Impact of Chronic Kidney Disease on Platelet Reactivity and Outcomes of Patients Receiving Clopidogrel and Undergoing Percutaneous Coronary Intervention

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The impact of chronic kidney disease (CKD) on residual platelet reactivity (PR) in patients undergoing percutaneous coronary intervention (PCI) is still debatable. We sought to investigate the interaction between PR and renal function and the related clinical outcomes in patients with coronary artery disease treated with PCI. Immediately before PCI, we measured PR (as P2Y12 reaction units [PRUs]) in 800 patients on clopidogrel with the VerifyNow P2Y12 assay. High PR was defined as a PRU value of ≥240 and low PR as a PRU value of ≤178. Based on a glomerular filtration rate of < or ≥60 ml/min/1.73 m^2, patients were respectively grouped into those with or without moderate-to-severe CKD. Primary end point was the incidence of 30-day net adverse clinical events (NACEs). Patients with moderate-to-severe CKD (n = 173, 21.6%) and those without showed similar PRU values (208 ± 67 vs 207 ± 75, p = 0.819). Yet, NACEs were significantly higher in patients with moderate-to-severe CKD (19.7% vs 9.1%, p <0.001), in terms of both ischemic (12.1% vs 7.2%, p = 0.036) and bleeding events (8.7% vs 2.1%, p <0.001). NACEs were significantly higher when moderate-to-severe CKD was associated with either high PR or low PR (25.4%, p for trend <0.001); this association was the strongest predictor of NACE at multivariate analysis (odds ratio 3.4, 95% confidence interval 2.0 to 5.6, p <0.001). In conclusion, we did not find an association between moderate-to-severe CKD and residual PR on clopidogrel. However, the association of moderate-to-severe CKD with either high or low PR was a strong determinant of adverse events after PCI. © 2014 Elsevier Inc. All rights reserved. (Am J Cardiol 2014;113:1124−1129)

Recent findings suggest that renal function might affect the clinical efficacy of clopidogrel. It has been hypothesized that patients with chronic kidney disease (CKD) might have reduced clopidogrel-induced platelet inhibition due to a specific impairment of the P2Y12 pathway.[1] However, conflicting data have been reported concerning the impact of CKD on residual platelet reactivity (PR) on clopidogrel in patients with coronary artery disease (CAD).[2−4] Aim of the present study is to further investigate the relation between PR and renal function and to evaluate their impact on clinical outcomes after percutaneous coronary intervention (PCI).

Methods

This prospective observational study enrolled consecutive patients undergoing PCI for stable CAD or non−ST elevation acute coronary syndrome at the Department of Cardiovascular Sciences, Campus Bio-Medico University, Rome, Italy, and at Cardiovascular Center Aalst, Aalst, Belgium. Exclusion criteria were ST elevation myocardial infarction (MI), radial approach, upstream use of glycoprotein IIb/IIIa inhibitors, platelet count $<70 \times 10^9$/L, active bleeding or bleeding diathesis, dialysis, and any malignancy. The study was performed in accordance with the Declaration of Helsinki and the protocol was approved by the institutional ethics committees, with all patients giving written informed consent. All interventions were performed with standard technique by way of the femoral approach. Before the procedure, patients were given unfractionated heparin (70 to 100 IU/kg body weight). All patients received aspirin before PCI. Patients received a 600-mg clopidogrel loading dose ≥6 hours before intervention or were pretreated with clopidogrel 75 mg/day for ≥5 days. Technicalities of the procedure, including use of drug-eluting stents and glycoprotein IIb/IIIa inhibitors, were left to the operator's discretion. Procedural success was defined as a reduction in percent diameter stenosis to below 30% and presence of Thrombolysis In Myocardial Infarction (TIMI) flow grade 3 in the main vessel and all side branches ≥2 mm in diameter.

Baseline serum creatinine levels were assessed at hospital admission in all patients. The estimated glomerular filtration rate (GFR) was calculated using the abbreviated Modification of Diet in Renal Disease formula.[5] CKD was defined according to the National Kidney Foundation's classification as follows: normal renal function to mild renal impairment with a GFR of ≥60 ml/min/1.73 m^2 and moderate-to-severe CKD with a GFR of <60 ml/min/1.73 m^2.[6]

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Table 1
Clinical and procedural features

Variable	Overall (n = 800)	GFR <60 ml/min/1.73 m^2 (n = 173)		p Value
		No (n = 627)	Yes (n = 173)	
Age (yrs)	67 ± 10	66 ± 10	68 ± 10	0.008
Men	590 (74)	457 (73)	133 (77)	0.291
Body mass index (kg/m^2)	26.1 ± 3.3	26.0 ± 3.2	26.3 ± 3.5	0.432
Hypertension	630 (79)	627 (78)	143 (83)	0.156
Diabetes mellitus	236 (30)	225 (36)	58 (34)	0.566
Dyslipidemia	598 (75)	468 (75)	130 (75)	0.587
Current smoking	162 (20)	131 (21)	31 (18)	0.389
Clinical presentation				0.635
Stable angina pectoris	569 (71)	411 (72)	158 (70)	
Non−ST elevation ACS	231 (29)	163 (28)	68 (30)	
Previous MI	199 (25)	182 (29)	56 (32)	0.395
Previous coronary revascularization	274 (34)	211 (34)	63 (36)	0.498
LVEF <40%	75 (9)	47 (7)	15 (9)	0.595
Clopidogrel therapy				0.178
Maintenance dose, 75 mg	105 (13)	77 (12)	28 (16)	
Loading dose, 600 mg	695 (87)	550 (88)	145 (84)	
Laboratory data				
Serum creatinine (mg/dl)	1.0 ± 0.3	1.0 ± 0.2	1.4 ± 0.2	<0.001
Estimated GFR (ml/min/1.73 m^2)	76.9 ± 24.2	83 ± 21	52 ± 7	<0.001
Multivessel CAD	336 (42)	252 (40)	84 (49)	0.048
Target coronary vessel				0.477
Left main	6 (1)	5 (1)	1 (1)	
Left anterior descending	429 (54)	343 (55)	86 (50)	
Left circumflex	133 (17)	111 (18)	32 (18)	
Right	217 (27)	163 (26)	54 (31)	
Saphenous vein graft	5 (1)	5 (1)	0 (0)	
Stent implanted	1.4 ± 0.9	1.4 ± 0.9	1.5 ± 1.0	0.089
Drug-eluting stents	231 (29)	174 (28)	57 (33)	0.182
Total stent length (mm)	22.8 ± 13.4	21.4 ± 12.1	25.6 ± 15.8	0.005
Glycoprotein IIb/IIIa inhibitors	87 (11)	66 (11)	21 (12)	0.546
Sheath size				0.717
6Fr	713 (89)	555 (89)	158 (91)	
7Fr	87 (11)	72 (11)	15 (9)	

Data are presented as mean ± SD or n (%).
ACS = acute coronary syndrome; LVEF = left ventricular ejection fraction.

PR was measured in the catheterization laboratory using the VerifyNow P2Y12 assay (Accumetrics, Inc., San Diego, California) immediately before PCI. Blood was drawn from the femoral artery immediately after sheath insertion. After discarding the first 5 ml of blood to avoid unwanted platelet activation, samples were collected into a 2-ml tube containing 3.2% sodium citrate. The VerifyNow P2Y12 assay is a turbidimetry-based optical detection system that measures platelet-induced aggregation by P2Y12 antagonist as an increase in light transmittance.[7] The assay contains 20-mol adenosine diphosphate and 22-nmol prostaglandin E1 to reduce the activation contribution from adenosine diphosphate binding to P2Y12 receptors. Values are expressed as P2Y12 reaction units (PRUs). The lower the PRU value, the greater the degree of P2Y12 receptor inhibition by clopidogrel and vice versa. According to previous studies, high platelet reactivity (HPR) was defined as a PRU value of $\geq$240[8–11] and low platelet reactivity (LPR) as a PRU value of $\leq$178.[11]

The primary end point was the 30-day incidence of net adverse clinical events (NACEs), defined as the occurrence of both ischemic and bleeding events. Secondary end point was the occurrence of any of the components of the primary end point. Ischemic events included death, MI, and target vessel revascularization. MI accounted for both periprocedural and spontaneous events. Periprocedural MI was defined as a postprocedural increase in creatine kinase-MB >3 times the ninety-ninth percentile of the upper reference limit for patients with baseline negative myocardial necrosis markers.[12] In patients with increased baseline levels of creatine kinase-MB, a subsequent increase >50% of the baseline value fulfilled the criteria for periprocedural MI.[13] Occurrence of spontaneous MI was defined as the presence of symptoms compatible with recurrent ischemia associated with electrocardiographic changes indicative of new ischemia (new ST-T changes or new left bundle branch block).[12] Definite stent thrombosis was defined according to the Academic Research Consortium definition.[14] Target vessel revascularization included bypass surgery or clinically driven repeat PCI of the target vessel(s). Bleeding events were defined as major bleeding according to the TIMI criteria or large entry-site hematoma (>10 cm in diameter).[15,16] Entry-site hematomas were repeatedly monitored throughout the hospitalization and the largest size detected was used for the analysis.