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"The Impact of Clinical Pharmacists on the Blood Pressure Control"

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THE IMPACT OF CLINICAL PHARMACIST ON THE BLOOD PRESSURE CONTROL OF PATIENTS WITH HYPERTENSION

by

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Abstract

Background and Goals

Hypertension is an important contributor to morbidity and mortality from cardiovascular disease. The morbidity and mortality associated with hypertension is significantly mitigated by control of blood pressure. Currently there is a significant gap between the estimated 31 percent of hypertensive Americans with a blood pressure controlled to the recommended goal of less than 140/90 mm Hg and the Healthy People 2010 target of 50 percent. New population-based solutions are being sought to help close this gap.

The knowledge, training and experience of clinical pharmacists suggest that they may be well suited for many aspects of hypertension management including, design of antihypertensive regiments, patient education, and blood pressure monitoring. It is common for specialty-trained clinical pharmacists work with physicians in a collaborative relationship to manage chronic illness, such as hypertension. The impact of pharmacists in the management of hypertension, however, has not yet been thoroughly investigated.

In an effort to identify solutions to improve blood pressure control in a large patient population, Providence Primary Care Research Network in Oregon investigated the impact of clinical pharmacists on hypertension management. They conducted a randomized controlled trial to evaluate the effectiveness of collaborative drug therapy management intervention by a clinical pharmacist targeted at lowering blood pressure as compared with usual care.

The primary objective of this study was attainment of blood pressure goals. Data on secondary outcomes including medication compliance, patient satisfaction, quality of life score, and patient hypertension knowledge were also assessed and provided for this thesis project. The thesis also evaluated the effect of demographic imbalance in the study samples introduced by the withdrawal of patients from the study.

Study Design

The 2001 Providence Hypertension Study was a prospective, randomized, controlled trial. Subjects were eligible to participate if they had a diagnosis of hypertension (ICD-9-CM[1] codes of 401.x) and a last systolic blood pressure ≥160 mm Hg and/or a last diastolic blood pressure ≥100 mm Hg. Consented subjects were randomized into two groups: (A) usual care from a primary care provider (PCP) who has received hypertension education, treatment guidelines, and a list of patients with blood pressures fitting the study inclusion criteria and (B) collaborative drug therapy management by a clinical pharmacist in addition to the usual care delivered by a PCP.

Results

Blood pressure: Although blood pressure decreased significantly in both arms, more subjects in the intervention group achieved the target blood pressure goal than did patients in the control group (62 percent as compared with 44 percent, odds ratio=2.13, 95% CI: 1.29-3.53).

Compliance: Within-group analysis for medication compliance indicated no significant increase in the usual care group from baseline to final assessment (p=0.52). Although the pharmacist group demonstrated an increase in the proportion of subjects

[1] *Internal Classification of Disease, ninth edition, clinical modification*

reporting high compliance from baseline to final assessment, the difference was not statistically significant (p=0.08).

Knowledge: Subjects in the intervention group demonstrated a statistically significant increase in the hypertension knowledge; however, between-group comparison revealed no difference at final assessment between the intervention and control groups.

Patient Satisfaction: No statistically significant difference in overall satisfaction was detected between study arms at final assessment (8.49 vs. 8.55, p=0.75). Within-group analysis revealed no difference in mean satisfaction in the usual care group from baseline to final assessment (p=0.16). However, there was an increase in the patient aggregate mean satisfaction from baseline to final assessment in the pharmacist-managed group (p<0.0001).

Quality of Life: The quality-of-life analysis results revealed that the between-group measurements at baseline indicated no statistically significant differences for any of the domains and aggregate scores.

Conclusions

An evidence-based, systematic approach using collaborative drug therapy management by clinical pharmacists in addition to the usual care delivered by a PCP for patients with uncontrolled hypertension resulted in improved blood pressure control. However, patient satisfaction, medication compliance, and quality of life were not significantly altered.

Further research is needed to determine if use of clinical pharmacists in the management of hypertension is a cost-effective strategy. Economic evaluation of the cost-effectiveness should assess prescribing patterns—if the clinical pharmacists

prescribe more effectively—and, therefore, reduce drug costs while improving blood pressure control. Furthermore, health care utilization information, which includes hypertension-related emergency room visits and hospitalizations, needs to be gathered to evaluate total costs associated with treatment of hypertension. This information will assist in determining the overall value of clinical pharmacists as a possible solution to the public health issue associated with poorly controlled hypertension in the U.S.

Specific Aims

Despite medical awareness and the availability of numerous antihypertensive medications, hypertension is not well controlled in the United States. Hypertension affects approximately 50 million American adults, one-third of whom are unaware of their condition (Vivian, 2002). An untreated hypertensive patient is at higher risk of experiencing a disabling or fatal event—such as heart attack, stroke or renal failure—than those who do not have high blood pressure (Merck Manual, Arterial Hypertension, 2005). Fortunately, effective control of blood pressure prevents or forestalls complications, and prolongs life in patients with systolic or diastolic hypertension.

Numerous papers have suggested that clinical pharmacists can be valuable team members in the management of many chronic conditions, including hypertension. Specialty-trained clinical pharmacists work in collaboration with primary care practitioners to decrease the prevalence of untreated and uncontrolled hypertension. A systematic review of the role of the clinical pharmacist in the management of chronic illness suggested several areas warranting further investigation, including, but not limited to, delineation of the costs and the effects of pharmacist intervention (Beney et al., 2002).

Providence Primary Care Research Network in Oregon attempted to address several of these areas by conducting a randomized controlled trial to evaluate the effectiveness of collaborative drug therapy management by clinical pharmacy specialists in patients with poorly controlled hypertension. Providence's study, "The Impact of Clinical Pharmacy Specialists in Management of Uncontrolled Hypertension," compared the collaborative pharmacy model with the usual care provided by primary care practitioners (Hunt, 2005).

To evaluate the impact of the involvement of a clinical pharmacy specialist on blood pressure control in patients with hypertension, Providence provided data for this thesis project. The thesis will achieve the following aims:

A. Evaluate the effectiveness of collaborative drug management of hypertension by clinical pharmacists compared with usual care practice. The primary outcome is attainment of a blood pressure target of 140/90 mm Hg, or below, at final assessment 12 months following randomization (while statistically adjusting for baseline concomitant variables);

B. Evaluate the effectiveness of collaborative drug management in hypertension by clinical pharmacists compared with usual care in secondary outcomes: medication compliance, patient satisfaction, quality of life score, patient hypertension knowledge, and blood pressure monitoring at home;

C. Evaluate the effect of a demographic imbalance introduced by the patients' withdrawal from the study.

Background and Significance

Hypertension continues to be a common condition in the general U.S population and worldwide. The age-adjusted prevalence of hypertension in Sweden and Italy was found to be 38 percent, 42 percent in England, 47 percent in Spain, 55 percent in Germany, and 27 percent in the United States and Canada (Wolf-Maier, 2004). Nearly one in four Americans have hypertension, which is the most common chronic condition prompting a visit with a healthcare provider.

The World Health Organization (WHO) recently concluded that hypertension is the most common attributable cause of preventable death in developed nations and, increasingly, a risk factor in developing countries (Elliot, 2004). Elevated blood pressure levels are positively and continuously related to risk of cerebral hemorrhage and infarction, as well as risk of major coronary heart disease (CHD) events such as fatal and nonfatal myocardial infarctions. The increased risks of heart failure and of renal disease have also been observed to be associated with hypertension. There is evidence that patients with a history of hypertension have at least a six-fold greater risk of heart failure than do individuals without such a history (WHO, 1999). Fortunately, decreasing high blood pressure through lifestyle management and pharmacotherapy does decrease the risk of negative events. For example, a sustained 5 mm Hg decrease in diastolic blood pressure is associated with a 35–40 percent decrease in the risk of stroke (WHO, 1999).

An analysis of the National Health and Nutrition Examination Survey (NHANES) data from 1999–2000 demonstrated that only 69 percent of hypertensive respondents were aware of their condition; 58 percent were treated, and 31 percent were controlled (Hajjar, 2003). This study suggests that hypertension remains an important public health problem and presents significant public health implications. In recognition of this public health crisis, hypertension target goals were established by the U.S. Department of Health and Human Services as part of Healthy People 2010 (Office of Public Health and Science, 2000). Cost-efficient and clinically effective interventions need to be developed and implemented to reach the Healthy People 2010 goal of 50 percent of hypertensives with blood pressure at 140/90 mm Hg.

There are numerous challenges to overcome to reach the Healthy People 2010 target goals for hypertension. A recent article by Hyman and Pavlik examined the NHANES III data and found that most cases of uncontrolled hypertension occur in patients who are older than 65 years, with good access to health care, and relatively frequent contact with physicians. It has been suggested that poor blood pressure control is a result of several factors including practitioner's visit time constraints, the practitioner's failure to prescribe lifestyle modifications, administer an adequate antihypertensive drug dose, or choose the appropriate drug combinations (Chobonian et al., 2003, Barter et al, 2003). Overcoming these barriers will require a focused intervention by healthcare providers with innovative and effective approaches directed at the populations at risk. Lifestyle modifications recommended by healthcare providers through health education, and appropriate pharmacological treatment are critical components of blood pressure treatment and control (Chobonian et al., 2003).

Clinical pharmacists are an important part of the healthcare delivery system and represent one available healthcare provider with the knowledge and training to assist patients and physicians in the management of hypertension. The sixth report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC VI) states that, "pharmacists should be encouraged to monitor patients' use of medications, to provide information about potential adverse effects, and to avoid drug interactions" (Joint National Committee, 1997). Clinical pharmacists, particularly those who pursue residency training, receive extensive training on blood pressure assessment and use of antihypertensive agents, with respect to efficacy, cost, and adverse effects. In the management of hypertension, clinical pharmacists select the appropriate treatment to

maximize clinical benefits (Okamoto et al., 2001). Several studies have demonstrated the effect of a clinical pharmacist's contribution in the management of hypertensive patients resulted in improved blood pressure control, as well as reduced potential drug interactions, unnecessary hospitalizations, and emergency room visits. Okamoto and colleagues reported significantly lower blood pressure measurements in a pharmacist-managed hypertension clinic compared with a physician-managed clinic during a six-month study. Moreover, patient satisfaction was significantly higher in the intervention group (Okamoto et al., 2001). Research by Bogden and others reported that subjects managed by pharmacists were significantly more likely to achieve the JNC-VI national goal compared with the usual care group (55 percent versus 20 percent) (Bogden et al., 1998). Mehos reported that, at a six-month follow-up appointment, only 22 percent of those in the control group had blood pressure measurements below 140/90 mm Hg, compared with 44 percent of the intervention patients (Mehos et al., 2000). Erickson and colleagues in a controlled study demonstrated significant decreases in mean blood pressure for the intervention group receiving drug management assistance from the pharmacists from baseline to final assessment, and non-significant changes in mean pressures in the control group that did not receive pharmacotherapy intervention (Erickson et al., 1997). A systematic review of the role of clinical pharmacist in the management of chronic illness, suggested several areas warranting further investigation, including:

- Delineate the cost, as well as the effect of pharmacist intervention
- Compare pharmacist intervention with care delivered by other healthcare providers

- Evaluate pharmacy interventions beyond a single site
- Provide a better assessment of adverse drug reactions and quality of life (Beney et al., 2002).

The Impact of Clinical Pharmacy Specialists in Management of Uncontrolled Hypertension study conducted by Hunt and colleagues at Providence Primary Care Research Network in Oregon attempted to evaluate the impact of adding pharmacy practitioners to the hypertension treatment team in a large, controlled multi-site intervention study. Clinical, economic and quality of life outcomes were measured for those receiving clinical pharmacist care, and compared with usual care provided by primary care practitioners alone. The Providence research team conducted a preliminary analysis, the goal of which was to evaluate the difference in mean blood pressure between patients receiving usual care and patients managed by a clinical pharmacy specialist (Hunt, 2005). In this thesis, this analysis was extended by: (1) evaluating the effect of clinical pharmacists' intervention on patients' achievement of the blood pressure target while controlling for baseline concomitant variables, (2) completing patients' quality-of-life analysis, (3) conducting thorough between-group and within-group analysis for the secondary outcomes including medication compliance, hypertension knowledge, patient satisfaction, and prevalence of blood pressure monitoring at home, and (4) determining if the high subject withdrawal rate from the study could bias study findings.

Subject withdrawal is a common phenomenon in clinical trials involving pharmacotherapy evaluations and longitudinal assessments for a fixed duration of follow-up (Gillum et al., 1979). It is common in clinical trials to be challenged with missing data

because patients drop out, die, withdraw (actively or passively), fail to complete certain study forms, and many other reasons. A major source of bias in trials can arise from patients who withdraw during the course of the trial (Murray et al., 1988), as those who withdraw may have different characteristics than those who complete the entire study. This is true for hypertension trials such as the one analyzed here. To make unbiased comparison between the intervention and control groups, it was important to thoroughly evaluate the issues of withdrawal, particularly because the proportion of people who withdrew varied between the study arms. Therefore, an additional analysis was completed to identify factors that are most predictive of a patient's decision to withdraw from the study and possibly to adjust for those in the analysis of the intervention effect.

In summary, hypertension is a common problem in U.S., affecting 27 percent of the adult population. Clinical pharmacists may be an untapped resource in assisting patients to manage their condition. This study evaluated the effectiveness of collaborative drug management of hypertension by clinical pharmacy specialists as compared to usual care in achieving blood pressure target of 140/90 mm Hg and improving other secondary outcomes

Research Design and Methods

Study Design

The Providence hypertension study was a prospective, randomized, controlled trial conducted in 2000–2001. According to randomization scheme, each participant had an equal chance of being assigned to an intervention or a control group. Baseline demographic and clinical characteristics of participants were distributed equally in the

experimental and control groups. This was an important feature allowing for control of risk factors that potentially could confound the relationship between intervention effect and outcome.

The study was conducted within the Providence Primary Care Research Network in Oregon (Providence Research Network, 2005). Network clinics participating in the study comprised approximately 80 internal medicine and family practice providers caring for approximately 110,000 patients in nine clinic locations. All nine participating Research Network clinics utilize Logician®, a standardized electronic medical record (EMR), to facilitate and document all patient care activities.[1]

The Providence institutional review board (IRB) approved the original Providence study. All enrolled patients provided verbal informed consent in an IRB-approved format.

This thesis used the main features of the original randomized intervention study. However, one of the study arms (group education) was not considered for analysis. The Oregon Health & Science University institutional review board approved this thesis project.

Study Population

The study population for the Providence hypertension study was identified from the Logician® database using the following criteria:

- active patients with documentation of an office visit within the past two years;
- age 18 years or older;

[1] Logician® is an electronic medical record system that enables ambulatory care physicians and clinical staff to document patient encounters, streamline clinic workflows, and securely exchange clinical data with other providers, patients, and information systems.

- documented diagnosis of hypertension on the problem list[2] based on ICD-9-CM[3] codes of 401.x .

The study population was stratified into two groups according to the JNC-VI blood pressure classifications as following:

- Patients with a last systolic blood pressure of 160 to 179 mm Hg and/or diastolic blood pressure of 100 to 109 mm Hg (Stage 2 hypertension)

and

- Patients with a last systolic blood pressure of greater than, or equal to, 180 mm Hg; or diastolic blood pressure greater than, or equal to, 110 mm Hg (Stage 3 hypertension).

Subjects were excluded prior to randomization for any of the following conditions: (a) being disenrolled from the medical group, (b) the primary care provider (PCP) excluded the patient, (c) the patient refused to participate, or (d) there was no blood pressure reading in the chart in the two years prior to the EMR query. To limit contamination, subjects were excluded if they or their spouse were enrolled in another hypertension study. A small percent of subjects was excluded after randomization based on the following conditions: death, transfer of care, disconnected phone, or a previous visit with clinical pharmacist identified from chart review. Eighteen subjects (8 percent) from the usual care group and 23 subjects (10 percent) from the pharmacist group were excluded after randomization. Figure 1 displays patient allocation in the study.

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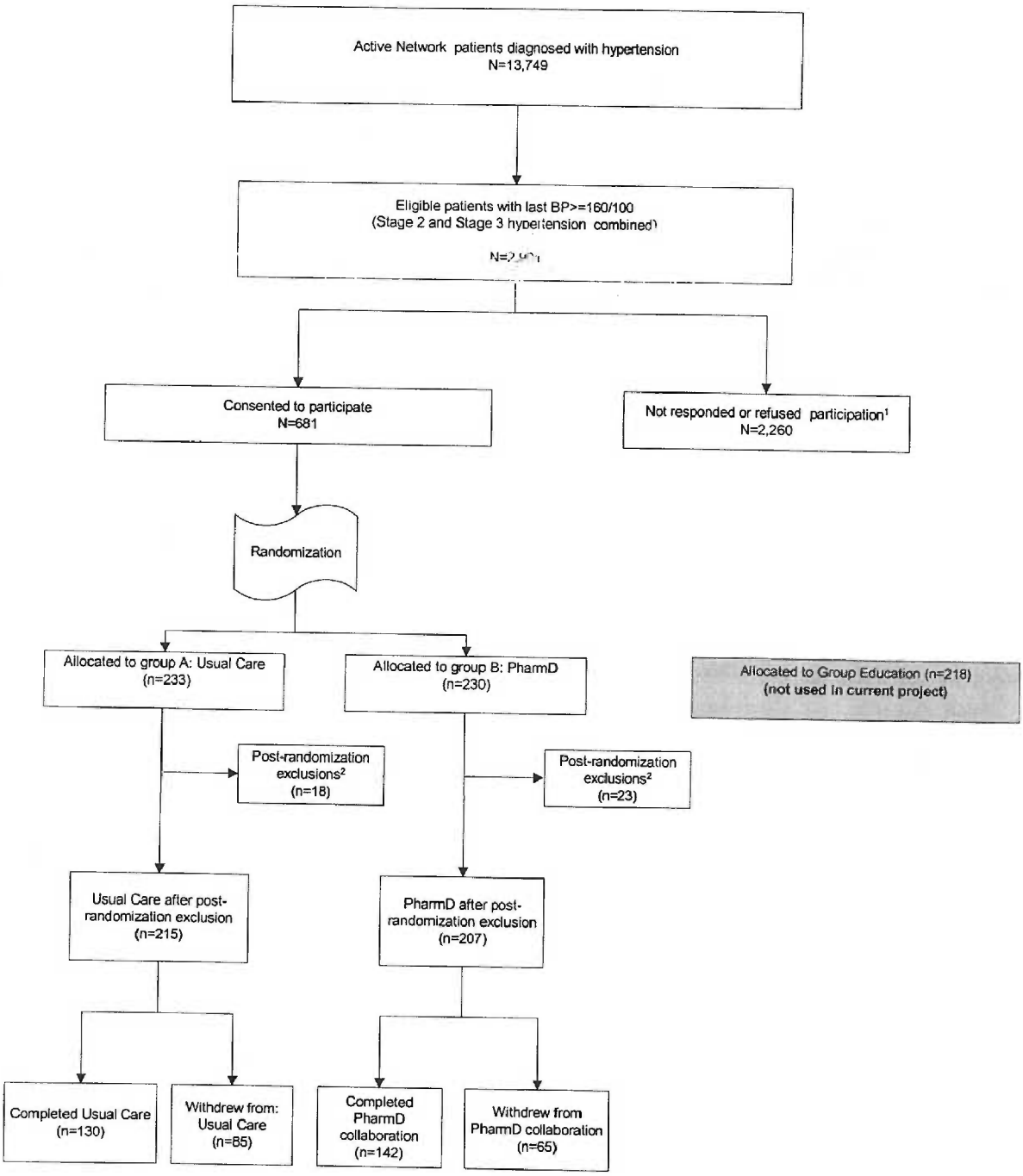
[2] Problem lists are generated and maintained through physician entry of patient diagnosis, analogous to the traditional paper chart. Problem list entries are stored in a searchable format, based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) system.

[3] *Internal Classification of Disease, ninth edition, clinical modification*

Figure 1. Patient population eligibility, participation and randomization flow diagram



[1] Subjects who refused participation by phone or did not return the consent card.
[2] Reasons for post-randomization exlcusions: transferred care, death, disconnected phone, or previous visit with clinical pharmacist.

Patients with hypertension stages 2 and 3 were combined for the purpose of this study. Therefore, the thesis population was defined as patients with a last systolic blood pressure ≥160 mm Hg and/or a last diastolic blood pressure ≥100 mm Hg, with the exclusions outlined above (Figure 1).

Initial Randomization

All eligible patients received a series of educational mailers and a Providence IRB-approved invitation for participation. Patients not responding to the letter were contacted by phone. The patients who responded positively by phone or returned the IRB-approved consent card were randomly assigned, with equal allocation, to one of the study groups receiving the following:

(A) usual care from a PCP who has received hypertension education, treatment guidelines, and a list of patients with blood pressures fitting the study inclusion criteria

(B) collaborative drug therapy management by a clinical pharmacist in addition to the usual care delivered by a PCP.

Stage 2 and 3 subjects were followed for 12 months (+/-3 months) following randomization. Another group of patients that was allocated into a group education study arm was not evaluated in this paper.

Thesis Intervention Subgroups

Randomization was completed separately for stage 2 and stage 3 patients in the Providence hypertension study; this paper, however, combined equivalent intervention groups from two stages for a comprehensive assessment of the intervention impact across stage 2 and stage 3 hypertension groups.

Providence Study Interventions

All patients received a series of education mailers. Subjects allocated to the usual care arm were instructed to continue their normal schedule of care. Patients with a blood pressure reading of ≥180/110 mm Hg, based on last measurement in the EMR, were given an appointment with their primary care provider if one did not already exist.

Patients allocated to the pharmacy practitioner intervention group had an initial appointment scheduled with one of five clinical pharmacy specialists employed by Providence Medical. Appointments with the pharmacists occurred in the patients' primary care clinics. During the initial visit, the clinical pharmacist reviewed the medications, provided hypertension education, screened for adverse drug reactions and interactions, and optimized the regimen to meet the needs of the patient according to signed guidelines. At the end of each clinic visit, a note documenting the interaction was placed in the EMR and forwarded to the primary care provider for co-signature.

Providence Hypertension Study Data Collection

The Providence hypertension study data collection was completed using a standardized questionnaire. The hypertension-specific questionnaire was developed by the study investigators to evaluate patient views on their own health, blood pressure, hypertension self-management progress, basic knowledge of hypertension, self-reported medication compliance, and satisfaction with different aspects of hypertension care (Hunt, 2005). Demographic data obtained for each patient from the EMR and this hypertension survey were date of birth, gender, marital status, height, educational level, ethnicity, estimate of the total household income, comorbidities, insurance status, and smoking status.

The patients' health status was evaluated based on the Medical Outcomes Study (MOS) SF-36 survey questions (Ware et al., 2001). The SF-36 is one of the most widely used generic measures of health status and has shown to be a reliable and valid quality-of-life assessment tool in many populations, including hypertensives (Ware, 2000). Patient satisfaction questions were derived from the previous satisfaction surveys commonly used in primary care medical group practice. The assessment of medication compliance consisted of four validated questions. Morisky et al. (1986) demonstrated the concurrent and predictive validity of these questions with regard to blood pressure control. Seventy-five percent of the patients who scored high on the four-item scale had their blood pressure under adequate control compared with 47 percent with blood pressure under control for patients scoring low (Morisky et al., 1986). The study investigators constructed a hypertension knowledge quiz to assess patients' understanding of hypertension and the principles of self-management.

The self-administered survey questionnaire was tested for readability, face and content validity with local experts, and for and internal validity in a sample of patients. The participants completed the survey twice during the study. The baseline survey was completed at home and mailed back to the investigator when the study was initiated (stage 2 patients), or completed in the office at the time of the first visit with pharmacist or PCP (stage 3 patients). The final assessment was completed by the study participants at the clinic during the exit interview.

Thesis Data Management and Scoring Methods

A Microsoft Access database was developed by Providence research team to enter and store the hypertension study data. A data entry form was created to facilitate accurate and simple data entry. However, due to the lack of built-in validation rules and accuracy checks, data entry errors were not prevented. Therefore, intensive data cleaning and recoding was necessary before a meaningful analysis was possible.

Patient smoking status was coded in two different ways. First, smoking survey responses were collapsed into three categories: "never smoked," "quit," or "smoker." Second, the variable was coded as a combination of responses from the survey and the current smoking status information from Logician with only two possible responses: "current smoker," and "otherwise."

Income categories were combined into four subgroups, patients with a total annual household income: (1) of less than $20,000; (2) from $20,000 to $40,000; (3) greater than $40,000 to $60,000; and (4) greater than $60,000.

Due to an insufficient number of patients in African American, American Indian, Native Alaskan, Hispanic, or Asian ethnic categories, self-reported race and ethnicity was recoded into two categories of "white" and "other." Marital status responses were recoded into a non-married category (e.g. divorced, separated, etc.) and married, based on the self-reported survey data.

Self-reported educational levels were also regrouped into three sufficiently sized categories of (1) those with less than a high school diploma, (2) high school graduate or equivalent, (3) and some college, college graduate, or above.

In addition, an ordinal variable was created based on the number of chronic conditions the patient reported having: diabetes, asthma or chronic obstructive pulmonary disease (COPD), stroke, coronary artery disease (CAD), or renal impairment. Patients were scored 0 for no co-morbidities, 1 for presence of one condition, 2 for two conditions, and 3 for presence of three or more chronic conditions. The body-mass index (BMI) measuring height to weight ratio, was calculated as patient's weight in kilograms divided by the square of patient's height in meters.

Assuming that most of the patient demographics characteristics (e.g., gender) would not change from the baseline period to the one-year final assessment, the demographic data missing in the baseline survey responses were replaced by data from the final assessment survey if the information was provided by the patients during the exit interview.

Measuring Primary Outcome

The clinical effectiveness of the intervention was defined by achievement of the blood pressure target goal of 140/90 mm Hg or lower at final assessment. Therefore, the primary outcome measure was the proportion of patients achieving the blood pressure target goal of 140/90 mm Hg or lower at the final assessment one year after study initiation. At the final assessment visit, the patient's blood pressure was evaluated in the primary care office by a registered nurse recently exposed to updated training in blood pressure measurement. The study was blinded so the nurse was unaware of subjects' randomization allocation. Three blood pressure measurements were taken with no less than five minutes, and no more than ten minutes, between measurements. The results of

the second and third measurements were averaged to give a final blood pressure value that used for this analysis.

The blood pressure readings retrieved from the EMR to identify the study population were used as baseline values for the study. These blood pressure values were recorded in the EMR based on an assessment by a medical assistant, administered during the course of a busy clinic schedule. Blood pressure measurements were not repeated, thus only one baseline reading for each subject was available for the study. Due to differences in quality and measurement, we did not attempt to record change in blood pressure over time, and restricted our outcome of interest to proportion in each group achieving target goals at 1-year follow-up.

Medication compliance. Overall compliance to the prescribed medications was measured by patient responses to four questions concerning their usual patterns of medication taking:

(1) Do you forget to take your medicine?

(2) Are you careless at times about taking your medicine?

(3) When you feel better do you sometimes stop taking your medicine?

(4) If you feel worse when you take the medicine, do you stop taking it?

The range of possible scores was 0 to 4, in which 4 points represented high medication compliance. A high compliance flag was assigned if a subject answered 'No' to all four questions. A medium compliance category was based on responding 'Yes' to one or two of the questions. A low compliance category was assigned if a subject responded 'Yes' to three or more questions. Preliminary data analysis revealed a small

number of respondents in the low compliance category. Therefore, the low and medium compliance categories were collapsed into one category for the purpose of this paper.

Patient satisfaction. Patient satisfaction was assessed for all patients receiving a survey at baseline and during an exit interview. Patients were asked to rate their satisfaction with 11 different components of healthcare and the treatment of hypertension on a scale from 0 to 10 in which 0 indicates lowest satisfaction and 10 indicates highest satisfaction. Overall satisfaction was evaluated at baseline and final assessment with a calculation of mean satisfaction levels across all components per subject.

Patient Quality of Life (QOL). Patient QOL was evaluated at baseline and final assessment one year later using the SF-36® battery of questions which yielded an eight-point scale profile of scores as well as physical and mental health summary measures. The SF-36 questions measured the health concepts or domains of physical functioning such as:

(1) limitations performing daily physical activities,

(2) physical health,

(3) bodily pain,

(4) general health perceptions,

(5) vitality (energy and fatigue),

(6) social functioning,

(7) emotional well being, and

(8) mental health domain.

The answers were scored based on the SF-36 manual and interpretation guide (Ware et al., 2001) using SAS analytic algorithm (Hays, 1997). The SAS code derived

the eight SF-36 scales as well as the SF-36 physical and mental health composite scores. The scoring was a multi-step process. First, each item was scored on a 0 to100 range so that the lowest and highest possible scores were set at 0 and 100, respectively. The scores represented the percentage of total possible scores achieved. Second, items in the same scale were averaged to create the eight-subscale scores. Then, all eight-subscale scores were standardized using a linear *z*-score transformation. *Z*-scores were calculated by subtracting subscale means from the general U.S. population sample from each individual's subscale scores and dividing the difference by the standard deviation of the U.S. sample. The *z*-scores were multiplied by the subscale factor score coefficients to calculate the physical component summary (PCS) and mental component summary (MCS), and summed over all eight subscales. Finally, *t*-scores were calculated by multiplying the obtained PCS and MCS sums by 10 and adding the resulting product to 50, to yield a mean of 50 and a standard deviation of 10 for the U.S. norm population. Conceptually the PCS reflects physical morbidity and etiology, whereas the MCS reflects psychological and mental morbidity and etiology. A very high PCS score requires more than freedom from physical limitations and role disability; it requires an evaluation of current health as "excellent". The same logic is reflected in the scoring of the MCS (Ware et al., 2001).

Patient hypertension knowledge. A hypertension knowledge quiz assessed patients' basic understanding of hypertension and self-management. The quiz was validated and used in a previously published study (Hunt et al., 2004). Patients' knowledge was assessed at baseline and final assessment using a set of the 10 questions from the hypertension health survey. An aggregate score was calculated based on the

number of correctly answered questions at baseline and final assessment with the range of possible scores as 0 to 10 in which 10 points represented a perfect score. The principal investigator of the Providence Hypertension Study provided the key of correct responses for scoring.

Home blood pressure monitoring. Patients were asked whether they used a sphygmomanometer to monitor their blood pressure at home. They were also asked whether they recorded or charted their blood pressure readings with possible answers of yes or no.

Statistical Analysis

Descriptive statistics were used to compare baseline demographic variables in intervention and groups. Continuous variables were described by means and standard deviations, while categorical variables were described using percentages. The differences in the proportion of patients who achieved the blood pressure target goal of 140/90 mm Hg or lower in each intervention group was evaluated using the χ^2 test of homogeneity from 2x2 contingency tables. Contingency tables and the χ^2 test of homogeneity were also used to evaluate association between independent categorical predictors and the outcome. Contingency tables were also used to evaluate the effect of random assignment on producing control and intervention groups that were similar when the study began and the effect of participant withdrawal from the study.

An intention-to-treat analysis was also used to compare the study groups with respect to achieving the blood pressure target goal, regardless of whether participants actually stayed in the study. Although the intention-to-treat analysis may underestimate

the full effect of the intervention, it attempts to guard against biased results in clinical trials (Hulley et al., 2001).

Analysis of Blood Pressure Response

To address the first research aim, a logistic regression model was built to evaluate the effectiveness of collaborative drug management of hypertension compared with usual [illegible] care [illegible]. Achievement of the blood pressure target goal of 140/90 mm Hg or lower was the dependent, or response, variable in the model. In a controlled experiment, the primary investigator controls the levels of the explanatory variables, assigns a treatment to each experimental unit, and observes the response. In this study, the control variable was the experimental group, to which the study participants were assigned. To adjust statistically for some baseline differences between the groups, the following supplemental factors were investigated for inclusion in the model: gender, smoking status, educational level, total household income, marital status, and others.

To assess the fit of the model, overall measures of fit were examined. The value of the Hosmer-Lemeshow goodness-of-fit statistic was calculated based on the deciles-of-risk of the approach. The tested null hypothesis is that the observed and the expected values were close (Hosmer and Lemeshow, 2003).

Analysis of Secondary Outcomes

To address the second research aim, evaluating the effectiveness of intervention with regard to secondary outcomes, several approaches were employed.

Repeated measures analyses of variance were used to evaluate continuous variables such as patient satisfaction, hypertension knowledge, and quality-of-life

composite scores. A principal advantage of repeated measures analysis is that it provides good precision for comparing treatments (i.e. baseline and final assessment) because all sources of variability between subjects are excluded from the experimental error. Only variation within subjects enters the experimental error, since two treatments can be compared directly for each subject. Thus, the subjects can be viewed as serving as their own controls (Neter et al., 2002). These analyses were completed using GLM procedure in SAS version 9.1 (SAS Institute).

To model binary variables such as medication compliance, repeated measures analysis with the generalized estimating equations (GEE) method was used (Diggle, 1999). The GEE approach estimates the population-averaged estimates while accounting for the dependency between the repeated measures. The dependency or correlation between repeated measures is taken into account by robust estimation of the variances of the regression coefficients. The GEE approach treats time dependency as a nuisance and specifies a "working" correlation matrix for the vector of repeated observations from each subject to account for dependency among the repeated observations. The "working correlation" is assumed to be the same for all subjects, reflecting average dependence among the repeated observations over subjects (Hu et al., 1998). The GENMOD procedure in SAS version 9.1 was used to complete this analysis (SAS Institute).

In addition to the repeated measures analyses, between-group and within-group analyses were conducted separately. Between-group analysis for categorical variables such medication compliance was completed using contingency tables and the χ^2 test of homogeneity. Within-group baseline-to-final assessment comparisons for medication compliance were completed using the McNemar test for paired proportions. The null

hypothesis is that paired proportions are equal. The McNemar test follows a χ^2 distribution with one degree of freedom.

Between-group analysis for continuous variables such as patient satisfaction, age, and quality-of-life composite scores were analyzed using the Student's *t*-test for independent samples. Within-group comparisons for these continuous variables were analyzed with paired *t*-tests.

The *t*-test required that three assumptions be met: normality of the two groups being compared, homogeneity of variance for the groups, and independence of the groups as established through the randomization procedure. If one or more of the assumptions for the *t-test* were violated (e.g., a score is not normally distributed) a nonparametric alternative to the *t*-test was used. The Mann-Whitney U test, also called Mann-Whitney-Wilcoxon rank-sum test, was used for between-group comparisons of patient hypertension knowledge that was not normally distributed. The null hypothesis tested is that the mean ranks are equal in the two groups. If the mean ranks are equal, the groups are similar. The sign test for paired samples was used for within-group comparisons of patient hypertension knowledge (Dawson-Saunders, 1994). To compare baseline and final assessment knowledge score, the difference between the two measurements was created.

Analysis of Withdrawal Determinants

To address the third research aim, a logistic regression model was built to determine factors most predictive of a patient's decision to withdraw from the Providence hypertension study. Of the 422 patients across both intervention and control groups, 150 people withdrew from the study after randomization but before follow-up was completed.

To investigate this phenomenon further and statistically adjust for its effect in the analysis of the intervention effectiveness, a group of demographic and co-morbid characteristics was analyzed. The following variables were included in the model: insurance type, gender, systolic and diastolic blood pressure, asthma or COPD, CAD, patient's smoking status, history of stroke, age, diabetes, and renal impairment. All data were retrieved from the EMR problem list with an exception of the patient's smoking status The patient's smoking status was coded as a combination of responses from the survey and data from EMR. Asthma or COPD, CAD, diabetes, stroke, and renal impairment were coded as "yes" or "no" variables with yes indicating the presence of a condition and no indicating the absence of a condition. The patient's insurance type was coded with 1 for commercial coverage and 0 for Medicare, Medicaid, or self-insured status. The rationale for combining Medicare, Medicaid, and self-insured into one category was supported by a low representation of Medicaid (3 subjects or 0.7 percent) and self-insured (5 subjects or 1.2 percent) subjects in the sample. A univariate analysis was used to assess the association between a patient's decision to withdraw and independent predictors. The results obtained from the univariate analysis assisted in the process of building a logistic regression model to evaluate factors most predictive of patients' decision to withdraw. Any variable whose univariate test had a p-value <0.25 was a candidate for the multivariate model. To evaluate scaling of all continuous variables, the quartiles were calculated using a SAS ranking procedure. In addition, a smoothed scatter-plot was examined to assess whether continuous variables are linear in the logit. A smoothed scatter-plot for the age variable showed that age was nonlinear in the logit and, therefore, was categorized into the quartiles. The smoothed logit and

quartiles method supported treating systolic blood pressure as a continuous linear variable in the logit.

The significance level was set at 0.05. SAS version 9.1 (SAS Institute) was used to complete all statistical analyses for this paper.

Power analysis. The initial power analysis was completed when the Providence hypertension study was designed. A total sample size of 302 subjects was required to detect a 4 mm Hg difference in mean systolic and mean diastolic blood pressures between intervention and usual care groups for 90 percent power at a significance level of $p<0.05$ (two-sided), assuming a standard deviation for systolic and diastolic blood pressures of 8 mm Hg. A power analysis was completed for the thesis on the basis of the sample size available for analysis. Sample sizes of 272 subjects provided a power of 80 percent to detect a 15 percent group difference in achieving the blood pressure target goal between the study groups, assuming a 0.05 level of significance.

Results

Baseline Demographics

From the total population of patients with hypertension eligible for the study, 681 patients consented to participate in the study (439 with stage 2 and 242 with stage 3 hypertension). After randomization was completed, 233 patients were assigned into the PCP usual care group and 230 patients were assigned to an intervention group (stage 2 and stage 3 combined). After post-randomization exclusions and withdrawals, 130 patients remained in the study's PCP usual care group and 142 patients remained in the intervention group (Figure 1, page 11).

Table 1 shows the baseline demographic characteristics and comorbidities of the study participants before and after withdrawal from the study. The intervention and control groups were comparable at baseline (before withdrawal) for age, gender, body mass index, insurance status, and comorbid conditions. The only statistically significant difference seen was in the patients' history of strokes. The subjects in the pharmacist group were slightly more likely to have had a history of stroke (7 percent compared with 2 percent, p=0.03) (Table 1)

A comparative analysis of the baseline patient demographics and comorbid conditions between groups for subjects who completed the study (after withdrawal) is also presented in Table 1. There was some imbalance with regard to some demographic and socioeconomic characteristics, and co-morbid conditions. The pharmacist-managed group had more males, more married patients, more patients with college degrees, more patients with diabetes and heart disease, and fewer patients without the chronic conditions listed above; but none of the differences were statistically significant at the 0.05 level.

After withdrawal from the study, the overall sample had the following demographic profile: fewer males with hypertension participated in the study compared with female participants (35 percent as compared to 65 percent). Of the total study participants, 65 percent were married. One third of the sample had a college degree or post-graduate education. Approximately 30 percent of the study participants reported a total family income of $20,000 or less.

Table 1. Baseline demographic characteristics for eligible population before and after withdrawal[4]

	Before Withdrawal			After Withdrawal		
	Usual Care (n=215)	Pharmacist Group (n=207)	p-value	Usual Care (n=130)	Pharmacist Group (n=142)	p-value
Age, mean (SD)	68 (13)	69 (12)	0.78	68 (13)	69 (12)	0.52
Male (%)	35	37	0.59	31	38	0.21
Ethnicity (%)						
White	NA	NA		95	93	0.56
Body mass index, mean (SD)	31 (7)	30 (6)	0.39	30 (7)	30 (6)	0.98
Married (%)	NA	NA		61	69	0.23
Education (%)						
Less than a high diploma	NA	NA		7	9	0.60
High school graduate or some college				65	59	
College graduate or above				28	32	
Family income (%)	NA	NA				
$0–19,999				29	25	0.38
$20,000–39,999				29	36	
$40,000–59,999				24	17	
$60,000 or more				18	22	
Commercial insurance (%)	30	34	0.43	29	28	0.85
Asthma or COPD (%)	11	12	0.77	9	12	0.46
Current smoker (%)	8	10	0.52	6	6	0.86
Diabetes (%)	24	25	0.73	21	27	0.19
History of stroke (%)	2	7	0.03 *	2	6	0.16
Coronary artery disease (%)	18	21	0.42	18	22	0.39
Renal impairment (%)	3	3	0.72	2	3	0.47
Chronic conditions (%)						
0	56	53		59	54	
1	32	31		31	28	
2	10	12		8	12	
3	2	4	0.47	2	6	0.17

* Statistically significant difference ($p<0.05$). NA represents variables collected only among subjects who completed the hypertension survey. Therefore, data are not available for subjects who withdrew from the study.

[4] After post-randomization exclusions

Determinants of Withdrawal from the Study

To evaluate the effectiveness of pharmacists' intervention and make unbiased comparisons between the study groups, it was important to evaluate the issues of withdrawal particularly because the proportion of withdrawals varied between the study arms. Therefore, to address the third research aim, the analysis was completed to identify factors that were most predictive of a patient decision to withdraw from the study and possibly to adjust for those in the analysis of the intervention effect. Proportionally more subjects withdrew from the usual care group than from the pharmacist-managed group (40 percent compared with 31 percent). This association was marginally significant (p=0.08) (Figure 2).

Figure 2. Percentage of participation and withdrawal from study in intervention and control groups

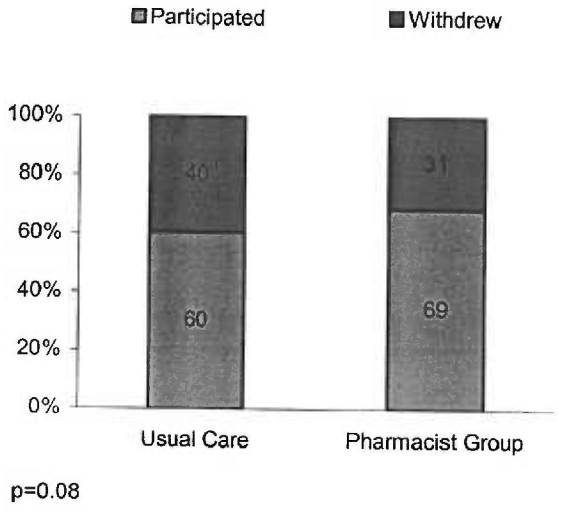


Table 2 shows the association of withdrawal status with selected demographic and clinical characteristics. Among the categorical characteristics, only patients' smoking status and type of insurance were significantly associated with patients' decision to

withdraw from the hypertension study. Smokers were more likely to withdraw from the study than nonsmokers (57 percent as compared to 34 percent, $p<0.01$). Medicare and/or Medicaid beneficiaries were less likely to withdraw from the hypertension study than those with commercial coverage (32 percent compared with 42 percent, $p=0.04$). No significant association was found between chronic conditions and participants' decision to withdraw from the hypertension study.

Table 2. Association between withdrawal from the Providence hypertension study and selected demographic and clinical characteristics[a]

Variables	Likelihood Ratio Chi-square	p-value	Significant
Intervention arm	3.05	0.08	
Gender	0.30	0.57	
Asthma or COPD	0.17	0.67	
Diabetes	0.01	0.92	
Smoking	7.58	0.01	*
Type of insurance	3.82	0.04	*
CAD	0.21	0.64	
Stroke	0.36	0.54	
Renal impairment	1.87	0.17	
Number of chronic conditions	2.95	0.40	

[a] All characteristics are compared to χ^2 with one degree of freedom except the number of chronic conditions (2 degrees of freedom).

Table 3 shows the association between continuous variables and withdrawal from the study. People who withdrew from the study were, on average, younger than people who completed; though statistical significance was not reached (66.7 years as compared to 68 years, $p=0.24$). With regard to blood pressure, there was a marginally statistically significant difference in the baseline mean systolic blood pressure between patients who completed the hypertension study and patients who decided to withdraw. People who withdrew, on average, had a higher systolic blood pressure (176 mm Hg mean systolic

blood pressure for withdrawals as compared with 173 mm Hg mean systolic blood pressure for those who stayed, p=0.05).

Table 3. Association between withdrawal from the Providence hypertension study and selected demographic and clinical variables

	Withdrew	Completed	p-value	Significant
	Mean	Mean		
Age	66	68	0.24	
Baseline systolic blood pressure	175	172	0.05	*
Baseline diastolic blood pressure	92	90	0.33	

Insurance status was highly associated with age: most of the younger people had commercial insurance and the majority of older people were covered by Medicare and/or Medicaid (p<0.0001) and, therefore, only age was included in the model.

Table 4 shows the results of the fitted best model evaluating predictors of withdrawal adjusted for the group randomization.

Table 4. Relationship between withdrawal and independent demographic and clinical characteristics

Parameter	OR	95% Confidence limits	p-value
Intervention group	0.69	(0.45, 1.04)	0.07
Baseline systolic blood pressure	1.01	(1.00, 1.03)	0.07
Smoking status	2.49	(1.21, 5.09)	0.01
Age quartiles 0 vs. 3	1.42	(0.79, 2.55)	0.24
Age quartiles 1 vs. 3	0.89	(0.50, 1.61)	0.71
Age quartiles 2 vs. 3	0.59	(0.32, 1.08)	0.08

Table 5. Odds ratios for 5-increment change in baseline systolic blood pressure

Effect	Unit	OR	95% Confidence limits
Baseline systolic blood pressure	5	1.06	(1.04, 1.19)

With a one-unit increase in baseline systolic blood pressure, the risk of withdrawal from the study increased 1.01 times. Scaling these results to more meaningful units: for every increase of 5 units in systolic blood pressure, the odds of withdrawal increase 1.06 times. The odds of withdrawal from the study among smokers were 2.49 times greater than among nonsmokers, and could be as low as 1.21 and as high as 5.09 with 95% confidence. The odds of withdrawal from the study decreased with an increase in age. In other words, the younger were the subjects the more likely they would withdraw from the study. However, a significance of this association was only marginal.

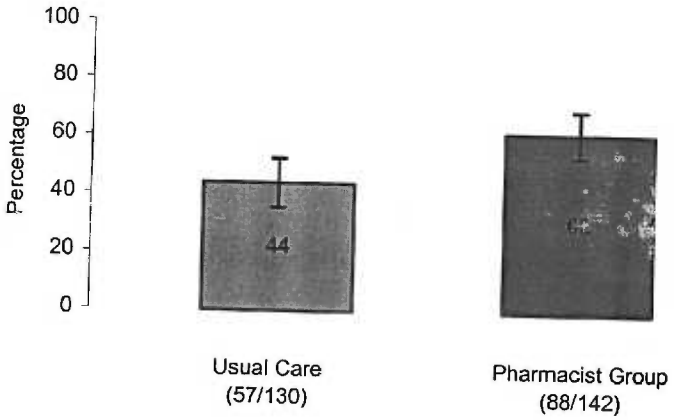
To assess the fit of the model, overall measures of fit were examined. The value of the Hosmer-Lemeshow goodness-of-fit statistic was calculated based on the deciles-of-risk approach. The null hypothesis tested here was that the observed and the expected values were close. Based on the overall measure of fit represented by the Hosmer-Lemeshow goodness-of-fit statistic (χ^2=9.48, df=8, and p=0.3), the model fit the data adequately. Although the model fit the data well, only a few variables were identified as significant predictors of patients' decision to withdraw from the hypertension study. None of the comorbidities (e.g. diabetes, CAD, etc.) were significantly associated with the patients' decision to withdraw from the hypertension study.

Intervention Effectiveness: Blood Pressure Response

This section of analysis addressed the first research aim. In the preliminary assessment of the crude differences between intervention and control groups in achieving blood pressure goals one year after enrollment in the study, more patients in the intervention group achieved blood pressure control than did patients in the control group (62 percent as compared to 44 percent respectively, p=0.0028) (Figure 3). The odds of

achieving the target goals of 140/90 in the pharmacy group were 2.08 times higher than in the usual care group (95% CI: 1.29-3.38, p=0.0028)

Figure 3. Between-group analysis examining the intervention effect on the percentage of patients who achieved target blood pressure goal



The results of the intention-to-treat analysis showed that blood pressure control was still favorably influenced by the pharmacist intervention: 43 percent of subjects achieved the target goal in the pharmacist group compared with 27 percent in the usual care group (p=0.0005).

Table 6 provides results of the best–fit model of the intervention effect with respect to target blood pressure goal controlling for gender, baseline systolic blood pressure, and insurance status.

Table 6. Results of logistic regression examining the effect of the intervention (odds of achieving the target blood pressure)

Parameter	OR	95% Confidence limits	p-value
Intervention group	2.13	(1.29, 3.53)	0.003
Gender (male vs. female)	0.63	(0.37, 1.07)	0.08
Baseline systolic blood pressure (per mm Hg)	0.98	(0.96, 0.99)	0.01
Insurance type (Commercial vs. Medicare/Medicaid)	1.68	(0.95, 2.97)	0.07

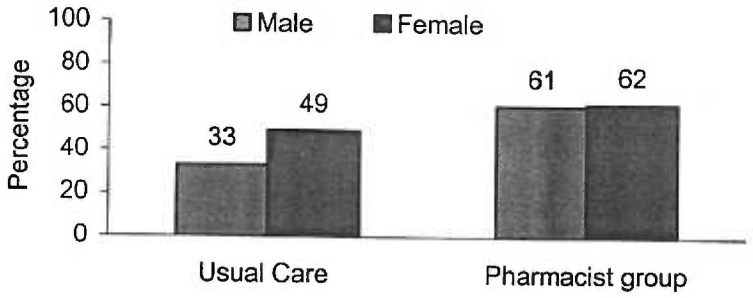
Table 6a. Odds ratios for 2 and 5-increment change in systolic blood pressure for achieving the target blood pressure

Effect	Unit (mm Hg)	OR	95% Confidence limits
Baseline systolic blood pressure	2	0.96	(0.93, 0.99)
Baseline systolic blood pressure	5	0.90	(0.83, 0.98)

The analysis results revealed the effectiveness of collaborative drug management of hypertension by a clinical pharmacist compared with usual care in achieving blood pressure target of 140/90 mm Hg. There was a strong association between the outcome and intervention effect: the odds of achieving the target goals of 140/90 in the pharmacy group were 2.13 times higher than in the usual care group (95% CI: 1.29-3.53, p=0.003) while controlling for gender, baseline systolic blood pressure, and type of insurance. Based on the overall measure of fit represented by the Hosmer-Lemeshow goodness-of-fit statistic (χ^2=7.15 and p=0.52), the model fit the data adequately.

The usual care group results showed a noteworthy gender difference in achieving blood pressure goal: the percentage of females achieving the target goal was higher than percent of males achieving the target goal with a marginally significant p=0.07. However, the percentage of females and males in the pharmacist group was nearly identical with respect to achieving the target blood pressure goal (p=0.99) (Figure 4).

Figure 4. Gender comparison with respect to achieving target blood pressure goal



Marital status, whether the patient had diabetes, smoking status, and a number of chronic conditions that were previously identified as potential confounders, did not improve the model significantly. The individual predicted probabilities from the withdrawal investigation model were categorized into four categories and were included in the intervention effect model as withdrawal propensity scores to control for withdrawal effect. However, the withdrawal propensity score did not contribute much to the model and was removed.

Secondary Outcomes

Medication Compliance. Results of the repeated measures analysis showed that the subjects in the usual care group were less likely to improve medication compliance from baseline to final assessment, although this association was only marginally significant (p=0.08). The group effect was not statistically significant (p=0.59). In other words no difference was found between the pharmacists and usual care groups with regard to medication compliance.

To investigate the medication compliance issue further, comparisons between the groups and within the groups were completed (Table 7). The number of subjects who provided a response to the medication compliance questions varied for the baseline and final assessment. Sample sizes per study arm are provided in Table 7.

Table 7. Medication compliance

	Usual Care		Pharmacist Group	
	Baseline (n=81)	Final Assessment (n=91)	Baseline (n=106)	Final Assessment (n=101)
	Column 1	*Column 2*	*Column 3*	*Column 4*
High compliance (%)	67.9	69.2	61.3	67.3
Medium or low compliance (%)	32.1	30.7	38.7	32.7

The between-groups comparison revealed no statistically significant difference in medication compliance at baseline (column 1 vs. column 3) and final assessment (column 2 vs. column 4) (p=0.35 and p=0.77 respectively). The within-group analysis indicated no significant increase in medication compliance from baseline to final assessment in the usual care group (p=0.52). Although the pharmacist group demonstrated an increase in the high compliance category from baseline to final assessment (61.3 percent compared with 67.3 percent), the difference was only marginally significant (p=0.08). Similar findings were demonstrated by the repeated measures analysis.

Medication compliance was evaluated in relation to the achievement of the target blood pressure goal of 140/90 mm Hg. In the usual care group, 43 percent of the patients who scored high on the four-item scale had achieved their blood pressure goal compared with 46 percent with the blood pressure under control for patients scoring medium or low (p=0.75). Sixty percent of the patients who scored high on the four-item scale achieved their blood pressure goal compared with 60 percent with blood pressure under control for patients scoring medium or low in the pharmacist group (p=0.98). Therefore, we can conclude that no statistically significant association found between medication compliance and achievement of the blood pressure target goal.

Patient Satisfaction. Patients were asked to rate their satisfaction with their care, and with the treatment and management of hypertension. At final assessment, patients in both groups were very satisfied with various aspects of the hypertension care they received (Table 8). Patients in both groups reported very high satisfaction with their personal doctors and the respect shown to them by the physicians and staff. Patients in the intervention group also reported a higher level of satisfaction with how their personal

doctors and staff explained information about high blood pressure and with their access to their personal doctors. The lowest reported satisfaction levels in both groups were regarding the cost of blood pressure medications. Overall, the mean levels satisfaction at final assessment for the usual care and the pharmacist groups were similar: 8.5 (STD 1.1) ranging 3.8 to 10 and 8.6 (STD 1.2) ranging from 5 to 10 respectively.

Table 8. Patient satisfaction with hypertension management at final assessment

	Usual care (n=93)		Pharmacist group (n=102)	
	Mean	Std. dev.	Mean	Std. dev.
Satisfaction with treatment	8.6	1.5	8.8	1.4
Satisfaction with personal doctor	9.0	1.5	9.0	1.3
Satisfaction with health plan	8.1	2.0	8.1	2.3
Satisfaction with access to PCP	8.3	1.9	8.6	1.7
Explanations regarding high BP	8.7	1.5	9.0	1.4
Explanations regarding medications for high BP	8.7	1.6	8.8	1.7
Respect shown by doctor and staff	9.4	1.1	9.3	1.2
Satisfaction with medications	8.9	1.5	8.7	1.9
Monitoring of BP	8.5	1.8	8.6	1.8
Time to discuss BP	8.4	1.9	8.6	1.6
Cost of current BP medications	6.9	3.1	6.6	3.1

Note: scores have upper limit of 10.

The results of changes in aggregate mean patient satisfaction were evaluated using the repeated measures analysis of variance and using *t-test* for between- and within-groups comparisons. The repeated measures analysis of variance detected a significant time within subject effect (p=0.0002), indicating a statistically significant improvement from baseline to final assessment overall.

Between-group analysis revealed no statistically significant difference between study arms at final assessment (8.49 as compared to 8.55, p=0.75). A within-group analysis showed no difference in mean satisfaction in the usual care group from baseline to final assessment (p=0.16). However, there was an increase in the aggregate patient mean satisfaction from baseline to final assessment in the pharmacist-managed group (p<0.0001) (Tables 9 and 10). These findings are consistent with the results obtained from the repeated measures analysis of variance.

Table 9. Between-group comparison of aggregate mean satisfaction

	Usual care (n=93)	Pharmacist group (n=102)	p-value
Mean satisfaction	8.5	8.6	0.75

Table 10. Within-group comparison of aggregate mean satisfaction

	Usual care (n=93)	Pharmacist group (n=102)
Difference in mean satisfaction	+0.25	+0.56
p-value	0.16	<0.0001

An analysis of the association between patient satisfaction and achievement of the target blood pressure goal revealed no statistically significant difference in the mean satisfaction for patients who achieved the goal compared with patients who did not. These results were found in both of the study arms (Table 11).

Table 11. Relationship between patient satisfaction and target blood pressure goal

	Usual care (n=93)	Pharmacist group (n=102)
At target goal	8.6	8.7
Not at target goal	8.4	8.4
p-value	0.4	0.2

Quality-of-Life Measurements. The quality-of-life assessments resulted in eight categories and two aggregate scores (Table 12). The domain scores and two aggregate measures were also compared to norms for the U.S. population with hypertension (Ware et al., 2001). All computed scores with the exception of bodily pain and social functioning were within one standard deviation of national norms.

Table 12. Quality-of-life mean scores at baseline and final assessment one year later

SF-36 Domains	Usual Care		Pharmacist Group	
	Baseline (n=82)	Final Assessment (n=96)	Baseline (n=110)	Final Assessment (n=102)
	Mean ± STD	Mean ± STD	Mean ± STD	Mean ± STD
Physical functioning	42± 12	42 ± 12	44 ± 11	44 ± 11
Role limitation, physical	47 ± 9	49 ± 7	49 ± 8	48 ± 7
Bodily pain	34 ± 9	33 ± 11	33 ± 10	32 ± 10
General health	43 ± 5	44 ± 6	43 ± 5	42 ± 6
Vitality (energy and fatigue)	49 ± 5	49 ± 5	49 ± 5	48 ± 5
Social functioning	36 ± 4	35 ± 6	37 ± 4	35 ± 5
Role limitations, emotional	48 ± 11	48 ± 12	47 ± 11	49 ± 11
Mental health	42 ± 5	42 ± 6	43 ± 6	44 ± 6
PCS	41 ± 5	42 ± 6	42 ± 6	41 ± 6
MCS	45 ± 6	44 ± 6	45 ± 6	46 ± 7

PCS: physical component summary score
MCS: mental component summary score

Consistently lower scores than for other domains were found for two domains: bodily pain and social functioning. The repeated measures analysis of variance of PCS score detected a statistically significant interaction between time effect (baseline vs. final assessment) and group effect (intervention vs. control groups) with a p-value of 0.02. This finding can be interpreted as follows: the PCS score in the pharmacist group slightly worsened, while the PCS score in the usual care group slightly improved. There were no significant effects identified for the MCS score as reported by the repeated measures analysis.

The results of the quality-of-life questions were evaluated between and within groups using the *t-test* and revealed no statistically significant differences at the end of the study for any of the domains and aggregate scores between-group measurements with exception of the general health domain (p=0.006), in which scores were slightly higher in the usual care group than in the pharmacists group. Within-group comparisons of the quality-of-life scores indicated that no significant changes occurred in the usual care group except in the physical limitation domain, in which the score improved two points on average (p=0.036) (Table 13). In the pharmacist group, reduction occurred in the bodily pain domain and PCS score (p=0.0016 and p=0.0064 respectively).

Table 13. Mean score changes from baseline to final assessment for each group

SF-36 Domains	Usual Care (n=88)	Pharmacist Group (n=94)
Physical functioning	-0.43	-0.14
Role limitation, physical	2.03*	-0.36
Bodily pain	-0.46	-2.67*
General health	0.99	-1.23
Vitality (energy and fatigue)	0.95	-0.24
Social functioning	0.45	-0.98
Role limitations, emotional	0.10	0.60
Mental Health	-0.29	1.17
PCS	0.57	-1.82*
MCS	0.79	1.23

* Statistically significant change from baseline to final assessment ($p<0.05$).

Mean PCS and MCS scores at final assessment were not significantly different for patients who achieved the target goal compared with those who did not. This finding was consistent across two study groups (Table 14).

Table 14. Quality-of-life scores at final assessment for patients who achieved target blood pressure goal compared with those who did not

	Achievement of blood pressure goal					
	Usual Care (n=88)			Pharmacist Group (n=94)		
QOL scores	Yes	No	p-value	Yes	No	p-value
PCS	43	41	0.13	41	40	0.36
MCS	44	45	0.69	45	47	0.22

Patient Hypertension Knowledge. Repeated measures analysis of variance revealed a non-significant between-subjects effect for hypertension knowledge. In other words, the groups were not statistically different with regard to hypertension knowledge ($p=0.7$) at both time points. There was a statistically significant interaction between time

and group (p=0.0013). The two study arms demonstrated different effects with respect to hypertension knowledge: there was an increase in hypertension knowledge within the pharmacist group and decrease in knowledge within the usual care group.

Similar findings were reported from between- and within- groups analysis using the Wilcoxon test. Between-group comparisons at final assessment revealed no statistically significant difference between groups (p=0.23). Although the mean rank in the pharmacist group at final assessment was slightly higher than in the usual care group indicating more individuals with higher scores in the pharmacist-managed group, a statistical significance was not achieved.

Within-group comparisons were completed using the sign test for paired samples on the difference in the hypertension knowledge scores between the baseline and final assessment. The large p-value (p=0.64) of the sign test for the usual care group provided insufficient evidence of a difference in score medians. In contrast, a within-group comparison for the pharmacist group indicated a statistically significant difference in score medians (p<0.0001), therefore, providing strong evidence of improvement in the hypertension knowledge for patients managed by a clinical pharmacist.

Additional analysis was completed to evaluate the relationship between hypertension knowledge and a patient's ability to achieve the target goal. Subjects who achieved the blood pressure target goal had a tendency to be more knowledgeable in the area of hypertension. In the group managed by a clinical pharmacist, the final assessment revealed a statistically significant difference in hypertension knowledge between those who achieved the target blood pressure goal and those who did not (with medians 9 and 8 respectively, p=0.03).

Blood pressure monitoring at home. An analysis revealed a statistically significant difference in blood pressure home monitoring between the pharmacist group and the usual care group (71 percent compared with 51 percent, p=0.004). Of the subjects who reported use of a sphygmomanometer to monitor their blood pressure at home, 80 percent in the pharmacist group reported recording or charting their blood pressure readings compared with 53 percent in the usual care group (p=0.002). In addition, subjects were asked about the number of days they checked their blood pressure. Subjects in the pharmacist group reported that they charted their blood pressure 14 days, on average, out of the last 30 days, compared with 9 days reported by the subjects from usual care (p=0.01).

Results Summary. In summary, the analysis revealed the effectiveness of collaborative drug management of hypertension by a clinical pharmacist compared with usual care in achieving blood pressure target of 140/90 mm Hg. The pharmacist group demonstrated a greater increase in medication compliance and hypertension knowledge. The pharmacist-managed group was more likely to monitor blood pressure at home and record the results.

Discussion

Management of hypertension is an important public health concern. Inadequate blood pressure control contributes to the major morbidity and mortality of cardiovascular disease and stroke. The purpose of this study was to investigate the effectiveness of clinical pharmacist intervention on patients' achievement of the blood pressure goal of 140/90 mm Hg. A notable finding of this study is that a total of 53 percent of subjects achieved the blood pressure target for both study arms combined; this exceeds the 50

percent goal established by Healthy People 2010. Despite the impressive improvement in hypertension goal attainment, subjects randomized to the pharmacy intervention were significantly more likely to achieve blood pressure control compared with the control group. This finding is consistent with other studies evaluating similar interventions that also reported a positive impact of pharmacists on hypertension control (Borestein et al., 2003, Okamoto et al., 2001. Bogden et al., 1998, Carter et al., 1997).

The Providence hypertension study is unique in that it was multi-site and involved multiple clinical pharmacy specialists. Relative to similar published studies examining the impact of pharmacist intervention, this study enrolled a large number of subjects. The features of the study involving large subject sample size and numbers of clinics/pharmacists, suggest that this intervention is scalable beyond a single clinic location and patient population. Another unique feature of the Providence hypertension study is that it examined blood pressure control in combination with other important outcomes, including medication compliance, patient quality of life, patient satisfaction, knowledge in the area of hypertension, and blood pressure monitoring at home. These secondary outcomes facilitate the further elucidation into the interim steps that may explain why pharmacy-treated subjects were significantly more likely to attain their blood pressure goal. Potential interim steps available for evaluation include the number of antihypertensive medications prescribed, or patient compliance with the medication regimen, patient knowledge or self-management skills.

The Providence research team determined that there was not a significant difference in the number of antihypertensive medications that were prescribed to patients in the pharmacy and usual care groups (Hunt, 2005). This thesis included an evaluation to

determine whether the difference in blood pressure control could be attributed to better compliance with prescribed antihypertensive regimens in the pharmacy-treated group. Unlike another published study (McKenney et al., 1973), in this study, subjects exposed to the pharmacy intervention did demonstrate a statistically significant increase in the proportion of subjects categorized as highly compliant with their medications from baseline to final assessment. However the pharmacy and usual care groups were not different with respect to medication compliance at final assessment. The improvement in blood pressure control that occurred when pharmacists were involved in hypertension management was either not a result of improved medication compliance or the 4-question survey selected to ascertain compliance was not sufficiently sensitive to detect the difference if it were present. Although the selected questionnaire has been validated in another setting, this study did not include any validation process. Ideally, self-reported medication compliance would be compared to a gold standard, such as prescription claims information. This study did not include that validation process because the analysis would have been limited to subjects with commercial insurance with a prescription benefit, which represents a small portion of the study participants. A 4-question self-reported survey to determine medication compliance would be a useful, convenient instrument to assess compliance with antihypertensive medications. Further investigation of the compliance assessment reliability is warranted.

It has been theorized that improved disease state knowledge is a basis for better patient healthcare choices (ICIC, 2005). This study included a 10-question quiz completed by all subjects at the beginning and end of the study. Hypertension knowledge was significantly improved over baseline in the intervention group, however, the

difference between the study arms at the final assessment was not significant. Although the knowledge quiz was tested and had been previously used (Hunt, 2004), further investigation is needed to evaluate sensitivity of the quiz to assess the patients' hypertension knowledge.

Another potential patient behavior that can be hypothesized to result in improved blood pressure control is self-management skills. This study evaluated use of home blood pressure monitoring as evidence of self-management skills. The pharmacist-managed group was more likely to monitor blood pressure at home and record the results. It is conceivable that the clinical pharmacists promoted self-management more aggressively, which in part can be responsible for more patients with prior uncontrolled hypertension achieving their blood pressure goal.

In this study, the only explanation for the improved blood pressure control in the pharmacist-treated group that could be identified was improved home blood pressure monitoring. Further investigation to identify the provider and patient behaviors that led to improved control would be valuable. Other secondary outcomes evaluated in the study include quality-of-life and patient satisfaction.

Quality-of-life, as measured by the SF-36, was also not positively impacted by the pharmacy intervention. The interpretation of this finding is unclear. This finding may have occurred because (1) no differences were perceptible in quality of life, (2) the tool that was used was not responsive enough to detect the change, or (3) differences may be detectable only after a longer period of follow-up than was used in this study. Several clinical trials with similar interventions reported the same results (Mehos et al., 2000, Erickson et al., 1997, Okamoto et al., 2001). If the SF-36 was not responsive enough to

detect change in the population of patients with hypertension, future evaluations of the impact of clinical pharmacy specialists on management of hypertension and patient quality of life may consider incorporating a more disease-specific instrument.

At final assessment, patients in both groups were very satisfied with various aspects of the hypertension care they received. Patients in both groups reported a high level of satisfaction with their personal doctor and the respect shown by the physicians and staff. Patients in the intervention group also reported a higher level of satisfaction with how their personal doctor and staff explained information about high blood pressure and with their access to their personal doctor. No statistically significant difference in patient satisfaction between study arms was detected at final assessment. There was an increase in the aggregate patient mean satisfaction from baseline to final assessment in the pharmacist-managed group. This study was not able to demonstrate a higher patient satisfaction in the intervention group than in the usual care group. However, the measure of overall study impact is that the study participants from both study arms reported a high level of satisfaction with the various aspects of hypertension care. A reservation mentioned by some physicians when entering into a collaborative relationship with the clinical pharmacist is the concern that continuity of patient care would be interrupted by the introduction of another healthcare professional into the relationship. This study demonstrated that, from the patient perspective, the physician - patient relationship was not degraded.

This study had several limitations. First, subjects were recruited for the study using a low-intensity screening and consent process: subjects either mailed in a postcard providing their consent or provided telephonic consent after discussing the study purpose

and process with a member of the research staff. Patients who responded positively by phone or postcard were randomly assigned, with equal allocation, to one of the study groups.

The low-intensity screening and consent process resulted in several occurrences of patient exclusion after randomization. This problem was anticipated when the study was designed, but was considered unavoidable since allowing patients to know the details of the intervention to which they were randomized before requesting their participation was considered the most compatible to real-world practice. However, the low-intensity screening and consent process resulted in the high withdrawal rate experienced in the study. Because subjects did not have to undergo a more rigorous consent process, subjects without a strong commitment to the study were not screened out prior to randomization.

A high subject withdrawal potentially jeopardizes the internal validity of the study results. However, thorough evaluation of withdrawal effect demonstrated that withdrawal did not imbalance the intervention and control groups with respect to subject demographic characteristics and comorbidities. Additionally, withdrawal propensity scores were not significant in the model assessing the primary outcome, implying that biases potentially introduced by subject withdrawal did not significantly impact results regarding blood pressure control. The strength of the low-intensity consent process and the relaxed inclusion criteria is that it facilitated improved generalizibility of the study results to other primary care settings and real-world patient-population with hypertension.

Another limitation of the study occurs because the baseline blood pressure was not assessed at the same level of rigor as the blood pressure obtained at the final

evaluation. The blood pressure readings retrieved from the EMR to identify the study population were also used as baseline values for the study. These blood pressure values were recorded in the EMR based on an assessment that occurs in the course of a busy clinic schedule by a medical assistant, which is not considered a research-quality measure. In contrast, at the final assessment visit, blood pressure was evaluated in the primary care office by a registered nurse recently exposed to updated training in blood pressure assessment. Therefore, attainment of the blood pressure target at final assessment was used as the primary outcome measure

Another blood-pressure-related limitation is that according to the Providence hypertension study protocol, the baseline blood pressures could have been recorded in the EMR within the last two years prior to the hypertension study initiation. Thus, patients with controlled undocumented hypertension could have been selected on the basis of old, inaccurate information with respect to the blood pressure values. However, such patients are likely equally distributed across the groups. This non-differential misclassification may bias the results towards the null. It is also conceivable that patients with uncontrolled hypertension, but whose last blood pressure reading (used as baseline value) was below 160/100 mm Hg at the time of measurement, were excluded from the eligible patient population. Thus, it is likely that the criteria of a last blood pressure 160/100 mm Hg or higher prevented some proportion of subjects with uncontrolled hypertension from inclusion in the study.

Clinical pharmacists, particularly those who pursue residency training, are an important part of the healthcare delivery system. Improvement in the blood pressure control in the intervention group suggests that the pharmacists may successfully assume

increased responsibilities for the long-term health care of patients with hypertension. The clinical pharmacist can provide a means to adequately address the importance of proper medication usage. Proper drug selection and safer usage of these drugs is also a major benefit of pharmacist intervention in the management of hypertension. Effective and rational management of increasingly complex drug therapies is important to the health of patients and to the efficient economic performance of health care systems and organizations. Because of the knowledge and skills of the clinical pharmacists in drug therapy and their accessibility to patients, clinical training and professional education, they are well-positioned to help patients and healthcare systems achieve more effective and efficient drug therapy outcomes (Hammond et al., 2003).

Conclusion and Future Directions

Given the prevalence and health risks posed by hypertension, establishing a means to reduce the frequency of this disease has far-reaching implications. This study demonstrated that, compared with usual care, physician-pharmacist comanagement of patients with uncontrolled hypertension resulted in a larger proportion of patients achieving blood pressure control. However, the study did not measure long-term clinical outcomes associated with uncontrolled hypertension, such as stroke, myocardial infarction, and mortality. Improvements in these outcomes would require persistence of the blood pressure reduction over a prolonged period (Borenstein et al., 2003). Therefore, many years of follow-up period would require measuring these end points.

Further research is needed to determine whether the use of clinical pharmacists in the management of hypertension is a cost-effective strategy. Economic evaluation of the

cost-effectiveness should assess prescribing patterns—whether clinical pharmacists prescribe more effectively and therefore, reduce drug costs while improving blood pressure control. Furthermore, healthcare services utilization information, which includes hypertension-related emergency room visits and hospitalizations, needs to be gathered to evaluate the total costs associated with treatment of hypertension. This information will assist in determining the overall value of clinical pharmacists as a possible solution to the public health issue associated with poorly controlled hypertension in the U.S.

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