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Evaluating the Utility of CYP2C219 Genetic Testing for P2Y12 Inhibitor Prescribing Within an Inpatient Setting

Thomas E. Maslo, Pharm.D. and Carolyn Null, Pharm.D.

Background

The emergence of pharmacogenomics offers the opportunity to practice precision medicine across healthcare, including within patients presenting with acute coronary syndrome (ACS).

In patients presenting with ACS and undergoing percutaneous coronary intervention (PCI) with stent placement, dual antiplatelet therapy (DAPT) is routinely prescribed for a minimum of 12 months post-PCI. DAPT consists of a P2Y12 inhibitor (clopidogrel, ticagrelor, or prasugrel) plus aspirin.

The American College of Cardiology (ACC), the American Heart Association (AHA), and the European Society of Cardiology (ESC) favor ticagrelor or prasugrel over clopidogrel in patients diagnosed with ACS who receive DAPT post-PCI. These guidelines do not recommend for routine genetic testing. Comparatively, the Clinical Pharmacogenetics Implementation Consortium provides guidance on tailored P2Y12 inhibitor therapy dependent on CYP2C19 status, with ticagrelor or prasugrel being favored in poor or intermediate metabolizers. Consequently, selection of a P2Y12 inhibitor may be influenced by both prescribing practices and patient-specific factors.

Approximately 30% of the North American population carry at least one CYP2C19 allele associated with reduced metabolism of clopidogrel, potentially increasing their risk for adverse outcomes and treatment failure. Ticagrelor and prasugrel are not impacted by CYP2C19 metabolism, but are associated with increased bleeding risk and cost.

The utilization of CYP2C19 genetic testing could optimize P2Y12 inhibitor prescribing, potentially resulting in improved clinical outcomes and cost savings. Recent studies have provided increasingly positive evidence that a genotype-guided strategy for DAPT results in reduced adverse events. Additionally, future guideline recommendations may be impacted by these studies. This retrospective cohort analysis aims to identify how CYP2C19 genetic testing may impact clinical practice within an inpatient setting.

Objectives

Primary
- Evaluate the incidence of optimal P2Y12 inhibitor prescribing in a retrospective cohort
  o Defined as those projected with a loss of function allele being prescribed ticagrelor or prasugrel (30%), and those projected without a loss of function allele being prescribed clopidogrel (70%)

Secondary
- Evaluate readmissions associated with major cardiovascular adverse events (MACE) at 30 days and 1 year
- Evaluate readmissions associated with stent thrombosis at 30 days and 1 year
- Perform a cost analysis between the study cohort and a simulated cohort utilizing a genotype-guided strategy at 1 year

Methodology

Study period:
- September 2016 through September 2019

Data collection:
- Electronic health record-based retrospective cohort

Study population:
- Patients ≥18 years old undergoing PCI with drug-eluting stent placement
- Patients prescribed DAPT – consisting of clopidogrel, ticagrelor, or prasugrel – upon discharge
- Patients presenting with acute coronary syndrome

Exclusion criteria:
- Past/current diagnosis of cancer
- Pregnancy
- To ensure appropriate length of follow-up, patients were also excluded if they did not have a documented chart encounter after 30 days of the index PCI

Outcomes measured:
- MACE, defined as myocardial infarction (MI) or ischemic stroke (ST)
- Other ischemic events, defined as stent thrombosis (ST) or unstable angina (UA)

Results

Figure 1. Prescribing Rates Over Time

Figure 2. Prescribing Rates Per Index Diagnosis

Figure 3. Initial Readmission Events Over 30 Days

Figure 4. Initial Readmission Events Over 1 Year

Figure 5. Cumulative Failure Rates Over Time

Figure 6. Cost-analysis Among Cohorts

Table 1. Event Rates Over 30 Days and 1 Year

Table 2. Evaluation of Genotype-guided DAPT over 1 year

Table 3. CYP2C19 Genetic Testing for P2Y12 Inhibitor Prescribing

Discussion

From September 2016 through September 2019, overall P2Y12 inhibitor prescribing rates compared favorably to the optimal prescribing rates noted in the primary objective. Ticagrelor or prasugrel were prescribed at an overall rate of 36.9%, while clopidogrel was prescribed at a rate of 73.1%. Additionally, prescribing of ticagrelor has increased over time, being possibly influenced by ACC/AHA and ESC guideline updates.

Prescribing habits showed that ticagrelor is more likely to be prescribed with an index diagnosis of STEMI, compared to NSTEMI or unstable angina. Within the past year, the POPular Genetics trial suggests that a genotype-guided strategy, with 61% of patients receiving clopidogrel, was non-inferior to those receiving ticagrelor in patients diagnosed with STEMI and undergoing PCI. The genotype-guided arm also experienced significantly fewer minor bleeding events. Thus, CYP2C19 screening may help support prescriber decision-making in consideration of the index diagnosis.

Event rates among both groups are more pronounced within the initial 30 days post-PCI, with 90% of total initial readmissions occurring during this period. These rates highlight the necessity of early, targeted P2Y12 inhibitor prescribing. Additionally, individuals receiving clopidogrel showed a significantly higher incidence of MACE plus other ischemic events (p<0.01) occurring after 1 year. Cumulative failure rates for the clopidogrel group were also comparatively higher throughout the entirety of this period.

A potential explanation for the increased readmission rates in the clopidogrel group is individuals, with one or more loss of function alleles, are being sub-optimally prescribed clopidogrel. A genotype-guided strategy could help mitigate these risks by allowing for targeted P2Y12 inhibitor prescribing, resulting in improved clinical outcomes.

A simulated analysis was completed utilizing incidence rates associated with a genotype-guided strategy, and also utilizing prescribing frequencies demonstrated by this study. The rate of MACE and other ischemic events was reduced by 57% in the simulated cohort. This reduction equated to savings of $577,377, or $1,325 per person, with savings attributed to reduced readmissions due to adverse outcomes.

Limitations of this retrospective cohort study include the potential for missed events not documented within the electronic medical record and the inability to control for other confounding factors. There was also notable attrition within the ticagrelor group, with 45 patients being discontinued therapy after a median of 37 days. Discontinuation of ticagrelor was most commonly associated with cost and dyspnea, at 49% and 39%, respectively. However, this high rate of discontinuation supports the utilization of a genotype-guided strategy in matching patients with the most optimal agent in regards to tolerability and cost. Lastly, CYP2C19 status is not the only contributor associated with a poor response to clopidogrel, and this study did not assess other factors contributing towards platelet reactivity.

Conclusion

This retrospective cohort study at two large, tertiary medical centers demonstrates that overall P2Y12 inhibitor prescribing rates compared favorably to the expected distribution of CYP2C19 phenotypes among the North American population, with a trend towards increased prescribing of ticagrelor. However, significantly increased MACE plus other ischemic events over 1 year in the clopidogrel group demonstrate that P2Y12 inhibitor prescribing can be optimized utilizing a genotype-guided strategy.

As event rates were higher within the initial 30 day period post-PCI, initiating CYP2C19 genetic screening promptly and during inpatient admission may help minimize early readmission. CYP2C19 genetic screening may also help guide optimal prescribing practices in consideration of other factors, such as the tolerability of the medication regimen. Lastly, a genotype-guided strategy may reduce costs for both the health system and the patient.

References