Randomized Trial of the Effect of Pharmacist Prescribing on Improving Blood Pressure in the Community

The Alberta Clinical Trial in Optimizing Hypertension (RxACTION)

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Background—Hypertension control rates remain suboptimal. Pharmacists' scope of practice is evolving, and their position in the community may be ideal for improving hypertension care. We aimed to study the impact of pharmacist prescribing on blood pressure (BP) control in community-dwelling patients.

Methods and Results—We designed a patient-level, randomized, controlled trial, enrolling adults with above-target BP (as defined by Canadian guidelines) through **c**ommunity pharmacies, hospitals, or primary care teams in 23 communities in Alberta. Intervention group patients received an assessment of BP and cardiovascular risk, education on hypertension, prescribing of antihypertensive medications, laboratory monitoring, and monthly follow-up visits for 6 months (all by their pharmacist). Control group patients received a wallet card for BP recording, written hypertension information, and usual care from their pharmacist and physician. Primary outcome was the change in systolic BP at 6 months. A total of 248 patients (mean age, 64 years; 49% male) were enrolled. Baseline mean±SD systolic/diastolic BP was 150±14/84±11 mm Hg. The intervention group had a mean±SE reduction in systolic BP at 6 months of 18.3±1.2 compared with 11.8±1.9 mm Hg in the control group, an adjusted difference of 6.6±1.9 mm Hg (P=0.0006). The adjusted odds of patients achieving BP targets was 2.32 (95% confidence interval, 1.17–4.15 in favor of the intervention).

Conclusions—Pharmacist prescribing for patients with hypertension resulted in a clinically important and statistically significant reduction in BP. Policy makers should consider an expanded role for pharmacists, including prescribing, to address the burden of hypertension.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00878566.

(*Circulation*. 2015;132:93-100. DOI: 10.1161/CIRCULATIONAHA.115.015464.)

Key Words: delivery of health care ■ hypertension ■ outcome assessment (health care) ■ pharmacists

Hypertension is a key risk factor for cardiovascular disease and premature mortality worldwide, affecting 1 in 5 North American adults and with 35% to 50% remaining uncontrolled.[1,2] Because the prevalence of hypertension increases with age,[2,3] it is expected that an aging population will lead to an even higher prevalence of hypertension and a greater burden on existing healthcare resources to manage elevated blood pressure (BP) and its sequelae in the coming years.

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Given the increasing workloads placed on primary care physicians, pharmacists are well positioned to take on a greater role in the management of chronic disease. Indeed, research has demonstrated the effectiveness of pharmacist-provided disease management activities, including for hypertension.[4–10] Specific to hypertension, a recent systematic

Received January 18, 2015; accepted May 6, 2015.

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The online-only Data Supplement is available with this article at http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIRCULATIONAHA.115.015464/-/DC1.

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Circulation **is available at http://circ.ahajournals.org** **DOI: 10.1161/CIRCULATIONAHA.115.015464**

review and meta-analysis assessing the effect of pharmacist intervention for outpatients with hypertension identified 39 randomized, controlled trials comprising >14 000 patients.[11] Compared with usual care, interventions including pharmacists resulted in improvements in both systolic (−7.6 mm Hg; 95 % confidence interval, −9.0 to −6.3) and diastolic BP (−3.9 mm Hg; 95 % confidence interval, −5.1 to −2.8). Of note, a greater effect size was observed among the 23 studies in which the pharmacist led the intervention, resulting in mean systolic and diastolic BP differences of −8.5 and −4.6 mm Hg, respectively, compared with usual care. However, the pharmacist interventions provided largely involved patient education, medication management activities (defined as monitoring activities with medication adjustment), and recommendations to physicians. Therefore, the effectiveness of these interventions largely remains dependent on physician follow-through on drug therapy recommendations made by the pharmacists, a type of "ceiling effect."

It is postulated that allowing pharmacists to independently prescribe drug therapy may result in even better patient outcomes than interventions based solely on providing recommendations. Since 2007, the Health Professions Act of Alberta, Canada has allowed pharmacists to apply for authorization to prescribe.[12] To receive this authorization, pharmacists must have a minimum of 1 year of practice experience and must successfully complete an application process, including the submission of patient care cases documenting their clinical involvement to demonstrate skills in patient assessment, judgment, care planning, and follow-up.[13] To ensure continuity of care, pharmacists must communicate all prescribing decisions to the patient's primary care physician and are responsible for conducting follow-up on their prescribing decisions. Additionally, all Alberta pharmacists are able to order laboratory studies for patients under their care as required. Pharmacists are required to maintain professional liability insurance.

The present study was designed to test the hypothesis that pharmacist prescribing for community-dwelling patients with uncontrolled hypertension would result in improved BP reduction over usual care.

Methods

The design and methods of this study have been published previously and are outlined in Figure 1.[14] Briefly, we conducted a multicenter, randomized, controlled trial comparing enhanced pharmacist care (which included independent patient assessment, counseling, and prescribing) with usual care in the province of Alberta, Canada. All participating pharmacists had prescribing authorization and practiced in community (20 pharmacists), hospital outpatient clinics (2 pharmacists), or primary care clinic settings (6 pharmacists). Pharmacists received training in BP assessment and treatment that was based on the Canadian Hypertension Education Program (CHEP) guidelines[15] and had access to hypertension experts for consultation as required.

Eligible patients were identified opportunistically through BP screening events, through case finding[16] by identifying patients at high risk of elevated BP, and through the course of providing routine care. Patients were enrolled in the study by participating pharmacists but could also be referred for assessment of study eligibility by a physician, nurse, or other health professionals. Patients were eligible for the study if they were adult outpatients and had uncontrolled BP as defined by the CHEP guidelines (which mandated multiple visits to define uncontrolled BP, with the exact number depending on the level of BP). Overall, this meant a BP >140/90 mm Hg for most and >130/80 mm Hg for those with diabetes mellitus. Because the CHEP guidelines specify a number of diagnostic scenarios with different BP cutoffs and the number of readings required, readers are referred to the guidelines for the clinical definitions of uncontrolled BP for the purpose of this study.[15,17–20] Patients meeting any of the criteria for diagnosis or, if already diagnosed, remaining above the specified target given their age and comorbidities could be included. Any changes to these guideline definitions over the course of the study were concurrently applied to the inclusion criteria for the study.

Exclusion criteria included hypertensive urgency or emergency (defined as systolic BP ≥200 or diastolic BP ≥130 mm Hg with/without symptoms), pregnancy, or unwillingness or inability to provide consent to participate. The study received ethics approval from the University of Alberta Health Research Ethics Board, and written informed consent was obtained from all participants.

All BP measurements performed by the pharmacist were made with the automated BpTRU (BpTRU Medical Devices, Coquitlam, BC, Canada), which takes 6 readings, discarding the first and taking the average of the remainder. Home measurements were performed with the LifeSource UA-787 home BP monitor. Both devices are validated or approved by CHEP, and pharmacists were to ensure that proper cuff sizes were used for all measurements.[21,22] Home measurement was used for those patients requiring >2 office screening visits, as defined by the CHEP guidelines,[15,17–20] as a guideline-concordant option for obtaining these additional BP readings. All patients using home measurement were provided verbal and written instruction on proper measurement technique by the pharmacist and were provided a cuff of proper size to ensure accuracy.

Randomization was conducted at the level of the patient and was performed via a centralized secure Web site at the Epidemiology Coordinating and Research (EPICORE) Center (http://www.epicore.ualberta.ca) to ensure randomization concealment. Patients were randomized in a 2:1 ratio to either intervention or usual care. Because of the nature of the intervention, blinding was not possible.

The intervention group received enhanced pharmacist care, which was guided by the CHEP guidelines and consisted of pharmacist assessment of and counseling about cardiovascular risk and BP control, review of antihypertensive medications, and prescribing/titrating of drug therapy if deemed necessary, in addition to a wallet card for recording BP measurements, lifestyle advice, and written information on hypertension developed by CHEP. The patient's primary care physician was notified of all assessment results and drug therapy changes in person or by fax. Intervention group patients were followed up at monthly intervals until their BP was at target for 2 consecutive visits and thereafter at 3-month intervals for the duration of the study period as per CHEP recommendations.

The usual care group received a wallet card for recording BP, lifestyle advice as required, written information on cardiovascular disease, and BP measurement by the pharmacist at 3-month intervals. Patient education was provided at the discretion of each pharmacist. Patients' primary care physicians were sent a notice that the patients were enrolled in the study on the basis of their elevated BP, and patients were advised to see their physicians for further treatment. All patients were followed up for a total of 6 months.

The primary outcome was the difference in change in systolic BP from baseline to 6 months between the intervention and usual care groups. Secondary outcomes included the change in diastolic BP and the number of patients at their CHEP-recommended target BP (defined as both systolic and diastolic BPs at target, ie, <130/80 mm Hg for those with diabetes mellitus and <140/90 mm Hg for all others) after 6 months and, in the intervention group, the number of new antihypertensive medications started, the number of antihypertensive dose changes, the number of antihypertensive drug changes, and the number of new prescriptions for acetylsalicylic acid and cholesterol-lowering medications. Drug therapy changes were enumerated at the level of the drug therapy class; in other words, an individual patient with 2 new antihypertensive drug classes initiated would be counted as having 2 new starts. All outcomes were

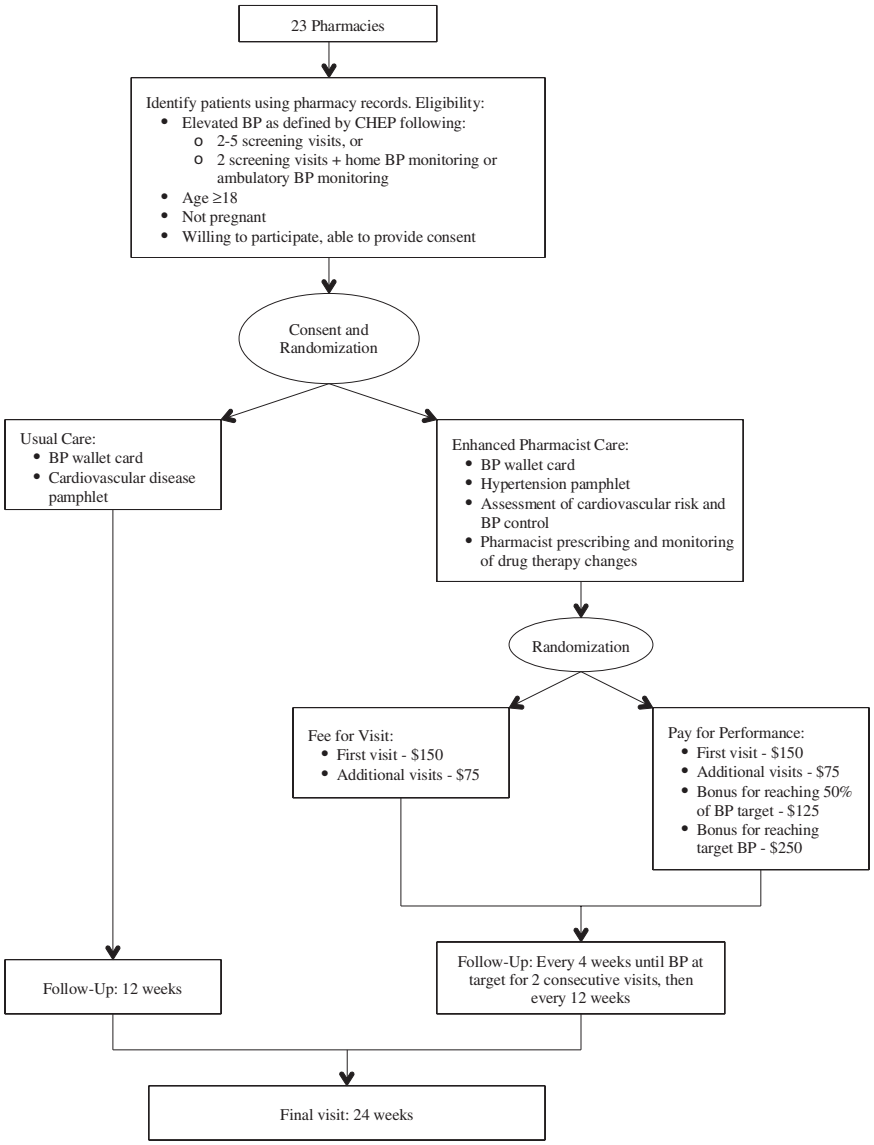

Figure 1. Study design. All fees are in Canadian dollars. BP indicates blood pressure; and CHEP, Canadian Hypertension Education Program.

measured by the pharmacist investigators in the process of providing care to study patients.

Since the initial publication of the methods for the study, some protocol modifications were made to remain consistent with updated hypertension guidelines and to enhance participant recruitment. Although the study was initially limited to rural communities, the enrollment criteria were revised to include urban centers in January 2012. Additionally, reflecting changes in the CHEP recommendations in 2012, undiagnosed and uncomplicated patients with an average BP across 2 visits of 140 to 179/90 to 109 mm Hg could be further screened through 24-hour ambulatory BP monitoring. Patients could be enrolled in the study with an average 24-hour BP of systolic ≥130 mm Hg or diastolic ≥80 mm Hg or average awake-hours BP of systolic ≥135 mm Hg or diastolic ≥85 mm Hg. Target BP for patients with chronic kidney disease in the absence of diabetes mellitus also changed from <130/80 to <140/90 mm Hg in the 2012 CHEP guidelines[17] and was incorporated into study targets from that point onward.

As outlined in our methods publication,[14] our prespecified sample size was 340 patients, including 90 in the usual care arm and 250 in the enhanced pharmacist care arm. All analyses were conducted with IBM SPSS Statistics version 21 (IBM Corp, Armonk, NY) and SAS version 9.4 (SAS Institute Inc, Cary, NC) and followed the intent-to-treat principle, with significance set at a value of $P<0.05$. A generalized, multivariable, linear regression with changes in systolic and diastolic BPs as the dependent variables was performed to adjust for baseline imbalances between groups (defined as those characteristics with $P<0.20$). Thus, we adjusted for a history of myocardial infarction, presence of diabetes mellitus, and a first-degree relative with a history of stroke. Similarly, a logistic model was also used to obtain an adjusted odds ratio for those achieving the target BP. To account for within-pharmacist correlation, all models used robust estimates of variance, clustered by every pharmacist who recruited patients into the study. Missing values were imputed by use of the last-observation-carried-forward method.

Results

Between July 2009 and May 2013, investigators at 23 pharmacies screened 754 patients and enrolled 248 (181 randomized to intervention, and 67 to usual care; Figure 2). Enrollment was stopped before accrual of the full sample size as a result of funding limitations. Of the 506 patients who were not randomized, 495 were ineligible on the basis of not having

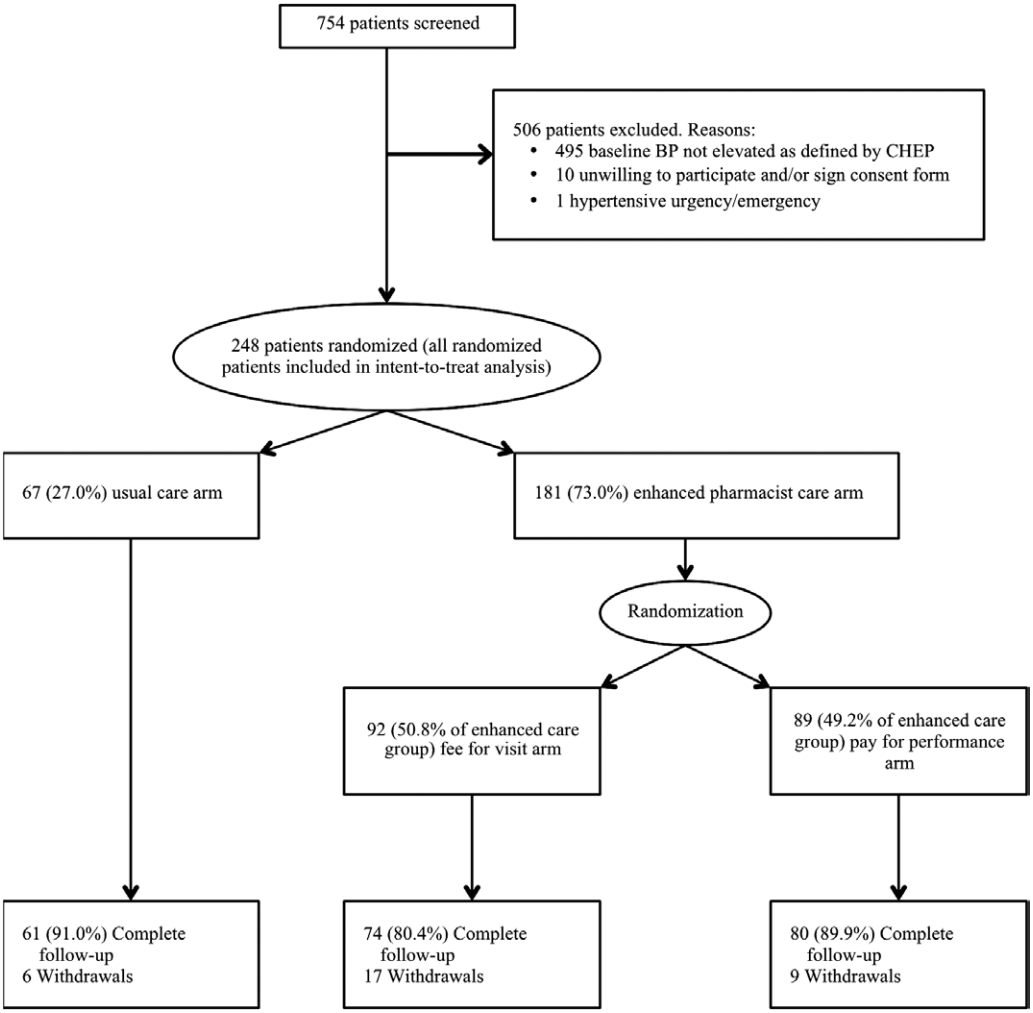

Figure 2. Trial flow. CHEP indicates Canadian Hypertension Education Program.

elevated BP as defined by CHEP at the time of measurement,[15,17–20] 10 did not provide consent, and 1 was referred for immediate care of hypertensive urgency/emergency. A total of 32 patients withdrew from the study (26 [14%] in the intervention group and 6 [9%] in the usual care group). Patients who withdrew from the study generally did not differ from those who continued in the trial, with the exceptions of being older (mean, 68 versus 62 years; P=0.02) and living a greater distance from the pharmacy (mean, 25 versus 12 km; P<0.001). Completeness of follow-up was 85% in the intervention group and 91% in the usual care group.

The intervention and usual care groups were similar at baseline (Table 1). Patients' average±SD age was 64±12 years, and 49% were male. The overall mean±SD systolic/diastolic BP was 150±14/84±11 mm Hg at baseline, and the majority of patients (78%) were already on antihypertensive drug therapy, taking an average of 1.7 medications. Patients already receiving antihypertensive therapy at baseline were older (mean, 65 versus 58 years; P=0.001); had lower diastolic BP (mean, 82.6 versus 86.6 mm Hg; P=0.02); were more likely to have a history of myocardial infarction (P=0.02), atrial fibrillation (P=0.05), stroke (P=0.02), peripheral artery disease (P=0.03), and family history of myocardial infarction (P=0.04); and were less likely to have a history of dyslipidemia (P=0.04) than those not on drug therapy. Of those not receiving antihypertensive therapy at enrollment, nearly half (49%) had been previously diagnosed with hypertension.

Systolic BP decreased in both groups over the 6-month trial, with a greater reduction observed in the intervention group (Figure 3). After adjustment, the mean±SE difference in systolic BP between groups was 6.6±1.9 mm Hg, which was statistically significant (P=0.0006). Diastolic BP also decreased in both groups, with an adjusted mean±SE difference of 3.2±1.3 mm Hg (P=0.01).

The proportion of patients achieving CHEP-recommended target BP was also significantly higher in the intervention than in the usual care group (crude rate, 58% in the intervention group versus 37% in the usual care group; P=0.02) with an adjusted odds ratio of 2.32 (95% confidence interval, 1.17–4.15).

Antihypertensive medication use for each group is provided in Table 2. In the intervention group (n=181), 103 new antihypertensive drugs were initiated, 94 dose changes were made (80 dose increases, 14 dose decreases), and 76 antihypertensive drugs were discontinued. In addition, 12 patients were prescribed low-dose acetylsalicylic acid and 14 were

Table 1. Patient Characteristics

Variable	Intervention (n=181)	Usual Care (n=67)
Demographics		
Male sex, n (%)	89 (49)	32 (48)
Age, mean (SD), y	63 (13)	65 (11)
Urban residence, n (%)	103 (57)	33 (49)
Cardiovascular risk factors:		
Systolic BP at baseline, mean (SD,) mm Hg	149 (14)	151 (11)
Diastolic BP at baseline, mean (SD), mm Hg	84 (12)	83 (10)
First-degree relative history of MI, n (%)	87 (48)	32 (48)
First-degree relative history of angina, n (%)	47 (26)	20 (30)
First-degree relative history of stroke, n (%)	57 (32)	27 (40)*
BMI, mean (SD), kg/m^2	32 (7)	32 (7)
Waist circumference, mean (SD), cm	106 (17)	109 (14)
Elevated waist circumference (>102 cm in men, >88 cm in women), n (%)	126 (70)	51 (76)
Smoking, n (%)		
Current	32 (18)	9 (13)
Ex-smoker	78 (43)	28 (42)
Never	68 (38)	30 (45)
Alcohol consumption, n (%)		
≥1 servings per day	28 (16)	8 (12)
Occasional	90 (50)	37 (55)
Salt added to food, n (%)		
Often/always	31 (17)	11 (16)
Sometimes	41 (23)	22 (33)
Self-reported cardiovascular comorbidities, n (%)		
Diabetes mellitus	71 (39)	38 (57)*
Chronic kidney disease	31 (17)	7 (10)
History of MI	8 (4)	8 (12)*
History of angina	23 (13)	13 (19)
History of heart failure	2 (1)	0
History of atrial fibrillation	22 (12)	5 (8)
History of stroke	10 (6)	6 (9)
Dyslipidemia	93 (51)	37 (55)
Peripheral artery disease	11 (6)	4 (6)
Prior revascularization procedure	11 (6)	6 (9)
On antihypertensive drug therapy at baseline, n (%)	137 (76)	56 (84)
Drugs taken, n (SD)	1.7 (1.2)	1.7 (1.2)

BMI indicates body mass index; and MI, myocardial infarction.

*Characteristics with baseline differences between groups at $P<0.20$ and therefore included in multivariable models.

prescribed a statin by the pharmacist. In the usual care group (n=67), 20 new antihypertensive drugs were initiated, 9 dose changes were made (8 dose increases, 1 dose decrease), 15 antihypertensive drugs were discontinued, 2 patients were initiated on low-dose acetylsalicylic acid, and 2 patients were initiated on a statin.

Discussion

An expanding scope of practice for pharmacists is increasingly being adopted worldwide for a number of reasons, including pharmacists' accessibility and drug therapy expertise and the increasing prevalence of chronic diseases, which are managed largely through lifestyle interventions and pharmacotherapy. To the best of our knowledge, our study is the first randomized trial of independent pharmacist prescribing in community-dwelling patients with hypertension. Our results demonstrated significant reductions in systolic and diastolic BPs and significant improvements in the proportion of patients reaching recommended BP targets compared with usual pharmacist and physician care. Given the accessibility of community pharmacies and high burden of illness from hypertension, these findings could have an important impact on public health.

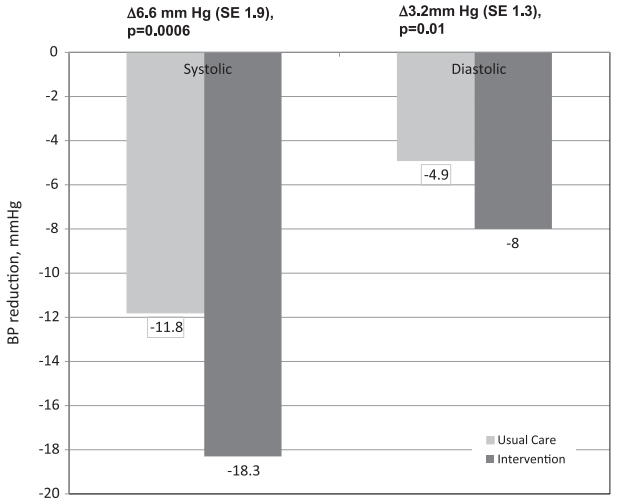

Figure 3. Adjusted difference in systolic and diastolic blood pressure (BP) over 6 months. Adjusted for history of myocardial infarction, diabetes mellitus, and first-degree relative with stroke.

An innovation of our study was the independent prescribing authorization of pharmacists. We hypothesized that pharmacist prescribing could overcome the ceiling effect that may be associated with recommendation-based care, and we expected that the difference in change in systolic BP from this intervention would be even greater than the 6.6 mm Hg observed. However, we observed a higher-than-expected BP reduction among the usual care group of 11.8 mm Hg, more than double that observed in the control arm of the Study of Cardiovascular Risk Intervention by Pharmacists–Hypertension (SCRIP-HTN) in a similar population.[23]

Table 2. Use of Antihypertensive Medications

	Intervention (n=181), n (%)		Usual Care (n=67), n (%)	
	Baseline	6 mo	Baseline	6 mo
Thiazide diuretic	77 (43)	99 (55)	25 (37)	30 (45)
ACE inhibitor	65 (36)	68 (38)	29 (43)	26 (39)
β-Blocker	34 (19)	35 (19)	9 (13)	10 (15)
Calcium channel blocker	52 (29)	67 (37)	21 (31)	22 (33)
Angiotensin receptor blocker	63 (35)	76 (42)	25 (37)	29 (43)
Other	13 (7)	12 (7)	5 (8)	6 (9)

ACE indicates angiotensin-converting enzyme.

Potential contributing factors could be the Hawthorne effect among patients and their primary care physicians, the effectiveness of the knowledge translation efforts of the CHEP program to improve awareness and control of hypertension in Canada,[24] case-finding efforts by pharmacists who may have preferentially enrolled patients with other comorbidities and therefore potentially differing motivation than identified via general population screening,[16] or the provision of interventions other than prescribing by the pharmacist that may have resulted in improved BP management. Because we relayed BP measurements to the patient and their family physician in the usual care group (thus functioning as an audit and feedback intervention in our usual care arm, which actually represents more than usual care), this may have also improved their BP care. Nevertheless, all such contaminating factors would have biased our findings toward the null hypothesis. Additionally, it should be noted that a slightly greater proportion of intervention patients were lost to follow-up than usual care patients; however, we used a last-value-carried-forward approach to impute missing values, which would have also biased toward the null hypothesis.

Compared with the results of a very comprehensive recent meta-analysis of 39 randomized trials examining the effectiveness of pharmacist interventions by Santschi and colleagues,[11] our study sample was similar in terms of participants' age and sex and frequency of intervention visits, but our study had a slightly shorter intervention duration (6 months versus a mean of 8.2 months). We found slightly lower mean differences in both systolic BP (−6.6 versus −7.6 mm Hg) and diastolic BP (−3.2 versus −3.9 mm Hg); however, as mentioned above, the marked improvements noted among the usual care group from potential contamination offset the absolute BP reductions observed in the intervention group of 18.3 and 8.0 mm Hg for systolic and diastolic BP, respectively. In contrast to the Santschi et al meta-analysis,[11] our study involved primarily community pharmacies, which may provide more generalizability in terms of potential public health impact.

It is also important to note that pharmacists providing care for intervention group patients were also remunerated for their services as part of the study. As described in the study protocol,[14] this remuneration was part of a secondary randomization process to function as a substudy of the main analysis (which will be reported separately). In the substudy, each patient randomized to the intervention group was further randomized in a 1:1 ratio to pharmacist payment in the form of fee for service (a flat rate per visit regardless of outcome) or pay for performance (a flat rate per visit with incentive payments for achieving BP goals). One cannot ignore the potential impact of this arrangement on the pharmacists choosing to participate in the study, the number of patients enrolled, or the nature of the care provided. Since July 2012, Alberta pharmacists have been able to claim a fee from the Alberta government for medication management services.[25] Pharmacists enrolling patients into the study before this date would therefore have received remuneration for providing care for study patients that otherwise would not have been offered. Conversely, after July 2012, this fee discrepancy would have been reduced because fee-for-service remuneration would have been available for these patients outside the study environment.

This study is not without limitations. Because of the nature of the intervention, neither the patients nor the pharmacist investigators could be blinded to the treatment group to which patients were allocated. However, our outcomes were objective (measured BP) and captured by automated devices, removing any potential for differential measurement bias between arms. Additionally, by design, patients were seen more frequently by the pharmacist if randomized to intervention versus usual care, which may have contributed to the BP reduction observed owing to reduced white coat hypertension over time or regression to the mean. To minimize the impact of white coat hypertension, a well-validated automated BP device (BpTRU) was used for all study measurements. Pharmacists were also asked to vacate the room when these measurements were taken to further reduce patient anxiety. Additionally, with ≈10% of Alberta pharmacists possessing additional prescribing authorization at the time of the study (personal communication, Dale Cooney, Alberta College of Pharmacists), it is possible that the early adopters choosing to apply for additional prescribing authorization and to participate in this study may differ from the typical pharmacist,[26] affecting the generalizability of the results. Similarly, one cannot assume that those patients volunteering for the study are representative of the population in terms of health motivation, potentially explaining some of the BP reduction noticed even among usual care patients. One also must consider the possibility for contamination among the usual care group because we did not use cluster randomization (as a result of logistics and the small number of pharmacists with additional prescribing authorization when the study was launched); thus, the usual care provided by pharmacists in our study may differ from the usual care provided by all pharmacists. Furthermore, although most drug therapy changes in the intervention group were likely implemented by the pharmacist, one cannot rule out that some medication adjustments were performed by the patient's primary care physician. However, the small number of drug changes in the usual care arm would argue against this being a major confounder. Finally, we did not achieve our target sample size of 340 patients and, because of funding limitations, terminated enrollment at 248 patients. It should be noted, however, that the sample size of 340 was required for the remuneration substudy (our a priori sample size calculation for the main study was 240 patients).

The results of our study demonstrate that pharmacist prescribing, when provided in addition to usual care, results in a clinically significant reduction in BP and a substantial improvement in the proportion of patients with initially uncontrolled hypertension reaching their target BP, even though a very high proportion, 78%, were already taking antihypertensive therapy at baseline.

Although Alberta was the first Canadian jurisdiction to allow pharmacists to independently prescribe antihypertensive drug therapy for patients, the Canadian provinces of Manitoba and New Brunswick have recently adopted similar legislation for pharmacists with specialty training and working as part of a collaborative practice,[27] and independent pharmacist prescribing has been in place in the United Kingdom since 2006.[28] The generalizability of our study results to these and future regions using independent pharmacist prescribing is unknown, and ongoing evaluation of these programs is encouraged. The results from this study, the first randomized,

controlled trial of pharmacist prescribing, and prodigious evidence from 39 nonprescribing trials[11] support recent efforts to expand pharmacists' scope of practice to include medication management activities in an effort to address clinical inertia in hypertension management.[29–31]

Acknowledgments

Drs Tsuyuki and Houle had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. We acknowledge the assistance of Dr Jeff Bakal with the statistical modeling.

Sources of Funding

RxACTION was supported by grants from the Canadian Institutes of Health Research, Alberta Innovates–Health Solutions, Merck, the Canadian Foundation for Pharmacy, and the Cardiovascular Health and Stroke Strategic Clinical Network of Alberta Health Services. The study was further supported by ManthaMed through the in-kind provision of BpTRU devices. Dr Houle received funding as a graduate student from the Canadian Institutes of Health Research, the Interdisciplinary Chronic Disease Collaboration (funded by Alberta Innovates–Health Solutions), and Hypertension Canada. Dr McAlister is supported by a salary award from Alberta Innovates–Health Solutions and the University of Alberta Chair in Cardiovascular Outcomes Research.

Disclosures

Dr Tsuyuki has received research funds for investigator-initiated trials from AstraZeneca, Sanofi, and Merck and has provided consulting for PharmaSmart International and Boehringer Ingelheim. The other authors report no conflicts.

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CLINICAL PERSPECTIVE

Hypertension is the leading risk factor worldwide for premature death and disability, yet treatment and control rates remain suboptimal. This problem requires some fresh thinking. The Alberta Clinical Trial in Optimizing Hypertension (RxACTION) study was the first randomized trial to evaluate independent prescribing by community pharmacists for patients with poorly controlled blood pressure. We enrolled 248 patients in 23 communities in Alberta, Canada. The 6-month pharmacist intervention (assessment, patient education, prescribing, and follow-up) reduced blood pressure by 6.6/3.2 mm Hg more than usual pharmacist and physician care (P=0.0006). In addition, patients were 2.3 times more likely to reach the recommended blood pressure targets. Pharmacists are primary care providers who are well situated to help address the burden of hypertension in the community. Our findings could have important public health implications.