Reference-based pricing of prescription drugs: exploring the equivalence of angiotensin-converting-enzyme inhibitors

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Abstract

Background: Reference-based pricing is a cost-containment policy applied to prescription drugs that are in the same class and deemed to be therapeutically equivalent. Recent reference-based pricing measures have targeted several drug classes, including angiotensin-converting-enzyme (ACE) inhibitors. The objective of this study was to assess whether patients treated for hypertension with various ACE inhibitors differed in their utilization of health care services and hence, whether the various ACE inhibitors should be considered therapeutically equivalent.

Methods: A retrospective cohort was formed from 4709 Saskatchewan residents aged 40–79 years who initiated treatment for hypertension with 1 of the 3 most frequently prescribed ACE inhibitors (captopril, enalapril or lisinopril) between Jan. 1, 1991, and Dec. 31, 1993. Information obtained from universal insurance databases included prescription drug use, the number of visits to a general practitioner (GP) or specialist and the number of hospital admissions during the year before treatment was initiated and during a follow-up period of up to 4 years. Rates were statistically adjusted for potential confounding variables and compared across treatment groups.

Results: Of the 4709 patients, 529 were prescribed captopril initially, 2939 enalapril and 1241 lisinopril. After treatment was initiated patients prescribed captopril were dispensed more medications on average, with an overall rate of 18.6 prescriptions per patient per year (v. 16.4 and 14.7 for enalapril and lisinopril users respectively); they were admitted to hospital more often, and they made more visits to GPs and specialists. The adjusted rate ratio of the number of visits to a GP for patients receiving enalapril, relative to captopril, was 0.84 (95% confidence interval [CI] 0.80–0.88), and for those receiving lisinopril it was 0.79 (95% CI 0.74–0.83). The adjusted rate ratios for the number of visits to a specialist were similar but lower, and for the number of hospital admissions they were 0.82 for patients prescribed enalapril initially (95% CI 0.73–0.93) and 0.65 (95% CI 0.56–0.75) for those prescribed lisinopril.

Interpretation: Patients with hypertension who are initially prescribed captopril used health care services more than those initially prescribed enalapril or lisinopril. This suggests that ACE inhibitors may not be therapeutically equivalent.

In response to increasing expenditures for prescription drugs,[1] many cost-containment measures have been proposed.[2–4] Reference-based pricing is a direct cost-sharing measure whereby the amount of money reimbursed for a drug is determined by the cost of the lowest priced "interchangeable agent" in that therapeutic class of drugs; any cost above that is borne by the patient. Randomized clinical trials have shown that many drugs within a therapeutic class are equally effective and safe on average.[5] Policies for reference-based pricing are based on the premise that, if this is the case, insurance and reimbursement should equal that of the lowest priced drug within the class.[6] Although reference-based pricing has been implemented in several countries, claims have been made that such policies are insensitive to the clinical differences between drugs[7] and that they promote drug substitution without adequate

Evidence

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scientific evaluation.[8,9] It has also been suggested that the savings produced by reference-based pricing may be offset by increased health care expenditures.[7,8,10–12]

Numerous randomized clinical trials have demonstrated the safety and efficacy of angiotensin-converting-enzyme (ACE) inhibitors for reducing blood pressure.[13–25] Indeed, ACE inhibitors are considered a homogeneous drug class[26,27] and have been targeted for reference-based pricing. However, some studies have reported that ACE inhibitors differ in potency, duration and site of action, dosage form, drug interactions, side-effect profile and efficacy.[22–41] If these differences lead to variations in the use of health care services (e.g., physician visits, hospital admissions and prescription drug use) the assumption of the equivalence of drugs underlying reference-based pricing would be violated.

We examined the potential impact of reference-based pricing of ACE inhibitors on the use of health care services. Specifically, we assessed whether hypertensive patients initially prescribed captopril, enalapril or lisinopril differed in their use of health care services and, hence, whether ACE inhibitors should be considered equivalent.

Methods

We used the prescription, medical care and hospital admission databases for Saskatchewan residents[42–45] to construct a cohort of patients aged 40–79 years who were initiating pharmacologic therapy for hypertension with an ACE inhibitor between Jan. 1, 1991, and Dec. 31, 1993. There was no policy for reference-based pricing of ACE inhibitors in Saskatchewan at that time. For each prescription dispensed on an outpatient basis, the following information was obtained: the dispensing date, the nature, strength and dosage form of the drug, the quantity dispensed and the cost. For each visit to a physician the date of the visit and the specialty of the physician were recorded; for hospital admissions, the dates of admission and discharge, the primary and secondary discharge diagnoses (coded using the *International Classification of Diseases*, 9th revision[46]) and the vital status at discharge were recorded. Demographic data included sex, date of birth, date of death (if applicable) and socioeconomic status at treatment initiation (evaluated by whether patients were receiving social assistance or not).

To identify only patients initiating therapy, we excluded patients dispensed an antihypertensive agent in the preceding 12 months. Several measures were taken to exclude patients receiving an antihypertensive agent for indications other than uncomplicated hypertension. Patients prescribed an ACE inhibitor for chronic heart failure or renal scleroderma were excluded based on their use of digoxin, oral corticosteroids or pencillamine in the year before treatment initiation. Patients prescribed anticoagulants, loop diuretics or other cardiac agents, or those admitted to hospital with heart disease (ICD-9 codes 402, 404, 410, 420.9–429.9 or 745.4–746.9) in the same period were also excluded because they may have had pre-existing cardiac disease. Finally, patients possibly presenting with transient hypertension were excluded by retaining only those dispensed 3 or more antihypertensive prescriptions in the first year.

To ensure that a sufficient number of observations were obtained for each treatment group, only patients dispensed 1 of the 3 most frequently prescribed ACE inhibitors (captopril, enalapril and lisinopril) when treatment was initiated were included in the study. The cohort entry date was the date of receipt of the first prescription, and the patient was categorized by the drug he or she was prescribed initially. Patients were followed until Dec. 31, 1994, they left the province, their insurance coverage ended or they died, whichever came first.

Poisson regression models for rates accounting for extra-Poisson between-subject variation[47] were used to compare the 3 treatment groups. These regression techniques permitted adjustment for potential confounding by age, sex, socioeconomic status and year of treatment initiation. Differences in comorbidity were partially accounted for by statistically adjusting for physician visits, hospital admissions and drug use (NSAIDs, psychotropic agents and drugs for respiratory illness, diabetes mellitus, rheumatism, ulcers, epilepsy and hyperlipidemia) in the year preceding treatment initiation. Crude and fully adjusted models with 95% confidence intervals (CIs) were calculated.

To assess the use of health care services after treatment was initiated, we compared the number of visits to general practitioners (GPs) and specialists and the number of hospital admissions across subjects according to the ACE inhibitor first prescribed, with captopril as the reference. Rates were computed as incidence-density rates, with outpatient time (number of events per patient per year) as the denominator to account for differences in the length of follow-up. Analyses included all health care services utilization, including any that arose secondary to the treatment of hypertension (e.g., changing drugs, adjusting dose) or related to side effects.

Results

Of the 27 710 patients who were prescribed any antihypertensive agent between Jan. 1, 1991, and Dec. 31, 1993, and satisfied the inclusion criteria, 529 patients were prescribed captopril initially, 2939 enalapril and 1241 lisinopril. Table 1 presents characteristics of these patients at treatment initiation and in the year preceding treatment. A greater proportion of patients prescribed captopril were older, male and receiving social assistance at treatment initiation than patients initially prescribed enalapril or lisinopril. They also received their first antihypertensive prescription at an earlier date, particularly when compared with patients given lisinopril at first; lisinopril was not available in Saskatchewan until July 1991. Health care services utilization in the year before the antihypertensive treatment was initiated also differed between the 3 groups. Patients in the captopril group were more likely to have received a prescription drug for a respiratory illness or diabetes, whereas a smaller proportion of patients received an anticonvulsant, NSAID, psychotropic agent or a drug for ulcer, asthma or rheumatism. Although a greater proportion of patients initially prescribed captopril were admitted to hospital in the year before treatment, patients in this group made fewer visits to GPs than those first prescribed enalapril or lisinopril.

After treatment was initiated patients prescribed captopril were dispensed more medications on average, with an overall rate of 18.6 prescriptions per patient per year (v. 16.4 and 14.7 for enalapril and lisinopril users respectively [Table 2]). Patients in the captopril group were also admitted to hospital more often and made more visits to

GPs and specialists after treatment initiation than those in the other 2 groups.

After adjustment for potential confounders, the rates for visits to a GP or specialist and admissions to hospital were significantly higher among patients prescribed captopril initially than among those prescribed enalapril or lisinopril (Table 3).

To test the consistency of these results across different levels of comorbidity, a stratified analysis was performed based on the number of hospital admissions in the year before treatment (Table 4). The rates of visits to a GP remained significantly higher among patients taking captopril for patients with one or no admissions to hospital in the previous year. This suggests that patients prescribed enalapril and lisinopril made fewer subsequent visits to a GP only if they were healthier before treatment was initiated. The greater number of visits to a specialist among the captopril users was attenuated for patients admitted to hospital once; among those not admitted or admitted to hospital twice or more, enalapril and lisinopril still showed a "protective" effect when compared with captopril. This variability could be a result of random error, as indicated by overlapping confidence intervals.

We carried out additional analyses to address the comparability of the groups and the role of potential confounding variables (data not shown). First, we stratified the comparisons according to patients' health status (as indicated by prescription drug use or hospital admissions) in the year preceding treatment; the results were similar to those of the main analyses and indicated that treatment initiation with lisinopril or enalapril was associated with lower rates of health care utilization than treatment with captopril. We also restricted the analyses to the 1580 patients who used a single agent at treatment initiation, who did not switch to another antihypertensive drug during the course of their treatment and who had not been admitted to hospital in the year preceding treatment initiation. When this was done most of the previously observed significant differences be-

Table 1: Patient characteristics at initiation of antihypertensive treatment with 1 of 3 ACE inhibitors

Characteristic	Drug initially prescribed; no. (and %) of subjects*		
	Captopril *n = 529*	Enalapril *n = 2939*	Lisinopril *n = 1241*
At treatment initiation			
Mean age (and SD), yr	62.7 (10.7)	60.9 (10.6)	59.9 (10.4)
Male sex	273 (51.6)	1413 (48.1)	630 (50.8)
Receiving social assistance	28 (5.3)	119 (4.0)	49 (3.9)
Mean length of follow-up† (and SD), mo	36.3 (11.1)	34.4 (10.6)	29.3 (8.5)
In year before treatment initiated			
Drugs prescribed			
Respiratory agents	32 (6.0)	143 (4.9)	64 (5.2)
Antidiabetic agents	48 (9.1)	244 (8.3)	77 (6.2)
Antiasthmatics or glucocorticoids	20 (3.8)	142 (4.8)	51 (4.1)
Antiulcer agents	43 (8.1)	263 (8.9)	129 (10.4)
Anticonvulsants	2 (0.4)	46 (1.6)	20 (1.6)
Antilipemics	9 (1.7)	50 (1.7)	45 (3.6)
NSAIDs	130 (24.6)	779 (26.5)	345 (27.8)
Psychotropic agents	70 (13.2)	498 (16.9)	209 (16.8)
Any medication	262 (49.5)	1481 (50.4)	631 (50.8)
Mean no. of hospital admissions (and range)‡	0.43 (0–6)	0.32 (0–7)	0.22 (1–10)
Frequency of hospital admissions, no. (and %) of patients			
0	380 (71.8)	2280 (77.6)	1041 (83.9)
1	106 (20.0)	488 (16.6)	161 (13.0)
≥ 2	43 (8.1)	171 (5.8)	39 (3.1)
Mean no. of visits to GP (and range)‡	6.9 (0–96)	7.2 (0–104)	8.1 (0–105)
Mean no. of visits to specialist (and range)‡	3.2 (0–62)	3.7 (0–113)	3.2 (0–64)

Note: ACE = angiotensin-converting-enzyme, SD = standard deviation, NSAIDs = nonsteroidal anti-inflammatory drugs, GP = general practitioner.
*Unless otherwise specified.
†Excludes time spent in hospital.
‡Ranges are provided rather than SDs because these distributions are skewed.

tween groups disappeared; this could have been due to the substantially reduced sample size, however.

Interpretation

Our study showed that patients with hypertension who are initially prescribed enalapril or lisinopril visit a physician less frequently and appear to be at lower risk for admission to hospital than patients initially prescribed captopril. Our results suggest that ACE inhibitors may not be therapeutically equivalent, as previously suggested,[22–41] and this would contradict the fundamental assumption underlying reference-based pricing. Thus, the anticipated savings from such a policy may be offset by the subsequent costs arising from an increase in the use of health care services.[48,49]

Several concerns have been raised about the reference-based pricing of prescription drugs and the potential impact such a policy may have on patient care and overall expenditures.[7–11] Uncontrolled studies involving patients with hypertension have reported substantial cost savings and equal therapeutic efficacy when substituting benazepril for enalapril,[50] lisinopril for captopril[51] or quinapril for either captopril, enalapril or lisinopril.[52] However, most of these clinical studies suffered from small samples, short follow-up or a lack of control over potential confounding variables. No randomized controlled trial has yet demonstrated the differential impact of ACE inhibitors on health care outcomes; any differences between inhibitors beyond those of initial cost remain to be determined.[48,49]

The usefulness of nonexperimental studies in evaluating the efficacy of a particular drug treatment in the population is well known.[53,54] However, without randomization these studies may be confounded by selective prescribing as a function of disease status or comorbidity as well as other characteristics of the patient or GP. This may not have been a major problem in our study because official guide-

Table 2: Annual rates of health resources utilization after treatment initiation*

Utilization	Drug initially prescribed; mean no. of events per subject per year		
	Captopril	Enalapril	Lisinopril
Prescription drug use			
ACE inhibitors	6.4	6.8	6.8
β-adrenergic blockers	0.8	0.6	0.5
Calcium-channel blockers	1.4	1.1	0.9
Diuretics	3.0	1.9	1.4
Any antihypertensive	11.6	10.4	9.6
Any prescribed agent†	18.6	16.4	14.7
Health services utilization			
Hospital admissions	0.6	0.4	0.3
Visits to a GP	11.5	9.5	9.1
Visits to a specialist	5.2	4.3	3.3

*Annual rates were computed as the mean number of events per subject per year using outpatient time as the denominator.
†Including antihypertensive medications.

Table 3: Crude and adjusted* rate ratios of health services utilization after treatment initiation

Utilization; drug group	Crude RR	Adjusted RR (and 95% CI)
Visits to a GP		
Captopril	1.00	1.00
Enalapril	0.83	0.84 (0.80–0.88)
Lisinopril	0.82	0.79 (0.74–0.83)
Visits to a specialist		
Captopril	1.00	1.00
Enalapril	0.84	0.82 (0.75–0.90)
Lisinopril	0.69	0.73 (0.65–0.82)
Hospital admissions		
Captopril	1.00	1.00
Enalapril	0.78	0.82 (0.73–0.93)
Lisinopril	0.57	0.65 (0.56–0.75)

Note: RR = rate ratio, CI = confidence interval.
*Adjusted for sex, age, social assistance at treatment initiation, year of treatment initiation and comorbidity (as measured by the use of NSAIDs, psychotropic agents and drugs for the treatment of diabetes, ulcers, respiratory illness and hyperlipidemia and the number of physician visits and hospital admissions in the year preceding treatment initiation).

Table 4: Adjusted rate ratios of health services utilization after treatment initiation, by number of hospital admissions in year preceding treatment initiation

Utilization; drug group	No. of admissions; RR		
	0 *n = 3701*	1 *n = 755*	≥ 2 *n = 253*
Visits to a GP			
Captopril	1.00	1.00	1.00
Enalapril	0.84 (0.79–0.88)	0.84 (0.75–0.95)	0.94 (0.77–1.14)
Lisinopril	0.79 (0.74–0.85)	0.78 (0.67–0.91)	0.83 (0.64–1.08)
Visits to a specialist			
Captopril	1.00	1.00	1.00
Enalapril	0.84 (0.75–0.93)	1.14 (0.89–1.45)	0.58 (0.41–0.81)
Lisinopril	0.77 (0.68–0.87)	0.93 (0.68–1.28)	0.38 (0.22–0.67)
Hospital admissions			
Captopril	1.00	1.00	1.00
Enalapril	0.76 (0.66–0.88)	0.99 (0.75–1.32)	0.93 (0.63–1.38)
Lisinopril	0.63 (0.53–0.75)	0.79 (0.54–1.15)	0.54 (0.30–0.98)

lines and medical textbooks do not differentiate between specific ACE inhibitors for treatment initiation. Moreover, we adjusted for factors that we thought might affect health care services utilization;[55] for example, we excluded patients with suspected cardiovascular disease and also examined subgroups of patients thought to be healthier. However, differences may have remained between the groups that could have biased the results.

Another limitation of our study stems from the use of computerized databases of drug dispensing; dispensing data may not accurately reflect actual drug use. Furthermore, we did not account for different patterns of prescription drug use, and this may have distorted our results, particularly if nonadherence to the initial treatment was systematically associated with the use of health care services.

Our study illustrates the complexities involved in evaluating reference-based pricing and confirms the need for more research. Ideally, increasing costs of prescribed drugs should be offset by improvements in health care services, and the short-term benefits of reference-based pricing should be weighed against long-term impact. Whether reference-based pricing really achieves its objectives and the implications the policy may have for access to health care and efficiency and quality of health care need to be examined.

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