ORIGINAL RESEARCH

Safety of Dual-Antiplatelet Therapy After Myocardial Infarction Among Patients With Chronic Kidney Disease

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***Background*—**Although recommended in the guidelines, the safety of chronic $P2Y_{12}$ inhibitor therapy in patients with chronic kidney disease (CKD) after an acute myocardial infarction (MI) is not well studied.

***Methods and Results*—**The TRANSLATE-ACS (Treatment with ADP Inhibitors: Longitudinal Assessment of Treatment Patterns and Events After Acute Coronary Syndrome) study included 11 108 MI patients treated with percutaneous coronary intervention and discharged alive on a $P2Y_{12}$ inhibitor from 233 US hospitals. We compared rates of GUSTO (Global Use of Strategies to Open Occluded Arteries) severe/moderate bleeding and premature discontinuation of $P2Y_{12}$ inhibitor by 1 year after MI among patients with varying CKD severity. The majority of MI patients treated with percutaneous coronary intervention had CKD: 42% had stage 2 (mild), 27% had stage 3 (moderate), and 4% had stage ≥4 (severe/end stage). Higher potency $P2Y_{12}$ inhibitors (prasugrel or ticagrelor) were prescribed at discharge in 39%, 35%, 23%, and 15% ($P<0.01$) of patients with stages 1, 2, 3, and ≥4, respectively. One-year GUSTO severe/moderate bleeding rates were higher with each stage of CKD: 1% in patients with CKD stage 1 or no CKD, 2% with an adjusted hazard ratio of 1.61 (95% CI, 1.05–2.35) for CKD stage 2, 4% with an adjusted hazard ratio of 1.92 (95% CI, 1.21–3.02) for CKD stage 3, and 10% with an adjusted hazard ratio of 2.44 (95% CI, 1.40–4.23) for patients with CKD stage ≥4. By 1 year after MI, 16% of patients overall had prematurely discontinued $P2Y_{12}$ inhibitor therapy; however, this rate was not largely affected by CKD stage. Premature $P2Y_{12}$ inhibitor–discontinuation rates were higher for patients discharged on higher potency $P2Y_{12}$ inhibitors in patients with CKD stage ≥2 ($P<0.01$).

***Conclusions*—**CKD severity was associated with a higher bleeding risk among those with acute MI treated with a $P2Y_{12}$ inhibitor. Patients with more advanced CKD were not significantly more likely than those with less advance CKD to prematurely discontinue $P2Y_{12}$ inhibitor therapy. **(*J Am Heart Assoc*. 2019;8:e012236. DOI: 10.1161/JAHA.119.012236.)**

Key Words: antiplatelet therapy • chronic kidney disease • discontinuation

Chronic kidney disease (CKD) is prevalent among patients with cardiovascular disease; between 33% and 50% of patients presenting with an acute myocardial infarction (AMI) have CKD.[1] Patients with CKD often have impaired hemostasis as well as other comorbid factors that place them at higher risk of bleeding.[2,3] The American College of Cardiology/American Heart Association (ACC/AHA) guidelines provide a class 1 recommendation for all patients to receive 12 months of $P2Y_{12}$ inhibitor therapy after a myocardial infarction (MI) and a class 2a recommendation in favor of higher potency $P2Y_{12}$ inhibitor therapy, such as prasugrel or ticagrelor, for MI patients treated with percutaneous coronary intervention (PCI).[4,5] However, because patients with CKD were often excluded from large clinical trials in MI patients, little is known about the bleeding risk associated with prolonged $P2Y_{12}$ inhibitor therapy or the use of higher potency $P2Y_{12}$ inhibitor therapy in post-MI patients with CKD.[2,3,6] In addition, bleeding often leads to premature discontinuation of $P2Y_{12}$ inhibitor therapy[7] and increased risk for subsequent cardiovascular events.[8,9] However, rates of persistence of $P2Y_{12}$ inhibitors are not well described as a function of CKD class in current practice.

In this study of TRANSLATE-ACS (Treatment with ADP Inhibitors: Longitudinal Assessment of Treatment Patterns and Events After Acute Coronary Syndrome),[10] a longitudinal observational registry of MI patients treated with PCI, we examined the risk of post-MI bleeding among patients with

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Clinical Perspective

What Is New?

- Among myocardial infarction patients treated with percutaneous coronary intervention, higher potency $P2Y_{12}$ inhibitors were less likely to be prescribed at discharge for patients with advanced chronic kidney disease.
- Patients with more advanced chronic kidney disease were not significantly more likely than those with less advance CKD to prematurely discontinue $P2Y_{12}$ inhibitor therapy.
- However, premature $P2Y_{12}$ inhibitor–discontinuation rates were higher for patients discharged on higher potency $P2Y_{12}$ inhibitors among those with chronic kidney disease stage ≥2.

What Are the Clinical Implications?

- Further studies are needed to better predict which patients with chronic kidney disease are most likely to experience bleeding events and to consider initiating clopidogrel in those patients to avoid premature $P2Y_{12}$ inhibitor discontinuation and temporary interruptions.

CKD and rates of premature $P2Y_{12}$ inhibitor discontinuation and interruptions in treatment due to bleeding. We hypothesized that patients with more advanced CKD, compared with less advanced disease, will have (1) higher risk of bleeding and (2) higher rates of premature $P2Y_{12}$ inhibitor discontinuation and bleeding-related interruptions in $P2Y_{12}$ inhibitor therapy and that (3) bleeding and $P2Y_{12}$ inhibitor discontinuation rates will be highest among those patients with more advanced CKD discharged on higher potency $P2Y_{12}$ inhibitors.

Methods

Study Population

The TRANSLATE-ACS study design has been described previously.[11] Between April 2010 and October 2012, 12 365 patients with or without ST-segment–elevation MI who were treated with PCI at 233 hospitals in the United States were enrolled in the TRANSLATE-ACS study. All treatment decisions were left to the practicing physicians because TRANSLATE-ACS was an observational study. The TRANSLATE-ACS study received approval from the Duke University institutional review board and the institutional review boards of all participating sites. All participants provided written informed consent. The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure. Of the total 12 365 enrolled patients, we excluded 14 who died in hospital, 1190 nondialysis patients who were missing creatinine clearance (CrCl) data, and 53 patients who were not discharged on a $P2Y_{12}$ inhibitor. Our final study population included 11 108 AMI patients discharged from 230 hospitals.

Data Collection and Definitions

Baseline clinical characteristics, demographics, past medical history, and discharge medications were abstracted from medical records or patient interviews into the TRANSLATE-ACS data collection form using standardized data elements and definitions.[11] In telephone interviews at 6 weeks, 6 months, and 12 months after MI discharge, patients were asked to describe their use of a $P2Y_{12}$ inhibitor, including any permanent or temporary discontinuation of treatment. Medical bills and records were collected to permit independent adjudication by study physicians of any hospitalized bleeding events and to classify bleeding severity according to the GUSTO (Global Use of Strategies to Open Occluded Arteries) definition.[12]

Patients were grouped by CrCl calculated with the serum creatinine level on admission using the Cockcroft–Gault equation: stage 1, CrCl ≥90 mL/min per 1.73 m^2; stage 2, CrCl 60 to 89 mL/min per 1.73 m^2; stage 3, CrCl 30 to 59 mL/min per 1.73 m^2; and stage ≥4, CrCl <30 mL/min per 1.73 m^2 or need for dialysis.

The primary outcomes of this analysis were the incidence of 1-year postdischarge GUSTO moderate/severe bleeding events by CKD group, premature $P2Y_{12}$ inhibitor–discontinuation rate by CKD group, and $P2Y_{12}$ inhibitor interruption due to bleeding or severe bruising by CKD group. GUSTO moderate/severe bleeding was defined as intracranial hemorrhage, bleeding that caused hemodynamic compromise requiring intervention, or bleeding that required blood transfusion. $P2Y_{12}$ inhibitor discontinuation was defined as cessation of any $P2Y_{12}$ inhibitor for >7 days. $P2Y_{12}$ inhibitor interruption was defined as a temporary cessation <7 days in duration for any reason. Ticagrelor and prasugrel were considered high-potency $P2Y_{12}$ inhibitors.

Statistical Analysis

Baseline patient characteristics, in-hospital treatments, and in-hospital events were compared across increasing severity of CKD. For Table 1, differences among CKD groups were assessed using the Cochran–Mantel–Haenszel statistical method based on rank score. For Tables 2 and 3, differences among CKD stages were compared with CKD stage 1 or no CKD using χ^2 tests for categorical variables and Wilcoxon rank sum tests for continuous variables.

To examine the cumulative incidence of GUSTO moderate/severe bleeding within 12 months of discharge, Kaplan–Meier

Table 1. Baseline Patient Characteristics by CKD Group

	Stage 1 or No CKD	Stage 2 (Mild CKD)	Stage 3 (Moderate CKD)	Stage ≥4 (Severe/End-Stage CKD)	
	n=2965	n=4685	n=2988	n=470	*P* Value
Demographics					
Age, y	52.0 (46.0–58.0)	59.0 (53.0–65.0)	69.0 (62.0–76.0)	71.0 (62.0–79.0)	<0.01
Female	363 (12.2)	1101 (23.5)	1411 (47.2)	283 (60.2)	<0.01
Nonwhite	285 (9.6)	530 (11.3)	373 (12.5)	98 (20.9)	<0.01
Uninsured	2268 (76.5)	3955 (84.4)	2694 (90.2)	440 (93.6)	<0.01
Household income, $	47 704 (40 582–57 881)	48 023 (41 504–57 347)	47 405 (40 582–55 431)	47 387 (40 582–56 243)	<0.01
Past medical history					
Prior MI	531 (17.9)	824 (17.6)	731 (24.5)	150 (31.9)	<0.01
Prior PCI	566 (19.1)	933 (19.9)	822 (27.5)	153 (32.6)	<0.01
Prior CABG	150 (5.1)	367 (7.8)	463 (15.5)	93 (19.8)	<0.01
Prior HF	98 (3.3)	198 (4.2)	294 (9.8)	116 (24.7)	<0.01
Prior stroke	81 (2.7)	198 (4.2)	278 (9.3)	67 (14.3)	<0.01
Diabetes mellitus	716 (24.2)	1090 (23.3)	939 (31.4)	271 (57.7)	<0.01
Hypertension	1723 (58.1)	3033 (64.7)	2348 (78.6)	439 (93.4)	<0.01
Prior PAD	93 (3.1)	241 (5.1)	311 (10.4)	92 (19.6)	<0.01
Dyslipidemia	1765 (59.5)	3075 (65.6)	2193 (73.4)	373 (79.4)	<0.01
In-hospital features					
NSTEMI (vs STEMI)	1486 (50.1)	2288 (48.8)	1595 (53.4)	292 (62.1)	<0.01
BMI, kg/m^2	29.7 (26.4–33.8)	29.4 (26.2–33.2)	29.1 (25.7–33.5)	29.0 (25.2–34.3)	<0.01
Preprocedure creatinine, mg/dL	0.8 (0.7–0.9)	1.0 (0.9–1.1)	1.2 (1.0–1.4)	2.0 (1.5–3.7)	<0.01
Preprocedure hemoglobin, g/dL	14.8 (13.7–15.8)	14.5 (13.4–15.6)	13.6 (12.3–14.8)	11.7 (10.4–13.3)	<0.01
DES implanted	2062 (69.5)	3445 (73.5)	2140 (71.6)	312 (66.4)	<0.01
Major bleeding	79 (2.7)	133 (2.8)	120 (4.0)	28 (6.0)	<0.01
RBC transfusion	22 (0.7)	55 (1.2)	83 (2.8)	62 (13.2)	<0.01
LOS, d	2 (2–3)	3 (2–3)	3 (2–4)	4 (3–6)	<0.01

Data are shown as n (%) or median (interquartile range). BMI indicates body mass index; CABG, coronary artery bypass grafting; CKD, chronic kidney disease; DES, drug-eluting stent; HF, heart failure; LOS, length of stay; MI, myocardial infarction; NSTEMI, non–ST-segment–elevation myocardial infarction; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; RBC, red blood cells; STEMI, ST-segment–elevation myocardial infarction.

cumulative incidence rates of bleeding were calculated. To assess the adjusted association of CKD groups on bleeding, we fit a Cox proportional hazards model with robust standard errors to account for within-hospital clustering. We adjusted for the following a priori specified covariates: age, sex, race, uninsured status, prior MI, PCI, coronary artery bypass grafting, stroke or transient ischemic attack, heart failure, diabetes mellitus, hypertension, peripheral arterial disease, smoking, gastrointestinal/genitourinary bleeding, ST-segment–elevation MI, body mass index, femoral access site, preprocedure hemoglobin, in-hospital major bleeding, in-hospital heart failure or cardiogenic shock, ejection fraction <40%, multivessel PCI, baseline EuroQol 5-dimensional questionnaire (EQ-5D) index, and higher potency $P2Y_{12}$ inhibitor at discharge. We tested for an interaction among CKD groups and discharge on higher potency (ie, prasugrel or ticagrelor) $P2Y_{12}$ inhibitors versus clopidogrel at discharge.

We then examined discharge $P2Y_{12}$ inhibitor and rates of $P2Y_{12}$ inhibitor use at the 12-month interview by CKD groups among patients who were still alive at 12 months. We also examined rates of $P2Y_{12}$ inhibitor switches from higher to lower potency $P2Y_{12}$ inhibitors, such as clopidogrel; premature discontinuations; and interruptions. $P2Y_{12}$ inhibitor use at the 12-month interview and $P2Y_{12}$ inhibitor switches,

Table 2. Rates of Antiplatelet Discharge Medications and Switching From a High-Potency $P2Y_{12}$ Inhibitor to Clopidogrel Within 1 Year of Discharge, Stratified by CKD Group

	Stage 1 or No CKD	Stage 2 (Mild CKD)		Stage 3 (Moderate CKD)		Stage ≥4 (Severe/Ends Stage CKD)	
	n=2965	n=4685	*P* Value*	n=2988	*P* Value*	n=470	*P* Value*
Discharge medications							
Aspirin	2911 (98.6)	4613 (98.8)	0.42	2932 (98.6)	0.94	456 (98.3)	0.57
Dose >81 mg daily	1943 (66.8)	3014 (65.3)	0.21	1797 (61.3)	<0.01	276 (60.5)	<0.01
Clopidogrel	1815 (61.2)	3034 (64.8)	<0.01	2311 (77.3)	<0.01	401 (85.3)	<0.01
Higher potency $P2Y_{12}$ inhibitor							
Prasugrel	1084 (36.6)	1522 (32.5)	<0.01	582 (19.5)	<0.01	59 (12.6)	<0.01
Dose <10 mg daily	3 (0.3)	9 (0.6)	0.24	9 (1.6)	<0.01	1 (1.7)	0.07
Ticagrelor	65 (2.2)	129 (2.8)	0.13	92 (3.1)	0.03	9 (1.9)	0.70
Dose <90 mg twice daily	10 (15.4)	15 (11.6)	0.46	7 (7.7)	0.12	0	0.21
Switch from high-potency $P2Y_{12}$ inhibitor to clopidogrel within 1 y							
Switch	132 (11.5)	215 (13.0)	0.23	120 (17.8)	<0.01	11 (16.2)	0.24
Days to switch	61.0 (22.0–168.5)	51.0 (18.0–167.0)	0.57	65.0 (27.0–173.5)	0.81	12.0 (1.00–64.0)	<0.05

CKD indicates chronic kidney disease.
**P* values compare each preceding column against stage 1 or no CKD.

discontinuations, and interruptions reported during the other interviews will be presented as frequencies (percentages). $P2Y_{12}$ inhibitor use, switches, discontinuations, and interruptions among stage 2, 3, and ≥4 CKD groups will be compared with patients in the stage 1 CKD group using χ^2 tests, and pairwise *P* values will be reported. Rates of premature discontinuation of $P2Y_{12}$ inhibitors, time to premature discontinuation, rates of $P2Y_{12}$ inhibitor interruptions, and time to first interruption were further stratified by type of stent (drug eluting or bare metal) and type of $P2Y_{12}$ inhibitor (clopidogrel versus higher potency). Patients missing the 12-month interview but still taking a $P2Y_{12}$ inhibitor at 15 months were assumed to be still taking $P2Y_{12}$ inhibitors at 12 months.

Results

Among 11 108 PCI-treated patients at 230 hospitals, 2965 (24.3%) had stage 1 or no CKD, 4685 (42%) had stage 2 (mild) CKD, 2988 (27%) had stage 3 (moderate) CKD, and 470 (4%) had stage ≥4 (severe/end stage) CKD. Among patients with stage ≥4 CKD, 144 (31%) were on dialysis.

Table 1 demonstrates the baseline demographic and clinical characteristics stratified by CKD group. Patients with stage ≥4 CKD or on dialysis were older and more likely to be female and of nonwhite race than patients with less advanced CKD (*P*<0.01). Patients with stage ≥4 CKD had significantly higher prevalence of diabetes mellitus and prior cardiovascular disease, including prior MI and prior heart failure (*P*<0.01). Patients with more advanced CKD were more likely to present with non-STEMI than patients with less advanced CKD (*P*<0.01). Drug-eluting stents were frequently implanted and, used in more than two thirds of patients across CKD severity groups. Patients with advanced CKD were more likely to have lower preprocedure hemoglobin levels (*P*<0.01).

Bleeding

During the index hospitalization, patients with stage ≥4 CKD or on dialysis were significantly more likely than those at lower stages to experience major bleeding (6.0%, 4.0%, 2.8%, and 2.7% for CKD stages ≥4, 3, 2, and 1 or no CKD, respectively; *P*<0.01) and require red blood cell transfusion (13.2%, 2.8%, 1.2%, and 0.7% for CKD stages ≥4, 3, 2, and 1 or no CKD, respectively; *P*<0.01).

By 1 year after discharge, 284 (2.6%) patients had GUSTO moderate/severe bleeding; the cumulative incidence of bleeding was 1.0%, 2.1%, 4.1%, and 10.0% for patients with CKD stages 1, 2, 3, and ≥4, respectively (Figure). Patients with higher CKD stage remained at significantly higher risk of bleeding after multivariable adjustment: compared with patients with normal kidney function, adjusted hazard ratios were 2.44 (95% CI, 1.40–4.23) for CKD stage ≥4, 1.92 (95% CI, 1.21–3.02) for CKD stage 3, and 1.61 (95% CI, 1.05–2.45) for CKD stage 2.

Table 3. Discontinuation and Interruption of $P2Y_{12}$ Inhibitors Within 1 Year After MI

	Stage 1 or No CKD	Stage 2 (Mild CKD)		Stage 3 (Moderate CKD)		Stage ≥4 (Severe/ End Stage CKD)	
	n=2965	n=4685	*P* Value*	n=2988	*P* Value*	n=470	*P* Value*
Premature $P2Y_{12}$ inhibitor discontinuation							
Overall	472 (15.9)	706 (15.1)	0.32	464 (15.5)	0.68	79 (16.8)	0.63
DES	208 (10.1)	359 (10.4)	0.69	229 (10.7)	0.51	41 (13.1)	0.10
BMS	242 (29.7)	325 (29.1)	0.80	216 (29.5)	0.95	36 (25.4)	0.30
Clopidogrel	278 (15.3)	434 (14.3)	0.34	343 (14.8)	0.67	62 (15.5)	0.94
Prasugrel/ticagrelor	193 (16.8)	272 (16.5)	0.82	119 (17.7)	0.64	16 (23.5)	0.15
Time to $P2Y_{12}$ inhibitor discontinuation							
Overall	161 (58–308)	167 (53–317)	0.65	173 (50–317)	0.36	133 (60–242)	0.18
DES	249 (127–339)	261 (91–336)	0.57	260 (136–339)	0.76	174 (108–209)	0.10
BMS	94 (34–230)	104 (39–232)	0.61	115.5 (31–252.5)	0.85	104 (28.5–149)	0.18
Clopidogrel	174 (60–309)	145 (45–300)	0.21	166 (43–316)	0.85	133 (60–220)	0.07
Prasugrel/ticagrelor	141 (58–299)	202 (66–335)	0.03	193 (87–324)	0.04	159 (85–286)	0.69
Temporary $P2Y_{12}$ inhibitor interruption (<7-d gap) due to bleeding or severe bruising							
Overall	49 (1.8)	116 (2.6)	0.03	90 (3.2)	<0.01	18 (4.3)	<0.01
DES	34 (1.8)	79 (2.5)	0.13	51 (2.5)	0.12	14 (4.9)	<0.01
BMS	15 (2.1)	35 (3.4)	0.10	33 (4.8)	<0.01	3 (2.5)	0.76
Clopidogrel	24 (1.4)	65 (2.3)	0.05	56 (2.6)	0.02	14 (3.9)	<0.01
Prasugrel/ticagrelor	25 (2.4)	51 (3.3)	0.19	34 (5.4)	<0.01	4 (6.7)	0.05

BMS indicates bare-metal stent; CKD, chronic kidney disease; DES, drug-eluting stent; MI, myocardial infarction.
**P* values compare each preceding column against stage 1 or no CKD.

$P2Y_{12}$ Inhibitor Discontinuation and Interruption

Rates of aspirin use were similar across CKD groups, although patients with stage 3 and ≥4 CKD were less likely to be prescribed high-dose aspirin (Table 2). Patients with more severe CKD were more likely to be prescribed clopidogrel than a higher potency $P2Y_{12}$ inhibitor at discharge (Table 2). Among patients prescribed a higher potency $P2Y_{12}$ inhibitor at discharge, patients with stage 3 and ≥4 CKD were more likely to switch to clopidogrel within 1 year after discharge compared with patients with stage 1 or no CKD (Table 2). The median number of days to switching was substantially fewer among patients with CKD stage ≥4 (median: 12 days after discharge; interquartile range: 1–64 days) compared with other patients.

Table 3 shows the rate of premature discontinuation of $P2Y_{12}$ inhibitor therapy within the first year after MI overall and then stratified by stent type and $P2Y_{12}$ inhibitor type. By 1 year, 15.5% of patients had prematurely discontinued $P2Y_{12}$ inhibitor therapy. Patients with CKD stage ≥4 had the highest rate of premature $P2Y_{12}$ inhibitor discontinuation (16.8%). Although not statistically significant, patients with stage 3 or ≥4 CKD who were treated with drug-eluting stents trended toward higher rates of premature $P2Y_{12}$ inhibitor discontinuation compared with drug-eluting-stented patients with CKD stage 1 or no CKD. Overall, patients with CKD (stage ≥2) discharged on a higher potency $P2Y_{12}$ inhibitor had higher rates of premature discontinuation than those discharged on clopidogrel ($P<0.01$). Among patients discharged on a higher potency $P2Y_{12}$ inhibitor, almost 1 in 4 patients with stage 4 CKD had discontinued $P2Y_{12}$ inhibitor therapy within the first year.

The median time to $P2Y_{12}$ inhibitor discontinuation was 161, 167, 173, and 133 days for patients with CKD stages 1 (or no CKD), 2, 3, and ≥4, respectively (Table 3). Among patients treated with drug-eluting stents, those with stage ≥4 CKD had the shortest time to $P2Y_{12}$ inhibitor discontinuation (median: 174 days; interquartile range: 108–309 days).

Temporary interruptions in $P2Y_{12}$ inhibitor use (<7-day gap) due to bleeding or severe bruising were uncommon but reported more frequently by patients with advanced CKD (Table 3). This pattern persisted regardless of discharge on clopidogrel or a higher potency $P2Y_{12}$ inhibitor. The rate of interruptions was significantly higher among stage ≥4 CKD or dialysis patients treated with drug-eluting stents compared with those with stage 1 CKD or patients with normal CrCl (4.9% versus 1.8%, $P<0.01$).

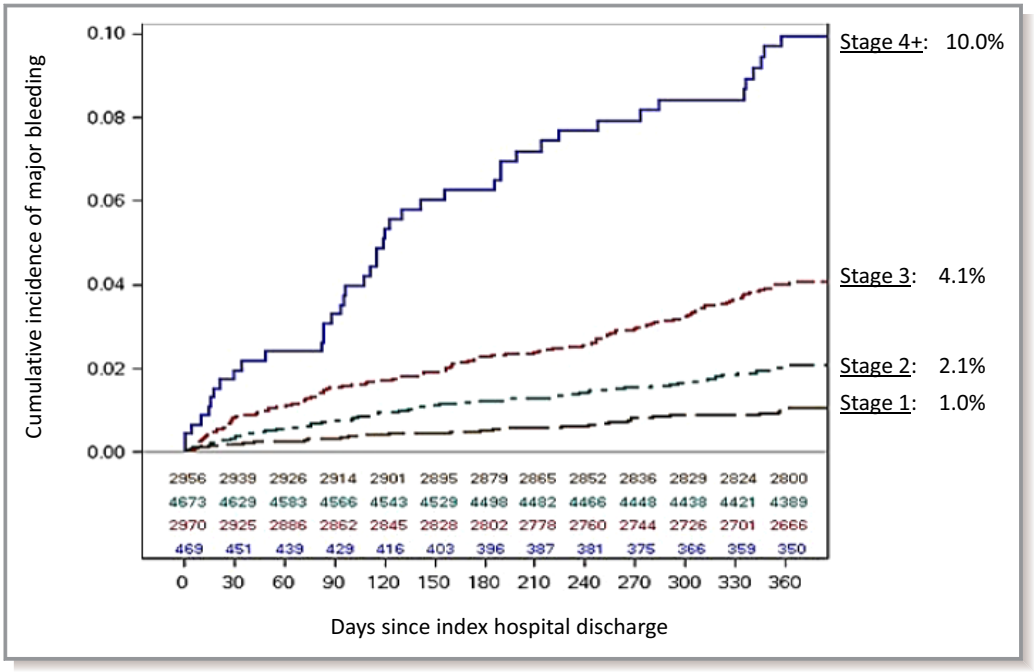

Figure. Cumulative incidence of moderate/severe bleeding after discharge, stratified by chronic kidney disease group.

Discussion

In this nationwide study of MI patients treated with PCI, we observed a high prevalence of CKD. While nearly all MI patients received dual-antiplatelet therapy and more than a third received higher potency $P2Y_{12}$ inhibitors, the use of higher potency $P2Y_{12}$ inhibitors declined with worsening renal function. Patients with CKD discharged on a higher potency $P2Y_{12}$ inhibitor had higher rates of major bleeding and were more likely to be prematurely discontinued than those discharged on clopidogrel. Patients with more advanced CKD were also more likely to report temporary interruptions in $P2Y_{12}$ inhibitor use due to bleeding or severe bruising than patients with less severe or no CKD.

Patients with advanced CKD or on dialysis with concomitant cardiovascular disease are a particularly vulnerable population with limited existing data supporting $P2Y_{12}$ inhibitor selection after an AMI. Pharmacodynamic studies have demonstrated increased platelet inhibition when using higher potency $P2Y_{12}$ inhibitors compared with clopidogrel in patients with CKD.[13,14] Subgroup analyses of the large randomized control trials of ticagrelor and prasugrel compared with clopidogrel in CKD patients found no reduction in recurrent MI or mortality with the use of prasugrel but did show a reduction in composite cardiovascular outcomes with the use of ticagrelor.[6,15] However, a large meta-analysis of $P2Y_{12}$ inhibitor therapy in post-MI patients with CKD suggested an increased risk of bleeding with minimal mortality benefit.[2] Current guidelines provide the same recommendations for the use of $P2Y_{12}$ inhibitors in CKD and non-CKD patients.[4,5] Our study demonstrated that more than a third of MI patients with CKD are treated with higher potency $P2Y_{12}$ inhibitors. Patients with advanced kidney disease are less often discharged on higher potency $P2Y_{12}$ inhibitors, perhaps secondary to bleeding events occurring at the time of the index MI hospitalization or because of provider concern for increased risk of bleeding in this population. These results echo a recent observational study of patients with diabetes mellitus and a recent acute coronary syndrome event showing CKD to be associated with lower likelihood of being initiated on prasugrel (odds ratio: 0.91; 95% CI, 0.83–0.98) or ticagrelor (odds ratio: 0.80; 95% CI, 0.70–0.92) versus clopidogrel.[16]

Post-MI patients with concomitant CKD compose a challenging population to manage because they are at higher risk for both ischemic and bleeding complications.[2,17,18] Derangements in platelet function and the coagulation cascade can lead to both bleeding tendencies and a prothrombotic state for patients with severe renal dysfunction.[19] In this study, we show that patients with advanced CKD had significantly higher risk of bleeding during the index hospitalization as well as within 1 year after discharge compared with patients with stage 1 or no CKD, despite being less often discharged on high-dose aspirin or higher potency $P2Y_{12}$ inhibitors. Because bleeding early after an MI is associated with premature discontinuation of $P2Y_{12}$ inhibitors,[7] this analysis then examined the rates of switching, premature discontinuation, and interruptions in $P2Y_{12}$ inhibitor therapy.

Guidelines recommend at least 1 year of $P2Y_{12}$ inhibitor treatment after MI for patients treated with PCI.[4,5] In our

PCI-treated MI population, the majority of patients persisted with $P2Y_{12}$ inhibitor therapy through the first year. The rate of premature $P2Y_{12}$ inhibitor discontinuation was not statistically significantly different among CKD severity groups. Patients with stage ≥4 CKD or on dialysis had the highest rate of $P2Y_{12}$ inhibitor discontinuation and shorter time to discontinuation. Overall, in patients with CKD stage ≥2, we observed higher discontinuation rates among patients discharged on higher potency $P2Y_{12}$ inhibitors compared with those discharged on clopidogrel. Patients with advanced CKD more frequently reported temporary interruptions in $P2Y_{12}$ inhibitor therapy due to bleeding. We also observed that patients with advanced CKD are more likely to switch earlier from a higher potency $P2Y_{12}$ inhibitor to clopidogrel. Presumably, in the setting of higher bleeding risk, patients and clinicians used temporary interruptions and drug-switching strategies to attempt to stay on $P2Y_{12}$ inhibitor therapy for the guideline-recommended course. Further studies are needed to better predict which patients with CKD are most likely to experience bleeding events and to consider initiating clopidogrel in those patients to avoid premature $P2Y_{12}$ inhibitor discontinuation and temporary interruptions.

Limitations

This study has several limitations. TRANSLATE-ACS gathered CrCl data at the time of index MI, but it does not capture whether the patient's renal function worsened or improved over the follow-up period. In addition, $P2Y_{12}$ inhibitor switching, discontinuation, and interruption after discharge were self-reported by patients and could not be verified. The use of higher potency $P2Y_{12}$ inhibitors may have increased since 2010–2012 because ticagrelor was relatively new to the US market at the time of the study.

Conclusions

In this post-MI population with CKD, higher potency $P2Y_{12}$ inhibitors were prescribed in more than a third of patients with CKD. Although patients with advanced CKD were less likely to be prescribed higher potency $P2Y_{12}$ inhibitors or high-dose aspirin at discharge, they had the greatest risk of moderate or severe bleeding after discharge. Patients with CKD discharged on a higher potency $P2Y_{12}$ inhibitor had higher rates of premature discontinuation than those discharged on clopidogrel. Patients with more advanced CKD were not significantly more likely to prematurely discontinue $P2Y_{12}$ inhibitor therapy but were more likely to report temporary interruptions in $P2Y_{12}$ inhibitor use due to bleeding or severe bruising and to switch to clopidogrel than patients with less severe or no CKD.

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