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Ticagrelor Use in Acute Myocardial Infarction: Balancing Evidence-Based Medicine with Affordability

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Abstract

STUDY OBJECTIVE—Data from randomized controlled trials support a mortality benefit with ticagrelor versus clopidogrel among patients with acute myocardial infarction (AMI). Many healthcare providers preferentially treat patients with AMI with ticagrelor. The goal of this study was to determine the association between out-of-pocket drug costs and ticagrelor continuation compared with switching to clopidogrel among patients hospitalized for AMI, following a pharmacist-led discussion on outpatient co-payment costs for ticagrelor.

DESIGN—Retrospective cohort study.

SETTING—A tertiary care academic medical center.

PATIENTS—Patients hospitalized with AMI between February 15, 2015 and January 23, 2017, who were loaded with ticagrelor on presentation.

MAIN RESULTS—Of 143 patients with AMI loaded with ticagrelor, 70 (49%) switched to clopidogrel after cost discussion. The median monthly ticagrelor co-payment was \$268.29 (interquartile range [IQR] \$45–\$350) for switchers, versus \$18 (IQR \$6–\$24) for non-switchers ($p < 0.001$). Patients with co-payments of \$100/month or more were 3.4 times more likely to switch to clopidogrel (relative risk 3.41, 95% confidence interval 2.12 to 5.47), compared with patients with co-payments of less than \$100/month.

CONCLUSIONS—Following a discussion of outpatient costs, half of patients with AMI switched from ticagrelor to clopidogrel when given the choice.

Keywords

P2Y₁₂ inhibitor; acute myocardial infarction; ticagrelor; clopidogrel; cost; acute coronary syndrome

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Dual antiplatelet therapy with aspirin and a P2Y₁₂ inhibitor is the cornerstone of acute myocardial infarction (AMI) treatment.¹ Data from randomized controlled trials support a mortality benefit and a reduction in major adverse cardiac events without significantly increasing the risk of bleeding when ticagrelor is administered instead of clopidogrel.^{1,2} Compared with clopidogrel, ticagrelor is a reversible direct-acting agent with faster onset of action, greater platelet inhibitory potency, and quicker elimination from the body.¹ For patients who require coronary artery bypass grafting (CABG), the quicker elimination of ticagrelor may facilitate shorter time to surgery.^{1,2} Given these benefits and contemporary analysis that support cost-effectiveness, health systems may consider adopting a policy to preferentially use ticagrelor in patients with AMI as a part of a value-based care approach to health care delivery.³ The association between out-of-pocket P2Y₁₂ inhibitor drug costs and patient drug preference, however, is unknown. The purpose of our study was to examine patient preferences for ticagrelor and clopidogrel when outpatient co-payment costs are openly discussed prior to hospital discharge.

Methods

In February 2015, University of Utah Health (U of U Health) implemented a standardized treatment protocol for patients presenting with AMI which included loading patients with AMI with 180mg of ticagrelor. The motivation behind this protocol was to ensure uniform treatment with an evidence-based medication proven to have mortality benefit.¹ Providers were encouraged to administer a loading dose of ticagrelor, in the absence of a contraindication, to patients who presented to the emergency department with AMI. For outside hospital referrals, ticagrelor was used if available at that facility. A pharmacist engaged the patients in a medication preference discussion within 24 hours after their first dose of a P2Y₁₂ inhibitor specifically addressing monthly, out-of-pocket costs, differences in dosing regimens between clopidogrel and ticagrelor, and the advantage of ticagrelor over clopidogrel with regards to mortality and bleeding. The discussion included the \$18/month manufacturer discount program, if it was available for patients with non-federal insurance.⁴ A P2Y₁₂ inhibitor was then selected in conjunction with the patients' values and preferences; patients were given the loading dose of the new drug if the agreed upon decision was to switch.⁵ Patients were defined as switchers if they were initially loaded with ticagrelor but were discharged with clopidogrel from the hospitalization. The primary goal of these analyses was to determine the rate of patient switching from ticagrelor to clopidogrel, and determine the association between out-of-pocket cost and switching.

Data from patients who had AMIs are collected routinely for quality control at U of U Health using the ACTION (Acute Coronary Treatment and Intervention Outcomes Network) Registry®. The ACTION Registry® is a voluntary program through the National Cardiovascular Disease Registry (NCDR)® that allows hospitals to collect outcome data and benchmark performance against other hospitals.⁶ The data includes collection of key demographic and clinical variables; we repurposed these data for our analyses. Patients presenting directly to our facility and outside hospital referrals hospitalized for AMI who were loaded with ticagrelor on presentation between February 2015 and January 2017 were included in the study. Patients were excluded who required coronary artery bypass graft

(CABG) for treatment of their AMI, died, left against medical advice, did not require a P2Y12 inhibitor at discharge, and any subsequent readmissions of the same patient during the study period. Monthly out-of-pocket ticagrelor costs, demographics, and comorbidities were compared between patients who switched and did not switch to clopidogrel using chi-squared tests for categorical variables and the Wilcoxon rank-sum test for continuous variables. Poisson multivariable regression was used to determine the association between cost and switching, using a stepwise regression sequentially removing variables with p values >0.20 . Candidate variables included: demographics (sex, race [white versus non-white], primary insurance payer [Medicare/private/other versus Medicaid/self], smoking status), co-morbid conditions (atrial fibrillation, dyslipidemia, currently on dialysis, diabetes mellitus, prior AMI, prior percutaneous coronary intervention [PCI], prior heart failure, prior CABG, hypertension, cerebrovascular disease, prior stroke, peripheral arterial disease, oral anticoagulant use at discharge, prior aspirin use), and presentation characteristics (ST-elevation myocardial infarction [STEMI], whether PCI was performed, and if the patient was an outside facility transfer).

This study was exempt by the U of U Health Institutional Review Board. Stata version 13 was used for analyses.

Results

Among 424 hospitalizations for AMIs between February 2015 and January 2017, 175 (41.2%) patients were loaded with ticagrelor; after exclusions, 143 patients remained for analyses (Figure 1). Among the final cohort of 143 patients with AMI, 70 (49%) switched to clopidogrel following the medication preference discussion. Patient characteristics from ACTION Registry® are presented in Table 1. The median monthly ticagrelor out-of-pocket cost was \$268.29 (interquartile range [IQR] \$45–\$350) for switchers, versus \$18 (IQR \$6–\$24) for non-switchers ($p<0.001$). In addition to cost, patients who switched were more likely to have Medicaid or be self-insured (including uninsured), be on an oral anticoagulant medication, and to be a smoker.

Out-of-pocket cost was categorized into three groups: less than \$100/month, \$100/month or more, and missing. In the unadjusted, stepwise regression model, patients with an out-of-pocket cost \$100/month or more were 3.8 times more likely to switch to clopidogrel (relative risk [RR] 3.78, 95% confidence interval [CI] 2.29 to 6.22), compared with patients with an out-of-pocket cost less than \$100/month. In the adjusted model, patients with an out-of-pocket cost \$100/month or more were still 3.4 times more likely to switch to clopidogrel (RR 3.41, 95% CI 2.12 to 5.47), compared with patients with an out-of-pocket cost less than \$100/month.

Missing cost data was more common among non-switchers (8.2%) than switchers (31%; $p<0.001$). To address this limitation, we used a sensitivity analysis excluding patients with missing cost data. The adjusted RR of switching to clopidogrel, excluding missing cost data, of patients with out-of-pocket cost \$100/month or more versus less than \$100/month was 4.42 (95% CI 2.71 to 7.22).

Discussion

Randomized controlled trials support the use of ticagrelor over clopidogrel and analyses suggest that ticagrelor is cost-effective from a societal perspective.¹⁻³ Despite this evidence, we found that half of patients with AMI switch from ticagrelor to clopidogrel following an open discussion of outpatient cost. While cost-effective, ticagrelor may not be affordable from an individual's perspective. Others have noted in-hospital switch rates of 24%, but our findings suggest that the true switch rate is higher when cost is included in P2Y12 inhibitor choice.⁷ To our knowledge, this study is the first to associate higher out-of-pocket cost with P2Y12 inhibitor choice. High cost is associated with non-adherence, so a cost-conscience process is prudent to identify patients who cannot afford ticagrelor.⁸

Our finding that half of patients with an AMI will choose a cheaper P2Y12 inhibitor when given the choice is critical to balancing evidenced-based medicine with real-world application. Non-adherence to P2Y12 therapy after AMI is of particular concern among patients who receive PCI, given the risk of stent thrombosis.⁹ Prior data from the MI FREEE trial suggests that identifying more affordable medication options increases medication adherence and improves outcomes.¹⁰ Other healthcare systems could choose to systematically evaluate patients preference in post-AMI management as part of a learning healthcare system, particularly as evolving healthcare policy proposals may place a greater cost burden directly on patients.¹¹

Pharmaceutical companies often provide discounts for patients who are prescribed brand-name medications, including the makers of ticagrelor. Under this program, the copayment for ticagrelor at the time of publication can be reduced to \$18/month for patients with non-federal insurance (i.e., not applicable to Medicare and the Veterans Affairs Health System).⁴ Given the importance of cost in the decision making process, such programs could increase access to ticagrelor in the immediate post-AMI setting. Indeed, our results suggest that several patients benefitted from this program: 58% (56 out of 96) of patients with commercial insurance faced co-pays of less than \$100 and the median co-payment was \$18/month. Still, healthcare providers must be aware of the fact that if the patients' insurance plan changes, deductibles are reset, or the maximum benefit under the manufacturer discount program is reached, patients may abruptly stop their medication, which may be concerning for patients post-AMI.

Our local process focused on a discussion of cost, but often includes other topics such as dosing regimens and bleeding concerns. The process was not, however, a fully scripted shared decision making approach. Shared decision making is a way to ensure medical care is in line with patients' values and preferences and is associated with increased patient knowledge, improved risk perceptions, and better medication adherence.¹² Other limitations in this retrospective analysis include a single-center experience among a predominantly white population. We were unable to account for other socioeconomic factors, such as patient income. Missing cost data was common in 8.2% of non-switchers and 30% of switchers. In a post-hoc discussion with our pharmacy team, if a patient was admitted around a holiday or at a time with limited pharmacy, the pharmacist may have been unable to meet with the patient to calculate ticagrelor co-payment cost and engage in the medication

preference discussion prior to discharge. In addition, the co-payment cost of ticagrelor is always more than \$300 after the first month for self-payers (most of whom are uninsured), and the decision making process may not have been documented in the electronic medical record for these patients. However, when we used a sensitivity analysis excluding patients with missing cost data, we found that increasing ticagrelor cost was still associated with switching (adjusted RR 4.42 [95% CI 2.71 to 7.22] for every \$100 increase in monthly out-of-pocket cost). In addition, factors other than cost may contribute to the decision making process. As suggested by the univariate analyses (Table 1), patients on oral anticoagulants were more likely to switch to clopidogrel (12.9% versus 1.4%, $p=0.007$), as clopidogrel is the guideline-recommended treatment when P2Y12 inhibitors are used with oral anticoagulants.¹³ Additionally, the association with smoking and switching (19.2% versus 37.1%, $p=0.017$) is likely multifactorial including, but not limited to, higher rates of atrial fibrillation and subsequent oral anticoagulant use among smokers and possibly even differences in primary payer type.¹⁴ The sample size, however, limited the evaluation of other, non-cost factors in the multivariable model.

Despite a protocol encouraging the use of ticagrelor in the absence of a contraindication, only 41% of our patients with AMI during the study period were loaded with ticagrelor. Our facility covers an extensive area of very rural hospitals, many of which do not routinely stock ticagrelor. Additionally, the distance to many of these hospitals necessitates the use of fibrinolytics prior to transfer, and clopidogrel is the only P2Y12 approved to be co-administered.¹³ Therefore, in addition to cost-related challenges in implementing a ticagrelor policy, other logistical barriers limited implementation as well.

Our findings are part of a learning healthcare system and demonstrate an important role for cost consideration in patients with AMI. Ongoing efforts should include standardized discussions and a systematic approach to shared decision making for all patients.

Conclusions

Among patients presenting with AMI who are loaded with ticagrelor, half switch to clopidogrel following a discussion on outpatient cost. Other healthcare systems should systematically evaluate patients' drug preference based on affordability as part of routine post-AMI management.

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Figure 1. Consort Diagram for Patients Presenting with Acute Myocardial Infarction. AMI = acute myocardial infarction, CABG = coronary artery bypass graft.

Table 1

Characteristics of Patients Loaded With Ticagrelor for AMI Who Continue Ticagrelor Compared With Patients Switching to Clopidogrel Prior to Discharge

Variable	Patients who continued ticagrelor (n=73)	Patients who switched to clopidogrel (n=70)	p-value
Age (mean years $\pm$ SD)	62.8 $\pm$ 11.6	62.8 $\pm$ 12.1	
Female gender (%)	30.1	27.1	0.692
Monthly out-of-pocket cost (median cost \$, IQR)	18, 6–24	268.29, 45–350	<0.001
Monthly out-of-pocket cost (%)			<0.001
<\$100	80.8	22.9	
\$100	11.0	47.1	
Missing Cost Data	8.2	30.0	
Primary payer (%)			0.001
Medicare/commercial/other [†]	91.8	70.0	
Medicaid/self-pay	8.2	30.0	
Race (%)			0.301
White	87.7	81.4	
Non-white	12.3	18.6	
Co-morbid conditions (%)			
Atrial fibrillation	5.5	8.6	0.469
Current or recent smoker	19.2	37.1	0.017
Hypertension	56.2	47.1	0.280
Dyslipidemia	64.4	54.3	0.219
Currently on dialysis	1.4	4.3	0.290
Diabetes mellitus	24.7	27.1	0.734
Prior MI	13.7	24.3	0.106
Prior heart failure	9.6	14.3	0.386
Prior PCI	15.1	22.9	0.234
Prior CABG	5.5	8.6	0.469
Cerebrovascular disease	5.5	10.0	0.311
Prior stroke	5.5	5.7	0.201
Peripheral arterial disease	5.5	4.3	0.741
STEMI or STEMI equivalent	71.2	67.1	0.596
Transferred from outside facility	24.7	28.6	0.596
PCI during hospitalization	97.3	90.0	0.074
Oral anticoagulant at discharge	1.4	12.9	0.007

AMI = acute myocardial infarction; CABG = coronary artery bypass graft; IQR = interquartile range; MI = myocardial infarction; PCI = percutaneous coronary intervention; SD = standard deviation; STEMI = ST elevation myocardial infarction.

[†]This insurance group includes 12 Medicare patients, 96 commercially insured patients, and 6 other types of insurance.