

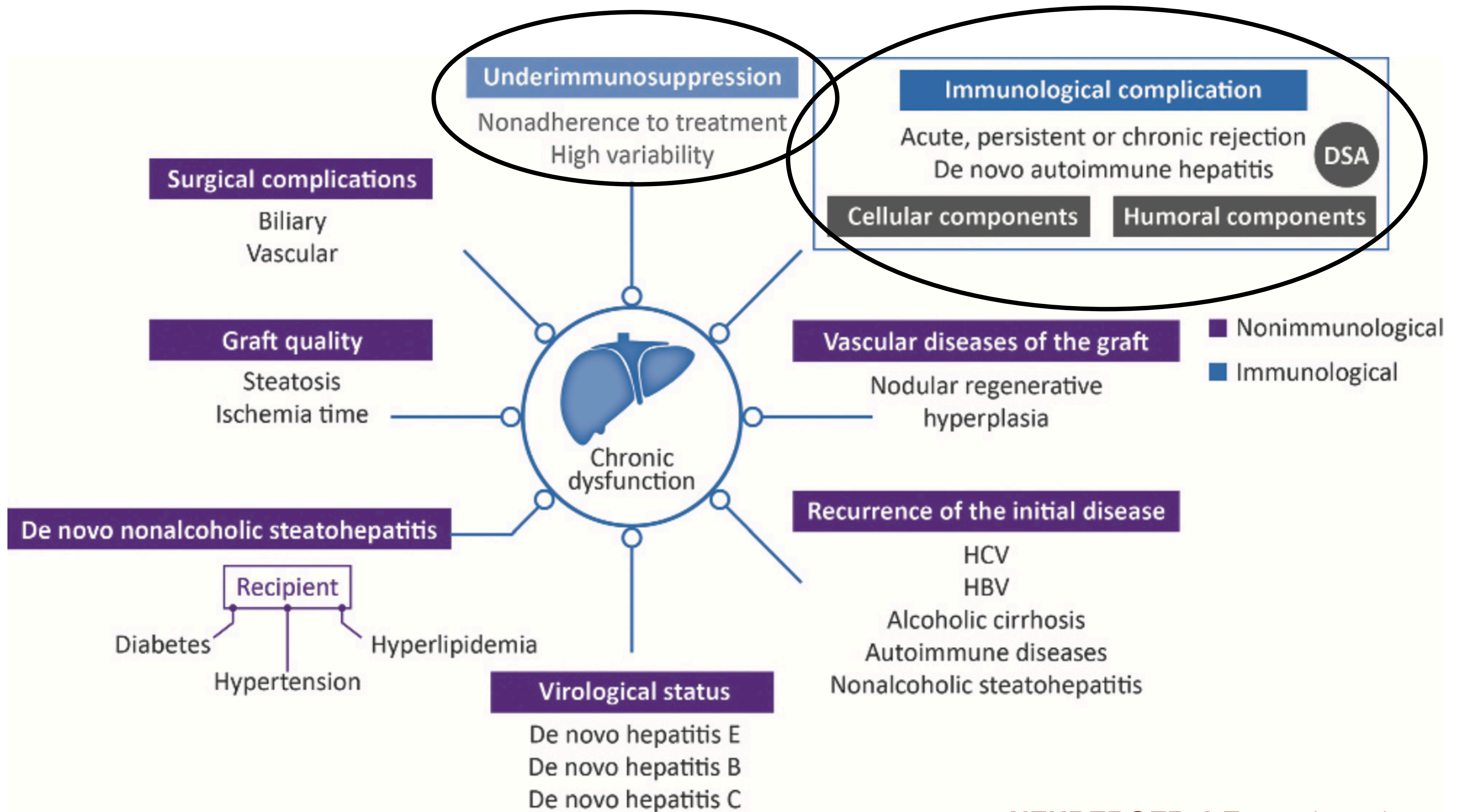
Less goes further

Contribución de Advagraf® a los resultados a largo plazo en trasplante hepático

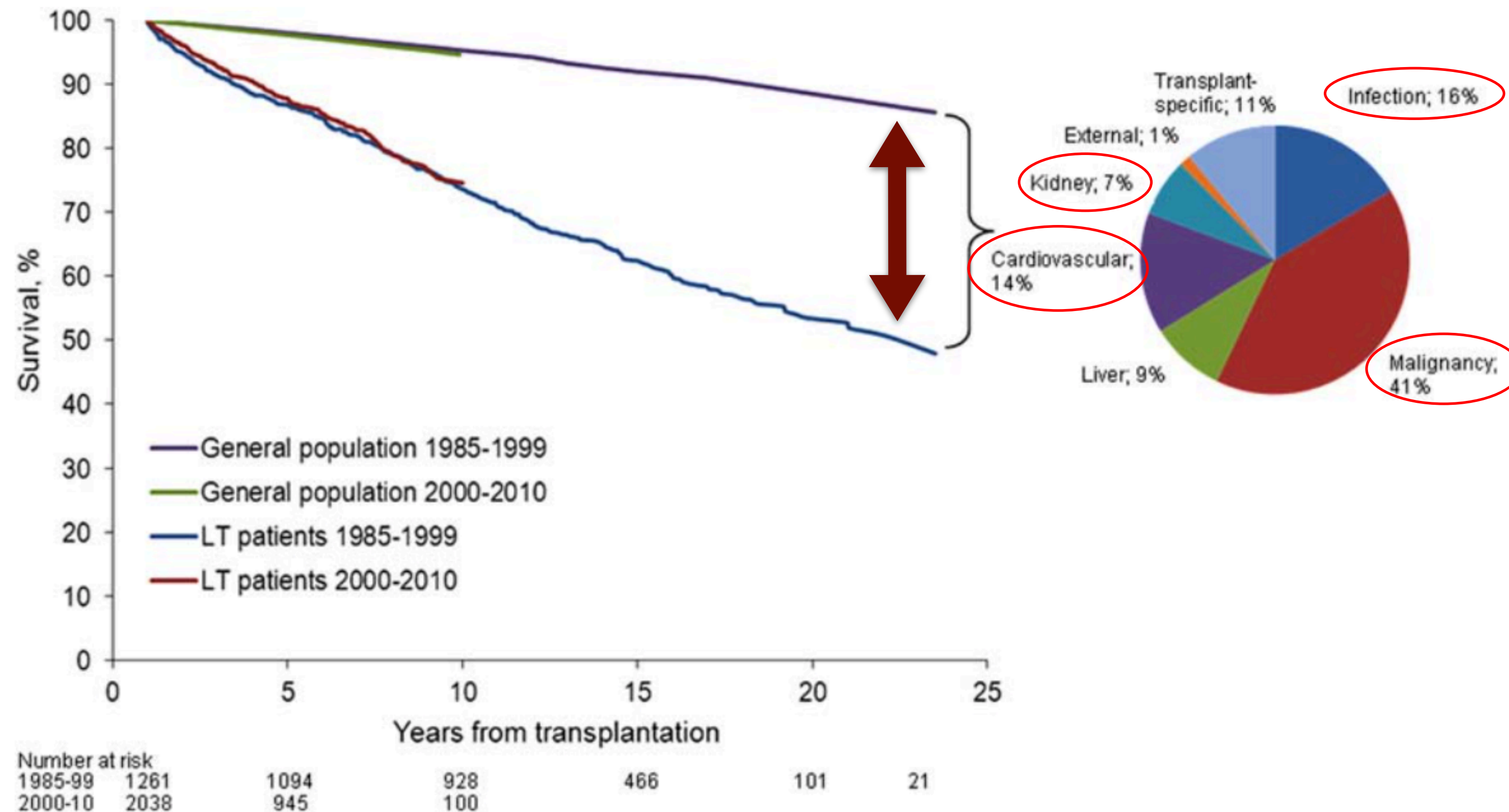
SETH2019

Javier Briceño



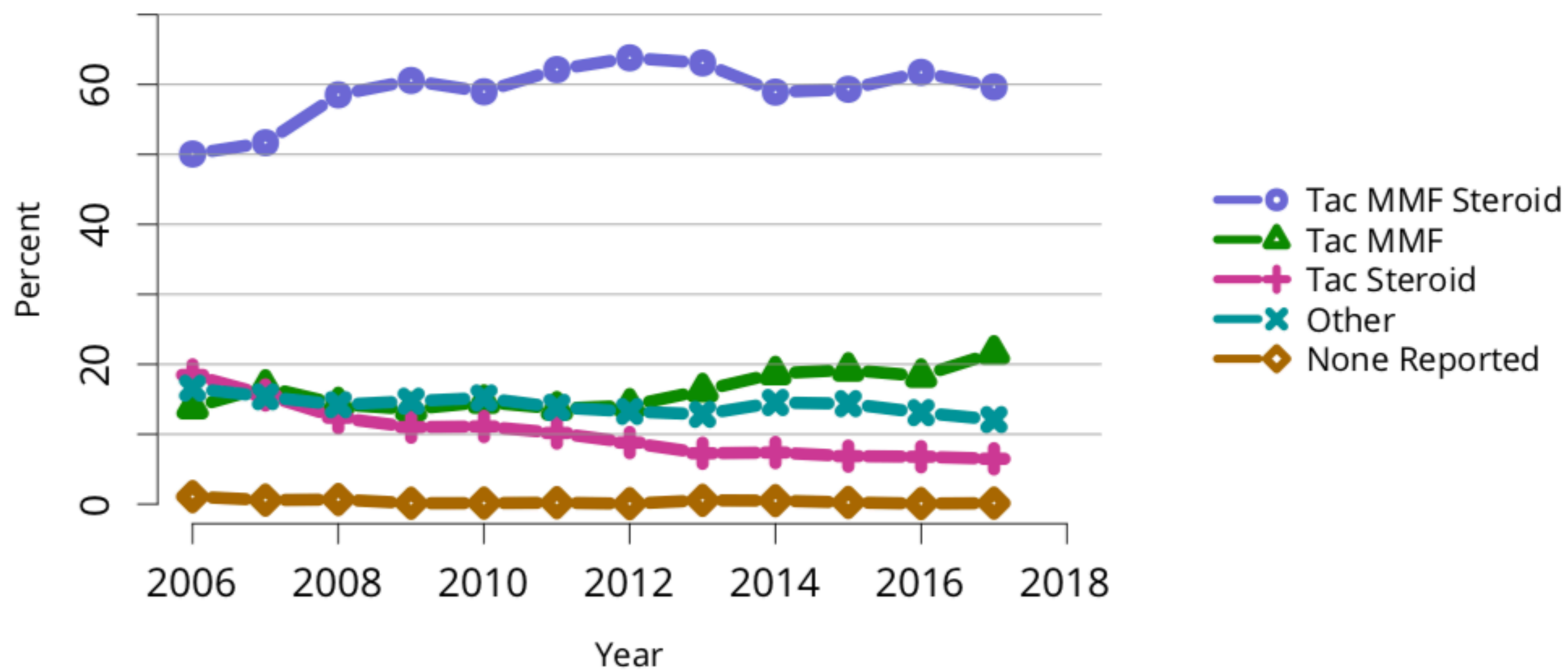


Incremento de mortalidad en trasplante hepático

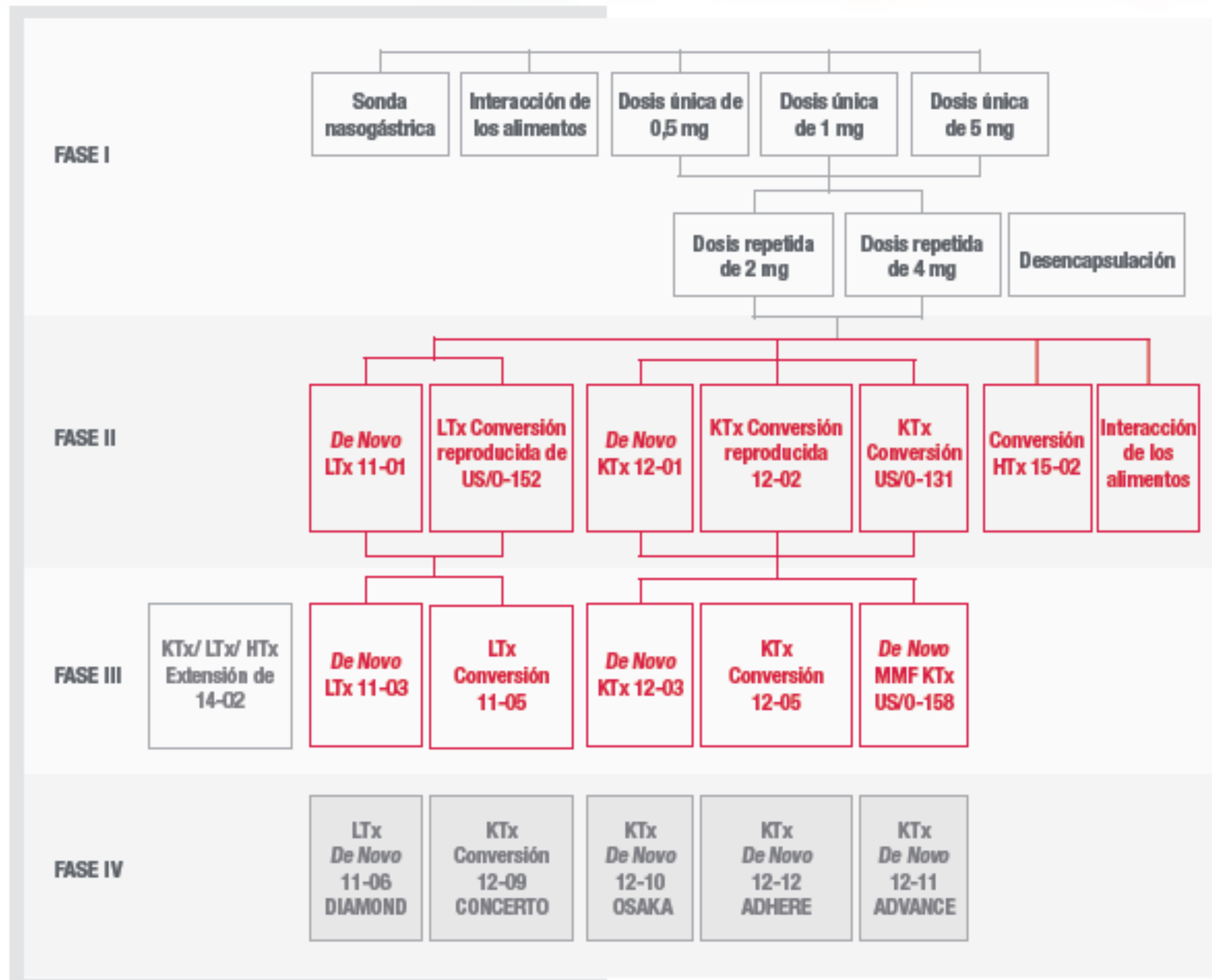


*20% exceso de mortalidad a 10 años
*4 de cada 5 fallecimientos potencialmente asociados a inmunosupresión

EVOLUCIÓN PAUTAS INMUNOSUPRESIÓN



Desarrollo clínico de ADVAGRAF

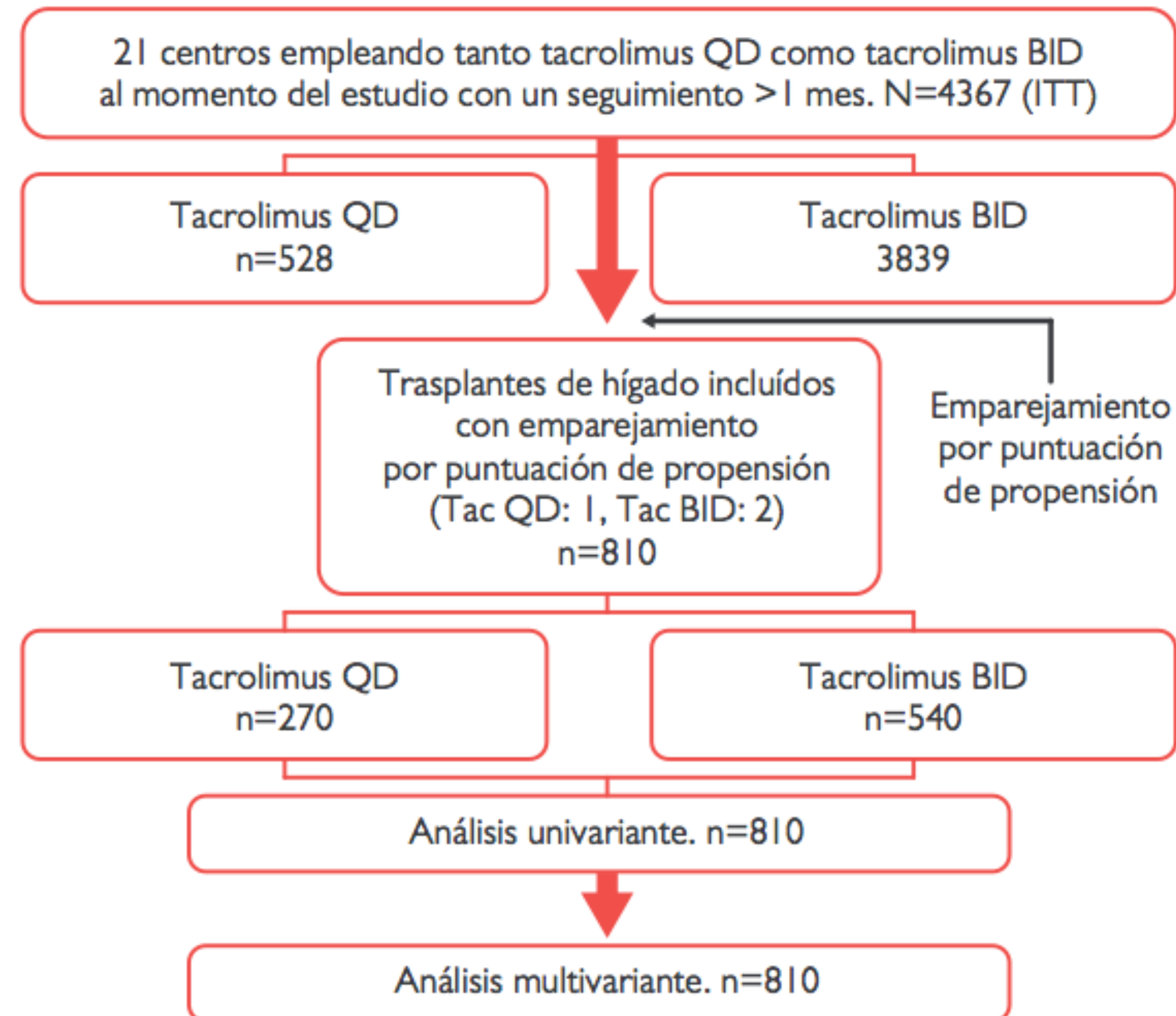




**European
Liver
Transplant
Registry**

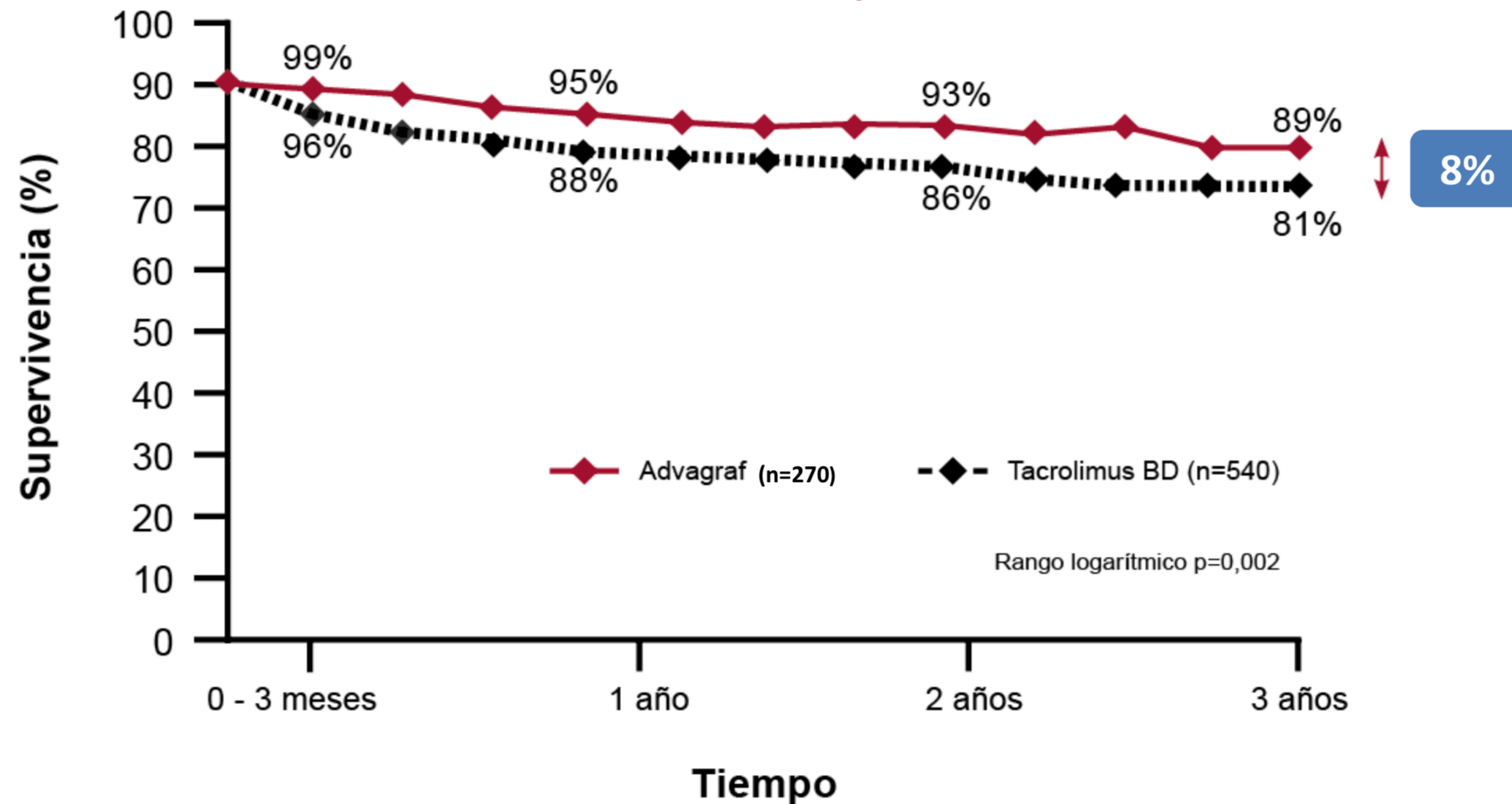
Advagraf vs TAC BID

Diseño del estudio

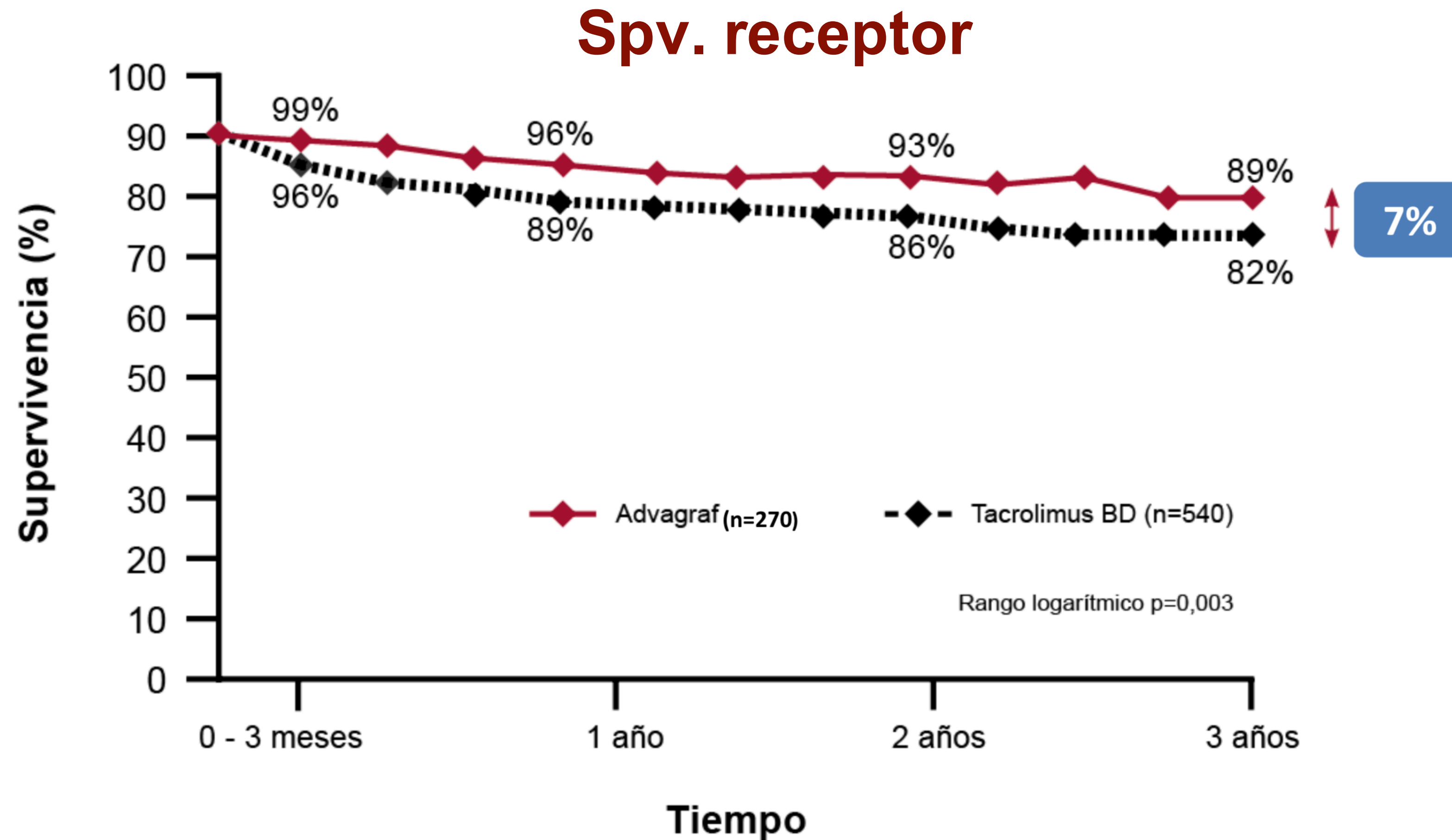


Advagraf vs TAC BID

Spv. injerto



Advagraf vs TAC BID

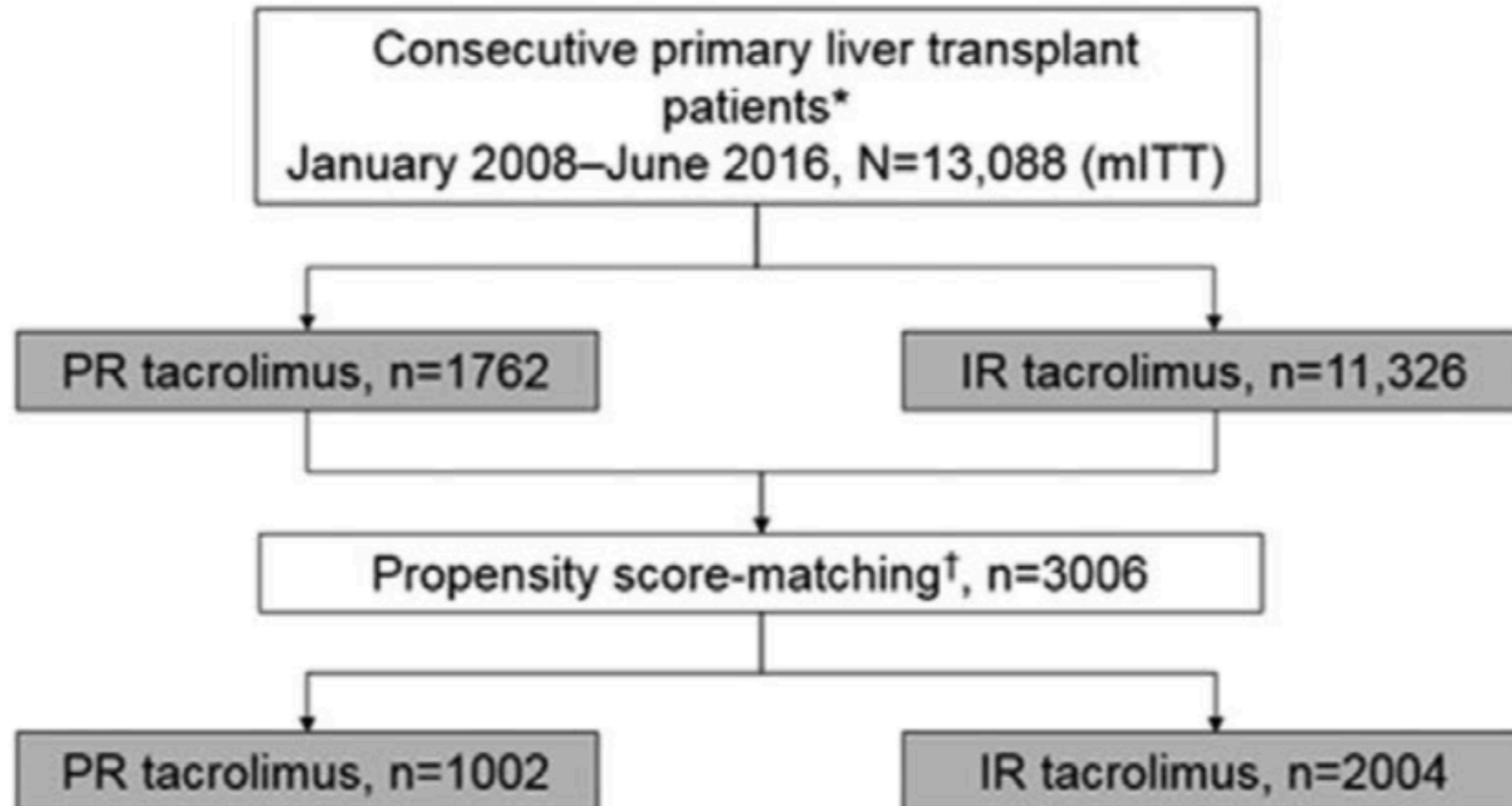


Advagraf vs TAC BID

RECEPTOR	<i>RR</i>
Incompatibilidad AB0	6.35
Tacrolimus BID	3.33
UNOS 1 & 2	2.53
CIT >6h	2.09
Donante >50	1.72

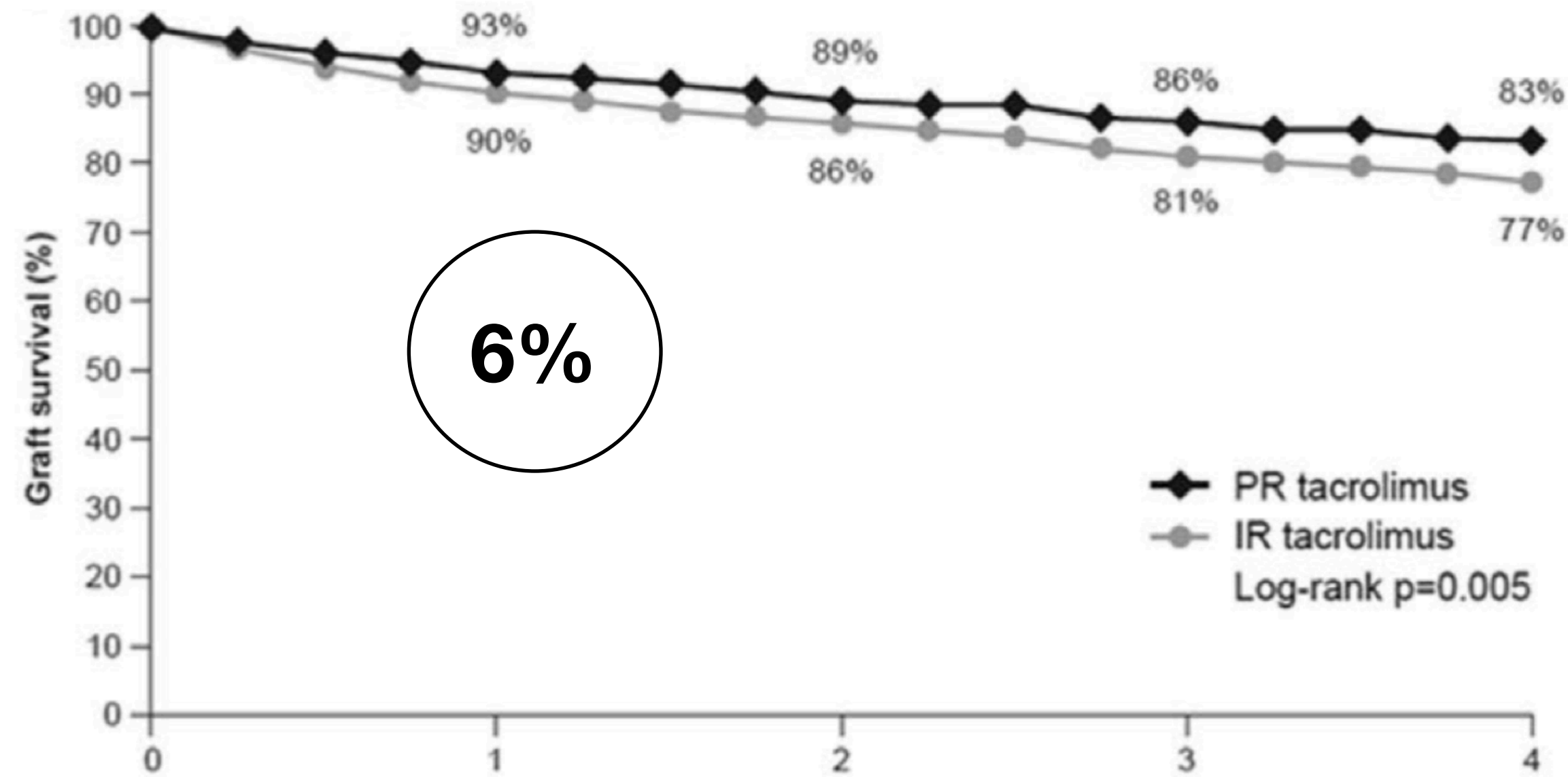
INJERTO	<i>RR</i>
Incompatibilidad AB0	6.22
Tacrolimus BID	3.33
UNOS 1 & 2	2.62
CIT> >6h	2.34
Donante >50	1.79

Improved Survival in Liver Transplant Patients Receiving Prolonged-release Tacrolimus-based Immunosuppression in the European Liver Transplant Registry (ELTR): An Extension Study

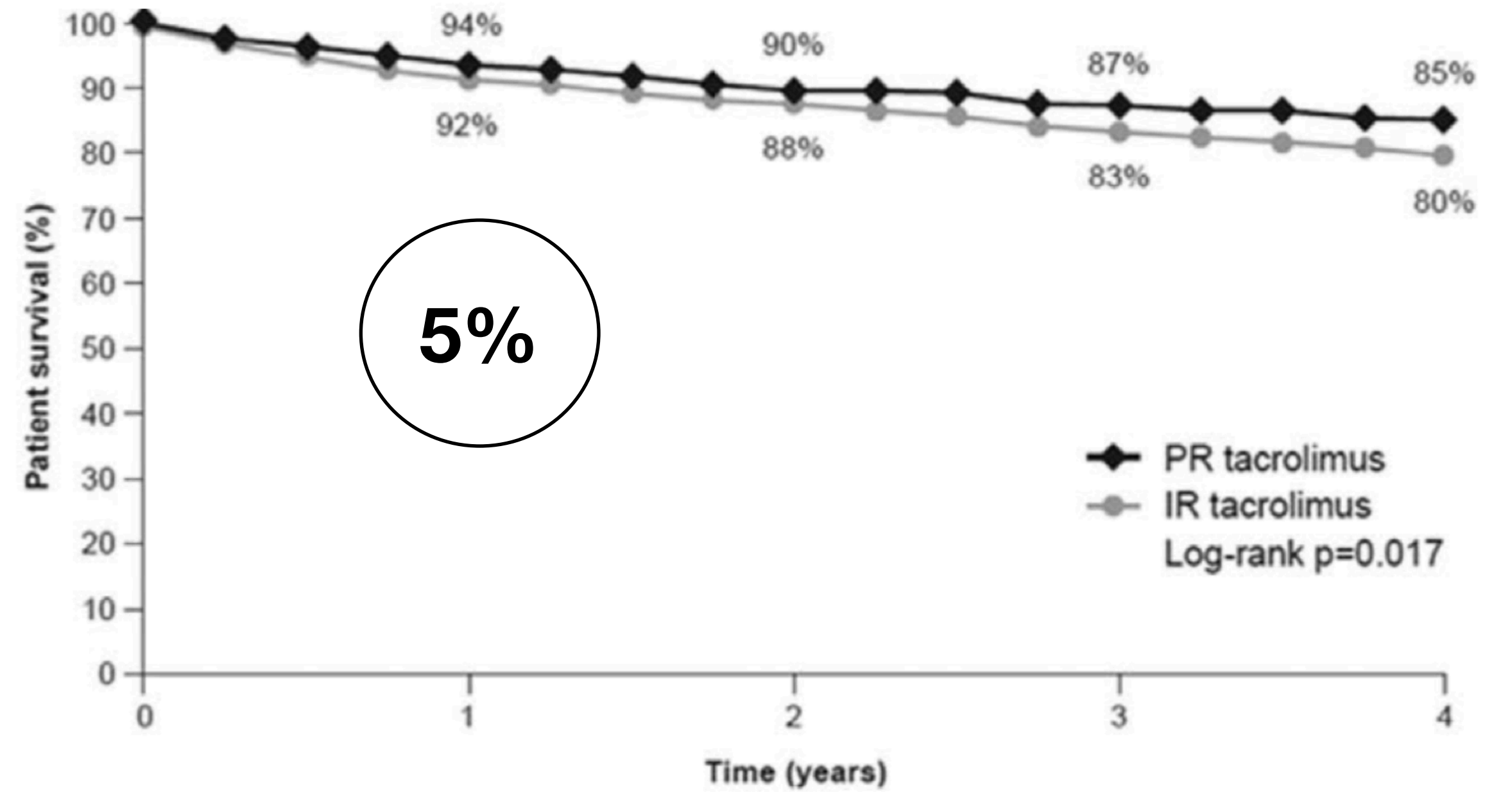


Improved Survival in Liver Transplant Patients Receiving Prolonged-release Tacrolimus-based Immunosuppression in the European Liver Transplant Registry (ELTR): An Extension Study

Spv. injerto

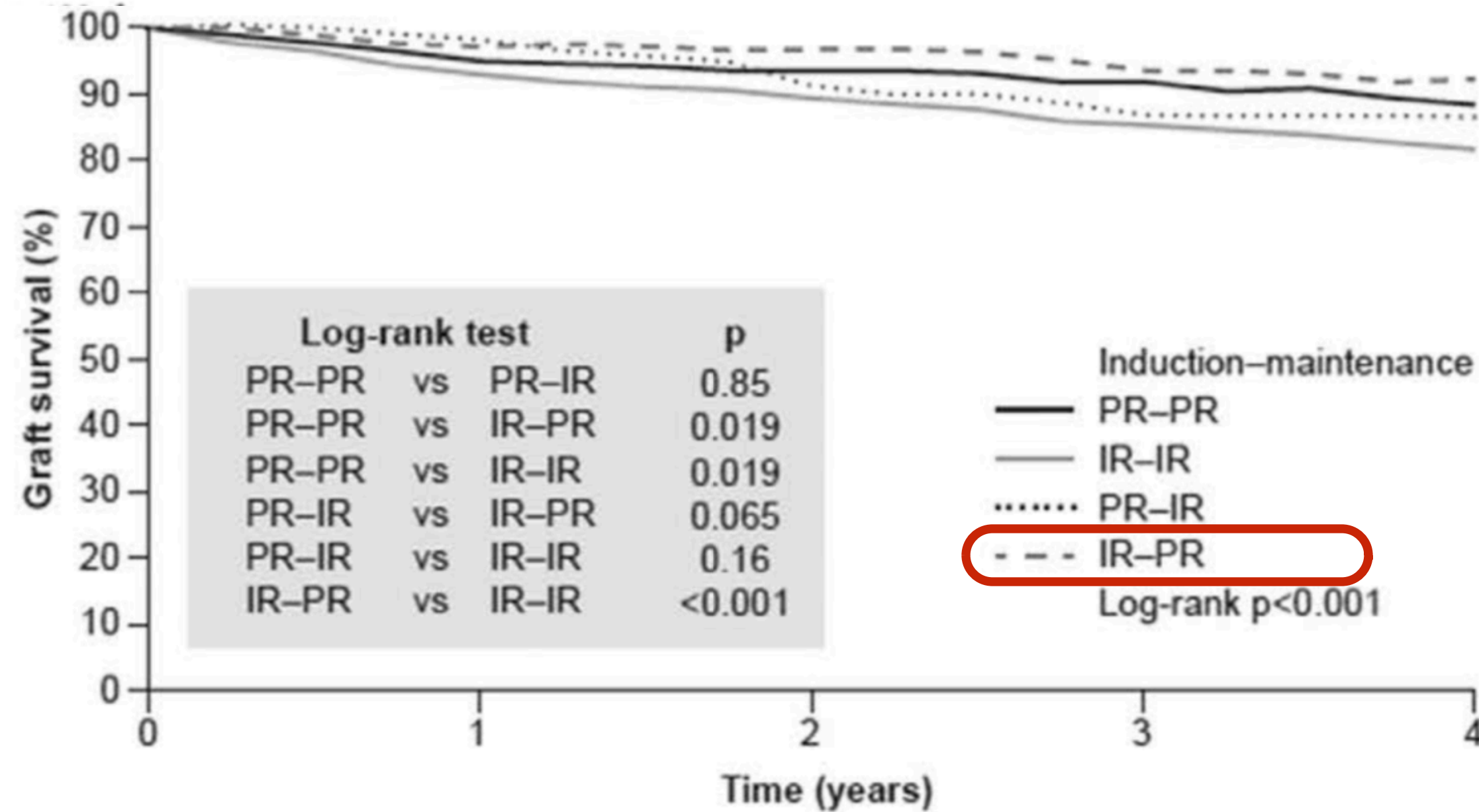


Spv. receptor

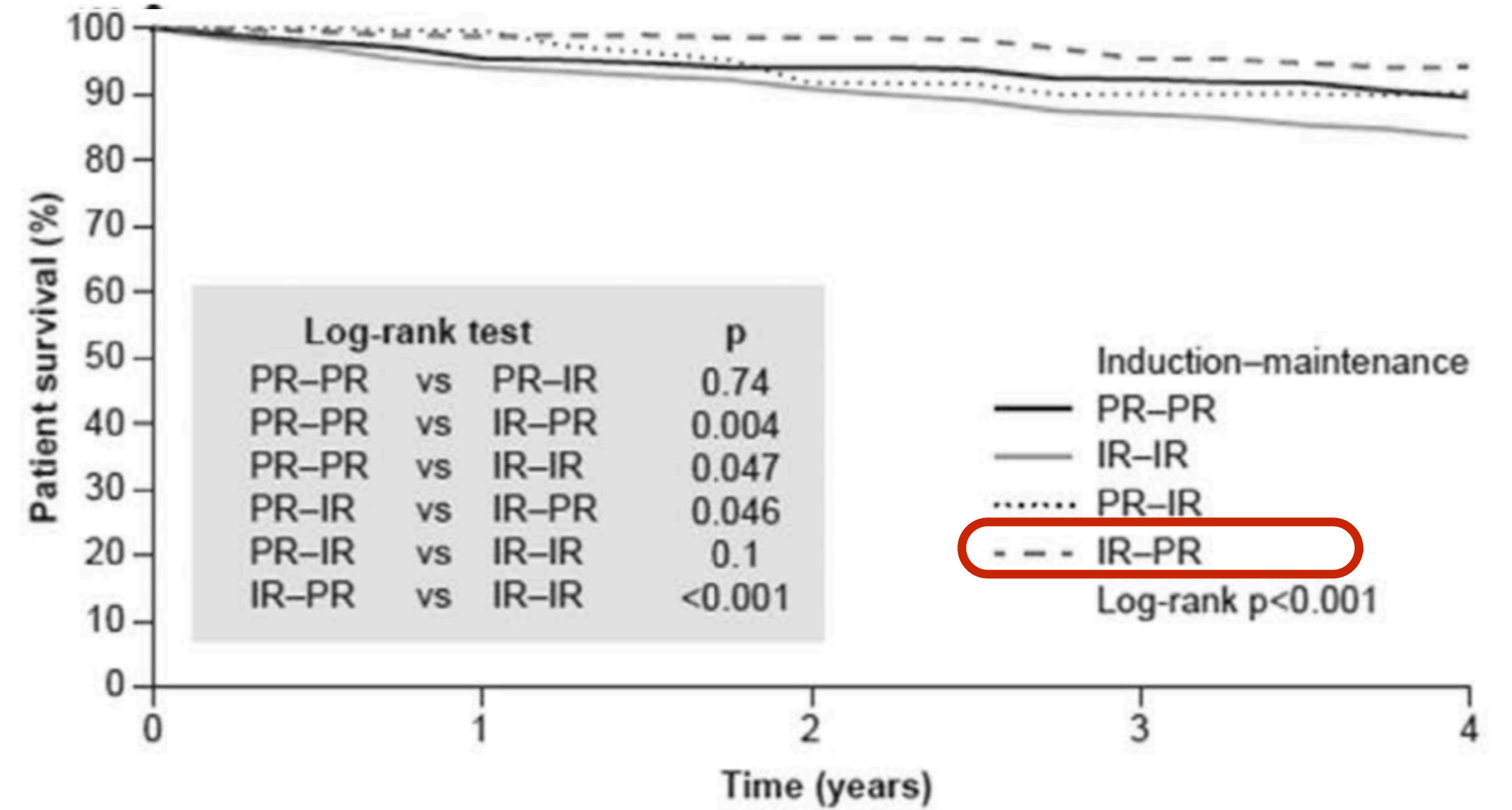


Improved Survival in Liver Transplant Patients Receiving Prolonged-release Tacrolimus-based Immunosuppression in the European Liver Transplant Registry (ELTR): An Extension Study

Spv. injerto



Spv. receptor



Crossover groups

Advagraf vs TAC BID

RECEPTOR	<i>RR</i>
Incompatibilidad AB0	6.35
Tacrolimus BID	3.33
UNOS 1 & 2	2.53
CIT >6h	2.09
Donante >50	1.72

INJERTO	<i>RR</i>
Incompatibilidad AB0	6.22
Tacrolimus BID	3.33
UNOS 1 & 2	2.62
CIT> >6h	2.34
Donante >50	1.79

Advagraf vs TAC BID

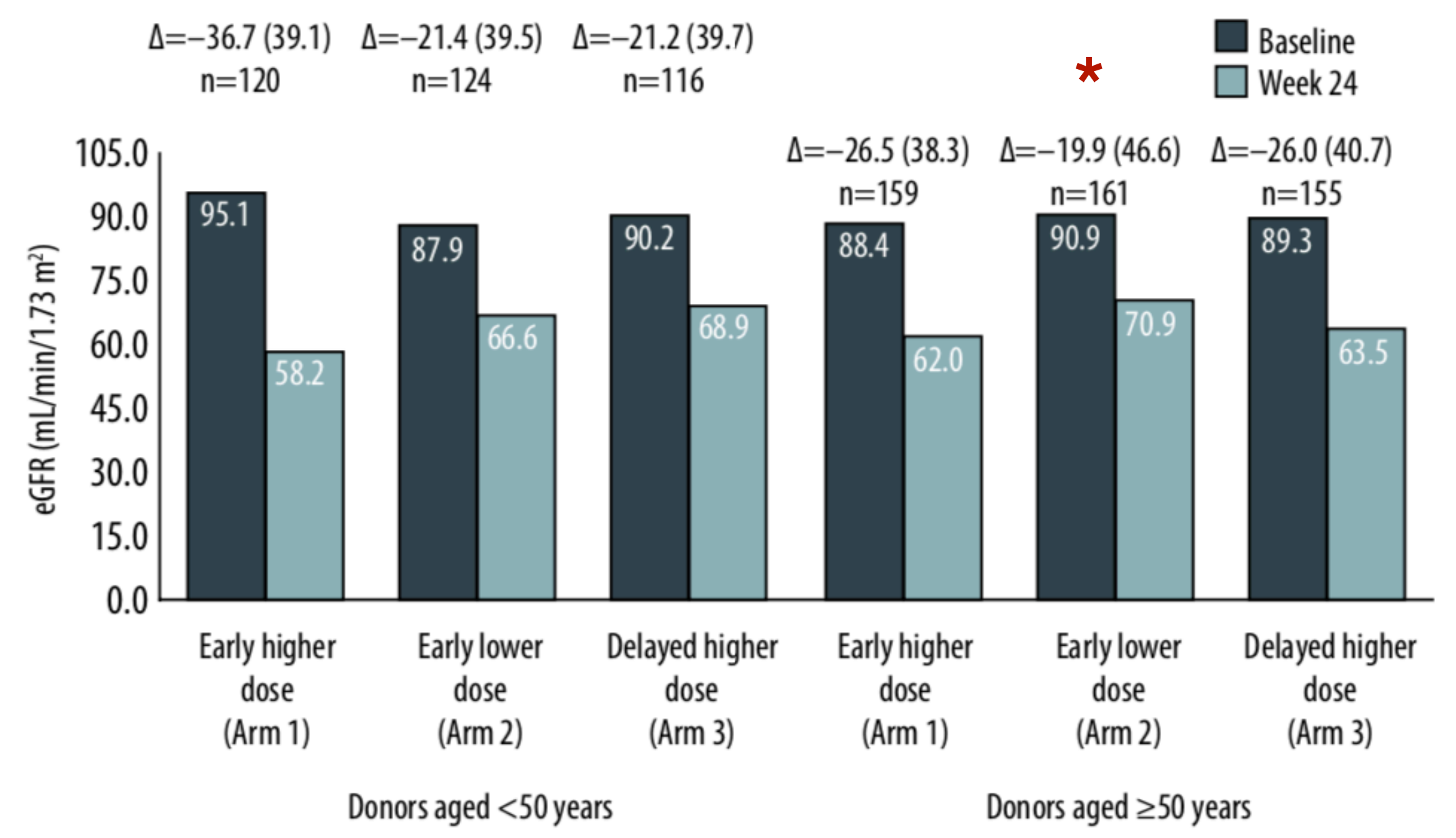
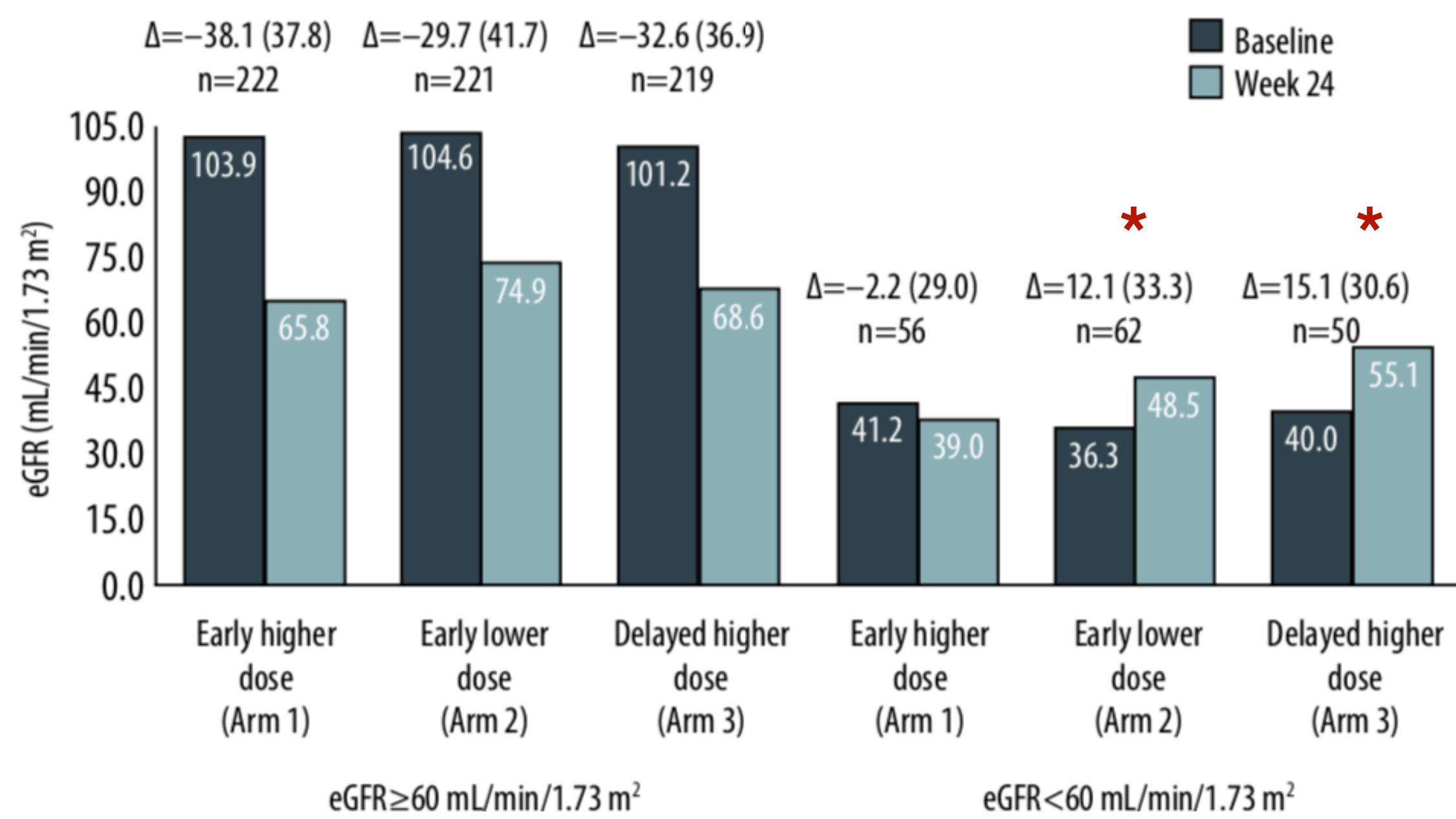
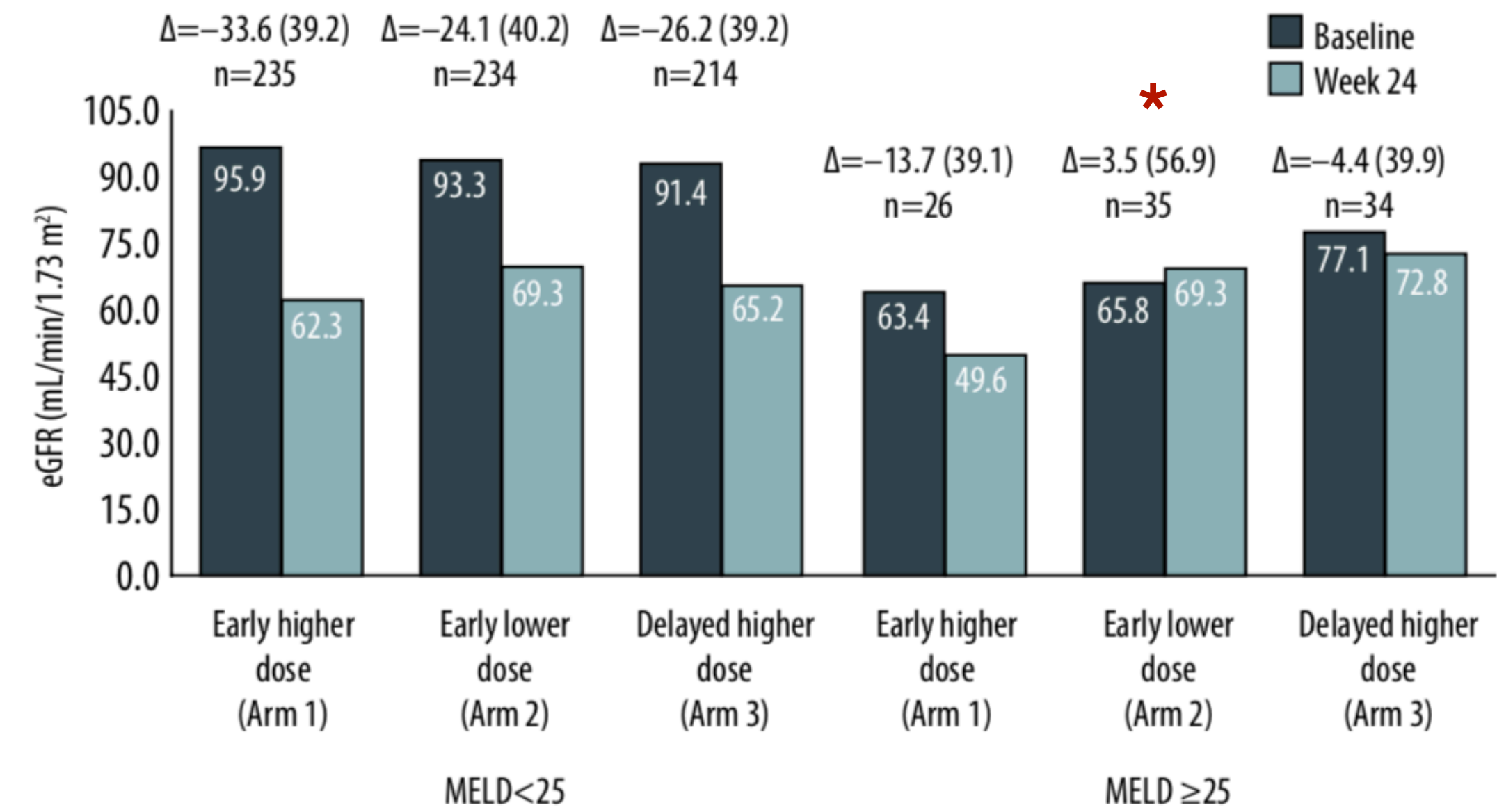
RECEPTOR	<i>RR</i>
Receptor VHC+	<i>1.91</i>
Creatinina >2mg/dL	<i>1.90</i>
UNOS 1 & 2	<i>1.89</i>
Tacrolimus BID	<i>1.40</i>
HCC	<i>1.35</i>
Donante >50	<i>1.33</i>

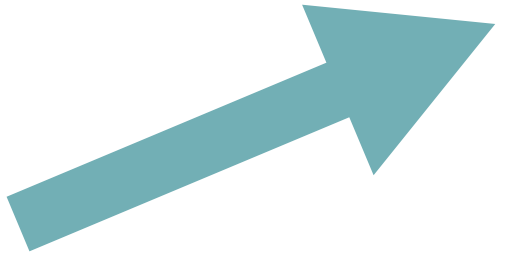
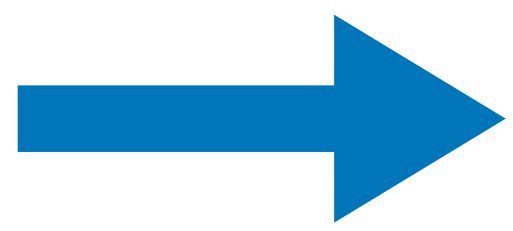
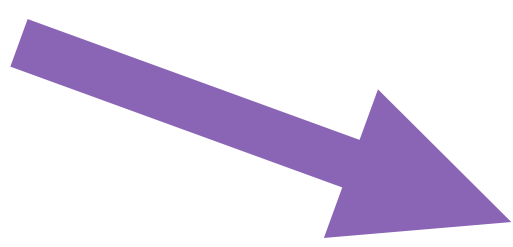
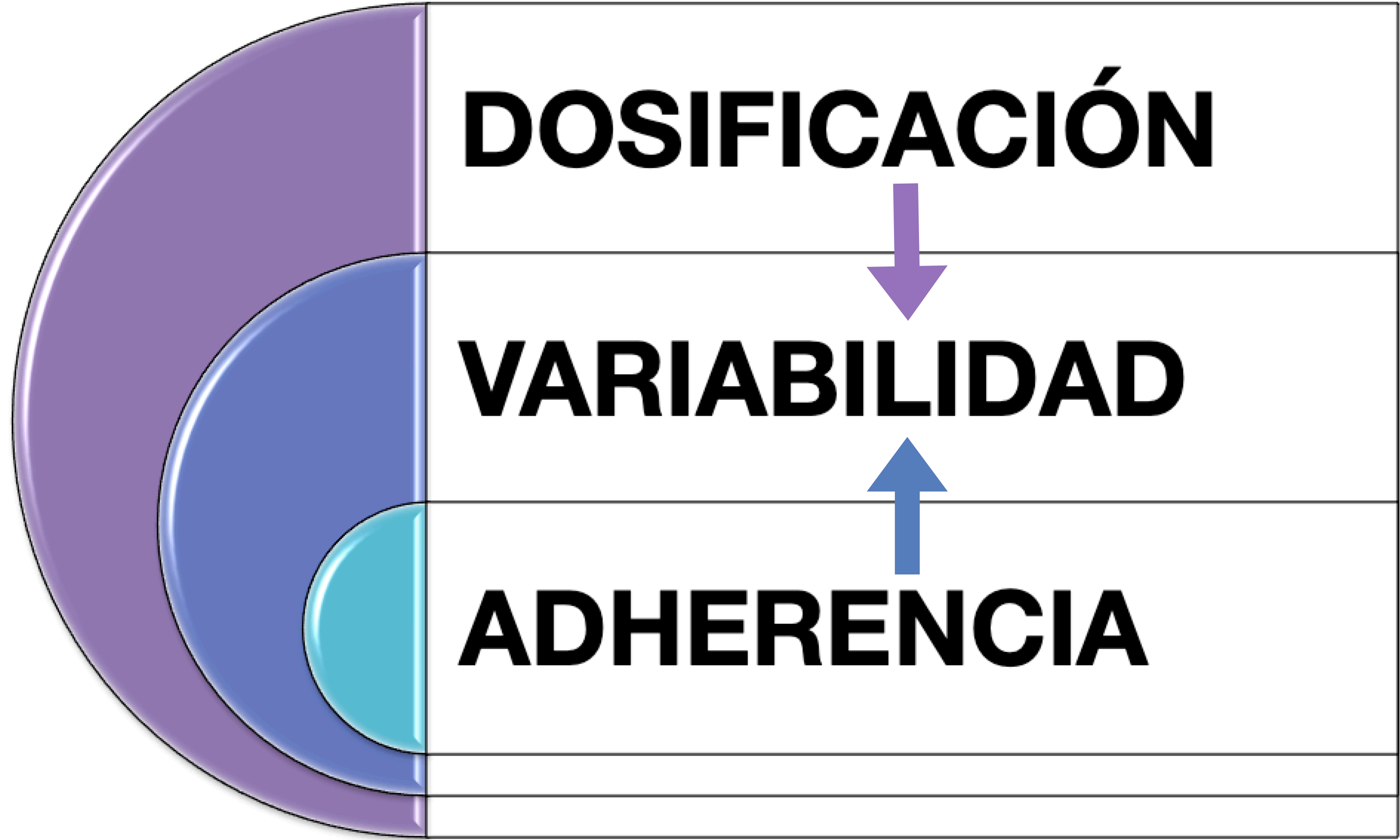
INJERTO	<i>RR</i>
Receptor HCV+	<i>2.05</i>
Edad receptor >55	<i>1.74</i>
UNOS 1 & 2	<i>1.69</i>
Creatinina 2mg/dL	<i>1.66</i>
Tacrolimus BID	<i>1.49</i>
Donante >50	<i>1.35</i>

The Effect of Donor Age and Recipient Characteristics on Renal Outcomes in Patients Receiving Prolonged-Release Tacrolimus After Liver Transplantation: Post-Hoc Analyses of the DIAMOND Study

Trunecka P, Ann Transplant 2019

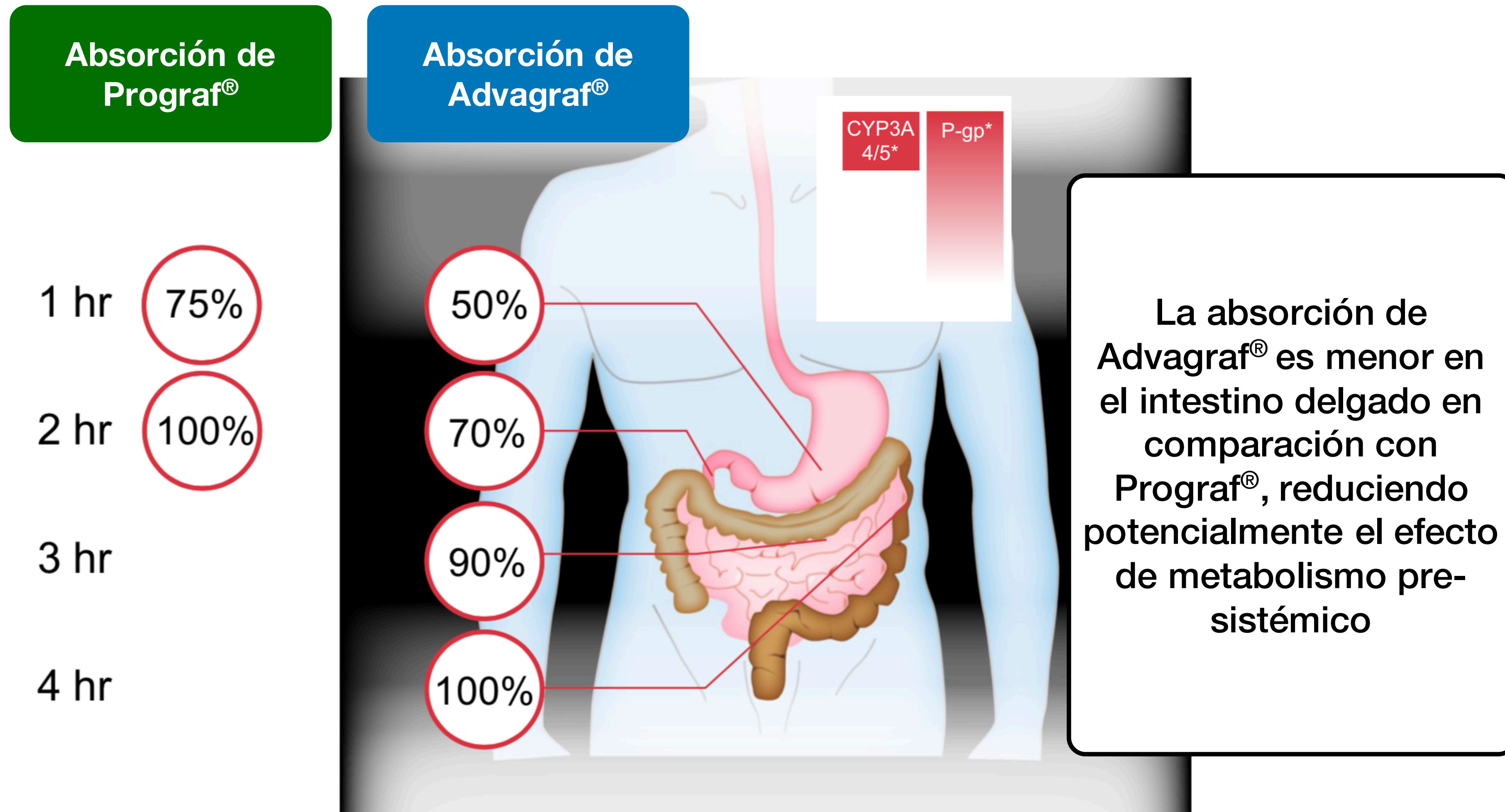
Arm 1: Advagraf 2 mg/kg/d
Arm 2: Advagraf 0.15-0.175 mg/kg/d } + Basiliximab
Arm 3: (+5) Advagraf 2 mg/kg/d



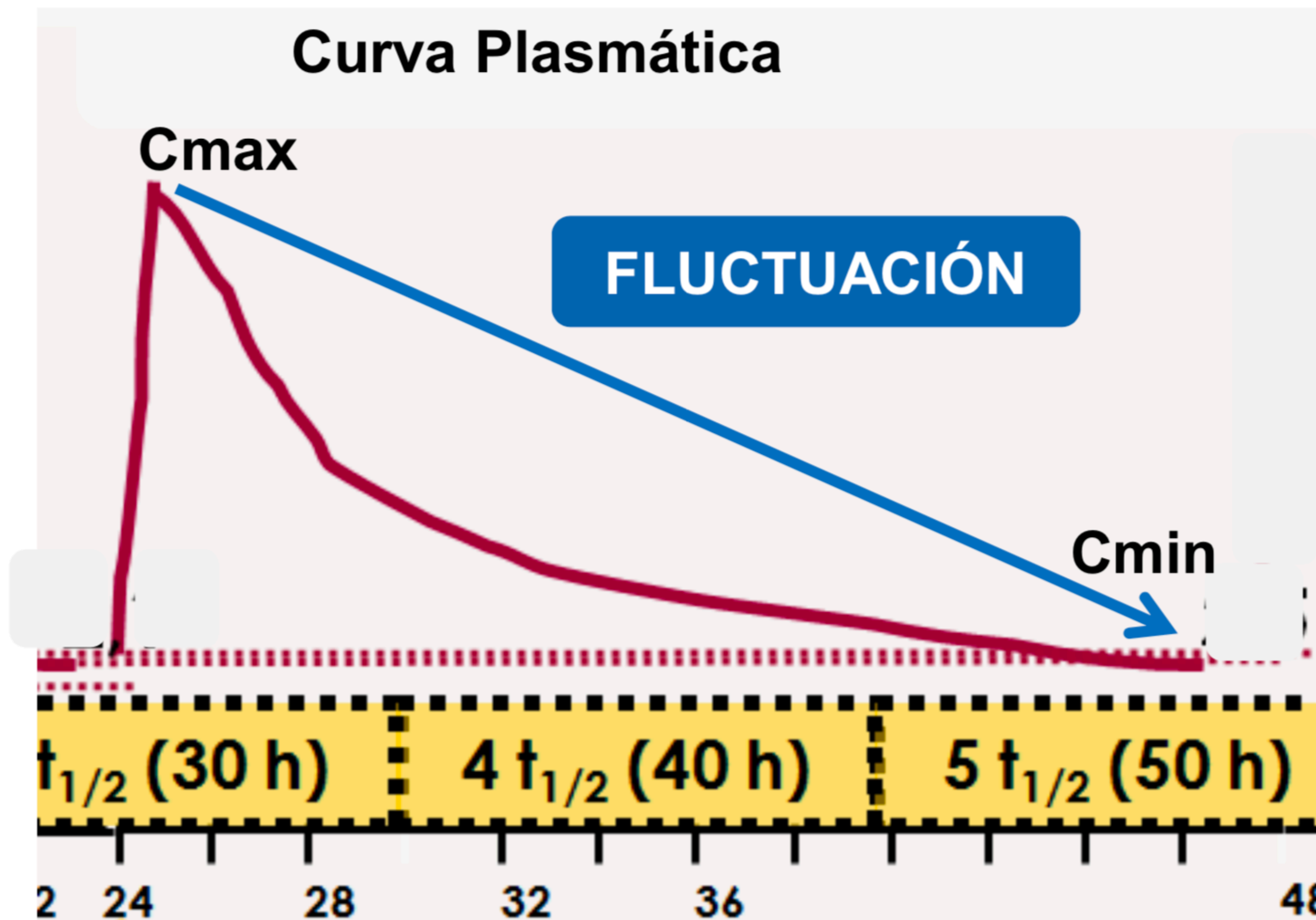


**RESULTADOS A
LARGO PLAZO**

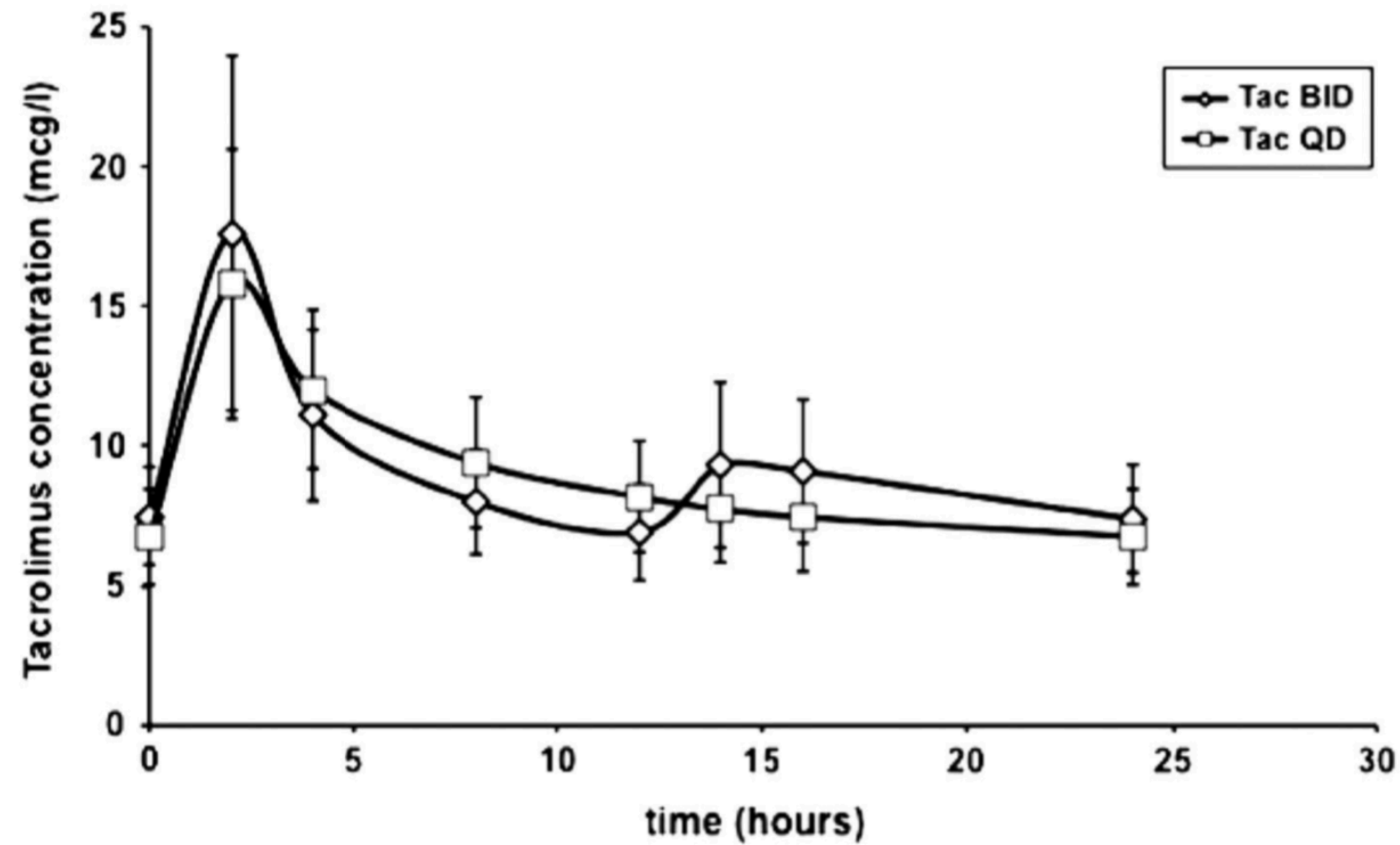
COMPARACIÓN DEL PERFIL TEÓRICO DE ABSORCIÓN EN EL TIEMPO ADVAGRAF® (liberación retardada) vs PROGRAF® (liberación inmediata)



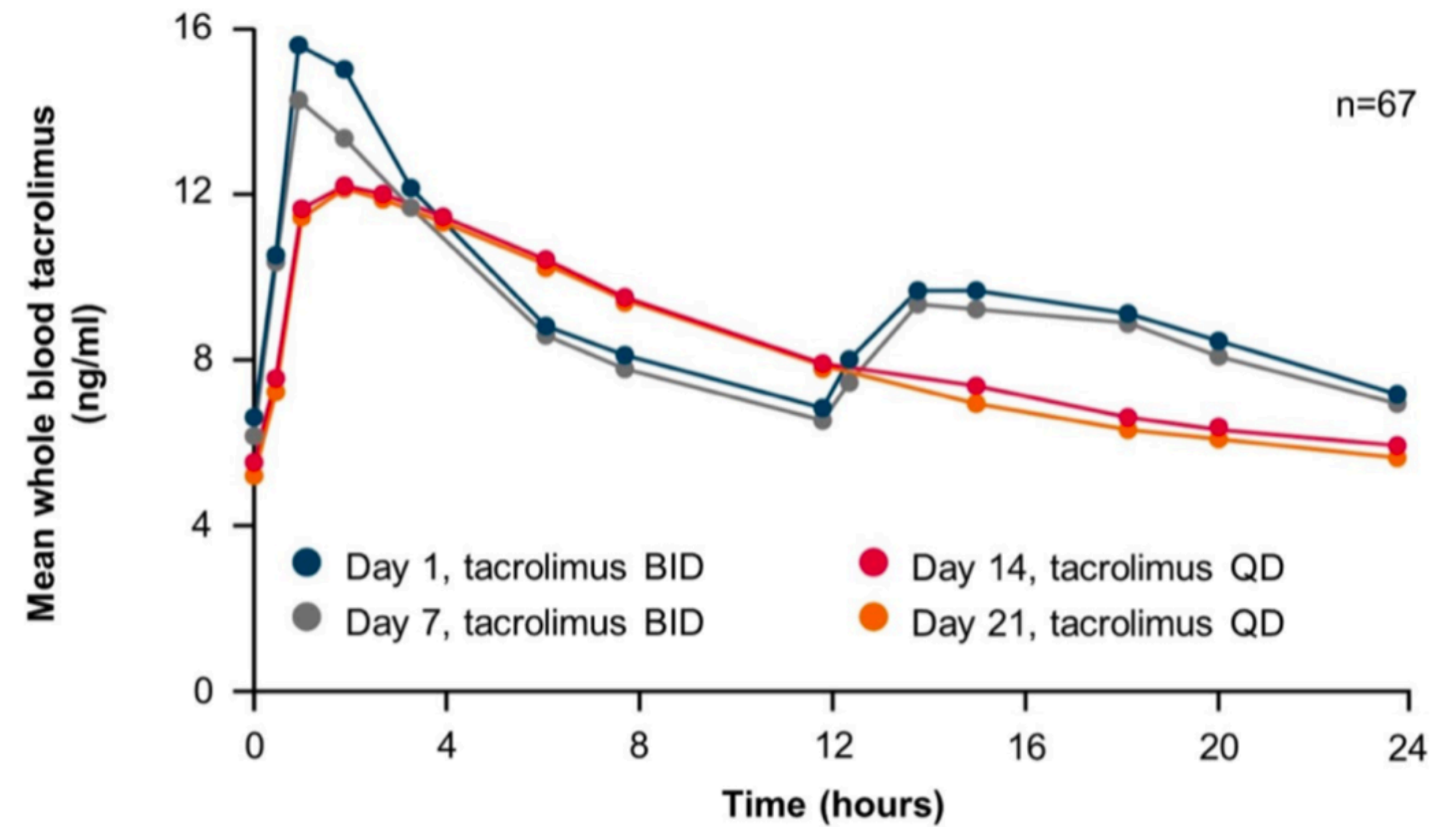
Fluctuación: parámetro farmacocinético



PERFIL FARMACOCINÉTICO DE ADVAGRAF® (liberación retardada) vs PROGRAF® (liberación inmediata)



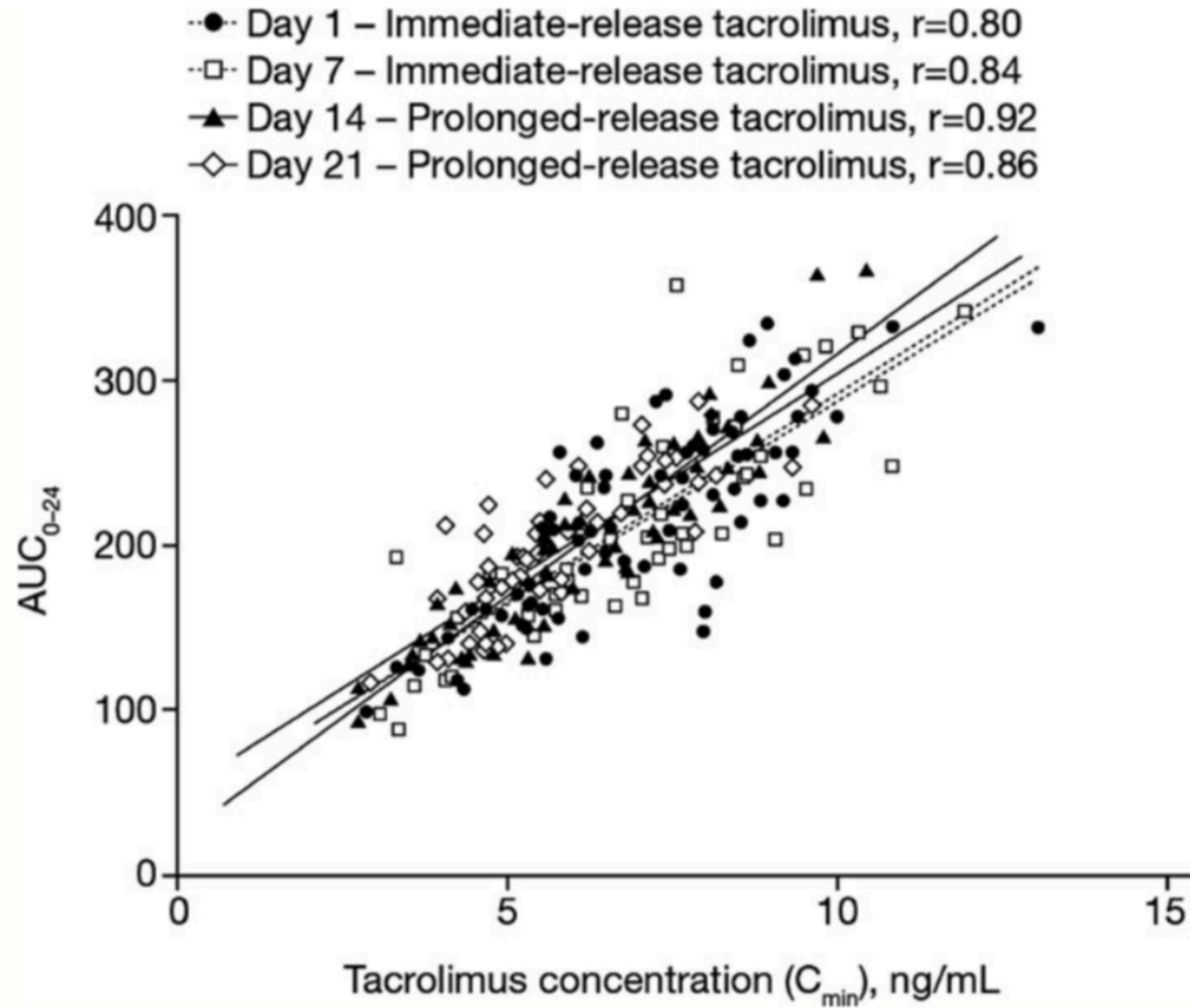
Staatz CE, *Clin Pharmacokinet* 2015



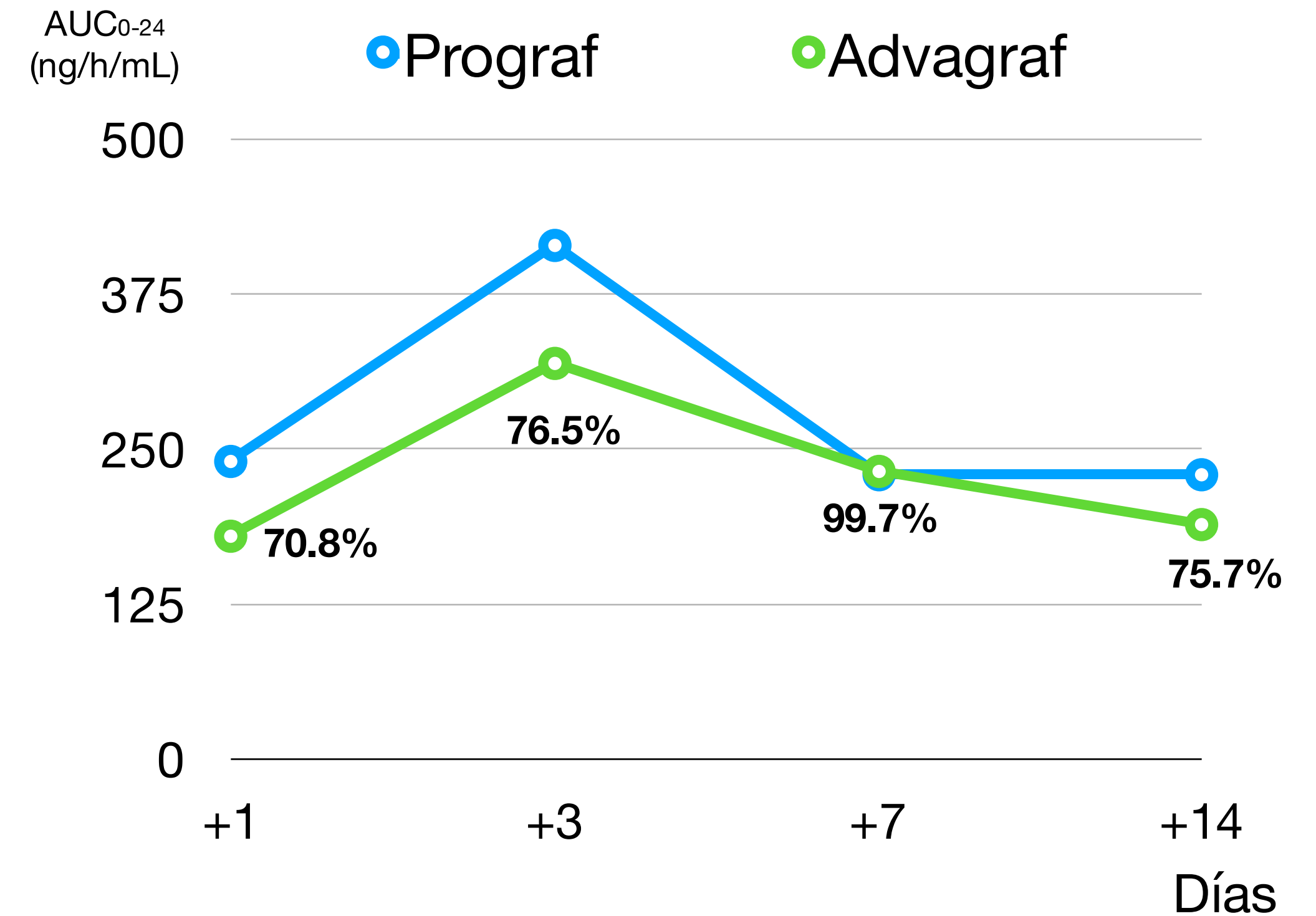
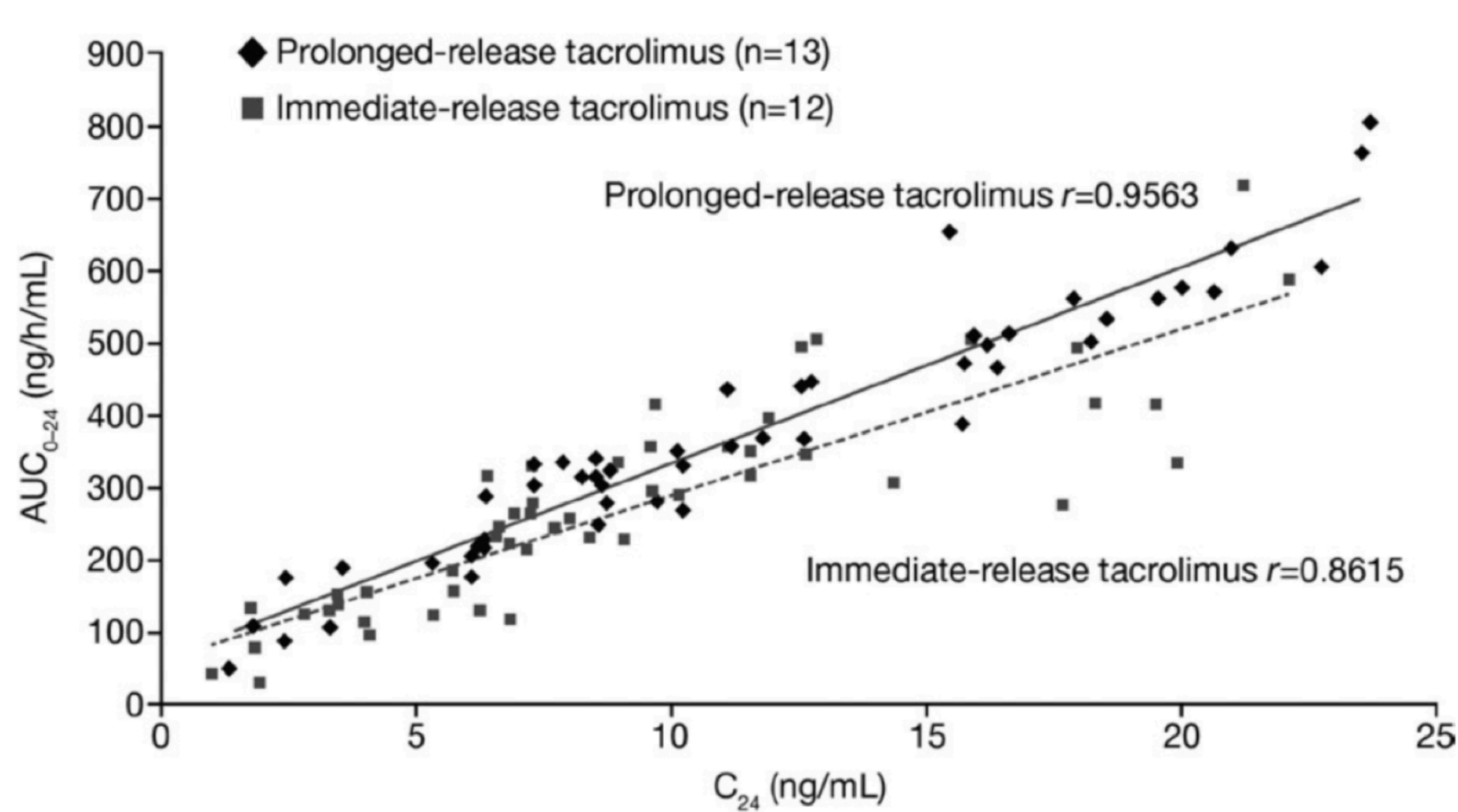
Tanzi MG, *Clin Transplant* 2016

- * Curva concentración-tiempo más suave
- * Perfil farmacocinético más plano
- * No dosis nocturna

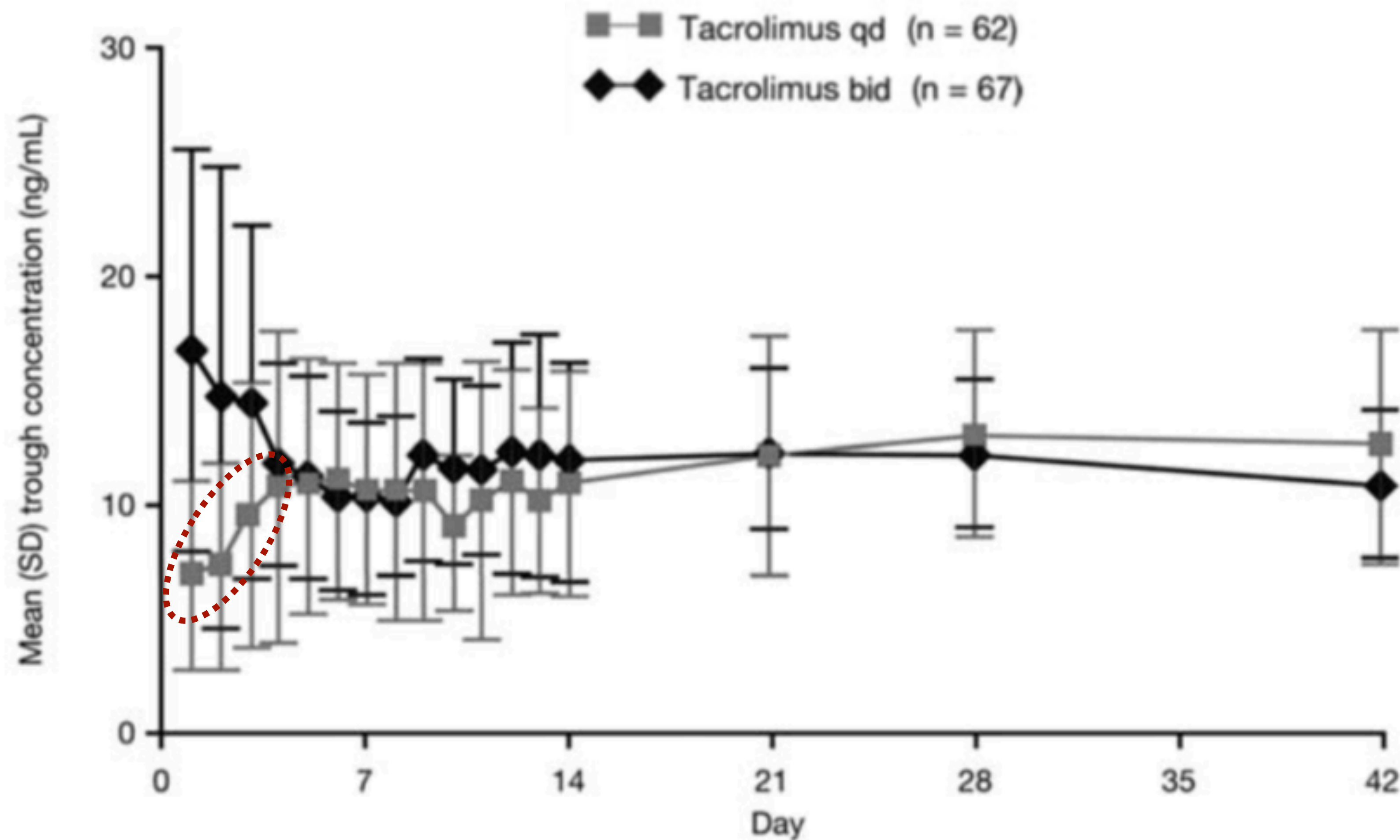
Pharmacokinetics of prolonged-release tacrolimus and implications for use in solid organ transplant recipients



Pharmacokinetics of prolonged-release tacrolimus versus immediate-release tacrolimus in de novo liver transplantation: A randomized phase III substudy

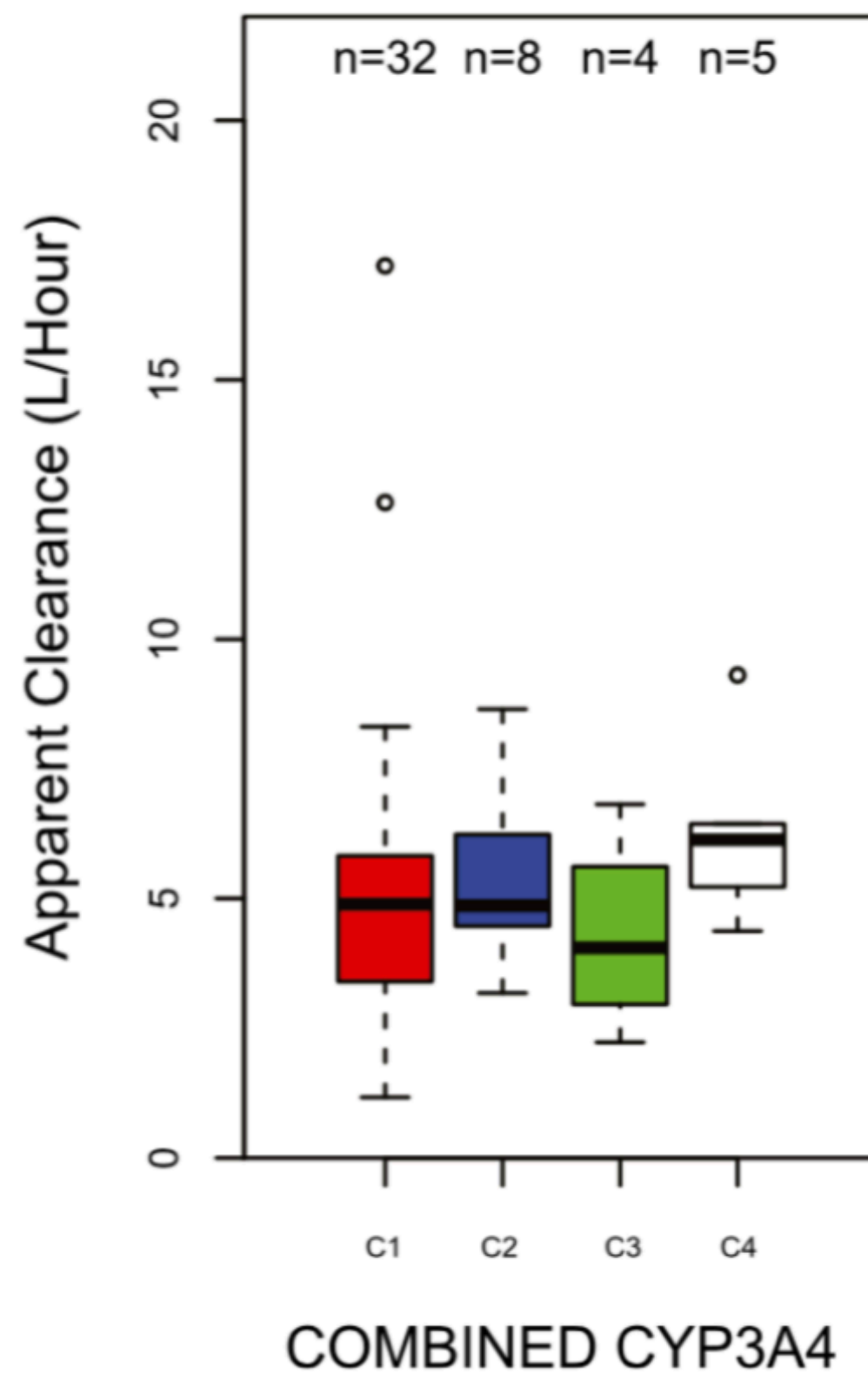


PERFIL FARMACOCINÉTICO DE ADVAGRAF® (liberación retardada) vs PROGRAF® (liberación inmediata)

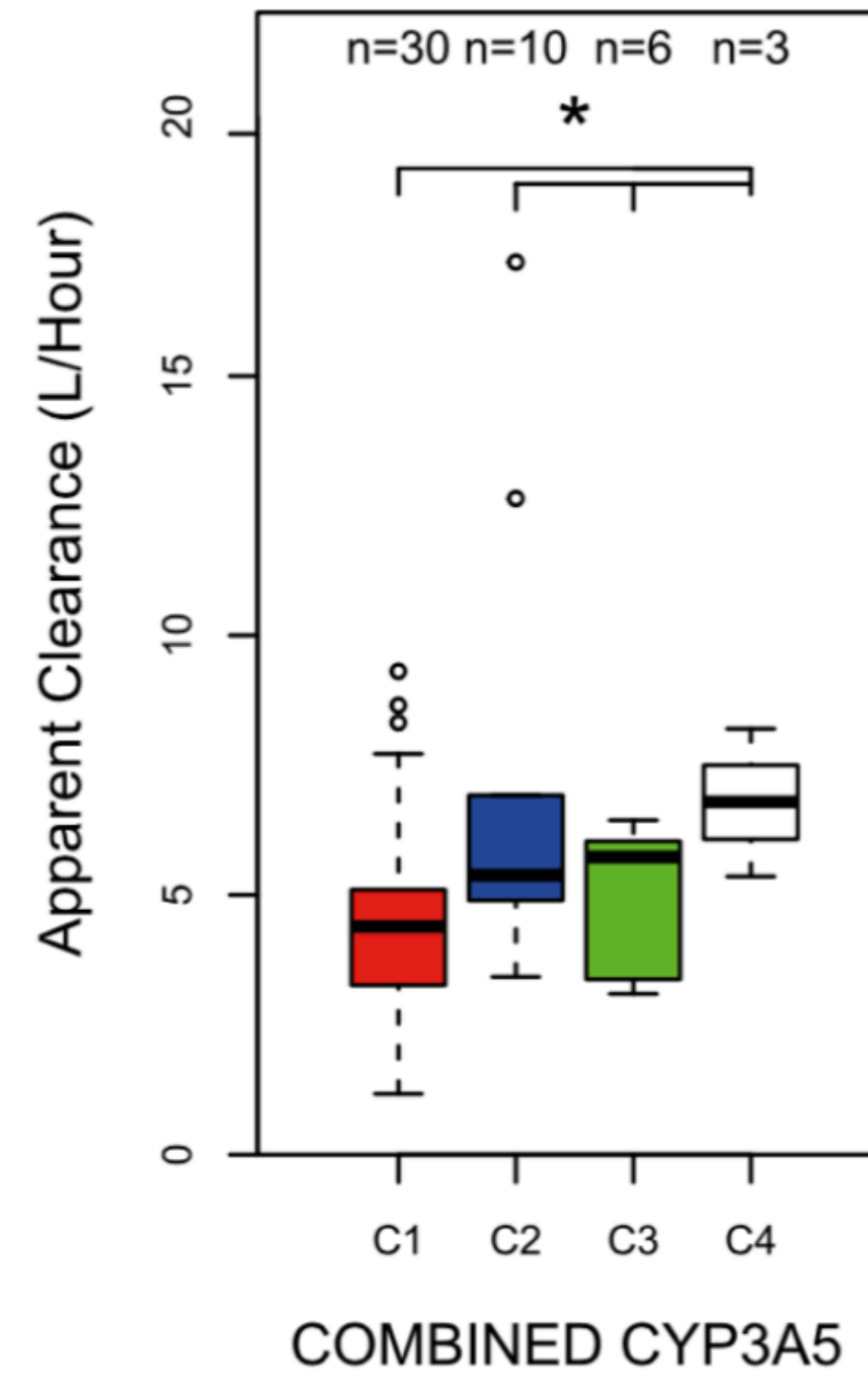


Population pharmacokinetics and pharmacogenetics of once daily tacrolimus formulation in stable liver transplant recipients

CYP3A4

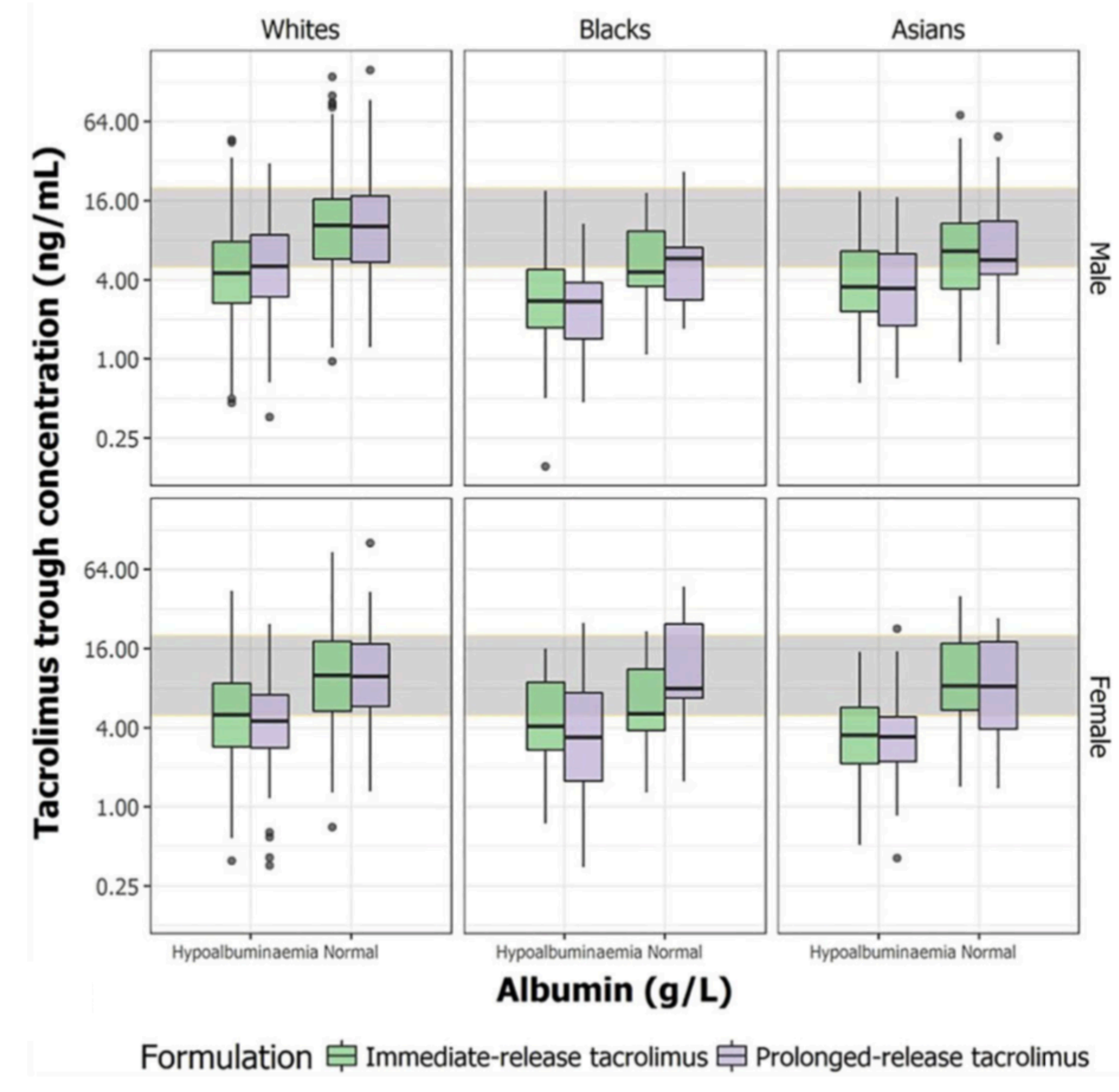
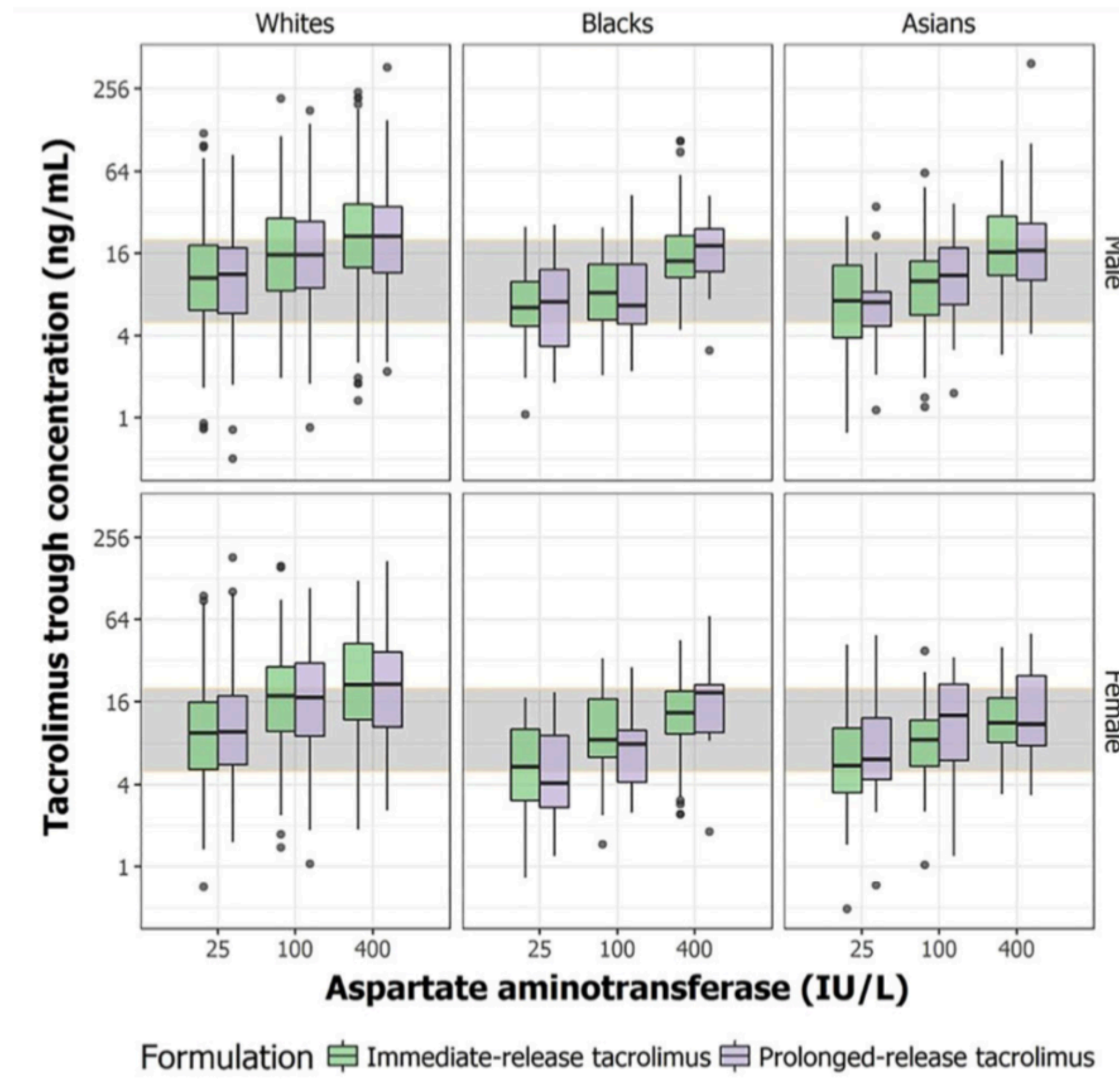


CYP3A5

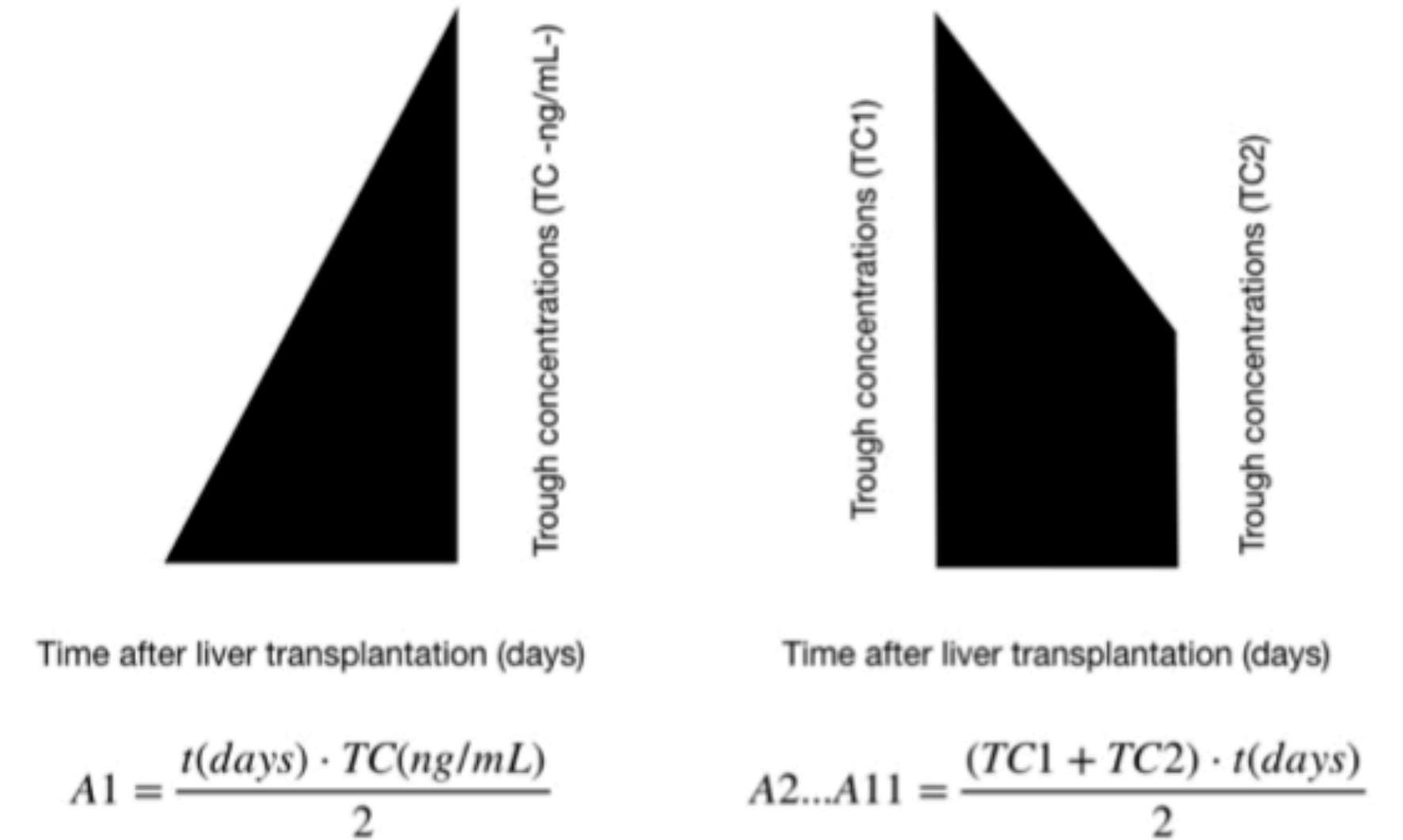
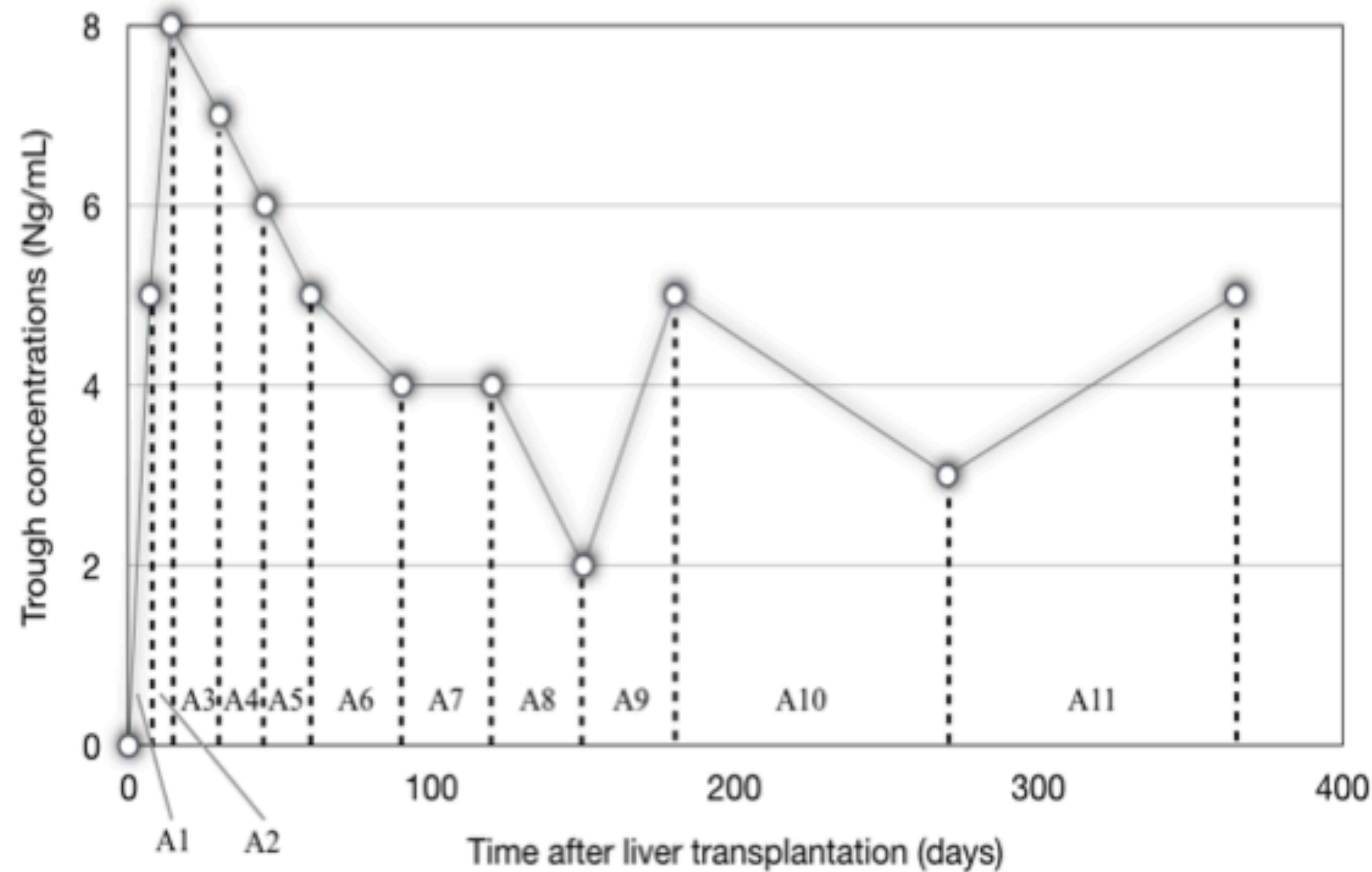


C1 R- / D-	1.0 (Ref.)
C2 R+ / D-	1.3>
C3 R- / D+	1.3>
C4 R+ / D+	1.7>

Population pharmacokinetics of immediate- and prolonged-release tacrolimus formulations in liver, kidney and heart transplant recipients

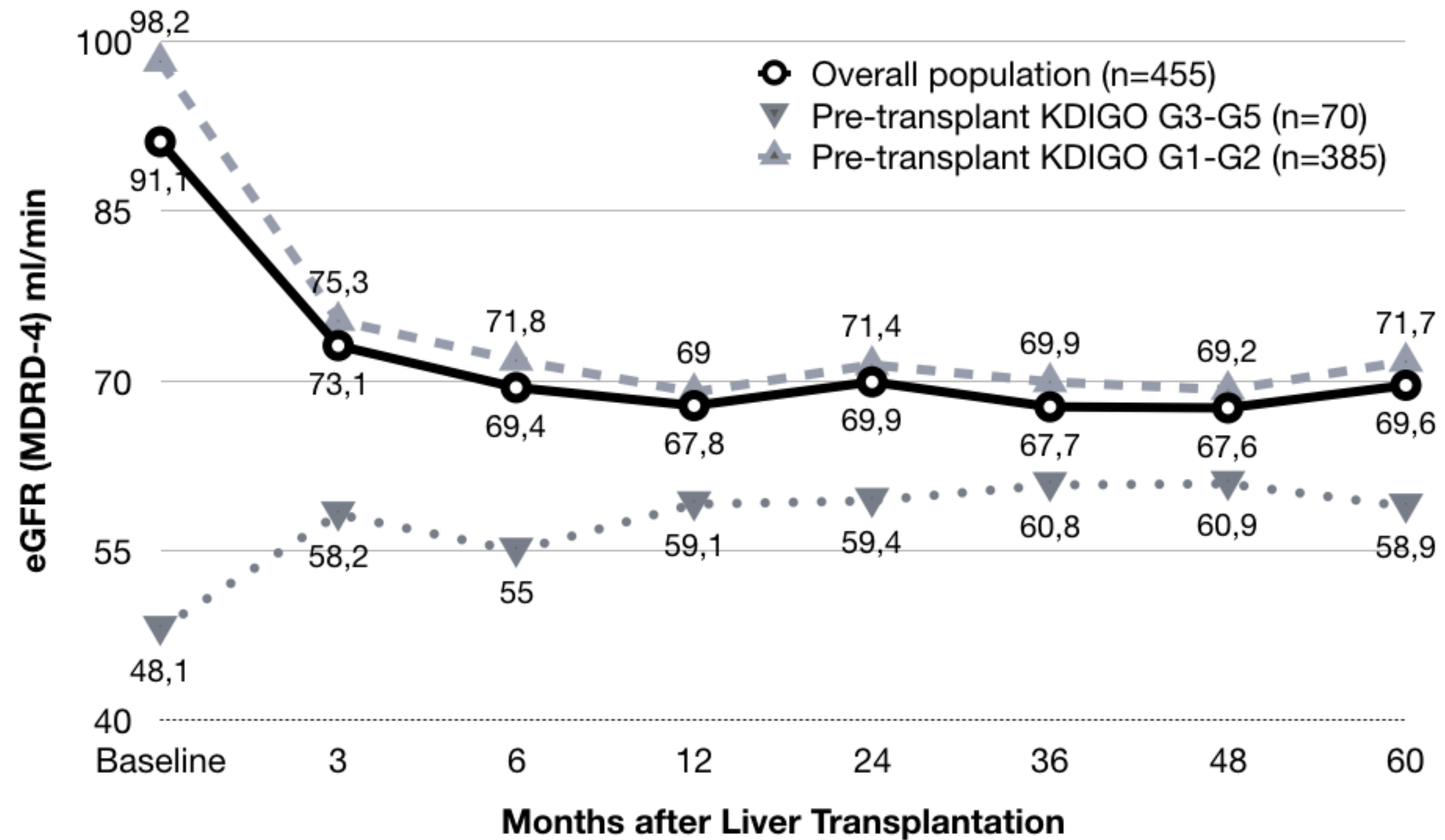


Area under trough concentrations of tacrolimus as a predictor of progressive renal impairment after liver transplantation

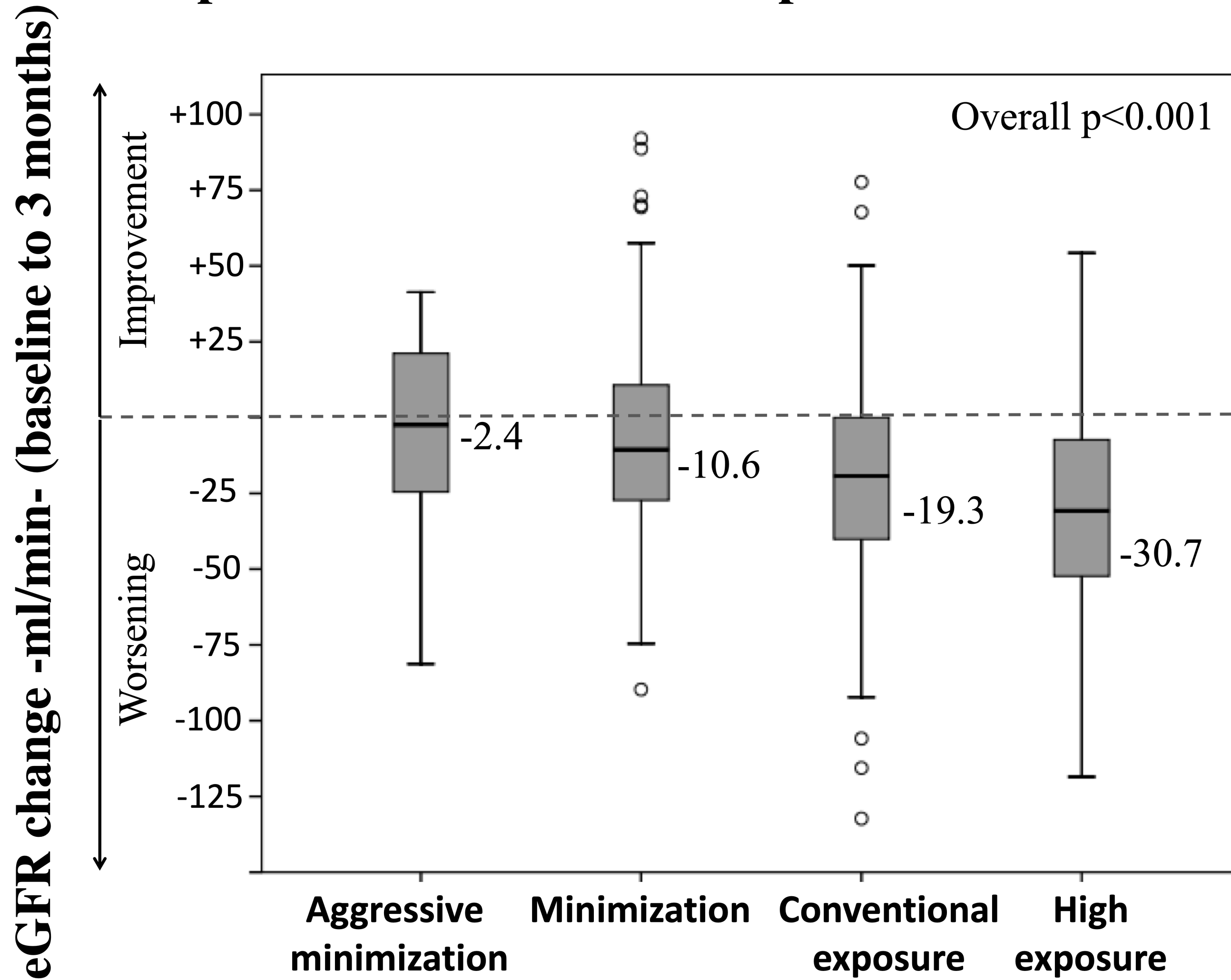


$$AUC_{tc} = A1 + A2 + A3 + \dots + A11$$

Area under trough concentrations of tacrolimus as a predictor of progressive renal impairment after liver transplantation

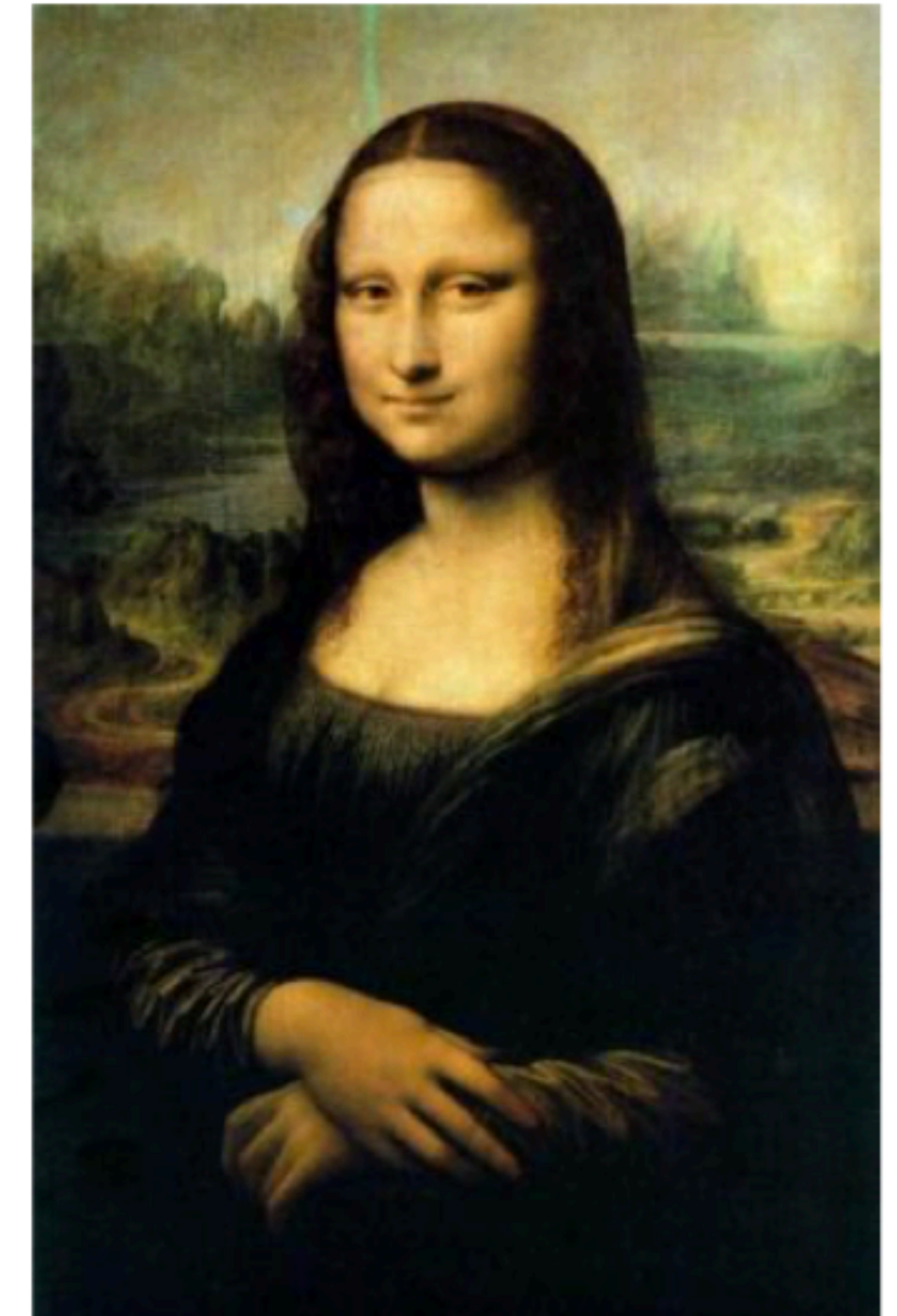
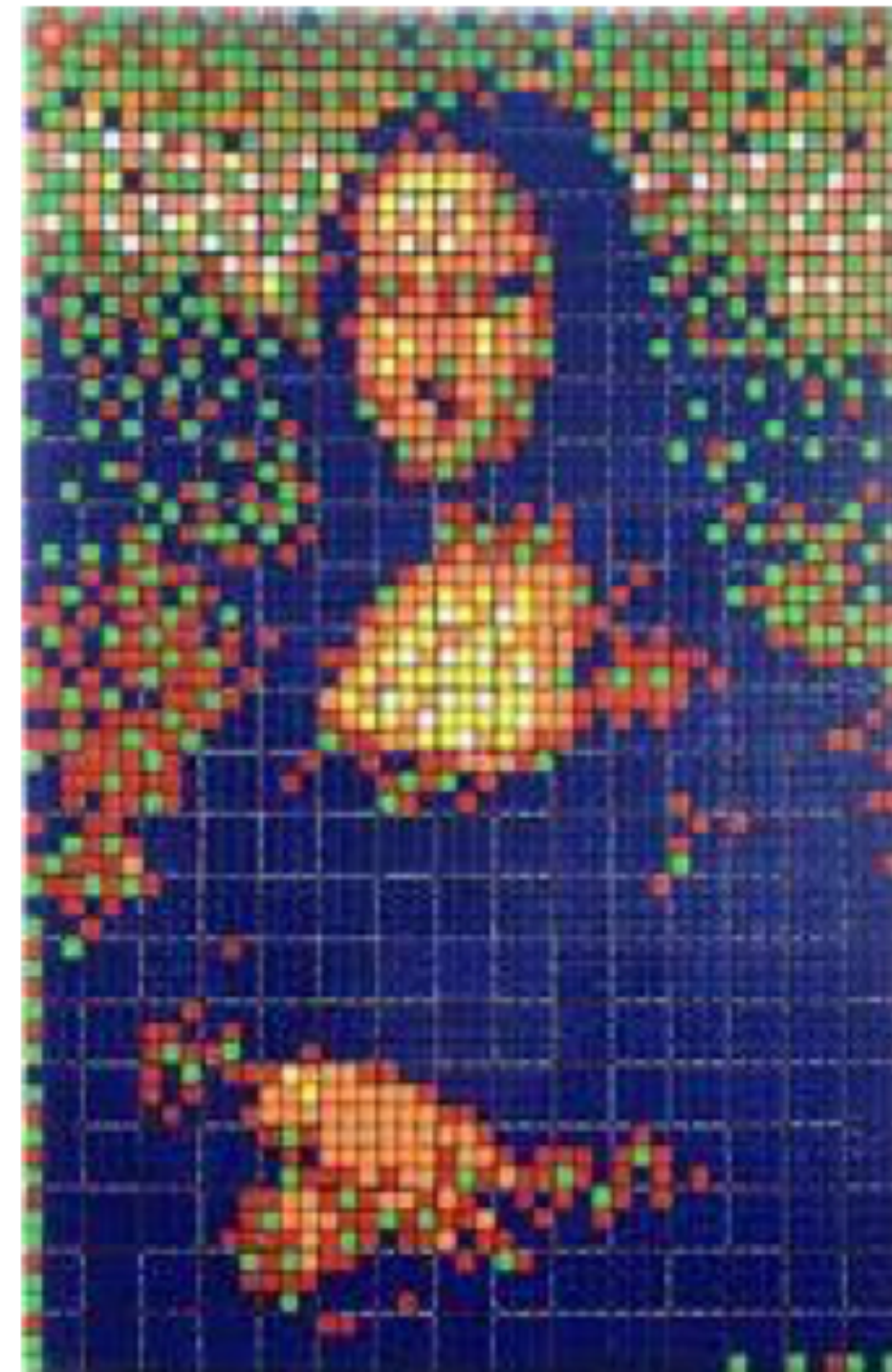


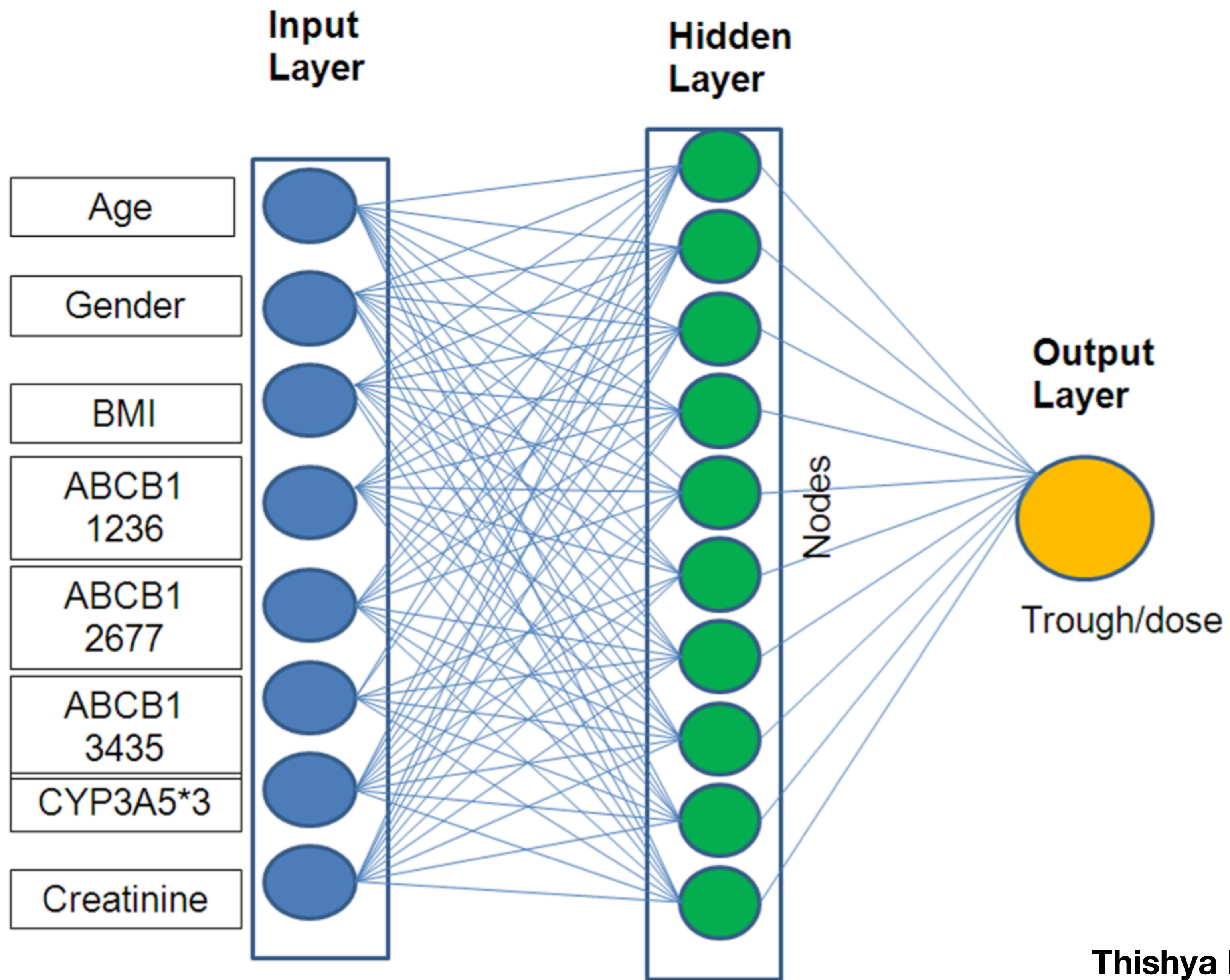
Area under trough concentrations of tacrolimus as a predictor of progressive renal impairment after liver transplantation



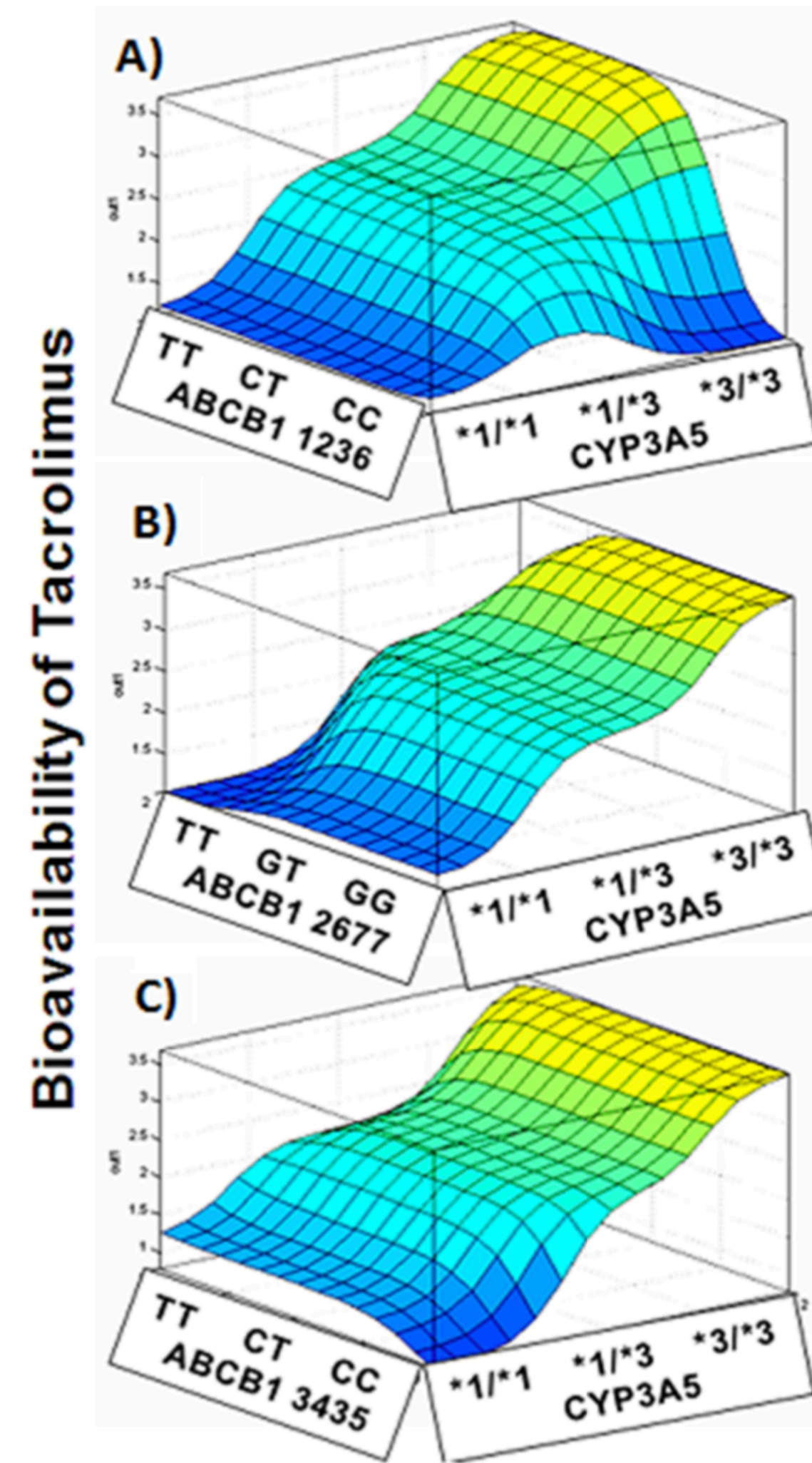
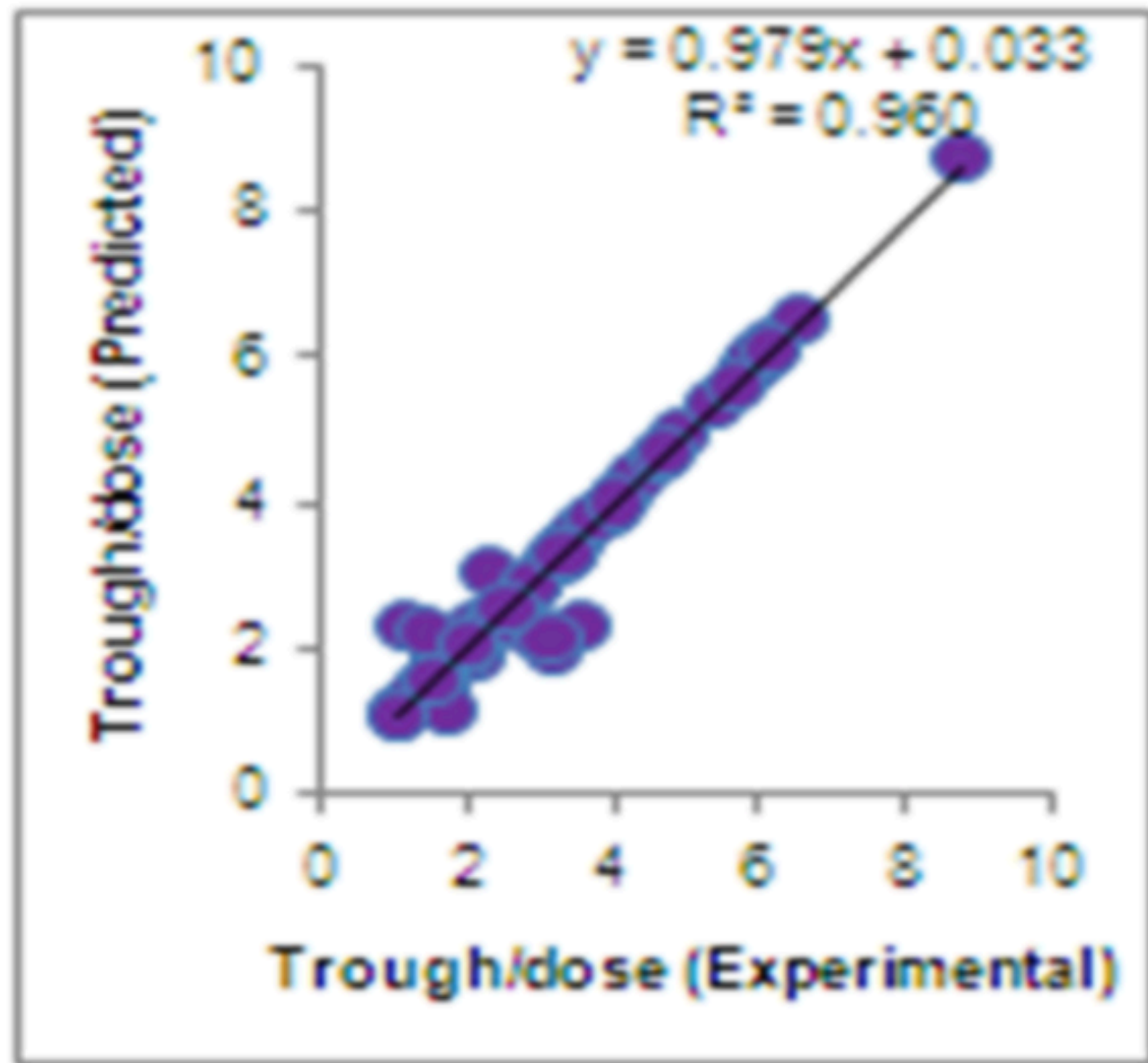
Category	Target trough concentrations (ng/mL)	AUCtc 3 months	AUCtc 6 months	AUCtc 12 months
Aggressive minimization	<4 (first month) <3 (thereafter)	<320	<590	<1,150
Minimization	4-6 (first month) 4 (thereafter)	321-579	591-1,109	1,151-2,219
Conventional	7-10 (first month) 6-8 (thereafter)	580-839	1,110-1,569	2,220-3,049
High exposure	>10 (first month) >8 (thereafter)	>840	>1,570	>3,050

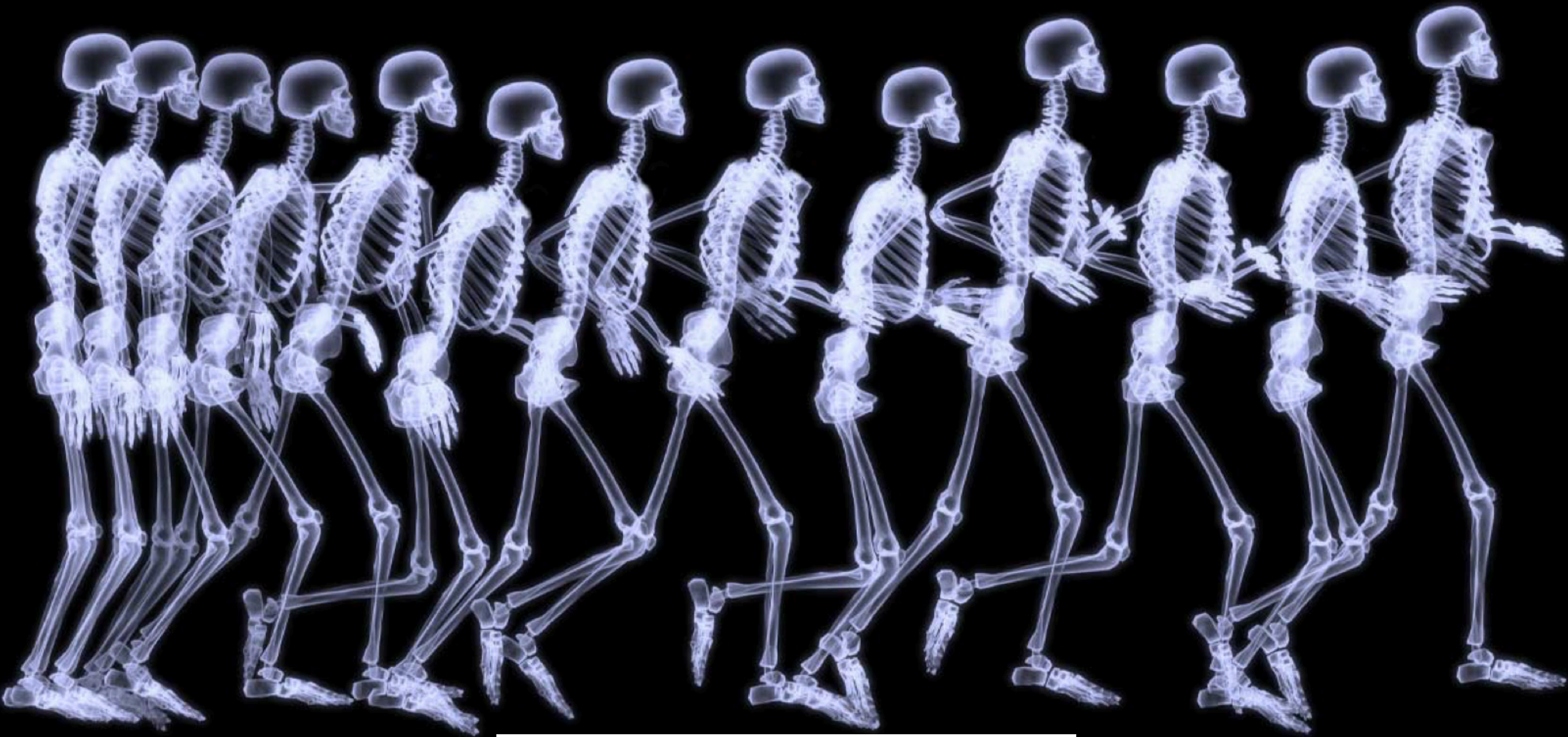
SIMPLIFICACIÓN





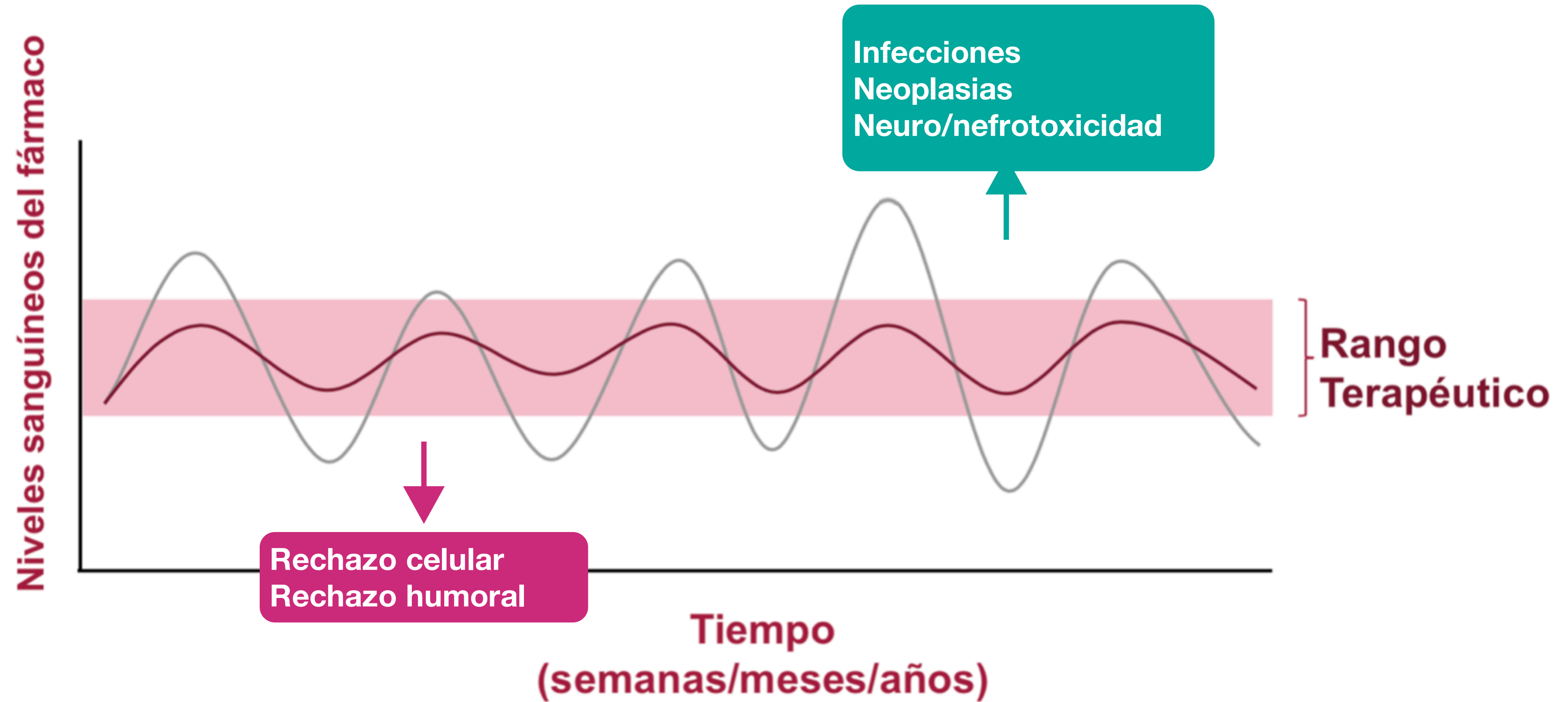
Thishya K, PlosOne 2018
Tang J, Sci Rep 2017



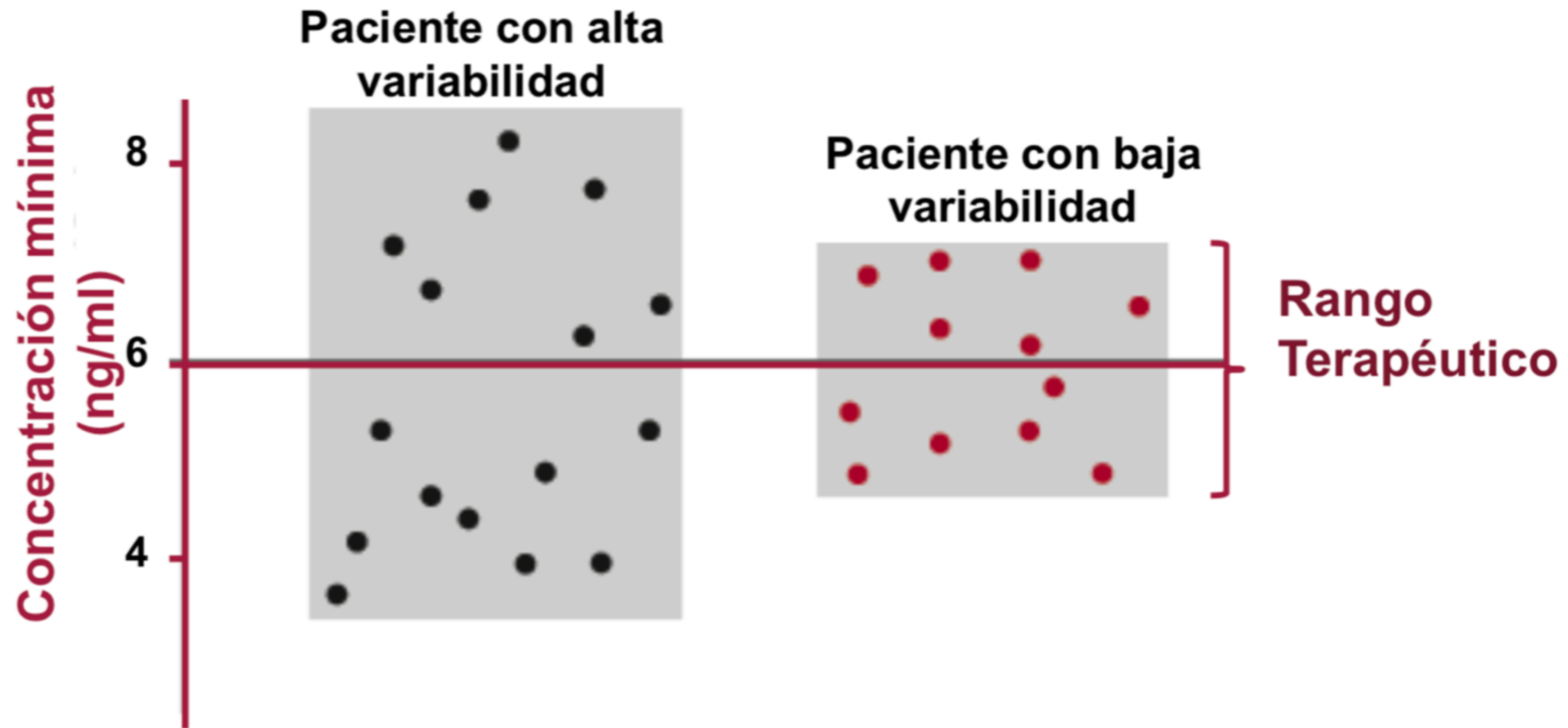


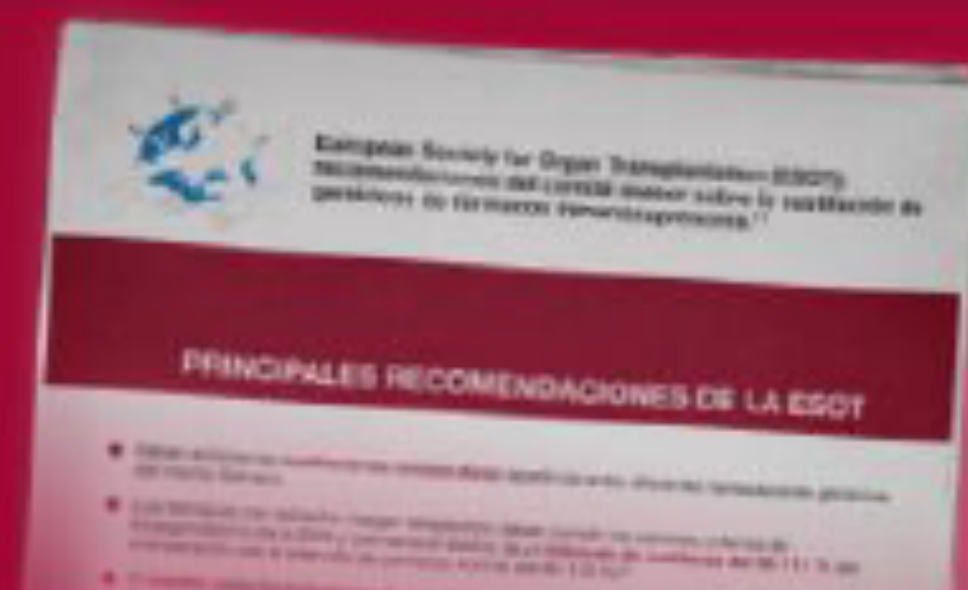
VARIABILIDAD

RANGO TERAPÉUTICO



Variabilidad intraindividual





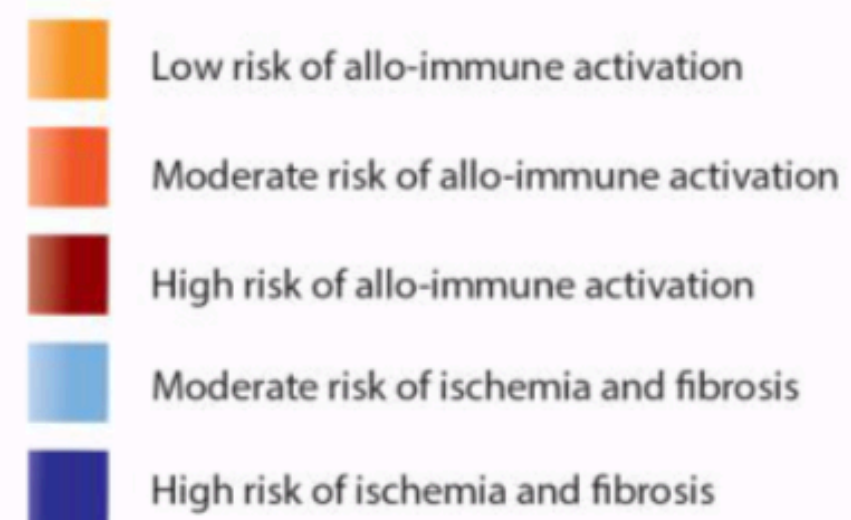
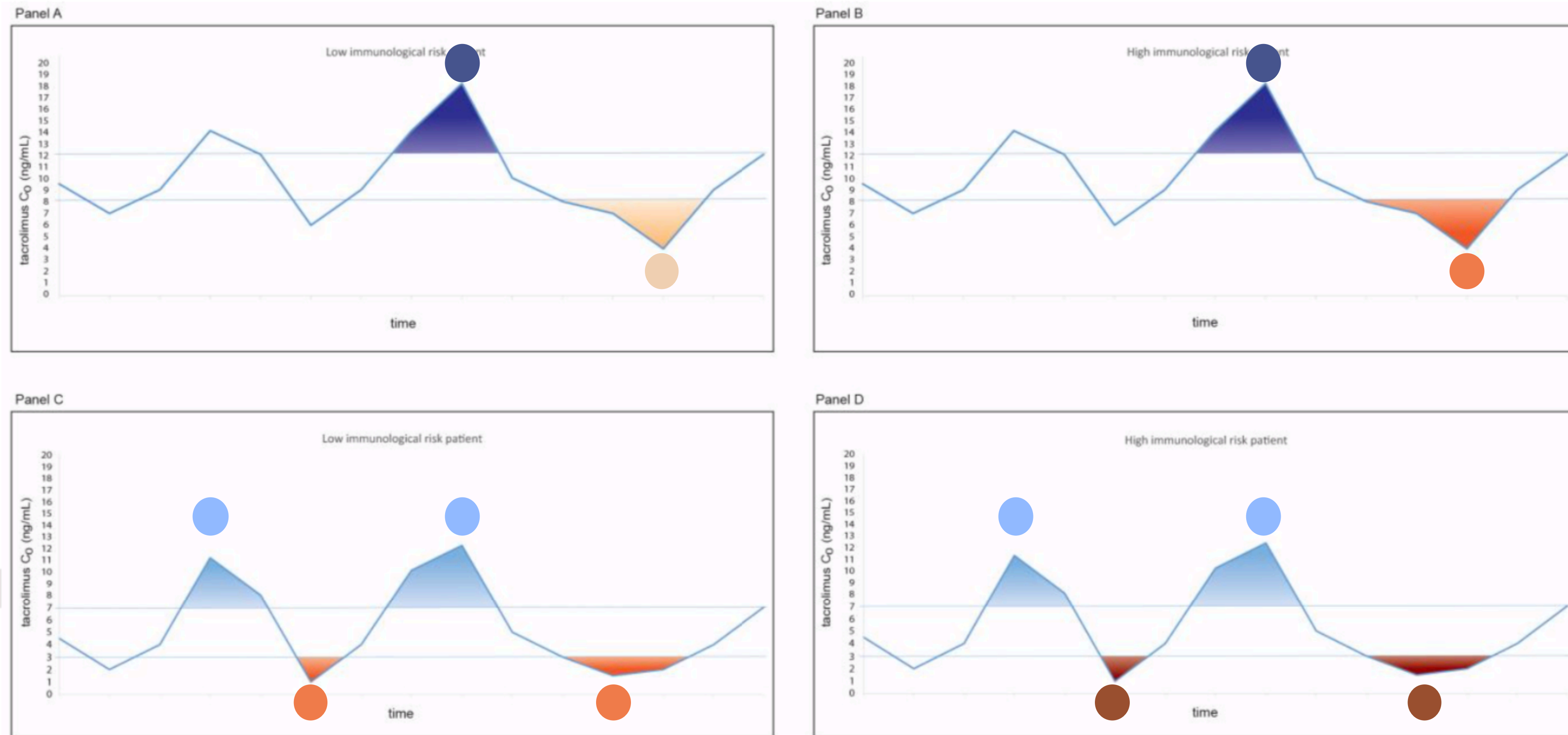
PRINCIPALES RECOMENDACIONES DE LA ESOT

- Deben evitarse las **sustituciones consecutivas** repetitivas entre diferentes formulaciones genéricas del mismo fármaco.
- Los fármacos con estrecho margen terapéutico deben cumplir los estrictos criterios de bioequivalencia de la EMA y permanecer dentro de un **intervalo de confianza del 90-111 %** (en comparación con el intervalo de confianza normal del 80-125 %)²
- El **cambio entre formulaciones de tacrolimus** (ya sean de marca o genéricas) debe ser iniciado exclusivamente por el **especialista** en trasplante.
- Cada cambio debe ser estrechamente **monitorizado** para garantizar que los niveles de tacrolimus en sangre permanezcan dentro del margen terapéutico definido.
- Debe **instruirse a los pacientes** sobre la sustitución de genéricos y sobre el modo de identificar las distintas formulaciones para que puedan alertar a los médicos en caso de **sustitución no controlada**.

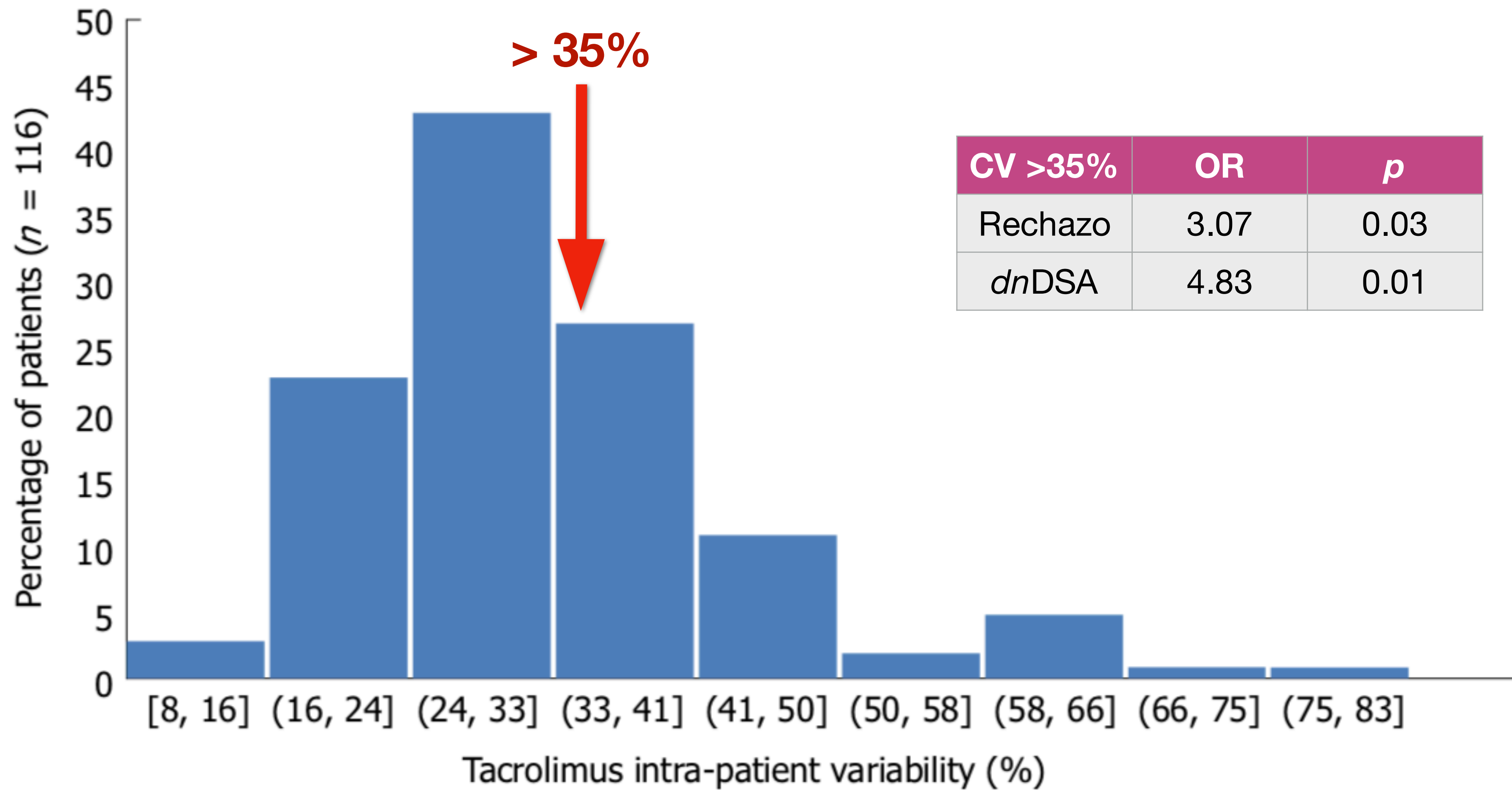
La variabilidad elevada en la exposición a CNI es un factor de riesgo significativo de un peor resultado a largo plazo...



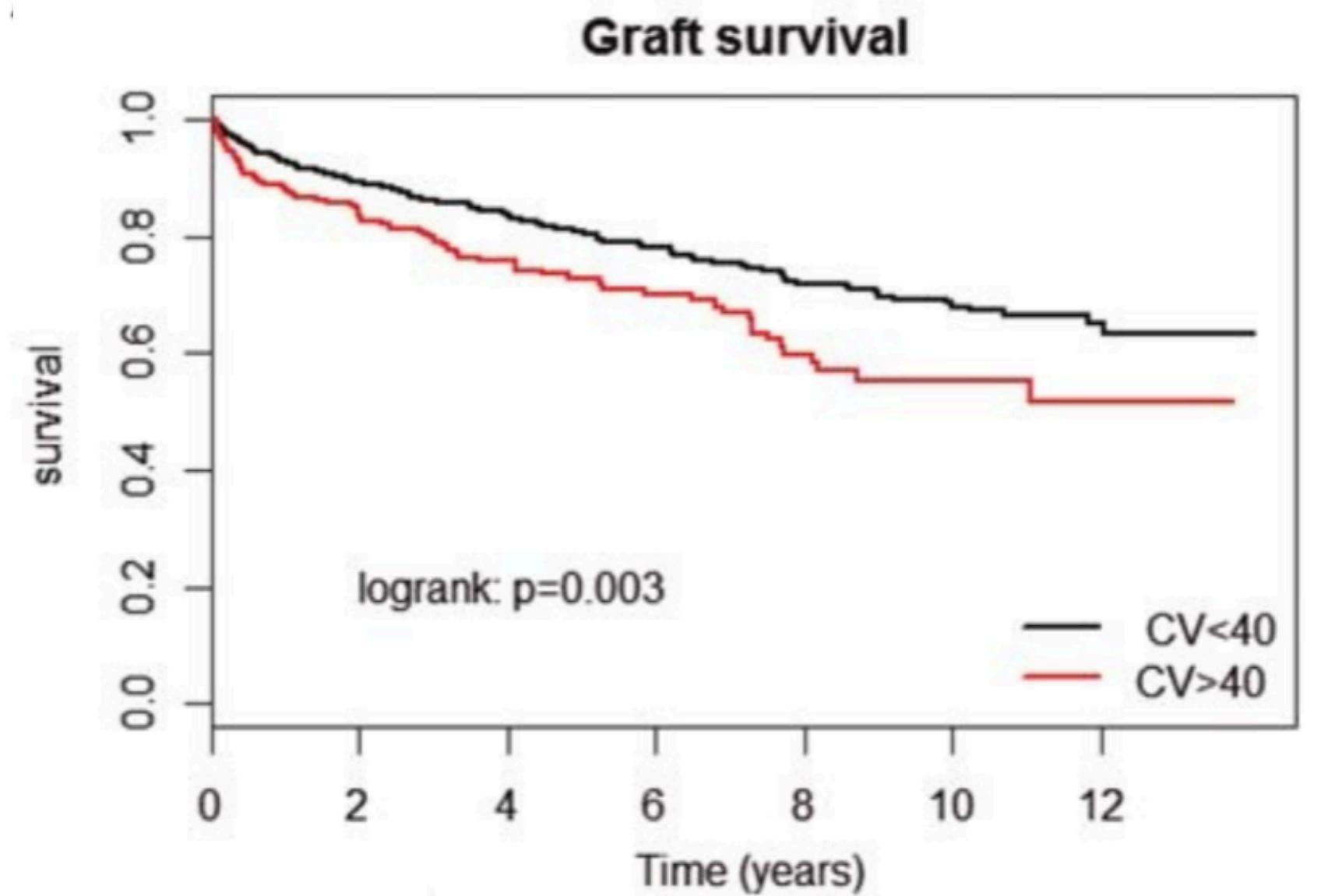
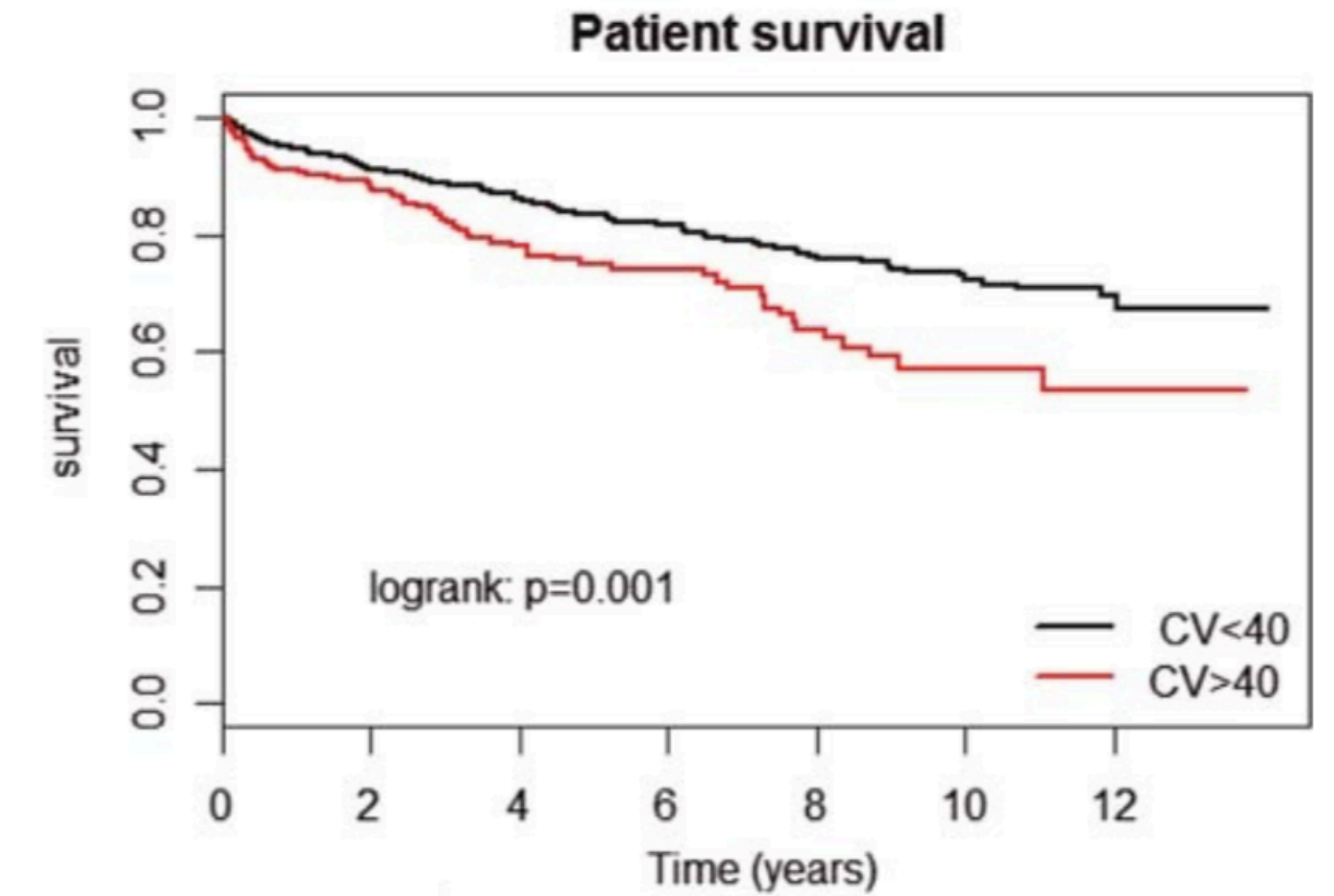
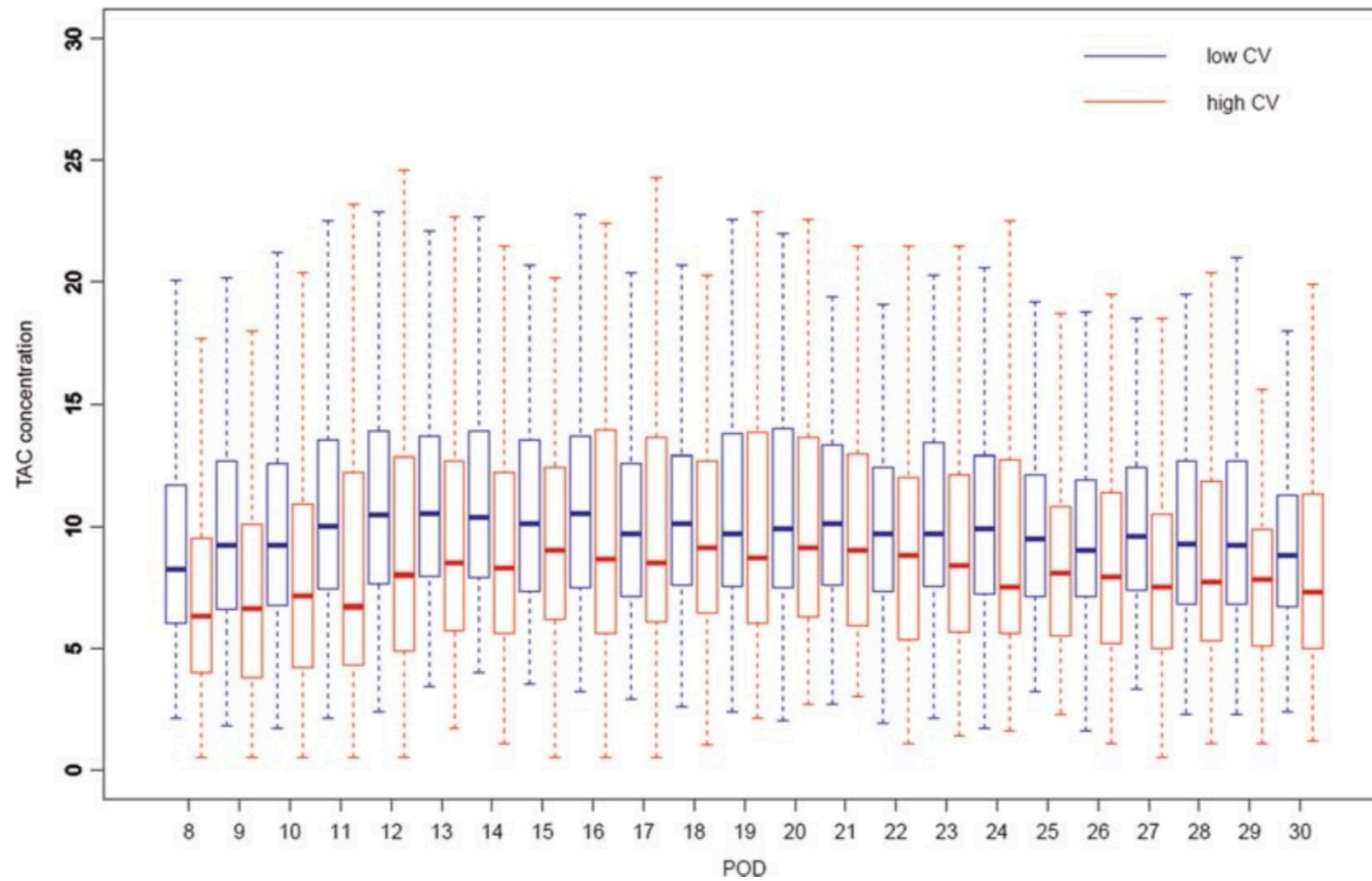
Intra-Patient Variability of tacrolimus exposure in solid organ transplantation: a novel marker for clinical outcome



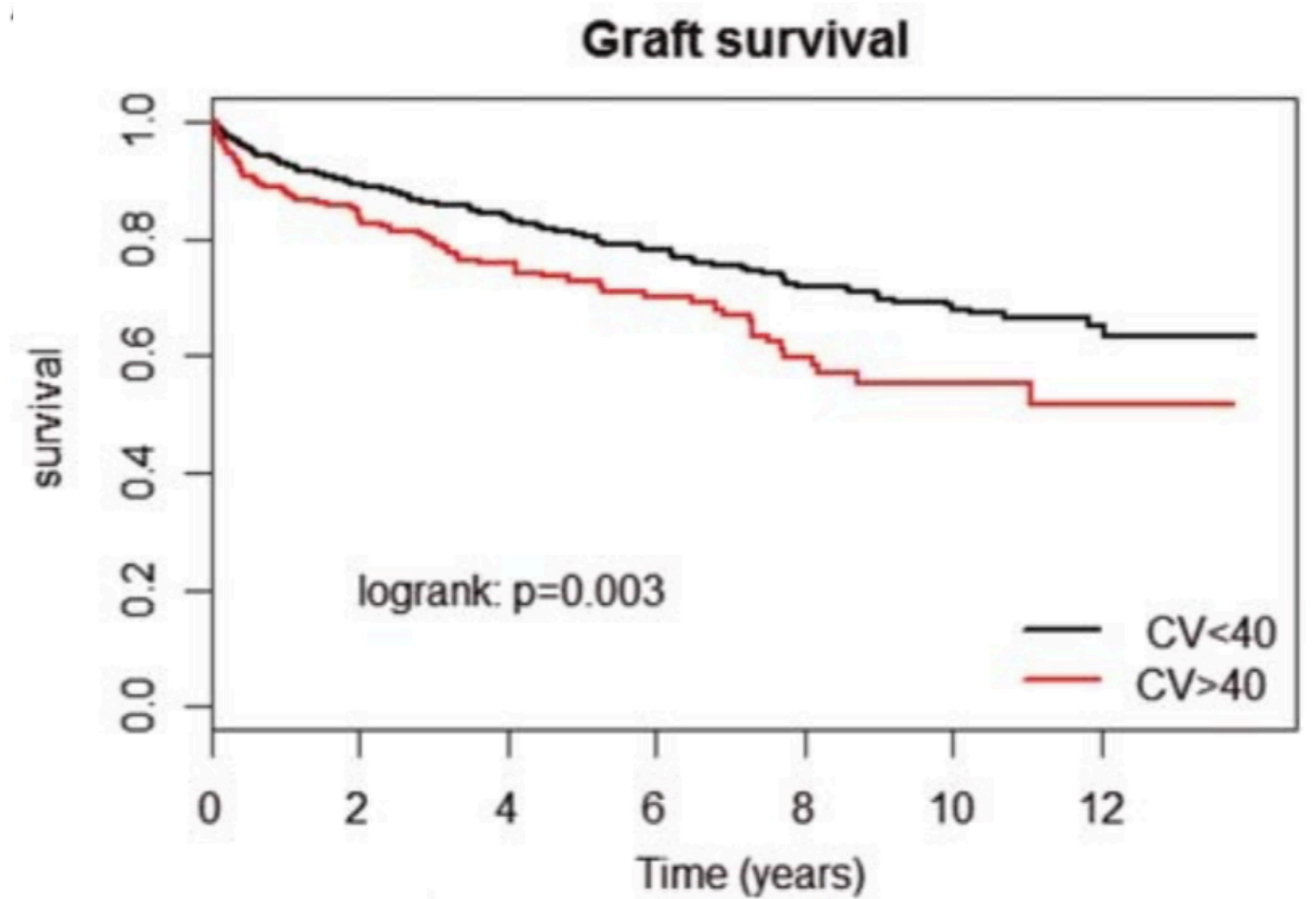
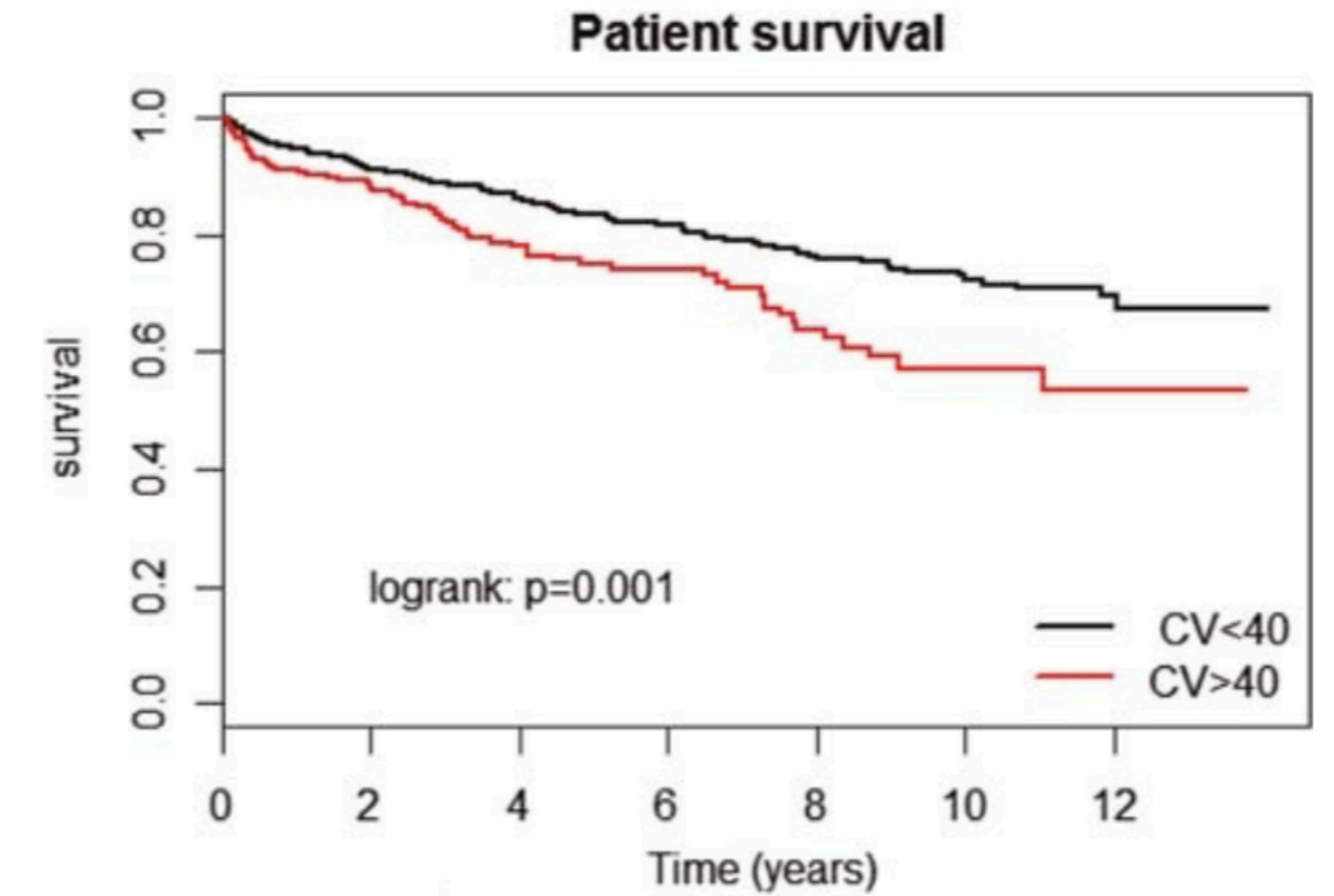
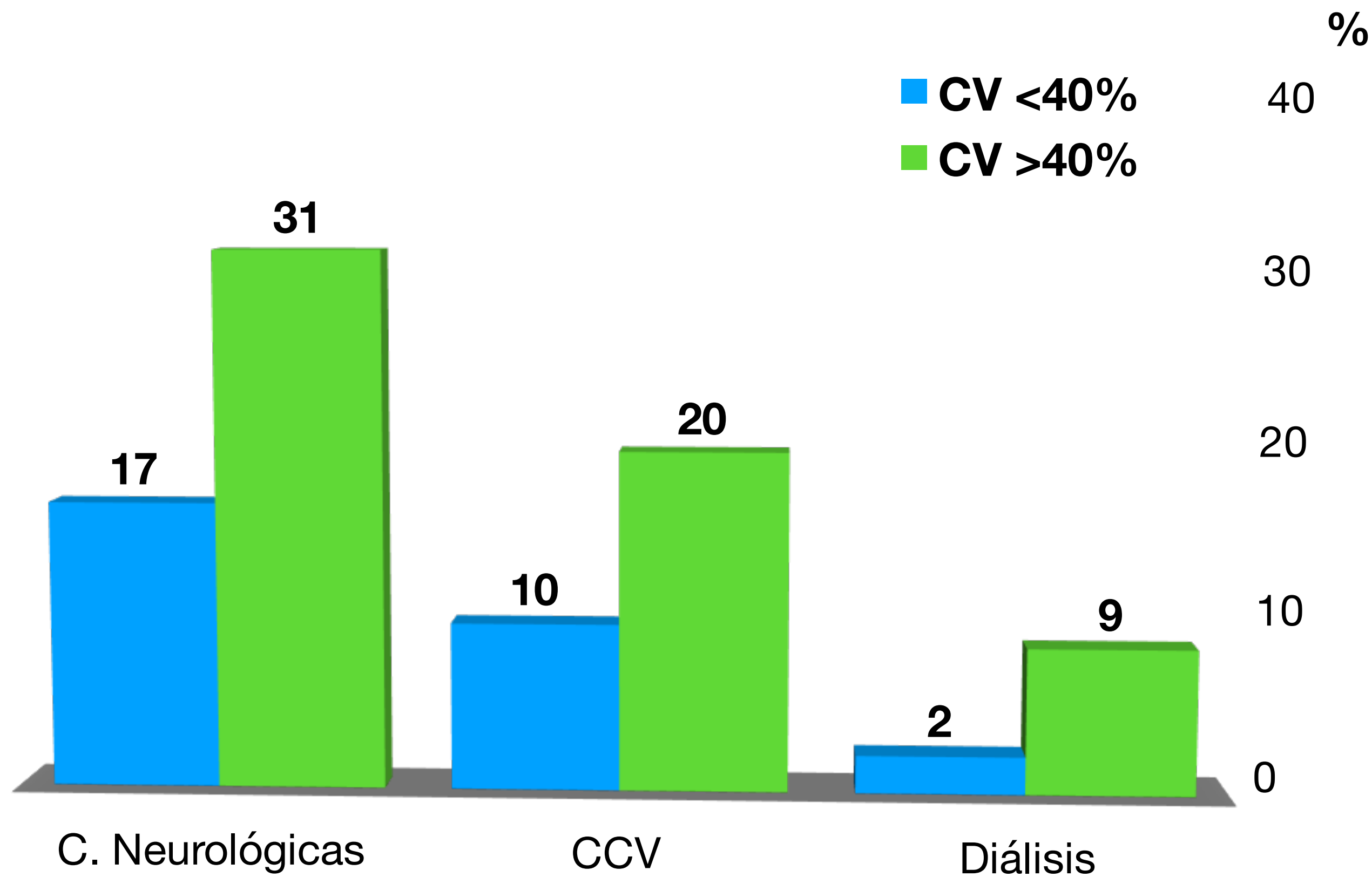
High tacrolimus intra-patient variability is associated with graft rejection, and *de novo* donor-specific antibodies occurrence after liver transplantation



High Inpatient Variability of Tacrolimus Exposure in the Early Period After Liver Transplantation Is Associated With Poorer Outcomes



High Inpatient Variability of Tacrolimus Exposure in the Early Period After Liver Transplantation Is Associated With Poorer Outcomes

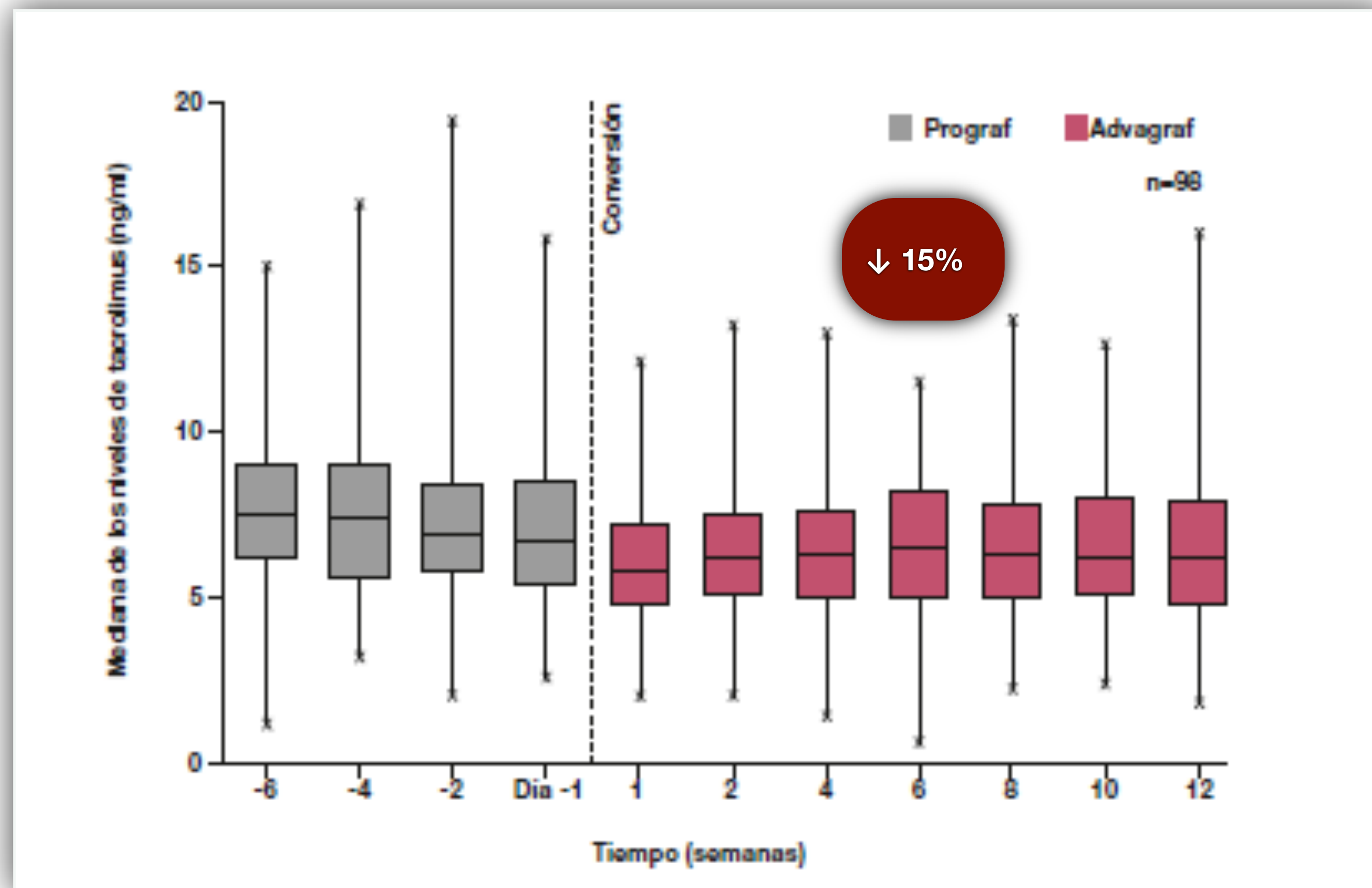


Advagraf reduce la variabilidad intra-paciente

Advagraf reduce la variabilidad y mantiene una exposición a tacrolimus más estable

- * Exposición más constante
- * Menor variabilidad inter e intrapaciente

Trasplante hepático



No modificables

- * Polimorfismos genéticos
- * Ritmo circadiano Tac

VARIABILIDAD

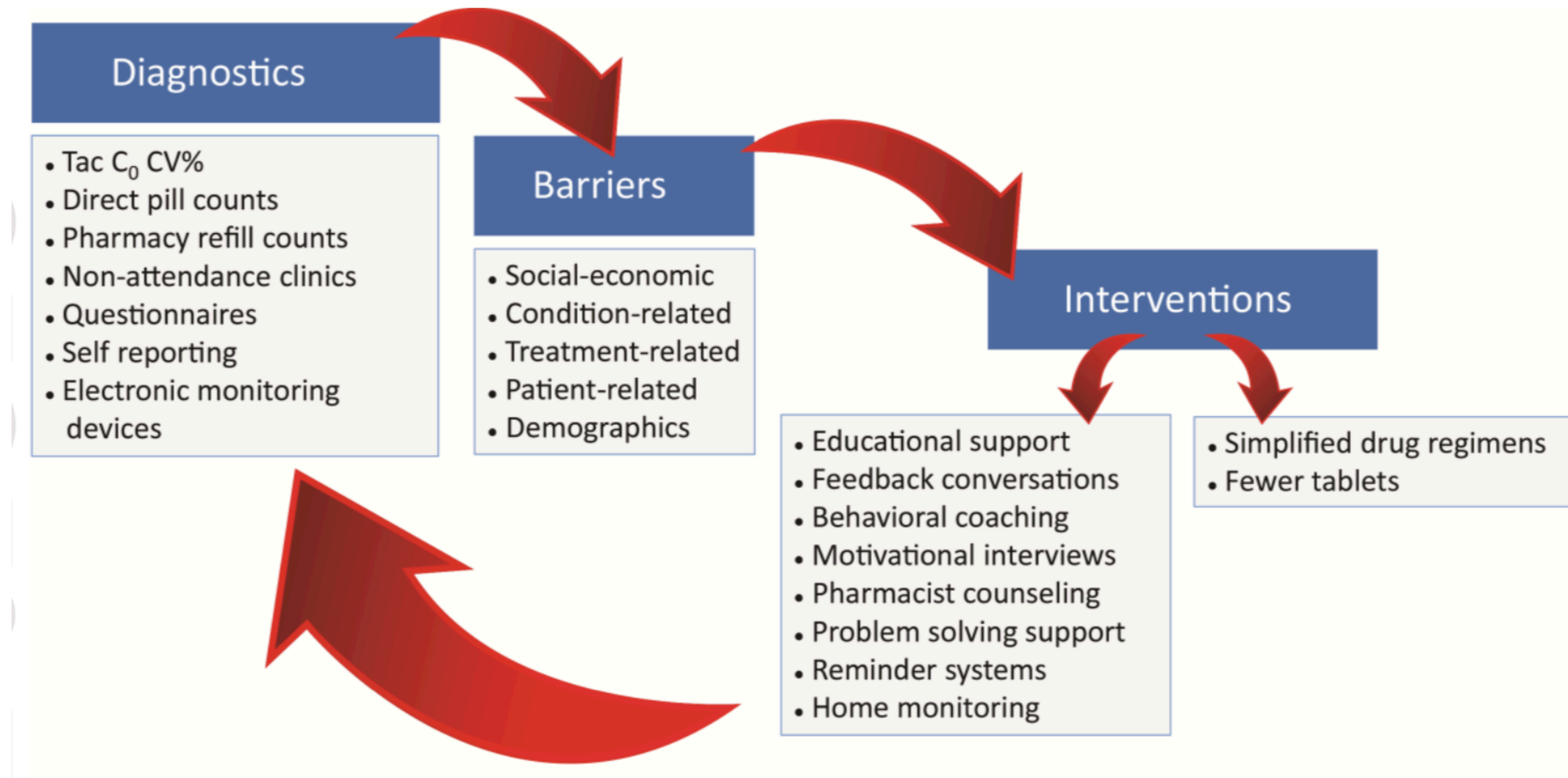
Poco modificables

- * **No Adherencia**
- * Alteraciones gastrointest.
- * Hipoalbuminemia
- * Anemia
- * Disfunción injerto

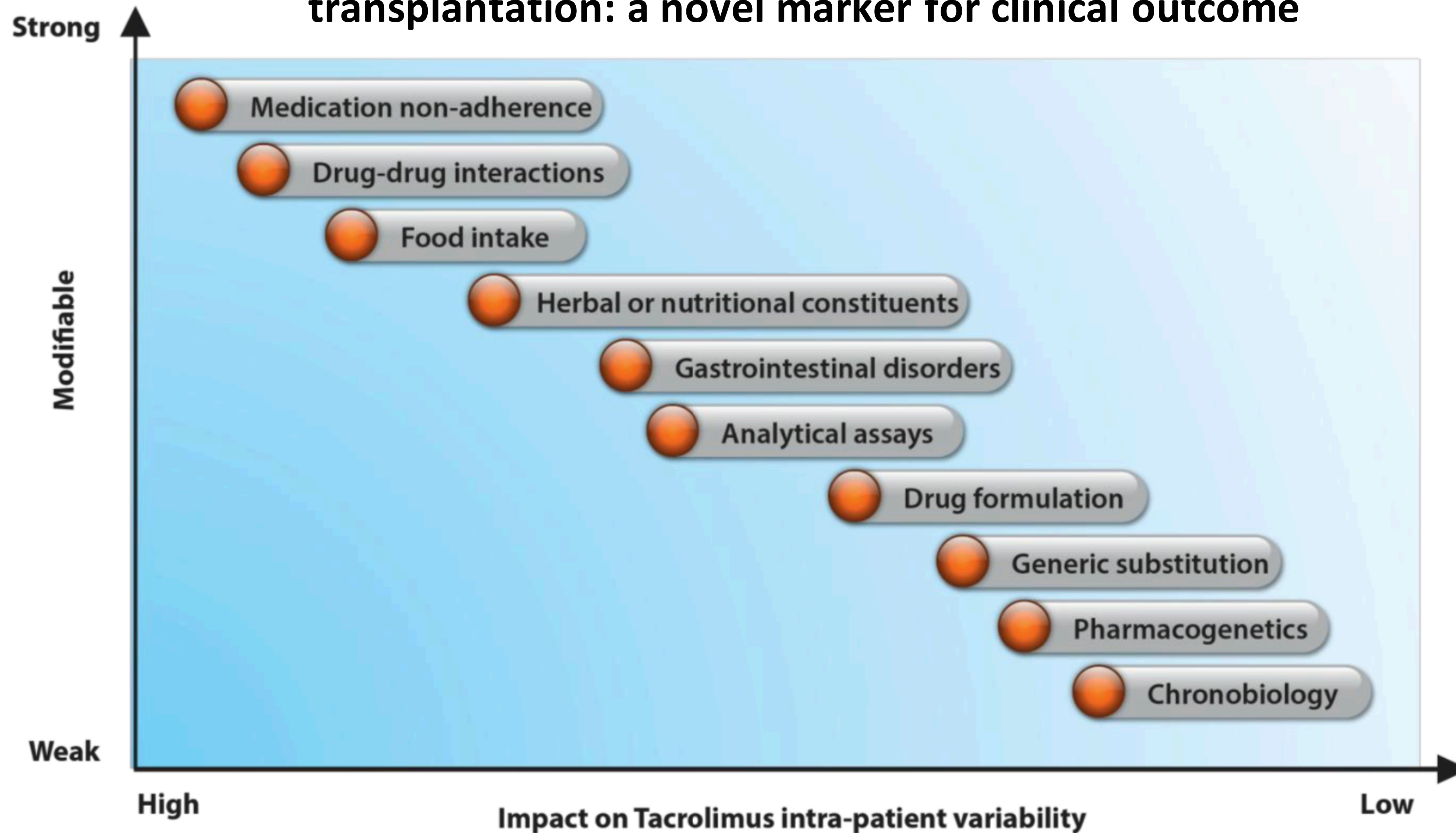
Muy modificables

- * **Alimentación**
- * Interacción fármacos
- * P. Herboristería
- * **Sustitución genéricos**

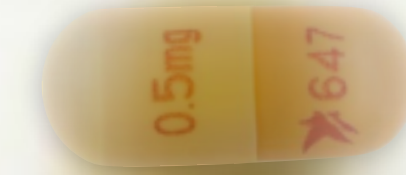
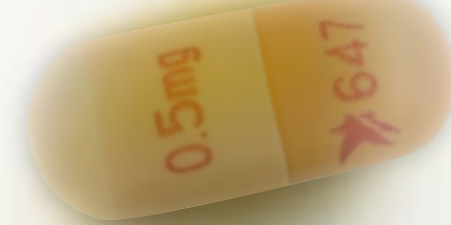
Intra-Patient Variability of tacrolimus exposure in solid organ transplantation: a novel marker for clinical outcome



Intra-Patient Variability of tacrolimus exposure in solid organ transplantation: a novel marker for clinical outcome



ADHERENCIA



97

60

10

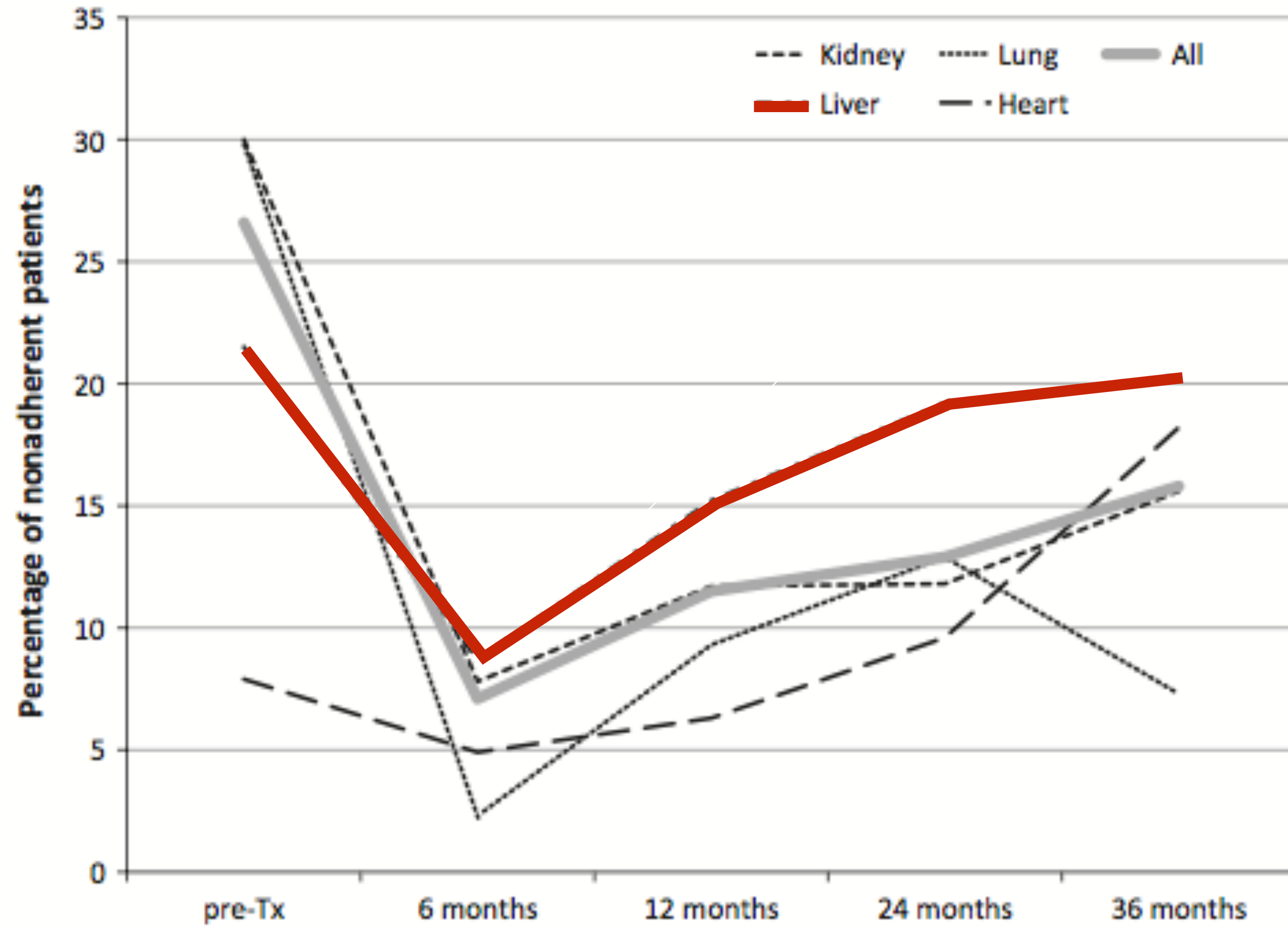


12

20

1

No ADHERENCIA



Factores paciente

Factores Sistema sanitario

**No
ADHERENCIA**

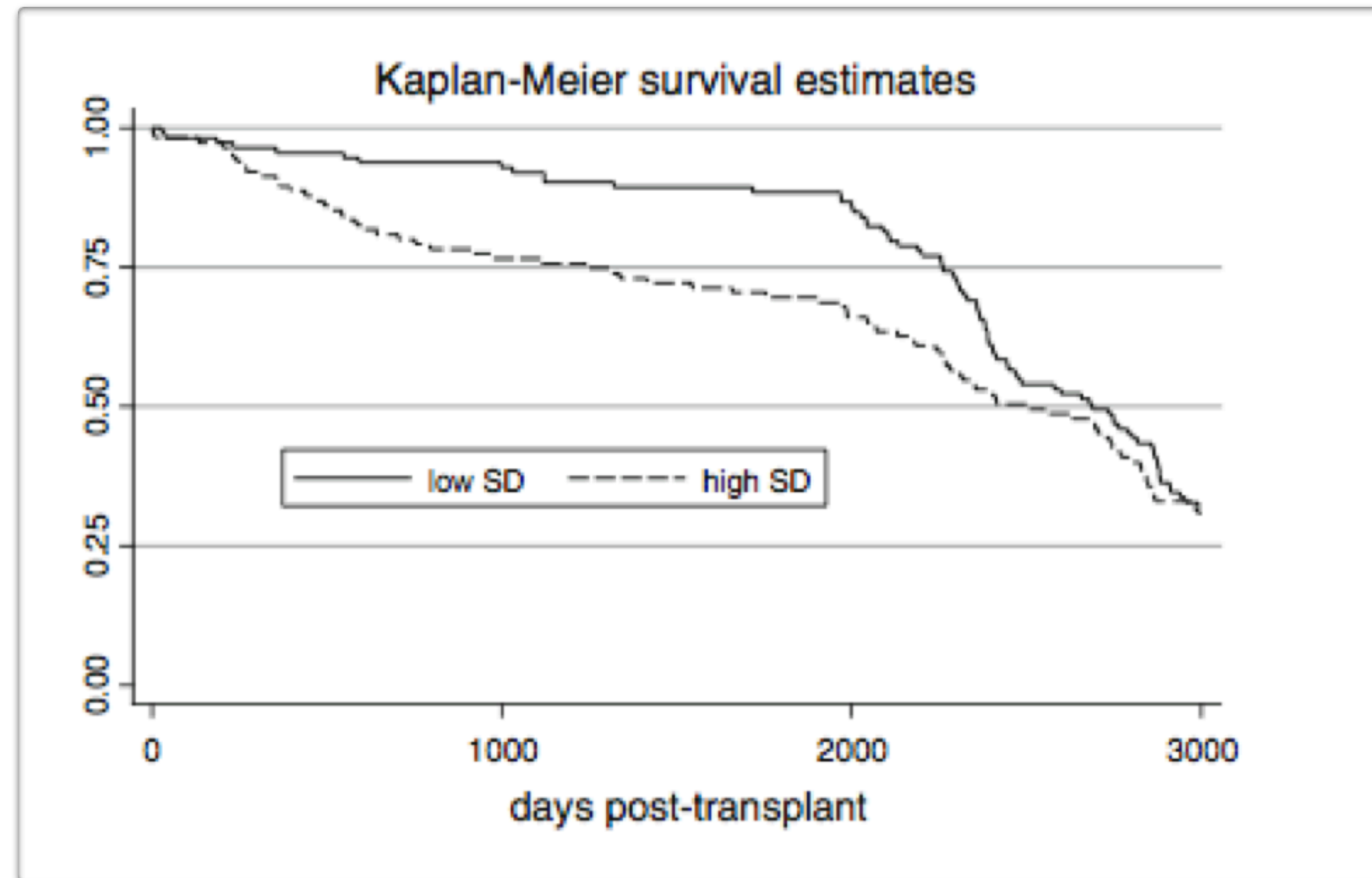
Factores Sociodemográficos

Factores Tratamiento

- * Larga duración
- * Complejidad
- * Número de píldoras

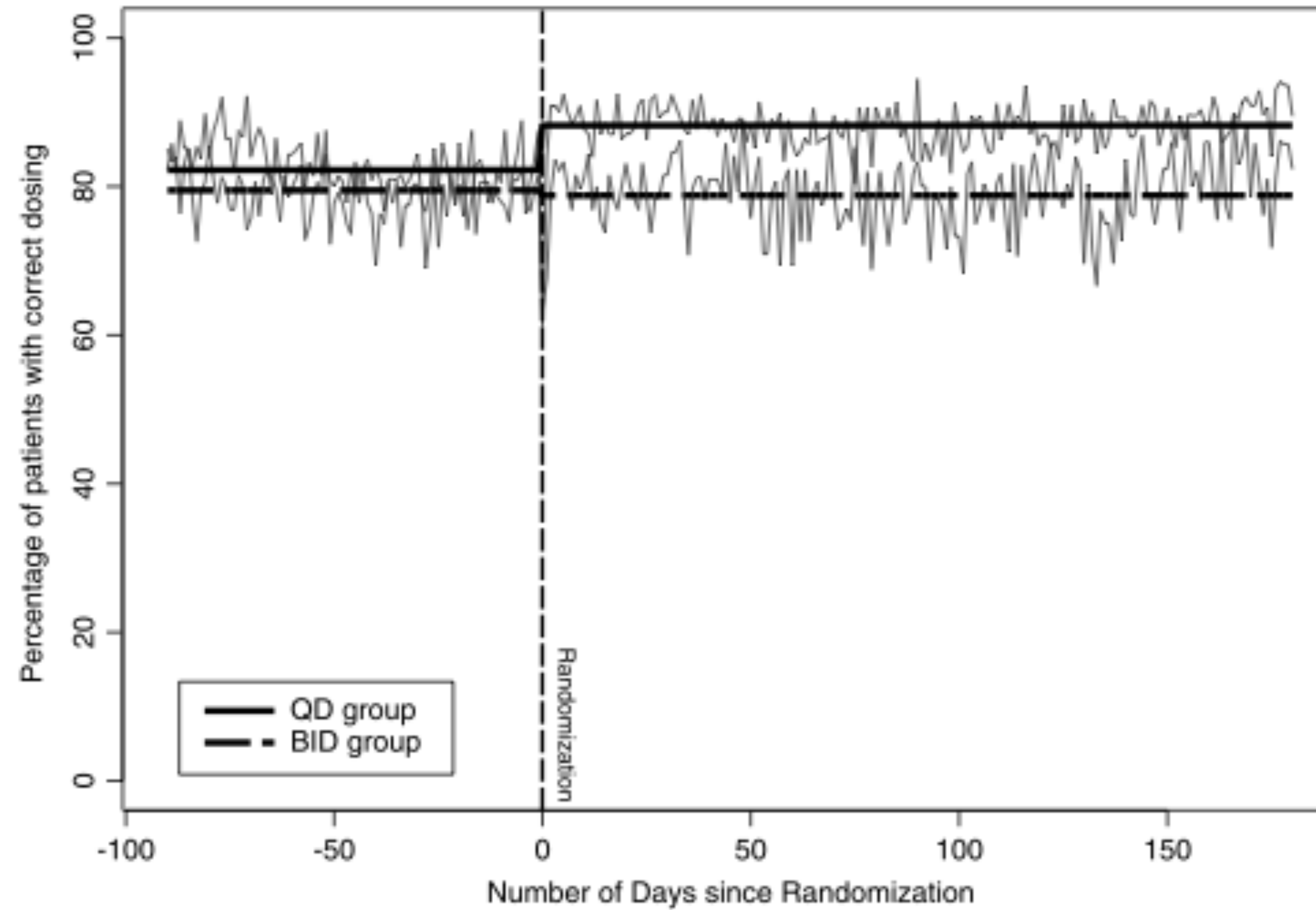
Nivel I

ADHERENCIA & SUPERVIVENCIA






Trasplante hepático

Número dosis & adherencia

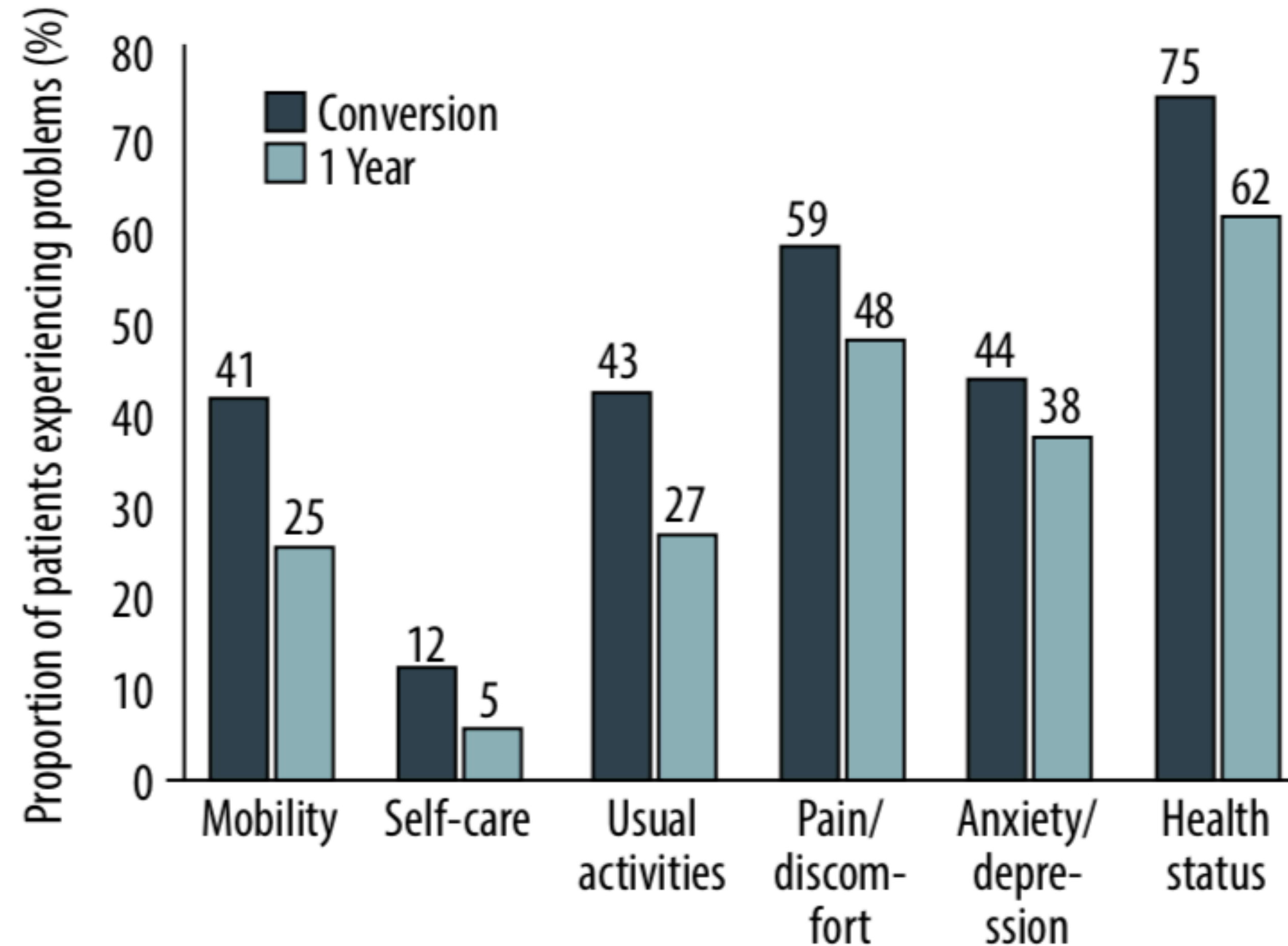


Presentaciones de tacrolimus disponibles en Astellas

	Producto	Formulación	Dosis	Cantidad
	ADVAGRAF	Oral	0,5 mg	30
			1 mg	30, 60
			3 mg	30
			5 mg	30
	PROGRAF	Oral	0,5 mg	30
			1 mg	30, 60
			5 mg	30
		Sol. i.v.	5 mg/ml	10 ml
	MODIGRAF	Granulado para suspensión oral	0,2 mg	50 sobres
			1 mg	50 sobres

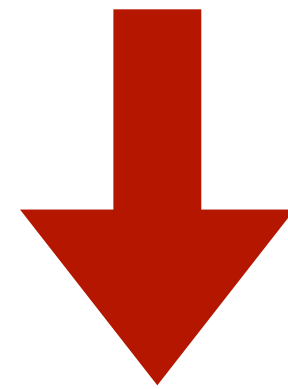
Fichas técnicas de Advagraf, Prograf y Modigraf

COBALT study: Calidad de vida



Amplio desarrollo clínico que ha demostrado que Advagraf® aporta:

- **Menor variabilidad** interpaciente e intrapaciente
- **Dosis acumulada** más fácil de predecir



- **Mayor supervivencia** de injerto y receptor a largo plazo
- **Menor daño renal**
- **Mayor adherencia**



Advagraf® no debe considerarse una “me-too drug” sino una entidad diferente por su valor terapéutico

Trunecka P, Curr Opin Organ Transplant 2017

¡Gracias!

