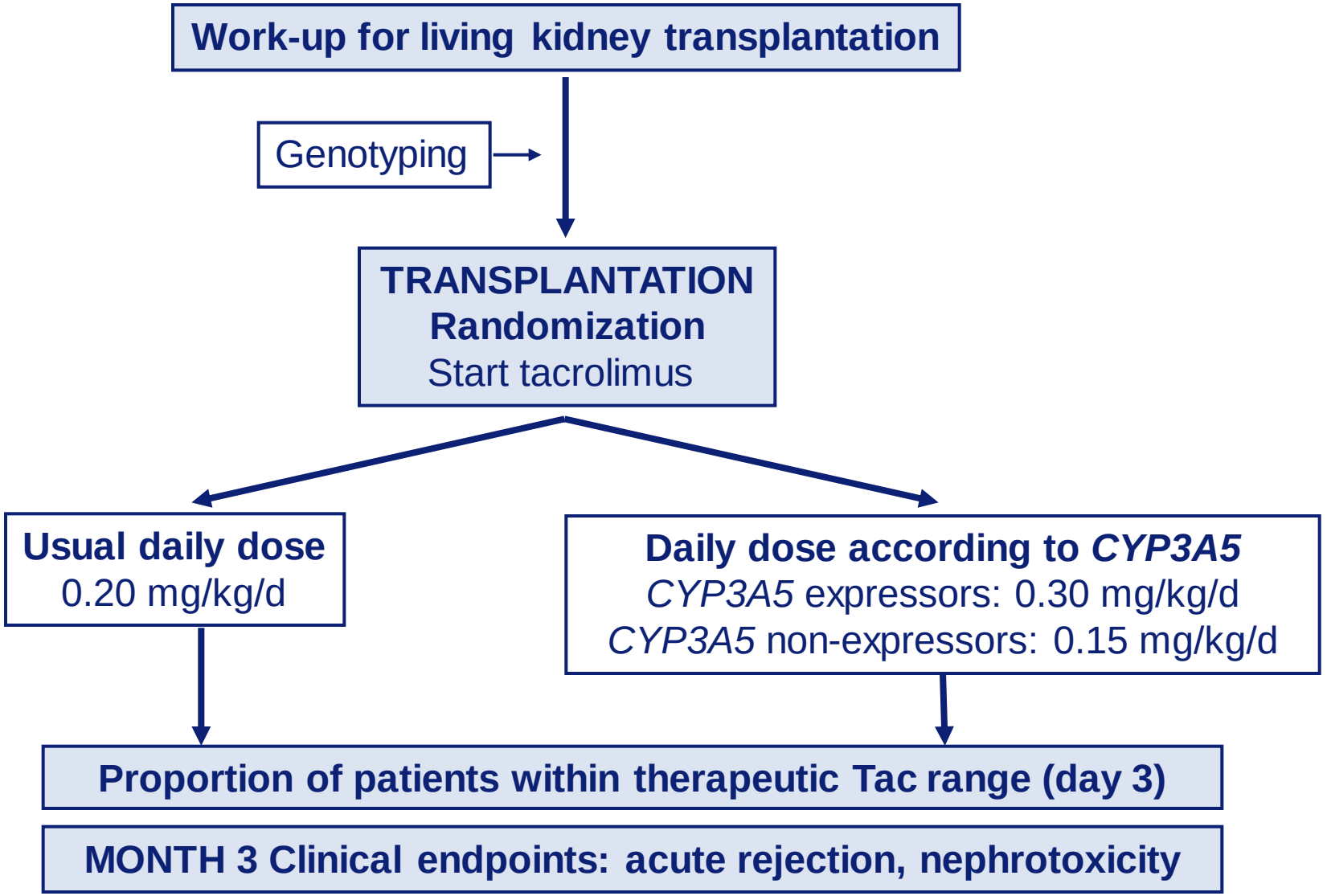
# Trial Design

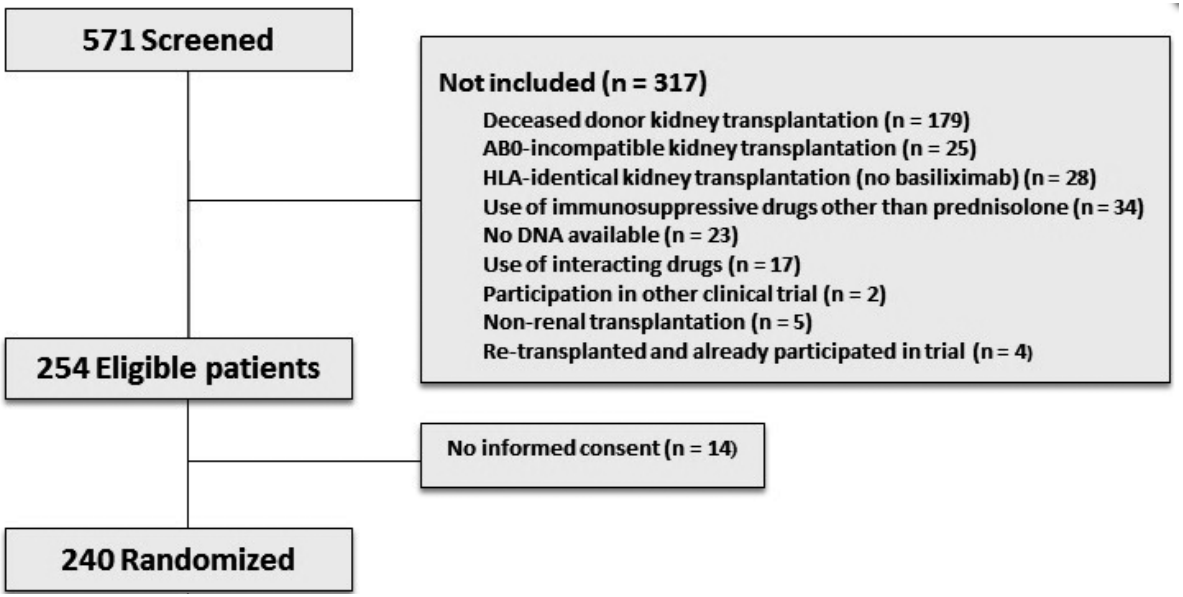


# Trial Design



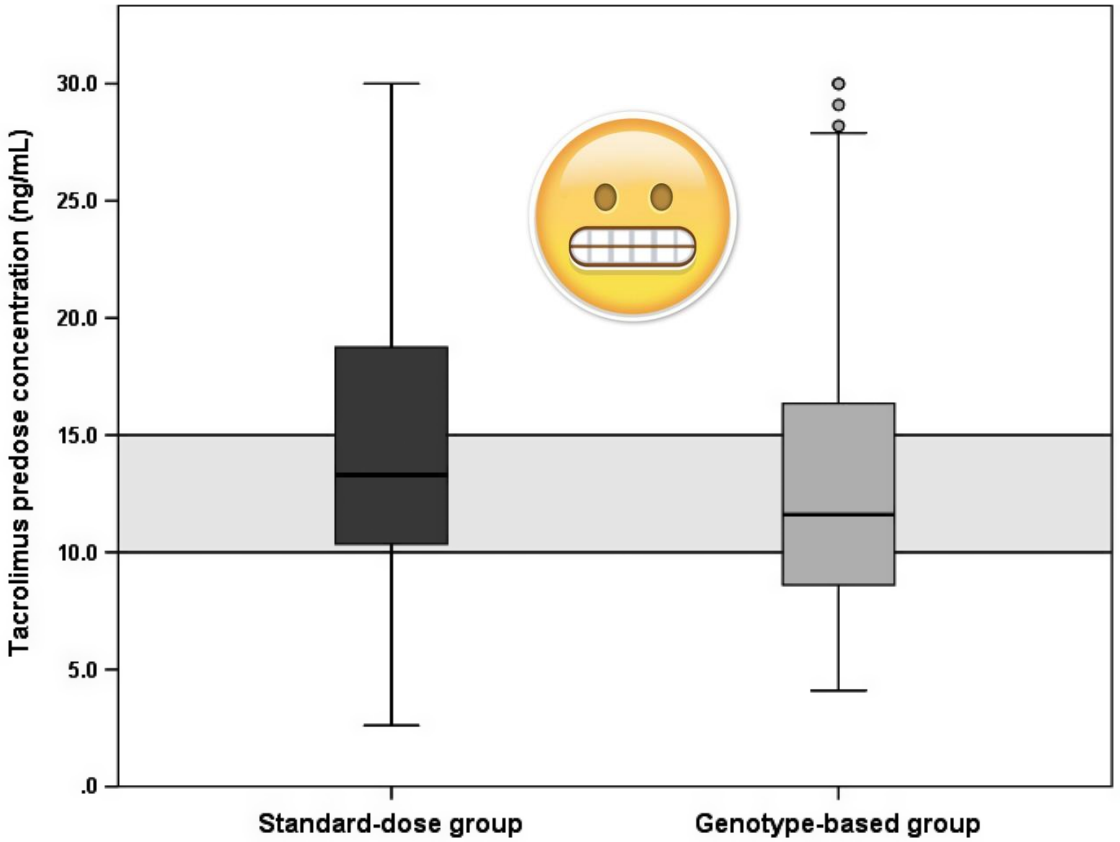
# Trial Design





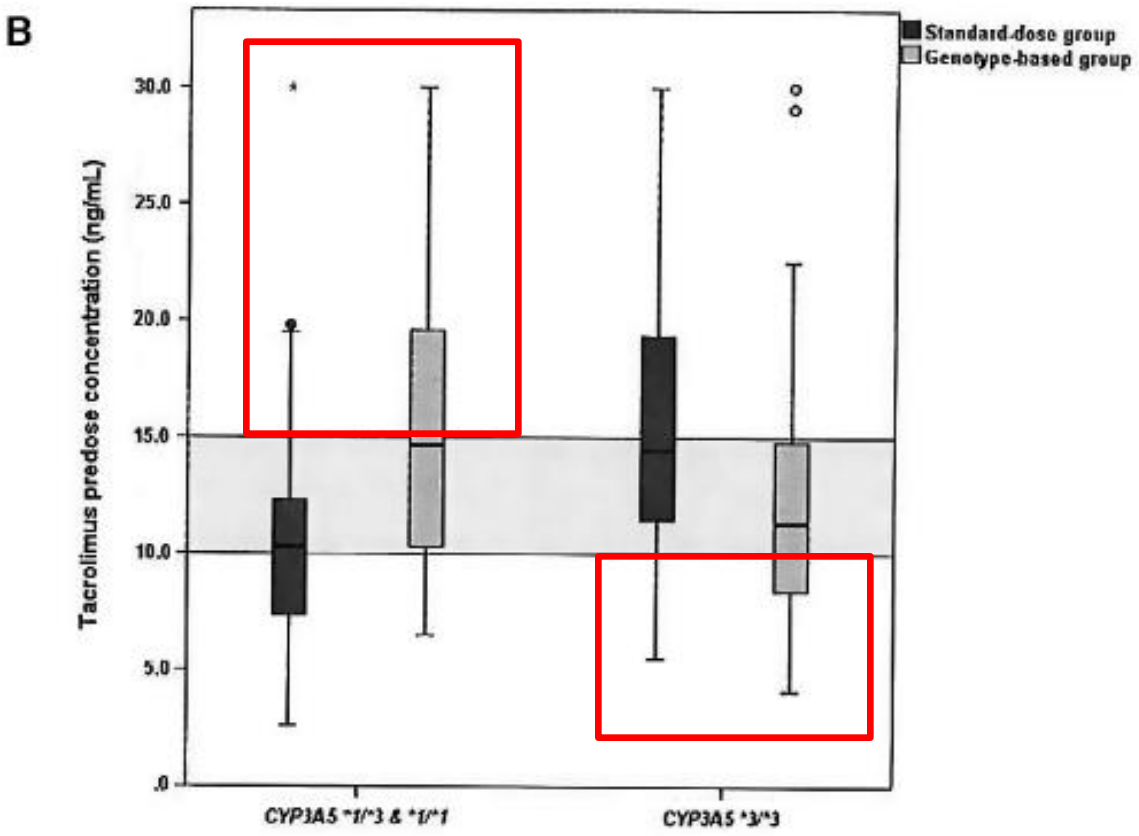

Shuker et al., Am J Transplant 2016;16:2085-96

# Primary endpoint

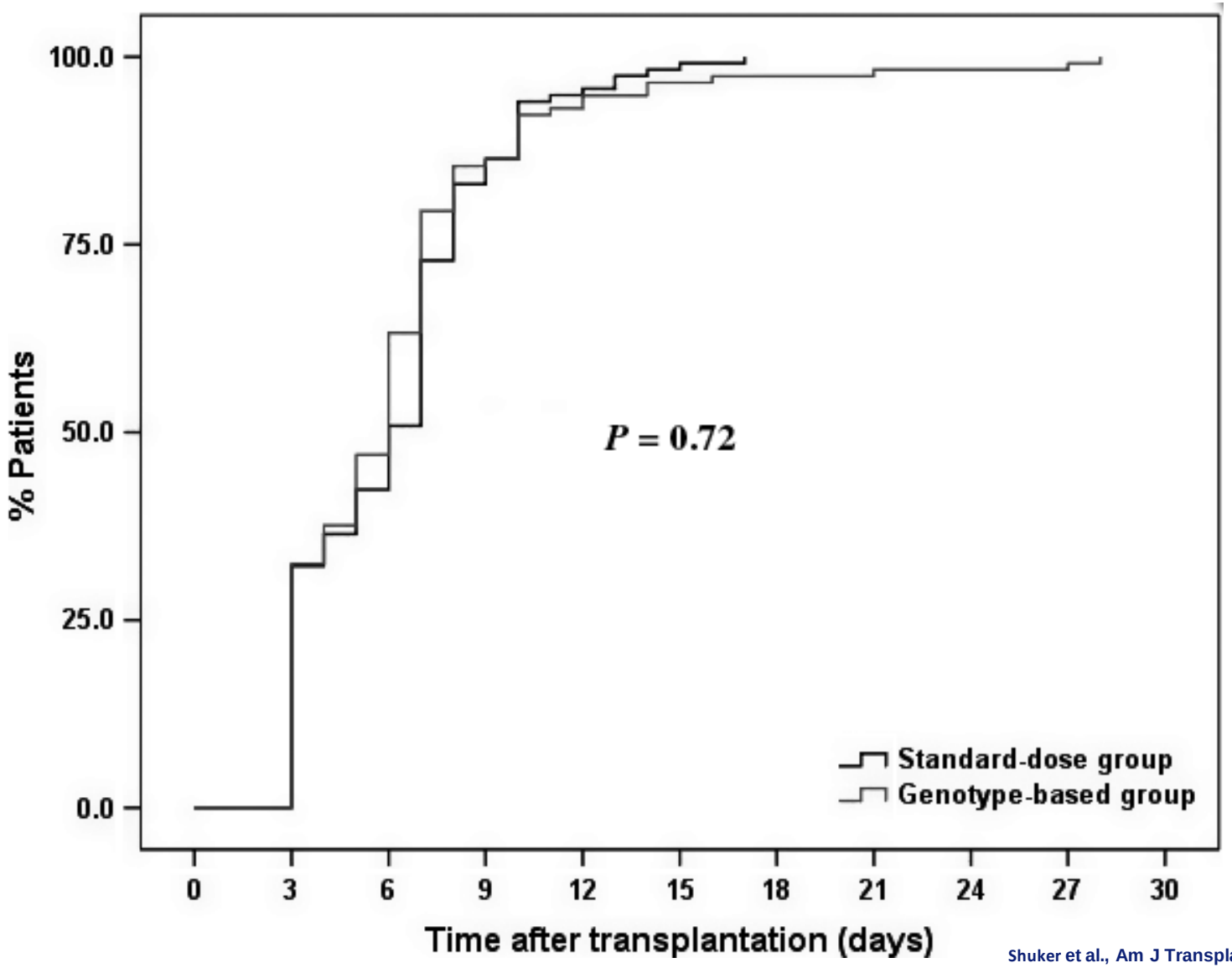



| | Standard-dose group | Genotype-based group | *p* |
|---|---|---|---|
| | n = 99 | n = 104 | |
| Supra-therapeutic concentration | 39 (39.4%) | 31 (29.8%) | 0.20 |
| Therapeutic concentration | 37 (37.4%) | 37 (35.6%) | 0.79 |
| Sub-therapeutic concentration | 23 (23.2%) | 36 (34.6%) | 0.10 |

Shuker et al., Am J Transplant 2016;16:2085-96


B
Standard-dose group
Genotype-based group
Tacrolimus predose concentration (ng/mL)
30.0
25.0
20.0
15.0
10.0
5.0
.0
CYP3A5 *1/*3 & *1/*1
CYP3A5 *3/*3

# Comparable time-to-target Tac concentration range




Shuker et al., Am J Transplant 2016;16:2085-96

# Safety

- AEs: 728 (SDG) *versus* 750 (GBG); $p = 0.56$
- SAEs: 148 (SDG) *versus* 167 (GBG); $p = 0.40$
- 1x death from bacterial peritonitis (SDG)
- Graft survival 97.5% *versus* 99.2% (3-month)
- 4 graft losses (all vascular complications)

Shuker et al., Am J Transplant 2016;16:2085-96

# No difference in BPAR

| Rejection type | Whole group (n = 237) | Standard-dose group (n = 119) | Genotype-based group (n = 118) |
|---|---|---|---|
| Borderline | 5 (2.1%) | 3 (2.5%) | 2 (1.7%) |
| Type I | | | |
| 1A | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| IB | 1 (0.4%) | 1 (0.8%) | 0 (0.0%) |
| Type 2 | | | |
| 2A | 9 (3.8%) | 4 (3.4%) | 5 (4.2%) |
| 2B | 7 (3.0%) | 3 (2.5%) | 4 (3.4%) |
| Type 3 | 1 (0.4%) | 1 (0.8%) | 0 (0.0%) |
| ABMR | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Mixed ACR and AMBR | 7 (3.0%) | 3 (2.5%) | 4 (3.4%) |
| Total BPAR[1] | 25 (10.5%) | 12 (10.1%) | 13 (11.0%) |

Shuker et al., Am J Transplant 2016;16:2085-96

## Conclusions

- *CYP3A5* genotype-based Tac dosing does not lead to:

  ✓an earlier achievement of the tacrolimus target concentration

or

  ✓an improvement of clinical outcomes

as compared with standard, bodyweight-based dosing

- Routine genotyping for *CYP3A5* cannot be recommended

Shuker et al., Am J Transplant 2016;16:2085-96

# Conclusions (2)

- Only ~35% “on target” at first steady state
- Considerable & unexplained residual variability in Tac exposure
- Rapid achievement of target exposure in both groups with TDM

Shuker et al., Am J Transplant 2016;16:2085-96

# General conclusions *CYP3A5* genotyping

- Pharmacogenetics-assisted Tac dosing

  … may get patients on target faster

  … may limit Tac over -and underexposure

- No demonstrated clinical benefit

- Other SNPs may explain residual variability in Tac PK

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WHERE DO WE GO FROM HERE?

# Algorithms to aid tacrolimus dosing

Clin Pharmacokinet
DOI 10.1007/s40262-016-0491-3

ORIGINAL RESEARCH ARTICLE

## A New *CYP3A5**3* and *CYP3A4**22* Cluster Influencing Tacrolimus Target Concentrations: A Population Approach

Franc Andreu[1,2] · Helena Colom[2] · Laure Elens[3,6] · Teun van Gelder[4,5,6] · Ronald H. N. van Schaik[5,6] · Dennis A. Hesselink[4,6] · Oriol Bestard[1] · Joan Torras[1] · Josep M. Cruzado[1] · Josep M. Grinyó[1] · Nuria Lloberas[1]

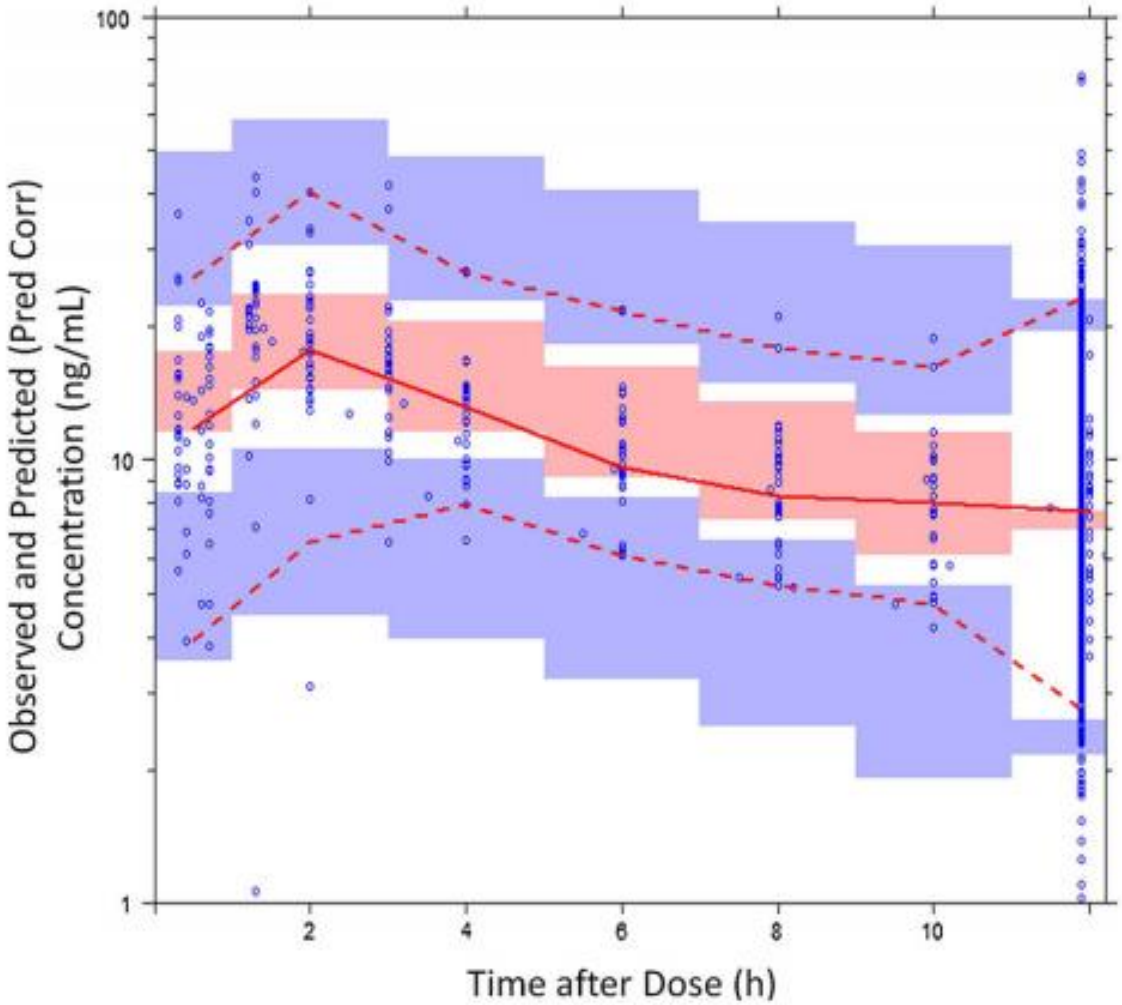
Andreu, Clin Pharmacokinet 2017; Jan 3. doi: 10.1007/s40262-016-0491-3. [Epub ahead of print]

Passey, Br J Clin Pharmacol 2011;72:948-87; Passey, Pharmacogenomics 2012;13:1141-7

Elens, Br J Clin Pharmacol 2013;75:1545-7; Åsberg, Transplant Int 2013;26:1198-1207;

Boughton, Br J Clin Pharmacol 2013;76:425-31

# Algorithms to aid tacrolimus dosing



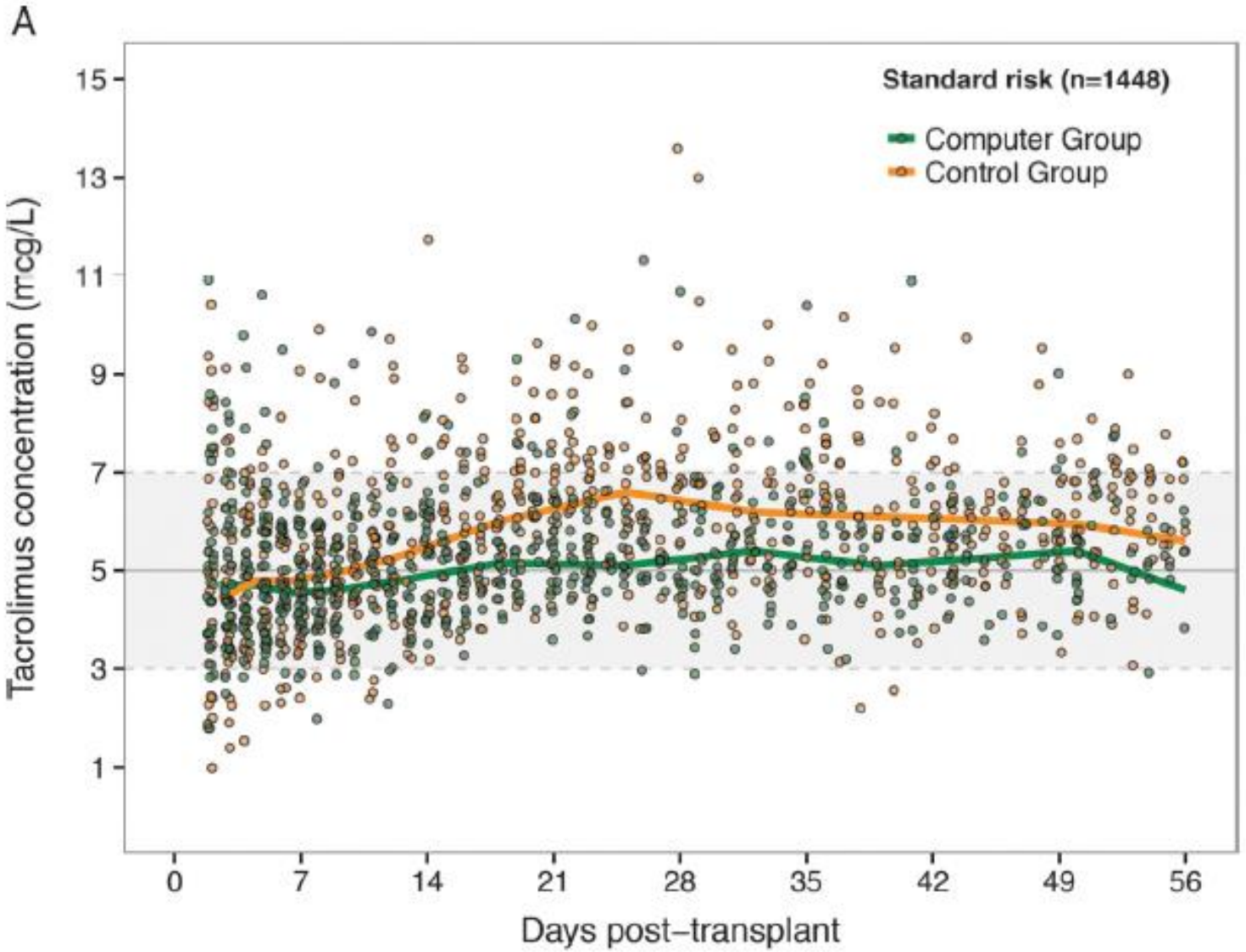

**Key Points**

This is the first population PK study combining CYP3A5 and CYP3A4 genotype, age, and hematocrit that influence tacrolimus concentrations in renal transplant recipients.

This a externally validated prediction model to propose new clear dosage guidelines for each genotype.

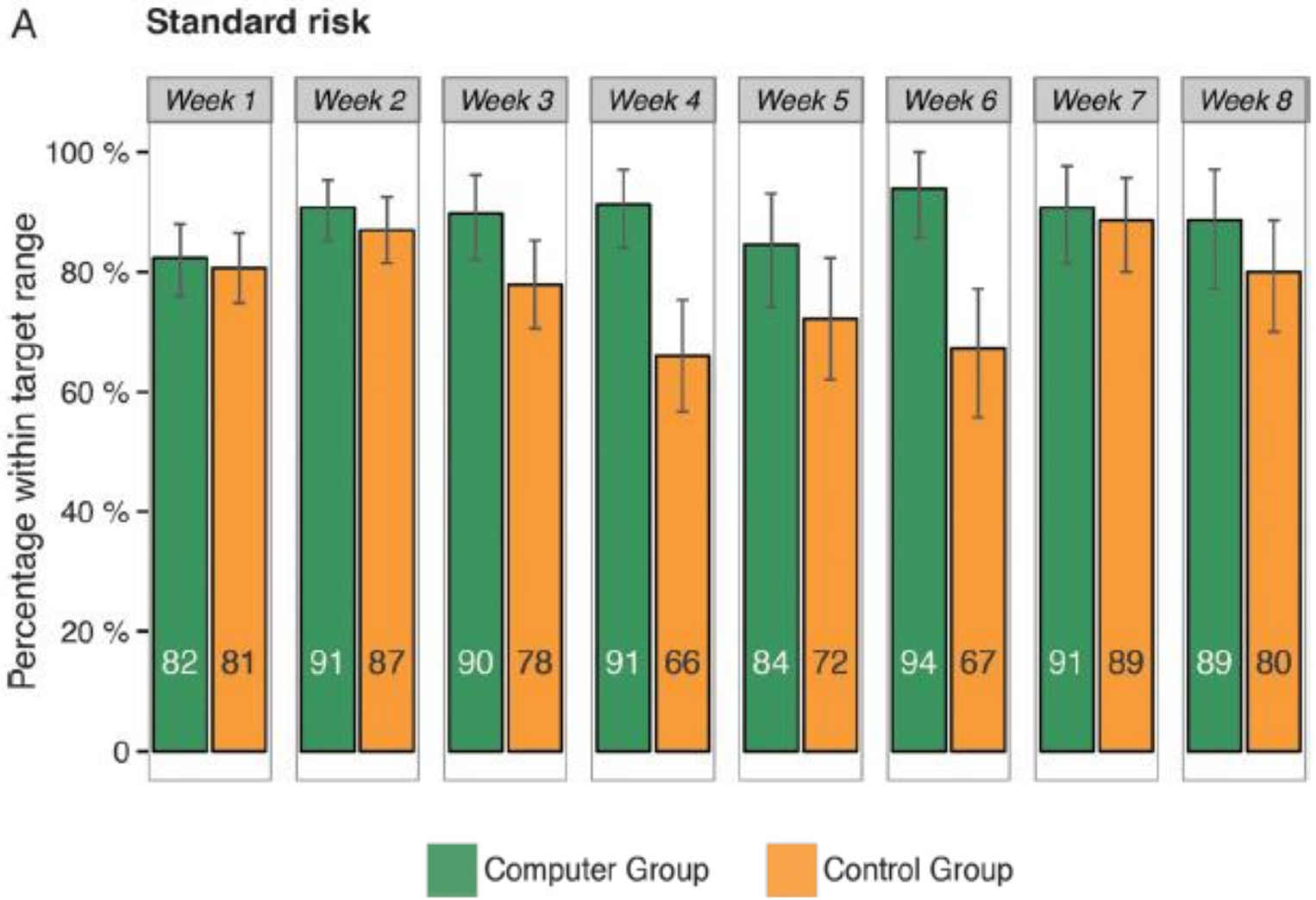
Andreu, Clin Pharmacokinet 2017; Jan 3. doi: 10.1007/s40262-016-0491-3. [Epub ahead of print]

# Algorithms to aid tacrolimus dosing




Størset, Transplantation 2015;99:2158-66

# Algorithms to aid tacrolimus dosing




Størset, Transplantation 2015;99:2158-66

# Algorithms to aid tacrolimus dosing

**TABLE 3.**

**Overview of clinical outcome at 8 weeks**

| | Computer group | | Control group | | |
|---|---|---|---|---|---|
| | Number/median (95% CI) | Range | Number/median (95% CI) | Range | *P* |
| Biopsy-proven acute rejections | 3 | | 5 | | 0.455[a] |
| Recorded infections | 6 | | 3 | | 0.289[a] |
| Glomerular filtration rate (mL/min per 1.73 $m^2$)[b], mean | 59 (55-64) | 30-87 | 53 (48-57) | 31-80 | 0.046[c] |
| Fasting plasma glucose, mmol/L[d] | 5.3 (5.1-5.5) | 4.3-6.7 | 5.5 (5.4-5.7) | 4.6-8.5 | 0.058[e] |
| 2-h plasma glucose, mmol/L[d] | 5.9 (5.6-6.6) | 2.9-9.3 | 6.8 (6.1-8.1) | 4.2-13.5 | 0.008[e] |

Størset, Transplantation 2015;99:2158-66

## Future

- Further development of algorithm-based tacrolimus dosing
- Implementation of such algorithms into clinical practice
- Need for end-point studies
- Unmet need for prediction of pharmacodynamics / adverse events

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University Medical Center Rotterdam

# BACK UP

# Example - Azathioprine

- Treatment of:

  - Neoplasia (ALL)
  - Autoimmune disease (rheumatoid arthritis)
  - Inflammatory bowel disease (Crohn's disease)
  - Prevention of rejection after transplantation

- Metabolized to 6-thioguanine nucleotides:

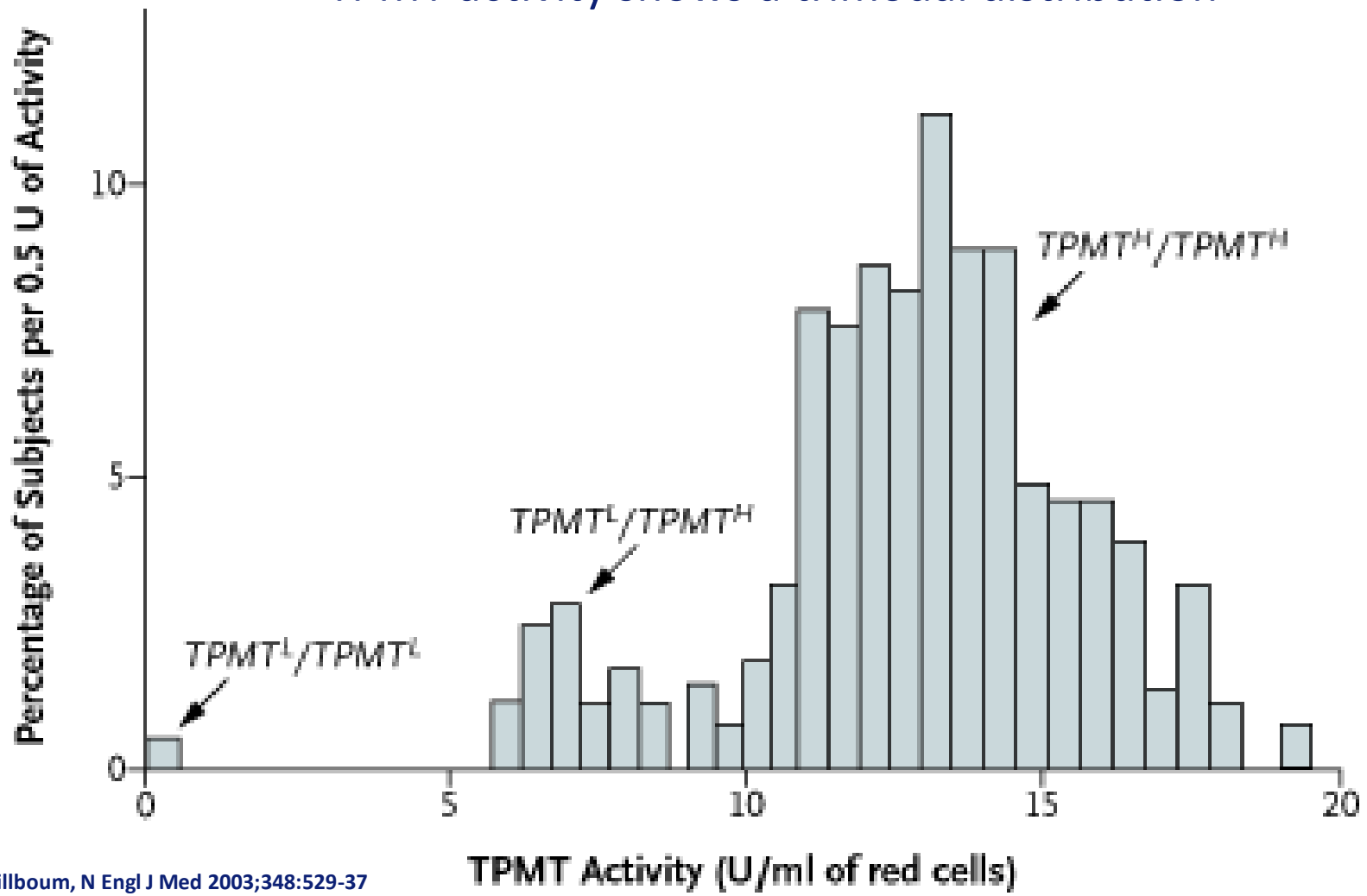
  - Immunosuppressive effect
  - Myelotoxicity, hepatotoxicity, pancreatitis, gastro-intestinal disturbances

# Azathioprine (2)

- Thiopurine *S*-methyl transferase (TPMT) inactivates azathioprine
- TPMT deficiency leads to accumulation of active 6-thioguanine metabolites, resulting in severe hematologic toxicity

# Thiopurine S-methyltransferase (TPMT) phenotype

TPMT activity shows a trimodal distribution




Weinshillboum, N Engl J Med 2003;348:529-37

# Clinical Pharmacogenetics Implementation Consortium guideline

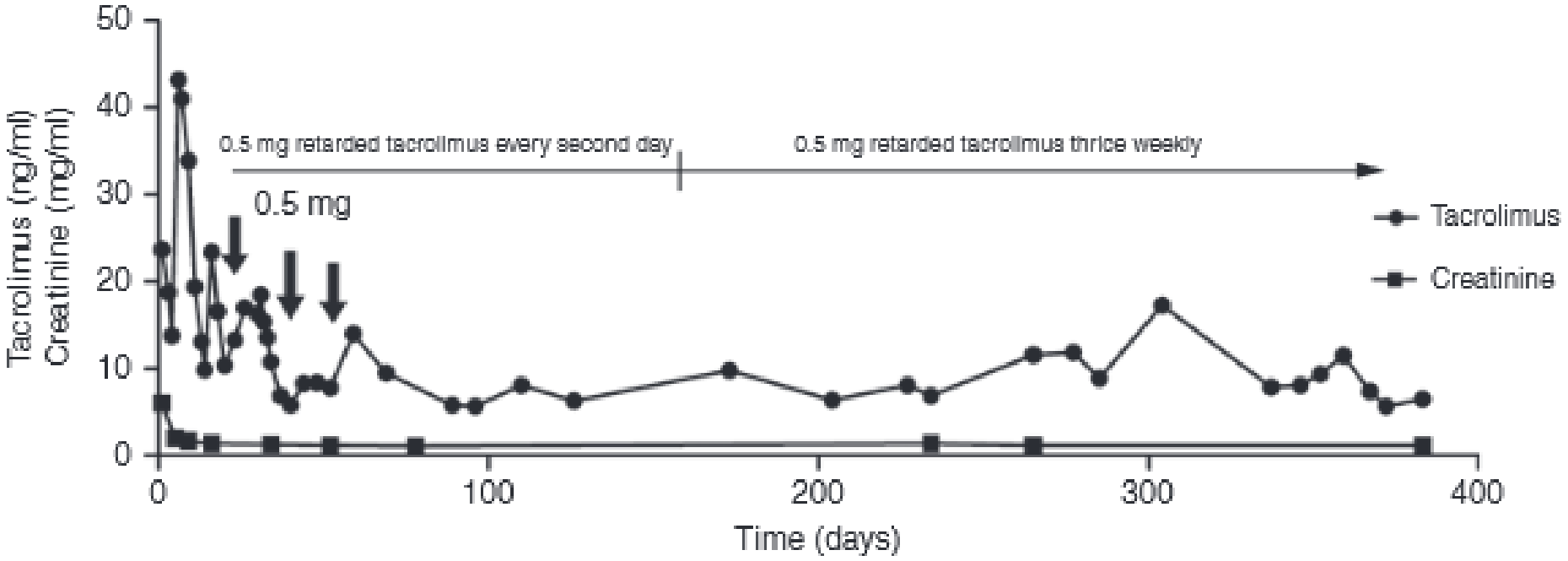
| Phenotype | Dosing recommendations for Aza | Classification of recommendations |
|---|---|---|
| Homozygous wildtype or normal, high activity | Start with normal starting dose (*e.g.* 2-3 mg/kg/d).<br>Allow 2 weeks to reach steady-state after each dose adjustment. | Strong |
| Heterozygote or intermediate activity | Start at 30-70% of "target-dose" (*e.g.* 1-1.5 mg/kg/d) and titrate based on tolerance.<br>Allow 2-4 weeks to reach steady state after each adjustment. | Strong |
| Homozygous variant, deficient activity | Consider alternative agents.<br>If necessary start at 10% of "target dose" and dose thrice weekly instead of daily.<br>Allow 4-6 weeks to reach steady-state after each dose adjustment. | Strong |

http://www.pharmgkb.org

Relling et al. Clin Pharmacol Ther 2011;89:387-94

# Residual variability

**… Exome sequencing revealed a novel SNP (c.802C>T) resulting in a premature stop codon in *CYP3A4* exon 5. … This is, to our knowledge the first case of a complete failure of CYP3A4 in humans.**




Werk, Clin Pharmacol Ther 2014;95:416-22