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Clopidogrel Use and Early Outcomes Among Older Patients Receiving a Drug-Eluting Coronary Artery Stent

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Background—Clopidogrel use after drug-eluting stent (DES) coronary artery implantation is essential for the prevention of early in-stent thrombosis, but clopidogrel use among older DES recipients has not been widely studied. We sought to identify characteristics associated with failure to fill a clopidogrel prescription and to examine the relationship between a clopidogrel prescription fill and hospitalization for acute myocardial infarction (AMI) or death.

Methods and Results—This study was a retrospective analysis of administrative data (20% sample) of 15 996 Medicare Part D enrollees who received a DES in 2006 to 2007. We modeled the adjusted probability and odds of clopidogrel prescription fill within 7 and 90 days of discharge and its association with AMI hospitalization or death. Of the study sample, 19.7% did not fill a clopidogrel prescription within 7 days of discharge, falling to 13.3% by day 90. The adjusted probability of filling a clopidogrel prescription within 7 or 90 days of discharge was lower for patients with dementia (20.2% less likely; 95% CI, 10.4%–30.1%), depression (10.7% less likely; 95% CI, 6.9%–14.5%), age >84 years compared to age 65 to 69 years (10.6% less likely; 95% CI, 8.6%–12.7%), black race (6.6% less likely; 95% CI, 4.2%–9.0%), intermediate levels of medication cost share (5.2% less likely; 95% CI, 2.9%–7.6%), and female sex (3.3% less likely; 95% CI, 2.1%–4.5%). It was higher for patients initially hospitalized for an AMI (12.5% more likely; 95% CI, 11.3%–13.6%). Failure to fill a clopidogrel prescription within 7 days of discharge was associated with a higher adjusted odds ratio of death during days 8 to 90 (2.44; 95% CI, 1.76–3.38) but was not associated with an increased risk of hospitalization for AMI.

Conclusions—One in 5 patients failed to fill a prescription for clopidogrel at 7 days after DES placement, and 1 in 7 failed to do so by 3 months. Individual characteristics available at the time of hospital discharge were associated with a clopidogrel prescription fill. Those characteristics most strongly associated with nonadherence, including age >84 years, not having an AMI, depression, and dementia, may guide clinicians and health systems seeking to target this high-risk population and improve health outcomes after percutaneous coronary intervention. (***Circ Cardiovasc Qual Outcomes***. 2012;5:103-112.)

Key Words: stents ■ coronary disease ■ medication adherence

D rug-eluting stents (DES) within the coronary artery are the second most commonly implanted medical devices among older Americans.[1] Unlike most implanted medical devices, the safety of a DES depends on adherence to a potent oral antiplatelet agent such as clopidogrel, a thienopyridine platelet aggregation inhibitor, taken daily for at least 3 to 12 months after stent placement. Premature discontinuation of clopidogrel after DES placement has been associated with a 30-fold increase in the risk of in-stent thrombosis and a 10-fold increase in the risk of death.[2–8] Because older Americans are at high risk for medication nonadherence, use of a DES in this population may carry additional risk.[9]

Almost all prior studies examining very early discontinuation of clopidogrel focus on patients with acute myocardial infarction (AMI). These studies include patients younger on average than most Medicare enrollees.[10–13] The availability of Medicare Part D prescription data now permits an analysis of clopidogrel prescription fill patterns in a national sample of older DES recipients with or without an AMI treated outside clinical trials.

We analyzed a large sample of Medicare Part D beneficiaries receiving a DES during an acute care hospitalization to identify characteristics associated with failure to fill a clopidogrel prescription within 7 and 90 days of discharge. We then examined the relationship between a clopidogrel fill and the health outcomes of hospitalization for AMI or death. We hypothesized that factors known at the time of hospital discharge, such as age, sex, race, income, comorbidities, and prescription cost share, would be associated with a lower likelihood of prescription fill and could identify individuals at risk for nonadherence. Based on previous literature, we also hypothesized that failure to fill a

clopidogrel prescription would be associated with increased risk of cardiovascular events and death.[14]

WHAT IS KNOWN

- Premature discontinuation of clopidogrel after receiving a drug-eluting stent (DES) increases the risk of in-stent thrombosis and death after percutaneous coronary intervention (PCI).
- Prior studies report prescription fill rates between 86% and 88% by 30 days after discharge.
- The Medicare Prescription Drug Benefit was designed to improve access to medications for older Americans, but the current rates for filling a prescription for clopidogrel after DES implantation are unknown.

WHAT THE STUDY ADDS

- Almost 1 in 5 patients treated with DES between 2006 and 2007 did not fill a prescription for clopidogrel within 1 week of hospital discharge, and 1 in 7 had not filled it within 90 days.
- Patient characteristics associated with not filling a prescription for clopidogrel included dementia or depression, age >84 years, black race, female sex, and intermediate levels of medication copay.

Methods

Data

From a 20% sample of Medicare beneficiaries, we used Medicare Denominator and Inpatient Files to create a principal cohort of individuals aged ≥65 years enrolled in fee-for-service Parts A, B, and D; residing in the United States; hospitalized in an acute care facility; and discharged to home between April 1, 2006, and September 30, 2007, with a discharge billing code indicative of receiving a DES (ICD-9 [*International Classification of Diseases, Ninth Edition*] 36.07; diagnosis-related groups 526, 527, 246, and 247). We excluded patients with any managed care enrollment or discontinuous Part D enrollment in the 90 days before or after index hospitalization. Because we sought to assess outpatient prescription fills, we excluded individuals who died or were admitted to an acute or nonacute care facility (eg, nursing home) in the first 7 days after hospital discharge. To account for individuals who did not fill a prescription for clopidogrel because they had been using it before their index hospitalization and, thus, may have had a supply at home, we excluded those who filled a prescription for clopidogrel in the 90 days preceding index admission. A cohort creation flow chart is shown in the Figure.

Prescription Fill Measures and Health Outcomes

We used the Medicare Part D Prescription Drug Event file to create dichotomous variables that indicate whether a patient filled at least 1 prescription for clopidogrel in the first 7 and the first 90 days after the day of discharge from the index hospitalization for DES implantation. Hospital readmission for AMI in the 90 days after the index discharge was determined by identifying acute care admissions with a diagnosis of AMI in the first or second claims position.[15] The online-only Data Supplement Table lists all ICD-9 and diagnosis codes used in the present analysis. Date of death was obtained from the Denominator Files.

Covariates

The analysis also included covariates that we hypothesized could influence filling a clopidogrel prescription. We determined age at time of index admission and race (classified as black or nonblack) from the Denominator File. We followed a modified version of the Iezonni methods to identify up to 13 comorbidities for each patient based on ICD-9 diagnosis codes present on index DES hospitalization discharge claims.[16–18] We similarly identified significant hemorrhage following the methods of Buresly et al,[19] which are defined as follows: intracranial, gastrointestinal, or intraocular hemorrhages; aortic rupture; aortic dissection; hematuria; hemoptysis; epistaxis; or hemorrhage not otherwise specified. From Prescription Drug Event files, we identified prescription fills for warfarin because its use might affect the decision to prescribe clopidogrel. We also identified other medications commonly prescribed after DES to compare fill rates, including β-blockers, statins, and proton pump inhibitors. Residential zip code was used to assign each patient an estimated race-specific, household income and a proportion of the population living in poverty based on 2000 Census data.[20] We ascertained Part D low-income subsidy status through the Denominator Files and categorized it dichotomously. This resource-tested subsidy is offered to enrollees with an annual income <150% of the federal poverty level.[21] Hospitals were categorized as academic medical centers using the American Association of Medical Colleges definition.[22,23] We recorded calendar year of index hospitalization (2006 or 2007) as well because of reported temporal trends in the selection criteria for DES.[24]

Patient prescription expenditures were measured in 2 ways: as a patient payment per pill and as a coinsurance or cost-share rate (patient payment/total prescription cost). Patient payment allows an assessment of the absolute cost paid by an individual for clopidogrel but is unavailable for those individuals who did not fill a prescription. To study the impact of cost exposure for all individuals, we calculated an individual-level, mean coinsurance rate using all of each patient's Part D prescription fills (both clopidogrel and nonclopidogrel medications). This coinsurance rate reflects the patient's comprehensive prescription cost-share experience. For patients with no prescription drug fills (2.0% of the cohort), we followed the methods of Goldman et al[25] in setting coinsurance rates equal to the mean of other cohort members of the same race, race-specific median household income quartile, Part D subsidy status, and state. Cost share was categorized on the basis of natural data breaks as <10%, 10% to 19%, 20% to 40%, and >40%.

Statistical Analysis

Prescription Fill Models Using Restricted Cohort

To assess characteristics associated with a clopidogrel prescription being filled by individuals residing in the community, we created a restricted cohort by excluding from the main cohort patients who died in the 90 days following hospital discharge and those who spent >20% of the first 90 postdischarge days institutionalized (eg, in an acute care facility or a skilled nursing home). We hypothesized that the remaining individuals would have sufficient opportunity to fill prescriptions at an outpatient pharmacy. We assessed clopidogrel fill within 7 and 90 days of index discharge using logistic models with random facility-level effects. To build a model that would be useful to hospital providers, we used only those covariates that would be available at the time of hospital discharge. Because odds ratios do not approximate relative risk for these common outcomes, we used these logistic models to calculate the adjusted probability of fill associated with each variable using the STATA 11.0 Margin (dydx) function (StataCorp). This derivative function provides the adjusted probability associated with each variable, assuming all other variables remain unchanged.[26] Results are also provided in the form of odds ratios in the online-only Data Supplement.

Health Outcomes Models Using Unrestricted Cohort

To determine the association between clopidogrel fill within 7 days of hospital discharge and risk of death, we included all members of the original cohort in logistic models for which the dependent
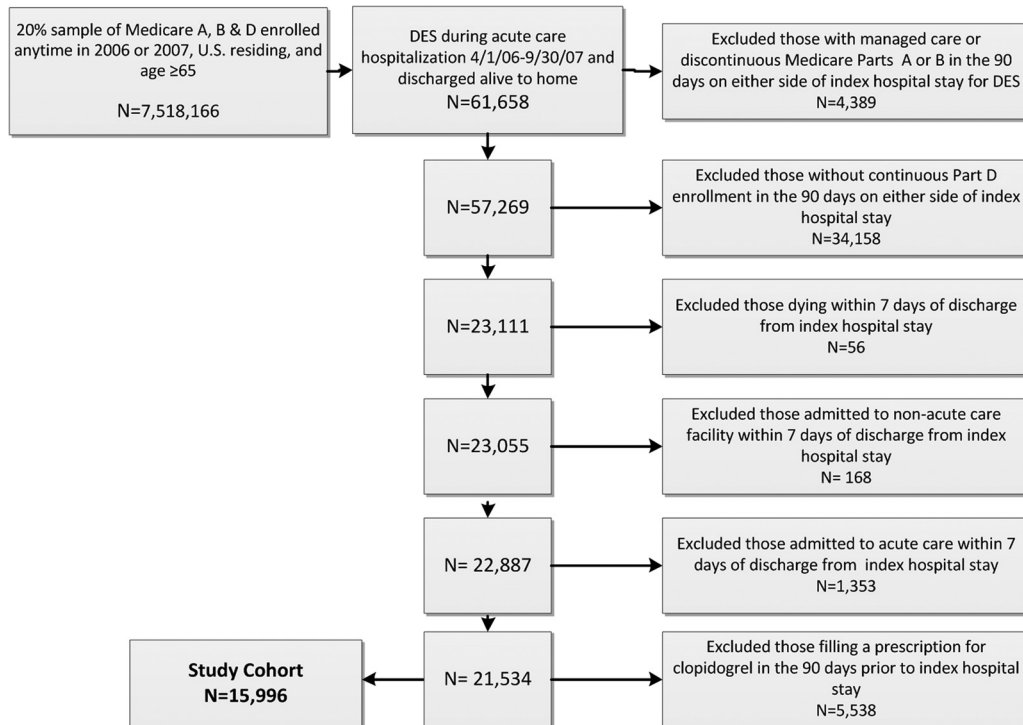
Figure. Cohort creation flow chart.

variables were death, hospitalization for AMI, and a combined end point of death and AMI in days 8 to 90 after the index hospitalization. We used the same covariates as in the prescription fill model, except coinsurance rate was replaced by receipt of the low-income subsidy, which we hypothesized to be a more likely determinant of health outcomes.

All analyses were conducted using SAS version 9.2 (SAS Institute Inc) and STATA 11.0 statistical software. All statistical tests were 2-sided, with significance defined as $P<0.05$. To account for multiple comparisons, we also report $P<0.01$. This study was approved by the institutional review board of Dartmouth College.

Results

Cohort Characteristics
For the principal cohort, we identified 15 996 US-residing patients aged ≥65 years who received a DES during acute hospitalization, were discharged to home alive, did not die, were not admitted to an acute or nonacute care facility in the first 7 days after hospitalization, and did not fill a clopidogrel prescription in the 90 days preceding the index hospitalization (Figure). Table 1 shows the characteristics of the main study cohort stratified by whether the patients filled a prescription for clopidogrel in the first 7 days after discharge from the index hospitalization. Mean cohort age was 74.5 years, 50.2% were women, and 6.9% were black. Only a minority (26.1%) of DES placements occurred during an admission with a primary diagnosis of AMI. Comorbidities were common, with diabetes, chronic pulmonary disease, and congestive heart failure diagnosed in 30.4%, 13.2%, and 16.9% of individuals, respectively. Diagnoses associated with hemorrhage were rare (1.3%).

Cost
The Medicare Part D low-income subsidy was common (33.9%) and had a significant impact on out-of-pocket ex-

pense for clopidogrel (median cost, \$0.98 per pill without the subsidy and \$0.10 per pill with the subsidy) (Table 2). The mean coinsurance or cost-share rate that individuals faced for all their prescriptions was 28.5%.

Prescription Fills
For the restricted cohort of those surviving 90 days after discharge, we identified 15 542 individuals of whom 19.7% did not fill a clopidogrel prescription within 7 days of discharge, falling to 13.3% by day 90 (Table 2). The mean±SD time to prescription fill was 2.8±10.3 days, with a median time of 0 days. This group differed significantly from those who did fill a prescription in terms of race, sex, economic status, and comorbidities (Table 1). They were less likely to see a cardiologist over the subsequent 3 months (54.1% versus 79.0%, $P<0.001$), and there was no difference in primary care follow-up visits.

Table 3 shows the adjusted probability of filling a clopidogrel prescription associated with each covariate. The strongest independent predictors of failing to fill a prescription for clopidogrel at both 7 and 90 days were age >84 years (compared to age 65–69 years), black race (compared to nonblack race), female sex, prescription coinsurance of 10% to 19% (compared to <10%), and diagnosis of depression or dementia. Dementia was the strongest predictor of not filling a clopidogrel prescription after discharge (by 7 days, 22.0% less likely [95% CI, 11.9–32.2]; by 90 days, 20.2% less likely [95% CI, 10.4–30.1]). AMI was the strongest predictor of successfully filling a prescription (by 7 days, 13.2% more likely [95% CI, 11.8–14.6]; by 90 days, 12.5% more likely [95% CI, 11.3–13.6].

Table 1. Cohort Characteristics

	Total	No Clopidogrel Fill in Days 0–7	Any Clopidogrel Fill in Days 0–7	P
No. patients	15 996	3159 (19.7%)	12 837 (80.3%)	
Demographics				
Age, y	74.5±6.5	75.6±7.1	74.2±6.3	<0.001
Female sex	50.2	55.7	48.9	<0.001
Black race	6.9	10.8	6	<0.001
Low-income subsidy	33.9	37.3	33.1	<0.001
Income by zip code, $	41 687±17 644	41 561±18 188	41 718±17 508	0.66
Poverty rate by zip code	10.7	11.3	10.6	<0.001
Mean prescription cost share	28.5	27.8	28.7	0.03
Comorbidities				
AMI, index hospitalization	26.1	14.0	29.1	<0.001
STEMI	10.5	5.3	11.7	<0.001
NSTEMI	15.6	8.6	17.3	<0.001
Unstable angina	37.7	27.3	40.3	<0.001
Depression	3.5	5.2	3.1	<0.001
Heart failure	16.9	17.4	16.7	0.33
Renal disease	7.6	9	7.2	0.0009
Cancer	3.9	4.8	3.7	0.0044
Hemorrhage	1.3	1.2	1.3	0.87
Liver disease	0.3	0.4	0.3	0.32
Diabetes mellitus	30.4	32.3	29.9	0.01
Dementia	0.7	1.7	0.5	<0.001
Peptic ulcer disease	0.7	0.6	0.7	0.42
Cerebrovascular disease	2.8	3.2	2.7	0.12
Pulmonary disease	13.2	13.2	13.2	0.98
Hospitalization				
Year 2007 vs 2006	44.8	44.9	44.8	0.91
Academic medical center	8.4	7.6	8.6	0.06
Length of stay, d	2.8±2.7	2.7±2.5	2.8±2.7	0.54
Follow-up care during days 0–90				
Cardiology outpatient visit	74.1	54.1	79	<0.001
Primary care outpatient visit	74.3	73.1	74.6	0.08
Proton pump inhibitor fill	29	23.3	30.4	<0.001
Statin fill	71.1	43.7	77.8	<0.001
β-blocker	69.2	47.7	74.4	<0.001
Warfarin fill	9.9	11.3	9.5	0.0025
Outcomes during days 8–90				
Acute care days	1.5±6.0	2.4±8.4	1.3±5.3	<0.001
Revascularization	6.2	4.2	6.7	<0.001
PCI	5.9	4	6.4	<0.001
CABG	0.3	NR	NR	0.74
AMI	1.0	1.0	0.9	0.7158
Deaths	1.1	2.2	0.8	<0.001
MI and death	1.9	3.0	1.7	<0.001

Data are presented as mean±SD or %. AMI type and comorbidities are based on diagnoses from index admission. AMI outcomes were based on the diagnosis code for AMI found in any position in the administrative data. Residential zip code was used to assign each patient an estimated race-specific, household income and a proportion of the population living in poverty based on 2000 Census data. Chi-square and *t* tests were used to assess statistical difference across the 2 clopidogrel fill strata/groups.

AMI indicates acute myocardial infarction; CABG, coronary artery bypass graft; MI, myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; NR, not reported due to Centers for Medicare & Medicaid Services restrictions on reporting cell counts <11; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

Table 2. Clopidogrel Prescription Fill Characteristics

Fill Characteristic	Value
Filled in day 0–7	80.3%
Filled in day 0–90	86.7%
Time to fill, d	2.8±10.3
Patient out-of-pocket cost per pill, median	$0.67
Without low-income subsidy, median	$0.98
With low-income subsidy, median	$0.10

Health Outcomes

In the 90 days following index hospitalizations, those who did not fill a prescription for clopidogrel in the 7 days after discharge spent more days hospitalized (2.4 versus 1.3 days, $P<0.001$) and were more likely to die (2.2% versus 0.8%, $P<0.001$) but underwent fewer PCIs (4.0% versus 6.4%, $P<0.001$) than those who filled a prescription (Table 1). Rates of bypass surgery and hospitalization for AMI in the 90 days after index hospitalization did not differ between groups. Failure to fill a clopidogrel prescription in the first 7 days after discharge carried an adjusted odds ratio of 2.44 for death during days 8 to 90 (95% CI, 1.76–3.38) (Table 4).

Sensitivity Analyses

We performed sensitivity analyses to assess the underlying assumptions of our models. We repeated our analysis on a larger cohort that included individuals who had filled a

Table 3. Adjusted Probabilities of a Clopidogrel Prescription Fill in the First 7 and First 90 Days Following Hospitalization With Receipt of a Drug-Eluting Stent in the Coronary Artery

	Clopidogrel Fill Days 0–7 (95% CI)	Clopidogrel Fill Days 0–90 (95% CI)
Age 70–74 y	−0.016 (−0.034 to 0.002)	−0.008 (−0.024 to 0.008)
Age 75–79 y	−0.016 (−0.035 to 0.003)	−0.01 (−0.027 to 0.007)
Age 80–84 y	−0.029 (−0.050 to −0.008)*	−0.024 (−0.043 to −0.006)†
Age >84 y	−0.102 (−0.126 to −0.077)*	−0.106 (−0.127 to −0.086)*
Black race	−0.084 (−0.112 to −0.057)*	−0.066 (−0.090 to −0.042)*
Female sex	−0.032 (−0.046 to −0.019)*	−0.033 (−0.045 to −0.021)*
Income 2nd quartile	0.007 (−0.013 to 0.027)	0.003 (−0.015 to 0.021)
Income 3rd quartile	−0.016 (−0.038 to 0.005)	−0.01 (−0.029 to 0.009)
Income top quartile	−0.011 (−0.035 to 0.012)	−0.012 (−0.033 to 0.009)
Poverty	−0.081 (−0.190 to 0.028)	−0.079 (−0.174 to 0 .016)
Coinsurance 10%–19%	−0.069 (−0.097 to −0.041)*	−0.052 (−0.076 to −0.029)*
Coinsurance 20%–40%	−0.030 (−0.048 to −0.013)*	−0.017 (−0.033 to −0.002)†
Coinsurance >40%	0.002 (−0.016 to 0.020)	0.020 (0.004 to 0.036)†
Stent in 2007 vs 2006	0.002 (−0.011 to 0.015)	−0.004 (−0.016 to 0.007)
Length of stay >median	−0.026 (−0.042 to −0.011)*	−0.031 (−0.045 to −0.017)*
AMI	0.132 (0.118 to 0.146)*	0.125 (0.113 to 0.136)*
Peptic ulcer	0.01 (−0.070 to 0.090)	−0.015 (−0.090 to 0.060)
Liver disease	−0.068 (−0.207 to 0.072)	−0.12 (−0.260 to 0.020)
Cerebrovascular disease	−0.017 (−0.057 to 0.023)	0.002 (−0.031 to 0.035)
Renal disease	−0.036 (−0.063 to −0.008)†	−0.033 (−0.057 to −0.008)*
Congestive heart failure	0 (−0.018 to 0.018)	0.008 (−0.008 to 0.023)
Hemorrhage	−0.005 (−0.066 to 0.055)	0.021 (−0.027 to 0.069)
Depression	−0.090 (−0.129 to −0.050)*	−0.107 (−0.145 to −0.069)*
Diabetes mellitus	−0.015 (−0.029 to −0.000)†	−0.002 (−0.015 to 0.010)
Dementia	−0.220 (−0.322 to −0.119)*	−0.202 (−0.301 to −0.104)*
Pulmonary disease	−0.001 (−0.021 to 0.019)	−0.006 (−0.024 to 0.011)
Cancer	−0.046 (−0.084 to −0.009)†	−0.067 (−0.103 to −0.030)*
Warfarin prescription	−0.024 (−0.047 to −0.001)†	−0.031 (−0.052 to −0.010)*
Academic medical center	0.040 (0.008 to 0.072)†	0.051 (0.019 to 0.083)*

Estimates are the adjusted probabilities obtained using the margin dydx function in STATA 11.0 following logistic regression modeling with random facility-level effects. Age is compared with age 65–69 y. Black race is compared to nonblack. Income is compared to first quartile. Coinsurance is compared to <10%. Residential zip code was used to assign each patient an estimated race-specific, household income and a proportion of the population living in poverty based on 2000 Census data. Coinsurance rate is the mean individual-level coinsurance for all Part D events; reference rate is <10%.

AMI indicates acute myocardial infarction.

*$P<0.01$.

†$P<0.05$.

Table 4.   Adjusted Odds of Death and AMI in the 8 to 90 Days Following Discharge From Hospitalization With Receipt of a Drug-Eluting Stent in the Coronary Artery

	Death Days 8–90	AMI Days 8–90	AMI or Death Days 8–90
No clopidogrel prescription fill within 7 d of discharge	2.44 (1.76–3.38)*	1.16 (0.78–1.74)	1.83 (1.42–2.37)*
Age 70–74 vs 65–70 y	1.17 (0.73–1.86)	1.11 (0.72–1.71)	1.08 (0.78–1.49)
Age 75–79 vs 65–70 y	1.24 (0.77–2.00)	1.07 (0.68–1.70)	1.06 (0.76–1.49)
Age 80–84 vs 65–70 y	1.57 (0.96–2.58)	0.87 (0.50–1.50)	1.07 (0.74–1.56)
Age >84 vs 65–70 y	2.50 (1.47–4.27)*	0.97 (0.50–1.88)	1.63 (1.08–2.45)†
Black race	0.72 (0.39–1.32)	0.82 (0.40–1.68)	0.82 (0.51–1.31)
Female sex	0.85 (0.62–1.18)	1 (0.72–1.40)	0.92 (0.72–1.17)
Income 2nd quartile vs 1st	0.82 (0.52–1.28)	1.33 (0.83–2.14)	1 (0.72–1.39)
Income 3rd quartile vs 1st	0.87 (0.55–1.39)	0.98 (0.58–1.67)	0.85 (0.59–1.22)
Income top quartile vs 1st	0.78 (0.46–1.31)	1.28 (0.73–2.22)	0.98 (0.66–1.44)
Poverty	2.5 (0.27–23.67)	0.45 (0.03–6.42)	1.35 (0.24–7.69)
Low-income subsidy	1.48 (1.06–2.08)	1.84 (1.30–2.60)*	1.55 (1.21–1.98)*
Stent in 2007 vs 2006	0.86 (0.63–1.18)†	1.2 (0.87–1.65)	0.98 (0.78–1.23)
Length of stay >median	1.92 (1.36–2.70)	1.21 (0.84–1.74)	1.56 (1.21–2.01)*
AMI	0.93 (0.65–1.35)	1.84 (1.28–2.63)*	1.38 (1.06–1.79)†
Peptic ulcer disease	0	1.73 (0.42–7.20)	0.94 (0.23–3.88)
Liver disease	1.71 (0.22–13.07)	1.61 (0.22–11.99)	1.76 (0.41–7.50)
Cerebrovascular disease	2.03 (1.01–4.06)†	0.98 (0.36–2.68)	1.6 (0.91–2.84)
Renal disease	2.73 (1.86–4.01)*	2.00 (1.29–3.11)*	2.40 (1.78–3.23)*
Congestive heart failure	1.81 (1.29–2.55)*	1.54 (1.06–2.24)†	1.65 (1.27–2.14)*
Hemorrhage	0.5 (0.12–2.10)	1.13 (0.35–3.62)	0.8 (0.32–1.98)
Depression	0.8 (0.32–1.99)	1.5 (0.73–3.11)	1.09 (0.60–1.97)
Diabetes mellitus	1.13 (0.81–1.58)	1.24 (0.88–1.74)	1.11 (0.87–1.42)
Dementia	1.33 (0.40–4.44)	1.81 (0.43–7.59)	1.66 (0.65–4.20)
Pulmonary disease	2.02 (1.42–2.89)*	1.67 (1.14–2.46)*	1.84 (1.40–2.41)*
Cancer	4.51 (2.85–7.14)*	0.92 (0.37–2.27)	2.78 (1.85–4.17)*
Warfarin prescription	1.31 (0.86–2.00)	1.21 (0.74–1.96)	1.26 (0.90–1.75)
Academic medical center	1.09 (0.64–1.85)	1.26 (0.76–2.11)	1.14 (0.78–1.67)

Data are presented as odds ratio (95% CI). Death and AMI measured in 8 to 90 d after index hospitalization. Odds ratios are from logistic regression modeling with random facility-level effects. Black race is compared to nonblack race. Residential zip code was used to assign each patient an estimated race-specific, household income and a proportion of the population living in poverty based on 2000 Census data. Of the 0.7% with pulmonary artery disease, no one died, so the coefficient in the first column predicts survival with certainty.

AMI indicates acute myocardial infarction.

*$P<0.01$.

†$P<0.05$.

prescription for clopidogrel in the 90 days before index hospitalization. We also used a Poisson regression to model predictors of prescription fills. These approaches attenuated the strength but not the direction of associations. Predictors of prescription fills did not differ significantly. To further investigate the relationship between early prescription fill and AMI, we excluded individuals who died in the first 30 and 90 days after discharge. To investigate survival bias, we repeated the analysis of prescription fills using the unrestricted cohort that included individuals dying within days 8 to 90 after discharge (online-only Data Supplement). We also included covariates for β-blocker, statin, and proton pump inhibitor prescription fills. These alternate analyses produced estimates very similar to the original models.

Discussion

We found that one fifth of individuals in this national cohort of Part D–enrolled, older DES recipients failed to fill the prescription for clopidogrel within 1 week of hospital discharge and that 1 in 7 had not filled a prescription by 90 days. Patients who were black, were aged >80 years, had not had an AMI, or were given a diagnosis of depression or dementia were significantly less likely to fill a prescription for clopidogrel. This is particularly concerning given that failure to fill a prescription was associated with a significant increase in the adjusted risk of death. Overall, these findings suggest that expanded prescription coverage through the Medicare Part D benefit is not, by itself, sufficient to address barriers in effectively delivering clopidogrel to those who need it after PCI.

Medication adherence is an issue of growing concern for those working to improve health system performance and offers a rare opportunity to simultaneously improve health outcomes while reducing costs.[27] Professional societies have recognized the problem of clopidogrel nonadherence in particular with the publication of a joint statement in 2007 recommending broad collaboration among the healthcare industry, insurers, government, and pharmaceutical industry to eliminate barriers to appropriate clopidogrel therapy.[28]

Unfortunately, nonadherence remains both common and difficult to detect.[29] The current results offer one possible approach for stakeholders addressing this issue—identification of those at high risk for medication nonadherence before hospital discharge. Using patient characteristics associated with failure to fill a prescription, providers can identify individuals less likely to receive appropriate clopidogrel therapy after leaving the hospital. This may appeal to hospitals as they seek to improve quality of care at the time of hospital discharge.

For example, patients who had been coded as having dementia during their index hospitalization were 20.5% less likely to fill any prescriptions for clopidogrel over the ensuing 90 days. Inadvertent medication nonadherence has been associated with dementia among elderly patients.[30] Cognitive function among older patients appears inversely related to ability to manage medications,[31] which may explain why depression was also significantly associated with failure to fill a prescription. Hospitals and physicians should consider additional efforts to improve adherence to clopidogrel therapy when a DES is placed in an older individual with depression or dementia.

Another possible explanation for nonadherence to clopidogrel after DES implantation may be found in the design of the low-income subsidy of the Medicare Part D benefit. The low-income subsidy is, by definition, related to a patient's financial resources and determines a patient's coinsurance or cost share. The low-income subsidy had a profound impact on the median cost to the patient of a clopidogrel tablet, lowering it from $0.98 to $0.10 per pill. We found those who paid 10% to 19% of the total cost of all their prescriptions were significantly less likely to fill their clopidogrel prescription than patients who paid 0% to 9% of the cost. This association was not as clear for individuals responsible for larger proportions of their medication costs perhaps because patients become less sensitive to cost as their income rises. This sensitivity to the cost of clopidogrel has been shown previously with elderly Medicare beneficiaries increasing their use of clopidogrel by 11% over a single year after transitioning from no prescription insurance to Medicare Part D coverage.[32] These results suggest that bundling a low-cost-share clopidogrel benefit with DES procedures might improve early delivery of this essential medication and decrease health disparities.

Although we found that black race predicted a lower probability of filling a prescription for clopidogrel, it remains unclear why this is the case. One possibility is that clopidogrel is underprescribed for these patients. According to the CRUSADE (Can Rapid Risk Stratification of Unstable An-gina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines) registry, which tracks individuals with non-ST-segment elevation myocardial infarction, black patients were significantly less likely to receive a prescription for clopidogrel at the time of hospital discharge.[33] It has been suggested that difference between black and nonblack health outcomes after AMI are due to variations in practice patterns that occur at the hospital rather than at the individual level.[34] Racial differences in both prescribing practices and medication adherence after placement of a DES should remain a focus of investigation and quality improvement efforts.

We found that patients who received a DES outside the setting of an AMI were significantly less likely to fill a prescription for clopidogrel by 90 days, an association also found in the use of statin therapy following a recent cardiac event.[35] For patients who do not experience a recent AMI, we cannot determine whether failure to use clopidogrel is due to the patient's own perception of risk or a consistent difference in how health care is delivered during and after hospital discharge.[36,37] The importance of this latter factor is suggested by the finding that patients who failed to fill their clopidogrel prescription were significantly less likely to see a cardiologist in the following 90 days, even though they were no less likely to see a primary care provider. For individuals with AMI, both inpatient care by a cardiologist and predischarge medication counseling have been shown to predict improved medication adherence.[13]

In the present study, we observed a clopidogrel prescription fill rate of 86.7% by 90 days, which is similar to rates reported for other cohorts both in Canada and in the United States. Using a registry of PCI performed in Ontario, Canada, Jackevicius et al[11] reported a clopidogrel prescription fill after stent placement of 64% at time of hospital discharge, 88% within 30 days of discharge, and 91% within 90 days of discharge. Spertus et al,[12] using the PREMIER (Prospective Registry Evaluating Myocardial Infarction: Events And Recovery) multicenter AMI registry, found that 30 days after discharge, 86.4% of patients self-reported clopidogrel use. It is notable that they found not completing high school to be the only independent predictor of premature discontinuation of clopidogrel, possibly because of a lack of statistical power. In a study of 7402 individuals who received a DES through large managed care organizations in California, Colorado, and Minnesota, Ho et al[38] found that 83.7% filled a prescription for clopidogrel on the day of discharge. In a prospective study of Spanish patients, Ferreira-Gonzalez et al[39] found that only 3% of individuals had discontinued clopidogrel by 3 months of follow-up, rising to 14.4% by 12 months.

Taken together, these studies support the present finding of a large and persistent subpopulation that does not receive guideline-recommended antiplatelet therapy following implantation of a coronary artery DES. In the current study, these individuals were significantly less likely to receive their DES during an AMI, visit a cardiologist, or receive repeat revascularization during the following 3 months, even though they were equally likely to follow up with their primary care

provider. In light of this, it is remarkable that they experienced the same risk of hospitalization for AMI as those who did fill a prescription for clopidogrel. One possible explanation is that lack of clopidogrel in this particular subpopulation leads to in-stent restenosis and stable angina more often than in-stent thrombosis and recurrent AMI. Another possibility is that they are less likely to be rehospitalized for AMI because they do not survive to admission. Finally, it is possible that Medicare Part D enrollees who receive stents electively have, overall, less severe coronary artery disease but worse overall health.

Limitations

The present study has limitations common to claims-based analyses. The coding of comorbidities we rely on may reflect regional variation in diagnostic or billing practices rather than actual disease prevalence.[40] Claims data do not reflect severity of each disease. For example, repeat revascularization may represent PCI for stable angina among individuals who are more likely to follow up with and be treated more aggressively by a cardiologist. Alternately, it may represent a group with more severe coronary artery disease that is associated with recurrent and symptomatic obstructive coronary disease. Despite this, previous studies have shown that models built on Medicare claims data capture cardiovascular disease patterns well.[41] The associations we report may be biased by unobserved confounders. For example, sicker patients or patients known to be dying may be less likely to obtain outpatient prescriptions. Furthermore, our analysis excludes those who do not survive 7 days from hospital discharge. These results may not be generalizable outside the population of fee-for-service Medicare Part D beneficiaries.

We relied on prescription fill records as a measure of prescription use. We have no data on prescriptions written and not filled. Fill records may overestimate true adherence to medications. A prescription fill is an essential early step in prescription drug adherence, and in studies of other medications, prescription fill has been shown to correlate with prescription use and clinical outcomes.[42–45] Numerous provider and patient factors have been identified as causes of failure to fill prescriptions.[46]

Strengths

To our knowledge, the present study is the first to assess clopidogrel use among a broad cross-section of older Americans, a group that commonly reports nonadherence to medications.[47] Patients without employer-sponsored prescription insurance and dual eligibility (Medicare and Medicaid) are disproportionately represented in the Medicare Part D program, and although this limits generalizability, the present cohort reflects the general population of seniors enrolled in Part D program in terms of sex, race, and income.[48]

We avoided indication bias, seen when illness severity is associated with the likelihood of receiving the treatment, by restricting our study to a population in which almost every individual should receive the treatment of interest, regardless of illness severity.[49] Restriction of this sort has proven particularly useful when analyzing administrative data, as was recently shown in an analysis of stress testing before PCI.[50]

Disagreement remains regarding the optimal length of therapy with clopidogrel after receiving a DES. Guidelines have moved in the direction of longer therapy, and although at least 12 months is now recommended after PCI with DES, stent package inserts still recommend only 3 to 6 months.[51] The current cohort data are from a time period between the release of the 2005 American Heart Association/American College of Cardiology/Society for Cardiovascular Angiography and Intervention practice guidelines for post-PCI care and the release of the 2007 update. During this period, clopidogrel therapy was recommended for at least 3 months after placement of all DES (3 months for sirolimus-coated stents and 6 months for paclitaxel-coated stents).

Conclusions

A significant portion of older adults enrolled in Medicare Part D fail to fill a prescription for clopidogrel in the 90 days following PCI with DES. This is worrisome in light of the association we and others have found between failure to fill a prescription for clopidogrel and the adjusted risk of death. Individual characteristics available at the time of hospital discharge, including sex, age, race, the diagnoses of dementia or depression, and the absence of AMI, identify patients at highest risk of failing to initiate this essential therapy. Clinicians should identify patients at high risk of nonadherence with clopidogrel. Health systems should develop quality improvement initiatives that target this high-risk population to improve health outcomes following PCI.

Disclosures

None.

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SUPPLEMENTAL MATERIAL

Appendix A. Diagnoses and ICD-9 Codes used to identify index myocardial infarction, comorbidities and procedures

Diagnoses	*ICD-9 Codes*
Myocardial Infarction	ST-segment elevation MI: ICD-9 Dx codes: 410.0-6, 410.8 5th digit 0 or 1 for all Non-ST segment elevation MI: ICD-9 Dx codes 410.71, 410.70, 410.90, 410.91 5th digit 0 or 1 for all
Chronic Renal Disease	ICD-9 Dx and V codes: 585-586, V420, V451, V56.x
Cancer	ICD-9 Dx and V codes: 140-171.9, 174-195.9, 196-199.9, 200-208.9, 273.0-273.3, V1046
Heart Failure	ICD-9 Dx code: 402.01, 402.11, 402.91, 425.0-9, 428.0-428.9, 429.3, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93
Unstable Angina	ICD-9 Dx codes: 411.x, 413.x
Pulmonary Disease	Chronic Non-Asthmatic Lung Disease: ICD-9 Dx code: 415.0, 416.8, 416.9, 491.0, 492.0, 494.0, 496.0 Asthmatic Lung Disease: ICD-9 Dx code 493.xx
Dementia	ICD-9 Dx code: 290.xx, 331.0-331.2
Diabetes and Diabetes with Complications combined	ICD-9 Dx code: 250.xx
Cerebrovascular Disease	ICD-9 Dx code: 362.34, 430-436.9, 437.0, 437.1, 437.9, 781.4, 784.3 997.0

Peptic Ulcer Disease	ICD-9 Dx code: 531- 534
Mild and Moderate Liver Disease	ICD-9 Dx code: 571.2, 571.5, 571.6, 571.8, 571.9, 572.2-572.4, 456.0x-456.29
Depression	ICD-9 Dx codes: 293.83,296.2,296.3, 296.90, 296.99, 298.0, 300.4,301.12,309.0,309.1,311
Cardiac catheterization	ICD-9 procedure codes, 37.22, 37.23, 88.55, 88.56, 88.57, 88.52, 88.53, 88.54
Percutaneous coronary intervention	ICD-9 procedure codes, 36.06, 36.07, 36.09, 00.66
Drug Eluting Stent	ICD-9 36.07, DRG 526, 527, 246, 247
Coronary artery bypass graft	ICD-9 procedure codes 36.10- 36.19

Appendix B. Prescription Fill Sensitivity Analysis Using Unrestricted Cohort:

Adjusted Probabilities of a Clopidogrel Prescription Fill in the First 7 and First 90 Days Following Hospitalization with Receipt of a Drug Eluting Coronary Artery Stent.

	Clopidogrel Fill 0 to 7	95% CI	Clopidogrel Fill 0 to 90	95% CI
Age 70 to 74	-0.017	[-.036,.001]	-0.009	[-.025,.008]
Age 75 to 79	-.019*	[-.038,-.000]	-0.013	[-.029,.004]
Age 80 to 84	-.032**	[-.053,-.011]	-.029**	[-.048,-.011]
Age >84	-.111**	[-.135,-.086]	-.114**	[-.135,-.093]
Black	-.090**	[-.118,-.063]	-.073**	[-.097,-.049]
Female	-.032**	[-.045,-.018]	-.033**	[-.045,-.021]
Income 2nd Quartile	0.007	[-.013,.027]	0.003	[-.015,.020]
Income 3rd Quartile	-0.016	[-.037,.005]	-0.012	[-.031,.007]
Income Top Quartile	-0.009	[-.032,.015]	-0.011	[-.032,.010]
Poverty	-0.078	[-.187,.030]	-0.082	[-.177,.013]
Co-insurance 10%-19%	-.075**	[-.102,-.047]	-.057**	[-.080,-.033]
Co-insurance 20%-40%	-.031**	[-.049,-.013]	-.018*	[-.034,-.002]
Co-insurance > 40%	0	[-.018,.018]	.018*	[.002,.034]
Stent in 2007 vs. 2006	-0.001	[-.014,.012]	-0.007	[-.018,.005]
Length Of Stay > Median	-.029**	[-.044,-.014]	-.033**	[-.047,-.019]
AMI	.139**	[.125,.153]	.131**	[.120,.143]
Peptic Ulcer	0.019	[-.059,.098]	-0.007	[-.080,.067]
Liver Disease	-0.083	[-.217,.052]	-.136*	[-.271,-.000]
Cerebrovascular Disease	-0.019	[-.059,.020]	0.001	[-.032,.034]
Renal Disease	-.037**	[-.063,-.010]	-.032**	[-.055,-.008]
Congestive Heart Failure	0.003	[-.015,.021]	0.009	[-.006,.025]
Hemorrhage	0.001	[-.058,.060]	0.024	[-.024,.072]
Depression	-.094**	[-.134,-.055]	-.113**	[-.151,-.075]
Diabetes Mellitus	-.017*	[-.032,-.003]	-0.005	[-.018,.007]
Dementia	-.211**	[-.306,-.116]	-.201**	[-.293,-.108]
Pulmonary Disease	-0.003	[-.022,.017]	-0.009	[-.026,.009]
Cancer	-.057**	[-.094,-.020]	-.073**	[-.109,-.038]
Warfarin Prescription	-.025*	[-.047,-.002]	-.033**	[-.054,-.013]
Academic Medical Center	.042*	[.010,.074]	.053**	[.021,.085]

* p<0.05, ** p<0.01

Estimates are the adjusted probabilities obtained using the margin dydx function in STATA 11.0, following logistic regression modeling with random facility level effects.

Appendix C. Prescription Fill Analysis Reported as Odds Ratios

Adjusted Odds of a Clopidogrel Prescription Fill in the First 7 and First 90 Days Following Hospitalization with Receipt of a Drug Eluting Coronary Artery Stent

	Clopidogrel Fill 0 to 7	95% CI	Clopidogrel Fill 0 to 90	95% CI
Age 70 to 74	0.9	[0.8,1.01]	0.93	[0.8,1.08]
Age 75 to 79	0.9	[0.8,1.02]	0.91	[0.78,1.07]
Age 80 to 84	0.83**	[0.72,0.95]	0.8**	[0.68,0.95]
Age >84	0.52**	[0.44,0.61]	0.38**	[0.31,0.45]
Black	0.58**	[0.48,0.69]	0.55**	[0.44,0.68]
Female	0.81**	[0.74,0.89]	0.74**	[0.66,0.83]
Income 2nd Quartile	1.04	[0.92,1.19]	1.03	[0.87,1.21]
Income 3rd Quartile	0.9	[0.78,1.03]	0.91	[0.77,1.08]
Income Top Quartile	0.93	[0.79,1.08]	0.9	[0.74,1.09]
Poverty	0.59	[0.29,1.2]	0.48	[0.2,1.16]
Co-insurance 10%-19%	0.64**	[0.53,0.76]	0.62**	[0.5,0.77]
Co-insurance 20%-40%	0.82**	[0.73,0.92]	0.85**	[0.74,0.98]
Co-insurance > 40%	1.01	[0.9,1.14]	1.21**	[1.04,1.4]
Stent in 2007 vs. 2006	1.01	[0.93,1.1]	0.96	[0.87,1.07]
Length Of Stay > Median	0.84**	[0.77,0.93]	0.76**	[0.67,0.85]
AMI	2.72**	[2.41,3.07]	4.61**	[3.88,5.47]
Peptic Ulcer	1.07	[0.62,1.83]	0.87	[0.46,1.65]
Liver Disease	0.67	[0.32,1.42]	0.42*	[0.19,0.96]
Cerebrovascular Disease	0.9	[0.7,1.15]	1.02	[0.75,1.39]

Renal Disease	0.8**	[0.68,0.94]	0.76**	[0.62,0.92]
Congestive Heart Failure	1	[0.89,1.13]	1.08	[0.93,1.25]
Hemorrhage	0.97	[0.66,1.42]	1.23	[0.74,2.05]
Depression	0.6**	[0.49,0.73]	0.45**	[0.36,0.57]
Diabetes Mellitus	0.91*	[0.83,1]	0.98	[0.87,1.1]
Dementia	0.32**	[0.21,0.51]	0.27**	[0.17,0.45]
Pulmonary Disease	0.99	[0.87,1.13]	0.94	[0.81,1.1]
Cancer	0.75**	[0.61,0.94]	0.59**	[0.46,0.76]
Warfarin Prescription	0.86*	[0.75,0.99]	0.77**	[0.65,0.9]
Academic Medical Center	1.3*	[1.05,1.6]	1.6**	[1.19,2.14]

* p<0.05, ** p<0.01