ORIGINAL RESEARCH

Impact of Cost Sharing on Therapeutic Substitution: The Story of Statins in 2006

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***Background*—**Cost sharing is widely used to encourage therapeutic substitution. This study aimed to examine the impact of increases in patient cost-sharing differentials for brand name and generic drugs on statin utilization on entry into the Medicare Part D coverage gap.

***Method and Results*—**Using 5% Medicare Chronic Condition Warehouse files from 2006, this quasi-experimental study examined patients with hyperlipidemia who filled prescriptions for atorvastatin or rosuvastatin between January and March 2006. Propensity score matching and difference-in-difference regressions were used to compare changes in statin utilization for the study group (patients who were not eligible for low-income subsidies [non–LIS] and had generic-only gap coverage) to those of a control group (LIS patients who faced the same cost sharing before and during the Part D coverage gap). In the final sample, 801 patients in the study group were matched to 801 patients in the control group. We found that, compared to the control group, the study group had a larger decline in any monthly brand-name statin use (−0.24 30-day fills, $P<0.001$). This was only partially offset by increased monthly generic statin use (+0.06 30-day fill, $P<0.001$), with an overall drop in any monthly statin use (−0.18 30-day fills, $P<0.001$). Overall adherence with statins declined (OR 0.81, $P<0.001$), and statin discontinuation increased (OR 1.62, $P<0.001$) in the study group as compared to the control group.

***Conclusions*—**Increases in cost-sharing differentials for brand name and generic drugs on coverage gap entry were associated with discontinuation of statins in Medicare Part D patients with hyperlipidemia. **(*J Am Heart Assoc*. 2016;5:e003377 doi: 10.1161/JAHA.116.003377)**

Key Words: cost • Medicare • medication adherence • medication discontinuance • statin • therapeutic substitution

To control increasing drug spending, insurers have tried to encourage and incentivize substitution of generic drugs, which are relatively less expensive, for proprietary products. Substitution can occur through generic substitution (switching from a brand name drug to the generic version of the same drug) or through therapeutic substitution (switching from a brand name drug to the generic version of an alternative drug in the same drug class).[1-3] In 2013, generic drugs accounted for ~86% of dispensed prescriptions in the United States.[4] This likely reflects the fact that achieving high levels of generic substitution has generally been straightforward for most payers (eg, generic substitution by pharmacies is mandated in many states).[5,6]

Therapeutic substitution has been less common for a variety of reasons, including physicians' reluctance to prescribe and/or patients' reluctance to take generic medications that are not identical to the desired brand-name drugs.[2] In order to encourage therapeutic substitution, employers, payers, and policymakers have widely used cost-sharing structures.[1-3] Insurers have often used tiered formularies, which usually require higher cost sharing and more restrictions for higher-cost drugs (placed on higher tiers) and lower cost sharing for alternative cheaper drugs (placed on lower tiers).[7] A large number of studies have examined the relationship between cost-sharing differentials (tiers) and medication utilization; however, the findings have been mixed.[8-14] For example, some studies showed an increase in generic drug use as a result of higher brand versus generic cost-sharing differentials,[9,10] whereas others did not.[11-13] Potential reasons for these inconsistent findings are that studies examined different drug classes and different therapeutic substitution scenarios and/or used

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different study designs, some of which may be less suitable for a rigorous assessment of the impact of therapeutic substitution.

We sought to gain additional insight into issues surrounding cost-sharing policies and therapeutic substitution by examining a unique period in the history of Medicare. The Medicare outpatient prescription benefit (Part D) was implemented on January 1, 2006 to increase access to prescription drugs. At that time, standard Part D plans for patients who did not qualify for any low-income subsidies involved variable cost sharing over the course of the year based on total drug spending. Beneficiaries were responsible for the first $250 of drug costs per year, paid 25% of drug costs in excess of $250 and up to $2250, and then faced a coverage gap (commonly referred to as the "donut hole") for drug expenditures between $2250 and $5100, at which time they became eligible for catastrophic coverage, where cost sharing dropped to 5% of subsequent drug costs for the remainder of the calendar year.[15,16] Some "enhanced" Part D plans offered generic-only coverage during the coverage gap, whereby enrollees who did not qualify for any low-income subsidies (ie, non-LIS patients) faced large increases in cost sharing for brand-name drugs but no change in the cost for generic drugs during the coverage gap. At the same time, patients fully eligible for low-income subsidies (ie, full-LIS patients) were not subject to the coverage gap and continued to pay copayments of $1 for generic drugs and $3 for brand name drugs throughout the year.

The introduction of Medicare Part D happened to coincide with changes in the availability of generic versions of commonly used medications for hypercholesterolemia, a major risk factor for both fatal and nonfatal cardiac events. Given that coronary heart disease (CHD) is the leading cause of mortality in America and a major cause of morbidity worldwide, use of medications to treat hypercholesterolemia has significant public health significance.[17] Statins (or HMG-CoA reductase inhibitors) represent the primary treatment for low-density lipoprotein cholesterol (LDL-C) reduction.[17] In 2006 in the United States, atorvastatin, rosuvastatin, simvastatin, and pravastatin were the most commonly used statins and were generally considered as therapeutic equivalents.[1,5,18] The FDA approved generic versions of simvastatin and pravastatin soon after their patents expired in April and June of 2006, respectively, while atorvastatin and rosuvastatin (which still were within their patent exclusivity period in the United States) remained available only as branded products. Thus, the benefit design of Medicare Part D and the new availability of generic versions of simvastatin and pravastatin in 2006 created a unique opportunity to examine how increases in cost-sharing differentials for brand name and generic drugs impacted use of individual statin agents and use of statins as a group.

Specifically, non-LIS beneficiaries using atorvastatin or rosuvastatin in Part D plans with generic-only gap coverage would have had to pay 100% of the cost of these branded drugs during the coverage gap. In contrast, beneficiaries could substantially reduce their out-of-pocket payments by switching to generic versions of simvastatin or pravastatin (ie, therapeutic substitution). The aim of this study was to examine the impact of increases in patient cost-sharing differentials for brand name and generic statins with entry into the Part D coverage gap on statin use among Medicare beneficiaries with hyperlipidemia.

Methods

Study Sample and Design

We identified beneficiaries from the 5% Chronic Condition Data Warehouse (CCW) database (which includes Medicare Part A, B, and D files) with a diagnosis of hyperlipidemia in 2005 (ICD-9-CM code 272.0–272.4) who had full years of fee-for-service coverage in 2005 and 2006 and stand-alone Medicare Part D coverage in 2006. From this sampling frame, we selected beneficiaries who had total drug spending that reached the Part D coverage gap in 2006; beneficiaries had either full-LIS status (LIS group) or had non-LIS status and were enrolled in plans with generic-only coverage or both generic and brand drug coverage during the coverage gap (non-LIS groups). The final sample included patients who filled either atorvastatin or rosuvastatin alone (ie, the 2 statins still covered by patent exclusivity in the United States) between January and March of 2006 (ie, who did not fill any other lipid-lowering drugs during the first 3 months of 2006). A very small proportion of patients (0.3%) with missing values on a key variable (county identification code) were excluded (Figure 1).

We used a quasi-experimental study design to examine changes in statin use across the pre–coverage gap and post–(during) coverage gap periods. The study group was comprised of non-LIS beneficiaries enrolled in plans with generic-only coverage during the coverage gap, who thereby experienced increased cost sharing for brand medications in the post-period. The contemporaneous control group was comprised of full-LIS beneficiaries who faced no increase in cost sharing for brand (or generic) medications during the coverage gap. Non-LIS patients enrolled in a subset of Part D plans that provided both generic and brand drug coverage during the coverage gap, who thereby faced similar copayments before and during the gap, were used as the second contemporaneous control group in sensitivity analyses. The contemporaneous control groups were used to adjust for changes not related to the increase in cost sharing faced by the study group (ie, factors unrelated to cost sharing that led

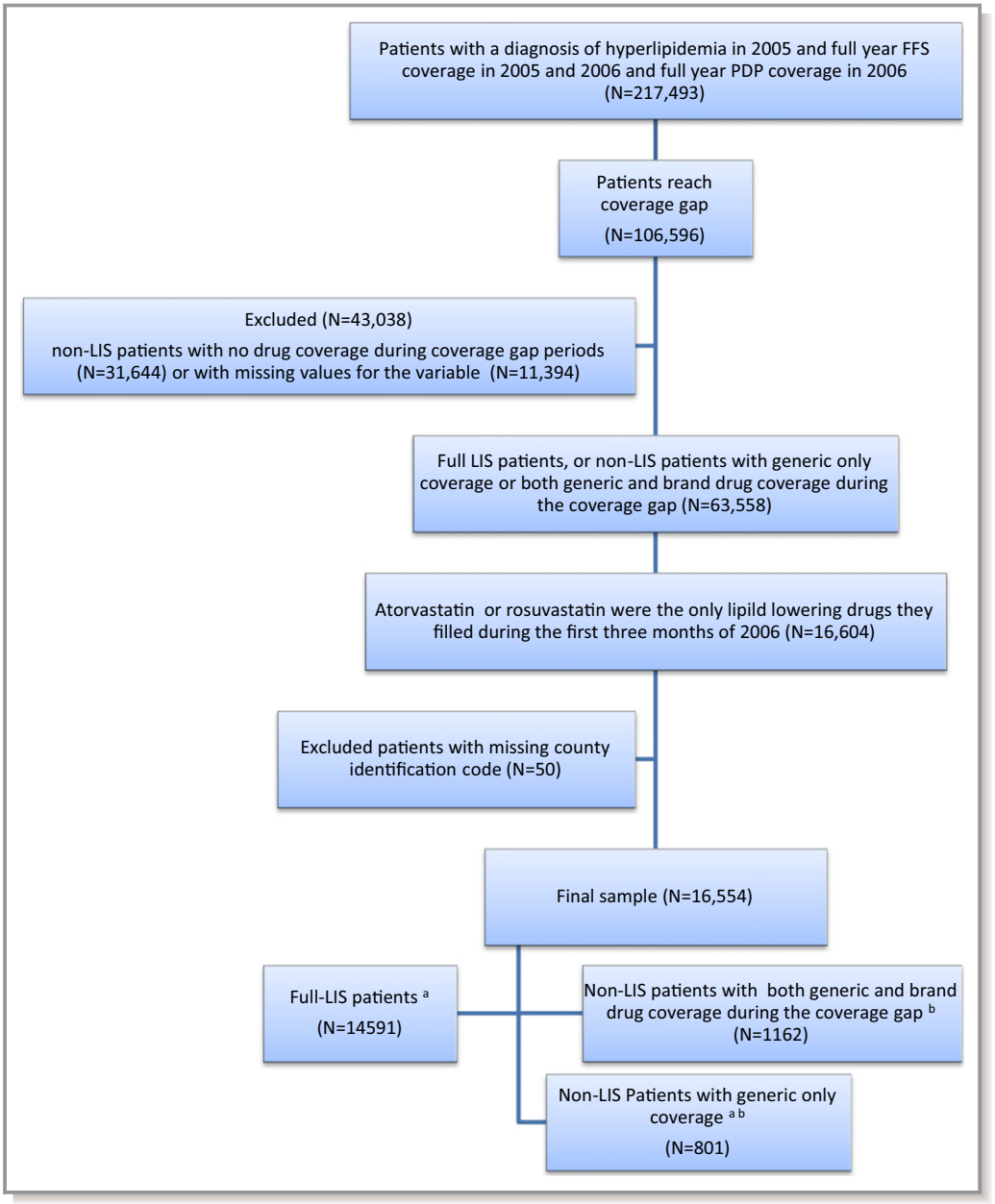

Figure 1. Sample flow chart. [a]After PS matching between non-LIS with generic coverage and full-LIS patients (N=801 for both groups). [b]After PS matching between patients with generic coverage and patients with both brand and generic coverage (N=743 for both groups). FFS indicates fee-for-service; LIS, low-income subsidies; PS, propensity score.

to changes in statin use). Propensity score matching was used to balance the study and control groups on patient demographics and clinical risk factors.

Assessment of Study Outcomes

We used a patient-month data structure to examine the impact of copayment changes due to entry into the coverage gap on the number of 30-day supply prescription fills (30-day fills) for statins and the proportion of these fills that were for brand-name and generic statins. We measured 30-day fills by a patient in each month before and during the coverage gap. The reported days' supply from each prescription was spread from the dispensing date to the date the prescription would have been exhausted. The cumulative days' supply available in each month was divided by the number of days in the month to obtain a standardized number of 30-day prescriptions filled by a patient in each month. The proportions of all 30-day statin fills that were for brand-name statins (including atorvastatin, rosuvastatin, and other brand-name statins) and generic statins (including generic simvastatin, pravastatin, and other generic statins) were calculated in each month. We

also examined the number of 30-day prescription fills for any lipid-lowering drug (including statin and nonstatin lipid-lowering drugs).

To examine how increases in generic and brand-name cost-sharing differentials affected discontinuation of brand-name statins, any statin, and any lipid-lowering drugs, drug switching from brand-name statins to generic statins, and overall adherence to any statin or lipid-lowering drugs, we assessed all these outcome measures for each patient separately for the period prior to entering the donut hole (before the coverage gap) and during the donut hole (during the coverage gap). Discontinuation was defined as the incidence of a 30-consecutive-day period without any days' supply of a study drug class on hand. If a patient started using generic statins after discontinuing brand statins, it was defined as switching from brand-name statins to generic statins. Overall adherence to any statin or lipid-lowering drugs was calculated via the proportion of days covered (PDC) measure and defined as PDC $\geq$0.80,[19-24] in keeping with the threshold used by the Centers for Medicare and Medicaid Services (CMS) to evaluate plan quality.[25] We limited analyses to patients who spent at least 1 month in the initial coverage period (ie, before the coverage gap) and 1 month during the coverage gap to allow enough time to observe the gap measure.

Control Variables

Covariates included age, sex, race/ethnicity, Medicare entitlement (LIS) status, metropolitan status (urban/rural), census region of residence, relevant comorbidities (diagnosis of coronary heart disease [CHD], diabetes mellitus, or cerebrovascular disease), use of atorvastatin versus rosuvastatin in early 2006, the number of months to reach coverage gap, the number of months spent in the coverage gap, area-level characteristics (per capita income, unemployment rate, education level) in the beneficiary's county of residence, and prescription drug hierarchical condition category (RxHCC) risk score. The RxHCC score was created using the RxHCC model, which generates indicators for 197 medical conditions based on diagnoses recorded on beneficiaries' previous year's Medicare claims.[26] It then applies previously calibrated weights, based on regression coefficients, to create a single risk score used to predict each beneficiary's total drug spending in the subsequent year. Although designed for Part D plan risk-adjusted payments, the RxHCC risk score is widely used to adjust for potential selection biases in medical and drug use studies among Medicare patients.[22,27-30]

Statistical Analyses

All analyses were based on a difference-in-difference approach[31] that compared pre-post changes in outcomes among the study group with pre-post changes in outcomes among the control group. Study-group patients (non-LIS beneficiaries with generic-only coverage during the gap) and control-group patients (full-LIS patients whose copayment remained $1 for generic drugs and $3 for brand-name drugs before and during coverage gap) were matched using propensity scores.[32] Propensity scores were estimated for each patient using a logit model with the dependent variable coded as a binary indicator for study group and adjusting for each of the covariates listed above. Monthly measures were examined using patient-level fixed-effects models. Two-period (before coverage gap and during coverage gap) difference-in-difference generalized estimating equation (GEE) logistic regressions[33] were used to model changes in the odds of having a continuous medication gap of $\geq$30 days, odds of drug switching, and odds of adherence (PDC $\geq$0.80) before and after entering the coverage gap. We conducted subgroup analyses among patients with CHD, diabetes mellitus, or cerebrovascular disease, and among patients reaching the coverage gap after June 2006 (when both simvastatin and pravastatin were available as generics). In sensitivity analyses, we repeated our analyses based on all patients in the study group (non-LIS with gap coverage) and control group (entire LIS sample without propensity score matching). In another sensitivity analysis, we excluded the "months to reach coverage gap" and "months in the coverage gap" as control variables from the logistic regression model that was used to generate propensity scores. This was because these 2 variables may be related to drug use, given that high-volume medication users would reach the coverage gap and transition out of the coverage gap more quickly. Finally, we also examined non-LIS patients with brand and generic gap coverage as an alternative contemporaneous control group.

All statistical analyses were carried out using SAS 9.4 and STATA version 12 (Stata Corp, College Station, TX). The study was reviewed and approved by the Institutional Review Board of the University of Pennsylvania. Requirement to obtain informed consent from subjects was waived.

Results

The nonmatched study sample consisted of 801 patients in the study group (non-LIS beneficiaries with generic-only gap coverage) and 14 591 patients in the control group (LIS beneficiaries). During the first quarter of 2006, nearly 90% of patients in both groups were atorvastatin users and 10% were rosuvastatin users. Using propensity score matching, we matched 801 patients from the control group to 801 patients in the study group. The 2 matched groups were very similar on relevant characteristics, with the standardized difference for all covariates smaller than 0.1 (indicating negligible

differences between groups).[34] The mean age for the sample was 75, and 43% were male (Table 1). Before they entered the coverage gap, non-LIS patients with generic-only gap coverage paid an average of $28.1 for atorvastatin or rosuvastatin, whereas LIS patients paid $3.5. After entering the coverage gap, non-LIS patients with generic-only gap coverage faced an increase in out-of-pocket payment from $28.1 to $81.7 per 30-day fills if they continued to use atorvastatin or rosuvastatin, compared to a mean out-of-pocket cost of $6.9 per 30-day fill if they switched to generic simvastatin or pravastatin. While in the coverage gap, LIS patients continued to face $3.5 copayments for atorvastatin and rosuvastatin compared with $1.4 copayments for generic simvastatin or pravastatin (Figure 2).

Figure 3A through 3C and Table 2 illustrate the monthly 30-day fills of statins for each group. Atorvastatin, rosuvastatin, generic simvastatin, and generic pravastatin represented 96% to 100% of statin use among patients in the sample before and during the coverage gap periods. Patients in the study group had a substantial reduction in monthly 30-day fills of brand-name statins after entering the coverage gap (atorvastatin or rosuvastatin: 0.81 to 0.53 monthly 30-day fills; any brand name statin: 0.82 to 0.54 monthly 30-day fills). In contrast, their monthly 30-day fill of generic statins

Table 1. Patient Characteristics Before and After Propensity Score Matching

	Before Propensity Score Matching			After Propensity Score Matching		
	Study Group	Control Group		Study Group	Control Group	
Patient Characteristics	N=801	N=14 591	D*	N=801	N=801	D*
Age, y (mean)	74.8	67.7	0.671	74.8	74.9	0.001
Male	43.1%	32.4%	0.222	43.1%	44.2%	0.023
Race						
White	97.0%	68.2%	0.822	97.0%	96.4%	0.035
Black	1.3%	15.9%	0.541	1.3%	1.1%	0.012
Other race	1.8%	16.0%	0.518	1.8%	2.5%	0.052
ESRD	0.9%	2.3%	0.115	0.9%	0.3%	0.083
RxHCC, mean	0.9	1.0	0.354	0.9	0.9	0.013
CHD	26.2%	26.2%	0.000	26.2%	26.8%	0.014
Diabetes mellitus	33.6%	45.5%	0.246	33.6%	35.3%	0.037
Cerebrovascular disease	9.4%	7.9%	0.054	9.4%	10.6%	0.042
Atorvastatin users, January to March 2006	89.5%	87.4%	0.067	89.5%	88.1%	0.043
Rosuvastatin users, January to March 2006	10.5%	12.6%	0.067	10.5%	11.9%	0.043
Number of months to reach coverage gap, mean	7.5	6.4	0.476	7.5	7.4	0.044
Months in coverage gap, mean	4.1	4.0	0.055	4.1	4.2	0.042
Region						
West	16.2%	22.1%	0.150	16.2%	16.4%	0.003
Midwest	20.5%	21.3%	0.021	20.5%	19.4%	0.028
Northeast	16.1%	27.1%	0.269	16.1%	16.2%	0.004
South	47.2%	29.5%	0.371	47.2%	48.1%	0.017
Urban residence	75.4%	76.1%	0.016	75.4%	74.9%	0.012
Median county-level income, mean	$30 372	$30 387	0.002	$30 372	$29 825	0.068
Residence in a county with low education levels†	12.5%	22.9%	0.277	12.5%	12.6%	0.004
County-level unemployment rate, mean	0.06	0.07	0.462	0.06	0.06	0.021

Study group were patients without low-income subsidy with generic-only coverage during the coverage gap, and control group were patients with low-income subsidy receiving generic and brand prescription drug coverage; ESRD, Medicare-eligible due to end-stage renal disease (ESRD) rather than age or disability; RxHCC, modified prescription drug hierarchical condition category (RxHCC) risk score wherein coefficients for age and sex are zeroed out in the score calculation because regression models separately control for these variables; CHD, with diagnosis of coronary heart disease.

*D indicates standardized difference; 2 groups are considered balanced if D<0.1.[34]

†Residing in a county with ≥25% adults without a high school diploma.

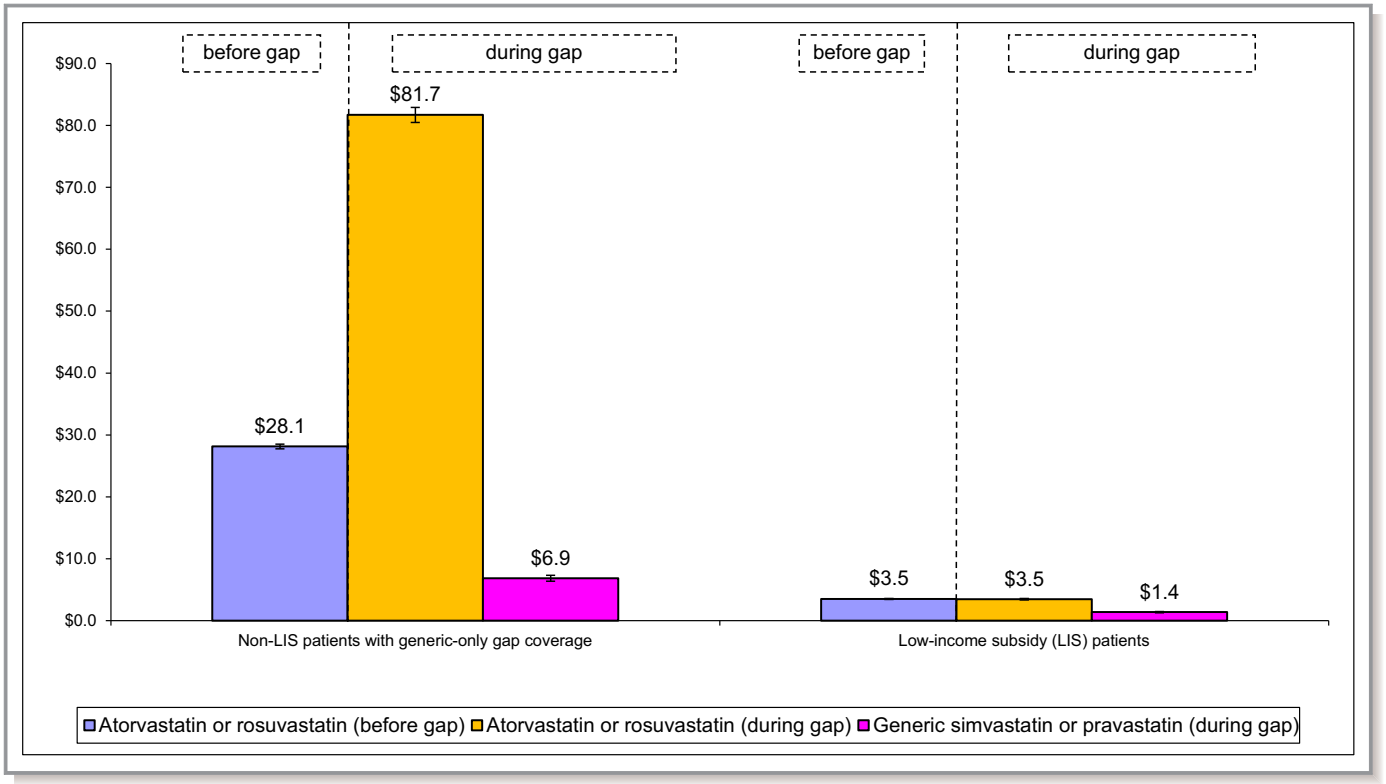

Figure 2. Mean out-of-pocket payment per 30-day fill before and during the coverage gap among non-LIS patients with generic-only gap coverage and LIS patients with both brand and generic gap coverage. Standard errors of means are shown as error bars. LIS indicates low-income subsidies.

increased during the coverage gap compared to the pre–coverage gap period (generic simvastatin or pravastatin: 0.00 to 0.07 monthly 30-day fills; any generic statin: 0.01 to 0.09 monthly 30-day fills). This resulted in a reduction in the percentage of statin fills that were for brand-name drugs (from 99% to 87%). However, the increase in generic statin fills did not compensate fully for the observed reduction in brand-name statin fills. Hence, there was a substantial drop in mean 30-day fills of any statin and any lipid-lowering drug among the study group of non-LIS patients with generic-only gap coverage. In contrast, the corresponding changes among the control group of LIS patients were minimal.

Risk-adjusted difference-in-difference estimates (changes among non-LIS patients with generic-only gap coverage compared with changes among LIS patients) confirmed the descriptive results (Table 2). The coverage gap was associated with reductions in mean monthly 30-day fills of atorvastatin or rosuvastatin (−0.24; 95% CI [−0.29, −0.19]), mean monthly 30-day fills of any brand-name statin (−0.24; 95% CI [−0.29, −0.19]), proportion of any 30-day statin fills that were for atorvastatin or rosuvastatin (−8%; 95% CI [−9%, −7%]), and proportion of any 30-day statin fills that were for brand-name statins (−8%; 95% CI [−9%, −7%]). At the same time, the coverage gap was associated with increases in mean monthly 30-day fills of generic simvastatin or pravastatin (0.04; 95% CI [0.03, 0.05]), mean monthly 30-day fills of any generic statin (0.06; 95% CI [0.04, 0.07]), and proportion of any 30-day statin fills that were for generic simvastatin or pravastatin (6%; 95% CI [5%, 7%]). Overall, the coverage gap was associated with reductions in mean monthly 30-day fills of any statin (−0.18; 95% CI [−0.23, −0.13]) and any lipid-lowering drug (−0.17; 95% CI [−0.22, −0.12]).

Analyses of discontinuation, switching, and overall adherence showed findings consistent with the patient-month analyses (Table 3). Compared to patients in the control group of LIS patients, patients in the study group had greater odds of discontinuing atorvastatin and rosuvastatin (OR: 1.72; 95% CI [1.33, 2.23]), of switching from atorvastatin and rosuvastatin to generic simvastatin or pravastatin (OR: 1.47; 95% CI [1.05, 2.06]), and of switching from a brand-name statin to a generic statin (OR: 1.56; 95% CI [1.10, 2.19]) during the coverage gap. Overall, the odds of discontinuing any statin and any lipid-lowering drug (statin or nonstatin) increased during the coverage gap relative to the period before the coverage gap for the study group compared with the control group (any statin OR: 1.62, 95% CI [1.24, 2.12]; any lipid-lowering drugs OR: 1.66, 95% CI [1.25, 2.20]). Similarly, the coverage gap was associated with lower odds of overall adherence to statins and any lipid-lowering drugs among

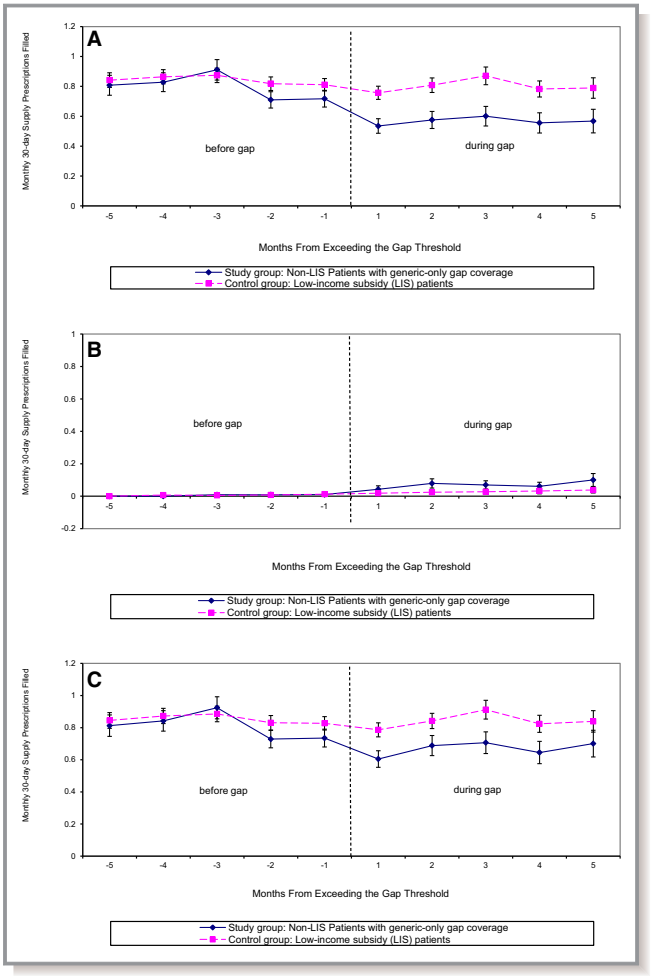

Figure 3. A, Monthly 30-day fills for atorvastatin or rosuvastatin. Standard errors of means are shown as error bars. B, Monthly 30-day fills for generic simvastatin or pravastatin. Standard errors of means are shown as error bars. C, Monthly 30-day fills for any statin. Standard errors of means are shown as error bars.

patients in the study group compared with patients in the control group (statin OR: 0.81, 95% CI [0.75, 0.88]; any lipid-lowering drugs OR: 0.83, 95% CI [0.77, 0.89]). Even among patients who did not discontinue atorvastatin or rosuvastatin (persistent on atorvastatin or rosuvastatin), a small but statistically significant decrease in PDC was observed among patients in the study group compared to patients in the control group (−0.02; 95% CI [−0.03, −0.01]; $P<0.001$).

The results of sensitivity analyses among the entire sample (without propensity score matching), using an alternative control group (non-LIS patients with brand and generic gap coverage), and using alternative covariates to create propensity score were similar to and consistent with the main analysis findings (Figure 4, Tables 4 through 6). Similar results were also found in subgroup analyses of patients with CHD, diabetes mellitus, or cerebrovascular disease and patients reaching the coverage gap after June 2006 (Tables 5 and 6).

Discussion

In 2006, the introduction of the Medicare Part D drug benefit, which subjected beneficiaries to variable cost sharing over the course of the coverage year, coincided with the introduction of generic versions of 2 common statin medications (simvastatin and pravastatin). For non-LIS patients enrolling in Part D plans with generic-only gap coverage and taking a statin available only as a brand name medication (ie, atorvastatin or rosuvastatin), this provided a unique opportunity to examine how increased cost-sharing differentials for brand name and generic drugs during Part D's coverage-gap phase was associated with therapeutic substitution (switching from a brand medication to an alternate generic medication in the same class) and overall use of statin or lipid-lowering drugs. This is because they faced a substantial increase in cost sharing for brand name statins during the Medicare Part D coverage gap (from $28 to $82 per 30-day fill, on average) and could substantially reduce their monthly copayments to an average of $7 by switching to generic simvastatin or pravastatin. Using a quasi-experimental study design, we found that beneficiaries who faced this increased brand/generic cost-sharing differential during the coverage gap did have greater odds of therapeutic substitution, as compared to patients who faced stable cost sharing due to low-income subsidies. Yet we also observed that the reductions in brand-name statin use were not accompanied by equal (compensatory) increases in generic statin use and hence resulted in lower overall statin use during the coverage gap. This indicated that some patients discontinued their statin medication rather than switching to a therapeutic substitute.

These findings are consistent with studies that have found that a larger cost-sharing difference between brand-name and generic drugs was associated with a higher proportion of generic drug use.[5,9-11,14,35-38] Our finding that increased use of generic statins only partially offset the reduction in branded statin use, resulting in decreased overall statin use, is consistent with results observed by Gilman and Kautter[14] and Motheral and Henderson.[11] The coverage gap was also associated with higher odds of discontinuing and lower odds of overall adherence to statins and other lipid-lowering drugs, even among subgroups of patients at higher risk for future cardiovascular events (ie, those with CHD, diabetes mellitus, or cerebrovascular disease) who might have increased motivation to remain on their medication. These findings raise concerns about the potential clinical impact of these utilization changes. Although some patients may have discussed statin discontinuation with their prescribing clinicians, others likely stopped their medication without such discussion. Our study did not evaluate clinical outcomes, but others have found that reduced adherence to lipid-lowering drugs is associated with worse physiological outcomes, higher rates of emergency

Table 2. Statin Utilization Before and During Coverage Gap Among Initial Atorvastatin or Rosuvastatin Users in 2006 (Measures at Monthly Level)

Outcomes	Study Group: Patients With Generic-Only Gap Coverage			Control Group: LIS Patients			Difference in Difference (Column3-Column6)	Risk-Adjusted Estimate*	95% CI	*P* Value
	(1) Before Coverage Gap	(2) During Coverage Gap	(3) Difference (During Minus Before)	(4) Before Coverage gap	(5) During Coverage Gap	(6) Difference (During Minus Before)				
Mean monthly 30-day fills of atorvastatin or rosuvastatin	0.81	0.53	−0.28	0.83	0.79	−0.04	−0.23	−0.24	−0.29 to −0.19	<0.001
Mean monthly 30-day fills of any brand name statin	0.82	0.54	−0.27	0.84	0.80	−0.04	−0.23	−0.24	−0.29 to −0.19	<0.001
Mean monthly 30-day fills of generic simvastatin or pravastatin	0.00	0.07	0.06	0.00	0.03	0.01	0.05	0.04	0.03 to 0.05	<0.001
Mean monthly 30-day fills of any generic statin	0.01	0.09	0.08	0.01	0.03	0.03	0.06	0.06	0.04 to 0.07	<0.001
Proportion of 30-day atorvastatin or rosuvastatin fills among all 30-day statin fills	99%	86%	−13%	99%	95%	−4%	−9%	−8%	−9% to −7%	<0.001
Proportion of 30-day generic simvastatin or pravastatin fills among all 30-day statin fills	1%	10%	9%	1%	4%	3%	6%	6%	5% to 7%	<0.001
Proportion of 30-day brand name statin fills among all 30-day statin fills	99%	87%	−12%	99%	96%	−4%	−9%	−8%	−9% to −7%	<0.001
Mean monthly 30-day fills of any statin	0.82	0.63	−0.19	0.84	0.83	−0.01	−0.18	−0.18	−0.23 to −0.13	<0.001
Mean monthly 30-day fills of any lipid-lowering drugs	0.84	0.69	−0.15	0.85	0.87	0.01	−0.17	−0.17	−0.22 to −0.12	<0.001

LIS indicates low-income subsidies. Sample included patients using only atorvastatin or rosuvastatin (available only as brand-name drugs in 2006) as their lipid-lowering drug during the first 3 months of 2006. Non–low-income-subsidy patients with generic-only gap coverage were propensity score (PS) matched to low-income-subsidy patients.
*Based on coefficients for the interaction term of study group indicator (reference group is control group) and postperiod indicator (reference group is pre–coverage gap period) from patient-level fixed-effects models.

department visits and nonelective hospitalizations, and increased mortality.[23]

The impact of cost-sharing differentials between brand and generic drugs on statin use has important implications for current Medicare policy as well as implications for other payers. On the one hand, greater use of generic statins could substantially lower drug spending[5] and potentially increase adherence because lower copayments reduce financial barriers to treatment.[39] Medicare uses tiered formularies that put generic drugs on the lowest tier with lower copayments and put brand-name drugs on higher tiers with higher cost sharing in an effort to influence prescription drug utilization, as do virtually all US payers. In 2013, copayments in employer-sponsored health insurance plans averaged $10 for first-tier drugs and $80 for fourth-tier drugs (the highest tier)[40]—a comparable copayment differential to that observed among our study group for Medicare beneficiaries in the coverage gap. Furthermore, coinsurance often leads to higher out-

Table 3. Statin Utilization Before and During the Coverage Gap Among Initial Atorvastatin or Rosuvastatin Users in 2006 (Measures at Benefit Phase Level)

	Study Group: Patients With Generic-Only Gap Coverage			Control Group: LIS Patients						
	(1) Before Coverage Gap	(2) During Coverage Gap	(3) Difference (During Minus Before)	(4) Before Coverage Gap	(5) During Coverage Gap	(6) Difference (During Minus Before)	Difference in Difference (Column3-Column6)	Odds Ratio or Risk-Adjusted Estimate*	95% CI	*P* Value
Binary outcomes								Odds ratio†		
Discontinued atorvastatin and rosuvastatin‡	29%	44%	15%	23%	25%	2%	13%	1.72	1.33 to 2.23	<0.001
Switched from atorvastatin and rosuvastatin to generic simvastatin or pravastatin	18%	24%	6%	17%	17%	0%	6%	1.47	1.05 to 2.06	0.027
Switched from brand name statins to generic statins	18%	23%	5%	17%	16%	−1%	6%	1.56	1.10 to 2.19	0.012
Discontinued statins‡	27%	35%	8%	22%	21%	−1%	9%	1.62	1.24 to 2.12	<0.001
Discontinued any lipid-lowering drug‡	25%	32%	7%	22%	19%	−3%	10%	1.66	1.25 to 2.20	<0.001
Adherent to statins (PDC ≥0.80)	71%	58%	−13%	74%	74%	0%	−13%	0.81	0.75 to 0.88	<0.001
Adherent to any lipid-lowering drug (PDC ≥0.80)	72%	61%	−10%	75%	76%	1%	−11%	0.83	0.77 to 0.89	<0.001
Continuous outcome								Risk-adjusted estimate§		
Mean PDC among patients persistent on atorvastatin or rosuvastatin	0.93	0.91	−0.02	0.93	0.93	0.00	−0.02	−0.02	−0.04 to −0.01	<0.001

LIS indicates low-income subsidies. Sample included patients using only atorvastatin or rosuvastatin (available only as brand-name drugs in 2006) as their lipid-lowering drug during the first 3 months of 2006. Non-LIS patients with generic gap coverage were propensity score matched to LIS patients. PDC indicates proportion of days covered.

*Based on coefficients for the interaction term of study group indicator (reference group is control group) and postperiod indicator (reference group is pre–coverage gap period).

†Based on generalized estimating equation logit model.

‡Discontinuation defined as 30-day continuous gap. Alternate definition of discontinuation as a 90-day continuous gap resulted in consistent findings (odds ratio=2.2, *P*=0.01 for statin; odds ratio=2.05, *P*=0.005 for any lipid-lowering drugs).

§Based on generalized estimating equation log gamma model.

of-pocket costs for patients as compared to fixed copayments, and a recent report by Avalere noted that the use of coinsurance versus copayments for both preferred and nonpreferred brand medication tiers has increased in Medicare Part D plans.[41] Further, a recent Medicare Payment Advisory Commission (MedPAC) proposal recommended modifying brand/generic copayment differentials to encourage the use of generic drugs.[42] On the other hand, our findings suggest that using copayment differential as a standalone strategy may be insufficient as a means of encouraging therapeutic substitution. Our data suggest that some patients ultimately decide to fill the medication as written, some switch to a lower–copayment drug, and some seem to have forgone any treatment.

Although our study data do not offer specific insight into why some patients opted not to fill their prescriptions or seek out a less expensive alternative, these effects are likely due to differences between the expected theoretical effects of cost-sharing policies and how these policies play out in the real world. Theoretically, when a cost-sharing structure increases

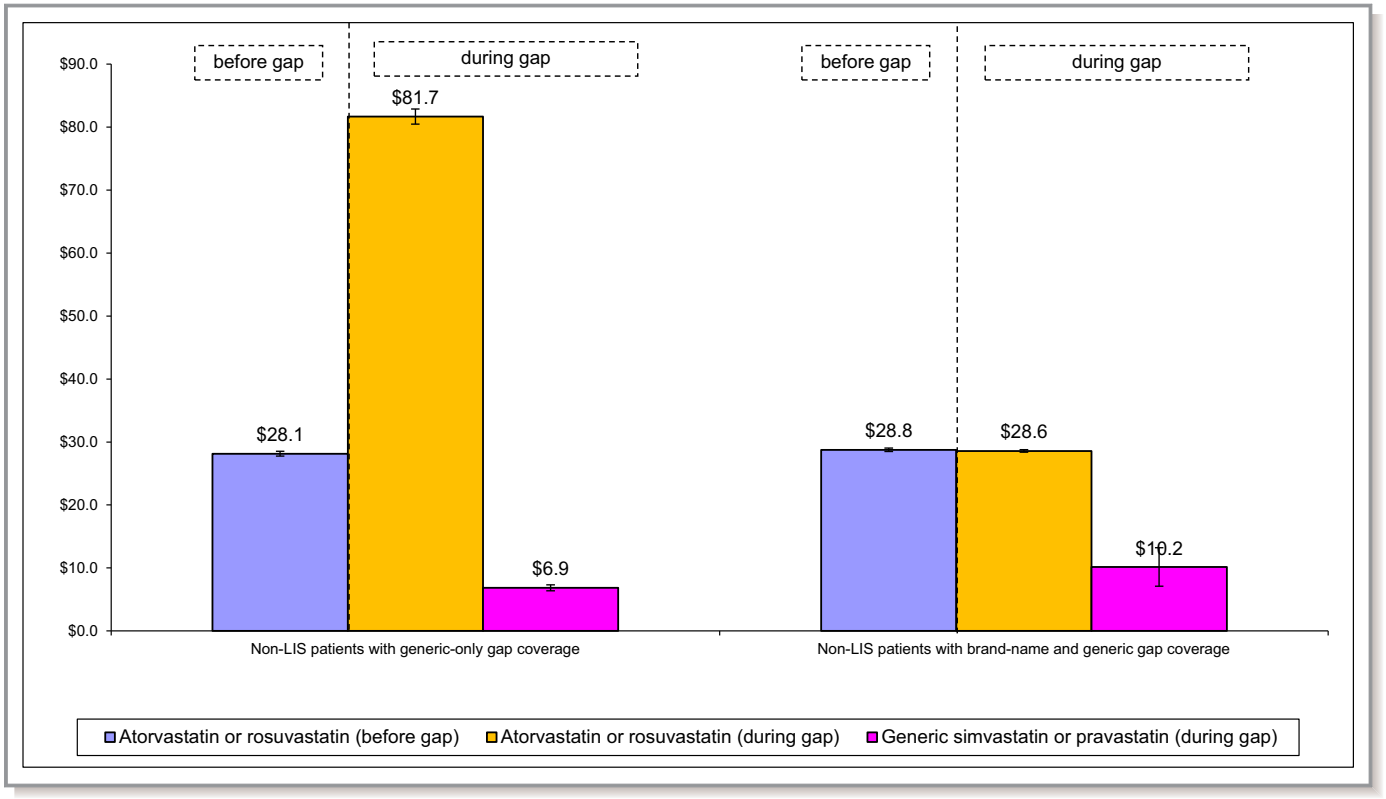

Figure 4. Mean out-of-pocket payment per 30-day fill before and during the coverage gap among non-LIS patients with generic-only gap coverage and non-LIS patients with both brand and generic gap coverage. Standard errors of means are shown as error bars. LIS indicates low-income subsidies.

copayments for brand drugs relative to copayments for generic drugs, it is assumed that patients will make rational decisions about medication purchasing based on out-of-pocket costs alone and be able to follow up on those decisions, resulting in utilization of a generic substitute for brand-name drug formulations. For this to happen, however, patients must be aware of the availability of generic alternatives, informed of the marginal benefits of brand-name versus generic drugs relative to their increased costs, willing to inform their prescribers about cost considerations, and willing and able to follow through with a change in medication. However, our results demonstrate that this does not always occur. Multiple factors may be contributing to our observed effects. First, research in behavioral economics has demonstrated a "status quo bias," whereby people tend to continue with their current choice, on the "path of least resistance," even when better alternatives exist.[43] Second, limited patient awareness of generic statins, and patient attitudes toward generic medication (such as thinking that generic statins are less effective or have more side effects than brand-name statins), may have contributed to the observed results.[44] Third, even when patients are open to therapeutic substitution, achieving it requires communication between clinicians and patients. Physicians and other prescribers, who often see patients from a wide variety of insurance plans with different policies, may not be aware of or adequately consider patient out-of-pocket costs when prescribing medications, reducing the likelihood that they would consider a therapeutic alternative.[45,46] Unless informed by the patient, a prescriber is also unlikely to know when a Medicare patient transitions into the donut hole and, even then, is unlikely to know how much any individual drug costs the patient. Therefore, the burden of conveying this information to providers falls on the patients. Patients, in turn, may not be aware of plan policies until after they attempt to fill a prescription. This scenario may have been especially likely during our study period, given that 2006 was the first year of the Medicare Part D program. Even when patients are aware of their options, potential barriers remain. By definition, Medicare beneficiaries whose drug expenditures place them in the coverage gap are more likely to have multiple medical providers, diagnoses, and medications and thus to be sicker, more vulnerable, and often overwhelmed. Advanced age, cognitive issues, and/or reluctance to discuss financial concerns can also inhibit patients' willingness or ability to raise cost concerns in medical appointments.[47] Even when patients are willing to request an alternative

Table 4. Characteristics of Patients With Generic Gap Coverage and Brand and Generic Gap Coverage

	Before PS Matching			After PS Matching		
	Study Group: Generic Gap Coverage	Control Group: Brand Generic Gap Coverage		Study Group: Generic Gap Coverage	Control Group: Brand Generic Gap Coverage	
Patient Characteristics	Mean (N=801)	Mean (N=1162)	D*	Mean (N=743)	Mean (N=743)	D*
Age	75.0	74.8	0.025	74.8	74.8	0.008
Male	38.6%	43.1%	0.090	42.1%	42.3%	0.003
Race			0.000			0.000
White	98.2%	97.0%	0.078	97.4%	97.3%	0.008
Black	1.2%	1.3%	0.005	1.6%	1.2%	0.035
Other race	0.6%	1.8%	0.107	0.9%	1.5%	0.049
ESRD	0.3%	0.9%	0.068	0.5%	0.7%	0.017
RxHCC	93.3%	90.9%	0.075	91.0%	91.5%	0.016
CHD	31.0%	26.2%	0.105	27.9%	27.2%	0.015
Diabetes mellitus	35.5%	33.6%	0.041	33.2%	34.1%	0.017
Cerebrovascular disease	9.2%	9.4%	0.005	8.9%	9.4%	0.019
Lipitor users during January to March 2006	87.6%	89.5%	0.060	88.3%	89.1%	0.026
Crestor users during January to March 2006	12.4%	10.5%	0.060	11.7%	10.9%	0.026
The month reaching coverage gap	7.0	7.5	0.240	7.3	7.5	0.070
Months in coverage gap	4.3	4.1	0.068	4.2	4.2	0.020
Region			0.000			0.000
West	10.1%	16.2%	0.183	14.7%	15.1%	0.011
Midwest	48.9%	20.5%	0.625	24.1%	22.1%	0.048
Northeast	8.1%	16.1%	0.247	12.4%	14.9%	0.075
South	33.0%	47.2%	0.293	48.9%	47.9%	0.019
Urban	62.0%	75.4%	0.293	73.0%	74.0%	0.024
Median county-level income	$29 508	$30 372	0.112	$30 068	$30 429	0.044
Residence in a county with low education levels†	6.9%	12.5%	0.190	10.0%	11.3%	0.044
County-level unemployment rate (mean)	0.06	0.06	0.148	0.06	0.06	0.047

Both study-group and control-group patients did not have low-income subsidy. Study-group patients had generic-only coverage during the coverage gap, and control group had generic and brand prescription drug coverage drug coverage gap; ESRD, Medicare-eligible due to end-stage renal disease (ESRD) rather than age or disability; RxHCC, Modified prescription drug hierarchical condition category (RxHCC) risk score wherein coefficients for age and sex are zeroed out in the score calculation because regression models separately control for these variables; CHD: with diagnosis of coronary heart disease.

*D indicates standardized difference; 2 groups are considered balanced if D<0.1.[34]

†Residing in a county with ≥25% adults without a high school diploma.

prescription, difficulty scheduling or traveling to appointments may present additional obstacles.

Further, in the subset of cases where physicians write brand-only prescriptions based on a patient's specific health status (eg, need for more intensive lipid-lowering effect), lack of awareness of financial barriers may create a missed opportunity to discuss whether switching to a generic statin is preferable to discontinuing statin therapy altogether. Overall, our findings suggest that shifts in cost-sharing policies may need to be accompanied by patient education and other strategies to promote uninterrupted treatment. Clinicians and health plans may be able to reduce unintended effects of cost-sharing changes on adherence by helping patients identify lower-cost alternatives for their cardiovascular medication regimens.

This quasi-experimental study has several inherent limitations. Because this was an observational study rather than a randomized controlled trial, it was critical to rule out or mitigate potential confounders. We used several approaches toward this end. First, we used extensive covariates in an effort to balance study and control groups through propensity score matching. It is important to note that whereas this approach reduced the influence of potential confounders between our study group and control group as a strategy to

Table 5. Sensitivity Analysis: Impact of Copayment Differential on Lipid-Lowering Drug Utilization Among Initial Lipitor or Crestor Users in 2006 (Measures at Monthly Level)

	1		2		3		4		5		6	
Outcomes	Estimate	*P* Value	Estimate	*P* Value	Estimate	*P* Value	Estimate	*P* Value	Estimate	*P* Value	Estimate	*P* Value
Monthly measures based on patient-level fixed-effects models: coefficients were reported												
Mean monthly 30-day fills of atorvastatin or rosuvastatin	−0.236	<0.001	−0.225	<0.001	−0.225	<0.001	−0.238	<0.001	−0.276	<0.001	−0.220	<0.001
Mean monthly 30-day fills of any brand name statin	−0.235	<0.001	−0.224	<0.001	−0.223	<0.001	−0.231	<0.001	−0.276	<0.001	−0.220	<0.001
Mean monthly 30-day fills of generic simvastatin or pravastatin	0.042	<0.001	0.043	<0.001	0.045	<0.001	0.069	<0.001	0.054	<0.001	0.031	<0.001
Mean monthly 30-day fills of any generic statin	0.057	<0.001	0.057	<0.001	0.061	<0.001	0.088	<0.001	0.066	<0.001	0.048	<0.001
Proportion of 30-day atorvastatin or rosuvastatin fills among all 30-day statin fills	−0.081	<0.001	−0.081	<0.001	−0.093	<0.001	−0.123	<0.001	−0.091	<0.001	−0.066	<0.001
Proportion of 30-day generic simvastatin or pravastatin fills among all 30-day statin fills	0.059	<0.001	0.059	<0.001	0.068	<0.001	0.088	<0.001	0.073	<0.001	0.044	<0.001
Proportion of 30-day brand name statin fills among all 30-day statin fills	−0.08	<0.001	−0.08	<0.001	−0.091	<0.001	−0.118	<0.001	−0.093	<0.001	−0.068	<0.001
Mean monthly 30-day fills of any statin	−0.178	<0.001	−0.166	<0.001	−0.163	<0.001	−0.142	<0.001	−0.21	<0.001	−0.172	<0.001
Mean monthly 30-day fills of any lipid-lowering drugs	−0.172	<0.001	−0.164	<0.001	−0.16	<0.001	−0.14	<0.001	−0.217	<0.001	−0.163	<0.001

CHD indicates coronary heart disease. 1, Main model: propensity score (PS)-matched, low-income subsidy (LIS) as the control group; 2, non-PS-matched: all LIS patients were compared to generic gap coverage; 3, PS-matched, brand generic gap coverage as the control group; 4, PS-matched, LIS as the control group, among subsample of patients with CHD, diabetes mellitus or cerebrovascular disease; 5, PS-matched, LIS as the control group, patients reaching donut hole after June 2006; 6, PS-matched, LIS as the control group, removing "months to reach coverage gap" and "months in the coverage gap" from PS factors. Estimates were based on coefficients for the interaction term of study group indicator (reference group is control group) and postperiod indicator (reference group is pre–coverage gap period) from patient-level fixed-effects models.

isolate the effects of cost sharing, it also resulted in a study population that resembled our study group (eg, predominantly white with lower rates of diabetes mellitus and a lower likelihood of living in a county with low education levels). As a result, our results may not be generalizable to the broader Medicare population. Second, the use of a difference-in-difference study design and patient-level fixed-effects models further reduced the effect of potential time-invariant confounders. Third, each of our control groups had strengths and limitations. Although the propensity score–matched control group of LIS patients was similar to the study group in observed covariates, they could have differed in unobserved confounders. To address this concern, we used non-LIS patients with both brand name and generic coverage as an alternative control group in sensitivity analyses. Although this control group may have been more similar to the non-LIS study group on both observed and unobserved covariates, there might be more potential selection bias associated with this control group because, unlike LIS patients, non-LIS patients could choose plans based on their needs. For example, non-LIS patients with higher demand for drug utilization could have selected more enhanced part D plans (eg, plans with brand and generic gap coverage). Nonetheless, our analysis of 2 different control groups showed consistent findings.

Our study is also subject to the limitations inherent in the use of claims-based prescription refill information as a proxy

Table 6. Sensitivity Analysis: Impact of Copayment Differential on Lipid-Lowering Drug Utilization Among Initial Lipitor or Crestor Users in 2006 (Measures at Benefit Phase Level)

	1		2		3		4		5		6	
Outcomes	Odds Ratio	*P* Value	Odds Ratio	*P* Value	Odds Ratio	*P* Value	Odds Ratio	*P* Value	Odds Ratio	*P* Value	Odds Ratio	*P* Value
Binary outcomes*												
Discontinued atorvastatin and rosuvastatin	1.721	<0.001	1.474	<0.001	2.04	<0.001	2.136	<0.001	2.046	<0.001	1.829	<0.001
Switched from atorvastatin and rosuvastatin to generic simvastatin or pravastatin	1.468	0.027	1.032	0.800	1.257	0.195	1.745	0.018	1.782	0.006	1.342	0.095
Switched from brand-name statins to generic statins	1.556	0.012	1.093	0.469	1.303	0.134	1.868	0.009	1.874	0.003	1.422	0.047
Discontinued statins	1.619	<0.001	1.255	0.013	1.806	<0.001	1.848	0.001	1.933	<0.001	1.689	<0.001
Discontinued any lipid-lowering drug	1.659	<0.001	1.264	0.014	1.79	<0.001	1.952	0.001	2.056	<0.001	1.709	<0.001
Adherent to statins (PDC ≥0.80)	0.811	<0.001	0.863	<0.001	0.83	<0.001	0.798	<0.001	0.772	<0.001	0.650	<0.001
Adherent to any lipid-lowering drug (PDC ≥0.80)	0.827	<0.001	0.879	<0.001	0.845	<0.001	0.819	<0.001	0.783	<0.001	0.680	0.002
Continuous outcome†	Estimate	*P* Value	Estimate	*P* Value	Estimate	*P* Value	Estimate	*P* Value	Estimate	*P* Value	Estimate	*P* Value
Mean PDC among patients persistent on atorvastatin or rosuvastatin	−0.025	<0.001	−0.019	0.003	−0.016	0.029	−0.014	0.169	−0.036	<0.001	−0.015	0.029

1, Main model: propensity score (PS)-matched, low-income subsidy (LIS) as the control group; 2, non-PS-matched: all LIS patients were compared to generic gap coverage; 3, PS-matched, brand generic gap coverage as the control group; 4, PS-matched, LIS as the control group, among subsample of patients with CHD, diabetes mellitus or cerebrovascular disease; 5, PS-matched, LIS as the control group, patients reaching donut hole after June 2006; 6, PS-matched, LIS as the control group, removing "months to reach coverage gap" and "months in the coverage gap" from PS factors. CHD indicates coronary heart disease; PDC, proportion of days covered.

*Based on odds ratios for the interaction term of study group indicator (reference group is control group) and postperiod indicator (reference group is pre–coverage gap period) from patient-level fixed-effects models using generalized estimating equation logit model.

†Based on coefficients for the interaction term of study group indicator (reference group is control group) and postperiod indicator (reference group is pre–coverage gap period) using generalized estimating equation log gamma model.

for drug use and adherence. Although this indirect measure cannot confirm whether patients actually took their medication as prescribed, the validity of prescription refill data as a measure of adherence has been demonstrated independently by several studies.[48,49] In addition, if a patient filled a medication prescription outside the Part D plan, this information would not be available in Medicare claims and could result in our measure underestimating true adherence. Of note, the discounts offered by some large chain pharmacies for many generic drugs (eg, $4 copays) did not start until late 2006, and, even when these programs began, simvastatin and pravastatin were often excluded from these programs. Therefore, this potential limitation was unlikely to significantly affect our results.

Finally, it is possible that our data from the first year of Medicare Part D are not fully representative of enrollment during a typical post–Part D year. In 2006, beneficiaries qualifying for LIS were autoenrolled, and non-LIS beneficiaries

had extensions in the time for enrollment (with a deadline in June 2006), so some non-LIS beneficiaries who enrolled later would have been excluded from our analysis. At the same time, our use of data from the first year of the Part D program may have resulted in less bias related to adverse selection across study groups (ie, patients self-selecting among plans with varying levels of generosity based on their need for medication), given that patients would not have been factoring prior experience with the coverage gap into their choice of plans. This should have improved the validity of our results.

It is worth noting that although the data used in our study are 10 years old, we believe that our study is still highly policy relevant because these circumstances provided a unique natural experiment opportunity, but the findings place a spotlight on the issue of generic and therapeutic substitution and cost sharing more generally. We found that patients facing an increase in their brand/generic cost-sharing differential had greater odds of generic substitution as well as lower overall statin use. That is, the reductions in brand name statin use were not accompanied by equal (compensatory) increases in generic statin use. The fact that such cost-sharing changes appeared to lead to unintended consequences is relevant to both current and future policy. For example, coinsurance often leads to higher out-of-pocket costs for patients as compared to fixed copayments, and the use of coinsurance versus copayments for both preferred and nonpreferred brand medication tiers has increased in Medicare Part D plans.[41] Further, as mentioned previously, a recent Medicare Payment Advisory Commission (MedPAC) proposal would again modify copayments to encourage the use of generic drugs.[42] Because policy discussions and revisions about how to control prescription drug costs are ongoing, the themes and results of our study are broadly relevant even though our study methods capitalized on a unique set of circumstances in 2006.

Conclusions

In an effort to control pharmaceutical spending, insurers, employers, and policymakers are increasing the differential in patient cost-sharing levels for brand-name and generic drugs as a way to encourage generic and therapeutic substitution. Our findings suggest that cost-sharing differentials for brand-name and generic drugs were associated with unintended consequences (eg, discontinuation of any statin use) in Medicare patients with hyperlipidemia. In light of the established efficacy of these medications in reducing risk of serious and expensive cardiac outcomes, these findings raise concern. Additional interventions (eg, informing prescribers and patients of the availability of therapeutic equivalent agents at relevant decision points, such as via educational material in medical offices) are likely needed to eliminate or minimize such unintended consequences.

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Disclosures

Dr Li reports no conflicts. Dr Schwartz has served as a member of an advisory board for Pfizer Inc and received a grant from Pfizer. Dr Doshi has served as a member of an advisory board for Alkermes, Boehringer Ingelheim, Forest, Merck, and Shire, all unrelated to this study; and has received grant funding from Pfizer, Janssen, PhRMA, Sanofi, Amgen, National Pharmaceutical Council, and Humana; and whose spouse owns stock in Merck & Co. Inc and Pfizer, Inc.

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