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**ORIGINAL ARTICLES**

# Impact of clopidogrel resistance on stroke severity in patients with acute ischemic stroke

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### *Abstract*

*Background:* Prior use of antiplatelet agents is associated with reduced severity in patients with ischemic stroke. However, clopidogrel resistance, which is characterized by a suboptimal platelet response to clopidogrel, diminishes the drug's efficacy. This study aimed to investigate the impact of clopidogrel resistance on stroke severity in patients receiving clopidogrel. *Methods:* A total of 116 patients who developed acute ischemic stroke while on clopidogrel, presented to two hospitals within 72 h of symptom onset, and underwent clopidogrel resistance testing using the VerifyNow assay were enrolled. The relationship between the VerifyNow parameters and stroke severity was analyzed using correlation and multivariable regression analyses. *Results:* Among the VerifyNow parameters, percent inhibition showed a significant inverse correlation with National Institutes of Health Stroke Scale (NIHSS) score at admission ($r = -0.387$, $p < 0.001$), whereas the P2Y12 reaction unit (PRU) exhibited a significant positive correlation ($r = 0.207$, $p = 0.028$). Multivariable analysis confirmed a significant inverse relationship between percent inhibition and NIHSS score at admission (B = -0.107, 95% confidence interval = -0.163 to -0.051; $p < 0.001$). However, PRU was not significantly associated with NIHSS score at admission in the multivariable analysis.
*Conclusions:* Clopidogrel resistance, particularly lower percent inhibition, was associated with greater stroke severity in patients receiving clopidogrel.

*Keywords:* Stroke, platelet function test, clopidogrel resistance, outcome

## INTRODUCTION

Stroke is a leading cause of long-term disability worldwide, highlighting the need for effective treatment and prevention strategies to improve clinical outcomes.[1] Antiplatelet therapy has been established as a cornerstone in the prevention of ischemic stroke.[2] In addition, prior use of antiplatelet agents has been shown to reduce stroke severity and improve functional outcomes.[3,4] Clopidogrel, a selective inhibitor of the P2Y12 receptor, is one of the widely used antiplatelet agents and is frequently recommended in clinical guidelines to reduce the risk of ischemic stroke.[2,5] However, a suboptimal platelet response to clopidogrel therapy, known as clopidogrel resistance, has been associated with increased thrombotic events in patients with ischemic stroke.[6-10] Given this evidence, clopidogrel resistance may influence stroke severity in patients already receiving clopidogrel therapy. Nevertheless, the relationship between clopidogrel resistance and stroke severity remains poorly understood, warranting further investigation.

Clopidogrel resistance can be evaluated using various methods, including light transmission aggregometry, flow cytometry, and genetic testing.[11] The VerifyNow system is a simple and rapid platelet function test that measures the blockade of the platelet P2Y12 receptor.[11] This system provides two key indicators of clopidogrel resistance: the P2Y12 reaction unit (PRU) and the percent inhibition. PRU is an absolute measure of platelet reactivity in response to adenosine diphosphate (ADP), whereas percent inhibition quantifies platelet reactivity to ADP compared

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to its activation by a reference agent. However, data on which of these indicators is more closely associated with the outcome of ischemic stroke are lacking.

Therefore, this study had two main objectives. First, it aimed to assess the impact of clopidogrel resistance, as measured using the VerifyNow assay, on stroke severity in patients receiving clopidogrel. Second, it sought to determine whether PRU or percent inhibition is a better predictor of ischemic stroke severity.

## METHODS

### *Study population*

The medical records of consecutive patients with acute ischemic stroke who presented to the neurology departments of two tertiary hospitals within 72 h of symptom onset between September 2020 and December 2023 were retrospectively reviewed. From these patients, those who had been taking clopidogrel for at least 7 consecutive days and underwent clopidogrel resistance testing upon admission were included in this study. The exclusion criteria were as follows: (1) blood samples for the clopidogrel resistance test collected more than 48 h after the last clopidogrel dose; (2) unclear timing of the last clopidogrel dose; (3) pre-existing functional disability, with a modified Rankin Scale (mRS) score of ≥ 2 before the onset of stroke; and (4) concomitant use of antiplatelet agents or anticoagulants other than clopidogrel. Ultimately, 116 patients were included in this study. This study was approved by the Institutional Review Boards of the participating hospitals. Each board waived the requirement for patient consent owing to the retrospective nature of this study.

### *Clinical information*

Data on baseline characteristics and vascular risk factors, such as hypertension, diabetes mellitus, hyperlipidemia, cigarette smoking, and atrial fibrillation, were collected. Smoking status was categorized as current smoker or non-smoker. In addition, data regarding each patient's history of ischemic stroke and ischemic heart disease were obtained.

Stroke subtypes were established based on the Trial ORG 10172 in Acute Stroke Treatment (TOAST) classification system.[12] Stroke severity was determined using the National Institutes of Health Stroke Scale (NIHSS) score at admission. Neurological deterioration was defined as an increase of ≥ 2 points in NIHSS score or an increase of ≥ 1 point on the NIHSS motor score within 7 days of symptom onset. Functional outcomes were evaluated according to the mRS score at 3 months after stroke onset, with scores of 3-6 classified as an unfavorable outcome.

The results of laboratory tests performed on admission, including hemoglobin, platelet count, admission glucose, prothrombin time international normalized ratio (PT INR), and high-sensitivity C-reactive protein (hs-CRP) levels, were obtained. Low-density lipoprotein cholesterol levels were measured in blood samples collected in the morning after admission following an overnight fast.

### *Clopidogrel resistance test*

Clopidogrel resistance was evaluated using the VerifyNow system (Accriva Diagnostics, San Diego, CA, USA), a turbidimetric method that quantifies platelet aggregation based on changes in light transmittance through a whole blood sample. This system uses a disposable cartridge containing two reaction chambers. The first chamber measures the platelet aggregation mediated by ADP, a potent agonist of the P2Y12 receptor on platelets, and expresses the results as PRU. In patients with clopidogrel resistance, platelet aggregation remains active, increasing the transmission of light through the blood samples and yielding higher PRU values. The second chamber measures platelet reactivity in response to thrombin receptor activating peptide (TRAP), a synthetic agonist that selectively activates protease-activated receptor 1 (PAR1) on platelets. As this pathway is independent of the P2Y12 receptor, it reflects the maximal aggregation of platelets independent of clopidogrel action and is referred to as baseline platelet reactivity (BASE). By comparing PRU and BASE, the VerifyNow system calculates percent inhibition according to the following formula: [(BASE–PRU)/BASE] × 100. This parameter indicates the extent to which clopidogrel reduces platelet aggregation relative to the maximal platelet aggregation measured in the TRAP chamber. Therefore, a higher percent inhibition reflects greater suppression of platelet activity by clopidogrel, demonstrating its effectiveness in inhibiting the P2Y12 receptor. Conversely, a lower percent inhibition suggests reduced responsiveness to clopidogrel, indicative of clopidogrel resistance.

*Statistical analysis*

Categorical variables are presented as frequency (percentage), whereas continuous variables are expressed as median (interquartile range [IQR]). The study population was stratified into tertiles based on percent inhibition values. Trends of variables across the tertiles of percent inhibition were analyzed using the chi-square test for categorical data and correlation analysis for continuous data. Correlations among BASE, PRU, percent inhibition, and admission NIHSS scores were assessed using the Pearson correlation test. Multivariable linear regression analysis was performed to determine independent variables associated with NIHSS score at admission. Variables with a p-value < 0.05 in the univariable analysis were included in the multivariable model. The results of multivariable analysis are expressed as B (95% confidence interval [CI]). Statistical significance was set at p-value < 0.05. All statistical analyses were performed using SPSS for Windows (version 27.0; IBM Corp., Armonk, NY, USA).

## RESULTS

*Baseline characteristics*

The study included 116 patients with a median age of 73 years (IQR, 67–79), of whom 84 (72.4%) were male. The median time from symptom onset to hospital arrival was 10.7 h (IQR, 3.8–20.2), and the median time from hospital arrival to the reporting of clopidogrel resistance test results was 14.3 h (IQR, 8.2–24.4). The median NIHSS score at admission was 2.0 (IQR, 1.0–5.0). Among the VerifyNow parameters, the median values for BASE, PRU, and percent inhibition were 233.0 (IQR, 198.3–267.8), 191.0 (IQR, 162.0–239.5), and 16.0 (IQR, -4.0–32.0), respectively.

Table 1 presents the baseline characteristics grouped by tertiles of percent inhibition. The time from symptom onset to hospital arrival (p for trend = 0.005), admission NIHSS score (p for trend < 0.001), prevalence of hypertension (p for trend = 0.008), cardioembolic stroke subtype (p for trend = 0.011), hs-CRP level (p for trend = 0.043), BASE value (p for trend = 0.046), and PRU value (p for trend < 0.001) showed significant linear trends from the lowest to the highest tertiles of percent inhibition. Unfavorable functional outcomes at 3 months were most frequently observed in the 1st tertile (22 patients, 61.1%) and least frequently in the 3rd tertile (7 patients, 19.4%), showing a significant linear trend (p for trend < 0.001). However, neurological deterioration did not demonstrate a significant trend across the tertiles.

*Clopidogrel resistance and stroke severity*

A significant positive correlation was observed between PRU and NIHSS score at admission (r = 0.207, p = 0.028). In contrast, percent inhibition exhibited a significant negative correlation with the NIHSS score at admission (r = -0.387, p < 0.001). The BASE value was not significantly correlated with the NIHSS score at admission (Figure 1). In the univariable linear regression analysis, older age (B = 0.116, 95% CI = 0.019 to 0.213; p = 0.020), shorter time from symptom onset to hospital arrival (B = -0.059, 95% CI = -0.113 to -0.004; p = 0.035), higher prevalence of atrial fibrillation (B = 3.359, 95% CI = 1.106 to 5.612; p = 0.004), lower prevalence of prior ischemic stroke (B = -2.051, 95% CI = -3.920 to -0.181; p = 0.032), higher PRU (B = 0.017, 95% CI = 0.002 to 0.033; p = 0.028), and lower percent inhibition (B = -0.086, 95% CI = -0.125 to -0.048; p < 0.001) were significantly associated with an increased NIHSS score at admission (Table 2). After adjusting for significant confounders, older age (B = 0.097, 95% CI = 0.004 to 0.191; p = 0.042), higher prevalence of atrial fibrillation (B = 2.677, 95% CI = 0.496 to 4.858; p = 0.017), and lower percent inhibition (B = -0.107, 95% CI = -0.163 to -0.051; p < 0.001) remained independent and significant predictors of higher NIHSS scores at admission (Table 2). The PRU value did not demonstrate a significant association with the NIHSS score at admission in the multivariable analysis.

## DISCUSSION

This study demonstrated that clopidogrel resistance, particularly a lower percent inhibition, was significantly associated with more severe stroke in patients undergoing clopidogrel therapy. Clopidogrel resistance refers to the inability of clopidogrel to achieve its expected inhibitory effect on platelet activation.[13] Therefore, it is speculated that high residual platelet reactivity due to clopidogrel resistance may promote larger thrombus formation and enhanced thrombus propagation, potentially increasing the severity of stroke events. Significant association between clopidogrel resistance and a higher risk of recurrent vascular events has been observed in stroke patients.[6-10] Moreover, the frequency of early neurological deterioration and unfavorable functional outcomes was significantly higher in

**Table 1: Clinical characteristics according to tertiles of percent inhibition**

| | Tertiles of percent inhibition | | | |
|---|---|---|---|---|
| | **1st (n=39)** | **2nd (n=38)** | **3rd (n=39)** | **p-value** |
| Age, year | 74.0 (67.0-79.0) | 74.5 (68.0-79.0) | 70.0 (64.0-77.0) | 0.178 |
| Male | 25 (64.1) | 28 (73.7) | 31 (79.5) | 0.130 |
| Onset to arrival, hours | 5.0 (2.3-12.7) | 13.7 (4.9-21.4) | 12.7 (4.2-36.4) | 0.005* |
| Arrival to CRT result, hours | 10.6 (5.1-21.3) | 18.2 (13.5-41.9) | 14.3 (6.8-23.3) | 0.354 |
| Admission NIHSS score | 4.0 (2.0-10.0) | 2.0 (1.0-4.0) | 2.0 (1.0-3.0) | <0.001* |
| Risk factors | | | | |
| Hypertension | 33 (84.6) | 32 (84.2) | 23 (59.0) | 0.008* |
| Diabetes mellitus | 15 (38.5) | 17 (44.7) | 14 (35.9) | 0.818 |
| Hyperlipidemia | 22 (56.4) | 26 (68.4) | 16(41.0) | 0.174 |
| Smoking | 9 (23.1) | 8 (21.1) | 3 (7.7) | 0.073 |
| Atrial fibrillation | 11 (28.2) | 9 (23.7) | 4 (10.3) | 0.051 |
| Prior ischemic stroke | 20 (51.3) | 22 (57.9) | 23 (59.0) | 0.496 |
| Prior ischemic heart disease | 12 (30.8) | 8 (21.1) | 8 (20.5) | 0.292 |
| TOAST classification | | | | |
| Large artery atherosclerosis | 6 (15.4) | 5 (13.2) | 2 (5.1) | 0.153 |
| Cardioembolism | 12 (30.8) | 8 (21.1) | 3 (7.7) | 0.011* |
| Small vessel occlusion | 11 (28.2) | 12 (31.6) | 18 (46.2) | 0.099 |
| Other determined | 2 (2.6) | 1 (2.6) | 0 (0.0) | 0.386 |
| Undetermined | 9 (23.1) | 12 (31.6) | 16 (41.0) | 0.090 |
| Laboratory findings | | | | |
| Hemoglobin, g/dL | 13.2 (12.5-15.5) | 13.0 (12.0-15.0) | 13.7 (12.4-14.9) | 0.782 |
| Platelet count | 231.0 (188.0-263.0) | 192.0 (159.0-245.8) | 213.0 (194.0-268.0) | 0.732 |
| Admission glucose, mg/dL | 143.0 (125.0-191.0) | 133.0 (106.0-170.5) | 128.0 (113.0-163.0) | 0.075 |
| LDL-C, mg/dL | 81.0 (62.5-111.3) | 74.0 (53.5-97.5) | 79.5 (58.8-102.0) | 0.478 |
| PT INR | 0.99 (0.95-1.10) | 1.03 (0.98-1.04) | 1.03 (0.97-1.06) | 0.318 |
| hs-CRP, mg/dL | 0.16 (0.08-0.49) | 0.10 (0.05-0.28) | 0.09 (0.04-0.31) | 0.043* |
| BASE | 223.0 (186.0-253.0) | 242.5 (203.8.0-284.0) | 237.0 (197.0-282.0) | 0.046* |
| PRU | 230.0 (197.0-277.0) | 199.0 (166.5-240.3) | 144.0 (100.0-182.0) | <0.001* |
| Outcome | | | | |
| Neurological deterioration | 10 (25.6) | 9 (23.7) | 6 (15.4) | 0.273 |
| Unfavorable 3-month outcome | 22 (61.1) | 12 (32.4) | 7 (19.4) | <0.001* |

Values are number (column %) or median (interquartile range).
*$p < 0.05$.
CRT, clopidogrel resistance test; NIHSS, National Institutes of Health Stroke Scale; TOAST, Trial ORG 10172 in Acute Stroke Treatment; LDL-C, low-density lipoprotein cholesterol; PT INR, prothrombin time international normalized ratio; hs-CRP, high-sensitivity C-reactive protein; BASE, baseline platelet reactivity; PRU, P2Y12 reaction unit.

stroke patients with clopidogrel resistance.[9,14-17] However, the present study is unique in that it specifically focused on patients who were already receiving clopidogrel therapy prior to their index stroke. This patient group has not been adequately investigated in previous studies. Through this approach, this study sought to evaluate the impact of clopidogrel resistance at the time of stroke onset on stroke severity. The findings further underscore the importance of monitoring clopidogrel resistance in patients undergoing treatment, even though it is not yet routinely recommended.[18]

A second important finding of this study was that only percent inhibition showed a significant inverse relationship with stroke severity. In contrast, PRU was not independently associated with stroke severity. PRU represents an absolute measure that evaluates the reactivity of platelets to ADP without considering the intrinsic activation potential of platelets. However, percent inhibition is a relative measure that evaluates how platelets respond to ADP compared to their maximal activation induced by TRAP. Therefore, these findings highlight the importance of considering the extent of change in platelet reactivity from

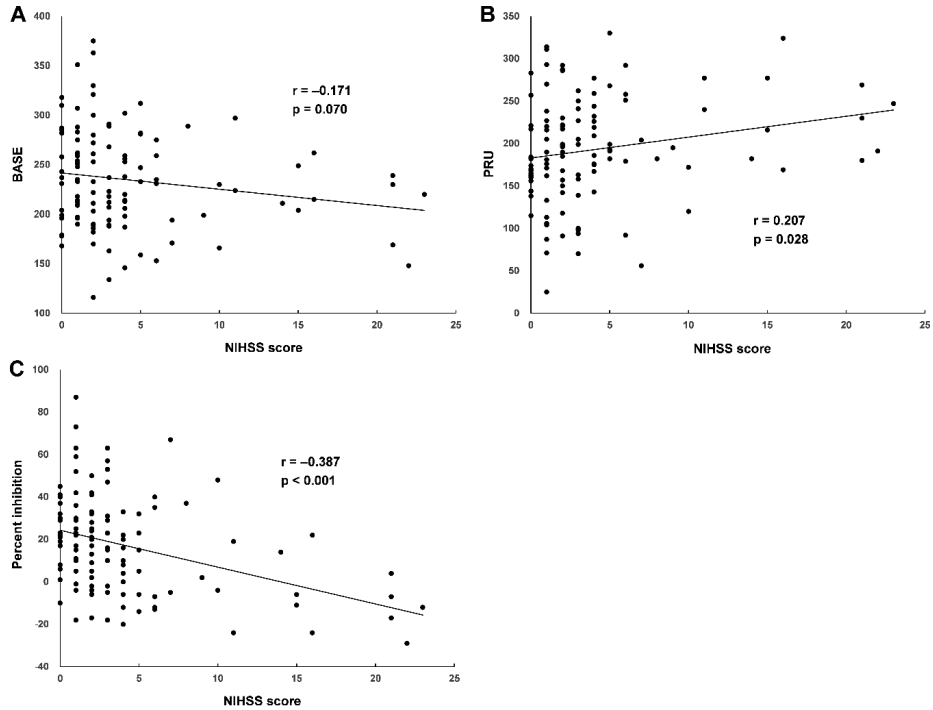


Figure 1. Correlations between stroke severity and BASE (A), PRU (B), and percent inhibition (C). BASE, baseline platelet reactivity; NIHSS, National Institutes of Health Stroke Scale; PRU, P2Y12 reaction unit.

**Table 2: Linear regression analysis of the factors associated with stroke severity**

| | Univariable | | Multivariable | |
|---|---|---|---|---|
| | **B (95% CI)** | **p-value** | **B (95% CI)** | **p-value** |
| Age | 0.116 (0.019 to 0.213) | 0.020* | 0.097 (0.004 to 0.191) | 0.042* |
| Male | -1.564 (-3.663 to 0.535) | 0.143 | | |
| Onset to arrival time | -0.059 (-0.113 to -0.004) | 0.035* | -0.026 (-0.077 to 0.026) | 0.331 |
| Risk factors | | | | |
| Hypertension | 1.526 (-0.669 to 3.720) | 0.171 | | |
| Diabetes mellitus | 0.189 (-1.645 to 2.224) | 0.296 | | |
| Hyperlipidemia | -0.855 (-2.752 to 1.043) | 0.374 | | |
| Smoking | -0.044 (-2.550 to 2.463) | 0.972 | | |
| Atrial fibrillation | 3.359 (1.106 to 5.612) | 0.004* | 2.677 (0.496 to 4.858) | 0.017* |
| Prior ischemic stroke | -2.051 (-3.920 to -0.181) | 0.032* | -1.556 (-3.283 to 0.172) | 0.077 |
| Prior ischemic heart disease | 2.005 (-0.176 to 4.186) | 0.071 | | |
| Laboratory findings | | | | |
| Hemoglobin | -0.055 (-0.565 to 0.455) | 0.831 | | |
| Platelet count | -0.002 (-0.016 to 0.013) | 0.827 | | |
| Admission glucose | 0.004 (-0.011 to 0.018) | 0.617 | | |
| LDL-C | 0.015 (-0.018 to 0.048) | 0.371 | | |
| PT INR | 8.165 (-5.514 to 21.845) | 0.239 | | |
| hs-CRP | 0.034 (-0.717 to 1.325) | 0.556 | | |
| BASE | -0.018 (-0.037 to 0.001) | 0.070 | | |
| PRU | 0.017 (0.002 to 0.033) | 0.028* | -0.021 (-0.042 to 0.001) | 0.057 |
| Percent inhibition | -0.086 (-0.125 to -0.048) | <0.001* | -0.107 (-0.163 to -0.051) | <0.001* |

*$p < 0.05$.

B, standard coefficient; CI, confidence interval; LDL-C, low-density lipoprotein cholesterol; PT INR, prothrombin time international normalized ratio; hs-CRP, high-sensitivity C-reactive protein; BASE, baseline platelet reactivity; PRU, P2Y12 reaction unit.

the baseline activation potential when assessing clopidogrel resistance, rather than relying solely on PRU during clopidogrel therapy. Taken together, the percent inhibition may serve as a more appropriate indicator for assessing clopidogrel resistance and tailoring antiplatelet therapy in clinical practice.

Clopidogrel is a prodrug that requires conversion into an active metabolite after oral administration.[19] CYP2C19 is a major enzyme involved in the generation of the clopidogrel active metabolite.[19] The CYP2C19 loss-of-function allele has been associated with clopidogrel resistance and a higher risk of vascular events.[20] In addition, multiple factors, such as drug-drug interaction and noncompliance, contributes to the development of clopidogrel resistance.[11] In this study, clopidogrel resistance was evaluated using the VerifyNow assay, a commonly used platelet function test, because it was hypothesized that platelet reactivity is the final consequence of complex interactions among these various factors. Therefore, by assessing platelet reactivity, the VerifyNow assay may capture these diverse influences and provide a reliable indicator of clopidogrel resistance.

This study has several limitations. First, it was a retrospective study with a relatively small sample size. Consequently, unrecognized biases may have affected the validity of the results. Although this study included patients from two institutions, the limited sample size could be attributed to the low incidence of ischemic stroke among patients taking clopidogrel. Larger prospective studies are warranted to confirm the findings of the present study. Second, this study was conducted in an Asian population, and the generalizability of the findings to other racial and ethnic groups remains uncertain. Research involving diverse ethnic populations is essential to ensure the broader applicability of the results. Third, although several factors, including coagulopathy and inflammatory response, are known to be associated with stroke severity,[21] these factors were not fully considered or adjusted for in this study. Finally, patients who presented within 72 h of symptom onset were enrolled. This time window may be overly extended, as the clopidogrel resistance test results may not accurately reflect the state of resistance at the time of stroke onset. However, 90 (77.6%) patients presented within 24 h of symptom onset, and 106 (91.4%) presented within 48 h, which likely mitigated the potential bias caused by the time lag between symptom onset and hospital arrival.

In conclusion, this study demonstrated that clopidogrel resistance, as assessed using the VerifyNow assay, is associated with increased stroke severity in patients receiving clopidogrel. Notably, percent inhibition, a relative measure that considers the baseline activation potential of platelets, showed a stronger association with stroke severity than the absolute PRU value. More clinical data are required to support the findings of our study.

## DISCLOSURE

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Conflict of interest: None

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