

Characterization and Evaluation of Clopidogrel Response Testing in a Community Hospital Setting

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Abstract

Purpose: To describe how VerifyNow P2Y₁₂ testing for clopidogrel response is being utilized at a community hospital.

Methods: A retrospective chart review was conducted at a 411-bed community hospital in patients who tested positive for poor clopidogrel response.

Results: There were 95 positive P2Y₁₂ tests evaluated in this study. Positive P2Y₁₂ tests were obtained 40.0% of the time for cardiovascular indications, 28.4% for neurologic indications, 1.1% for hematologic indications, and 30.5% were obtained to evaluate patients prior to surgery. The medication regimens of 38.8% of patients did not change as a result of a positive test for poor clopidogrel response. The clopidogrel dose was increased in 16.3% of patients, and clopidogrel was discontinued in 10.2% of patients positive for poor clopidogrel response not undergoing surgical evaluation. Rehospitalization rates of non-surgical patients for recurrent thrombosis or bleeding at 90 days were highest for patients who had an additional antiplatelet agent or anticoagulant added due to poor clopidogrel response. The lowest rehospitalization rate was seen in patients switched to an alternative agent.

Conclusions: The most common findings after a positive P2Y₁₂ test in non-surgical patients were no change in therapy and increasing the dose of clopidogrel. Adding an additional antiplatelet agent or anticoagulant was associated with the highest risk of rehospitalization.

Keywords: Clopidogrel; VerifyNow P2Y₁₂; Antiplatelet; Clopidogrel response testing

Abbreviations: ACS: Acute Coronary Syndrome; CABG: Coronary Artery Bypass Graft; LTA: Light Transmittance Aggregometry; MACE: Major Adverse Cardiac Events; MI: Myocardial Infarction; PCI: Percutaneous Coronary Intervention; PGE1: Prostaglandin E₁; PRU: P2Y₁₂ Reaction Unit; STEMI: ST-Segment-Elevation Myocardial Infarction

Background

Clopidogrel is a thienopyridine antiplatelet agent approved for a wide variety of indications including thrombosis prophylaxis after stenting and percutaneous coronary interventions (PCIs), secondary prevention of atherothrombotic events (myocardial infarction [MI], stroke, and vascular death) after a recent MI or stroke, and secondary prophylaxis of atherothrombotic events in patients with acute coronary syndrome (ACS) [1]. Clopidogrel is metabolized by hepatic CYP 450 enzymes (CYP 3A4, CYP3A5, CYP 2C19) to its active form and works by irreversibly inhibiting the P2Y₁₂ receptor on platelets thereby blocking ADP-induced platelet activation and aggregation.

Despite its proven benefit, some patients taking clopidogrel have been deemed "clopidogrel resistant" [2,3]. This has been attributed to the fact that there is a great deal of interpatient variability in clopidogrel's ability to block platelet aggregation. Most patients experience 40-60% inhibition of platelet activity with clopidogrel at steady-state [1]. Some proposed hypothesis for why there is such variability include the level of platelet reactivity before clopidogrel therapy, individual differences in clopidogrel absorption, and genetic polymorphisms altering the ability to metabolize clopidogrel to its active form [3].

The VerifyNow P2Y₁₂ Test is a point of care blood test that measures platelet reactivity at the P2Y₁₂ receptor in order to determine clopidogrel's effectiveness in blocking platelet aggregation in patients

[4]. The test measures P2Y₁₂ aggregation with fibrinogen-coated beads through changes in light transmittance and reports results as P2Y₁₂ reaction units (PRU), with higher levels indicating greater platelet reactivity. In one channel, the system uses ADP as a platelet agonist, and prostaglandin E₁ (PGE1). PGE1 suppresses ADP-induced aggregation at the P2Y₁ receptor, which is a receptor that clopidogrel does not block. The second channel measures the baseline platelet function of a sample by using thrombin receptor activating peptide and PAR-4 activating peptide to induce platelet aggregation which is not blocked by clopidogrel. The test reports the PRUs in the ADP channel, baseline PRUs from the second channel, and the % PRU inhibition, which is a calculation of the percent change from the baseline aggregation [4]. The VerifyNow P2Y₁₂ Test has been tested and validated against light transmittance aggregometry (LTA) using ADP and PGE1 as agonists, with a strong agreement between both tests (95% vs. 93% average inhibition) and a coefficient of variance less than 8% [5].

Patients with lower levels of platelet inhibition while taking clopidogrel are more likely to experience atherothrombotic events than patients with higher levels of platelet inhibition. In one prospective study, 60 patients undergoing PCI and stenting after an ST-segment-elevation myocardial infarction (STEMI) were evaluated to determine

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Received August 30, 2011; **Accepted** October 05, 2011; **Published** October 15, 2011

Citation: Lalama J, Brackbill M (2011) Characterization and Evaluation of Clopidogrel Response Testing in a Community Hospital Setting. J Clin Exp Cardiol 2:155. doi:10.4172/2155-9880.1000155

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how clopidogrel's interpatient variability affects clinical outcomes [6]. Patients were stratified into four quartiles based on their platelet inhibition, which was measured by LTA. Significantly more recurrent cardiovascular events (STEMI, ACS, subacute stent thrombosis, and acute peripheral arterial occlusion) after six months of follow-up were seen in the patients with the least response to clopidogrel. While no events were seen in the third and fourth quartiles, 40% and 6.7% of patients in the first and second quartiles respectively experienced recurrent cardiovascular events ($p=0.007$) [6]. A prospective observational cohort study was conducted in 804 patients receiving drug-eluting stents looking at the occurrence of stent thrombosis after 6 months of follow-up [7]. Clopidogrel responsiveness was measured using LTA. Overall stent thrombosis was 3.1%; however this rate was 8.6% in nonresponders to clopidogrel compared to 2.3% in patients responding to clopidogrel ($p<0.001$) [7]. Similar results have been published in several other trials demonstrating the correlation between higher atherothrombotic events and lower platelet inhibition [8-11]. There are also studies using the VerifyNow P2Y₁₂ Test which demonstrate the correlation between higher atherothrombotic events and lower platelet inhibition [12-16].

Point of care testing makes it easier for clinicians to identify which patients respond to clopidogrel poorly and are at higher risk for recurrent atherothrombotic events. Unfortunately, there is no consensus for how to prevent atherothrombotic events in patients who respond to clopidogrel poorly. There have also been no prior studies researching therapeutic decision making after positive tests indicating poor clopidogrel response are reported using point of care devices. This study aims to describe how VerifyNow P2Y₁₂ testing for clopidogrel response is being utilized at a community hospital and determine how a positive test changes subsequent medication management in non-surgical patients. The secondary objective is to determine which type of medication change associated with a positive P2Y₁₂ test has the highest 90 day readmission rates for recurrent thrombosis or bleeding in non-surgical patients.

Methods

A retrospective chart review was conducted at a 411-bed not-for-profit hospital that serves as a regional referral center for cardiovascular care. Patients were included in the study if they were older than 18 years and had a positive P2Y₁₂ test from January 2008 to December 2009. A positive test was defined using our institution's cut off as less than 50% inhibition of PRUs for the P2Y₁₂ receptor, which is based upon the package labeling for clopidogrel [1]. Appropriate use of the P2Y₁₂ test was defined as testing of non-surgical patients at clopidogrel steady-state (after a loading dose or seven days of therapy), and testing in patients where clopidogrel is being held either prior to surgery to assess for bleeding risks or to assess clopidogrel's contribution to a bleeding event. Inappropriate testing was defined as testing in non-surgical patients when clopidogrel was not at steady-state, testing in patients with inherited platelet disorders, with platelet counts $<100 \times 10^9/L$, and with recent use of interfering antiplatelet agents (abciximab within 14 days, eptifibatid or tirofiban within 48 hours, cilostazol within 12 hours).

Clinical decisions as a result of positive P2Y₁₂ test in non-surgical patients were categorized as: no change, increased clopidogrel dose, switched clopidogrel to an alternative antiplatelet or anticoagulant, addition of another antiplatelet or anticoagulant, discontinuing clopidogrel without replacement therapy, increased aspirin dose, and multiple interventions. Multiple interventions were defined as a change in therapy with at least two different interventions. The ultimate

therapeutic intervention for a patient was counted when there was more than one positive P2Y₁₂ test during a hospitalization. Medication histories obtained during admission and discharge medication lists were used to characterize medication changes. Rehospitalization at 90-days for recurrent thrombosis or bleeding was evaluated for each patient by electronically reviewing the readmission history. Descriptive statistics were utilized to analyze the data. The institution's Institutional Review Board approved this study protocol.

Results

P2Y₁₂ tests were ordered for cardiovascular indications (ACS, PCI, or ordered by cardiology service), neurologic indications (transient ischemic attacks, cerebrovascular accidents, or ordered by neurologic service), cardiovascular surgery evaluations, general surgery evaluations, and hematologic indications (evaluation to see if clopidogrel was contributing to a GI bleed) (Table 1).

A total of 95 positive P2Y₁₂ tests were evaluated in 82 patients out of 100 P2Y₁₂ tests performed during the study period. The mean age at testing was 64.5 ± 13.9 years (range, 33-93). Of the positive tests, 43% were conducted in female patients and 57% were conducted in male patients. For positive tests performed appropriately for cardiovascular or neurologic indications ($n=53$), the mean inhibition of PRUs at the P2Y₁₂ receptor was $20.3 \pm 15.5\%$ (range 0-49%). The mean inhibition of PRUs at the P2Y₁₂ receptor for tests taken appropriately while clopidogrel was being held to assess patients for surgery bleeding risks or to evaluate clopidogrel's contribution to a GI bleed ($n=27$) was $7.3\% \pm 10.7\%$ (Range 0-37%). Two patients ultimately did not undergo surgery; however, results of P2Y₁₂ testing were not the reason to cancel surgery for either patient.

Eighty-four percent of the P2Y₁₂ tests evaluated were performed appropriately (Table 2). The most common reasons for inappropriate use were testing when clopidogrel was not at steady-state (9%) and when patients had not yet recovered from an interfering antiplatelet agent (6%). Tests that were taken inappropriately were not included in the results for the primary and secondary objectives of this study.

Primary Therapeutic Indication	Number of Tests Ordered (%)
Cardiovascular	38 (40.0%)
Neurologic	27 (28.4%)
Cardiovascular Surgery	23 (24.2%)
General Surgery	6 (6.3%)
Hematologic	1 (1.1%)

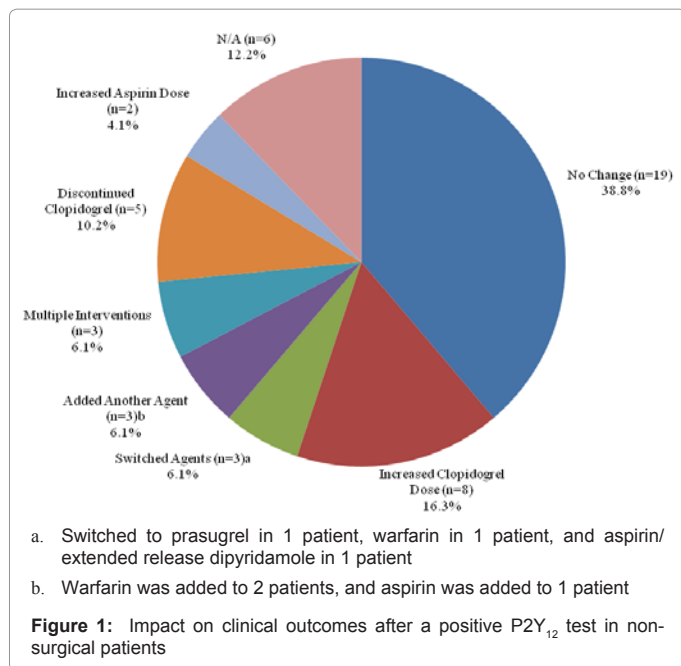
Table 1: Primary Therapeutic Indication for Positive P2Y₁₂ Tests.

Factor Impacting Reliability	Number of Tests (%)
Tests taken in patients loaded with clopidogrel or at steady-state	53 (56%)
Tests taken when clopidogrel was being held to assess for surgery or reason for bleeding	27 (28%)
Tests taken in patients not at steady-state	9 (9%)
Tests taken when platelet function had not recovered from interfering agents ^a	6 (6%)
Tests taken in thrombocytopenic patients ^b	1 (1%)
Tests taken in patients with inherited platelet disorders	0 (0%)
Tests taken appropriately	80 (84%)

a. Abciximab within the past 14 days, eptifibatid or tirofiban within the past 48 hours, or cilostazol within the past 12 hours before testing

b. Patient's platelet function had also not recovered from an interfering agent

Table 2: Factors Impacting P2Y₁₂ Testing Reliability.



Therapeutic intervention group	Number of tests in group	Number of patients rehospitalized after 90 days (%)
No change	19	7 (37%)
Increased clopidogrel dose	8	2 (25%)
Switched agents	3	0 (0%)
Added another agent	3	2 (67%)
Multiple interventions	3	0 (0%)
Discontinued clopidogrel	5	3 (60%)
Increased aspirin dose	2	0 (0%)

Table 3: Rehospitalization rates for bleeding or recurrent thrombosis after 90 days in non-surgical patients

Of the 53 positive tests taken appropriately in non-surgical patients, there were 49 separate hospitalizations. After a positive P2Y₁₂ test in non-surgical patients, no change in antiplatelet regimen, increased clopidogrel dose, and discontinued clopidogrel was most commonly seen (Figure 1).

Fifteen non-surgical patients out of 49 patients (30.6%) who tested positive for poor clopidogrel response (53 tests) were rehospitalized within 90 days with symptoms of either recurrent thrombosis or bleeding. Patients who had an additional antiplatelet or anticoagulant added as a result of a positive P2Y₁₂ test had the highest rehospitalization rate at 90 days (n=2, 67%) for either recurrent thrombosis or bleeding. Discontinuing clopidogrel had the second highest 90 day rehospitalization rate (n=3, 50%). No rehospitalizations for recurrent thrombosis or bleeding were observed in the groups where clopidogrel was switched to an alternative antiplatelet or anticoagulant, the group where multiple interventions were performed, and the group where the aspirin dose was increased (Table 3). The clinical decision for one of the rehospitalized patients was unable to be determined from chart review.

Discussion

This study demonstrates how point of care P2Y₁₂ testing is being utilized in one community institution. During the study period of two years, it was observed that the tests were commonly used for cardiovascular or neurologic indications as well as for evaluating

patients for subsequent surgical interventions after clopidogrel administration. Almost all of the tests conducted were positive. One possible explanation for the high positivity rate is that physicians only tested in patients in whom a high suspicion of clopidogrel non-response was suspected. For example, a physician may suspect clopidogrel non-response for a patient readmitted for recurrent MI while on clopidogrel therapy.

P2Y₁₂ testing occurred in about 30% of patients where clopidogrel was being held. Testing in these patients was performed to evaluate residual clopidogrel effects to assess for bleeding risks. Therefore, the testing was performed for reasons other than predicting clopidogrel response. It also explains why the % PRU inhibition was much lower for this group. There currently is little data to support the use of point-of-care P2Y₁₂ testing to assess for bleeding risks with clopidogrel [17,18]. One case report documents using the VerifyNow P2Y₁₂ Test to minimize both thrombotic and bleeding risks for a patient who needed to have a right radical nephrectomy five weeks after receiving a drug-eluting stent [19]. Clopidogrel and aspirin were discontinued seven and five days prior to surgery respectively. Platelet function was tested daily using the VerifyNow P2Y₁₂ and VerifyNow Aspirin tests until function began to return to normal. Tirofiban and enoxaparin were then given to bridge the patient to surgery. The surgery was successful, clopidogrel and aspirin were restarted eight hours later with loading doses, and the patient did not experience any thrombotic or bleeding events during the perioperative period [19]. Small studies have shown that adenosine diphosphate aggregometry, multiple electrode platelet aggregometry, and thromboelastography platelet mapping may be able to predict bleeding risks for patients receiving coronary artery bypass grafts (CABG) [20-22]. However, one of those studies showed that the point-of-care tests Platelet Function Analyzer 100 and Platelet Works were not predictive of which patients receiving CABG would bleed [20]. The VerifyNow P2Y₁₂ Test has not yet been studied to predict bleeding risks in CABG or other surgeries in patients taking clopidogrel [17].

The most common clinical outcome observed in this study for patients with cardiovascular or neurologic indications was that no changes were made about 40% of the time after a positive test. Clopidogrel was also discontinued in about 10% of patients without anything prescribed to take its place. While this may seem surprising, there is currently no consensus on how to effectively treat patients who respond poorly to clopidogrel. Without any treatment recommendations for positive tests, the utility of point of care P2Y₁₂ testing is still up for debate [23]. Unfortunately, there was a trend towards increased 90 day rehospitalization rates due to recurrent thrombosis or bleeding in both the patients where no changes to therapy were made and patients where clopidogrel was discontinued without anything to take its place. These results are similar to prior studies demonstrating that patients with low platelet inhibition are more likely to experience rethrombosis and ischemia than patients with higher levels of platelet inhibition [2-4,6-11].

The most common medication change observed during this study was increasing the dose of clopidogrel. There is mixed evidence supporting this treatment modality. One observational study compared a conventional maintenance dose of clopidogrel 75mg/day to a higher maintenance dose of 150mg/day in clopidogrel resistant patients after undergoing PCI and stenting (n=52) [24]. Patients in the high maintenance group experienced both significantly less stent thrombosis (p=0.002) and major adverse cardiac events (MACE) (p=0.001) when compared to the conventional dosing group. There was no difference in hemorrhagic accidents between both groups indicating that higher

maintenance doses of clopidogrel may be as safe as conventional dosing while being more effective for clopidogrel resistant patients [24]. These results contrast with the results from the GRAVITAS trial [25]. The GRAVITAS trial was a prospective, double-blinded, active control trial with a large patient population ($n=2214$). Patients with high on-treatment platelet reactivity with clopidogrel ($PRU \geq 230$ measured by the VerifyNow P2Y₁₂ Test) were randomized to receive either standard-dose clopidogrel (75mg daily) or high-dose clopidogrel (additional 600mg loading dose followed by 150mg daily). PRUs were significantly reduced in the high-dose clopidogrel group, but no differences were seen between the groups in the primary composite endpoint of death from CV causes, non-fatal MI, or stent thrombosis in 6 months and no differences between the groups were seen in moderate or severe bleeding. However, despite the large number of patients included in the GRAVITAS trial, there was a lower event rate than predicted so the trial was underpowered [25].

Another treatment option observed less frequently in this study was to add additional antiplatelet or anticoagulant to therapy. Agents observed in this study include cilostazol, warfarin, and aspirin. By adding additional agents to therapy, atherothrombotic events could be prevented by further blocking platelet activity or inhibiting the clotting cascade, but potentially at the risk of increasing bleeding events. The ACCEL-AMI study was a prospective trial randomizing AMI patients to receive clopidogrel 75mg/day ($n=30$), clopidogrel 150mg/day ($n=30$), or clopidogrel 75mg/day and cilostazol 100mg twice daily ($n=30$) as maintenance therapy after receiving coronary stents [26]. Patients in each group were also treated with aspirin 200mg/day throughout the study. After 30 days, platelet inhibition was assessed for each group using many different tests. Fewer patients in the triple antiplatelet group had high-postclopidogrel platelet reactivity compared to patients in the clopidogrel 75mg/day and 150mg/day ($p < 0.001$) and triple antiplatelet therapy was found to significantly inhibit platelets more than the other groups in all assessments measured. This study did not present any outcomes or safety data however [26]. Only one patient had cilostazol added to therapy in this study. Adding additional antiplatelet or anticoagulant agents to therapy in this study was associated with the highest rehospitalization rate at 67%.

Switching clopidogrel to another agent was another common intervention observed in this study. This group also had the lowest 90 day rehospitalization rate with no patients needing to be rehospitalized for recurrent thrombosis or bleeding. Patients were switched from clopidogrel to prasugrel, warfarin, or aspirin/extended release dipyridamole in this study. Patients who respond poorly to clopidogrel may be able to obtain optimal platelet inhibition when switching to another agent. This is demonstrated in a case series published by Pena et al. [27]. Seven patients with stent thrombosis were tested and found to be clopidogrel resistant. Clopidogrel maintenance doses were titrated from 75mg/day to 150mg/day, then to 225mg/day for six of the seven patients, and then up to 300mg/day for four patients because they all continued to not respond to the escalating clopidogrel doses. Compassionate use of prasugrel was able to be obtained for four of the patients and adequate platelet inhibition was observed in all of the patients after four weeks [27]. The RESPOND trial was a crossover designed trial in 98 patients comparing both responders and non-responders of clopidogrel to ticagrelor which is an oral reversible P2Y₁₂ inhibitor [28]. Ticagrelor was able to significantly inhibit more platelet aggregation than clopidogrel in non-responders ($p < 0.05$) and platelet aggregation fell significantly when patients were switched from clopidogrel to ticagrelor ($p < 0.0001$). One major and three minor bleeding events occurred either during or after ticagrelor therapy,

while no bleeding events were reported for patients taking clopidogrel. Only five serious adverse events (MI, hypotension, atrial fibrillation, and bradycardia) were reported during this study and they all occurred either during or after ticagrelor therapy [28]. Although switching agents might be able to significantly reduce platelet aggregation, this may not translate to a reduction in clinical outcomes such as MACE. The TRIGGER-PCI trial, which randomized patients who underwent successful elective PCI with high platelet reactivity to receive either clopidogrel 75mg daily or prasugrel 10mg daily, was halted early [29]. Like the GRAVITAS trial, there was a lower event rate for the primary endpoint (MI or cardiovascular death within 6 months) than expected causing the study to be underpowered even if the enrollment target of 2150 patients was reached [29].

There are limitations to this study. This study was retrospective, conducted in only one institution, and had a small sample size. Because the sample size was so small, only descriptive studies were able to be performed. Another limitation is that only 90 days was used as follow-up for rehospitalizations; readmission rates may be different if patients were followed for a longer period of time. The timing of when the P2Y₁₂ tests were taken in relation to when clopidogrel doses were given was not collected. This might have had an impact on the appropriateness of some of the tests taken. Also, more than halfway through the study prasugrel became commercially available and was added to the formulary at the institution this study was conducted. Because of this, clinical decisions after a positive test were different at the end of the study than at the beginning. P2Y₁₂ testing also can be used to test the efficacy of prasugrel so this test might be used to determine prasugrel responsiveness in the near future. Larger prospective trials should be conducted to determine the best treatment modality to use for patients with poor clopidogrel response to help make point-of-care testing devices more useful.

Conclusions

This study shows that the VerifyNow P2Y₁₂ Test is most commonly utilized for cardiovascular and neurologic indications and approximately 30% of all the tests taken are to evaluate patients for surgical interventions after clopidogrel administration. The majority of the P2Y₁₂ tests were taken appropriately. No change to antiplatelet regimens was the most common observation after a positive P2Y₁₂ test in non-surgical patients. However, these patients also experienced one of the highest rates of rehospitalizations for recurrent thrombosis or bleeding. Switching clopidogrel to another antiplatelet or anticoagulant, conducting multiple interventions, and increasing the dose of aspirin were associated with the lowest risk of rehospitalization. Larger prospective studies are needed in order to corroborate the results of this study.

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