A n extensive literature has documented the impact of high copayments on medication use. These studies suggest that for each 10% increase in cost sharing, prescription drug use decreases by 2% to 6%, depending on the class of drug and indication for its use. In the case of “essential” medications, these reductions in medication consumption should be associated with adverse clinical consequences. After all, if randomized trials and other forms of high-quality evidence have established the relationship between the (greater) use of a drug and improvements in health outcomes, then the opposite must logically be true. Numerous studies demonstrate this apparent association. For example, patients who discontinue evidence-based medications after an acute myocardial infarction or stroke are 3 times more likely to die than patients who remain adherent.

However, the validity of these observations is threatened by an important bias: patients who stop therapy are often sicker than patients who do not, either because of true clinical differences or their likelihood of engaging in healthy activities (see Figure). This “sick stopper bias” is a direct analog of the “healthy user effect,” whereby patients who adhere to preventive therapies are more likely than nonadherent patients to engage in a broad spectrum of healthy behaviors such as use of preventive services. As a result, adherent patients are less likely to experience adverse health outcomes (eg, motor vehicle accidents) that are related and unrelated to the therapeutic effects of the drugs being evaluated. In this way, the apparent association between medication discontinuation and adverse clinical outcomes (Figure line 3) may actually be due to confounding by a patient’s healthy lifestyle and health choices (Figure lines D-F), even in analyses that use multivariable models to carefully adjust for observable clinical covariates (Figure lines B-E).

In this issue of The American Journal of Managed Care, Philipson and colleagues evaluate the association between cost sharing for clopidogrel, medication discontinuation, and rates of acute coronary syndrome (ACS) rehospitalization. Clopidogrel is an essential drug in the management of patients who have experienced an ACS and undergone percutaneous coronary intervention. It also is very expensive, and its underuse is common. Thus, an evaluation of the implications of high cost sharing for this drug is an important contribution to the literature. The authors demonstrate that patients with 10% higher coinsurance for clopidogrel have a 0.74 percentage point greater risk per quarter of medication discontinuation and a 0.76 percentage point greater risk per quarter of ACS rehospitalization.

The authors recognize the pitfalls of directly evaluating the association between the observed reductions in clopidogrel use related to higher cost sharing and the subsequent changes in the rate of hospitalization, and thus do not do so. Nevertheless, their results clearly imply this relationship, and the 2 associations they do evaluate may be confounded by the same factors they seek to avoid (see the Figure). The relationship between higher cost sharing and reduced medication use (line 1) may be confounded by observable (lines A-B) and unobservable (lines C-D) characteristics. Similar concerns could exist for the relationship between cost sharing and utilization (line 2 compared with lines A-E and C-F).

If, for example, sicker patients chose or ended up in plans with higher levels of cost sharing, the apparent association between higher cost sharing and lower utilization may be the result (in part or in whole) of these patient characteristics. Philipson et al evaluated selection effects by measuring the average number of patient comorbidities in the year after the index ACS discharge. Other factors inherent to the variations in plan design that are the focus of the authors’ investigation are more difficult to address. For example, patients with certain preferences or medical histories (ie, before their index ACS) may seek employers or jobs with less or more generous benefits (even if these factors don’t influence plan choice after the ACS has occurred). More directly, the generosity of drug coverage for clopidogrel is likely related to cost sharing for other evidence-based medications which, if stopped, also confer near-term risks. Thus, it may not be accurate to attribute all of the observed effects of high cost sharing to clopidogrel alone, especially since the primary independent variable in Philipson et al’s analysis is an overall measure of plan generosity (ie, for all drugs and not specifically for clopidogrel).
Clinical Outcomes

Regression analyses. High-dimensional propensity scores and other medications might be included as parameters in the especially when a control group is used.

When a natural cost-sharing change occurs, interrupted time-series methods limit confounding to co-occurring events, especially when a control group is used.

A rebound phenomenon has been associated with stopping clopidogrel, but the expected event rate is far lower than that observed. Further, the actual cost for an ACS hospitalization for patients with high drug cost sharing was greater than that for patients with low cost sharing. This too may reflect the characteristics of patients who discontinued clopidogrel (ie, sick patients stop therapy and sick patients also have longer and more complicated hospitalizations), rather than the consequences of the discontinuation itself.

How might such confounding be addressed? In the absence of randomized cost-sharing evidence, a variety of design and analytic strategies might help. Markers of health-seeking behavior, such as receipt of immunizations or adherence to other medications, might be included as parameters in the regression analyses. High-dimensional propensity scores and instrumental variable methods may provide for better covariate balance and more valid inferences of treatment effects. When a natural cost-sharing change occurs, interrupted time-series methods limit confounding to co-occurring events, especially when a control group is used.

Perhaps most telling is the fact that the increased rate of clopidogrel discontinuation associated with higher cost sharing is almost identical to the increased rate of cardiac rehospitalization. This implies that all patients who discontinued clopidogrel were rehospitalized because of it or that a smaller number of patients had multiple subsequent hospitalizations all as a result of cost-related medication discontinuation.

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High Cost Sharing and Adverse Outcomes


