



Original Article

# Antihypertensive Prescribing for Uncomplicated, Incident Hypertension: Opportunities for Cost Savings

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## ABSTRACT

**Background:** A range of first-line similarly effective medications ranging in price are recommended for treating uncomplicated hypertension. Considering drug costs alone, thiazides and thiazide-like diuretics are the most cost-efficient option. We determined incident prescribing of thiazides for newly diagnosed hypertension as first-line treatment in Alberta, factors that predicted receiving thiazides vs more costly medications, and how much could be saved if more patients were prescribed thiazides.

Hypertension affects 23% of Canadian adults, accounting for an estimated 10% of overall health care spending.<sup>1</sup> A number of medications at various prices are recommended by guidelines as initial pharmacotherapy to treat hypertension without other compelling indications.<sup>2</sup> More highly-priced medicines can have considerable financial implications for individuals and the health care system.<sup>3</sup> In Canada, approximately 10% of patients experience cost-related nonadherence, which affects outcomes and increases health care costs.<sup>4,5</sup> Forgoing treatment because of cost barriers might lead to preventable morbidity, hospital visits, and costs, or even premature death.<sup>6,7</sup>

For therapeutic areas such as hypertension in which multiple treatments are available at different prices, physician

## RÉSUMÉ

**Contexte :** De nombreux médicaments tous aussi efficaces les uns que les autres, mais de prix variable, sont recommandés pour le traitement de première intention de l'hypertension non compliquée. Si l'on tient compte du coût du médicament seulement, les thiazides et les diurétiques apparentés aux thiazides sont les options les plus économiques. Nous avons évalué le taux de prescription d'un thiazide pour le traitement de première intention de l'hypertension nouvellement diagnostiquée en Alberta, les facteurs de prédiction de la

prescribing behaviour and its responsiveness to medicine prices (ie, prescribing lower-cost medicines with comparative effectiveness whenever appropriate) represents an opportunity to contain costs (to the patient and to the health system) while simultaneously improving patient outcomes (as a result of also reducing cost-related nonadherence).<sup>5</sup> Physicians and other prescribers rarely interact with pricing data in their daily practices and have been shown to often be unaware of drug pricing.<sup>8</sup> Consequently, higher-cost medications might be prescribed when lower-cost alternatives exist with equivalent expected effectiveness.

A variety of successful interventions have increased physicians' access to and awareness of drug prices to encourage physicians to prescribe lower-cost therapies when appropriate.<sup>9-12</sup> Since 2013, one such effort to increase physicians' awareness of higher-priced medicines in the province of Alberta specifically, has been the publication of an annual report by the Alberta College of Family Physicians (ACFP). These reports list lower-cost alternatives according to therapeutic area, including an estimate of the out-of-pocket cost to the patient to fill their prescription.<sup>13</sup> For example, the lowest-cost generic angiotensin converting enzyme inhibitors (ACEIs; ie, ramipril, lisinopril) were priced at \$30 for a 90-day supply whereas the lowest-cost generic diuretics (ie, indapamide, hydrochlorothiazide) were half that cost (ie, \$15 for a

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**Ethics Statement:** The reported research has adhered to the relevant ethical guidelines.

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See page 712 for disclosure information.

**Methods:** Using a retrospective cohort design, factors predicting receiving thiazides vs other agents were determined using mixed effects logistic regression. Cost savings were simulated by shifting patients from other antihypertensive medications to thiazides and calculating the difference.

**Results:** Within our cohort of 89,548 adults, only 12% received thiazides as first-line treatment whereas 44% received angiotensin converting enzyme inhibitors, 17% received angiotensin receptor blockers, 16% received calcium channel blockers, and 10% received  $\beta$ -blockers. Antihypertensive medications were typically prescribed by office-based, general practitioners (88%). Being male and receiving a prescription from a physician with  $\geq 20$  years of practice and a high clinical workload were associated with increased odds of receiving nonthiazides. In the extreme case that all patients received thiazides as their first prescription, spending would have been reduced by a maximum of 95% (CAD\$1.8 million).

**Conclusions:** Only 12% of Albertan adults with incident, uncomplicated hypertension were prescribed thiazides as first-line treatment. With the opportunity for drug cost savings, future research should evaluate the risk of adverse events and side effects across the drug classes and whether the costs associated with managing those risks could offset the savings achieved through increased thiazide use.

prescription d'un thiazide plutôt que d'un autre médicament plus coûteux, ainsi que les économies qui pourraient être réalisées si on prescrivait un thiazide à un plus grand nombre de patients.

**Méthodologie :** Dans le cadre de notre étude de cohorte rétrospective, nous avons déterminé les facteurs de prédiction de la prescription d'un thiazide plutôt que d'un autre agent à l'aide d'une régression logistique à effets mixtes. Nous avons simulé les économies qui pourraient être réalisées en faisant passer à un thiazide les patients à qui un autre médicament antihypertenseur a été prescrit et en calculant la différence.

**Résultats :** Dans notre cohorte de 89 548 adultes, seulement 12 % des patients ont reçu un thiazide en première intention; 44 % ont reçu un inhibiteur de l'enzyme de conversion de l'angiotensine; 17 %, un antagoniste des récepteurs de l'angiotensine; 16 %, un inhibiteur calcique; et 10 %, des bêtabloquants. Les agents antihypertenseurs sont généralement prescrits par des omnipraticiens en cabinet (88 %). Le fait d'être un homme et le fait d'obtenir une prescription auprès d'un médecin exerçant depuis au moins 20 ans et ayant une lourde charge de travail clinique étaient associés à une probabilité supérieure de recevoir un agent autre qu'un thiazide. Dans le cas extrême où tous les patients se verraient prescrire un thiazide en première intention, la réduction des dépenses pourrait atteindre 95 % (soit 1,8 million de dollars canadiens).

**Conclusions :** En Alberta, un thiazide a été prescrit en première intention à seulement 12 % des adultes venant de recevoir un diagnostic d'hypertension non compliquée. Compte tenu des économies qui pourraient être réalisées si un thiazide était prescrit dans ce contexte, il conviendrait d'effectuer des recherches plus poussées pour évaluer le risque de manifestations indésirables et d'effets secondaires associé aux différentes classes de médicaments, et pour déterminer si les coûts liés à la prise en charge de ce risque annuleraient les économies réalisées en augmentant le recours aux thiazides.

90-day supply).<sup>13</sup> Over time and at a system level, initiating patients' treatment with drugs that are twice the price of other equivalent options can amount to large cost differences.

As stated in the ACFP reports and elsewhere,<sup>13</sup> thiazide and thiazide-like diuretics (referred to collectively as "thiazides" in this article) are the least expensive class of antihypertensive medications in Canada. This treatment choice is supported by practice guidelines with "grade A" evidence as a single-pill monotherapy.<sup>2</sup> A recently updated Cochrane systematic review and observational studies also support low-dose thiazides as a similarly effective first-line treatment for incident hypertension relative to other available classes of guideline-recommended antihypertensive medications.<sup>14-17</sup>

Therefore, in this study, we sought to determine how often thiazides and higher-cost alternatives were prescribed as first-line treatment in Alberta, factors that predict receiving thiazides vs other antihypertensive medications, and how much could be saved if more patients with incident uncomplicated hypertension were prescribed lower-cost thiazides first.

## Methods

### Setting

This study was conducted in the province of Alberta, Canada, where access to physician and laboratory services are available without charge. Although currently there is no

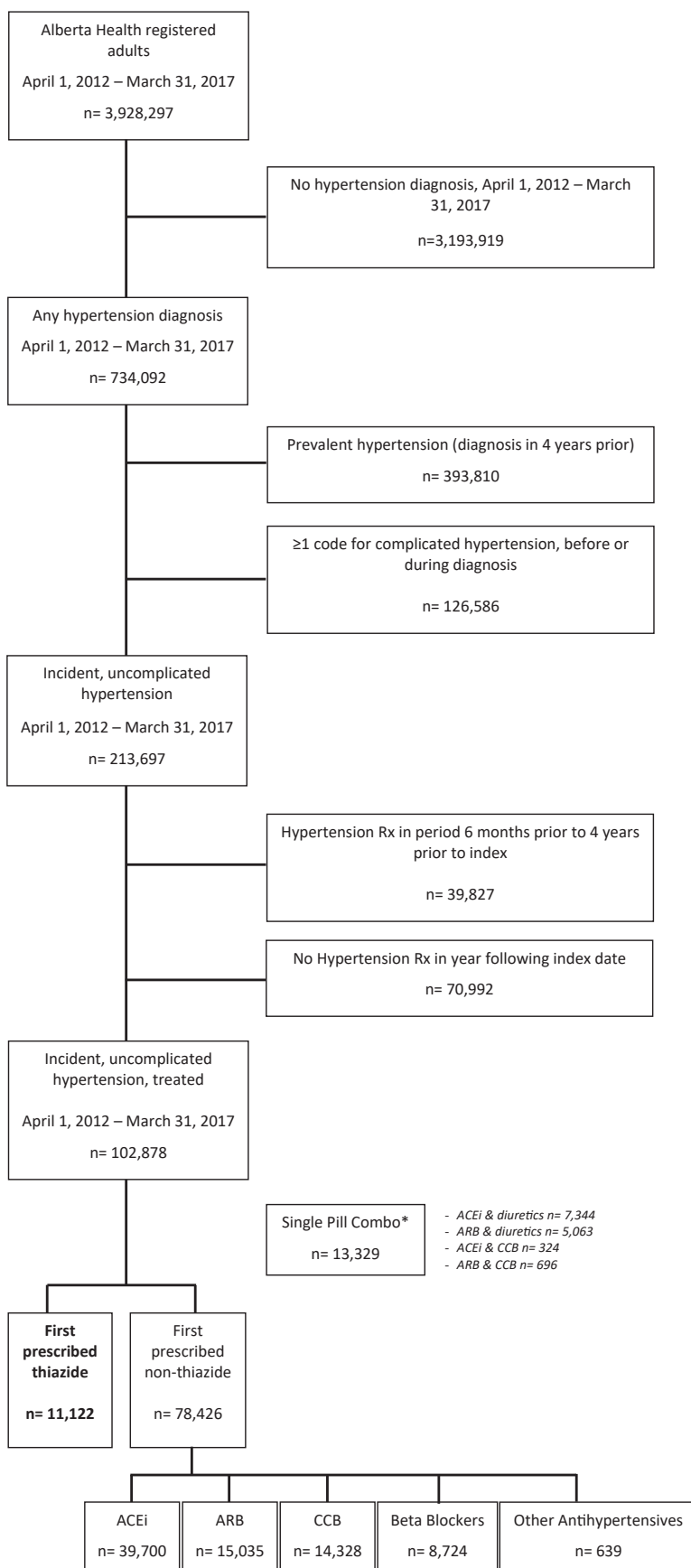
universal pharmacare system, a provincial government-sponsored (premium-free) program is available for prescription drug benefits for people aged 65 and older such that most patients will not need to pay more than \$25 for a 3-month supply of medications. Although most patients are insulated from drug costs in Canada through public or employer-based insurance programs (which might have varying levels of coverage and restrictions), there is a small proportion of patients (estimated to be approximately 10%), such as the underemployed, who might experience cost-related nonadherence because of a lack of adequate coverage for pharmaceuticals.<sup>4,18</sup>

### Ethics

The Conjoint Health Research Ethics Board of the University of Calgary approved this study and granted waiver of patient consent.

### Data sources

We used a provincial data repository, which includes administrative, laboratory, and pharmaceutical claims for nearly all residents of Alberta.<sup>19</sup> Specifically, pharmaceutical claims were captured within the Pharmaceutical Information Network, which includes all medications that have been dispensed at an Alberta pharmacy, regardless of patient medication coverage. Data files were linked using scrambled patient or physician identification numbers for privacy



**Figure 1.** Inclusion and exclusion flow to derive a cohort of first Rx for uncomplicated, incident hypertension. ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; Rx, prescription.

protection. At the time of study, the most recent data available were from March 31, 2017.

## Cohort

We created a population-based retrospective cohort of adult Albertans (18 years of age or older) with incident, uncomplicated, treated hypertension diagnosed between April 1, 2012 and March 31, 2017 (Fig. 1). A 5-year time frame was selected to avoid the idiosyncrasies of any given year, but still provide a large enough observation window to observe typical prescribing and prescription filling behaviours for patients who are initiating pharmacotherapy after an uncomplicated hypertension diagnosis. Hypertension was identified using a validated algorithm (1 hospital claim [International Classification of Diseases 10th Revision code I10-I13, I15] or 2 physician claims [International Classification of Diseases ninth Revision 401-405] within 2 years or less).<sup>20</sup> The hypertension diagnosis date was defined as either the date of their hospital claim or the first of 2 physician claims. To focus on incident hypertension, we excluded patients with a previous claim for hypertension within a 4-year lookback window.

Patients were excluded if they had other compelling indications for pharmacological therapy, as defined by Hypertension Canada's guidelines, because these patients might have additional benefit from non-thiazide antihypertensive medications.<sup>21</sup> We excluded patients with previous ischemic heart disease (coronary artery disease and recent myocardial infarction), heart failure, stroke, left ventricular hypertrophy, atrial fibrillation, supraventricular tachycardia, chronic kidney disease, liver cirrhosis, renovascular disease, and diabetes (Supplemental Table S1). We also excluded patients who were prescribed metolazone or who had at least 1 diagnostic code for "complicated hypertension" during the study period (Supplemental Table S2). These conditions were identified using hospital discharge data and physician claims.

We included patients who had their first antihypertensive prescription dispensed (list of included medications is available in Supplemental Table S3) within the same time frame as the hypertension diagnosis date (ie, within the 6 months before or 12 months after the prescription date because some patients might start taking medication when blood pressure is elevated but have not met the administrative data definition for hypertension). We excluded patients who had a hypertension diagnosis, but no hypertension prescription filled in the year after their diagnosis date to maintain a cohort of patients with an incident hypertension diagnosis who subsequently initiated treatment (ie, primary adherence was observed by the patient after the initial hypertension diagnosis in which pharmacotherapy was recommended). Finally, we excluded patients who initiated treatment using single-pill combination medicines to maintain our study's focus on interchangeable hypertension monotherapies. These exclusions were all made using prescription dispensation data.

## Outcomes

A patient's first prescription for hypertension was identified using prescription dispensation data and categorized into thiazides (including thiazide and thiazide-like medicines: hydrochlorothiazide, chlorthalidone, metolazone, and indapamide) or other antihypertensive agents (including ACEIs,

angiotensin receptor blockers [ARBs], calcium channel blockers [CCBs], and  $\beta$ -blockers).

The cost of first prescriptions was estimated at the individual product level on the basis of the products' Health Canada Drug Identification Number (DIN). For each DIN, the cost per prescription was estimated as the median number of days dispensed, the median number of pills per day, and the price per pill according to the contemporaneous Alberta Drug Benefit Formulary, which lists individual drug prices for provincial pharmaceutical insurance programs.<sup>22</sup>

## Covariates of interest

Our covariates included patient and prescriber characteristics. Patient demographic and illness characteristics were defined using registry, hospital, claims, and laboratory data and measured at the date of hypertension diagnosis. We defined patients' age (mean and categorical), sex, urban/rural status, neighbourhood income quintile,<sup>23</sup> comorbidities (defined using validated algorithms<sup>24</sup>), and indicators of kidney function, proteinuria, and glycemic control. We demarcated relational continuity of primary care using the Usual Provider Continuity index on the basis of the number of visits to the same physician.

We defined prescriber characteristics at the patient level at the first prescription dispensation date. Number of unique prescribers and their specialty were identified using the pharmacy data. If prescriber information was missing from the first prescription, we obtained it from the patient's second antihypertensive prescription. For prescribers who were physicians (rather than a nurse or pharmacist<sup>25</sup>), we used physician claims data to define their years practicing since 1994 (when our database started), proportion of clinical workload on the basis of the number of days billing, practice location in the province (urban/rural), and practice facility type (eg, hospital, office, other).<sup>26</sup>

## Analysis

Differences in baseline characteristics of patients and prescribers (on the basis of whether the patient's first hypertension prescription was a thiazide or other antihypertensive medication) were determined using  $\chi^2$  tests for binary variables, *t* test for age (which was normally distributed), and rank sum test for kidney function, proteinuria, and glycemic control (which were not normally distributed). All tests were 2-way and considered significant at the 5% level.

Factors associated with receiving another antihypertensive agent compared with thiazides were determined using a mixed effects logistic regression model, including a random intercept for prescribers and bootstrapped standard errors to address patients' clustering within prescribers. We initially included all patient and prescriber characteristics in the model and then used a backward elimination approach to remove collinear and nonsignificant variables from the model. When the final model was determined, we estimated the intraclass correlation coefficient, the ratio of between-physician variance to the total variance.

Potential cost savings were estimated by shifting patients who were first prescribed other antihypertensive medications to thiazides and calculating the difference in total costs. Recognizing that legitimate reasons might exist for some

**Table 1. Patient characteristics**

Characteristic	Overall	Thiazide	Other antihypertensive*	<i>P</i> <sup>†</sup>
Overall, n	89,548	11,122	78,426	
First-line treatment				
Thiazides	12.4 (11,122)	100.0 (11,122)		
ACEI	44.3 (39,700)		50.6 (39,700)	
ARB	16.8 (15,035)		19.2 (15,035)	
CCB	16.0 (14,328)		18.3 (14,328)	
β-Blocker	9.7 (8724)		11.1 (8724)	
Other blood pressure medications <sup>‡</sup>	0.7 (639)		0.8 (639)	
Age group				
18-44.99	27.3 (24,433)	27.1 (3008)	27.3 (21,425)	0.545
45-64.99	53.5 (47,876)	53.6 (5958)	53.5 (41,918)	0.812
≥ 65	19.1 (17,127)	19.3 (2146)	19.1 (14,981)	0.628
Mean age (SD), years	53.4 (13.4)	53.6 (13.3)	53.4 (13.4)	0.134
Sex				
Male	53.8 (48,206)	43.5 (4837)	55.3 (43,369)	< 0.001
Female	46.2 (41,342)	56.5 (6285)	44.7 (35,057)	
Urban/rural				
Urban	87.2 (78,117)	86.6 (9634)	87.3 (68,483)	0.038
Rural	12.5 (11,171)	13.2 (1463)	12.4 (9708)	0.021
Missing	0.3 (260)	0.2 (25)	0.3 (235)	0.170
Income quintile				
Lowest quintile	23.7 (21,195)	22.8 (2532)	23.8 (18,663)	0.017
Highest quintile	16.6 (14,816)	16.8 (1864)	16.5 (12,952)	0.516
Missing	0.9 (825)	0.9 (98)	0.9 (727)	0.636
GP attachment <sup>§</sup>				
Infrequent	0.9 (788)	0.8 (91)	0.9 (697)	0.456
Low	22.5 (20,164)	23.9 (2655)	22.3 (17,509)	< 0.001
Medium	32.7 (29,252)	33.9 (3771)	32.5 (25,481)	0.003
High	43.5 (38,986)	41.0 (4565)	43.9 (34,421)	< 0.001
Missing	0.4 (358)	0.4 (40)	0.4 (318)	0.473
Comorbidities				
0	58.9 (52,743)	56.7 (6308)	59.2 (46,435)	< 0.001
1	26.7 (23,897)	27.9 (3099)	26.5 (20,798)	0.003
2	9.7 (8697)	10.5 (1172)	9.6 (7525)	0.002
≥ 3	4.7 (4211)	4.9 (543)	4.7 (3668)	0.339
Kidney function: mean eGFR (SD)	89.40 (17.77)	89.13 (16.76)	89.44 (17.92)	0.106
Glycemic control: mean HbA1c (SD)	5.76 (0.78)	5.70 (0.67)	5.77 (0.79)	< 0.001
Proteinuria				
Normal	82.6 (73,992)	83.2 (9257)	82.5 (64,735)	0.073
Mild	7.3 (6570)	6.5 (727)	7.5 (5843)	0.001
Heavy	2.2 (1977)	1.8 (197)	2.3 (1780)	0.001
Not measured	7.8 (7009)	8.5 (941)	7.7 (6068)	0.008

Data are presented as % (n) except where otherwise noted.

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; eGFR, estimated glomerular filtration rate; GP, general practitioner; HbA1c, hemoglobin A1c.

\* Other hypertension medications: ACEI, ARB, CCB, β-blocker, and other antihypertensive medications.

<sup>†</sup> For comparison between thiazide and other hypertension medications. Calculated using  $\chi^2$  test for binary variables, *t* test for age, and rank sum test for kidney function, proteinuria, and glycemic control.

<sup>‡</sup> Other blood pressure medications included methyl dopa (n = 144), clonidine (n = 358), guanfacine (n = 8), prazosin (n = 50), doxazosin (n = 22), hydralazine (n = 49), bosentan (n = 2), ambrisentan (n = 4), or antihypertensive medications for pulmonary arterial hypertension (n = 2).

<sup>§</sup> Primary care attachment (also called relational continuity) categories are defined as infrequent (1 to 2 primary care visits), high (> 75% of patients with 3 or more primary care visits made to the same physician), medium (50%-75% of 3 or more visits made to the same physician), and low (< 50% of visits made to any one primary care physician).

patients to initiate therapy using nonthiazide drugs, we estimated potential savings for different proportions of patients (ie, 20%, 40%, 60%, 80%, 100%) from the other drug classes and switching them into the thiazide prescription group (while maintaining the original distributions of patients across the DINs within each of the classes).

## Results

Our cohort included 89,548 adults with incident, uncomplicated, treated hypertension. We excluded 393,810 patients with prevalent hypertension, 126,586 with complications, 39,827 with an antihypertensive prescription filled

before 6 months before their hypertension diagnosis, 70,922 with no hypertension prescription in the year after their diagnosis index date, and 13,329 who started treatment with a single pill combination (Fig. 1).

## Type of antihypertensive prescribed

Among our cohort, 12.4% (11,122/89,548) received thiazides as a first prescription (Table 1), including hydrochlorothiazide, chlorthalidone, and indapamide. Hydrochlorothiazide accounted for 86.8% of all thiazides. The most commonly first prescribed other antihypertensive medication among our cohort were ACEIs (44.3%; 39,700/89,548), most of which were

brand-name versions of perindopril erbumine (56.6%; 22,447/39,700) or trandolapril (12.1%; 4,474/39,700). Smaller proportions of patients in the cohort received ARBs (16.8%; 15,035/89,548), most of which were brand-name versions of olmesartan medoxomil (26%; 3943/15,059). Generic use was more predominant for the smaller proportion of patients who received CCBs (16.0%; 14,328/89,548) and  $\beta$ -blockers (9.7%; 8724/89,548). A small number of patients (0.7%; 639/89,548) received other antihypertensive medications not recommended as first-line treatment for uncomplicated hypertension.

### Patient and prescriber characteristics

Patients who received thiazides as first-line treatment were similar overall to those receiving other antihypertensive medications. The mean age was 53.4 (SD 13.4) years, with approximately a quarter of patients (27.3%) under the age of 45 years, half (53.5%) between 45 and 65 years, and approximately a fifth (19.1%) age 65 years and older. Approximately 87% of patients lived in urban areas. Those who started treatment with thiazides were more likely to be female (56.5% vs 43.5%;  $P < 0.001$ ). There were some significant differences between the groups with respect to income, number and type of comorbidities (Supplemental Table S2), proteinuria, and glycemic control, but these differences were typically small and not in a consistent direction. There was no difference in kidney function between the 2 groups (Table 1).

First-line antihypertensive medications were prescribed by 6743 prescribers (data not shown). Most of the prescribers were physicians, including 4346 general practitioners who prescribed to 88.0% of patients, 336 internal medicine specialists who prescribed to 3.3% of patients, 134 cardiologists who prescribed to 2.5% of patients, and 72 nephrologists who prescribed to 0.3% of patients. Nearly all physicians worked in an office setting (84%). A small number of patients saw other prescribers, such as pharmacists or nurse practitioners, without specialties indicated (2.1%;  $n = 1865$ ). Prescribers saw a mean of 19.4 patients with incident, treated, hypertension, ranging from 1 to 416 patients (Table 2).

Patients who saw general practitioners vs specialists were slightly more likely to receive thiazides as first-line treatment than other antihypertensive medications (90.8% vs 87.6%;  $P < 0.001$ ). Patients who saw physicians with fewer years of practice were somewhat more likely to receive thiazides than other antihypertensive medications. Similarly, patients who saw physicians with more years in practice were more likely to receive antihypertensive medications other than thiazides. Patients who saw physicians with higher clinical workloads (> 60%) were also less likely to receive thiazides compared with other antihypertensive medications (52.2% vs 59.1%;  $P < 0.001$ ). Finally, patients with higher relational continuity to their general practitioner (75% or more of visits to the same physician) were less likely to receive thiazides as their first prescription (41.0% vs 43.9%;  $P < 0.001$ ).

### Patient and physician factors associated with not receiving thiazides

Male patients were at increased odds of receiving non-thiazides compared with female patients (adjusted odds ratio [OR], 1.67; 95% confidence interval [CI], 1.59-1.75). Physician factors associated with an increased odds of prescribing non-thiazides included being a specialist (OR, 1.84;

95% CI, 1.62-2.09) and having a high clinical workload (OR, 1.99; 95% CI, 1.61-2.44; Table 3). Physician clustering accounted for 30.7% (95% CI, 29.0%-32.3%) of the variation in being prescribed another antihypertensive medication compared with thiazides, which suggests a high level of variation in prescribing between physicians.

### Cost savings

The total cost of the initial prescriptions within our cohort was CAD\$1,868,873. Thiazides made up 1% of the share of the initial cost, whereas ACEIs made up 52%, ARBs 31%, CCBs 12%, and  $\beta$ -blockers 4% of the share of the initial costs (Fig. 2). Only ACEIs and ARBs consumed larger shares of the total expenditure (52% and 31%, respectively) than their share of the total prescriptions filled (45% vs 17%, respectively), which was because of the heavy reliance on brand-name drugs within those drug classes, in contrast to the other 3 drug classes investigated. If 20% of patients who started treatment using other antihypertensive medications instead of thiazides, approximately \$355,000 would have been saved (Fig. 3). The savings increased as more patients were switched from other antihypertensive medications to thiazides. If all patients received thiazides as their first prescription, \$1,773,409 could have been saved during the study period on first prescriptions alone. More than half (\$980,664) of these savings would have resulted from a reduction in the prescribing of ACEIs.

### Discussion

In our study of a cohort who initiated antihypertensive pharmacotherapy after a new diagnosis of uncomplicated hypertension, we found that initiating treatment with thiazides was the second least common start for patients of the 5 drug classes studied, only representing approximately 12% of patients. Instead, patients most commonly started treatment with brand-name ACEIs. Assuming thiazides were an appropriate treatment option for more patients than status quo, there might be opportunities for reducing system-level spending by as much as 95% (from \$1,893,648 to \$97,981 in the extreme case that all patients started treatment with thiazides). This illustrates the difference that treatment choice can make, even when restricting those choices to guideline-recommended options. Potential interventions to increase reliance on thiazides might be considered, particular those focused on general practitioners (as opposed to other practice areas) because they are most often in the position of recommending patients' initial treatment. However, because the risk of adverse events and side effects is not uniform across all 5 drug classes, the costs associated with managing those risks might vary and offset the initial drug cost savings in the longer term; therefore, more research is needed before recommending interventions to increase thiazide use.

Previous studies have shown greater reliance on thiazides than was observed in our study. For example, a 2004 survey showed that thiazide diuretics consistently accounted for approximately 30% of antihypertension prescriptions across countries in Western Europe and the United States, but use of other antihypertensive medications varied widely according to country.<sup>27</sup> A study that investigated Canadian antihypertensive utilization showed that thiazides consistently comprised

**Table 2. Prescriber characteristics (measured at the patient level)**

Measure	Overall	Thiazide	Other hypertension medications*	P
Overall, n	89,548	11,122	78,426	
Specialty				
General practitioner	88.0 (78,766)	90.8 (10,097)	87.6 (68,669)	< 0.001
Internal medicine	3.3 (2980)	2.2 (247)	3.5 (2733)	< 0.001
Cardiologist	2.5 (2235)	0.5 (58)	2.8 (2177)	< 0.001
Nephrologist	0.3 (306)	0.1 (16)	0.4 (290)	< 0.001
Other†	3.8 (3396)	3.8 (427)	3.8 (2969)	0.782
Missing	2.1 (1865)	2.5 (277)	2.0 (1588)	0.001
Years of practice in Alberta since 1994				
≤ 5 years	26.2 (23,433)	28.7 (3194)	25.8 (20,239)	< 0.001
6-10 years	21.3 (19,110)	22.8 (2540)	21.1 (16,570)	< 0.001
11-15 years	15.5 (13,835)	15.0 (1665)	15.5 (12,170)	0.135
16-20 years	9.2 (8213)	8.3 (927)	9.3 (7286)	0.001
> 20 years	25.9 (23,165)	22.7 (2526)	26.3 (20,639)	< 0.001
Missing	2.0 (1792)	2.4 (270)	1.9 (1522)	0.001
Mean (SD)	12.1 (7.4)	11.4 (7.3)	12.2 (7.4)	< 0.001
Clinical workload‡				
≤ 25%	1.8 (1577)	2.6 (285)	1.7 (1292)	< 0.001
26%-60%	38.0 (33,998)	42.8 (4760)	37.3 (29,238)	< 0.001
> 60%	58.2 (52,147)	52.2 (5806)	59.1 (46,341)	< 0.001
Missing	2.0 (1821)	2.4 (271)	2.0 (1550)	0.001
Practice facility type				
Hospital	12.4 (11,137)	12.9 (1429)	12.4 (9708)	0.160
Doctor office	84.1 (75,300)	82.9 (9223)	84.3 (66,077)	< 0.001
Other	1.4 (1285)	1.8 (199)	1.4 (1086)	0.001
Missing	2.0 (1821)	2.4 (271)	2.0 (1550)	0.001
Practice location				
Calgary	36.8 (32,977)	35.3 (3925)	37.0 (29,052)	< 0.001
Central	10.7 (9609)	10.5 (1163)	10.8 (8446)	0.319
Edmonton	31.5 (28,178)	31.1 (3463)	31.5 (24,715)	0.423
North	11.8 (10,531)	13.6 (1513)	11.5 (9018)	< 0.001
South	6.9 (6211)	6.9 (768)	6.9 (5443)	0.892
Missing	2.3 (2042)	2.6 (290)	2.2 (1752)	0.014

Data are presented as % (n) except where otherwise noted.

\* Other hypertension medications: ACEI, ARB, CCB, β-blocker, and other antihypertensive medication.

† Other prescribers include pharmacists and nurses who were trained and authorized to write prescriptions.

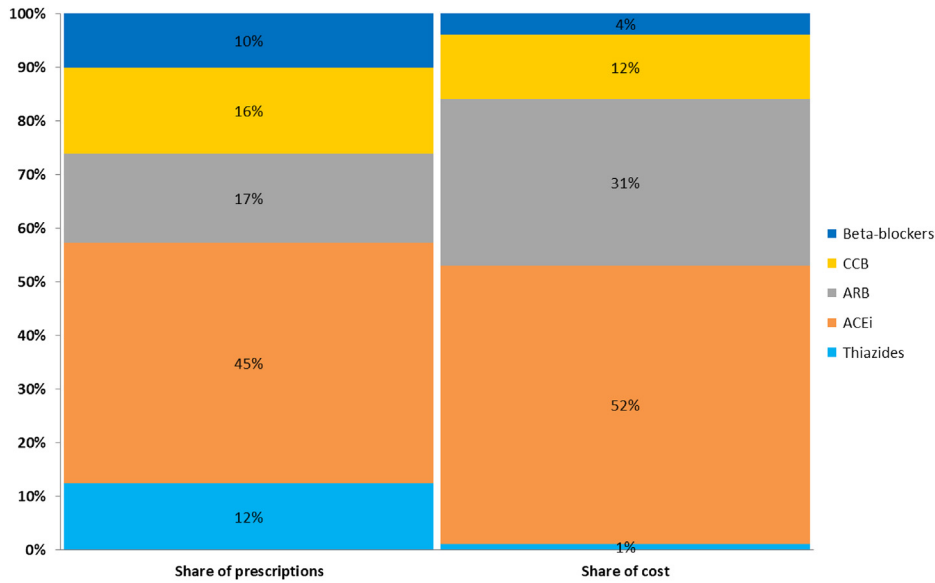
‡ Clinical workload indicates the proportion of days physicians billed in one year.

**Table 3. Association of patient and physician characteristics and the likelihood of receiving an antihypertensive medication other than thiazide for uncomplicated incident hypertension 2012-2017**

Characteristic	OR	95% CI		P
		Lower bound	Upper bound	
Patients' biological sex				
Male	1.67	1.59	1.75	< 0.001
Female	Reference			
Provider type				
Specialist	1.84	1.62	2.09	< 0.001
General practitioner	Reference			
Missing	1.27	0.51	3.21	0.608
Providers' years of practice				
0-5 Years	0.82	0.73	0.92	0.001
6-10 Years	0.76	0.67	0.87	< 0.001
11-15 Years	0.77	0.66	0.88	< 0.001
16-20 Years	0.91	0.77	1.07	0.257
≥20 Years	Reference			
Missing	0.10	0.01	0.85	0.035
Providers' clinical workload*				
≤ 25%	Reference			
26%-60%	1.40	1.14	1.72	0.001
> 60%	1.99	1.61	2.44	< 0.001
Missing	9.19	0.94	4.11	0.057
Constant	0.20	0.16	0.24	< 0.001

CI, confidence interval; OR, odds ratio.

\* Clinical workload indicates the proportion of days physicians billed in one year.



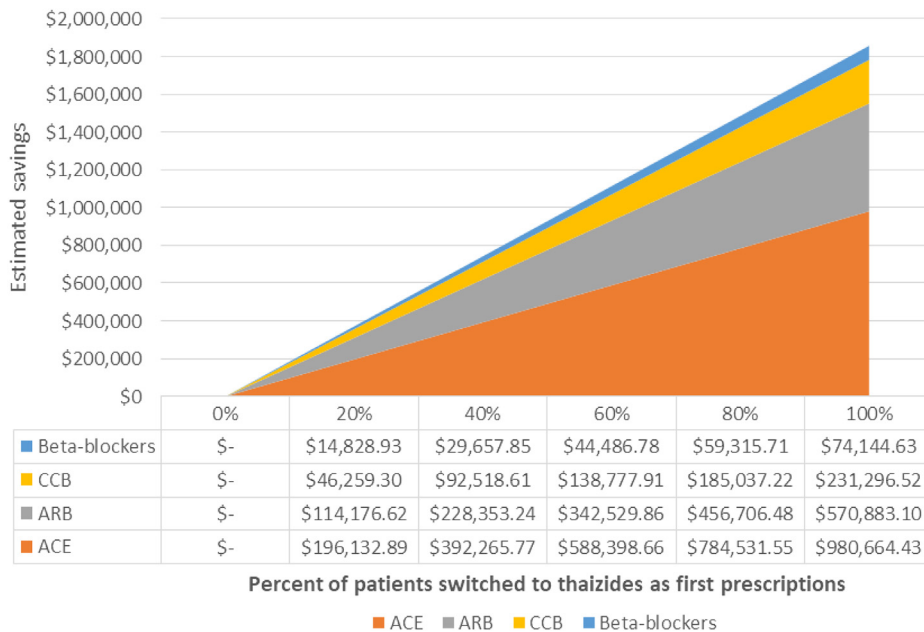
**Figure 2.** Share of antihypertensive prescriptions vs the associated estimated expenditure.

approximately 20% of all hypertensive prescribing across all provinces and across time (from 1996 to 2006).<sup>28</sup> These previous observations might suggest that Canada’s use of thiazides has historically been lower than other countries, and that, at least within Alberta, thiazide use might have declined even further since 2006.

Similarly, in a previous study in Alberta, it was reported that ACEIs consistently represented approximately 30% of the prescriptions written for hypertension from 1996 to 2006,<sup>28</sup> which might suggest that ACEI use in the province has increased considerably since then (now approximately 44%). Although in the current study we observed the highest

level of reliance on ACEIs in Alberta to date, it is important to acknowledge that there is some precedent for such levels internationally; ACEIs have previously represented more than 40% of hypertension drug utilization in Germany, Italy, and the United States.<sup>27</sup>

Our study showed that disproportionately high expenditures on ACEIs was largely because of the high number of those prescribed perindopril erbumine or trandolapril, which were under patent protection with only brand-name versions available during our observation window. The same was also true for brand-name olmesartan medoxomil, which was the most commonly prescribed ARB. Generic equivalents of other



**Figure 3.** Savings per first prescription per percentage of patients who started receiving thiazides, April 2012 to March 2017. ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker.



ACEIs and ARBs were available, but these brand name products were dispensed, nonetheless. Today generic equivalents of perindopril erbumine, trandolapril, and olmesartan are available and eligible for automatic substitution, but these generic versions remain at 6.3, 6.3, and 9.7 times more costly than thiazides, respectively. Other generic ACEIs and ARBs are less costly, but still more compared with thiazides. The most commonly prescribed generic ACEI (ie, ramipril) and ARB (ie, valsartan) remain 2.5 and 6.7 times more expensive than the most commonly prescribed thiazide (ie, hydrochlorothiazide), respectively. Nevertheless, we acknowledge that now with generic entry occurring for these frequently prescribed drugs (ie, perindopril erbumine, trandolapril, and olmesartan), the magnitude of differences between drug class expenditures has likely been markedly reduced relative to those observed during this study's observation window, especially now that within-class substitution was recently implemented in Alberta's public programs for ACEIs (as well as CCBs).<sup>29,30</sup>

Automatic between-class substitution does not currently exist in Alberta when it comes to drugs for treating uncomplicated hypertension. A number of intricacies exist between these drug classes, which make interchangeability beyond generic substitution challenging. Dosing equivalencies need to be established from clinical evidence and trial outcomes, which can be confused by differing dose frequency, titration requirements, subgroup differences, as well as varying levels of renal function and individual disease states.<sup>31</sup> Furthermore, the range of side effects and risks are not the same for the therapeutic agents, particularly when individual patient factors are considered.<sup>32</sup> For example, patients with atrial fibrillation are more often prescribed medications for rate control (such as  $\beta$ -blockers and nondihydropyridine CCBs), which is a compelling clinical indication to started treatment with a medication that is not a thiazide diuretic. Because of these important nuances, automatic substitution with other drugs between classes might not be advisable. For this reason, we have been careful to not suggest that all patients should started treatment with thiazide monotherapies, but rather that, thiazides might be a very suitable treatment option for more patients than are currently being prescribed.

Because of challenges such as these with between-class interchangeability, should an intervention be considered to encourage the use of thiazide or thiazide-like diuretics (or other less expensive treatment options) where appropriate within this context, those that provide drug price information to prescribers at the point when treatment decisions are being made might be preferable to policy approaches that would mandate switches. Physicians and other prescribers rarely interact with pricing data in their daily practices and have been shown to be poor predictors of drug prices.<sup>8</sup> Interventions that create electronic prompts or display pricing information and/or less expensive alternatives when prescriptions are written have shown success elsewhere in encouraging price-conscious prescribing while still achieving similar outcomes, particularly when these tools can provide personalized feedback and reporting.<sup>9-11,33</sup> Other complementary education-based approaches might include booster courses on available antihypertensive pharmacotherapies and their relative costs. These might prove effective, particularly if focused on primary care providers who are most often

positioned to initiate treatment by writing a patients' first prescription.

However, we acknowledge that our study has several important limitations. First, our study did not consider the associated health care utilization costs, which might result later because of side effects of the different antihypertension drug classes, each of which have their own risk profiles (eg, increased risk of thiazide-induced hyponatremia,<sup>34-36</sup> risk of hyperkalemia, and reduced glomerular filtration rate with ACEIs and ARBs<sup>37,38</sup>). The costs of these side effects might vary among hypertension drug classes.<sup>39</sup> Relatedly, the fact that thiazides were prescribed to a small proportion of patients might reflect the perception that they are less well tolerated by patients compared with newer agents; therefore, for a meaningful shift toward increasing reliance on thiazides to occur, more than just drug cost savings will need to be shown with compelling empirical and scientific rigour. Although this matter was deemed beyond the scope of our current study, it will be a valuable next step for future research and is required before recommending any of the aforementioned interventions to increase thiazide use. This work might also bring insight to other open questions regarding important differences that might exist between populations' (eg, sex, race) responses to different hypertension drugs and dosing regimens, including thiazides and thiazide-like drugs.<sup>21,40,41</sup>

Second, in our study we considered monotherapy only. Other studies have noted that after initial treatment with a thiazide, many patients will soon need to use an additional antihypertensive medication,<sup>16</sup> which was a key finding in a number of clinical trials.<sup>42-48</sup> Some practitioners might initiate pharmacotherapy with single-pill combinations with this in mind; whereas such an approach is supported by guideline recommendations and earlier initiation of combination therapies might be one instance in which cost savings with equivalent therapeutic effect is possible, our study was focused on prescribers who take a comparable approach in using monotherapy to initiate antihypertensive treatment. Future research might address cost-effectiveness of combination therapies.

Third, because of our focus on system-level drug costs, our cost estimates do not include pharmacist dispensing fees, which patients pay out-of-pocket (in contrast to the previously-mentioned ACFP reports). Furthermore, our cost estimates do not factor in rebates and are exclusively on the basis of Alberta Health Blue Cross' formulary prices. Because the size of rebates are kept in confidence between payor and suppliers and because the actual negotiated prices might vary according to insurer,<sup>49</sup> the exact absolute amount of possible savings through more price-conscious prescribing might also vary to some extent. That said, our study has also provided relative estimates of possible savings (eg, the most commonly prescribed brand name ACEIs are 6.3 times more expensive than the most commonly prescribed thiazide), an indicator that might be less sensitive to variation because rebate and price variations apply equally to all drug classes, and brand and generic drugs regardless of insurer.

In conclusion, the choice between guideline-recommended monotherapies for treating incident, uncomplicated hypertension carries very different cost implications, particularly at the system level for larger populations and considering that the initial prescription sets precedent for many patients' care

going forward. Our finding that only 12% of Albertans were prescribed thiazides as first-line treatment suggests that there might be opportunity for drug cost savings by increasing use of thiazides and thiazide-like diuretics when appropriate. However, before recommending interventions to increase thiazide use, more research is needed to investigate the relative risk of adverse events and side effects across the 5 drug classes and whether the costs associated with managing those risks might offset any shorter-term drug cost savings gained through changing initial prescribing patterns.

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### Disclosures

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### References

- Weaver CG, Clement FM, Campbell NRC, et al. Healthcare costs attributable to hypertension. *Hypertension* 2015;66:502-8.
- Hypertension Canada. Choice of therapy for adults with hypertension without compelling indications for specific agents. Available at: <https://guidelines.hypertension.ca/prevention-treatment/uncomplicated-hypertension-therapy>. Accessed April 12, 2021.
- Patra J, Popova S, Rehm J, et al. Economic cost of chronic disease in Canada. Ontario chronic disease prevention alliance and the Ontario public health association (2007). Available at: [https://www.ocdpa.ca/sites/default/files/publications/OCDPA\\_EconomicCosts.pdf](https://www.ocdpa.ca/sites/default/files/publications/OCDPA_EconomicCosts.pdf). Accessed April 12, 2021.
- Law MR, Cheng L, Dhalla IA, Heard D, Morgan SG. The effect of cost on adherence to prescription medications in Canada. *CMAJ* 2012;184:297-302.
- Choudhry NK, Denberg TD, Qaseem A. Improving adherence to therapy and clinical outcomes while containing costs: opportunities from the greater use of generic medications: best practice advice from the clinical guidelines committee of the American College of Physicians. *Ann Intern Med* 2016;164:41-9.
- Kane S, Shaya F. Medication non-adherence is associated with increased medical health care costs. *Dig Dis Sci* 2008;53:1020-4.
- Bender BG, Rand C. Medication non-adherence and asthma treatment cost. *Curr Opin Allergy Clin Immunol* 2004;4:191-5.
- Allan GM, Lexchin J, Wiebe N. Physician awareness of drug cost: a systematic review. *PLoS Med* 2007;4:e283.
- Frazier LM, Brown J, Divine GW, et al. Can physician education lower the cost of prescription drugs?: A prospective, controlled trial. *Ann Intern Med* 1991;115:116-21.
- Guterman JJ, Chernof BA, Mares B, et al. Modifying provider behavior: a low-tech approach to pharmaceutical ordering. *J Gen Intern Med* 2002;17:792-6.
- McMullin ST, Lonergan TP, Rynearson CS, et al. Impact of an evidence-based computerized decision support system on primary care prescription costs. *Ann Fam Med* 2004;2:494-8.
- Alexander GC, Casalino LP, Tseng CW, McFadden D, Meltzer DO. Barriers to patient-physician communication about out-of-pocket costs. *J Gen Intern Med* 2004;19:856-60.
- Alberta Collage of Family Physicians. Price comparison of commonly prescribed pharmaceuticals in Alberta 2018. Available at: <https://www.acfp.ca/wp-content/uploads/2018/03/ACFPPrisingDoc2018.pdf>. Accessed April 12, 2021.
- Wright JM, Musini VM, Gill R. First-line drugs for hypertension. *Cochrane Database Syst Rev* 2018;4:CD001841.
- Wright JM, Musini VM. First-line drugs for hypertension. *Cochrane Database Syst Rev* 2009;3:CD001841.
- Machado MADÁ, de Moura CS, Wang Y, et al. Comparative effectiveness of antihypertensive drugs in nondiabetic patients with hypertension: a population-based study. *J Clin Hypertens (Greenwich)* 2017;19:999-1009.
- Moura CS, Daskalopoulou SS, Levesque LE, et al. Comparison of the effect of thiazide diuretics and other antihypertensive drugs on central blood pressure: cross-sectional analysis among nondiabetic patients. *J Clin Hypertens (Greenwich)* 2015;17:848-54.
- Tang KL, Ghali WA, Manns BJ. Addressing cost-related barriers to prescription drug use in Canada. *CMAJ* 2014;186:276-80.
- Hemmelgarn BR, Clement F, Manns BJ, et al. Overview of the Alberta Kidney Disease Network. *BMC Nephrol* 2009;10:30.
- Quan H, Khan N, Hemmelgarn BR, et al. Validation of a case definition to define hypertension using administrative data. *Hypertension* 2009;54:1423-8.
- Nerenberg KA, Zarnke KB, Leung AA, et al. Hypertension Canada's 2018 guidelines for diagnosis, risk assessment, prevention, and treatment of hypertension in adults and children. *Can J Cardiol* 2018;34:506-25.
- Government of Alberta. Interactive drug benefit list. Available at: <https://idbl.ab.bluecross.ca/idbl/load.do>. Accessed April 12, 2021.
- Trachtenberg AJ, Quinn AE, Ma Z, et al. Association between change in physician remuneration and use of peritoneal dialysis: a population-based cohort analysis. *CMAJ Open* 2020;8:E96-104.
- Tonelli M, Wiebe N, Fortin M, et al. Methods for identifying 30 chronic conditions: application to administrative data. *BMC Med Inform Decis Mak* 2015;15:31.
- Marra C, Johnston K, Santschi V, Tsuyuki RT. Cost-effectiveness of pharmacist care for managing hypertension in Canada. *Can Pharm J (Ott)* 2017;150:184-97.
- Knight JC, Dowden JJ, Worrall GJ, Gadag VG, Murphy MM. Does higher continuity of family physician care reduce hospitalizations in elderly people with diabetes? *Popul Health Manag* 2009;12:81-6.
- Wang YR, Alexander GC, Stafford RS. Outpatient hypertension treatment, treatment intensification, and control in Western Europe and the United States. *Arch Intern Med* 2007;167:141-7.
- Walker RL, Chen G, Campbell NRC, et al. Canadian provincial trends in antihypertensive drug prescriptions between 1996 and 2006. *Can J Cardiol* 2011;27:461-7.
- Alberta Blue Cross. Alberta Health announces an important change to coverage for select angiotensin-converting enzyme inhibitors (ACEIs), HMG-COA reductase inhibitors (statins) and calcium-channel blocking agents (CCBs) under Alberta government sponsored programs. Available at: <https://www.ab.bluecross.ca/pdfs/pharmacy-benefacts/818-Alberta-Health-announces-important-coverage-change-for-select-medications-under-government-sponsored-programs.pdf>. Accessed April 12, 2021.

30. Alberta Health. Alberta Maximum Allowable Cost (MAC) program: angiotensin converting enzyme inhibitors, (2019). Available at: <https://www.ab.bluecross.ca/pdfs/MAC-pricing-ACE-inhibitors-details.pdf>. Accessed April 12, 2021.
31. Sica DA. Class-effect with antihypertensive medications: pharmacologic considerations. *J Clin Hypertens (Greenwich)* 2009;11(suppl 12):S13-8.
32. Burnier M, Bakris G, Williams B. Redefining diuretics use in hypertension: why select a thiazide-like diuretic? *J Hypertens* 2019;37:1574-86.
33. Fretheim A, Aaserud M, Oxman AD. Rational prescribing in primary care (RaPP): economic evaluation of an intervention to improve professional practice. *PLoS Med* 2006;3:e216.
34. Leung AA, Wright A, Pazo V, Karson A, Bates DW. Risk of thiazide-induced hyponatremia in patients with hypertension. *Am J Med* 2011;124:1064-72.
35. Ernst ME, Carter BL, Goerd CJ, et al. Comparative antihypertensive effects of hydrochlorothiazide and chlorthalidone on ambulatory and office blood pressure. *Hypertension* 2006;47:352-8.
36. Alderman MH, Piller LB, Ford CE, et al. Clinical significance of incident hypokalemia and hyperkalemia in treated hypertensive patients in the antihypertensive and lipid-lowering treatment to prevent heart attack trial. *Hypertension* 2012;59:926-33.
37. Bandak G, Sang Y, Gasparini A, et al. Hyperkalemia after initiating renin-angiotensin system blockade: the Stockholm Creatinine Measurements (SCREAM) project. *J Am Heart Assoc* 2017;6:e005428.
38. Sadjadi SA, McMillan JI, Jaipaul N, Blakely P, Hline SS. A comparative study of the prevalence of hyperkalemia with the use of angiotensin-converting enzyme inhibitors versus angiotensin receptor blockers. *Ther Clin Risk Manag* 2009;5:547-52.
39. Cutler DM, Ghosh K, Messer KL, et al. Explaining the slowdown in medical spending growth among the elderly, 1999-2012. *Health Aff (Millwood)* 2019;38:222-9.
40. Tamargo J, Rosano G, Walther T, et al. Gender differences in the effects of cardiovascular drugs. *Eur Heart J Cardiovasc Pharmacother* 2017;3:163-82.
41. Helmer A, Slater N, Smithgall S. A review of ACE inhibitors and ARBs in black patients with hypertension. *Ann Pharmacother* 2018;52:1143-51.
42. Leenen FHH. ALLHAT: what has it taught us so far? *CMAJ* 2004;171:719-20.
43. Wright JT Jr, Williamson JD, Whelton PK, et al. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med* 2015;373:2103-16.
44. Cushman WC, Ford CE, Cutler JA, et al. Success and predictors of blood pressure control in diverse North American settings: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *J Clin Hypertens (Greenwich)* 2002;4:393-404.
45. The ALLHAT Officers. Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002;288:2981-97.
46. Hansson L, Zanchetti A, Carruthers SG, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. *Lancet* 1998;351:1755-62.
47. Julius S, Kjeldsen SE, Weber M, et al. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. *Lancet* 2004;363:2022-31.
48. Dahlöf B, Sever PS, Poulter NR, et al. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. *Lancet* 2005;366:895-906.
49. Memedovich KA, Manns B, Beall R, Hollis A, Clement F. The impact of pharmaceutical rebates on patients' drug expenditures. *CMAJ* 2019;191:E308-12.

### Supplementary Material

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