

Pharmacist Interventions to Improve Cardiovascular Disease Risk Factors in Diabetes

A systematic review and meta-analysis of randomized controlled trials

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OBJECTIVE—This systematic review and meta-analysis of randomized controlled trials (RCTs) assesses the effect of pharmacist care on cardiovascular disease (CVD) risk factors among outpatients with diabetes.

RESEARCH DESIGN AND METHODS—MEDLINE, EMBASE, CINAHL, and the Cochrane Central Register of Controlled Trials were searched. Pharmacist interventions were classified, and a meta-analysis of mean changes of blood pressure (BP), total cholesterol (TC), LDL cholesterol, HDL cholesterol, and BMI was performed using random-effects models.

RESULTS—The meta-analysis included 15 RCTs (9,111 outpatients) in which interventions were conducted exclusively by pharmacists in 8 studies and in collaboration with physicians, nurses, dietitians, or physical therapists in 7 studies. Pharmacist interventions included medication management, educational interventions, feedback to physicians, measurement of CVD risk factors, or patient-reminder systems. Compared with usual care, pharmacist care was associated with significant reductions for systolic BP (12 studies with 1,894 patients; -6.2 mmHg [95% CI -7.8 to -4.6]); diastolic BP (9 studies with 1,496 patients; -4.5 mmHg [-6.2 to -2.8]); TC (8 studies with 1,280 patients; -15.2 mg/dL [-24.7 to -5.7]); LDL cholesterol (9 studies with 8,084 patients; -11.7 mg/dL [-15.8 to -7.6]); and BMI (5 studies with 751 patients; -0.9 kg/m² [-1.7 to -0.1]). Pharmacist care was not associated with a significant change in HDL cholesterol (6 studies with 826 patients; 0.2 mg/dL [-1.9 to 2.4]).

CONCLUSIONS—This meta-analysis supports pharmacist interventions—alone or in collaboration with other health care professionals—to improve major CVD risk factors among outpatients with diabetes.

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Cardiovascular disease (CVD) is the major cause of death in patients with diabetes and is about two times more frequent in these patients compared with people without diabetes (1). Although studies have demonstrated that control of major CVD risk factors, such as hypertension or dyslipidemia, reduces the risk of cardiovascular complications

among patients with diabetes (2–5), CVD risk factors remain poorly controlled in these patients (5–7). Therefore, effective interventions and new models of care are needed to improve management of CVD risk factors among patients with diabetes, particularly in light of the increase in health care costs and the increasing problems with access to primary care

physicians in most health care systems (8). A recent systematic review evaluating the effect of pharmacists as team members on patient care in the United States has underlined the integration of pharmacists as a health care team member and provider of health services (9).

Pharmacists can therefore help fill the gap as primary care providers and can contribute to the control of CVD risk factors by their knowledge of medications, their easy accessibility for patients, and their collaborative practice with physicians (9–13). More specifically, pharmacists have the opportunity to provide medication instructions to patients at each prescription, to improve safe medication use, and to assist physicians in chronic care (12,14,15). In a recent meta-analysis, we showed that pharmacist care improves the management of outpatients with major modifiable CVD risk factors (15). However, studies conducted solely in outpatients with diabetes were not included in that meta-analysis. Other reviews have evaluated pharmacist interventions in the management of diabetes but focused solely on glycemic control (16), did not include only randomized controlled trials (RCTs), or did not pool data (17–19). Consequently, the objective of this systematic review and meta-analysis of RCTs is to assess the effect of pharmacist care on major CVD risk factors among outpatients with diabetes.

RESEARCH DESIGN AND METHODS

—We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement to conduct our systematic review (20).

Inclusion criteria and outcomes

We included studies that 1) had a RCT design; 2) evaluated the effect of pharmacist care delivered by a community, hospital, or clinical pharmacist; 3) among adults outpatients with diabetes (type 1 or 2) and with any modifiable major CVD risk factors (hypertension, dyslipidemia, smoking, or obesity); and 4) compared with a usual

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care group. Outcomes were systolic and diastolic BP, total cholesterol (TC), LDL cholesterol, HDL cholesterol, and BMI. We did not consider fasting blood glucose or glycosylated hemoglobin (A1C) as outcomes because they are not classical CVD risk factors and, in addition, were recently the subject of a systematic review assessing the effect of pharmacist care on metabolic control among patients with diabetes (16).

Search strategy

In collaboration with a research medical librarian (A.L.C.), electronic databases including MEDLINE via PubMed (1950 to March 2012), EMBASE (1980 to March 2012), CINAHL (1937 to March 2012), and the Cochrane Central Register of Controlled Trials (up to March 2012) were searched for randomized controlled studies of the impact of pharmacist care on major CVD risk factors among outpatients with diabetes, published in any language. Inclusion criteria and methods of analysis were specified in advance and documented in a protocol available upon request.

The PubMed search syntax served as the basis for all search strategies, using Medical Subject Headings (MeSH) and text terms with Boolean operators. The syntax consisted of three search themes intersected by the Boolean term "AND." MeSH terms included cardiovascular disease-related terms ("Cardiovascular Diseases," "Dyslipidemias," "Diabetes Mellitus," "Smoking," "Overweight") and pharmacist-related terms ("Pharmacists," "Pharmaceutical Services," "Pharmacy Service, Hospital," "Pharmacies," "Pharmacy"). The search was focused on randomized controlled studies 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 database searches, we also conducted a hand search of bibliographies of all relevant articles. The detailed search strategy used is described in the Supplementary Data online.

Methods of the review

Two reviewers (V.S. and A.C.) independently screened all titles and abstracts and then examined the full text of each potentially eligible article using prespecified inclusion criteria (Fig. 1). Disagreements about study selection were resolved by discussion.

Data extraction

Two reviewers (V.S. and A.C.) independently extracted data using a standardized

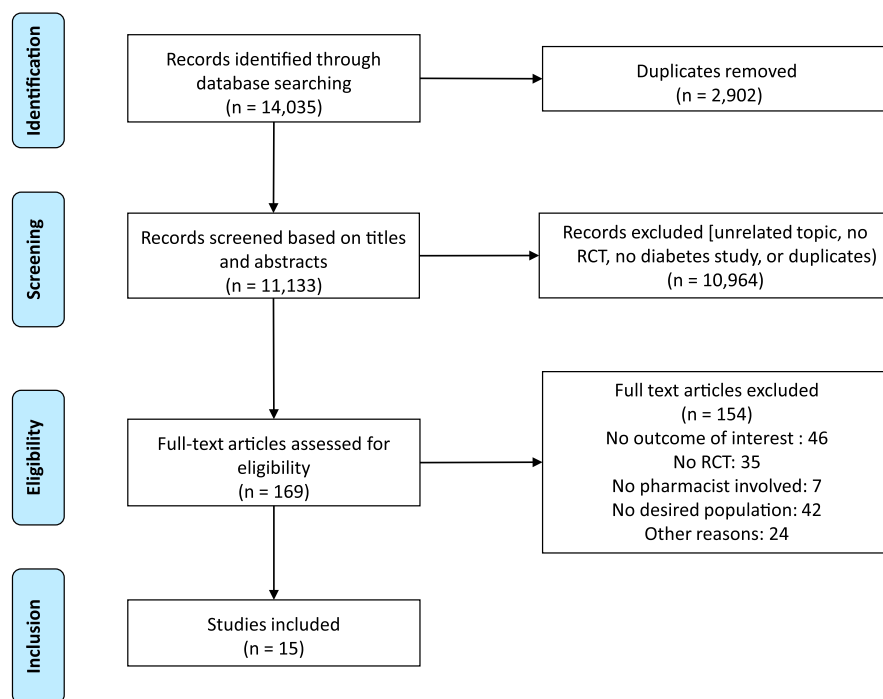


Figure 1—Selection of studies for systematic review of pharmacist care interventions. (A high-quality color representation of this figure is available in the online issue.)

collection form. From each included study, the following characteristics were abstracted: 1) study authors and country and year of the publication; 2) study characteristics (study setting and design, duration of follow-up, sample size); 3) characteristics of participants (sex, age, CVD risk factors, medications); 4) characteristics of interventions (description and frequency of the pharmacist intervention); 5) characteristics of the usual care group; and 6) outcome measures (change in BP, TC, LDL cholesterol, HDL cholesterol, and BMI between baseline and follow-up).

Pharmacist interventions were classified using a priori–defined categories based on a recent systematic review of pharmacist care of patients with heart failure (21) as pharmacist-directed care (pharmacist initiated and managed interventions) and pharmacist collaborative care (pharmacist collaborated in interventions conducted by a multidisciplinary healthcare team).

Assessment of the methodological quality of individual studies

Using the Cochrane Risk of Bias Tool (22), two reviewers (V.S. and A.C.) independently assessed the quality (risk of bias) of each study regarding the following domains: adequacy of randomization, concealment of allocation, blinding of outcome assessors, completeness of data, selective outcome reporting, and “other bias.”

As recommended, we rated each item as 1) “low risk of bias” if it is unlikely that a bias seriously alters the results; 2) “unclear” if it is plausible that a bias raises some doubt about the results; and 3) “high risk of bias” if it is plausible that a bias seriously weakens confidence in the results. Disagreements were resolved by discussion.

Statistical analysis

Statistical analyses were conducted following the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions (22) and the PRISMA statement (20). Data were analyzed using STATA 11.0 software (StataCorp LP, College Station, TX). The meta-analysis was conducted using a random-effects model because of the a priori heterogeneity (15). Pooled intervention effect estimates are reported as weighted mean differences with 95% CI. We calculated SDs from SEs or CIs presented in the reports, if required. The χ^2 and I^2 statistics were used to assess statistical heterogeneity across studies, with I^2 values of 50% or more indicating a substantial level of heterogeneity (22). Post hoc subgroup analyses were conducted according to the type of pharmacist care, the type and the number of interventions, and the setting of care. Funnel plots were drawn, and Egger tests were computed to explore a potential publication bias. Sensitivity analyses were conducted

by excluding relatively small studies and restricting analysis to good-quality studies.

RESULTS

Results of the research and the included studies

Initially, 14,035 citations were identified (Fig. 1). After initial screening of titles and abstracts, 169 potentially relevant full-text

articles were reviewed for eligibility. The review included 15 RCTs, all published in English, involving 9,111 participants.

Details of the included studies, including the characteristics of the participants, the interventions of the pharmacist, and the outcome are given in Tables 1 and 2. The 9,111 participants (52% women) were a mean age of 63 years (range 49–70). The mean duration of follow-up was 11 months

(range 4–24). Participants were most often followed up in outpatient clinics (12 studies); for example, Veterans Affairs Medical Centers or primary care clinics. Three studies were conducted in community pharmacies (8,23,24). Nine of the 15 studies were conducted in North America (7 in the U.S. and 2 in Canada), 4 in Asia (Thailand, China, United Arab Emirates, and India), 1 in Europe (Spain), and 1 in Australia.

Table 1—Characteristics of the included studies: study setting and design, sample size, and study participants

Source; country	Study setting	Study design, duration	Sample size (intervention/usual care)	Study participants; mean age
Pharmacist-directed care				
Al Mazroui et al., 2009 (25); United Arab Emirates	Outpatient clinic	RCT, 12 months	234 (117/117)	Patients with type 2 diabetes taking oral hypoglycemic Med; 49 years
Chan et al., 2012 (26); Hong Kong	Outpatient clinic	RCT, 9 months	105 (51/54)	Patients with uncontrolled type 2 diabetes (A1C ≥ 8%), taking at least 5 Meds including one hypoglycemic Med; 62 years
Fornos et al., 2006 (23); Spain	Community pharmacy	RCT, 13 months	112 (56/56)	Patients with diabetes taking oral antidiabetic Med; 64 years
Kraemer et al., 2012 (24); U.S.	Community pharmacy	RCT, 12 months	67 (36/31)	Employees with type 1 or 2 diabetes; 54 years
Phumipamorn et al., 2008 (27); Thailand	Outpatient clinic	RCT, 8 months	A1C, TC, HDL-C, 130 (63/67); LDL-C, 108 (53/55)	Patients with diabetes (A1C >7%); 54 years
Planas et al., 2009 (28); U.S.	Community pharmacy	RCT, 9 months	40 (25/15)	Patients with uncontrolled diabetes (A1C >7.0%) and hypertension (BP ≥130/80 mmHg) or taking antihypertensive Med; 65 years
Rothman et al., 2005 (29); U.S.	Outpatient clinic	RCT, 12 months	194 (99/95)	Patients with type 2 diabetes (A1C ≥8.0%); 55 years
Sriram et al., 2011 (30); India	Outpatient clinic	RCT, 8 months	120 (60/60)	Patients with type 2 diabetes; 56 years
Pharmacist-collaborative care				
Clifford et al., 2005 (31); Australia	Outpatient clinic	RCT, 12 months	180 (92/88)	Patients with type 2 diabetes taking at least one prescribed Med; 70 years
Edelman et al., 2010 (32); U.S.	Outpatient clinic	RCT, 12 months	239 (133/106)	Patients with uncontrolled diabetes (A1C>7.5%) and hypertension (BP>140/90 mmHg) taking Med for diabetes; 62 years
McLean et al., 2008 (8); Canada	Community pharmacy	RCT, 6 months	227 (115/112)	Adult patients with diabetes and BP >130/80 mmHg taking insulin or oral hypoglycemic Med for >6 months; 65 years
Pape et al., 2011 (33); U.S.	Outpatient clinic	Cluster-RCT, 24 months	6,963 (2,047/4,916)	Patients with type 1 or 2 diabetes; 64 years
Scott et al., 2006 (34); U.S.	Outpatient clinic	RCT, 9 months	131 (64/67)	Patients with type 2 diabetes; 51 years
Simpson et al., 2011 (35); Canada	Outpatient clinic	RCT, 12 months	260 (131/129)	Patients with type 2 diabetes; 59 years
Taveira et al., 2010 (36); U.S.	Outpatient clinic	RCT, 4 months	109 (58/51)	Patients with uncontrolled type 2 diabetes (A1C between 7 and 9%); 64 years

HDL-C, HDL cholesterol; LDL-C, LDL cholesterol; TC, total cholesterol; Med, medication; HTA, hypertension.

Table 2—Characteristics of the included studies: key components of pharmacist interventions, intervention frequency, description of usual care group, and outcomes extracted

Source, country	Key components of pharmacist interventions	Intervention frequency	Description of usual care group	Outcomes extracted
Pharmacist-directed care				
Al Mazroui et al., 2009 (25); United Arab Emirates	Pharmaceutical care including: 1) Patient education regarding Med (side effects, storage of medication), disease (risk on diabetes complications), lifestyle and compliance; distribution of printed leaflet; 2) behavioral modification support (advice on self-monitoring of glycemic control; physical exercise; Med compliance and smoking cessation); and 3) discussion with physician and, if necessary recommendation (dosage simplification) to physician regarding Med changes.	Not applicable	Usual care from medical and nursing staff; no patient education; no treatment plan	BP, TC, LDL-C, HDL-C, and BMI at follow-up
Chan et al., 2012 (26); Hong Kong	Face-to-face interview with pharmacist before each physician visit including: 1) Assessment of Med history (prescription Med, such as over-the-counter drugs, vitamins, and herbal supplements); 2) evaluation of patient Med adherence; 3) education about CVDs and lifestyle modifications; 4) distribution of color stickers for pillboxes or Med bags of patients; and 5) DRPs identification with notification to physician.	Every patient encounter	Usual care without pharmacist intervention	Change in BP, HDL-C, LDL-C, TC, and BMI from baseline
Fornos et al., 2006 (23); Spain	Pharmacotherapy follow-up program including: 1) Patient interview regarding Med, health problems, and lifestyle; 2) patient education regarding diabetes, lifestyle (physical activity, healthy diet, smoking cessation) and Med; 3) distribution of verbal and written information about the correct use of Med; and 4) detection and resolution of DRPs.	Monthly	Usual care	BP, TC, LDL-C, HDL-C, and BMI at follow-up
Kraemer et al., 2012 (24); U.S.	Multiple scheduled educational appointments including: 1) Patient education and empowerment; and 2) progress note to patient's physician by fax, e-mail, or mail after each visit.	1, 2, 3 months; thereafter, every 1–3 months	Usual care received written and postal educational information about diabetes	Change in BP, HDL-C, LDL-C, and TC
Phumipamorn et al., 2008 (27); Thailand	Check Med pill count; patient education regarding Med, diabetic treatment and lifestyle; distribution of diabetic pamphlet.	Every 2 months (7 visits over 12 months)	Usual care provided by physicians; usual Med dispensation by pharmacist	Change in TC, LDL-C, and HDL-C from baseline
Planas et al., 2009 (28); U.S.	A community-based MTM program including: 1) Med review related to current prescribed and nonprescribed Med to identify DRPs; 2) DRPs identification; 3) if DRP identified, recommendations to physicians regarding adjustment HTA Med dose and addition Med by fax or telephone; 4) patient education regarding Med, lifestyle and diet; and 5) a copy of the visit note sent to physician.	Monthly	Usual care	Change in BP and TC from baseline
Rothman et al., 2005 (29); U.S.	Intensive diabetes management: 1) Patient education and counseling regarding diabetes and Med; 2) Med adjustments (initiation or increase) based on BP, cholesterol, and glucose evidence-based algorithms with the approval of physicians; and 3) proactive management of clinical parameters using a database to track patient outcomes and proactively improve care.	Every 2–4 weeks or more frequently if necessary	Usual care	Change in BP and TC from baseline

Continued on p. 2710

Table 2—Continued

Source; country	Key components of pharmacist interventions	Intervention frequency	Description of usual care group	Outcomes extracted
Striram et al., 2011 (30); India	Pharmaceutical care including: 1) Patient education including Med counseling, dietary, exercise, and lifestyle modifications; 2) distribution of educational materials, including information leaflet and diabetic diary; and 3) contact by telephone to monitor patient progress.	Not applicable	Usual care receiving no pharmaceutical care	BMI at follow-up
Pharmacist-collaborative care				
Clifford et al., 2005 (31); Australia	Pharmaceutical care program including: 1) Med review including complementary and diabetes Meds by patient questionnaire; 2) listing and ranking of DRPs; 3) recommendations to physician regarding Meds; and 4) patient education related to Meds, diet, exercise, and home glucose monitoring (distribution of educational pamphlets). Team members: physician	At baseline, 6 and 12 months plus 6 weekly telephone contacts	Usual care	Change in BP, TC, HDL-C, and BMI from baseline
Edelman et al., 2010 (32); U.S.	At each GMC session (7–8 patients with the care team): 1) Med review from medical records by pharmacist and physician; 2) review of BP and home blood glucose readings by pharmacist and physician; 3) development of individualized plan for Med or lifestyle management with pharmacist and physician; 4) adjustment of Med by pharmacist and physician and report to primary care providers; and 5) patient education and counseling related to Med and lifestyle. Team members: physician and nurse	Every 2 months (7 visits over 12 months)	Usual care; no active intervention	BP at follow-up
McLean et al., 2008 (8); Canada	Pharmacist-nurse team including: 1) Patient education and counseling regarding cardiovascular risk reduction; 2) distribution of HTA education pamphlet and wallet card documenting recorded patient BP measures faxed to physicians; and 3) patient's risk factors, current Med and BP measures with any suggestions for further management based on guidelines faxed to physicians. Team member: nurse	Every 6 weeks	Usual care with distribution of BP wallet card, pamphlet on diabetes; with general counseling from nurse and pharmacist	Change in SBP from baseline
Pape et al., 2011 (33); U.S.	Physician-pharmacist team including: 1) Reviewing of medical charts of patients with an elevated LDL-C; 2) recommendations on Med and follow-up laboratory monitoring sent electronically to physician; 3) if recommendation is accepted by physician, telephonic pharmacist intervention to patient (confirmation of Med history and previous adverse reactions, identification of barriers of adherence); and 4) documentation of patient communication and care in medical record and consignment by physician. Team member: physician	Not applicable	Usual care	LDL-C and BP at follow-up

Continued on p. 2711

Table 2—Continued

Source; country	Key components of pharmacist interventions	Intervention frequency	Description of usual care group	Outcomes extracted
Scott et al., 2006 (34); U.S.	Pharmacist-managed diabetes care program (6–8 patients) including: 1) Review of nutrition and basic diabetes management; 2) patient education and counseling about lifestyle, compliance and diabetes (goal setting); and 3) encouragement to monitor blood glucose. Team members: physician, nurse, and dietitian	At 3, 6, and 9 months	Usual care	Change in BMI and BP from baseline
Simpson et al., 2011 (35); Canada	Med review from patient discussion, measurement of CVD risk factors (BP, height, weight and heart rate), recommendations to physician regarding Med management of BP and other risk factors, discussion and approval of recommendations by physician, implementation of recommendations by pharmacist. Team member: physician	At pharmacists', physicians', or patients' discretion	Usual care; no contributions from pharmacists	Change in BP, TC, and LDL-C from baseline
Taveira et al., 2006 (36); U.S.	Pharmacist-led group medical visit program (4 to 8 patients) including: 1) Educational intervention (education of Med, disease and lifestyle); and 2) pharmacologic and behavioral intervention (education of Med, disease and lifestyle; Med changes; exercises, prescriptions, and distribution of report card containing medical history, Med, and laboratory values). Team members: nurse, nutritionist, and physical therapist	Once a week	Usual care	Change in BP and LDL-C from baseline

GMC, group medical clinic including pharmacist and primary care internist; HDL-C, HDL cholesterol; HT, hypertension; LDL-C, LDL cholesterol; Med, medication; MTM, medication therapy management; TC, total cholesterol; Med, medication; SBP, systolic BP.

Types of pharmacist interventions

Eight studies were pharmacist-directed care (23–30) and seven were pharmacist collaborative care (8,31–36) (Tables 1 and 2). Pharmacist interventions were 1) medication management (monitoring of drug therapy such as adjustment and change of medications, medication review from patient interviews, or assessment of medication compliance) in 14 studies (8,23–29,31–36); 2) educational interventions to patients (education and counseling about medications, lifestyle and physical activity or about compliance; distribution or use of educational material; educational workshop) in 14 studies (8,23–34,36); 3) feedback to health care professional (drug-related problems [DRPs] identification, recommendation and discussion with physician regarding medication changes or problems of compliance, development of treatment plans) in 12 studies (8,23–26,28,29,31–35); 4) measurement of CVD risk factors (measurement of BP or review of laboratory data by the pharmacist during follow-up) in 3 studies (8,32,35); and 5) patient-reminder systems (telephone contact) in 5 studies (26,29,30,32,33).

Methodological quality of included studies

As assessed by the Cochrane Risk of Bias Tool (22), the quality of the 15 included studies varied (Supplementary Fig 1). Most studies adequately described randomization sequence generation, were free of selective outcome reporting, and were free of other bias (e.g., important baseline imbalance in patient characteristics). Allocation concealment and blinding to outcome assessors was not described in most studies. In all studies, participants were not blinded to pharmacist intervention.

Outcomes

The outcome was systolic BP in 12 studies (including 1,894 patients) (8,23–26,28,29,31,32,34–36), diastolic BP in 9 studies (1,496 patients) (23–26,29,31,32,35,36), TC in 8 studies (1,280 patients) (23–27,29,31,35), LDL cholesterol in 9 studies (8,084 patients) (23–27,33–36), HDL cholesterol in 6 studies (826 patients) (23–27,31), and BMI in 5 studies (751 patients) (23,25,26,30,31). No study reported smoking as an outcome.

BP

Of the 12 studies reporting systolic BP (8,23–26,28,29,31,32,34–36), 7 demonstrated statistically significant reductions with pharmacist care. Of the nine

studies reporting diastolic BP (23–26,29,31,32,35,36), three demonstrated statistically significant reductions with pharmacist care. Pooled analyses indicate that pharmacist care showed greater reductions in systolic BP (weighted mean difference -6.2 mmHg [-7.8 to -4.6], $P < 0.001$) and diastolic BP (weighted mean difference -4.5 mmHg [-6.2 to -2.8], $P < 0.001$) compared with usual care (Fig. 2A and B). Heterogeneity was negligible for systolic BP ($I^2 = 2\%$) but moderate for diastolic BP ($I^2 = 46\%$).

TC, LDL cholesterol, and HDL cholesterol

Two of the eight studies reporting TC demonstrated statistically significant reductions with pharmacist care (25,27), and the pooled estimate showed a significant reduction in TC (weighted mean difference -15.2 mg/dL [-24.7 to -5.7], $P = 0.002$; Fig. 3A). Five of the nine studies reporting LDL cholesterol demonstrated statistically significant reductions with pharmacist care (25–27,33,34), and the pooled estimate showed a significant reduction in LDL cholesterol (weighted mean difference -11.7 mg/dL [-15.8 to -7.6], $P < 0.001$; Fig. 3B). Six studies reported HDL cholesterol (Fig. 3C). The pooled estimate did not show a statistically significant change in HDL cholesterol (weighted mean difference 0.2 mg/dL [-1.9 to 2.36], $P = 0.846$). There was substantial heterogeneity for TC ($I^2 = 75\%$) and HDL cholesterol ($I^2 = 72\%$) and moderate heterogeneity for LDL cholesterol ($I^2 = 41\%$).

BMI

Five studies reported BMI (Fig. 3D). Two studies (30,31) showed a statistically significant benefit of pharmacist care. The pooled estimate showed a significant reduction in BMI (weighted mean difference -0.9 kg/m² [-1.7 to -0.1], $P = 0.026$) with a substantial heterogeneity between studies ($I^2 = 92\%$).

Subgroup analyses

We conducted post hoc subgroup analyses to explore the possible differences between studies according to the type of pharmacist care, the type and the number of interventions and the setting of care (Supplementary Table 1). These analyses, conducted only for the outcome systolic BP available in 12 studies, showed a statistically and clinically significant reduction in systolic BP for both pharmacist-directed care and pharmacist-collaborative care, with a tendency to a greater reduction in

systolic BP for pharmacist-directed care compared with pharmacist-collaborative care (weighted mean difference -8.1 mmHg [-12.3 to -3.7] vs. -5.7 mmHg [-7.7 to -3.7]). Studies conducted in community pharmacies inclined to a greater reduction in systolic BP compared with other studies (weighted mean difference -10.0 mmHg [-16.4 to -3.7] vs. -5.5 mmHg [-7.3 to -3.7]). We found no major differences in systolic BP reductions according to the type and the number of interventions.

Publication bias

We explored the possibility of publication bias for the 12 studies in which the outcome was systolic BP. The funnel plot for the outcome systolic BP showed a slight asymmetry, with a borderline P value using the Egger test ($P = 0.08$), indicating a potential publication bias.

Sensitivity analyses

Because of a potential publication bias and to explore the impact of study quality on the effect estimates, we conducted two sensitivity analyses. After excluding the six smallest studies (8,25,29,31,32,35), with fewer than 80 participants per randomization group, the six remaining studies demonstrated a statistically significant reductions in systolic BP for pharmacist care compared with the usual care group (weighted mean difference -5.7 mmHg [-7.8 to -3.6], $I^2 = 0\%$) and of the same magnitude that was observed when all studies were included. The second sensitivity analysis was restricted to studies of “good quality.” Of 12 studies with the systolic BP outcome, 5 were of good quality, with a low risk of bias on at least 4 of 6 items using the Cochrane Risk of Bias Tool (22), and showed again statistically significant and similar reductions for the pharmacist care (weighted mean difference -5.6 mmHg [-8.2 to -2.9], $I^2 = 0\%$).

CONCLUSIONS—Our systematic review and meta-analysis supports the benefits of pharmacist interventions in the management of major CVD risk factors among outpatients with diabetes. Pharmacist interventions were associated with significant reductions in systolic and diastolic BP, TC, LDL cholesterol, and BMI compared with the usual care group. No significant change was observed with HDL cholesterol. The most frequent pharmacist interventions were medication management (monitoring of drug therapy such as adjustment and change of medications,

medication review from patient interviews, or assessment of medication compliance), educational interventions to patients (education and counseling about medications, lifestyle and physical activity or about compliance; distribution or use of educational material; educational workshop), and feedback to another health care professional (DRPs identification; recommendation and discussion with physician regarding medication changes or problems of compliance; development of treatment plans).

Beyond the individual studies included in our review, no other systematic review has examined the efficacy of pharmacist interventions in the management of major CVD risk factors among patients with diabetes. Nevertheless, these beneficial results are consistent with our recent systematic review on the effect of pharmacist care in CVD care among outpatients (15) and extend this earlier work by including data from trials focusing specifically on pharmacist care among outpatients with diabetes.

The benefit of pharmacist interventions on CVD risk factors in patients with diabetes combined with the impact of pharmacist care on metabolic control (A1C and fasting blood glucose), as shown in a recent systematic review (16), could translate in substantial benefits on patient morbidity and mortality as well as on health care costs. Our review indicates that pharmacist care improves in a comprehensive manner all major CVD risk factors among outpatients with diabetes, except smoking, for which no study was identified. Because smoking amplifies the risk of CVD among patients with diabetes (37) and may have deleterious effect on diabetes control (38), studies are needed to assess the impact of pharmacist care to reduce the risk of smoking among patients with diabetes. The beneficial effect of pharmacist care on BMI that we observed is encouraging because, like smoking cessation, weight loss is difficult to achieve but of major importance among patients with diabetes to help reduce CVD risk and control blood glucose (39).

We could not identify which type of intervention was more potent to control CVD risk factors among patients with diabetes. Our subgroup analyses restricted to studies assessing systolic BP did not reveal clear differences in effect size according to the type of pharmacist care, the type and the number of interventions, or the setting of care. Moreover, we could not estimate from this review how much training the pharmacist needs, which elements of the intervention have a real impact, the

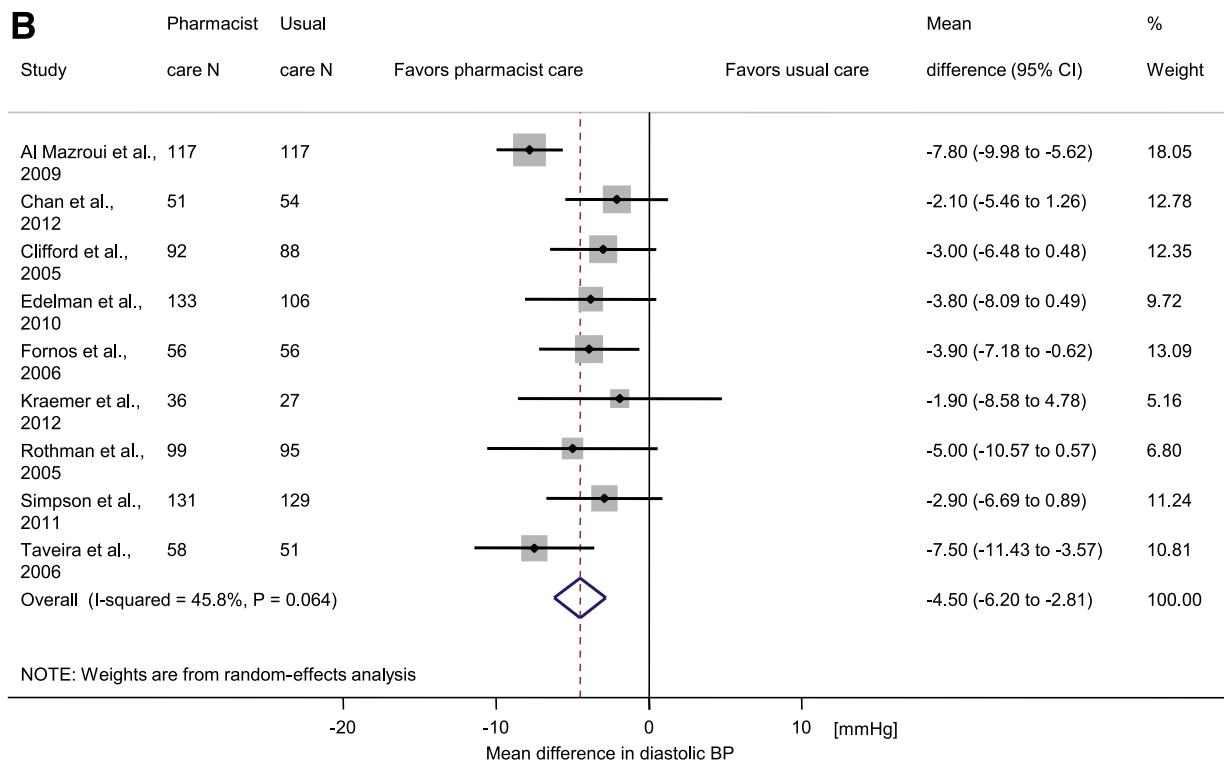
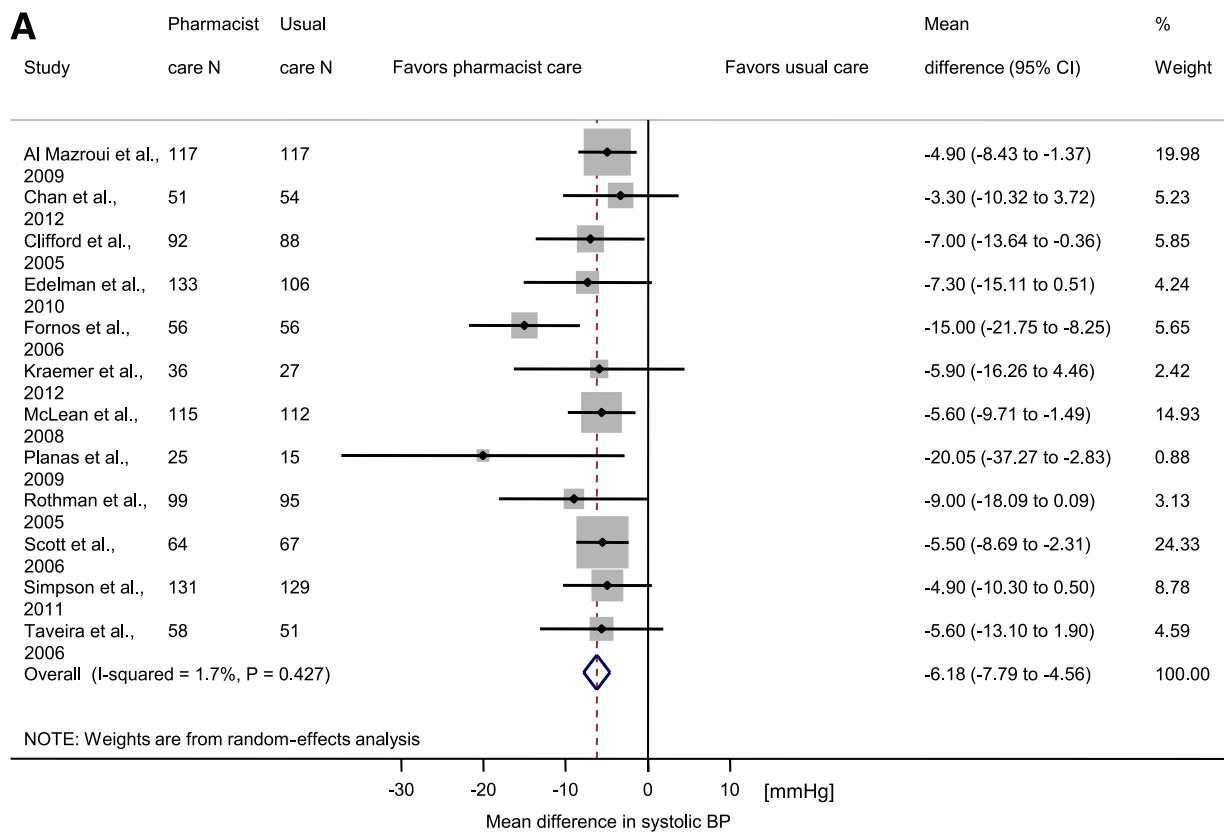


Figure 2—Forest plots show the effect of pharmacist care on the mean difference in systolic BP (A) and in diastolic BP (B). Mean differences of less than 0 between pharmacist care and usual care groups indicate an effect in favor of pharmacist care. (A high-quality color representation of this figure is available in the online issue.)

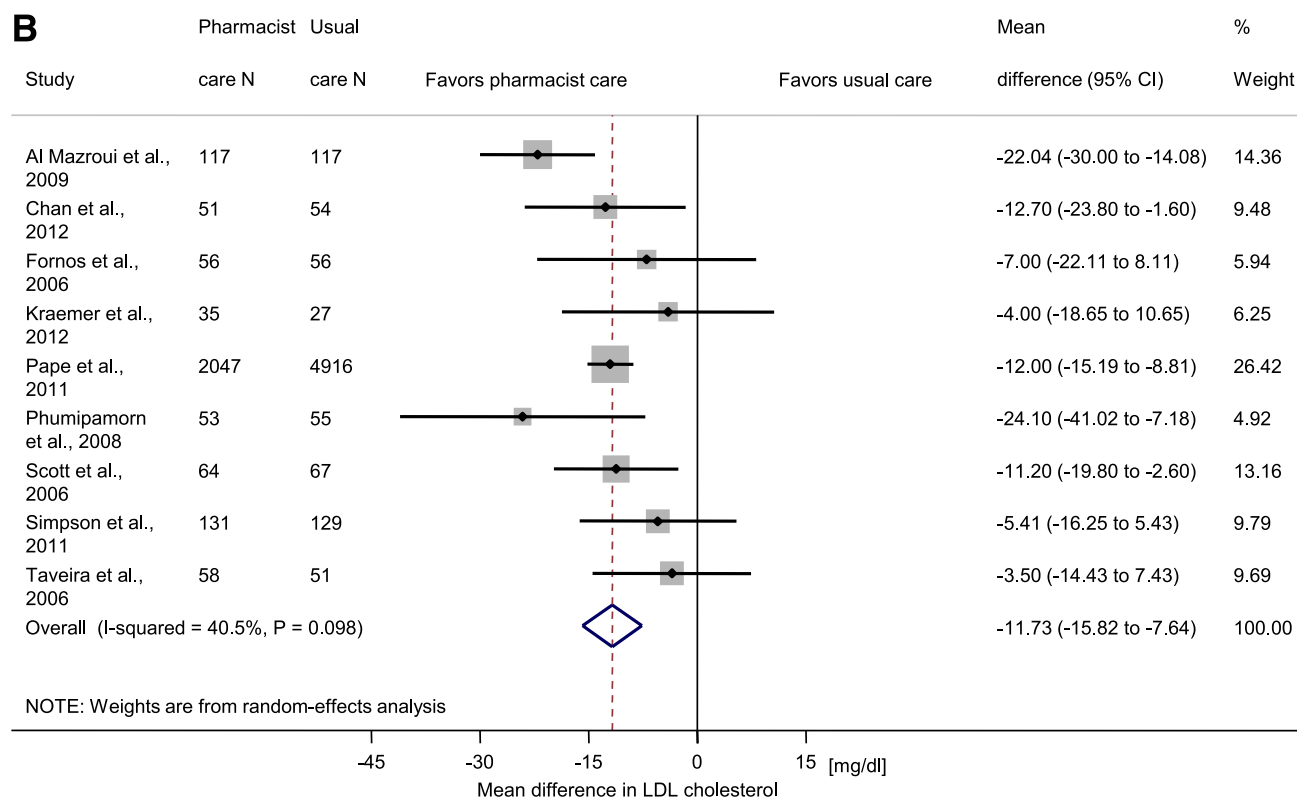
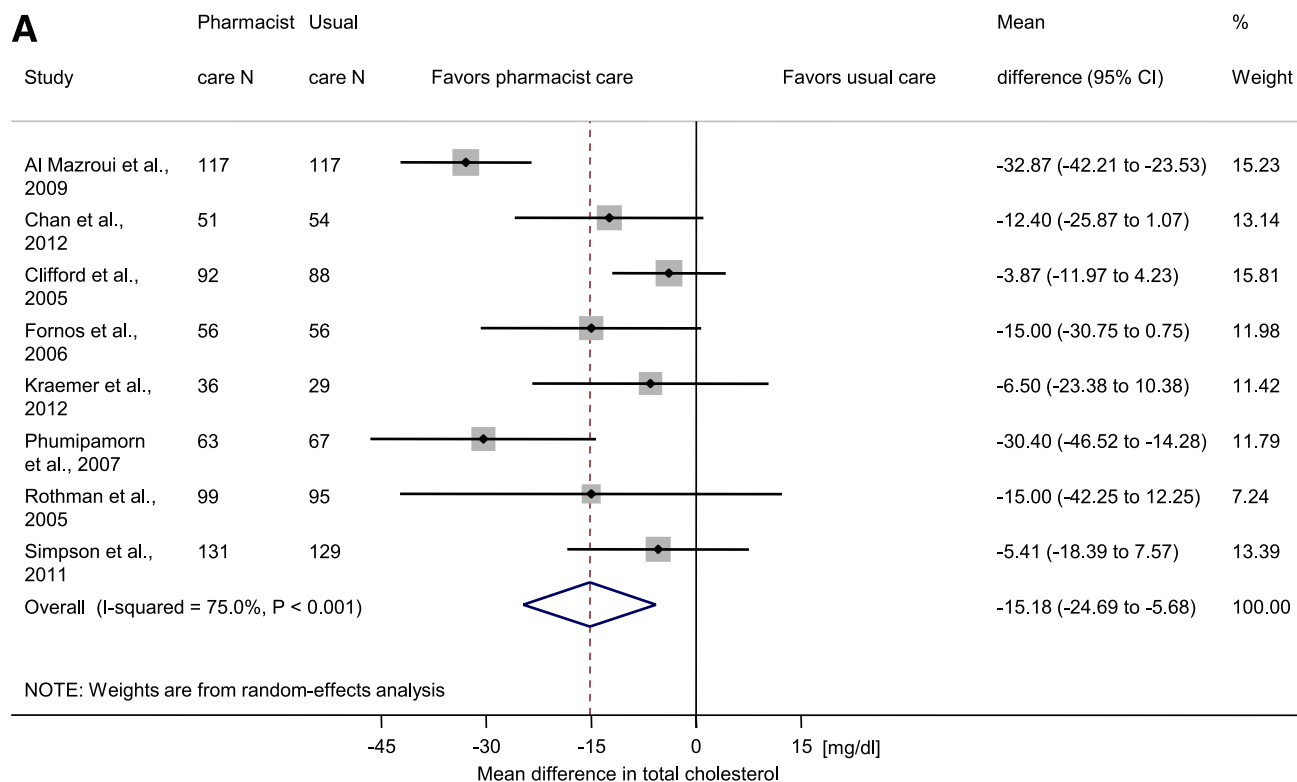


Figure 3—Forest plots show the effect of pharmacist care on the mean difference in TC (A), LDL cholesterol (B), HDL cholesterol (C), and BMI (D). Mean differences of less than 0 between pharmacist and usual care groups indicate an effect in favor of pharmacist care. (A high-quality color representation of this figure is available in the online issue.)

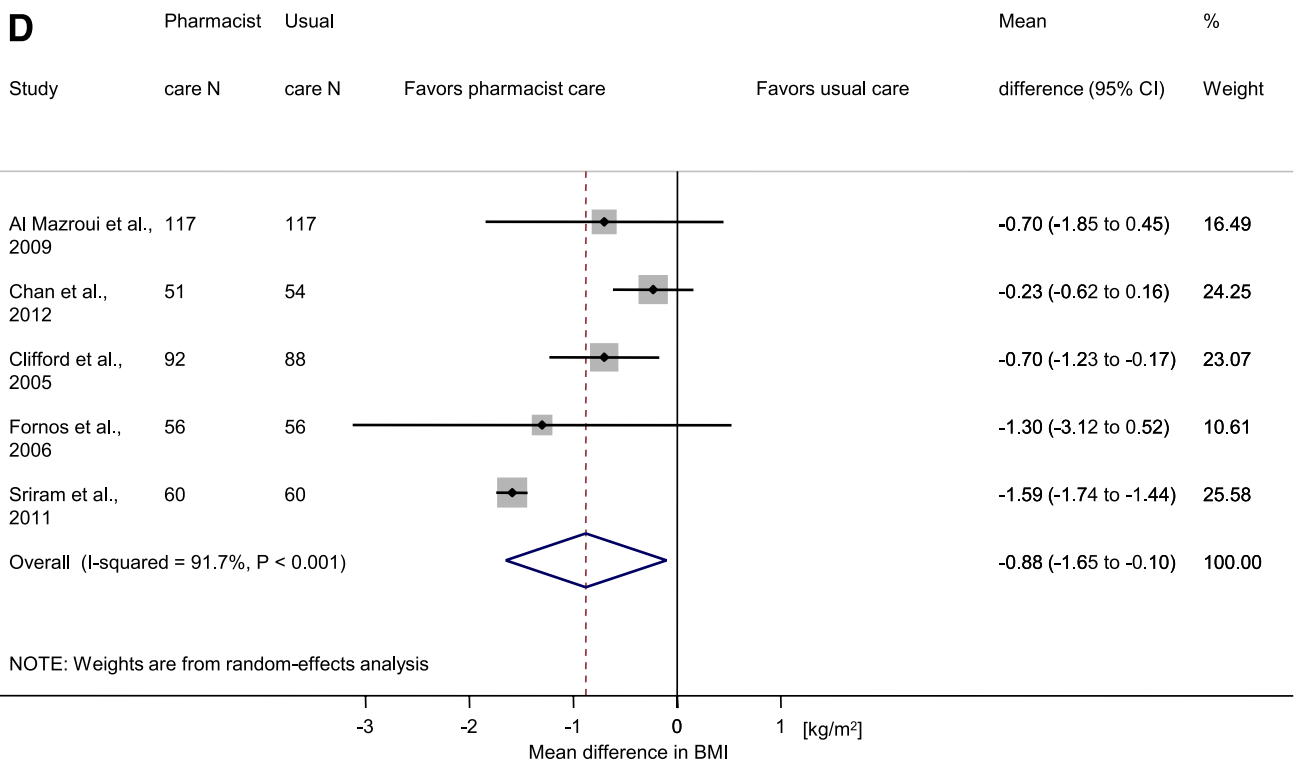
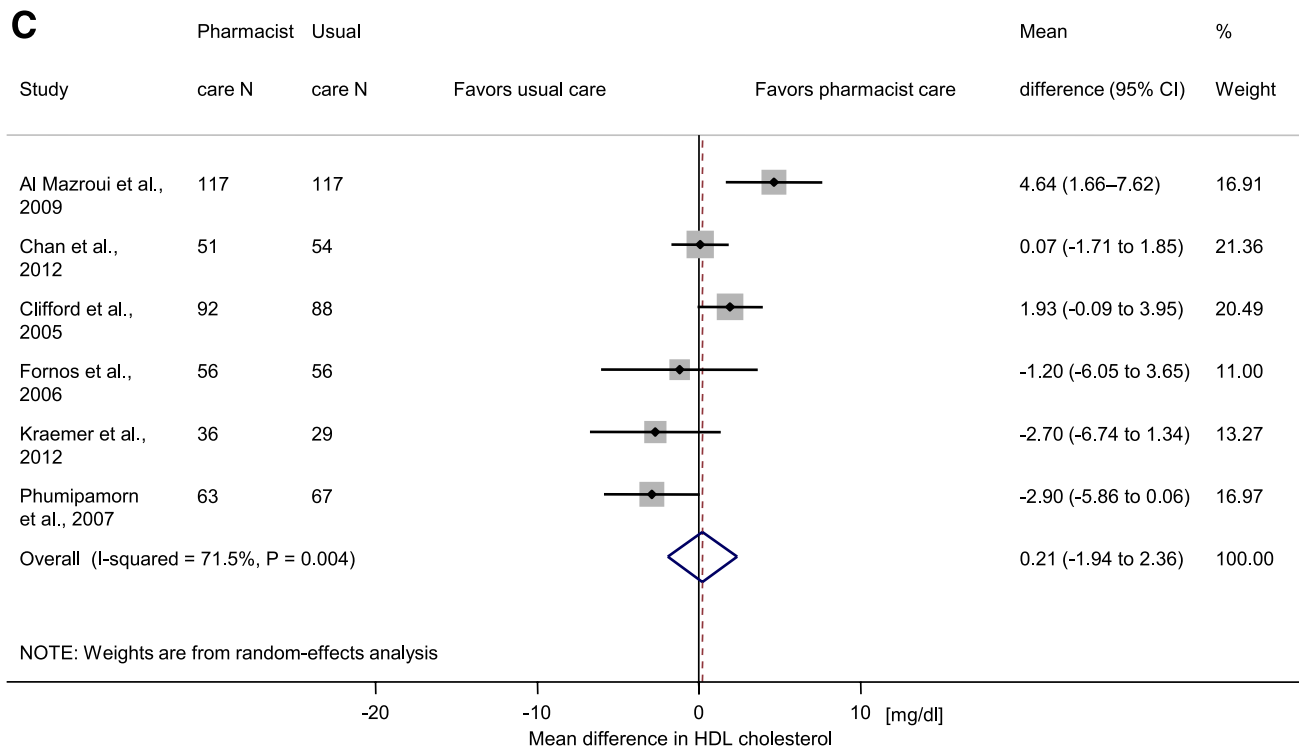


Figure 3—Continued

frequency with which the pharmacist has to intervene, or if there is an impact on CVD risk factors beyond the period of intervention. Nevertheless, identification of the more potent intervention was hampered because pharmacist interventions varied

among the identified studies and often included a combination of several interventions. Heterogeneity was found in the effect of interventions on diastolic BP, TC, LDL cholesterol, and HDL cholesterol and may be attributable to differences in terms

of interventions, care setting, and co-interventions between studies (15).

Strengths and limitations

The strengths of our review include a comprehensive systematic review of the

literature, the assessment of the impact of pharmacist interventions on all major CVD risk factors, and the inclusion of different types of pharmacist interventions. Limitations include the variation in pharmacist interventions between studies, preventing the definite identification of the most beneficial intervention, and the absence of direct evidence of the effect of pharmacist interventions on CVD events or death among patients with diabetes. Another limitation includes the absence in many studies of a detailed description of the intervention provided to the control group. In addition, we could not explain the observed heterogeneity between studies for some outcomes. We also identified a potential publication bias. However, our sensitivity analysis restricted to relatively large studies as well as our analyses restricted to good quality studies did not suggest any substantial bias in the estimation of the effect of pharmacist interventions. Finally, most studies were conducted in the U.S. and Canada, reflecting an advanced role of the pharmacist in these health care systems.

Summary and perspectives

Our review provides evidence that pharmacist interventions—conducted alone or in collaboration with other health care professionals—improve management of major CVD risk factors among outpatients with diabetes. However, our work also indicates that more research is needed to assess which pharmacist interventions are most effective, implementable, and less time-consuming in various types of health care systems or jurisdictions. Future research should also demonstrate cost-effectiveness of pharmacist interventions for patients with diabetes and CVD risk factors. There is also a significant need to develop and evaluate interprofessional education initiatives during pharmacy, medical, and nursing training to enhance future collaborative care among patients with diabetes.

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