

Special Article

OUTCOMES OF REFERENCE PRICING FOR ANGIOTENSIN-CONVERTING-ENZYME INHIBITORS

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ABSTRACT

Background In January 1997, reference pricing for angiotensin-converting-enzyme (ACE) inhibitors for patients 65 years of age or older was introduced in British Columbia, Canada. For medications within a specific class, insurance covers the cost up to the reference price, and patients pay the extra cost of more expensive medications. Although reference pricing may reduce the costs of prescription drugs, there is concern that patients may switch to less effective medications or stop treatment.

Methods We analyzed data from the Ministry of Health on all 37,362 residents of British Columbia who were 65 or older and were enrolled in the provincial health insurance program, received ACE inhibitors priced higher than the reference price of \$27 a month in 1996, and were potentially affected by the new policy. We identified 5353 residents who switched to an ACE inhibitor not subject to cost sharing during the first six months and compared them with 27,938 residents who received only ACE inhibitors subject to cost sharing.

Results Reference pricing for ACE inhibitors was not associated with changes in the rates of visits to physicians, hospitalizations, admissions to long-term care facilities, or mortality. The probability of stopping antihypertensive therapy decreased as compared with the probability before the change in policy (relative risk, 0.76; 95 percent confidence interval, 0.65 to 0.89). Eighteen percent of patients who had been prescribed ACE inhibitors subject to cost sharing switched to lower-priced alternatives. As compared with patients who did not switch, those who did had a moderate transitory increase in the rates of visits to physicians (rate ratio, 1.11; 95 percent confidence interval, 1.07 to 1.15) and hospital admissions through the emergency room (rate ratio, 1.19; 95 percent confidence interval, 0.99 to 1.42) during the two months after switching, but not subsequently.

Conclusions We found little evidence that when reference pricing for ACE inhibitors was introduced in British Columbia, patients stopped treatment for hypertension or that health care utilization and costs increased. (N Engl J Med 2002;346:822-9.)

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IN the United States, \$117 billion — that is, 8.9 percent of overall health care expenditures — was spent for prescription drugs in 2000.¹ Drug expenditures grew 2.5 to 3 times as fast as total health care expenditures between 1998 and 2000¹⁻³ and are about to exceed hospital expenditures for some health plans.⁴ Recently, reference pricing has been suggested as a cost-control mechanism for proposed Medicare drug benefits.⁵

Reference pricing is based on the assumption that medications within a specific class are interchangeable and a common level of reimbursement can be established. If a physician prescribes a medication priced higher than the reference price, the patient is required to pay the difference. Typically, the cost of drugs priced at or below the reference price is fully covered by insurance.

The main issues of concern about reference pricing are that patients may switch to less effective medications, become noncompliant, see their physician more frequently, or be hospitalized more frequently.^{6,7} For example, an uncontrolled study found an increase in thrombotic vascular complications when patients switched from simvastatin to fluvastatin under a system of reference pricing in New Zealand.⁸ Studies of fixed copayments for prescriptions have reported reductions in overall drug use (e.g., the number of prescriptions filled) of 5 to 10 percent.^{7,9-13} Nonetheless, there are almost no rigorous evaluations of the effect of reference pricing on health care utilization or costs.^{14,15} We studied the consequences of reference pricing for angiotensin-converting-enzyme (ACE) inhibitors, a class of antihypertensive medications that are particularly effective in patients with con-

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gestive heart failure,¹⁶ diabetes,¹⁷ or chronic renal disease.¹⁸

METHODS

Patients

Beginning on January 1, 1997, residents of British Columbia, Canada, 65 years of age or older were fully covered for the least expensive ACE inhibitors — captopril (Capoten), quinapril (Accupril), and ramipril (Altace). Benazepril (Lotensin), cilazapril (Inhibace), enalapril (Vasotec), fosinopril (Monopril), and lisinopril (Prinivil, Zestril) were covered up to a maximum of \$27 per month. For these medications subject to cost sharing, patients paid an extra \$2 to \$62 for a one-month supply. Previously, the costs of all these medications had been covered in full.¹⁹

In 1995, reference pricing for nitrates, histamine H₂ blockers, and nonsteroidal antiinflammatory medications was instituted in British Columbia. In 1997, reference pricing for calcium-channel blockers was also introduced. We analyzed changes in expenditures and the rates of health care utilization, admissions to long-term care facilities, and mortality after the introduction of reference pricing for ACE inhibitors among elderly patients in British Columbia. The requirement for reference pricing had generous exemptions, including frailty or previous failure of treatment. Thirty-nine percent of those potentially affected obtained individual exemptions as “frail elderly patients.” No other major health policy interventions were initiated during the study period.

All residents of British Columbia who are 65 or older are eligible for publicly funded health care, including pharmaceutical benefits, with prescriptions limited to a 100-day supply. For all prescriptions, the medications, dose, and dispensed quantity are entered into a single computer by retail pharmacists through a province-wide network. Underreporting and misclassification appear to be minimal.²⁰ The Ministry of Health holds data on all drug claims, physicians’ claims for services in offices and hospitals, hospitalizations, admissions for long-term care, and deaths for the study cohort. Up to 16 diagnoses for hospital discharges and 1 diagnosis for each medical service were coded in the data base. A previous report indicated high accuracy and completeness of data on health care utilization.²¹ The human-subjects review boards of Harvard Medical School, the Harvard School of Public Health, Brigham and Women’s Hospital, and the University of British Columbia approved the protocol. The Ministry of Health supplied complete data bases linked by a unique, anonymous study number assigned to each patient.

We selected a cohort of all 59,074 patients who were 65 or older in December 1995, who received an ACE inhibitor between December 1995 and March 1996, and who were not in a long-term care institution at the time of their first use of an ACE inhibitor. The population was further restricted to 37,362 patients who were recipients of higher-priced drugs that required cost sharing after the change in policy and who were not using any medications to treat diabetes or asthma, since patients taking such drugs were exempt from the policy.

The subgroup of 5353 “switchers” who received an ACE inhibitor subject to cost sharing during the four months before the change in policy and started an ACE inhibitor not subject to cost sharing during the first six months after the implementation of reference pricing was compared with a subgroup of 27,938 patients who received only ACE inhibitors subject to cost sharing (“non-switchers”) during both periods. Data collection stopped in June 1998. The remaining 4071 patients were the 1015 who stopped all drug therapy for hypertension and the 3056 who switched from ACE inhibitors to other antihypertensive medications.

Statistical Analysis

To compare trends in health care utilization in switchers and non-switchers for the period from 10 months before to 10 months after

the date of the switch, we used a longitudinal repeated-measures design. Each patient was assigned an index date; the index date for switchers was the day of switching from ACE inhibitors subject to cost sharing to those not subject to cost sharing between November 1, 1996 (the time the policy was announced), and June 30, 1997. The index date for nonswitchers was the first date that an ACE inhibitor subject to cost sharing was dispensed between January 1, 1997, and June 30, 1997.

For each of 10 30-day intervals before and after the index date, event rates were calculated for days on which patients visited a physician, hospital admissions through an emergency room, nonemergency hospital admissions, and admissions to long-term care facilities. We divided the sum of all events by the total number of eligible patients for each period. Admissions to long-term care facilities were treated as one-time events because patients almost never returned to the community. We compared event rates for switchers for each 30-day period with the corresponding rates for nonswitchers using Poisson regression models that included interactions between switching status (switching vs. nonswitching) and indicators for the 30-day initiation period before the index date, the early period (2 30-day periods after the index date), and the late period (3 to 10 30-day periods after the index date).^{11,22-24} Other covariates included in the models were age in years at the beginning of each 30-day interval, sex, household adjusted income (\leq \$11,000 vs. $>$ \$11,000 per year), and chronic disease score²⁵ computed from prescription medications used during a specified three-month period and the preceding three months. The chronic disease score ranges from 0 to 35, with an increase in score indicating a decrease in health status.²⁶ Thus, a new chronic disease score was computed for every quarter and treated as a time-varying covariate. Additional covariates included the diagnoses of coronary heart disease, heart failure, or chronic renal failure (a primary diagnosis at hospital discharge or three claims for physician services with *International Classification of Diseases*²⁷ codes for the above diagnoses).

To further control for differences between switchers and non-switchers, we adjusted for quintiles of a score for the propensity to switch medications.^{28,29} The propensity to switch was calculated as the linear predictor of a logistic regression that modeled switching as a function of characteristics of patients and physicians, prior health care utilization, expenditures, chronic disease scores,²⁵ and statistically significant interactions. The propensity score had slight predictive power ($c=0.60$; a c score of 0.5 indicates random prediction of future switching, and a c score of 1.0 indicates perfect predictive power³⁰). We combined prognostic covariates and propensity scores in our multivariate models for increased robustness against selection bias.³¹ We estimated the relative rates of utilization as compared with base-line rates in switchers and nonswitchers with 95 percent confidence intervals.

We corrected for overdispersion by including a scale parameter.³² Within-patient correlation between the repeated events was corrected for with the use of the generalized estimating equations.³³ Because of the delay between switching and events, an autoregressive covariance structure with lags of one month was adopted.³⁴ We modeled payments for physicians’ services in a linear regression assuming gamma-distributed errors for the right-skewed distribution of payments in Canadian dollars.³⁵

The large number of study patients provided sufficient statistical power to detect a 3 percent change in the overall rate of visits to physicians.³⁶ Any increase in health care utilization among people who switched ACE inhibitors would be diminished by the constant utilization among the majority of patients who did not switch and thus reduced the statistical power.³⁷

We computed standardized mortality ratios to control for strong seasonal variation in mortality by dividing the monthly mortality rates for the study cohort by the monthly mortality rates for all other residents of British Columbia who were 65 years or older during the same time period. The standardized mortality ratios were further adjusted for age and sex and reported with their 95 percent confidence intervals.³⁸

RESULTS

The base-line characteristics of the switchers and nonswitchers are shown in Table 1. Table 2 shows the overall effect of the policy on the 37,362 people in the cohort. After seasonal variation was accounted for, there were no significant changes in health care utilization. The probability of discontinuing antihypertensive therapy after the implementation of reference pricing was lower than the probability before the change in policy (relative risk, 0.76; 95 percent confidence interval, 0.65 to 0.89). Eighteen percent of patients receiving ACE inhibitors subject to cost sharing switched to lower-priced alternatives. Four percent of patients receiving ACE inhibitors not subject to cost sharing switched to higher-priced drugs during the first six months of the policy. There was no significant difference between switchers and nonswitchers in the proportion of patients who continued therapy with ACE inhibitors six months after the implementation of reference pricing (89.5 percent vs. 89.2 percent, $P=0.50$).

Visits to Physicians

Switchers had an 11 percent increase in visits to physicians (95 percent confidence interval, 7 to 15 percent) as compared with nonswitchers during the two months after switching (Table 3). Both switchers and nonswitchers had additional visits to physicians just before the index date to receive or change prescriptions. There was a 39 percent decrease in the median time between two prescriptions for antihypertensive medications during the first three months after switching — from 82 days to 50 days. The increase in visits to physicians among switchers after the index date was specific to cardiovascular conditions. It was not found for acute respiratory infections, which are common during winter and spring (Fig. 1). Three months after switching, the rates of visits to physicians in switchers and nonswitchers were the same (Table 3).

Hospitalizations

Although switchers appeared to have a higher rate of hospital admissions through emergency rooms for the first two months after the change in policy (rate ratio, 1.27; 95 percent confidence interval, 1.07 to 1.51), the association was no longer significant after adjustments were made for hospitalizations in the three months before switching (rate ratio, 1.19; 95 percent confidence interval, 0.99 to 1.42). The rate ratio for the entire period after the change in policy was 1.03 (95 percent confidence interval, 0.92 to 1.14) (Table 3). Analyses of patient subgroups defined by a low income, a high chronic disease score, or diagnoses of coronary heart disease, heart failure, or renal failure did not show any group-specific effects of the policy on any of the outcomes we studied (data not shown).

TABLE 1. BASE-LINE CHARACTERISTICS OF THE 33,291 PATIENTS WHO RECEIVED ACE INHIBITORS BEFORE AND AFTER THE IMPLEMENTATION OF REFERENCE PRICING.

CHARACTERISTIC	SWITCHERS (N=5353)*	NONSWITCHERS (N=27,938)†	P VALUE
	no. (%)‡		
Sex			<0.001
Female	3150 (59.9)	15,201 (55.5)	
Male	2108 (40.1)	12,188 (44.5)	
Age in April 1996			<0.001
65–70 yr	1253 (23.7)	7,277 (26.5)	
71–75 yr	1428 (27.0)	7,332 (26.7)	
76–80 yr	1185 (22.4)	6,097 (22.2)	
≥81 yr	1422 (26.9)	6,727 (24.5)	
Annual income§			<0.001
High (>\$19,000)	2827 (55.2)	15,671 (57.7)	
Moderate (\$11,001–\$19,000)	771 (15.1)	3,823 (14.1)	
Low (\$0–\$11,000)	1521 (29.7)	7,681 (28.3)	
No. of hospitalizations through the emergency room¶			
0–4	4720 (89.8)	24,802 (90.5)	
≥5	536 (10.2)	2,604 (9.5)	
No. of visits to a physician¶			
0–4	963 (18.4)	5,001 (18.4)	
≥5	4268 (81.6)	22,181 (81.6)	
No. of different diagnoses¶			
0–4	2898 (54.6)	15,023 (54.4)	
≥5	2410 (45.4)	12,592 (45.6)	
Chronic disease score¶**			<0.001
0–4	2778 (51.9)	13,550 (48.5)	
≥5	2575 (48.1)	14,388 (51.5)	
Diagnosis			
Coronary heart disease	958 (17.9)	5,196 (18.6)	
Heart failure	1226 (22.9)	6,482 (23.2)	
Chronic renal failure	182 (3.4)	866 (3.1)	

*Switchers were defined as patients who received ACE inhibitors subject to cost sharing during the four months before the implementation of reference pricing and who received an ACE inhibitor not subject to cost sharing during the first six months after the implementation of reference pricing.

†Nonswitchers were defined as patients who received ACE inhibitors subject to cost sharing before and during the six months after the implementation of reference pricing.

‡Percentages were calculated on the basis of the number of patients for whom data were available, except for the percentages for the diagnoses, which were calculated on the basis of the total number of patients in the study.

§Income is shown in Canadian dollars. To convert to U.S. dollars, multiply by 0.62.

¶Measures based on the rate of health care utilization were assessed during the six months before implementation of the policy.

||The classification systems used for diagnoses were those of the ninth revision of the *International Classification of Diseases*.²⁷

**Computed on the basis of the use of prescription medication, the chronic disease score ranges from 0 to 35, with an increase in score indicating a decrease in health status.²⁶

Admissions to Long-Term Care Facilities and Mortality

Rates of admission to long-term facilities decreased in switchers as compared with nonswitchers (Table 3). The monthly mortality rate, adjusted for seasonal variation, for the cohort of recipients of ACE inhibitors, which was 20 percent higher than that for all other residents in British Columbia who were 65 years or

REFERENCE PRICING FOR ACE INHIBITORS

TABLE 2. CHANGES IN HEALTH CARE UTILIZATION AND COMPLIANCE AFTER THE INTRODUCTION OF REFERENCE PRICING AMONG THE 37,362 RECIPIENTS OF HIGH-PRICED ACE INHIBITORS THAT REQUIRED COST SHARING.*

OUTCOME	AVERAGE BASE-LINE VALUES (JULY TO SEPTEMBER 1996)	CHANGE FROM BASE-LINE TO TRANSITION PERIOD AFTER IMPLEMENTATION OF THE POLICY (JANUARY TO JUNE 1997)	
		CRUDE RATE RATIO (95% CI)	MULTIVARIATE ADJUSTED RATE RATIO (95% CI)†
Visits to a physician	169	1.03 (1.01 to 1.05)	1.01 (0.98 to 1.04)
Hospital admissions through the emergency room	1.96	1.03 (1.00 to 1.07)	0.98 (0.91 to 1.04)
Nonemergency hospital admissions	1.25	1.02 (0.98 to 1.05)	0.99 (0.94 to 1.05)
Admissions to long-term care facilities (per 10,000 patients)	0.184	1.15 (1.10 to 1.21)	1.07 (0.96 to 1.19)
ABSOLUTE DIFFERENCE‡			
Paid claims for physicians' services (\$)	8,900	12.5 (7.9 to 17.0)	3.7 (-1.1 to 8.6)
RELATIVE RISK			
Monthly probability of switching from cost-sharing to non-cost-sharing ACE inhibitors (%)§	0.3	21.7 (18.2 to 26.0)	—
Monthly probability of switching from non-cost-sharing to cost-sharing ACE inhibitors (%)§	1.6	1.52 (1.34 to 1.71)	—
Monthly probability of stopping all antihypertensive medications (%)§	2.6	0.76 (0.65 to 0.89)	—

*The study cohort was followed from July 1996 to June 1997. Rates for visits and admissions were calculated as the number of events per 100 eligible patients except where noted. Patients' data were censored at the time the patients died or emigrated from the province. CI denotes confidence interval.

†Rates were adjusted for age, sex, income, chronic disease score, seasonal variation (with the use of an identically defined historical control cohort one year earlier), overdispersion, and autoregression (see the Methods section).

‡The change in Canadian dollars is expressed as an absolute difference, not as a ratio.

§We calculated the probability as the percentage of patients who switched or discontinued antihypertensive medications during the index month among those who were receiving ACE inhibitor therapy at the beginning of the index month. Patients who discontinued medication were defined as those who had had no antihypertensive medication dispensed during the previous six months. We assumed that the last dispensed antihypertensive medication was used by the patient (with an average three-month supply). Therefore, the date of discontinuation was defined as three months after the last antihypertensive medication was dispensed. The observation period was extended to September 1997.

TABLE 3. DIFFERENCES IN HEALTH CARE UTILIZATION AND ADMISSION TO LONG-TERM CARE FACILITIES IN 5353 SWITCHERS AS COMPARED WITH 27,938 NONSWITCHERS.*

OUTCOME	RELATIVE CHANGE IN RATE RATIOS BETWEEN SWITCHERS AND NONSWITCHERS AS COMPARED WITH BASE-LINE VALUES (95% CI)†		
	INITIATION PERIOD (1 MONTH BEFORE INDEX DATE)	EARLY PERIOD (1 TO 2 MONTHS AFTER INDEX DATE)	LATE PERIOD (3 TO 10 MONTHS AFTER INDEX DATE)
	Visits to a physician	1.01 (0.97 to 1.05)	1.11 (1.07 to 1.15)
Hospital admissions through the emergency room	1.39 (1.20 to 1.61)	1.27 (1.07 to 1.51)	0.97 (0.86 to 1.09)
Nonemergency hospital admissions	1.17 (0.94 to 1.44)	1.05 (0.83 to 1.32)	0.90 (0.77 to 1.05)
Paid claims for physicians' services (\$)‡	10.9 (4.4 to 17.4)	13.4 (7.3 to 19.6)	1.3 (-2.8 to 5.3)
Admissions to long-term care facilities	0.66 (0.39 to 1.15)	0.45 (0.26 to 0.80)	0.53 (0.35 to 0.82)

*Values are rates per patient per month. Base-line values were measured 2 to 11 months before the index date. The index date for switchers was the day of switching from ACE inhibitors subject to cost sharing to ACE inhibitors not subject to cost sharing. For those who continued to receive drugs subject to cost sharing, the index date was the first day that an ACE inhibitor was dispensed between January 1, 1997, and June 30, 1997.

†Relative changes in rate ratios were adjusted for age, sex, income, chronic disease score, quintiles of the propensity score, and a time-varying covariate for prior hospitalizations through the emergency room. A rate ratio of 1.11, for example, indicates that for switchers, the rate of the outcome is 11 percent higher than at base line; the rates are adjusted for an underlying difference between switchers and nonswitchers. CI denotes confidence interval.

‡The change in Canadian dollars is expressed as an absolute difference, not as a ratio.

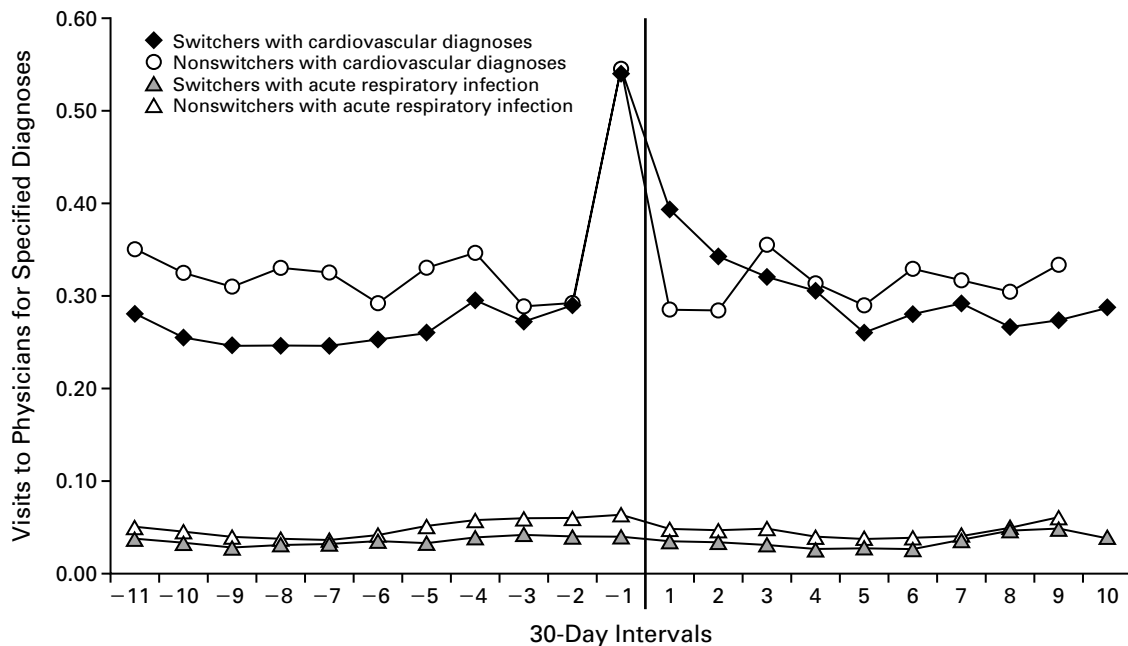


Figure 1. Average Monthly Number of Visits to a Physician per Patient for Cardiovascular Conditions and Acute Respiratory Infection in Patients Who Switched from ACE Inhibitors Subject to Cost Sharing to ACE Inhibitors Not Subject to Cost Sharing as Compared with Patients Who Did Not Switch.

The vertical line indicates the index date — that is, the day of switching, which occurred between November 1, 1996, and June 30, 1997, in those who switched, or the day an ACE inhibitor was first administered, which occurred after January 1, 1997, in those who received only drugs subject to cost sharing.

older (mortality ratio standardized for age and sex, 1.20; 95 percent confidence interval, 1.00 to 1.44), did not change after the implementation of reference pricing ($P=0.58$) (Fig. 2).

Economic Effects

Switchers had a temporary increase in expenditures for medical services of approximately \$11 per patient (95 percent confidence interval, \$4 to \$17) just before switching and of \$13 (95 percent confidence interval, \$7 to \$20) afterward (Table 3); this reflected the increased number of visits to physicians. Under the conservative assumption that this difference in expenditures between switchers and nonswitchers was due entirely to the change in policy, the total cost of the policy in terms of payments to physicians from October 1996 to March 1998 would have been about \$700,000 (95 percent confidence interval, \$450,000 to \$950,000). This cost was calculated by integrating payments to physicians that were temporarily above an average base-line difference of \$10 per month between switchers and nonswitchers. This compares with savings in expenditures for antihypertensive drugs during the first year after the change in policy of about

\$6.7 million, resulting in a net savings of approximately \$6 million (95 percent confidence interval, \$5.75 million to \$6.25 million).

DISCUSSION

Our study was designed to address the concern that reference pricing of ACE inhibitors may cause discontinuations of antihypertensive therapy and unintended increases in health care utilization and health care costs because of inappropriate substitutions of medications.^{6,8,39,40} We found little evidence to support this concern. After reference pricing was implemented, there was no increase in the overall rate of visits to physicians, hospitalizations, or drug discontinuations. Despite the high statistical power of our overall analysis, we could have missed an effect on visits to physicians and hospitalizations among the 18 percent of patients who switched from higher-priced to lower-priced medications soon after the policy change.

When we examined the effects of switching ACE inhibitors as a consequence of the change in policy, as compared with expected outcomes if those patients had not switched, we found a transitory increase in visits to physicians and claims for physicians' services

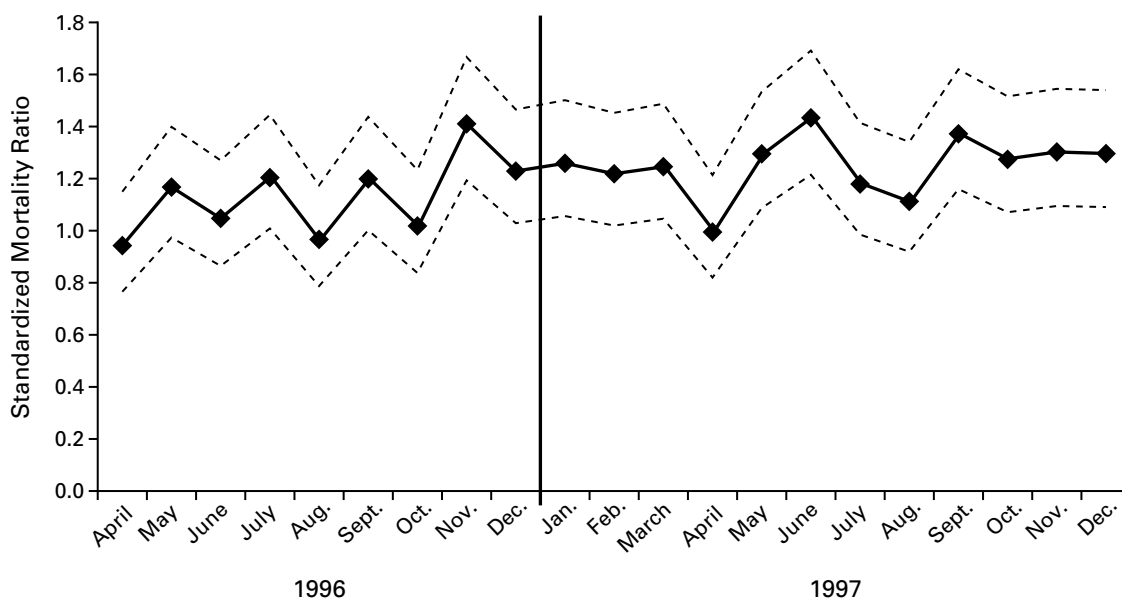


Figure 2. Standardized Mortality Ratios for the Study Cohort.

The dotted lines indicate the 95 percent confidence intervals. Standardized mortality ratios of over 1.00 indicate that the corresponding cohort has a higher mortality rate than the population in British Columbia excluding the study cohort. Standardized mortality ratios were calculated by indirect standardization, with adjustment for sex and age.

for the two months after the switch. This may be explained by the need to see a doctor for a new prescription and increased monitoring by physicians of the new medication.

Because hospitals excluded ACE inhibitors subject to cost sharing from their formularies after the implementation of reference pricing,⁴¹ patients admitted to hospitals were more likely to switch medications and because of their prior hospitalization were more likely to be readmitted. The temporary increase in hospitalizations after switching was largely explained by readmissions of patients who were hospitalized before switching and was based on only two months of data.

Determining the effects of switching drugs requires careful attention to the patients affected by the change in policy. Since patients who did not switch were presumed to be either sicker (the basis for an exemption) or to have higher incomes (i.e., to be able to pay the higher copayment for their drug of first choice), simultaneous adjustment was required for factors influencing the choice and outcomes of therapy.⁴² The data included in the propensity score, particularly before health care utilization, were not strong enough predictors of switching to discriminate between patients who switched and those who did not. Previous studies suggest that if switching is not related to prior health care utilization (a marker for health status),

it is most likely related to the preferences of patients or physicians.⁴³ We believe our control for selection bias was adequate because the best predictor of health care utilization is prior health care utilization, which we measured in many ways. The association between the preferences of patients or physicians and switching remains unclear. Preferences are unlikely to cause sudden changes in health care utilization as compared with base-line utilization. Our longitudinal design, comparing changes in trends between the two groups, controlled for unmeasured confounding, because it can be reasonably assumed that differences in outcomes caused by selection factors are the same before and after the index date.

Taking the savings in drug expenditures and the increase in physicians' services into account, we estimated the net savings from the policy to be \$6 million Canadian during the first 12 months of reference pricing. This estimate is conservative, because it does not include the savings for patients who initiated ACE-inhibitor therapy after reference pricing began.

We found similar results in vulnerable groups of the elderly, including those patients with low income, chronic diseases, or diagnoses of myocardial infarction or heart failure at base line. However, the diagnostic information in the claims data might be too crude to identify these groups reliably. In general, misclassification of patients according to risk factors at base line

attenuates the contrast between subgroups and decreases the power to detect adverse effects.

Our findings apply to the approach to reference pricing in British Columbia during a period of stability of health services in the province. That a relatively small proportion of patients switched ACE inhibitors is due mainly to the fact that the reference price was set at \$27 per month and was independent of dose. Therefore, low doses of the drugs that were subject to cost sharing were fully covered, and the policy disproportionately affected patients needing higher doses. Another contribution to the low switching rate was the fact that about two fifths of patients who were potentially affected obtained individual exemptions as "frail elderly patients" through prior approval. Thus, our findings may not be generalizable to similar systems that lack such generous exemptions, such as three-tiered copayment systems in some health maintenance organizations in the United States.

The analysis is restricted to ACE inhibitors, a frequently prescribed and important class of medications for the treatment of hypertension and congestive heart failure. ACE inhibitors have a low within-class variability of effectiveness and thus represent particularly safe candidates for reference pricing. More caution may be necessary for other drug classes, such as calcium-channel blockers, in which there are more pharmacologic differences between the most common agents — verapamil, diltiazem, and the dihydropyridines. Our study focuses on the short-term outcomes of the change in policy. Longer-term data would be desirable but would also be difficult to attribute to one intervention, since many patient-level and system-level factors change over longer periods of observation. We could not directly measure all changes in the health status of patients but only changes that led to contact with health care professionals. Future research should include direct measures of health outcomes and randomized control groups to rule out potential selection biases.

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REFERENCES

- Iglehart JK. Medicare and prescription drugs. *N Engl J Med* 2001;344:1010-5.
- Levit K, Cowan C, Braden B, Stiller J, Sensenig A, Lazenby H. National health expenditures in 1997: more slow growth. *Health Aff (Millwood)* 1998;17(6):99-110.
- Kane NM. Pharmaceutical cost containment and innovation in the United States. *Health Policy* 1997;41:Suppl:S71-S89.
- Steinhauer J. Rising cost of drugs take a bigger share of health insurance outlays. *New York Times*. October 29, 1999.
- Huskamp HA, Rosenthal MB, Frank RG, Newhouse JP. The Medicare prescription drug benefit: how will the game be played? *Health Aff (Millwood)* 2000;19(2):8-23.
- Bourgault C, Elstein E, Le Lorier J, Suissa S. Reference-based pricing of prescription drugs: exploring the equivalence of angiotensin-converting-enzyme inhibitors. *CMAJ* 1999;161:255-60.
- Tamblin R, Laprise R, Hanley JA, et al. Adverse events associated with prescription drug cost-sharing among poor and elderly persons. *JAMA* 2001;285:421-9.
- Thomas M, Mann J. Increased thrombotic vascular events after change of statin. *Lancet* 1998;352:1830-1.
- Roemer MI, Hopkins CE, Carr L, Gartside F. Copayments for ambulatory care: penny-wise and pound-foolish. *Med Care* 1975;13:457-66.
- Nelson AA Jr, Reeder CE, Dickson WM. The effect of a Medicaid drug copayment program on the utilization and cost of prescription services. *Med Care* 1984;22:724-36.
- Soumerai SB, Avorn J, Ross-Degnan D, Gortmaker S. Payment restrictions for prescription drugs under Medicaid: effects on therapy, cost, and equity. *N Engl J Med* 1987;317:550-6.
- Reeder CE, Nelson AA. The differential impact of copayment on drug use in a Medicaid population. *Inquiry* 1985;22:396-403.
- Harris BL, Stergachis A, Ried LD. The effect of drug co-payments on utilization and cost of pharmaceuticals in a health maintenance organization. *Med Care* 1990;28:907-17.
- Schneeweiss S, Schöffski O, Selke GW. What is Germany's experience on reference based drug pricing and the etiology of adverse health outcomes or substitution? *Health Policy* 1998;44:253-60.
- Holbrook A, O'Brien B, Grootendorst P. Reference-based pricing (RBP) of prescription drugs. *Can J Cardiol* 1997;13:689-90.
- Garg R, Yusuf S. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. *JAMA* 1995;273:1450-6. [Erratum, *JAMA* 1995;274:462.]
- Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. *N Engl J Med* 1993;329:1456-62. [Erratum, *N Engl J Med* 1993;330:152.]
- Maschio G, Alberti D, Janin G, et al. Effect of the angiotensin-converting-enzyme inhibitor benazepril on the progression of chronic renal insufficiency. *N Engl J Med* 1996;334:939-45.
- Antihypertensives: information on reference drug pricing in British Columbia. Victoria, B.C.: Pharmcare, 1997.
- Anderson GM, Kerluke KJ, Pulcins IR, Hertzman C, Barer ML. Trends and determinants of prescription drug expenditures in the elderly: data from the British Columbia Pharmcare Program. *Inquiry* 1993;30:199-207.
- Williams JL, Young W. Inventory of studies on the accuracy of Canadian health administrative databases: technical report. Toronto: Institute for Clinical Evaluative Sciences (ICES), December 1996.
- Gillings D, Makuc D, Siegel E. Analysis of interrupted time series mortality trends: an example to evaluate regionalized perinatal care. *Am J Public Health* 1981;71:38-46.
- Veney JE, Kaluzny AD. Evaluation and decision making for health services. 2nd ed. Part 5. Trend analysis. Ann Arbor, Mich.: Health Administration Press, 1991.
- Hallas J. Evidence of depression provoked by cardiovascular medication: a prescription sequence symmetry analysis. *Epidemiology* 1996;7:478-84.
- Von Korff M, Wagner EH, Saunders K. A chronic disease score from automated pharmacy data. *J Clin Epidemiol* 1992;45:197-203.
- Schneeweiss S, Seeger JD, Maclure M, Wang PS, Avorn J, Glynn RJ. Performance of comorbidity scores to control for confounding in epidemiologic studies using claims data. *Am J Epidemiol* 2001;154:854-64.
- International classification of diseases, 9th rev., clinical modification: ICD-9-CM. 4th ed. Los Angeles: Practice Management Information, 1992.
- Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika* 1983;70:41-55.
- Idem*. Reducing bias in observational studies using sub-classification on the propensity score. *J Am Stat Assoc* 1984;79:516-24.
- Hosmer DW Jr, Lemeshow S. Applied logistic regression. 2nd ed. New York: John Wiley, 2000:162.
- Rubin DB, Thomas N. Combining propensity score matching with additional adjustments for prognostic covariates. *J Am Stat Assoc* 2000;95:573-85.
- Glynn RJ, Buring JE. Ways of measuring rates of recurrent events. *BMJ* 1996;312:364-7.

- 33.** Liang K-Y, Zeger SL. Longitudinal data analysis using generalized linear models. *Biometrika* 1986;73:13-22.
- 34.** Kennedy P. *A guide to econometrics*. 4th ed. Cambridge, Mass.: MIT Press, 1988:123-5.
- 35.** Diehr P, Yanez D, Ash A, Hornbrook M, Lin DY. Methods for analyzing health care utilization and costs. *Annu Rev Public Health* 1999;20:125-44.
- 36.** Goodman SN, Berlin JA. The use of predicted confidence intervals when planning experiments and the misuse of power when interpreting results. *Ann Intern Med* 1994;121:200-6. [Erratum, *Ann Intern Med* 1995;122:478.]
- 37.** Zelen M. Compliance, bias, and power in clinical trials. *Biometrics* 1991;47:778-9.
- 38.** Esteve J, Bernhamou E, Raymond L. *Statistical methods in cancer research*. Vol. 4. Descriptive epidemiology. Lyon, France: International Agency for Research on Cancer, 1994:62-6. (IARC scientific publications no. 128.)
- 39.** McLaughlin PR. Reference-based pricing of prescription drugs. *Can J Cardiol* 1997;13:31-2.
- 40.** Boulet AP, Tessier G. Reference-based pricing in British Columbia: implications for cardiologists — an analysis. *Can J Cardiol* 1997;13:46-51.
- 41.** Gill NJ, Frighetto L, Marra C, Jewesson P. Influence of the British Columbia reference drug program on hospital formularies: a survey of hospital pharmacy managers. *Can J Clin Pharm* 2000;7:109-14.
- 42.** Schneeweiss S, Maclure M, Walker AM, Grootendorst P, Soumerai SB. On the evaluation of drug benefits policy changes with longitudinal claims data: the policy maker's versus the clinician's perspective. *Health Policy* 2001;55:97-109.
- 43.** Mitler LK, Rizzo JA, Horwitz SM. Physician gender and cesarean sections. *J Clin Epidemiol* 2000;53:1030-5.

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