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Research Article

Premature Discontinuation of Ticagrelor among Patients who underwent PCI for ACS in a Large Urban Safety Net Hospital

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Abstract

Background: Dual anti-platelet therapy for one year after placement of drug eluting stent (DES) is guideline indicated for the prevention of stent thrombosis. The prevalence of ticagrelor nonadherence has not been fully elucidated.

Methods: All patients who received DES from January 2011 – June 2016 at Parkland Health and Hospital System and were initially prescribed ticagrelor were included; those lost to follow up before 1 year, who were transitioned to clopidogrel within that time, or did not have a Parkland specific financial subsidy were excluded. We collected refill data from a large, closed pharmacy system for 1 year post-DES. For each patient, ticagrelor adherence was categorized as proportion of days covered (PDC) > 80%, PDC 40 - 79% or PDC < 40%. Statin PDC was calculated and compared to ticagrelor PDC to assess the relative impact of drug- vs. patient-specific adherence factors. Survival models using time to first failure to obtain a ticagrelor refill, allowing a 5-day grace period, were created. Logistic regression models were used to assess for clinical predictors of low PDC (< 40%).

Results: Our cohort (N = 160) was 75% male, 70% White, 21% African American, and Asians were 9%. The PDC at one year for ticagrelor (61% ± 32%) was modestly lower than for statin medications (65% ± 34%, $p < 0.02$). At one year, 43.6% of the cohort had good adherence (PDC > 80%) to ticagrelor and 33.0% had poor adherence (< 40%). In comparison, 49.0% of the same cohort had good adherence to statin and 25.0% had poor adherence ($p < 0.001$). Statin and ticagrelor adherence were highly correlated ($r = 0.73$). Median time to first failure to refill ticagrelor was 90 days. A multivariable model showed African American race/ethnicity and a copay of > $5 were associated with lower adherence, while speaking Spanish as a primary language was associated with higher PDC. However, the overall discrimination of our logistic model was poor.

Conclusions: In this urban safety net cohort of patients receiving DES, overall adherence to ticagrelor was suboptimal. Statin and ticagrelor adherence differed only modestly, suggesting that non-adherence was driven by patient-level factors rather than being ticagrelor-specific.

Keywords: *Ticagrelor; Medical Adherence; Acute Coronary Syndrome*

Introduction

Dual antiplatelet therapy (DAPT), the use of aspirin and a P2Y12 receptor blocker in combination, remains a cornerstone of treatment in patients undergoing percutaneous coronary intervention (PCI). DAPT has been shown to reduce combined endpoints for major adverse

cardiovascular events (MACE) and to reduce cardiovascular mortality. Clopidogrel was the first approved agent and has been followed by more potent oral agents including ticagrelor. In comparison to clopidogrel, ticagrelor has been shown to be more effective in lowering MACE and cardiovascular mortality in stented patients after ACS [1] and it is now considered first line therapy. In order for patients to receive the full benefit of DAPT, adherence to medication is essential. Premature discontinuation of clopidogrel after DES has been shown to be common and associated with both in-stent thrombosis (IST) and mortality [2].

Clopidogrel adherence after PCI was shown to be poor in work by our group and others [3,4]. Beyond the increased bleeding risk common to all DAPT, ticagrelor has unique adverse side effects, such as dyspnea and bradycardia [5-7], which may further decrease adherence as compared with clopidogrel [8]. As prescription of ticagrelor becomes more common, it is important to examine ticagrelor adherence overall and in comparison with drugs that do not have the same side effect profile. Parkland Health and Hospital System (PHHS) is a large academic medical center serving as the sole safety net hospital for Dallas County and provides subsidized care to indigent patients. Medications are provided within the system pharmacies at subsidized cost, leading patients to preferentially fill expensive medications such as ticagrelor only at system pharmacies. Therefore, we sought to (1) assess ticagrelor adherence over the year after DES, (2) compare ticagrelor adherence with statin adherence (acting in this case as a "control" without the ticagrelor-specific side effects), and (3) to assess whether there were strong clinical predictors of low ticagrelor adherence.

Methods

We performed a retrospective cohort study to characterize the overall medication adherence of ticagrelor and statin medications. During the study period, financial assistance was given to uninsured low-income Dallas County residents who qualified based on income and household size. Medications were provided to patients who filled within the closed system at low cost ($0 - $10 per month, income based). We identified patients who underwent DES and received an initial ticagrelor prescription using the Parkland cardiac catheterization lab database. We used medication refill data from the Parkland pharmacy database.

Study population

The patient population selected includes all patients between the dates of April 1st, 2011 and June 30th 2016 who underwent DES placement, were prescribed ticagrelor at discharge, who had ≥ 1 year of post-PCI follow up, and who received Parkland subsidies for drugs filled at Parkland. Any patient that was initially prescribed ticagrelor but was switched to clopidogrel within one year, who had prescriptions sent to an outside pharmacy, or obtained alternative health insurance during follow up was excluded (Figure 1). Identified patients were then chart reviewed for patient demographics, laboratory data, electrocardiograms, cardiac catheterization reports, echocardiographic reports, clinical follow up and duration of ticagrelor therapy using the EPIC electronic medical record. The frequency of comorbid conditions including diabetes mellitus, hypertension, hyperlipidemia, ischemic heart disease, prior smoking, congestive heart failure, prior acute coronary syndrome (ACS), prior PCI and peripheral vascular disease were determined by chart review. Ticagrelor related side effects and one year clinical outcomes for refractory angina, heart failure hospitalization, recurrent ACS, ticagrelor related dyspnea and bleeding were evaluated by chart review. This study protocol was approved by the University of Texas Southwestern institutional review board and Parkland.

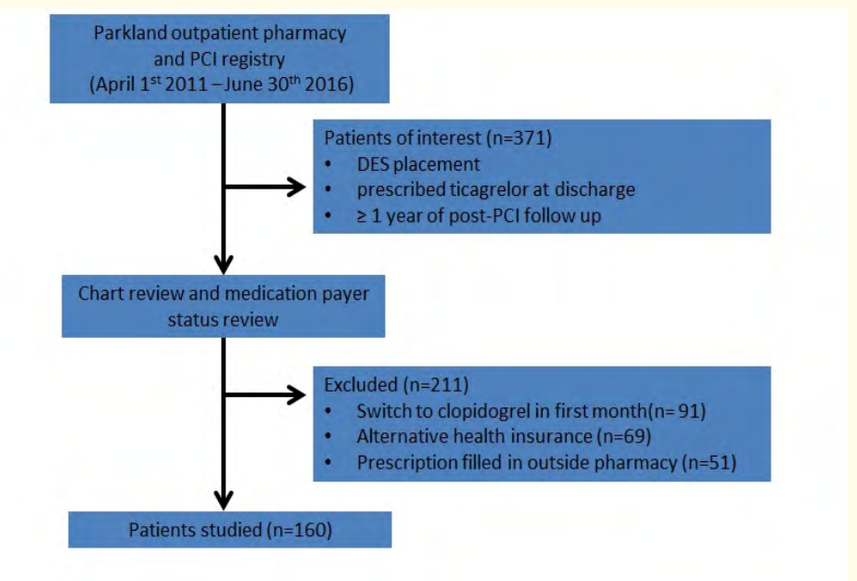

Figure 1: *Study flow diagram.*

Outcome measures

The PDC is a ratio where the denominator refers to the number of days between the first fill, hospital day of discharge, and the end of the follow up period of one year. The numerator is the number of days covered by the prescription fills (each 90 days) during the denominator period. For refills identified near the end of the observation period, only the days supplied between that refill date and end of the follow-up period were counted. PDC has been well validated as a surrogate outcome measure for adherence, with clinically relevant implications such as readmission to the hospital [9,10]. The PDC of ticagrelor and statin medications were determined from the same study cohort. Statin PDC was measured as an internal control to assess the relative contribution of drug-specific versus patient-specific effects on patient adherence. PDC for both ticagrelor and statin were categorized as: high (> 80%), intermediate (40 - 79%), and low (< 40%). These values have been used in prior studies investigating adherence to treatment in hypertension and hyperlipidemia [11,12]. In the same cohort, we also sought to determine the ticagrelor time to failure over the period of one year. Because the anti-platelet effect of ticagrelor persists after medication discontinuation and order to be more conservative we allowed a 5 day grace period after a prescription should have been refilled [13].

Statistical Analysis

Descriptive statistics are reported in table 1. Student's t test was used to compare overall differences in mean PDC of ticagrelor and statin medications. Categorical variables were analyzed for differences using the Chi square test. Continuous ticagrelor PDC versus statin PDC was graphed and Pearson correlation coefficient was calculated from these continuous data. Kaplan Meier analysis was used to categorize time to failure to refill ticagrelor within the 5 days grace period and plotted over the course of one year. Odds of low ticagrelor PDC compared to the referent group (high and intermediate PDC) were modeled using a stepwise approach with multivariable adjustment for age, sex, and comorbidities to determine whether patient characteristics, payer status and clinical factors could predict low ticagrelor adherence. All statistical tests were two sided with p values < 0.05 considered statistically significant. Analyses were performed using STATA 14 software (STATA, College Station, Texas).

Results

The study cohort had a mean age of 55 ± 9.0 years and BMI of 30 ± 5.6 kg/m2 and was predominately male (Table 1). The majority of patients were White and the percentages of African American and Hispanic patients were 21% and 53% respectively. The predominant indication for PCI was ACS (98%) rather than elective (2%) consistent with ticagrelor's guideline supported role. By one year of follow-up, PDC for ticagrelor as compared with statin were (PDC > 80%, 43.9% vs. 48.8%, n = 80), (PDC 40 - 79%, 23.0% vs. 30.0%, n = 27) and (PDC < 40%, 33.0% vs. 25.0%, n = 53) (Chi Square, p < 0.001) (Figure 2). The mean statin PDC was 65% vs. 61% for ticagrelor (p < 0.02). PDC of ticagrelor and statin medications were highly correlated (Pearson r = 0.73). Kaplan Meier analysis for ticagrelor time to failure was plotted over one year. The median time to failure to refill ticagrelor was 90 days (Figure 3). By one year, 93.8% of patients had failed to fill at least one ticagrelor prescription within a 5-day grace period of their home supply running out.

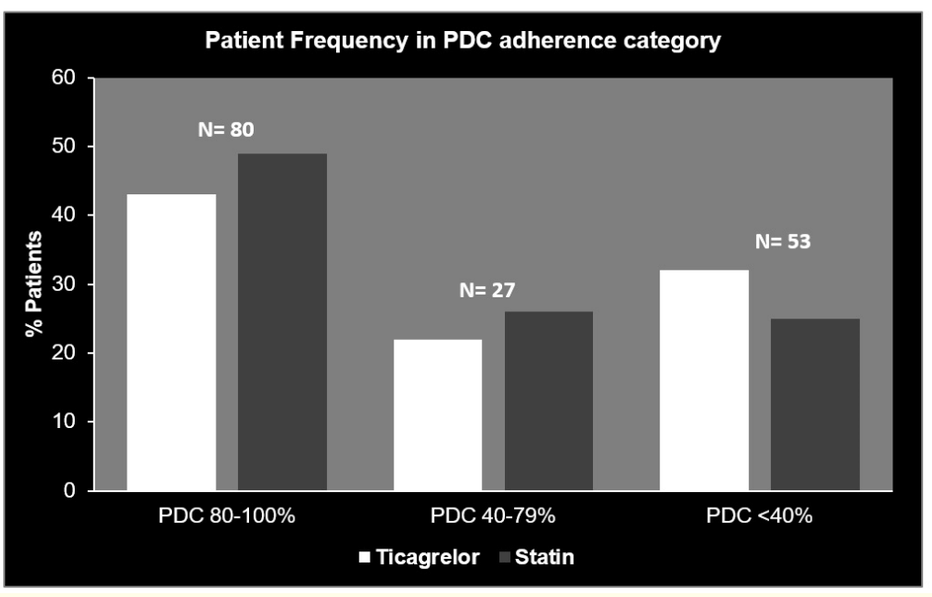

Figure 2: *Patients stratified by PDC adherence category for ticagrelor (black) and statin (gray). PDC (80 - 100%) highly adherent, PDC (40 - 79%) intermediate adherence, and PDC (< 40%) low adherence.*

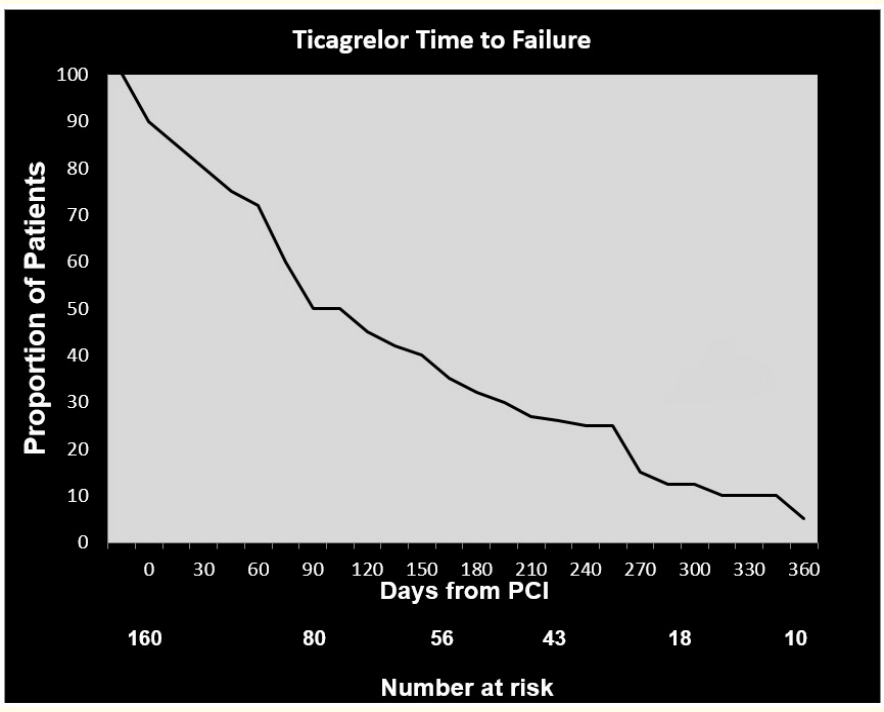

Figure 3: *Kaplan-Meier plot of time to failure to fill ticagrelor prescription within a 5 day grace period. Median time to failure was 90 days.*

A prediction model for low ticagrelor adherence using logistic regression for pre-specified clinical predictors, social and ethnic determinants, known side effects to medication, and hospital outcomes at 1 year was generated using variables in table 1. Significant associations with low ticagrelor adherence were found among patients who were African American versus white and Hispanic patients [OR: 2.76, 95% CI (1.14 - 6.70)] and Co-payment cost for 30-day supply of > $5 versus <= $5 [OR: 3.09, 95% CI (1.26 - 7.55)]. Paradoxically, patients that were primary Spanish speakers versus primary English speakers at one year were likely to have higher adherence [OR: 0.27, 95% CI (0.11 - 0.67)]. All other variables including the presence of drug side effects were not associated with low adherence.

Characteristics	Overall N = 160
Age (years)	55 ± 8.98
Female	26%
BMI (kg/m^2)	30 ± 5.61
Race	
White	70%
African American or Black	21%
Asian	9%
Ethnic Groups	
Hispanic	53%
Non-Hispanic	47%
Indication for PCI	
STEMI	34%
NSTEMI	53%
Unstable Angina	11%
Positive functional test	2%
Comorbidities	
Diabetes Mellitus	49%
Hypertension	93%
Hyperlipidemia	84%
Former or current Tobacco use	40%
Asthma/COPD	9%
Chronic Kidney Disease III or greater	10%
Depression	10%
Cardiovascular disease history	
Ischemic heart disease	32%
Prior ACS	21%
Prior CABG	9%
Prior PCI	21%
Mean LVEF	48%
CHF (systolic heart failure)	19%
LVEF < 35%	23%
Presence of ICD	6%
History of CVA	8%
Atrial Fibrillation	4%
Peripheral Vascular Disease	14%
Medications	
On warfarin?	4.3%
On NOAC	0%
Procedural Characteristics	
Radial Access	39%
Single Vessel PCI	70%
Two Vessel PCI	21%
Three Vessel PCI	4%
Bypass graft PCI	3%
Marital Status	
Married	30%
Single	42%
Divorced/Separated	20%
Widowed	4%
Unknown	4%
Language	
English	62%
Spanish	37%
Payer status	
Parkland Health Plus	39%
Parkland Financial Assist	33%
Dallas County Tax Support	28%
Ticagrelor Related Side Effects	
Dyspnea	12%
Bradycardia	12%
Hyperuricemia	2%
Gout Flare	< 1%
Cardiovascular outcomes one year	
Refractory Angina	13%
Staged PCI	14%
Recurrent ACS	9%
Heart failure hospitalization	14%

Table 1: *Demographics and patient characteristics.*

Discussion

Medication adherence research in the areas of cardiovascular care aims to address the possible factors involved in non-adherence to treatment of hypertension and hypercholesterolemia as well secondary prevention strategies after myocardial infarction. Indeed patients identified with low levels of adherence had higher rates of MACE and those with higher PDC had lower rates of MACE over subsequent years [14].

In this retrospective cohort study from a large urban safety net hospital evaluating patient adherence to ticagrelor after PCI, we found that ticagrelor adherence was poor despite a highly subsidized medication cost. Approximately 44% of patients were considered highly adherent and one third of the patients were considered poorly adherent. There are few reports of ticagrelor adherence in the literature however rates of ticagrelor discontinuation are reported from clinical trials and patient registries. In PLATO there was 23.4% discontinuation rate at one year. Similarly high rates of discontinuation, 20.7%, were encountered in a registry from Saskatchewan where the discontinuation rate attributed to lack of adherence was 7.9% [1,15].

We also sought to determine whether adherence to ticagrelor differed from other medications the patient was prescribed. Statin PDC was used as the control since the medication is a class I guideline recommended treatment in our patient cohort, was universally prescribed, and whose cost was similarly subsidized, encouraging patients to fill within the system. As compared to adherence to statin medications using overall PDC, our patients were modestly less adherent to ticagrelor overall. Levels of statin adherence correlated strongly with ticagrelor which suggests that factors contributing to low adherence among ticagrelor are less likely drug specific and more likely patient related. Ticagrelor median time to failure was shorter than clopidogrel adherence from a previously reported study on from our center [4].

Possible contributors to poor adherence include duration of therapy, patient comorbidities, side effects of medications, financial barriers, polypharmacy, tablet manipulation, health literacy, lack of patient motivation and lack of 30 day follow up [16-18]. Ticagrelor is not available as a generic at this time and patients are therefore expected to pay more for the medication. While this was mitigated in the present cohort by financial subsides, this may be a very relevant concern in patients expected to bear the full medication cost.

We considered a multitude of predictors for low ticagrelor adherence including clinical presentation, comorbid conditions, social determinants, ticagrelor related side effects, and clinical outcomes at one year. We found that low adherence was not strongly associated with indication for PCI, comorbidities, clinical outcomes at one year, ticagrelor related dyspnea, bleeding, or bradycardia, although our study was underpowered to test for weak associations. Twice daily dosing maybe a relevant factor although we cannot say with certainty that this is the case. Finally, vulnerable minorities such as African American and Hispanic patients are at higher risk for medication non-adherence to beta blocker, ace inhibitor and statin after acute myocardial infarction [19].

Our study included a disproportionate representation of both African American and Hispanic patients compared with national demographics. In our analysis, African Americans were 2.8 times more likely to be within the category of low adherence (PDC < 40%) than were white patients. In contrast, primarily Spanish speaking patients were found to be more adherent than primarily English speaking patients. Institution wide difficulties for vulnerable minorities are largely seen as daunting; however, paying attention to provider level factors such as quality of the visit, effective follow up with primary care, and provider communication strength may help address medication adherence [20,21]. PHHS provides a wide range of services for primarily Spanish-speaking patients to overcome the language barrier including round the clock translation services, training in cultural sensitivity and patient education materials translated to Spanish. Success in these areas may explain why our primarily Spanish speaking population was 73% less likely than primarily English speakers to be among the low adherence category.

Despite providing medication at a highly subsidized cost, non-adherence to ticagrelor was common. Our findings were similar to a prior report at our institution where clopidogrel adherence was observed to be poor despite subsidized prescription coverage [4]. The addition of copays or out of pocket costs did affect adherence negatively. We found that those who were required to pay a co-pay of greater than five dollars were 3.1 times more likely to be among the low adherence category. These findings are similar to the results of the Post-Myocardial Infarction Free Rx Event and Economic Evaluation (MI FREEE) Trial, which tested the effect of waiving co-pays for prescription coverage after acute myocardial infarction on medication adherence and found overall adherence was suboptimal with or without the usual copay, although modestly higher in the no-copay arm [22]. The level of social support is often considered when predicting successful follow up or adherence to medications. Multiple clinical and social predictors are considered important for the successful management of many chronic conditions [23,24].

Conclusions

In this diverse patient population within a large healthcare system, adherence to ticagrelor is poor in the year following PCI for ACS. While ticagrelor adherence was lower than statin adherence, this difference was modest and suggests overall non-adherence primarily reflects patient level differences rather than ticagrelor-specific reasons for non-adherence. We found that the median ticagrelor time to failure was generally similar to our prior study investigating clopidogrel adherence. Clinical predictors were not associated with low levels of adherence however greater odds for low adherence were found among African Americans and those required co-pay or out of pocket coverage of ticagrelor which suggest potentially important racial and socioeconomic disparities contributing to nonadherence. Recognizing the suboptimal rate of adherence to ticagrelor is important for effective ACS care.

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