Utilisation du clopidogrel chez les patients en IRCT

Yassine Bouatou

Médecin interne

Service de Pharmacologie et Toxicologie Cliniques, HUG

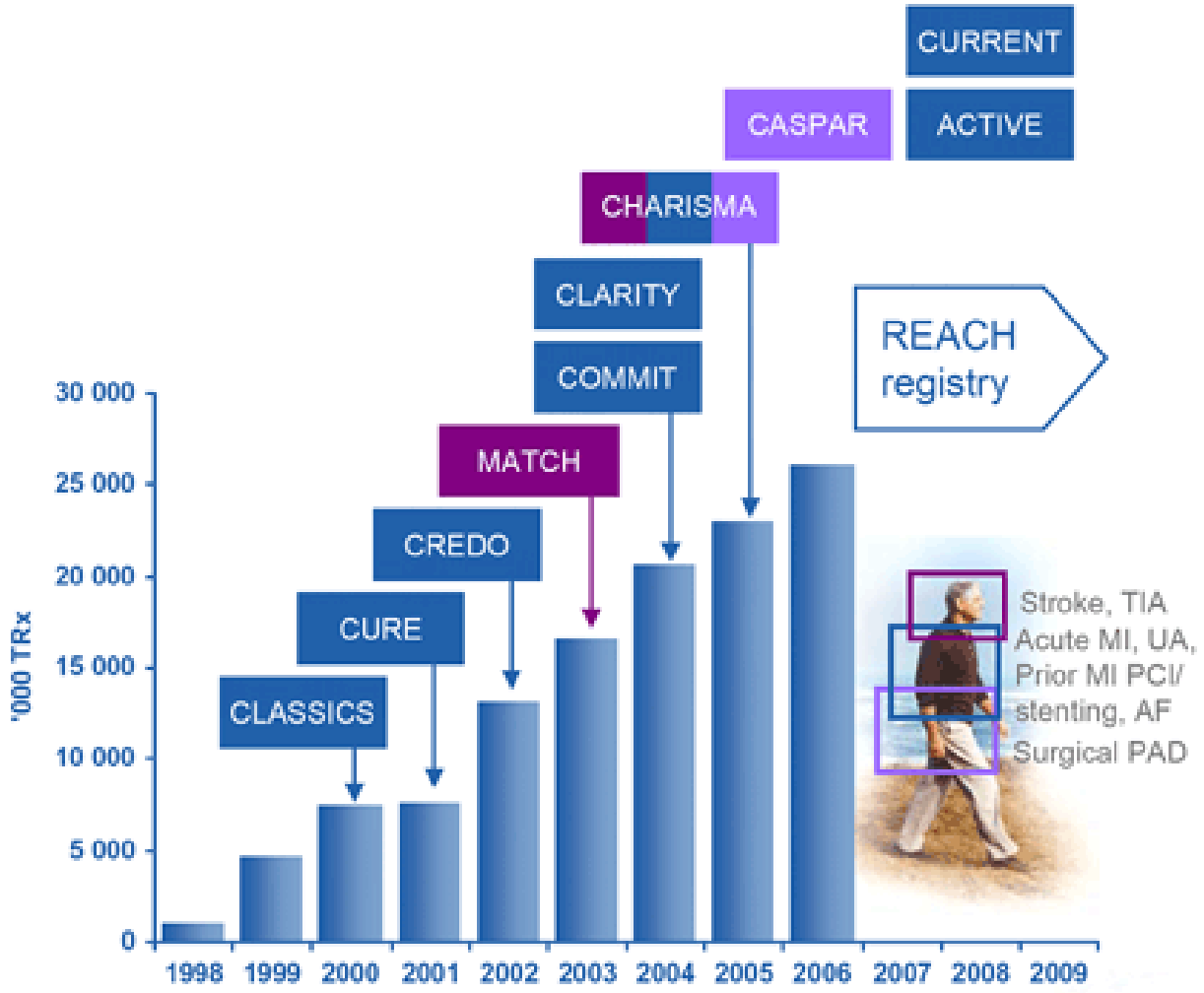
Cas clinique : M. A, 61 ans

- IRCT en hémodialyse depuis 3 ans (néph. HTA)
- ATCD : AVC aphasie, maladie coronarienne
- MH : sténose et thrombose partielle de FAV
- SCA – NSTEMI : sténose du tronc commun
- PCA – Stent. VASP > 75 %. Ad dose de charge.
- 3 mois après resténose sous clopidogrel

Plan

- Introduction : le clopidogrel en chiffres …
- EBM et clopidogrel dans le syndrome coronarien aigu
- Variabilité de la réponse clinique et outcome clinique
- Clopidogrel et insuffisance rénale
- Rappels pharmacocinétiques et pharmacodynamiques
- Causes de variabilité de réponse au clopidogrel dans la population générale
- Causes de variabilité de réponse au clopidogrel dans la population avec une maladie rénale chronique
- Métabolisme des médicaments dans l'insuffisance rénale
- Retour au cas clinique …
- Conclusion et perspectives

Introduction



Sanofi, site internet

EBM et clopidogrel dans le syndrome coronarien aigu

The exclusion of patients with chronic kidney disease from clinical trials in coronary artery disease

D Charytan[1] and RE Kuntz[2]

Créat de 176 à 264 µmol/L

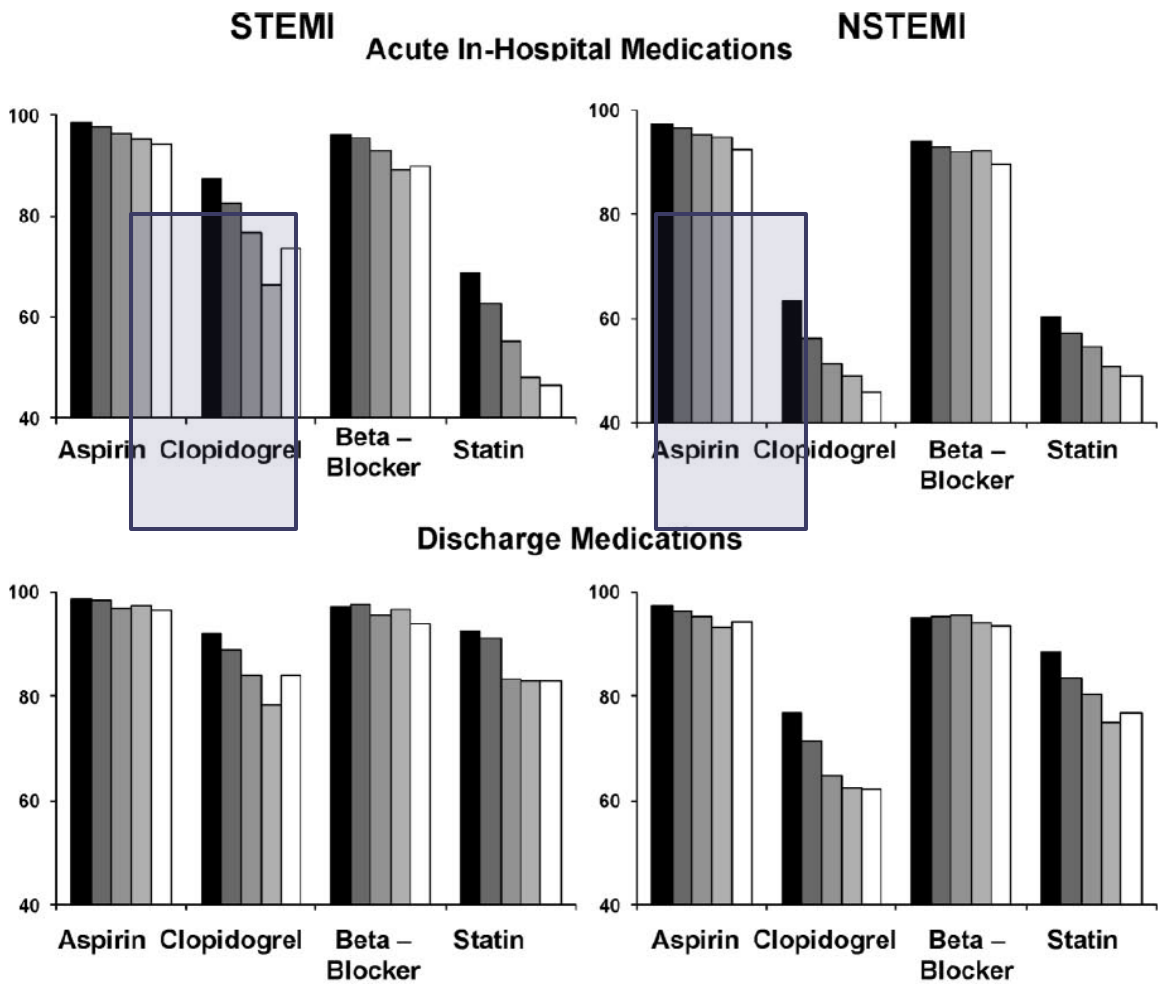
Table 6 | Non-GIIb/IIIa oral anti-platelet therapy

Trial	Intervention	Excluded	Creatinine (mg/dl)	Conditions Excluded	Function Reported	Other Conditions Reported
CLARITY-TIMI 28[98]	Clopidogrel vs placebo	Y	> 2.5	N	N	Y
CLASSICS[99]	3 regimens of plavix+ASA	Y	> 2.0	N	N	Y
CREDO[100]	Clopidogrel vs placebo	Y	> 3.0	N	N	Y

Intervention	Number of trials	Number excluding subjects with ESRD (%)	Number excluding subjects with renal insufficiency (%)
Anti-platelet agents	15	9 (60.0)	6 (46.6)

Kidney International (2006) **70**, 2021–2030

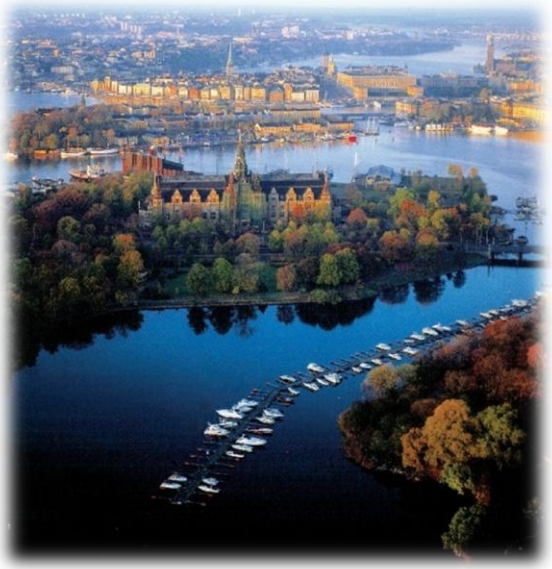
EBM et clopidogrel dans le syndrome coronarien aigu



- Rapport publié en 2010 par National CV Data Registry
- Sur 19029 STEMI 30.5 % IRC
- Sur 30462 NSTEMI 42.9% IRC
- Mortalité à court terme X2 dès le stade 3 de CKD

Circulation. 2010 Jan 26;121(3):357-65.

EBM et clopidogrel dans le syndrome coronarien aigu



Original Article | Journal of INTERNAL MEDICINE

doi: 10.1111/j.1365-2796.2009.02204.x

Relation between renal function, presentation, use of therapies and in-hospital complications in acute coronary syndrome: data from the SWEDEHEART register

Primary PCI versus thrombolysis in STEMI		*N*	Primary PCI (%)	Crude OR	95% CI	Adjusted OR	95% CI
eGFR	≥90	3225	70.8	1.00	–	1.00	–
	60–89	5382	61.3	0.65	0.60–0.71	0.70	0.63–0.77
	30–59	1612	56.5	0.55	0.49–0.62	0.65	0.56–0.74
	15–29	109	59.6	0.67	0.46–0.96	0.87	0.58–1.32
	<15/dialysis	40	42.5	0.34	0.20–0.59	0.41	0.21–0.79

J Intern Med. 2010 Jul;268(1):40-9

EBM et clopidogrel dans le syndrome coronarien aigu

J Am Soc Nephrol 15: 2462–2468, 2004

"Renalism": Inappropriately Low Rates of Coronary Angiography in Elderly Individuals with Renal Insufficiency

GLENN M. CHERTOW,* SHARON-LISE T. NORMAND,†‡ and BARBARA J. MCNEIL‡

↓ prescription des antiaggrégants (risque hémorragique ?)
↓ PCI (complications, précipitation de la dialyse)

	IRC – indication	Pas IRC - indication
PCI	25.2 %	46 %

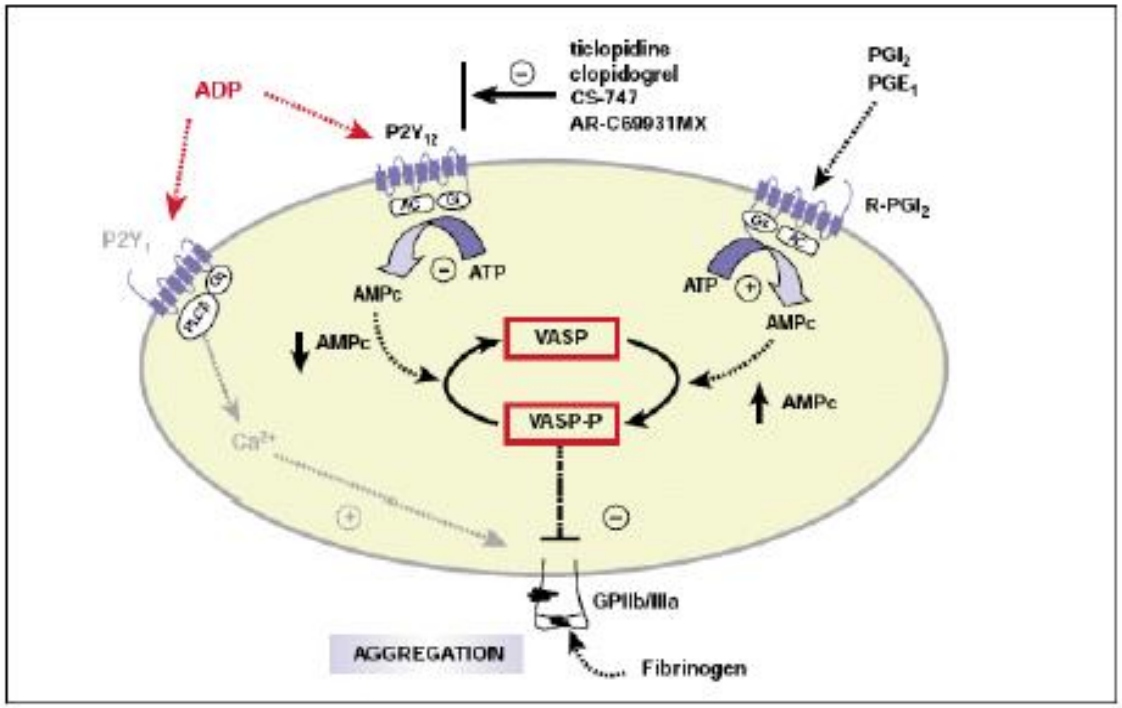
Patients IRC	Angiographie	Pas d'angiographie
Mortalité à 1 an	26.7	47 %

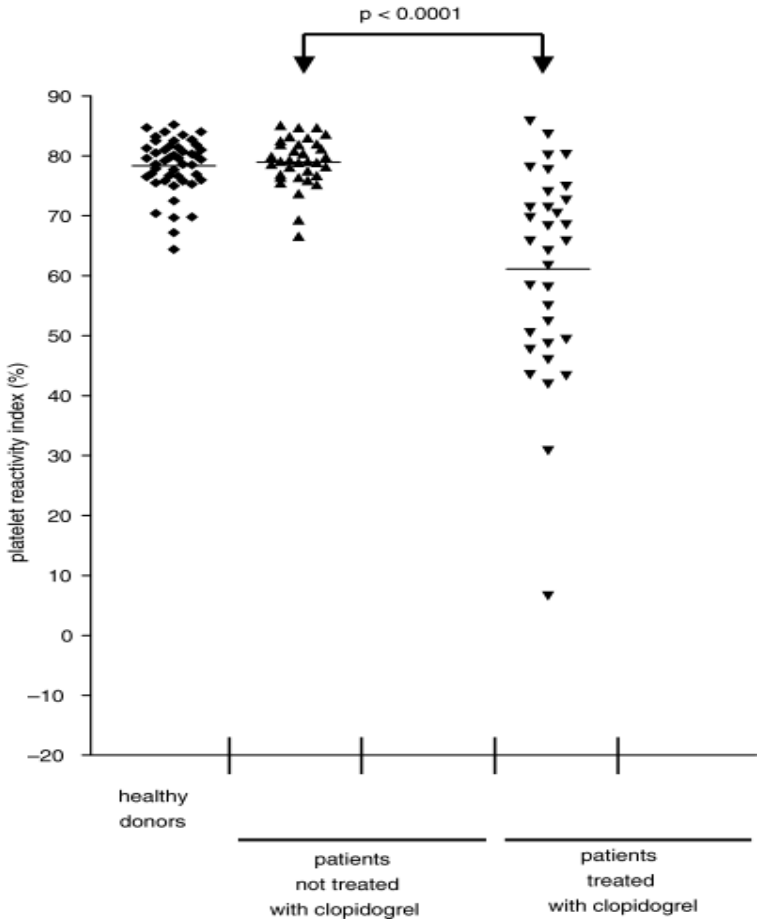
EBM et clopidogrel dans le syndrome coronarien aigu

All dialysis patients presenting with ACS should be treated as in the nondialysis population, with the exception of specific attention to drugs that have altered clearances in kidney failure (e.g., low molecular weight heparin). These therapies include percutaneous coronary intervention (PCI), CABG, antiplatelet agents, beta-blockers, thrombolytic therapy, and lipid-lowering agents. (C)

KDOQI

Variabilité de la réponse au clopidogrel

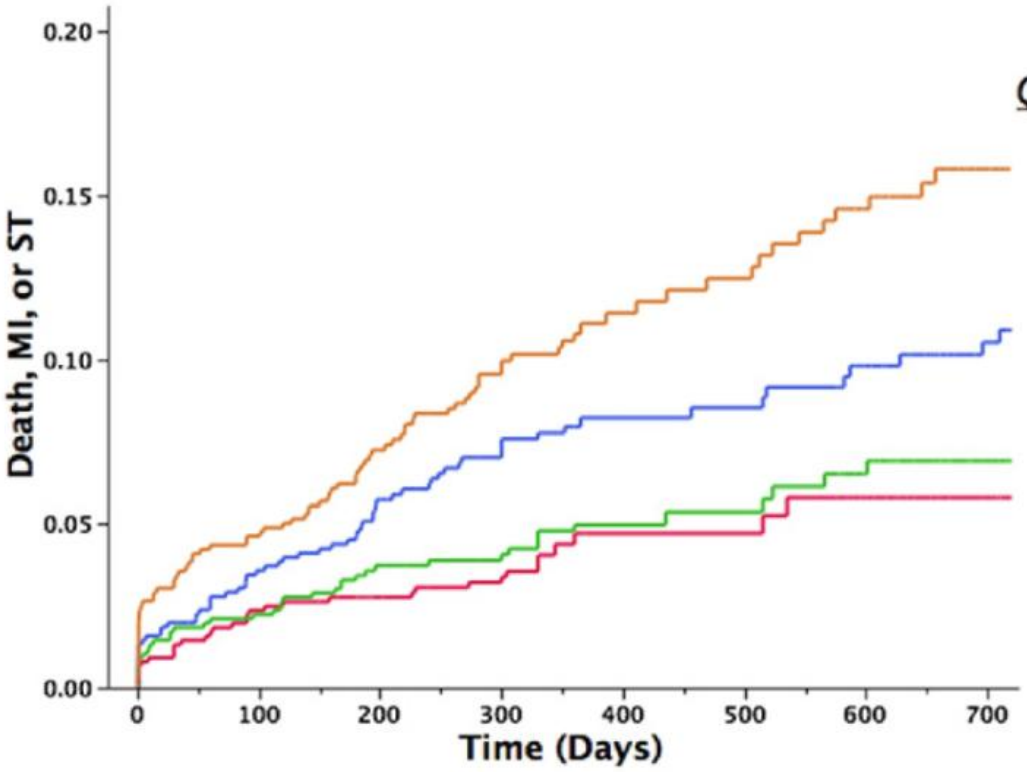




Index de réactivité plaquettaire (PRI)

Aleil B et al. *J Thromb Haemost* 2005

Impact clinique de la variabilité de la réponse au clopidogrel



Quartile	Event Rate	P-value*
Q4	15.8%	<0.001
Q3	10.9%	0.02
Q2	6.9%	0.97
Q1	5.8%	–

Journal of the American College of Cardiology Vol. 58, No. 19, 2011

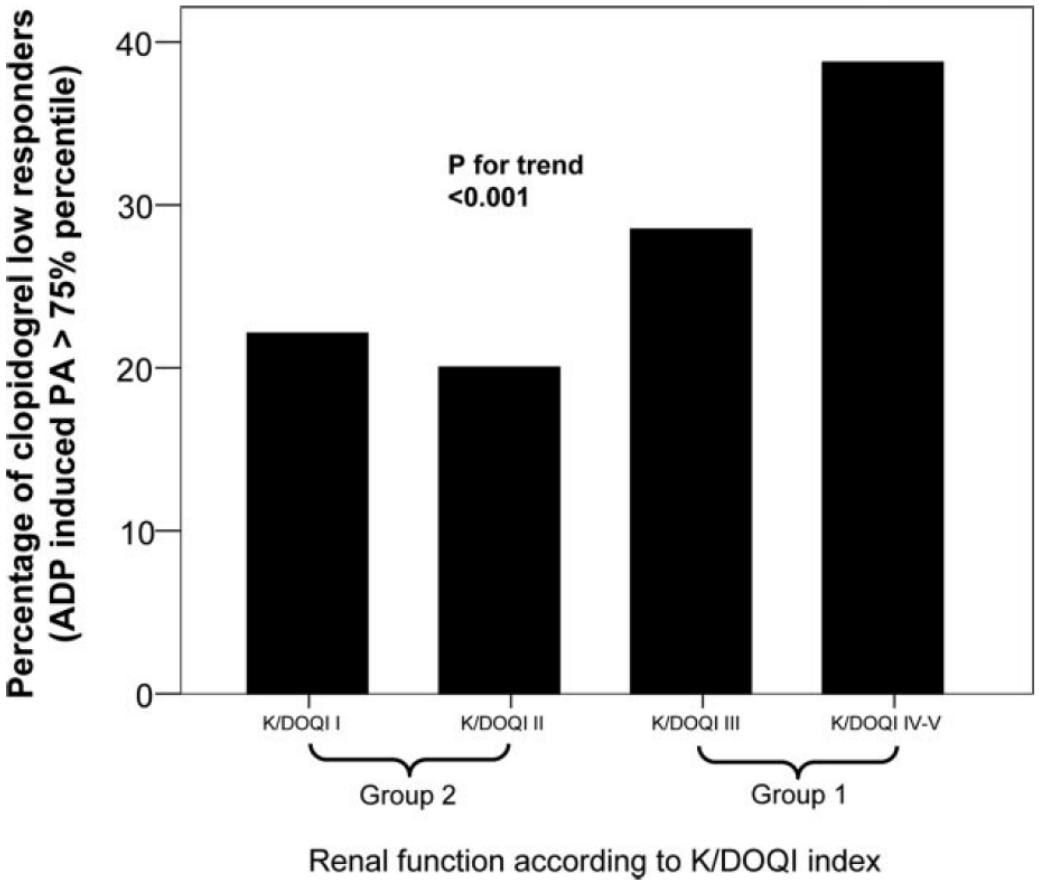
Impact clinique de la variabilité de la réponse au clopidogrel

Outcomes	No. (%) of Participants			*P* Value[a]
	Total (n = 1772)	LRPR (n = 1525)	HRPR (n = 247)	
Primary end point	168 (9.5)	132 (8.7)	36 (14.6)	.003
Cardiac death	89 (5)	65 (4.3)	24 (9.7)	<.001
Myocardial infarction	41 (2.3)	33 (2.2)	8 (3.2)	.30
Urgent coronary revascularization	16 (0.9)	15 (1.0)	1 (0.4)	.71[b]
Stroke	22 (1.2)	19 (1.2)	3 (1.2)	>.99[b]
Stent thrombosis	59 (3.3)	44 (2.9)	15 (6.1)	.01
Definite	30 (1.7)	23 (1.5)	7 (2.8)	.13
Probable	15 (0.8)	11 (0.7)	4 (1.6)	.15
Possible	14 (0.9)	10 (0.7)	4 (1.6)	.11

Abbreviations: HRPR, high residual platelet reactivity; LRPR, low residual platelet reactivity.
[a] The χ^2 test was used for comparison unless otherwise indicated.
[b] By Fisher exact test.

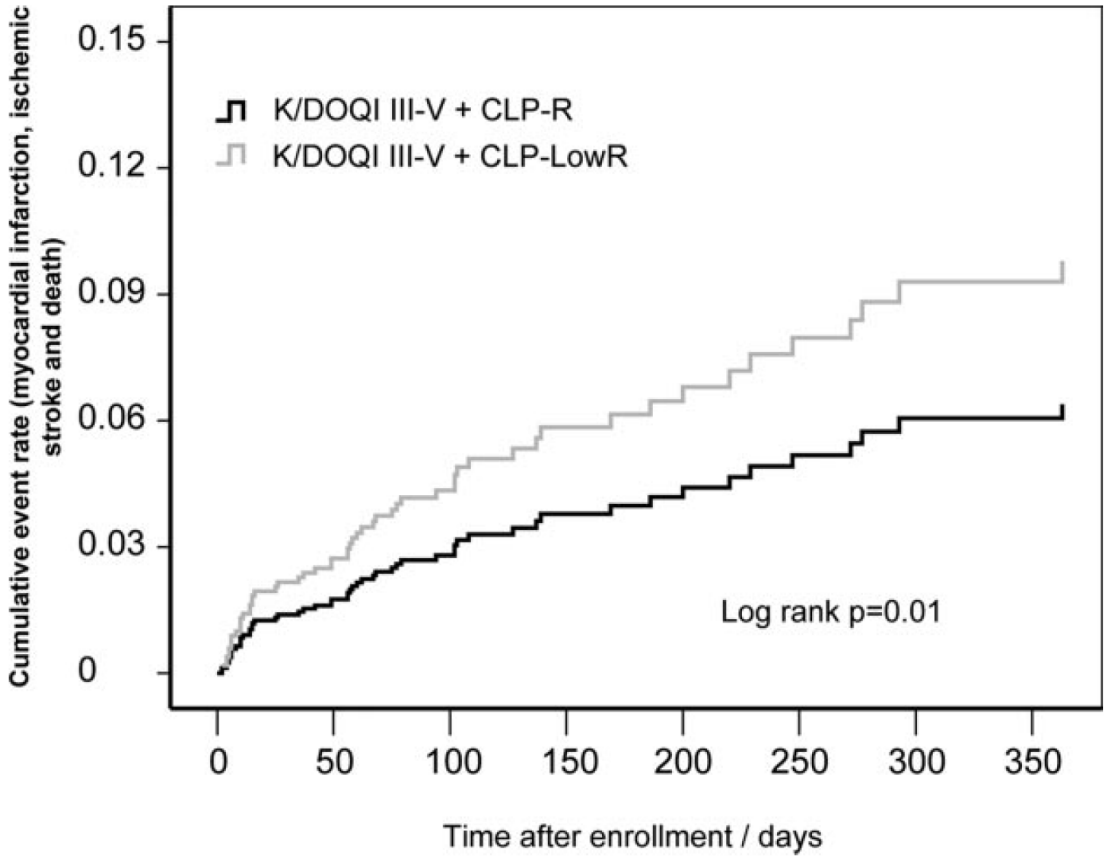
JAMA, September 21, 2011—Vol 306, No. 11

Clopidogrel et insuffisance rénale



J Am Soc Nephrol **22:** 627–633, 2011

Clopidogrel et insuffisance rénale



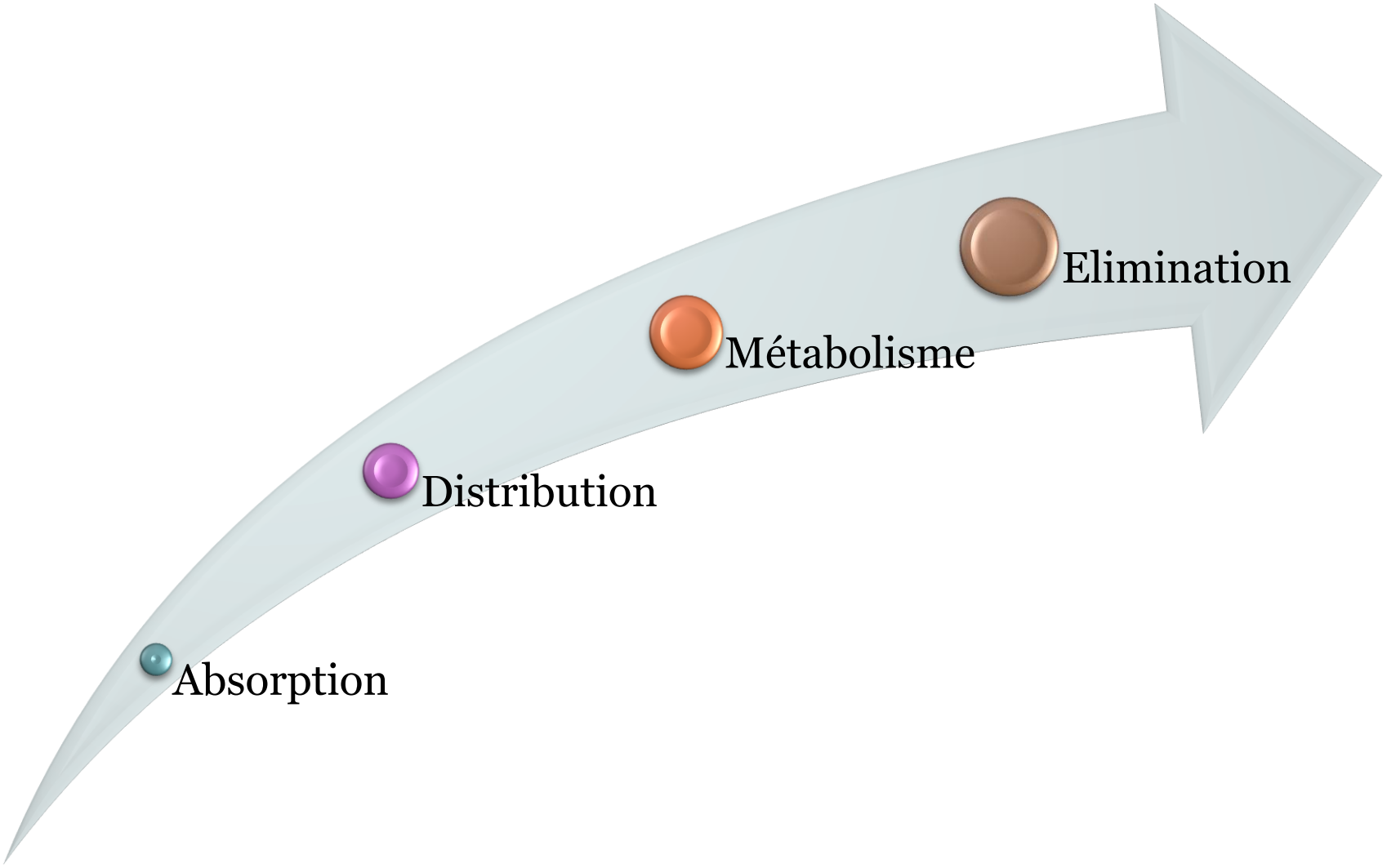
J Am Soc Nephrol **22:** 627–633, 2011

Clopidogrel chez le patient dialysé

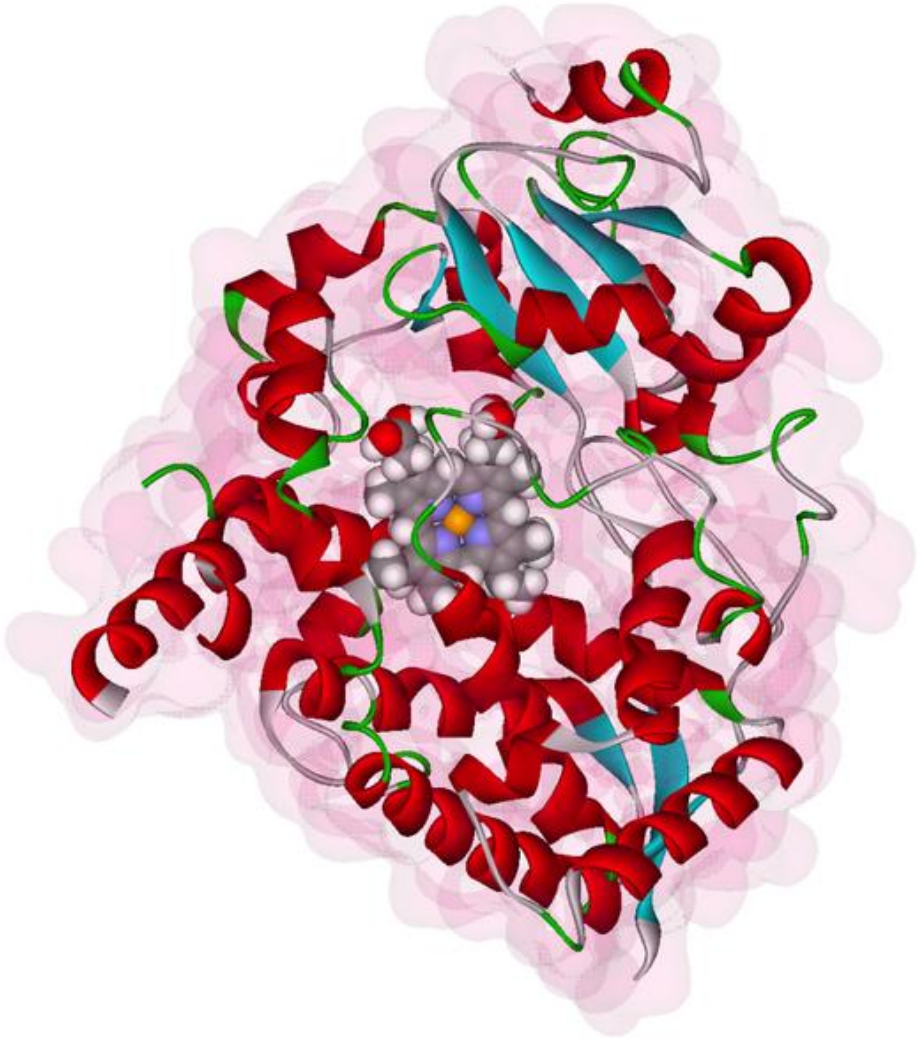
85 patients dialysés sous clopidogrel	• 70 non répondeurs • 15 répondeurs
Parmi les non répondeurs	• Hb, Ht : + d'anémie • Plaquettes : + de thrombopénie

Am J Kidney Dis. 2012;xx(x):xxx

Rappels pharmacocinétiques

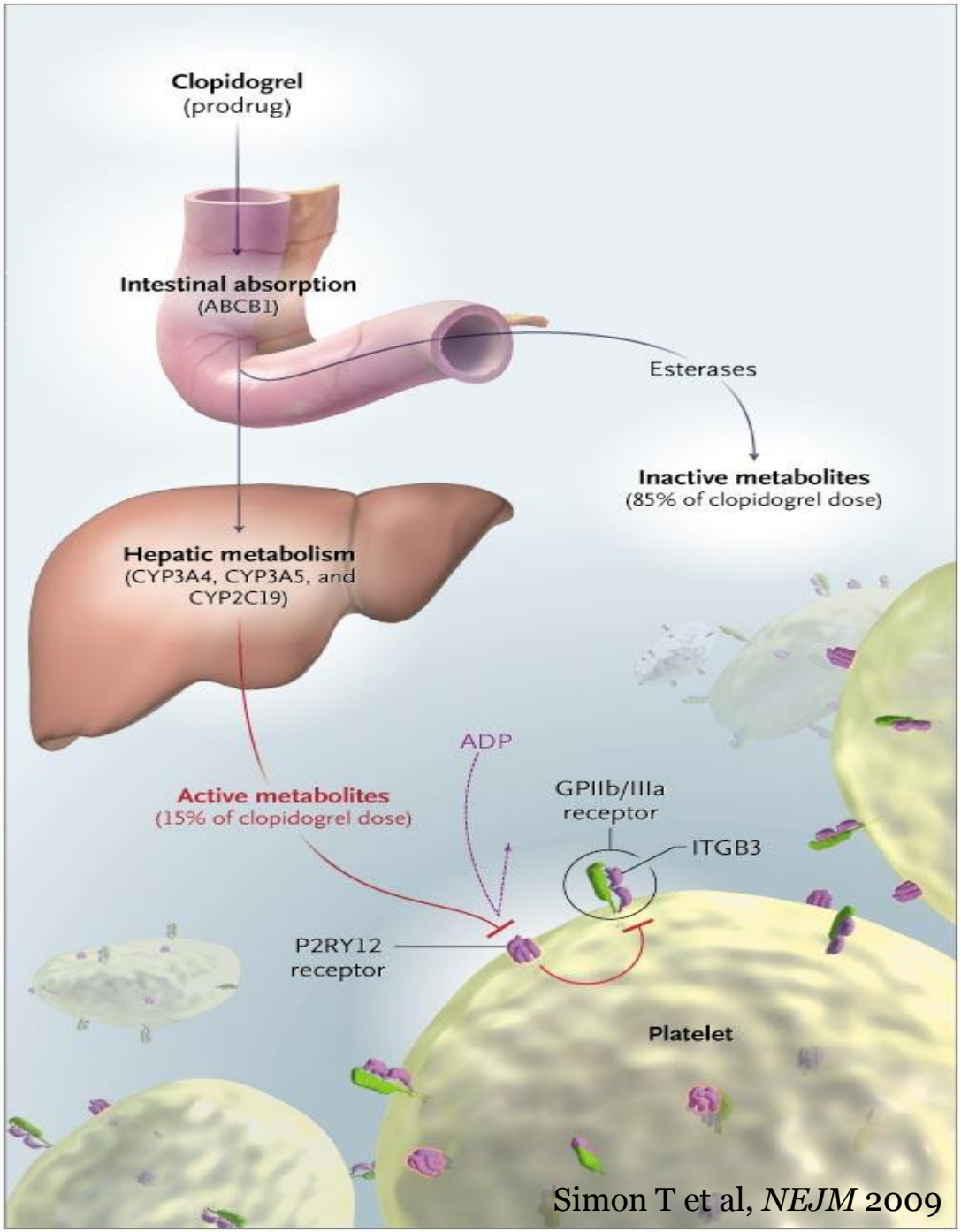


Rappels pharmacocinétiques



PK/PD

2ième génération: **clopidogrel**



Simon T et al, *NEJM* 2009

Absorption

↓

CYPs

↓

Récepteur P2Y12

Rappels pharmacocinétiques

Métabolite actif : 2 procédés oxydatifs successifs	• clopidogrel →2-oxo-clopi (CYP1A2, CYP2B6, and/or CYP2C19) • 2-oxo-clopi 19→ active (CYP3A4, CYP2B6, 2C9, and/or 2C19)
CYP2C19 et CYP3A4 +++	• Paramètres de cinétique enzymatique • Effets inhibiteurs de médics et Ac. dirigés contre les P450s.

Rappels pharmacodynamiques

Assay	Advantages	Limitations	Predicts outcome	Able to monitor Aspirin	Clopidogrel	GP IIb/IIIa
Platelet aggregometry						
Turbidometric light transmittance	Historical 'gold standard'	Time consuming, sample preparation, poor reproducibility, experienced technician required	Yes	Yes	Yes	Yes
Electrical impedance	Whole blood assay	Time consuming, sample preparation, experienced technician required	Yes	Yes	Yes	Yes
Flow cytometry						
Assessment of platelet surface P-selectin, activated GPIIb/IIIa, leucocyte-platelet aggregates	Whole blood assay, small sample volume	Sample preparation, experienced technician required	Yes	Yes	Yes	Yes
VASP phophorylation	Whole blood assay, sample volume, P_2Y_{12} specific	Sample preparation, experienced technician required	Yes	No	Yes	No
Point-of-care						
VerifyNow	Whole blood assay, ease of use, small sample volume, rapid	Further data required on optimal cut-off values	Yes	Yes	Yes	Yes
Thrombelastogram	Whole blood assay, measures platelet-fibrin clot formation and clot lysis	Sample preparation and manual pipetting required	Yes	Yes	Yes	Yes
Multiplate	Whole blood assay, rapid	Manual pipetting required	Yes	Yes	Yes	Yes
PFA-100	Whole blood assay, ease of use, rapid, small sample volume	Affected by VWF, haematocrit levels and platelet count, manual pipetting required	Yes	Yes	NR	NR
PlateletWorks	Whole blood assay, ease of use, rapid, small sample volume	Not extensively studied	No	Yes	Yes	Yes

NR, not recommended; VASP, vasodilator stimulated phosphoprotein; VWF, von Willebrands factor.

BJCP N. Sambu & N. Curzen

Variabilité de la réponse au clopidogrel dans la population générale

The Pharmacogenomics of Antiplatelet Intervention (PAPI) Study

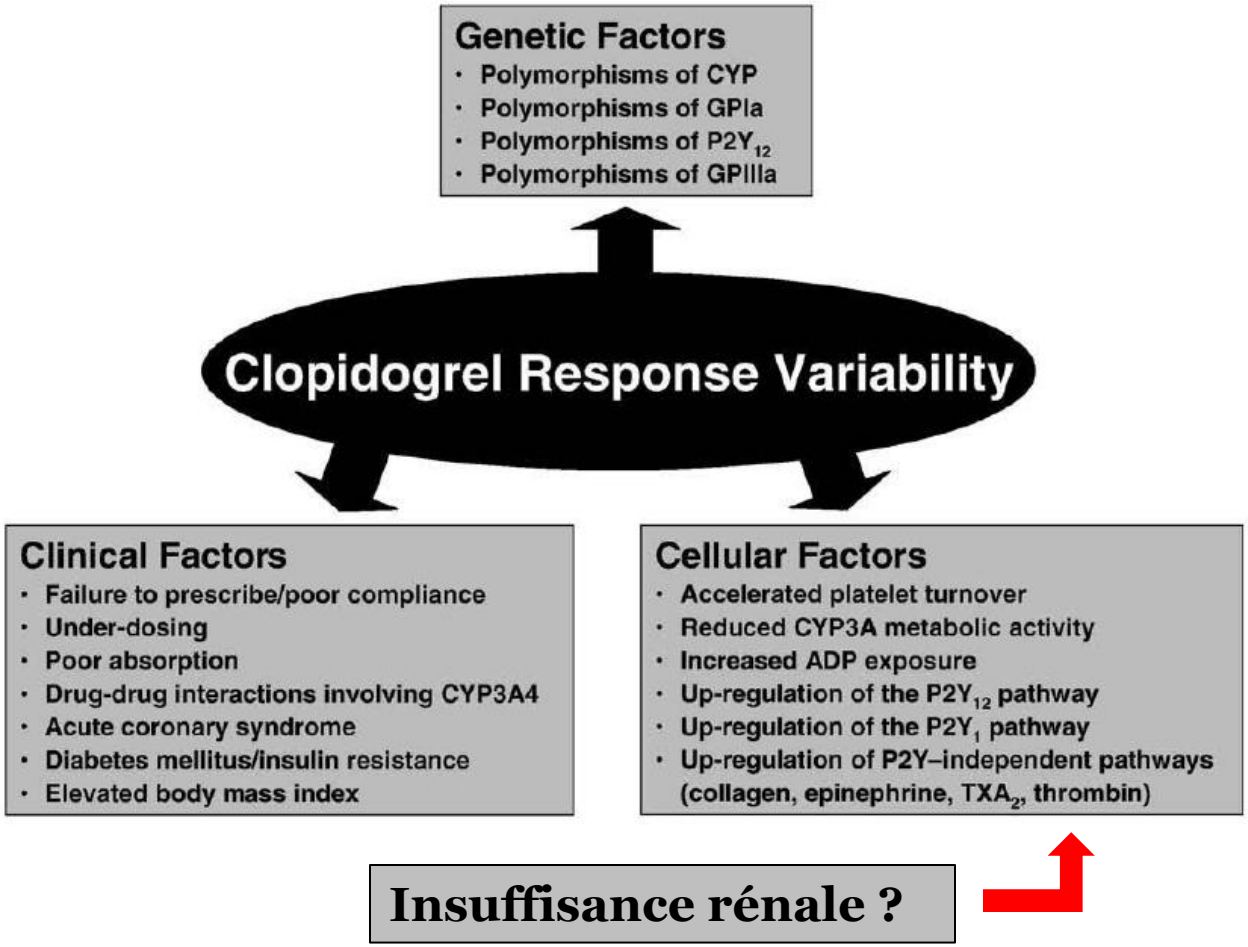
Etude pangénomique dans une population de sujets sains

- CYP 2C19*2 } 12%
- Age
- Profil lipidique } 22%
- IMC
- **?** } 66%

→ Interactions médicamenteuses ?

Shuldiner AR et al, *JAMA* 2009;302:849

Variabilité de la réponse au clopidogrel chez le patient ayant une maladie rénale chronique



Variabilité de la réponse au clopidogrel chez le patient ayant une maladie rénale chronique

Facteurs liés au patient et ses pathologies

Facteurs liés au traitements de la MRC

Variabilité de la réponse au clopidogrel chez le patient ayant une maladie rénale chronique

Filtre ?

- Réaction avec métabolite actif ?

Variabilité de la réponse au clopidogrel chez le patient ayant une maladie rénale chronique

↓ Absorption

Altération MDR1 /AAS *(CPT, 2011)*

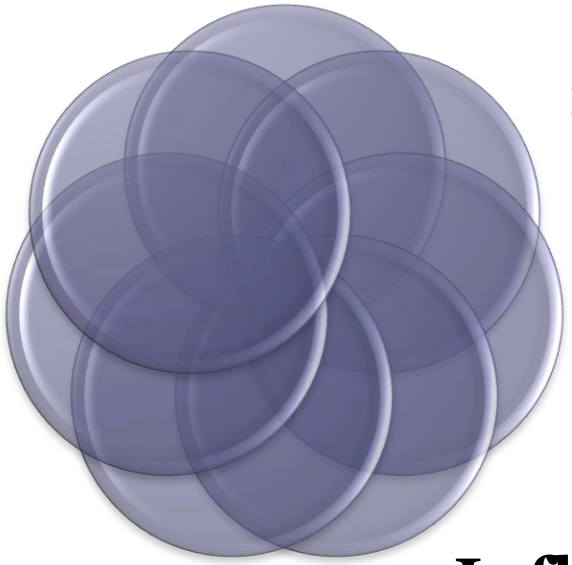
Anémie

Am J Cardiol, 2012

↓ Métabolisme

Interaction médicamenteuse

Diminution de la fonction des cytochromes ?



Urémie

Indoxyl – sulfate et toxicité vasculaire

(*J Ren Nutr. 2010 Sep;20(5 Suppl):S2-6*)

Dénutrition

↓ Ω3 *(JACC, 2010)*

Diabète

Angio, 2012

Inflammation

↑ IL-6 (*Circ J, 2011*) , ↑ IL-10 et Leuco (*J Thromb Thrombolysis. 2011*)

Variabilité de la réponse au clopidogrel chez le patient ayant une maladie rénale chronique

↓ Absorption

Altération MDR1 /AAS *(CPT, 2011)*

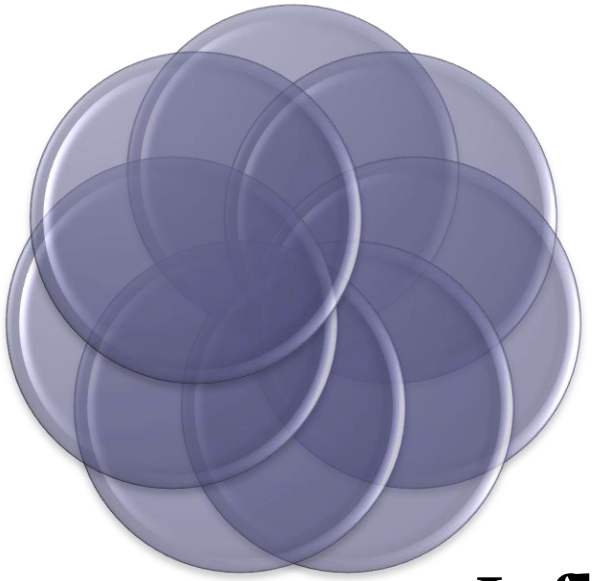
Anémie

Am J Cardiol, 2012

↓ Métabolisme

Interaction médicamenteuse

Diminution de la fonction des cytochromes ?



Urémie

Indoxyl – sulfate et toxicité vasculaire

(*J Ren Nutr. 2010 Sep;20(5 Suppl):S2-6*)

Dénutrition

↓ Ω3 *(JACC, 2010)*

Diabète

Angio, 2012

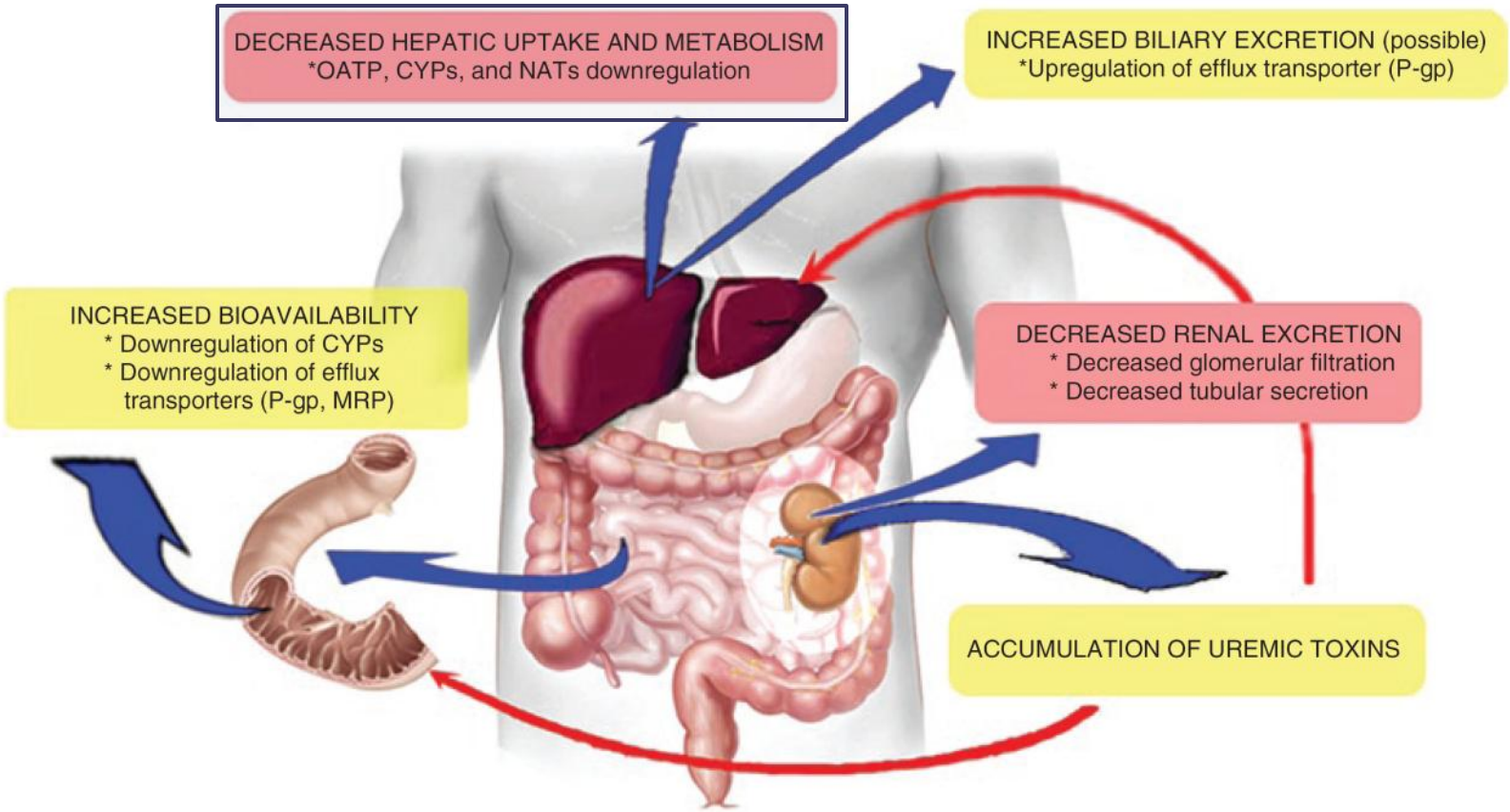
Inflammation

↑ IL-6 (*Circ J, 2011*) , ↑ IL-10 et Leuco (*J Thromb Thrombolysis. 2011*)

Métabolisme des médicaments dans l'insuffisance rénale : une explication ?

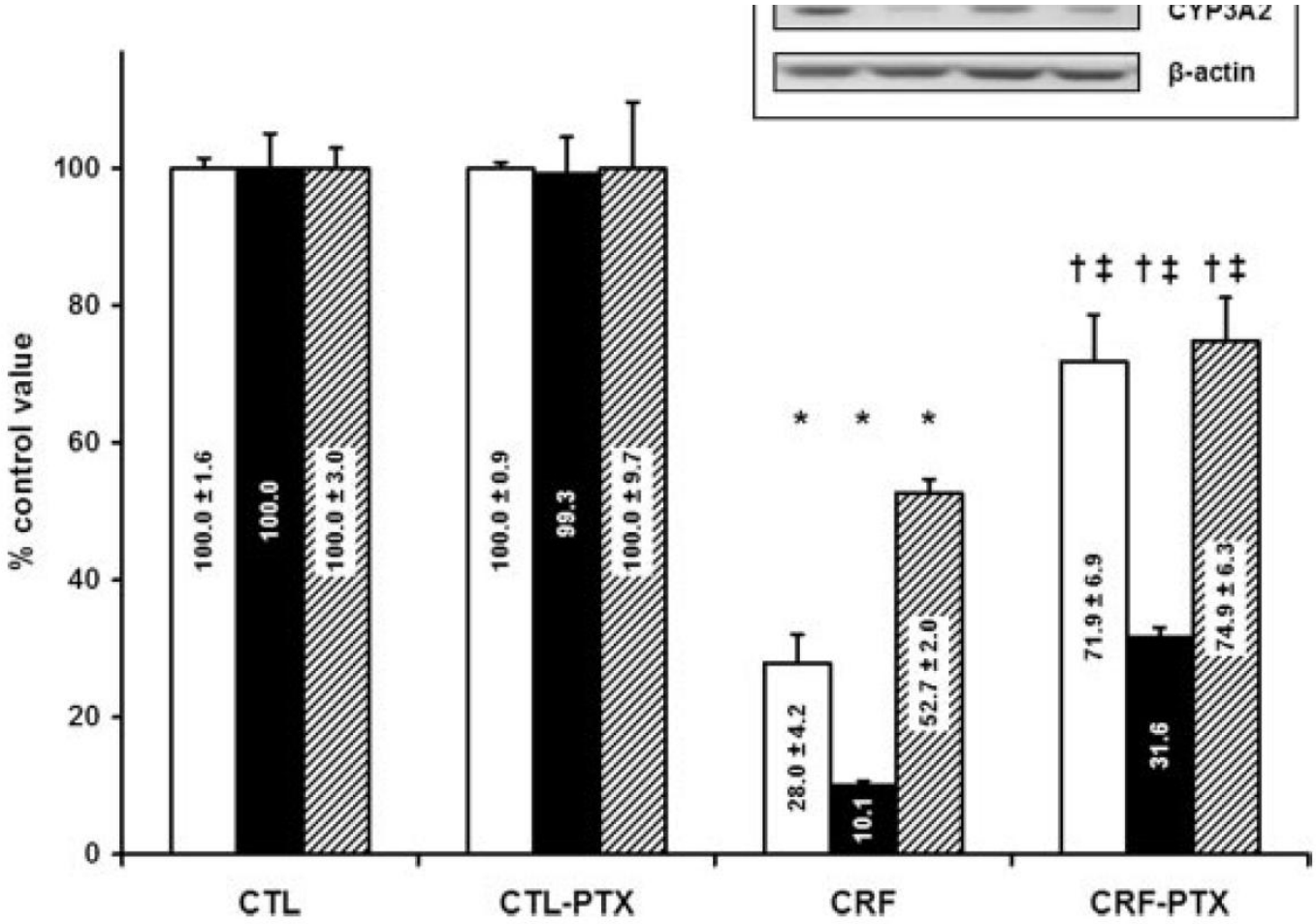
Emerging Evidence of the Impact of Kidney Disease on Drug Metabolism and Transport

TD Nolin[1,2], J Naud[3,4], FA Leblond[3] and V Pichette[3,4]



VOLUME 83 NUMBER 6 | JUNE 2008 | www.nature.com/cpt

Métabolisme des médicaments dans l'insuffisance rénale : une explication ?



J Am Soc Nephrol 17: 3041–3048, 2006.

Métabolisme des médicaments dans l'insuffisance rénale : une explication ?

Hepatic Clearance, but Not Gut Availability, of Erythromycin Is Altered in Patients With End-Stage Renal Disease

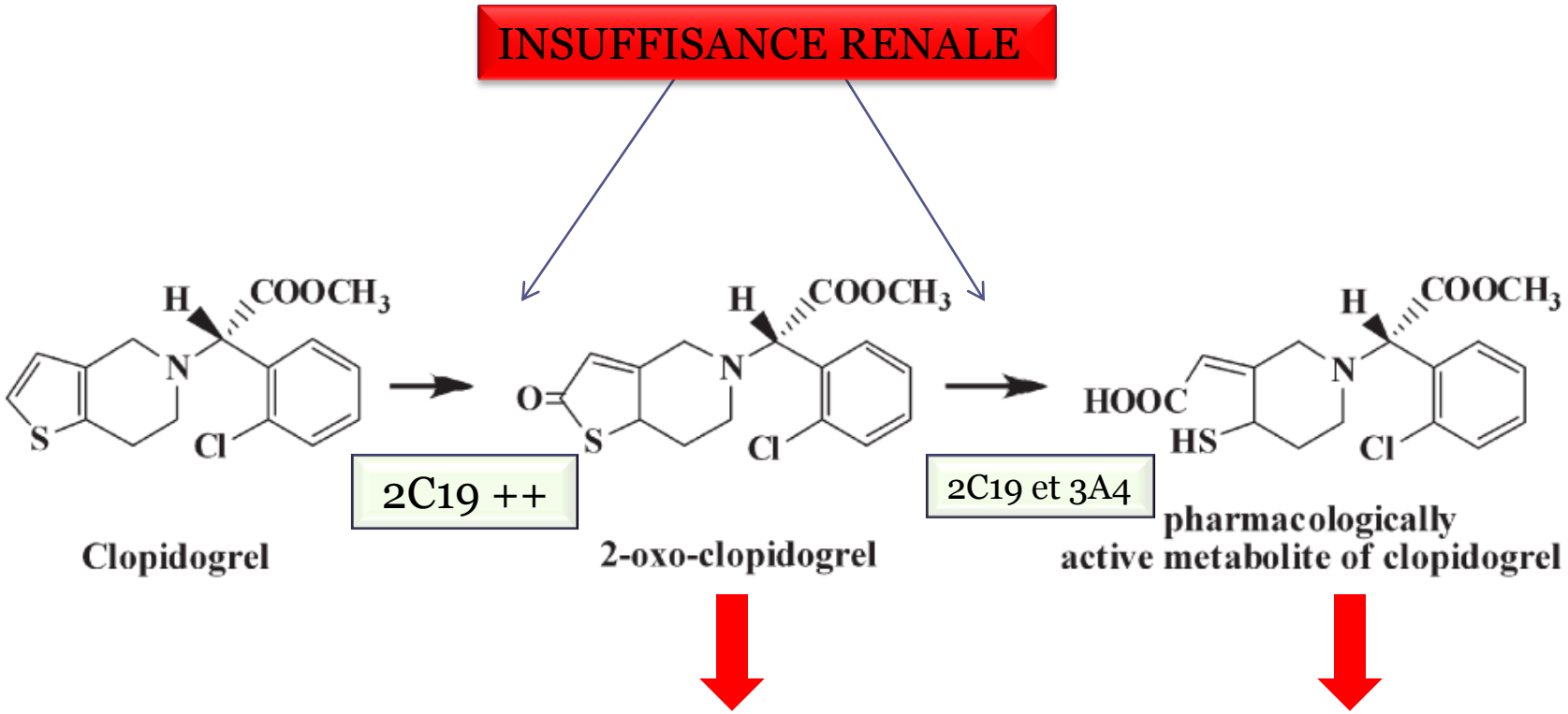
Table 3 Erythromycin pharmacokinetic parameters (mean ± SD) in ESRD patients and controls after oral administration of 250 mg erythromycin

	Healthy controls	ESRD patients	Percentage increase (*P* value)
T_{max} (h)	0.92 ± 0.56	1.08 ± 1.04	↔
C_{max} (µg/l)	446 ± 298	895 ± 714	137%[a] ↑ ($P = 0.01$)
AUC (µg·h/l)	1,040 ± 702	2,400 ± 1,950	51%[a] ↑ ($P = 0.007$)
AUC adjusted[b] (kg·h/l)	0.29 ± 0.19	0.74 ± 0.77	158%[a] ↑ ($P = 0.009$)
F (%)	15 ± 6	21 ± 17	36% ↑ ($P = 0.36$)
F_H (%)	50 ± 10	64 ± 15	28% ↑ ($P = 0.015$)
$F_{abs} \cdot F_G$ (%)	33 ± 30	35 ± 28	↔
$t_{1/2}$ (h)	2.86 ± 1.27	6.23 ± 3.17	118% ↑ ($P = 0.003$)
MAT (h)	1.52 ± 0.56	2.83 ± 2.50	86% ↑ ($P = 0.09$)
f_u (%)	27 ± 5	30 ± 4	↔

AUC, area under the concentration–time curve; C_{max}, peak plasma concentration; ESRD, end-stage renal disease; F, bioavailability; F_{abs}, fraction of the dose absorbed; F_G, gut bioavailability; F_H, hepatic bioavailability; f_u, unbound fraction; MAT, mean absorption time; $t_{1/2}$, elimination half-life; T_{max}, time to maximal concentration.

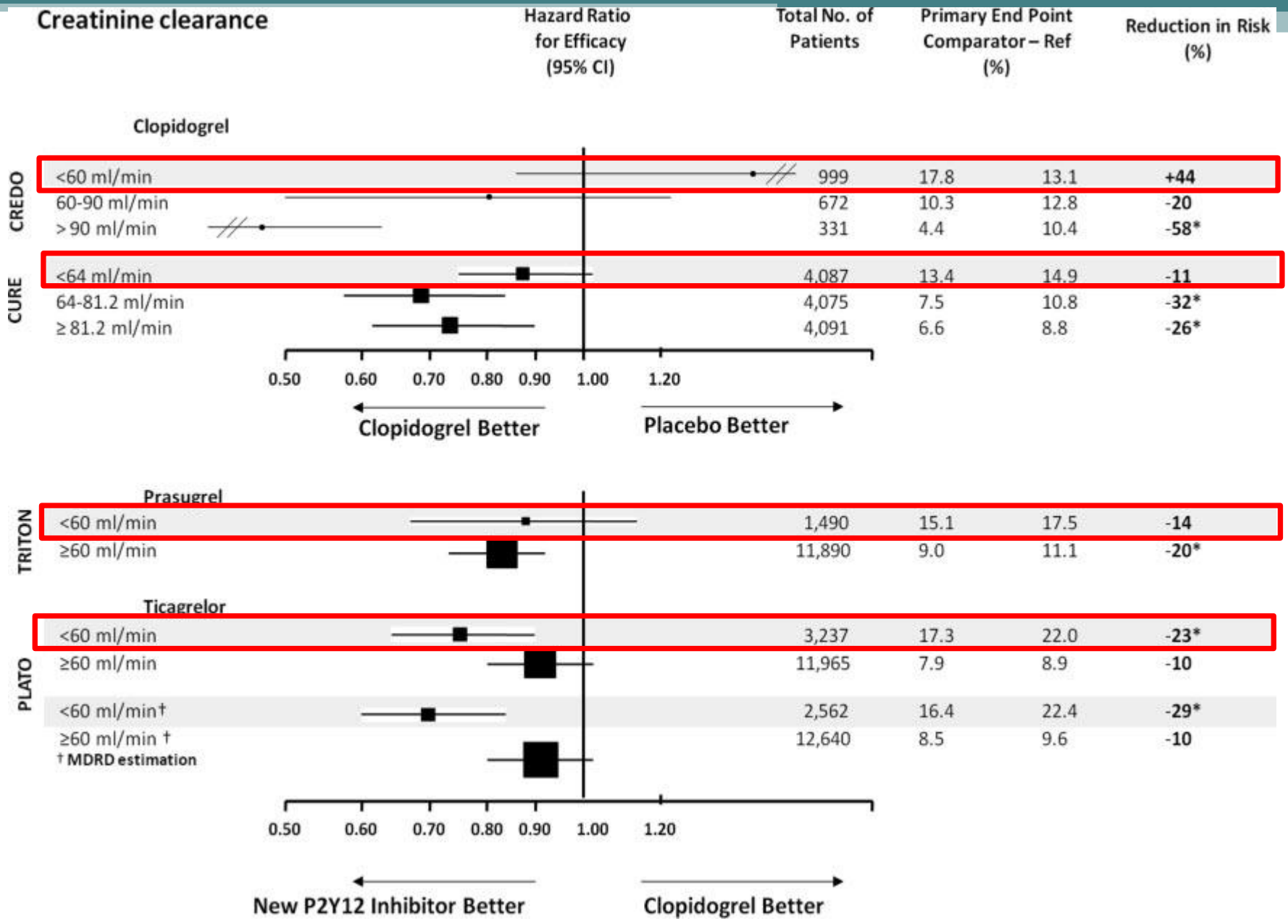
[a]Geometric mean difference (after log transformation). [b]AUC was adjusted by dose/weight.

Métabolisme des médicaments dans l'insuffisance rénale : une explication ?



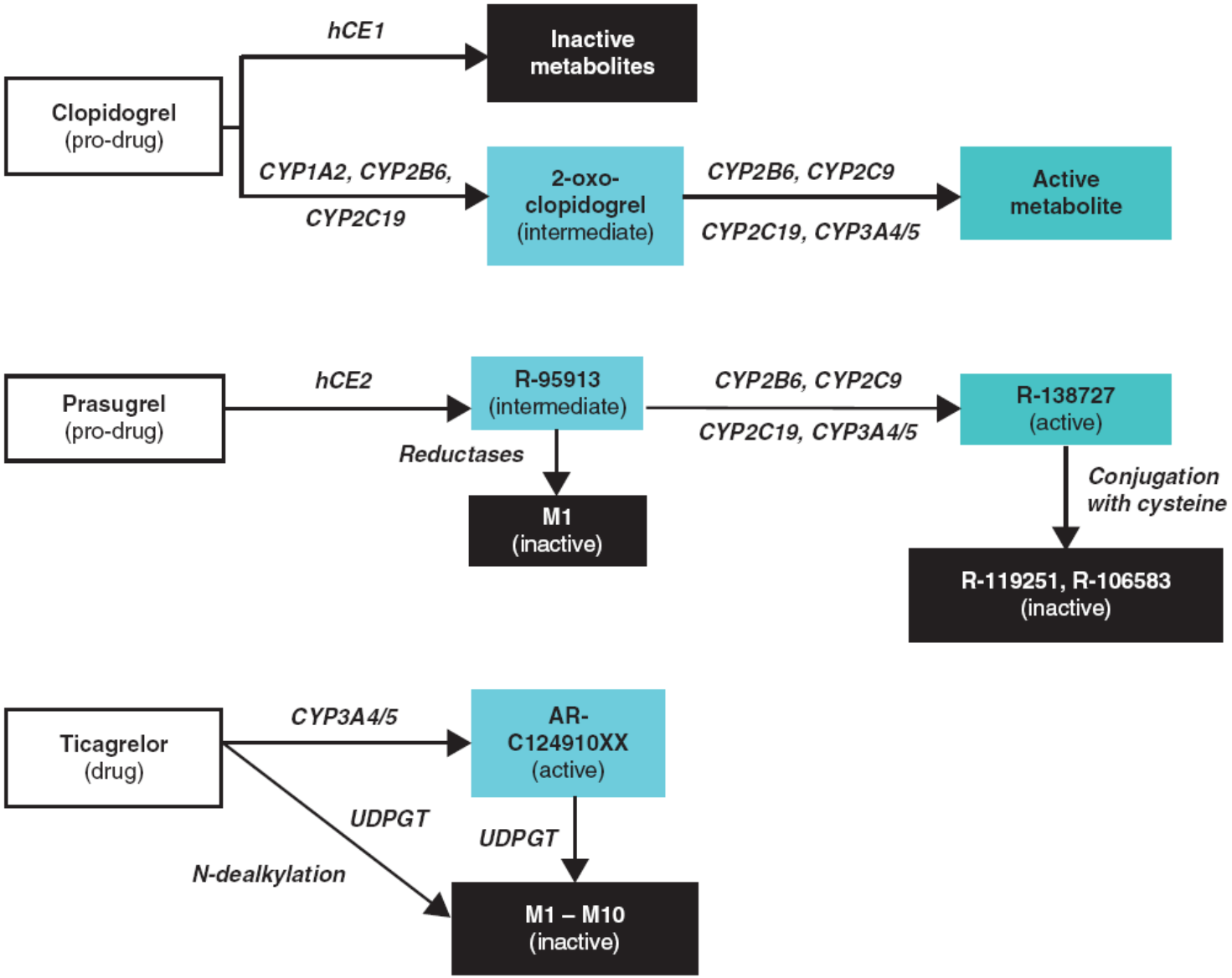
Cas clinique : M. A, 61 ans

- IRCT en hémodialyse depuis 3 ans (néph. HTA)
- ATCD : AVC aphasie, maladie coronarienne
- MH : sténose et thrombose partielle de FAV
- SCA – NSTEMI : sténose du tronc commun
- PCA – Stent. VASP > 75 %. Ad dose de charge.
- 3 mois après resténose sous clopidogrel



Montalescot G et al. *Circulation* 2010;122:1049

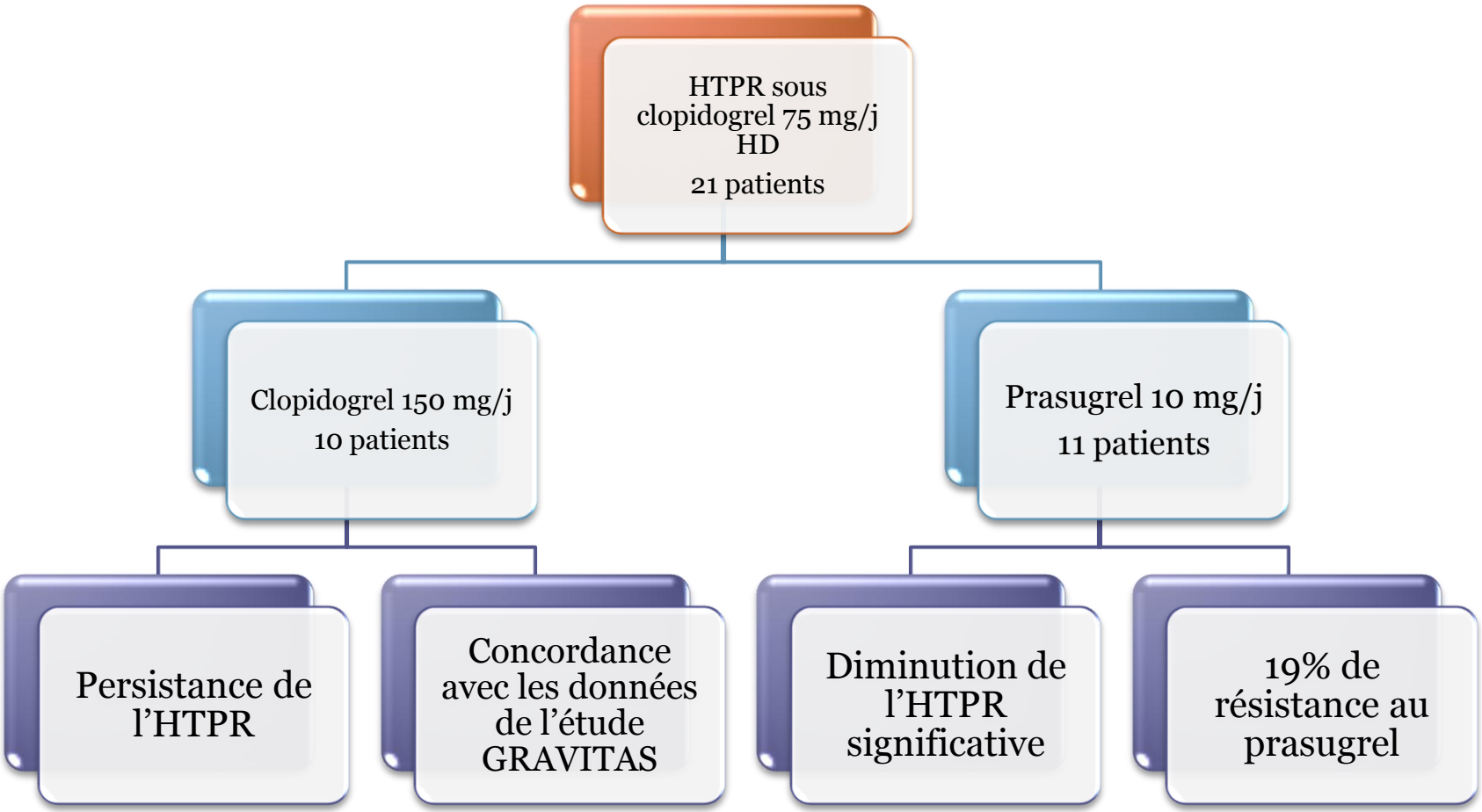
Perspectives



ORIGINAL ARTICLE

Antiplatelet effects of prasugrel vs. double clopidogrel in patients on hemodialysis and with high on-treatment platelet reactivity

D. ALEXOPOULOS,* A. PANAGIOTOU,* I. XANTHOPOULOU,* D. KOMNINAKIS,† G. KASSIMIS,*



J Thromb Haemost. 2011 Dec;9(12):2379-85.

Ticagrelor in Clopidogrel Resistant Patients Undergoing Chronic Hemodialysis

This study has been completed.

First Received on January 12, 2012. Last Updated on February 2, 2012 History of Changes

Sponsor:	University of Patras
Information provided by (Responsible Party):	Dimitrios Alexopoulos, University of Patras
ClinicalTrials.gov Identifier:	NCT01511471

Purpose

Clopidogrel administration is commonly prescribed in patients undergoing percutaneous coronary intervention, in patients with previous stroke and in patients under chronic hemodialysis via fistulae. Patients with chronic renal failure present lower clopidogrel response compared to those with normal renal function. Ticagrelor is a new oral direct-acting antagonist, which provides greater platelet inhibition in both clopidogrel responders and non-responders. It has also been shown that in patients with chronic kidney disease (creatinine clearance <60 mL/min)ticagrelor achieved an absolute risk reduction of cardiovascular death, myocardial infarction, and stroke greater than that of patients with normal renal function. Clopidogrel resistant patients as assessed by VerifyNow P2Y12(Accumetrics)will be administered after informed consent ticagrelor 90 mg twice daily for 15 days. Platelet reactivity will be determined at the end of the treatment period. Bleeding events, major adverse cardiac events and any side effects until Day 15 will be reported in a descriptive manner.

Condition	Intervention	Phase
Platelet Reactivity	Drug: Ticagrelor	Phase III

Study Type: Interventional
Study Design: Endpoint Classification: Pharmacodynamics Study
Intervention Model: Single Group Assignment
Masking: Single Blind (Outcomes Assessor)
Primary Purpose: Treatment

Official Title: Ticagrelor in Clopidogrel Resistant Patients Undergoing Chronic Hemodialysis

Resource links provided by NLM:

MedlinePlus related topics: Dialysis

Drug Information available for: Clopidogrel Clopidogrel Bisulfate

U.S. FDA Resources

Further study details as provided by University of Patras:

Primary Outcome Measures:

Conclusion et perspectives

- Il est recommandé d'administrer du clopidogrel chez le patient IRC terminal dans le cadre du syndrome coronarien aigu
- Le niveau de preuve est faible et le bénéfice du clopidogrel est moindre chez les patients insuffisants rénaux et ce d'autant que la prévalence de résistance est très élevée chez les IRCT
- Augmentation de la survenue d'évènements CV parmi les patients IRC sous clopidogrel :
  - Insuffisamment traité ?
  - Insuffisamment métabolisé ? Effet de l'IRC sur le métabolisme.
- Nécessité de changer de traitement ? Prasugrel ? Ticagrelor ?

Merci ☺