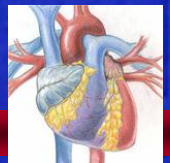
ANTIPLATELET THERAPY IN CHRONIC KIDNEY DISEASE

Dimitrios Alexopoulos, MD

ALPIC 2012
28.1.2012



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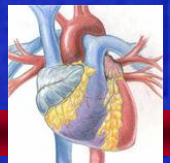
have received honoraria from:
Astra , Eli Lilly, Sanofi-Aventis

Advisory board: Astra, Boeringer Ingelheim



Chronic kidney disease is prevalent and affects an ever-increasing proportion of patients presenting with acute coronary syndrome.

The National Kidney Foundation estimates that 11% of the U.S. population has CKD.

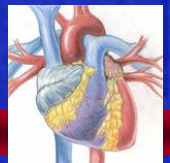


Table 1 National Kidney Foundation Classification of CKD Based on GFR

Classification	Definition
Normal	GFR >90 ml/min/1.73 m^2 with no evidence of kidney dysfunction
CKD 1	GFR >90 ml/min/1.73 m^2 with evidence of kidney dysfunction
CKD 2	GFR 60–90 ml/min/1.73 m^2
CKD 3	GFR 30–60 ml/min/1.73 m^2
CKD 4	GFR 15–30 ml/min/1.73 m^2
CKD 5	GFR <15 ml/min/1.73 m^2

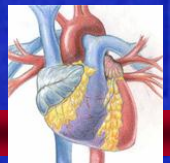
CKD = chronic kidney disease; GFR = glomerular filtration rate.

Data from clinical trials suggest that 35% to 40% of patients presenting with ACS have some degree of renal insufficiency.

Patients with CKD:
have a higher risk of ACS

have a significantly higher mortality

are predisposed to increased bleeding complications.



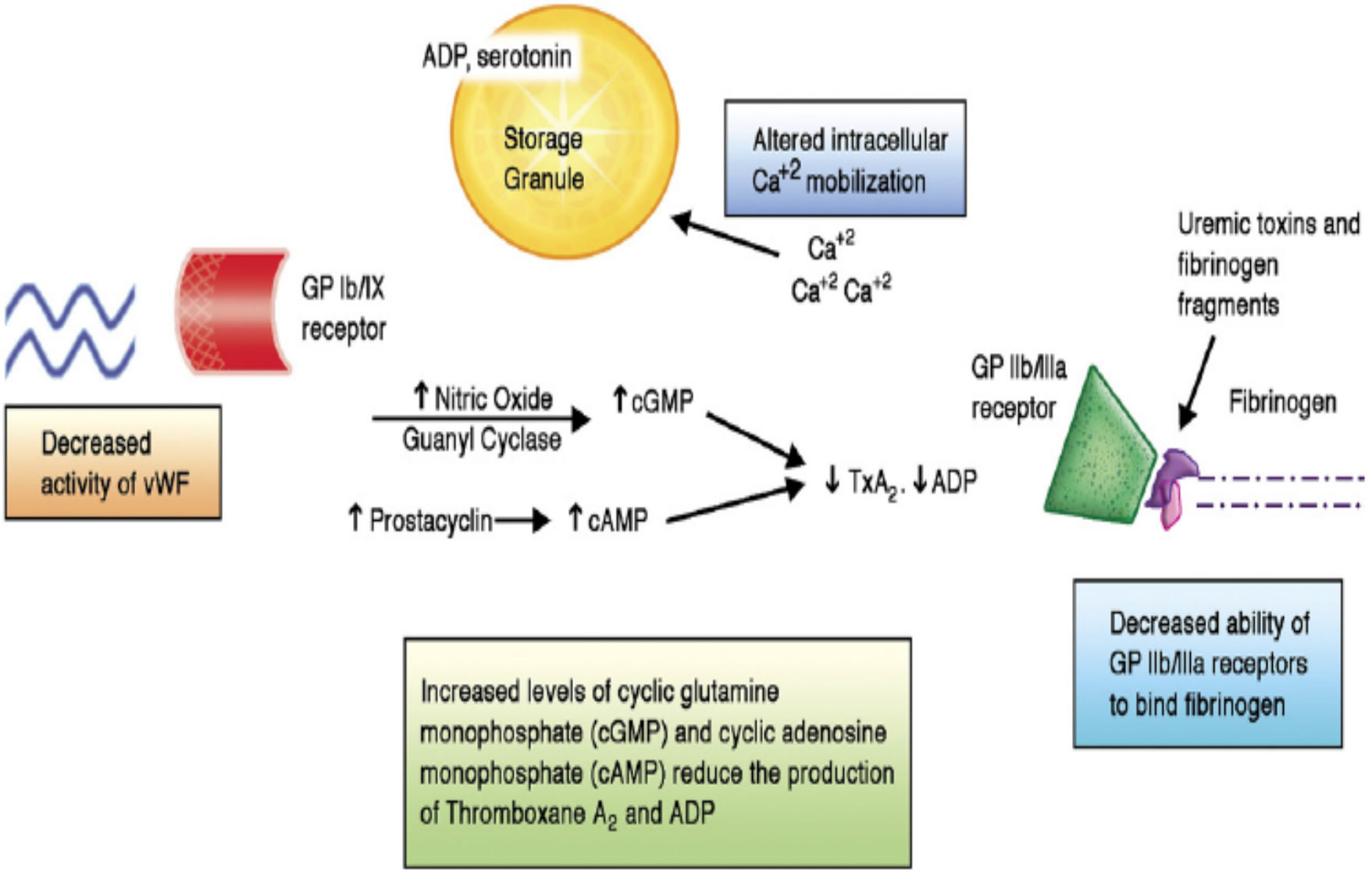


Figure 1 **Overview of Factors Contributing to Platelet Dysfunction in Uremia**

Shown are both intrinsic and extrinsic coagulation factors contributing to platelet dysfunction in uremia, demonstrating the mechanism of impaired platelet adhesion, activation, and aggregation in uremic patients. ADP = adenosine diphosphate. Adapted with permission from Washam and Adams (8).

Table 1. Thrombotic abnormalities in end-stage renal disease.

Platelet factors:

- Increased platelet stimulation
- Abnormal membrane receptor expression(Gp Ib, GpIIb/IIIa)
- Contact with artificial circuit
- Hyperfibrinogenemia
- Release of growth factors(PDGF) that reduce blood flow in the vascular access

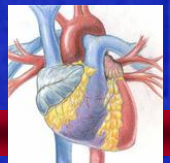
Endothelial factors:

- Increased levels of vWF
- Increased levels of thrombodulin
- Increased release of VCAM
- Oxidative stress and thus reduced NO synthesis
- Increased levels of PAI-1

D. Alexopoulos, et al Hell J Cardiol, 2011,52:509

Antiplatelet drugs form the bedrock of management of patients with ACS.

Most randomized trials of these drugs exclude patients with CKD, and current guidelines for management of these patients are largely based on these trials.



Aspirin

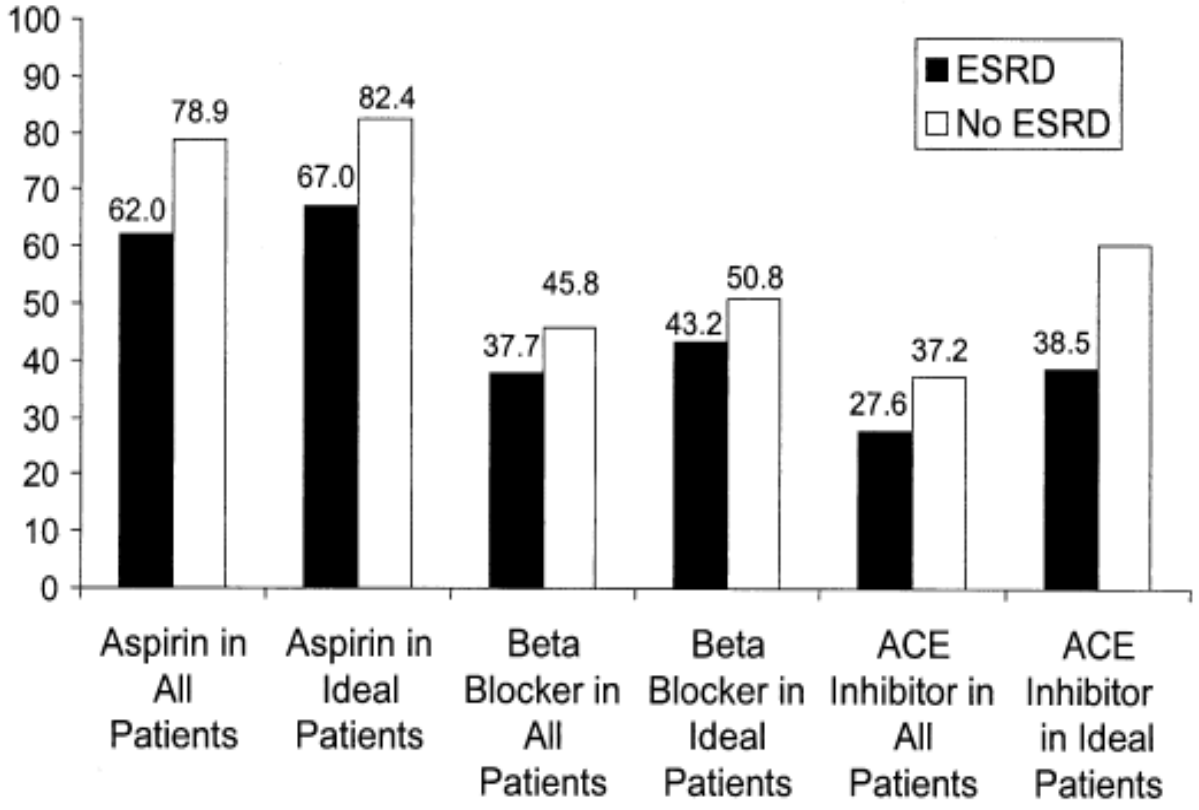


Figure 1. Aspirin, beta-blockers, and angiotensin-converting enzyme (ACE) inhibitors were less likely to be provided to patients with end-stage renal disease (ESRD) than those without ESRD. In an analysis of patients considered ideal for the individual therapies, the overall administration rates were higher, but patients with ESRD still remained less likely to receive the therapy than those without ESRD. The p value for each comparison between ESRD and non-ESRD patients was <0.001.

Berger AK, et al. JACC 2003

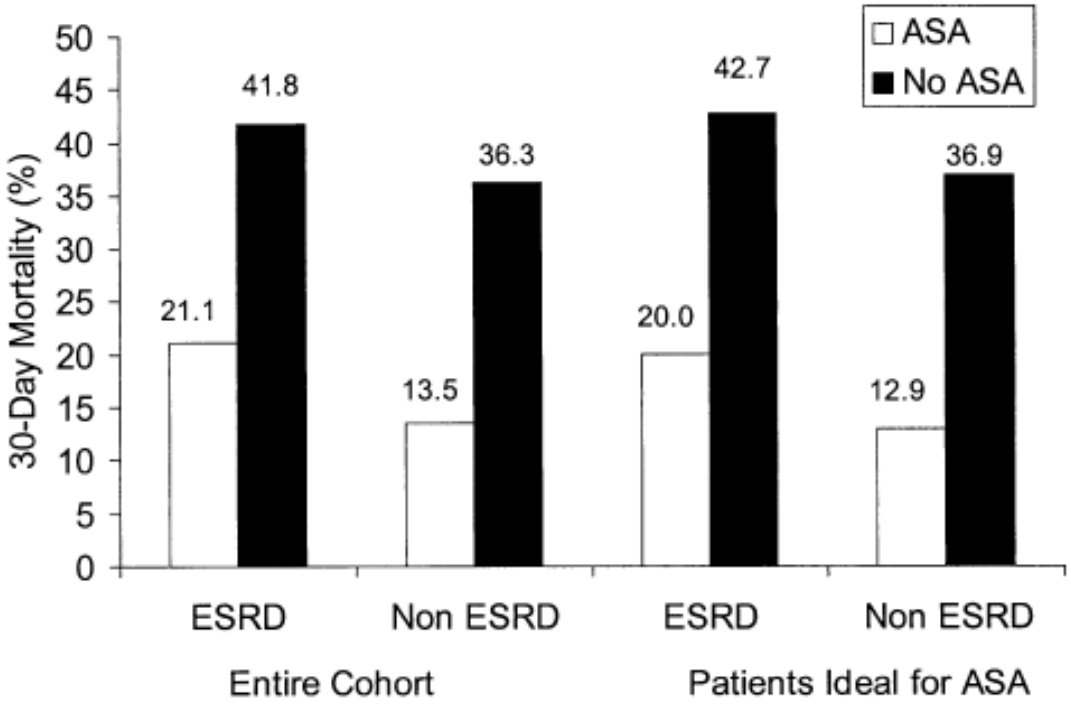
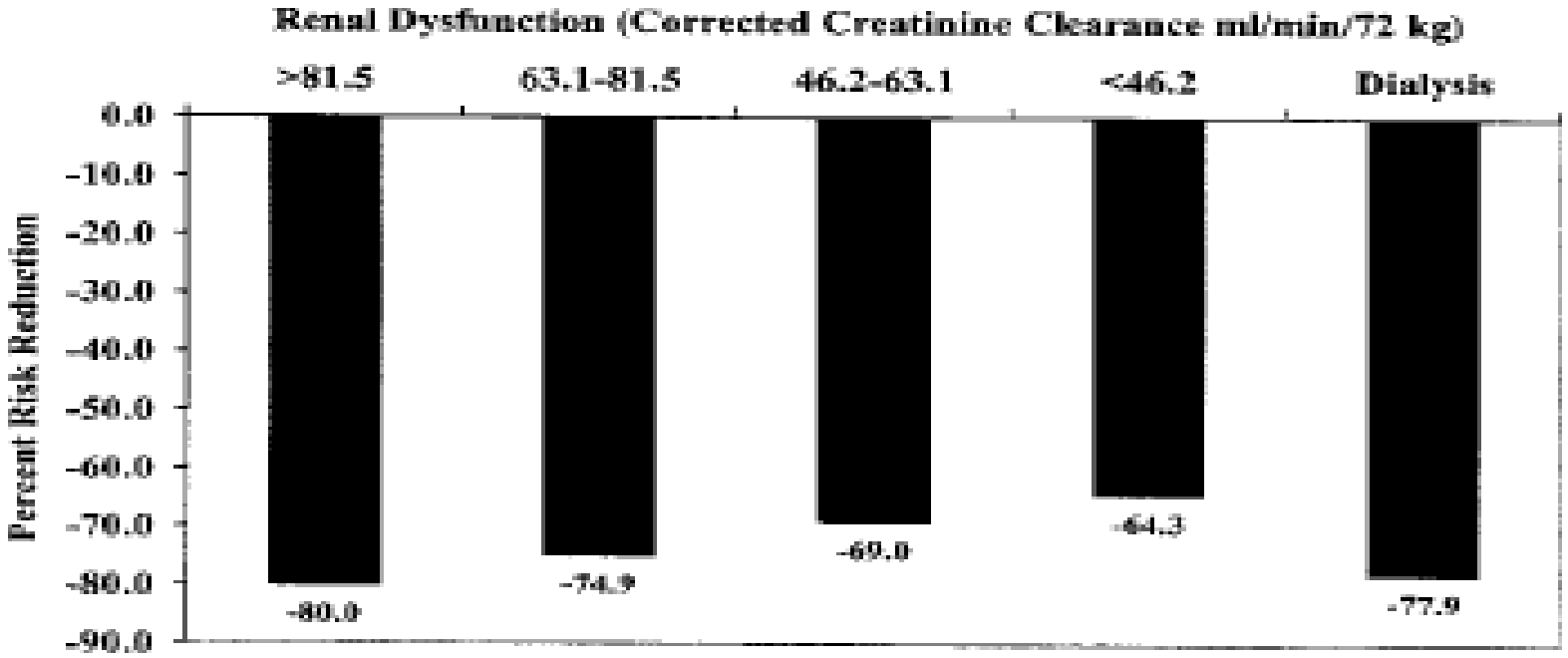


Figure 2. Thirty-day mortality was dramatically reduced by the administration of aspirin (ASA) during the hospitalization. The p value for each mortality comparison between patients taking ASA and those not receiving ASA was <0.001. The relative risk reduction in mortality was significantly greater for patients without end-stage renal disease (ESRD) than for those with ESRD in the entire cohort (63% vs. 50%, p = 0.01). After restricting the cohort to patients ideal for ASA, the reduction in mortality provided by aspirin therapy remained greater in the non-ESRD group, although it was no longer statistically significant (65% vs. 53%, p = 0.10).

Berger AK. et al. JACC 2003

1724 pts with STEMI



Age-adjusted relative risk reduction for the combination of ASA+BB on inhospital mortality, according to level of renal dysfunction in patients not in shock or heart block ($P < .0001$ for all). The referent group is made up of patients who received neither ASA nor BB.

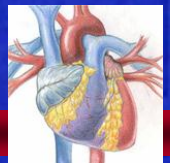
McCullough PA et al AHJ 2002

The low-dose aspirin (100 mg/day) in CKD patients is not associated with increased major bleeding or progression of CKD

(U.K. HARP (Heart and Renal Protection)-1 trial and the DOPPS (Dialysis Outcomes and Prescription Patterns Study)

Low-dose aspirin (75 to 160 mg) is as efficacious as high-dose aspirin (325 mg) for secondary prevention of coronary artery disease in patients with CKD and end-stage renal disease

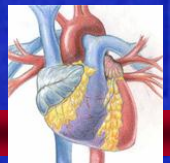
(Meta-analysis by the Antithrombotic Trialists Collaboration)



Clopidogrel

Recommended by the ACC/AHA and ESC guidelines in patients with ACS

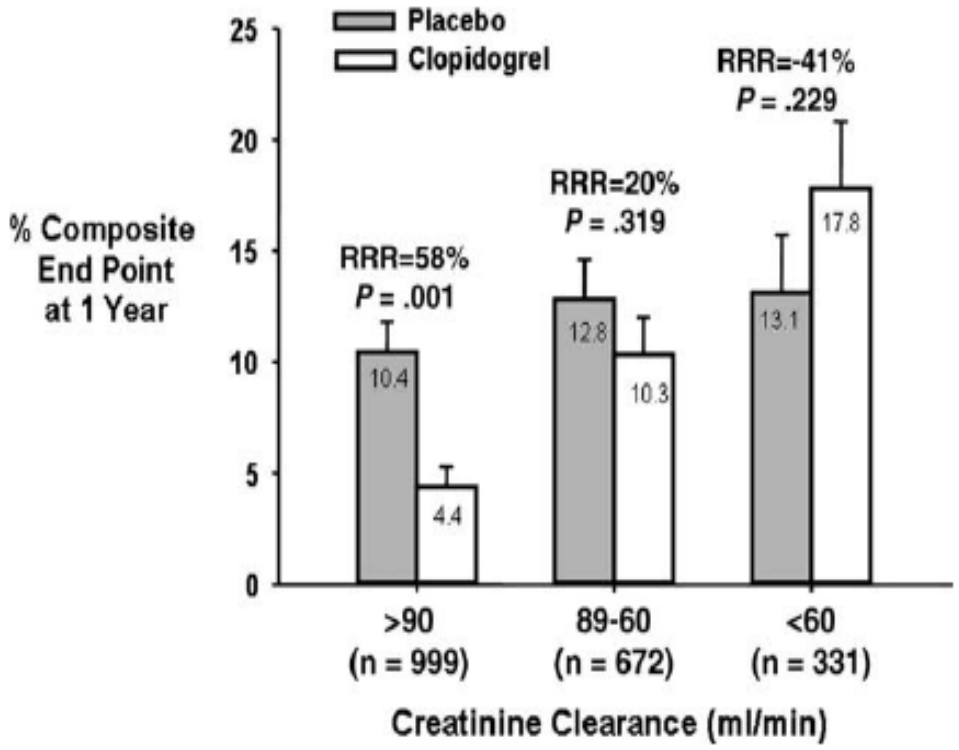
No specific recommendations exist for the adjustment of clopidogrel dosage in renal insufficiency.



The efficacy and safety of short- and long-term dual antiplatelet therapy in patients with mild or moderate chronic kidney disease: Results from the Clopidogrel for the Reduction of Events During Observation (CREDO) Trial

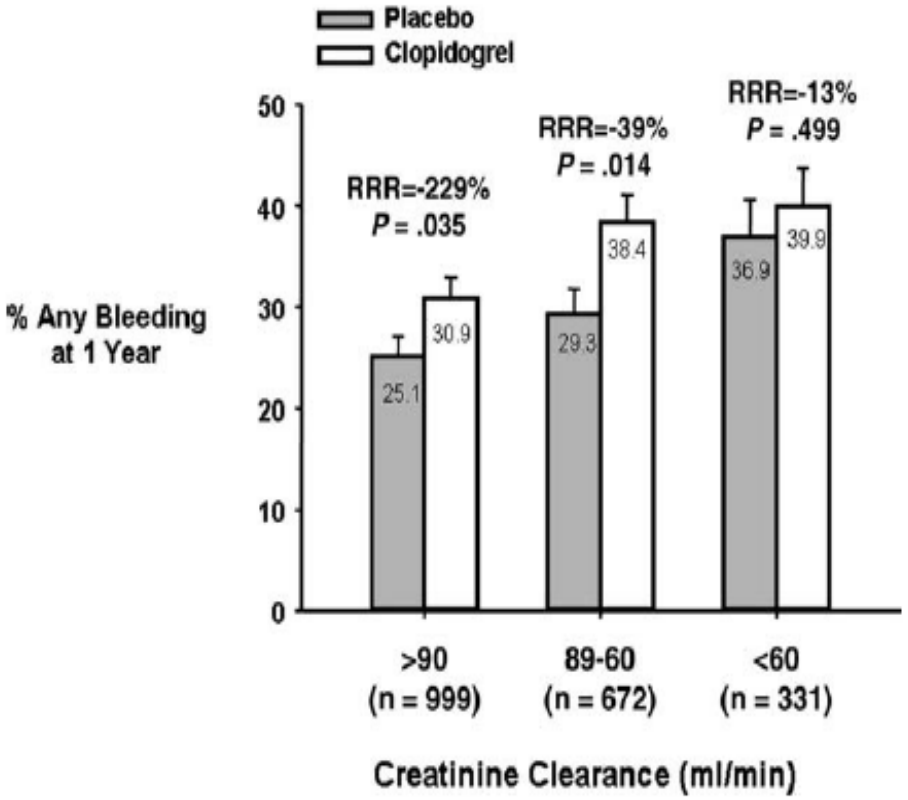
Patricia J.M. Best, MD, Steven R. Steinhubl, MD, Peter B. Berger, MD, Arijit Dasgupta, MD, Danielle M. Brennan, MS, Lynda A. Szczech, MD, Robert M. Califf, MD, and Eric J. Topol, MD for the CREDO Investigators *Rochester, MN*

Figure 2



The effect of clopidogrel therapy on the composite end point of death, myocardial infarction, and stroke at 1 year in all 3 creatinine clearance groups.

Figure 4



The effect of clopidogrel on any bleeding at 1 year in all 3 creatinine clearance groups.

Clinical Outcomes of Patients With Diabetic Nephropathy Randomized to Clopidogrel Plus Aspirin Versus Aspirin Alone (A post hoc Analysis of the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance [CHARISMA] Trial)

Arijit Dasgupta, MD[a,*], Steven R. Steinhubl, MD[b,c], Deepak L. Bhatt, MD, MPH[d], Peter B. Berger, MD[b], Mingyuan Shao, MSc[e], Koon-Hou Mak, MD[f], Keith A.A. Fox, MB, ChB[g], Gilles Montalescot, MD, PhD[h], Michael A. Weber, MD[i], Steven M. Haffner, MD[j], Alexios P. Dimas, MD[k], P. Gabriel Steg, MD[l], and Eric J. Topol, MD[m], for the CHARISMA Investigators

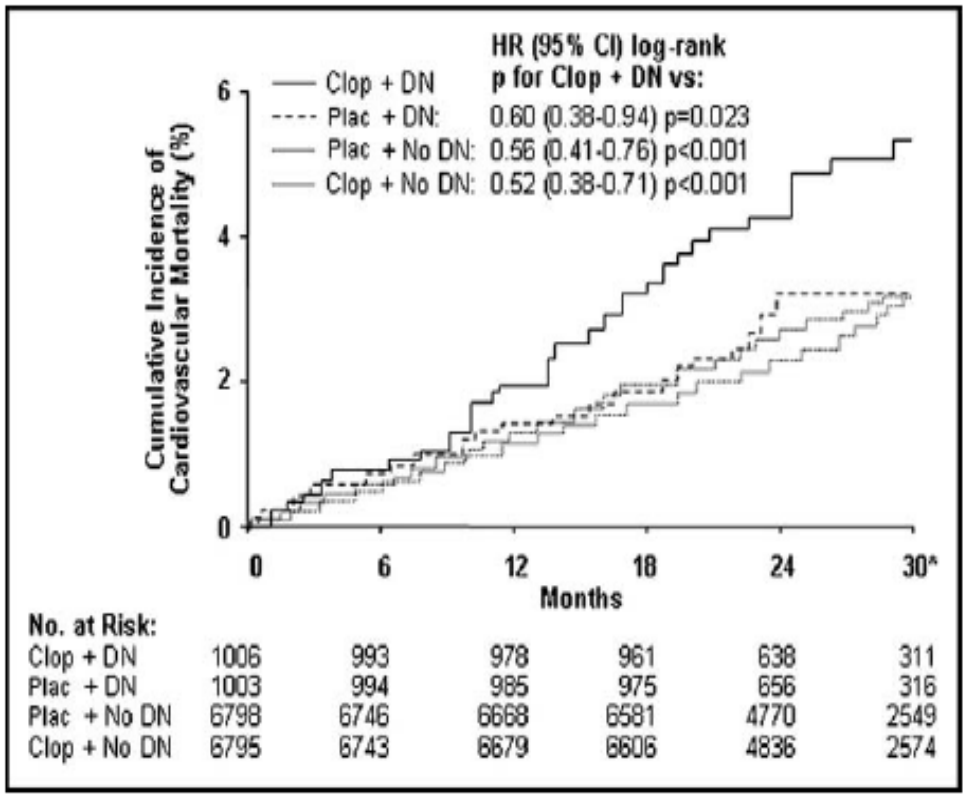


Figure 2. Kaplan-Meier estimates of cumulative incidence of CV mortality. *Kaplan-Meier curves truncated to 30 months. Clop = clopidogrel; DN = diabetic nephropathy; Plac = placebo.

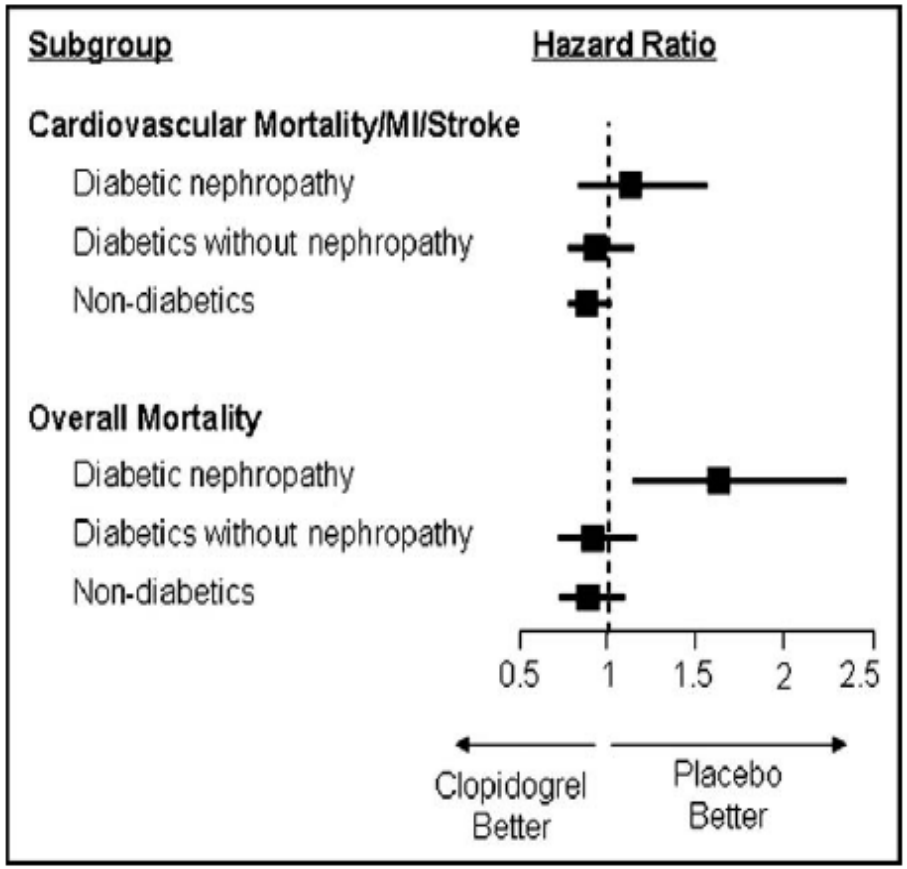


Figure 3. Forest plot of the effect of drug assignment and diabetic nephropathy status on the primary end point and overall mortality.

Table 2. Antiplatelet agents and access thrombosis rate in hemodialysis.

Study	Year	Trial (N)	Intervention	Duration (months)	Access thrombosis rate
Dypiridamole:					
Sreedhara[24]	1994	RCT (N=107)	Dipyridamole 75 mg, aspirin 325 mg, both, placebo Type I: new graft Type II: recurrent thrombosis	72	Type I: 17% vs. 50% vs. 23% vs. 32% Type II: 83% vs. 50% vs. 100% vs. 80%
Dixon[25]	2009	RCT (N=649)	Dipyridamole 200 mg + aspirin 25 mg vs. placebo	60	40% vs. 42%
Aspirin:					
Kooistra[26]	1994	RCT crossover (N=153)	Aspirin 30 mg vs. placebo	3	16% (9.4% aspirin vs. 6.5% placebo, NS)
Clopidogrel:					
Trimarchi[36]	2005	Prospective (N=24)	Clopidogrel 75 mg vs. no antithrombotic therapy	Until diagnosis of thrombosis	8% vs. 92% (p=0.001)
Dember[37]	2008	RCT (N=877)	Clopidogrel (300 mg LD and 75 mg daily) vs. placebo	5 after AVF creation or 1 after dialysis initiation	12.2% vs. 19.5% (p=0.018)
Kaufman[38]	2003	RCT (N=200)	Clopidogrel 75 mg + aspirin 325 mg vs. double placebos	24	HR 0.81 (95% CI: 0.47-1.40) in favor of aspirin and clopidogrel therapy, (p=0.45)

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Table 2. Fistula Thrombosis

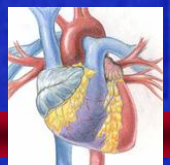
	No. (%) of Patients		
	Clopidogrel (n = 435)[a]	Placebo (n = 431)[a]	Relative Risk (95% Confidence Interval)[b]
Thrombosis at 6 wk (all patients)	53 (12.2)	84 (19.5)	0.63 (0.46-0.97)[c]
By location			
Forearm fistula	31 (12.9)	60 (24.7)	0.53 (0.36-0.77)
Upper arm fistula	22 (11.3)	24 (12.8)	0.89 (0.52-1.53)

[a] Six of the 441 patients randomized to clopidogrel and 5 of the 436 patients randomized to placebo were not included because patency was not evaluated.

[b] Relative risks were stratified for fistula location and center.

[c] The 95% confidence interval reported is the repeated confidence interval adjusted for interim monitoring. The repeated *P* value adjusted for interim monitoring is .018.

Dember, JAMA 2008: 299:2164



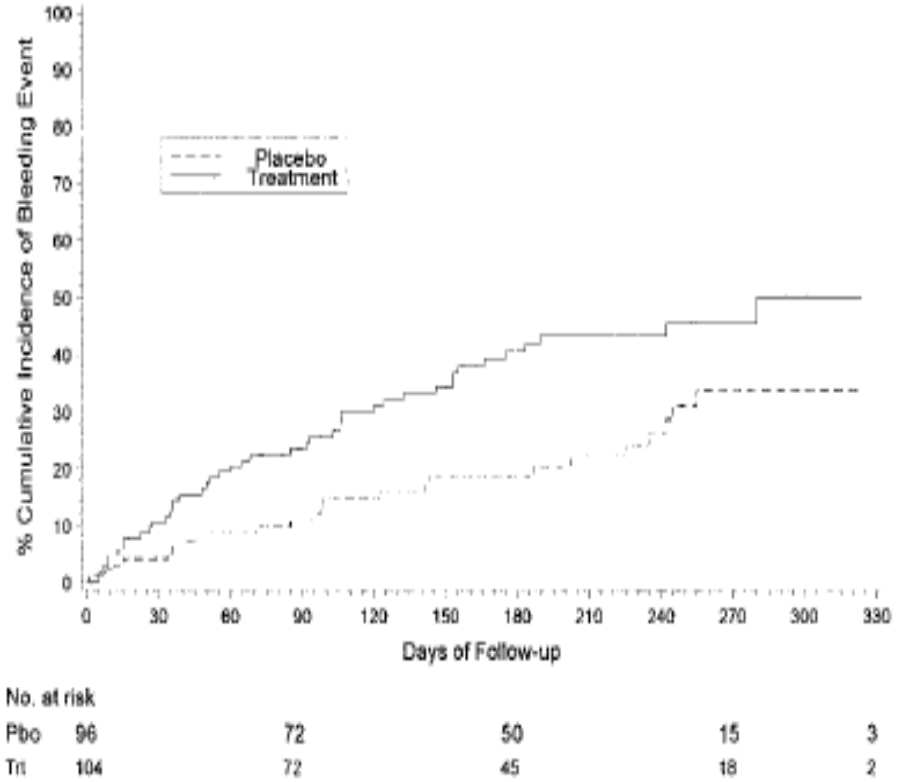


Figure 1. Cumulative incidence of first bleeding events. The incidence was significantly ($P = 0.007$) greater for the aspirin/clopidogrel-treated group [hazard ratio, 1.98; 95% confidence interval (CI), 1.19 to 3.28]. Pbo, placebo; Trt, treatment.

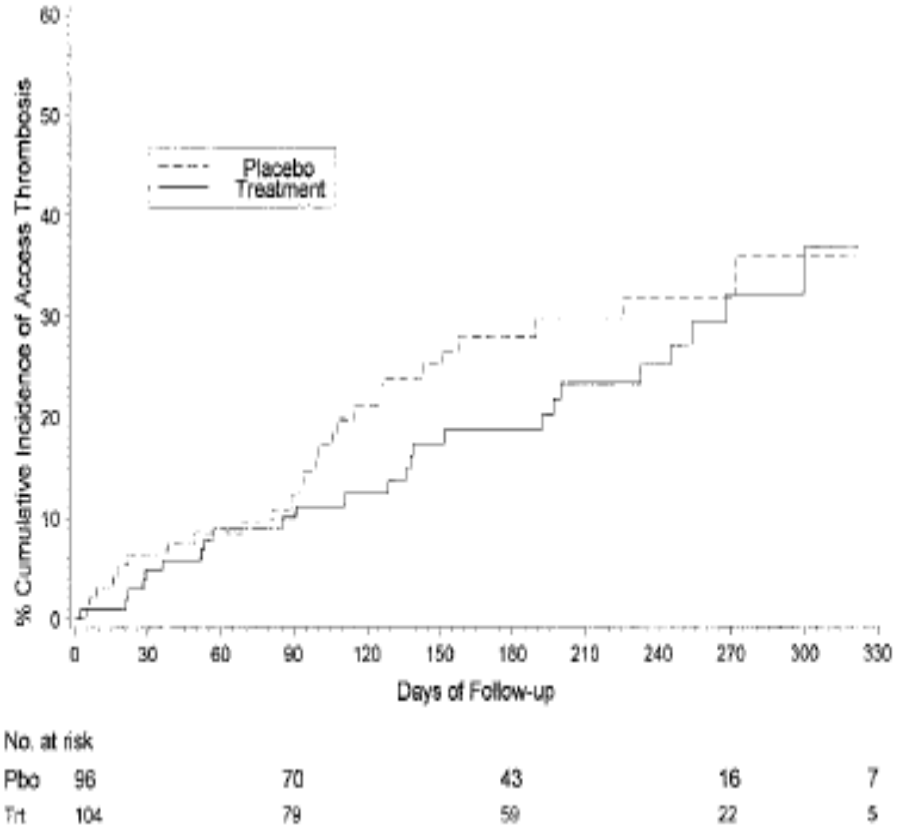


Figure 2. Cumulative incidence of first graft thromboses. The incidences were not significantly different ($P = 0.45$) for the two groups (hazard ratio, 0.81; 95% CI, 0.49 to 1.40). Pbo, placebo; Trt, treatment.

Kaufman JS et al, JASNE 2003, 14:2313

Journal of Thrombosis and Thrombolysis 10,127–131,2000.

A Pharmacodynamic Study of Clopidogrel in Chronic Hemodialysis Patients

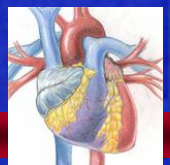
James S. Kaufman,[1] Louis Fiore,[2] James A. Hasbargen,[3] Theresa Z. O'Connor,[4] and Gilles Perdriset[5]

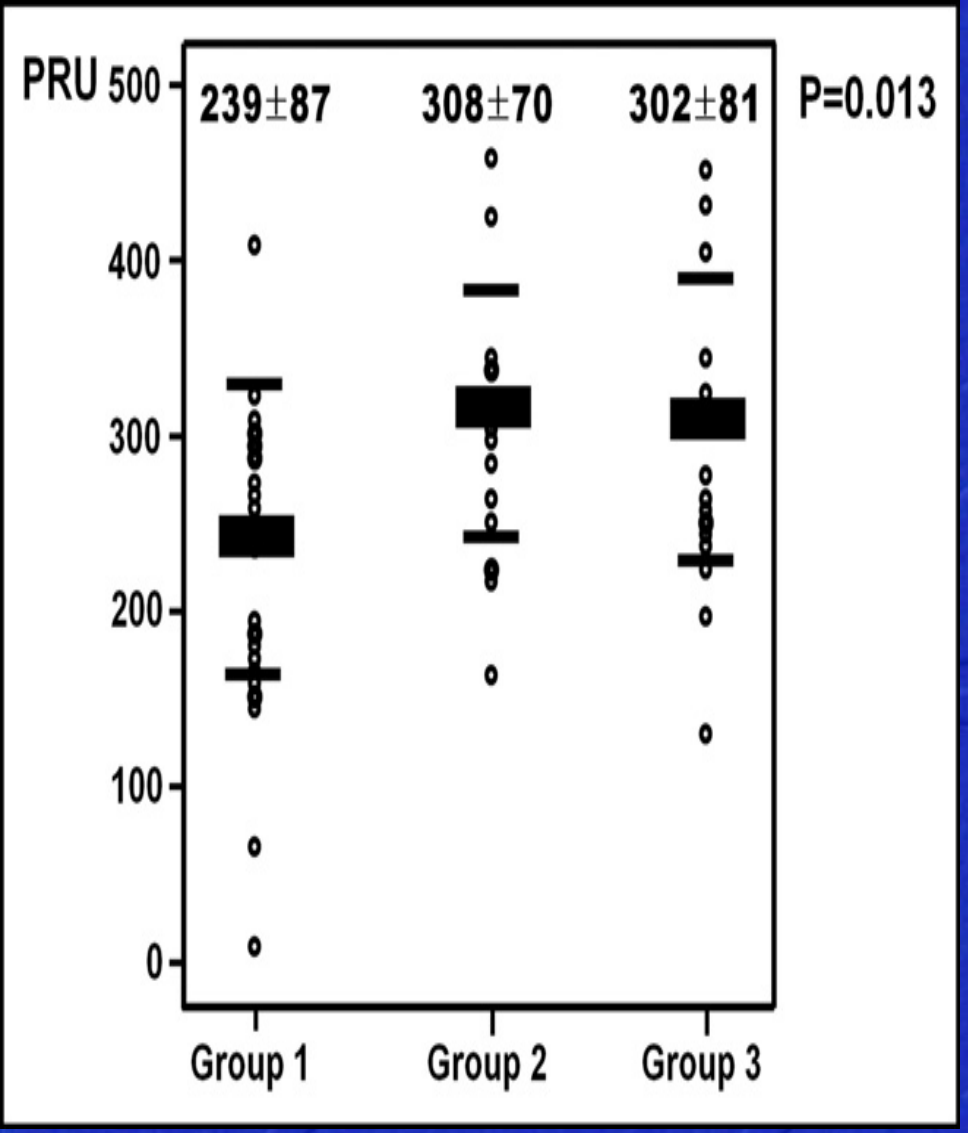
9 chronic HD patients were studied.
Baseline platelet aggregation studies
Clopidogrel 75mg daily for 14 days.
Platelet aggregation studies
Drug stopped -final set of platelet aggregation studies 7 days later.

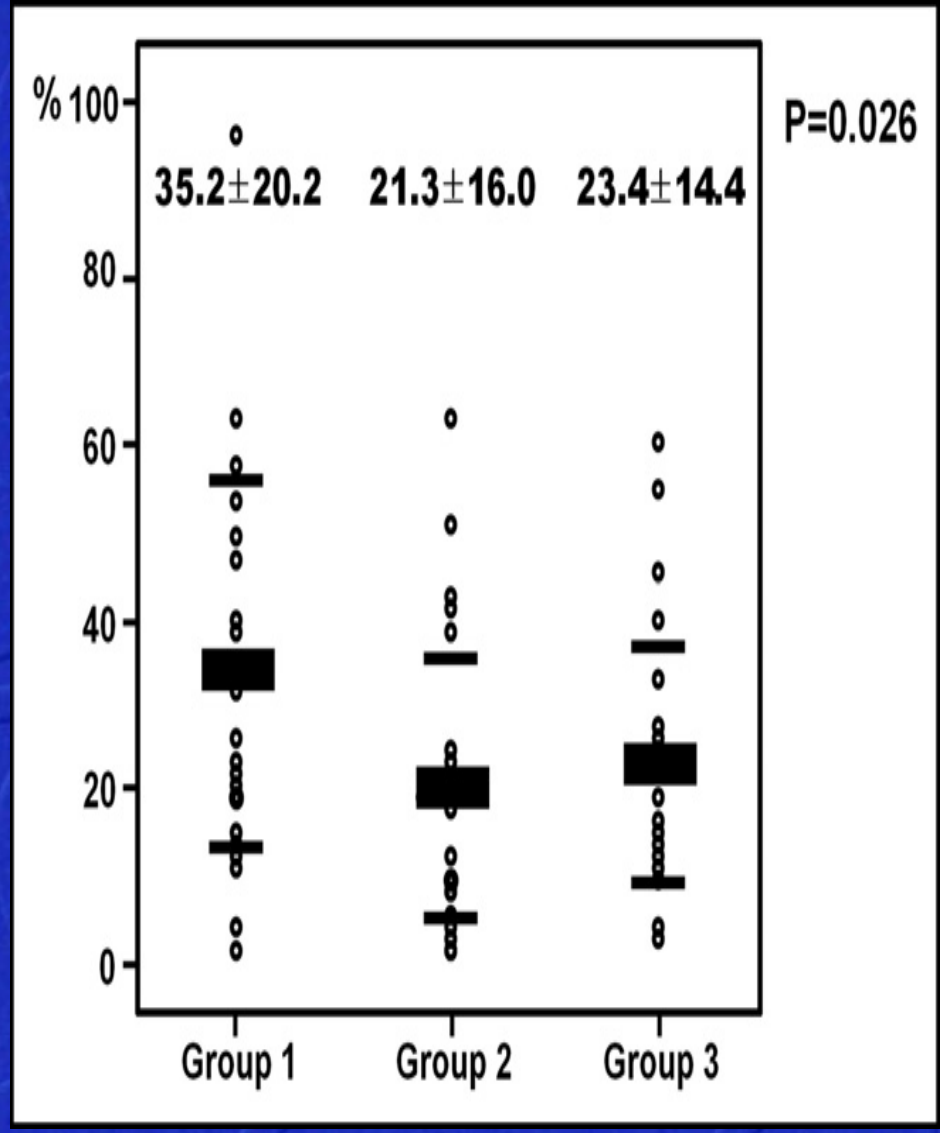
ADP-induced platelet aggregation was inhibited from 48 to 23% with ADP 2mM (P.0.0113), from 59 to 38% with ADP 5mM (P.0.0166), and from 66 to 44% with ADP 10mM (P.0.0172).

This inhibition was reversed 7 days after stopping clopidogrel.

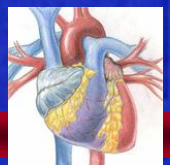
No adverse reactions were noted. No patient had evidence of bleeding, rash or gastro-intestinal (GI) upset







Park SH et al, *Am J Cardiol*. 2009; 104: 1292



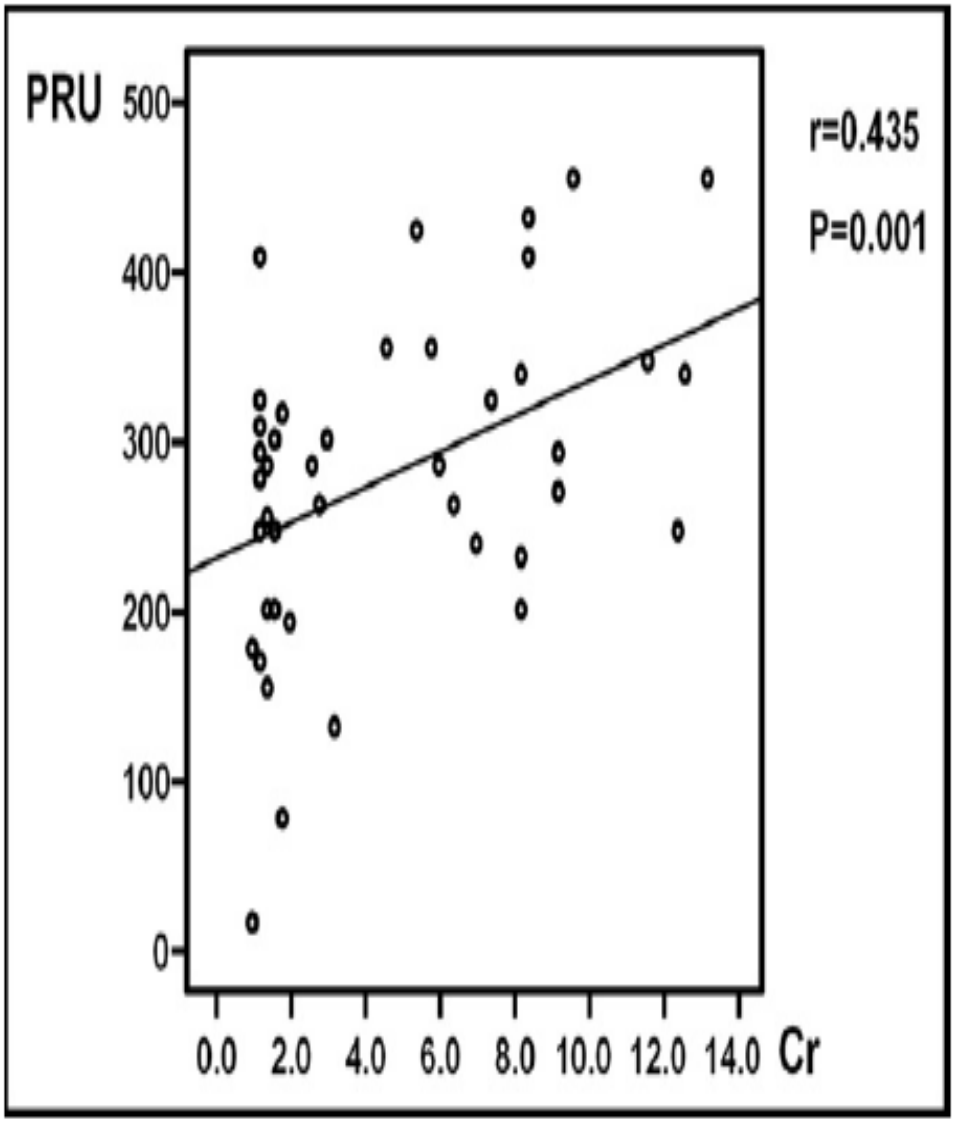


Figure 3. Correlation of creatinine (Cr) with PRU.

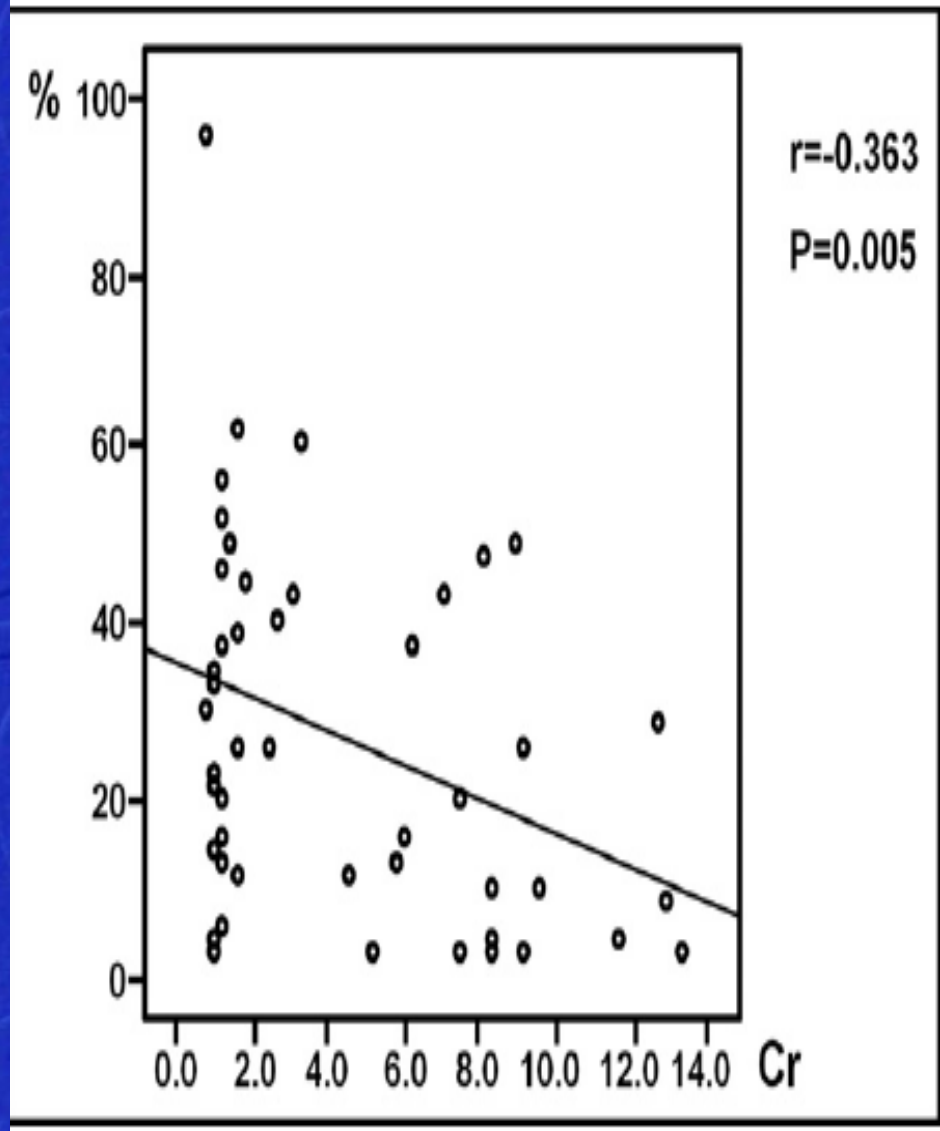


Figure 4. Correlation of creatinine (Cr) with percentage of inhibition.

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doi:10.1016/j.jacc.2009.10.043

Impact of Chronic Kidney Disease on Platelet Function Profiles in Diabetes Mellitus Patients With Coronary Artery Disease Taking Dual Antiplatelet Therapy

Dominick J. Angiolillo, MD, PHD,* Esther Bernardo, BSC,† Davide Capodanno, MD,* David Vivas, MD,† Manel Sabaté, MD, PHD,† José Luis Ferreiro, MD,* Masafumi Ueno, MD,* Pilar Jimenez-Quevedo, MD, PHD,† Fernando Alfonso, MD, PHD,† Theodore A. Bass, MD,* Carlos Macaya, MD, PHD,† Antonio Fernandez-Ortiz, MD, PHD†

Jacksonville, Florida; and Madrid, Spain

Objectives We sought to assess the impact of renal function on platelet reactivity in patients with diabetes mellitus (DM) and coronary artery disease on aspirin and clopidogrel therapy.

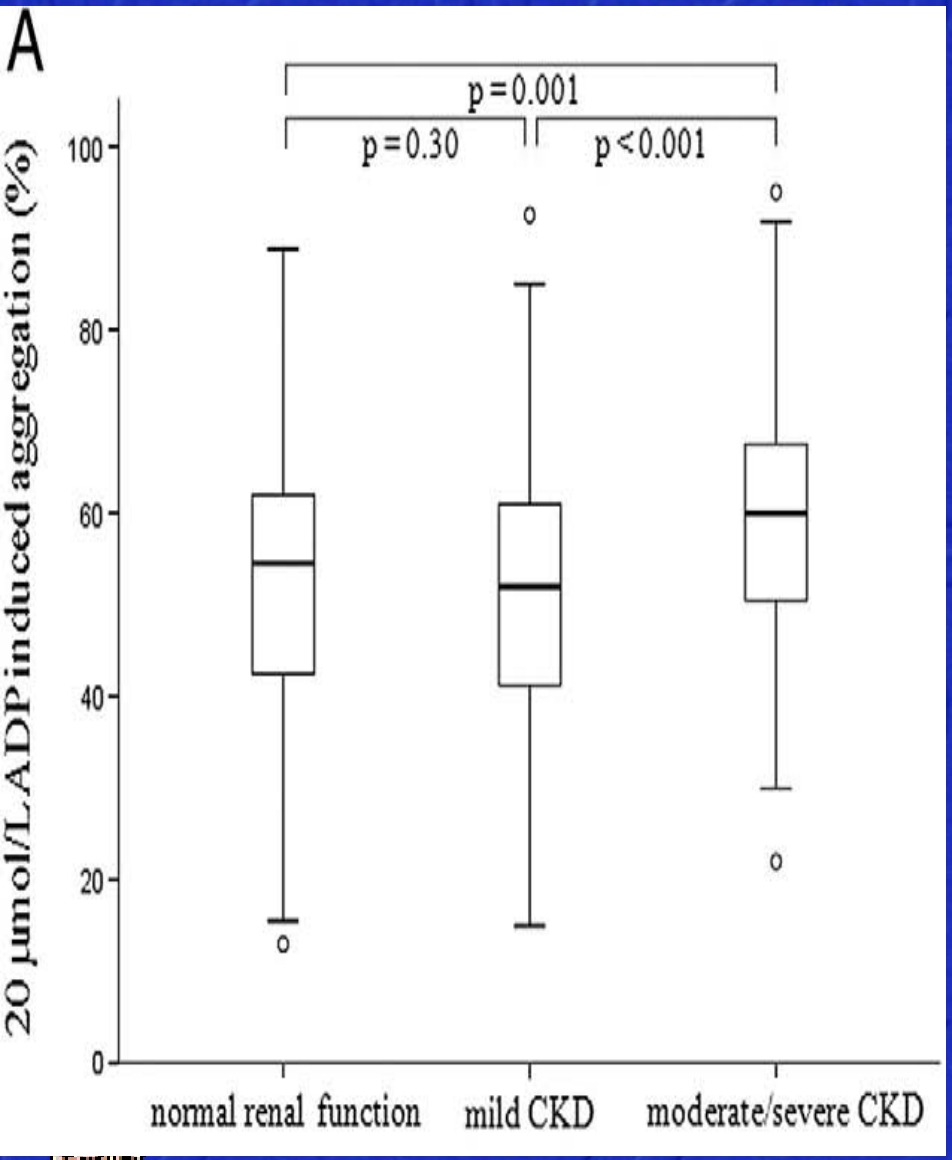
Background Diabetes mellitus is a key risk factor for chronic kidney disease (CKD). In aspirin-treated DM patients the presence of moderate/severe CKD is associated with reduced clinical efficacy of adjunctive clopidogrel therapy. Whether these findings may be attributed to differences in clopidogrel-induced effects is unknown.

Methods This was a cross-sectional observational study in which DM patients taking maintenance aspirin and clopidogrel therapy were studied. Patients were categorized into 2 groups according to the presence or absence of moderate/severe CKD. Platelet aggregation after adenosine diphosphate (ADP) and collagen stimuli were assessed with light transmittance aggregometry and defined patients with high post-treatment platelet reactivity (HPPR). Markers of platelet activation, including glycoprotein IIb/IIIa activation and P-selectin expression, were also determined using flow cytometry.

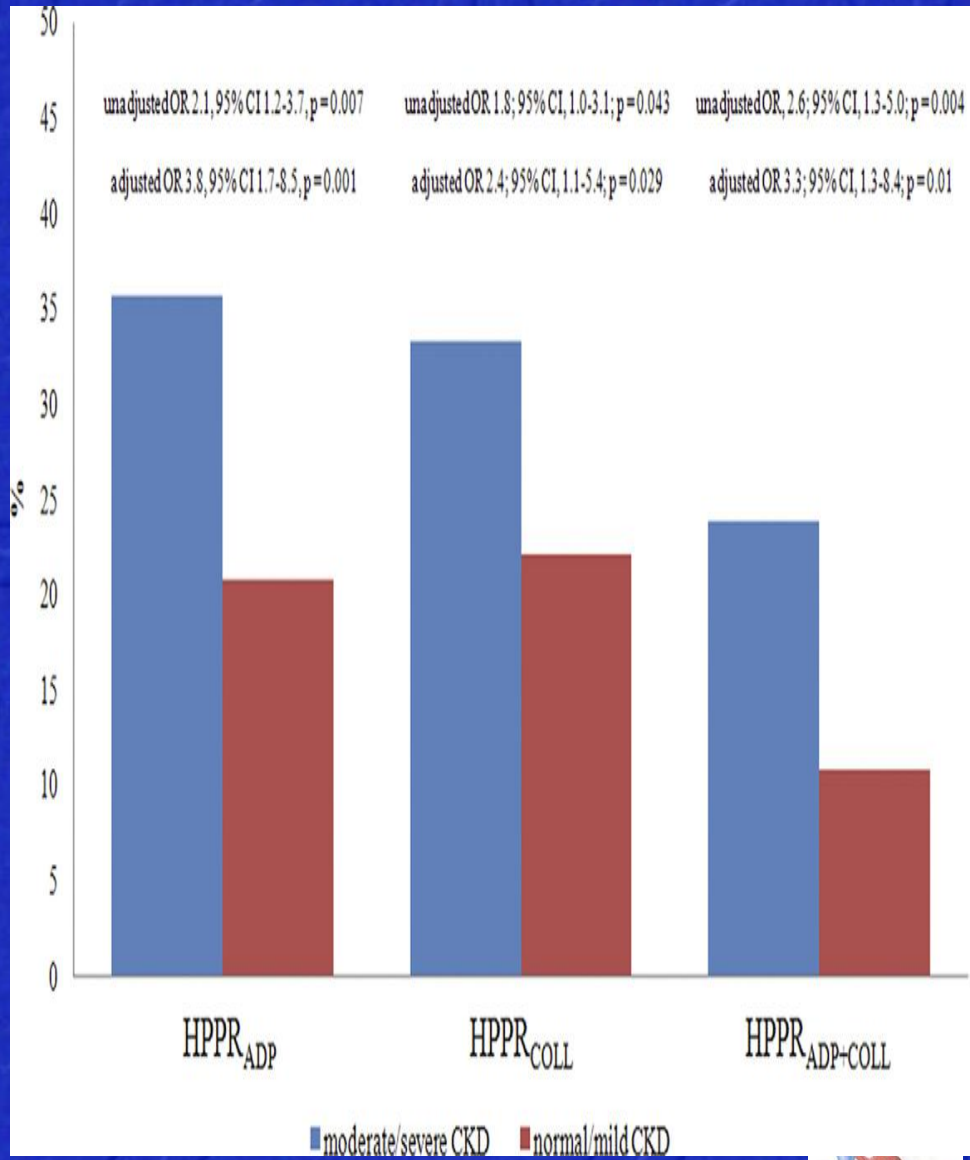
Results A total of 306 DM patients were analyzed. Patients with moderate/severe CKD ($n = 84$) had significantly higher ADP-induced ($60 \pm 13\%$ vs. $52 \pm 15\%$, $p = 0.001$) and collagen-induced ($49 \pm 20\%$ vs. $41 \pm 20\%$, $p = 0.004$) platelet aggregation compared with those without ($n = 222$). After adjustment for potential confounders, patients with moderate/severe CKD were more likely to have HPPR after ADP (adjusted odds ratio: 3.8, 95% confidence interval: 1.7 to 8.5, $p = 0.001$) and collagen (adjusted odds ratio: 2.4; 95% confidence interval: 1.1 to 5.4; $p = 0.029$) stimuli. Markers of platelet activation were significantly increased in patients with HPPR.

Conclusions In DM patients with coronary artery disease taking maintenance aspirin and clopidogrel therapy, impaired renal function is associated with reduced clopidogrel-induced antiplatelet effects and a greater prevalence of HPPR. (J Am Coll Cardiol 2010;55:1139–46) © 2010 by the American College of Cardiology Foundation

Platelet Aggregation According to Renal Function

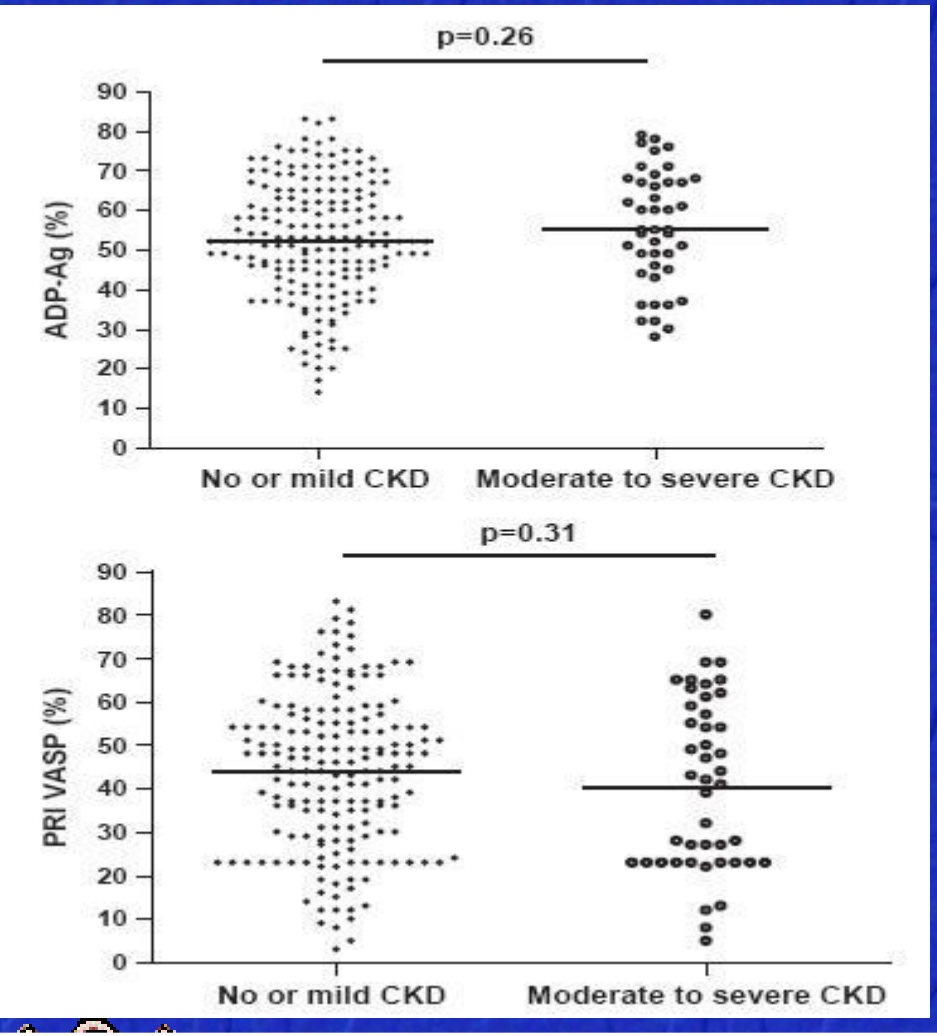


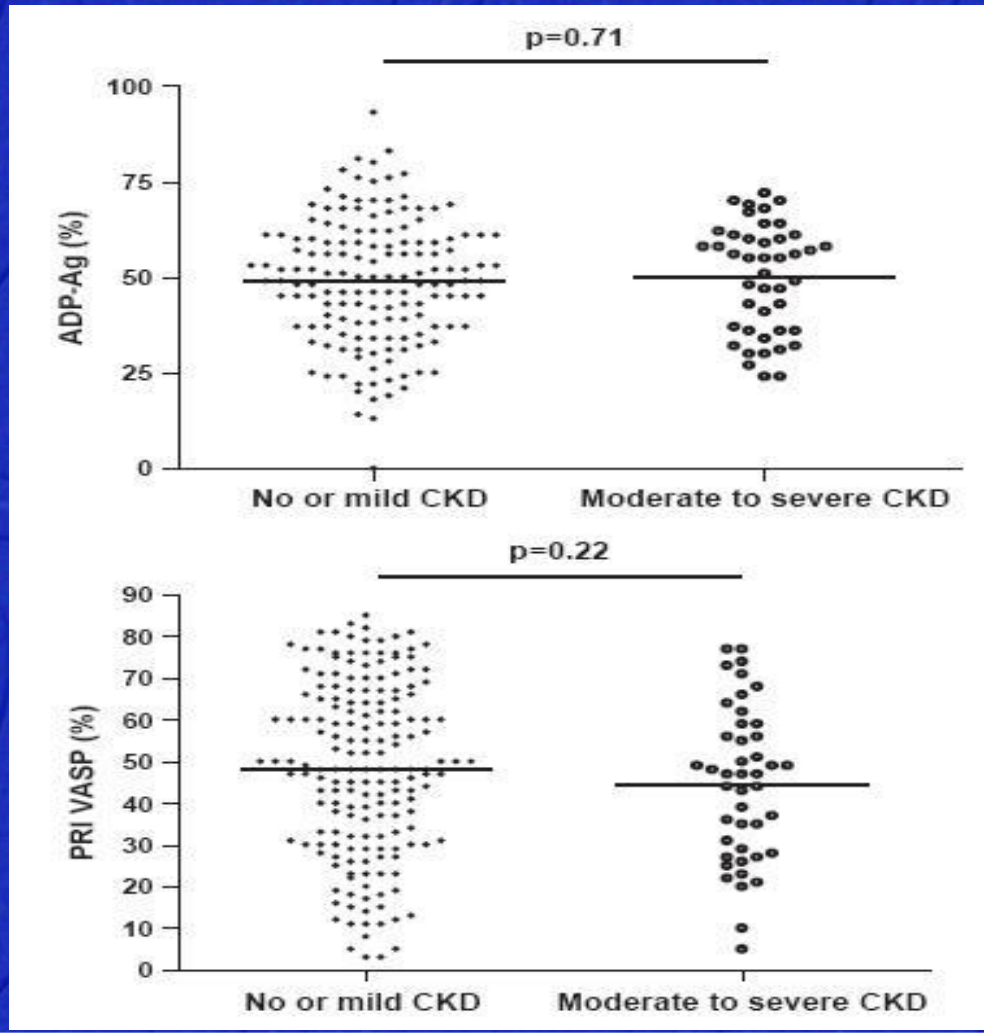
Prevalence of Moderate/Severe CKD and Normal Renal Function/Mild CKD in Patients With HPPR



Initial Clopidogrel response according to renal function after a 600 mg loading dose.

One month Clopidogrel response according to renal function after a 150 mg maintenance dose.





Lack of effect of chronic kidney disease on clopidogrel response with high loading and maintenance doses of clopidogrel after Acute Coronary Syndrome

Cuisset T, et al. *Thromb Res*. 2010; 126: e400-402.

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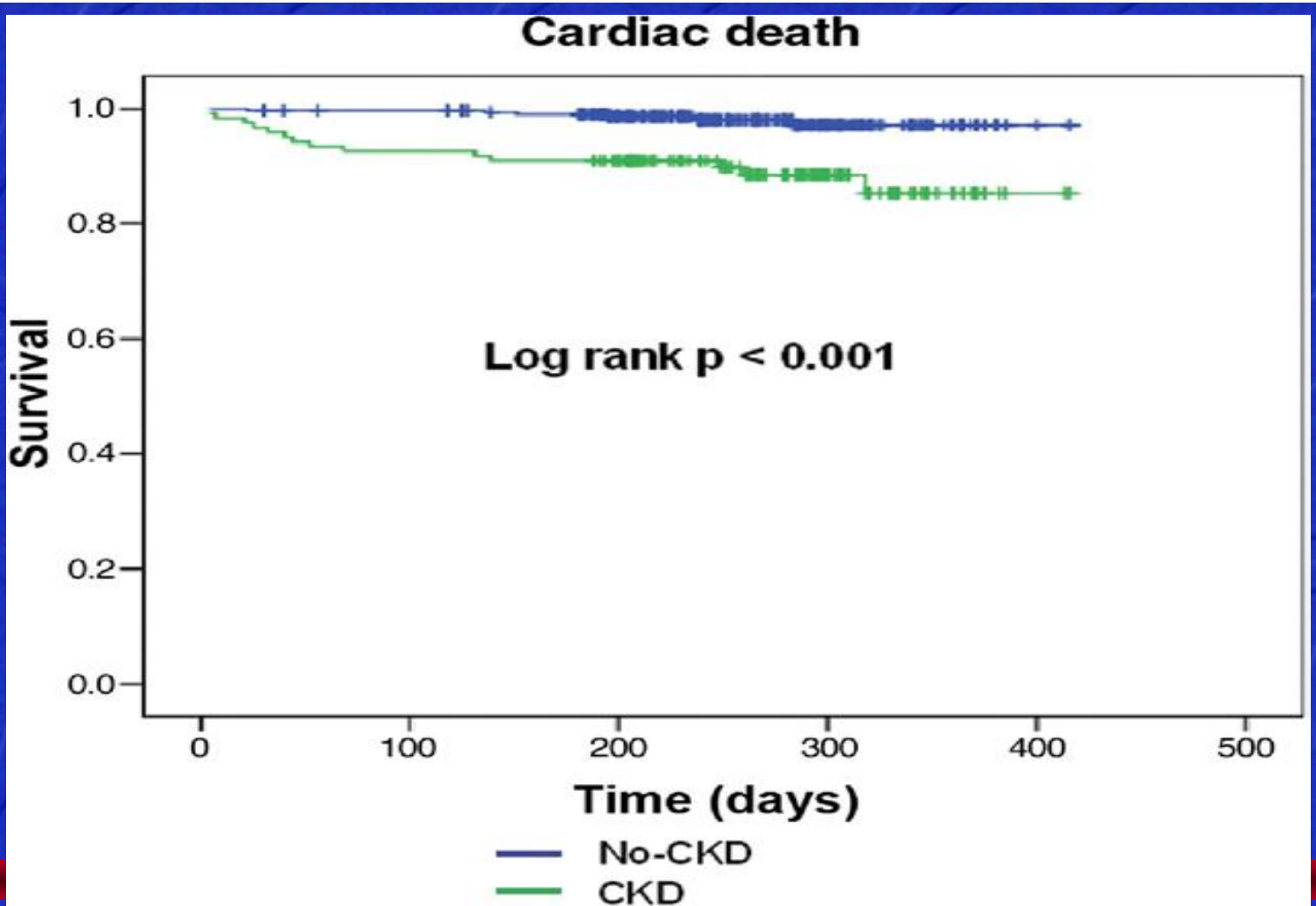
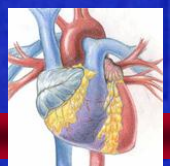
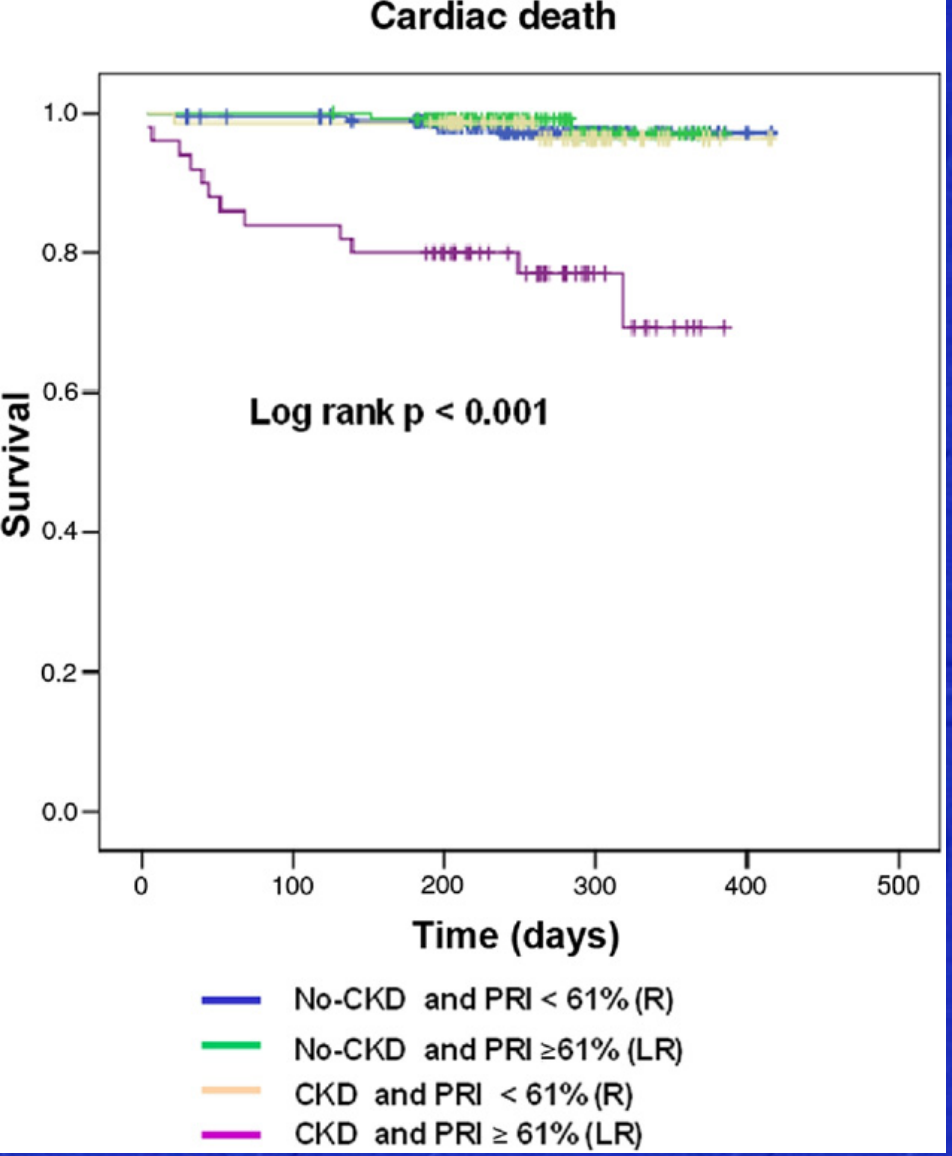
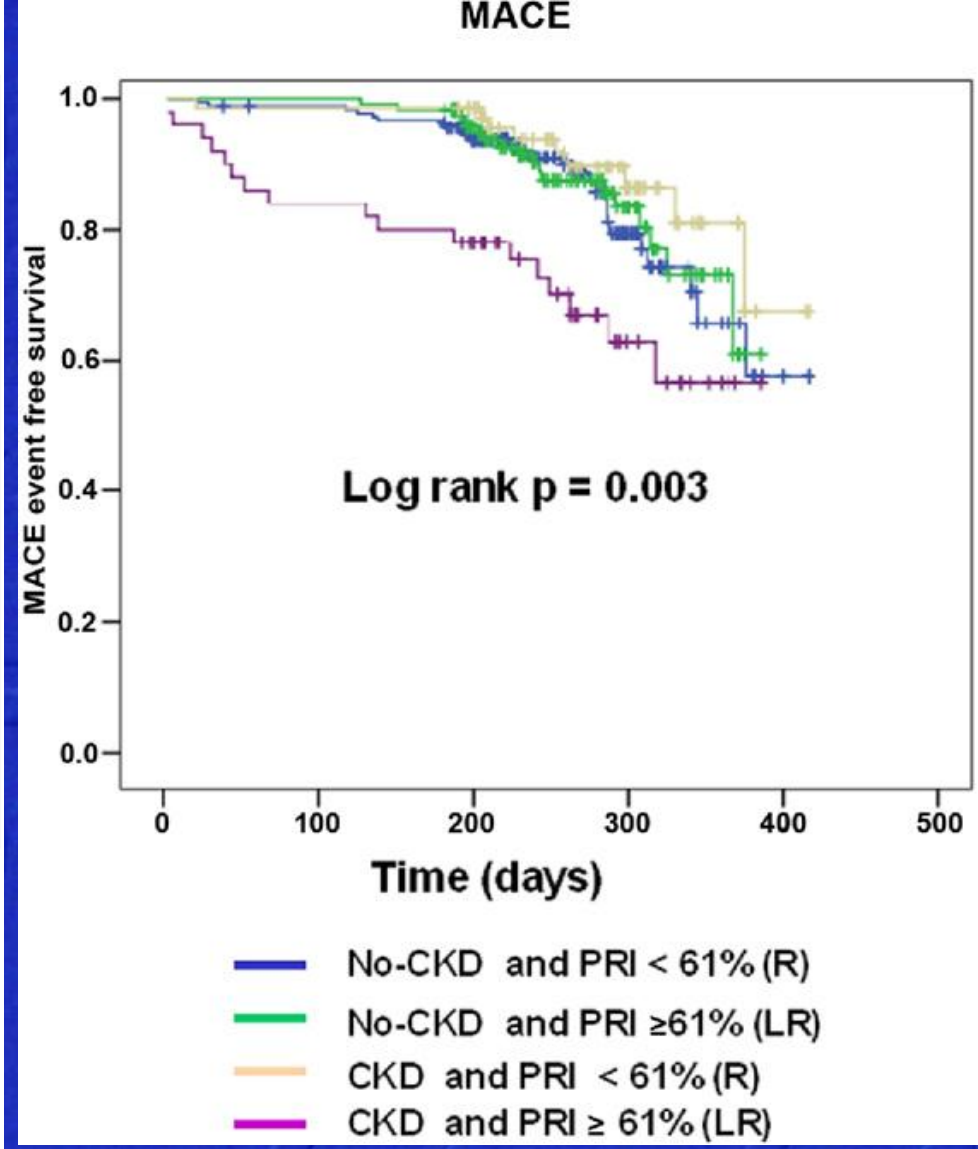
Cardiovascular Mortality in Chronic Kidney Disease Patients Undergoing Percutaneous Coronary Intervention Is Mainly Related to Impaired $P2Y_{12}$ Inhibition by Clopidogrel

Olivier Morel, MD, PHD,*† Soraya El Ghannudi, MD,* Laurence Jesel, MD,* Bogdan Radulescu, MD,* Nicolas Meyer, MD, PHD,‡ Marie-Louise Wiesel, MD,§ Sophie Caillard, MD, PHD,‖ Umberto Campia, MD,¶ Bruno Moulin, MD, PHD,‖ Christian Gachet, MD, PHD,§ Patrick Ohlmann, MD, PHD*

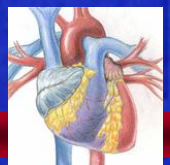


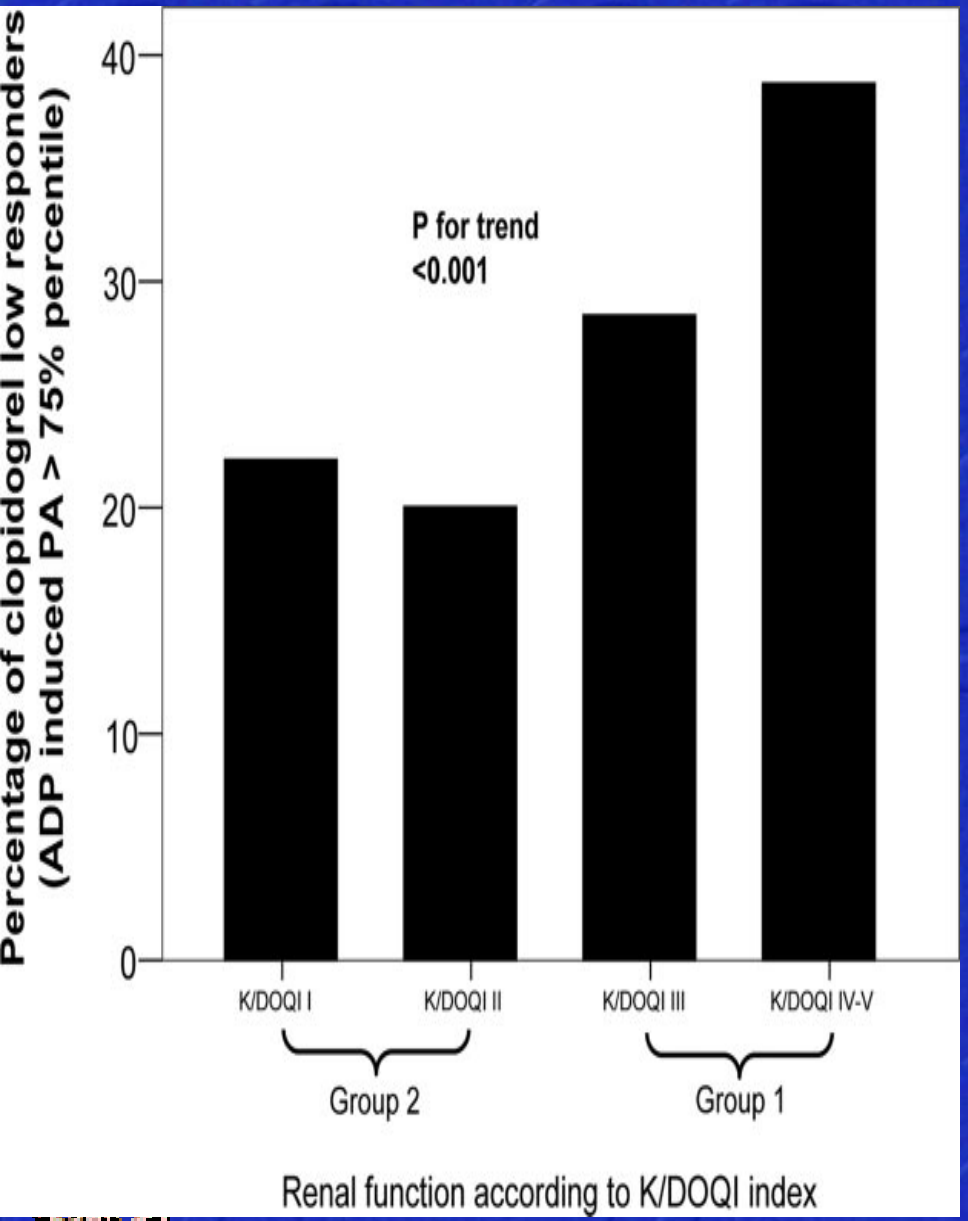


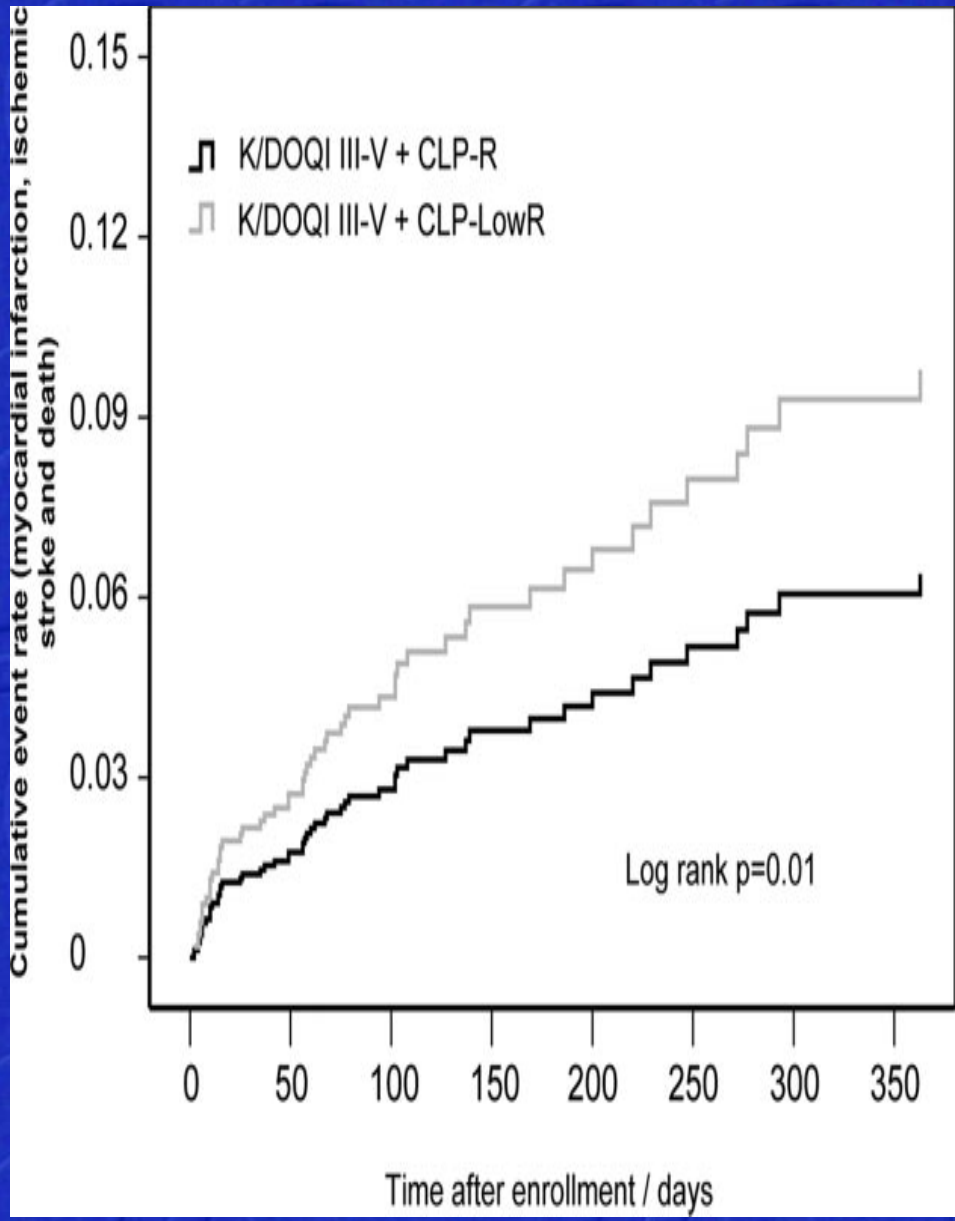




Morel O, et al *J Am Coll Cardiol*. 2011; 57: 399-408







Htun P, et al. *J Am Soc Nephrol*. 2011; 22: 627-633

AJKD

Correspondence

RESEARCH LETTER

Prevalence of Inadequate Platelet Inhibition by Clopidogrel in Patients Receiving Hemodialysis

To the Editor:

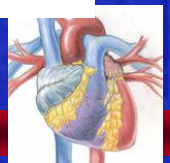
A variable antiplatelet response to clopidogrel is a well-recognized phenomenon studied mostly in patients with percutaneous coronary intervention (PCI), for whom high on-treatment platelet reactivity is associated with an elevated risk of adverse events, including stent thrombosis. Patients undergoing maintenance hemodialysis (HD) therapy present enhanced platelet reactivity, and clopidogrel often is prescribed to prevent atherothrombotic or, specifically, vascular access thrombotic complications.[1,2] However, few and contradictory data for clopidogrel's platelet inhibitory effect in HD patients are available.[3,4] In a randomized comparison of prasugrel versus high clopidogrel in HD patients,[5] we identified 21 of 25 (84%) with high on-treatment platelet reactivity. In the present prospective multicenter study, we extend this observation by defining the prevalence of high on-treatment platelet reactivity in a larger number of HD patients.

In one tertiary center and 2 regional hospitals, all maintenance HD patients receiving ongoing (≥2 months) treatment with clopi-

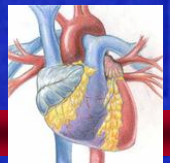
dogrel, 75 mg/d, were approached for platel
ment. Exclusion criteria included long-term
treatment, acute coronary syndrome, hemo
PCI or coronary artery bypass grafting withi
count $<100 \times 10^3/\mu L$, and hematocrit <28%
blood samples were drawn with a loose tourni
venous catheter inserted into a forearm vein
HD. Platelet-function testing was performed
(Accumetrics Inc, www.accumetrics.com) p
assay. Results are reported as P2Y12 reactio
≥235 PRU considered high on-treatment pl
used Fisher exact test and 2-sample *t* test to ana
normally distributed continuous data and Man
data with skewed distribution (presented as
several log-binomial models did not converge
Poisson regression models with a robust estim
mates the log-binomial maximum likelihood
the crude relative risks of clopidogrel hyp
various patient characteristics. A final multipl
model (enter method) was fitted including all
related to clopidogrel hyporesponsiveness st
level in univariate analyses. All tests were 2 t

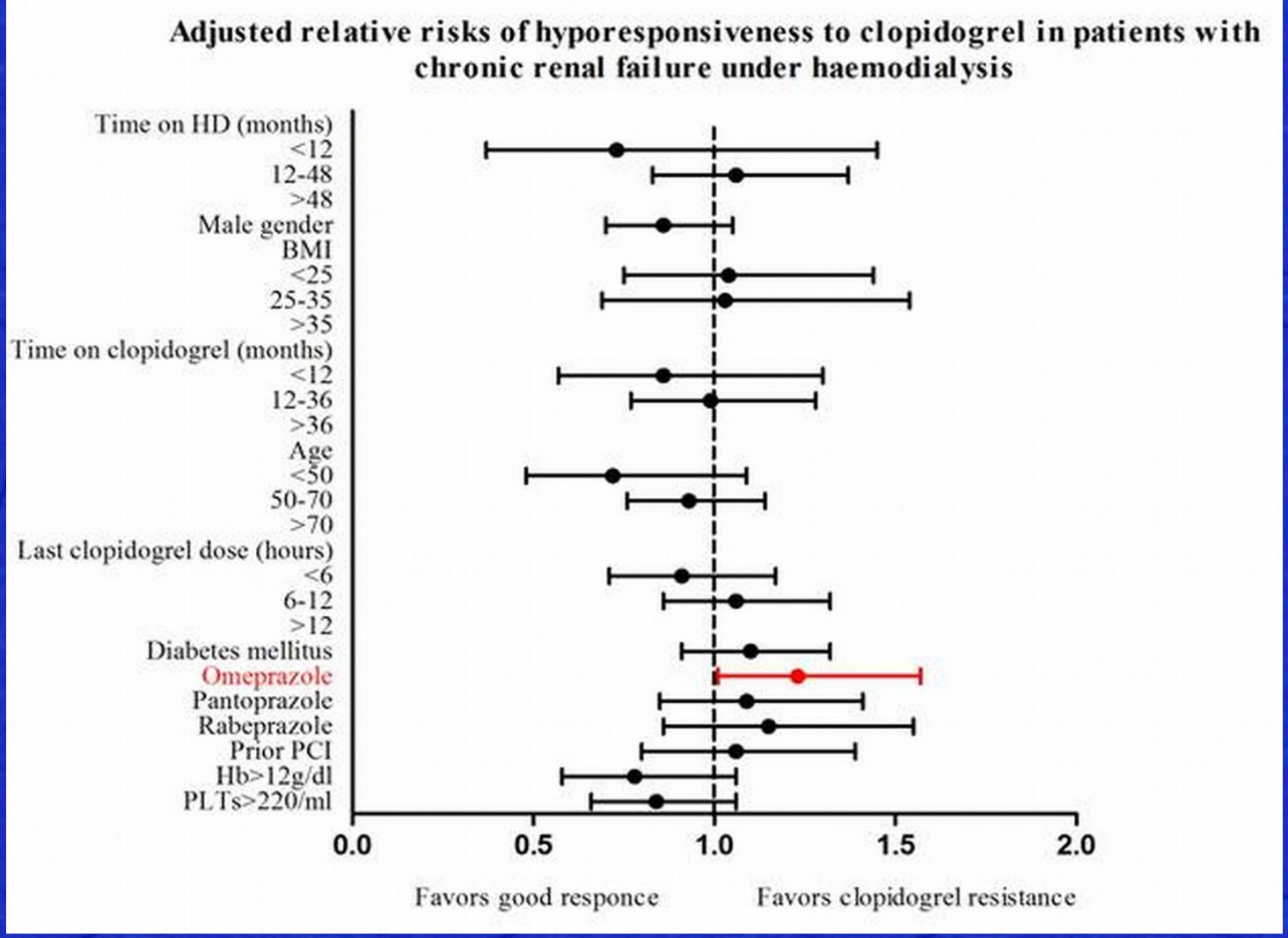
Alexopoulos D, et al, Dec 10, 2011

Patras University Hospital



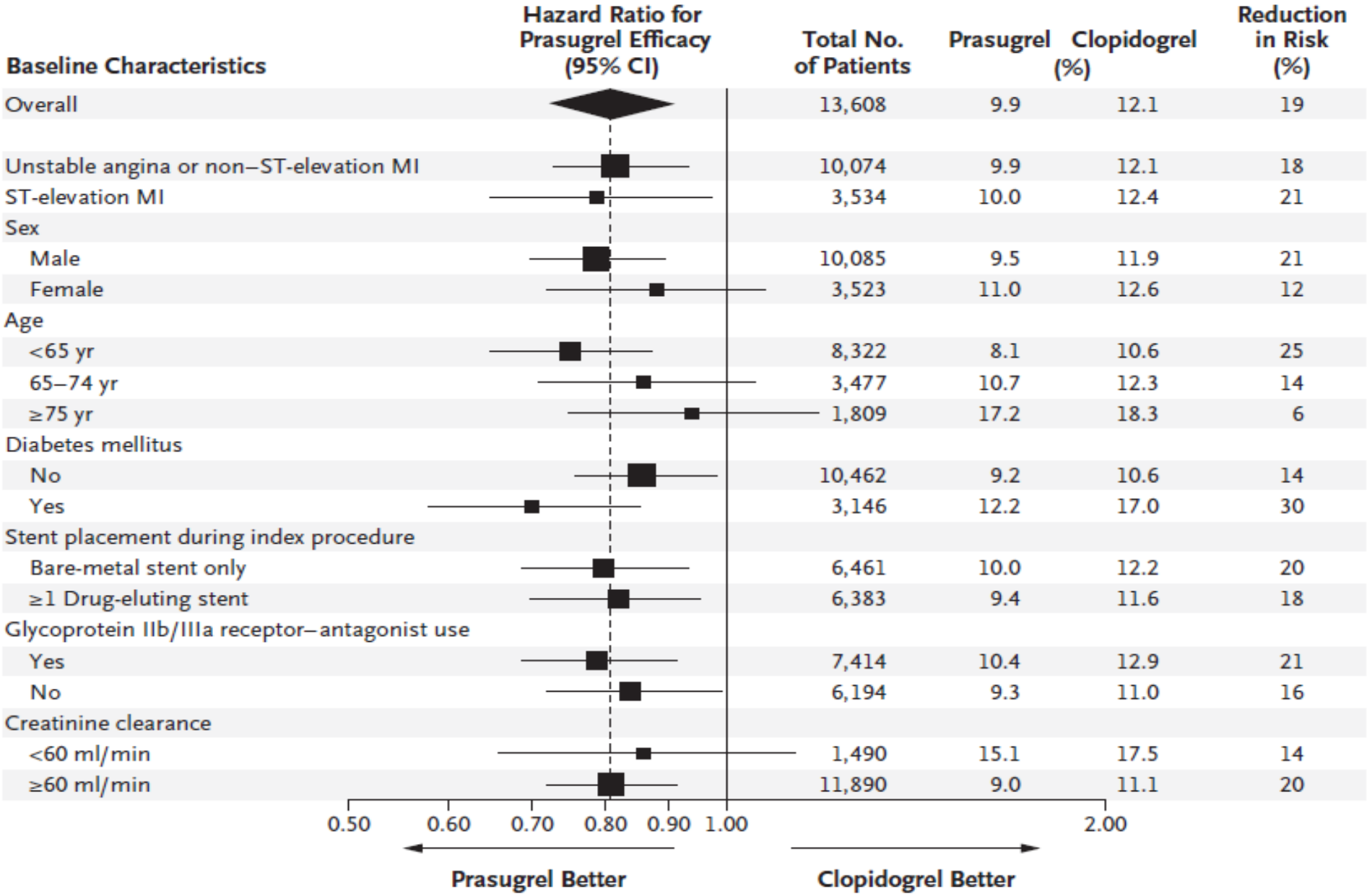
- Out of 85 screened HD patients, 70 patients (82.4%) exhibited HTPR.
- The mean PR for the overall cohort was 294.5±69.2 PRU.





In multivariate analysis (Poisson regression model) , the use of omeprazole was independently associated with a higher risk for HTPR (Relative risk=1.23, 95% CI 1.01-1.57, p=0.04).

Prasugrel TRITON- TIMI 38



Journal of Clinical Pharmacy and Therapeutics (2009) 34, 585–594 doi:10.1111/j.1365-2710.2009.01068.x

PHARMACOKINETICS

Prasugrel pharmacokinetics and pharmacodynamics in subjects with moderate renal impairment and end-stage renal disease

D. S. Small* PhD, R. E. Wrishko* PhD, C. S. Ernest II* MS, L. Ni* PhD, K. J. Winters* MD, N. A. Farid* PhD, Y. G. Li* MS, J. T. Brandt* MD, D. E. Salazar† PhD, A. G. Borel* PhD, K. A. Kles* PhD and C. D. Payne‡ MS

Eli Lilly and Company, Indianapolis, IN, USA, †Daiichi Sankyo, Inc., Parsippany, NJ, USA and ‡Eli Lilly and Company, Windlesham, UK

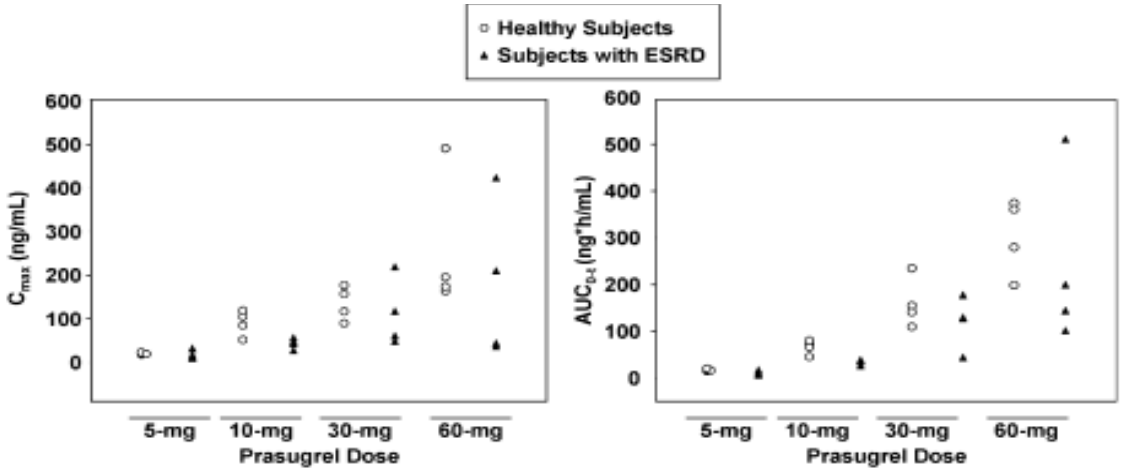
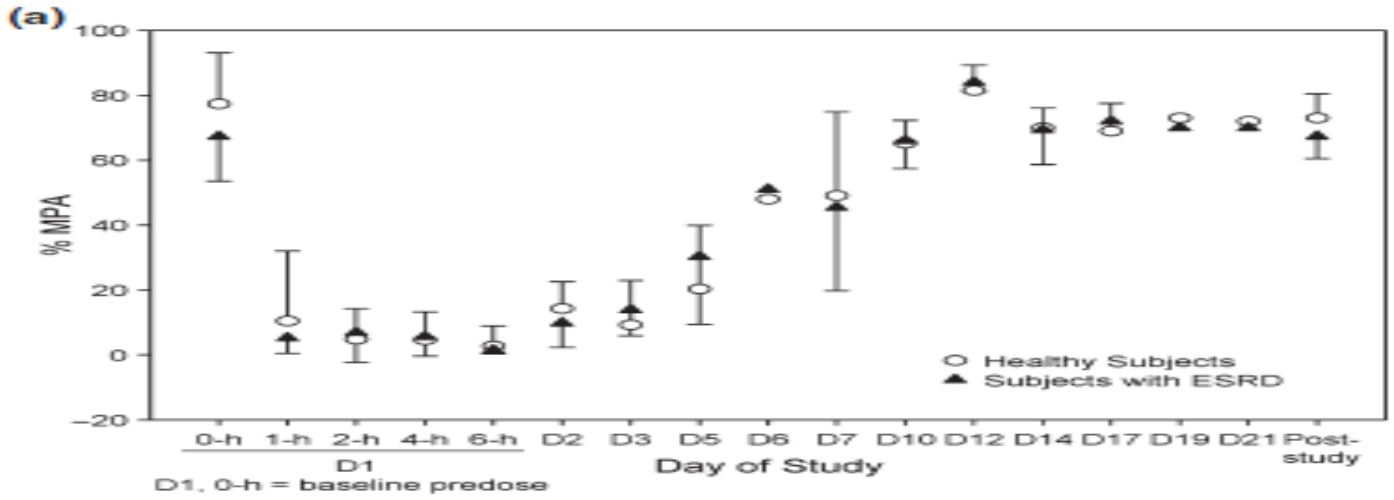


Fig. 3. C_{max} and AUC following prasugrel doses in subjects with ESRD and healthy matched subjects from Study 3.



Journal of Thrombosis and Haemostasis, 9: 1–8 DOI: 10.1111/j.1538-7836.2011.04531.x

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,* P. DAVLOUROS,* C. FOURTOUNAS† and D. GOUMENOS†
*Departments of *Cardiology; and †Nephrology, Patras University Hospital, Patras, Greece*

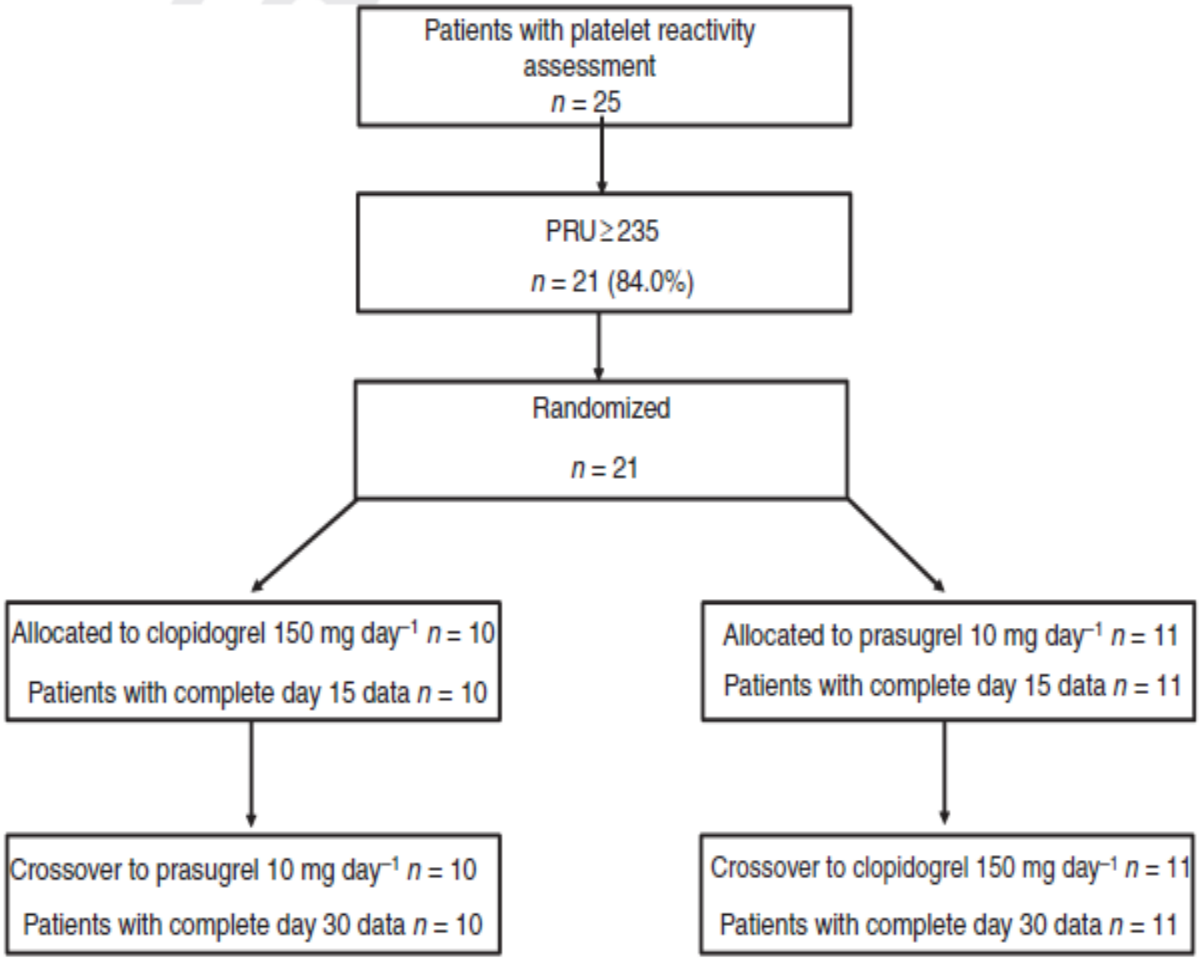


Table 1 Baseline characteristics of randomized patients

	Overall, $N = 21$	Clopidogrel, $N = 10$	Prasugrel, $N = 11$	P
Age (years)	61.2 ± 12.0	58.2 ± 12.2	64.0 ± 11.6	0.3
Male gender	14 (66.7)	6 (60)	8 (72.7)	0.7
BMI	26.2 ± 3.5	27.3 ± 4.3	25.2 ± 2.3	0.2
Time on HD (months)	96 (6–204)	80 (6–187)	96 (11–204)	0.9
Hyperlipidemia	15 (71.4)	7 (70.0)	8 (72.7)	1.0
Hypertension	18 (85.7)	10 (100)	8 (72.7)	0.2
DM	10 (47.6)	5 (50.0)	5 (45.5)	1.0
Smoking	5 (23.8)	3 (30.0)	2 (18.2)	0.6
PAD	10 (47.6)	5 (50.0)	5 (45.5)	1.0
History of CAD	13 (61.9)	5 (50.0)	8 (72.7)	0.4
Ht (%)	33.3 ± 3.2	32.2 ± 2.8	34.4 ± 3.2	0.1
Hb (g dL^{-1})	10.5 ± 1.2	10.1 ± 1.0	10.8 ± 1.3	0.1
Platelets (μL^{-1})	226520 ± 67359	247800 ± 64323	207180 ± 66981	0.2
Albumin (mg dL^{-1})	3.9 ± 0.3	3.8 ± 0.3	4.1 ± 0.1	0.03
Parathormone (pg mL^{-1})	218.9 ± 171.9	262 ± 228.4	170.4 ± 53.1	0.3
Medication				
Omega-3 fatty acids	8 (38.1)	3 (30.0)	5 (45.5)	0.7
Statin	9 (42.9)	5 (50.0)	4 (36.4)	0.7
PPIs	16 (76.2)	8 (80.0)	8 (72.7)	1.0
β-Blocker	13 (61.9)	7 (70.0)	6 (54.5)	0.7
Nitrates	5 (23.8)	2 (20.0)	3 (27.3)	1.0
ACE inhibitors	3 (14.3)	2 (20.0)	1 (9.1)	0.6
CCBs	4 (19.0)	3 (30.0)	1 (9.1)	0.3
Aspirin	10 (47.6)	5 (50.0)	5 (45.5)	1.0
PR day 0 (PRU)	335.1 ± 54.2	342.5 ± 68.0	328.5 ± 40.2	0.6
At least one *CYP2C19*2* allele	6 (28.6)	2 (20)	4 (36.4)	0.6
Two *CYP2C19*2* alleles	2 (9.5)	0 (0)	2 (18.2)	0.5

ACE, angiotensin-converting enzyme; BMI, body mass index; CAD, coronary artery disease; CCB, calcium channel blocker; DM, diabetes mellitus; Hb, hemoglobin; HD, hemodialysis; Ht; PAD, peripheral artery disease; PPI, proton pump inhibitor; PR, platelet reactivity; PRU, P2Y12 reaction units. Values are expressed as means ± SD, medians (range) or n (%). P-value refers to comparison between patients initially randomized

Table 2 Platelet reactivity analysis

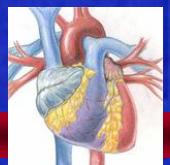
Platelet reactivity	Prasugrel LS estimates (95% CI)	Clopidogrel LS estimates (95% CI)	LS mean difference (95% CI)	*P*-value
Combined data (pre-crossover and post-crossover)	*N* = 21 156.7 (132.2–181.1)	*N* = 21 279.9 (255.5–304.4)	− 123.2 (− 157.8 to − 88.7)	< 0.001
Combined data (pre-crossover and post-crossover) for non-carriers of the *CYP2C19*2* allele	*N* = 15 162.1 (134.1–190.0)	*N* = 15 275.5 (247.5–303.4)	− 113.4 (− 152.9 to − 73.8)	< 0.001
Combined data (pre-crossover and post-crossover) for carriers of at least one *CYP2C19*2* allele	*N* = 6 135.1 (97.6–172.6)	*N* = 6 298.9 (261.4–336.4)	− 163.8 (− 218.3 to − 109.2)	< 0.001

CI, confidence interval; LS, least squares. Maximum likelihood linear mixed model, with patient ID as random effect, period, treatment sequence and treatment as fixed effects, and baseline P2Y12 reaction units as a covariate.

Table 3 High on-treatment platelet reactivity rates

	Prasugrel	Clopidogrel	*P*-value
Combined data (pre-crossover and post-crossover)	*N* = 21 4 (19.0)	*N* = 21 18 (85.7)	< 0.001
Combined data (pre-crossover and post-crossover) for non-carriers	*N* = 15 4 (26.7)	*N* = 15 12 (80.0)	0.003
Combined data (pre-crossover and post-crossover) for carriers	*N* = 6 0 (0)	*N* = 6 6 (100)	0.07

Values are expressed as *n* (%).



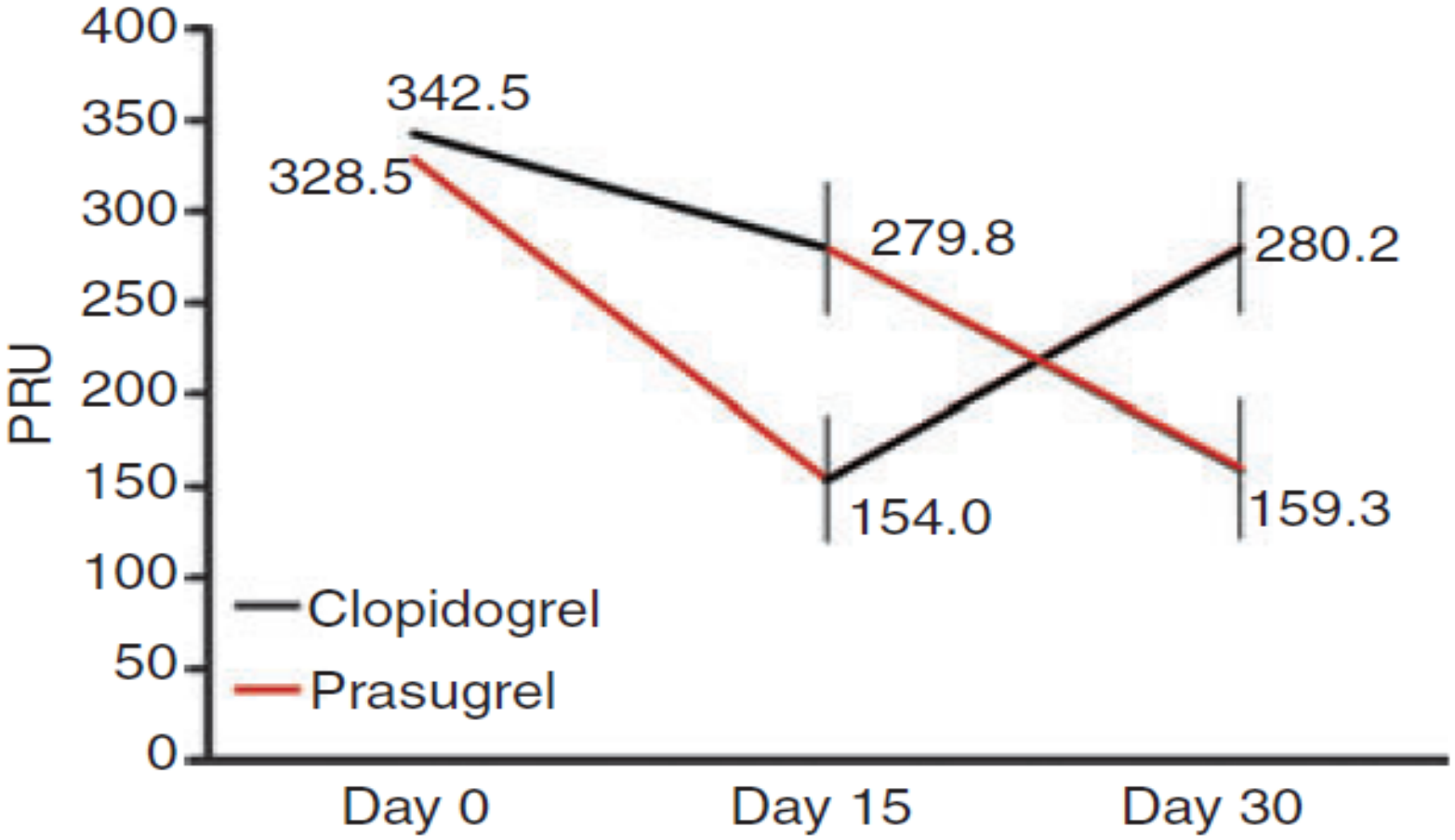


Fig. 2. Platelet reactivity PR (in P2Y12 reaction units [PRU]) by treatment sequence. PR is significantly lower in patients receiving prasugrel than in those receiving high-dose clopidogrel. Least squares estimates with 95% confidence intervals are presented.

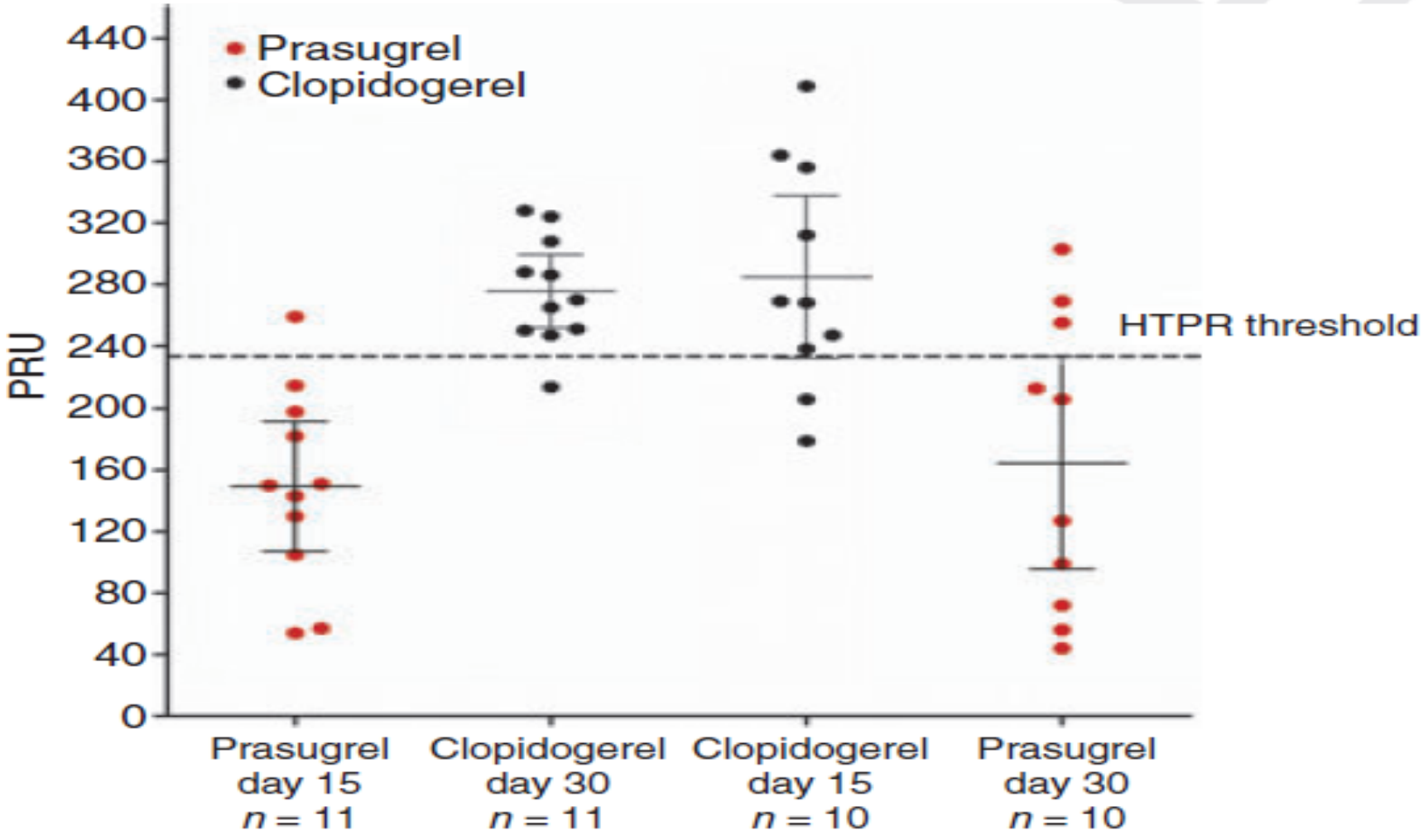


Fig. 3. Individual platelet reactivity responses according to treatment. Lines represent means, and error bars represent 95% confidence intervals. PRU, P2Y12 reaction units; HTPR, high on-treatment platelet reactivity.

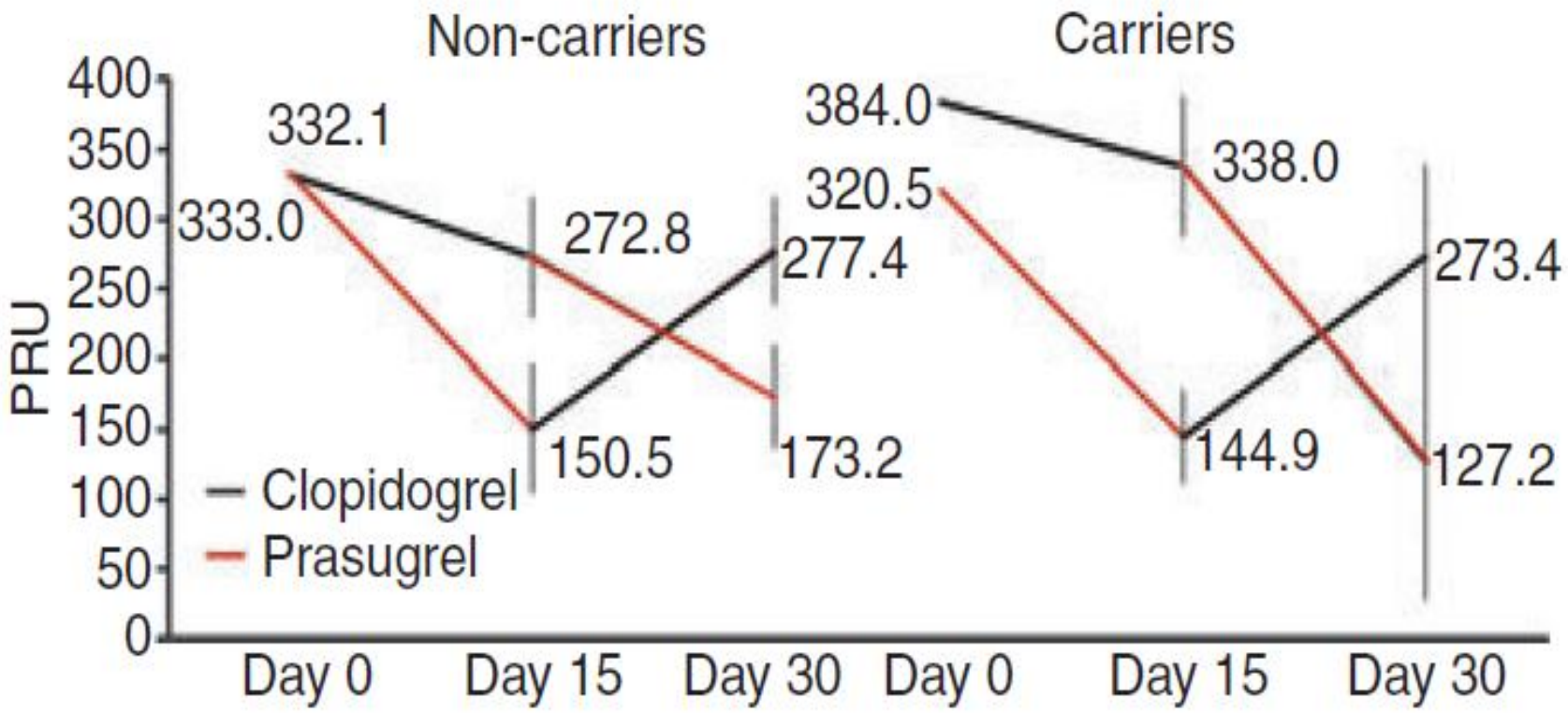
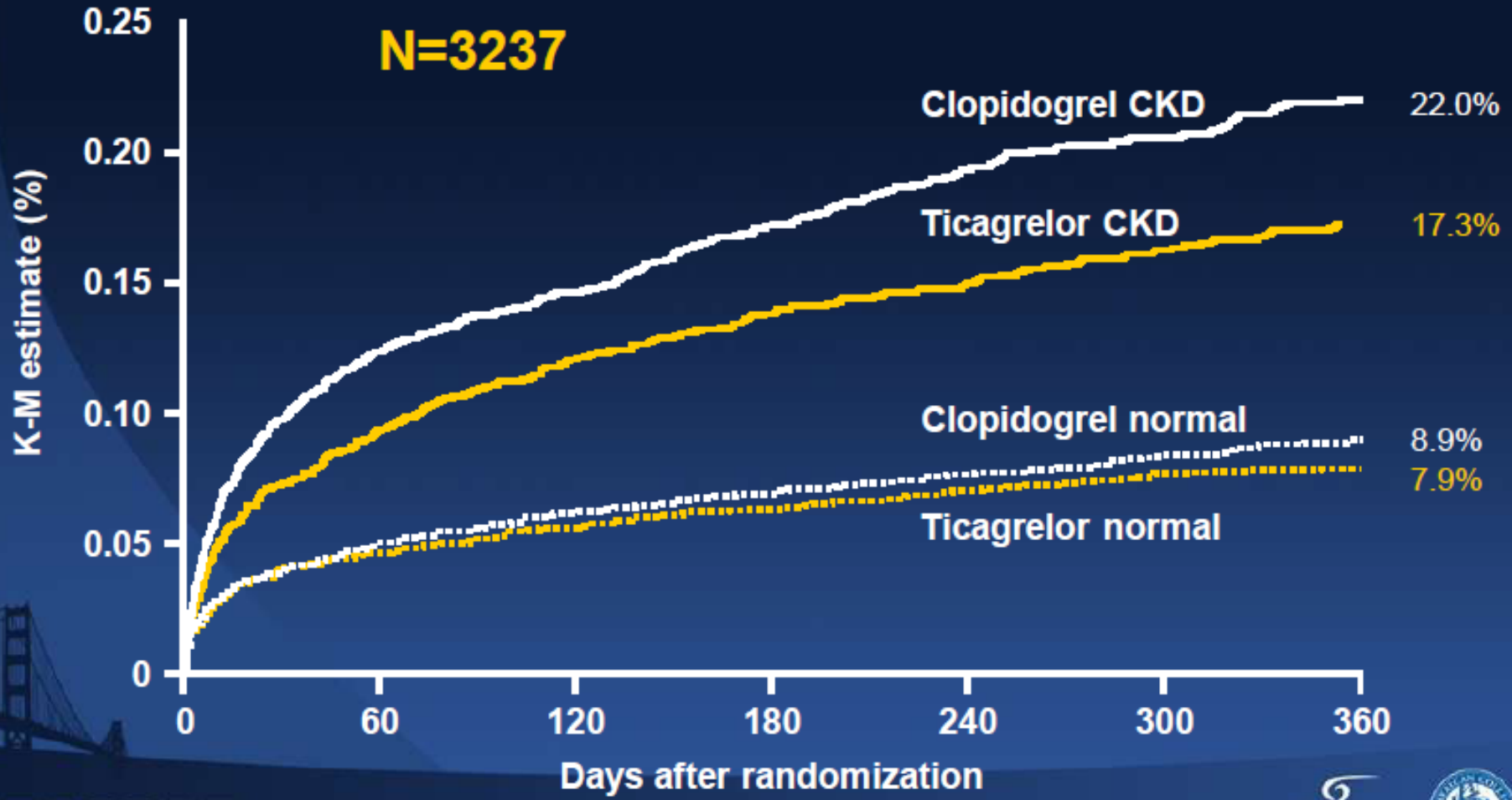


Fig. 4. Platelet reactivity (PR) by treatment sequence in non-carriers and carriers of the *CYP2C19*2* allele. Least squares estimates with 95% confidence intervals are presented. PR is significantly lower for prasugrel in both carriers and non-carriers. PRU, P2Y12 reaction units.

PLATO

Renal

Primary endpoint (creatinine clearance <60 mL/min),



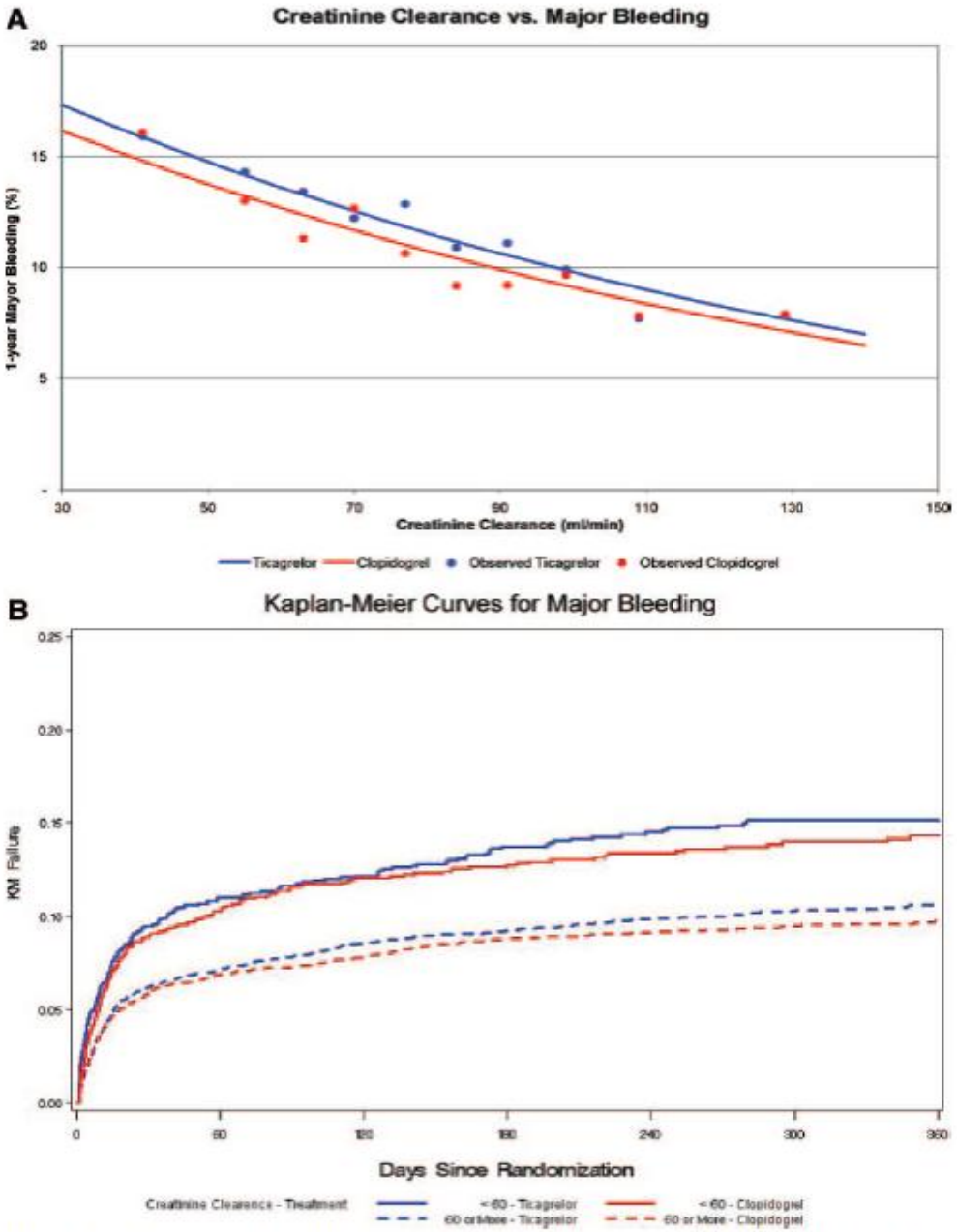
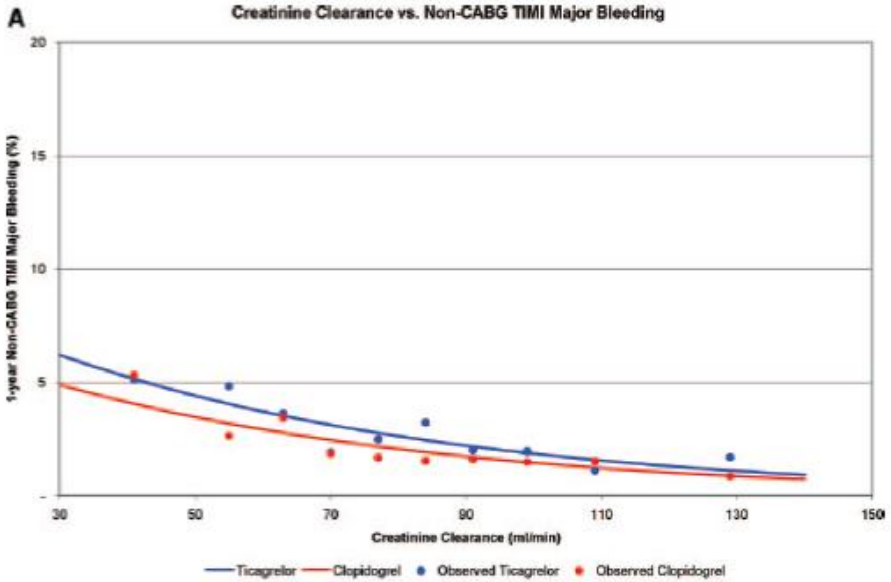


Figure 4. Deciles of baseline levels of CrCl by treatment are on the horizontal axis. A, Kaplan-Meier (KM) estimate of the yearly event rate for PLATO major bleeding. B, Kaplan-Meier estimate of the yearly event rate for non–CABG-related TIMI major bleeding.

James S, et al *Circulation*. 2010; 122: 1056-1067



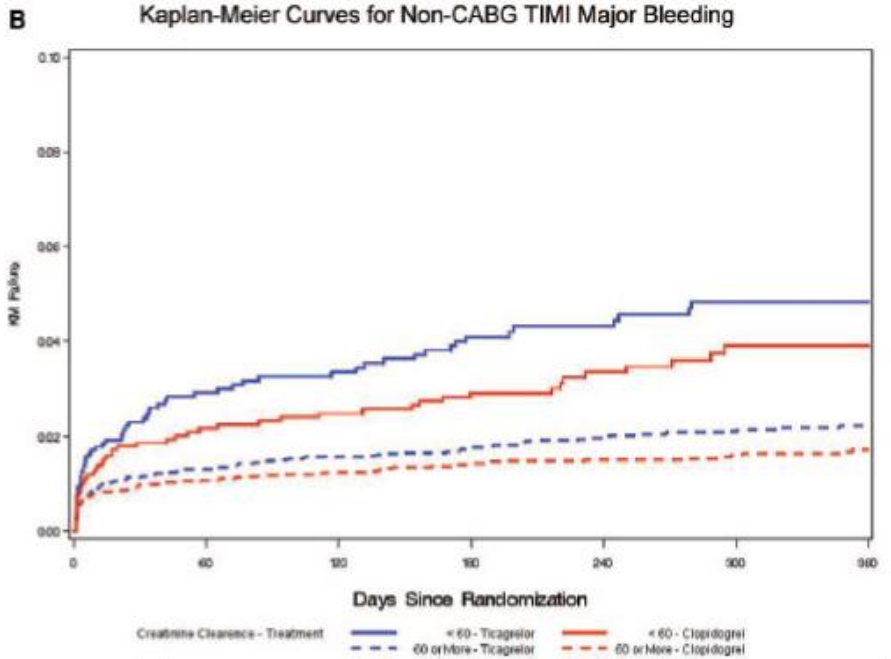
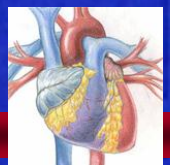


Figure 5. Kaplan Meier event rate curves of (A) PLATO major bleeding and (B) non–CABG-related TIMI major bleeding in patients in the ticagrelor (blue lines) and clopidogrel (red lines) groups stratified by renal function. Patients with CKD(solid lines) and normal renal function (dotted lines) were determined by calculated CrCl at baseline.



James S, et al *Circulation*. 2010; 122: 1056-1067

Pharmacokinetics, Pharmacodynamics, and Safety of Ticagrelor in Volunteers With Severe Renal Impairment

Kathleen Butler, MD, and Renli Teng, PhD

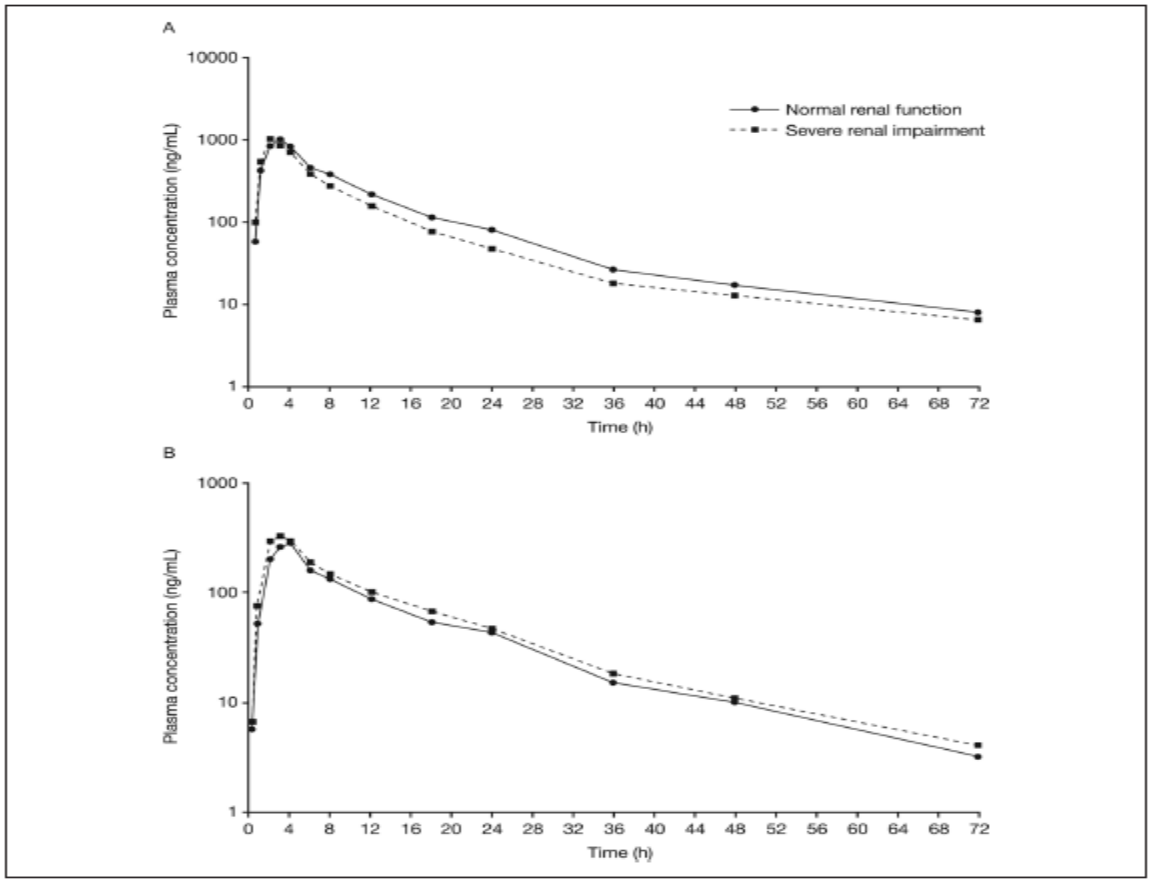
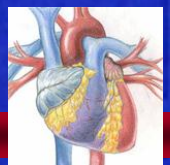


Figure 1. Geometric mean plasma concentration-time profiles of ticagrelor (A) and AR-C124910XX (B) in volunteers with severe renal impairment (n = 10) and volunteers with normal renal function (n = 10) after a single 180-mg ticagrelor dose.

J Clin Pharmacol 2011



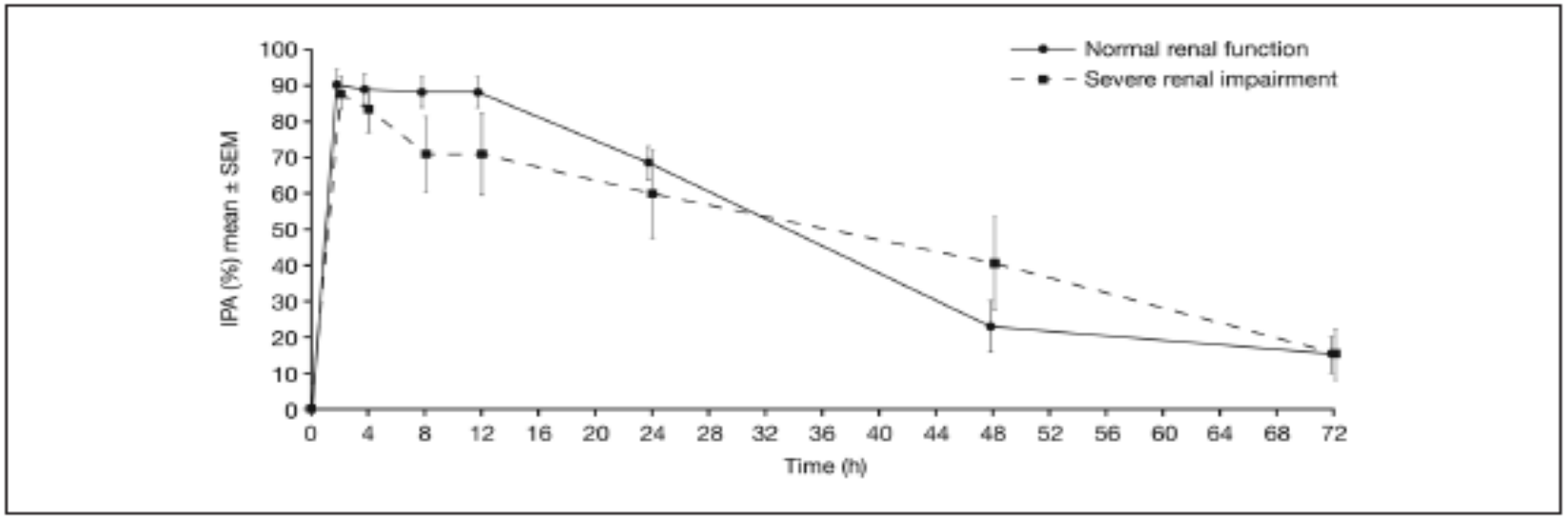


Figure 4. Mean (± standard error of the mean [SEM]) final-extent IPA versus time in volunteers with severe renal impairment (n = 10) and normal renal function (n = 10) after a single 180-mg dose of ticagrelor. IPA, inhibition of platelet aggregation.

Table III Inhibition of Platelet Aggregation (IPA) Parameters at Final-Extent Adenosine Diphosphate–Induced Aggregation After a Single Oral 180-mg Dose of Ticagrelor in Volunteers With Either Normal Renal Function or Severe Renal Impairment

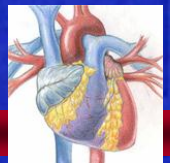
Parameter[a]	Normal Renal Function[b] (n = 10)	Severe Renal Impairment[c] (n = 10)	LS Mean Difference: Point Estimate (95% CI)[d]
IPA_{max}, %	93 (9)	90 (12)	−3 (−12 to 5)
$TIPA_{max}$, h	3.0 (2.0 to 12.0)	2.0 (2.0 to 8.0)	NA
$AUEC_{0-24}$, %·h	1916 (242)	1633 (666)	−273 (−704 to 159)
$AUEC_{0-72}$, %·h	3467 (889)	3499 (2137)	26 (−1371 to 1423)

$AUEC_{0-24}$, area under the effect curve 0 to 24 hours; $AUEC_{0-72}$, area under the effect curve 0 to 72 hours; CI, confidence interval; IPA_{max}, maximum IPA; $TIPA_{max}$, time to IPA_{max}.
a. Data are mean (SD) for IPA_{max} and AUEC; median (range) for $TIPA_{max}$.
b. Creatinine clearance (CrCL) ≥ 80 mL/min.
c. CrCL < 30 mL/min.
d. Least square (LS) mean difference = severe impairment − normal.

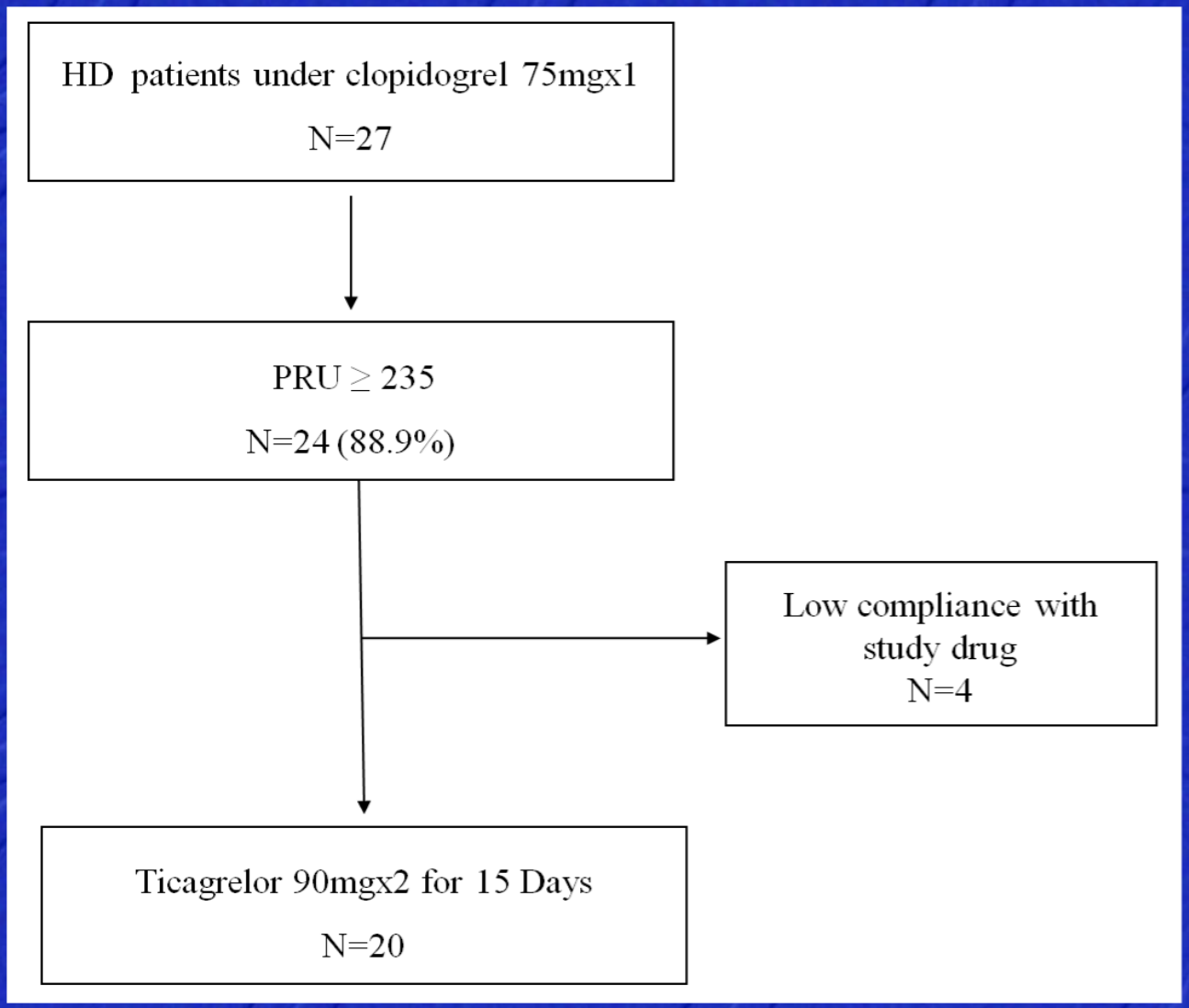
Ticagrelor first-in-man experience in patients on hemodialysis with high on clopidogrel platelet reactivity

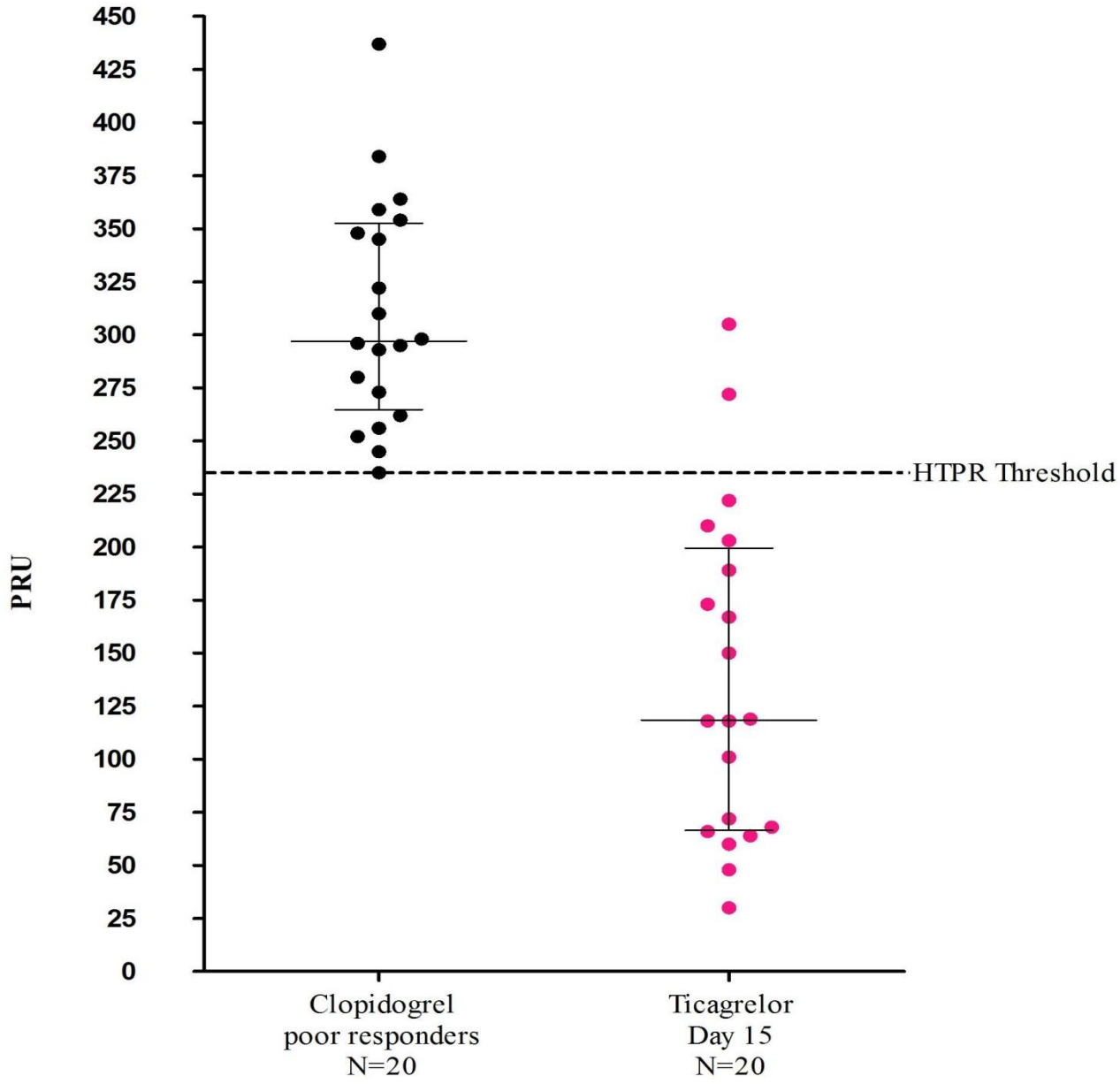
Dimitrios Alexopoulos, MD, FESC, FACC,* Ioanna Xanthopoulou MD,* Pavlos Goudas MD,§ Eleni Koutroulia MD,§ Dimitrios Goumenos, MD†

(Submitted)



Study flow chart

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HTPR Threshold
Clopidogrel
poor responders
N=20
Ticagrelor
Day 15
N=20

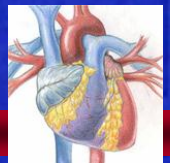
Glycoprotein IIb/IIIa inhibitors.

Abciximab in normal and CKD patients:

Similar clinical outcomes.

CKD patients more episodes of major bleeding

(Frilling et al, AJC 2002)



The relation of renal function to ischemic and bleeding outcomes with 2 different glycoprotein IIb/IIIa inhibitors: The Do Tirofiban and ReoPro Give Similar Efficacy Outcome (TARGET) trial

Peter B. Berger, MD,[a] Patricia J.M. Best, MD,[a] Eric J. Topol, MD,[b] Jennifer White, MS,[c] Peter M. DiBattiste, MD,[d] Albert W. Chan, MD,[b] Steen D. Kristensen, MD,[f] Howard C. Herrmann, MD,[c] and David J. Moliterno, MD[g]
Rochester, Minn, Cleveland, Ohio, Philadelphia, Pa, Wilmington, Del, Durham, NC, Aarhus, Denmark, and Lexington, Ky

Table III. Primary end points of patients in TARGET based on quartile of estimated creatinine clearance

End points at 30 d (%)	Creatinine clearance (mL/min) <70 (n = 1186)	70-90 (n = 1114)	90-114 (n = 1140)	≥114 (n = 1183)	P
Death	0.5	0.7	0.1	0.3	.096
MI	6.9	7.8	4.6	5.2	.004
Urgent TVR	0.8	1.2	0.6	0.4	.197
Primary composite end point	7.3	8.5	5.1	5.8	.005

Table IV. Composite end point of death, MI, and TVR at 30 days in TARGET based on drug treatment received and the creatinine clearance

Patient group	Abciximab	Tirofiban	P
All patients	6.0	7.5	.034
Creatinine clearance (mL/min)			
<70	6.0	8.7	.074
70-90	8.2	8.9	.693
90-114	4.4	5.8	.293
<114	5.6	6.1	.704

Data are presented as percentages.

Table V. Thirty-day end point of MI in TARGET based on drug treatment received and the creatinine clearance

Patient group	Abciximab	Tirofiban	P
All patients	5.4	6.9	.037
Creatinine clearance (mL/min)			
<70	5.5	8.4	.052
70-90	7.3	8.3	.530
90-114	4.0	5.1	.409
<114	5.1	5.4	.789

Data are presented as percentages.

Table VI. Multivariable logistic model for the composite end point of death, MI, or urgent TVR at 30 days

Variable	OR (95% CI)	P
Tirofiban	1.21 (0.95-1.54)	.13
Creatinine clearance (log transformation)	0.72 (0.53-0.99)	.041
Country of origin (US vs non-US)	1.47 (1.04-2.07)	.031
Acute coronary syndrome	1.53 (1.17-2.04)	.002
Multivessel coronary artery disease (2 or 3)	1.47 (1.1-1.97)	.010
Diabetes	0.68 (0.49-0.93)	.016
Heart failure	1.60 (1.12-2.28)	.010
Clopidogrel use 3 d before the procedure	0.60 (0.41-0.90)	.012
Maximum lesion length (0-10, 10-20,>20 mm)	1.76 (1.45-2.13)	<.001

Treatment Effects of *Eptifibatide* in Planned Coronary Stent Implantation in Patients With Chronic Kidney Disease (ESPRIT Trial)

Donal N. Reddan, MB, MHS, John Conor O'Shea, MD, Ian J. Sarembock, MB, ChB, MD, Kathryn A. Williams, MS, Karen S. Pieper, MSc, Edward Santoian, MD, PhD, William F. Owen, Jr., MD, Michael M. Kitt, MD, and James E. Tcheng, MD

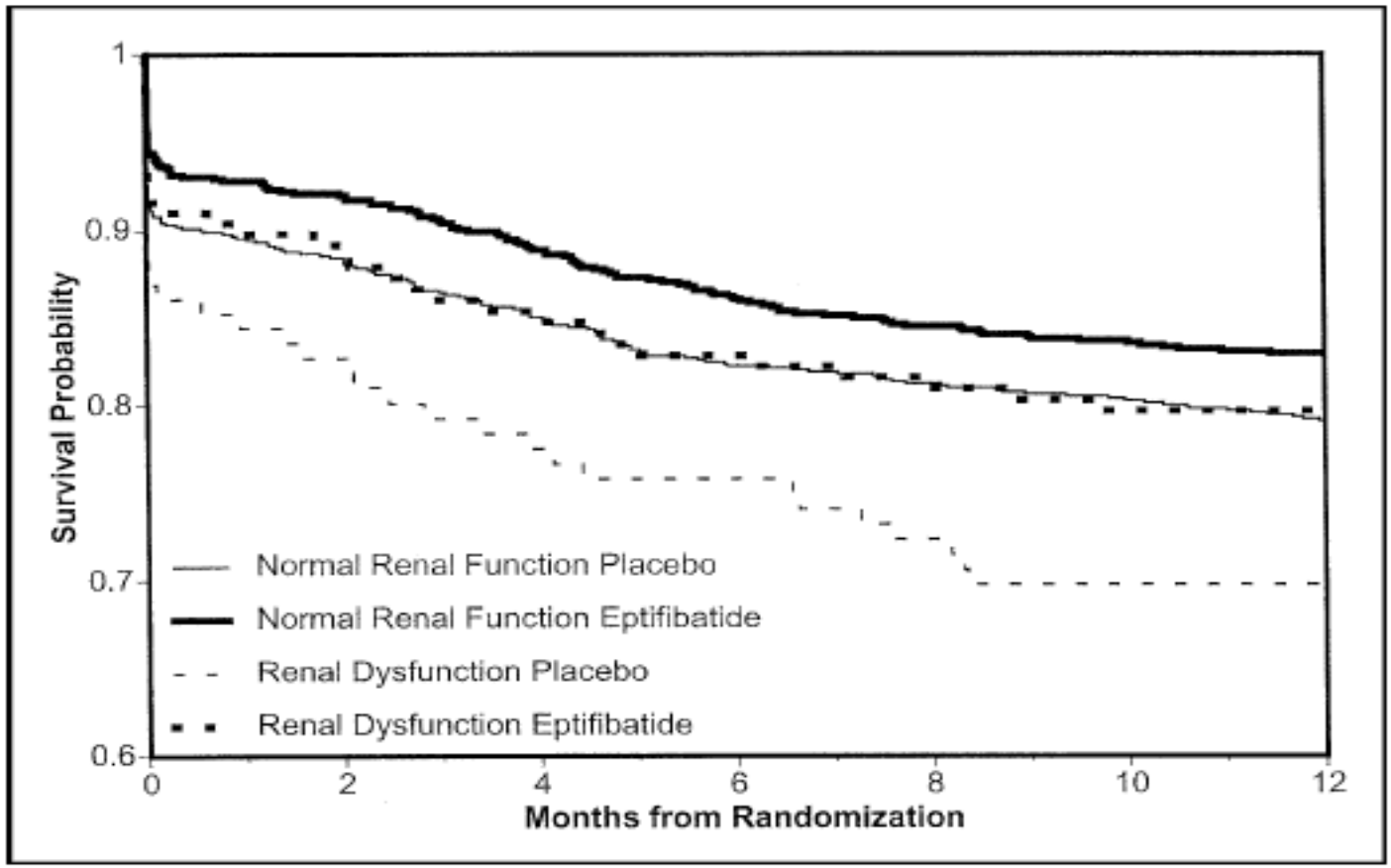
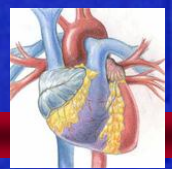


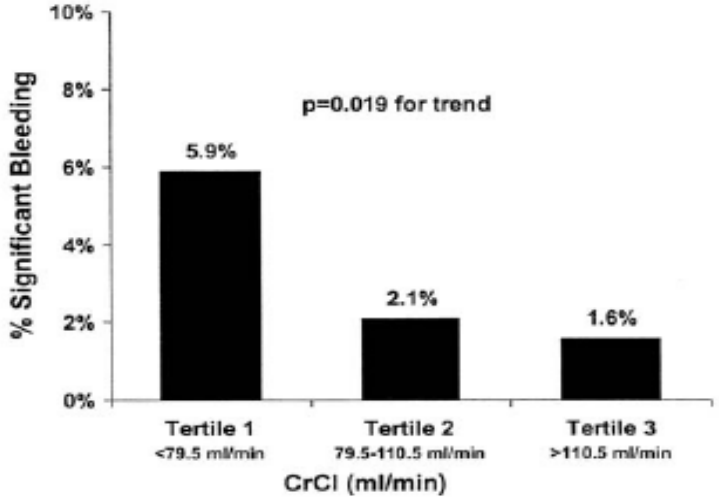
FIGURE 1. Kaplan-Meier curves by treatment group stratified by renal function categories for the outcome of death, MI, and urgent target vessel revascularization up to 12 months.

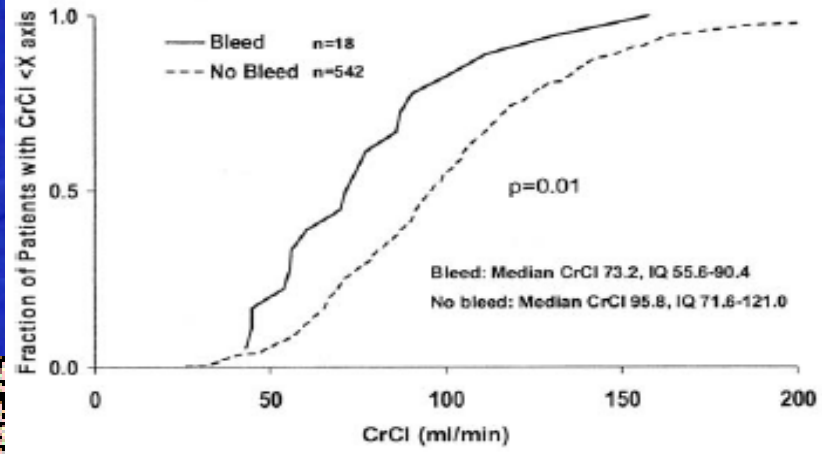


Correlates of Bleeding Events Among Moderate- to High-Risk Patients Undergoing Percutaneous Coronary Intervention and Treated With Eptifibatide

Observations From the PROTECT–TIMI-30 Trial

Ajay J. Kirtane, MD, SM,* Gregory Piazza, MD,* Sabina A. Murphy, MPH,† Daniela Budiu, MD,† David A. Morrow, MD, MPH, FACC,† David J. Cohen, MD, MSc,* Eric Peterson, MD, MPH, FACC,‡ Nasser Lakkis, MD, FACC,§ Howard C. Herrmann, MD, FACC,‖ Theresa M. Palabrica, MD,¶ C. Michael Gibson, MS, MD, FACC,*† for the TIMI Study Group





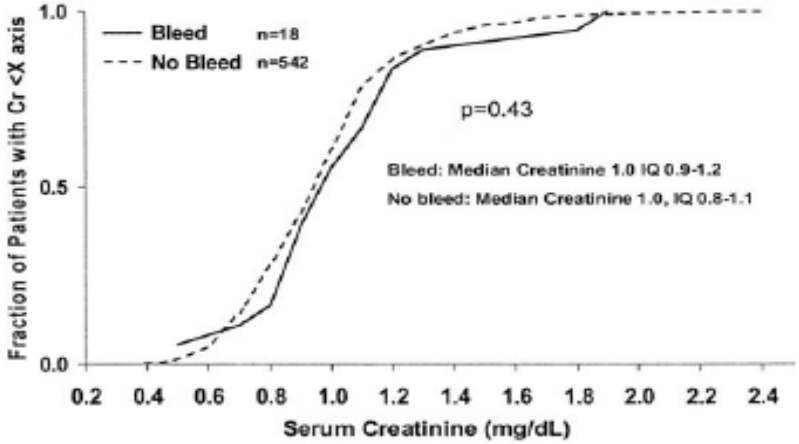


Figure 2. Relation of creatinine clearance (CrCl) and bleeding. IQ = interquartile range.

Excess Dosing of Antiplatelet and Antithrombin Agents in the Treatment of Non–ST-Segment Elevation Acute Coronary Syndromes

Table 3. Patient-Level and Practice-Level Predictors of Excess Antithrombotic Dose

Patient Characteristics	Likelihood of Receiving Excess Dose, Adjusted OR (95% CI)*		
	Unfractionated Heparin	Low-Molecular-Weight Heparin	Glycoprotein IIb/IIIa Inhibitor
Age, y			
65-74	0.93 (0.79-1.11)	0.76 (0.65-0.89)	4.23 (3.67-4.86)
≥75	0.81 (0.68-0.96)	0.75 (0.63-0.89)	14.39 (12.24-16.90)
Renal insufficiency	1.25 (1.07-1.46)	0.82 (0.67-1.00)	4.12 (2.95-5.75)
Women	0.92 (0.80-1.06)	0.73 (0.63-0.84)	3.74 (3.29-4.25)
Diabetes mellitus	1.04 (0.93-1.16)	1.16 (1.03-1.31)	1.35 (1.20-1.51)
Prior congestive heart failure	0.86 (0.73-1.02)	1.14 (0.97-1.33)	1.49 (1.23-1.81)
Weight, per 5-kg decrease	1.28 (1.22-1.35)	1.26 (1.23-1.29)	1.02 (1.00-1.04)
Academic hospital	1.02 (0.66-1.58)	1.26 (1.03-1.54)	0.93 (0.76-1.15)
Cardiologist	0.90 (0.77-1.06)	1.17 (1.02-1.34)	0.94 (0.82-1.06)
Medication adherence, per 5% decrease	1.12 (0.97-1.30)	1.02 (0.97-1.08)	1.06 (1.01-1.12)

Abbreviations: CI, confidence interval; OR, odds ratio.

*Among those patients receiving each therapy, the likelihood of receiving excess dose by patient and physician characteristic in a model containing all variables above, including (not shown) number of hospital beds, race (nonwhite vs white), insurance status (Medicaid, Medicare, self/none vs health maintenance organization/private), and positive cardiac markers. Reference groups include aged less than 65 years, men, no diabetes mellitus, serum creatinine level of less than 2.0 mg/dL (<176.8 µmol/L), no prior congestive heart failure, nonacademic hospital, and care provided by noncardiologist.

Alexander et al-CRUSADE, JAMA 2005

Table 2 Antiplatelet and Antithrombotic Agents, Recommended Doses, Routes of Elimination, Effect of Renal Failure on Dose, and Potential Strategies to Reverse Their Effect

Drug	Recommended Dose	Route of Elimination	Half-Life	Effect of Renal Failure on Dose
Aspirin	81–325 mg	Renal (pH-dependent)	2–19 h	None
Clopidogrel and active metabolite	Loading dose: 300–600 mg Maintenance dose: 75 mg	Renal (50%), feces (50%)	6 h	None
Prasugrel	Loading dose: 60 mg Maintenance dose: 10 mg	Renal (60–70%)	2–15 h	None
Ticagrelor	Loading dose: 180 mg Maintenance dose: 90 mg PO BID	Biliary	6–13 h	None
Abciximab	250 μg/kg bolus followed by 0.125 μg/kg/min for 12 h	Spleen, RES	30 min	None
Tirofiban	0.4 μg/kg/min 30-min bolus followed by 0.1 μg/kg/min	Renal (40%–70%)	1.4–1.8 h	CrCl <30 ml/min/1.73 m^2: 0.2 μg/kg/min 30-min bolus followed by 0.05 μg/kg/min
Epitifibatide	180 μg/kg bolus followed by 2.0 μg/kg/min for 72 h	Renal (50%)	25 min	CrCl <50 ml/min/1.73 m^2: 180 μg/kg/min bolus followed by 1 μg/kg/min for 72 h; contraindicated in patients on hemodialysis

Basra et al, JACC 2011

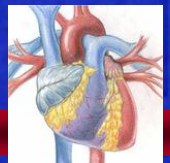
CONCLUSIONS

There is a clear dearth of studies evaluating the safety and efficacy of antiplatelet drugs for treating CKD patients.

Most of the recommendations are based on single-center data or post-hoc analyses.

Novel therapies may help overcome some of the complications observed in these patients

Further randomized trials are warranted to objectively evaluate their efficacy for this increasingly common subgroup of patients.



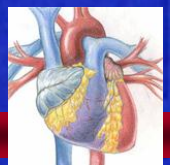


Table 3 Safety and Efficacy of Antiplatelet and Antithrombotic Agents Stratified by Category of CKD

Drug	CKD 1	CKD 2	CKD 3	CKD 4	CKD 5	Comments	RCT/RP/SC/R/MA/SA	Evidence
Aspirin	S, E	S, E	S, E	S, E	S, E		RCT (12,16,17), RP (13), R (14), MA (18)	Sufficient
Clopidogrel	S, E	S, E	US, NE	US, NE	US, NE	Increased risk of minor bleeding and risk of blood transfusions in CKD 3–5. Lack of efficacy in CREDO (20) and CURE (22) trials in CKD 3–5. Further studies needed to establish efficacy of standard dose vs. double dose clopidogrel in patients with CKD	RCT (23), SA (20,22)	Further studies of CKD 3–5 patients needed
Prasugrel	S, E	S, E	UK	UK	UK	No studies currently available on safety and efficacy in patients with CKD. No difference based on pharmacokinetic and pharmacodynamic data.	RCT (29)	Further studies of CKD patients needed
Ticagrelor	S, E	S, E	S, E	S, E	S, E	May be considered over standard dose clopidogrel. Further trials needed to assess efficacy vs. double dose clopidogrel.	RCT (33), SA (34)	Sufficient
Abciximab	S, E	S, E	S, E	S, E	S, E	No interaction observed between abciximab, worsening renal function and ischemic/bleeding outcomes.	SA (40), SC (37), R (36)	Sufficient
Tirofiban	S, E	S, E	S, E	S, E	S, E	No interaction observed between tirofiban, worsening renal function, and ischemic/bleeding outcomes. Dose needs to be adjusted for CrCl <30 ml/min/1.73 m^2	SC (38), SA (39,40)	Sufficient
Eptifibatide	S, E	S, E	S, E	S, E	S, E	No interaction observed between eptifibatide, worsening renal function, and ischemic/bleeding outcomes. Dose needs to be adjusted for CrCl <50 ml/min/1.73 m^2	SA (43)	Sufficient

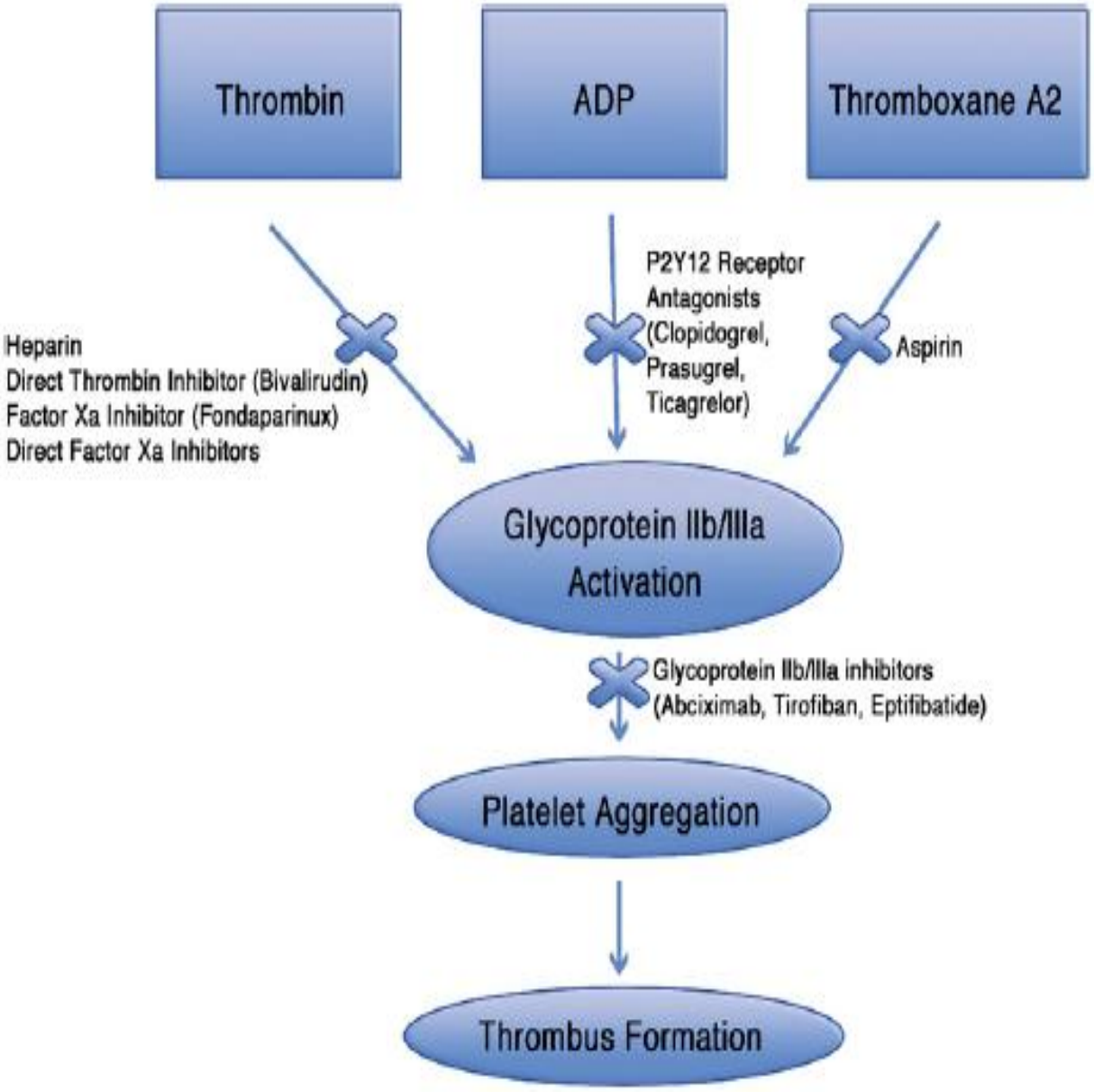


Figure 2 Sites of Inhibition of Platelet Activation and Aggregation

Hellenic J Cardiol 2011; 52: 509-515

Review Article

Oral Antiplatelet Agents and Chronic Kidney Disease

DIMITRIOS ALEXOPOULOS, AGELLIKI PANAGIOTOU

Department of Cardiology, Patras University Hospital, Patras, Greece.

Key words: **Platelets, clopidogrel, hemodialysis, chronic kidney disease.**

Chronic kidney disease (CKD) is recognized as an independent predictor for myocardial infarction, stroke and all-cause mortality due to accelerated atherosclerosis.[1] Cardiovas-

normalities varies from deep vein thrombosis and pulmonary embolism to hemodialysis vascular access thrombus formation, atherosclerosis-associated thrombosis (mainly in the form of acute coronary

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STATE-OF-THE-ART PAPER

Safety and Efficacy of Antiplatelet and Antithrombotic Therapy in Acute Coronary Syndrome Patients With Chronic Kidney Disease

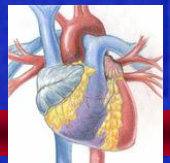
Sukhdeep S. Basra, MD, MPH,* Peter Tsai, MD,† Nasser M. Lakkis, MD*‡

Houston, Texas

Chronic kidney disease (CKD) is prevalent and affects an ever-increasing proportion of patients presenting with acute coronary syndrome (ACS). Patients with CKD have a higher risk of ACS and significantly higher mortality, and are also predisposed to increased bleeding complications. Antiplatelet and antithrombotic drugs form the bedrock of management of patients with ACS. Most randomized trials of these drugs exclude patients with CKD, and current guidelines for management of these patients are largely based on these trials. We aim to review the safety and efficacy of these drugs in patients with CKD presenting with ACS. (J Am Coll Cardiol 2011;58:2263–9)

Effect of renal failure on dose

Abciximab	250 μg/kg bolus followed by 0.125 μg/kg/min for 12 h	Spleen, RES	30 min	None
Tirofiban	0.4 μg/kg/min 30-min bolus followed by 0.1 μg/kg/min	Renal (40%–70%)	1.4–1.8 h	CrCl <30 ml/min/1.73 m^2: 0.2 μg/kg/min 30-min bolus followed by 0.05 μg/kg/min
Epitifibatide	180 μg/kg bolus followed by 2.0 μg/kg/min for 72 h	Renal (50%)	25 min	CrCl <50 ml/min/1.73 m^2: 180 μg/kg/min bolus followed by 1 μg/kg/min for 72 h; contraindicated in patients on hemodialysis



Prasugrel pharmacokinetics and pharmacodynamics in subjects with moderate renal impairment and end-stage renal disease

D. S. Small* PhD, R. E. Wrishko* PhD, C. S. Ernest II* MS, L. Ni* PhD, K. J. Winters* MD, N. A. Farid* PhD, Y. G. Li* MS, J. T. Brandt* MD, D. E. Salazar† PhD, A. G. Borel* PhD, K. A. Kles* PhD and C. D. Payne‡ MS

Eli Lilly and Company, Indianapolis, IN, USA, †Daiichi Sankyo, Inc., Parsippany, NJ, USA and ‡Eli Lilly and Company, Windlesham, UK

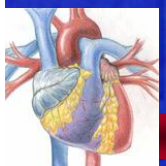
ABSTRACT

Objective: The pharmacokinetic (PK) and pharmacodynamic (PD) responses to prasugrel were compared in three studies of healthy subjects vs. those with moderate or end-stage renal impairment.
Methods: Two of the three protocols were parallel-design, open-label, single dose (60-mg prasugrel) studies in subjects with end-stage renal disease (ESRD; $n = 12$) or moderate renal impairment ($n = 10$) and matched healthy subjects with normal renal function ($n = 10$). The third protocol was an open-label, single-dose escalation (5, 10, 30 and 60 mg prasugrel) study in subjects with ESRD ($n = 16$) and matched healthy subjects with normal renal function ($n = 16$). Plasma concentrations of prasugrel's active metabolite were determined and pharmacokinetic parameter estimates were derived. Maximum platelet aggregation (MPA) was measured by light transmission aggregometry using 20 μM adenosine diphosphate as agonist.
Results: Across all studies, prasugrel's C_{max} and AUC_{0-t} were 51% and 42% lower in subjects with ESRD than in healthy subjects. AUC_{0-t} did not differ between healthy subjects and subjects with moderate renal impairment. The magnitude of change and time-course profiles of MPA was
Conclusion: There was no difference in pharmacokinetics or PD responses between subjects with moderate renal impairment and healthy subjects. Despite significantly lower exposure to prasugrel's active metabolite in subjects with ESRD, MPA did not differ between healthy subjects and those with ESRD.

Keywords: pharmacodynamics, pharmacokinetics, prasugrel, renal impairment, thienopyridine

INTRODUCTION

Prasugrel, a new thienopyridine prodrug, is metabolized *in vivo* to an adenosine diphosphate (ADP) receptor antagonist, which binds irreversibly to platelet $P2Y_{12}$ receptors and inhibits ADP-induced platelet aggregation (1). A simplified metabolic pathway for the formation of prasugrel's active metabolite and its inactive metabolites is shown in Fig. 1. In a phase 3 study (TRITON-TIMI 38) in patients with acute coronary syndromes (ACS) with planned percutaneous coronary intervention (PCI), prasugrel given as a 60-mg loading dose (LD) followed by daily 10-mg maintenance doses (MD), co-administered with aspirin, significantly reduced rates of ischaemic events when compared with the standard-dose regimen



Lack of effect of chronic kidney disease on clopidogrel response with high loading and maintenance doses of clopidogrel after Acute Coronary Syndrome

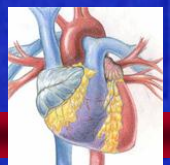
Objectives: The aim was to assess the effect of CKD on high doses clopidogrel effect in the acute phase after 600 mg and one month after high 150 mg maintenance dose.

Methods: 223 consecutive patients admitted for NSTE ACS have been prospectively included in the study, including 179 with normal renal function or mild CKD and 44 with moderate to severe CKD. All patients underwent PCI during initial hospitalisation. Patients received a 600 mg loading dose of clopidogrel and 250 mg of aspirin at least 12 hours before coronary angiography and assessment of clopidogrel response. After PCI, all patients received aspirin 75 mg and clopidogrel 150 mg at discharge. After one month, platelet function tests were repeated to assess chronic response to clopidogrel. Blood samples were examined with two methods: VASP and ADP-Ag.

Results: In hospital, no significant difference was observed between patients with or without CKD neither for ADP-Ag (mean±SD=49.8%±14.15 vs. 48.9%±16.4, p=0.71), nor for PRI VASP (mean±SD=44.6%±18.3 vs. 48.4%±20.7, p=0.22). One month after hospital discharge, clopidogrel response showed no significant difference between patients with or without CKD neither for ADP-Ag (mean±SD=55.4%±14.4 vs. 52.5%±14.9, p=0.26), nor for PRI VASP(mean±SD=10.5%±19.5 vs. 43.8%±17.7, p=0.31).

Conclusions: CKD showed no significant effect on clopidogrel response, neither for acute response, nor for chronic response with high clopidogrel doses on board.

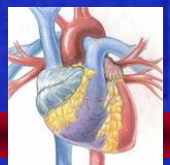
Cuisset T, Frere C, Moro PJ et al. *Thromb Res*. 2010; 126: e400-402.



Aspirin. The efficacy of aspirin for patients with CKD presenting with ACS is well established. In the Cooperative Cardiovascular Project (11), McCullough et al. (12) showed that aspirin reduced in-hospital mortality by 64.3% to 80% across all quartiles of creatinine clearance (CrCl). In addition, patients who were not receiving aspirin on admission were more likely to be in heart failure or cardiogenic shock.

A recent retrospective review of 595 patients with ACS found that the use of aspirin was associated with a decreased rate of ST-segment elevation myocardial infarction in patients with GFR 60 ml/min (odds ratio [OR]: 0.5, 95% confidence interval [CI]: 0.2 to 1.0; p 0.05) (13). Data from the National Cardiovascular Data ACTION (Acute Coronary Treatment and Intervention Outcomes Network) registry, including 19,029 patients with ST-segment elevation myocardial infarction and 30,462 with non–STsegment elevation myocardial infarction, documented decreasing use of aspirin with worsening severity of CKD (14,15). The U.K. HARP (Heart and Renal Protection)-1 trial and the DOPPS (Dialysis Outcomes and Prescription Patterns Study) showed that low-dose aspirin (100 mg/day) in CKD patients was not associated with increased major bleeding or progression of CKD (16,17).

In a recent meta-analysis by the Antithrombotic Trialists Collaboration, low-dose aspirin (75 to 160 mg) was found to be as efficacious as high-dose aspirin (325 mg) beyond the acute phase for secondary prev ntion of coronary artery disease in patients with CKD and end-stage renal disease (18).



Clopidogrel. The current ACC/AHA guidelines recommend the use of clopidogrel in patients with ACS (9,19). No specific recommendations exist for the adjustment of clopidogrel dosage in renal insufficiency. A post-hoc analysis from the CREDO (Clopidogrel for Reduction in Events During Observation) trial, patients with mild and moderate CKD did not have any significant difference in outcomes (mild 10.3 % vs. 12.8%, p 0.30; moderate 17.8% vs. 13.1%, p 0.24) with increased risk of bleeding with clopidogrel (20).

A post-hoc analysis of the CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) trial (21–23) showed no interaction between clopidogrel and renal function (p value for homogeneity 0.11). However, there was no significant benefit from using clopidogrel for patients in the lowest tertile (relative risk: 0.89 [95% confidence interval [CI]: 0.76 to 1.05]), and patients in this group had a significant increase in minor bleeding (hazard ratio: 1.5, 95% CI: 1.21 to 1.86) and blood transfusion (3.5%).

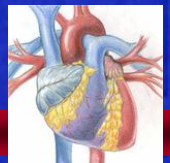


Table 3. Clopidogrel pharmacodynamic studies in patients with chronic kidney disease.

Study	Year	Population (N)	Clopidogrel dose	Assay	Results
Kaufman[31]	2000	Hemodialysis (N=9)	75 mg for 14 days	ADP-induced platelet aggregation 2 mM, 5 mM, 10 mM	From 48% to 23% From 59% to 38% From 66% to 44% p=0.01
Park[32]	2009	CKD (groups II, III) vs. normal renal function (group I) (N=59)	group I: 75 mg group II: 75 mg group III: 150 mg	VerifyNow (PRU)	Group I 239 ± 87 Group II 308 ± 70 Group III 302 ± 81 p=0.013
Angiolillo[33]	2010	Diabetic CAD patients categorized by the presence or absence of moderate/severe CKD (N=306)	75 mg	ADP and collagen platelet aggregation	60 ± 13% vs. 52 ± 15%, p=0.001 49 ± 20% vs. 41 ± 20%, p=0.004
Cuisset[34]	2010	PCI patients, 44 moderate/severe CKD 179 normal/mild CKD (N=223)	600 mg LD + 150 mg MD	ADP-induced platelet aggregation and VASP	1 month: 55.4% vs. 52.5% 10.5% vs. 43.8%

CKD – chronic kidney disease; ADP – adenosine diphosphate; VASP – vasodilator-stimulated phosphoprotein phosphorylation assay; LD – loading dose; LR – low responder; MD – maintenance dose; PCI – Percutaneous coronary intervention; PRU – platelet reactivity units; R – responder.

D. Alexopoulos, et al Hell J Cardiol, 2011,52:509

CLINICAL STUDY

Impact of Chronic Aspirin and Statin Therapy on Presentation of Patients With Acute Myocardial Infarction and Impaired Renal Function

Alessandro Sciahbasi, MD;[1] Romano Arcieri, MD;[2] Maria Quarto, MS;[3] Gianluca Pendenza, MD;[4] Chiara Lanzillo, MD;[1] Francesco Summaria, MD;[1] Enrico Romagnoli, PhD, MD;[1] Cosimo Commisso, MD;[1] Maria Penco, MD;[4] Ernesto Lioy, MD[1]

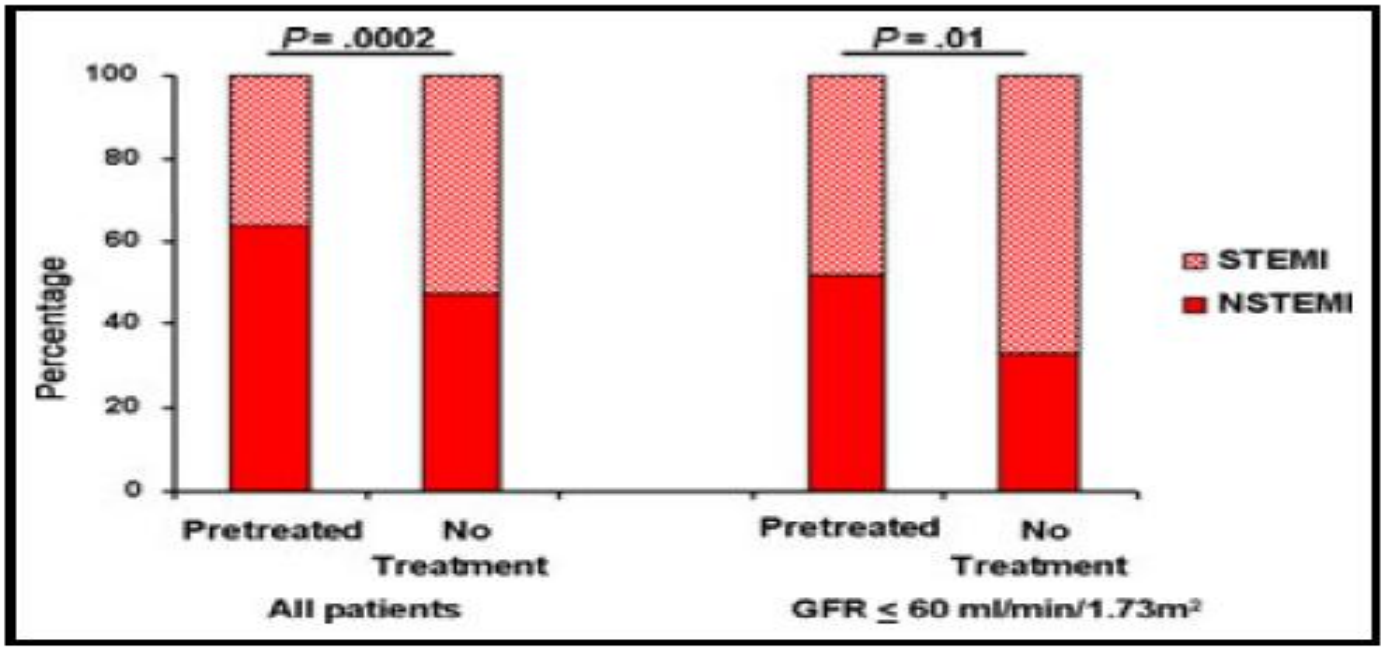
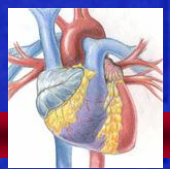


Figure 1. Patients pretreated with aspirin or statins had a significantly lower incidence of ST-segment elevation myocardial infarction (STEMI) compared with patients not pretreated. These results are confirmed also in patients with impaired renal function. GFR indicates glomerular filtration rate; NSTEMI, non–ST-segment elevation acute myocardial infarction.



J Am Soc Nephrol 14: 2313–2321, 2003

Randomized Controlled Trial of Clopidogrel plus Aspirin to Prevent Hemodialysis Access Graft Thrombosis

JAMES S. KAUFMAN,* THERESA Z. O'CONNOR,† JANE HONGYUAN ZHANG,† ROBERT E. CRONIN,‡ LOUIS D. FIORE,* MICHAEL B. GANZ,§ DAVID S. GOLDFARB,‖ and PETER N. PEDUZZI,† FOR THE VETERANS AFFAIRS COOPERATIVE STUDY GROUP ON HEMODIALYSIS ACCESS GRAFT THROMBOSIS

**Department of Veterans Affairs Boston Healthcare System and Department of Medicine, Boston University School of Medicine, Boston, Massachusetts; †Department of Veterans Affairs Cooperative Studies Program Coordinating Center, West Haven, Connecticut; ‡Veterans Affairs North Texas Health Care Center, Dallas, Texas; §Cleveland Veterans Affairs Medical Center, Cleveland, Ohio; and ‖New York Veterans Affairs Medical Center, New York, New York.*

Abstract. Thrombosis of hemodialysis vascular access grafts represents a major medical and economic burden. Experimental and clinical models suggest a role for antiplatelet agents in the prevention of thrombosis. The study was designed to determine the efficacy of the combination of aspirin and clopidogrel in the prevention of graft thrombosis. The study was a randomized, double-blind trial conducted at 30 hemodialysis units at Veterans Affairs medical centers. Participants undergoing hemodialysis with a polytetrafluoroethylene graft in the arm were randomized to receive either double placebos or aspirin (325 mg) and clopidogrel (75 mg) daily. Participants were to be monitored while receiving study medications for a minimum of 2 yr. The study was stopped after randomization of 200 participants, as recommended by the Data Safety and Monitoring Board because of a significantly increased risk of bleeding among the participants receiving aspirin and clopidogrel therapy. The cumulative incidence of bleeding events was significantly greater for those participants, compared with participants receiving placebos [hazard ratio, 1.98; 95% confidence interval (CI), 1.19 to 3.28; $P = 0.007$]. Twenty-three participants in the placebo group and 44 participants in the active treatment group experienced a bleeding event ($P = 0.006$). There was no significant benefit of active treatment in the prevention of thrombosis (hazard ratio, 0.81; 95% CI, 0.47 to 1.40; $P = 0.45$), although there was a trend toward a benefit among participants who had not experienced previous graft thrombosis (hazard ratio, 0.52; 95% CI, 0.22 to 1.26; $P = 0.14$). In the hemodialysis population, therapy with aspirin and clopidogrel was associated with a significantly increased risk of bleeding and probably would not result in a reduced frequency of graft thrombosis.

Low Responsiveness to Clopidogrel Increases Risk among CKD Patients Undergoing Coronary Intervention

Patrik Htun,* Suzanne Fateh-Moghadam,* Christian Bischofs,* Winston Banya,†
Karin Müller,* Boris Bigalke,* Konstantinos Stellos,* Andreas E. May,* Marcus Flather,†
Meinrad Gawaz,* and Tobias Geisler*†

*Medizinische Klinik III, Abteilung für Kardiologie und Kreislauferkrankungen, Universitätsklinikum der Eberhard-Karls-Universität Tübingen, Tübingen, Germany; and †Clinical Trials and Evaluation Unit, Royal Brompton and Harefield National Health Service Foundation Trust and Imperial College, Royal Brompton Hospital, London, United Kingdom

ABSTRACT

Patients with CKD are at higher risk for major events after percutaneous coronary intervention (PCI) compared with subjects with normal renal function. The aims of this study were to evaluate responsiveness to clopidogrel in patients with CKD and to examine the effect of antiplatelet drug response on post-PCI outcome. We retrospectively evaluated a consecutive cohort of 1567 patients with symptomatic coronary artery disease undergoing PCI, 648 (41%) of whom had stage 3 to 5 CKD. We assessed responsiveness to clopidogrel by ADP-induced platelet aggregation after oral administration of a 600-mg clopidogrel loading dose and 100 mg of aspirin. In a multivariate survival analysis that included 1335 (85%) of the cohort, stage 3 to 5 CKD and low response to clopidogrel were independent predictors of the primary end point (composite of myocardial infarction, ischemic stroke, and death within 1 year). In summary, a low response to clopidogrel might be an additional risk factor for the poorer outcomes in patients with stage 3 to 5 CKD compared with patients with better renal function.

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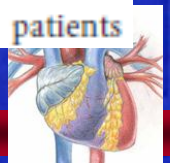
reactivity in patients receiving dual antiplatelet therapy with aspirin and clopidogrel and the prognostic effect of antiplatelet drug responsiveness on the outcome in patients with chronic kidney disease.

RESULTS

1567 patients were enrolled in the platelet aggregation study. The cohort consisted of consecutive, unselected patients who underwent coronary stenting for symptomatic coronary artery disease. Baseline characteristics for patients



Effect of Clopidogrel on Early Failure of Arteriovenous Fistulas for Hemodialysis

A Randomized Controlled Trial

Laura M. Dember, MD
Gerald J. Beck, PhD
Michael Allon, MD
James A. Delmez, MD
Bradley S. Dixon, MD
Arthur Greenberg, MD
Jonathan Himmelfarb, MD
Miguel A. Vazquez, MD
Jennifer J. Gassman, PhD
Tom Greene, PhD
Milena K. Radeva, MS
Gregory L. Braden, MD
T. Alp Ikizler, MD
Michael V. Rocco, MD, MSCE
Ingemar J. Davidson, MD
James S. Kaufman, MD
Catherine M. Meyers, MD
John W. Kusek, PhD
Harold I. Feldman, MD, MSCE
for the Dialysis Access Consortium Study Group

Context The arteriovenous fistula is the preferred type of vascular access for hemodialysis because of lower thrombosis and infection rates and lower health care expenditures compared with synthetic grafts or central venous catheters. Early failure of fistulas due to thrombosis or inadequate maturation is a barrier to increasing the prevalence of fistulas among patients treated with hemodialysis. Small, inconclusive trials have suggested that antiplatelet agents may reduce thrombosis of new fistulas.

Objective To determine whether clopidogrel reduces early failure of hemodialysis fistulas.

Design, Setting, and Participants Randomized, double-blind, placebo-controlled trial conducted at 9 US centers composed of academic and community nephrology practices in 2003-2007. Eight hundred seventy-seven participants with end-stage renal disease or advanced chronic kidney disease were followed up until 150 to 180 days after fistula creation or 30 days after initiation of dialysis, whichever occurred later.

Intervention Participants were randomly assigned to receive clopidogrel (300-mg loading dose followed by daily dose of 75 mg; n=441) or placebo (n=436) for 6 weeks starting within 1 day after fistula creation.

Main Outcome Measures The primary outcome was fistula thrombosis, determined by physical examination at 6 weeks. The secondary outcome was failure of the fistula to become suitable for dialysis. Suitability was defined as use of the fistula at a dialysis machine blood pump rate of 300 mL/min or more during 8 of 12 dialysis sessions.

Results Enrollment was stopped after 877 participants were randomized based on a stopping rule for intervention efficacy. Fistula thrombosis occurred in 53 (12.2%) participants assigned to clopidogrel compared with 84 (19.5%) participants assigned to placebo (relative risk, 0.63; 95% confidence interval, 0.46-0.97; $P=.018$). Failure to attain suitability for dialysis did not differ between the clopidogrel and placebo groups (61.8% vs 59.5%, respectively; relative risk, 1.05; 95% confidence interval, 0.94-1.17; $P=.40$).

Conclusion Clopidogrel reduces the frequency of early thrombosis of new arteriovenous fistulas but does not increase the proportion of fistulas that become suitable for dialysis.

Trial Registration clinicaltrials.gov Identifier: NCT00067119

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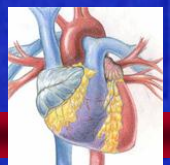
APPROXIMATELY 470 000 Americans have end-stage renal disease, and most are treated with hemodialysis.[1] A major challenge in caring for patients undergoing hemodialysis is maintaining a functioning vascular access, which is essential for performing the dialysis procedure. The effect of vascular access dysfunction is substantial—it is a leading reason for hospitalization among patients with end-stage renal disease and has asso-

Author Affiliations and Members of the Dialysis Access Consortium Study Group are listed at the end of this article.
Corresponding Author: Laura M. Dember, MD,



A Comparison of Clopidogrel Responsiveness in Patients With Versus Without Chronic Renal Failure

Sang Hyun Park, MD[a], Weon Kim, MD[b,*], Chung Su Park, MD[a], Won Yu Kang, MD[a], Sun Ho Hwang, MD[a], and Wan Kim, MD[a]

We sought to compare the platelet responsiveness to clopidogrel between patients with chronic renal failure and those with normal renal function. We conducted a prospective, randomized, open-label, single-center trial. A total of 23 patients with normal renal function received a usual daily dose of 75 mg of clopidogrel (group I, 61 ± 7 years). Also, 36 patients with chronic renal failure (60 ± 5 years) were divided into 2 groups according to their daily dose of clopidogrel: a daily dose of 75 mg of clopidogrel for 30 days (group II, n = 18) or a daily dose of 150 mg (group III, n = 18). The primary efficacy variables among the study groups using the VerifyNow P2Y12 assay were the P2Y12 reaction unit value and the percentage of inhibition. A significant difference was found in the P2Y12 reaction unit value among the 3 groups (239 ± 87 in group I, 308 ± 70 in group II, 302 ± 81 in group III (p = 0.013) and in the percentage of inhibition (35 ± 20 in group I, 21 ± 16 in group II, 23 ± 14 in group III, p = 0.026). No significant difference was found in the P2Y12 reaction units or percentage of inhibition between groups II and III. In conclusion, platelet responsiveness to clopidogrel decreased more in patients with chronic renal failure than in those with normal renal function, and this decreased platelet responsiveness to clopidogrel was not improved by an increase in the clopidogrel dosage. (Am J Cardiol 2009;104:1292–1295)

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Cardiovascular Mortality in Chronic Kidney Disease Patients Undergoing Percutaneous Coronary Intervention Is Mainly Related to Impaired $P2Y_{12}$ Inhibition by Clopidogrel

Olivier Morel, MD, PHD,*† Soraya El Ghannudi, MD,* Laurence Jesel, MD,* Bogdan Radulescu, MD,* Nicolas Meyer, MD, PHD,‡ Marie-Louise Wiesel, MD,§ Sophie Caillard, MD, PHD,‖ Umberto Campia, MD,¶ Bruno Moulin, MD, PHD,‖ Christian Gachet, MD, PHD,§ Patrick Ohlmann, MD, PHD*

Strasbourg and Le Kremlin Bicêtre, France; and Chicago, Illinois

Objectives We sought to determine whether low platelet response to the $P2Y_{12}$ receptor antagonist clopidogrel as assessed by vasodilator-stimulated phosphoprotein flow cytometry test (VASP-FCT) differentially affects outcomes in patients with or without chronic kidney disease (CKD) undergoing percutaneous coronary intervention (PCI).

Background Although both CKD and impaired platelet responsiveness to clopidogrel are strong predictors of unfavorable outcome after PCI, the impact of their association is unknown. The platelet VASP-FCT assay is specific for the $P2Y_{12}$ ADP receptor pathway. In this test, platelet activation is expressed as the platelet reactivity index (PRI).

Methods Four-hundred forty unselected patients (CKD: 126, estimated glomerular filtration rate [eGFR] <60 ml/min/1.73 m^2), no-CKD: 314 eGFR >60 ml/min/1.73 m^2) undergoing urgent (n = 336) or planned (n = 104) PCI were prospectively enrolled. In each subgroup, patients were classified as low-responders (LR: PRI ≥61%) or responders (R: PRI <61%) to clopidogrel.

Results At a mean follow-up of 9 ± 2 months, all-cause mortality, cardiac death, and possible stent thrombosis were higher in CKD than in no-CKD patients. Within the CKD group, the LR status was associated with higher rates of all-cause mortality (25.5% vs. 2.8%, $p < 0.001$), cardiac death (23.5% vs. 2.8%, $p < 0.001$), all stent thrombosis (19.6% vs. 2.7%, $p = 0.003$), and MACE (33.3% vs. 12.3%, $p = 0.007$). Conversely, in no-CKD patients, the LR status did not affect outcomes. Multivariate analysis identified Killip class ≥3, drug-eluting stent implantation, and the interaction between LR and CKD (hazard ratio: 11.96, 95% confidence interval: 1.22 to 116.82; $p = 0.033$) as independent predictors of cardiac death.

Conclusions In CKD patients, the presence of low platelet response to clopidogrel is associated with worse outcomes after PCI. (J Am Coll Cardiol 2011;57:399–408) © 2011 by the American College of Cardiology Foundation

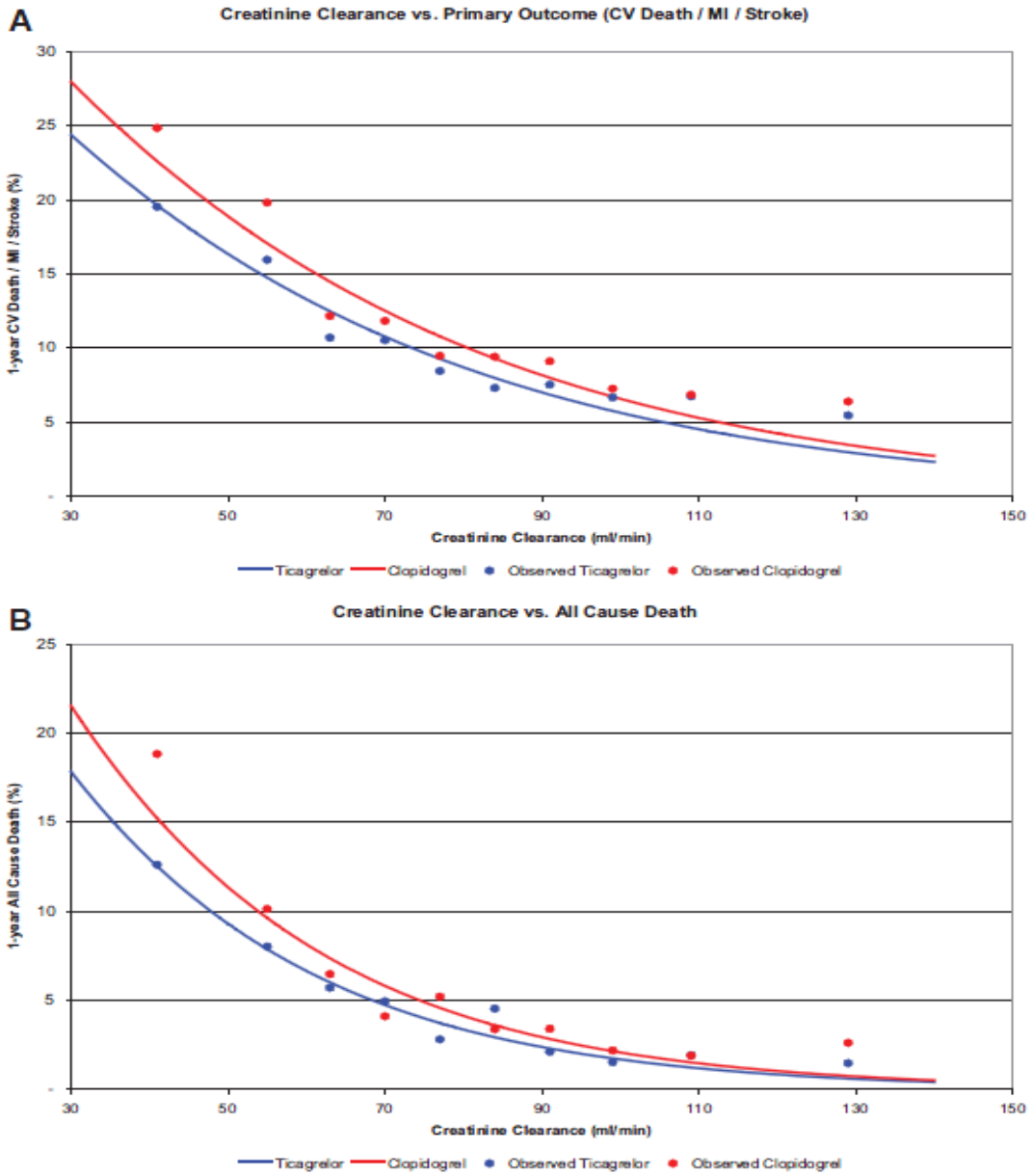

Figure 1. Deciles of baseline levels of CrCl by treatment are on the horizontal axis. A, Kaplan-Meier estimate of the yearly event rate for the primary composite end point of cardiovascular (CV) death, myocardial infarction (MI), and stroke on the vertical axis. B, Total mortality on the vertical axis. Each plot includes smoothed estimates of the relationships.

James S, et al *Circulation*. 2010; 122: 1056-1067

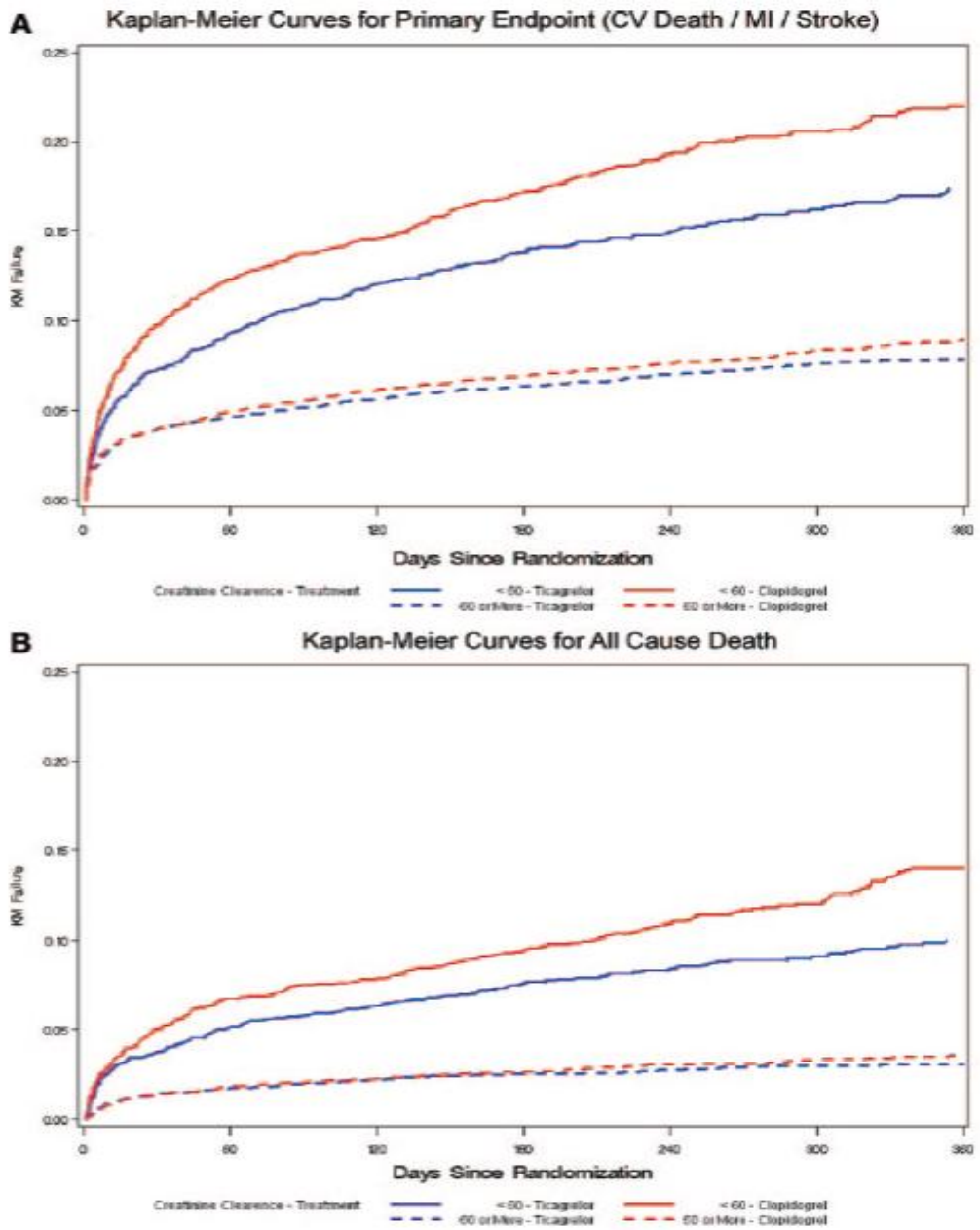

Figure 2. Kaplan-Meier (KM) event rate curves of (A) the primary composite of cardiovascular death, myocardial infarction, and stroke and (B) total mortality in the ticagrelor (blue lines) and clopidogrel (red lines) groups stratified by renal function. Patients with CKD (solid lines) and normal renal function (dotted lines) were determined by calculated CrCl at baseline.

James S, et al *Circulation*. 2010; 122: 1056-1067

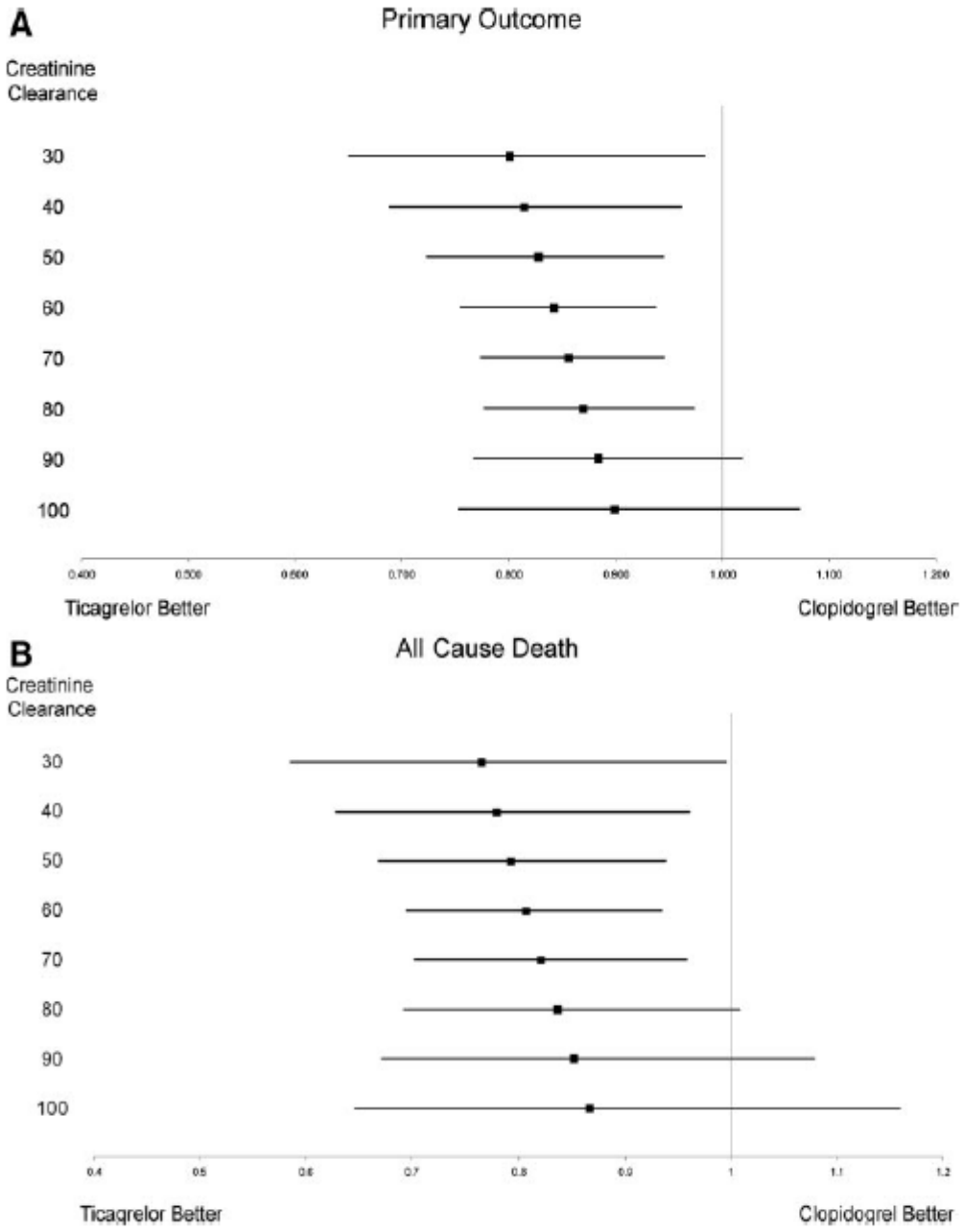

Figure 3. HRs with 95% CIs for (A) the primary composite end point of cardiovascular death, myocardial infarction, and stroke and (B) total mortality for ticagrelor vs clopidogrel at different cut points of CrCl.

James S, et al *Circulation*. 2010; 122: 1056-1067

Ticagrelor Versus Clopidogrel in Acute Coronary Syndromes in Relation to Renal Function

Results From the Platelet Inhibition and Patient Outcomes (PLATO) Trial

Stefan James, MD, PhD; Andrzej Budaj, MD, PhD; Philip Aylward, MD, PhD; Kristen K. Buck, MD; Christopher P. Cannon, MD; Jan H. Cornel, MD, PhD; Robert A. Harrington, MD; Jay Horrow, MD; Hugo Katus, MD, PhD; Matyas Keltai, MD, PhD; Basil S. Lewis, MD, PhD; Keyur Parikh, MD; Robert F. Storey, MD, PhD; Karolina Szummer, MD, PhD; Daniel Wojdyla, MSc; Lars Wallentin, MD, PhD

Background—Reduced renal function is associated with a poorer prognosis and increased bleeding risk in patients with acute coronary syndromes and may therefore alter the risk-benefit ratio with antiplatelet therapies. In the Platelet Inhibition and Patient Outcomes (PLATO) trial, ticagrelor compared with clopidogrel reduced the primary composite end point of cardiovascular death, myocardial infarction, and stroke at 12 months but with similar major bleeding rates.

Methods and Results—Central laboratory serum creatinine levels were available in 15 202 (81.9%) acute coronary syndrome patients at baseline, and creatinine clearance, estimated by the Cockcroft Gault equation, was calculated. In patients with chronic kidney disease (creatinine clearance <60 mL/min; n=3237), ticagrelor versus clopidogrel significantly reduced the primary end point to 17.3% from 22.0% (hazard ratio [HR], 0.77; 95% confidence interval [CI], 0.65 to 0.90) with an absolute risk reduction greater than that of patients with normal renal function (n=11 965): 7.9% versus 8.9% (HR, 0.90; 95% CI, 0.79 to 1.02). In patients with chronic kidney disease, ticagrelor reduced total mortality (10.0% versus 14.0%; HR, 0.72; 95% CI, 0.58 to 0.89). Major bleeding rates, fatal bleedings, and non–coronary bypass–related major bleedings were not significantly different between the 2 randomized groups (15.1% versus 14.3%; HR, 1.07; 95% CI, 0.88 to 1.30; 0.34% versus 0.77%; HR, 0.48; 95% CI, 0.15 to 1.54; and 8.5% versus 7.3%; HR, 1.28; 95% CI, 0.97 to 1.68). The interactions between creatinine clearance and randomized treatment on any of the outcome variables were nonsignificant.

Conclusions—In acute coronary syndrome patients with chronic kidney disease, ticagrelor compared with clopidogrel significantly reduces ischemic end points and mortality without a significant increase in major bleeding but with numerically more non–procedure-related bleeding.

Clinical Trial Registration—URL:http://www.clinicatrials.gov. Unique identifier: NCT00391872.

(***Circulation***. **2010;122:1056-1067.**)

Key Words: acute coronary syndrome ■ bleeding ■ clopidogrel ■ mortality ■ myocardial infarction ■ renal function

Pharmacokinetics, Pharmacodynamics, and Safety of Ticagrelor in Volunteers With Severe Renal Impairment

Kathleen Butler, MD, and Renli Teng, PhD

Ticagrelor, a $P2Y_{12}$ receptor antagonist, is approved in the European Union and the US for the prevention of thrombotic events in patients with acute coronary syndromes. Renal dysfunction potentially affects drug disposition. Ticagrelor pharmacokinetics, pharmacodynamics, and safety in renal impairment were assessed. A single 180-mg ticagrelor dose was administered to volunteers with severe renal impairment (creatinine clearance [CrCL] < 30 mL/min) and normal renal function (CrCL ≥ 80 mL/min; n = 10/group). Severe renal impairment did not significantly affect ticagrelor's pharmacokinetics, pharmacodynamics, or safety. Ticagrelor absorption and AR-C124910XX (active metabolite) formation were rapid. In renally impaired volunteers, ticagrelor mean maximum concentration (C_{max}) and area under the plasma concentration-time curve from zero to infinity were 20% lower and for AR-C124910XX was 17% higher versus normal volunteers. Ticagrelor systemic exposure was low in 3 volunteers (CrCL < 20 mL/min), but data were variable. Onset and offset of final-extent inhibition of platelet aggregation were comparable in both groups. Inhibition of platelet aggregation parameters and profiles were similar between groups, indicating that platelet sensitivity to ticagrelor was not affected by severe renal impairment. Ticagrelor was well tolerated in both groups with few adverse events. No ticagrelor dose adjustment is required for renally impaired patients.

Keywords: *Ticagrelor; antiplatelet therapy; renal insufficiency; pharmacokinetics; pharmacodynamics*

Journal of Clinical Pharmacology, XXXX;XX:xxx-xxx

Extrinsic factors:

- Uremic toxins
- Anemia
- Hyperhomocysteinemia

Plasma factors:

- Increased levels of d-dimers
- Reduced levels of protein C anticoagulant activity
- Increased levels of prothrombin fragments 1+2
- Increased levels of thrombin-antithrombin complex (ongoing coagulation)
- Decreased levels and reduced activity of antithrombin III
- Reduced levels of protein S
- Increased levels of tissue factor
- Elevation of antiphospholipid antibodies
- Increased levels of plasmin-antiplasmin complex (i.e. ongoing fibrinolysis)

Does Hemodialysis Affect *Clopidogrel* Resistance as Measured by VerifyNow® P2Y12 Test?

21 HD patients after therapy with clopidogrel
Blood sample was drawn from each patient before starting and at the end of the HD session using the dialysis access.
VerifyNow P2Y12.

Difference in PRUs before and after HD (299.71 ± 48.4 vs 274.09 ± 60, p = 0.029)

In this pilot study, defining platelet reactivity in HD patients using the VerifyNow P2Y12 has serious pitfalls in terms of the difference in the values of pre- and post-HD blood samples.

Geara AS, et al. Am J Cardiol. 2011;107(7):1103-4

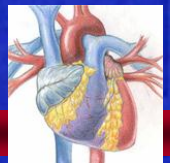

Table 1. Patient Demographic Characteristics

	Overall (n = 85)	Clopidogrel Responders (n = 15)	Clopidogrel Poor Responders (n = 70)	*P*
Age (y)	64.9 ± 12.9	62.5 ± 15.6	65.4 ± 12.4	0.4
Men	61 (71.8)	13 (86.7)	48 (68.6)	0.2
BMI (kg/m^2)	25.1 ± 4.2	24.8 ± 4.2	25.2 ± 4.2	0.8
Time on HD therapy (mo)	55 (2-262)	48 (2-132)	56 (2-262)	0.2
Time on clopidogrel therapy (mo)	33 (2-312)	24 (2-59)	36 (2-312)	0.1
Time since last clopidogrel dose (h)	17 (0.5-24)	17 (1-24)	15 (0.5-24)	0.3
Hyperlipidemia	44 (51.8)	7 (46.7)	37 (52.9)	0.8
Hypertension	73 (85.9)	12 (80.0)	61 (87.1)	0.4
Diabetes	28 (32.9)	3 (20.0)	25 (35.7)	0.4
Smoking	22 (25.9)	3 (20.0)	19 (27.1)	0.8
Prior MI	12 (14.1)	2 (13.3)	10 (14.3)	0.9
Prior CABG	9 (10.6)	2 (13.3)	7 (10.0)	0.7
Prior PCI	14 (16.5)	1 (6.7)	13 (18.6)	0.4
Hematocrit (%)	36.5 ± 4.1	39.0 ± 5.0	35.9 ± 3.7	0.007
Hemoglobin (g/dL)	11.8 ± 1.5	12.7 ± 1.6	11.6 ± 1.4	0.007
Platelets ($\times 10^3/\mu$L)	221.9 ± 74.3	265.1 ± 102.4	212.7 ± 64.0	0.01
Medication				
Omega-3 fatty acids	27 (31.8)	5 (33.3)	22 (31.4)	0.9
Statins	23 (27.1)	6 (40.0)	17 (24.3)	0.2
PPIs	41 (48.2)	4 (26.7)	37 (52.9)	0.09
Omeprazole	24 (28.2)	2 (13.3)	22 (31.4)	0.2
Pantoprazole	9 (10.6)	0 (0)	9 (12.9)	0.4
Esomeprazole	5 (5.9)	2 (13.3)	3 (4.3)	0.2
Rabeprazole	3 (3.5)	0 (0)	3 (4.3)	0.9
ACE inhibitors	16 (18.8)	3 (20.0)	13 (18.6)	0.9
CCBs	22 (25.9)	5 (33.3)	17 (24.3)	0.5
Aspirin	22 (25.9)	4 (26.7)	18 (25.7)	0.9
Insulin	20 (23.5)	3 (20.0)	17 (24.3)	0.9