

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

Supplementary File

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Supplementary Tables

Table S1. List of administrative databases and variables used

| Database | Description | Variables |
|---|--|---|
| PharmaNet repository | Records of all prescription drugs and medical supplies dispensed from community pharmacies. | <ul style="list-style-type: none"> • Drug identification number (DIN) • Generic name • Therapeutic group • Days supply • Service date • Cost accepted by PharmaCare |
| Medical Services Plan (MSP) Payment Information | Records of medically necessary physician services provided by fee-for-service practitioners. | <ul style="list-style-type: none"> • Diagnosis code • Fee item (procedure) code • Service date |
| Discharge Abstract Database (DAD) | Administrative, clinical, and demographic information on hospital discharges. | <ul style="list-style-type: none"> • Diagnosis code • Procedure code • Admission date • Discharge date |
| National Ambulatory Care Reporting System (NACRS) | Records of hospital-based and community-based ambulatory care, including day surgery, outpatient and community-based clinics, and emergency departments. | <ul style="list-style-type: none"> • Diagnosis code • Procedure code • Registration date |
| Medical Services Plan (MSP) Registration and Premium Billings | Records of provincial health plan enrollment and demographics | <ul style="list-style-type: none"> • Birthdate • Sex • Enrollment start date • Enrollment end date • Death |

Table S2. 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 C09BA02 C09BA03 C09BA04 C09BA04 C09BA05 C09BA06 C09BA08 C09BB04 C09BB10 | trandolapril enalapril/hydrochlorothiazide lisinopril/hydrochlorothiazide perindopril erbumin/indapamide perindopril arg/indapamide ramipril/hydrochlorothiazide quinapril/hydrochlorothiazide cilazapril/hydrochlorothiazide perindopril arg/amlodipine bes trandolapril/verapamil hcl |
| Angiotensin receptor blocker | C09CA01 C09CA02 C09CA03 C09CA04 C09CA06 C09CA07 C09CA08 C09CA09 C09DA01 C09DA02 C09DA03 C09DA04 C09DA06 C09DA07 C09DA08 C09DA09 C09DB04 C09DX04 | losartan potassium eprosartan mesylate valsartan irbesartan candesartan cilexetil telmisartan olmesartan medoxomil azilsartan medoxomil losartan/hydrochlorothiazide eprosartan/hydrochlorothiazide valsartan/hydrochlorothiazide irbesartan/hydrochlorothiazide candesartan/hydrochlorothiazid telmisartan/hydrochlorothiazid olmesartan/hydrochlorothiazide azilsartan med/chlorthalidone telmisartan/amlodipine sacubitril/valsartan |
| Calcium Channel Blocker | C08CA01 C08CA02 C08CA05 C08CA55 C09BB04 C09DB04 C10BX03 | amlodipine besylate felodipine nifedipine nifedipine/acetylsalicylic ac perindopril arg/amlodipine bes telmisartan/amlodipine amlodipine/atorvastatin |
| Potassium-sparing diuretic | C03DA01 C03DB01 C03DB02 C03EA01 C03EA01 C03EA01 | spironolactone amiloride hcl triamterene amiloride/hydrochlorothiazide triamterene/hydrochlorothiazid spironolact/hydrochlorothiazid |
| Loop diuretic | C03CA01 C03CA02 | furosemide 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 S3. List of diagnosis and procedure codes used to identify conditions

| Condition | Diagnosis Codes | | Procedure Codes | | |
|--|--|--|--|--|---|
| | 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 | - | - | - |
| Toxemia of pregnancy | 642.5-642.7 | O11, O14-O15 | - | - | - |

| Condition | Diagnosis Codes | | Procedure Codes | | |
|--------------------------------|------------------|--|---|------------------------------------|----------------|
| | ICD-9 | ICD-10 | CCP | CCI | MSP fee Items* |
| 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.

* List of MSP fee items are available from <https://www2.gov.bc.ca/assets/gov/health/practitioner-pro/medical-services-plan/msc-payment-schedule-may-2021.pdf>.

Table S4. 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] |
| PharmaCare coverage | Total accepted amount by PharmaCare > \$0 for the initial antihypertensive drug class [covered; not covered] |
| Geographical area | Based on forward sortation area of individuals' residence in British Columbia [north; east; central; west-rural; west-urban] |

Table S5. 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 S6. Discontinuation of any antihypertensive therapy in the incident user cohort by PharmaCare coverage

| With PharmaCare Coverage | | | | | |
|---------------------------------------|---------------------------|-------------------|-----------------------|---------------------------|-------------------------------|
| Initial Drug Class | Discontinued n (%) | Died n (%) | Censored n (%) | Crude SHR (95% CI) | Adjusted SHR (95% CI)* |
| Thiazide Monotherapy n = 84,897 | 54,972 (64.7) | 987 (1.2) | 28938 (34.1) | Reference | Reference |
| ACEI Monotherapy n = 98,157 | 59,881 (61.0) | 1324 (1.3) | 36952 (37.6) | 0.95 (0.94-0.96) | 0.94 (0.93-0.96) |
| ARB Monotherapy n = 1002 | 635 (63.4) | 18 (1.8) | 349 (34.8) | 0.98 (0.90-1.06) | 0.99 (0.91-1.07) |
| Thiazide with ACEI/ARB n = 10,957 | 6560 (59.8) | 173 (1.6) | 4224 (38.6) | 0.92 (0.90-0.94) | 0.92 (0.90-0.94) |
| Calcium Channel Blocker n = 14,510 | 9198 (63.4) | 189 (1.3) | 5123 (35.3) | 1.06 (1.03-1.08) | 1.04 (1.01-1.06) |
| Without PharmaCare Coverage | | | | | |
| Initial Drug Class | Discontinued n (%) | Died n (%) | Censored n (%) | Crude SHR (95% CI) | Adjusted SHR (95% CI)* |
| Thiazide Monotherapy n = 1111 | 756 (68.0) | 12 (1.1) | 343 (30.9) | Reference | Reference |
| ACEI Monotherapy n = 2513 | 1957 (77.9) | 13 (0.5) | 543 (21.6) | 1.50 (1.37-1.63) | 1.48 (1.36-1.62) |
| ARB Monotherapy n = 10,447 | 6788 (65.0) | 77 (0.7) | 3582 (34.3) | 0.91 (0.84-0.98) | 0.92 (0.86-0.99) |
| Thiazide with ACEI/ARB n = 7952 | 4965 (62.4) | 70 (0.9) | 2917 (36.7) | 0.86 (0.80-0.93) | 0.89 (0.82-0.96) |
| Calcium Channel Blocker n = 1235 | 887 (71.8) | 9 (0.7) | 339 (27.4) | 1.24 (1.12-1.36) | 1.22 (1.11-1.35) |

SHR Subdistribution hazard ratio; CI confidence interval; ACEI Angiotensin-converting enzyme inhibitor; ARB angiotensin II receptor blocker.

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

Table S7. Discontinuation of any antihypertensive therapy in the incident user cohort, with discontinuation defined as a 60-day gap.

| Initial Drug Class | Discontinued n (%) | Died n (%) | Censored n (%) | Crude SHR (95% CI) | Adjusted SHR (95% CI)* |
|--------------------------------------|--------------------|------------|----------------|--------------------|------------------------|
| Thiazide Monotherapy n = 85,909 | 62,633 (72.9) | 831 (1.0) | 22445 (26.1) | Reference | Reference |
| ACEI Monotherapy n = 100,526 | 70,496 (70.1) | 1105 (1.1) | 28,925 (28.8) | 0.98 (0.97-0.99) | 0.97 (0.96-0.98) |
| ARB Monotherapy n = 11,430 | 8421 (73.7) | 77 (0.7) | 2932 (25.7) | 1.10 (1.07-1.13) | 0.90 (0.87-0.93) |
| Thiazide with ACEI/ARB n = 18,882 | 13,241 (70.1) | 200 (1.1) | 5441 (28.8) | 0.99 (0.97-1.01) | 0.91 (0.89-0.93) |
| CCB n = 15,728 | 11,156 (70.9) | 171 (1.1) | 4401 (28.0) | 1.04 (1.02-1.07) | 1.01 (0.99-1.03) |

SHR Subdistribution 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, PharmaCare coverage, geographical area.

Table S8. Discontinuation of any antihypertensive therapy in the incident user cohort, with discontinuation defined as a 120-day gap.

| Initial Drug Class | Discontinued n (%) | Died n (%) | Censored n (%) | Crude SHR (95% CI) | Adjusted SHR (95% CI)* |
|--------------------------------------|--------------------|------------|----------------|--------------------|------------------------|
| Thiazide Monotherapy n = 86,008 | 51,051 (59.4) | 1089 (1.3) | 33,868 (39.4) | Reference | Reference |
| ACEI Monotherapy n = 100,670 | 56,044 (55.7) | 1484 (1.5) | 43,142 (42.9) | 0.95 (0.94-0.96) | 0.95 (0.94-0.96) |
| ARB Monotherapy n = 11,449 | 6685 (58.4) | 102 (0.9) | 4662 (40.7) | 1.03 (1.01-1.06) | 0.78 (0.75-0.81) |
| Thiazide with ACEI/ARB n = 18,909 | 10,411 (55.1) | 266 (1.4) | 8232 (43.5) | 0.94 (0.92-0.96) | 0.83 (0.81-0.85) |
| CCB n = 15,745 | 9314 (59.2) | 215 (1.4) | 6216 (39.5) | 1.10 (1.08-1.13) | 1.06 (1.04-1.09) |

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

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

Supplementary Figures

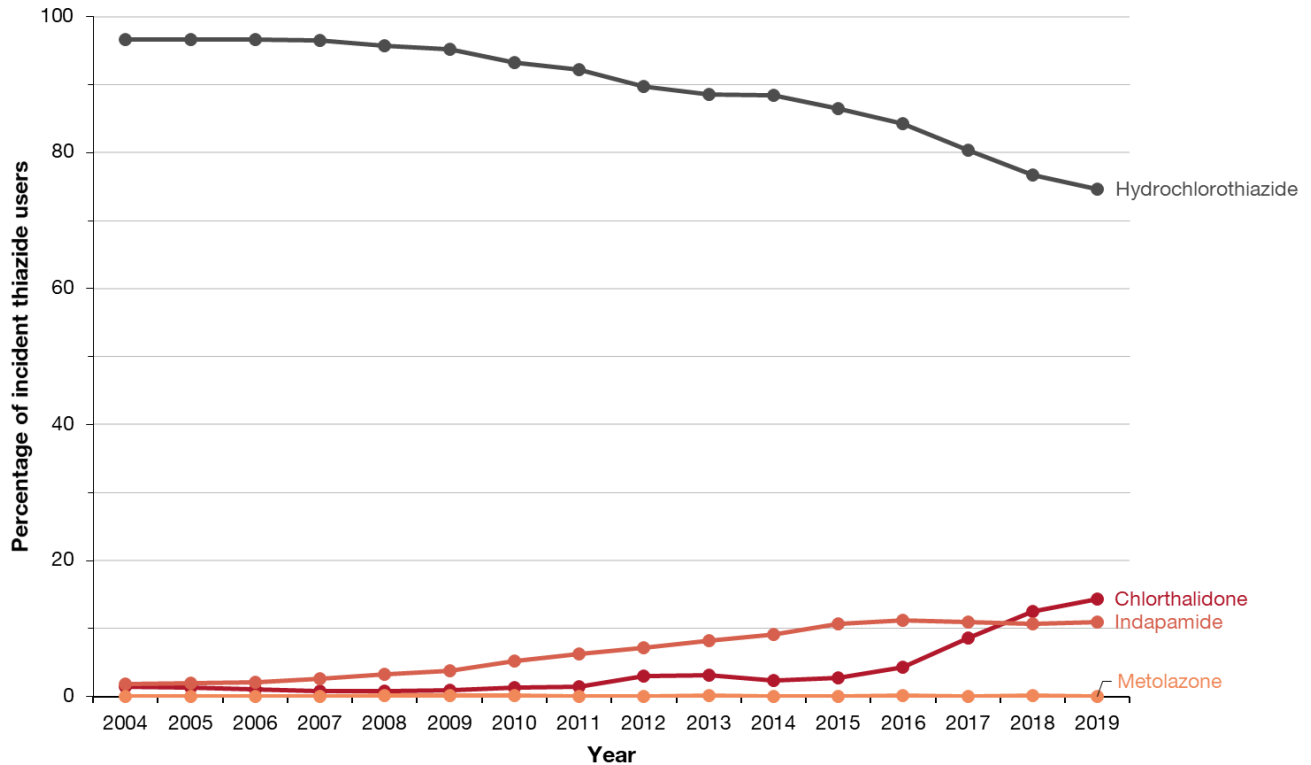


Figure S1. Percentage of incident thiazide users between 2004 and 2019.