Trends in Antihypertensive Drug Utilization in British Columbia, 2004–2019

Jason D. Kim MPH, Anat Fisher MD PhD, Colin Dormuth ScD

Department of Anesthesiology, Pharmacology and Therapeutics, The University of British Columbia, Vancouver, British Columbia, Canada

Corresponding author:

Jason D. Kim

Department of Anesthesiology, Pharmacology and Therapeutics

2176 Health Sciences Mall, Vancouver, BC Canada V6T 1Z3

Email: jason.kim@ubc.ca

Funding statement: This project was funded by the British Columbia Ministry of Health, Pharmaceutical, Laboratory & Blood Services Division. All inferences, opinions, and conclusions drawn in this manuscript are those of the authors, and do not reflect the opinions or policies of the British Columbia Ministry of Health.

Competing interest statement: The authors declare that they have no competing interests.

Word count: Abstract 250; Text 2500

ABSTRACT

Background: The real-world impact of recent changes to clinical guidelines for hypertension is currently unknown. We aimed to evaluate trends in antihypertensive drug utilization over a 16-year period (2004–2019) in British Columbia.

Methods: Our two-part study included: 1) a longitudinal study that described the annual prevalence and incidence rate of using five antihypertensive drug classes (thiazide, angiotensin-converting enzyme inhibitor (ACEI), angiotensin II receptor blocker (ARB), calcium channel blocker, beta-blocker) in individuals aged 30 to 75 years (2004–2019); and 2) a cohort study comparing the risk of discontinuation, switch or add-on therapy between incident users of the above drug classes (2004–2014). We performed Cox regression analysis adjusted for age, sex, income level, and geographical area to estimate hazard ratios (HR).

Results: The incidence rate of using one of the five drug classes decreased by 22.9% from 2004 to 2014, and increased by 23.8% from 2014 to 2019. The prevalence and incidence rate of thiazide use decreased by 18.4% and 64.0% respectively, from 2004 to 2019, while those for the other drug classes increased. Incident users on thiazide monotherapy were more likely to discontinue any antihypertensive treatment versus ACEI monotherapy (HR=0.96, 95% CI: 0.95–0.97) and thiazide with ACEI/ARB (HR=0.96, 95% CI: 0.94–0.98), and were most likely to switch or add on.

Interpretation: Increasing incidence rates of antihypertensive therapy after 2014 followed the publication of new evidence and guidelines recommending lower blood pressure targets. The prevalence and incidence rate of thiazide use decreased compared with other drug classes.

INTRODUCTION

Hypertension is a modifiable risk factor for cardiovascular disease and accounts for 10% of the Canadian healthcare budget.[1] In Canada, five antihypertensive drug classes are recommended for the initial treatment of individuals with hypertension and without other compelling indications.[2] Of the five drug classes, thiazide-type and thiazide-like diuretics ("thiazides") have shown to significantly reduce mortality and cardiovascular events, including stroke and coronary heart disease in individuals with moderate to severe primary hypertension.[3] Thiazides are also the least expensive treatment option in Canada, presenting an opportunity for cost-savings. Other recommended drug classes include angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blocker (ARBs), dihydropyridine calcium channel blockers (CCBs), and beta-blockers[2,4,5], although the evidence supporting them are not as robust.

Clinical guidelines for the treatment and management of hypertension continue to be updated with new evidence. In 2017, the American College of Cardiology and American Heart Association (ACC/AHA) redefined the diagnostic blood pressure (BP) threshold for hypertension from 140/90 to 130/80 mmHg regardless of individuals' cardiovascular risk, lowered BP targets to under 130/80 mmHg, and recommended earlier initiation of pharmacotherapy for low-risk individuals at a threshold of 140/90 mmHg.[4] Hypertension Canada, for selected high-risk individuals, lowered the diagnostic threshold from 140/90 to 130/80 mmHg and recommended a systolic BP target under 120 mmHg.[6] The BP targets were informed by the results of two meta-analyses,[7,8] and the Systolic Blood Pressure Intervention Trial (SPRINT), which concluded that intensive lowering of systolic BP targets to <120 mmHg compared with <140 mmHg resulted in a 25% reduction in major cardiovascular events and all-

cause mortality among high-risk individuals without diabetes.[9] These changes were expected to impact the prevalence and incidence of hypertension (i.e., reclassification of previously non-hypertensive individuals) and the use of antihypertensive drugs (i.e., initiation of pharmacotherapy in treatment-naïve individuals or intensification of treatment to reach BP targets).[10,11] Trends in antihypertensive drug use have been responsive to the findings of clinical trials and changes in guidelines up to 2014;[12] however, the impact of more recent guidelines on antihypertensive prescribing is not currently known. In this study, we aimed to 1) evaluate trends in antihypertensive drug utilization in British Columbia (BC) over a 16-year period (2004–2019), and 2) compare the risk of discontinuation and switch or add-on therapy in incident users of antihypertensive drugs.

METHODS

Setting and data source

The study was conducted in the province of BC and comprised two parts: 1) utilization trends and 2) time to discontinuation, switch or add-on therapy analyses. We used anonymized, linkable administrative health databases of the BC Ministry of Health. The data consisted of prescription drug dispensing records at community pharmacies, registry data on enrollment in the provincial health plan and demographics, outpatient physician services, and inpatient hospitalizations.

Trends in antihypertensive drug utilization

We identified a source population of BC residents aged 30 to 75 years who were enrolled in the provincial health plan between January 1, 2004 and December 31, 2019. We excluded

beneficiaries of the First Nations Health Authority and federal programs for whom we had no access to drug data. From the source population, we identified prevalent and incident users of the following antihypertensive drug classes: thiazides, ACEIs, ARBs, CCBs, and beta-blockers. We defined "prevalent use" as a dispensing of at least one antihypertensive drug during the year, and "incident use" as a dispensing of an antihypertensive drug with no record of any antihypertensive drug (listed in **Table S1**) dispensed in the previous five years. Prevalence was expressed as a percentage, computed as the number of prevalent users divided by the total number of individuals in the source population during the calendar year. Incidence was expressed as a rate per 1000 person-years, computed as the number of incident users divided by the total person-years of health plan enrollment for the source population during the calendar year.

Discontinuation, switch or add-on therapy

Incident user cohort

From the source population, we constructed an incident user cohort comprising individuals who initiated antihypertensive treatment on thiazide monotherapy, ACEI monotherapy, ARB monotherapy, combination thiazide with ACEI/ARB, or CCB between January 1, 2004 and December 31, 2014. Cohort entry was defined as 91 days after initial dispensing. Individuals were excluded from the cohort if they were not continuously enrolled in the provincial health plan during the previous two years, had missing information on age or sex, were under 30 or over 75 years of age, died before cohort entry, received both ACEI and ARB at initial dispensing, or were diagnosed with cancer, renal failure, secondary hypertension, or other conditions indicated for the antihypertensive drug classes (**Table S2**) anytime before cohort

entry. Individuals were also excluded if they experienced the outcome between initial dispensing and cohort entry.

Outcomes

Two outcomes were assessed: 1) discontinuation of any antihypertensive therapy and 2) switch to or add-on of a different antihypertensive drug class. Discontinuation was assigned using the refill-sequence model,[13] where the first medication-free gap of 90 days for any antihypertensive drug (**Table S1**) was considered discontinuation of antihypertensive therapy. The discontinuation date was defined as the expected date of the next prescription refill. We did not adjust for stockpiling. Individuals who switched between antihypertensive drug classes before a 90-day gap were considered persistent users.

Switch or add-on therapy was defined as the first dispensing of an antihypertensive drug class different from the initial drug class (**Table S1**). Switching from a combination product to its different components was not considered a switch or add-on. Individuals were censored in the case of death, end of MSP enrollment, or end of follow-up. Additionally, for the switch or add-on analysis, individuals were censored if they discontinued antihypertensive therapy.

Statistical analysis

Cox regression models compared the hazards of discontinuation, switch or add-on between incident users on thiazide monotherapy and incident users on ACEI monotherapy, ARB monotherapy, thiazide with ACEI/ARB, and CCB. The multivariate models included adjustment for age, sex, income level, and geographical area (defined in **Table S3**). Analyses were performed using R software version 3.6.1. The study protocol was approved by the University of British Columbia Clinical Research Ethics Board (H19-03491).

RESULTS

Trends in antihypertensive drug utilization

The overall prevalence of the five antihypertensive drug classes increased by 19.3% (from 17.2% [in 2004] to 20.6% [in 2019]) (**Figure 1**). Prevalent use of ACEIs, the most prescribed drug class throughout the study period, increased by 15.5% (from 8.7% [in 2004] to 10.1% [in 2019]). Prevalent use of ARBs and CCBs also increased, by 84.9% for ARBs (from 3.1% [in 2004] to 5.7% [in 2019]) and by 109.4% for CCBs (from 2.9% [in 2004] to 6.0% [in 2019]). Prevalent use of thiazides increased by 12.8% in the first five years (from 8.5% [in 2004] to 9.5% [in 2009]) and subsequently decreased by 27.6% (from 9.5% [in 2009] to 6.9% [in 2019]) (**Figure 2**).

The overall incidence rate for the five drug classes decreased by 22.9% in the first ten years (from 23.7 [in 2004] to 18.3 [in 2014] per 1000 person-years) and subsequently increased by 23.8% (from 18.3 [in 2014] to 22.6 [in 2019] per 1000 person-years) (**Figure 1**). Incident use of thiazides decreased by 64.0% (from 8.9 [in 2004] to 3.2 [in 2019] per 1000 person-years) (**Figure 2**). After 2014, incidence rates increased for ACEIs by 25.8% (from 7.7 [in 2014] to 9.7 [in 2019] per 1000 person-years) and for ARBs by 29.8% (from 1.2 [in 2014] to 1.7 [in 2019] per 1000 person-years). Incidence rates increased for CCBs by 225.9% (from 1.2 [in 2004] to 4.0 [in 2019] per 1000 person-years) and for beta-blockers by 8.5% (from 6.5 [in 2004] to 7.1 [in 2019] per 1000 person-years). In an ad hoc analysis of incident users on thiazides, the percentage initiating hydrochlorothiazide decreased by 15.6% (from 88.4% [in 2014] to 74.6% [in 2019]) in favour of chlorthalidone (from 2.4% [in 2014] to 14.4% [in 2019]) and indapamide (from 9.2% [in 2014] to 10.9% [in 2019]) (**Figure S1**).

Discontinuation, switch or add-on therapy

After pre-defined inclusion and exclusion criteria were applied to the source population, the incident user cohort consisted of 232,781 individuals who initiated antihypertensive treatment between 2004 and 2014 (**Table S4**). Most incident users initiated ACEI monotherapy (n=100,670 [43.2%]) and thiazide monotherapy (n=86,008 [36.9%]).

Among all incident users of antihypertensive drugs, the overall median time to discontinuation was 5.58 years (95% CI: 5.53–5.64). Incident users on ARB monotherapy had the shortest median time to discontinuation (4.72 years, 95% CI: 4.48–4.95), and incident users on combination thiazide with ACEI/ARB had the longest (5.93 years, 95% CI: 5.70–6.13) (**Table 1, Figure 3**). In an adjusted Cox regression model, we estimated a 3.8% lower risk of discontinuation for thiazide with ACEI/ARB and 4.1% lower risk for ACEI monotherapy compared with thiazide monotherapy. In an ad hoc analysis stratified by PharmaCare drug coverage (covered/not covered), we found better persistence with ARB monotherapy compared with thiazides in each stratum (**Table S5**).

The overall median time to switch or add-on was 4.76 years (95% CI: 4.72–4.82). Incident users on thiazide monotherapy had the shortest median time to switch (4.26 years, 95% CI: 4.18–4.35) and those on thiazide with ACEI/ARB had the longest (6.95, 95% CI: 6.75–7.21) (**Table 2, Figure 4**). Incident users on thiazide monotherapy had the highest risk of switching or adding on.

INTERPRETATION

This study described trends in antihypertensive drug utilization in BC over a 16-year period (2004–2019). We observed a historical decrease in incident antihypertensive therapy from 2004 to 2014, followed by an increase from 2014 to 2019. Despite this recent increasing trend, initiation on thiazides continued to decrease, while initiation on ACEIs, ARBs, CCBs, and beta-blockers increased. Although the prevalence of antihypertensive therapy increased by 20.6% from 2004 to 2019, prevalent thiazide use increased by 12.8% from 2004 to 2009 and subsequently decreased by 27.6% from 2009 to 2019. Incident users on thiazide monotherapy had a higher risk of discontinuing any antihypertensive therapy compared with those on ACEI monotherapy and thiazide with ACEI/ARB, as well as a higher risk of switching to or adding on a different antihypertensive drug class compared with those in the other initial drug class groups.

Our finding of a decrease in incident antihypertensive therapy between 2004 and 2014 was consistent with a previously reported decrease in the hypertension age-standardized incidence rate of 6 per 1000 population from 1999 to 2012 in BC.[14] The increase in incident antihypertensive therapy from 2015 onwards corresponded in time with the publication of SPRINT (2015) and updated Hypertension Canada (2016) and ACC/AHA (2017) guidelines that lowered recommended BP thresholds and targets.[4,6] Muntner and co-authors estimated that implementation of the revised ACC/AHA BP standards would increase initiation of pharmacological therapy by 1.9% and increase intensified treatment by 14.4% in existing users.[11] We observed a 2.3% greater annual increase in incident antihypertensive therapy between 2017 and 2018 versus the annual increase of the previous year. Increases in prevalence

for non-thiazide drug classes may be partially explained by add-on therapy related to treatment intensification.

We observed a decrease in the prevalence and incidence of thiazide use consistent with previous studies.[12,15,16] Contributing factors to the decrease may be related to concerns around potential adverse effects associated with thiazides,[17] as well as evidence from the ACCOMPLISH (2008) trial which concluded that an ACEI/CCB combination was superior in reducing adverse cardiovascular events in high-risk individuals compared with a thiazide/ACEI combination.[12,18] However, reasons for the continued decrease in thiazide use remains unclear. No new trials on first-line drugs for hypertension were identified in the 2017 update to the original Cochrane systematic review,[3] and studies of real-world evidence on the comparative effectiveness and safety of antihypertensives provide further support for thiazides as a preferred first-line option.[19,20] From 2017 to 2018, three Danish observational studies reported an association between hydrochlorothiazide and skin cancer.[21–23] Following these studies, hydrochlorothiazide use decreased by 44% in Denmark.[24] We did not observe a similar impact in BC; however, we found that the proportion of incident thiazide use on hydrochlorothiazide (thiazide-type diuretics) has decreased since 2014, as preference for chlorthalidone and indapamide (thiazide-like diuretics) has increased due to their cardioprotective effects.[2,25–27]

Initiation on thiazide monotherapy was associated with a higher risk of treatment discontinuation compared with initiation on ACEI monotherapy and thiazide with ACEI/ARB. Previous studies showed similar patterns,[19,28,29] and risk differences ranged from +8.9% to +32.8%. Individuals who perceive side effects from their initial medication are more likely to discontinue;[30] thus side effects of thiazides may be a potential factor in discontinuation

patterns. In our study, incident users on ARB monotherapy had the shortest median time to discontinuation, which was unexpected given good tolerability profiles of ARBs.[31] Provincial drug coverage for ARBs differed from other drug classes; less than 9% of individuals on ARB monotherapy had coverage for their initial prescription compared with 98% of individuals on other drug classes. Higher drug payment is associated with antihypertensive drug non-adherence;[30,32] thus drug coverage was considered an intermediate variable in the exposure-discontinuation pathway and not included as a covariate for adjustment. Simpson's paradox was observed in ad hoc stratified analysis (i.e., reversal of effect),[33] where we found superior persistence for ARB monotherapy. We found that incident users on thiazide monotherapy were more likely to switch to or add on a different antihypertensive drug class compared with incident users on other drug classes, which was consistent with other studies.[19,28] We also found they were earlier to switch or add on than to discontinue. These findings may indicate less optimal BP control with thiazides monotherapy, thus leading to treatment intensification to reach BP targets.

Factors influencing treatment decisions are complex. It is unclear why thiazide use has declined given their effectiveness and potential for cost-savings.[3,34] Future research areas include evaluating the impact of prescriber and patient preferences on antihypertensive utilization, as well as real-world prescribing trends among individuals with specific clinical and demographic characteristics.[35] Future studies on treatment persistence might also consider accounting for differences in drug coverage policies across drug exposures in their jurisdiction.

A limitation of administrative data is the absence of clinical and laboratory data. Comorbid conditions, BP measurements, and biochemical markers are important considerations in individualized treatment.[36] Without these data, we could not evaluate utilization trends according to clinical characteristics, examine adherence to guidelines, or ascertain reasons for

discontinuation, switching or adding. Additionally, individuals were not required to have a hypertension diagnosis; thus, patients with other conditions (e.g., beta-blocker users with heart failure) were included and may have resulted in an overestimation of utilization rates.

Incidence rates of antihypertensive therapy increased after 2014, following the publication of new evidence and updated guidelines recommending lower BP thresholds and targets. Initiation on thiazides decreased from 2004 to 2019 and prevalent thiazide use decreased from 2009 to 2019, while the use of other first-line antihypertensive drugs increased. Incident users on thiazide monotherapy were more likely to discontinue antihypertensive treatment compared with those on ACEI monotherapy and thiazide with ACEI/ARB, and more likely to switch to or add on. Further research on factors influencing treatment decisions, and utilization trends according to clinical characteristics could provide insight into prescribing patterns.

Acknowledgements

The authors thank Ellen Reynolds for editing a version of this manuscript. The BC Ministry of Health approved access to and use of BC data facilitated by Population Data BC. All inferences, opinions, and conclusions drawn in this manuscript are those of the authors, and do not reflect the opinions or policies of the Data Stewards. The following data sources were used (https://www2.gov.bc.ca/gov/content/health/conducting-health-research-evaluation/data-access-health-data-central):

- British Columbia Ministry of Health [creator] (2021): Medical Services Plan (MSP) Payment Information File. BC Ministry of Health [publisher]. MOH (2019);
- British Columbia Ministry of Health [creator] (2021): PharmaNet. BC Ministry of Health [publisher]. Data Stewardship Committee (2019);
- Canadian Institute for Health Information [creator] (2021): National Ambulatory Care Reporting System. BC Ministry of Health [publisher]. MOH (2019);
- Canadian Institute for Health Information [creator] (2021): Discharge Abstract Database (Hospital Separations). BC Ministry of Health [publisher]. MOH (2019);
- British Columbia Ministry of Health [creator] (2021): Consolidation File (MSP Registration & Premium Billing). BC Ministry of Health [publisher]. MOH (2019)

TABLES

Table 1. Discontinuation of any antihypertensive therapy in the incident user cohort.

Initial Drug Class	Discontinued n (%)	Censored n (%)	Median (years)	Crude HR (95% CI)	Adjusted HR (95% CI)*
Thiazide Monotherapy n = 86,008	55,728 (64.8)	30,280 (35.2)	5.42 (5.33-5.51)	Reference	Reference
ACEI Monotherapy n = 100,670	61,838 (61.4)	38,832 (38.6)	5.89 (5.81-5.97)	0.96 (0.95-0.97)	0.96 (0.95-0.97)
ARB Monotherapy n =11,449	7423 (64.8)	4026 (35.2)	4.72 (4.48-4.95)	1.07 (1.04-1.09)	1.06 (1.03-1.08)
Thiazide with ACEI/ARB n = 18,909	11,525 (60.9)	7384 (39.1)	5.93 (5.70-6.13)	0.96 (0.94-0.98)	0.96 (0.94-0.98)
CCB n = 15,745	10,085 (64.1)	5660 (36.0)	4.87 (4.71-5.05)	1.08 (1.06-1.11)	1.06 (1.04-1.09)

HR Hazard ratio; *CI* confidence interval; *ACEI* angiotensin-converting enzyme inhibitor; *ARB* angiotensin II receptor blocker; *CCB* calcium channel blocker.

* Adjusted for age, sex, income level, geographical area.

Table 2. Switch to or add-on of a different antihypertensive drug class in the incident user cohort.

Initial Drug Class	Switched or Added n (%)	Censored n (%)	Median (years)	Crude HR (95% CI)	Adjusted HR (95% CI)*
Thiazide Monotherapy n =75,214	39,992 (53.2)	35,222 (46.8)	4.26 (4.18-4.35)	Reference	Reference
ACEI Monotherapy n = 89,500	44,254 (49.4)	45,246 (50.6)	4.53 (4.45-4.62)	0.98 (0.96-0.99)	0.93 (0.92-0.95)
ARB Monotherapy n = 10,763	4781 (44.4)	5982 (55.6)	5.48 (5.21-5.67)	0.84 (0.82-0.87)	0.82 (0.80-0.85)
Thiazide with ACEI/ARB n = 17,469	7184 (41.1)	10,285 (58.9)	6.95 (6.75-7.21)	0.74 (0.72-0.76)	0.71 (0.69-0.73)
CCB n = 14,925	6338 (42.5)	8587 (57.5)	6.59 (6.32-6.92)	0.75 (0.73-0.77)	0.74 (0.72-0.76)

HR Hazard ratio; *CI* confidence interval; *ACEI* angiotensin-converting enzyme inhibitor; *ARB* angiotensin II receptor blocker; *CCB* calcium channel blocker.

* Adjusted for age, sex, income level, geographical area.

FIGURES

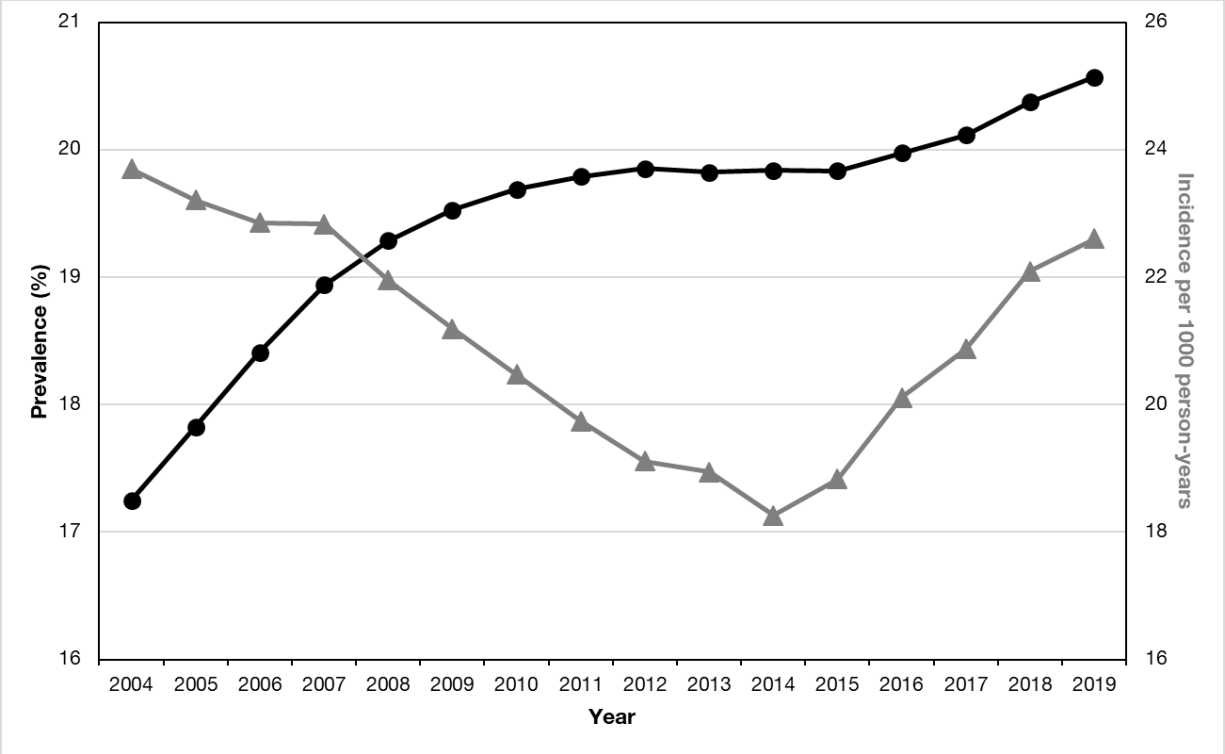

Figure 1. Prevalence and incidence of antihypertensive drug use among residents of British Columbia aged 30–75 years between 2004 and 2019. Prevalence was computed as the number of prevalent users of thiazides, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, calcium channel blockers, or beta-blockers divided by the number of British Columbia residents aged 30–75 years during the calendar year. Incidence was computed as the number of incident users of the five antihypertensive drug classes per 1000 person-years of health plan enrollment among British Columbia residents aged 30–75 years during the calendar year. Prevalent use was defined as at least one of the five antihypertensive drug classes dispensed during the year. Incident use was defined as one of the five antihypertensive drug classes dispensed in the absence of a record for any antihypertensive drug dispensed in the five years prior (drug list available in Supplementary Table S1).

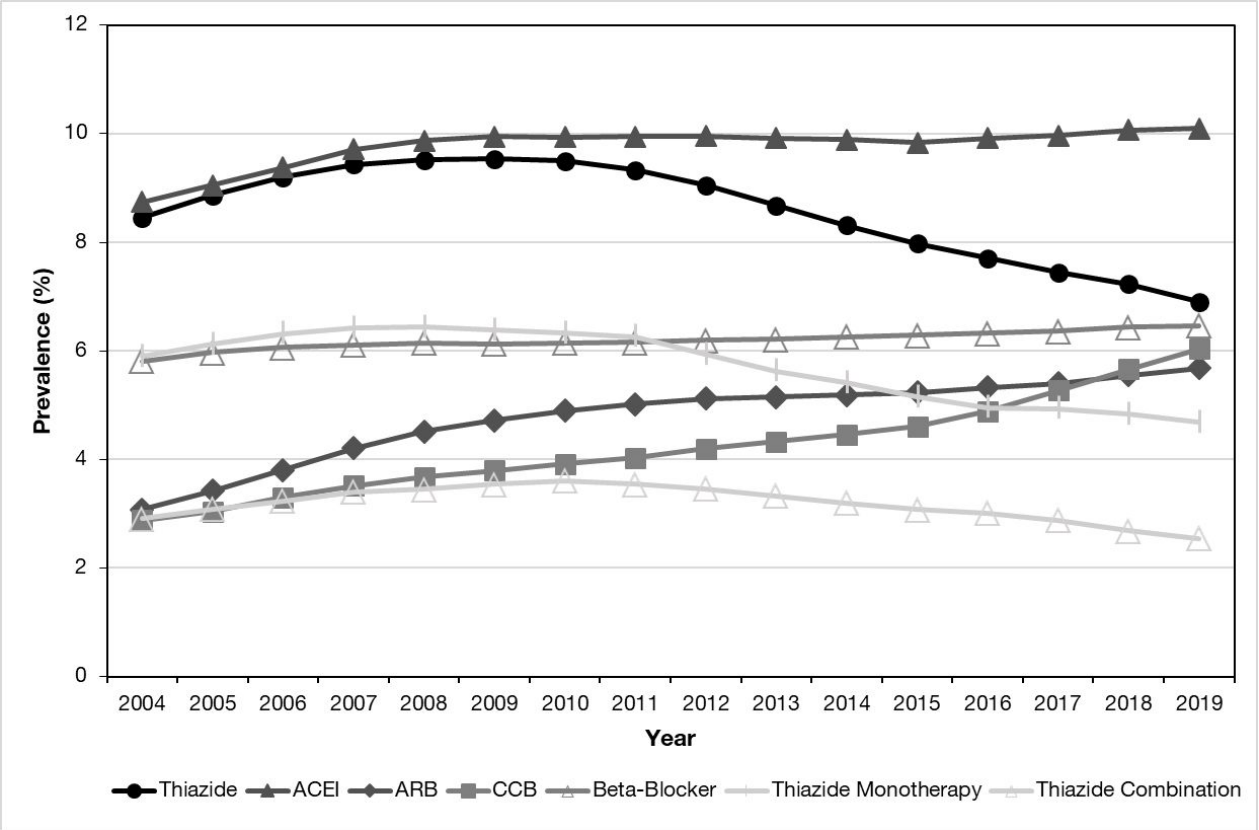

Figure 2. Prevalence of antihypertensive drug use among residents of British Columbia aged 30–75 years between 2004 and 2019, by drug class. Prevalence was computed as the number of prevalent users of an antihypertensive drug class divided by the number of British Columbia residents aged 30–75 years during the calendar year. *ACEI* Angiotensin-converting enzyme inhibitor; *ARB* angiotensin II receptor blocker; *CCB* calcium channel blocker.

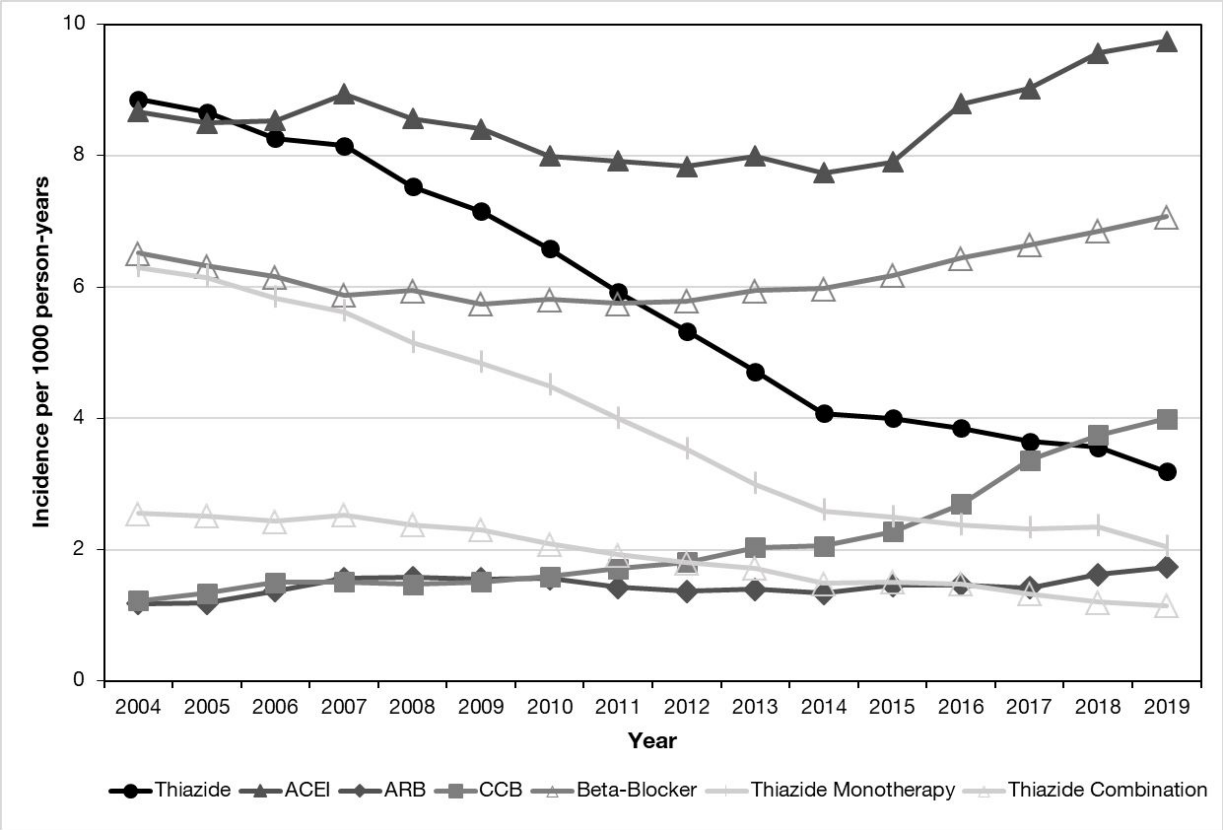

Figure 3. Incidence of antihypertensive drug use among residents of British Columbia aged 30-75 years between 2004 and 2019, by drug class. Incidence was computed as the number of incident users per 1000 person-years of health plan enrollment among British Columbia residents aged 30–75 years during the calendar year. Incident use was defined as one of the five antihypertensive drug classes dispensed in the absence of a record for any antihypertensive drug dispensed in the five years prior (drug list available in Supplementary Table S1). *ACEI* Angiotensin-converting enzyme inhibitor; *ARB* angiotensin II receptor blocker; *CCB* calcium channel blocker.

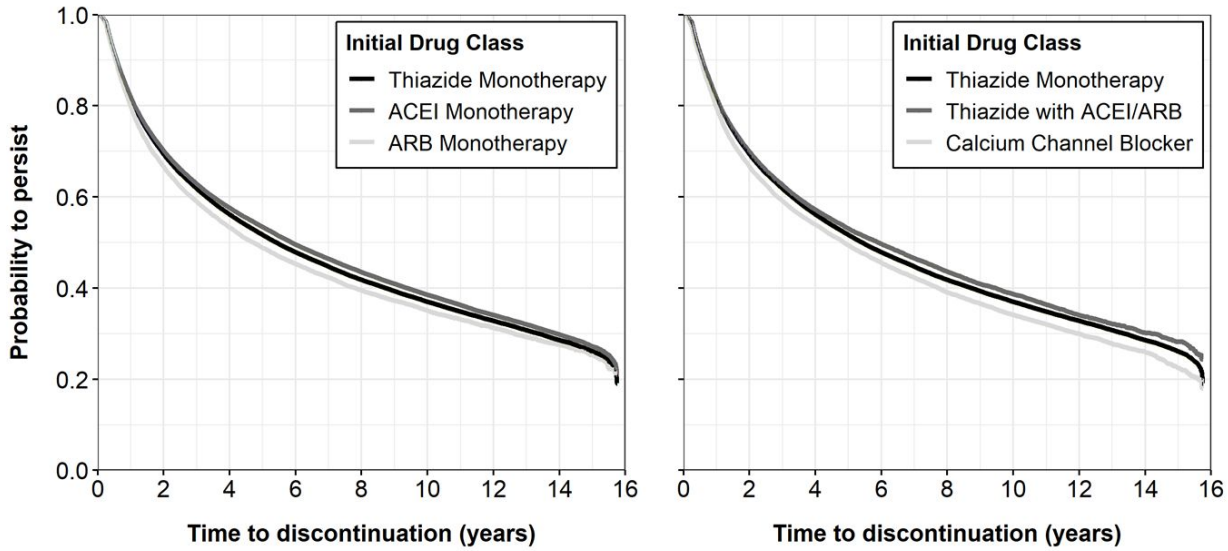

Figure 4. Time to discontinuation of any antihypertensive therapy by initial drug class.

Discontinuation was assigned using the refill-sequence model, where the first medication-free gap of 90 days for any antihypertensive drug was considered discontinuation of antihypertensive therapy (drug list available in Supplementary Table S1). The discontinuation date was defined as the expected date of the next prescription refill. Individuals were censored in the case of death, end of health plan enrollment, or end of follow-up. *ACEI* Angiotensin-converting enzyme inhibitor; *ARB* angiotensin II receptor blocker.

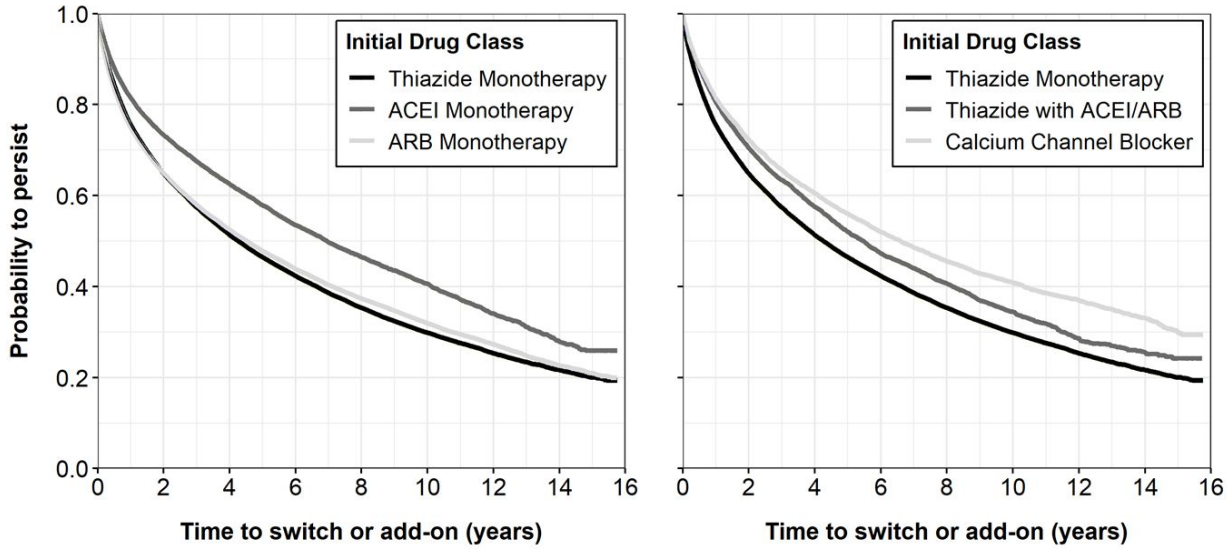

Figure 5. Time to switch to or add-on of a different antihypertensive drug class by initial drug class. Switch or add-on therapy was defined as the first dispensing of an antihypertensive drug class different from the initial drug class (drug list available in Supplementary Table S1). Switching from a combination product to its different components was not considered a switch or add-on event. Individuals were censored in the case of death, end of health plan enrollment, discontinuation of antihypertensive therapy, or end of follow-up. *ACEI* Angiotensin-converting enzyme inhibitor; *ARB* angiotensin II receptor blocker.

REFERENCES

1. Weaver CG, Clement FM, Campbell NRC, James MT, Klarenbach SW, Hemmelgarn BR, et al. Healthcare Costs Attributable to Hypertension. Hypertension. 2015;66(3):502–8.

2. Rabi DM, McBrien KA, Sapir-Pichhadze R, Nakhla M, Ahmed SB, Dumanski SM, et al. Hypertension Canada's 2020 Comprehensive Guidelines for the Prevention, Diagnosis, Risk Assessment, and Treatment of Hypertension in Adults and Children. Can J Cardiol. 2020;36(5):596–624.

3. Wright JM, Musini VM, Gill R. First-line drugs for hypertension. Cochrane Db Syst Rev. 2018;4(4):CD001841.

4. Whelton PK, Carey RM, Aronow WS, Casey DE, Collins KJ, Himmelfarb CD, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Executive Summary A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Soc Hypertens. 2018;12(8):579.e1-579.e73.

5. Williams B, Mancia G, Spiering W, Rosei EA, Azizi M, Burnier M, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J. 2018;39(33):3021–104.

6. Leung AA, Nerenberg K, Daskalopoulou SS, McBrien K, Zarnke KB, Dasgupta K, et al. Hypertension Canada's 2016 Canadian Hypertension Education Program Guidelines for Blood

Pressure Measurement, Diagnosis, Assessment of Risk, Prevention, and Treatment of Hypertension. Can J Cardiol. 2016;32(5):569–88.

7. Ettehad D, Emdin CA, Kiran A, Anderson SG, Callender T, Emberson J, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. Lancet. 2016;387(10022):957–67.

8. Xie X, Atkins E, Lv J, Bennett A, Neal B, Ninomiya T, et al. Effects of intensive blood pressure lowering on cardiovascular and renal outcomes: updated systematic review and meta-analysis. Lancet. 2016;387(10017):435–43.

9. Group SR, Wright JT, Williamson JD, Whelton PK, Snyder JK, Sink KM, et al. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. New Engl J Medicine. 2015;373(22):2103–16.

10. Garies S, Hao S, McBrien K, Williamson T, Peng M, Khan NA, et al. Prevalence of Hypertension, Treatment, and Blood Pressure Targets in Canada Associated With the 2017 American College of Cardiology and American Heart Association Blood Pressure Guidelines. Jama Netw Open. 2019;2(3):e190406.

11. Muntner P, Carey RM, Gidding S, Jones DW, Taler SJ, Wright JT, et al. Potential U.S. Population Impact of the 2017 ACC/AHA High Blood Pressure Guideline. J Am Coll Cardiol. 2017;71(2):109–18.

12. Sundbøll J, Adelborg K, Mansfield KE, Tomlinson LA, Schmidt M. Seventeen-Year Nationwide Trends in Antihypertensive Drug Use in Denmark. Am J Cardiol. 2017;120(12):2193–200.

13. Caetano PA, Lam JMC, Morgan SG. Toward a standard definition and measurement of persistence with drug therapy: Examples from research on statin and antihypertensive utilization. Clin Ther. 2006;28(9):1411–24.

14. Hamm NC, Pelletier L, Ellison J, Tennenhouse L, Reimer K, Paterson JM, et al. Trends in chronic disease incidence rates from the Canadian Chronic Disease Surveillance System. Heal Promot Chronic Dis Prev Can Res Policy Pract. 2019;39(6–7):216–24.

15. Johansen ME, Niforatos JD, Sussman JB. The Ecology of Antihypertensives in the United States, 1997–2017. J Gen Intern Med. 2021;36(3):699–704.

16. Walker RL, Chen G, Campbell NRC, McAlister FA, Quan H, Tu K, et al. Canadian Provincial Trends in Antihypertensive Drug Prescriptions Between 1996 and 2006. Can J Cardiol. 2011;27(4):461–7.

17. Ellison DH, Loffing J. Thiazide Effects and Adverse Effects. Hypertension. 2009;54(2):196–202.

18. Jamerson K, Weber MA, Bakris GL, Dahlöf B, Pitt B, Shi V, et al. Benazepril plus Amlodipine or Hydrochlorothiazide for Hypertension in High-Risk Patients. New Engl J Medicine. 2008;359(23):2417–28.

19. Machado MA de Á, Moura CS, Wang Y, Danieli C, Abrahamowicz M, Bernatsky S, et al. Comparative effectiveness of antihypertensive drugs in nondiabetic patients with hypertension: A population-based study. J Clin Hypertens. 2017;19(10):999–1009.

20. Suchard MA, Schuemie MJ, Krumholz HM, You SC, Chen R, Pratt N, et al. Comprehensive comparative effectiveness and safety of first-line antihypertensive drug classes: a systematic, multinational, large-scale analysis. Lancet. 2019;394(10211):1816–26.

21. Pottegård A, Hallas J, Olesen M, Svendsen MT, Habel LA, Friedman GD, et al. Hydrochlorothiazide use is strongly associated with risk of lip cancer. J Intern Med. 2017;282(4):322–31.

22. Pedersen SA, Gaist D, Schmidt SAJ, Hölmich LR, Friis S, Pottegård A. Hydrochlorothiazide use and risk of nonmelanoma skin cancer: A nationwide case-control study from Denmark. J Am Acad Dermatol. 2018;78(4):673-681.e9.

23. Pottegård A, Pedersen SA, Schmidt SAJ, Hölmich LR, Friis S, Gaist D. Association of Hydrochlorothiazide Use and Risk of Malignant Melanoma. Jama Intern Med. 2018;178(8):1120.

24. Pottegård A, Bech BH, Pedersen SA, Christensen B. Use of hydrochlorothiazide in Denmark following publication of skin cancer risk findings. Pharmacoepidem Dr S. 2021;

25. Roush GC, Ernst ME, Kostis JB, Tandon S, Sica DA. Head-to-Head Comparisons of Hydrochlorothiazide With Indapamide and Chlorthalidone. Hypertension. 2015;65(5):1041–6.

26. Pareek AK, Messerli FH, Chandurkar NB, Dharmadhikari SK, Godbole AV, Kshirsagar PP, et al. Efficacy of Low-Dose Chlorthalidone and Hydrochlorothiazide as Assessed by 24-h Ambulatory Blood Pressure Monitoring. J Am Coll Cardiol. 2016;67(4):379–89.

27. Engberink RHGO, Frenkel WJ, Bogaard B van den, Brewster LM, Vogt L, Born B-JH van den. Effects of thiazide-type and thiazide-like diuretics on cardiovascular events and mortality: systematic review and meta-analysis. Hypertens Dallas Tex 1979. 2015;65(5):1033–40.

28. Bourgault C, Sénécal M, Brisson M, Marentette MA, Grégoire J-P. Persistence and discontinuation patterns of antihypertensive therapy among newly treated patients: a population-based study. J Hum Hypertens. 2005;19(8):607–13.

29. Burke TA, Sturkenboom MC, Lu S, Wentworth CE, Lin Y, Rhoads GG. Discontinuation of antihypertensive drugs among newly diagnosed hypertensive patients in UK general practice. J Hypertens. 2006;24(6):1193–200.

30. Grégoire J-P, Moisan J, Guibert R, Ciampi A, Milot A, Gaudet M, et al. Determinants of discontinuation of new courses of antihypertensive medications. J Clin Epidemiol. 2002;55(7):728–35.

31. Abraham HMA, White CM, White WB. The Comparative Efficacy and Safety of the Angiotensin Receptor Blockers in the Management of Hypertension and Other Cardiovascular Diseases. Drug Safety. 2015;38(1):33–54.

32. Laan DM van der, Elders PJM, Boons CCLM, Beckeringh JJ, Nijpels G, Hugtenburg JG. Factors associated with antihypertensive medication non-adherence: a systematic review. J Hum Hypertens. 2017;31(11):687–94.

33. Tu Y-K, Gunnell D, Gilthorpe MS. Simpson's Paradox, Lord's Paradox, and Suppression Effects are the same phenomenon – the reversal paradox. Emerg Themes Epidemiology. 2008;5(1):2–2.

34. Quinn AE, Ronksley PE, Bresee L, Au F, Wick J, Leung AA, et al. Antihypertensive Prescribing for Uncomplicated, Incident Hypertension: Opportunities for Cost Savings. Cjc Open. 2021;3(6):703–13.

35. Ma J, Lee K-V, Stafford RS. Changes in Antihypertensive Prescribing During US Outpatient Visits for Uncomplicated Hypertension Between 1993 and 2004. Hypertension. 2006;48(5):846–52.

36. Mancia G, Grassi G. Individualization of Antihypertensive Drug Treatment. Diabetes Care. 2013;36(Supplement_2):S301–6.

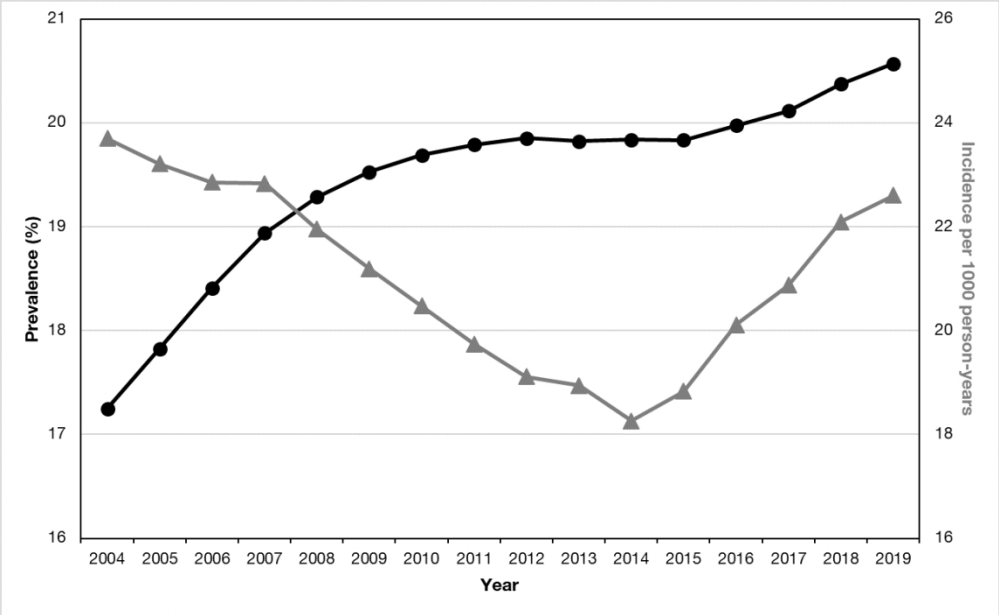

Figure 1. Prevalence and incidence of antihypertensive drug use among residents of British Columbia aged 30–75 years between 2004 and 2019. Prevalence was computed as the number of prevalent users of thiazides, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, calcium channel blockers, or beta-blockers divided by the number of British Columbia residents aged 30–75 years during the calendar year. Incidence was computed as the number of incident users of the five antihypertensive drug classes per 1000 person-years of health plan enrollment among British Columbia residents aged 30–75 years during the calendar year. Prevalent use was defined as at least one of the five antihypertensive drug classes dispensed during the year. Incident use was defined as one of the five antihypertensive drug classes dispensed in the absence of a record for any antihypertensive drug dispensed in the five years prior (drug list available in Supplementary Table S1).

220x135mm (150 x 150 DPI)

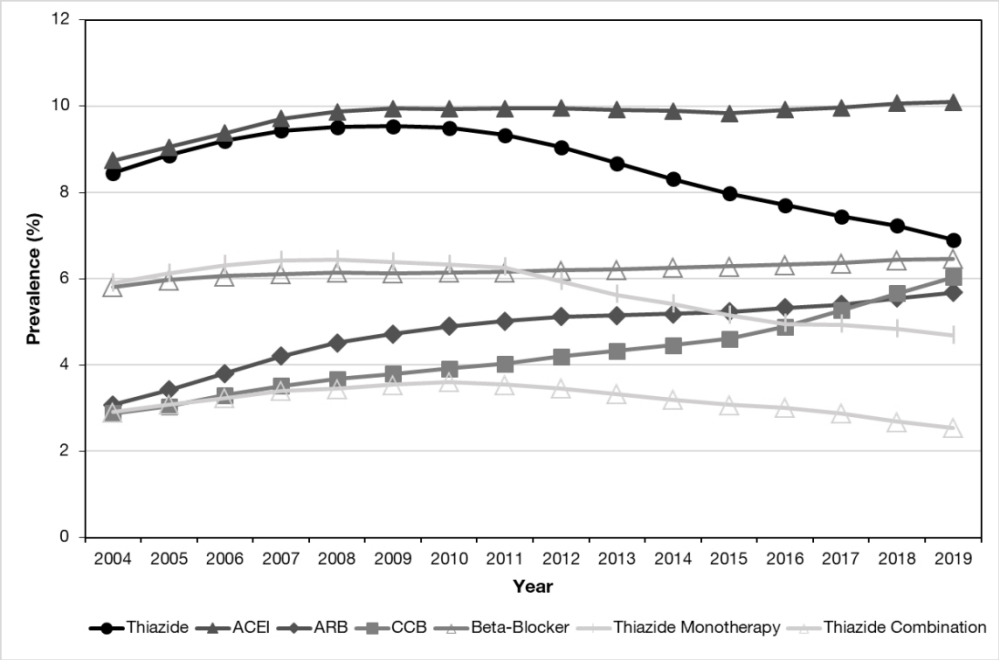

Figure 2. Prevalence of antihypertensive drug use among residents of British Columbia aged 30–75 years between 2004 and 2019, by drug class. Prevalence was computed as the number of prevalent users of an antihypertensive drug class divided by the number of British Columbia residents aged 30–75 years during the calendar year. ACEI Angiotensin-converting enzyme inhibitor; ARB angiotensin II receptor blocker; CCB calcium channel blocker.

210x139mm (150 x 150 DPI)

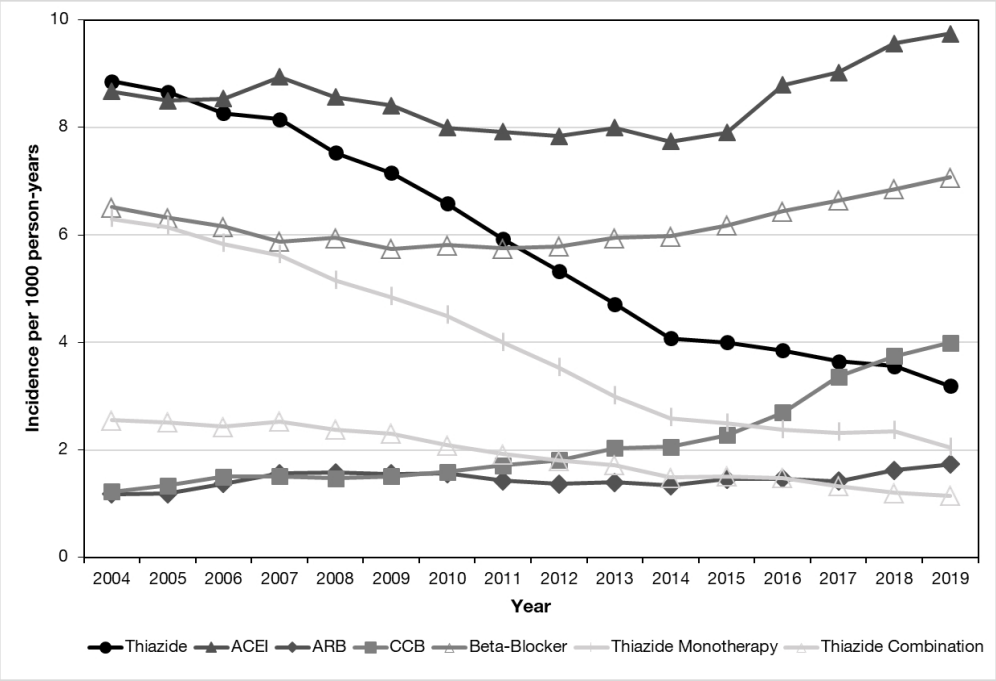

Figure 3. Incidence of antihypertensive drug use among residents of British Columbia aged 30-75 years between 2004 and 2019, by drug class. Incidence was computed as the number of incident users per 1000 person-years of health plan enrollment among British Columbia residents aged 30–75 years during the calendar year. Incident use was defined as one of the five antihypertensive drug classes dispensed in the absence of a record for any antihypertensive drug dispensed in the five years prior (drug list available in Supplementary Table S1). ACEI Angiotensin-converting enzyme inhibitor; ARB angiotensin II receptor blocker; CCB calcium channel blocker.

210x142mm (150 x 150 DPI)

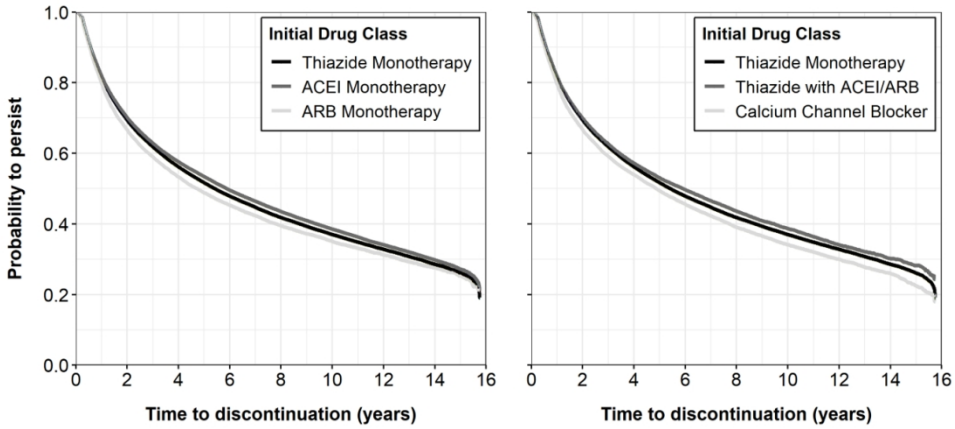

Figure 4. Time to discontinuation of any antihypertensive therapy by initial drug class. Discontinuation was assigned using the refill-sequence model, where the first medication-free gap of 90 days for any antihypertensive drug was considered discontinuation of antihypertensive therapy (drug list available in Supplementary Table S1). The discontinuation date was defined as the expected date of the next prescription refill. Individuals were censored in the case of death, end of health plan enrollment, or end of follow-up. ACEI Angiotensin-converting enzyme inhibitor; ARB angiotensin II receptor blocker.

239x114mm (150 x 150 DPI)

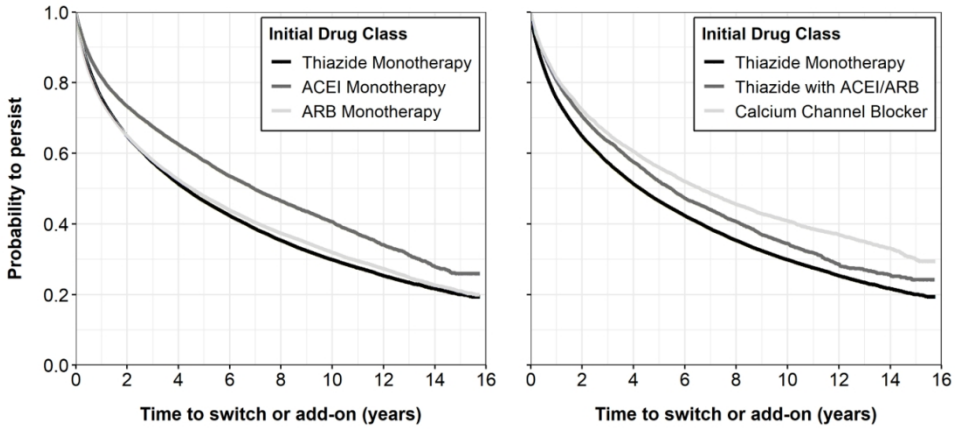

Figure 5. Time to switch to or add-on of a different antihypertensive drug class by initial drug class. Switch or add-on therapy was defined as the first dispensing of an antihypertensive drug class different from the initial drug class (drug list available in Supplementary Table S1). Switching from a combination product to its different components was not considered a switch or add-on event. Individuals were censored in the case of death, end of health plan enrollment, discontinuation of antihypertensive therapy, or end of follow-up. ACEI Angiotensin-converting enzyme inhibitor; ARB angiotensin II receptor blocker.

239x114mm (150 x 150 DPI)

Table 1. Discontinuation of any antihypertensive therapy in the incident user cohort.

Initial Drug Class	Discontinued n (%)	Censored n (%)	Median (years)	Crude HR (95% CI)	Adjusted HR (95% CI)*
Thiazide Monotherapy n = 86,008	55,728 (64.8)	30,280 (35.2)	5.42 (5.33-5.51)	Reference	Reference
ACEI Monotherapy n = 100,670	61,838 (61.4)	38,832 (38.6)	5.89 (5.81-5.97)	0.96 (0.95-0.97)	0.96 (0.95-0.97)
ARB Monotherapy n =11,449	7423 (64.8)	4026 (35.2)	4.72 (4.48-4.95)	1.07 (1.04-1.09)	1.06 (1.03-1.08)
Thiazide with ACEI/ARB n = 18,909	11,525 (60.9)	7384 (39.1)	5.93 (5.70-6.13)	0.96 (0.94-0.98)	0.96 (0.94-0.98)
CCB n = 15,745	10,085 (64.1)	5660 (36.0)	4.87 (4.71-5.05)	1.08 (1.06-1.11)	1.06 (1.04-1.09)

HR Hazard ratio; *CI* confidence interval; *ACEI* angiotensin-converting enzyme inhibitor; *ARB* angiotensin II receptor blocker; *CCB* calcium channel blocker.

* Adjusted for age, sex, income level, geographical area.

Table 2. Switch to or add-on of a different antihypertensive drug class in the incident user cohort.

Initial Drug Class	Switched or Added n (%)	Censored n (%)	Median (years)	Crude HR (95% CI)	Adjusted HR (95% CI)*
Thiazide Monotherapy n =75,214	39,992 (53.2)	35,222 (46.8)	4.26 (4.18-4.35)	Reference	Reference
ACEI Monotherapy n = 89,500	44,254 (49.4)	45,246 (50.6)	4.53 (4.45-4.62)	0.98 (0.96-0.99)	0.93 (0.92-0.95)
ARB Monotherapy n = 10,763	4781 (44.4)	5982 (55.6)	5.48 (5.21-5.67)	0.84 (0.82-0.87)	0.82 (0.80-0.85)
Thiazide with ACEI/ARB n = 17,469	7184 (41.1)	10,285 (58.9)	6.95 (6.75-7.21)	0.74 (0.72-0.76)	0.71 (0.69-0.73)
CCB n = 14,925	6338 (42.5)	8587 (57.5)	6.59 (6.32-6.92)	0.75 (0.73-0.77)	0.74 (0.72-0.76)

HR Hazard ratio; *CI* confidence interval; *ACEI* angiotensin-converting enzyme inhibitor; *ARB* angiotensin II receptor blocker; *CCB* calcium channel blocker.

* Adjusted for age, sex, income level, geographical area.

Trends in Antihypertensive Drug Utilization in British Columbia, 2004–2019

Supplementary File

Table of Contents

Supplementary Tables

Table S1. List of antihypertensive medications dispensed in British Columbia.

Therapeutic Group	ATC Code	Generic Name
Thiazide diuretic	C02LA01	reserpine/hydrochlorothiazide
	C02LA01	hydralazine/reserpin/hcthiazid
	C02LB01	methyldopa/hydrochlorothiazide
	C02LC01	clonidine hcl/chlorthalidone
	C03AA03	hydrochlorothiazide
	C03BA04	chlorthalidone
	C03BA08	metolazone
	C03BA11	indapamide
	C03EA01	spironolact/hydrochlorothiazid
	C03EA01	amiloride/hydrochlorothiazide
	C03EA01	triamterene/hydrochlorothiazid
	C07BA05	propranolol/hydrochlorothiazid
	C07BA06	timolol/hydrochlorothiazide
	C07CA03	pindolol/hydrochlorothiazide
	C07CB03	atenolol/chlorthalidone
	C09BA02	enalapril/hydrochlorothiazide
	C09BA03	lisinopril/hydrochlorothiazide
	C09BA04	perindopril arg/indapamide
	C09BA04	perindopril erbumin/indapamide
	C09BA05	ramipril/hydrochlorothiazide
	C09BA06	quinapril/hydrochlorothiazide
	C09BA08	cilazapril/hydrochlorothiazide
	C09DA01	losartan/hydrochlorothiazide
	C09DA02	eprosartan/hydrochlorothiazide
	C09DA03	valsartan/hydrochlorothiazide
	C09DA04	irbesartan/hydrochlorothiazide
	C09DA06	candesartan/hydrochlorothiazid
	C09DA07	telmisartan/hydrochlorothiazid
	C09DA08	olmesartan/hydrochlorothiazide
	C09DA09	azilsartan med/chlorthalidone
	C09XA52	aliskiren/hydrochlorothiazide
Angiotensin-converting enzyme (ACE) inhibitor	C09AA01	captopril
	C09AA02	enalapril sodium
	C09AA02	enalapril maleate
	C09AA03	lisinopril
	C09AA04	perindopril erbumine
	C09AA05	ramipril

	C09AA06	quinapril hcl
	C09AA07	benazepril hcl
	C09AA08	cilazapril
	C09AA09	fosinopril sodium
	C09AA10	trandolapril
	C09BA02	enalapril/hydrochlorothiazide
	C09BA03	lisinopril/hydrochlorothiazide
	C09BA04	perindopril erbumin/indapamide
	C09BA04	perindopril arg/indapamide
	C09BA05	ramipril/hydrochlorothiazide
	C09BA06	quinapril/hydrochlorothiazide
	C09BA08	cilazapril/hydrochlorothiazide
	C09BB04	perindopril arg/amlodipine bes
	C09BB10	trandolapril/verapamil hcl
Angiotensin receptor blocker	C09CA01	losartan potassium
	C09CA02	eprosartan mesylate
	C09CA03	valsartan
	C09CA04	irbesartan
	C09CA06	candesartan cilexetil
	C09CA07	telmisartan
	C09CA08	olmesartan medoxomil
	C09CA09	azilsartan medoxomil
	C09DA01	losartan/hydrochlorothiazide
	C09DA02	eprosartan/hydrochlorothiazide
	C09DA03	valsartan/hydrochlorothiazide
	C09DA04	irbesartan/hydrochlorothiazide
	C09DA06	candesartan/hydrochlorothiazid
	C09DA07	telmisartan/hydrochlorothiazid
	C09DA08	olmesartan/hydrochlorothiazide
	C09DA09	azilsartan med/chlorthalidone
	C09DB04	telmisartan/amlodipine
	C09DX04	sacubitril/valsartan
Calcium Channel Blocker	C08CA01	amlodipine besylate
	C08CA02	felodipine
	C08CA05	nifedipine
	C08CA55	nifedipine/acetylsalicylic ac
	C09BB04	perindopril arg/amlodipine bes
	C09DB04	telmisartan/amlodipine
	C10BX03	amlodipine/atorvastatin
Potassium-sparing diuretic	C03DA01	spironolactone
	C03DB01	amiloride hcl
	C03DB02	triamterene
	C03EA01	amiloride/hydrochlorothiazide

	C03EA01	triamterene/hydrochlorothiazid
	C03EA01	spironolact/hydrochlorothiazid
Loop diuretic	C03CA01	furosemide
	C03CA02	bumetanide
Beta-blocker	C07AA03	pindolol
	C07AA05	propranolol hcl
	C07AA06	timolol maleate
	C07AA12	nadolol
	C07AB02	metoprolol tartrate
	C07AB03	atenolol
	C07AB07	bisoprolol fumarate
	C07AB12	nebivolol hcl
	C07AG01	labetalol hcl
	C07BA05	propranolol/hydrochlorothiazid
	C07BA06	timolol/hydrochlorothiazide
	C07BA12	nadolol/bendroflumethiazide
	C07CA03	pindolol/hydrochlorothiazide
	C07CB03	atenolol/chlorthalidone
Other	C02AA02	reserpine
	C02AB02	methyldopa
	C02AC01	clonidine hcl
	C02AC02	guanfacine hcl
	C02CA01	prazosin hcl
	C02CA04	doxazosin mesylate
	C02DB02	hydralazine hcl
	C02DC01	minoxidil
	C02LA01	reserpine/hydrochlorothiazide
	C02LA01	hydralazine/reserpin/hcthiazid
	C02LB01	methyldopa/hydrochlorothiazide
	C02LB01	methyldopa/chlorothiazide
	C02LC01	clonidine hcl/chlorthalidone
	C03DA01	spironolactone
	C08DA01	verapamil hcl
	C08DB01	diltiazem hcl
	C09BB10	trandolapril/verapamil hcl
	C09XA02	aliskiren fumarate
	C09XA52	aliskiren/hydrochlorothiazide
	G04CA03	terazosin hcl
	N02CX02	clonidine hcl

ATC Anatomical Therapeutic Chemical.

Table S2. List of diagnosis and procedure codes used to identify conditions

	Diagnosis Codes		Procedure Codes		
Condition	**ICD-9**	**ICD-10**	**CCP**	**CCI**	**MSP fee Items**
Cancer	140-209, V58.0, V58.1	C00-C97, Z51.0, Z51.1, Z51.2	06.2 (radiotherapy), 06.3 (radiotherapy), 13.55 (chemotherapy)	X.XX.35.XX-G6 (chemotherapy), X.XX.35.XX-M0 to X.XX.35.XX-M9 (chemotherapy), X.XX.27 (radiotherapy), X.XX.26 (brachytherapy)	33581, 33582, 33583 (chemotherapy)
Renal failure	584-586	N17-N19	-	-	-
Dialysis (peritoneal or hemodialysis)	V45.1, V56.0, V56.8, E870.2, E871.2, E872.2, E874.2	E10.220-E10.224, E10.229, E11.220-E11.224, E11.229, E13.220-E13.224, E13.229, E14.220-E14.224, E14.229, T82.4, Y60.2, Y61.2, Y62.2, Y84.1, Z49.0-Z49.2, Z99.2	51.27, 51.42, 51.43, 51.95, 66.98	1PZ21HPD4, 1PZ21HQBR, 1PZ21HQBS	33750, 33751, 33752, 33708, 33756, 33758, 33723, 33759, 33761
Diseases associated with secondary hypertension	194.0, 227.0, 237.3, 255.1, 255.6, 405, 447.3, 447.8	C74.1, C75.5, D13.2, D35.0, D44.6, D44.7, E26, E27.5, I15, I77.3,	-	-	-
Congestive heart failure	428	I50	-	-	-
Coronary artery disease	410.x-414.x	I20.x-I25.x	48.0, 48.1, 48.2	1.IJ.76, 1.IJ.50	07908, 0790, 07990, 00839, 00840, 00842, 00841
Cirrhosis and liver disease	570-573	K70-K75	-	-	-

	Diagnosis Codes		Procedure Codes		
Condition	**ICD-9**	**ICD-10**	**CCP**	**CCI**	**MSP fee Items**
Toxemia of pregnancy	642.5-642.7	O11, O14-O15	-	-	-
Premenstrual tension and edema	625.4	N94.3	-	-	-
Nephrotic syndrome	581	N04	-	-	-
Kidney stones	593-594	N20-N23	68.0, 68.2, 67.01, 69.0, 69.13, 70.5, 71.96	1.PG.59, 1.PE.59, 1.PL.59, 1.PM.59	
Hypercalcemia	275.42	E83.52	-	-	-
Diabetes Insipidus	253.5, 588.1	E23.2, N25.1	-	-	-
Migraine	346	G43	-	-	-
Diabetic nephropathy	249.4, 250.4	E10.2, E10.7, E11.2, E11.7, E14.2, E14.7	-	-	-
Other chronic kidney diseases	580-589, 590-593	N00-N20, N25-N29	-	-	-
Marfan syndrome	759.82	Q87.4	-	-	-

ICD International Classification of Disease; *CCP* Canadian Classification of Diagnostic, Therapeutic, and Surgical Procedures; *CCI* Canadian Classification of Health Interventions; *MSP* Medical Services Plan.

Table S3. Covariate definitions

Covariate	Definition
Age	Age at initiation of antihypertensive therapy [discrete]
Sex	Based on provincial health insurance registry data [female; male]
Income level	Any prescription drug claim paid by an assisted basic or senior $0 deductible plan or social services plan in the 1 year before cohort entry. [assisted; not assisted]
Geographical area	Based on forward sortation area of individuals' residence in British Columbia [north; east; central; west-rural; west-urban]

Table S4. Patient flow

	No. of individuals remaining	No. of individuals excluded	% Excluded
Source population	5,669,128		
Individuals with a new prescription for a thiazide, ACEI, ARB, or CCB between January 1, 2004 and December 31, 2014.	502,743		
Exclusion criteria			
Lack of continuous enrollment in the 2 years before cohort entry	430,415	72,328	14.4
Lost MSP enrollment within the first 3 months of the initial prescription	429,697	718	0.1
Missing information on age or sex	429,677	20	0.0
Age under 30 or over 75 on date of the initial prescription	373,364	56,313	11.2
Died before cohort entry	373,347	17	0.0
Dispensed both ACEI and ARB on date of the initial prescription	373,301	46	0.0
Cancer	303,741	69,560	13.8
Renal failure or dialysis	298,430	5,311	1.1
Secondary hypertension	297,622	808	0.2
Heart failure	291,821	5,801	1.2
Coronary artery disease	264,202	27,619	5.5
Edema-causing conditions (except steroid use)	261,098	3,104	0.6
Steroid use	255,881	5,217	1.0
Kidney stones or hypercalcemia	254,400	1,481	0.3
Diabetes Insipidus	254,380	20	0.0
Migraine	250,854	3,526	0.7
Diabetic nephropathy	250,641	213	0.0
Other chronic kidney diseases	248,539	2,102	0.4
Marfan syndrome	248,533	6	0.0
Discontinued any antihypertensive therapy within the first 3 months of the initial prescription	232,781	15,752	3.1
Final Cohort	**232,781**		

Table S5. Discontinuation of any antihypertensive therapy in the incident user cohort by PharmaCare coverage

PharmaCare Coverage					
Initial Drug Class	**Discontinued n (%)**	**Censored n (%)**	**Median (years)**	**Crude HR (95% CI)**	**Adjusted HR (95% CI)***
Thiazide Monotherapy, n = 84,897	54,972 (64.7)	29,925 (35.2)	5.44 (5.35-5.53)	Reference	Reference
ACEI Monotherapy, n = 98,157	59,881 (61.0)	38,276 (39.0)	6.05 (5.96-6.14)	0.95 (0.94-0.96)	0.95 (0.93-0.96)
ARB Monotherapy, n = 1002	635 (63.4)	367 (36.6)	5.78 (5.20-6.77)	0.98 (0.91-1.06)	0.98 (0.91-1.06)
Thiazide with ACEI/ARB, n = 10,957	6560 (59.8)	4397 (40.1)	6.44 (6.15-6.75)	0.92 (0.90-0.95)	0.92 (0.90-0.95)
Calcium Channel Blocker, n = 14,510	9198 (63.4)	5312 (36.6)	5.08 (4.91-5.30)	1.06 (1.04-1.08)	1.04 (1.02-1.06)
Without PharmaCare Coverage					
Initial Drug Class	**Discontinued n (%)**	**Censored n (%)**	**Median (years)**	**Crude HR (95% CI)**	**Adjusted HR (95% CI)***
Thiazide Monotherapy, n = 1111	756 (68.0)	355 (32.0)	4.21 (3.76-4.88)	Reference	Reference
ACEI Monotherapy, n = 2513	1957 (77.9)	556 (22.1)	1.79 (1.63-1.92)	1.50 (1.37-1.63)	1.47 (1.35-1.60)
ARB Monotherapy, n = 10,447	6788 (65.0)	3659 (35.0)	4.61 (4.37-4.85)	0.91 (0.84-0.98)	0.91 (0.84-0.98)
Thiazide with ACEI/ARB, n = 7952	4965 (62.4)	2987 (37.6)	5.24 (4.94-5.59)	0.86 (0.80-0.93)	0.87 (0.81-0.94)
Calcium Channel Blocker, n = 1235	887 (71.8)	348 (28.2)	2.69 (2.36-3.10)	1.24 (1.12-1.36)	1.21 (1.09-1.33)

ACEI Angiotensin-converting enzyme inhibitor; *ARB* angiotensin II receptor blocker.

* Adjusted for age, sex, income level, geographical area.

Supplementary Figures

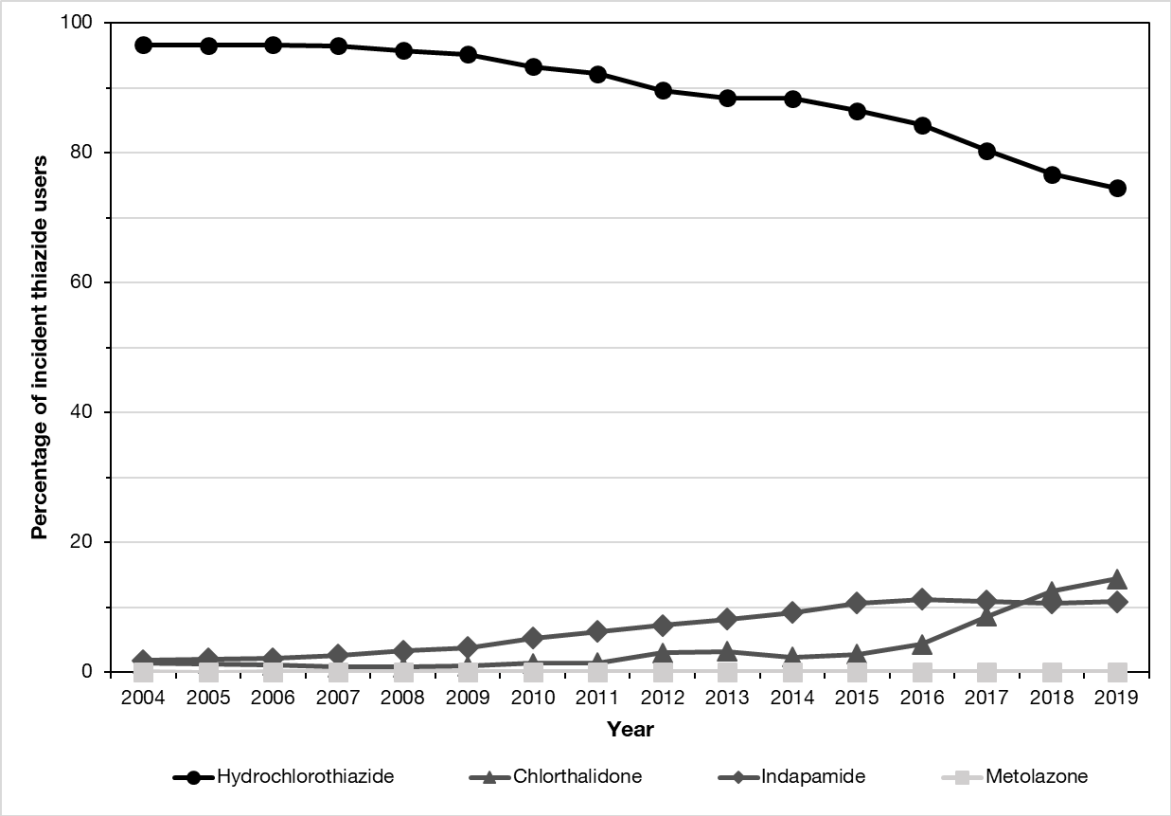

Figure S1. Percentage of incident thiazide users between 2004 and 2019.