Contemporary Profile of Chronic Dialysis Patients Receiving Oral P2Y$_{12}$ Inhibitors: A Single Center Experience

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Abstract

Background: Oral P2Y$_{12}$ inhibitors including clopidogrel, prasugrel, and ticagrelor are FDA-approved for patients presenting with acute coronary syndrome. Due to systematic exclusion of patients with end stage renal disease (ESRD) on outpatient dialysis from major trials, scarce data exist to report contemporary use of these drugs in ESRD patients.

Study design: Retrospective chart review of patient records.

Setting and participants: From 2011-2015, 848 ESRD patients (32%) had prescriptions for oral P2Y$_{12}$ inhibitors such as clopidogrel, prasugrel, and ticagrelor. Differences in patient characteristics as well as major adverse events (MAEs) defined as a composite of new coronary stent placement, heart valve replacement, coronary artery bypass graft or amputation; and all-cause death, nose and gastrointestinal (GI) bleeding were collected.

Results: Of the 85 patient records that were reviewed, there were 68.2% males, 66.7% whites, 21.4% African Americans and 9% on peritoneal dialysis. There were no differences in baseline characteristics of patients who were prescribed the three drugs. 18 (21.2%) deaths, 57 (67.1%) MAEs, 9 (10.6%) nose bleeds and 13 (15.3%) GI bleeds were identified over 16.5 months follow up. There was no difference in clinical outcome variables between the three groups.

Conclusion: Oral P2Y$_{12}$ inhibitors were commonly prescribed to ESRD patients despite the inadequacy of data and there were no differences in the profiles of ESRD patients who were prescribed the three drugs or their outcome variables. All-cause death, MAEs, nose and GI bleeds were common in these patients. Future studies are needed to investigate clinical benefits and risks associated with use of P2Y$_{12}$ inhibitors in this high-risk patient population.

Keywords: Clopidogrel; Prasugrel; Ticagrelor; Oral P2Y$_{12}$ inhibitors; Dialysis

Introduction

Nearly 600,000 patients with end stage renal disease (ESRD) on outpatient dialysis have coronary heart disease, and one-third experience thrombotic cardiovascular (CV) events such as acute coronary syndrome (ACS) [1,2]. Antiplatelet agents (APA), such as aspirin and P2Y$_{12}$ inhibitors, are the cornerstone of ACS management [2,3]. In fact, in ESRD patients, oral P2Y$_{12}$ inhibitors (clopidogrel, prasugrel or ticagrelor) are one of the top fifteen prescribed drugs [1]. However, it must be noted that both, efficacy of oral P2Y$_{12}$ inhibitors in ESRD patients as well as its safety in these patients (who are already predisposed to bleeding), are not established due to systematic exclusion of these patients from the landmark ACS randomized trials [2]. Given the ambiguity and complexity surrounding use of P2Y$_{12}$ inhibitors in ESRD patients, the goal of this study was to characterize contemporary use of clopidogrel, prasugrel, and ticagrelor in ESRD patients. In addition, we report important clinical outcome variables identified in the electronic medical record (EMR) of patients who were prescribed oral P2Y$_{12}$ inhibitors.

Methods

Study population

The Institutional Review Board approval was obtained. In this retrospective cohort study, we identified a local cohort of

ESRD patients from the Healthcare Enterprise Repository for Ontological Narration system (HERON) of the University of Kansas Medical Center (KUMC) between 07.20.2011 and 12.31.2015 using the Informatics for Integrating Biology and the Bedside (i2b2) query and analysis tool (CTSA Award # UL1TR000001) [4]. HERON is the local repository of the KUMC EMR.

Since ticagrelor was approved by the FDA in July 2011, all three drugs have been available in the market since 07.20.2011 [5-7]. Therefore, we chose 07.20.2011 as the start date to create a contemporary ESRD cohort and limit bias in the results during the time period when any one of the three APA was unavailable in the market.
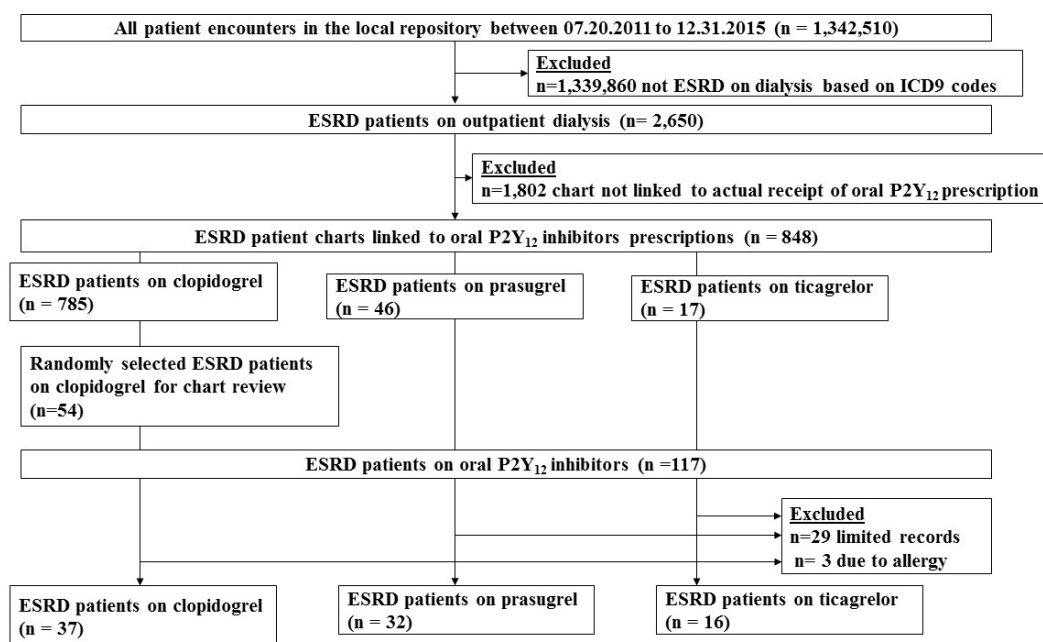

Figure 1 Derivation of the study cohort of end stage renal disease (ESRD) patients on chronic dialysis who were prescribed clopidogrel, prasugrel, and ticagrelor.

ESRD patients were identified from the HERON repository using the International Classification of Disease 9th Revision (ICD 9) codes 585.6 or V45.11.8. **Figure 1** shows the derivation of the study cohort. Among 1,342,510 patients aged 18 years and older identified from the HERON, 2,650 (0.2%) ESRD patients were on outpatient dialysis (hemodialysis or peritoneal dialysis).

Of the 2,650 ESRD patients, charts of 848 patients (32%) were linked to the actual receipts of prescriptions for oral $P2Y_{12}$ inhibitors: 785 patients on clopidogrel (92.6%), 46 patients on prasugrel (5.4%) and 17 patients on ticagrelor (2%). We reviewed EMR of all those who were prescribed prasugrel (n=46) or ticagrelor (n=17).

In addition, we randomly selected a convenient sample of 54 (6.9%) of the 785 patients identified on clopidogrel for detailed chart review, thus, yielding a total of 117 ESRD patients on the three oral $P2Y_{12}$ inhibitors. From the 117 ESRD patients, we further excluded 32 patients due to limited record in the EMR (n=29) or allergy reported from drug use (n=3). A final cohort of 85 ESRD patients on outpatient dialysis who were prescribed oral $P2Y_{12}$ inhibitors at our academic hospital was identified for detailed chart review.

Baseline data collection

We collected data from the EMR. From the admission encounter when a prescription for an oral $P2Y_{12}$ inhibitor first appeared in the chart of a patient, we deemed the prescription to be a new prescription and that date to be the index date. Since the three drugs are FDA-approved for patients presenting with acute coronary syndrome (ACS), they are usually prescribed for the first time in the inpatient settings (index admission).

Baseline characteristics including demographic information, co-morbidities, medications and laboratory data were derived from the index admission notes or outpatient encounters prior to the index date. If there were multiple encounters for a patient, baseline data were collected from the index admission note. Dialysis vintage was reported in months and reflected the time period between dialysis initiation and the index date. Patients were followed until the end of the observation period.

Clinical variables

The clinical variables were recorded from the index date to the end of the observation period. These included

• All-cause death;

- Major adverse events (MAE) defined as a composite of new coronary stent placement (coronary stent placement after 5 days of the index date), heart valve replacement, coronary artery bypass graft (CABG), amputation or the number of all-cause hospitalizations defined as the number of inpatient admissions to the university hospital following the index admission;
- Bleeding events including GI bleeding requiring hospitalization or nose bleeds during index hospitalization.

Statistical analysis

Baseline comorbidities were coded as binary variables. Descriptive statistics were performed for all study variables.

The analysis of variance (ANOVA) was used to compare the mean values of continuous variables such as age, dialysis vintage, and BMI while the Kruskal-Wallis test (the non-parametric version of ANOVA) was used to compare the median values of variables such as follow-up period, number of baseline comorbidities, number of baseline medications, and number of post-index all-cause hospitalizations. In addition, frequencies of baseline characteristics were compared among patients who were prescribed the three drugs using Pearson's chi square tests. Data analyses were performed using IBM SPSS Statistics Version 23 (SPSS Inc, Chicago, IL). An alpha value was set a priori at <0.05 to be statistically significant.

Table 1 Demographic and baseline characteristics of ESRD patients who were prescribed clopidogrel, prasugrel and ticagrelor during hospital admission for acute coronary syndrome.

Variables	All (n=85)	Clopidogrel (n=37)	Prasugrel (n=32)	Ticagrelor (n=16)	p-value
Demographics					
Age, mean (SD)	62.7 (10.3)	63.2 (11.9)	61.5 (9.5)	64.1 (8.0)	0.68
Gender, n (%)					
Female	27 (31.8)	12 (32.4)	9 (28.1)	6 (37.5)	0.80
Male	58 (68.2)	25 (67.6)	23 (71.9)	10 (62.5)	
Race, n (%)					
White	56 (66.7)	26 (72.2)	17 (53.1)	13 (81.3)	0.19
African American	18 (21.4)	5 (13.9)	11 (34.4)	2 (12.5)	
Other	10 (11.9)	5 (13.9)	4 (12.5)	1 (6.3)	
BMI, mean (SD)	30.3 (6.4)	29.0 (5.9)	31.6 (6.5)	30.9 (7.4)	0.23
Follow-up period in months, median (IQR)	16.5 (4.0, 34.3)	16.8 (3.9, 34.0)	20.8 (6.9, 34.7)	11.3 (1.0, 30.0)	0.31
Dialysis type, n (%)					
Hemodialysis	77 (90.6)	34 (91.9)	28 (87.5)	15 (93.8)	0.73
Peritoneal dialysis	16 (18.8)	6 (16.2)	7 (21.9)	3 (18.8)	
Dialysis vintage in months, mean (SD)	29.8 (34.0)	33.5 (40.4)	33.1 (33.0)	12.4 (11.0)	0.25
Baseline comorbidities, n (%)					
Number of baseline comorbidities, median (IQR)	5 (3, 7)	5 (3, 7)	5 (4, 7)	5.5 (3, 6)	0.72
Diabetes mellitus	60 (70.6)	27 (73.0)	24 (75.0)	9 (56.3)	0.37
Hypertension	83 (97.6)	36 (97.3)	32 (100.0)	15 (93.8)	0.39
CHF	38 (44.7)	20 (54.1)	11 (34.4)	7 (43.8)	0.26
PVD	29 (34.1)	15 (40.5)	11 (34.4)	3 (18.8)	0.31
Amputation	13 (15.3)	5 (13.5)	5 (15.6)	3 (18.8)	0.89
CAD/CABG	74 (87.1)	30 (81.1)	30 (93.8)	14 (87.5)	0.29
Previous coronary stent	42 (49.4)	15 (40.5)	19 (59.4)	8 (50.0)	0.30
MI	33 (38.8)	13 (35.1)	15 (46.9)	5 (31.3)	0.48
Previous bleed	16 (18.8)	4 (10.8)	9 (28.1)	3 (18.8)	0.19

Atrial fibrillation	14 (16.5)	4 (10.8)	5 (15.6)	5 (31.3)	0.18
Stroke/TIA	14 (16.5)	12 (32.4)	2 (6.3)	0 (0.0)	0.01
Baseline medications, n (%)					
Number of baseline medications, median (IQR)	5 (4, 7)	5 (4, 6.5)	6 (5, 7)	5 (4, 6.75)	0.52
Beta-blockers	65 (76.5)	30 (81.1)	24 (75.0)	11 (68.8)	0.61
ACE-I/ARB	43 (50.6)	19 (51.4)	18 (56.3)	6 (37.5)	0.47
Statin	62 (72.9)	28 (75.7)	24 (75.0)	10 (62.5)	0.58
Warfarin	6 (7.1)	4 (10.8)	2 (6.3)	0 (0.0)	0.36

Abbreviations: ACE-I: Angiotensin-Converting Enzyme Inhibitors; ARB: Angiotensin Receptor Blockers; BMI: Body Mass Index; CABG: Coronary Artery Bypass Grafting; CAD: Coronary Artery Disease; CHF: Congestive Heart Failure; IQR: Interquartile Range; MI: Myocardial Infarction; PVD: Peripheral Vascular Disease; SD: Standard Deviation; TIA: Transient Ischemic Attack.

Results

Prescriptions for clopidogrel, prasugrel and ticagrelor

From 2011-2015, 848 (32%) of the 2,650 ESRD patients were prescribed oral P2Y$_{12}$ inhibitors: 785 (92.6%) patients on clopidogrel 75 mg/day, 46 (5.4%) patients on prasugrel 10 mg/day and 17 (2.0%) patients on ticagrelor 90 mg twice daily. All these patients were on aspirin 81 mg/day and were prescribed APA during the index admission for ACS.

Demographic information of ESRD patients on oral P2Y$_{12}$ inhibitors

Of the 85 ESRD patients on oral P2Y$_{12}$ inhibitors who had detailed chart review, more than two-thirds (n=58, 68.2%) of the chart review patients were male. The mean age of the cohort was 62.7 ± 10.3 years. Two thirds were white (66.7%) and 21.4% were African American. The mean BMI was 30.3 ± 6.4 kg/m^2 for the overall cohort. There were no differences in the demographics including age, gender, race, and BMI of patients who were prescribed the three APA **(Table 1)**.

Almost 91% (n=77) were on chronic hemodialysis, and only 9% (n=8) were on peritoneal dialysis. There was no difference between dialysis modality and the type of P2Y$_{12}$ inhibitor prescribed: 91.9% of patients on clopidogrel, 87.5% on prasugrel and 93.8% ticagrelor were on hemodialysis, (p=0.73). In addition, dialysis vintage was similar between the three groups: 33.5 months for patients who were prescribed clopidogrel, 33.1 months for prasugrel, and 12.4 months for ticagrelor (p=0.25).

Baseline comorbidities and concomitant medication use

For the overall cohort (n=85), a median (IQR) of 5 (3,7) baseline comorbidities was reported **(Table 1)**. However, there were no differences in the comorbid disease burden between the treatment groups (p=0.72). More than two-thirds (70.6%)

of the cohort was diabetic and most of the patients (97.6%) had hypertension. Prevalence of baseline cardiovascular disease was high in the cohort, 44.7% had congestive heart failure, 87.1% had either coronary artery disease or previous CABG and 49.4% had previous coronary stents. However, there were no between group differences in the baseline comorbidities **(Table 1)**. The median (IQR) number of baseline medications documented during the index admission for the cohort was 5 (4,7). Only 76.5% of the patients were on beta-blockers, whereas 7.1% were on warfarin. There were no between group differences in the use of baseline medications **(Table 1)**.
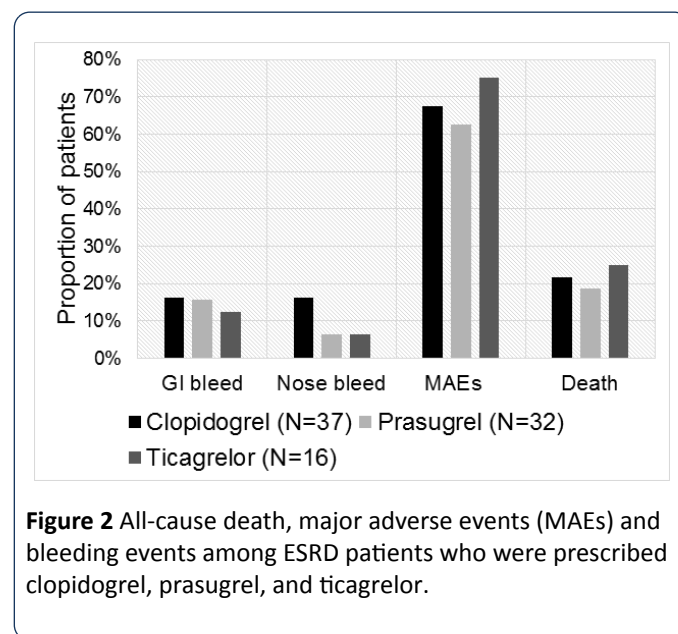

Figure 2 All-cause death, major adverse events (MAEs) and bleeding events among ESRD patients who were prescribed clopidogrel, prasugrel, and ticagrelor.

Clinical variables

There were 18 deaths (21.2%) during the median (IQR) follow up of 16.5 (4.0, 34.3) months: 8 deaths in the clopidogrel group, 6 in prasugrel group and 4 in the ticagrelor group (p>0.05). In the overall cohort, 57 patients (67.1%) encountered MAE, including eight (9.4%) new coronary stent placements and 11 (12.9%) procedures related to either HVR, CABG or amputation occurred during the follow up.

Furthermore, we found 13 (15.3%) episodes of GI bleeds and 9 (10.6%) episodes of nose bleeds during the follow up period (p>0.05) **(Figure 2).** In the exploratory analyses, we did not observe any differences in outcomes between the three drugs.

Discussion

We report contemporary prescription practices of oral $P2Y_{12}$ inhibitors in ESRD patients at our university hospital. Our major findings are: 1) 32% of the ESRD patients on dialysis were prescribed oral $P2Y_{12}$ inhibitors between 2011 and 2015 and 92.6% of these prescriptions were clopidogrel; 2) there were no major differences in baseline characteristics including demographics, dialysis modality, dialysis vintage, baseline comorbidities and baseline medication use of patients who were prescribed the three drugs; and, 3) among those who were prescribed oral $P2Y_{12}$ prescriptions following admissions for ACS, all-cause deaths, MAEs, and bleeding events were common during the short-term follow up and there were no differences in the outcomes between three drugs.

Of the three oral $P2Y_{12}$ inhibitors, prasugrel and ticagrelor are FDA approved for use in patients experiencing ACS, whereas clopidogrel has an additional indication for patients with stable CAD [2,8,9]. There are important pharmacokinetic and pharmacodynamic differences between the three oral $P2Y_{12}$ inhibitors [10-12]. Clopidogrel is a prodrug. It requires 2-step metabolism by cytochrome P450 (CYP450) enzymes to become active before binding to $P2Y_{12}$ receptor on the platelet surface [3,10]. Theoretically, this multistep process renders clopidogrel less favorable for inhibiting platelet aggregation in CKD patients because: a) Genetic polymorphisms in CYP450 enzymes result in high inter- and intra-individual variability in clopidogrel effects; and, b) Uremic toxins can alter CYP450 system and thus affect availability of clopidogrel active metabolite [2]. Newer oral $P2Y_{12}$ inhibitors such as prasugrel and ticagrelor compared to clopidogrel have more desirable pharmacological properties. Prasugrel requires only 1-step to become metabolically active whereas ticagrelor is an active drug. The resulting higher bioavailability as well as the reduced inter- and intra-individual variability in their antiplatelet effects are likely responsible for the superior antiplatelet efficacy of newer oral $P2Y_{12}$ inhibitors versus clopidogrel [13-15].

There is growing popularity of newer oral $P2Y_{12}$ inhibitors in patients experiencing ACS [16,17]. However, no study has reported efficacy, safety or prescribing trends of oral $P2Y_{12}$ inhibitors in ESRD patients [2]. ESRD is a special clinical condition with multiple defects in hemostatic pathways that increase risk of thrombotic CV events compared to the general population [2,18,19]. In our study, approximately one-third of our ESRD cohort was prescribed oral $P2Y_{12}$ inhibitors after admission for acute coronary syndrome. Majority (92.6%) of the study patients received prescriptions for clopidogrel, 5.4% for prasugrel and 2.0% for ticagrelor. A recent study in the general population analyzed EMR from several hospitals across the USA and found 77% of all patients undergoing percutaneous coronary intervention (PCI) and/or diagnostic coronary angiography (n=37,964) received clopidogrel, 13% received prasugrel and 10% received ticagrelor as of June 2013

[20]. Studies from Michigan and Australia found similar distribution of these agents [4,21]. We were unable to find studies that compared differences in prescription allocation ratios of the three drugs in ESRD patients. However, we anticipate that the newer oral $P2Y_{12}$ inhibitors will gain popularity in this high-risk patient population despite lack of evidence.

We found no differences in baseline characteristics including demographics, dialysis modality, dialysis vintage, baseline comorbidities and baseline medication use of patients who were prescribed the three drugs. A recent study in the general population reported that compared to patients receiving clopidogrel, majority of patients receiving ticagrelor were white, younger and had fewer comorbidities [17]. This may suggest that patients who receive newer oral $P2Y_{12}$ inhibitors may be working and may have better insurance providers compared to those who received prescriptions for clopidogrel. Since >93% of the chronic dialysis patients are covered by Medicare in the USA, these differences in baseline demographics of patients who were prescribed the three drugs were not noted in our study patients [17]. Moreover, demographics of our study cohort were similar to the national ESRD cohort except age, gender and presence of diabetes mellitus [21]. Our study patients compared to the U.S. Renal Data Sharing (USRDS) cohort were older (62.7 years versus 56.9 years), comprised of more males (68.2% versus 56.3%), included fewer African Americans (21.4% versus 35.2%) and had higher prevalence of diabetes mellitus (70.6% versus 43.6%) [22].

We found 21.2% of the ESRD patients who were prescribed oral $P2Y_{12}$ inhibitors died during a short follow up of 16.5 months. Almost two-thirds of hemodialysis patients and half of peritoneal dialysis patients have cardiovascular disease, with <60% survival rate 2-years post-PCI [23,24]. Therefore, mortality rates in our study patients are similar to the national cohort. Notably, these rates are significantly higher than post-PCI mortality rates in the general population, and underline the urgent need for studies to examine cardiovascular and/or mortality benefits of oral $P2Y_{12}$ inhibitors post-PCI in this high-risk patient population. Approximately two-thirds of our study patients experienced MAE and 20% experienced bleeding events (GI or nose bleeding), numbers that are six- and five-fold higher than that reported in the general population, respectively [25,26]. Only 7.1% were on concomitant warfarin therapy. In the exploratory analyses, we did not observe any differences in outcomes between the three drugs. Recent RCTs in the general population (TRITON-TIMI and PLATO trials) reported higher efficacy of newer oral $P2Y_{12}$ inhibitors compared to clopidogrel in reducing mortality and future CV events among patients presenting with ACS [25,26]. However, these trials enrolled few patients with mild to moderate CKD and excluded patients with advanced CKD and ESRD, precisely those with highest risk of thrombotic CV events. Among a small subgroup of participants that had mild CKD (defined as creatinine clearance of <60 ml/min), use of ticagrelor over clopidogrel was associated with 23% reduction in mortality and future CV events without any increased risk of bleeding [26,27].

Our pilot study has several strengths. The study protocol followed the best practices recommended for conducting retrospective chart review. Chart review of patient record is still considered to be a gold standard. Data abstractors were trained before starting the data abstraction. In addition, variables were adequately operationalized before starting the study and we used a standardized abstraction form for collecting study variables. Furthermore, we were systematic in including eligible patients.

Our study has several limitations that are generally associated with retrospective chart review. Selection bias, confounding by indication and lead-time bias are known limitations of the retrospective studies. Therefore, in this pilot study, we have carefully interpreted our results. In addition, due to lack of data on various confounders, we have not investigated any associations between drug exposure and outcomes and avoided over-interpretation of our data. Despite these limitations, we believe that our findings are meaningful as this patient population is systematically excluded from major studies and data remain scarce in this topic. Second, this is a pilot study examining contemporary use of oral $P2Y_{12}$ inhibitors in a small sample of ESRD patients from a single center. Therefore, our study may be under-powered to detect meaningful differences and limit its generalizability. In addition, we were not able to determine the temporal drug exposure of patients who were prescribed oral $P2Y_{12}$ inhibitors. We report small number of clinical events linked to the charts of the ESRD patients after being prescribed oral $P2Y_{12}$ inhibitors. As a result, our analyses is exploratory and not powered to detect association between the drug prescription at index admission and clinical outcomes. Finally, we were not able to collect information regarding the type of stent, the number of vessels intervened and the type of ACS with certainty due to poor documentation in the EMR and missing data. We chose not to include this information in the manuscript. We believe this pilot data will lay the foundation for further studies that evaluate the comparative efficacy and safety of these increasingly used agents in this high-risk population.

Conclusion

Oral $P2Y_{12}$ inhibitors are commonly prescribed to ESRD patients although there is insufficient data to support their overall use as well as inadequate guidance regarding individual agent choice in this patient population. In contemporary practice, clopidogrel was the predominant agent used although it is likely we will see a surge in use of the other agents. There were no differences in the profiles of ESRD patients who were prescribed these drugs or clinical outcomes associated with the three agents, but all-cause death, MAEs, nose and GI bleeds were common in these patients. There is a pressing need for further studies to investigate clinical benefits and risks associated with use of $P2Y_{12}$ inhibitors in this growing high-risk patient population.

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