ORIGINAL RESEARCH ARTICLE

Effect of cost sharing on adherence to evidence-based medications in patients with acute coronary syndrome

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ABSTRACT

Objectives Cost-sharing scheme for pharmaceuticals in Spain changed in July 2012. Our aim was to assess the impact of this change on adherence to essential medication in patients with acute coronary syndrome (ACS) in the region of Valencia.

Methods Population-based retrospective cohort of 10 563 patients discharged alive after an ACS in 2009–2011. We examined a control group (low-income working population) that did not change their coinsurance status, and two intervention groups: pensioners who moved from full coverage to 10% coinsurance and middle-income to high-income working population, for whom coinsurance rose from 40% to 50% or 60%. Weekly adherence rates measured from the date of the first prescription. Days with available medication were estimated by linking prescribed and filled medications during the follow-up period.

Results Cost-sharing change made no significant differences in adherence between intervention and control groups for essential medications with low price and low patient maximum coinsurance, such as antiplatelet and beta-blockers. For costlier ACE inhibitor or an angiotensin II receptor blocker (ACEI/ARB) and statins, it had an immediate effect in the proportion of adherence in the pensioner group as compared with the control group (6.8% and 8.3% decrease of adherence, respectively, p<0.01 for both). Adherence to statins decreased for the middle-income to high-income group as compared with the control group (7.8% increase of non-adherence, p<0.01). These effects seemed temporary.

Conclusions Coinsurance changes may lead to decreased adherence to proven, effective therapies, especially for higher priced agents with higher patient cost share. Consideration should be given to fully exempt high-risk patients from drug cost sharing.

INTRODUCTION

The use of proven, effective and safe medications has contributed substantially to reductions in cardiovascular morbidity and mortality.[1] Accordingly, clinical practice guidelines recommend that all patients with an acute coronary syndrome (ACS) receive treatment with a beta-blocker, a statin, an ACE inhibitor (ACEI) or an angiotensin II receptor blocker (ARB) and antiplatelet agents,

unless a contraindication exists. But important gaps in adherence to prescribed therapies arise: some patients never fill their first prescriptions,[2] and most have poor adherence to medication regimens over time.[3,4] Not surprisingly, non-adherent patients are at a substantially higher risk of death.[5] Patients with ACS who discontinue all of their medications are more than three times as likely to die as those who remain adherent.[6] Therefore, improving medication adherence could further reduce the burden of ACS.

Patient cost sharing is among the many factors that contribute to medication non-adherence, and evidence shows that reducing patient out-of-pocket expenses is generally associated with improved drug adherence.[7] Patient cost-sharing policies that take into account patient characteristics, patient risks and published evidence (with regard to the efficacy and the relative effectiveness of interventions) could improve the rational use of drugs and produce savings for insurers without having a negative effect on health outcomes. However, interventions targeting high-value therapies on high-risk patients may affect adherence and lead to undesired outcomes. A large number of studies have analysed the relationship between cost sharing and adherence to drug treatments and found that cost sharing may unintentionally negatively impact the use of and adherence to essential medications for chronic diseases.[8–11] With regard to ACS medications, there is evidence that even in the absence of cost-sharing schemes, patient adherence is suboptimal.[8–16] This situation highlights the need for careful consideration of the appropriateness of subjecting essential medications to patient cost sharing that could further compromise the achievement of benefits observed in clinical trials.

In 2012, the Spanish drug cost-sharing scheme was reformed. This affected mainly pensioners, who had been exempt from cost sharing until this reform, when a 10% coinsurance (percentage of the price of the drug which has to be paid by the patient) with a monthly copayment (total amount to be paid by the patient) ceiling of €8 or €18, according to income, was set up for the vast majority. In addition, the scheme affected the middle-income to high-income working population, for whom coinsurance rose from 40% to 50% of drug price (or to 60%, depending on income), with no ceiling. Low-income

working population coinsurance remained unchanged at 40% with no ceiling. These differential copayment schemes resulted in a natural experiment, with the latter group acting as a control group and pensioners and the middle-income to high-income working population as intervention groups, which provided an opportunity to evaluate the consequences of the changes in the patient drug cost-sharing scheme on adherence for a cohort of population with available information before and after the reform. The aim of this study was to assess the impact of the cost-sharing reform on medication adherence in patients with ACS in the Spanish region of Valencia.

METHODS
Design
Population-based retrospective cohort of patients discharged alive after an ACS to any Valencia Health System (VHS) hospital from January 2009 to December 2011, who were followed throughout the health information systems from hospital discharge to December 2013.

Setting
The study was conducted in the Valencia region, an autonomous region in Spain with 5.11 million inhabitants in 2010. Specifically, in the VHS, an extensive network of hospitals, primary care centres and other facilities managed by the regional government, which provides universal free healthcare services (except for drug copayment) to 97% of the region's population.

Population
All patients of both sexes aged 35 years and over with an emergency admission and discharged from any of the 24 acute care VHS hospitals with a main diagnosis of ACS (International Classification of Diseases, Ninth Revision, Clinical Modification - ICD9CM=410.xx—except 410.x2—and 411.xx) between 1 January 2009 and 31 December 2011. Exclusion criteria were as follows: (1) government employees whose prescriptions are reimbursed by civil service insurance mutualities, not included in the pharmacy databases of the VHS; (2) patients not registered in the municipal census, who left the region or who were discontinued from VHS coverage for other causes, because of limitations on follow-up; (3) patients who died before July 2012, when the cost-sharing change came into force; and (4) patients who changed their cost-sharing status during the study period; (5) non-treated patients (patients who had no prescription for any of the four therapeutic groups within the first 3 months after discharge).

Data sources
We combined data from several electronic information systems of the VHS (outpatient electronic medical record, Minimum Basic Dataset at discharge and the population information system) to create a database with sociodemographic characteristics, including all physician prescriptions written, all prescriptions filled at the pharmacy, ambulatory diagnoses and procedures, outpatient and emergency department visits, hospitalisations, and deaths for all patients studied.

Study cohorts
We created three cohorts, one control group and two intervention groups, as follows: the working population not affected by the cost-sharing scheme change (patients with an annual income lower than €18 000 and subject to 40% coinsurance with no changes during the period studied) made up the control group; pensioners, who were previously exempt from cost sharing and moved to 10% coinsurance with a monthly ceiling for all medications (including ACS drugs) of €8 or €18 depending on income, made up one of the intervention groups. The second intervention group comprised the middle-income to high-income working population (earning more than €18 000 annually) who had previous coinsurance of 40% and increased to 50% or 60%, depending on income (table 1). Pensioners earning more than €100 000 per year, with 60% coinsurance and €60 ceiling were excluded, though group is barely relevant as it accounts for <0.1% of the population.

ACS medications
We studied four therapeutic groups: antiplatelet agents (acetylsalicylic acid at doses of 100 mg), beta-blockers, ACEI/ARB and statins. Clopidogrel was excluded as it is indicated as a short-term treatment, and thus the majority of patients do not reach the policy change time point under treatment. Independently of the cost-sharing scheme, patient expense in beta-blockers, ACEI or ARB as single agents was limited to 10% of the package cost (chronic medication scheme). Antiplatelet agents, statins, ACEI or ARB in fixed-dose combinations had no package cost limit. Table 2 shows the average prices per package (calculated on the date at which the cost-sharing change occurred) and the corresponding patients' cost-share amounts before and after the scheme change.

Primary outcome
We evaluated the impact of the cost-sharing change on medication adherence. For this purpose, we employed a novel,

Table 1 Cost-sharing scheme characteristics before and after the July 2012 reform

Study groups	Population groups	Before the reform		After the reform	
		Coinsurance (% price)	Monthly ceiling	Coinsurance (% price)	Monthly ceiling
Pensioners group	Pensioners (annual income lower than €18 000)	0	–	10	€8
	Pensioners (annual income between €18000 and €100 000)	0	–	10	€18
	Pensioners (annual income>€100 000)*	0	–	60	€60
Low-income working population (control group)	Working population (annual income lower than €18 000)	40	No ceiling	40	No ceiling
Middle-income to high-income working population	Working population (annual income between €18 000 and €100 000)	40	No ceiling	50	No ceiling
	Working population (annual income>€100 000)	40	No ceiling	60	No ceiling

*Pensioners with annual income>€100.000 account for 0.097% of the Spanish population, and in practice this group is barely relevant for analysis.

Table 2 Average prices and maximum patient cost sharing before and after the reform

		Average price per package (maximum patient cost-sharing before and after policy change), in €		
		Control group	Pensioners group	Middle-income to high-income group
Total maximum medication monthly patient share after the scheme change	Max patient share per drug	No ceiling	€8 to €18 per month*	No ceiling
Antiplatelet	No	4.3 (1.76)	4.2 (0 to 0.42)	4.1 (1.64 to 2.05 or 2.46)
Beta-blockers	10%	2.9 (0.29)	3.1 (0 to 0.31)	3.0 (0.30)
ACEI/ARB (single molecule)	10%	7.4 (0.74)	7.5 (0 to 0.75)	7.0 (0.70)
ACEI/ARB combined with another molecule	No	22.6 (9.04)	21.5 (0 to 2.15)	20.6 (8.24 to 10.3 or 12.36)
Statins	No	21.4 (8.56)	19.0 (0 to 1.9)	21.3 (8.52 to 10.65 or 12.78)

*The changes in the cost-sharing scheme defined a third group of pensioners earning >€100 000 annually, with a 60% coinsurance and a €60 ceiling. In practice, this group is barely relevant for analysis as it accounts for <0.1% of the population.
ACEI, ACE inhibitor; ARB, angiotensin II receptor blocker.

pinpointed approach to assess adherence taking into account both prescriptions issued by the physician and prescriptions filled by the patient at the pharmacy (linked by a single identifier). Thus, adherence was only assessed during the periods the patient had prescriptions written by their physicians, obtaining more precise adherence estimates. Days with available medication during the follow-up period were estimated through the dose regimen defined by the physician and the number of pills per package (eg, for a regimen of one pill every 12 hours and packages of 30 tablets, each dispensation would entail 15 days of medication available). In our study, 85% of the prescriptions provide 30 days' supply, 10% provide 15 days' supply, with the remaining 5% of prescriptions providing between 30 and 60 days covered with medication. After issuing a prescription, this remains valid for a period of 10 days. If a refill occurred before the previous refill should have run out, we assumed that the new refill began the day after the end of the old refill, and days with a drug supply were accumulated. We allowed for a maximum of an accumulated daily supply (stockpiling) of 180 days. Different agents within a therapeutic class were considered interchangeable. Weekly adherence was measured from the time of the first prescription (definition of being adherent as having ≥80% of the time covered), obtaining a repeated dichotomous measure for each week of follow-up and patient. Considering that we are working with time series, we translate these adherence estimates into calendar time units. Once we have adherence estimates (as a dichotomous outcome) for each individual and calendar week, we calculate average adherence rates for the population under treatment at each calendar week of the period of assessment.

Ethics
The study was approved by the Institutional Review Board of the Public Health General Directorate of the Valencia Health Authority and the Center for Public Health Research. All patient data were transferred to the research team anonymised and de-identified prior to analysis. The Regulatory Commission of Access to Ambulatory Care Information of the Valencia Health Authority approved the cession of this anonymised data.

Statistical analysis
We constructed weekly series of adherence rates for the intervention and control cohorts from January 2011 to December 2013, for 18 months before the cost-sharing policy change and 18 months after, totalling 156 weeks. We estimated

difference-in-difference (DiD) models by ordinary least squares through segmented linear regression for the weekly rates of adherence to the four therapeutic groups assessed.[17] The models compared intervention groups (pensioners and the middle-income to high-income working group) with the control group (low-income working population), and detected the occurrence of an immediate effect (level change) and trend effect (slope changes) attributable to the cost-sharing policy change. The DiD method accounts for unobserved variables that can be different between the groups but are assumed to remain fixed over time, as is the case of age-sex composition of the groups as well as other baseline characteristics. Also, the DiD analysis takes into account and controls for counterfactual temporal trends to provide estimates of differences in trends.

The general model is as follows:

$$Y_t = \alpha_0 + \alpha_1 t + \alpha_2 RD + \alpha_3.RD + \alpha_4 I + \alpha_5 t.I + \alpha_6.RD.I + \alpha_7 t.RD.I + \epsilon,$$

where I is the dummy=1 for the intervention group, t is the temporal trend (=1 for the first week of the study time span) and RD is the dummy=1 from July 2012. The model also includes a dummy for August, as preliminary bivariate tests found a significant drop in adherence that month. The DiD estimator for the immediate short-term effect on adherence after the policy change, in the intervention groups, as compared with the control group is α_6 and the estimator for the differential effect on slope change is α_7. Thus, the total effect of the policy change at week t is $\alpha_6 + \alpha_7 t$. We calculated the model predictions of adherence rates for each group at t=1, 2,…,18 months after the change in cost sharing, and compared them with the counterfactual rates (no change scenario) to evaluate medium-term effects. All analyses were done using Stata v13 and R.

RESULTS
Patient characteristics
From 10 563 patients who were discharged alive after an ACS between 2009 and 2011 and survived at least until the cost-sharing scheme change in July 2012, 1839 patients did not experience any change in their cost-sharing status (control group), 8715 were pensioners (pensioners group) and 639 belonged to the middle-income to high-income group. Patients in the pensioners group were older (mean age 71.3 years old vs 51 in the control and 51.3 in the middle-income to high-income groups), had a higher proportion of women (32.4% vs 16.2% in the control group and 10.7% in the middle-income to high-income group) and a lower frequency of myocardial

Table 3 Patient characteristics per cohort and adherence rates in the 18 months previous to the cost-sharing change

	Control group	Intervention groups	
Characteristics	Low-income working population	Pensioners	Middle-income to high-income working population
Number of patients	1839	8715	639
Average age	51.0	71.3	51.3
% Females	16.2	32.4	10.7
% Acute myocardial infarction	84.1	73.4	85.1
Average time from the event occurred (days)	702	717	709
Average weekly adherence rates before the cost sharing change (%)*			
Antiplatelet	84.2 (1609)	94.0 (7632)	86.9 (533)
Beta-blockers	88.5 (1543)	94.9 (6943)	90.4 (547)
ACEI/ARB	90.7 (1349)	95.1 (7198)	92.0 (458)
Statins	83.2 (1748)	94.2 (7970)	86.9 (611)

*The number of patients on treatment with each therapeutic group is shown in parentheses. Patients on treatment are defined as those patients receiving one prescription within 3 months from the ACS event.

ACEI, ACE inhibitor; ACS, acute coronary syndrome; ARB, angiotensin II receptor blocker.

infarction as main index admission diagnosis (73.4% vs 84.1% and 85.1%, respectively). Time from the index event to the policy change was similar for the three groups (table 3).

Medication adherence

Medication adherence was already suboptimal before the cost-sharing change, particularly for working groups (table 3). Weekly rates of adherence for the four therapeutic groups before and after the scheme change are shown in figure 1. *Weekly rates of adherence for the drugs considered for the three cohorts.* For the whole period, adherence rates in the pensioners group were higher than for the working population for all therapies. Among the working population, middle-income to high-income patients had higher adherence figures than patients in the control group (low income), even before the cost-sharing change.

The cost-sharing change had an immediate effect on the proportion of adherence for ACEI/ARB (single-agent and fixed-dose combinations all considered) and statins, in the pensioner group as compared with the control group (6.8% and 8.3% decrease of adherence, respectively, p<0.01 for both). However, there was a significant change in trend after the policy modification indicating a possible recovery of adherence in the pensioners group as compared with the control group (p<0.01 for both). For the middle-income to high-income group as compared with the control group, only adherence to statins significantly decreased after the reform (7.8% decrease in adherence, p<0.01). As observed for pensioners, the differential change in trend for the middle-income to high-income group after the reform suggests that the effect of increased coinsurance on adherence attenuated with time (p<0.01), showing these effects may be temporary. No effect was found for low-priced essential medications and low patient maximum coinsurance (such as antiplatelet and beta-blockers) in either intervention group as compared with the control group.

Regarding the duration of the effect of the cost-sharing policy change, pensioners seemed to move back to counterfactual expected rates of adherence to antiplatelet agents within 15 months of the change, and 18 months or longer for the rest of the medications. The apparent recovery to counterfactual expected rates for the middle-income to-high-income working population was faster for all medications, this being around 1 year (table 4).
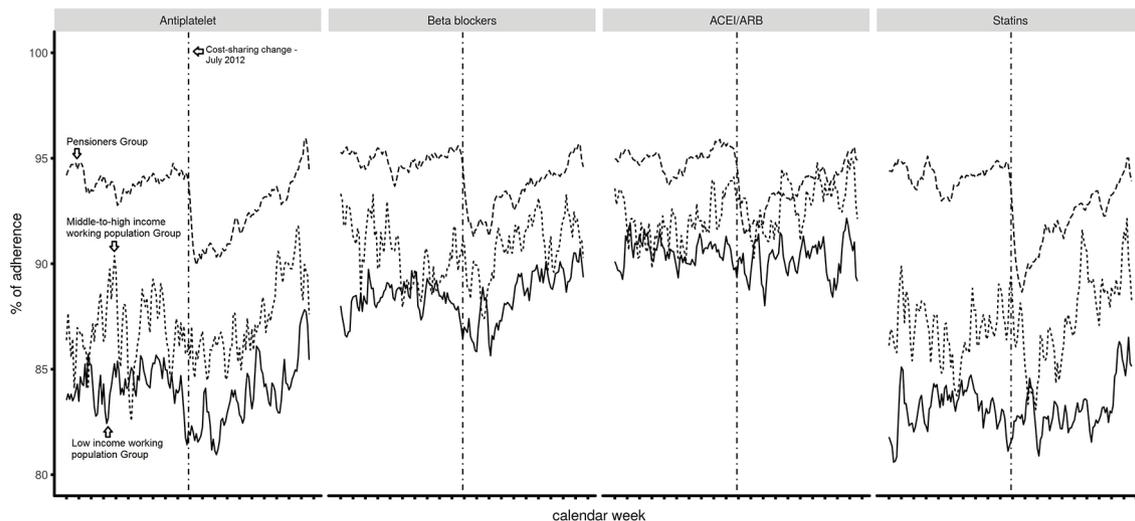

Figure 1 Weekly rates of adherence for the drugs considered for the three cohorts. ACEI, ACE inhibitor; ARB, angiotensin II receptor blocker.

Table 4 Effect of the cost-sharing change on adherence to essential medications

		Antiplatelet	Beta-blockers	ACEI/ARB	Statins
Pensioners group versus control group	Level change (%)	−1.790 (1.24)	−1.021 (0.97)	−6.792 (6.35)**	−8.293 (5.61)**
	Slope change (%)	0.004 (0.50)	0.000 (0.03)	0.023 (3.84)**	0.031 (3.67)**
	Time to counterfactual adherence rates for pensioners (months)	15.4	17.9	>20.7	18.4
	R^2	0.97	0.96	0.92	0.97
Middle-income to high-income group versus control group	Level change (%)	−1.120 (0.54)	−2.295 (1.41)	0.066 (0.04)	−7.806 (3.57)**
	Slope change (%)	0.010 (0.83)	0.028 (3.03)**	−0.001 (0.17)	0.044 (3.50)**
	Time to counterfactual adherence rates for middle-income to high-income population (months)	12.4	12.0	11.7	13.6
	R^2	0.73	0.68	0.64	0.76

n=312

Antiplatelet, acetyl salicylic acid; ACEI/ARB, ACE inhibitors and angiotensin II receptor blockers.

t-ratios in parentheses *p<0.05; **p<0.01.

DISCUSSION

This evaluation of a population-based natural experiment showed that adherence to some essential treatments for secondary prevention of ACS was reduced in the short term as a consequence of the increase of the drug cost sharing in Spain. We found that after the cost-sharing policy reform, pensioners, who moved from full insurance to 10% coinsurance with a monthly ceiling of €8 or €18 depending on income, significantly reduced adherence to relatively expensive ACEI/ARB and statins, but not to low-priced antiplatelet agents and beta-blockers. Also, the coinsurance change from 40% to 50 or 60% with no monthly ceiling for the middle-income to high-income working population decreased adherence to statins, the costlier therapy. However, effects seemed temporary, with patients returning to adherence rates equivalent to those observed in the period previous to the reform. According to the model predictions, 18 months after the reform all groups had recovered or were close to adherence figures expected if no change in cost sharing had occurred. The temporality of effects could be explained by the relatively low levels of total coinsurance, even after the reform, or by the relatively low increase of coinsurance due to the reform. Even if effects appear to be temporary, this 18-month gap in adherence on a highly vulnerable population is expected to have a relevant impact on clinical outcomes as observed in previous studies,[8 9 18 19] and probably also on costs.[9 19]

Furthermore, it is also worth noting that before the cost-sharing change, patients with free full coverage—pensioners—were more adherent than the working population who were subject to 40% coinsurance. Among the latter, the low-income workers had poorer adherence than the middle-income to high-income working population, suggesting an income gradient.

Our findings confirm those of earlier studies[8 10] but in a universal free healthcare setting using a robust methodology to define the outcome, that is, adherence to essential medications on a high-risk population. It has been shown that cost-sharing policies that simply share the financial burden of buying drugs with patients can lead to suboptimal utilization and adherence to medications in both high-risk and general populations.[8 10 11] The detrimental effect on adherence to essential medications in vulnerable populations is particularly important because it is more likely to cause harm, as shown in the only clinical trial assessing the effect of eliminating cost sharing for secondary prevention after myocardial infarction.[19] The differential effect observed on distinct therapeutic agents is supported by previous evidence. For relatively low-price and low patient cost-share medications, the effect of increased coinsurance on adherence has shown to be small,[20] whereas for higher price and high patient cost-share medications the effect is stronger.[21]

The effect on pensioners, who moved from no participation in costs to a very limited cost share but experienced a significant level change in adherence, is consistent with economic literature showing that price elasticity of demand for medical care is not linear and that with regard to the impact of cost-sharing schemes on drug utilisation and adherence, effects are stronger with the initial introduction of cost sharing rather than with increases on already set copayments.[22] Middle-income to high-income working population supported a much higher share of pharmaceutical costs before the reform (40% coinsurance) and increased their cost share after it (to 50% or 60%), resulting also in effects on adherence, but only for statins, and to a less extent than for pensioners. For instance, for statins pensioners shared €0 before the policy reform and up to €1.9 per package after the reform, when the middle-income to high-income working population moved from €8.52 to €10.65 or €12.78 per package.

Our work is subject to some limitations. First, we used prescription and dispensing data to measure adherence, but patients do not necessarily consume all the drugs they are prescribed or filled. Nevertheless, several studies have shown a high consistency between dispensation and patient consumption.[23 24] To our knowledge, this is the first study to assess the effects of cost sharing on medication adherence linking prescription and dispensing data, which enables to estimate adherence based on days with available medication more precisely using electronic databases. Furthermore, patients may have anticipated the cost-sharing change resulting in a stockpiling effect during the weeks prior to the reform.[25] However, stockpiling could not have skewed our results because we accounted for the quantities dispensed when we calculated adherence. Second, although our analytic approach is considered one of the strongest non-experimental approaches for evaluating time-delimited policy changes/interventions, our groups may follow different trends in the prechange period, resulting in a breach of the parallel trend assumption required in DiD analysis. This assumption implies that outcomes for the intervention and comparison groups would be expected to change at the same rate in lack of intervention.[26] Moreover, our analysis is subject to the possibility that the changes in adherence we observed were due to other events that occurred simultaneously with the policy change. Third, our

middle-income to high-income group was of relatively small size, which could hinder the robustness of the DiD analysis for this group. However, our results were consistent for both intervention groups. Finally, the exclusion of clopidogrel from analysis (due to methodological considerations associated with its pattern of use as a short-term medication) may have a bearing on the comprehensiveness nature of our results.

In conclusion, our results show that coinsurance increments may lead to increased adherence to proven, effective therapies, especially for higher priced agents with a higher patient cost share. We also observed that adherence was already suboptimal before the cost-sharing policy change, with a clear cost/income gradient—lower adherence in pricier drugs and among poorer people. Earlier in 2011, the Post-Myocardial Infarction Free Rx Event and Economic Evaluation (MI FREEE) trial had already demonstrated that eliminating copayments for statins, beta-blockers, ACEI and ARBs for secondary prevention after myocardial infarction increased medication adherence and reduced the rates of total major vascular events.[19] In the light of the consistency of these results in a universal free healthcare setting, consideration should be given to fully exempting high-risk patients (as patients after an ACS) from drug cost sharing. Reducing financial/economic barriers to evidence-based medication use could improve health outcomes while reducing total cost of care by reducing the number of costly non-fatal events, resulting in a cost-effective strategy for the Spanish National Health System and healthcare insurers worldwide.[27–30]

Key messages

What is already known on this subject?
Even in the absence of patient cost sharing, adherence to essential medication after an acute coronary syndrome(ACS) is suboptimal. Cost sharing may further affect medication adherence in high-risk patients.

What might this study add?
We obtained more precise adherence estimates through a novel approach. Using this improved outcome measure, we confirmed a detrimental effect of increasing drug patient out-of-pocket expenses on adherence to evidence-based medications in the short term, in a high-risk population-based cohort in a universal healthcare setting.

How might this impact on clinical practice?
Reducing financial barriers to evidence-based medication use could improve health outcomes while reducing total cost of care. Accordingly, consideration should be given to fully exempting high-risk patients, as are patients after an ACS, from drug cost sharing.

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