

Platelet function testing to predict hyporesponsiveness to clopidogrel in patients with chest pain seen in the emergency department

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Background: A dual antiplatelet regimen has been shown to reduce the risk of major adverse cardiovascular events after percutaneous coronary intervention. However, there is little information available on inhibition of platelet aggregation in patients with a prior coronary stent presenting with chest pain. This study evaluated the prevalence of hyporesponsiveness to clopidogrel and factors associated with this in patients presenting to our emergency department with chest pain who had previously undergone coronary stent placement and were prescribed dual antiplatelet therapy.

Methods: Responsiveness to clopidogrel was evaluated in a cohort of 533 consecutive stented patients presenting to the emergency department with chest pain. P2Y₁₂ reaction units (PRU) and percent P2Y₁₂ inhibition with clopidogrel were measured in all patients. Of 533 patients, 221 (41.6%) had PRU \geq 230. A multivariate logistic regression model was used to determine the relationship between hyporesponsiveness to clopidogrel (defined as PRU \geq 230) and several potential risk factors, ie, gender, age, race, type 1 or type 2 diabetes, hypertension, smoking, chronic renal failure, and obesity.

Results: There was a greater risk of hyporesponsiveness in African Americans than in non-African American patients (adjusted odds ratio [OR] = 2.165), in patients with type 2 diabetes than in those without (adjusted OR = 2.109), and in women than in men (adjusted OR = 1.813), as well as a greater risk of hyporesponsiveness with increasing age (adjusted OR = 1.167 per decade).

Conclusion: There was a high prevalence of hyporesponsiveness to clopidogrel in patients presenting with chest pain and a prior coronary stent. Non-insulin-dependent diabetes mellitus and African American race were the strongest predictors of hyporesponsiveness to clopidogrel, followed by gender and age.

Keywords: clopidogrel, platelet function testing, chest pain, emergency department

Introduction

Dual antiplatelet treatment has been shown to reduce the risk of major adverse cardiovascular events after percutaneous coronary intervention. Premature cessation of dual antiplatelet therapy, including aspirin and thienopyridine drugs, such as ticlopidine, clopidogrel, or prasugrel, and non-thienopyridines, such as ticagrelor, is associated with an increased risk for major cardiovascular events and stent thrombosis.¹ Dual antiplatelet therapy is recommended for 12 months after placement of a drug-eluting stent.²

Thienopyridine drugs, including ticlopidine, clopidogrel, and prasugrel, and the non-thienopyridine agent, ticagrelor, interact with P2Y₁₂, an adenosine diphosphate receptor. It is known that the pharmacodynamic response to clopidogrel

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is less than desirable in 15%–40% of patients.^{3–6} The clinical significance of this variable response to antiplatelet agents has been debated in the medical community, and the US Food and Drug Administration has responded by issuing three sequential “boxed warnings” for clopidogrel.⁷ It is believed that a suboptimal response to an antiplatelet regimen may be associated with adverse cardiovascular and cerebrovascular outcomes.^{8,9}

During coronary intervention, there is a need for adequate P2Y₁₂ inhibition using P2Y₁₂ receptor blockers and inhibition of thromboxane production with aspirin in addition to antithrombotic regimens.¹⁰ Many trials have shown that poor inhibition of platelet aggregation may lead to a higher risk of stent thrombosis in such patients.^{8,11–13}

We report here the prevalence of hyporesponsiveness to clopidogrel assessed by platelet function assay in patients with chest pain who had previously received a coronary stent and presented in the community hospital setting. We now report the distinctive finding that a large proportion of such patients have inadequate inhibition of platelet aggregation.

Materials and methods

A platelet function assay was performed in all patients presenting to the emergency department of a community hospital with chest pain, a history of coronary artery stenting, and prescribed clopidogrel and aspirin. A cohort of 533 consecutive patients was studied prospectively, consistent with the clinical protocol of the hospital emergency department chest pain center. Characteristics of study patients are shown in Table 1.

The platelet function assay included measurement of platelet reactivity, reported as P2Y₁₂ reaction units of clopidogrel (PRU), baseline PRU (preclopidogrel), percent inhibition of P2Y₁₂, and aspirin reaction units in all patients who gave a history of taking aspirin and clopidogrel after coronary intervention. Hyporesponsiveness to clopidogrel is defined as a PRU > 230 or percent inhibition of P2Y₁₂ < 30%. The data were also analyzed using a hyporesponsiveness threshold of PRU > 208. Emergency department attendance records were reviewed for pertinent clinical factors. The protocol was approved by the institutional review board.

Platelet function assay

Assessment of platelet function was done using the commercially available VerifyNow[®] test (Accumetrics, San Diego, CA, USA) and has been described in detail elsewhere.¹⁴ Many trials, including GRAVITAS (Gauging Responsiveness with a VerifyNow Assay Impact on Thrombosis and Safety), have used a PRU > 230¹⁵ as the threshold for hyporesponsiveness.

Table 1 Patient characteristics stratified by clopidogrel hyporesponsiveness, with PRU = 230 as the cutoff

	PRU < 230	PRU ≥ 230	P value
Gender			
Male	187 (60.1%)	96 (43.2%)	<0.001
Female	124 (39.9%)	126 (56.8%)	
Age			
Mean (SD)	63.6 (12.3)	65.4 (13.2)	0.110
Race			
Caucasian	244 (78.5%)	142 (64.0%)	<0.001
African American	66 (21.2%)	75 (33.8%)	
Asian	1 (0.3%)	2 (0.9%)	
Other	0 (0.0%)	3 (1.4%)	
Type 1 diabetes			
Yes	6 (1.9%)	5 (2.3%)	1.000
No	304 (97.7%)	217 (97.7%)	
Unknown	1 (0.3%)	0 (0.0%)	
Type 2 diabetes			
Yes	76 (24.4%)	90 (40.5%)	<0.001
No	234 (75.2%)	131 (59.0%)	
Unknown	1 (0.3%)	1 (0.5%)	
Hypertension			
Yes	266 (85.5%)	194 (87.4%)	0.795
No	42 (13.5%)	28 (12.6%)	
Unknown	3 (1.0%)	0 (0.0%)	
Smoking			
Yes	136 (43.7%)	83 (37.4%)	0.153
No	173 (55.6%)	138 (62.2%)	
Unknown	2 (0.6%)	1 (0.5%)	
Chronic renal failure			
Yes	57 (18.3%)	48 (21.6%)	0.378
No	253 (81.4%)	174 (78.4%)	
Unknown	1 (0.3%)	0 (0.0%)	
Obesity			
Yes	133 (42.8%)	98 (44.1%)	0.790
No	177 (56.9%)	123 (55.4%)	
Unknown	1 (0.3%)	1 (0.5%)	

Notes: Fisher's Exact test (or Student's *t*-test for age) was used to test for dependence between hyporesponsiveness and each patient characteristic. There was a statistically significant bivariate association with gender, race, and type 2 diabetes, with the higher risk of hyporesponsiveness associated with female gender, African American race, and having type 2 diabetes. There is a marginally significant (*P* = 0.110) association with increasing age.

Abbreviations: PRU, P2Y₁₂ reaction units; SD, standard deviation.

The logic of this cutoff has been discussed previously.¹⁵ Furthermore, post hoc analysis of GRAVITAS using a PRU ≥ 208 was identified as a predictor of death, myocardial infarction, and stroke at one year, with fewer cardiovascular events in the GRAVITAS trial.¹⁶ Thus, our primary analysis was based on a PRU > 230 and the secondary analysis was done using PRU > 208.

The platelet function assay uses arachidonic acid, adenosine diphosphate (ADP), and thrombin receptor-activating peptide to assess platelet responsiveness to the P2Y₁₂ inhibitor, clopidogrel. The assay uses whole blood in a turbidometric assay and fibrinogen-coated beads to measure differences in platelet aggregation in response to various

agonists.¹⁷ Whole blood from a patient is exposed to 20 μ mol ADP and 22 nmol prostaglandin E1. Prostaglandin E1 helps to increase the specificity of the P2Y12 assay by suppressing ADP-mediated P2Y1 platelet activation and aggregation. The patient's platelets agglutinate around the fibrinogen-coated beads with an increase in light transmittance. The results are reported as PRU.

The platelet function assay reported three values in this cohort of patients:

- PRU which represents the extent of inhibition of the P2Y12 ADP receptor by thienopyridines or non-thienopyridines, and the test takes advantage of different receptors on platelets stimulated by different agonists. P2Y12 subreceptors of ADP and thrombin receptors are strong platelet activators and function independently of each other.
- baseline PRU is calculated by stimulating thrombin receptors on platelets to estimate the total possible platelet aggregation in the preclopidogrel state.
- percent inhibition of P2Y12 ADP receptors is determined by the difference between baseline PRU and PRU determined after exposure to an ADP agonist; however, percent inhibition of P2Y12 may not be accurate, because

baseline PRU is not actually preclopidogrel PRU, but rather estimated by the thrombin agonist response while the patient is taking clopidogrel, and thrombin-induced platelet aggregation may not be an adequate reflection of baseline ADP-induced platelet aggregation.¹⁸

Results

A cohort of 533 consecutive patients presenting to the emergency department with chest pain and a history of being prescribed clopidogrel were studied. Two patients were excluded from analysis because they had no baseline PRU reading. Of 531 patients with baseline PRU readings, 221 (41.6%) had high platelet reactivity on treatment (PRU \geq 230) and 287 (54.0%) had percent P2Y12 inhibition $<$ 30%; hyporesponsiveness based on these two indicators was concordant in 439 patients (82.7%). A total of 268 patients (50.5%) had PRU \geq 208. Determination of hyporesponsiveness to clopidogrel based on PRU \geq 208 and percent P2Y12 inhibition $<$ 30% thresholds was concordant in 456 patients (85.9%), as shown in Figure 1.

A multivariate logistic regression model was used to determine the relationship between hyporesponsiveness

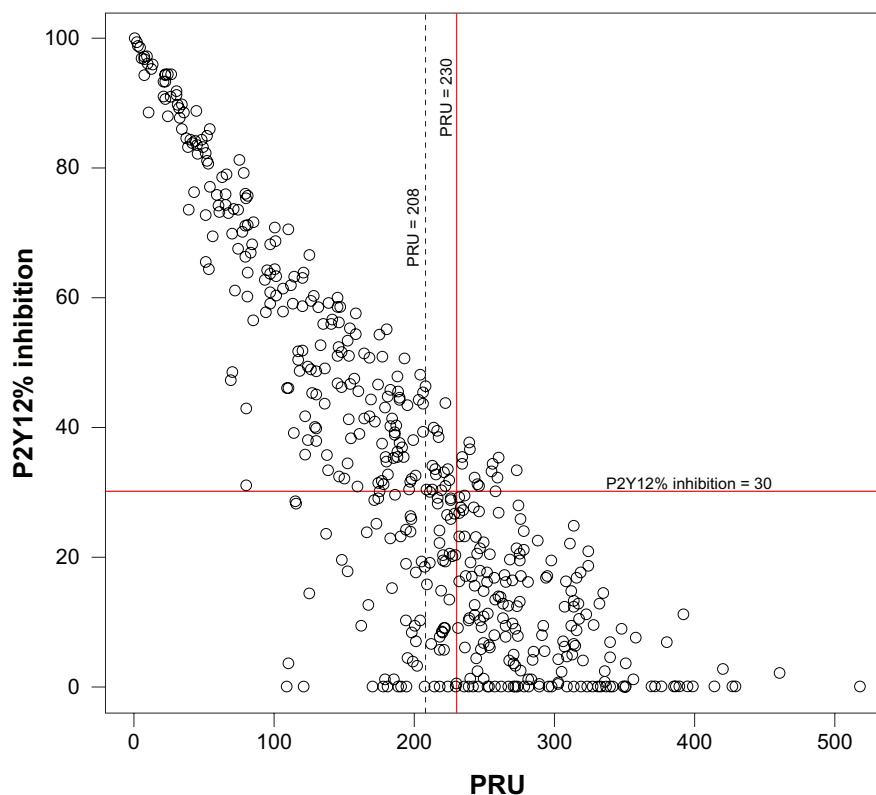


Figure 1 Scatter plot of percent P2Y12 inhibition versus PRU.

Notes: Points to the right of the vertical red line are patients for whom PRU was \geq 230, while points below the horizontal red line are for patients in whom percent P2Y12 inhibition was $<$ 30. Points in the lower right quadrant ($n = 208$, 39.2%) are judged clopidogrel-hyporesponsive by both criteria, while points in the upper left quadrant ($n = 231$, 43.5%) are judged clopidogrel-responsive by both criteria. Points in the upper right and lower left quadrants ($n = 92$, 17.3%) have discordant judgments based on the two criteria. For comparison, a dotted gray line is drawn at the alternative PRU = 208 cutoff.

Abbreviation: PRU, P2Y12 reaction units.

to clopidogrel ($\text{PRU} \geq 230$) and several potential risk factors for variation in platelet function and ischemic heart disease. The results of this modeling are shown in Table 2. There are three predictors that are statistically significant at $P < 0.05$, and one (ie, age) at $P < 0.06$. Specifically, there was a greater risk of hyporesponsiveness in patients with type 2 diabetes than those without (adjusted odds ratio [OR] = 2.109), in African American compared with non-African American patients (adjusted OR = 2.165), and in women compared with men (adjusted OR = 1.813), and there was also a greater risk of hyporesponsiveness with increasing age (adjusted OR = 1.167 per decade). When adjusted for other risk factors, smoking was not a statistically significant predictor of hyporesponsiveness to clopidogrel.

Discussion

This study reports distinctive findings on the prevalence of inadequate platelet inhibition in patients with a coronary stent who are prescribed clopidogrel and return to a community hospital emergency department with chest pain. Depending on the definition of inadequate platelet inhibition used, 42%–54% of such patients had poor inhibition of platelet function. This is a remarkable failure of efficacy of a drug treatment strategy. Whether or not these patients prove to have an acute coronary syndrome at the time of the emergency department visit, or chest pain of other etiology, this determination of the efficacy of the current treatment strategy produces results that are concerning. The quantitative analysis of inadequate platelet inhibition varies somewhat, depending on whether percent inhibition or PRU is the metric, although concordance is reasonable (Figure 1).

Noncompliance with medication may have contributed to inadequate platelet inhibition. The incidence of

non adherence with dual antiplatelet therapy in the “real-world” international observation registry was 2% at 30-day follow-up.¹⁹ Nonetheless, the current study does provide a distinctive analysis of the incidence of adequate and inadequate platelet inhibition in a group of patients with coronary stents and chest pain, and such patients are commonly seen in emergency departments.

The individual biological response to clopidogrel is variable. Multiple studies support the hypothesis that this variable pharmacodynamic effect of clopidogrel may be responsible for atherothrombotic events following stent deployment.^{9,20–22} Diabetes and African American race were strong predictive factors. Hyporesponsiveness to clopidogrel can be secondary to several factors, including age, body mass index, diabetes, dyslipidemia, chronic renal disease, genetic polymorphism, and pharmacokinetic and pharmacodynamic interactions arising from concomitant use of other drugs.^{23,24} Failure to take the drug as prescribed certainly can produce hyporesponsiveness. Studies have found that platelets from diabetic patients are generally more reactive^{25,26} and less responsive to antiplatelet therapy.²⁷ Our findings are consistent with those observations. Several factors may explain this global hyper-reactive platelet in diabetes, such as insulin resistance, poor glycemic control, increased inflammatory status, increased response to ADP, increased reactivity on contact with collagen,²⁸ increased fibrinogen levels,²⁹ and increased production of epinephrine and thrombin receptor agonist peptide.^{28,30}

Mangicapra et al used the VerifyNow assay in diabetic patients undergoing percutaneous coronary intervention and found them to have higher platelet reactivity and worse periprocedural outcomes.³¹ Diabetic patients also have a poor response to aspirin (aspirin reaction units > 550).³² In our study, patients with type 2 diabetes presenting with

Table 2 Multivariable logistic regression model of hyporesponsiveness to clopidogrel ($\text{PRU} \geq 230$)

Variable	Estimate	SE	Z value	P value	Adjusted OR		
					Estimate	95% CI	
Intercept	−1.827	0.618	−2.957	0.0031*			
Gender (female)	0.595	0.191	3.113	0.0019*	1.813	1.248	2.641
Age (decades)	0.155	0.082	1.899	0.0575	1.167	0.996	1.372
Race (African American)	0.772	0.215	3.589	0.0003*	2.165	1.423	3.312
Type 1 diabetes	−0.109	0.692	−0.158	0.8747	0.897	0.212	3.432
Type 2 diabetes	0.746	0.206	3.618	2.97E-04*	2.109	1.410	3.166
Hypertension	−0.299	0.287	−1.041	0.2980	0.742	0.424	1.309
Smoking	−0.038	0.202	−0.190	0.8496	0.962	0.648	1.431
Chronic renal failure	0.110	0.233	0.475	0.6349	1.117	0.706	1.760
Obesity	0.015	0.194	0.076	0.9396	1.015	0.693	1.485

Notes: Parameter estimates, standard errors, P values ($H_0: \beta = 0$ versus nonzero alternative), and adjusted OR for each of nine predictors and 95% CI. * $P > 0.05$.

Abbreviations: CI, confidence interval; OR, odds ratio; SE, standard error; PRU, P2Y₁₂ reaction units.

chest pain had a higher prevalence of hyporesponsiveness (adjusted OR = 2.1409), as shown in Table 2.

This analysis also shows a greater risk of hyporesponsiveness in African American patients than in non-African Americans (adjusted OR = 2.165). Collins et al³³ have shown the African American race to be an independent risk factor for developing stent thrombosis after placement of a drug-eluting stent. Despite higher compliance with clopidogrel in African American patients, they were nearly three times more likely to develop stent thrombosis than non-African Americans (1.71% versus 0.59%). However, no platelet function testing was done in these patients to probe any relationship between stent thrombosis and hyporesponsiveness despite higher compliance with clopidogrel. Higher stent thrombosis may be due to genetic polymorphism making African American patients less responsive to clopidogrel.

As suggested by this and other studies, mechanisms of hyporesponsiveness to clopidogrel, such as genetic polymorphism, may need to be assessed. Previous studies have demonstrated that carriers of the cytochrome P450 (CYP) 2C19 hypofunctioning allele may produce a factor leading to decreased clopidogrel metabolites, causing diminished platelet inhibition and an increased rate of cardiovascular events.^{34,35} Such polymorphism is seen more frequently in African American and East Asians than in Caucasians.³⁶ The CYP 2C19*2 allele is present in 13% of Caucasians, 18% of African Americans, and 29% in East Asians.³⁷ Rapid point-of-care genotyping at the bedside is evolving in clinical practice, which will help personalization of antiplatelet therapy.³⁸ While the importance of the platelet function assay is evolving, the platelet function test may be useful in high-risk patients, such as those with diabetes, left main stem stenosis, and diffuse atherosclerotic disease with complex coronary lesions undergoing percutaneous coronary intervention.³⁹

Limitations

Limitations of this study include its lack of clinical outcome data or biomarkers for ischemia. Because inclusion in the study was dependent on the patient stating that they were taking clopidogrel and aspirin, the level of actual, as opposed to stated, patient compliance with the antiplatelet regimen is not known. Therefore, this was not a study of drug efficacy but rather a study of platelet inhibition in the clinical syndrome of chest pain evaluated in the emergency department for patients who have been prescribed clopidogrel and aspirin.

Tailoring antiplatelet therapy according to platelet function testing

Use of the platelet function assay to guide antiplatelet therapy has received considerable attention. This study and others have identified clinical risk factors for inadequate platelet inhibition by clopidogrel. However, clinical profiling clearly has inadequate predictive value in itself, and a platelet function assay may add value. Results from the large ADAPT-DES (Assessment of Dual AntiPlatelet Therapy With Drug Eluting Stents) registry suggest that hyporesponsiveness to clopidogrel after implantation of a drug-eluting stent is an independent predictor of stent thrombosis and myocardial infarction.⁴⁰ A platelet function assay may help screen for hyporesponders and nonresponders, and could also identify patients in whom medication compliance may be the main issue.

There are several alternatives to clopidogrel for patients with a suboptimal response to antiplatelet therapy. Newer antiplatelet agents, such as prasugrel and ticagrelor, have demonstrated superiority in patients with an acute coronary syndrome.^{41,42} These new drugs are not affected by genetic variants of CYP 2C19, and are more effective, with a more predictable pharmacodynamic response, than the standard dose of clopidogrel. However, it is likely that clopidogrel will remain a valuable and widely used inhibitor of platelet function. This study demonstrates that the therapeutic goal, ie, platelet inhibition, assessed by an in vitro assay, is not achieved by a large proportion of patients prescribed clopidogrel to prevent coronary stent thrombosis. Ongoing trials will expand our understanding of dual antiplatelet regimens and the role of the platelet function assay. The use of in vitro testing may be useful to guide treatment and to identify hyporesponders or nonresponders.

Disclosure

The authors report no conflicts of interest in this work.

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