Pharmacy Cost Sharing, Antiplatelet Therapy Utilization, and Health Outcomes for Patients With Acute Coronary Syndrome

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Objectives: To examine how cost sharing for prescription drugs affects compliance with antiplatelet therapy and subsequent health outcomes among patients with acute coronary syndrome (ACS).

Study Design: Retrospective outcomes study using administrative data from medical and pharmaceutical claims of patients enrolled at health plans offered by 26 large employers drawn from all regions of the country.

Methods: A total of 14,325 patients were diagnosed as having ACS and underwent coronary stent implantation between 2002 and 2005. Each patient was followed up for a maximum of 2 years. Primary outcomes measures were adoption of outpatient antiplatelet therapy, adherence to outpatient therapy, hospital admissions, and healthcare expenditures.

Results: Patients with ACS who face higher coinsurance are less likely to adopt outpatient antiplatelet therapy within the first month after stent implantation and are more likely to discontinue treatment in the first year after stent implantation (P <.01). Higher coinsurance is also associated with an increased number of ACS rehospitalizations (P <.01). For patients in health plans with higher coinsurance rates, expected costs from ACS hospitalizations are $2796 (38%) higher in the first year after stent implantation (P <.01).

Conclusions: Higher copayments for prescription drugs are associated with lower utilization of antiplatelet therapy and with higher likelihood of rehospitalization among patients with ACS. As a consequence, total healthcare spending for patients with ACS increases by approximately $615 in the first year after stent implantation.

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For author information and disclosures, see end of text.

Increased cost sharing for prescription drugs is often proposed as a cost-cutting mechanism to help curb rising healthcare costs. Evidence suggests that higher cost sharing substantially lowers pharmaceutical expenditures on the part of health plans.[1-4] However, there is a growing body of evidence that higher cost sharing worsens patient adherence to therapy. Because pharmaceuticals with a proven risk-benefit profile are often cost-effective treatments, this reduced adherence can lead to poorer health outcomes and eventually increase total healthcare costs.[5-8] This has led many to argue that cost sharing should be minimized for therapies with the highest expected clinical benefits.[9-11]

This study assesses how cost sharing for antiplatelet therapy affects utilization of therapy and attendant health outcomes among patients with acute coronary syndrome (ACS). This syndrome includes acute myocardial infarction and unstable angina. In 2006, approximately 1.4 million patients were hospitalized with a primary or secondary diagnosis of ACS.[12] The use of antiplatelet drugs (clopidogrel bisulfate plus aspirin) for up to 12 months after hospital discharge has been shown to significantly improve health outcomes for patients with non–ST-segment elevation ACS.[13,14] Clinical guidelines recommend the use of antiplatelet therapy for patients with ACS undergoing percutaneous coronary intervention with the implantation of a coronary stent.[15]

Antiplatelet drugs, and clopidogrel in particular, are among the most widely used prescription drugs. This makes them potentially attractive targets for health plans looking to decrease expenditures through higher cost sharing. However, there is evidence that more restrictive benefit designs such as prior authorization delay adoption of antiplatelet therapy among patients with acute myocardial infarction and are associated with significantly worse health outcomes.[16] The potential effect of higher cost sharing on antiplatelet therapy utilization and the health consequences for patients have not been explored to date.

METHODS

The data and methods used in our analysis are briefly described herein. More detail is available in an online technical **eAppendix** (available at **www.ajmc.com**). This study uses a

In this article
Take-Away Points / p291
www.ajmc.com
Full text and PDF
Web exclusive
eAppendix

longitudinal database of medical and pharmacy claims linked to benefit design information for a group of large private employers. We identify all patients in the sample who were diagnosed as having ACS between 2002 and 2005, defined as the presence of 1 or more of the following *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) diagnosis codes: 410.xx, 411.xx, 412.xx, or 414.xx. This definition of ACS is somewhat more expansive than the most commonly used alternative, which includes only acute myocardial infarction and unstable angina. We restrict the ACS sample to patients who underwent implantation of 1 or more coronary stents during this period (*ICD-9-CM* procedure code 36.06 or 36.07 or *Current Procedural Terminology* code 92980 or 92981 for outpatient treatment).

Take-Away Points

While cost sharing for pharmaceuticals is often suggested as a means to curb healthcare expenditures, it can sometimes reduce patient utilization of therapy and worsen health outcomes. This study examines the association of pharmacy cost sharing with discontinuation of antiplatelet therapy and with more rehospitalizations for acute coronary syndrome (ACS).

- Higher cost sharing is associated with lower utilization of antiplatelet therapy and with more ACS rehospitalizations.
- The expenditures associated with more rehospitalizations lead to a net increase in the costs paid by health plans for these patients.
- These findings suggest that imposing higher cost sharing for antiplatelet therapy as a means to reduce healthcare costs could be counterproductive.

We use 2002 as the start date for our study because this was the year in which clinical guidelines began recommending antiplatelet therapy as the method of treatment for patients with a coronary stent.[15] To focus on treatment for new ACS, we sample only patients who had no prior hospital admissions with an ACS diagnosis and no prescription for antiplatelet therapy in the 12 months preceding the first stent implantation in our study period. Our final analytic sample includes 14,325 patients with ACS covered by 265 plan-years provided by 26 different employers (because some health plans change benefit design over time, we use the term *plan-year* to refer to a plan in a specific year). We refer to the first stent as the index stent and the date of first stent as the index date.

Using our data on pharmacy claims, we are able to identify the fill date, dosage, and days supplied for all antiplatelet drugs. Most antiplatelet prescriptions (>90%) are for clopidogrel. The use of other antiplatelet drugs is so infrequent that we do not distinguish between the use of clopidogrel and other antiplatelet drugs.

Adoption

Total drug utilization depends on adoption and adherence. *Adoption* is defined as filling an outpatient prescription for clopidogrel after discharge (we use adoption to distinguish the start of therapy after discharge in contrast to initiation of therapy during the hospitalization). Most patients having ACS with stent implantation first receive antiplatelet therapy in the hospital. In some cases, delay might occur in high-cost health plans if physicians provide a greater quantity of free samples to patients (which we cannot observe). However, because it is unlikely that physicians provide even a full month's worth of free samples, we study adoption over the 40 days after implantation of the index stent.

Adherence

Past researchers have divided samples into discrete groups based on the proportion of days covered.[7,17-23] In this study, we define *discontinuation* as a 3-month period after implantation of the index stent during which the patient has 0 days covered. Although discontinuation represents just one component of adherence, we believe that it is the most salient measure for a treatment regimen as short as antiplatelet therapy. Discontinuation of clopidogrel therapy has been shown to be associated with worse health outcomes in past research.[24]

Hospitalizations and Expenditures

An *ACS hospitalization* is defined as a hospitalization after implantation of the index stent and with an associated diagnosis of ACS in the claim. We compute the total number of unique ACS hospitalizations in each 3-month period for the first 2 years after implantation of the index stent. We also compute total medical expenditures across all payers associated with each ACS hospitalization. As with hospitalizations, these expenditures are summed over each 3-month period for 2 years after stent implantation.

Cost Sharing

We use the observed coinsurance rate, the percentage of total pharmaceutical expenditures paid out of pocket by patients, as our measure of plan generosity. Changes in the coinsurance rate have been shown to be associated with utilization effects similar to those associated with changes in drug copayments.[25]

We define *high cost-sharing health plans* and *low cost-sharing health plans* as those with coinsurance in the top quartile and in the bottom quartile, respectively, across all plan-years in our sample. In our hypothetical scenarios, we replace the actual coinsurance rate in a plan-year with the mean coinsurance rate in the high cost-sharing health plans or the low

cost-sharing health plans. The mean coinsurance rates for the high cost-sharing health plans and the low cost-sharing health plans are 37% and 14%, respectively. In terms of US dollars, patients in the high cost-sharing health plans have mean copayments of $41.19 for antiplatelet medication compared with $9.41 in the low cost-sharing health plans.

An important consideration is the extent to which patients randomly choose their health plans. Our strategy requires that the unobserved baseline health status of patients at the time of the index stent is uncorrelated with plan generosity. In the technical appendix, we verify that the observed correlation between health plan choice and health status is not large. If anything, sicker patients are more likely to select low cost-sharing health plans; this would bias our approach toward finding more hospitalizations in the low cost-sharing health plans rather than less. This may render our estimated effects on hospitalization conservative. Moreover, our estimates include employer fixed effects, meaning that the identifying variation in coinsurance comes largely from changes in employer coverage, which are unlikely to be correlated with unobserved health status of workers.

Other Covariates

We include age, sex, marital status, and sponsorship status (employee or dependent). Measures of comorbidities come from the claims directly as a sequence of binary indicators for whether the patient had 2 or more claims for a specific condition during the year (we require ≥2 claims to avoid rule-out diagnoses). We use a full set of 30 separate comorbidities in our analyses. To incorporate effects from other pharmaceutical utilization, we also use the number of 30-day equivalent prescriptions for all other drugs that an individual fills.

Statistical Analysis

We use multivariate regression analysis to estimate the linear relationship between health plan cost sharing and other control variables on the following dependent variables: utilization, adoption, discontinuation, ACS hospitalizations, and total expenditures on ACS hospitalizations. The unit of analysis is a person-quarter; we aggregate the number of days a patient is covered by antiplatelet therapy and the number of ACS hospitalizations over 3-month intervals after implantation of the index stent. We conduct the analysis by quarter because this is the shortest period over which we can observe discontinuation of mail-order prescriptions.

Regressions are weighted by the number of individuals covered in a plan-year. Standard errors allow for correlation within employers (using the sandwich variance estimator of the "cluster" command in Intercooled STATA version 10; StataCorp LP, College Station, TX). Employer and year fixed effects are included in all regression models. The models for discontinuation and hospitalizations study only the first 4 quarters after implantation of the index stent. For the hospital expenditures model, we follow up patients for 2 years after implantation of the index stent but allow the effect of cost sharing to differ in the first and second years. Because clinical guidelines recommend antiplatelet therapy for up to 12 months after implantation of the index stent,[15] we expect effects on health outcomes within the first year. We examine outcomes in the second year as a validation test.

We use a continuous measure of cost sharing. To illustrate the effect of different cost-sharing levels, we use the regression models to predict values for high (top quartile) and low (bottom quartile) cost-sharing health plans. Specifically, we compute 2 sets of predicted values from the models. The first assigns all health plans the mean cost-sharing level among high cost-sharing health plans but overall mean values for the other covariates. The second assigns all health plans the mean cost-sharing level among low cost-sharing health plans. We interpret the resulting difference as the predicted effect of moving from high to low cost sharing (regression results are reported in the technical eAppendix). All tests of statistical significance are based on the significance of the underlying coefficients from the continuous model.

RESULTS

Table 1 gives summary statistics. The first column contains statistics for the full patient sample. Because our sample is restricted to patients having ACS with stent implantation, the sample consists of more older males than the general US population. Individuals in the western United States are underrepresented in the data, as they comprise just 6% of the sample. Patients in the sample filled approximately 6.9 thirty-day equivalent prescriptions for antiplatelet therapy in the first year after implantation of the index stent. The mean coinsurance rate for antiplatelet drugs (17%) is slightly lower in the sample than the mean coinsurance rate for all other drugs (21%). Patients average 0.3 and 0.4 total ACS rehospitalizations over the first and second years after implantation of the index stent, respectively.

The second and third columns in Table 1 give statistics for patients in the low and high cost-sharing samples, respectively. Patients with low cost sharing have lower copayments and coinsurance rates but higher drug utilization. The table also summarizes observable differences between patients in the 2 groups. Patients with high cost sharing are more likely to be male, married, and have higher income.

Figure 1 shows Kaplan-Meier estimates of the probability that a patient adopts antiplatelet therapy over the first 40

■ **Table 1.** Characteristics of 14,325 Privately Insured Patients With Acute Coronary Syndrome (ACS) Undergoing Coronary Stent Implantation Between 2002 and 2005[a]

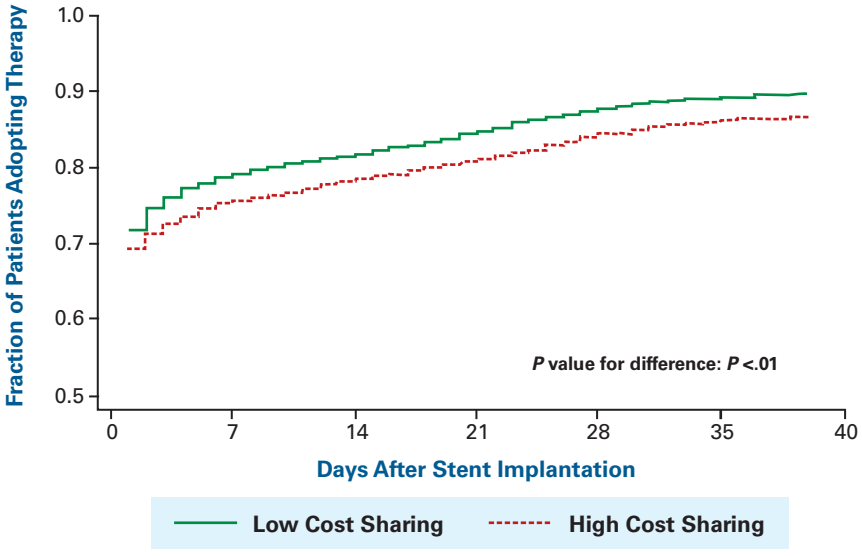
Variable	All Patients	Patient Subgroup	
		Low Cost-Sharing Health Plan	High Cost-Sharing Health Plan
Demographics			
Age, y			
Mean (SD)	67 (11)	68 (10)	67 (10)
≥65, No. (%)	57 (50)	63 (48)	64 (48)
Male sex, No. (%)	70 (46)	64 (48)	78 (42)
Married, No. (%)	72 (45)	67 (47)	81 (39)
Patient is primary insured, No. (%)	71 (45)	71 (46)	73 (44)
Annual household income, median (SD), $[b]	42,071 (9149)	40,188 (7571)	44,516 (10,361)
No. of comorbidities, mean (SD)	2.2 (1.3)	2.3 (1.4)	2.1 (1.2)
Geographic Region, No. (%)			
Northeast	20 (40)	12 (33)	30 (46)
Midwest	36 (48)	47 (50)	22 (42)
West	6 (23)	2 (14)	12 (32)
South	39 (49)	39 (49)	36 (48)
Prescription Drug Utilization and Benefits			
No. of 30-day equivalent antiplatelet prescriptions after stent implantation, mean (SD)			
First year	6.9 (4.1)	6.7 (4.3)	5.8 (4.1)
Second year	9.2 (7.1)	9.3 (7.5)	7.4 (6.6)
Copayment for antiplatelet drugs, mean (SD), $	31.2 (23.5)	12.9 (8.1)	61.6 (19.1)
Coinsurance rate, mean (SD), %			
Antiplatelet drugs	17 (11)	8 (3)	31 (8)
All other drugs	21 (11)	11 (2)	36 (6)
No. of 30-day equivalent prescriptions for all other drugs in the first year after stent implantation, mean (SD)	48.5 (34.3)	55.4 (35.9)	42.0 (30.4)
No. of ACS Hospitalizations After Stent Implantation, Mean (SD)			
First year	0.3 (0.7)	0.4 (0.7)	0.3 (0.7)
Second year	0.4 (0.9)	0.5 (0.9)	0.4 (0.8)
Observations			
No.	14,325	6600	3192

[a]Data are weighted by the total number of patients in the plan-year.
[b]Defined at the 3-digit zip code tabulation area level in the 2000 US census.

days after the index date for high cost-sharing and low cost-sharing health plans. The dashed line represents high cost-sharing health plans. We restrict the analysis to the first 40 days after implantation of the index stent because our data indicate that this is the period during which most prescriptions are filled. Both the high and low cost-sharing health plans have high rates of adoption immediately after implantation of the index stent; approximately 70% adopt therapy 1 day after implantation. Adoption occurs more rapidly and frequently in low cost-sharing health plans (P <.01). Adoption is higher in low cost-sharing health plans at every point. At 40 days after implantation of the index stent, approximately 90% of patients with low cost sharing have adopted antiplatelet therapy compared with approximately 86% of patients with high cost sharing.

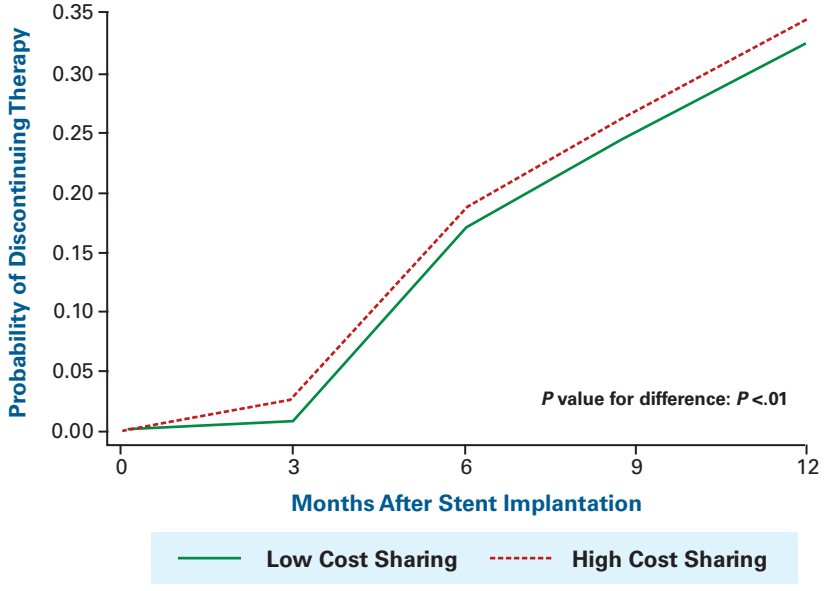
Figure 2 shows the relationship between cost sharing and likelihood of discontinuation. The 2 lines represent the predicted probabilities of discontinuation by month after the

Figure 1. Proportion of Patients Adopting Antiplatelet Therapy in High Cost-Sharing and Low Cost-Sharing Health Plans[a]



[a]The figure shows the Kaplan-Meier failure function of the number of days after implantation of the index stent until adoption of antiplatelet therapy. Adoption date is the date on which the first outpatient prescription for antiplatelet drugs is filled. Failure functions are graphed between 1 and 40 days after implantation of the index stent.

Figure 2. Predicted Probability of Discontinuing Antiplatelet Therapy in High Cost-Sharing and Low Cost-Sharing Health Plans[a]



[a]The predicted probability of discontinuation is generated using multivariate regression of the probability that a patient discontinues therapy in a quarter against the mean coinsurance rate in the health plan, controlling for year effects, employer fixed effects, demographic characteristics, and comorbidities. Predicted values are computed in each quarter at the mean values of all characteristics and at the coinsurance rates for high cost-sharing and low cost-sharing health plans. The estimated change in the probability of discontinuation during a quarter in response to a 10% increase in the coinsurance rate is 0.007 (P <.01). Regressions are weighted by the total number of individuals in the plan-year, and variance estimates are calculated allowing for dependence (ie, clustering) within employers.

index date, evaluated at the mean coinsurance rates for high and low cost-sharing health plans. The likelihood of discontinuation rises over time for patients in both groups, but discontinuation is more likely in high cost-sharing health plans. Each month, the probability of discontinuation is 1.8 percentage points higher for patients in high cost-sharing health plans (P <.01). These findings indicate that higher cost sharing reduces utilization through delayed adoption and greater discontinuation.

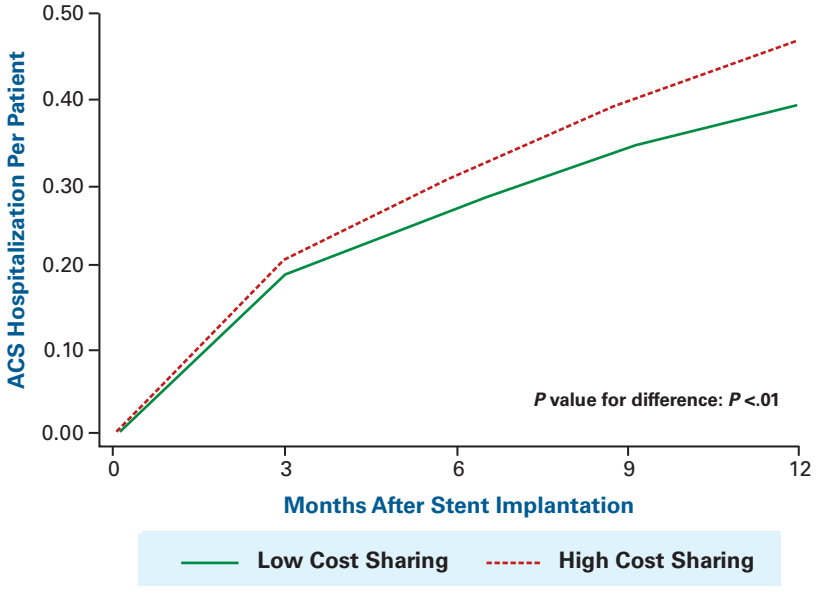
Figure 3 shows the predicted number of rehospitalizations per patient over the first 12 months after the index date for patients in high and low cost-sharing health plans. Higher cost sharing is associated with more rehospitalizations. On average, patients with low cost sharing experience approximately 0.19 ACS hospitalizations over the first 3 months after implantation of the index stent compared with 0.21 for patients with high cost sharing (P <.01). Through 12 months after implantation of the index stent, these numbers were 0.40 and 0.47 for patients in low and high cost-sharing health plans, respectively (P <.01). Note that these values do not represent the probability of rehospitalization because some patients will have multiple ACS rehospitalizations in the year.

Table 2 gives the differences in predicted healthcare expenditures resulting from ACS rehospitalizations for high cost-sharing and low cost-sharing health plans. During the first year after implantation of the index stent, the mean cumulative cost of ACS rehospitalizations per patient was $7361 in low cost-sharing health plans compared with $10,157 in high cost-sharing health plans, for a difference of $2796 or 38% ($P$ <.01). This

is higher than the difference implied by just the number of hospitalizations between the 2 groups, suggesting that patients with ACS in high cost-sharing health plans also have longer, more expensive hospitalizations. The mean coinsurance rate for inpatient care in our sample is 22%, so patients pay approximately $615 of the total increase in costs given in Table 1.

Table 2 also gives the predicted expenditures for the second year after stent implantation. Patients with low cost sharing have cumulative costs of $5146 for ACS hospitalizations in the second year compared with $4904 for patients with high cost sharing, for a difference of $242 or 4.7% ($P$ = .82). This suggests that there is no statistical difference in expected costs from ACS rehospitalizations during the second year after the index date, although cumulative costs over both years are lower for low cost-sharing health plans.

■ **Figure 3.** Predicted Number of Acute Coronary Syndrome (ACS) Hospitalizations per Patient in High Cost-Sharing and Low Cost-Sharing Health Plans[a]



[a]The predicted number of hospitalizations is generated using multivariate regression to estimate the number of hospitalizations with an ACS diagnosis in a quarter against the mean coinsurance rate in the health plan, controlling for year effects, demographic characteristics, and comorbidities. Predicted values are computed in each quarter at the mean values of all characteristics and at the coinsurance rates for high cost-sharing and low cost-sharing health plans. The estimated change in the number of hospitalizations during a quarter in response to a 10% change in the coinsurance rate is 0.008 (P <.01). Regressions are weighted by the total number of individuals in the plan-year, and variance estimates are calculated allowing for dependence (ie, clustering) within employers.

Compared with low cost-sharing health plans, our results suggest that high cost-sharing health plans experience a $2180 increase in rehospitalization costs per patient with ACS during the first year after stent implantation. Apart from health outcomes for patients, health plans face the question of how the expected increase in hospitalization costs compares with the overall savings from increasing cost sharing for pharmaceuticals. The patients in our sample have mean expenditures on prescription drugs of $4845 in the year following implantation of the index stent. Accounting for the estimated effect of higher cost sharing on the utilization of all drugs, the total pharmaceutical cost savings to a high cost-sharing health plan rise to about $1577. This suggests a net increase in the mean expenditures to health plans of $603 per patient with ACS during the year after stent implantation, or $2180 minus $1577. This figure is conservative because it ignores additional costs that could arise from decreased utilization of prescription drugs other than antiplatelet therapy, which could lead to other adverse health outcomes unrelated to ACS. It also ignores costs associated with ACS events that do not result in a hospitalization, as well as the patient's private cost of enduring poorer health.

DISCUSSION

Our findings suggest that increased cost sharing for antiplatelet therapy among patients having ACS with stent implantation is associated with worse health outcomes and with a net increase in expenditures by health plans. Although higher cost sharing may sometimes prove to be a cost-effective means for reducing costs and for discouraging waste, our findings suggest that it may not be desirable in all instances. Higher cost sharing seems less likely to be cost-effective in cases where there is proven clinical benefit from adhering to a fixed course of treatment, as with antiplatelet therapy after coronary stent implantation. Compounding this effect are the costly consequences of failure to adhere, which ultimately raises the risk of hospitalizations. Most of the costs accrue within a short period of less than 1 year, suggesting that even high-turnover health plans face this trade-off. This result is consistent with the proposal by Fendrick et al[9] to reduce copayments for drugs with high therapeutic benefits.

The estimated effects on utilization are somewhat smaller than other estimates, but we find a strong effect on health outcomes. This may be due to the fact that patients having

Table 2. Predicted Annual Expenditures on Acute Coronary Syndrome (ACS) Hospitalizations in High Cost-Sharing and Low Cost-Sharing Health Plans During the First and Second Years After Stent Implantation[a]

Variable	First Year	Second Year
Low cost-sharing health plan, mean, $	7361	5146
High cost-sharing health plan, mean, $	10,157	4904
Difference (%)	2796 (38.0)	–242 (–4.7)

[a]Reported are the estimated cumulative expected costs from ACS hospitalizations. Annual costs are estimated using multivariate regression of the total expenditures associated with ACS hospitalizations in a quarter against the mean coinsurance rate in the plan, controlling for year effects, demographic characteristics, and comorbidities. Predicted values are computed at the mean values of all characteristics and at the coinsurance rates for high cost-sharing and low cost-sharing health plans and are summed over all quarters. The estimated differences in costs associated with a 10% change in the coinsurance rate are $377.20 ($P$ <.01) per quarter in the first year after implantation of the index stent and –$24.40 ($P$ = .82) per quarter in the second year. Regressions are weighted by the total number of individuals in the plan-year, and variance estimates are calculated allowing for dependence (ie, clustering) within employers.

ACS with stent implantation are sicker on average than the patient populations that have been the focus of many prior studies on prescription drug utilization. Goldman et al[26] show that chronically ill patients receiving ongoing treatment are less price responsive than others. Given that antiplatelet use is strongly associated with improved health outcomes for patients having ACS with stent implantation, it is not surprising that a decline in utilization is associated with substantially worse health outcomes.

Several limitations to this study should be noted. While we focus on the utilization of antiplatelet therapy, our cost-sharing measure reflects benefit generosity for all drugs. An alternative approach would have been to calculate the actual coinsurance rate that each patient faces for antiplatelet therapy. However, the use of actual payment data is problematic because it reflects choices made by patients. This leads to systematic bias if patients switch to lower-cost medications because of high costs or if patients enjoy lower copayments because of high spending levels that exceed deductibles or out-of-pocket maximums. To overcome these limitations, we use aggregate measures of cost sharing at the plan-year level.

Our results should be interpreted as reporting the association between overall plan generosity and health outcomes for patients with ACS. In principle, this association could be generated by antiplatelet therapy or by several other pharmaceutical products such as statins or β-blockers. Higher cost sharing in a health plan could reduce utilization of these alternative therapies, which could contribute to worse health outcomes experienced by patients with ACS. However, it is important to note that these therapies are typically associated with long-term benefits of utilization, whereas antiplatelet therapy has been shown to have an immediate effect on health outcomes.[13,27,28] The fact that the positive health outcomes associated with lower cost sharing all accrue in the first year after stent implantation suggests that utilization of antiplatelet therapy is an important factor in the causal relationship. Nevertheless, future work should address the extent to which cost sharing reduces adherence for the full range of pharmaceutical products used to treat ACS, as well as how each affects health outcomes.

A related point is that our data do not include the use of over-the-counter therapies such as aspirin. Clinical evidence supports the use of antiplatelet therapy in addition to aspirin,[13,14] and it is unclear whether aspirin use is correlated with plan-level cost sharing.

Another limitation is the lack of evidence on how failure to adhere directly affects patients. Our findings suggest that higher cost sharing increases the likelihood of hospitalization for ACS, but we have no means for quantifying the cost of this to patients. Furthermore, our data do not allow us to address the effect of cost sharing on mortality of individual patients. The evidence from clinical trials clearly indicates that antiplatelet therapy reduces mortality among patients having ACS with stent implantation.[13,14]

In conclusion, in the face of rising medical expenditures, there has been increasing pressure on health plans to take steps to contain costs by increasing patient cost sharing for prescription drugs. However, some patients will fail to adopt or will prematurely discontinue therapy when faced with higher out-of-pocket expenditures. This study shows that higher coinsurance rates for antiplatelet therapy are associated with early discontinuation of therapy and with a higher rate of rehospitalization among patients with ACS. These findings suggest that imposing higher cost sharing for antiplatelet therapy as a means to reduce healthcare costs could be counterproductive.

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company. Dr Maclean is an employee of Bristol-Myers Squibb, the manufacturer of the antiplatelet therapy discussed in this study, and reports owning stock in the company.

Authorship Information: Concept and design (TJP, EM, JRM); acquisition of data (TJP); analysis and interpretation of data (TJP, EM, JRM); drafting of the manuscript (TJP); critical revision of the manuscript for important intellectual content (TJP, EM, JRM); statistical analysis (TJP); obtaining funding (TJP); administrative, technical, or logistic support (TJP); and supervision (TJP).

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