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Original Article

Ticagrelor use in patients after percutaneous coronary intervention: one year follow up in a community hospital

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Abstract: Background: Current guidelines from American College of Cardiology (ACC) recommend ticagrelor over clopidogrel in patients with acute coronary syndrome. We have observed many patients being switched from ticagrelor to clopidogrel after percutaneous coronary intervention (PCI) in our hospital. Our goal is to evaluate the use rate of ticagrelor and categorize the reasons for non-use. Methods: We performed a retrospective data analysis of all patients who underwent PCI at Unity Hospital of Rochester, New York, from January 2019 to January 2020. A total of 330 patients underwent PCI for ACS over the year. After exclusions, 277 patients were enrolled in the analysis. Results: Of the 277 patients, 179 (65%) completed one year of ticagrelor therapy, and 98 (35%) stopped ticagrelor and transitioned to clopidogrel. The most common reason for switching from ticagrelor was dyspnea (42 patients), followed by cost concerns (41 patients). Conclusion: At our community hospital, completion of one-year use of ticagrelor post-PCI occurred in 65% of patients. The most common reasons for discontinuation are dyspnea and medication cost.

Keywords: Ticagrelor, clopidogrel, dual antiplatelet therapy, acute coronary syndrome, percutaneous coronary intervention, medication compliance/adherence

Introduction

As per the AHA/ACC and European Society of Cardiology (ESC) guidelines for ACS, antiplatelet antithrombotic therapy is a very essential part of medical therapy along with PCI. Previously clopidogrel, along with aspirin was considered gold standard. But with newer studies ticagrelor and prasugrel was found to be superior to clopidogrel.

Ticagrelor is direct, selective and reversible adenosine diphosphate (ADP) receptor antagonist that inhibits platelet activation and aggregation. On the other hand, Clopidogrel is a prodrug, and its active metabolite blocks the ADP receptor irreversibly. In a 6-week study comparing the inhibition of platelet aggregation (IPA) to a loading dose of 180 mg ticagrelor and 600 mg of clopidogrel, the IPA was consistently higher in the ticagrelor group. After ticagrelor, the most significant effect of IPA was attained at 2 hours and lasted for at least 8 hours [1].

After the last dose of ticagrelor and clopidogrel, the maximum IPA was 88% with ticagrelor and 62% with the clopidogrel, and after 24 hours, the IPA was 58% and 52%, respectively [1].

Clopidogrel has a disadvantage of variable response, with 15-30% of patients being non-responsive [2, 3]. The occurrence of ischemic events in patients with a previous history of the acute coronary syndrome despite being on P2Y12 inhibitors is related to non-responsiveness to antiplatelets [4]. Compared to Clopidogrel, ticagrelor has faster action, more significant effect and more consistent platelet inhibition.

The American Heart Association (AHA)/American College of Cardiology (ACC) Focused Update on Dual Antiplatelet Therapy Guidelines from 2016 recommend ticagrelor as the preferred P2Y12 receptor antagonist after acute coronary syndrome with or without coronary intervention [5]. The PLATO trial supported the

preference of ticagrelor. In this trial, ticagrelor was associated with a reduced vascular death rate, myocardial infarction or stroke compared to clopidogrel in patients with acute coronary syndrome with or without ST elevation. There was no difference in the rate of major bleeding between both groups [6].

The practice at our institution is to start ticagrelor in nearly all Acute Coronary Syndrome patients. However, we observe that many patients ultimately are switched to clopidogrel due to cost and adverse effects. Changing antiplatelet medication is substantially undesirable from a medical standpoint, as it can inadvertently result in periods without full antiplatelet coverage. We seek to quantify the number of patients who transition between the two medications at our institution, quantify the timing of the transition, and look at the association of this transition outcome with various factors. The goal is to guide our clinicians and others who work in a similar setting to choose initial outpatient antiplatelet therapy after percutaneous coronary intervention. For example, if a patient has a high probability of requiring transition, the patient could be started on clopidogrel rather than ticagrelor.

Methods

A retrospective data analysis of all patients who underwent Percutaneous coronary intervention (PCI) for Acute coronary syndrome (ACS) at our hospital between January 2019 to January 2020 was conducted. Institutional Review board approval for ethical clearance was sought and was approved. Approval number-IRB 2093 A Ritter. Patient charts were accessed, and clinical details were noted. The reason for premature switching of antiplatelet were noted from the cardiology outpatient or phone call documentation.

Inclusion criteria

All patients who underwent PCI for a period of 12 months for ACS and was started on ticagrelor post PCI at Unity hospital.

Exclusion criteria

1. Patients who needed antithrombotic for any other reason, for example stroke or atrial fibrillation. 2. Patients who died during the time period of study. 3. Patients who underwent CABG during the time period of study. 4. Patients who were never started on ticagrelor. 5. Patients who were lost to follow up during the one-year period.

Analysis

Data was collected by conducting a thorough chart review and was compiled on a spreadsheet. Patient data included the age, sex and race of the patients. The duration of days on ticagrelor was recorded for the patients who discontinued the medication. The reasons for discontinuing ticagrelor were also enumerated.

Statistical analyses were performed using SAS Studio (SAS Institute). Descriptive statistics for all the study variables were done. Logistic regression results of these analyses were reported with point estimates, 95% confidence intervals and *P* values. $P < 0.05$ is considered to be statistically significant in multivariate analysis.

Patients that stopped taking ticagrelor before completion of 1 year were categorized based on the reason for cessation: Shortness of breath, drug interaction, development of Gout, insurance issues, rash, non-compliance.

Results

We reviewed the charts of 330 patients who underwent PCI during the span of one year at our institution from January 1, 2019, to January 1, 2020. After excluding patients already on antithrombotic for any other reason, patients who died during the study period, patients who underwent CABG during the one year and patients who were never started on ticagrelor, 277 patients were included in the study. The mean age was 69.7 years (56.2-79.6 years). 229 patients (82.7%) were males, and 48 (17.3%) were females.

Of 277 patients, 179 (65%) patients completed one year of ticagrelor therapy and 98 (35%) patients stopped ticagrelor and transitioned to clopidogrel.

Shortness of breath was the leading cause for ticagrelor discontinuation in 42.8%, followed by cost-related reasons in 41.8%. Other reasons for discontinuation included reaction to existing medications like phenytoin, HIV medica-

Table 1. Demographic and treatment status characteristics

Parameter Statistic	N = 277
Age (Year)	
Number	277
Mean (SD)	68.0 (11.701)
Standard error of mean	0.7
Median	68
Q1; Q3	60; 76
Min; Max	33; 98
Sex, n (%)	
Female	48 (17.3%)
Male	229 (82.7%)
Race, n (%)	
Asian	2 (0.7%)
Black	80 (28.9%)
White	195 (70.4%)
Ticagrelor completed, n (%)	
No	98 (35.4%)
Yes	179 (64.6%)
Reason for Withdrawal, n (%)	
Drug reaction (phenytoin, HIV medications etc)	4 (4.0%)
Economical concerns	41 (41.8%)
Gout	2 (2.0%)
Lack of compliance	4 (4.0%)
Rash	5 (5.0%)
Shortness of breath	42 (42.8%)
Duration (Days)	
Number of days	98
Mean (SD)	40.7 (38.8)
Standard error of mean	3.924
Median	30
Q1; Q3	30; 60
Min; Max	1; 300

Table 2. Logistic regression model

Parameter	OR	CI	*P*-value
Age	1.03	1.003-1.048	0.0286
Sex	1.46	0.733-2.904	0.2821
Race	1.68	0.943-2.979	0.0783

Abbreviation: OR = Odds Ratio, CI = Confidence Interval. Only non-missing value were included. Dependent variable: Ticagrelor completed/Not. Independent variables: Age, Gender (ref = 'Female'), Race (ref = 'Black').

tions (4%), rash and allergic reactions (5%), inability to comply with the twice a day regimen (4%) and induction of gout attacks (2%). The mean value observed for days on ticagrelor among the patients who stopped it was 40.7 ± 38.8. **Table 1** shows the demographic and treatment status characteristics.

Table 2 shows the results of logistic regression analysis to determine the association between the patients who withdrew the treatment and the covariates. Dependent dichotomized variable (Ticagrelor completed/Not completed (Ref = Not completed)) and independent covariates were, Age, Gender (ref = 'Female'), Race (ref = 'African American'). Significant correlations were noted for: Age (OR, 1.03; 95% CI, 1.00 to 1.05; P = 0.03).

Discussion

After ACS, ticagrelor In the PLATO trial was associated with less vascular death, myocardial infarction and stroke at 12 months compared to clopidogrel, 9.8% vs. 11.7% (HR, 0.84; 95% confidence interval [CI], 0.77 to 0.92; P < 0.001). In light of this finding, the use of ticagrelor for 12 months is preferred. We found that only 65% of the patients completed one year of ticagrelor after PCI, and 35% were transitioned to clopidogrel. Shortness of breath was the most common cause for stopping ticagrelor in 42.8%. Dyspnea is a well-known side effect of ticagrelor with a poorly understood mechanism. You et al., in a retrospective cohort study of patients with ACS, found that the use of ticagrelor is associated with a higher risk of dyspnea (27.3%) compared to clopidogrel (22.6%) HR, 1.21 [95% CI, (1.17-1.26); P < .001] [7]. The PLATO trial found that 14% of the patients who received ticagrelor developed dyspnea, but only 0.9% discontinued the medication because of the side effect. In the ONSET/OFFSET study, 25% of patients in the ticagrelor group reported shortness of breath, but only three patients stopped the medication [8]. A Dutch registry enrolled 354 patients and evaluated the adherence rate. It was found that 24% discontinued the medication and the most common reason was dyspnea in 11% of the total ticagrelor patients [9]. Our data is in line with the Dutch registry data, as we saw that 15% of all ticagrelor patients

stopped the medication due to dyspnea. Industry-funded, blinded studies (PLATO and ONSET/OFFSET) showed much greater continued use despite dyspnea. These studies had the highest motivation to coax patients through their dyspnea to continue using the study drug, and they also had study-level resources (Nursing), which likely contributed to this. In the community, where there is no nursing staff dedicated to the sole task of getting patients to continue the study drug, it is not surprising that the discontinuation rate for dyspnea in our patients is greater than ten times what was seen in these initial industry studies.

In the PLATO study, most dyspnea developed in the first week of treatment. However, a meta-analysis showed that the risk of dyspnea remained high beyond six months [10]. The pathophysiology of dyspnea is unknown. Adenosine has been considered a potential cause, but the HI-TECH study showed no difference in serum adenosine levels in ticagrelor, clopidogrel and prasugrel patients, and there was no association between the adenosine level and the occurrence of dyspnea [11]. However, the ticagrelor level itself was higher in patients who developed dyspnea. Association of ticagrelor level and dyspnea was confirmed in the PEGASUS-TIMI 54 study, where the incidence of dyspnea was less with 60 mg twice daily ticagrelor compared to 90 mg twice daily (16%, 18%, respectively), and the discontinuation rate was 4.5% in the lower dose compared to 6.5% with the higher dose [12]. It is worthy to note that both doses effectively lowered cardiovascular mortality and myocardial infarction compared to placebo in patients with myocardial infarction more than one year previous. In patients greater than one year out from myocardial infarction, decreasing the dose of ticagrelor may be one of the approaches to lessen the incidence of dyspnea.

Most of the reported dyspnea is mild to moderate in degree and, according to *post hoc* analysis of PLATO data, is not associated with worsened outcomes. In an industry-supported article by Parodi et al., dyspnea in ticagrelor patients should be evaluated carefully with history, physical exam and testing to rule out common specific pathologies. Patients should be observed and reassured that symptoms may improve with time. Given the proven benefit, if the dyspnea is persistent but tolerated, it is reasonable to continue the ticagrelor. However, if the dyspnea is severe or the patient cannot tolerate it, discontinuation of the medication and transition to clopidogrel or prasugrel is an option [14].

The second most common reason for discontinuing ticagrelor was the cost of the medication. Ticagrelor expense is a well-known potential issue for patients [15, 16]. While clopidogrel can be obtained for as low as $5 a month, ticagrelor costs nearly 100 times as much, at $415-$480 a month [17]. On analysis of patients from PLATO, treating patients for 12 months with ticagrelor was associated with a cost per quality-adjusted life-year (QALY) meeting a criterion for cost-effectiveness [16]. At our hospital, patients were given a coupon for 30 free days of ticagrelor to enhance use for this critical first month. Early switching of ticagrelor to clopidogrel prior to hospital discharge was studied and associated with increased platelet reactivity and adverse cardiovascular events [15]. If the coupon program were to be stopped, we would have many more patients exposed to these increased risks, as they would experience “sticker shock” when they went to pick up their discharge medications and require a switch to clopidogrel. Essentially, in our system, the possible efficacy of ticagrelor hinges on a coupon program. We hypothesize that clopidogrel or ticagrelor for acute coronary syndrome should be informed by financial status. Further study is needed in this regard.

The average US household income is $67,521 in 2020 [17]. Zipcode analysis shows our hospital serves households with a median income of $67,749 [17, 18]. As these income numbers are similar, our finding regarding the stoppage of ticagrelor due to financial issues is likely to be similar for the rest of the nation.

Other reasons for abbreviated use of ticagrelor included: inability to comply with the twice a day regimen (4 patients), and gout attack (2 patients), which is a known side effect of the medication [20], rashes from allergic etiology (5 patients) and having other medications with interaction with ticagrelor (4 patients). As per the center preference, clopidogrel was used and other options like prasugrel was seldom used as a second option to ticagrelor.

The other known complications of ticagrelor are increased bleeding, brady arrythmias and thrombotic thrombocytopenic purpuras. Interestingly, none of the patients we followed had to prematurely switch ticagrelor due to these complications [21].

Adherence to medications is utmost importance in reducing post-PCI complications including ischemic events, stent thrombosis and restenosis. Initiating other antiplatelets instead of ticagrelor in selected patients could help in avoiding switching antiplatelet mid-therapy. Further studies are required to identify optimal antithrombotic strategy in patients.

Limitations

This study is a retrospective study. As data was compiled from chart review, there is potential for discrepancies in documentation of the real reason for premature discontinuation that could potentially have changed study outcomes. Patients were not followed up to detect any difference in occurrence of clinical events in patients who remained on ticagrelor compared to the premature discontinuation group. Another limitation is that the study did not include any CABG, or previously on medical therapy patients, or patients requiring anticoagulation for atrial fibrillation and so the results cannot be fully extrapolated to these groups. Finally, these results were obtained from a community hospital in north-east United states of America. The premature discontinuation rates could be different as influenced by the cost factor in other countries.

Conclusion

In our community hospital, 65 percent of patients completed their one-year ticagrelor treatment after PCI. Dyspnea and pharmaceutical costs are the most common reasons for stopping treatment. Counseling and reassuring the patient about the shortness of breath and explaining the expense of the prescription may help reduce non-compliance. Initiating other antiplatelets instead of ticagrelor in selected patients could help in avoiding switching antiplatelet mid-therapy.

Disclosure of conflict of interest

None.

Abbreviations

ACS, Acute coronary syndrome; PCI, Percutaneous coronary intervention; IPA, Inhibition of platelet aggregation; ADP, Adenosine diphosphate; CABG, Coronary artery bypass graft.

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