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# Association of Medicare Part D Low-Income Cost Subsidy Program Enrollment with Increased Fill Adherence to Clopidogrel After Coronary Stent Placement

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## Abstract

**Study Objective—**To determine the association between enrollment in the Medicare Part D low-income cost subsidy (LIS) program, which reduces out-of-pocket medication costs, and fill adherence to the antiplatelet drug, clopidogrel, after coronary stent placement.

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**Author Contributions:** Study concept and design (Duru, Ettner, Mangione); Acquisition of data (Mangione); Analysis and interpretation of data (Edgington, Turk, Tseng, Duru, Ettner, Mangione, Kimbro); Preparation of manuscript (Duru, Ettner, Mangione, Edgington, Turk, Tseng, Kimbro)

**Design—**Retrospective cohort study.

**Data Source—**Pharmacy claims database of a large, national Medicare Part D insurer.

**Patients—**A total of 2967 beneficiaries of a national Medicare Part D plan who had a coronary stent placed between April and December 2006 and were prescribed clopidogrel but were not preexisting users of clopidogrel; of these patients, 504 were enrolled in the LIS program and 2463 were not enrolled in the LIS program.

**Measurements and Main Results—**We defined LIS status as being enrolled in the LIS program at any point during the 12 months after the procedure. We examined the association between LIS status and good medication fill adherence to clopidogrel, defined as proportion of days covered ≥ 80%, or discontinuation of clopidogrel over the 12-month window starting from the date of their stent placement. We also identified patients with claims-based diagnoses of major bleeding events while taking clopidogrel. For those patients, we calculated fill adherence only for the period between medication initiation and the onset of major bleeding and/or did not classify them as having inappropriately discontinued the medication. We created a propensity score predicting the propensity of being eligible for the LIS benefit and used inverse propensity score weighting with regression adjustment to generate estimates of the effect parameters. LIS enrollment was associated with a higher predicted likelihood of good clopidogrel fill adherence after stent placement (54.8% for LIS enrollees vs 47.6% for non-enrollees, p=0.008). No significant difference was noted between the two groups in predicted risk of discontinuing clopidogrel after stent placement (18.3% for LIS enrollees vs 21.0% for non-enrollees, p=0.21).

**Conclusion—**The LIS benefit was associated with better clopidogrel fill adherence after stent placement. Although clopidogrel is now available in generic form, our work underscores the need for efforts to identify and enroll patients in the LIS benefit who require costly antiplatelet medications for coronary heart disease.

## Keywords

Prevention; Coronary Heart Disease; Medication Fill Adherence; Medicare Part D

Coronary heart disease (CHD) remains the leading cause of death in the United States, and the combined direct and indirect costs of CHD exceed $100 billion annually.[1, 2] Patients who survive an initial myocardial infarction are at high risk for a successive event, and almost 500,000 Americans have a recurrent myocardial infarction each year.[2] Many patients with CHD require coronary stent placement, and the initiation of dual antiplatelet therapy, such as aspirin and clopidogrel, after coronary stent placement is the standard of care in modern medicine.[3] As with younger patients, the data from older adults indicate a clear benefit of revascularization in clinically appropriate settings.[4,5] Unfortunately, many high-risk patients do not realize the full benefit of antiplatelet agents such as clopidogrel because of inadequate adherence. After coronary stent placement, 10–20% of patients inappropriately stop taking clopidogrel within the first 30 days after the procedure, and rates of nonadherence and/or complete discontinuation at 12 months are even greater.[6–10] The risk of adverse events is particularly alarming for patients with drug-eluting stents who discontinue clopidogrel prematurely. These individuals have at least a 30-fold increased risk

of stent thrombosis over 9 months of follow-up compared with similar patients with good adherence.[11]

Although nonadherence to clopidogrel is multifactorial in etiology, the burden of medication copayments has been consistently reported as an important underlying problem, particularly before the drug was available in generic form.[9, 13–20] This relationship has been observed within low-income cohorts for whom an increase in medication out-of-pocket costs has been linked to decreased use of essential medications, including cardiovascular medications.[21, 22] The Medicare Part D drug benefit includes a low-income cost subsidy (LIS) program designed to reduce medication copayments for beneficiaries with low income and limited assets, and also to eliminate the Part D "coverage gap."[23] Almost 10 million older adults are enrolled in the LIS program,[23] and the program has been linked to better adherence and decreased use of cost-reducing behaviors such as borrowing money or going without necessities.[24,25] The LIS benefit is associated with improved adherence to essential cardiovascular medications after a myocardial infarction[26] and should also result in improved adherence among older adults who have had coronary revascularization with a stent, with or without a previous myocardial infarction.

Using 2006 and 2007 claims data from a large, national Medicare Part D insurer, we investigated whether enrollment in the LIS program was associated with clopidogrel adherence and persistence after coronary stent placement. We hypothesized that enrollment in the LIS program would be associated with a higher likelihood of good fill adherence to clopidogrel. We also hypothesized that LIS-enrolled beneficiaries would be less likely to discontinue clopidogrel prematurely. Our data predate the availability of clopidogrel in generic form, but we believe that examining this research question remains applicable to newer antiplatelet medications that are still only available in branded form (e.g., ticagrelor, prasugrel).

## Methods

### Study Design

In this study, we compared two groups of Medicare Part D beneficiaries who underwent coronary stent placement: those enrolled in the LIS program (exposed group) and those not enrolled in the LIS program (control group). We used a retrospective cohort design, following each individual in both groups forward in time from the date of their stent placement for up to 12 months.

### Data Source and Patient Population

We analyzed 2006 and 2007 national pharmacy claims of Medicare Part D beneficiaries enrolled in Medicare Advantage Prescription Drug (MAPD) plans offered by a large national insurer. We limited the sample to beneficiaries who were aged 65 years or older by January 1, 2006; had a coronary stent placement between April 1, 2006, and December 31, 2006; were not preexisting users of clopidogrel, defined by not having filled this medication over the 3 months prior to the coronary stent placement; and were continuously enrolled in the plan for 12 months after the coronary stent placement.

We classified beneficiaries as being the exposed group if they were enrolled in the LIS program during the month of their stent placement in 2006 or at any point in the following 12 months. Since LIS eligibility is based on the calendar year, beneficiaries enrolled at the time of their stent placement would have been enrolled for all of 2006, provided there was no change in their income or family size. Beneficiaries enrolled at any point in 2007 also retained eligibility for that calendar year and were included in the exposed group. We classified beneficiaries as being in the control group if they were not enrolled in the LIS program at any point in 2006 or 2007. As described below, we conducted a sensitivity analysis limiting the exposed group to beneficiaries who were enrolled in the LIS program for both the 2006 and 2007 calendar years, and dropping those beneficiaries only enrolled in the LIS program in either 2006 or 2007. We identified index events from the *International Classification of Diseases, Ninth Revision* (ICD-9), Current Procedural Terminology (CPT), and Healthcare Common Procedure Coding System (HCPCS) lists. Specifically, we defined coronary stent placement using ICD-9 codes 36.01–36.02, 36.05–36.07, and 36.09, or CPT/HCPCS codes 92980, 92981, G0290, and G0291. For patients with multiple coronary stent placements, we defined the study window based on the first recorded procedure. We included patients with primary nonadherence, defined as having no fills for clopidogrel over the 12 months after stent placement, in the fill adherence analyses. However, we excluded these patients from the analyses examining clopidogrel discontinuation since they never started taking the medication in the first place.

## Key Study Variables

Our two dependent variables were medication fill adherence for clopidogrel and medication discontinuation of clopidogrel. We calculated medication fill adherence using a pharmacy utilization-based measure, the proportion of days covered (PDC).[27] The PDC uses refill data from pharmacy claims to determine the cumulative period for which medication was available to the patient. PDC values range from 0% (completely nonadherent) to 100% (completely adherent). We defined good fill adherence as having a PDC ≥ 80% over an 11-month period after the coronary stent placement. We did not include the initial 30-day window after stent placement in calculating the PDC since patients may have received an initial supply of clopidogrel on discharge that was bundled with the cost of the procedure and possible inpatient stay. We allowed drug supply to carry over from month to month in calculating the PDC, including any medications patients received in the initial 30 days.

We assumed that patients with major bleeding while taking clopidogrel would likely be instructed to discontinue the medication, so the absence of subsequent refills would not necessarily indicate patient nonadherence. Therefore, we right-censored the analyses to exclude the time period after the first recorded date of major bleeding from the adherence calculations. We defined major bleeding as any record of the following ICD-9 codes indicating bleeding: 430–432 (intracerebral); 578.X (gastrointestinal); 719.1X (hemarthrosis); 423.0 (hemopericardium); 599.7 (hematuria); 626,2, 626.6, 626.8, 627.0, 627.1 (vaginal); 786.3 (hemoptysis); 784.7 (epistaxis); or 459.0 (hemorrhage not otherwise specified)[28].

Since medications administered in skilled nursing facilities and inpatient hospitals are not covered by Medicare Part D, we subtracted the number of days that beneficiaries were admitted in either of these facilities from the denominator used to calculate clopidogrel fill adherence. We did not include fills for any other antiplatelet agents in our measure of adherence to clopidogrel. We defined persistence with clopidogrel as a 90-day gap between the estimated date of running out of medication (calculated from the date and days' supply of the last clopidogrel refill) and the date exactly 12 months after coronary stent placement. Beneficiaries who had greater than a 90-day gap without any evidence of major bleeding as defined above were classified as nonpersistent and were considered to have discontinued clopidogrel prematurely.

Our primary predictor was enrollment in the Medicare Part D LIS program, which has been ongoing since 2006 with the same income inclusions relative to the federal poverty level. The LIS program automatically enrolls beneficiaries with incomes at or below 135% of the federal poverty level or who qualify for Medicaid, including those in long-term care nursing facilities, as well as patients who receive some assistance from Medicare cost-sharing programs for other low-income individuals (e.g., Specified Low-Income Medicare Beneficiary program). The LIS program is also open to voluntary enrollment for non–Medicaid-eligible beneficiaries with incomes < 150% of the federal poverty level who also meet prespecified asset thresholds. We were not able to differentiate among LIS beneficiaries based on eligibility criteria and combined them into a single group.

The LIS program discounts the costs of medications in two ways, by reducing copayments and by eliminating the standard Part D coverage gap; these benefits are mandated by Medicare and must be provided by all Medicare Part D insurers to their LIS beneficiaries. Copayments for LIS enrollees who were Medicaid eligible or had incomes < 135% of the federal poverty level in 2006 ranged from $1.00–2.15 for generic medications and $3.00–5.35 for tier 1 brand name medications. LIS enrollees with incomes between 135% and 150% of the federal poverty level were responsible for 15% of their total medication costs until they reached a threshold at which the LIS copayments were applied. All LIS enrollees are exempted from the Medicare Part D coverage gap (i.e., their medication subsidies were year round). In contrast, Part D beneficiaries in our dataset who were not enrolled in the LIS program had benefit designs that varied in terms of medication generosity. The most frequent benefit design for non-LIS enrollees in 2006 included copayments of $7.50 for generic medications and $15 for tier 1 brand-name medications. All non-LIS enrollees were responsible for 100% of their medication costs after entering the coverage gap.

## Propensity Score Estimation

We used a combination of individual-level variables to calculate a propensity score predicting the propensity of patients to be eligible for the LIS benefit by using Stata software, version 13.[29] These variables were drawn directly from the enrollment and claims files, and included age measured as a continuous variable, sex, each of 16 comorbidities (hypertension, coronary artery disease, congestive heart failure, dementia, schizophrenia, mental health condition other than schizophrenia, osteoarthritis, rheumatoid arthritis, non-skin cancer, chronic obstructive pulmonary disease, atrial fibrillation/arrhythmia, end-stage

renal disease, cerebrovascular accident, peripheral arterial disease, diabetes mellitus, hyperlipidemia), and an indicator for whether the last refill was for a 90-day supply.

### Statistical Analysis

The two main study outcomes were good clopidogrel fill adherence (PDC ≥ 80%) and early discontinuation of clopidogrel. We calculated Average Treatment Effects using inverse-probability–weighted regression adjustment, a "doubly robust" approach implemented using the teffects command in Stata 13.[30] Using inverse probability weights obtained from the propensity score model, we fit weighted regression models separately for each treatment level and then predicted adherence or discontinuation for the entire sample. This resulted in treatment-specific outcome predictions for each individual. The average treatment effect is the difference of the average prediction from the LIS treatment model minus the average prediction from the non-LIS treatment model. We used $p<0.05$ as a significance test for all comparisons.

We evaluated several sensitivity analyses to evaluate the robustness of our findings with changes in the definitions of key study variables. We conducted two key sensitivity analyses to assess the potential impact of clinical variation on our findings, including limiting the sample to patients with ICD-9 codes that were specific for drug-eluting stents (78% of all stents in the sample). We also increased the threshold for good fill adherence to a PDC of 90%, given the potential devastating consequences for CAD patients of even limited nonadherence to antiplatelet therapy, and we report the results of both analyses.

We conducted additional sensitivity analyses related to LIS exposure and the timing of medication fills. We limited the LIS-enrolled group to beneficiaries with claims reflecting LIS enrollment in both 2006 and 2007, comparing them to the subsample that were never enrolled in the LIS program during either year. We also included in the regressions an indicator if the last medication refill was for a 90-day supply and occurred more than 30 days prior to the end of the study window. We included this indicator to adjust for the possibility that beneficiaries with "terminal" 90-day refills may have falsely elevated fill adherence compared with beneficiaries who received 30-day refills, if part of the 90-day supply was discarded and not actually consumed. Finally, we also included beneficiaries who were noncontinuously enrolled and who were known to have died during the study window, and included them as nonadherent after their last recorded refill. Each of these sensitivity analyses yielded findings consistent with the main analyses, so we report only the sensitivity analyses described in the previous two paragraphs.

## Results

A total of 2967 beneficiaries were enrolled in the study: 504 LIS enrollees and 2463 non-LIS enrollees (Table 1). Descriptive characteristics of the two comparison groups were more balanced after propensity score weighting, and no statistically significant differences were observed. Overall, 18% of patients had a major bleeding event within 12 months after stent placement. In the adjusted analyses, LIS enrollees were more likely to have good fill adherence (> 80% PDC) to clopidogrel over the 12 months after coronary stent placement compared to beneficiaries not enrolled in the LIS program (54.8% vs. 47.6%, p=0.008

[Table 2]). We observed findings of similar magnitude when the fill adherence threshold was set at 90% PDC (42.2% vs. 35.3%, p=0.006) and for the subset of patients with drug-eluting stents (59.1% vs. 51.7%, p=0.022). However, we found no significant difference in the likelihood of premature clopidogrel discontinuation among non-LIS enrollees compared to LIS enrollees (21.0% vs. 18.3%, p=0.21).

## Discussion

These analyses found that Medicare Part D beneficiaries receiving the LIS were more likely to have good adherence to clopidogrel after coronary stent placement compared with those not receiving the LIS. This was also true for the subgroup who received a drug-eluting stent. However, there was no difference between the groups in the likelihood of discontinuing clopidogrel altogether, suggesting that LIS status is not associated with this critical risk behavior that greatly increases the risk of stent thrombosis. Although clopidogrel is now available in generic form, these results are relevant when considering adherence to newer brand-name antiplatelet agents such as prasugrel and ticagrelor. Based on findings from large epidemiologic studies and clinical trials, this improvement in adherence we observe among Medicare beneficiaries enrolled in the LIS program should be associated with fewer cardiovascular events.[31,32]

For example, analysis of the Patterns of Non-Adherence to Anti-Platelet Regimens in Stented Patients (PARIS) registry found that 14% of patients had a “disruption” of therapy, including for as little as < 7 days. Compared to adherent patients, the patients with disrupted therapy had a 3.2–percentage point increase in any major cardiovascular event (composite of cardiac death, definite or probable stent thrombosis, myocardial infarction, or revascularization)[33]. Although our definitions for patient inclusion criteria and study variables differ, extrapolation from these numbers suggests that an approximate excess burden up to 0.23% of cardiovascular events (or 2.3 events/1000 patients) might be linked to differences in fill adherence associated with LIS benefit status.

Our findings are consistent with another recently published study examining the association with the LIS benefit and adherence to cardiovascular medications. This study found that Medicare beneficiaries with CHD enrolled in the LIS program were more likely to have good overall adherence to a group of medications, including angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, and beta-blockers, compared to patients not enrolled in the LIS program.[34] However, this study included all patients with prevalent CHD, rather than examining adherence in the critical post-revascularization procedure period.

A recently published randomized clinical trial found that providing free medications after myocardial infarction improved medication adherence and decreased the rates of major vascular events, although no significant change was seen in revascularization rates.[35] This type of value-based design, in which copayments for key evidence-based medications are reduced or eliminated, has been shown to improve adherence and other health outcomes in different settings.[36] Patients who successfully enroll in LIS will benefit from lower out-of-pocket costs, including a copayment reduction as well as an exemption from the Medicare

coverage gap. The Center for Medicare and Medicaid Services estimates that as of 2010, more than 1.5 million beneficiaries are eligible for the LIS subsidy based on their income and assets but have not applied.[22] Aggressive outreach efforts are underway to identify and enroll these eligible beneficiaries, including routinized screening of all patients in the Connecticut and New Jersey state pharmaceutical assistance programs.[37] However, such efforts will only reach a minority of low-income, eligible Part D patients with chronic conditions such as CHD.

One reason that eligible Medicare beneficiaries may not enroll in the LIS program is the complexity of the enrollment process. Only 30% of Medicare beneficiaries who are eligible for the LIS program, but are not automatically enrolled, have signed up.[23] Half of eligible beneficiaries are enrolled in Part D but are in unsubsidized plans with higher cost sharing.[23] A survey of patients with incomes < 150% of the federal poverty level found that LIS enrollment is particularly low among patients with less than a high school education and that lack of understanding about the program is an important barrier to enrollment.[38] A separate study produced similar findings, showing that among older adults, cognitive impairment and lower health numeracy are linked to lower rates of LIS enrollment.[39] Another reason why some eligible patients may not enroll is that they are taking relatively few prescription medications and do not expect to save money with medication subsidies.[38] However, low-income Medicare beneficiaries with relatively high copayments who are prescribed multiple medications for CHD upon discharge, including antiplatelet medications, a statin, a beta-blocker, and, potentially, an ACE inhibitor and an aldosterone antagonist, will likely benefit from LIS enrollment.

The use of critical pathways and toolkits has proven very successful in ensuring that the appropriate evidence-based medications are started in all eligible patients after myocardial infarction while hospitalized.[40] Many of these standardized protocols also include patient education prior to discharge and incorporate a multidisciplinary team, including nurses and pharmacists. However, these protocols do not routinely address financial barriers to medication adherence. The interaction with the health care system after a myocardial infarction or for a cardiac revascularization procedure may represent an ideal opportunity to screen Medicare patients to identify a subset that may be eligible for the LIS program, and help them with applying to the program in order to decrease their medication out-of-pocket costs. As many patients are likely to have difficulty applying on their own, the index hospitalization and immediate outpatient follow-up period may represent an important window to provide assistance with the process. Patients can apply online or over the telephone and in most cases are not required to submit proof of income or resources since the Social Security Administration verifies patient-reported estimates against government records.[41] We believe that pilot studies evaluating this type of practical approach are indicated as a potential adjunct to improve the quality of comprehensive care and secondary prevention for older patients of low socioeconomic status who have coronary heart disease.

Our study has several limitations. We were unable to differentiate between LIS enrollees who were automatically enrolled and those who applied voluntarily, so we were unable to report on the association of specific copayment levels and LIS status with medication adherence. We could not determine the physician intent for specific duration of therapy with

clopidogrel. Although guidelines for the duration of antiplatelet therapy after coronary stent placement have not changed significantly over the last 10 years, the data we analyzed for this study are several years old and may not reflect other recent changes in clinical practice and patient management. Finally, as with many studies using administrative claims data, we were not able to include such variables as prescribing physician specialty, use of tobacco or alcohol, race/ethnicity, or level of education in our propensity score. The absence of potential confounders increases the possibility of omitted variable bias, and future studies that can include these variables will be better able to demonstrate causal inference.

## Conclusion

For patients with a chronic disease such as CHD, maintaining good adherence to an evidence-based medication regimen is critical to optimize self-care and decrease the risk of bad outcomes. Improving adherence among these patients is a public health priority, and addressing system-level barriers to adherence is an important direction of research and practice. Our findings indicate that the medication subsidies provided by the Medicare LIS program are associated with increased fill adherence to clopidogrel. Although clopidogrel is now available in generic form, other brand-name antiplatelet medications are now available, such as prasugrel and ticagrelor, for which good adherence after coronary stent placement is critical. The results of this study therefore suggest the need for ongoing research and creative interventions to increase LIS uptake among patients with coronary heart disease who are financially eligible for the subsidy program but are not currently enrolled.

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## Table 1

Characteristics of Patients with a Coronary Stent by Low-Income Cost Subsidy Status, Before and After Inverse Propensity Score Weighting

| | Inverse Propensity Score Unweighted | | Inverse Propensity Score Weighted | |
|---|---|---|---|---|
| **Characteristic** | **LIS Enrollees (n=504)** | **Not Enrolled in LIS (n=2463)** | **LIS Enrollees (n=504)** | **Not Enrolled in LIS (n=2463)** |
| Age (yrs), mean ± SD | 73.8 ± 5.8 | 74.4 ± 5.9 | 74.4 ± 5.8 | 74.3 ± 5.9 |
| Female sex | 61% | 37% | 42% | 41% |
| Comorbidities | | | | |
| Hypertension | 84% | 75% | 76% | 77% |
| Coronary artery disease | 90% | 86% | 85% | 86% |
| Mental health condition (not schizophrenia) | 13% | 8% | 9% | 9% |
| Dementia | 4% | 3% | 3% | 3% |
| Osteoarthritis | 23% | 17% | 18% | 18% |
| Rheumatoid arthritis | 2% | 2% | 2% | 2% |
| Cancer (not skin cancer) | 17% | 20% | 19% | 19% |
| Chronic obstructive pulmonary disease | 35% | 19% | 22% | 22% |
| Congestive heart failure | 32% | 22% | 25% | 24% |
| Atrial fibrillation/arrhythmia | 37% | 33% | 33% | 34% |
| End-stage renal disease | 7% | 4% | 5% | 5% |
| Cerebrovascular accident | 22% | 17% | 18% | 17% |
| Peripheral arterial disease | 28% | 18% | 20% | 20% |
| Diabetes mellitus | 45% | 29% | 33% | 32% |
| Hyperlipidemia | 72% | 69% | 68% | 70% |
| Schizophrenia | 2% | 1% | 1% | 1% |
| Last index fill was a 90-day supply | 11% | 18% | 16% | 17% |

LIS = low-income cost subsidy

## Table 2

Adjusted Predicted Probabilities of Good Clopidogrel Fill Adherence and Early Discontinuation of Clopidogrel by Low-Income Cost Subsidy Status, After Inverse Probability Weighting Estimation[a]

| Variable | Predicted Percentage Among LIS Enrollees | Predicted Percentage Among Non-LIS Enrollees | Average Treatment Effect (95% CI) | p Value |
|---|---|---|---|---|
| Fill adherence to clopidogrel (PDC > 80%) for the 12 months after coronary stent placement (n=2967) | 54.8% | 47.6% | 7.2% (1.9–12.5%) | 0.008 |
| Fill adherence to clopidogrel (PDC > 90%) for the 12 months after coronary stent placement (n=2967) | 42.2% | 35.3% | 6.9% (2.0–11.8%) | 0.006 |
| Patients with drug-eluting stents: fill adherence to clopidogrel (PDC > 80%) for the 12 months after coronary stent placement (n=2174) | 59.1% | 51.7% | 7.4% (1.1–13.6%) | 0.022 |
| Early discontinuation of clopidogrel after coronary stent placement (n=2550) | 18.3% | 21.0% | −2.7% (−6.8–1.5%) | 0.21 |

LIS = low-income cost subsidy; CI = confidence interval; PDC = proportion of days covered.

[a] Adjusted for age, sex, 16 separate comorbidities, and whether the last index medication fill was for a 30-day or 90-day supply.