KI REPORTS
KIReports.org
CLINICAL RESEARCH

Comparative Effectiveness and Safety of Oral P2Y12 Inhibitors in Patients on Chronic Dialysis

Nishank Jain[1,2], Milind A. Phadnis[3], Suzanne L. Hunt[3], Junqiang Dai[3], Theresa I. Shireman[4], Clayton L. Davis[1], Jawahar L. Mehta[1,2], Rafia S. Rasu[5] and S. Susan Hedayati[6]

[1]Department of Internal Medicine, University of Arkansas for Medical Sciences, Little Rock, Arkansas, USA; [2]Medicine Service, Central Arkansas Veterans Affairs Medical Center, Little Rock, Arkansas, USA; [3]Department of Biostatistics and Data Science, University of Kansas School of Medicine, Kansas City, Kansas, USA; [4]Department of Health Services, Policy and Practice, School of Public Health, Brown University, Providence, Rhode Island, USA; [5]Department of Pharmacotherapy, College of Pharmacy, University of North Texas Health Sciences, Fort Worth, Texas, USA; and [6]Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, Texas, USA

Introduction: Although oral $P2Y_{12}$ inhibitors (P2Y12-Is) are one of the most commonly prescribed medication classes in patients with end stage kidney disease on dialysis (ESKD), scarce data exist regarding their benefits and risks.

Methods: We compared effectiveness and safety of clopidogrel, prasugrel, and ticagrelor in a longitudinal study using the United States Renal Data System registry of Medicare beneficiaries with ESKD. Individuals who filled new P2Y12-I prescriptions between 2011 and 2015 were included and followed until death or censoring. The primary exposure variable was P2Y12-I assignment. The primary outcome variable was death. Secondary outcomes included cardiovascular (CV) death, coronary revascularization, and gastrointestinal (GI) hemorrhage. Survival analyses were performed after propensity matching.

Results: Of 44,619 patients with ESKD who received P2Y12-Is, 95% received clopidogrel ($n = 42,523$), 3% prasugrel ($n = 1205$), and 2% ticagrelor ($n = 891$). To balance baseline differences, propensity-matching was performed: 1:6 for prasugrel ($n = 1189$) versus clopidogrel ($n = 7134$); 1:4 for ticagrelor ($n = 880$) versus clopidogrel ($n = 3520$); and 1:1 for ticagrelor versus prasugrel ($n = 880$). Prasugrel was associated with a reduced risk for death versus clopidogrel and ticagrelor (adjusted hazard ratio [HR] = 0.82; 95% CI: 0.73–0.93 and 0.78; 95% CI: 0.64–0.95). Compared with clopidogrel, prasugrel reduced risk for coronary revascularization (HR = 0.91; 95% CI: 0.86–0.96). There were no differences in GI hemorrhage between P2Y12-Is.

Conclusion: In patients with ESKD, prasugrel compared with others reduced risk of death possibly by reducing risk for coronary revascularizations and without worsening gastrointestinal hemorrhage. Future trials are imperative to compare efficacy and safety of P2Y12-Is in patients with ESKD.

Kidney Int Rep (2021) **6,** 2381–2391; https://doi.org/10.1016/j.ekir.2021.06.031
KEYWORDS: cardiovascular; clopidogrel; dialysis; P2Y12; prasugrel; ticagrelor

More than 600,000 patients in the United States are affected with ESKD and dependent on chronic dialysis.[1] This population is at a ≥4-fold increased risk of thrombotic CV events, such as acute myocardial infarction (AMI), as compared with the general population.[2] Thrombotic events frequently lead to percutaneous coronary interventions and dual antiplatelet therapy with aspirin plus an oral P2Y12-I. Not surprisingly, P2Y12-Is are one of the most often prescribed drugs in patients with ESKD.[1]

Ticagrelor and prasugrel are approved by the United States Food and Drug Administration in the AMI settings, whereas clopidogrel is also indicated in non-AMI settings, including for broader clinical use in peripheral arterial disease or stroke.[3,4] Ticagrelor is an active drug.[5] Prasugrel is converted into a metabolite by esterases in the intestine to become active.[6] Clopidogrel, however, becomes active after multiple activation steps by the cytochrome P450 system.[7] Thus, ticagrelor and prasugrel have greater antiplatelet effects than clopidogrel,[8,9] with reduced interindividual and

Correspondence: Nishank Jain, Department of Internal Medicine, University of Arkansas for Medical Sciences, 4301 West Markham Street, Slot 501, Little Rock, Arkansas 72211, USA. E-mail: njain2@uams.edu

Received 2 June 2021; revised 22 June 2021; accepted 28 June 2021; published online 3 July 2021

intraindividual variabilities, resulting in 15% lower CV events and mortality in the general population.[10,11]

Nevertheless, no head-to-head randomized clinical trials (RCTs) compared P2Y12-I treatments in patients with ESKD, and scarce observational data exist to support the use of prasugrel or ticagrelor over clopidogrel.[12,13] The proportion of patients with ESKD receiving ticagrelor has increased, the proportion receiving prasugrel remains unchanged, and clopidogrel remains the most often prescribed P2Y12-I.[14] On one hand, ESKD may result in alterations of platelet receptors and impairment in drug conformational changes, which can potentially render newer P2Y12-Is less efficacious.[15] On the other hand, these patients are at a disproportionately higher risk for bleeding that might be worse with more potent antiplatelet therapy.[16,17] Therefore, comparative effectiveness and safety data on P2Y12-I in ESKD would help fill a knowledge gap that is less likely to be filled by a RCT to guide evidence-based care and help clinicians balance between thrombotic and bleeding risks in these patients.

To address these knowledge gaps, we used Medicare claims data to compare the effectiveness and safety of prasugrel, ticagrelor, and clopidogrel among individuals with ESKD newly prescribed a P2Y12-I, using propensity score matching to minimize bias by indication. We hypothesized that patients with ESKD on prasugrel and ticagrelor, compared with those on clopidogrel, have a reduced risk of all-cause death and CV events but an increased risk of GI hemorrhage.

METHODS

Data Source

The United States Renal Data System (USRDS) is a national registry that tracks >93% of all adult patients on dialysis from initiation of dialysis to kidney transplantation or death and incorporates Medicare parts A, B, and D claims. The registry includes demographic and comorbidity for every patient documented on initiation of dialysis in the Centers for Medicare and Medicaid Services form 2728, tracks health updates, and records date and cause(s) of death by extracting patient-level claims.

Design and Cohort

We created a national cohort of patients with ESKD who initiated P2Y12-I therapy from files dated January 1, 2011, to December 30, 2015. The cohort identification period started on July 20, 2011, and ended on September 30, 2015. The start date corresponds to when ticagrelor became available on the market. The end date is the last date when the International Classification for Diseases, Ninth Revision, Clinical Modification code was switched to the International Classification for Diseases, Tenth Revision, Clinical Modification. After applying exclusions, we identified every patient who was continuously eligible for Medicare and filled a new prescription. The following 2 steps identified new prescriptions: first, P2Y12-I was identified by nonproprietary drug names, and, second, any such prescription appearing after a 6-month period without any previous patient exposure was flagged as new. The index date was defined as the date of the first prescription. The earliest and the latest possible index dates were July 20, 2011, and September 29, 2015. Comorbidities were assessed 6 months before the index dates. Participants were followed from the index date to death or censorship. Once individuals were censored, they were not allowed back into the cohort. Our final analysis was based on the intention-to-treat approach in which we followed censored-at-switch strategy.[18]

All prevalent patients undergoing chronic dialysis including those on dialysis after failed transplantation were considered if they survived ≥6 months from the first recorded service. Continuous eligibility for Medicare parts A, B, and D was confirmed during the 6-month period before the index dates and throughout the follow-up period. Beneficiaries taking anticoagulants before the index dates were included. Finally, new prescription criterion was applied. Patients were excluded if <18 years of age; had missing first service date; initiated chronic dialysis after the study end date; were not prescribed P2Y12-I; or new prescription criterion was not met. Institutional Review Board approval was obtained.

Variables

Comorbidities were collected from the Centers for Medicare and Medicaid Services form 2728. In addition, we combined data obtained with codes appearing on 2 different days in outpatient claims data or once in hospital claims data before the index dates (see Supplementary Table S1).[19,20]

Exposure

The primary exposure variable was assignment to a P2Y12-I type. Date of outpatient fill and days' supply were used to flag dates covered by a prescription. This allowed us to calculate time-dependent cumulative drug exposure, which was defined as the number of weeks covered by a P2Y12-I divided by the number of weeks of follow-up and expressed as a percentage. Adjustments in run-out dates and days' supply for overlapping prescriptions were made. If the strength of the second overlapping prescription was similar to the first one and was filled within 7 days of the run-out

date of the first, the second prescription start date was adjusted to 1 day after the run-out date of the first prescription. Subsequently, the second prescription run-out date was extended to account for the number of overlapping days. If the second prescription was for a different strength, the first prescription run-out date was shortened to 1 day before the service date of the second prescription. The first prescription day supply was shortened accordingly. To account for length of hospitalization, days' supply and run-out dates were extended by length of hospital stay for prescriptions spanning hospitalization. We also measured time-dependent cumulative drug exposure and "user status" to account for medication adherence in the sensitivity analysis.[19] When there were gaps in possession of drug for ≥2 weeks, "non-user" status was flagged for a given week as antiplatelet effects of P2Y12-I washout in 2 weeks; otherwise, "user" status was flagged.

Outcomes

From the index date to the study end date, we flagged outcomes in the hospitalization claims (see Supplementary Table S2). The primary outcome was all-cause death. Nephrologists are mandated to submit to their regional network a Death Notification Form, including time and cause of death, within 45 days of the event. Each network then forwards the information to the USRDS Coordinating Center, which then becomes part of the USRDS registry. The secondary effectiveness outcomes were CV death and any occurrence of coronary revascularization during the survival period.[19] CV death was defined as death from cardiac cause, including AMI, coronary artery disease, cardiomyopathy, cardiac arrhythmia, and cardiac arrest. The secondary safety outcome was any occurrence of GI hemorrhage during the survival period.

Censoring

Right censoring occurred during follow-up for discontinuation of Medicare eligibility, transplantation of kidney, switching from one P2Y12-I to another, initiation of anticoagulant therapy, loss to USRDS follow-up, or September 30, 2015.

Statistical Analyses

Comparisons across groups were performed with Kruskal–Wallis test for continuous variables and Cochran-Mantel-Haenszel χ^2 tests for categorical variables. Crude event rates were calculated per 1000 person-years.

To compare all-cause death events based on each P2Y12-I category, univariable survival analyses using Kaplan–Meier curves were performed, with statistical significance determined using a log-rank test. We, subsequently, constructed semiparametric Cox proportional hazards models to compare prasugrel with clopidogrel, ticagrelor with clopidogrel, and ticagrelor with prasugrel. Models included P2Y12-I exposure, demographics, dialysis-related factors, comorbidities, year of index date, concomitant medications, and interim events. Because an individual having an interim CV event (including AMI, ischemic stroke, hospitalization for congestive heart failure, or coronary revascularization) on P2Y12-I therapy may have a higher risk of death as compared with those without such events, "interim" event was added as a time-dependent covariate to our model for all-cause death. Specifically, our models allowed comparisons between ticagrelor/clopidogrel, prasugrel/clopidogrel, and prasugrel/ticagrelor expressed in terms of % hazard reduction after Bonferroni multiplicity adjustment. Cox proportional hazards model assumptions were evaluated using log-log survival plots for categorical covariates and a plot of Schoenfeld residuals versus time for continuous covariates.

To minimize confounding by indication, we performed propensity score matching. We initially considered using the inverse probability of treatment weighting method of propensity analysis but rejected this approach because of concerns that it would assign disproportionately higher weights for prasugrel and ticagrelor over clopidogrel given disproportionately higher use of clopidogrel and underutilization of prasugrel and ticagrelor in the cohort. Instead, for generating propensity scores, we used polychotomous (3 drugs) logistic regression models to investigate associations between prescriptions to a P2Y12-I type and various patient characteristics, including demographics, dialysis-related factors, and comorbidities, such as CV events within 6 months of index dates. Predicted probabilities from these logistic regression models were used to generate propensity scores. These scores were generated based on the main effect, and, subsequently modified the model to include higher order interactions between risk factors until observed versus expected differences were no longer significant using a similar approach to the Hosmer-Lemeshow test applied to the regression models. Subsequently, variable optimal matching was performed for each patient on prasugrel to 6 patients on clopidogrel, without replacement for each prasugrel-treated patient, and using an algorithm match with a caliper width of 0.25 SD of the logit of propensity score. For each patient on ticagrelor therapy, there were 4 patients on clopidogrel therapy and 1 patient on prasugrel therapy using a similar approach. Finally, matched sets (prasugrel-clopidogrel, prasugrel-ticagrelor, and ticagrelor-

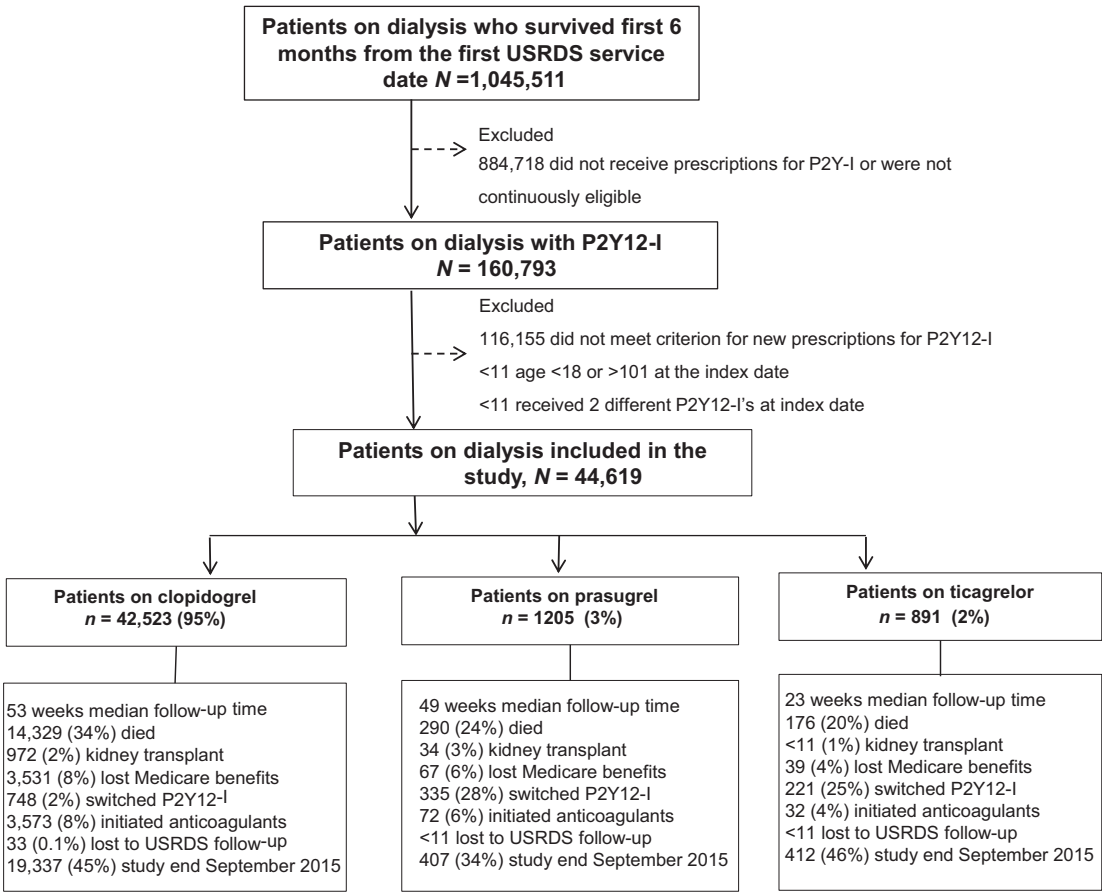

Figure 1. Derivation of the study cohort. P2Y12-I, $P2Y_{12}$ inhibitor; USRDS, United States Renal Data System.

clopidogrel) were compared to ensure balance in covariates, that is, a standardized difference for each covariate to be <10%. After matching, associations between P2Y12-I therapy and outcomes were analyzed using Cox proportional hazards models stratified by matched sets to estimate HRs and corresponding 95% CIs.

Analyses of random-effect recurrent events of coronary revascularization and GI hemorrhage were performed by maximizing a Weibull likelihood using a nonlinear mixed model by incorporating a random disturbance term that represents unobserved heterogeneity owing to recurrent events on an individual.[21]

To account for differences in indications for P2Y12-Is, we created a prespecified subgroup of those with AMI claims before the index dates and performed the above-mentioned survival analyses. For sensitivity analysis to account for drug adherence, we incorporated 2 different time-dependent covariates of drug exposure in separate models.[22]

All CIs used a 2-sided α of 0.05. Analyses were generated with SAS software, version 9.4, for Windows (SAS Institute Inc., Cary, NC), and with R software, version 3.6.0, for Windows.

RESULTS

Baseline Characteristics

During the observation period, 160,793 patients with ESKD received prescriptions for a P2Y12-I (Figure 1). Our final cohort was 44,619 patients; 95% received clopidogrel ($n = 42,523$), 3% prasugrel ($n = 1205$), and 2% ticagrelor ($n = 891$). Overall, 56,851.5 person-years follow-up accrued with median (interquartile range) follow-up of 52 weeks (20 weeks, 101 weeks). After censoring, 20,156 patients (45.2%) remained at the study end (Figure 1).

Median age was 64.0 years, and 20% were ≥75 years of age; 53.9% were men, 36.0% African American, and 17.8% Hispanic. Furthermore, 93% were on hemodialysis, and the remaining on peritoneal dialysis. A total of 8% of the cohort was on oral anticoagulants. There were between-group differences in baseline characteristics which were successfully matched and balanced—1189 patients on prasugrel with 7134 patients on clopidogrel; 880 patients on ticagrelor with 3520 patients on clopidogrel; and 880 patients on ticagrelor with 880 patients on prasugrel (Table 1 and Supplementary Table S3).

Table 1. Characteristics of the study cohort before and after propensity matching

	Before propensity score matching			After propensity score matching P vs. C			After propensity score matching T vs. C		
Baseline characteristics	**C, *n* = 42,523**	**P, *n* = 1205**	**T, *n* = 891**	**P, *n* = 1189**	**C, *n* = 7134**	**Std. diff (%)**	**T, *n* = 880**	**C, *n* = 3520**	**Std. diff (%)**
Demographics									
Age in yr[a]	64.0 (55.0, 73.0)	60.0 (52.0, 68.0)[b]	64.0 (56.0, 72.0)[b]	60.0 (52.0, 68.0)	60.0 (51.0, 68.0)	−0.5	64.0 (56.0, 72.5)	64.0 (55.0, 72.0)	2.3
Male sex, *n* (%)	22,820 (53.7)	731 (60.7)[b]	490 (55.0)[b]	720 (60.6)	4,392 (61.6)	−2.1	484 (55.0)	1931 (54.9)	0.3
Race, *n* (%)									
African American	15,466 (36.4)	316 (26.2)[b]	274 (30.8)[b]	312 (26.2)	1852 (26.0)	1.2	273 (31.0)	1063 (30.2)	3.2
Caucasian	17,128 (40.3)	567 (47.1)[b]	423 (47.5)[b]	561 (47.2)	3,402 (47.7)		416 (47.3)	1656 (47.0)	
Hispanics	7578 (17.8)	238 (19.8)[b]	133 (14.9)[b]	234 (19.7)	1392 (19.5)		131 (14.9)	540 (15.3)	
Other races	1262 (5.3)	81 (6.7%)[b]	59 (6.6)[b]	80 (6.7)	478 (6.7)		59 (6.7)	255 (7.2)	
Unknown race	89 (0.2)	3 (0.2)[b]	2 (0.2)[b]	2 (0.2)	10 (0.1)		1 (0.1%)	6 (0.2)	
Dialysis-related factors									
Dialysis modality									
Hemodialysis, *n* (%)	39,636 (93.2)	1064 (88.3)[b]	808 (90.7)[b]	1051 (88.4)	6337 (88.8)	−1.4	798 (90.7)	3,163 (89.9)	2.8
Peritoneal dialysis, *n* (%)	1887 (6.8)	141 (11.7)[b]	83 (9.3)[b]	138 (11.6)	797 (11.2)		82 (9.3)	357 (10.1)	
Weeks on dialysis	201 (100, 351)	185 (89, 326)[b]	192 (97, 324)[b]	186 (89, 328)	187 (95, 325)	−0.5[c]	192 (97, 322)	183 (94, 318)	2.4[c]
Comorbidities, *n* (%)									
AMI	9555 (22.5)	461 (38.3)[b]	411 (46.1)[b]	451 (37.9)	3,207 (45.0)	0.1[d]	404 (45.9)	1778 (50.5)	0.1[d]
Coronary revascularization	10,782 (25.4)	931 (77.3)[b]	727 (81.6)[b]	915 (77.0)	4088 (57.3)	0.1[d]	717 (81.5)	1115 (60.1)	0.1[d]
Hypertension	38,203 (89.8)	1077 (89.4)	799 (89.7)	NA	NA	NA	NA	NA	NA
Diabetes mellitus	33,378 (78.5)	953 (79.1)	725 (81.4)	942 (79.2)	5631 (78.9)	0.7	717 (81.5)	1874 (81.6)	−0.4
Cancer	3,900 (9.2)	89 (7.4%)	84 (9.4%)	87 (7.3%)	524 (7.3%)	−0.1	83 (9.4%)	314 (8.9%)	1.8
Liver disease	3,339 (7.9%)	93 (7.7)	53 (5.9)	93 (7.8)	545 (7.6)	0.7	53 (6.0)	219 (6.2)	−0.8
GI bleed	3,374 (7.9)	75 (6.2)	61 (6.8)	74 (6.2)	434 (6.1)	0.6	60 (6.8)	224 (6.4)	1.8
COPD	13,304 (31.3)	324 (26.9)[b]	269 (30.2)[b]	320 (26.9)	1919 (26.9)	0.0	264 (30.0)	1048 (29.8)	0.5
Atrial fibrillation	8682 (20.4)	190 (15.8)[b]	154 (17.3)[b]	184 (15.5)	1075 (15.1)	1.1	150 (17.0)	589 (16.7)	0.8
CHF	26,303 (61.9)	763 (63.3)	575 (64.5)	755 (63.5)	4568 (64.0)	−1.1	570 (64.8)	1304 (65.5)	−1.4
PVD	18,548 (43.6)	399 (33.1)[b]	286 (32.1)[b]	394 (33.1)	1351 (33.0)	0.4	283 (32.2)	1154 (32.8)	−1.3
Ischemic stroke	5330 (12.5)	43 (3.6)[b]	51 (5.7)[b]	43 (3.6)	254 (3.6)	0.3	51 (5.8)	211 (6.0)	−0.8
Intracranial hemorrhage	426 (1.0)	<11[e]	<11[e]	NA	NA	NA	NA	NA	NA
Antihypertensive medicine	31,123 (73.2)	961 (79.8)[b]	718 (80.6)[b]	954 (80.2)	5710 (80.0)	0.5	713 (81.0)	1881 (81.8)	−2.1
Satins	21,499 (50.6)	723 (60.0)[b]	555 (62.3)[b]	717 (60.3)	4280 (60.0)	0.6	551 (62.6)	1185 (62.1)	1.1
Proton pump inhibitor	13,157 (30.9)	387 (32.1)	271 (30.4)	386 (32.5)	1215 (31.0)	3.0	269 (30.6)	1120 (31.8)	−2.7

AMI, acute myocardial infarction; C, clopidogrel; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; GI, gastrointestinal; NA, not applicable; P, prasugrel; PVD, peripheral vascular disease; Std. diff., standardized difference; T, ticagrelor.

[a]Ages were calculated on index date and reported as mean (range).

[b]$P < 0.01$ comparing C, P, and T before propensity score matching.

[c]Std. diff was calculated based on natural log of weeks on dialysis.

[d]Either presence of baseline AMI or coronary revascularization was used for propensity score matching.

[e]The number was masked as it was <11, in accordance with the USRDS policy.

Hypertension and intracranial hemorrhage were not used for propensity score matching.

Table 2. Number of events and crude event rates per 1000 person-years during follow-up

	Before propensity score matching			After propensity score matching P vs. C		After propensity score matching T vs. C		After propensity score matching P vs. T	
Outcome of interest	C, n = 42,523	P, n = 1205	T, n = 891	P, n = 1189	C, n = 7134	T, n = 880	C, n = 3,520	P, n = 880	T, n = 880
Primary outcomes									
All-cause death, n (rate)	14,329 (261.48)	290 (201.46)	176 (287.21)	286 (200.89)	1269 (243.31)	176 (290.31)	1194 (261.74)	228 (223.44)	176 (290.31)
Secondary effectiveness outcomes									
CV death, n (rate)	6203 (113.20)	154 (106.98)	90 (146.87)	152 (106.77)	1114 (119.46)	90 (148.45)	577 (126.49)	120 (117.60)	90 (148.45)
Coronary revascularization, n (rate)	18,592 (339.28)	836 (580.75)	378 (616.85)	827 (580.90)	4432 (475.26)	373 (615.26)	1298 (503.75)	618 (605.63)	373 (615.26)
Secondary safety outcomes									
Gastrointestinal hemorrhage, n (rate)	4769 (87.03)	116 (80.58)	78 (127.29)	116 (81.48)	683 (73.24)	76 (125.36)	381 (83.52)	102 (99.96)	76 (125.36)

C, clopidogrel; CV, cardiovascular; P, prasugrel; T, ticagrelor.

Outcomes

In the prasugrel/clopidogrel, ticagrelor/clopidogrel, and prasugrel/ticagrelor propensity-matched cohorts, 2555 (30.7%), 1370 (31.1%), and 404 (23.0%), respectively, died during the follow-up (Table 2). Kaplan–Meier analyses revealed fewer all-cause deaths among prasugrel users than clopidogrel or ticagrelor users and no differences among ticagrelor and clopidogrel users (Figure 2). Table 2 reveals the crude event rates for the secondary outcomes. There were 1266 (15.2%), 667 (15.1%), and 210 (11.9%) CV deaths in the prasugrel/clopidogrel, ticagrelor/clopidogrel, and prasugrel/ticagrelor propensity-matched cohorts. Of all coronary revascularizations, 21.7% were first, 11.9% second, and the remaining subsequent occurrences. Of all GI hemorrhages, 70.2% were first, 17.4% second, and the remaining subsequent occurrences.

Effect of P2Y12-I

All-Cause Death

After adjusting for covariates, prasugrel was associated with a reduced risk of all-cause death (adjusted HRs = 0.82, 95% CI: 0.73–0.93 versus clopidogrel, Figure 3a, and 0.83, 95% CI: 0.69–0.99 versus ticagrelor, Figure 3c). This association remained unchanged after matching for propensity of receiving prasugrel to clopidogrel or ticagrelor (HRs 0.80, 95% CI: 0.70–0.90 and 0.75, 95% CI: 0.57–0.98; Figure 3a and c). There were no significant differences in all-cause death between ticagrelor and clopidogrel users (Figure 3b).

Secondary Outcomes

We found no differences for reduced risk of CV death among prasugrel versus clopidogrel users (HR = 0.85; 95% CI: 0.72–1.01) (Figure 3a) or prasugrel versus ticagrelor users (HR = 0.80; 95% CI: 0.60–1.07) (Figure 3c) during follow-up and no difference between ticagrelor versus clopidogrel users (HR = 1.08; 95% CI: 0.86–1.35) (Figure 3b). There was reduced risk of coronary revascularization with prasugrel use over clopidogrel use (HR = 0.91; 95% CI: 0.86–0.96; Figure 3a) but not over ticagrelor use (HR = 0.92; 95% CI: 0.88–1.01; Figure 3c). GI hemorrhages were also not significantly different (Figure 3a–c).

Subgroup Analysis

A total of 451 prasugrel users and 404 ticagrelor users were retained and matched to clopidogrel users in ratios of 1:3 and 1:5. Similarly, 404 prasugrel users were retained and matched to ticagrelor users in 1:1 ratio. Propensity-matched analyses in the subgroups confirmed that risk associated with all-cause death was lower for prasugrel than for clopidogrel or ticagrelor

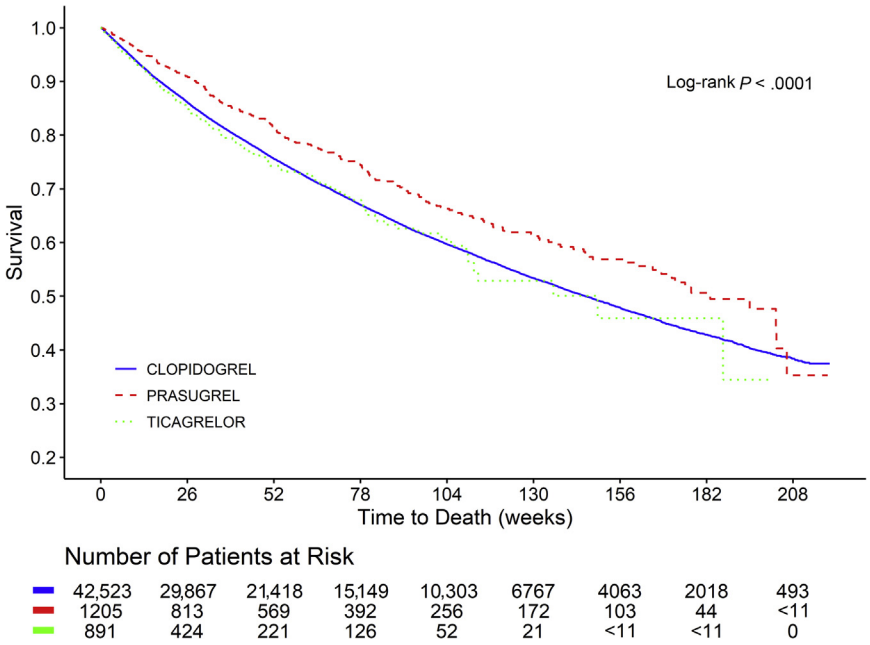

Figure 2. Kaplan–Meir curve representing survival probability of patients on chronic dialysis (ESKD) who were prescribed clopidogrel, prasugrel, and ticagrelor. ESKD, end-stage kidney disease.

(HRs = 0.83; 95% CI: 0.69–1.00 and 0.66; 95% CI: 0.50–0.86) (Figure 3a and c).

Sensitivity Analysis

After adding time-dependent cumulative drug exposure, the prasugrel effect persisted (HR = 0.81; 95% CI: 0.72–0.91) in reducing all-cause death. When we adjusted for time-dependent "user" status, the prasugrel effect persisted (HR = 0.75; 95% CI: 0.63–0.90).

DISCUSSION

Our important finding is that dialysis-dependent patients with ESKD who were treated with prasugrel, as

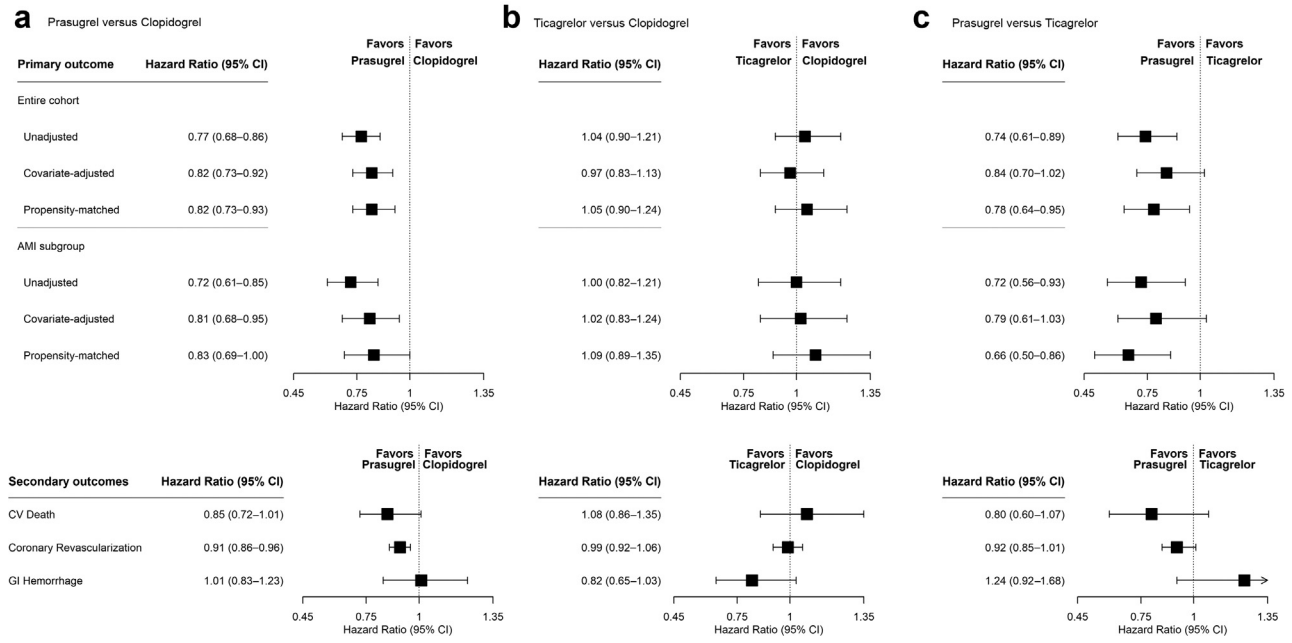

Figure 3. Forest plot for the entire cohort and the subgroup with AMI representing hazard ratio with its CI for primary outcome (all-cause death) in covariate-adjusted and propensity-matched cohorts. Panels represent results for comparison between (a) prasugrel versus clopidogrel, (b) ticagrelor versus clopidogrel, and (c) prasugrel versus ticagrelor. For the propensity-matched cohort, it also reveals comparison of the secondary effectiveness outcomes, CV death and coronary revascularization, and the secondary safety outcome, GI hemorrhage, between (a) prasugrel versus clopidogrel, (b) ticagrelor versus clopidogrel, and (c) prasugrel versus ticagrelor. AMI, acute myocardial infarction; CV, cardiovascular; GI, gastrointestinal.

compared with those treated with clopidogrel or ticagrelor, had a reduced risk of all-cause death and no added risk for GI hemorrhage, possibly by reducing risk for CV deaths and coronary revascularizations. These findings suggest that prasugrel may be more effective than clopidogrel or ticagrelor for reducing risk of death, primarily CV death, and of coronary revascularization among dialysis-dependent patients with ESKD. These findings can not only help guide future research in this field but importantly fill a knowledge gap that has not been filled by a trial to guide evidence-based care in this vulnerable patient population.

To date, there are no RCTs to guide P2Y12-I treatment specifically in patients with ESKD. Our findings, therefore, become important in that, in a large, propensity-matched national cohort, risk associated with all-cause death was lower with prasugrel than with clopidogrel or ticagrelor, as they extend the results of landmark trials in patients with non-ESKD with AMI.[23,24] In the Platelet Inhibition and Patient Outcomes trial, ticagrelor was found to be superior to clopidogrel in patients with AMI.[10] In 2 separate trials, prasugrel was found to be superior to clopidogrel only in those with AMI who underwent percutaneous coronary intervention[23] but not without percutaneous coronary intervention.[25] In the most recent Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment 5 trial, prasugrel was superior to ticagrelor in patients with AMI undergoing percutaneous coronary intervention.[22] These trials excluded patients with ESKD.[10,20–25] Finally, a recent analysis of patients with ESKD receiving drug-eluting stents revealed no benefit of prasugrel or ticagrelor over clopidogrel in reducing a composite of CV death, AMI, or stroke.[13] In the scarcity of previous evidence and systematic exclusion of patients with ESKD from landmark trials, our results highlight important findings regarding better effectiveness of prasugrel over others. It also lays groundwork for future trials to compare efficacy and safety of P2Y12-I use in patients with ESKD.

In our analysis, the risk of GI hemorrhage was not different among patients treated with each of the P2Y12-I drugs studied. Previous RCTs comparing prasugrel or ticagrelor with clopidogrel reported no increased risk of bleeding in patients without kidney disease, and a subgroup analysis of individuals with creatinine clearance $<$ 60 ml/min revealed similar results.[20–23] In addition, an RCT that followed patients with ESKD for 6 weeks investigated the efficacy of clopidogrel versus placebo in reducing arteriovenous fistula thrombosis and revealed no increased risk of bleeding with clopidogrel.[26] The overall bleeding rate of 16% was higher in our study than aforementioned studies, in which it was 2% to 4%, possibly owing to the presence of higher prevalence of comorbidities, and much longer follow-up.[26] Our findings are contrary to the current belief that prasugrel may be more harmful than others based on postmarketing data reporting higher risk of GI hemorrhage in patients with non-ESKD treated with prasugrel.[27] Given that patients with ESKD are at a significantly higher risk of GI hemorrhage than the general population, and antiplatelet therapy potentially worsens this risk, patients with ESKD were generally not well represented in RCTs of antiplatelet therapy, and questions surrounding safety of these newer P2Y12-Is in the setting of ESKD remain unanswered. Our results suggest that P2Y12-I type may not result in differential bleeding risk in this high-risk patient population.

We also reveal that treatment with ticagrelor was not associated with a mortality benefit over clopidogrel. In the subgroup analyses of the Platelet Inhibition and Patient Outcomes trial, the mortality benefit of ticagrelor over clopidogrel observed in patients with a creatinine clearance $<$ 60 ml/min was lost in the subgroup with clearance $<$ 30 ml/min.[28] This trial included only 15 participants with clearance $<$ 15 ml/min not on chronic dialysis, and patients with ESKD were excluded. Higher death rates were reported in participants with clearance $<$ 15 ml/min in the ticagrelor arm as compared with the clopidogrel arm.[14] A similar trend was reported from another registry, in which ticagrelor lost mortality benefit over clopidogrel as severity of kidney disease worsened from clearance $<$60 ml/min to $<$30 ml/min.[29] A Taiwanese study revealed that ticagrelor had no mortality benefit over clopidogrel in patients with ESKD with AMI.[30] Our results extend these findings to reveal no mortality benefit for ticagrelor in patients with the most severe kidney disease—ESKD—with clearance typically at $<$15 ml/min.

Our findings that patients with ESKD treated with prasugrel, as compared with those treated with clopidogrel or ticagrelor, had a reduced risk of all-cause death, CV death, and coronary revascularization without increasing risk of GI hemorrhage also reveal how little we understand on the use of these drugs in patients with ESKD. Prasugrel and ticagrelor are more potent antiplatelet drugs and achieve greater platelet inhibition than clopidogrel.[6,31] This may be particularly beneficial for patients with ESKD because platelet activation in these patients is greater than in those without kidney disease.[32] Nevertheless, pharmacologic properties of prasugrel and ticagrelor might be different in the ESKD milieu than that in the general population, thus altering their efficacy in patients with

ESKD. First, prasugrel binds to the $P2Y_{12}$ receptor directly and irreversibly, whereas ticagrelor binds reversibly to a site on the receptor remote from the adenosine diphosphate binding site and blocks adenosine diphosphate binding to the receptor by allosteric modulation.[6,31] This direct and irreversible inhibition of the $P2Y_{12}$ receptor by prasugrel may be more efficacious than the remote and reversible binding of ticagrelor owing to the presence of middle molecules in the ESKD milieu that may interfere with binding. Second, medication adherence may also be better with once-daily prasugrel in patients with ESKD on polypharmacy than with twice-daily ticagrelor.[12] Our results are, therefore, a significant first step to drive future research in this field of inquiry.

We observed significant association of prasugrel over clopidogrel with reduction in coronary revascularizations but not for CV deaths. One explanation could be that a proportion of CV events may have not been readily captured in the USRDS registry. As compared with the general population, patients with ESKD are known to experience a higher burden of sudden cardiac death and often die at home without even a chance for being diagnosed with a CV event or undergoing revascularization.[33] In addition, a large proportion have baseline elevated levels of circulating cardiac troponins.[34] This leads to possible underdiagnosis and undertreatment of CV events in patients with ESKD.[35] Therefore, CV events were probably undercaptured.

Several limitations deserve mentioning. First, because aspirin is available over-the-counter, data on its long-term use were not available in the registry. It would bias the study if concurrent aspirin users identified by prescriptions only were included because it would leave out a large proportion of patients who purchase aspirin over the counter. Nevertheless, our effect sizes may fail to capture aspirin effect. On one hand, aspirin alone may have some efficacy in reducing CV events in patients with ESKD. On the other hand, patients may be prescribed a P2Y12-I as monotherapy without (or instead of) aspirin owing to the bleeding risks associated with dual antiplatelet therapy in ESKD.[16,17] Second, prasugrel and ticagrelor were underused in ESKD because ticagrelor was approved by the US Food and Drug Administration on the study start date and prasugrel was approved in 2009.[14] Owing to lack of data related to the use of P2Y12-Is in patients with ESKD, there may be reluctance among prescribers to use prasugrel in ESKD given its greater reported risk for bleeding than clopidogrel or ticagrelor in the general population. Although we minimized presence of selection bias using a rigorous statistical approach, residual confounding could still exist. Third, we used data sets before the transition from the International Classification for Diseases, Ninth Revision, Clinical Modification, to the International Classification for Diseases, Tenth Revision, Clinical Modification, codes. Trends for use of P2Y12-Is could change with time, and future work could use more recent data sets to confirm our results. Fourth, switching between P2Y12-Is could be informative.[36] For instance, if P2Y12-Is were stopped, or changed to another P2Y12-I during follow-up, the reason for that decision may not be available in a study of this nature. Therefore, lack of an increase in GI hemorrhage may be hidden as administrative claims data are not granular enough to capture such occurrences. Finally, P2Y12-Is could be prescribed for various clinical indications, including AMI, stroke, or PVD. Although we performed subgroup analysis by indication for AMI, drug effects may not be uniform for other clinical indications that were not analyzed in this study. Despite these limitations, our study is strengthened by use of a large, national, multiethnic cohort of an understudied, high-risk patient population—precisely those who were systematically excluded from previous RCTs. Because of lack of evidence regarding P2Y12-I use in ESKD, our results will become even more relevant only when a large RCT in this patient population can be undertaken.

CONCLUSION

In patients with ESKD, treatment with prasugrel, as compared with clopidogrel or ticagrelor, may be more effective at reducing all-cause death without increasing risk for GI hemorrhage, possibly by reducing risk for CV deaths and coronary revascularizations. This is important because these patients are at a disproportionately higher risk than the general population not only for thrombotic events but also for bleeding. An RCT is imperative to investigate comparative effectiveness and safety of P2Y12-Is to guide evidence-based care and balance efforts to reduce thrombotic risks with those to minimize adverse bleeding events.

DISCLOSURE

All the authors declared no competing interests.

ACKNOWLEDGMENTS

We thank Judy A. Bielby, RHIA, for reviewing the International Classification of Diseases, Ninth Revision and diagnosis-related group codes for completeness and accuracy. We thank Deepa Raghavan, MD, and the Science Communication Group (University of Arkansas for Medical Sciences, Little Rock, AR) for editing the manuscript. We thank Robert F. Reilly, MD, and Bradley C. Martin, PhD, for critiques related to the study. A part of these findings was

recently submitted as an abstract to the American Heart Association 2021 Congress. A data-use agreement was signed and approved by the United States Renal Data System Program Director (DUA 2016-50). The University of Kansas Medical Center (Kansas City, KS) was the primary site for data collection, processing, and analysis. The manuscript was approved for publication by the United States Renal Data System Coordinating Center (approval #MS2020-28). The content is solely the responsibility of the authors and does not necessarily represent the official views of the American Heart Association, the American Society of Nephrology, and the National Institutes of Health.

FUNDING STATEMENT

This study was supported by the American Heart Association Scientist Development Grant 16SDG31000045 (NJ) and the American Society of Nephrology Foundation for Kidney Research (NJ). SSH is supported by the Yin Quan-Yuen Distinguished Professorship in Nephrology at the University of Texas Southwestern Medical Center, Dallas, Texas. The project described was also supported by the Translational Research Institute grant (TL1 TR003109) through the National Center for Advancing Translational Sciences of the National Institutes of Health.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1. Shows codes used to extract baseline characteristics of the cohort.

Table S2. Shows codes used to define outcomes.

Table S3. Shows characteristics of the propensity-matched cohort for prasugrel and ticagrelor.

STROBE Statement (PDF)

REFERENCES

1. United States Renal Data System. 2019 USRDS annual data report: epidemiology of kidney disease in the United States. Bethesda, MD: National Institutes of Health, National Institutes of Diabetes and Digestive and Kidney Diseases. Accessed April 24, 2021. https://www.usrds.org/annual-data-report/
2. Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. *Am J Kidney Dis*. 1998;32(suppl 3):S112–S119. https://doi.org/10.1053/ajkd.1998.v32.pm9820470.
3. Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines: an update of the 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention, 2011 ACCF/AHA guideline for coronary artery bypass graft surgery, 2012 ACC/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease, 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction, 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes, and 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery [published correction appears in *Circulation.* 2016;134:e192–e194] *Circulation*. 2016;134:e123–e155. https://doi.org/10.1161/CIR.0000000000000404.
4. Levine GN, Bates ER, Blankenship JC, et al. 2015 ACC/AHA/SCAI focused update on primary percutaneous coronary intervention for patients with ST-elevation myocardial infarction: an update of the 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention and the 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Society for Cardiovascular Angiography and Interventions [published correction appears in *Circulation*. 2016;133:e442–e443] *Circulation*. 2016;133:1135–1147. https://doi.org/10.1161/CIR.0000000000000336.
5. Teng R, Butler K. Pharmacokinetics, pharmacodynamics, tolerability and safety of single ascending doses of ticagrelor, a reversibly binding oral P2Y(12) receptor antagonist, in healthy subjects. *Eur J Clin Pharmacol*. 2010;66:487–496. https://doi.org/10.1007/s00228-009-0778-5.
6. Small DS, Wrishko RE, Ernest CS 2nd, et al. Prasugrel pharmacokinetics and pharmacodynamics in subjects with moderate renal impairment and end-stage renal disease. *J Clin Pharm Ther*. 2009;34:585–594. https://doi.org/10.1111/j.1365-2710.2009.01068.x.
7. Mullangi R, Srinivas NR. Clopidogrel: review of bioanalytical methods, pharmacokinetics/pharmacodynamics, and update on recent trends in drug–drug interaction studies [published correction appears in *Biomed Chromatogr.* 2009;23:334] *Biomed Chromatogr*. 2009;23:26–41. https://doi.org/10.1002/bmc.1128.
8. Storey RF, Melissa Thornton S, Lawrance R, et al. Ticagrelor yields consistent dose-dependent inhibition of ADP-induced platelet aggregation in patients with atherosclerotic disease regardless of genotypic variations in P2RY12, P2RY1, and ITGB3. *Platelets*. 2009;20:341–348. https://doi.org/10.1080/09537100903075324.
9. Siller-Matula JM, Akca B, Neunteufl T, et al. Inter-patient variability of platelet reactivity in patients treated with prasugrel and ticagrelor. *Platelets*. 2016;27:373–377. https://doi.org/10.3109/09537104.2015.1095874.
10. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2009;361:1045–1057. https://doi.org/10.1056/NEJMoa0904327.
11. Wiviott SD, Braunwald E, Angiolillo DJ, et al. Greater clinical benefit of more intensive oral antiplatelet therapy with prasugrel in patients with diabetes mellitus in the trial to assess improvement in therapeutic outcomes by optimizing platelet inhibition with prasugrel-thrombolysis in myocardial infarction 38. *Circulation*. 2008;118:1626–1636. https://doi.org/10.1161/CIRCULATIONAHA.108.791061.
12. Jain N, Reilly RF. Oral P2Y12 receptor inhibitors in hemodialysis patients undergoing percutaneous coronary interventions: current knowledge and future directions. *Semin Dial*. 2016;29:374–381. https://doi.org/10.1111/sdi.12484.

13. Mavrakanas TA, Kamal O, Charytan DM. Prasugrel and ticagrelor in patients with drug-eluting stents and kidney failure. *Clin J Am Soc Nephrol*. 2021;16:757–764. https://doi.org/10.2215/CJN.12120720.
14. Jain N, Hunt SL, Cui H, et al. Trends for and clinical factors associated with choice of oral P2Y12 inhibitors for patients on chronic dialysis. *Cardiovasc Drugs Ther*. 2019;33:511–521. https://doi.org/10.1007/s10557-019-06913-w.
15. Boccardo P, Remuzzi G, Galbusera M. Platelet dysfunction in renal failure. *Semin Thromb Hemost*. 2004;30:579–589. https://doi.org/10.1055/s-2004-835678.
16. Holden RM, Harman GJ, Wang M, et al. Major bleeding in hemodialysis patients. *Clin J Am Soc Nephrol*. 2008;3:105–110. https://doi.org/10.2215/CJN.01810407.
17. Hiremath S, Holden RM, Fergusson D, Zimmerman DL. Antiplatelet medications in hemodialysis patients: a systematic review of bleeding rates. *Clin J Am Soc Nephrol*. 2009;4:1347–1355. https://doi.org/10.2215/CJN.00810209.
18. Shen JI, Montez-Rath ME, Lenihan CR, et al. Outcomes after warfarin initiation in a cohort of hemodialysis patients with newly diagnosed atrial fibrillation. *Am J Kidney Dis*. 2015;66:677–688. https://doi.org/10.1053/j.ajkd.2015.05.019.
19. Shireman TI, Phadnis MA, Wetmore JB, et al. Antihypertensive medication exposure and cardiovascular outcomes in hemodialysis patients. *Am J Nephrol*. 2014;40:113–122. https://doi.org/10.1159/000365255.
20. Tang Y, Brooks JM, Wetmore JB, Shireman TI. Association between higher rates of cardioprotective drug use and survival in patients on dialysis. *Res Soc Admin Pharm*. 2015;11:824–843. https://doi.org/10.1016/j.sapharm.2014.12.007.
21. Allison PD. *Survival Analysis Using SAS: A Practical Guide*. 2nd ed. Cary, NC: SAS Institute Inc.; 2010.
22. Phadnis MA, Shireman TI, Wetmore JB, et al. Estimation of drug effectiveness by modeling three time-dependent covariates: an application to data on cardioprotective medications in the chronic dialysis population. *Stat Biopharm Res*. 2014;6:229–240. https://doi.org/10.1080/19466315.2014.920275.
23. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2007;357:2001–2015. https://doi.org/10.1056/NEJMoa0706482.
24. Schupke S, Neumann FJ, Menichelli M, et al. Ticagrelor or prasugrel in patients with acute coronary syndromes. *N Engl J Med*. 2019;381:1524–1534. https://doi.org/10.1056/NEJMoa1908973.
25. Roe MT, Armstrong PW, Fox KA, et al. Prasugrel versus clopidogrel for acute coronary syndromes without revascularization. *N Engl J Med*. 2012;367:1297–1309. https://doi.org/10.1056/NEJMoa1205512.
26. Dember LM, Beck GJ, Allon M, et al. Effect of clopidogrel on early failure of arteriovenous fistulas for hemodialysis: a randomized controlled trial. *JAMA*. 2008;299:2164–2171. https://doi.org/10.1001/jama.299.18.2164.
27. Koyabu Y, Abe S, Sakuma M, et al. Short-term safety and mid-term efficacy of prasugrel versus clopidogrel in patients undergoing percutaneous coronary intervention. *Intern Med*. 2019;58:2315–2322. https://doi.org/10.2169/internalmedicine.2262-18.
28. James S, Budaj A, Aylward P, et al. Ticagrelor versus clopidogrel in acute coronary syndromes in relation to renal function: results from the Platelet Inhibition and Patient Outcomes (PLATO) trial. *Circulation*. 2010;122:1056–1067. https://doi.org/10.1161/CIRCULATIONAHA.109.933796.
29. Edfors R, Sahlen A, Szummer K, et al. Outcomes in patients treated with ticagrelor versus clopidogrel after acute myocardial infarction stratified by renal function. *Heart*. 2018;104:1575–1582. https://doi.org/10.1136/heartjnl-2017-312436.
30. Lee CH, Tsai TH, Lin CJ, et al. Efficacy and safety of ticagrelor compared with clopidogrel in patients with end-stage renal disease with acute myocardial infarction. *Am J Cardiovasc Drugs*. 2019;19:325–334. https://doi.org/10.1007/s40256-018-00318-0.
31. Husted S, van Giezen JJ. Ticagrelor: the first reversibly binding oral P2Y12 receptor antagonist. *Cardiovasc Ther*. 2009;27:259–274. https://doi.org/10.1111/j.1755-5922.2009.00096.x.
32. Jain N, Li X, Adams-Huet B, et al. Differences in whole blood platelet aggregation at baseline and in response to aspirin and aspirin plus clopidogrel in patients with versus without chronic kidney disease. *Am J Cardiol*. 2016;117:656–663. https://doi.org/10.1016/j.amjcard.2015.11.029.
33. Makar MS, Pun PH. Sudden cardiac death among hemodialysis patients. *Am J Kidney Dis*. 2017;69:684–695. https://doi.org/10.1053/j.ajkd.2016.12.006.
34. Jain N, Hedayati SS. How should clinicians interpret cardiac troponin values in patients with ESRD? *Semin Dial*. 2011;24:398–400. https://doi.org/10.1111/j.1525-139X.2011.00912.x.
35. Fox CS, Muntner P, Chen AY, et al. Use of evidence-based therapies in short-term outcomes of ST-segment elevation myocardial infarction and non–ST-segment elevation myocardial infarction in patients with chronic kidney disease. *Circulation*. 2010;121:357–365. https://doi.org/10.1161/CIRCULATIONAHA.109.865352.
36. Rollini F, Franchi F, Angiolillo DJ. Switching P2Y12-receptor inhibitors in patients with coronary artery disease. *Nat Rev Cardiol*. 2016;13:11–27. https://doi.org/10.1038/nrcardio.2015.113.