Age Modifies Intracranial and Gastrointestinal Bleeding Risk from P2Y12 Inhibitors in Patients Receiving Dialysis

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Key Points
- In dialysis patients on P2Y12 inhibitors, annual incidence rates for intracranial bleeds were 2% in those aged <55 years and 3% in those ≥75 years, and gastrointestinal bleeds were 4% in those aged <55 years and 9% in those aged ≥75 years.
- On clopidogrel, prasugrel, and ticagrelor, for every decade increase in age of patients receiving chronic dialysis, risk of intracranial bleed increased by 9%, 55%, and 59%, and risk of gastrointestinal bleed increased by 21%, 28%, and 39%, respectively.
- Compared with clopidogrel, prasugrel was associated with a greater risk of intracranial bleed for those aged ≥75 years, and ticagrelor was worse for gastrointestinal bleeds for those aged ≥60 years.

Abstract
Background Individuals aged ≥75 years are the fastest-growing population starting dialysis for end-stage kidney disease (ESKD) due to living longer with coronary artery disease. ESKD alone can increase bleeding risk, but P2Y12 inhibitor (P2Y12-I) antiplatelet medications prescribed for cardiovascular treatment can exacerbate this risk in patients with ESKD. The age-specific rates of bleeding complications in dialysis patients with ESKD on P2Y12-I remain unclear, as does how age modifies the bleeding risk from P2Y12-I use in these patients.

Methods In a retrospective cohort study, we collected data on 40,972 patients receiving maintenance hemodialysis or peritoneal dialysis who were newly prescribed P2Y12-I therapy between 2011 and 2015 from the USRDS registry. We analyzed the effect of age on the time to first bleed and the interactions between age and P2Y12-I type on modifying the effects of a bleed.

Results Twenty percent of the cohort were aged ≥75 years. There were 3096 (8%) gastrointestinal (GI) and 1298 (3%) intracranial (IC) bleeding events during a median follow-up of 1 year. Annual incidence rates for IC bleeds were 2% in those aged <55 years and 3% in those aged ≥75 years. Rates for GI bleeds were 4% in those aged <55 years and 9% in those aged ≥75 years. On clopidogrel, prasugrel, and ticagrelor, for every decade increase in age of the cohort members, the risk of IC bleed increased by 9%, 55%, and 59%, and the risk of GI bleed increased by 21%, 28%, and 39%, respectively. At age ≥75 years, prasugrel was associated with a greater risk of IC bleed than clopidogrel. At age ≥60 years, ticagrelor was associated with a greater risk of GI bleed than clopidogrel.

Conclusions More potent P2Y12-Is (prasugrel and ticagrelor) were associated with a disproportionately higher risk of IC bleed with increasing age compared with that of clopidogrel—prasugrel was much worse than clopidogrel at age ≥75 years. All three drugs were associated with only modest increase in the risk of GI bleed with every decade increase in age—ticagrelor was much worse than clopidogrel at ≥60 years of age. These results highlight the need for head-to-head clinical trials for the use of P2Y12-Is in patients with ESKD to determine age cutoffs where the risk of bleeding outweighs the benefits of thrombosis prevention.

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**Introduction**

Patients with ESKD experience a two- to five-fold higher risk of bleeding complications such as gastrointestinal (GI) and intracranial (IC) bleeds, and their risk of dying from these complications is two-fold higher for GI bleeds and a four- to ten-fold higher for IC bleeds (1–4). This excessive bleeding risk may be exacerbated by the use of antiplatelet drugs (e.g., oral P2Y12 inhibitors [P2Y12-I]) prescribed for cardiovascular treatment of acute thrombotic events such as heart attack or stroke (5,6). Of the three P2Y12-Is, prasugrel and ticagrelor are more potent P2Y12-Is than clopidogrel. In a recent observational study, prasugrel was associated with a 28% reduced risk of mortality and a 9% reduced risk of coronary revascularizations over clopidogrel in ESKD patients (7). Another study, primarily a case series comprising hemodialysis patients with poor antiplatelet effects to clopidogrel, demonstrated superior antiplatelet effects with ticagrelor use (8). Due to the lack of randomized clinical trials of the use of this drug class in ESKD and bleeding risks associated with these drugs, these patients are seldom prescribed more potent P2Y12-I therapies (6). Surprisingly, recent observational studies in patients with ESKD reported no differences between these three drugs in the risk for GI bleed or major bleed, defined as a composite of death from bleed, any bleed requiring hospitalization, or bleed at crucial sites (7,9).

ESKD is a unique clinical condition involving multiple defects in the hemostatic pathway where risk factors for bleeding complications may not be the same as that in the general population (10). Although patients with ESKD are known to bleed more due to kidney failure, P2Y12-I therapies are frequently initiated for cardiovascular diseases in this patient population (6). Published literature on bleeding risks related to P2Y12-I therapy is limited by the small number of bleeding events, shorter duration of follow-up, lack of data on individuals >75 years of age, lack of data on more potent P2Y12-Is, failure to exclude the use of anticoagulants, and inclusion of only patients who did not have ESKD (3,4,11–18). Therefore, reliable estimates of event rates for GI and IC bleeds remain unclear among patients with ESKD on P2Y12-I therapy as do the age-specific rates and the risk factors associated with such complications.

ESKD is one of the most rapidly growing chronic diseases globally, with a patient population that includes individuals who are ≥75 years of age who are starting dialysis due to living longer with coronary artery disease (5,19). According to the Academic Research Consortium for high bleeding risk, individuals who are ≥75 years of age are also the fastest-growing population of patients undergoing percutaneous coronary interventions (20). Although this consortium identifies age ≥75 years as a minor criterion for high bleeding risk, it acknowledges limitations of the published literature that excluded this patient subgroup (20), and several of the validated risk scores for bleeding risk estimation related to P2Y12-I therapy do not even include age as a risk factor (21). Therefore, it is crucial to understand age-specific bleeding rates in patients with ESKD on P2Y12-I therapy, the risk factors associated with such complications, and whether age modifies the effect of this drug class on the bleeding complications. To accomplish the aforementioned objectives, we used the United States Renal Data System (USRDS) registry—a readily available national registry with a large population of patients with ESKD in the United States—to examine the age-specific event rates for GI and IC bleed among this patient population on P2Y12-I therapy, and we explored risk factors associated with such bleeding complications. We also investigated whether age modifies the effect of the drug class for bleeding complications by estimating the interactions between age and P2Y12-I therapies on bleeding risks.

**Materials and Methods**

**Study Design and Cohort**

We created a large retrospective multiracial national cohort of patients with ESKD who were prescribed P2Y12-I therapy by selecting data files between January 1, 2011, and December 30, 2015, collected in the USRDS registry. The cohort identification period started on July 20, 2011, corresponding to the date when ticagrelor became available on the US market. The period ended on September 30, 2015, when the International Classification for Diseases (ICD)-9-CM codes switched to ICD-10-CM codes. Every patient who was continuously eligible for Medicare Parts A, B, and D and who filled a new prescription for a P2Y12-I was identified. Two steps were followed to identify newly prescribed P2Y12-Is. First, P2Y12-I prescriptions were identified by nonproprietary drug names. Subsequently, any P2Y12-I prescription that appeared after a 6-month period without prior patient exposure was presumed to represent a new treatment episode. The index date was designated as the first date a patient began P2Y12-I therapy. Comorbidities were assessed using the date 6 months before a cohort member’s index date, starting at January 1, 2011. Each member was followed from the index date to the occurrence of death or censoring.

Patients included in the sample were undergoing chronic hemodialysis or peritoneal dialysis and those who returned to dialysis after failing a previous transplant during the cohort identification period. We confirmed the receipt of chronic dialysis before or on the index date. Included patients were also ≥18 years old, had survived at least 6 months from the first USRDS-recorded service for chronic dialysis, had continuous eligibility for Medicare Parts A, B, and D during the 6-month period before the index date (confirmed using the payer status file), and had a new P2Y12-I treatment episode (as previously described). Patients taking anticoagulants or other antiplatelet therapies before their index date were excluded. Patients were also excluded if the date of their first USRDS-recorded service for chronic dialysis was missing or if chronic dialysis started after the study end date.

Institutional Review Board approval was obtained (Protocol # 205782) for nonhuman subject research.

**Data Source**

The USRDS registry tracks >93% of dialysis patients from initiation of dialysis through transplantation or death (5). Upon initiation of dialysis, demographic and comorbidity conditions of patients are documented in the registry and are regularly updated with changes in insurance status, dialysis treatments, and transplantation. The registry also incorporates Medicare Parts A, B, and D claims data.
Variables, Exposure, Outcomes, and Censoring

Demographics were collected from the patient dataset collected from the USRDS registry. Baseline comorbidities were identified during the 6 months before the index dates using codes appearing in the inpatient and the outpatient claims data plus information available on the CMS form 2728 (Supplemental Table 1). Concomitant medicines were reported if present on the index date. On the basis of prescription data, patients were assigned to one of three P2Y12-I treatment groups and were assigned a corresponding exposure variable. Starting from the index date and running through the study end date, outcomes of interest were identified from the hospitalization claims (Supplemental Table 2). Outcome variables were time to first fatal or nonfatal GI or IC bleed during the observation window. Subjects were censored upon the loss of Medicare eligibility, receipt of a kidney transplant, switching from one P2Y12-I to another, initiation of anticoagulant therapy, loss to USRDS follow-up, study end date, or nonbleed-related death.

Statistical Analyses

Descriptive statistics were generated. Crude event rates were calculated by accounting for an individual’s contribution to person-years and were reported as events per 1000 person-years. Age-specific annual incidence rates and cumulative risk were calculated and expressed as percentages. Cox proportional hazard models were estimated using the forward stepwise selection for the time to first bleed, which included a comprehensive set of covariates such as demographics, dialysis-related factors, comorbidities, concomitant medicines, and P2Y12-I type. The proportional hazard model assumptions were assessed using log-log survival plots for categorical covariates and a plot of Schoenfeld residuals versus time for age (continuous covariate). We conducted multivariable analyses in a subgroup containing cohort members with a prior cardiovascular event (acute myocardial infarction [AMI] or coronary revascularization procedure claim) in the 6-month period before the index date to identify risk factors for bleeding complications, specifically among those with ESKD and recent cardiovascular event. Additional sensitivity analyses were similarly conducted for clopidogrel, prasugrel, and ticagrelor users after stratifying the cohort by P2Y12-I type. We also constructed a subdistribution hazards model in which death was treated as a competing risk. Interaction of age and P2Y12-I was investigated by introducing the interaction term age×P2Y12-I in the multivariable models. A P<0.1 was considered a significant interaction. Estimates of the regression coefficients of the interaction term age×P2Y12-I type were used to evaluate the relative performance of a pair of P2Y12-I types (e.g., prasugrel versus clopidogrel) by means of a hazard ratio as a function of age with a focus on

Figure 1. | Derivation of the cohort after applying inclusion and exclusion criteria and the remaining cohort at the end of follow-up after death and censoring. P2Y12-I, P2Y12 inhibitor.
the 50- to 80-year age range. Ninety percent confidence intervals (consistent with the P-value of 0.1 for the interaction term) were generated to assess the age range at which each P2Y12-I type performed most favorably compared with the other two types.

Results

Our final cohort comprised 40,972 patients (Figure 1). The median follow-up was 1 year, the median age was 64 years, and 20% of the cohort were aged ≥75 years (Table 1). Fifty-four percent were men, 36% were Black, 18% were Hispanic, and the majority received chronic hemodialysis. Within the cohort, 95% used clopidogrel, 3% used prasugrel, and 2% used ticagrelor (Supplemental Table 3). There were baseline differences between the three groups in the claims of AMI and coronary revascularization captured during the 6-month period before the index dates; a subgroup with these cardiovascular events was created, containing 15,452 patients (38% of the cohort; Supplemental Table 4). There were 3096 (8%) GI bleed events and 1298 (3%) IC bleeds over the entire cohort during the observation window (Table 2). Annual bleeding rates and cumulative risk increased with age (Figure 2).

### Risk Factors for Time to First GI Bleed during the Observation Window

History of previous GI bleed was the strongest independent predictor for GI bleed (adjusted hazard ratio [HR] = 2.76; 95% confidence interval [CI], 2.50 to 3.04). Subgroup analysis (Figure 3B) and sensitivity analysis (Supplemental Table 5) demonstrated similar associations. Age was the second most important independent predictor of GI bleed during follow-up (Figure 3A). Other significant predictors of GI bleed (Figure 3, A and B) were a history of chronic obstructive pulmonary disease, peripheral vascular disease, and cancer.

### Interaction of Age and P2Y12-I on GI Bleed

There was a significant interaction of age with P2Y12-I type in modifying the risk of GI bleed (P < 0.1). For every decade increase in age, the risk of GI bleed increased by
21% with clopidogrel use (HR = 1.21; 95% CI, 1.17 to 1.24), by 28% with prasugrel use (HR = 1.28; 95% CI, 1.08 to 1.52), and by 39% with ticagrelor use (HR = 1.39; 95% CI, 1.14 to 1.7; Supplemental Table 6). All of these results remained unchanged in the competing risk models (Supplemental Table 6). At age ≥ 60 years, ticagrelor was associated with a greater risk of GI bleed compared with clopidogrel (age 65: HR = 1.41; 95% CI, 1.12 to 1.78; age 75: HR = 1.63; 95% CI, 1.24 to 2.14) in the full model (Figure 5) and in the competing risk model (age 75: HR = 1.69; 95% CI, 1.09 to 2.62).

Risk Factors for Time to First IC Bleed during the Observation Window

History of previous ischemic stroke was the strongest independent predictor of IC bleed during follow-up (HR = 2.74; 95% CI, 2.42 to 3.11; Figure 4A). Similar associations were noted in the subgroup (Figure 4B) and sensitivity (Supplemental Table 7) analyses. Age was the second most important independent predictor of IC bleed during follow-up in the entire cohort. Other significant predictors of IC bleed were the presence of diabetes mellitus, being a woman, and peritoneal dialysis (worse than hemodialysis) in the entire cohort (Figure 4, A and B).

Interaction of Age and P2Y12-I on IC Bleed

There was a significant interaction of age with P2Y12-I type in modifying the risk of IC bleed (P < 0.1). For every decade increase in age, risk of IC bleed increased by 9% with clopidogrel use (HR = 1.09; 95% CI, 1.05 to 1.13), by 55% with prasugrel use (HR = 1.55; 95% CI, 1.15 to 2.09), and by 59% with ticagrelor use (HR = 1.59; 95% CI, 1.05 to 2.4; Supplemental Table 6). All of these results remained unchanged in the competing risk models (Supplemental Table 6). At age ≥ 75 years, prasugrel was associated with a greater risk of IC bleed than clopidogrel (age 75: HR = 1.60; 95% CI, 1.01 to 2.54) in the full model (Figure 5) and in the competing risk model (age 75: HR = 1.69; 95% CI, 1.09 to 2.62).

Discussion

Using a large national multiracial cohort of patients with ESKD who were prescribed P2Y12-I therapy, we found annual rates for IC and GI bleeds to be 3% and 6% that worsened with age. Although it is not surprising to find an increased risk of bleeding complications with older age in patients with ESKD prescribed P2Y12-Is, our new findings are related to the age-specific IC risk (1) how it worsens with age for this patient population, and (2) how age modifies the relative risks of P2Y12-I use in specific age groups. Our findings could help clinicians optimize prescriptions for P2Y12-Is for patients with ESKD by using the age-specific risk estimates, understanding the predictors associated with such risks, and realizing relative bleeding risks of P2Y12-Is for different age groups. These results also highlight the need for head-to-head clinical trials for the use of P2Y12-Is in patients with ESKD to determine age-specific risk estimates.
cutoffs where the risk of bleeding outweighs the benefits of thrombosis prevention.

We found that the annual rate of IC bleed in patients with ESKD on P2Y12-I therapy worsened significantly with age (2% in those <55 years and 3% in those $\geq 75$ years). Because patients with ESKD are known to bleed more, it is not surprising to find that the overall annual rate of IC bleed (3%) was much higher than that observed in the post-marketing real-world data of the general population (0.1%) (22) and of those with ESKD with kidney failure alone (approximately 0.8%) (23). The US Food and Drug Administration (FDA) issued a warning for bleeding risk related to prasugrel use in patients with a history of stroke and in individuals aged $\geq 75$ years (24). However, there are no warnings for the use of the other more potent P2Y12-I ticagrelor in this age subgroup, despite concerns raised during the secondary review of the PLATO trial data by the FDA where they found the risk of stroke to be two-and-a-half times higher among participants receiving ticagrelor compared with clopidogrel (25). In this study, we found the presence of previous ischemic stroke and age to be the most important predictors of IC bleed. Furthermore, we found this risk worsened disproportionately with every decade increase in age on treatment with more potent P2Y12-I's (55% or 59%) compared with that noted with clopidogrel (9%). More specifically, there was a 60% increased risk with the use of prasugrel over clopidogrel at age

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**Figure 3.** Predictors of gastrointestinal bleed in ESKD patients on P2Y12 inhibitors. Forest plot representing Cox proportional hazard ratios of selected risk factors associated with time to first gastrointestinal bleed in (A) the entire study cohort and (B) the subgroup with a cardiovascular event (CV) claim over the 6 months before the index dates. Only select covariates from the Cox model are shown in the forest plot.
Putting this all together and knowing that almost two thirds of ESKD patients with IC bleeds die within a median follow-up of 1.2 years, our findings highlight an urgency to conduct randomized trials for the use of more potent P2Y12-Is over clopidogrel in patients with ESKD with a goal to identify subgroups of individuals where safety risks might outweigh the potential benefits of thrombosis prevention (e.g., patients with a history of stroke or individuals ≥75 years).

We also report annual rates of GI bleed of patients with ESKD on P2Y12-I to be 6%, with lower rates (4%) in those <55 years of age and higher rates (9%) in those aged ≥75 years. The overall annual rate of 6% is somewhat similar to that reported in ESKD patients with kidney failure alone (approximately 6%), where data on the use of antiplatelet and anticoagulant drugs were not captured (26). Our annual rates cannot be directly compared with the post hoc randomized clinical trial data that reported a composite outcome of major bleeding rather than GI bleed. In these studies, the proportion of participants with “major bleeding” on P2Y12-Is is 7%–9% in the subgroups of non-dialysis CKD participants with an eGFR, 30 ml/min per 1.73 m² (13–15). However, it may be reasonable to infer that the risk of GI bleed in patients with ESKD on P2Y12-Is may not be too different from patients with CKD who are not on dialysis but are on antiplatelet therapies. In this study, we also found previous history of GI bleed and age to be the most important predictors of future GI bleeds in patients with ESKD on P2Y12-I therapies, where the risk worsened with every decade increase in age on treatment. 

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**Figure 4. Predictors of intracranial bleed in ESKD patients on P2Y12 inhibitors.** Forest plot representing Cox proportional hazard ratios of selected risk factors associated with time to first intracranial bleed in (A) the entire study cohort and (B) the subgroup with a CV claim over the 6 months before the index dates. Only select covariates from the Cox model are shown in the forest plot.

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| Entire cohort | CV claim subgroup |
|---------------|-------------------|
| Age           | Hazard Ratio (95% CI) |
| Male vs. Female | 1.010 (1.005, 1.014) |
| Hemodialysis vs. Peritoneal | 0.810 (0.724, 0.907) |
| History of Diabetes | 0.630 (0.516, 0.769) |
| CHF           | 1.410 (1.202, 1.654) |
| Ischemic stroke | 1.133 (1.003, 1.280) |
|               | 2.740 (2.417, 3.106) |

| Age           | Hazard Ratio (95% CI) |
|---------------|-------------------|
| Male vs. Female | 1.007 (0.998, 1.016) |
| Hemodialysis vs. Peritoneal | 0.843 (0.694, 1.024) |
| History of Diabetes | 0.851 (0.583, 1.244) |
| CHF           | 1.445 (1.097, 1.904) |
| Ischemic stroke | 1.223 (0.971, 1.539) |
|               | 1.854 (1.407, 2.443) |
with prasugrel (28%) and ticagrelor (39%) compared with that noted with clopidogrel (21%). More specifically, the risk of GI bleed increased by 41% at 65 years and by 63% at 75 years with the use of ticagrelor over clopidogrel. Overall, data from other studies on “major bleeds” and our new data on the age-specific event rates for GI bleed in patients with ESKD on P2Y12-Is and the relative risks of P2Y12-I at specific age groups suggest that it may be reasonable to choose a strategy to maximize thrombosis prevention with potent P2Y12-Is for patients with ESKD, 65 years of age and for those with no history of GI bleed.

In addition to the abovementioned findings, we also identified five risk factors ranked from the largest to the smallest hazard ratios that were associated with IC and GI bleeds in patients with ESKD. For IC bleed, the top five risk factors were history of ischemic stroke, age at index prescription, presence of diabetes mellitus, being a woman, and receipt of peritoneal dialysis (over hemodialysis). For GI bleed, the top five risk factors were history of GI bleed, age at index prescription, and history of chronic obstructive airway disease, peripheral vascular disease, or cancer. These risk factors in patients with ESKD are notably different from the risk factors in the general population for those on antiplatelet drugs included in validated bleeding scores, such as CRUSADE, ACUITY, and PRECISE-DAPT (21). The CRUSADE score includes eight variables (women, diabetes mellitus, chronic heart failure, valvular heart disease, heart rate, systolic blood pressure, glomerular filtration rate, and hematocrit), the ACUITY score includes seven variables (women, age, creatinine clearance, hemoglobin, white blood cell count, and previous spontaneous bleeding). Although our analyses using administrative claims data did not include laboratory values, the differences in the risk factors associated with bleeding events in patients with ESKD and the general population may be due to complex hemostatic disorder underlying ESKD (27). Moreover, these findings are also consistent with the poor performance of bleeding scores on oral anticoagulants in patients with ESKD that are otherwise widely used in the general population (10). Further work is required to use the aforementioned clinical characteristics in ESKD patients for risk stratifying them for use of P2Y12-Is (28).

Our study has several limitations, including missing claims data and lack of data on aspirin use, which is widely available over the counter. Second, the inclusion of a group of patients not on P2Y12-Is would have further strengthened the determination of whether age modifies the bleeding risks of this drug class for patients with ESKD; however, to offset this limitation, we analyzed interactions between age and P2Y12-I type in modifying effects on bleeding events. Our results are further strengthened in a competing risk analysis and a stratified analysis by P2Y12-I type where we noted an age effect across the 3 P2Y12-Is
with varying magnitudes by P2Y12-I type (age×P2Y12-I type). Third, this was an exploratory analysis to identify potential risk factors in this patient population, which might inform a risk stratification tool for these patients, but techniques, such as split-sample cross-validation or bootstrapping, to guard against model overfitting were not conducted. Fourth, there were baseline differences between the three groups in the claims of AMI and coronary revascularization captured during the 6-month period before index dates. We had anticipated this issue a priori, given the differences in the FDA-approved clinical indication of the three drugs (23,24). We therefore strengthened our findings by confirming the results in the entire cohort with a similar finding in a subgroup analysis of individuals with presence of these claims before index dates. Finally, the number of patients in the prasugrel and the ticagrelor groups was very small primarily because these drugs were relatively new on the market and were underutilized when data were collected from 2011 through 2015 (6). Future studies with more recent data files from the USRDS registry could be utilized to address this limitation.

In summary, we found annual rates of IC and GI bleeds in patients with ESKD on P2Y12-I therapy to be 3% and 6%, respectively, which worsened with age. More potent P2Y12-I s disproportionately increased the risk of IC bleed with every decade increase in age compared with that noted with clopidogrel—prasugrel was much worse than clopidogrel at age ≥75 years. All three P2Y12-I types only modestly increased the risk of GI bleed with every decade increase in age—ticagrelor was much worse than clopidogrel at age ≥60 years. These results highlight the need for head-to-head clinical trials for use of P2Y12-I s in patients with ESKD to determine age cutoffs where the risk of bleeding outweighs the benefits of thrombosis prevention.

Disclosures
S.S. Hedayati reports honoraria from the American College of Physicians for participation in Nephrology MKSAP and the American Society of Nephrology Post-Graduate Education Program; and an advisory or leadership role for the American Heart Association (study sections), ACP, and the MKSAP Nephrology Committee. B. Martin reports consultancy for eMaxHealth LLC; honoraria from the Institute of Clinical and Economic Review (ICER) as a member of the Midwest Comparative Effectiveness Public Advisory Council; and patents or royalties for Trestle Tree LLC. All remaining authors have nothing to disclose.

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The content is solely the responsibility of the authors and does not necessarily represent the official views of the AHA, ASN, or NIH.

Author Contributions
L. Al-Hindi was responsible for resources; L. Al-Hindi and N. Jain wrote the original draft of the manuscript; J. Dai was responsible for data curation; J. Dai and M.A. Phadnis were responsible for formal analysis; S.S. Hedayati, N. Jain, B.C. Martin, J.L. Mehta, M.A. Phadnis, and T.I. Shireman were responsible for supervision; S.S. Hedayati, N. Jain, B.C. Martin, J.L. Mehta, M.A. Phadnis, R.S. Rasu, and T.I. Shireman reviewed and edited the manuscript; N. Jain was responsible for conceptualization and funding acquisition; N. Jain and R.S. Rasu were responsible for the investigation; N. Jain, B.C. Martin, M.A. Phadnis, R.S. Rasu, and T.I. Shireman were responsible for the methodology; N. Jain and R.S. Rasu were responsible for validation; and R.S. Rasu was responsible for project administration.

Data Sharing Statement
The data cannot be shared as per a data use agreement between USRDS and the researchers.

Supplemental Material
This article contains the following supplemental material online at http://kidney360.asnjournals.org/lookup/suppl/doi:10.34067/KID.0002442021/-/DCSupplemental.

Supplemental Table 1. Methods for identifying baseline characteristics.

Supplemental Table 2. Codes used to define outcomes.

Supplemental Table 3. Baseline characteristics of the cohort stratified by P2Y12-I type.

Supplemental Table 4. Baseline characteristics of the cohort stratified by presence of a claim for acute myocardial infarction or coronary revascularization within the 6-month period before the index dates.

Supplemental Table 5. Multivariable Cox regression models analyzing associations between clinical risk factors and gastrointestinal bleed in the cohort stratified by P2Y12-I.

Supplemental Table 6. Change in hazard ratio of bleeding for every decade increase in age on the basis of type of P2Y12-I.

Supplemental Table 7. Multivariable Cox regression models analyzing associations between clinical risk factors and intracranial bleed in the cohort stratified by P2Y12-I.

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