CLINICAL RESEARCH STUDY

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Improving Medication Adherence in Patients with Hypertension: A Randomized Trial

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ABSTRACT

BACKGROUND AND PURPOSE: In patients with hypertension, medication adherence is often suboptimal, thereby increasing the risk of ischemic heart disease and stroke. In a randomized trial, we investigated the effectiveness of a multifaceted pharmacist intervention in a hospital setting to improve medication adherence in hypertensive patients. Motivational interviewing was a key element of the intervention.

METHODS: Patients (n = 532) were recruited from 3 hospital outpatient clinics and randomized to usual care or a 6-month pharmacist intervention comprising collaborative care, medication review, and tailored adherence counseling including motivational interviewing and telephone follow-ups. The primary outcome was composite medication possession ratio (MPR) to antihypertensive and lipid-lowering agents, at 1-year follow-up, assessed by analyzing pharmacy records. Secondary outcomes at 12 months included persistence to medications, blood pressure, hospital admission, and a combined clinical endpoint of cardiovascular death, stroke, or acute myocardial infarction.

RESULTS: At 12 months, 20.3% of the patients in the intervention group (n = 231) were nonadherent (MPR <0.80), compared with 30.2% in the control group (n = 285) (risk difference −9.8; 95% confidence interval [CI], −17.3, −2.4) and median MPR (interquartile range) was 0.93 (0.82-0.99) and 0.91 (0.76-0.98), respectively, $P = .02$. The combined clinical endpoint was reached by 1.3% in the intervention group and 3.1% in the control group (relative risk 0.41; 95% CI, 0.11-1.50). No significant differences were found for persistence, blood pressure, or hospital admission.

CONCLUSIONS: A multifaceted pharmacist intervention in a hospital setting led to a sustained improvement in medication adherence for patients with hypertension. The intervention had no significant impact on blood pressure and secondary clinical outcomes.

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Treatment of hypertension and dyslipidemia significantly reduces the risk of cardiovascular events and stroke,[1] but poor adherence and nonpersistence to antihypertensive and lipid-lowering agents are common and associated with severe health consequences for patients[2] and substantial costs for society.[3,4]

Interventions for improving medication adherence have been intensively studied for decades,[5-7] but even complex interventions have shown only modest effect.[7] One likely explanation is that nonadherence is multifactorial, thus making a fully effective intervention difficult to achieve.[8] The field of adherence research has therefore moved toward new strategies with individualized rather than standardized adherence interventions[9,10] and team-based care, for example, integrating a clinical pharmacist with particular focus on patients' drug-related problems and adherence behavior.[11-13] One approach with growing evidence for improving medication adherence is counseling based on motivational interviewing.[14]

CLINICAL SIGNIFICANCE

- A 6-month, multifaceted pharmacist intervention in a hospital setting improved adherence to medication for patients with hypertension for at least 12 months.
- The intervention comprised collaborative care, medication review, and adherence counseling including motivational interviewing and telephone follow-ups.
- The improvement in adherence was not associated with a statistically significant impact on clinical outcomes, and cost and effectiveness studies are warranted before routine implementation.

Pharmacist interventions have focused mostly on primary care,[6,12] and only a few researchers have studied motivational interviewing as a tool to improve adherence in hypertension patients in secondary care.[15-17] The aim of this randomized, controlled trial was thus to assess whether a multifaceted pharmacist intervention including collaborative care and motivational interviewing would improve medication adherence, persistence, and clinical outcomes in hypertensive patients treated in secondary care.

METHODS

Study Design, Setting, and Participants

This randomized, controlled trial was conducted at Odense University Hospital, Denmark. Patients with hypertension were included from one cardiology and 2 endocrinology outpatient clinics from December 2012 to July 2013. Patients were followed until 1 year after the first visit at the outpatient clinics.

Patients were eligible if they were 18 years or older and were prescribed at least one antihypertensive agent. Patients were excluded if they lived in a care home, received dose-dispensed medicine from a pharmacy, had medicine dispensed by a home nurse, had terminal illness, had conditions that precluded patient interview (eg, dementia), or lived outside the Region of Southern Denmark (RSD).

The eligible patients were randomized to an intervention group or a control group. The randomization process was performed by the clinical trial group at the hospital pharmacy. Because control subjects required very limited resources, the most rational use of resources to achieve a given statistical precision entailed a skewed randomization. Hence, a 4:5 allocation ratio and computer-generated randomization block sizes of 9 were used. Allocation was concealed in numbered opaque envelopes. Eligible patients were identified from the list of scheduled visits electronically generated 2 weeks before outpatient clinic days.

Patients randomized to the intervention group were mailed written information and an invitation to participate in the study. At the outpatient clinic, the pharmacist provided oral information and if the patient wished to participate, informed consent was obtained. Patients randomized to the control group were not contacted or informed about the study. The study protocol was approved by the Regional Scientific Ethical Committees for Southern Denmark and the Danish Data Protection Agency and registered at ClinicalTrial.gov as NCT01742923.

Usual Care

Both groups received usual care, which included 2-4 outpatient consultations with physicians or nurses per year. At the consultations, a broad range of risk factors, including lifestyle and adherence, were addressed. Blood pressure (BP), blood glucose, and lipid profiles were measured, and adjustments of the medications were made. Clinical pharmacists were not involved in usual care.

Clinical Pharmacist Intervention

The intervention group received usual care and a pharmacist intervention consisting of 3 elements: 1) a medication review focused on identifying drug-related problems for antihypertensive or lipid-lowering agents followed by advice to the physician in charge; 2) a patient interview; 3) 2 or more follow-up telephone calls to the patient within the first 6 months after inclusion.

The dialogue in the interview was based on principles of motivational interviewing.[18] To ensure standardization and to guide the pharmacist in assessing and addressing the various reasons for nonadherence, we used a medication adherence questionnaire validated in Danish users and filled out before the interview,[19] and an adapted version of the

DRug Adherence Work-up (DRAW)[20] tool, with suggested actions to address each problem identified during the interview.

The pharmacist interviewed the patients by telephone 1 month and 6 months after the first visit. Additional telephone follow-up calls were performed between the 2 scheduled telephone calls, if necessary. After the interview and telephone calls, the patients received a written summary including their own goals and actions to be taken. Five clinical pharmacists employed at the hospital pharmacy at Odense University Hospital carried out the intervention. The pharmacist training and further details regarding the intervention are described elsewhere.[21]

Baseline Data

Demographic data, diagnosis, risk factors, and prescribed medication were collected from the patient's electronic medical record and a local database hosting information on diabetes patients. Calculation of baseline adherence was similar to the main adherence outcomes described below, except that adjustment for prescribing changes and hospitalization were not performed.

Outcomes and Assessments

Adherence and persistence measures were estimated from data obtained from the Odense University Pharmacoepidemiological Database.[22] The register covers all prescriptions for reimbursed medicine redeemed at Danish pharmacies by inhabitants in RSD.

Primary Outcome. The primary outcome was overall adherence to antihypertensive and lipid-lowering agents 12 months after inclusion, reported as a continuous, as well as a binary outcome.

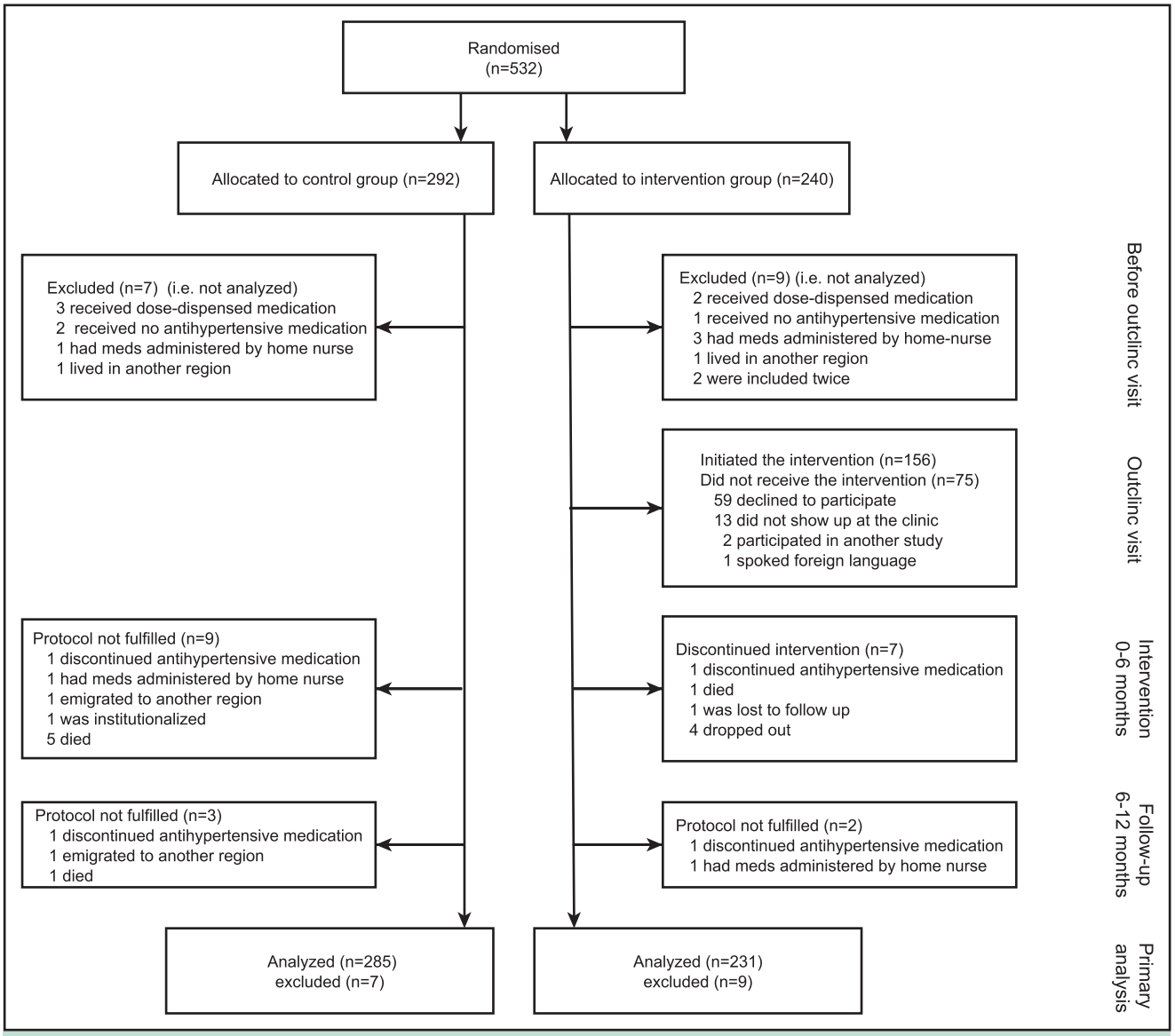

Figure 1 CONSORT diagram of flow of patients through the study protocol.

Table 1 Baseline Demographic and Clinical Characteristics

Variable	Intervention n = 231	Control n = 285
Men, n (%)	138 (59.7)	171 (60.0)
Age, median (IQR)	62 (54-68)	60 (52-68)
Systolic BP mm Hg, mean (SD)*	136.8 ± 15.6	136.6 ± 16.3
Diastolic BP mm Hg, mean (SD)*	78.1 ± 10.6	78.6 ± 11.3
BP controlled, n (%)*,†	65 (36.3)	89 (39.0)
Medications, n (%)		
Diuretics	62 (26.8)	65 (22.8)
Calcium antagonists	111 (48.1)	148 (51.9)
Beta-blockers	60 (26.0)	74 (26.0)
Renin-angiotensin agents	213 (92.2)	269 (94.4)
Lipid-lowering agents	170 (73.6)	208 (73.0)
Number of medications, median (IQR)		
Antihypertensive and lipid-lowering agents	3 (2-3)	3 (2-3)
Antihypertensive agents	2 (1-3)	2 (1-3)
Total number of unique medications	6 (5-9)	7 (5-10)
Baseline adherence		
Composite MPR, median (IQR)‡,§	0.95 (0.83-0.99)	0.93 (0.80-0.99)
Nonadherent (MPR <0.8), n (%)	47 (21.8)	64 (24.8)
Risk factors and complications, n (%)		
Diabetes, type 1	81 (35.1)	104 (36.5)
Diabetes, type 2	130 (56.3)	161 (56.5)
Dyslipidemia	184 (79.7)	234 (82.1)
Acute myocardial infarction	17 (7.4)	27 (9.5)
Arrhythmia	18 (7.8)	13 (4.6)
Other cardiovascular disease	48 (20.8)	70 (24.6)
Stroke or other cerebrovascular disease	17 (7.4)	33 (11.6)
Renal disease‖	36 (15.6)	54 (18.9)
Retinopathy	40 (17.3)	57 (20.0)
High alcohol consumption¶	10 (4.3)	20 (7.0)
Current smoker	42 (18.2)	54 (18.9)
Previous smoker	88 (38.1)	130 (45.6)
BMI 25-30 kg/m^2	68 (29.4)	80 (28.1)
BMI >30 kg/m^2	111 (48.1)	119 (41.8)

BP = blood pressure; IQR = interquartile range; MPR = mediation possession ratio.
*Included in BP analysis: Intervention (n = 179), Control (n = 228).
†BP <140/90 mm Hg or <130/80 for diabetics.
‡MPR for antihypertensive and lipid-lowering agents for a 1-year period ahead of the inclusion.
§Included in MPR analysis: Intervention (n = 216), Control (n = 258).
‖Estimated glomerular filtration rate <60 mL/min.
¶Weekly consumption, women >14 drinks, men >21 drinks.

Adherence was calculated using the medication possession ratio (MPR) measure,[23] defined as the amount of drug available from refills during the follow-up period relative to the amount prescribed. The estimate was refined in several ways[24,25] described in a previous study.[26] The calculation was adjusted for hospitalization stays, switch within drug class, and prescribing changes during the follow-up period. The continuous outcome, composite MPR, was a time-weighted mean of MPRs for antihypertensive and lipid-lowering agents, as described by Steiner et al.[27] The binary outcome was the number of nonadherent (composite MPR <0.80) and adherent (composite MPR ≥0.80) patients within the first year of follow-up. Patients were followed until the earliest of the following events: drugs discontinued by a hospital physician, death, use of dose-dispensed medicine, medicine dispensed by a home nurse, institutionalization, emigration from RSD, or the end of the study period.

Secondary Outcomes. Secondary outcomes were composite MPR at 3, 6, and 9 months, as well as adherence and persistence to diuretics, calcium antagonists, beta-blockers, renin-angiotensin agents, and lipid-lowering agents, all at 12 months.

Nonpersistence was defined by failure to redeem a prescription within 90 days after the last date covered by the preceding prescription[23] and was estimated for medication prescribed at study entry. The days to discontinuation were the number of days from study start to the day for which the

Table 2 Baseline Data of Intervention Group Patients with Performed and Not-performed Intervention

Variable	Intervention Performed n = 156	Intervention Not Performed n = 75
Men, n (%)	94 (60.3)	44 (58.7)
Age, median (IQR)	62 (54-68)	60 (54-69)
Systolic BP mm Hg, mean (SD)*	136.1 ± 14.0	137.8 ± 17.9
Diastolic BP mm Hg, mean (SD)*	78.1 ± 9.9	78.3 ± 12.1
BP controlled, n (%)*,†	79 (36.8)	19 (35.2)
Medications, n (%)		
Diuretics	36 (23.1)	26 (34.7)
Calcium antagonists	73 (46.8)	38 (50.7)
Beta-blockers	42 (26.9)	18 (24.0)
Renin-angiotensin agents	143 (91.7)	70 (93.3)
Lipid-lowering agents	121 (77.6)	49 (65.3)
Number of medications, median (IQR)		
Antihypertensive and lipid-lowering agents	3 (2-3)	3 (2-3)
Antihypertensive agents	2 (1-2)	2 (1-3)
Total number of unique medications	7 (5-9)	6 (5-8)
Baseline adherence		
Composite MPR, median (IQR)‡,§	0.94 (0.83-0.99)	0.96 (0.81-1.00)
Nonadherent (MPR <0.8), n (%)	31 (21.2)	16 (22.9)
Risk factors and complications, n (%)		
Diabetes, type 1	52 (33.3)	29 (38.7)
Diabetes, type 2	91 (58.3)	39 (52.0)
Dyslipidemia	126 (80.8)	58 (77.3)
Acute myocardial infarction	11 (7.1)	6 (8.0)
Arrhythmia	15 (9.6)	3 (4.0)
Other cardiovascular disease	32 (20.5)	16 (21.3)
Stroke or other cerebrovascular disease	12 (7.7)	5 (6.7)
Renal disease‖	21 (13.5)	15 (20.0)
Retinopathy	20 (12.8)	20 (26.7)
High alcohol consumption¶	6 (3.8)	4 (5.3)
Current smoker	30 (19.2)	12 (16.0)
Previous smoker	55 (35.3)	33 (44.0)
BMI 25-30 kg/m^2	52 (33.3)	16 (21.3)
BMI >30 kg/m^2	73 (46.8)	38 (50.7)

BP = blood pressure; IQR = interquartile range; MPR = mediation possession ratio.
*Included in BP analysis: Intervention (n = 125), Control (n = 54).
†BP <140/90 mm Hg or <130/80 for diabetics.
‡MPR for antihypertensive and lipid-lowering agents for a 1-year period ahead of the inclusion.
§Included in MPR analysis: Intervention (n = 146), Control (n = 70).
‖Estimated glomerular filtration rate < 60mL/min.
¶Weekly consumption, women >14 drinks, men >21 drinks.

final refill provided dosing.[23] Patients treated with more than one drug within a drug class were excluded from the analysis.

Secondary outcomes at 12 months included a combined endpoint of cardiovascular death, acute myocardial infarction or hemorrhagic or ischemic stroke,[28] hospital admissions, and BP and medication changes for antihypertensive and lipid-lowering agents.

Data on hospital admission, including admission due to stroke and acute myocardial infarction, were obtained from the Danish National Patient Register, which holds information on all Danish public hospital admissions. Mortality data were obtained from electronic medical records and the Danish Civil Registration system.

BP outcomes were systolic BP (SBP), diastolic BP (DBP), BP control at 12 months, and change from baseline to 12 months in SBP, DBP, and in proportion of patients with BP control.

To maintain a realistic set-up, we did not influence the BP measurement practice used by the individual outpatient clinics, and BP measures were extracted from the outpatient clinics' records. Baseline BP was defined as the measurement nearest to study start within 1 month, and end BP measurement nearest to study end within 3 months. Home and 24-hour measures were adjusted according to guidelines.[29]

Table 3 Adherence Between Treatment Groups

Variable	Intervention	Usual Care	H-L Median Difference/ Risk Difference (95% CI)	*P* Value
Primary endpoint, n	231	285		
Composite MPR†	0.93 (0.82-0.99)	0.91 (0.76-0.98)	0.02 (0.002-0.03)	*.02
Nonadherent (composite MPR <0.8)	47 (20.3)	86 (30.2)	−10 (−17, −2)	*.01
Antihypertensive agents, n	231	285		
Composite MPR‡	0.95 (0.82-1.00)	0.94 (0.77-0.99)	0.01 (0.02-0)	.07
Nonadherent (composite MPR <0.8)	53 (22.9)	80 (28.1)	−5 (−13-2)	.19
Lipid-lowering agents, n	175	224		
MPR	0.96 (0.81-1.00)	0.93 (0.71-1.00)	0.01 (0-0.03)	.06
Nonadherent (MPR <0.8)	41 (23.4)	74 (33.0)	−10 (−18, −1)	*.04
Diuretics, n	72	83		
MPR	0.99 (0.79-1.00)	0.96 (0.82-1.00)	0 (0-0.01)	.58
Nonadherent (MPR <0.8)	19 (26.4)	20 (24.1)	2 (−11-16)	.85
Beta-blockers, n	66	79		
MPR	1.00 (0.85-1.00)	0.99 (0.90-1.00)	0 (0-0.01)	.62
Nonadherent (MPR <0.8)	12 (18.2)	11 (13.9)	4 (−8-16)	.50
Calcium antagonists, n	128	159		
MPR	0.98 (0.84-1.00)	0.97 (0.76-1.00)	0 (0-0.01)	.11
Nonadherent (MPR <0.8)	27 (21.1)	43 (27)	−6 (−16-4)	.27
RAS agents - plain, n	148	199		
MPR	0.99 (0.88-1.00)	0.96 (0.80-1.00)	0.01 (0-0.03)	*<.01
Nonadherent (MPR <0.8)	24 (16.2)	50 (25.1)	−9 (−17, −0)	*.05
RAS agents - combinations, n	83	99		
MPR	0.98 (0.73-1.00)	0.99 (0.90-1.00)	0 (−0.01-0)	.32
Nonadherent (MPR <0.8)	23 (27.7)	16 (16.2)	12 (−1-24)	.07

Values denote n (%) or medians (interquartile range) unless specified otherwise.
CI = confidence interval; H-L = Hodges-Lehmann estimate; MPR = medication possession ratio; RAS = renin angiotensin system agents.
*Statistically significant $P < .05$.
†Composite MPR based on 2 groups of medications: antihypertensive and lipid-lowering agents.
‡Composite MPR based on diuretics, beta-blockers, calcium antagonists, RAS agents, moxonidine and doxazosin.

Sample Size

Sample size was chosen to ensure 80% power and a significance level at 5% to detect a difference of 12.5% in the proportion of patients who were adherent. Based on 150 performed interventions, and anticipated declination and dropout rates of 25% and 10%, respectively, an intervention group size of 220 patients was calculated. To ensure the power to detect a 12.5% difference, it was necessary to have 275 controls, that is, a 4:5 allocation ratio was chosen. More patients than expected declined to participate, and to reach 150 performed interventions, an additional 37 patients were randomized. No patient profiles had been analyzed when this decision was made.

Statistical Analysis

Binary outcomes were compared using Fisher's exact test and given as risk differences. Continuous outcomes were compared using an unpaired *t* test or the Wilcoxon-Mann-Whitney 2-sided test. Median difference estimate was derived from Hodges-Lehmann estimate. MPR over time was compared using a mixed-effect linear regression model with patient and time as random-effect parameters, and an interaction between follow-up time and treatment group was tested. Persistence was illustrated using Kaplan-Meier cumulative failure curves and compared using the Cox proportional hazard model. All *P* values were 2-tailed, with statistical significance set at .05. All confidence intervals were calculated at the 95% level. The analyses were performed for all patients with applicable medication data. All data for assessment of adherence were double-entered and corrected using EpiData version 3.1 (The EpiData Association, Odense, Denmark). Data were analyzed using Stata version 13 (StataCorp LP, College Station, TX). The researcher was blinded to the allocation when assessing and analyzing the outcomes. The study conformed to the CONSORT statement.[30]

RESULTS

Participants

Among 532 eligible patients, 292 were allocated to the control group and 240 to interventions (**Figure 1**). After excluding 16 patients for whom adherence could not be estimated, 285 and 231 evaluable patients remained in the control and intervention groups, respectively. In the intervention group, 156 received the intervention; 59 declined to participate and 13 did not show up at the clinic. In total, 112 patients had significant protocol deviations (**Figure 1**).

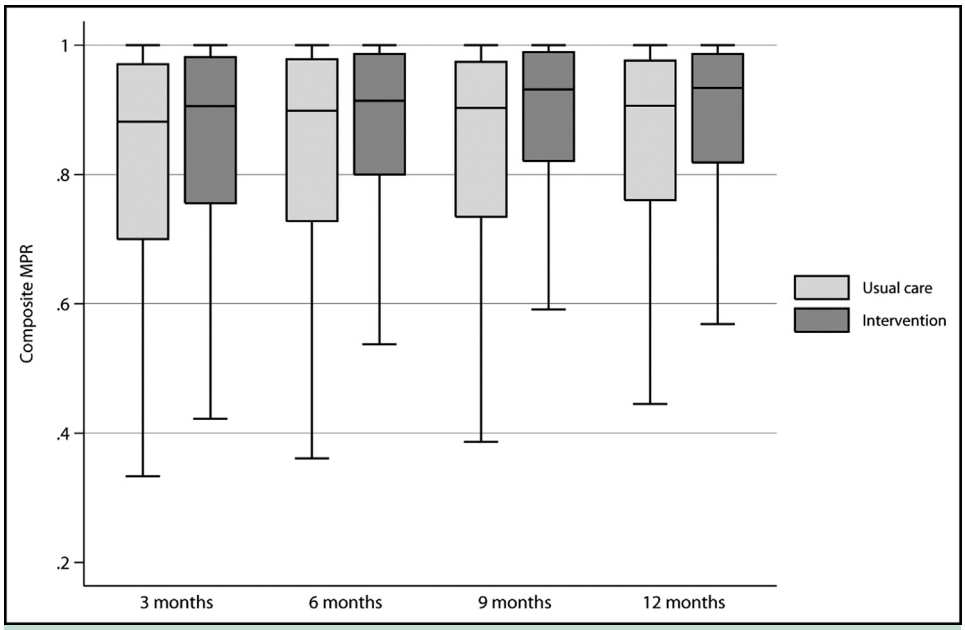

Figure 2 Boxplot of overall adherence score (composite MPR) over time. The composite MPR is based on antihypertensive and lipid-lowering agents. The box displays the interquartile range (IQR) and the median. The whiskers display 1.5 IQR. Outside values are excluded. Over time, MPR was significantly higher in the intervention group compared with the usual care group (P = .04). At 9 and 12 months, the difference in MPR between the groups was significant, P <.01 and P = .02, respectively. There was no evidence of an interaction between treatment groups and time. MPR = medication possession ratio.

Baseline Data

Baseline characteristics did not differ significantly by treatment group (Table 1). The median age of the patients was 62 years, and 60% were men. The majority of the patients suffered from diabetes (92%) and dyslipidemia (81%). BP was controlled in 38% of the patients. In the intervention group, patients without intervention performed differed from patients with performed intervention on 3 variables. They were more frequently treated with lipid-lowering drugs (77.6% vs 65.3%), had slightly lower SBP (136.1 mm Hg vs 137.8 mm Hg), and less frequently, retinopathy (12.8% vs 26.7%) (Table 2).

Medication Adherence and Persistence

At the primary endpoint, 12 months, median composite MPR was 0.91 (interquartile range [IQR] 0.76-0.98) in the control group, compared with 0.93 (IQR 0.82-0.99) in the intervention group (P = .02) (Table 3). A greater proportion of control group patients were nonadherent compared with intervention patients (30.2% vs 20.3%, P = .01). A trend toward improvement was evident at 3 months, and the difference was sustained at 9 months and 12 months (Figure 2).

A greater proportion of control patients were classified as nonadherent for lipid-lowering agents (33.0% vs 23.4%; P = .04) and plain renin-angiotensin agents (25.1% vs 16.2%; P = .05) at 12 months. For the remaining drug classes, there were no statistically significant differences in adherence rates (Table 3).

For all drug classes, except beta-blockers, nonpersistence was lower in the intervention group than in the control group, although none were statistically significant (Figure 3).

To assess whether informing and asking patients to participate in the study alone could improve adherence, data for intervention patients with performed intervention were compared with patients without intervention performed (Table 4) and with patients from the usual care group (data obtained from Table 3). As in the main analyses (Table 3), adherence rates were greater in patients with performed intervention than those without intervention (Table 4), though most differences were nonsignificant, possibly due to the smaller number of patients. Adherence rates in patients who did not receive the intervention did not differ markedly from the rates in the usual care group. Both results indicate that information alone is unlikely to be the cause of the improved adherence in the main analysis.

Clinical Outcomes

No significant differences were found for clinical outcomes, but all measures, except for change in DBP, pointed in the direction in favor of the intervention (Table 5). At 12

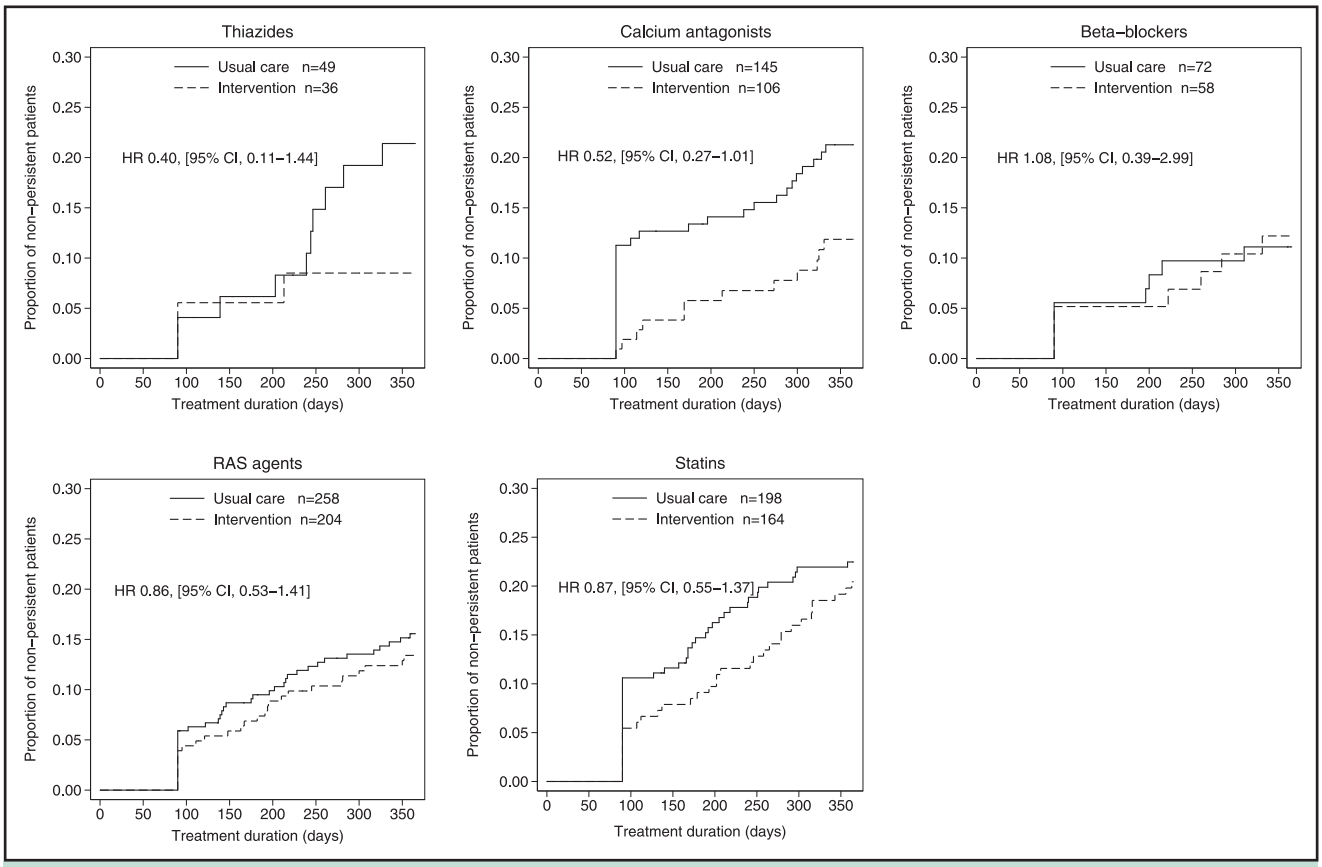

Figure 3 Cumulative incidence of nonpersistence of antihypertensive drug classes and statins. CI = confidence interval; HR = hazard ratio; RAS agents = renin angiotensin system agents.

months, 12 patients had a least one composite cardiovascular event: 3 (1.3%) in the intervention group and 9 (3.1%) in the control group (relative risk 0.41; 95% confidence interval, 0.11-1.50). For these 12 patients, the overall median (IQR) adherence rate was 0.73 (0.68-0.82), and 8 patients (67%) were nonadherent.

The pharmacists made 91 recommendations on drug-related problems, of which 64% were accepted by physicians. During patient interviews, 421 problems were identified: 60% related to medication and 40% to lifestyle. Problems identified are described in detail elsewhere.[21] Despite these recommendations, the proportion of patients with medication changes did not differ significantly between groups; 49% of the intervention patients vs 46% in the control group ($P = .54$) had medication changes (**Table 5**). The mean total time spent by pharmacists per intervention patient was 2 h 14 min (SD 40 min).

DISCUSSION

This multifaceted pharmacist intervention resulted in significant and sustained improvement in medication adherence for hypertension patients in an ambulatory secondary care setting, but without significant effect on persistence and clinical outcomes. Our results are in line with evidence from meta-analyses showing that pharmacist interventions alone or in collaboration with other health care professionals can improve medication adherence and BP control.[6,12]

According to observational studies, good adherence to cardiovascular medication is associated with a 20% lower risk of cardiovascular event and 35% decrease in mortality.[2] In our study, the effect on adherence was not translated into significant impact on persistence and clinical outcomes. Given the fairly low event rate and the relatively short follow-up time, the nonsignificant result on the composite endpoint is hardly surprising, and larger trials or meta-analyses are necessary for clarifying an effect on clinical events.

Motivational interviewing was a central element of the intervention. Motivational interviewing has shown promising results in medication adherence therapy in other health care settings.[14,31] Used as a single component intervention, it improved adherence with antihypertensive therapy by 14%, but without significant effect on BP.[31] We integrated motivational interviewing into a complex intervention with multiple components, as systematic reviews show that multifaceted approaches are essential to effectively improve adherence.[5,7,32]

There are several advantages to using pharmacy records to ascertain adherence. First, it is less interfering than, for

Table 4 Adherence of Intervention Group Patients with Performed and Not-performed Intervention

Variable	Intervention Performed	Intervention Not Performed	H-L Median Difference/ Risk Difference (95% CI)	*P* Value
Primary endpoint, n	156	75		
Composite MPR†	0.93 (0.83-0.99)	0.92 (0.79-0.99)	0.01 (−0.01-0.01)	.47
Nonadherent (composite MPR <0.8)	28 (17.9)	19 (25.3)	−7 (−19-4)	.22
Antihypertensive agents, n	156	75		
Composite MPR‡	0.95 (0.83-1.00)	0.94 (0.76-0.99)	0.01 (0-0.02)	.23
Nonadherent (composite MPR <0.8)	33 (21.2)	20 (26.7)	−6 (−17-6)	.40
Lipid-lowering agents, n	125	50		
MPR	0.97 (0.84-1.00)	0.89 (0.71-0.99)	0.03 (0-0.09)	*.02
Nonadherent (MPR <0.8)	25 (20)	16 (32)	−12.0 (−26.7-2.7)	.11

Values denote n (%) or medians (interquartile range) unless specified otherwise.
CI = confidence interval; H-L = Hodges-Lehmann estimate; MPR = medication possession ratio.
*Statistically significant $P < .05$.
†Composite MPR based on 2 groups of medications: antihypertensive and lipid-lowering agents.
‡Composite MPR based on diuretics, beta-blockers, calcium antagonists, renin angiotensin system agents, moxonidine and doxazosin.

example, pill counts, and may therefore affect patient behavior to a lesser extent. Second, pharmacy refill data are widely recognized as a valid measure of adherence.[23,27] Third, we were able to account for medication discontinuation, dose changes, and days spent in the hospital, which improved our estimate. Other strengths of the study included intention-to-treat analyses and the use of 5 extensively trained pharmacists at 3 different outpatient clinics.

To our knowledge, this is the first study on a pharmacist intervention including motivational interviewing to show a positive impact on medication adherence in hypertensive patients. It is also one of the first studies to demonstrate a sustained effect after intervention has stopped. A large study on a pharmacist intervention very similar to this one had no impact on BP 6 months after a 14-month intervention period[33] (adherence data not available). A recent study, the HAPPy trial,[34] on a pharmacist intervention including motivational interviewing, medication review, a reminder system, and BP self-monitoring in community pharmacies found, in contrast to our study, a significant reduction in BP but no difference in adherence at 6 months. Several factors can explain the divergent findings. First, the

Table 5 Clinical Outcomes and Medication Changes by Treatment Group

Variable	Intervention (n = 231)	Usual Care (n = 285)	Difference/Risk Difference (95% CI)
Combined endpoint, n (%)	3 (1.3)	9 (3.1)	−1.9 (−4.0-0.6)
Stroke, n	1	4	−1.0 (−2.5-0.6)
Myocardial infarction, n	0	2	−0.7 (−1.6-0.3)
Cardiovascular death, n	2	3	−0.2 (−1.9-1.5)
Readmission per patient mean (SD)	0.32 (0.83)	0.37 (1.43)	−0.06 (−0.15-0.26)
Patient readmitted, n (%)	42 (18.2)	56 (19.6)	−1.4 (−8.3-5.3)
BP mean (SD) mm Hg*			
SBP 12 mo	134.1 (13.8)	135.4 (14.4)	−1.3 (−4.4-1.9)
DBP 12 mo	76.4 (11.1)	76.7 (10.1)	−0.3 (−2.7-2.0)
Change in SBP	−1.7 (17.9)	−0.6 (17.0)	−1.1 (−5.0-2.8)
Change in DBP	−1.1 (11.0)	−1.5 (12.5)	0.4 (−2.2-3.1)
BP controlled 12 mo,† n/total‡ (%)	63/167 (37.7)	72/215 (33.5)	4.2 (−5.5-13.9)
Change in BP controlled, n/total* (%)	2/138 (1.4)	−10/176 (−5.7)	−7.1 (−20.3-6.0)
Medication changes,§ n (%)			
Any change	113 (49)	131 (46)	3.0 (−0.6-11.6)
Dose change	64 (28)	62 (22)	6.0 (−1.5-13.5)
Medication discontinued	59 (26)	72 (25)	0.3 (−7.2-7.8)
New medication	74 (32)	89 (31)	0.8 (−0.7-8.9)

BP = blood pressure; CI = confidence interval; DBP = diastolic blood pressure; SBP = systolic blood pressure.
*Total number with baseline and study end measurements; intervention n = 138, usual care n = 176.
†BP <140/90 mm Hg or <130/80 for diabetics.
‡Total number with measurements at study end.
§Number of patients with change of antihypertensive and lipid-lowering medications.

average baseline was higher in the HAPPy trial (3-5 mm Hg), leaving more room for improvement. Second, in our study, obesity and type 2 diabetes, which are both strongly associated with treatment-resistant hypertension,[35] were highly prevalent. Third, our study had greater power for adherence outcomes and used more reliable adherence measures (refill data vs self-reported measures), which may explain why only our study found a significant improvement in adherence. The HAPPy trial[34] used follow-up visits at the pharmacy, whereas we used telephone follow-ups, which may be more acceptable and convenient than in-person intervention.[36] Telephone-based motivational interviewing to improve medication adherence has been successful in other settings.[37] Bosworth et al[38,39] showed long-term and sustained effect after telephone counseling, like we did. Bimonthly calls delivered by nurses trained in motivational interviewing combined with home BP monitoring led to an 11% relative improvement in BP control at 24 months.[38,39]

We found no significant improvement in BP. A possible explanation is that, contrary to many other studies, we also included patients who already had reached their target BP.[12] This left us with a smaller margin for improvement. In studies with a positive effect on BP, pharmacists often adjust medication independently,[11] and even though a trend toward an intensified treatment among intervention patients was observed, this could also explain the discrepant effect on BP. Future studies should focus on patients at higher risk, for example, patients with uncontrolled BP or patients who had exhibited nonadherence, as these patients might benefit more from an adherence intervention.

There are some limitations of our study. First, one-third of the intervention patients declined to participate. Based on measurable variables, there is, however, no clear indication of substantial selection bias, as baseline data differed only slightly between patients who declined and patients who accepted the intervention. Second, we had adherence as our primary outcome, and not BP or clinical events. The BP data were not sufficiently accurate as primary outcome, and 12-month measurements were missing for 26% of the cohort. Standardized BP measurement is required for definitive conclusions on BP impact. Third, pharmacists and treating physicians could not be blinded with respect to the allocation. This problem is largest for subjective outcomes, and our main outcomes were objectively and blindly assessed using register data. Fourth, there is a risk of contamination bias, which represents a bias toward underestimating the true intervention effect. Fifth, in contrast to the control group, the intervention group was informed that their prescription data were monitored, which could introduce an intervention effect outside the effect of the pharmacist intervention. We believe that this effect is minimal, as being aware of this data collection method is less likely to influence adherence compared with, for example, pill count and electronic monitoring devices.[40] Further, we have analyzed adherence at study end for the patients from the intervention group who received the information but not the intervention, and their adherence was comparable with the control group, indicating that the information did not influence adherence. Finally, no measures concerning the economic impact were included, but most of the cost of the intervention was related to the pharmacist time (2.25 hours per patient). A similar multifaceted intervention, used after acute coronary syndrome, with similar results on adherence and BP, indicates a reasonable balance between costs and effect of our study.[13] In that study, the intervention was found to be cost neutral, even though the pharmacists spent nearly twice as much time on each patient than in our study.

CONCLUSION

This pragmatic trial showed that an in-hospital multifaceted pharmacist intervention including motivational interviewing significantly and persistently improved adherence to antihypertensive and lipid-lowering medication in patients with hypertension, but without significant impact on clinical outcomes. Cost-effectiveness studies and larger samples to assess whether the improvement in adherence can be translated into better clinical outcome are warranted before a routine implementation.

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