Effect of a 36-Month Pharmaceutical Care Program on Coronary Heart Disease Risk in Elderly Diabetic and Hypertensive Patients

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Received, March 16, 2011; Revised, May 10, 2011; Accepted, June 17, 2011; Published, June 22, 2011.

ABSTRACT - Purpose. To examine the effect of an implemented pharmaceutical care program on coronary heart disease risk in elderly diabetic and hypertensive patients. **Methods.** A total of 200 elderly (≥60 years) diabetic and/or hypertensive patients were recruited into a randomized, controlled, prospective clinical trial with a 36-month follow-up, developed in a public primary health care unit in a municipality in the Brazilian State of Sao Paulo. A range of clinical measurements was evaluated at baseline and for 36 months. The intervention-group patients received pharmaceutical care from a clinical pharmacist, whereas the control-group patients received their usual care from the medical and nursing staff. The Framingham scoring method was used to estimate changes in the 10-year coronary heart disease risk of all patients. **Results.** A total of 194 patients completed the study. Significant reductions ($P < 0.05$) in the mean values (baseline vs. 36 months) of systolic blood pressure (156.7 mmHg vs. 133.7 mmHg; $P < 0.001$), diastolic blood pressure (106.6 mmHg vs. 91.6 mmHg; $P < 0.001$), fasting glucose (135.1 mg/dL vs. 107.9 mg/dL; $P < 0.001$), hemoglobin A1C (7.7% vs. 7.0%; $P < 0.001$), triglycerides (206.0 mg/dL vs. 152.5 mg/dL; $P < 0.001$), low-density lipoprotein (LDL) cholesterol (112.4 mg/dL vs. 102.0 mg/dL; $P < 0.001$), high-density lipoprotein cholesterol (55.5 mg/dL vs. 65.5 mg/dL; $P < 0.001$), total cholesterol (202.5 mg/dL vs. 185.9 mg/dL; $P < 0.001$), body mass index (26.2 kg/m^2 vs. 26.1 kg/m^2; $P < 0.001$), and abdominal circumference (103.2 cm vs. 102.5 cm; $P = 0.001$) were observed in the intervention group, whereas no significant changes were verified in the control group. The mean Framingham risk prediction score in the intervention group was 6.8% at baseline and decreased to 4.5%; $P < 0.001$) after 36 months, but remained unchanged in the control group. **Conclusion.** The pharmaceutical care program resulted in better clinical measurements and reduced the cardiovascular risk scores in elderly diabetic and hypertensive patients over a 36-month period.

INTRODUCTION

Cardiovascular diseases (CVD) account for 17.1 million deaths per year worldwide, and coronary heart disease is responsible for 7.2 million of these deaths, most of them involving elderly individuals. Developing countries contribute more to overall mortality due to this disease than developed countries (1). In Brazil, approximately 2 million cases of severe CVD were reported in 2004**,** with an estimated annual cost of at least US$54.2 billion, and most of this cost is funded by the Brazilian public health system (2). An exploration of alternative strategies is needed to address this public health problem.

The intervention by pharmacists through pharmaceutical care can help other health professionals in the management of drug therapy by identifying, preventing, and resolving drug-related problems (3).

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Pharmaceutical care programs have been found useful in reducing coronary heart disease risk factors such as increased blood pressure, high blood glucose, and high lipid levels (4-6). However, most of these studies have focused on a research context rather than practices implemented within health care systems. The practice of pharmaceutical care is not fully implemented in any health system, but promising initiatives have been developed in some developed countries (7-9). More robustly designed pharmaceutical care studies of substantial duration are needed to confirm the positive effects of adding clinical pharmacists to the interdisciplinary teams employed by health systems.

To the authors' knowledge, randomized, controlled, prospective clinical trials of long duration evaluating the effect of implemented pharmaceutical care programs on coronary heart disease risk in elderly diabetic and hypertensive patients and conducted in developing countries such as Brazil are scarce. Previous pharmaceutical care studies conducted in developing countries involved small samples (10,11) or were nonrandomized (12,13), and were of short duration (10-14). Additionally, none evaluated coronary heart disease risk (10-14). It is therefore important to evaluate the role of the pharmacist in developing countries in the context of the health care team to promote new strategies to adequately control coronary heart disease risk. Pharmacists in developing countries work mainly in drug administration, including activities related to the acquisition and inventory control of drugs, with little clinical activity directed toward the patient. The practice of pharmaceutical care at the public primary health care level is scarce in developing countries.

Brazil's *Sistema Único de Saúde* (SUS) is a universal, publicly funded, rights-based public health system. The SUS states that every citizen, regardless of economic and social condition, has access to all levels of health care (primary, secondary, and tertiary), including medicines (15,16).

Primary care offered to outpatients at Primary Health Care Units (PHCUs) involves health education, prevention and surveying of disease spread, and drug dispensation. The supply of drugs occurs in pharmacies located within the PHCUs, which dispense medications on the basis of a municipal list of essential medicines. Family physicians, general practitioners, and nurses provide primary health care interventions (consultations, exams, education groups, and vaccinations), and pharmacies within PHCUs provide patients with the drugs prescribed by these professionals. Drug dispensation usually occurs without the presence or supervision of a pharmacist, since several PHCUs do not have a single pharmacist on staff. The SUS primary care level is the only choice for access to health care for approximately 70% of the Brazilian population, which does not have financial resources to pay directly for private health services or drugs.

This study aimed to evaluate the effect of an implemented pharmaceutical care program on coronary heart disease risk among elderly diabetic and hypertensive patients in the Brazilian public health system by verifying changes in the presence of risk factors for the development of the disease and by estimating the risk of developing the disease within 10 years (17).

METHODS

Study design

The study was a randomized, controlled, longitudinal, prospective clinical trial carried out from October 1, 2006 to October 31, 2009 in a PHCU of the Brazilian public health system located in the city of Salto Grande, Sao Paulo State. The study was approved by the Research Ethical Committee of the State University of Maringa, Brazil (CAAE 0182/09).

Pharmaceutical care program implementation process

The pharmaceutical care program was implemented in this PHCU in October 2005 by adding clinical pharmacists to the health care team for diabetic and hypertensive patients. The process was initiated by the institution of an interdisciplinary team composed of 1 clinical pharmacist, 1 nurse, and 2 general practitioners, based on the report prepared by the Academic Health Center Task Force on Interdisciplinary Health Team Development, University of Minnesota, USA (18). The team adopted a protocol to guide the operation process including attributions of each professional, mechanisms to resolve internal conflicts, mechanisms of communication, mechanisms of

evaluation and feedback, periodicity of meetings, and goals of therapy for several medical conditions. The stated goals of therapy varied according to the presence or absence of other risk factors or comorbidities and followed the Brazilian consensus guidelines for hypertension and diabetes (19,20). The clinical pharmacist performed centralized (e.g., in-service or continuing education about pharmacotherapy, drug information leaflets to health professionals and patients, drug use evaluation, and drug therapy protocol management) and decentralized activities (e.g., individual pharmacotherapy management, coordination of educative groups). Initially the clinical pharmacist performed these activities for 50% of their total working hours. As the service demonstrated good acceptance by the other health professionals and patients, in January 2006, the clinical pharmacist began to perform these activities full time. Based on the results of a pilot study, 3 other clinical pharmacists were included in the pharmaceutical care program in May 2006 (50% of their total working hours). The implementation process was finalized in August 2006, when all other health professionals at this PHCU (5 general practitioners and 2 nurses) began to integrate the interdisciplinary team. Before the beginning of this study, 260 patients aged over 60 years (37.0% of elderly diabetic and hypertensive patients attended in the PHCU) were receiving pharmaceutical care intervention.

The clinical pharmacists who performed pharmaceutical care were previously trained by a researcher (PON) from the State University of Maringá. The training was conducted individually and lasted 20 h for each pharmacist. Pharmaceutical care concepts and procedures comprised the first step of the training (8 h). The second step was an overview of the Brazilian consensus guidelines for hypertension, diabetes, and dyslipidemia (8 h) (19,20,21). Techniques for communication with other health professionals and patients comprised the third step of training (2 h). The final step involved techniques to coordinate educative groups (2 h). Before the completion of each step, a test was carried out with each pharmacist, with a minimum score of 80% correct answers required to pass to the next step (no pharmacist was reproved at any step). The assessment of the quality of the service performed by each pharmacist was carried out monthly during the first year of the implementation and consisted of 2 indicators: percent of patients reaching the therapeutic goals stated in the care plan and patient satisfaction level with the pharmaceutical care program according to a validated instrument (22).

Study subjects

Patients eligible for inclusion in the study were ≥ 60 years of age, diagnosed with diabetes and/or hypertension according to Brazilian national consensus guidelines (19,20), under drug treatment for diabetes and/or hypertension, regularly participated in medical, nursing, and educative activities offered at the PHCU, and had up-to-date results for their routine physical and laboratory tests (no more than 30 days prior to baseline measurements). Exclusion criteria included a diagnosis of dementia (registered by a psychiatrist in the medical records) and history of previous cerebrovascular accidents or myocardial infarction (registered by a physician in the medical records), as well as patients already followed by a clinical pharmacist.

Eligible patients were identified by 3 researchers (VR, MN, and AN) using an electronic database available in the PHCU (Cetil®). The information available in this electronic database includes patient identification (medical record number, name, sex, date of birth, and address), clinical information (diagnosed diseases, results and dates of clinical and laboratory exams, dates and description of consultations, and attendance frequency in educative groups) and drug therapy information (name of the drugs dispensed, name of prescriber, date of dispensation, and amount dispensed).

Sample size

The sample size of the trial was calculated to detect a 10% reduction in serum low-density lipoprotein (LDL) cholesterol, since it is the major lipid marker of coronary heart disease (17). It was estimated that 95 patients would be required in each group for a 2-tailed α of 0.05 and a 1-β of 80%. Based on these data, to ensure sufficient statistical power and to account for attrition during the study, a target sample size of 100 patients in each group was assumed. Eligible patients were invited by phone and/or personally (at home or in the

PHCU) by the researchers (VR, MN, and AN) to participate in the study. A total of 278 potential subjects were willing to participate in the study and gave oral and written consent to the ethics in research protocol. To reach the target sample size, 78 patients were randomly excluded.

Randomization

JMP software version 8.0.1 (SAS, Cary, NC, USA) provided computer-generated random sequences (100 patients each in the intervention and control groups) according to the medical record numbers of the 200 patients selected.

Description of interventions

All patients (intervention group and control group) were enrolled at the beginning of the study (October 1, 2006 to October 30, 2006) and followed for 36 months.

Patients enrolled in the control group received the usual care offered in the PHCU, consisting of appointments with physicians every 3 months and with nurses every month. Any procedures were registered in the patient records and could consist of alterations in the prescribed drugs, requests for laboratory exams, general information about patient health, and specialist referrals.

Patients received their prescription services without any pharmaceutical care approach. Patients randomized into the intervention group, besides the usual care offered, also received pharmaceutical care intervention. The pharmaceutical care intervention consisted of individual follow-ups (according to the Pharmacotherapy Workup developed at the University of Minnesota, USA (23)) and educative group activities. The Pharmacotherapy Workup was carried out by 4 pharmacists (staff of the pharmaceutical care program implemented at the PHCU) at a frequency of 1 visit every 6 months. This schedule was adopted so as not to disturb the routine activities of the PHCU pharmacy staff. During the Pharmacotherapy Workup, interventions were aimed at guaranteeing a high rate of compliance to the pharmacotherapy. These interventions included assessment of non-compliance problems, discussions with patients and family about the role of medication in their health status (including patients' active participation in choosing their drug treatment), suggestions to physicians concerning new drug regimens (taking into account patients' medication experience), orientation with respect to the correct use of drugs (including the method for insulin application), and the preparation of special packages to provide a visual reminder that a medication was taken.

The pharmaceutical care program was developed individually with regard to patients' individual needs as well as knowledge of their clinical conditions and drug therapy. Data concerning each patient's reason for the encounter, demographic information, pharmacotherapy history, medication experience, and other clinical information were elicited during the assessment and registered in the patient's medical records. After assessing whether the patient's drug-related needs were being met and whether any drug therapy problems were present, the pharmacists developed individual care plans for the patients, with patients participating actively in the elaboration of their care plan. The first step of the care plan was to determine the goals of therapy (parameters, values, and timeframes), which were determined via consensus between the pharmacist and patient. The pharmacists followed the goals of therapy stated for each medical condition in the protocol of the interdisciplinary team, and in situations not stated in the protocol, they consulted 1 general practitioner and 1 nurse to establish the goals of therapy. The pharmacists performed verbal and written orientations related to controlling the disease, compliance to therapeutic and non-therapeutic treatments, appropriate nutrition, and correct use of drugs. The pharmacists also worked in association with other health professionals for additional interventions such as adjustment of drug dosage, modification of the drug therapy (addition or withdrawal), modification of diet plan, and practice of physical activities. In the follow-up evaluation, the patient outcomes relative to the individual desired goals of therapy were evaluated, and the patients were reassessed to determine whether any new drug therapy problems had developed.

All decisions made in pharmaceutical care practice were documented in the patient's medical record. These medical records were accessed by the physicians during their attendance. Previous recommendations made to the patient and/or physicians were assessed for acknowledgment or implementation, based on interviews and medical reports. Two

researchers (RF and ST) collected the data on recommendations made to the patient or physician through analysis of the medical reports and interviews. Educative group activities were also organized once every 6 months, with groups of 20 patients. During these activities, themes such as adherence, dangers of self-medication, and the correct storage of medicines were discussed.

Previous data from the pharmaceutical care program implemented in the PHCU indicated a high number of diabetic and hypertensive patients with non-controlled levels of serum lipids (total cholesterol, LDL cholesterol, and triglycerides). This finding influenced the pharmacists to approach drug-related problems referent to lipid levels (e.g., non-compliance to lifestyle modification and necessity to add a pharmacotherapy to reduce lipid levels) more intensively during the meetings.

Outcome measurements

Each patient was interviewed by 2 researchers (LP and DP) to obtain details on his socio-demographic data, cigarette consumption, and medications being used. The researchers consulted the medical records of each patient to record the baseline values for blood pressure, fasting glucose, hemoglobin A1C, triglycerides, LDL cholesterol, high-density lipoprotein (HDL) cholesterol, total cholesterol, body mass index (BMI), abdominal circumference, and number of diseases diagnosed. These researchers were blinded to patient study status and played no role in the delivery of the interventions. The patients were asked to return to the PHCU once every 6 months for follow-up assessments. All patients were assessed as per the initial baseline assessments during their scheduled PHCU visit (6, 12, 18, 24, and 36 months).

The primary outcome of the study was the risk of coronary heart disease. Regarding coronary heart disease risk, a 10-year risk assessment was carried out for all patients (control and intervention groups) at baseline and at the end of the study period using the Framingham scoring method (17). The Framingham 10-year coronary heart disease risk categories are mild (<10%), moderate (10–20%), and severe (>20%) (17).

Blood pressure levels were determined by a trained nurse according to the procedures recommended by the Brazilian hypertension consensus guidelines (19), using a calibrated aneroid sphygmomanometer certified by the Brazilian Society of Cardiology. Laboratory exams were carried out in a certified laboratory. The patients were weighed by a trained nurse on a calibrated scale with a stadiometer. Abdominal circumference was measured using a certified tape, again by a trained nurse. The nurse who made the blood pressure, weight, height, and abdominal circumference measurements was blinded to patients' allocation in the study.

Drug-related problems

Drug-related problems detected in the intervention group were classified according to the Pharmacist's Workup of Drug Therapy (23). We carried out 2 assessments regarding drug-related problems: prevalence of acceptance of the general practitioner to the interventions proposed by pharmacists and prevalence of drug-related problems resolved.

Compliance was determined by 2 researchers (PON and RC) at baseline and after 36-month follow-up using 2 different methods: the Morisky-Green test translated into Portuguese (24) and the computerized dispensed medication history (25). These researchers were blinded to the group allocation of the patients. The Morisky-Green test translated into Portuguese is a validated self-reporting tool for compliance assessment that consists of 4 direct questions (24,26):

1 Do you ever 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 Sometimes if you feel worse when you take the medicine, do you stop taking it?

The patients were considered compliant to the pharmacotherapy when they correctly answered all 4 questions and were considered non-compliant to the pharmacotherapy when they correctly answered 3 or fewer questions (24,26).

The computerized dispensed medication history estimates the medication use of each patient by analyzing the periodicity of prescription pickups during the 6 months before the measurement. The quantity of prescribed and dispensed drugs over this period was

calculated. Patients with a quantity of dispensed medications within 80–115% of the prescribed medications were considered compliant, and patients with other values were considered non-compliant (25).

STATISTICAL ANALYSES

The data were entered into a Microsoft Excel database and imported into the Statistica software package version 7. Before selecting the tests, the data were tested for normal distribution. The baseline characteristics were compared between the control group and the intervention group using the chi-square test and the paired-sample t-test, as appropriate. For comparisons between the baseline and endpoint values in the control group and intervention group, the dependent-samples Student's t-test was used. P values < 0.05 were considered statistically significant.

RESULTS

Baseline characteristics

A population of 397 patients fulfilled the entrance criteria and presented no exclusion criteria. Of the 100 patients recruited to each group, 97 completed the study. Figure 1 illustrates the flow of patients throughout the study and describes the various stages at which data were collected. The statistical analyses indicated that the baseline characteristics of the patients in the intervention group closely matched those of the patients in the control group (Table 1).

Ten-year risk assessment for coronary heart disease

Patients at moderate risk for coronary heart disease decreased from 14.4% to 8.3% in the intervention group during the study period, and a corresponding increase was observed in the number of patients at mild risk in the same group, from 81.5% to 90.7%. In the control group, 1 patient transitioned from moderate to severe risk during the 36-month follow-up. The mean Framingham prediction scores at baseline were 6.8 ± 4.5% for the intervention group and 6.9 ± 4.5% for the control group. After 36 months of follow-up, the value decreased to 4.5 ± 2.8% (P < 0.001) in the intervention group, but remained unchanged at 6.9 ± 4.7% (P = 0.320) in the control group (Table 3). A significant difference in the change in Framingham score was observed between the 2 groups (P < 0.05) (Table 3).

Clinical outcomes Changes in clinical outcomes over 36 months of follow-up are shown in Table 2. Significant reductions (P < 0.05) in the mean values (baseline vs. 36 months; 95% confidence interval [CI]) of systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting glucose, hemoglobin A1C, triglycerides, LDL cholesterol, HDL cholesterol, total cholesterol, BMI, and abdominal circumference were observed in the intervention group, but no significant changes were found in the control group (Table 2). The difference between the groups in the change observed over 36-month follow-up was significant (P < 0.05) (Table 2).

Drug-related problems

In the intervention group, 92.3% of the patients presented at least 1 drug-related problem, with a mean of 2.93 drug-related problems per patient. Table 4 shows the prevalence of each type of drug-related problem identified in the intervention group. A high level of acceptance by the general practitioners for the interventions proposed by the pharmacists was observed (Table 4). Most of the identified drug-related problems were resolved (Table 4).

A high rate of non-compliant patients was observed at baseline. The intervention group showed a significant increase in pharmacotherapy compliance (P < 0.01). No significant difference was observed between the results of the 2 compliance assessment tools used (Figure 2).

DISCUSSION

To the authors' knowledge, this is the first controlled, longitudinal (36-month follow-up), prospective clinical trial conducted in a developing country to examine the effect of a pharmaceutical care program on the risk of coronary heart disease, using this range of clinical outcomes and the Framingham score.

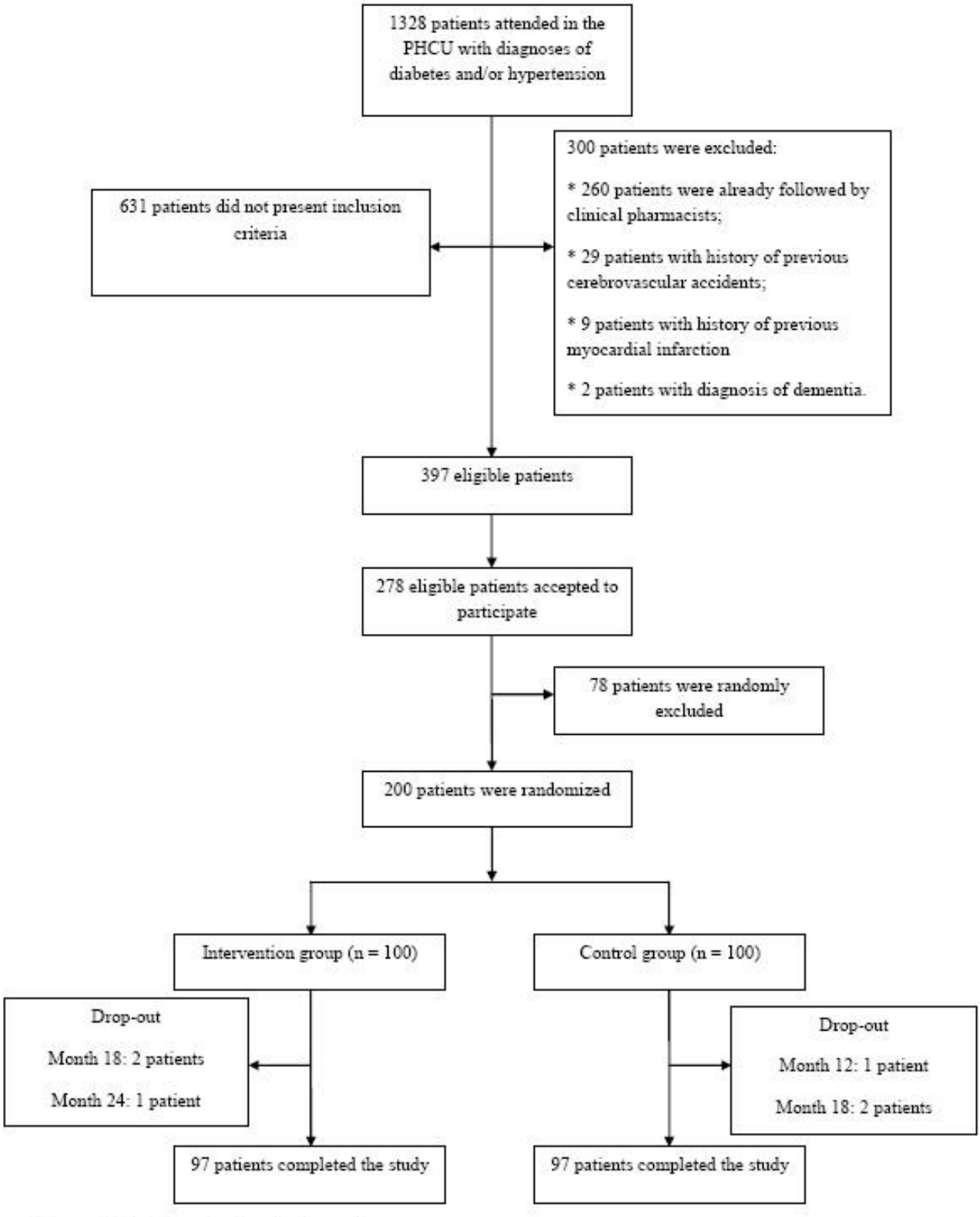

Figure 1. Flowchart of patients in the study

Table 1. Baseline characteristics of the study participants

Variable	Intervention group (n = 97)	Control group (n = 97)	*P* value[ab]
Female gender, n (%)	61 (62.9)	60 (61.8)	0.88
Mean age, years (SD)	65.3 (5.8)	65.3 (5.7)	0.99
Black ethnicity, n (%)	69 (71.1)	67 (69.1)	0.75
Mean monthly family income, US$ (SD)	314.9 (99.1)	317.7 (101.8)	0.32
Incomplete elementary school, n (%)[c]	76 (78.4)	75 (77.4)	0.93
Cigarette consumption, n (%)[c]	21 (22.0)	22 (23.0)	0.86
Mean SBP, mmHg (SD)	156.7 (21.8)	155.9 (20.8)	0.79
Mean DBP, mmHg (SD)	106.6 (17.7)	108.7 (16.9)	0.36
Mean fasting glucose, mg/dL (SD)	135.1 (55.6)	135.8 (55.4)	0.93
Mean hemoglobin A1C[d], % (SD)	7.7 (0.5)	7.7 (0.5)	0.69
Mean triglycerides, mg/dL (SD)	206.0 (134.8)	206.5 (134.6)	0.98
Mean LDL cholesterol, mg/dL (SD)	112.4 (12.7)	112.1 (12.7)	0.90
Mean HDL cholesterol, mg/dL (SD)	55.5 (8.5)	54.9 (6.6)	0.51
Mean total cholesterol, mg/dL (SD)	202.5 (35.7)	202.0 (35.4)	0.91
Mean BMI, kg/m^2 (SD)	26.2 (3.2)	26.2 (3.2)	0.97
Mean abdominal circumference,cm (SD)	103.2 (13.2)	103.2 (13.2)	0.99
Mean diagnosed diseases, n (SD)	2.40 (1.30)	2.40 (1.30)	0.98
Patients diagnosed with hypertension, n (%)[e]	46 (47.4)	44 (45.4)	0.77
Patients diagnosed with diabetes, n (%)[e]	17 (17.5)	18 (18.5)	0.85
Patients presenting both diabetes and hypertension, n (%)	34 (35.1)	35 (36.1)	0.88
Mean number of drugs for chronic use, n (SD)	3.3 (1.7)	3.3 (1.7)	0.17
Use of anti-hypertensive drugs			
Thiazide diuretics, n (%)	56 (57.7)	55 (56.7)	0.88
ACEI, n (%)	53 (54.6)	50 (51.5)	0.67
Calcium channel blockers, n (%)	28 (28.9)	26 (26.8)	0.75
Adrenergic beta-blockers, n (%)	19 (19.6)	16 (16.5)	0.58
ARB, n (%)	10 (10.3)	15 (15.5)	0.29
Loop diuretics, n (%)	6 (6.2)	8 (8.2)	0.59
Adrenergic alfa-2 agonist, (%)	4 (4.1)	3 (3.1)	0.72
Use of antidiabetic drugs			
Metformin, n (%)	47 (48.5)	49 (50.5)	0.78
Sulfonylureas, n (%)	38 (39.2)	39 (40.2)	0.88
Insulin, n (%)	10 (10.3)	13 (13.4)	0.52

Abbreviations used: SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high-density lipoprotein; BMI, body mass index; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.
[a]The chi-square test and paired-sample t-tests were used as appropriate.
[b]*P* values < 0.05 were considered statistically significant.
[c]Self reported.
[d]Only patients with a diagnosis of diabetes were subjected to this exam.
[e]Patients presenting only hypertension or diabetes.

To assess the effect of an intervention on reducing coronary heart disease risk, long-duration studies are superior to short-duration studies, since the patients are exposed to everyday living factors, like non-compliance and development of new risk factors, for a longer period. The results indicated that the pharmaceutical care program promoted better clinical measurements and reduced the cardiovascular risk scores in elderly diabetic and hypertensive patients over a 36-month period. By helping other health professionals in the process of care, the pharmacists were able to provide a better support to these patients.

Table 2. Changes during 36 months of follow-up

Variable	Intervention group (n = 97) Changes during 36 months	*P* value[a]	Control group (n = 97) Changes during 36 months	*P* value[a]	Difference between groups, *P* value[a]
Mean SBP, mmHg [95% CI]	-23.0 [-26.4-19.6]	<0.001[b]	-0.4 [-3.1-2.3]	0.765	<0.001[b]
Mean DBP, mmHg [95% CI]	-14.8 [-17.7 -11.9]	<0.001[b]	-1.9 [-3.7-0.0]	0.055	<0.001[b]
Mean fasting glucose, mg/dL [95% CI]	-27.2 [-35.7 -18.6]	<0.001[b]	1.1 [-3.2-5.4]	0.615	<0.001[b]
Mean hemoglobin A1C[c], % [95% CI]	-0.7 [-0.9-0.6]	<0.001[b]	0.0 [-0.1-0.1]	0.885	<0.001[b]
Mean triglycerides, mg/dL [95% CI]	-53.5 [-79.9-27.0]	<0.001[b]	-1.9 [-10.9-7.1]	0.680	<0.001[b]
Mean LDL cholesterol, mg/dL [95% CI]	-10.4 [-15.8- 0.8]	<0.001[b]	2.8 [-0.8-3.7]	0.522	<0.001[b]
Mean HDL cholesterol, mg/dL [95% CI]	10.0 [8.5-11.5]	<0.001[b]	0.0 [-0.6-0.6]	0.916	<0.001[b]
Mean total cholesterol, mg/dL [95% CI]	-16.6 [-22.1-11.6]	<0.001[b]	4.4 [-1.58-11.2]	0.054	<0.001[b]
Mean BMI, kg/m^2 [95% CI]	-0.1 [-0.2-0.1]	<0.001[b]	0.0 [0.0-0.1]	0.304	<0.001[b]
Mean abdominal circumference, cm [95% CI]	-0.6 [-1.0-0.3]	0.001[b]	0.1 [0.0-1.0]	0.502	<0.001[b]

Abbreviation used: SBP, systolic blood pressure; CI, confidence interval; DBP, diastolic blood pressure; HDL, high-density lipoprotein; BMI, body mass index.
[a]Paired-sample t-test was used.
[b]*P* values < 0.05 were considered statistically significant.
[c]Only patients with a diagnosis of diabetes were subjected to this exam.

Table 3. Comparison of the 10-year risk assessment for coronary heart disease using the Framingham score

Score	Intervention group (n = 97) Baseline n (%)	After 36-month follow-up n (%)	*P* value[ab]	Control group (n = 97) Baseline n (%)	After 36-month follow-up n (%)	*P* value[ab]	Difference between groups, *P* value[ab]
>20% (severe)	4 (4.1)	1 (1.0)	<0.001[c]	4 (4.1)	5 (5.1)	0.320	<0.001[c]
10–20% (moderate)	14 (14.4)	8 (8.3)		14 (14.4)	13 (13.4)		
<10% (mild)	79 (81.5)	88 (90.7)		79 (81.5)	79 (81.5)		

[a]The chi-square test was used.
[b]Comparison between baseline and after 36 months of follow-up.
[c]*P* values < 0.05 were considered statistically significant.

The present study was conceived to address a major public health problem in developing countries and a treatment gap between previous research evidence and clinical practice. It provides proof that pharmacists at the Brazilian public primary health care level working in partnership with other health professionals (interdisciplinary teams as described) and patients can have a major beneficial impact on reducing coronary heart disease risk. It is hoped that the pharmaceutical care program implemented in this PHCU can be adapted and used in other Brazilian PHCUs and other primary care settings of developing countries.

Our results suggest that the introduction of pharmaceutical care at the Brazilian public primary care level is viable. The expenditures to include a pharmacist at the PHCU are very low when compared to the economic outcomes achieved by the intervention of this professional

(14). Another important indicator supporting this viability was the high level of acceptance and satisfaction of both patients and other health professionals (general practitioners and nurses) with the pharmaceutical care interventions. Recent reforms in the Brazilian curriculum for Pharmacy graduates will also help to reinforce this viability, because clinical knowledge and skills are now part of the teaching content.

Table 4. Drug-related problems identified and resolved in the intervention group

DRP category	Number of DRP identified (%)	Prevalence of interventions proposed by the pharmacist accepted by GPs	Prevalence of DRP resolved
Unnecessary drug therapy	4 (1.41)	25.00%	25.00%
Needs additional drug therapy	22 (7.75)	95.45%	86.36%
Ineffective drug	2 (0.70)	50.00%	50.00%
Dosage too low	19 (6.70)	89.47%	78.95%
Adverse drug reaction	67 (23.59)	100%	100%
Dosage too high	12 (4.22)	66.67%	66.67%
Non-compliance	158 (55.63)	100%	89.87%
Total	284 (100)	96.13%	89.08%

Abbreviation used: DRP, drug-related problem; GPs, general practitioners.

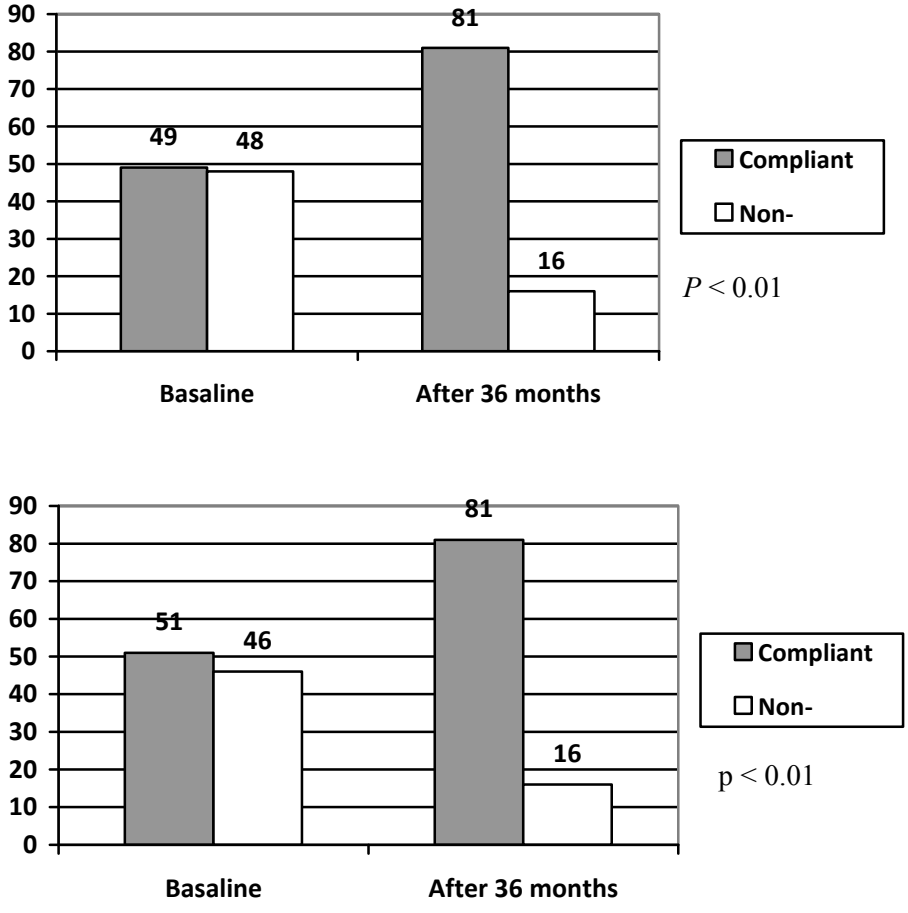

Figure 2. Number of compliant patients in the intervention group according to the Morisky-Green test (24,26) (top) and according to computerized dispensed medication history (25) (bottom). The chi-square test was used

Clinical outcomes

The present study demonstrated a positive impact of the pharmaceutical care program on blood pressure levels. Other studies have also reported a reduction in this parameter, which can be attributed to the effectiveness of pharmaceutical care in identifying and resolving drug-related problems and in optimizing adherence to lifestyle modifications (4,25,27,28). However, the changes observed in the present study were more significant. The Fremantle Diabetes Study identified a reduction in mean SBP and DBP values over 12 months (29). Significant reductions ($P < 0.001$) in SBP and DBP over 12 months were also reported by Al Mazroui et al. (28). In a study conducted by Lee et al. (30), patients who submitted to a pharmaceutical care program for 18 months significantly reduced their mean SBP values ($P = 0.005$) but demonstrated no significant differences in DBP. Castro et al. (31) reported a trend for better blood pressure control in uncontrolled hypertensive patients enrolled in a pharmaceutical care program over 6 months, although the differences were not statistically significant. Correr et al. (14) reported no significant reduction in SBP ($P = 0.251$), but did observe a significant reduction in DBP ($P = 0.003$) over 12 months. These variations in results may be attributed to different characteristics of patients enrolled in the studies (age, baseline blood pressure levels, diseases presented, scholastic level, and others), study duration, and the characteristics of the health systems where the studies were conducted (availability of medications, availability of medical and nursing consultation, and others).

Another important outcome observed in this study was a significant reduction in blood glucose levels (fasting glucose and hemoglobin A1C) in the intervention group compared with the control group.

These reductions can also be attributed to the effectiveness of pharmaceutical care in identifying and resolving drug-related problems and in optimizing adherence to lifestyle modifications (25-28). A study with a shorter duration than the present one reported a smaller reduction in fasting glucose (<15 mg/dL) and hemoglobin A1C (<0.5%) (29). Other studies (14,28) have shown a greater reduction in fasting glucose (>54.9 mg/dL) and hemoglobin A1C (>2.2%) over a shorter period (12 months), but from higher baseline values (>166 mg/dL and >8.5%, respectively) and in a different health system setting. These results suggest that the effectiveness of pharmaceutical care in the control of blood glucose levels depends on patient characteristics, the duration of the study, and the characteristics of the health system where the study is conducted.

The patients enrolled in the intervention group showed significant reductions in blood lipid levels over 36 months in comparison with the control group. Interventions to optimize adherence to lifestyle modifications and to identify and resolve drug-related problems, particularly drug-related problems concerning the need for additional therapy such as statins and fibrates, contributed to this result (28,32). Other studies have also demonstrated the effectiveness of pharmaceutical care programs in lowering lipid levels, but with varying results (28,29,32). The Fremantle Diabetes Study identified a reduction in mean triglyceride levels, an increase in mean HDL cholesterol levels, and a decrease in mean total cholesterol levels (29). Al Mazroui et al. (28) also obtained significant reductions in triglycerides, increases in HDL cholesterol, and reductions in total cholesterol levels over a 12-month period. A study with a mean duration of 21 months conducted by Mazzolini et al. (32) reported the effectiveness of pharmaceutical care interventions with respect to triglycerides and total cholesterol levels, but no effectiveness in HDL cholesterol, which in fact significantly decreased as opposed to increasing. These studies were developed in different health system settings, conducted over different periods of time, and involved patients with different characteristics.

Significant reductions in BMI and abdominal circumference over 36 months were observed in the intervention group compared with the control group. Obesity is a well-known risk factor for many diseases. Obese people (with BMI $\geq$ 30 kg/m^2) have an increased risk of death from heart disease, stroke, and cancers. Other studies have demonstrated that being overweight (i.e., BMI of 25.0 to 29.9) is also associated with increased mortality. The rate of death from any cause is the lowest in patients with BMI of 22.5 to 25.0 kg/m^2, and it increases with progressively higher and lower BMI levels (33). The progressive excess mortality above

this range is due mainly to vascular disease (34). Abdominal circumference is more reliable than BMI in stratifying mortality risk in patients with cardiovascular diseases; it is directly associated with mortality even in patients with normal BMI (35). According to these results, even the small reduction in BMI or abdominal circumference achieved in our study could significantly improve patient surveillance.

Published results regarding the effectiveness of pharmaceutical care for reducing BMI and abdominal circumference demonstrate considerable variability, which may be due to a variety of factors. Moreover, further discrepancies may arise from diverse health system settings, different patient characteristics, and different study durations. Over 12 months, a pharmaceutical care program reduced BMI from 30.0 kg/m^2 to 29.4 kg/m^2 in the Fremantle Diabetes Study (29). Ahrens et al. (36), in a study to assess the effectiveness of pharmaceutical care in body mass loss, reported an 8.1-cm reduction in abdominal circumference (baseline of 89.1 cm) over a mean of 21 months. Al Mazroui et al. (28) reported a greater reduction in BMI (-1.05 kg/m^2) over a shorter period (12 months), but from a higher baseline value (28.3 kg/m^2), in the United Arab Emirates health system. However, Correr et al. (14) demonstrated a smaller reduction in BMI (-0.2 kg/m^2) over 12 months from a higher baseline value (29.2 kg/m^2) in the Brazilian health system.

Risk assessment for coronary heart disease

The pharmaceutical care program significantly reduced the 10-year risk of coronary heart disease calculated using the Framingham score. This result suggests that better clinical outcomes were obtained by optimizing adherence to lifestyle modifications and identifying and resolving drug-related problems, resulting in a lower risk of coronary heart disease among the patients. The Fremantle Diabetes Study (29) demonstrated a significant reduction in the median 10-year estimated risk of a first coronary heart disease event (from 25.1% to 20.3%; $P = 0.002$) over 12 months; calculated using the United Kingdom Prospective Study risk engine for a 10-year absolute risk of coronary heart disease and stroke (37,38). In patients submitting to a pharmaceutical care program over 12 months, the mean Framingham prediction scores decreased from 10.6% to 7.7%; $P < 0.001$ (28). The variation in these results can be attributed to different coronary heart disease risks at baseline (patient characteristics), different study durations, different health system settings, and different prediction scores used.

Drug-related problems

Similar to others studies conducted in Brazil, a high prevalence of drug-related problems was observed (10,12,13,39), indicating the importance of the inclusion of pharmaceutical care practices directed to resolve drug-related problems in primary health care.

As observed in the present study and in previously published research, pharmaceutical care represent an effective strategy for the resolution of drug-related problems, and solving drug-related problems significantly improved patients' clinical outcomes (10,12,13,23,39). Studies with higher rates of drug-related problem resolution tended to demonstrate more concrete improvements in the patients' clinical outcomes. Our results indicated an 89.08% resolution rate of identified drug-related problems. Strand et al. (23) were able to resolve 88.0% of their drug-related cases, while Sá-Borges et al. (10) successfully resolved 62.7% of identified cases. These different resolution rates of drug-related problems may be attributable to different levels of clinical knowledge and skills between the pharmacists that performed pharmaceutical care, since our study and the study conducted by Strand et al. (23) were carried out with pharmacists who had greater practice experience than the study conducted by Sá-Borges et al. (10).

Another limiting factor in the resolution of drug-related problem is that several drug-related problems required the intervention of a general practitioner, such as drug and dosage change. This issue reinforces the need to establish good strategies for communication between members of the health care team. The implementation of the interdisciplinary team facilitated the communication process in our study, which suggests that this strategy is an important step in consolidating pharmaceutical care practice in health systems.

Treatment non-compliance was the most prevalent drug-related problem in the present study, with almost half of patients in the

intervention group considered non-compliant at baseline. In a study conducted in a secondary health care center in Brazil, non-compliance was also the most prevalent drug-related problem (10). As non-compliance to pharmacotherapy is associated with negative clinical outcomes in diabetic and hypertensive patients, interventions to improve compliance are very important (40,41).

The strategies carried out in the intervention group to improve compliance were targeted to specific risk factors and causes identified during the patient assessment. Multicomponent interventions, including external cognitive supports involving education strategies (patient education and counseling) and a behavioral component focused on the mechanism of medication delivery (blister packs), were tailored to the individual needs of each patient. The present pharmaceutical care program encouraged patients to assume an active role in their own treatment plans (promote self-efficacy), empowered patients and family members to become informed medication consumers, encouraged patients to develop a list of short-term and long-term goals for the drug therapy (to stimulate long-term compliance), provided medication instructions several times and in different formats (verbal and written), promoted convenience through reminder packaging, and conducted regular follow-up meetings to assess compliance rates and motivate the patient.

Limitations

This study had some limitations. Although the Framingham score has been used on a widespread scale to predict the 10-year risk of coronary heart disease, this method presents some limitations, such as underestimating the 10-year risk of coronary heart disease in type 2 diabetic patients (42). In the present study, self-reporting of cigarette consumption was used to calculate the Framingham score, which may have underestimated the number of non-smokers leading to lower 10-year coronary heart disease risk scores in the population studied. Only the diabetic patients were subjected to the hemoglobin A1C test in the health system setting analyzed, which reduced the sample size for this parameter and may have produced a bias in the study. The absence of a gold standard method to measure compliance (43) also complicated assessment of the interventions provided. Indirect methods are useful in daily practice (cheap, fast, and easy to apply) but tend to overestimate compliance (43). The present authors decided to use 2 indirect methods concomitantly to reduce this bias. The number of pharmacists who performed pharmaceutical care was small, and they received previous training not offered to all pharmacists who work in the SUS, so care must be taken before generalizing these results to all pharmacists working in the SUS. The study was only carried out in 1 PHCU, so future multicenter studies with larger sample populations are needed to generalize the results.

CONCLUSION

Ours results show that a pharmaceutical care program composed of pharmacotherapy follow-up and educative group activities organized by pharmacists reduced the cardiovascular risk scores in elderly diabetic and hypertensive patients. The observed reduction in cardiovascular risk scores suggests that such a program can lead to meaningful improvements in health outcomes and reduce health expenditures.

ACKNOWLEDGEMENTS

We acknowledge the pharmacists who provided pharmaceutical care to the intervention group, and the researchers involved in the randomization process. This study was supported by Fundação de Apoio ao Desenvolvimento Científico (FADEC).

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