Laboratory testing and antihypertensive medication adherence following initial treatment of incident, uncomplicated hypertension: A real-world data analysis

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Abstract
In this study on medication adherence among newly diagnosed patients with uncomplicated, incident hypertension, we conducted a retrospective cohort study using available administrative and laboratory data from April 1, 2012 to March 31, 2017 in Alberta, Canada to understand the extent to which baseline laboratory assessment and/or subsequent follow-up was associated with persistence with antihypertensive therapy. We determined the frequency of baseline and follow-up testing and compared the rates of medication persistence by patient-, neighbourhood-, and treatment-related factors. Of 103 232 patients with newly diagnosed, uncomplicated hypertension who filled their first prescription within our study timeframe, 52.5% were non-persistent within 6 months. Persistent patients were more often female and residing in neighbourhoods with higher social status (with exception to rurality). Aside from older age, the strongest predictor of persistence was performance of laboratory testing related to hypertension with an apparent effect in which higher levels of medication persistence were seen with more frequent laboratory testing. We concluded that medication persistence was far from optimal, dropping off considerably after 6 months for more than half of patients. Medication persistence is a substantial barrier to realizing the full societal benefits of antihypertensive treatment. Ongoing follow up with patients, including laboratory testing, may be a critical component of better long term treatment persistence.

KEYWORDS
adherence, gender differences, hypertension—general, primary care issues
1 | INTRODUCTION

Hypertension is one of the most prevalent chronic medical conditions globally, and a major risk factor for cardiovascular disease and early death.\(^1\) Incontrovertible evidence from randomized trials prove that hypertension treatment prevents cardiovascular disease and cardiovascular mortality\(^2\) but inappropriate discontinuation of medication remains a common concern that predisposes to worse outcomes.\(^3\) Accordingly, the choice of antihypertensive drug class, occurrence of medication side effects (e.g., hypokalemia), and monitoring for clinical outcomes (e.g., blood pressure targets) are important factors related to persistence with treatment.\(^13,14\)

Current clinical practice guideline recommendations for antihypertensive medication selection and monitoring are largely derived from results of clinical trials.\(^15\)–\(^17\) However, treatment-related adverse events are frequently underestimated in trials compared to real world settings.\(^18\) Trial participants are generally healthy and motivated individuals who can tolerate run-in periods compared to unselected patients encountered in clinical practice. This latter point is crucial when considering which antihypertensive medications are most likely to be tolerated and continued in routine clinical care.

Addressing this, we examined how baseline laboratory assessment and subsequent follow-up informed drug selection and persistence with antihypertensive therapy in a population-based cohort of patients with recent-onset, uncomplicated hypertension. We determined the frequency of baseline and follow-up testing and compared the rates of medication persistence according to the occurrence of medication-related laboratory abnormalities.

2 | METHODS

2.1 | Design

This real-world evidence investigation used a retrospective cohort study design to analyze archival provincial administrative healthcare records from Alberta, Canada from April 1, 2012 to March 31, 2017.

2.2 | Setting

This study was conducted in the province of Alberta, Canada (population ~4.5 million).

2.3 | Ethics

Ethics approval was obtained from the Conjoint Health Research Ethics Board at the University of Calgary.

2.4 | Data sources

Provincial data sources including administrative health data (i.e., Practitioner Claims, Discharge Abstract Database, Ambulatory Care Classification System, and the Alberta Health Care Insurance Plan), laboratory, and pharmaceutical claims for all adult Albertans was used. Pharmaceutical claims were captured in the Pharmaceutical Information Network (PIN) that includes all medications that have been dispensed at an Alberta pharmacy within the community, along with dates of dispensation, amount of medication dispensed, and number of days supplied to the patient. PIN does not capture inpatient medication dispensations. Data files were linked using the patient’s unique provincial health care number.

2.5 | Study cohort

A population-based retrospective cohort was created among Albertans 18 years or older with incident, uncomplicated, treated hypertension diagnosed between April 1, 2012 and March 31, 2017. The study cohort was assembled using the same methods as previously reported.\(^19\) Briefly, patients with hypertension were identified using a validated administrative algorithm\(^20\) and patients with prevalent hypertension were excluded using a 4-year lookback window. We defined “uncomplicated hypertension” as the absence of a compelling indication to use a specific antihypertensive agent and/or target organ damage (e.g., left ventricular hypertrophy, coronary artery disease, stroke, renal dysfunction, and peripheral arterial disease).\(^21\) Further, in line with previous studies,\(^19\) we excluded the following conditions: previous ischemic heart disease (coronary artery disease and recent myocardial infarction), heart failure, stroke, left ventricular hypertrophy, atrial fibrillation, supraventricular tachycardia, chronic kidney disease, liver cirrhosis, renovascular disease, diabetes, and those with at least one diagnostic code for “complicated hypertension” during the study period. Patients with incident, uncomplicated hypertension who received medication for hypertension within 1 year after hypertension diagnosis date were included to form the final cohort. The index date was defined as the dispensation date of the first antihypertensive medication within the same timeframe as the hypertension diagnosis date (6 months prior to or 12 months after).\(^20\) The list of eligible monotherapy and single pill combination (SPC) antihypertensive medications included in our study can be found in Supplementary Table 1.

Patients with medication dispenses for two of the above treatments on the same date were also included in the cohort.

2.6 | Outcome variable: persistence

Our primary outcome was treatment persistence to the index prescription within the first 6 months of initiating pharmacotherapy. Within the 6-month observation window for each patient in the cohort, non-persistence was defined as a 7-day or more gap between prescription dispenses of an antihypertensive prescription(s) for the same patient based on the number of days supplied, assuming they took their prescribed dose everyday (e.g., a patient was dispensed a 60-day supply, but did not refill their prescription until 90 days later). Seven days was chosen as the cut point for distinguishing persistent patients after examining the distribution of the duration of all treatment gaps.
observed. While 30 days has been used in some studies, it was evident this cut point would not be sensitive enough to capture a considerable number of observations wherein patients were delayed by several weeks in filling their next prescription, making it difficult to rationalize categorizing them as persistent. To address concerns that choosing a different cut point could change our overall conclusions, we performed a sensitivity test using a different measure for persistence that is not based upon a treatment interruption gap (see the below Sensitivity Analysis for more details). Note that our observation of persistence accounted for treatment switching, which was defined as discontinuation of the index prescription with a subsequent dispensation record in the PIN database of a different eligible antihypertensive treatment for the same patient, and for treatment additions, which was defined as a prescription record in the PIN database for a different treatment class added to the treatment regimen for the same patient without discontinuation of the index prescription.

2.7 Independent variables

Our independent variables of interest were whether laboratory testing related to hypertension as recommended by guidelines (i.e., serum electrolytes, kidney function, fasting plasma glucose, and glycated hemoglobin A1c) had been performed for the patient. Laboratory testing was divided into four groups: no testing, baseline testing only, follow-up testing only, or both baseline and follow up testing. Results of laboratory testing and other outcomes aside from persistence are provided in the web appendix.

We also tracked six other independent variables previously shown to be associated with persistence to help contextualize our findings. Firstly, we traced the type of antihypertensive medication prescribed as another factor under prescribers’ control that has previously been shown to impact the level of persistence given the differing treatment side effect profiles. The initial prescription for an antihypertensive drug was categorized as follows for monotherapies: angiotensin converting enzyme inhibitors (ACEi), angiotensin II receptor blockers (ARB), calcium channel blockers (CCB), thiazide and thiazide-like diuretics (TDS), and beta blockers (BBS). Dispensations for potassium supplementation were also examined during the follow-up period (listed in Supplementary Table 1). Two-drug therapies were categorized as SPCs or free-equivalent components (FECs) (i.e., two single-agent pills) as this has been found to facilitate adherence by reducing pill burden.

Other variables investigated beyond prescribers’ control that were found (or theorized) to be associated with persistence levels included two patient-level factors, that is, age and sex, and three neighborhood-level factors, that is, the proportion of visible minorities, the average income of that neighbourhood, and rurality. These neighbourhood-level factors were derived by linking the patients’ residential postal code to the corresponding dissemination area in the 2016 Canadian census. Rurality was determined based on the second character of the patients’ home address (a zero indicating a rural postal route).

2.8 Statistical analysis

Our analysis included descriptive statistics of baseline characteristics. We then described the relationship between persistence (i.e., whether there was a 7-day or more treatment disruption) and patient characteristics. We plotted these proportions side-by-side with the overall level of persistence observed for the entire cohort as a benchmark for above or below overall persistence. Statistically significant differences were determined using \( \chi^2 \) and Kruskal-Wallis tests for categorical and continuous variables, respectively. All tests were two-tailed and a statistical significance level of 5% was used.

2.9 Sensitivity analysis

To test the robustness of the apparent relationship between persistence and laboratory testing intensity, we used the percentage of prescription possession as the persistence outcome measure, rather than a 7-day treatment disruption measure. Similar to other studies, this was defined as whether the patient was on any antihypertensive at the end of their 6-month follow-up period (yes/no) – regardless of persistence on initial treatment, switching, or addition. The advantage of using the percentage of prescription possession measure is that it requires no definition of a treatment gap (e.g., 7 days) between prescriptions, but rather provides daily measure of the proportion of the cohort that had been dispensed enough medication to cover the prescribed dose for each day of the observation period. The disadvantage of this measure is that — depending upon when the measure is taken (e.g., 45, 90, 180 days) — one or more important gaps between prescription fills can be overlooked. We plotted the percentage of prescription possession over the entire observation window for the cohort grouped by whether they received baseline laboratory testing and/or follow-up laboratory testing.

3 RESULTS

3.1 Cohort characteristics

Between April 1, 2012 and March 31, 2017, 103,232 patients were diagnosed with incident, uncomplicated hypertension, and treated with an antihypertensive medication in Alberta (Figure 1). The mean age of the study cohort was 53.4 years (SD: 13.2) with the majority of patients being male (54.5%) (Table 1). Of patients diagnosed with incident, uncomplicated hypertension, 29.9% lived in a predominantly white neighbourhood, 27.4% lived in a neighbourhood with 15–30% visible minorities, and 19.0% lived in a neighbourhood with ≥50% visible minorities. Almost a quarter of patients lived in a neighbourhood income in the lowest quintile, and with the majority living in urban areas (82.5%).

Within this cohort, 9.5% (n = 9,796) received TDs as their index antihypertensive prescription, 49.7% received either an ACEi or ARB, 11.8% received a CCB, 6.4% received a beta blocker, 12.4% received...
**TABLE 1** Characteristics of adult patients diagnosed with uncomplicated hypertension between April 1, 2012 and March 31, 2017 who received antihypertensive medication stratified by persistence (n = 103,232)

| Characteristic                           | Total n (%) | Persistent (Yes less than 7-day treatment gap) | No (7-day or more treatment gap) | p-valueb |
|------------------------------------------|-------------|-------------------------------------------------|---------------------------------|----------|
| Total                                    | 103,232 (100) | 49,036 (47.5) | 54,196 (52.5) | <0.001   |
| Age, mean (SD)                           | 53.4 (13.2) | 55.0 (12.9) | 51.9 (13.3) | <0.001   |
| Age, categorical                         |             |                                                 |                                 |          |
| 18 to <45                                | 27,933 (27.1) | 10,895 (22.2) | 17,038 (31.4) | <0.001   |
| 45 to <65                                | 55,911 (54.2) | 27,547 (56.2) | 28,364 (52.3) |          |
| ≥65                                      | 19,388 (18.8) | 10,594 (21.6) | 8,794 (16.2) |          |
| Sex                                      |             |                                                 |                                 |          |
| Male                                     | 56,283 (54.5) | 25,906 (52.8) | 30,377 (56.1) | <0.001   |
| Female                                   | 46,949 (45.5) | 23,130 (47.2) | 23,819 (43.9) |          |
| Proportion of visible minority           |             |                                                 |                                 |          |
| <15%                                     | 30,892 (29.9) | 15,458 (31.5) | 15,434 (28.5) | <0.001   |
| 15–29%                                   | 28,302 (27.4) | 13,755 (28.1) | 14,547 (26.8) |          |
| 30–49%                                   | 23,985 (23.2) | 11,145 (22.7) | 12,840 (23.7) |          |
| ≥50%                                     | 19,662 (19.0) | 8,527 (17.4) | 11,135 (20.5) |          |
| Missing                                  | 391 (0.4) | 151 (0.3) | 240 (0.4) |          |
| Neighborhood income quintile             |             |                                                 |                                 |          |
| Lowest - 1                                | 24,465 (23.7) | 10,846 (22.1) | 13,619 (25.1) | <0.001   |
| 2                                        | 22,429 (21.7) | 10,647 (21.7) | 11,782 (21.7) |          |
| 3                                        | 20,274 (19.6) | 9,672 (19.7) | 10,602 (19.6) |          |
| 4                                        | 18,409 (17.8) | 8,901 (18.2) | 9,508 (17.5) |          |
| Highest - 5                               | 17,242 (16.7) | 8,793 (17.9) | 8,449 (15.6) |          |
| Missing                                  | 413 (0.4) | 177 (0.4) | 236 (0.4) |          |
| Urban/Rural                              |             |                                                 |                                 |          |
| Urban                                    | 85,123 (82.5) | 40,464 (82.5) | 44,659 (82.4) | 0.797    |
| Rural                                    | 17,721 (17.2) | 8,405 (17.1) | 9,316 (17.2) |          |
| Missing                                  | 388 (0.4) | 167 (0.3) | 221 (0.4) |          |
| Treatment class at index date            |             |                                                 |                                 |          |
| Thiazide/thiazide-like diuretic           | 9,796 (9.5) | 5,178 (10.6) | 4,618 (8.5) | <0.001   |
| ACE inhibitors                           | 37,110 (35.9) | 17,826 (36.4) | 19,284 (35.6) |          |
| ARBs                                     | 14,297 (13.8) | 6,721 (13.7) | 7,576 (14.0) |          |
| Calcium channel blockers                 | 12,170 (11.8) | 5,757 (11.7) | 6,413 (11.8) |          |
| Beta blockers                            | 6,584 (6.4) | 2,831 (5.8) | 3,753 (6.9) |          |
| Other antihypertensives*                 | 645 (0.6) | 296 (0.6) | 349 (0.6) |          |
| Single pill combinations (SPCs)          | 12,778 (12.4) | 5,518 (11.3) | 7,260 (13.4) |          |
| Free-equivalent components (FECs)        | 9,852 (9.5) | 4,909 (10.0) | 4,943 (9.1) |          |
| Treatment continuity                     |             |                                                 |                                 |          |
| Addition                                 | 26,339 (25.5) | 22,898 (46.7) | 0 (0.0) | <0.001   |
| Switch                                   | 22,870 (22.2) | 22,870 (46.6) | 0 (0.0) | <0.001   |
| Treatment disruption                      | 54,196 (52.5) | 0 (0.0) | 54,196 (100.0) | <0.001   |

(Continues)
TABLE 1 (Continued)

| Characteristic                  | Total n (%) | Persistent |              |              |              | p-valueb |
|---------------------------------|-------------|-----------|-------------|-------------|-------------|----------|
|                                 | N = 103,232 | Yes (less than 7-day treatment gap) | N = 49,036 | No (7-day or more treatment gap) | N = 54,196 |          |
| Labaratory testing              |             |           |             |             |             |          |
| No Test                         | 17,968 (17.4)| 6968 (14.2)| 11,000 (20.3)| <0.001      |             |          |
| Baseline test only              | 25,725 (24.9)| 10,864 (22.2)| 14,861 (27.4) |             |             |          |
| Follow-up test only             | 26,401 (25.6)| 13,543 (27.6)| 12,858 (23.7) |             |             |          |
| Baseline and follow-up test     | 33,138 (32.1)| 17,661 (36.0)| 15,477 (28.6) |             |             |          |

Notes: The percentages reported here were calculated using the denominators indicated at the top of each column (i.e., 103,232; 49,036; or 54,196) to provide an overview of cohort characteristics. See Figure 2 for percentages using row totals as the denominator for comparing relative levels of medication persistence by patient or treatment characteristics.

Statistical significance testing consisted of Kruskal-Wallis and χ² tests for continuous and categorical variables, respectively. The ‘missing’ categories were excluded from the statistical tests on the visible minority, neighbourhood income quintile or urban/rural variables.

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; SD, standard deviation.

3.2 | Persistence overall and by patient characteristics

Of the total cohort, 47.5% (n = 49,306) were considered persistent during the entire observation window (i.e., no treatment gaps were observed that were 7 days or more) (Figure 2). Regarding patient-level factors, a significantly higher persistence was observed among females (49.3%, p < 0.001) whereas a lower rate was seen among males (46.0%, p < 0.001). Increasingly higher persistence was observed by age group with 39.0% persistence among 18–44 year-olds; 49.3% among 45–64 year-olds, and 54.6% among 65+ year-olds—the highest level observed by our study. As for geographic characteristics, higher persistence was seen as neighbourhoods were increasingly white (from 43.4% to 50.0%) and wealthy (from 44.3% to 51.0%). However, no significant difference (p = 0.797) was observed among urban or rural patients (47.5% and 47.4%, respectively).

3.3 | Persistence by treatment-related factors

Higher persistence was seen among patients prescribed thiazides (52.9%, p < 0.001) with a considerably lower rate observed among those prescribed beta-blockers (43.0%, p < 0.001) (Figure 2). Among patients prescribed more than one agent, those prescribed FECs higher persistence (49.8%, p < 0.001) whereas those prescribed SPCS had a much lower level (43.2%, p < 0.001). Note that nearly half of persistent patients either switched from one antihypertensive medication to another agent (46.6%) and/or received an additional agent (46.7%) (Table 1).

3.4 | Patient persistence by laboratory testing

Persistence was statistically significantly associated (p < 0.001) with the intensity of testing with the highest levels of persistence seen among those who were tested multiple times and had follow-up testing at 6 months (Table 2). Patients with no laboratory testing had the lowest level of persistence after 6 months (n = 6968; 38.8%). In comparison, persistence levels were 3.4% higher in patients with baseline testing only (n = 10,864; 42.2%; p < 0.001), 12.5% higher in those with only follow up testing (n = 13,543; 51.3%; p < 0.001), and 14.5% higher in those with both baseline and follow-up lab testing (n = 17,661; 53.3%; p < 0.001) — corresponding to the highest level of persistence observed in our study (only exceeded by those who were aged 65+).

3.5 | Sensitivity analysis: treatment possession at end of follow-up and laboratory testing

The results comparing patients grouped by laboratory testing were broadly similar when the proportion of treatment possession at the end of the follow-up period was examined (rather than treatment persistence). There were statistically significant differences in treatment possession by testing intensity (p < 0.001), but the magnitude of these differences was less pronounced (Table 3). By the end of the observation period, patients with follow-up testing only or baseline and follow-up testing had a similar number of patients on an antihypertens-
Inclusion and exclusion flow chart of cohort of patients with uncomplicated, incident hypertension

4 | DISCUSSION

Among factors under prescriber control (e.g., choice of antihypertensive or single pill formulation), our real-world analysis of 103,232 newly diagnosed, uncomplicated hypertension patients who filled their first prescription found that persistence levels were highest among patients with baseline and follow-up laboratory testing related to hypertension. More specifically, we observed an effect in which fewer treatment disruptions occurred for those with more frequent and recent testing. Persistent patients were also more likely to be female, older, and from neighbourhoods with higher social status (with exception to rurality). However, regardless of treatment-related factors or patient characteristics investigated, patient persistence was low overall with only half continuing treatment after 6 months. These findings have important implications for clinical practice and highlight the need for strategies to improve long-term persistence for a common chronic condition with known sequelae.

A striking finding of our study was the low level persistence overall. Regardless of the measure of treatment adherence used, similarly low rates have also been reported elsewhere. For example, Abegaz et al's systematic review and meta-analysis of 28 studies using the eight-item Morisky medication adherence scale (MMAS-8) found that as many as 45% of patients treated for hypertension are non-adherent.43 A retrospective cohort study from Germany in 2016 investigated antihypertensive medication in 2016 and found 56.3% of patients to be non-adherent within 2 years.44 These findings appear to be consistent with medication adherence for many other chronic diseases.45 Roughly 50% of patients with coronary heart disease treated with statins discontinue within the first year.46–49 Similarly, 50% patients with osteoporosis treated with bisphosphonates become non-adherent after 1 year.50–53 This level of adherence extends beyond antihypertensive drugs as we found similar results in a related study focused on diabetes with 48% being non-adherent to metformin within 12 months.54 With such suboptimal adherence at a population level, it is important for future studies to continue to uncover ways to boost patient adherence to antihypertensive medications.25,55,56

Fortunately, our study does reveal some clues as to how prescribers may be able to encourage higher levels of medication persistence among their patients. Most important, we observed higher levels of persistence with more testing with a magnitude much larger than the other treatment-related factors under a prescribers’ control (e.g., medication class prescribed, SPC vs. FECs). Although this resonates with the findings of other studies,13,57 the reasons underlying this association remain elusive. While laboratory testing itself may foster higher levels of medication persistence (e.g., patients feel more closely monitored by their physicians), it also may simply signal patients who are able to follow physicians’ recommendations more closely. Regardless, a lack of follow up on laboratory work may be an indicator to physicians of patients who are at higher risk of discontinuing their medication. Another possibility is that laboratory work is reflective of a higher level of ongoing patient-provider communication, which has been found to foster ongoing medication persistence.58,59 This possibility also resonates with our observation that a large number of persistent patients either had a medication added during the observation window (which may address suboptimal blood pressure control with a single medication25) and/or switched drug classes (which may address patient concerns regarding side effects).20 Nevertheless, our study design only provides insight into the correlation between laboratory testing intensity and higher persistence. As correlation does not
Table 2: Number of patients who experienced treatment disruption of their index prescription dispense (a gap of 7 or more days between fills) during follow-up, among adult patients diagnosed with uncomplicated hypertension between April 1, 2012 and March 31, 2017 who received antihypertensive treatment (n = 103,232)

| Lab testing group            | Persistence observed for 6 months following index prescription, n (%) | p value |
|------------------------------|------------------------------------------------------------------------|---------|
|                              | Yes (n) | No (n) | Total (n) |
| No test                      | 6968 (38.8) | 11,000 (61.2) | 17,968 | <0.001 |
| Baseline test only           | 10,864 (42.2) | 14,861 (57.8) | 25,725 |
| Follow-up test only          | 13,543 (51.3) | 12,858 (48.7) | 26,401 |
| Baseline and follow-up test  | 17,661 (53.3) | 15,477 (46.7) | 33,138 |
| Total                        | 49,036 (47.5) | 54,196 (52.5) | 103,232 |

Note: The p value results from a χ² test, and the statistically significant result indicates that there is an association between lab testing and discontinuing the initial antihypertensive treatment.

Figure 2: Levels of persistence observed by patient-, neighbourhood-, and treatment-related factors. Note: Proportions of persistence observed in the cohort by individual level variables (i.e., age, sex), neighbourhood-level variables (i.e., income quintile, visible minority, rurality), and treatment-related factors within the prescribers’ control (i.e., combination formulation, antihypertensives class, laboratory testing). Red shading is the proportion persistent (i.e., no gap of 7 days or more between prescription fills) versus those that were not (shown in blue). The dotted line represents the overall level of persistence seen for the entire cohort in the first 6 months following their index prescription date. Table 1 was used to calculate all percentages shown here using row totals as the denominator.

Table 3: Number of patients who had received antihypertensive treatment at the end of follow-up, among adult patients diagnosed with uncomplicated hypertension between April 1, 2012 and March 31, 2017 who received antihypertensive treatment (n = 103,232)

| Lab testing group            | Antihypertensive treatment at end of follow-up, n (%) | p value |
|------------------------------|-------------------------------------------------------|---------|
|                              | Yes (n) | No (n) | Total (n) |
| No test                      | 10,424 (58.0) | 7,544 (42.0) | 17,968 | <0.001 |
| Baseline test only           | 15,068 (58.6) | 10,657 (41.4) | 25,725 |
| Follow-up test only          | 17,181 (65.1) | 9,220 (34.9) | 26,401 |
| Baseline and follow-up test  | 21,251 (64.1) | 11,877 (35.9) | 33,138 |
| Total                        | 63,924 (61.9) | 39,308 (38.1) | 103,232 |

Note: The p value results from a χ² test, and the statistically significant result indicates that there is an association between lab testing and having an antihypertensive prescription dispense at the end of follow-up.
FIGURE 3  Antihypertensive treatment patterns, among adult patients diagnosed with uncomplicated hypertension between April 1, 2012 and March 31, 2017 who received antihypertensive treatment (n = 103,232). Note: We calculated the proportion of patients that were dispensed enough medication to cover their prescribed dose for the day in question as the percentage of prescription possession. The dips in the percentage of prescription possession (e.g., day 30, 60, 90) occur because some patients ran beyond the days covered by their initial prescription (assuming perfect adherence to the prescribed daily dose) and either discontinued treatment (resulting in a lower percentage of prescription possession for the overall cohort) or waited a period of time before filling their next prescription (resulting in the percentage of prescription possession to rise again). In this analysis, the study cohort is divided into four groups based on whether their prescribing physician had also ordered laboratory testing associated with their prescription (the timing of these tests roughly runs in parallel to prescription refills, but is not indicated above). The analysis shows that irrespective of the treatment gaps in all groups, differences emerged between groups in the percentage of prescription possession around days when prescription refills typically occurred. By the end of the observation period, the two groups with follow-up lab testing had significantly higher percentages of prescription possession as compared to those without follow-up lab testing.

imply causation, future research is needed to investigate the extent to which there may be a causative effect at a play.

Our findings regarding the two other factors under the prescribers’ control are also of interest. Notably, there was better persistence among patients prescribed TDs, though their side effects have been noted elsewhere and are well-known among prescribers. Our study also found favourable results for prescribing FECs over SPCs which has been observed previously, despite the existence of evidence that SPCs can facilitate adherence by reducing pill burden. The relatively lower cost of TDs and FECs may partially explain our findings as larger co-payments associated with more costly therapeutics have been shown to reduce persistence.

Finally, our findings regarding patients’ age, sex, and neighbourhood are also notable and consistent with previous work. Lower levels of persistence among younger patients is well-established, though the ability to persist with medication has been theorized to peak at a certain age (e.g., 65) before again declining. We also detected lower levels of persistence in lower income and racialized neighborhoods, which may underscore the importance of the structural determinants of medication persistence noted by other studies (e.g., pharmacy deserts). We also observed differences in levels of persistence by biological sex, which resonates with previous and ongoing research that has documented differences in medication taking behaviours by gender. As these results illustrate the importance of the social determinants of medication persistence, it also raises caution about increasing the burden upon patients by assigning them laboratory work given the number of barriers they already face when adhering to a new medication regimen.

The results of this study should be interpreted in light of its limitations. First, our cohort was limited to patients with incident, uncomplicated hypertension with no major comorbidities. As a result, these findings may not be generalizable to patients with hypertension with compelling indications for specific agents or end-organ damage. Second, our measure of persistence was based upon prescriptions filled. It is possible that some patients may possess the medication but did not follow through with taking their medication as prescribed. Third, our measures of persistence track secondary persistence (i.e., whether the patient had ongoing persistence following the fill of their first prescription); but as our data sources do not contain a record of prescriptions that were prescribed but unfilled, our study cannot definitively shed light on the frequency of how often patients failed to fill their first prescription. Fourth, blood pressure measurements were not available in administrative records; therefore, we are unable to determine the proportion of patients achieving adequate blood
pressure control after 6 months. However, while a single drug may occasionally be sufficient, the vast majority of patients require multiple agents to achieve target blood pressure control.\textsuperscript{65, 66} Fifth, our study did not account for the reason for discontinuation, which may be appropriate. For example, although rare, if patients make major lifestyle changes after being diagnosed with hypertension (e.g., smoking cessation, significant weight loss), they could have their antihypertensives discontinued by the prescriber.\textsuperscript{67, 68} Similarly, our study cannot distinguish the reasons behind medication changes or discontinuation, which may be motivated by suboptimal blood pressure control, side effects, cost, supply shortages, or another unobserved factor. Finally, while our work established an association between persistence and lab testing regimen, we did not further explore whether these relationships were independent from other measured factors (e.g., prescribing TDs with both baseline and follow-up laboratory testing). Future research using logistic regression for multivariable adjustments to explore combinations of treatment-related variables theorized to be particularly advantageous for optimal treatment persistence is needed.

5 | CONCLUSION

Control of hypertension via persistence with antihypertensives is key to ensuring uncontrolled blood pressure does not lead to severe sequelae. However, persistence is suboptimal and drops off considerably after 6 months. With such considerable proportions of patients discontinuing treatment, medication persistence is a substantial barrier to realizing the proven benefits of antihypertensive treatment for reducing preventable cardiovascular disability and death. Ongoing follow up with patients is likely a critical component to ensure patients are more consistently taking an appropriately matched antihypertensive medication in the longer term. Our study points to laboratory testing as a potential tool for encouraging medication persistence and/or as a potential signal of patients who are more (or less) likely to take their medications.

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CONFLICT OF INTEREST

The authors declare they have no competing or conflicting interests.

AUTHOR CONTRIBUTIONS

All authors conceived and planned the study. T.D.S. and R.F.B. carried out the analysis. All authors contributed to the interpretation of the results. C.S. and R.F.B. took the lead in writing the manuscript. All authors provided input and critical feedback in revising the manuscript and responding to peer review.

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