ORIGINAL RESEARCH

American Heart Association | American Stroke Association

Thienopyridine Use After Coronary Stenting in Low Income Patients Enrolled in Medicare Part D Receiving Maintenance Dialysis

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***Background*—**Coronary stenting in patients on dialysis has increased by nearly 50% over the past decade, despite heightened risks of associated stent thrombosis and bleeding relative to the general population. We examined clopidogrel, prasugrel or ticlopidine use after percutaneous coronary intervention (PCI) with stenting in patients on dialysis. We conducted 3-, 6-, and 12-month landmark analyses to test the hypothesis that thienopyridine discontinuation prior to those time points would be associated with higher risks of death, myocardial infarction, or repeat revascularization, and a lower risk of major bleeding episodes compared with continued thienopyridine use.

***Methods and Results*—**Using the US Renal Data System, we identified 8458 patients on dialysis with Medicare Parts A+B+D undergoing PCI with stenting between July 2007 and December 2010. Ninety-nine percent of all thienopyridine prescriptions were for clopidogrel. At 3 months, 82% of patients who received drug-eluting stents (DES) had evidence of thienopyridine use. These proportions fell to 62% and 40% at 6 and 12 months, respectively. In patients who received a bare-metal stent (BMS), 70%, 34%, and 26% of patients had evidence of thienopyridine use at 3, 6, and 12 months, respectively. In patients who received a DES, there was a suggestion of higher risks of death or myocardial infarction associated with thienopyridine discontinuation in the 3-, 6-, and 12-months landmark analyses, but no higher risk of major bleeding episodes. In patients who received a BMS, there were no differences in death or cardiovascular events, and possibly lower risk of major bleeding with thienopyridine discontinuation in the 3- and 6-month landmark analyses.

***Conclusions*—**The majority of patients on dialysis who undergo PCI discontinue thienopyridines before 1 year regardless of stent type. While not definitive, these data suggest that longer-term thienopyridine use may be of benefit to patients on dialysis who undergo PCI with DES. **(*J Am Heart Assoc*. 2014;3:e001356 doi: 10.1161/JAHA.114.001356)**

Key Words: clopidogrel • end-stage renal disease • epidemiology • percutaneous coronary intervention • revascularization

Coronary heart disease affects 30% to 60% of patients with end-stage renal disease (ESRD)[1–3] on dialysis, and the number of percutaneous coronary interventions (PCI) in these patients has increased by nearly 50% over the past decade.[4] After PCI with stent placement, clinical practice guidelines recommend dual antiplatelet therapy with aspirin and either a thienopyridine (clopidogrel, ticlopidine, or prasugrel) or ticagrelor for at least 1 month and up to 12 months after receipt of bare-metal stents (BMS), and for at least 12 months following insertion of drug-eluting stents (DES) to prevent stent thrombosis, provided that the patient is not at increased risk for bleeding.[5] These guidelines were based on studies conducted in patients without significant kidney disease. Moreover, recent studies in non-ESRD cohorts have yielded conflicting results regarding the relative cardiovascular benefits and risks of bleeding associated with longer versus shorter durations of thienopyridine use, calling into question the optimal duration of thienopyridine use even in the general population.[6–11] Patients on dialysis are less responsive to the antiplatelet effects of clopidogrel[12] relative to patients with normal or near normal kidney function, which may contribute to the higher observed risk of stent thrombosis in the ESRD population.[13] Furthermore, patients on dialysis are at an increased risk of bleeding.[14,15]

Although thienopyridines, and clopidogrel in particular, are among the most commonly prescribed medications in patients on dialysis, both in terms of days supplied and total

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Accompanying Tables S1 through S7 and Figures S1 through S3 are available at http://jaha.ahajournals.org/content/3/5/e001356/suppl/DC1

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cost,[16] relatively little is known about their patterns of use, relative safety, and effectiveness in this population. Therefore, we conducted a national study on thienopyridine use and associated outcomes in patients on maintenance dialysis who were covered by Medicare Parts A, B, and D. We hypothesized that the majority of patients would discontinue thienopyridine use prior to 12 months after PCI with stenting, and that earlier discontinuation would be associated with higher risks of death, myocardial infarction (MI), or repeat revascularization, and a lower risk of major bleeding episodes compared with continued thienopyridine use.

Methods

Study Population

We used data on all fee-for-service claims between January 1, 2007 and December 31, 2011 from Medicare Parts A, B, and D that were reported through the United States Renal Data System (USRDS), the national registry of patients with ESRD.[16] As mandated in the Social Security Amendments of 1972,[17] almost all patients with ESRD qualify for federal health benefits through Medicare, irrespective of age or disability status. We selected all adult patients (≥18 years) who received a stent during PCI (International Classification of Diseases, Ninth Edition [ICD-9] procedure codes 36.00, 36.01, 36.02, 36.05, 36.06, 36.07, 36.09, or 00.66) between July 1, 2007 and December 31, 2010. This design allowed us to restrict the cohort to patients who had not undergone PCI in the prior 6 months and provided for a 6-month look-back window for baseline medication and comorbidity ascertainment in the full cohort (Figure 1). Since we had data through December 31, 2011, we had at least 1 year of follow-up data post-PCI in all patients studied. The hospitalization during which PCI was performed was defined as the index hospitalization.

We included patients with continuous coverage through Medicare Part A and B as primary payer for 6 months prior to the index hospitalization admission date. We further required continuous Medicare Part D coverage with a low-income subsidy for the 6 months prior to the index date in order to ascertain baseline medication use. The low-income subsidy provides full or partial waivers for premiums and copayments to patients based on household income levels, including during the medication coverage gap (ie, the "donut hole"), allowing observation of medication fill patterns without interruption.

We excluded patients undergoing any type of heart surgery during the index hospitalization, including coronary artery bypass grafting, ventricular reconstruction, pericardial, or valvular surgery (identified using ICD-9 procedure codes for 35.xx, 36.xx, 37.31, 37.32, 37.35, 37.4, or 37.5).

Because we were interested in outpatient thienopyridine use after PCI, we excluded patients who died during the index hospitalization. We also excluded patients with an index hospitalization (including any subsequent nursing facility stays) longer than 30 days. We included patients who were on hemodialysis or peritoneal dialysis at the time of their index hospitalization. All analyses were conducted separately by stent type (DES or BMS). Patients who received both DES and BMS were assigned to the DES group, since subsequent thienopyridine use would be driven by the presence of at least 1 DES.

Duration of Thienopyridine Use

Medication use was ascertained from Medicare Part D claims. We included patients with evidence of thienopyridine use within 30 days after discharge from the index hospitalization. Patients who used thienopyridines prior to the index admission were credited with any excess supply by adding these pills to the number of days supplied after index hospitalization discharge. Days spent in a hospital or nursing home were not counted towards the days supplied because these institutions generally provide medications to patients. We defined thienopyridine discontinuation as >30 day gap in drug supply from previous filled prescriptions.[8] When calculating the days from PCI discharge to thienopyridine discontinuation during the first year, we censored at the time of death, end of Medicare Part D coverage, or loss of a low-income subsidy since we would no longer be able to observe their medication fill patterns without interruption.

Landmark Analyses

We performed landmark analyses to evaluate the association of thienopyridine use with outcomes. Landmark analyses estimate time-to-event probabilities in different treatment groups conditional on group membership at a pre-specified point in time (ie, the "landmark" time point),[18] and has been used in several previous studies of thienopyridine use and outcomes.[7,8,10,19] We chose 3 landmark time points: 3, 6, and 12 months after the index hospitalization discharge date, since our available data overlap with the time period when guidelines changed from recommending 3 to 6 months of thienopyridine use after coronary stenting with DES to at least 12 months.[20] To create the landmark cohorts, we included patients who were alive, had continuous Medicare Part A, Part B, and Part D coverage with a low-income subsidy, and who were event-free (ie, not hospitalized for an MI, repeat revascularization or major bleeding episode) from index hospitalization discharge up to the landmark time point (Figures S1 through S3). The primary exposure of interest was

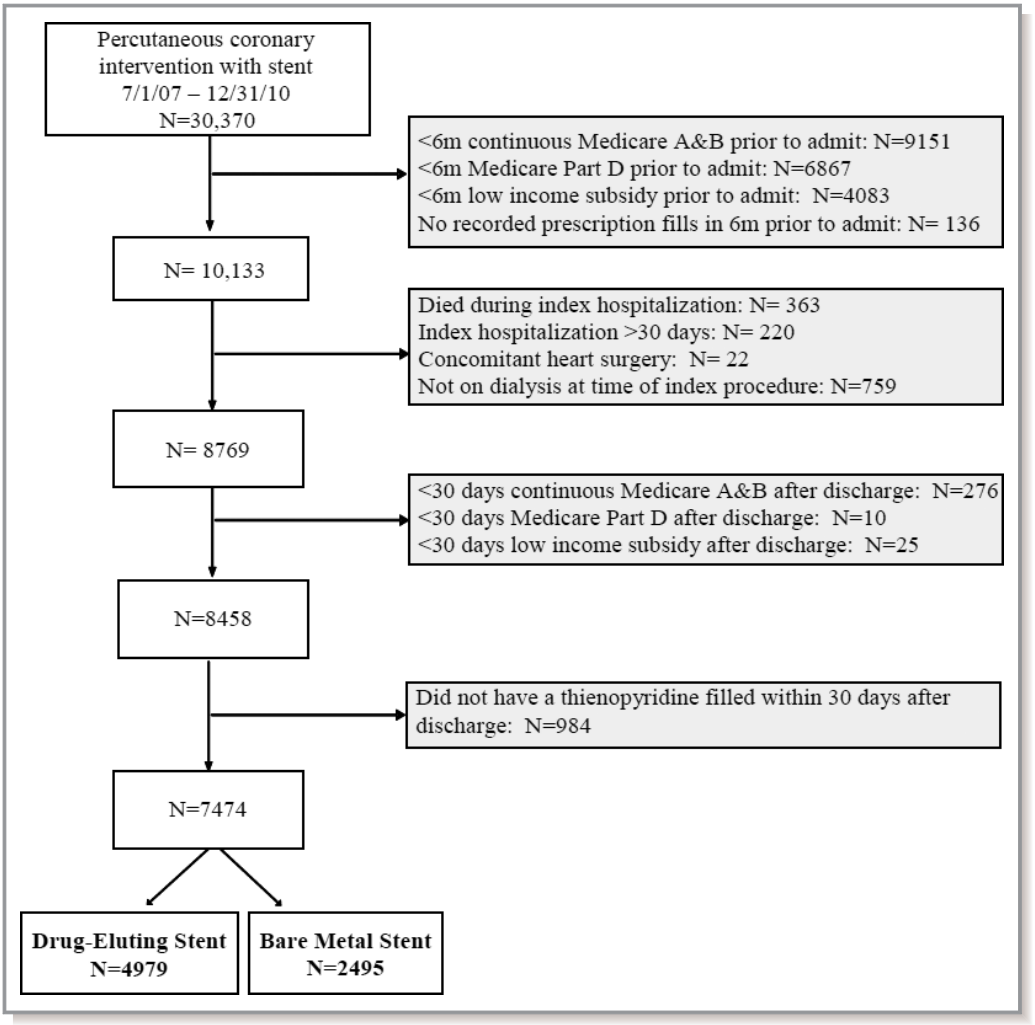


Figure 1. Cohort assembly. Patients in the USRDS with ESRD on dialysis who underwent PCI with stenting and met the inclusion and exclusion criteria. ESRD indicates end-stage renal disease; PCI, percutaneous coronary intervention; USRDS, United States Renal Data System.

whether patients had discontinued or continued thienopyridine use at the landmark time point.

Follow-Up and Outcomes

The primary outcome of interest was death from any cause, ascertained from the USRDS, which ascertains information on patient deaths irrespective of Medicare coverage status. Follow-up for the primary outcome was through December 31, 2011. We also examined 2 composite outcomes: (1) death or MI and (2) death, MI, or repeat revascularization (Table S1). An MI occurring during the index hospitalization was not considered an outcome, since it may have occurred prior to the revascularization. Because ascertainment of MI required hospitalization information, for the composite outcomes, follow-up was censored at the time of loss of Medicare Part A and B coverage.

We also examined major bleeding episodes, defined as a primary or secondary hospital discharge diagnosis of intracranial bleeding, or a primary discharge diagnosis code of bleeding at extra-cranial sites[21,22] (Table S1). We used the same censoring strategy as for the 2 composite outcomes, with the addition of censoring at the time of death.

Covariates

We obtained data on age, sex, race (white, black and other), Hispanic ethnicity, dialysis modality (hemodialysis or peritoneal dialysis), time since first treatment for ESRD, presumed cause of ESRD, and history of failed kidney transplant from the USRDS patient and treatment history files at the index date.

In the full cohort, we defined comorbid conditions using ICD-9 codes and procedure codes from ≥1 inpatient or ≥2

outpatient encounters separated by at least 1 day using all available historical data prior to (but not including) the index date (Table 1),[23] an approach that yields less bias than using fixed observation windows.[24] For each of the landmark cohorts, we ascertained comorbid conditions in an analogous way, using all historical data prior to and including the landmark time point. To adjust for differences in health care utilization,[23] we identified the number of non-nephrology outpatient visits, number of hospitalized days, and nursing home stays in the 6 months prior to the index date. We also categorized patients into 1 of 9 US census regions based on the zip code in which they received ESRD treatment during the index hospitalization.

Baseline use of other cardiovascular medications was ascertained from Medicare Part D claims in the 6 months prior to the index date for the full cohort, and the 6 months prior to the 6- and 12-month landmark time points. For the 3-month landmark cohort, baseline medication use was ascertained from index hospital discharge to the 3-month landmark time point.

Statistical Analysis

Differences in baseline characteristics among patients who continued versus discontinued thienopyridine use were assessed using standardized differences,[25] which are not influenced by sample size.[25,26] A standardized difference of >10% is thought to represent meaningful imbalance between treatment groups.

We used 3 analytic strategies. First, we conducted multivariable (MV)-adjusted proportional hazard regression, including all variables listed in Table 1. Second, we estimated exposure propensity scores[27] for each patient from a multivariable logistic regression model that included all baseline variables listed in Tables S2 through S7 for each of the landmark cohorts. Propensity scores were then used to conduct inverse probability of treatment weighted (IPTW) analyses with stabilized weights.[28,29] Third, we applied a greedy matching algorithm[30] to tightly match 1 patient who discontinued thienopyridines to 1 patient with continued thienopyridines in each of the landmark cohorts (maximum difference in propensity scores between matched pairs=0.1). We estimated hazard ratios (HR) and corresponding 95% confidence intervals (CI) for the outcomes of interest using proportional hazards regression models. Because all baseline variables were well balanced (ie, standardized differences <10%) in the IPTW and propensity-score-matched cohorts (Tables S2 through S7), no further adjustments were made to the models. In the IPTW analyses, we used robust standard errors. We tested the proportionality assumption using Schoenfeld residual plots.

The institutional review board of Stanford University approved the study. All analyses were conducted using SAS Enterprise Guide 4.3 (Cary, NC).

Results

We identified 8458 patients on maintenance dialysis who underwent PCI with stenting and met inclusion and exclusion criteria (Figure 1). Of these patients, 7474 (88%) had evidence of thienopyridine use by having at least 1 filled prescription or excess thienopyridine supply from prior to the index hospitalization within 30 days after discharge and constituted the study cohort. Patients excluded due to lack of evidence of thienopyridine use within 30 days (N=619 for DES, N=365 for BMS) tended to be older and had more comorbid conditions, including valvular disease, stroke or transient ischemic attack, and dementia (data not shown). Sixty-seven percent of the final cohort received a DES, while 33% received a BMS. The mean age of the cohort was 60 years, with high prevalences of diabetes, hypertension, and hyperlipidemia (Table 1).

Thienopyridine Use

Ninety-nine percent of all patients received clopidogrel as the first thienopyridine after hospital discharge; 0.8% received prasugrel and 0.2% received ticlopidine. Most prescriptions were for a 30-day supply of the thienopyridine, regardless of stent type (87% for DES, 86% BMS), with the remainder split evenly between a 90-day and other supply durations. Given our use of a 30-day grace period, all patients had a minimum of 30 days supplied. The median time from index hospitalization to discontinuation was 269 days (interquartile range [IQR] 120 to 507 days) in the DES group and 158 days (IQR 81 to 378 days) in patients receiving BMS (Figure 2). Duration of thienopyridine use did not differ significantly by index year (data not shown).

3-Month Landmark Cohort Analyses

Of the 4979 patients who received a DES, 4049 (81%) were alive and event-free at 3 months after the index hospitalization discharge (Figure S1). Of these patients, 550 (14%) discontinued thienopyridines and we matched 545 of these patients to an equal number of patients who continued thienopyridines (propensity score model *c*-statistic 0.70, Hosmer-Lemeshow *P*=0.1). Of the 2495 patients who received a BMS, 1952 (78%) were alive and event-free at 3 months after the index hospitalization discharge. We matched 469 patients who discontinued thienopyridines to

Table 1. Baseline Characteristics Ascertained 6 Months Prior to Index Date of the Overall Cohort and by Stent Type

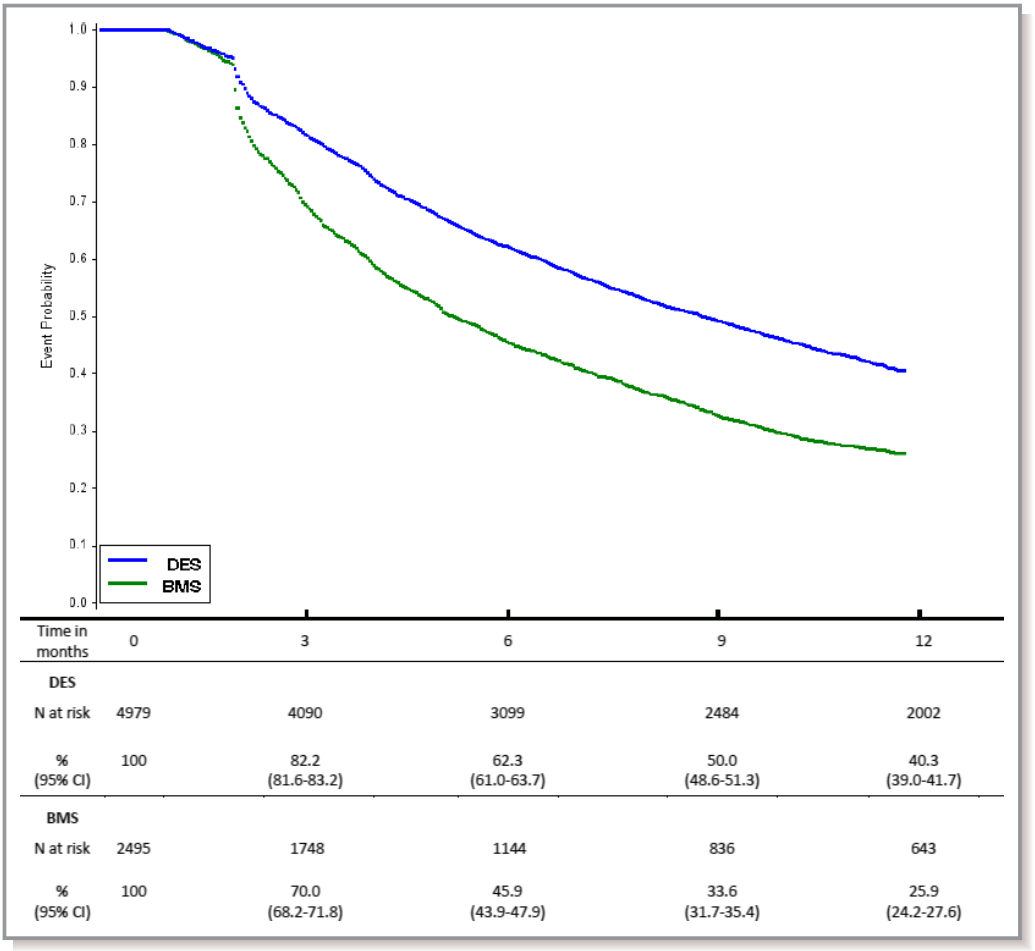
	Overall (N=7474)	DES (N=4979)	BMS (N=2495)
Demographics			
Age, mean (SD), y	60.1 (11.5)	60.1 (11.3)	60.2 (12.0)
Male	50.8	49.4	53.6
Race			
White	55.6	57.0	52.9
Black	36.1	34.5	39.4
Asian	5.7	6.0	5.2
Other/Unknown	2.5	2.6	2.4
Peritoneal dialysis	4.9	5.0	4.8
Time since end-stage renal disease, median (IQR), years	3.4 (1.7 to 5.9)	3.3 (1.7 to 5.7)	3.6 (1.9 to 6.4)
Cause of end-stage renal disease			
Diabetes	62.0	65.4	55.1
Hypertension	23.8	21.8	27.8
Glomerulonephritis	5.7	5.0	7.3
Other/unknown	8.5	7.8	9.9
Non-nephrology outpatient visits, median (IQR)	22 (13 to 33)	22 (13 to 34)	21 (12 to 32)
Hospital days, median (IQR)	3 (1 to 10)	3 (1 to 10)	4 (1 to 11)
Any nursing home stay	6.5	6.3	7.0
On kidney transplant waiting list	17.2	17.2	17.2
Multivessel intervention	19.0	20.9	15.2
Index presentation			
Stable coronary artery disease	62.6	63.6	60.7
ST elevation myocardial infarction	5.6	4.5	7.7
Non-ST elevation myocardial infarction	31.4	31.5	31.2
Unstable angina	0.4	0.4	0.4
Year of revascularization			
2007	15.0	13.4	18.4
2008	29.2	28.6	30.5
2009	28.1	29.4	25.7
2010	27.6	28.7	25.5
Cardiovascular comorbidities			
PCI prior to index	27.9	30.2	23.2
CABG prior to index	24.3	24.7	23.6
Myocardial infarction	30.7	30.3	31.3
Angina	46.6	47.7	44.5
Heart failure	78.0	78.0	78.1
Hypertension	100.0	100.0	100.0
Atrial fibrillation	21.9	21.2	23.3
Other arrhythmia	28.3	27.8	29.2
Stroke/transient ischemic attack	28.6	28.4	29.2
Valvular disease	42.0	40.7	44.7
Peripheral arterial disease	60.3	60.6	59.8
Cerebrovascular disease	28.8	28.9	28.7

Continued

Table 1. Continued

	Overall (N=7474)	DES (N=4979)	BMS (N=2495)
Other comorbid conditions			
Diabetes mellitus	87.3	89.1	83.6
Hyperlipidemia	83.3	84.5	80.8
Gastrointestinal bleeding	32.6	31.5	35.0
Peptic ulcer disease	9.8	9.4	10.7
Intracranial hemorrhage	2.9	2.6	3.4
Liver disease	21.0	20.2	22.7
Chronic lung disease	52.4	51.5	54.2
Smoking history	22.8	20.5	27.3
Dementia	8.5	8.2	9.1
Depression	30.5	30.6	30.4
Cancer	12.2	11.4	13.6
Hypothyroid	19.9	20.2	19.4
Obesity	24.5	24.9	23.7
Baseline medication use			
Thienopyridine	36.1	40.0	28.3
Other antiplatelet agents	3.2	3.1	3.4
Anticoagulants	9.8	9.0	11.5
Non-steroidal anti-inflammatory	9.2	9.3	8.9
Angiotensin converting enzyme inhibitors	41.3	41.4	41.1
Angiotensin II receptor blockers	23.6	24.1	22.6
Beta blockers	74.5	74.9	73.7
Calcium channel blockers	56.7	57.5	55.3
Central alpha receptor blocker	26.4	25.9	27.4
Alpha blocker	5.8	5.6	6.3
Diuretics	23.8	24.9	21.7
Nitrates	32.9	33.4	31.9
Vasodilators	25.0	24.8	25.6
Statins	56.9	58.8	53.2
Other lipid-lowering agents	15.1	16.0	13.2
Proton pump inhibitors	50.6	50.7	50.3
Census region			
Pacific	15.0	16.0	13.1
Mountain	4.6	5.0	3.8
West North Central	5.1	5.0	5.5
East North Central	15.0	14.0	16.9
Mid Atlantic	12.8	13.5	11.6
Northeast	2.6	2.2	3.4
West South Central	16.6	16.6	16.5
East South Central	8.4	8.7	7.8
South Atlantic	19.9	19.2	21.4

All values are % unless otherwise noted. BMS indicates bare metal stent; CABG, coronary artery bypass grafting; DES, drug-eluting stent; IQR, interquartile range; PCI, percutaneous coronary intervention; SD, standard deviation.



Time in months	0	3	6	9	12
DES					
N at risk	4979	4090	3099	2484	2002
% (95% CI)	100	82.2 (81.6-83.2)	62.3 (61.0-63.7)	50.0 (48.6-51.3)	40.3 (39.0-41.7)
BMS					
N at risk	2495	1748	1144	836	643
% (95% CI)	100	70.0 (68.2-71.8)	45.9 (43.9-47.9)	33.6 (31.7-35.4)	25.9 (24.2-27.6)

Figure 2. Days from PCI discharge to thienopyridine discontinuation in the first year. Patients censored at time of loss of Medicare Part D low-income subsidy or death. Discontinuation defined as a period of >30 days without thienopyridine supply. Abbreviations: BMS indicates bare metal stent; DES, drug eluting stent; PCI, percutaneous coronary intervention.

an equal number of patients who continued this medication (propensity score model *c*-statistic 0.65, Hosmer-Lemeshow *P*=0.9). After applying IPTW or propensity score-matching, all baseline variables were well balanced (Tables S2 and S3).

The crude incident rates for death and the composite outcomes of death or MI and death, MI or repeat revascularization were higher for patients who discontinued thienopyridines by 3 months for patients receiving a DES (Table 2). Thienopyridine discontinuation by 3 months was associated with a higher risk of death (HR 1.14, CI 1.01 to 1.29) in the MV-adjusted model, but there was no significant association with either composite outcome or with major bleeding episodes (Figure 3A). For patients receiving a BMS, thienopyridine discontinuation by 3 months was not associated with significantly higher risk of death or cardiovascular events (Table 3, Figure 3B). However, there was a non-significant trend towards lower risk of major bleeding episodes associated with thienopyridine discontinuation (HR 0.77, CI 0.58 to 1.02 in the MV-adjusted model). Results were qualitatively consistent across all 3 analytical methods.

6-Month Landmark Cohort Analyses

For patients who received a DES, 3393 (68%) were alive and event-free at 6 months after the index hospitalization discharge (Figure S2). We matched 939 out of 971 patients who discontinued thienopyridines to an equal number of patients who continued thienopyridines (*c*-statistic 0.68, Hosmer-Lemeshow *P*=0.8). Of the patients who received a BMS, 1555 (62%) were alive and event-free at 6 months after the index hospitalization discharge. We matched 625 out of 698 patients who discontinued thienopyridines prior to this time point to an equal number of patients who continued thienopyridines (propensity score model *c*-statistic 0.65, Hosmer-Lemeshow *P*=0.3). After applying IPTW or propensity score-matching, baseline variables were well balanced (Tables S4 and S5).

Table 2. Crude Event Rates in the 3, 6 and 12-Month Landmark Cohorts, in Patients Receiving Drug-Eluting Stents

	Death			Death or MI			Death, MI or Repeat Revascularization			Major Bleeding Episode		
	N Events	Total p-y	Events/ 100 p-y	N Events	Total p-y	Events/ 100 p-y	N Events	Total p-y	Events/ 100 p-y	N Events	Total p-y	Events/ 100 p-y
3 M full cohort												
Discontinued	345	965	35.8	384	792	48.5	406	733	55.4	82	839	9.8
Continued	1861	6417	29.0	2148	5242	41.0	2354	4718	49.9	484	5632	8.6
3 M matched cohort												
Discontinued	340	957	35.5	379	785	48.3	401	728	55.0	82	831	9.9
Continued	316	978	32.3	361	796	45.4	388	710	54.6	83	864	9.6
6 M full cohort												
Discontinued	527	1615	32.6	603	1329	45.4	643	1229	52.3	125	1408	8.9
Continued	1175	4175	28.1	1353	3510	38.5	1506	3166	47.6	295	3725	7.9
6 M matched cohort												
Discontinued	503	1577	31.9	579	1298	44.6	619	1198	51.7	119	1375	8.7
Continued	500	1621	30.8	568	1358	41.8	621	1218	51.0	127	1428	8.9
12 M full cohort												
Discontinued	514	1513	34.0	577	1270	45.4	620	1191	52.1	114	1335	8.5
Continued	514	1942	26.5	592	1697	34.9	667	1568	42.5	114	1762	6.5
12 M matched cohort												
Discontinued	405	1262	32.1	457	1068	42.8	496	1001	49.6	87	1120	7.8
Continued	384	1290	29.8	426	1129	37.7	476	1046	45.5	81	1164	7.0

M indicates month; MI, myocardial infarction; p-y, person-years.

The crude incidence rates for the combined outcome of death or MI were higher among patients who discontinued thienopyridine in the full cohorts, but more similar in the PS-matched cohorts irrespective of stent type (Tables 2 and 3). Results from our 3 analytical models showed a non-significant trend towards higher risks of death or MI associated with thienopyridine discontinuation in patients receiving a DES (HR 1.06, CI 0.96 to 1.17 in the MV-adjusted model, Figure 3A), and lower risk of major bleeding episodes in patients receiving a BMS (HR 0.80, CI 0.60 to 1.06 in the MV-adjusted model; Figure 3B).

12-Month Landmark Cohort Analyses

For patients who received a DES, 2460 (49%) were alive and event-free at 12 months after the index hospitalization discharge (Figure S3). We matched 908 out of 1101 patients who discontinued thienopyridines to an equal number of patients who continued thienopyridines (*c*-statistic 0.69, Hosmer-Lemeshow *P*=0.8). Of the patients who received a BMS, 1127 (45%) were alive and event-free at 12 months after the index hospitalization discharge. We matched 404 out of 688 patients who discontinued thienopyridines to an equal number of patients who continued thienopyridines (propensity score model *c*-statistic 0.68, Hosmer-Lemeshow *P*=0.9). After applying IPTW or propensity score-matching, baseline variables were well balanced, with the exception of the number of hospital days in the BMS cohort (Tables S6 and S7).

Among patients who received a DES, we again saw a trend towards higher risks of death or MI associated with thienopyridine discontinuation (Table 2, Figure 3A). Among patients who received a BMS, there were no associations with any of the outcomes, including risk of major bleeding episodes (Table 3, Figure 3B).

Discussion

Contemporaneous guidelines developed in patients without advanced kidney disease recommend thienopyridine use for at least 1 year after PCI with DES, and for at least 1 month and up to 12 months after BMS implantation.[5] Using a large national registry of low income patients on maintenance dialysis in the US, we found that patients commonly discontinued thienopyridine use prior to reaching 1 year after PCI, regardless of stent type. By 6 months after PCI, 62% of DES and 46% of BMS patients continued to use

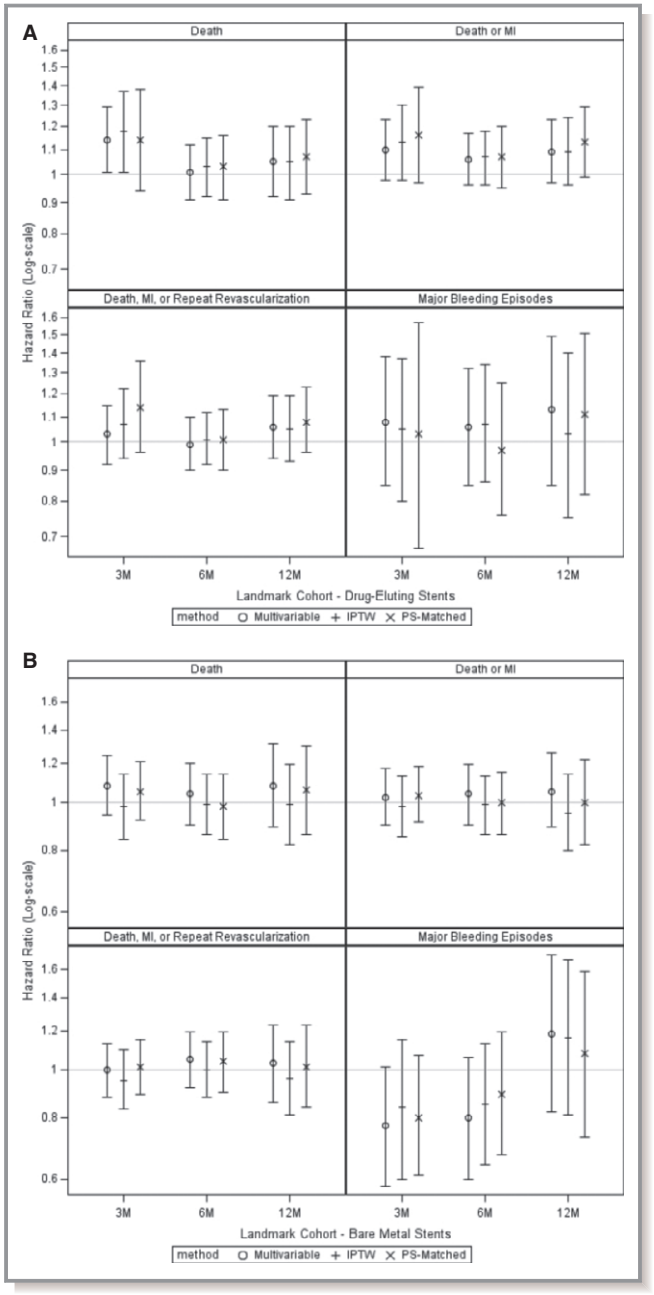


Figure 3. Association of discontinued vs continued thienopyridine use in the 3-, 6-, and 12-month landmark analyses using 3 analytic methods in patients receiving (A) drug-eluting stents and (B) bare metal stents. Abbreviations: multivariable=multivariable adjusted; IPTW indicates inverse probability of treatment weighting; MI, myocardial infarction; PS, propensity score.

thienopyridines, and by 1 year, the respective proportions fell to 40% and 26%. In patients who were event-free at 3 months after PCI with a DES, discontinuation of thienopyridines prior to this time point was associated with a 14% to 18% higher risk of death. We saw a trend towards higher risk of the composite outcome of death or MI after receipt of DES in patients who discontinued thienopyridines in the 3-, 6-, and 12-month landmark time analyses but the results were not statistically significant. In patients who received BMS, we did not see any significant differences in the risk of death or cardiovascular outcomes by thienopyridine use in any of the landmark analyses, but observed a possible lower risk of major bleeding episodes for patients who had discontinued thienopyridines in the 3- and 6-month landmark analyses; however, the results were not statistically significant.

Despite the current guidelines, observational studies and randomized trials in non-ESRD populations have yielded conflicting results regarding duration of thienopyridine use post-PCI, leading to ongoing controversy even in the general coronary artery disease population. In a 12-month landmark analysis of 29 175 patients in the Veterans Administration health care system,[8] continued clopidogrel use was associated with a 30% (CI 18% to 39%) lower risk of death after receipt of a DES, and a 15% (CI 4% to 24%) lower mortality risk after receipt of a BMS compared with clopidogrel discontinuation. However, the Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia Study (PRODIGY) showed no differences in the risk of death, MI, or stroke among patients who had a balanced mixture of DES and BMS randomized to receive 6 versus 24 months of clopidogrel and aspirin.[6] Other studies have shown a benefit from longer duration of thienopyridine use after DES implantation, but not BMS implantation. For example, in a 6-month landmark analysis of 3609 patients undergoing PCI at a single US center, continued clopidogrel use was associated with a significantly lower risk of death (2% versus 5.3%, P=0.03) and death or MI (3.1% versus 7.2%, P=0.02), but only among patients receiving DES; no significant differences were seen in patients who received BMS.[10] In contrast, in a 6-month landmark analysis of 7247 Japanese patients undergoing PCI with DES,[9] continued thienopyridine use was not associated with lower rates of death (3.4% versus 3.4%, P=0.9) or with death or MI (4.1% versus 4.1%, P=0.99). Differences among studies could stem from heterogeneity in demographic or racial/ethnic proportions in the study cohorts, definitions of thienopyridine discontinuation, or peri-procedural therapies used.

Patients on dialysis are at an increased risk of bleeding due to platelet dysfunction, systemic anticoagulation (heparin) use during dialysis, and the dialysis procedure itself.[14,15] Our study was limited by relatively few events and correspondingly wider confidence limits, but we did find a suggestion of a lower risk of major bleeding episodes among patients receiving BMS who discontinued thienopyridines in the 3- and 6-month landmark analyses. No trends in major bleeding episodes were observed among patients receiving DES. Our results are largely consistent with a recent meta-analysis of 21 trials in 4826 patients on hemodialysis, which showed that patients randomized to receive an antiplatelet agent for acute

Table 3. Crude Event Rates in the 3-, 6- and 12-Month Landmark Cohorts, in Patients Receiving Bare-Metal Stents

	Death			Death or MI			Death, MI or Repeat Revascularization			Major Bleeding Episode		
	N Events	Total p-y	Events/ 100 p-y	N Events	Total p-y	Events/ 100 p-y	N Events	Total p-y	Events/ 100 p-y	N Events	Total p-y	Events/ 100 p-y
3 M full cohort												
Discontinued	282	856	32.9	310	687	45.1	331	642	51.6	61	756	8.1
Continued	854	2737	31.2	963	2254	42.7	1034	2039	50.7	252	2387	10.6
3 M matched cohort												
Discontinued	279	854	32.7	307	685	44.8	328	640	51.2	61	754	8.1
Continued	281	852	33.0	322	698	46.1	337	638	52.8	85	732	11.6
6 M full cohort												
Discontinued	371	1233	26.4	411	1020	35.6	444	958	41.1	90	1091	8.0
Continued	455	1515	21.7	516	1294	29.2	548	1210	33.0	137	1340	7.3
6 M matched cohort												
Discontinued	325	1127	28.8	363	924	39.3	394	863	45.7	87	988	8.8
Continued	328	1119	29.3	378	963	39.2	399	908	43.9	98	986	9.9
12 M full cohort												
Discontinued	312	1033	17.2	343	893	22.1	369	857	24.5	90	905	5.9
Continued	195	672	26.6	217	569	35.1	228	540	38.7	54	594	8.6
12 M matched cohort												
Discontinued	178	601	29.6	197	518	38.0	210	497	42.3	53	533	10.0
Continued	179	623	28.7	200	529	37.8	209	502	41.7	51	550	9.3

M indicates month; MI, myocardial infarction; p-y, person-years.

coronary syndromes after undergoing PCI had no significant increased risk of major bleeding (relative risk 0.93, CI 0.58 to 1.49) compared with control.[31] However, only 34% of these patients were in trials including a thienopyridine; the other antiplatelet agents used included aspirin, sulfinpyrazone, or dipyridamole. The latter is known to have very weak antithrombotic effects, prolonging patency of arteriovenous grafts by mitigating intimal hyperplasia at the site of venous anastomosis.[32,33] In contrast, in an observational study of 41 425 hemodialysis patients, clopidogrel use (versus non-use) during the first 90 days of hemodialysis was associated with a 39% (CI 8% to 80%) higher risk of hospitalized bleeding in adjusted analyses.[34] However, the specific indication and duration of clopidogrel use in that study was not defined.

In our study, 12% of patients had no record of any thienopyridine use within 30 days after discharge post-PCI, despite the fact that all patients included in our study had a low-income subsidy, which provides very low or zero medication copayments. While we cannot exclude the possibility that some patients received a thienopyridine without using their pharmacy benefits, this rate of primary non-adherence after PCI is consistent with reports in other high-risk groups with minimal out-of-pocket costs.[35–37] Patients on dialysis are prescribed an average of 12 medications,[38] and the high pill burden is known to contribute to low adherence and poor outcomes in this population. Therefore, strategies other than reducing cost to improve medication adherence are needed.

Certain limitations of our study need to be considered. First, we were only able to reliably ascertain thienopyridine use in patients with Medicare Part D who received a low-income subsidy, who tend to be younger and more often black or Hispanic compared with the general dialysis population.[4] However, 65% of dialysis patients were covered by Medicare Part D during our study time period, with about 75% of hemodialysis and 64% of peritoneal dialysis patients receiving a low-income subsidy,[4] constituting a large proportion of the US dialysis population. We have no a priori reason to believe that the comparative effectiveness of different lengths of thienopyridine use would be modified by socioeconomic status or type of insurance. Second, we relied on outpatient pharmacy claims data as a measure of thienopyridine use. These data do not provide information on the reason for thienopyridine discontinuation, such as patient intolerance, non-adherence, or prescriber decisions. However, claims data provide an objective measure of medication use, unlike patient questionnaires, which may be subject to recall bias.

Further, we did not have information on outpatient aspirin use or inpatient peri-procedural medications such as glycoprotein IIb/IIIa inhibitors or loading doses of thienopyridines, which could have influenced the results. Third, clopidogrel accounted for nearly all the prescribed thienopyridines in our study, so our results may not be applicable to other antiplatelet drugs such as prasugrel and ticagrelor. Fourth, there are differences in the risks of MI, repeat revascularzation, and stent thrombosis among early generation DES (eg, paclitaxel- or sirolimus-eluting stents) and newer generation DES (eg, everolimus or zotarolimus-eluting stents),[39] but we were unable to identify the specific type of DES used with our claims-based data. Finally, although we ascertained an extensive list of comorbid conditions and healthcare utilization variables, the USRDS does not have information on left ventricular ejection fraction, coronary anatomy, bifurcation stenting, functional status, and other potentially important clinical variables. While we attempted to limit confounding further by using 3 complementary statistical methods, no method can fully account for the marginal contribution of unmeasured confounders. In addition, we may have had limited power to detect clinically significant differences, particularly for the relatively rare outcome of major bleeding episodes. A large randomized clinical trial would be required to obtain the least biased estimates of the treatment.

In summary, most patients with ESRD on maintenance dialysis enrolled in Medicare Part D with the low-income subsidy discontinue thienopyridines prior to reaching 1 year after PCI with stenting. In 3-, 6-, and 12-month landmark analyses, we found some evidence to support the use of thienopyridines for 12 months or longer among patients who received a DES, but not among patients who received only BMS. Moreover, there was a suggestion of decreased risk of major bleeding episodes among patients who received BMS and discontinued thienopyridines by 3 or 6 months. While our results cannot definitively determine the optimal length of thienopyridine use in patients on dialysis, they certainly call into question whether recommendations from clinical practice guidelines developed in non-ESRD populations should be applied. Given that we observed rates of death, MI, and repeat revascularization that were 6- to 10-fold higher than in general populations,[8,19] our study underscores the need for further dedicated research in patients with ESRD to provide guidance on treatment strategies for a variety of cardiovascular diseases.

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Disclosures

None.

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