REVIEW ARTICLE

HEALTH CARE REFORM

Impact of Pharmacist Care in the Management of Cardiovascular Disease Risk Factors

A Systematic Review and Meta-analysis of Randomized Trials

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Background: Pharmacists may improve the clinical management of major risk factors for cardiovascular disease (CVD) prevention. A systematic review was conducted to determine the impact of pharmacist care on the management of CVD risk factors among outpatients.

Methods: The MEDLINE, EMBASE, CINAHL, and Cochrane Central Register of Controlled Trials databases were searched for randomized controlled trials that involved pharmacist care interventions among outpatients with CVD risk factors. Two reviewers independently abstracted data and classified pharmacists' interventions. Mean changes in blood pressure, total cholesterol, low-density lipoprotein cholesterol, and proportion of smokers were estimated using random effects models.

Results: Thirty randomized controlled trials (11 765 patients) were identified. Pharmacist interventions exclusively conducted by a pharmacist or implemented in collaboration with physicians or nurses included patient educational interventions, patient-reminder systems, measurement of CVD risk factors, medication management and feedback to physician, or educational intervention to health care professionals. Pharmacist care was associated with significant reductions in systolic/diastolic blood pressure (19 studies [10 479 patients]; –8.1 mm Hg [95% confidence interval {CI}, –10.2 to –5.9]/–3.8 mm Hg [95% CI,–5.3 to –2.3]); total cholesterol (9 studies [1121 patients]; –17.4 mg/L [95% CI,–25.5 to –9.2]), low-density lipoprotein cholesterol (7 studies [924 patients]; –13.4 mg/L [95% CI,–23.0 to –3.8]), and a reduction in the risk of smoking (2 studies [196 patients]; relative risk, 0.77 [95% CI, 0.67 to 0.89]). While most studies tended to favor pharmacist care compared with usual care, a substantial heterogeneity was observed.

Conclusion: Pharmacist-directed care or in collaboration with physicians or nurses improve the management of major CVD risk factors in outpatients.

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CARDIOVASCULAR DISEASE (CVD) is the leading cause of mortality and morbidity in adults worldwide[1] and accounts for approximately one-third of mortality in Canada[2] and in the United States.[3] Randomized studies have demonstrated the efficacy of lowering blood pressure (BP) and cholesterol levels or smoking cessation to reduce CVD mortality and morbidity.[4] However, control of CVD risk factors is far from optimal in the population[5,6] and only a minority of patients with CVD risk factors achieved target goals for low-density lipoprotein cholesterol (LDL-C) levels[7] or BP.[6] Interventions to improve the management of CVD risk factors are therefore needed.

See also pages 1428, 1471, and 1480

Because patients have difficulties accessing primary care physicians and health care costs are rapidly rising, greater use of community-based models of care has been proposed.[8] Among these models is the greater integration of the pharmacist as a provider of health services and member of the health care team. Pharmacists are highly accessible health care professionals, and because of their knowledge of drug therapy and their computerized records of medications, they are particularly well positioned to provide the necessary medication instructions to patients to improve safe medication use and are in collaboration with primary care physicians to assist in preventive CVD care.[9,10] Studies have demonstrated beneficial interventions of pharmacists in medication use,[11] identification of patients at high risk of CVD,[12] and CVD management.[10] Interventions have included pharmacist-only

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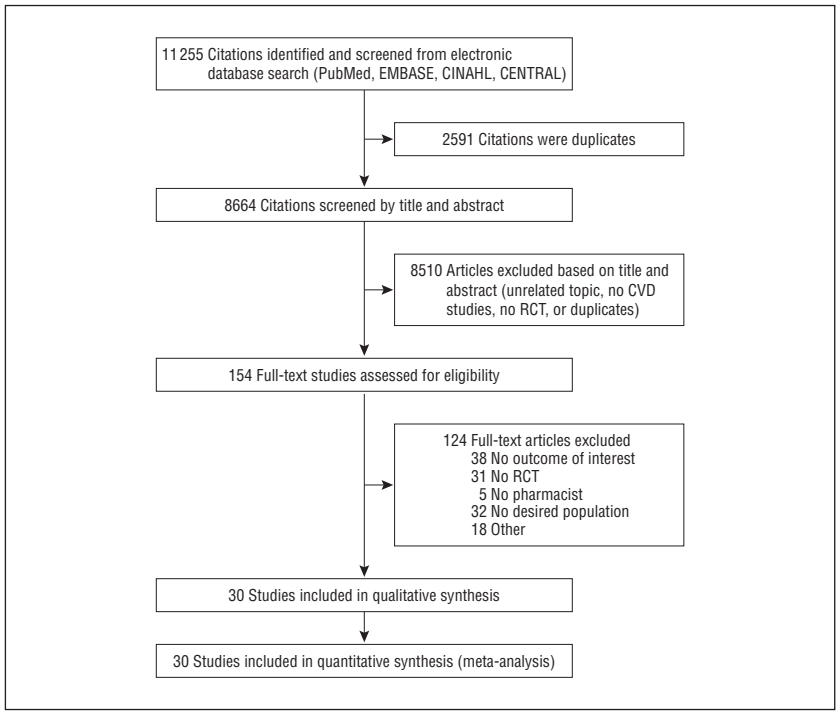

Figure 1. Flow diagram of studies assessed and included. CVD indicates cardiovascular disease; RCT, randomized controlled trial.

or pharmacist-collaborative care as part of disease management programs, clinical pharmacy cardiac risk services,[13-15] and community-based programs that focus on modifiable CVD risk factors.[10,16,17] Therefore, interventions delivered by pharmacists may be key to improve the management and outcomes among patients with CVD risk factors.[10]

Previous studies have shown that collaborative care involving pharmacists may help the management of diabetes,[16] dyslipidemia,[10] hypertension,[18,19] heart failure,[20] and CVD[17] and reduces the risk of all-cause and heart failure hospitalizations.[21] To more effectively use the expertise of pharmacists in CVD care, it is necessary to better understand their roles and contributions to patient care. A review of pharmacist interventions suggested that pharmacy-based interventions improve surrogate outcomes of CVD.[22] However, this review was not systematic in its coverage and did not aggregate the findings through meta-analysis. Therefore, we conducted a systematic review of randomized studies to determine the impact of pharmacist care on the management of major CVD risk factors among outpatients.

METHODS

DATA SOURCES AND SEARCHES

In collaboration with a medical research librarian (A.L.C.), we conducted a systematic literature search of the electronic databases MEDLINE via PubMed (1950 to November 2010), EMBASE (1980 to November 2010), CINAHL (1937 to November 2010), and the Cochrane Central Register of Controlled Trials (up to November 2010) for randomized controlled trials (RCTs). Inclusion criteria and methods of analysis were specified in advance and documented in a protocol available on request.

The PubMed search syntax served as the basis for all search strategies, using both Medical Subject Headings (MeSH) and text terms with Boolean operators (see eAppendix for the full electronic search strategy; http://www.archinternmed.com). MESH terms included cardiovascular disease-related terms (*Cardiovascular Diseases*, *Dyslipidemias*, *Diabetes Mellitus*, *Smoking*, and *Overweight*) and pharmacist-related terms (*Pharmacists*, *Pharmaceutical Services*, *Pharmacy Service, Hospital*, *Pharmacies*, and *Pharmacy*). The search was focused on RCTs using the Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE. The search strategy was then adapted for EMBASE, CINAHL, and the Cochrane Central Register of Controlled Trials. In addition to these automated searches, we conducted a hand search of bibliographies of all relevant articles. We considered publications in any language.

STUDY SELECTION

Two authors (V.S. and A.C.) independently screened titles, abstracts, and full articles from the literature search to determine eligibility (**Figure 1**). We included studies that (1) had a randomized control design; (2) evaluated the impact of pharmacist care delivered by pharmacist, community pharmacist, hospital pharmacist, or clinical pharmacist; and (3) were conducted among adults outpatients with any modifiable CVD risk factors (hypertension, dyslipidemia, diabetes, smoking, or obesity), irrespective of whether they were receiving CVD pharmacological treatment, compared with a usual care group. Outcomes of interest for this study were systolic and diastolic BP, total cholesterol (TC), LDL-C, or smoking. Studies involving only diabetic patients were not included. Disagreements were resolved by discussion. Based on a recent systematic review on pharmacist care of patients with heart failure,[21] the classification of pharmacist interventions was made using a priori–defined categories: pharmacist-directed care (pharmacist initiated and managed interventions) and pharmacist collaborative care (pharmacist collaborated in interventions conducted by a multidisciplinary health care team).

DATA EXTRACTION AND RISK OF BIAS IN INCLUDED STUDIES

Data extraction was independently performed by 2 authors (V.S. and A.C.) using a standardized data collection form. From each included study, information was abstracted on the following: (1) study author, year of the publication, and country where the study was conducted; (2) study characteristics (including study setting and design, duration of follow-up and sample size); (3) characteristics of participants (including sex, age, CVD risk factors, and medications); (4) characteristics of interventions (including description and frequency of the pharmacist intervention); (5) characteristics of usual care group; and (6) types of outcome measure (including change in BP from baseline, BP at follow-up; change in LDL-C and TC levels from baseline, LDL-C and

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Table 1. Characteristics of Included Studies: Study Setting and Design, Sample Size, and Study Participants

Source; Country	Study Setting	Study Design, Duration	Sample Size, Total No. (Intervention/Usual Care)	Study Participants; Mean Age
		Pharmacist-Directed Care		
Chiu et al,[26] 2008; Taiwan	Outpatient clinic	RCT, 6 mo	154 (78/76)	Patients with previous ischemic stroke; 65 y
Dent et al,[27] 2009; US	Outpatient clinic	RCT, 6 mo	101 (50/51)	Smokers with ≥1 cigarettes daily for 7 d and ready to quit in the next 2 wk; 56 y
Ellis et al,[28] 2000; US	Outpatient clinic	RCT, 12 mo	TC, 342 (162/180); LDL-C, 241 (117/124)	Controlled or uncontrolled dyslipidemic patients (LDL-C ≥130 mg/dL; LDL-C ≥100 mg/dL if diabetes or CAD present) at high risk for drug-related adverse events (high number of Meds); 66 y
Faulkner et al,[29] 2000; US	Outpatient clinic	RCT, 24 mo	30 (15/15)	Uncontrolled dyslipidemic patients (LDL-C >130 mg/dL) who had undergone CABG or PTCA and taking lipid-lowering Med; 63 y
Garção and Cabrita,[30] 2002; Portugal	Community pharmacy	RCT, 6 mo	82 (41/41)	Controlled or uncontrolled hypertensive patients taking antihypertensive Med; 65 y
Green et al,[31] 2008; US	Outpatient clinic	RCT, 12 mo	520 (261/259)	Uncontrolled hypertensive patients (BP, 140-199/90-109 mm Hg) taking antihypertensive Med; 59 y
Lee et al,[32] 2006; US	Outpatient clinic	RCT, 6 mo	BP, 135 (73/62); LDL-C, 121 (64/57)	Elderly (age ≥65 y) taking ≥4 long-term Med daily; 77 y
McKenney et al,[33] 1973; US	Community pharmacy	RCT, 5 mo	49 (24/25)	Uncontrolled hypertensive patients (diastolic BP ≥90 mm Hg) taking antihypertensive Med; 60 y
Mehos et al,[34] 2000; US	Outpatient clinic	RCT, 6 mo	36 (18/18)	Uncontrolled hypertensive patients (BP, 140-179/90-109 mm Hg) taking ≥1 antihypertensive Med; 59 y
McMillan Nola et al,[35] 2000; US	Community pharmacy	RCT, 6 mo	51 (25/26)	Dyslipidemic patients with uncontrolled LDL-C (according to NCEP ATP III guidelines) taking lipid-lowering Med or not; 60 y
Okamoto and Nakahiro,[36] 2001; US	Hypertensive clinic and general medicine clinic	RCT, 6 mo	330 (164/166)	Controlled or uncontrolled hypertensive patients (mild to moderate HT) taking antihypertensive Med; 62 y
Paulós et al,[37] 2005; Chile	Community pharmacy	RCT, 16 wk	42 (23/19)	Controlled or uncontrolled dyslipidemic patients taking lipid-lowering Med; 64 y
Peterson et al,[38] 2004; Australia	Home visit	RCT, 6 mo	81 (39/42)	Controlled or uncontrolled dyslipidemic patients (TC ≥4.0 mmol/L) discharged from hospital with CVD and taking lipid-lowering Med; 64 y
Sookaneknun et al,[39] 2004; Thailand	University community pharmacy and primary care units	RCT, 6 mo	235 (118/117)	Controlled or uncontrolled hypertensive patients (BP ≥140/90 mm Hg; BP ≥130/85 mm Hg if diabetes present) taking antihypertensive Med or not; 63 y
Vial et al,[40] 2002; Australia	Outpatient clinic and community pharmacy	RCT, 12 mo	64 (42/22)	Inpatient smokers with >10 cigarettes per day; 52 y
Villa et al,[41] 2009; Chile	Outpatient clinic and community pharmacy	RCT, 32 wk	138 (81/57)	Controlled or uncontrolled dyslipidemic patients taking lipid-lowering Med; 54 y
Vivian,[42] 2002; US	Outpatient clinic	RCT, 6 mo	53 (26/27)	Uncontrolled hypertensive patients (BP ≥140/90 mm Hg) taking antihypertensive Med; 65 y
Zillich et al,[43] 2005; US	Community pharmacy	Cluster RCT, 3 mo	125 (64/61)	Uncontrolled hypertensive patients (BP, 145-179/95-109 mm Hg; BP, 135-179/90-109 mm Hg if diabetes present) taking 1-3 antihypertensive Med; 65 y

(continued)

TC levels at follow-up; and prevalence of smoking cessation).

Risk of bias in the adequacy of randomization, concealment of allocation, blinding of outcome assessors, completeness of data, selective outcome reporting, and other bias (eg, important baseline imbalance in patient characteristics) was assessed by 2 authors (V.S. and A.C.) using the Cochrane Risk of Bias Tool.[23] For each item, the quality characteristics of each study were rated as (1) low risk of bias; (2) unclear; and (3) high risk of bias. Disagreements between the reviewers (V.S. and A.C.) were resolved by an open dialogue to develop

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Table 1. Characteristics of Included Studies: Study Setting and Design, Sample Size, and Study Participants (continued)

Source; Country	Study Setting	Study Design, Duration	Sample Size, Total No. (Intervention/Usual Care)	Study Participants; Mean Age
		Pharmacist-Collaborative Care		
Bogden et al,[44] 1998; US	Outpatient clinic	RCT, 6 mo	95 (49/46)	Uncontrolled hypertensive patients (BP ≥150/95 mm Hg; BP ≥140/90 if previous CVD or other CVD risk factors present) taking antihypertensive Med or not; 55 y
Bogden et al,[9] 1997; US	Outpatient clinic	RCT, 6 mo	94 (47/47)	Uncontrolled dyslipidemic patients (TC ≥240 mg/dL) taking lipid-lowering Med or not; 58 y
Borenstein et al,[45] 2003; US	Outpatient clinic	RCT, 12 mo	197 (98/99)	Uncontrolled hypertensive patients (BP ≥140/90 mm Hg; BP ≥160/90 mm Hg if age ≥65 y); 62 y
Carter et al,[18] 2008; US	Outpatient clinic	Cluster RCT, 9 mo	179 (101/78)	Uncontrolled hypertensive patients (BP, 145-179/95-109 mm Hg; BP 135-179/85-109 mm Hg if diabetes present) taking antihypertensive Med or not; 61 y
Carter et al,[46] 2009; US	Outpatient clinic	Cluster RCT, 6 mo	402 (192/210)	Uncontrolled hypertensive patients (BP, 140-179/90-109 mm Hg; BP, 130-179/80-109 mm Hg if diabetes present) taking 0 to 3 antihypertensive Med; 58 y
de Castro et al,[47] 2006; Brazil	Outpatient clinic	RCT, 6 mo	64 (30/34)	Uncontrolled hypertensive patients (BP ≥140/90 mm Hg) treated with hydrochlorothiazide; 61 y
Hennesy et al,[25] 2006; US	Outpatient clinic	Cluster RCT, 6 mo	7159 (3617/3542)	Controlled or uncontrolled hypertensive patients taking antihypertensive Med or not; 62 y
Hunt et al,[48] 2008; US	Outpatient clinic	RCT, 12 mo	463 (233/230)	Uncontrolled hypertensive patients (BP ≥160/100 mm Hg); 68 y
Lee et al,[49] 2009; China	Outpatient clinic	RCT, 12 mo	118 (58/60)	Dyslipidemic patients with uncontrolled LDL-C (according to ATP III guidelines goals) taking lipid-lowering Med; 62 y
Santschi et al,[50] 2008; Switzerland	GPs and outpatient clinic	Cluster RCT, 12 mo	68 (34/34)	Uncontrolled hypertensive patients (BP ≥140/90 mm Hg) taking antihypertensive Med; 66 y
Solomon et al,[51] 1998; US	Outpatient clinic	RCT, 6 mo	133 (63/70)	Controlled or uncontrolled hypertensive patients taking antihypertensive Med; 67 y
Villeneuve et al,[52] 2010; Canada	Outpatient clinic	Cluster RCT, 12 mo	225 (108/117)	Uncontrolled dyslipidemic patients (LDL-C ≥2.5 mmol/L; TC/HDL-C ≥4.0 mmol/L for high-risk patients; LDL-C ≥3.5 mmol/L; TC/HDL-C ≥5.0 mmol/L for moderate-risk patients) taking 1 lipid-lowering Med or not; 61 y

Abbreviations: ATP III, Adult Treatment Panel III; BP, blood pressure; CABG, coronary artery bypass graft; CAD, coronary artery disease; CVD, cardiovascular disease; GPs, general practitioners; HDL-C, high-density lipoprotein cholesterol; HT, hypertension; LDL-C, low-density lipoprotein cholesterol; Med, medication; NCEP, National Cholesterol Education Program; PTCA, percutaneous transluminal coronary angioplasty; RCT, randomized controlled trial; TC, total cholesterol.

SI and conventional conversion factor: To convert cholesterol to millimoles per liter, multiply by 0.0259; to convert to milligrams per deciliter, divide by 0.0259.

consensus which was reached without the involvement of a third author.

STATISTICAL ANALYSIS

Statistical analyses were conducted following the recommendations of the *Cochrane Handbook for Systematic Reviews of Interventions*[23] and the PRISMA statement.[24] Data were analyzed using STATA version 11.0 (StataCorp, College Station, Texas). Average intervention effects were calculated as relative risks with 95% confidence intervals (CIs) for dichotomous data using a random effects model. For continuous data, we used a random effects model to calculate weighted mean differences with 95% CIs. We calculated standard deviations from standard errors or 95% CIs presented in the articles if required. Heterogeneity was quantified using the I^2 and the χ^2 test of heterogeneity.[23] Funnel plots were drawn and Egger tests were computed to explore the possibility of publication bias. To explore possible determinants of heterogeneity, we conducted post hoc subgroup analyses according to selected study characteristics. We did not perform a meta-regression, given the relatively limited number of studies. Sensitivity analyses were conducted by (1) excluding relatively small studies (with fewer than 50 participants per randomization group); (2) excluding the study by Hennesy et al,[25] which was the only study in which the pharmacist did not have direct contact with patients; and (3) restricting analysis to studies of good quality.

RESULTS

Searches identified 11 255 potential citations. After initial screening of titles and abstracts, 154 full-text studies were assessed for eligibility and 30 RCTs, all published in the English language, met inclusion criteria (Figure 1).

DESCRIPTION OF STUDIES AND TYPES OF INTERVENTIONS

Table 1 and **Table 2** summarize the characteristics of the included studies. The outcome was BP in 19 studies (10 479 patients),* TC in 9 studies (1121 patients),† LDL-C in 7 studies (924 patients)[28,29,32,35,41,49,52] and smoking in 2 studies (165 patients).[27,40] No study reported obesity or overweight as outcome. Six

*References 18, 25, 26, 30-34, 36, 39, 42-48, 50, 51.

†References 9, 28, 29, 35, 37, 38, 41, 49, 52.

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Table 2. Characteristics of Included Studies: Key Components of Pharmacist Interventions, Intervention Frequency, Usual Care Group, and Outcomes

Source; Country	Key Components of Pharmacist Interventions	Intervention Frequency	Description of Usual Care Group	Outcomes Extracted
	Pharmacist-Directed Care			
Chiu et al,[26] 2008; Taiwan	Education and counseling of Med and lifestyle; counseling of Med compliance; verification of drug interactions	Monthly	No description	Change in BP from baseline
Dent et al,[27] 2009; US	Smoking cessation group program including 1. Education and counseling of Med, establishment of quit date; 2. Cognitive techniques to support change (ie, fear of weight gain); 3. Strategies for prevention of relapses (ie, maintenance of changes) via 3 face-to-face group sessions	3 Times over 5 wk	5- to 10-min Telephone assistance delivered by pharmacist	7-d Point prevalence smoking cessation biochemically confirmed
Ellis et al,[28] 2000; US	Pharmaceutical care including 1. Assessment and adjustment of Med regimen; 2. Identification and prevention of DRPs; 3. Laboratory tests ordered if necessary	At baseline, 6 and 12 mo	No pharmaceutical care	Change in LDL-C and TC from baseline
Faulkner et al,[29] 2000; US	Telephone contact including 1. Patient interview related to Med and prescriptions; 2. Assessment of compliance by pill and packet counts and reasons of noncompliance if applicable	Every week over 12 wk	No telephone contact	Change in LDL-C and TC from baseline
Garção and Cabrita,[30] 2002; Portugal	Pharmaceutical care program including 1. Monthly measure of BP; 2. HT and lifestyle habits education and counseling (educational leaflets about HT, food, and diet); 3. Identification of DRPs; 4. Recommendation to physician regarding Med regimen changes via letter, telephone	Monthly	Usual pharmacy dispensing services (brief counseling, medication review, monitoring for adverse drug reactions)	Change in BP from baseline
Green et al,[31] 2008; US	Pharmacist care management using Web site including 1. Home BP monitoring; 2. Patient education (instructions for home BP monitoring and medications); 3. Telephone call (Med history and cardiovascular risk factors); 4. Recommendation to physician regarding Med changes via Web communications (electronic copy to patients)	Every 2 wk until control BP	Home BP monitoring and patient Web site without pharmacist	Change in BP from baseline
Lee et al,[32] 2006; US	Pharmacy care program including 1. Med education; 2. Med adherence aid (blister pack) and adherence assessment by pill count; 3. Regular follow-up by pharmacists	Every 2 mo	No Med education and no Med adherence aid (blister packs)	BP at follow-up and change in LDL-C from baseline
McKenney et al,[33] 1973; US	Patient interview related to Med and prescriptions; Med education; identification and resolution of DRPs; recommendation to physician regarding Med changes; distribution of additional educational material;	Monthly	Usual care	BP at follow-up

(continued)

cluster RCTs were randomized at pharmacy[43] or provider care level.[18,25,46,50,52] The remaining trials were randomized at patient level.[9,26-42,44,45,47-49,51]

The included studies involved a total of 11 765 participants aged from 52 to 77 years and followed over a mean of 8 months (minimum, 3 months; maximum, 24 months) (Table 1 and Table 2). Overall, 54% of the participants were women. Patients had uncontrolled CVD risk factors in 17 studies and were receiving pharmacological treatment (antihypertensive or lipid-lowering drugs) in 18 studies. In the remaining studies, patients with controlled or uncontrolled CVD risk factors and with or without pharmacological treatment were included.

Most studies (n=20) were conducted in North America. Other studies were conducted in South America (n=3), Asia (n=3), Europe (n=2), and Australia (n=2). Participants were most often followed in outpatients clinics (20 studies), eg, primary care center or family medicine clinic. Five studies were conducted in community pharmacies[30,33,35,37,43] and 5 in both outpatients clinics and community pharmacies.[39-41,50,52] One study involved a pharmacist intervention delivered at home outside of a health care setting.[38]

Eighteen studies were pharmacist-directed care[26-43] and 12 pharmacist-collaborative care (Table 1 and

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Table 2. Characteristics of Included Studies: Key Components of Pharmacist Interventions, Intervention Frequency, Usual Care Group, and Outcomes (continued)

Source; Country	Key Components of Pharmacist Interventions	Intervention Frequency	Description of Usual Care Group	Outcomes Extracted
	Pharmacist-Directed Care (continued)			
McMillan Nola et al,[35] 2000; US	Lipid management program including 1. Education (potential adverse effects and goals of Med therapy) and counseling of Med and lifestyle; 2. Assessment of cholesterol levels; 3. Assessment of Med compliance (refill history and patient's discussion); 4. Communication with physician for DRPs via fax, letters, and telephone calls	Every 4 to 8 wk	Usual counseling	LDL-C and TC at follow-up
Mehos et al,[34] 2000; US	Education of HT and lifestyle using pamphlets; distribution and education of home BP device with diary to document home BP values; change in HT Med and missed doses; telephone contact to evaluate home BP measurements; Med recommendation to physician if BP ≥140/90 mm Hg	Telephone monthly. If BP ≥140/90 mm Hg: visit to physicians	No home BP monitor; counseling on HT medications and lifestyle modifications	Change in BP from baseline
Okamoto and Nakahiro,[36] 2001; US	Counseling of Med; education of HT Med and non-Med; verbally recommendations to physician regarding any Med changes	At pharmacists' or GPs' discretion	No intervention by pharmacist	Change in BP from baseline
Paulós et al,[37] 2005; Chile	Pharmaceutical care program including 1. Counseling of Med and education (brochures about disease and lifestyle); 2. Identification and resolution of DRPs; 3. Reference to physician	5 Times over 16 wk	Usual counseling by pharmacist	Change in TC from baseline
Peterson et al,[38] 2004; Australia	Education of lipid Med, lifestyle and compliance; assessment of DRPs; written clinical recommendations to GP if necessary; measurement of total blood cholesterol	Monthly	Usual care	TC at follow-up
Sookaneknun et al,[39] 2004; Thailand	Measurement of BP; education and counseling of Med, disease and lifestyle (educational leaflets and diary about HT and food); identification of DRPs, resolution, and prevention of DRPs; recommendation to physician regarding Med regimen changes via letter or patient medical record	Monthly	No pharmacist involvement	Change in BP from baseline
Vial et al,[40] 2002; Australia	Smoking cessation program including 1. Distribution of nicotine patch; 2. Weekly counseling visits; 3. Measurement of expired carbon monoxide	Weekly	Advice quitting smoking	Prevalence of continuous abstinence and point prevalence of abstinence
Villa et al,[41] 2009; Chile	Pharmaceutical care program including 1. Education of Med, non-Med, and disease using audiovisual aids and flashcards	Every 2 wk	No intervention	LDL-C and TC at follow-up
Vivian,[42] 2002; US	Counseling of Med and lifestyle; assessment of compliance; change in HT Med (drug selection and dosage)	Monthly	Usual pharmacy dispensing services, no monthly visits	Change in BP from baseline

(continued)

Table 2).[9,18,25,44-52] The interventions exclusively delivered by pharmacist or implemented in collaboration with physicians or nurses included (1) educational interventions directed to patients (defined as education and counseling about medications, lifestyle or compliance; distribution or use of educational material; patient educational workshop) in 26 studies[9,25-27,30-45,47-52]; (2) patient-reminder systems (defined as telephone contact; using Web site; home visit; or drug adherence aids) in 9 studies‡; (3) medication management (defined as medication review from medical records or patient interview; assessment of medication compliance; monitoring of medication therapy such as assessment, adjustment, or change of medications) in 22 studies§; (4) feedback to health care professional (defined as drug-related problems (DRPs) identification; recommendation to physicians regarding medications change; meeting with team to discuss care) in 24 studies‖; (5) measurement of CVD risk factors or reviewing of laboratory data by pharmacist during follow-up in 12 studies¶; and (6) an educational intervention directed to

‡*References 18, 29, 31, 32, 34, 38, 43, 49, 50.*

§*References 9, 18, 26, 28, 29, 31-33, 35, 38, 39, 41, 42, 44-52.*

‖*References 9, 18, 25, 28, 30, 31, 33-39, 41, 43-52.*

¶*References 9, 28, 30, 31, 34, 35, 38-40, 43-45.*

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Table 2. Characteristics of Included Studies: Key Components of Pharmacist Interventions, Intervention Frequency, Usual Care Group, and Outcomes

Source; Country	Key Components of Pharmacist Interventions	Intervention Frequency	Description of Usual Care Group	Outcomes Extracted
	Pharmacist-Directed Care (continued)			
Zillich et al,[43] 2005; US	Education of HT Med, disease (handouts about BP) and home BP technique; distribution of home BP device; suggestion of drug adherence aids if necessary; written treatment recommendations to physician regarding intensification of Med regimen; contact with physician to develop treatment plan; patient education related to treatment plan	4, 6-8, and 12 wk	Meeting with pharmacist, BP measurement, no education; no home BP monitors; no written recommendations; no contact with physician	Change in BP from baseline
	Pharmacist-Collaborative Care			
Bogden et al,[44] 1998; US	Review of HT Med; counseling of Med compliance; review of laboratory data with physicians; recommendation to physician regarding the least costly HT Med via patient medical chart **Team members: physician**	Every patient encounter	Access to pharmacy clerk to answer HT Med questions initiated by patient; no recommendations to physician	Change in BP from baseline
Bogden et al,[9] 1997; US	Review of Med; counseling of Med compliance; review of laboratory data with physicians; recommendation to physician regarding Med changes and the least costly Med via patient medical chart; no dietary advice **Team members: physician**	Every patient encounter	Access to pharmacy clerk to answer Med questions initiated by patient; no recommendations to physician	Change in TC from baseline
Borenstein et al,[45] 2003; US	Measurement of BP; patient interview related to HT Med, compliance and lifestyle; education of dietary and lifestyle; recommendation to physician regarding Med changes via telephone call **Team members: physician and nurse**	Every 2-4 wk at pharmacist's discretion	No intervention	Change in BP from baseline
Carter et al,[18] 2008; US	Patient interview related to Med; verbally or written recommendation to physician regarding HT Med changes; recommendation of Med compliance aids if necessary **Team members: physician and nurse**	2, 4, 6, and 8 mo; additional visit or telephone contact if BP was uncontrolled	No recommendations to physician	Change in BP from baseline
Carter et al,[46] 2009; US	Assessment and adjustment of HT Med approved by physicians; assessment of BP; verbally drug recommendations to physicians; education to physician if necessary **Team members: physician**	At baseline, 3 and 6 mo	Usual counseling by pharmacist	Change in BP from baseline
de Castro et al,[47] 2006; Brazil	Pharmaceutical care program including 1. Review of HT Med; 2. Patient interview related to HT Med, lifestyle and compliance; 3. Distribution of printed educational materials related to HT Med; 4. DRPs identification and resolution; 5. Discussion with physician related to identified DRPs **Team members: physician**	Monthly	No printed educational materials; no Med education	Change in BP from baseline

(continued)

health care professional (defined as a training program or distribution of educational material to other health care professionals including physicians) in 2 studies.[25,46]

METHODOLOGICAL QUALITY OF INCLUDED STUDIES

The studies were of variable methodological quality (see eFigure). Information on allocation concealment or blinding to outcome assessors was not described in most studies. None of the study blinded study participants to the pharmacist intervention. Most of the studies were free of selective outcome reporting.

OUTCOMES

Blood Pressure

The majority of the 19 studies demonstrated beneficial and statistically significant differences in systolic and diastolic BP between pharmacist and usual care groups (**Figure 2**). No study demonstrated a statistically significant difference in favor of the usual care group. The pooled estimate of the 19 RCTs showed a significant reduction in BP for pharmacist care compared with usual care (weighted mean difference in systolic BP, −8.1 mm Hg [95% CI, −10.2 to −5.9], $P<.001$; weighted mean difference in diastolic BP,

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Table 2. Characteristics of Included Studies: Key Componevnts of Pharmacist Interventions, Intervention Frequency, Usual Care Group, and Outcomes (continued)

Source; Country	Key Components of Pharmacist Interventions	Intervention Frequency	Description of Usual Care Group	Outcomes Extracted
	Pharmacist-Collaborative Care (continued)			
Hennesy et al,[25] 2006; US	Health care professionals education (educational materials about BP targets); presentation of audit report to health care professionals (proportion of patients with BP control); mailing of educational and motivational materials to patients **Team members: physician**	Once over 6 mo	No audit; no health professional education	BP at follow-up
Hunt et al,[48] 2008; US	Review of Med and lifestyle habits; DRPs assessment; written recommendation to physician regarding HT Med selection, dosage and changes **Team members: physician**	At pharmacist's discretion	Routine medical care	BP at follow-up
Lee et al,[49] 2009; China	Education and counseling of Med and lifestyle (leaflets about target LDL-C goal, Med compliance, adverse effects of Med and dietary suggestions); assessment of Med compliance (pill counts and patient's discussion); telephone follow-up related to drug intake and non-Med (over-the-counter drugs intake or Chinese medicine); assessment of DRPs; discussion with physicians related to DRPs; written recommendation to physician regarding reasons of noncompliance **Team members: physician**	Telephone follow-up every 4 wk	Routine conventional care; no pharmacist-initiated service provided	Change in LDL-C and TC from baseline
Santschi et al,[50] 2008; Switzerland	Monitoring and support Med adherence with electronic device (adherence report); discussion with GP and physician if necessary **Team members: GPs**	2, 4, 6, and 12 mo	Usual pharmacy dispensing services (no special effort being made to improve patient adherence)	BP at follow-up
Solomon et al,[51] 1998; US	Pharmaceutical care including 1. Education and counseling of HT Med and disease; 2. Assessment of Med compliance (self-reporting and pill counts); 3. Written recommendation to physician or patient regarding Med selection, regimen and compliance **Team members: physician**	Monthly	No access to pharmacist; no supplementary education	BP at follow-up
Villeneuve et al,[52] 2010; Canada	Primary care management program including 1. Patient counseling of Med and lifestyle changes using a patient decision aid; 2. Assessment of Med compliance and drug efficacy; 3. Adjustment of statin dosage; 4. Report to physician by fax **Team members: physician**	At baseline and every 2 mo	Usual care and counseling by pharmacist	Change in LDL-C and TC from baseline

Abbreviations: BP, blood pressure; DRPs, drug-related problems; GPs, general practitioners; HT, hypertension; LDL-C, low-density lipoprotein cholesterol; Med, medication; TC, total cholesterol.

−3.8 mm Hg [95% CI, −5.3 to −2.3], $P<.001$). A substantial heterogeneity was observed for both systolic (I^2=75.5%) and diastolic BP (I^2=85.3%).

TC and LDL-C

Of the 9 studies reporting TC level, 6 demonstrated a statistically significant benefit of pharmacist care (**Figure 3**A). Of the 7 studies reporting LDL-C level, 4 demonstrated a statistically significant benefit of pharmacist care (Figure 3B). For both outcomes no study demonstrated a statistically significant difference in favor of the usual care group. The pooled estimate showed a significant reduction in TC level (weighted mean difference, −17.4 mg/L [95% CI, −25.5 to −9.2], $P<.001$) and LDL-C (weighted mean difference, −13.4 mg/L [95% CI, −23.0 to −3.8], P=.006) for pharmacist care compared with usual care. A substantial heterogeneity was also observed for both TC (I^2=78.5%) and LDL-C (I^2=86.5%) levels.

Smoking

Two studies suggested that pharmacist care helped decrease smoking (**Figure 4**). The pooled estimate showed a statistically significant reduction in smoking for pharmacist care compared with the usual care (relative risk, 0.77 [95% CI, 0.67 to 0.89], P=.001). No significant heterogeneity was observed.

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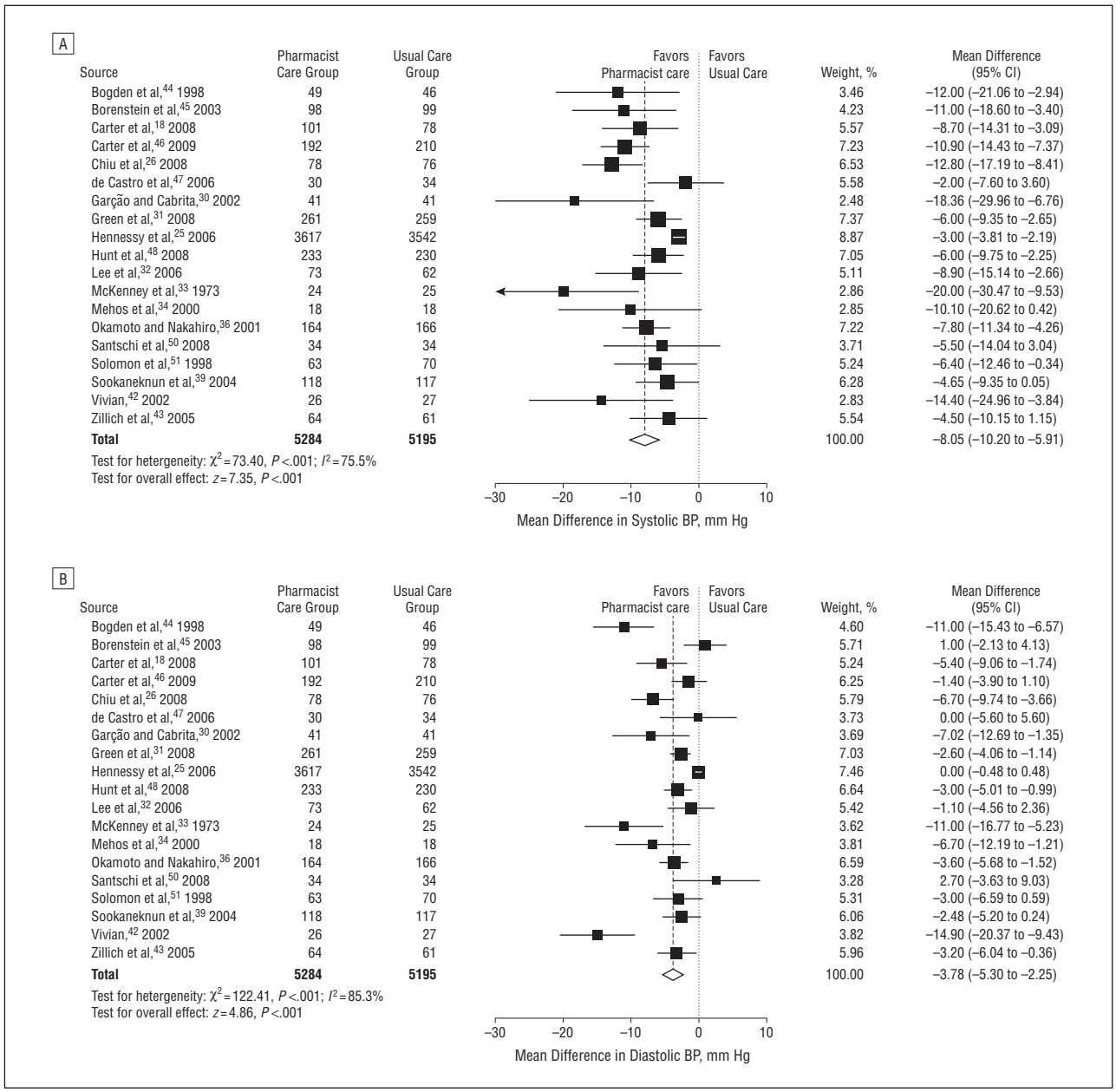

Figure 2. Forest plots of the mean difference in systolic (A) and diastolic (B) blood pressure (BP) with the pharmacist care group compared with the usual care group. CI indicates confidence interval.

Subgroup Analyses

To explore the possible differences between studies and in view of the substantial heterogeneity, post hoc subgroup analyses were conducted according to the type of pharmacist care, the type and number of interventions, and the inclusion of uncontrolled or a mix of controlled and uncontrolled hypertensive patients (**Table 3**). These analyses were conducted for the outcome BP, for which a relatively large number of studies were available (n = 19). Pharmacist-directed care and pharmacist-collaborative care were both associated with statistical reductions in systolic and diastolic BP, but no major differences were demonstrated between the 2 types of pharmacist care (pharmacist-directed care: weighted mean difference in systolic BP, −9.1 mm Hg [95% CI, −11.7 to −6.4]; weighted mean difference in diastolic BP, −5.1 mm Hg [95% CI, −7.0 to −3.1]; and pharmacist-collaborative care: weighted mean difference in systolic BP, −6.8 mm Hg [95% CI, −9.7 to −3.9]; and weighted mean difference in diastolic BP, −2.2 mm Hg [95% CI, −4.6 to −0.2]) (Table 3). Moreover, there were no major differences in BP reductions according to the type or the number of interventions or to the control of BP.

Publication Bias

We explored the possibility of publication bias for studies in which the outcome was BP (n = 19). For both systolic and diastolic BP, asymmetry in the funnel plots was observed and an Egger test result was statistically significant, indicating a potential publication bias.

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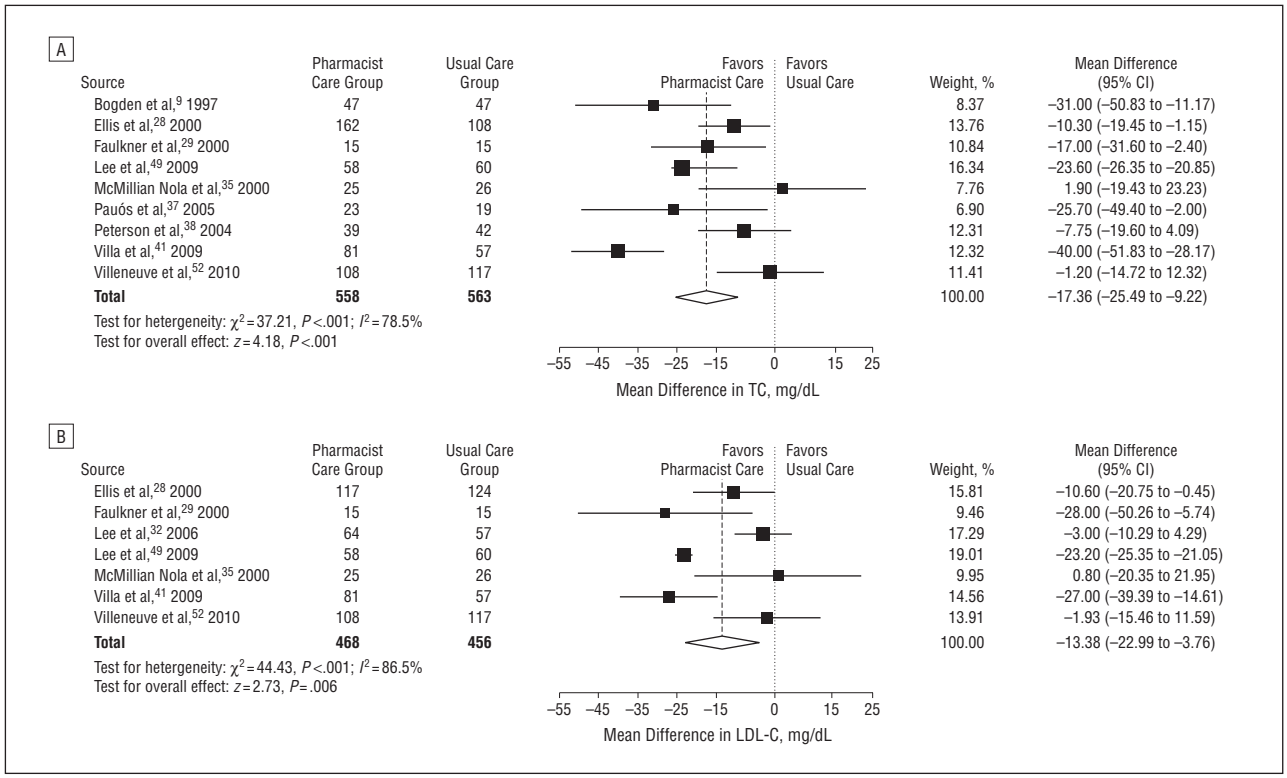

Figure 3. Forest plot of the mean difference in total cholesterol (TC) (A) and low-density lipoprotein cholesterol (LDL-C) (B) with the pharmacist care group compared with the usual care group. To convert LDL-C to millimoles per liter, multiply by 0.0259.

Sensitivity Analyses

Because of potential publication bias, a first sensitivity analysis was performed to explore the influence of relatively small studies (with fewer than 50 participants per randomization group; n=7).[30,33,34,42,44,47,50] After exclusion of these studies from the meta-analysis, a similar reduction in BP for pharmacist care compared with usual care group was observed (systolic BP mean difference, −7.3 mm Hg [95% CI, −9.6 to −5.0], I^2=78.5%; diastolic BP mean difference, −2.5 mm Hg [95% CI, −3.8 to −1.2], I^2=80.3%).

The second sensitivity analysis was performed to assess the influence of the study by Hennessy et al,[25] which was the only study in which the pharmacist had no direct contact with patients. After exclusion of this study from the meta-analysis, a similar reduction in BP for the pharmacist care group compared with the usual care group was observed (sys tolic BP mean difference, −8.3 mm Hg [95% CI, −10.1 to −6.5], I^2=41.9%; diastolic BP mean difference, −4.0 mm Hg [95% CI, −5.5 to −2.6], I^2=72.7%).

To explore the impact of study quality on the effect estimates, a third sensitivity analysis was conducted restricting analysis to studies of good quality. A study was of "good quality" if it had a low risk of bias on 3 items or more (of 6) using the Cochrane Risk of Bias Tool.[23] Of 19 studies with the BP outcome, 8[18,31,35,43,44,46,48,49] (assessing 1955 participants) were of good quality and showed similar significant reductions in BP for the pharmacist care group compared with the usual care group (systolic BP mean difference, −7.8 mm Hg [95% CI, −9.6 to −6.0], I^2=6.5%; diastolic BP mean difference, −3.8 mm Hg [95% CI, −5.3 to −2.3], I^2=64.4%).

COMMENT

Our systematic review, identifying 30 RCTs that assessed 11 765 outpatients, supports the benefit of pharmacist care interventions in the management of major CVD risk factors among outpatients. Pharmacist interventions achieved greater reductions in systolic and diastolic BP, TC, and LDL-C, and in the risk of smoking compared with the usual care group. The most frequent interventions, exclusively provided by pharmacists or implemented in collaboration with physicians or nurses, were (1) educational interventions for patients (education and counseling about medications, lifestyle, or compliance); (2) feedback to physician (DRPs identification, recommendation to physician regarding medications), and (3) medication management (medication review from medical records and monitoring of drug therapy such as adjustment or change of medications).

Our results underscore the significant benefits of pharmacist interventions in CVD risk factors and are in line with those of a previous narrative review, which suggested that pharmacist-led interventions were associated with a better control of some CVD risk factors (hypertension and dyslipidemia) in outpatients.[22] Furthermore, our findings are supported by a recent systematic review[53] evaluating the effect of pharmacist as team members on patient care. In this review, Chisholm-Burns et al[53] reported a mean differ-

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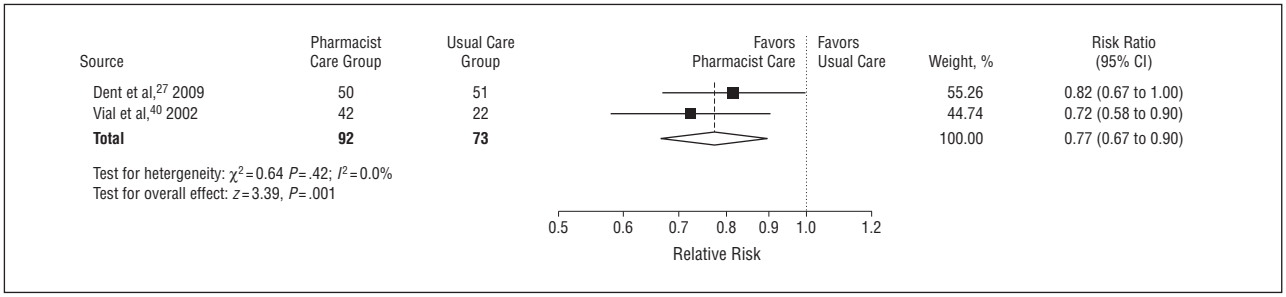

Figure 4. Forest plot of the relative risk of smoking with the pharmacist care group compared with the usual care group.

Table 3. Subgroup Analyses for the Difference in Systolic and Diastolic BP With Pharmacist Care Compared With Usual Care Group According to Selected Study Characteristics

Study Characteristics	No. of Studies	Mean Difference (95% CI)	
		Systolic BP	Diastolic BP
All studies	19	−8.1 (−10.2 to −5.9)	−3.8 (−5.3 to −2.3)
Type of pharmacist care			
Pharmacist-directed care	10	−9.1 (−11.7 to −6.4)	−5.1 (−7.0 to −3.1)
Pharmacist-collaborative care	9	−6.8 (−9.7 to −3.9)	−2.2 (−4.6 to −0.2)
Type of interventions			
Educational interventions to patients			
Yes	17	−7.7 (−9.9 to −5.5)	−3.9 (−5.5 to −2.2)
No	2	−10.3 (−13.3 to −7.3)	−3.2 (−7.1 to 0.7)
Patient-reminder systems			
Yes	6	−6.7 (−9.0 to −4.5)	−2.9 (−4.6 to −1.2)
No	13	−8.7 (−11.6 to −5.8)	−4.3 (−6.4 to −2.2)
Measurement of CVD risk factors			
Yes	7	−7.4 (−10.2 to −4.6)	−4.0 (−6.3 to −1.6)
No	12	−8.1 (−11.0 to −5.3)	−3.7 (−5.7 to −1.6)
Educational interventions to health care professionals			
Yes	2	−6.8 (−14.5 to −1.0)	−0.1 (−1.0 to 0.7)
No	17	−8.0 (−9.9 to −6.2)	−4.2 (−5.8 to −2.7)
Feedback to health care professionals			
Yes	16	−7.3 (−9.5 to −5.2)	−3.2 (−4.7 to −1.7)
No	3	−11.8 (−15.2 to −8.4)	−7.3 (−13.9 to −0.6)
Medication management			
Yes	14	8.4 (−10.4 to −6.3)	−3.9 (−5.8 to −2.1)
No	5	−6.7 (−10.6 to −2.7)	−3.4 (−6.2 to −0.6)
No. of interventions			
≤3	9	−9.7 (−13.6 to −5.7)	−4.5 (−7.2 to −1.8)
≥4	10	−6.5 (−8.2 to −4.8)	−3.3 (−4.9 to −1.6)
Type of hypertensive patients			
Uncontrolled	12	−9.3 (−12.4 to −6.1)	−4.9 (−7.3 to −2.6)
Mix of uncontrolled and controlled	7	−6.8 (−9.1 to −4.5)	−2.4 (−3.5 to −1.3)

Abbreviations: BP, blood pressure; CI, confidence interval; CVD, cardiovascular disease.

ence between the pharmacist group and the comparison group of −6.3 mg/dL (95% CI, −6.5 to −6.0) in LDL-C, −7.8 mm Hg (95% CI, −9.7 to −5.8) in systolic BP, and −2.9 mm Hg (95% CI, −3.8 to −2.0) in diastolic BP. Nevertheless, this review was restricted to studies conducted in the United States and evaluated only interventions of pharmacist as a team member, ie, pharmacist-collaborative care interventions. Furthermore, no sensitivity analyses were conducted in this review.

Pharmacist interventions varied among the identified studies and possibly included several cointerventions. Therefore, it was difficult to clearly delineate the different types of interventions, making it difficult to precisely identify which intervention was more efficient to help the management of CVD risk factors among outpatients. Our analyses that were restricted to studies assessing BP, the most frequently reported outcome, did not allow us to identify which intervention was more efficient to decrease BP. A systematic review of pharmacist care among patients with heart failure suggested that pharmacist interventions implemented in collaboration with physicians or nurses were more efficient to reduce the rate of hospitalizations compared with interventions exclusively provided by pharmacists.[21] Nevertheless, our review did not show better outcomes in favor of pharmacist interventions exclusively provided by pharmacists or in favor of pharmacist interventions implemented in collaboration with physicians or nurses. Therefore, further studies are needed to define and evaluate which pharmacist interventions are the most effective for the management of CVD risk factors in different health care system organizations or jurisdictions.

The traditional view of the pharmacist's role in primary care is medication distribution. Although this

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role remains an important part of the activity of a pharmacist, evidence documented in our systematic review and previous reviews[21,53] demonstrates a transformation of pharmacy practice toward a more clinical, patient-centered role and a collaborative approach toward pharmacist-physician in patient care. The enhanced role of the pharmacist as member of CVD health care is more successfully implemented and accepted in North America health care system compared with the European health care system. Indeed, most studies# identified in our review were conducted in North America and only 2 studies[30,50] were conducted in Europe.

Our review has some limitations. First, although we conducted a rigorous and systematic review, we did not search for unindexed and unpublished literature. Our analyses indicate a potential publication bias that suggests that studies reporting favorable results of pharmacist interventions were more likely published than those reporting negative results.[23] Consequently, the average estimates of the effect of pharmacist interventions may be overestimated. However, our sensitivity analysis, which excluded relatively small studies, showed that the estimate of the effect of pharmacist interventions on BP was similar to the analysis including all studies. Second, while most studies favored pharmacist care compared with usual care, a substantial heterogeneity was observed in the effect of pharmacists' interventions on BP, TC, and LDL-C, which suggests a large variation in the effect of pharmacist interventions.[53] As we expected heterogeneity, we used random effects analysis to allow for differences in the treatment effect from study to study.[54] Differences in terms of interventions and setting, disease severity of patients or cointerventions may explain this heterogeneity. We explored the potential sources of heterogeneity by conducting subgroup analyses by the type of pharmacist care and the type of pharmacist interventions. We found no difference in effect on BP according to the type of pharmacist care and the type of interventions. Moreover, sensitivity analyses accounting for study quality and study size reported similar effects on BP. We also investigated whether differences were observed between studies including uncontrolled or a mix of controlled and uncontrolled hypertensive patients but found no major differences. Other potential causes of heterogeneity could be comorbidities, number of medications, or age of the patients but would have required individual level data to be identified.[55]

Despite these limitations, our review had unique strengths. Our review was conducted following the *Cochrane Handbook for Systematic Reviews of Interventions*[23] and the PRISMA statement.[24] Our review was systematic in its coverage; considered major modifiable CVD risk factors, such as hypertension, dyslipidemia, and smoking; and included studies assessing the effect of pharmacist-directed care as well as pharmacist-collaborative care.

In conclusion, our results support the beneficial role of pharmacist care in the management of CVD risk factors among outpatients. Given the difficulties in accessing primary care physicians, the integration of pharmacist in the care of outpatients should be considered as a valuable solution for improving the management of CVD risk factors. Further studies are needed to identify which type of pharmacist interventions are best suited to help manage CVD risk factors and how this type of pharmacist care could be enhanced in various health care systems.

#References 9, 18, 25, 27-29, 31-36, 42-46, 48, 51, 52.

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Author Contributions: Drs Santschi and Chiolero had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Santschi, Chiolero, Burnand, and Paradis. *Acquisition of data:* Santschi, Chiolero, and Colosimo. *Analysis and interpretation of data:* Santschi, Chiolero, Burnand, and Paradis. *Drafting of the manuscript:* Santschi and Chiolero. *Critical revision of the manuscript for important intellectual content:* Santschi, Chiolero, Burnand, Colosimo, and Paradis. *Statistical analysis:* Santschi, and Chiolero. *Obtained funding:* Paradis. *Administrative, technical, and material support:* Santschi, Chiolero, and Paradis. *Study supervision:* Burnand and Paradis.

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Online-Only Material: The eAppendix and eFigure are available at http://www.archinternmed.com.

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