



Original Article

Prescription Trends of Thiazide Diuretics in a Canadian Primary Care Population From 2015 to 2021

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ABSTRACT

Background: Hypertension Canada 2017 guidelines favoured the use of thiazide (TZ)-like diuretics, such as CLTD (chlorthalidone) and indapamide (IND) over hydrochlorothiazide (HCTZ). Health Canada warned in 2019 that HCTZ may be associated with increased risk of skin cancer. Our study looked at the changes in TZ prescriptions from 2015 to 2021 in Ontario, Canada.

Methods: A retrospective cohort study was conducted of adults with hypertension, using electronic medical record data from the University of Toronto Practice-Based Research Network database covering mostly the Greater Toronto area. Outcomes included the proportion of patients who received a prescription of HCTZ, CLTD, or IND each month. Interrupted time-series analysis was used to evaluate the change in outcomes after publication of the 2017 guidelines and 2019 safety warning. Prescription trends were stratified by prescribing physicians' sex and year of medical school graduation.

Results: A total of 100,428 patients with hypertension were included in the cohort, with 31,700 patients who received at least one TZ prescription from 343 family physicians. We found a declining trend in HCTZ prescriptions over time, accompanied by an increase in IND and

RÉSUMÉ

Contexte : Les lignes directrices 2017 d'hypertension Canada accordaient la priorité à l'utilisation de diurétiques apparentés aux thiazidiques (TZ), comme la chlorthalidone (CLTD) et l'indapamide (IND), plutôt que l'hydrochlorothiazide (HCTZ). En 2019, Santé Canada a émis une mise en garde indiquant que le HCTZ pourrait être associé à un risque accru de cancer de la peau. Notre étude s'intéressait à l'évolution des taux de prescriptions des différents diurétiques TZ entre 2015 et 2021 en Ontario, au Canada.

Méthodologie : Une étude de cohorte rétrospective a été menée auprès d'adultes atteints d'hypertension à l'aide des données des dossiers médicaux électroniques du réseau de recherche fondé sur la pratique de l'Université de Toronto, qui couvre principalement la région du Grand Toronto. Les issues évaluées comprenaient la proportion de patients se faisant prescrire HCTZ, CLTD ou IND chaque mois. Une analyse de série chronologique interrompue a été réalisée pour évaluer l'évolution des issues après la publication des lignes directrices de 2017 et la mise en garde de 2019. Les tendances observées dans les prescriptions ont été stratifiées selon le sexe et l'année d'obtention du diplôme de médecine du médecin prescripteur.

Hypertension (HTN) is the most important modifiable risk factor for cardiovascular diseases and affects almost 1 in 4 Canadian adults.¹ Current mainstays of HTN prevention and treatment consist of adopting healthy behaviours and taking effective medications.² In a study on the prevalence and management of HTN based on data from the Canadian Primary Care Sentinel Surveillance Network published in 2015, 88% of patients with HTN were prescribed an

antihypertensive medication, including thiazide (TZ) diuretics.³ TZs have been a cornerstone of HTN treatment for decades, partly due to their being one of the least costly options.^{4,5}

TZ diuretics are divided into TZ-type and TZ-like diuretics based on their differing molecular structures, and pharmacokinetic and pharmacodynamic profiles.⁶ TZ-type diuretics include hydrochlorothiazide (HCTZ); and TZ-like diuretics, which are longer-acting, include chlorthalidone (CLTD) and indapamide (IND).⁶ HCTZ is the most commonly prescribed diuretic,⁷ but guidelines have changed in the past decade to further embrace the use of TZ-like diuretics. The United Kingdom National Institute for Health and Care Excellence (NICE) 2011 guidelines on HTN in adults recommended offering CLTD or IND in preference to HCTZ if a diuretic treatment is to be initiated or changed.⁸ The Hypertension

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See page 796 for disclosure information.

CLTD prescriptions, with statistically significant but transient changes in prescription rates after publication of the 2017 guidelines and the 2019 safety warning for all 3 medications. Female physician and early-career physician prescription rates changed faster than that of their counterparts immediately after the Health Canada safety warning was issued.

Conclusions: TZ diuretic prescription patterns have changed in recent years, but Hypertension Canada's 2017 guidelines and the 2019 Health Canada safety warning did not have a sustained significant impact on the change in prescription rates of HCTZ, IND, and CLTD.

Canada and the American College of Cardiology/American Heart Association guidelines were updated in 2017 to also give preference to the longer-acting TZ-like diuretics based on evidence at that time that the use of TZ-like diuretics resulted in additional risk reduction for cardiovascular events and heart failure, and in greater systolic and 24-hour blood pressure reduction, compared to short-acting HCTZ, without any detectable differences in adverse effects.^{9,10}

Updates in Hypertension Canada guidelines have been shown in the past to influence the prescription trends of antihypertensive drug classes in Canada.^{11,12} From 1996 to 2006, the number of prescriptions for antihypertensive agents increased significantly, and the greatest annual change in prescriptions occurred between 1999 to 2002 for the drug classes recommended in the first Canadian Hypertension Education Program guidelines in 1999.^{11,12} Other international studies have looked at TZ diuretic prescription trends more specifically.^{6,7,13} In the United Kingdom, the use of IND increased significantly from 2010 to 2017, following the NICE 2011 guidelines, but HCTZ was still used more widely than TZ-like diuretics.⁶ To our knowledge, antihypertensive drug prescription trends and specifically TZ diuretic prescriptions have not been studied in Canada recently in the context of the updated 2017 Hypertension Canada guidelines regarding TZ-like diuretics. Moreover, in January 2019, HCTZ was also the object of a Health Canada safety alert declaring that "prolonged use of hydrochlorothiazide may be associated with a risk of non-melanoma skin cancer that is at least four times the risk of not using hydrochlorothiazide" and suggesting to health providers to consider alternatives to HCTZ for patients who are at higher risk for nonmelanoma skin cancer.¹⁴ This new safety alert regarding HCTZ could have affected prescription rates also. The objective of this project therefore is to describe the prescription trends of TZ diuretics for adults with HTN in a Canadian primary care context; more specifically, the goal is to determine if the 2017 Hypertension Canada guidelines and the 2019 Health Canada safety alert have impacted prescribing trends, and to assess if any characteristics of the prescribing physicians are associated with changes in prescription trends.

Résultats : Au total, 100 428 patients atteints d'hypertension ont été inclus dans la cohorte; 31 700 d'entre eux se sont fait prescrire un TZ au moins une fois par l'un des 343 médecins de famille prescripteurs. Nous avons observé une tendance à la baisse quant aux prescriptions de HCTZ, laquelle s'accompagnait d'une augmentation du nombre de prescriptions d'IND et de CLTD. La variation des taux de prescriptions pour les trois médicaments était statistiquement significative, mais transitoire après la publication des lignes directrices de 2017 et de la mise en garde de 2019. Les taux de prescriptions immédiatement après la publication de la mise en garde de Santé Canada ont changé plus vite pour les femmes médecins et les médecins en début de carrière que pour les autres médecins.

Conclusions : Les habitudes de prescription des diurétiques thiazidiques ont changé dans les dernières années, mais les lignes directrices 2017 d'Hypertension Canada et la mise en garde émise en 2019 par Santé Canada n'ont pas eu un effet significatif durable sur la variation des taux de prescriptions de HCTZ, d'IND et de CLTD.

Methods

Study design

We conducted an observational retrospective cohort study using electronic medical records (EMRs) data from family medicine practices included in the University of Toronto Practice-Based Research Network (UTOPIAN) to assess TZ diuretic prescription trends among patients with HTN from January 2015 to December 2021.

Data source

We used data from the UTOPIAN Data Safe Haven, which is a secure research database comprised of de-identified patient records extracted from EMRs of contributing family medicine practices, with more than 80% of these family physicians practicing in the Greater Toronto area in Ontario, Canada (approximately 55% in the Metropolitan Toronto region, and 30% in the Central Ontario region, based on practice postal codes).^{15,16} About 10% of contributing family physicians are based in Northern Ontario, and less than 5% in Southwestern Ontario. From the UTOPIAN database, we extracted the sociodemographic characteristics (age, sex, and postal code to determine urban vs rural location, and neighborhood income quintile) and medication records of the patients included in the study population, and the sociodemographic characteristics (number of years in practice, sex, and urban vs rural clinical practice location) of the physicians prescribing medications to the patients included in the study population.

Study population

We created an open cohort of patients using the following inclusion criteria: (i) have a valid sex and date of birth recorded in their EMR; (ii) be at least 18 years old during the current month; (iii) have at least 2 visits recorded in their EMR (including at least 1 in the past 5 years); (iv) have at least one visit and/or billing record and/or prescription in the past 5 years; and (v) have a diagnosis of HTN established before the current month. Diagnosis of HTN was defined as follows: (i)

documentation of diagnosis in the patient's past medical history; OR (ii) prescription of an antihypertensive medication AND documentation of an elevated blood pressure $\geq 140/90$ mm Hg at any point in the EMR; OR (iii) prescription of an antihypertensive medication AND a billing record with the diagnostic code for HTN at any point in the EMR; OR (iv) a billing record with the diagnostic code for HTN at any point in the EMR AND documentation of an elevated blood pressure $\geq 140/90$ mm Hg at any point in the EMR. The open cohort was constructed monthly; once patients entered the cohort, they remained included unless they stopped meeting one of the data inclusion criteria above.

Outcome measures

Our 3 main outcome measures were the proportion of patients with HTN who received a prescription of (i) HCTZ and/or HCTZ-combination; (ii) CLTD and/or CLTD-combination; and (iii) IND and/or IND-combination medications each month (see [Supplemental Table S1](#) for list of medications included). These were calculated as the number of patients with HTN who received at least one prescription of the medication of interest, divided by the number of patients with HTN who received at least one prescription of any TZ or TZ-combination medication in each month. Other outcomes included the average proportion of patients with HTN who received a prescription for at least one antihypertensive medication each month, separately for each of the different classes of antihypertensive medications over the study period.

Data analysis

The study population's sociodemographic characteristics, as well as the characteristics of physicians who prescribed TZ or TZ-combination medications, were summarized using frequencies and percentages. We used interrupted time-series analysis to evaluate the change in the main outcomes after 2 events, as follows: Event A = publication of the 2017 Hypertension Canada guidelines in March 2017; and Event B = Health Canada safety alert issued in January 2019. These events defined 3 distinct time periods (T): T1 = January 2015 to February 2017; T2 = March 2017 to December 2018; T3 = January 2019 to December 2021. We fitted segmented regression models to the data using *prog autoreg* in SAS (SAS Institute, Cary, NC), and we modelled the residuals using autoregressive processes to account for autocorrelations. For each main outcome, we obtained estimates and 95% confidence intervals (CIs) for the outcome at baseline, the change in proportion in T1 (slope T1), as well as the change in level and change in slope after each event. We also compared the slope in T3 to the slope in T1 using the linear hypothesis test option in *prog autoreg*. We stratified the above analysis by physician sex and year of medical school graduation, but not by location, as the majority of physicians worked in an urban setting. Analyses were performed using SAS version 9.4 (SAS Institute), and figures were created in R, version 4.0.4 (R Foundation, Vienna, Austria).

Ethics approval

The study was approved by the University of Toronto Health Sciences Research Ethics Boards (#40170). Patient

consent was not applicable to this study, as it was a retrospective study using de-identified data. The research reported in this paper adhered to the Reporting of Studies Conducted Using Observational Routinely Collected Health Data (RECORD) guidelines.¹⁷

Results

A cumulative total of 100,428 patients with a diagnosis of HTN were included in the cohort during the study period from January 2015 to December 2021. Of these, 31,700 patients received at least one prescription for a TZ and/or TZ-combination medication during the study period (see [Supplemental Table S2](#) for the monthly number of patients with HTN included in the study cohort and the monthly number of included patients who received at least one TZ and/or TZ-combination medication prescription). Most of these patients were aged between 65 and 79 years (40.60%), were female (55.49%), and lived in an urban region (91.13%; [Table 1](#)). They were distributed across the neighborhood income quintiles (16.78% to 22.84%).

All antihypertensive medications, including the TZ and/or TZ-combination medications, were prescribed by 343 family physicians (see [Supplemental Table S2](#) for the monthly number of family physicians who prescribed the TZ and/or TZ-combination medications). Most of these physicians were female (61.52%) and practiced in an urban region (98.25%; [Table 2](#)).

Prescription of antihypertensive medications

During the study period, an average of 10.09% of patients with HTN received a prescription for at least one antihypertensive medication each month. [Table 3](#) shows the average monthly proportion of patients who received a prescription of

Table 1. Sociodemographic characteristics of patients included in the study population

Characteristic	Patients with hypertension, n (%)	Patients with hypertension with a thiazide and/or thiazide-combination medication prescription, n (%)
Total	100,428	31,700
Age, y		
18–49	11,147 (11.10)	2261 (7.13)
50–64	29,051 (28.93)	9222 (29.09)
65–79	36,307 (36.15)	12,871 (40.60)
≥ 80	23,923 (23.82)	7346 (23.17)
Sex		
Female	52,688 (52.46)	17,589 (55.49)
Male	47,740 (47.54)	14,111 (44.51)
Neighbourhood income quintiles		
1	21,756 (21.66)	7048 (22.23)
2	18,301 (18.22)	5863 (18.50)
3	16,722 (16.65)	5318 (16.78)
4	17,215 (17.14)	5425 (17.11)
5	23,574 (23.47)	7240 (22.84)
Missing	2860 (2.85)	806 (2.54)
Location of residence		
Rural	6995 (6.97)	2332 (7.36)
Urban	91,519 (91.13)	28,887 (91.13)
Missing	1914 (1.91)	481 (1.52)

Table 2. Characteristics of physicians who prescribed antihypertensive medications, including thiazide and/or thiazide-combination medications

Characteristic	n (%)
Total	343
Sex	
Female	211 (61.52)
Male	132 (38.48)
Year of medical school graduation	
1967–1994 (late-career)	117 (34.11)
1995–2007 (mid-career)	111 (32.36)
After 2007 (early-career)	110 (32.07)
Missing	5 (1.46)
Location of clinical site	
Urban	337 (98.25)
Rural	6 (1.75)

the different classes of antihypertensive medications over the study period (see [Supplemental Table S1](#) for list of medications included). The most prescribed class was calcium-channel blockers (CCBs), followed by angiotensin-converting enzyme inhibitors (ACEIs), beta-blockers, angiotensin receptor blockers (ARBs), and finally TZs. When considering TZs and TZ-combination medications together, the proportion increased to a similar number as that for ACEIs.

TZ and TZ-combination medication prescription trends

When looking at the monthly proportion of patients with HTN who received at least one TZ or TZ-combination medication prescription, an average of 65.35% (standard deviation [SD] 8.52) of these patients got a prescription for HCTZ or HCTZ-combinations over the study period, starting at 77.69% in January 2015 and progressively trending down to 54.88% in December 2021 ([Fig. 1](#)). For IND or IND-combination medication prescriptions, the average proportion of patients who received these was 28.12% (SD 6.31), starting at 18.73% in January 2015 and progressively trending up to 36.19% in December 2021. The average monthly proportion of patients who received a CLTD or CLTD-combination medication prescription was 6.95% (SD 2.44), starting at 3.84% at the beginning, and increased to 9.10% at the end of the study period.

Changes in prescription trends around different events (interrupted time series)

Between 2015 and 2017 (T1), the monthly proportion of patients who received an HCTZ or HCTZ-combination prescription progressively decreased by an estimated 0.14% (95% CI: -0.25, -0.04; T1 slope) each month ([Fig. 1](#); [Table 4](#)). After the Hypertension Canada’s 2017 guidelines were published (Event A), this proportion significantly decreased by an additional 0.21% (95% CI: -0.39, -0.04) each month (T2 vs T1 slopes). After the Health Canada safety warning was announced in January 2019 (Event B), an immediate significant decrease occurred in the proportion of HCTZ and/or HCTZ-combination monthly prescriptions by 3.63% (95% CI: -5.40, -1.86; change in level after Event B). This change was not sustained, as the change in monthly prescriptions in T3 returned to a slow decreasing rate, similar to that in the T2 and T1 time periods.

Table 3. Average monthly proportion of patients with hypertension who received a prescription of the different classes of antihypertensive medications, 2015–2021

Class of medications	Average proportion of patients, % (SD)
Calcium-channel blockers	33.68 (1.03)
Angiotensin-converting enzyme inhibitors	30.70 (1.83)
Beta-blockers	21.08 (1.11)
Angiotensin receptor blockers	20.68 (2.05)
Thiazides	
Thiazides only	17.27 (2.42)
Thiazides and thiazide-combination medications	30.23 (3.44)
Other classes of antihypertensives	1.90 (0.17)
Other combination medications	0.89 (0.56)

Denominator: monthly number of patients with hypertension who received a prescription for at least one antihypertensive medication. SD, standard deviation.

The proportion of IND and/or IND-combination prescriptions was increasing by an estimated 0.11% (95% CI: 0.04%, 0.18%) per month in T1 ([Fig. 1](#); [Table 4](#)). After the 2017 guidelines, the proportion increased significantly by an additional 0.13% (95% CI: 0.01%, 0.25%) per month (T2 vs T1 slopes). After the Health Canada safety warning, an immediate significant increase in the proportion of monthly prescriptions by 3.27% (95% CI: 1.98%, 4.57%; change in level after Event B) was observed. This increase was not sustained, as the change in monthly prescriptions of IND and/or IND-combination prescriptions returned to a slow increasing rate, similar to that in the T2 and T1 time periods.

The proportion of patients receiving CLTD and/or CLTD-combination prescriptions was also slowly increasing by 0.04% (95% CI: 0.01%, 0.08%) each month in T1 ([Fig. 1](#); [Table 4](#)). This proportion increased significantly by an additional 0.08% (95% CI: 0.03%, 0.14%) each month after the publication of the 2017 guidelines (T2 vs T1 slopes), and by another 1.73% (95% CI: 1.05%, 2.41%) right after the Health Canada safety warning (change in level after Event B). This increase was not sustained, as the change in monthly prescriptions of CLTD/CLTD-combination prescriptions decreased back to a similar almost-flat rate, as in the T1 time period.

Changes in prescription trends by physician characteristics

Some significant differences were found at the start of the study period, with female providers prescribing slightly more HCTZ than male providers (intercept, 78.23% vs 75.15%, *P*-value < 0.001), and slightly less IND (18.86% vs 20.70%, *P*-value < 0.001) and CLTD (2.94% vs 4.10%, *P*-value = 0.005; see [Supplemental Fig. S1](#)). No significant differences occurred between female and male providers for the baseline T1 prescription rate (slope T1), or in how the prescription rates changed after the Hypertension Canada’s 2017 guidelines (change in level after Event A and slopes T2 vs T1) for all 3 medications. Immediately after the Health Canada safety warning, female providers decreased their HCTZ prescriptions and increased their IND and CLTD prescriptions faster than male providers (change in level after Event B), but this difference was not sustained into T3 (slopes T3 vs T1).

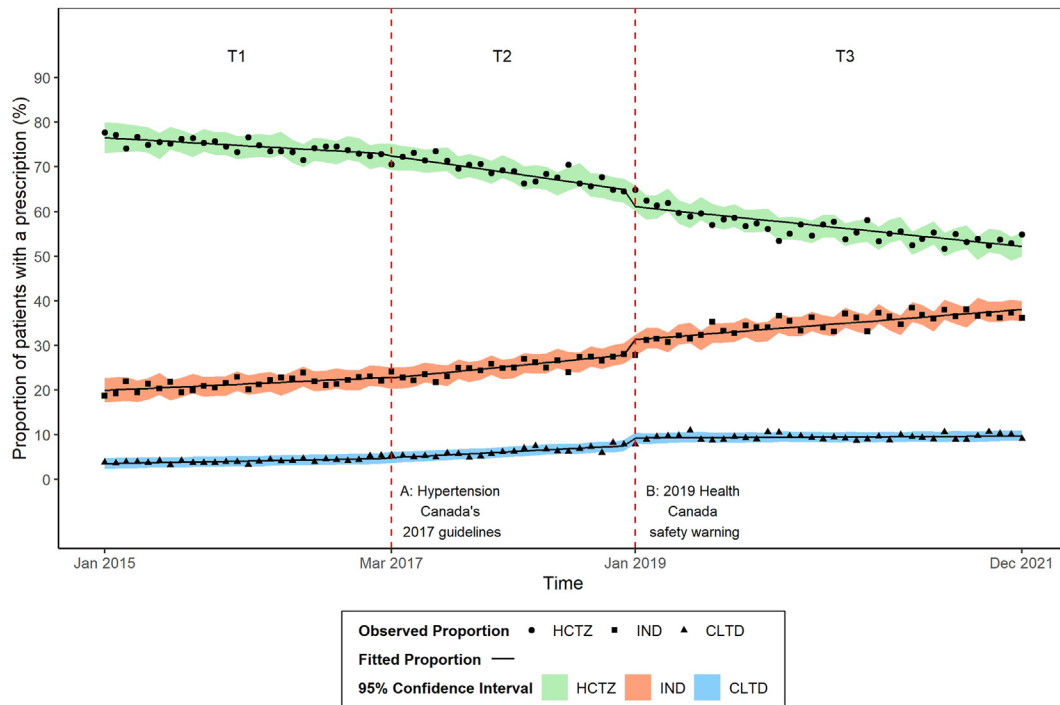


Figure 1. Monthly proportion of patients with a prescription of thiazide diuretic medications. A = publication of Hypertension Canada's guidelines in March 2017; B = Health Canada safety alert publication in January 2019. Hydrochlorothiazide (HCTZ) = HCTZ and/or HCTZ-combination medications; indapamide (IND) = IND and/or IND-combination medications; chlorthalidone (CLTD) = CLTD and/or CLTD-combination medications. T, time period. Denominator: monthly number of patients with hypertension who received a prescription for a thiazide or thiazide-combination medication.

When looking by physicians' graduation year from medical school, early-career physicians (graduated after 2007) prescribed more CLTD, mid-career physicians (graduated between 1995 and 2007) prescribed more HCTZ, and late-career physicians (graduated between 1967 and 1994) prescribed more IND at the start of the study (intercept), compared to the other 2 groups (Supplemental Fig. S1). No difference occurred in T1 prescription rates (slope T1) among the 3 groups for all 3 medications. Immediately after the Hypertension Canada 2017 guidelines, the only difference noted was that the early-career physicians increased their IND prescriptions faster than the late-career physicians (change in level after Event A), but this increase was not sustained into the T2 period. In T2, no difference occurred between groups in their decreasing rates of HCTZ prescription (slopes T2 vs T1); mid-career physicians increased their CLTD

prescriptions faster than the other 2 groups; and late-career physicians increased their IND prescriptions faster than the mid-career physicians only. Immediately after the Health Canada warning, early-career physicians decreased their HCTZ prescriptions faster than the other 2 groups, increased their IND prescriptions faster than the late-career physicians, and increased CLTD prescriptions faster than the mid-career physicians (change in level after Event B). Mid-career physicians also increased IND prescriptions faster than the late-career physicians. These changes were not sustained into the T3 period, in which no differences in the decreasing HCTZ and the increasing IND prescription rates were observed among the 3 groups (slopes T3 vs T1). For CLTD, the mid-career physicians' prescription rate increased slightly in T3, compared to T1, whereas the other 2 groups' prescription rates decreased in the T3, compared to the T1, period.

Table 4. Rate of change in monthly proportion of patients who received thiazide prescriptions

Measure	HCTZ	IND	CLTD
Intercept	76.69 (74.96, 78.42)*	19.83 (18.70, 20.96)*	3.51 (2.99, 4.03)*
T1 slope	-0.14 (-0.25, -0.04)*	0.11 (0.04, 0.18)*	0.04 (0.01, 0.08)*
Change in level after Event A	-0.24 (-2.09, 1.61)	-0.25 (-1.62, 1.12)	0.08 (-0.66, 0.82)
T2 vs T1 slopes	-0.21 (-0.39, -0.04)*	0.13 (0.01, 0.25)*	0.08 (0.03, 0.14)*
Change in level after Event B	-3.63 (-5.40, -1.86)*	3.27 (1.98, 4.57)*	1.73 (1.05, 2.41)*
T3 vs T2 slopes	0.10 (-0.05, 0.26)	-0.05 (-0.15, 0.06)	-0.11 (-0.16, -0.06)*
T3 vs T1 slopes	-0.11 (-0.24, 0.01)	0.08 (0.00, 0.17)	-0.03 (-0.07, 0.01)

Event A = publication of Hypertension Canada's guidelines in March 2017; Event B = Health Canada safety alert publication in January 2019.

CI, confidence interval; CLTD, chlorthalidone; HCTZ, hydrochlorothiazide; IND, indapamide; T, time period.

*Statistically significant, with P -value < 0.05.

Discussion

Our study found that among our cohort of primary care patients with HTN who received at least one antihypertensive medication prescription, the average monthly proportion of patients who received a TZ prescription was 17.27% over the study period, which was lower than that for other classes of antihypertensive medications (CCBs, ACEIs, beta-blockers, ARBs), but the proportion increased to 30.23% when TZ-combination medication prescriptions were included. When looking at the trends in TZ medication prescriptions over time, we found that the monthly proportion of patients receiving HCTZ and/or HCTZ-combination prescriptions decreased from 77.69% to 54.88% during the study period, with the prescription rate declining faster after publication of the Hypertension Canada's 2017 guidelines and immediately after the 2019 Health Canada safety warning was issued. On the other hand, monthly proportions of patients receiving IND and/or IND-combination and CLTD and/or CLTD-combination prescriptions doubled or more over the study period, with prescription rates increasing faster following the 2017 guidelines publication and immediately after the safety warning was issued for both medications. By the end of the study period, the prescription rates for the 3 medications returned to a level similar to that observed in the first period of the study (T1), so significant changes in prescription rates after the guidelines and safety alert were issued were temporary and did not affect the overall trends. When stratifying by physician characteristics, female physicians and early-career physicians notably decreased their HCTZ prescriptions and increased their IND and CLTD prescriptions faster than their counterparts right after the Health Canada 2019 safety alert was issued, but these differences were not sustained over time. Early-career physicians also transiently increased their IND prescriptions faster than the late-career physicians immediately after publication of the Hypertension Canada's 2017 guidelines.

Our finding that TZ medications were prescribed less than other classes of antihypertensive medications is similar to the results of other studies. In a study from Alberta, Canada, only 12.4% of patients with incident, uncomplicated HTN were prescribed TZs as first-line treatment (mainly HCTZ), behind the proportion of patients who received ACEIs, ARBs and CCBs.⁵ Another Canadian study that investigated antihypertensive utilization from 1996 to 2006 showed that TZs consistently comprised approximately 20% of all antihypertensive prescribing across all provinces and across time,¹² which is close to the 17.27% average found over our study period. TZ-combination medications were the main type of combination medications identified in our study, which increased the average monthly proportion of patients receiving a TZ or TZ-combination medication prescription to 30.23%.

In the United Kingdom, a study looked at prescription data in 2010 and 2016/2017 to analyze the impact of the 2011 NICE HTN guidelines on the trend in TZ prescribing and found that although prescriptions of TZs declined over the years, the most prescribed one was still the TZ-type diuretic bendroflumethiazide (equivalent to HCTZ) and TZ-type diuretics were still used more widely than TZ-like ones.⁶ IND use did increase significantly over their study period, but CLTD was rarely prescribed. These patterns are very similar to our results showing that HCTZ was the most prescribed, followed in order by IND and CLTD.

Our study has found some significant changes in prescription patterns after the publication of Hypertension Canada's 2017 guidelines. Although the new guidelines stated that longer-acting diuretics were preferred (Grade B recommendation based on 2 meta-analyses and 1 randomized controlled trial),⁹ new evidence published since then has questioned the superiority of TZ-like diuretics. A population-based retrospective cohort study conducted in Ontario, Canada found that among older adults, CLTD was associated with a higher risk of kidney function decline, cardiovascular events, and hypokalemia, compared with HCTZ use.¹⁸ Another large observational comparative cohort study of first-time users of antihypertensive monotherapy in the US published in 2020 concluded that CLTD was not associated with significant cardiovascular benefits and had a greater risk of renal and electrolyte abnormalities, compared to HCTZ¹⁹; but their results have been criticized for potential confounding, with a call to wait for more-definitive results from the long-awaited Veterans Affairs (VA) trial before changing clinical practice recommendations on diuretic choice.²⁰ A 2021 systematic review found that, in the long-term, CLTD is significantly more effective in reducing major cardiovascular events than HCTZ, but it also pointed to waiting for the VA trial for further guidance.²¹ In December 2022, the results of the VA pragmatic trial directly comparing commonly used doses of CLTD to HCTZ were finally published: Patients who received CLTD did not have a lower occurrence of major cardiovascular outcome events and had a higher incidence of hypokalemia than patients who received HCTZ.²² Given the inconsistent evidence in recent years, the Hypertension Canada's 2017 guidelines may have played only a partial role in the faster decrease of HCTZ prescriptions and the faster increase of IND and CLTD prescriptions in the T2 period of our study; other potential factors, such as commercial availability of new combination medications, should be considered.

Since the 2019 Health Canada safety alert, several studies looking further into the association between HCTZ and risk of skin cancer have been published, as this topic remains controversial.²³ The ongoing debate on whether HCTZ specifically is associated with an increased risk of skin cancer could explain the unsustainable impact of the Health Canada safety alert on prescription changes in our study. A population-based cohort study from Ontario published in 2021 assessed TZs and other antihypertensives, and concluded that higher cumulative exposure to TZs (no distinction made among HCTZ, CLTD, and IND) was associated with increased rates of skin cancer (keratinocyte carcinoma and melanoma) in older adults, but no evidence of association was found with other antihypertensive classes.²⁴ In response to this study, Hypertension Canada released a statement that although the cohort study was well-conducted, observational studies cannot provide proof of causality, that HTN itself is associated with cancer risk, and that TZs should not be stopped without evaluating the risk-benefit ratio.²⁵ A recent 2023 Canadian multisite population-based cohort study found that increased risks of keratinocyte carcinoma or melanoma were observed with longer duration of use and higher cumulative doses of HCTZ, but that HCTZ was not associated with an overall increased risk of keratinocyte carcinoma, compared to ACEIs or CCBs.²⁶ Another recently published, small, randomized, placebo-controlled trial concluded that HCTZ did not increase photosensitivity and was not associated with phototoxic or carcinogenic

reactions.²⁷ More research is needed given the heterogeneous conclusions of previous studies.

Based on our results, physician characteristics may be associated with prescription patterns, with early-career physicians potentially being faster to modify their prescriptions in response to recommendation changes. We have not found other studies looking at the association between physician characteristics and specific TZ prescriptions. One retrospective cohort study looked at factors predicting receiving TZs vs other antihypertensives and found that patients who saw physicians with more than 20 years of practice were more likely to receive antihypertensive medications other than TZs.⁵ More quantitative and qualitative studies are needed to better understand physician characteristics as determinants of prescription behaviour changes.

Finally, another important element that could have influenced the prescription rates is the COVID-19 pandemic, which started in March 2020 and therefore encompassed a majority of the T3 period of our study (January 2019 to December 2021) when prescriptions trends returned to baseline T1 patterns. During the pandemic, virtual care became the dominant care format; fewer visits for HTN occurred, and the majority of these visits were virtual and did not record a blood pressure measurement.^{28,29} This shift likely represented missed opportunities for antihypertensive medication review, with prescriptions being renewed automatically by physicians, given the limited bandwidth to conduct in-person visits during the height of the pandemic and the close monitoring required with medication changes.

Strengths and limitations

Given that HTN is mainly diagnosed and managed in primary care settings in Canada, clinical practice in this setting is important to study. Our study used primary care electronic medical record data from a practice-based research network, which is more comprehensive and representative of real-world family medicine practice than survey or administrative data that include only medication data for patients aged over 65 years in Ontario. However, some limitations should be considered. The UTOPIAN data included patients mostly living in the urban Greater Toronto area and who were attached to family medicine practices, so our results may not be generalizable to patients who do not have regular access to primary care nor to family physicians working in other areas and/or models of care. We also used medication data to track each prescription recorded in the patients' EMR, but this may not reflect whether the prescription was sent to the pharmacy, dispensed to the patients, or taken by the patients. One Canadian study found primary medication nonadherence (patients not filling their initial prescriptions) to be around 17% of prescriptions,³⁰ with another study showing that the nonadherence ranged from 13.7% for antidepressants up to 30.3% for antihypertensives among primary care patients.³¹ We therefore cannot comment on patients' adherence to prescribed medications based on our results and the potential impact of prescription changes on clinical outcomes.

Conclusions

TZ diuretic prescription patterns in our primary care patient population in Ontario have changed in recent years, with HCTZ becoming less prescribed, and IND and CLTD

gaining in popularity. The significant changes in prescription rates observed after publication of Hypertension Canada's 2017 guidelines and the 2019 Health Canada safety warning were not sustained over time; by the end of our study, prescription proportions for the 3 medications continued to decline or increase at rates similar to those from before 2017. More research, including qualitative studies, is needed to better understand potential factors, such as specific patient and physician characteristics, drug availability (eg, new combination medications), cost of medications, and drug coverage plans, that might influence prescription trends and uptake of clinical guidelines.

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Ethics Statement

The study was approved by the University of Toronto Health Sciences Research Ethics Boards (#40170). The research reported in this paper adhered to the Reporting of Studies Conducted Using Observational Routinely Collected Health Data (RECORD) guidelines.

Patient Consent

The authors confirm that patient consent is not applicable to this article. This is a retrospective observational study using de-identified data; therefore the research ethics board did not require consent from the patient.

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Disclosures

The authors have no conflicts of interest to disclose.

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Supplementary Material

To access the supplementary material accompanying this article, visit *CJC Open* at <https://www.cjopen.ca/> and at <https://doi.org/10.1016/j.cjco.2024.03.001>.