

Systematic Review and Meta-Analysis of Medication Reviews Conducted by Pharmacists on Cardiovascular Diseases Risk Factors in Ambulatory Care

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Background—Pharmacists-led medication reviews (MRs) are claimed to be effective for the control of cardiovascular diseases; however, the evidence in the literature is conflicting. The main objective of this meta-analysis was to analyze the impact of pharmacist-led MRs on cardiovascular disease risk factors overall and in different ambulatory settings while exploring the effects of different components of MRs.

Methods and Results—Searches were conducted in PubMed, Web of Science, Embase, the Cumulative Index to Nursing and Allied Health Literature, and the Cochrane Library Central Register of Controlled Trials database. Randomized and cluster randomized controlled trials of pharmacist-led MRs compared with usual care were included. Settings were community pharmacies and ambulatory clinics. The classification used for MRs was the Pharmaceutical Care Network Europe as basic (type 1), intermediate (type 2), and advanced (type 3). Meta-analyses in therapeutic goals used odds ratios to standardize the effect of each study, and for continuous data (eg, systolic blood pressure) raw differences were calculated using baseline and final values, with 95% CIs. Prediction intervals were calculated to account for heterogeneity. Sensitivity analyses were conducted to test the robustness of results. Meta-analyses included 69 studies with a total of 11 644 patients. Sample demographic characteristics were similar between studies. MRs increased control of hypertension (odds ratio, 2.73; 95% prediction interval, 1.05–7.08), type 2 diabetes mellitus (odds ratio, 3.11; 95% prediction interval, 1.17–5.88), and high cholesterol (odds ratio, 1.91; 95% prediction interval, 1.05–3.46). In ambulatory clinics, MRs produced significant effects in control of diabetes mellitus and cholesterol. For community pharmacies, systolic blood pressure and low-density lipoprotein values decreased significantly. Advanced MRs had larger effects than intermediate MRs in diabetes mellitus and dyslipidemia outcomes. Most intervention components had no significant effect on clinical outcomes and were often poorly described. CIs were significant in all analyses but prediction intervals were not in continuous clinical outcomes, with high heterogeneity present.

Conclusions—Intermediate and advanced MRs provided by pharmacists may improve control of blood pressure, cholesterol, and type 2 diabetes mellitus, as statistically significant prediction intervals were found. However, most continuous clinical outcomes failed to achieve statistical significance, with high heterogeneity present, although positive trends and effect sizes were found. Studies should use a standardized method for MRs to diminish sources of these heterogeneities. (*J Am Heart Assoc.* 2019;8:e013627. DOI: 10.1161/JAHA.119.013627.)

Key Words: cardiovascular risk factors • hypertension • medication reviews • pharmacist management • type 2 diabetes mellitus

Cardiovascular diseases (CVDs) are the main cause of morbidity and mortality worldwide, with more than 36% of adults in the United States and 40% in Europe at high risk for developing or with established CVD.^{1,2} The World Health

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Accompanying Tables S1 through S3 and Figures S1 through S8 are available at <https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.013627>

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Clinical Perspective

What Is New?

- Pharmacist-led medication reviews (MRs) seem to improve the control of hypertension, type 2 diabetes mellitus, and dyslipidemias in ambulatory settings despite differences in components implemented and high heterogeneity between studies.
- MRs in ambulatory clinics could have larger effects in the achievement of type 2 diabetes mellitus and dyslipidemia goals and in decreasing systolic blood pressure and low-density lipoprotein cholesterol in community pharmacies.
- Advanced MRs could have larger effects than intermediate MRs on diastolic blood pressure, glycated hemoglobin, fasting glucose, total cholesterol, and low- and high-density lipoprotein cholesterol, but more studies are needed.

What Are the Clinical Implications?

- Including pharmacists in care teams to provide MRs in both community pharmacies and ambulatory clinics could improve the management of hypertension, type 2 diabetes mellitus, and dyslipidemias.

Organization reported 17.9 million of CVD-related deaths in 2016, representing 44% of all deaths from noncommunicable diseases, with 85% of these deaths caused by strokes and ischemic heart diseases.^{3,4} Dyslipidemia, hypertension, and type 2 diabetes mellitus (T2DM) are the most common risk factors in adults, with an estimated 39%, 31%, and 8% affected worldwide, with great impact in mortality, morbidity, and costs of care. However, common strategies to control these diseases appear to be relatively ineffective.²⁻⁴

Pharmacists are increasingly having direct involvement in patient care usually by providing services that have the objective of improving medication management of patients and other healthcare professionals.⁵⁻⁸ There are various types of services, including medication reviews (MRs).^{8,9} MRs vary from a brief revision of the prescribed medicines to more complex interventions involving patients and physicians, which allow the detection of pharmacological interactions and drug-related problems such as adverse drug reactions, effectiveness problems, nonadherence, and self-medication.^{10,11} Pharmacist-led interventions have reportedly increased the achievement of therapeutic goals in CVD risk factors such as hypertension and T2DM, decreasing systolic blood pressure (BP) between 6 and 10 mm Hg and glycated hemoglobin (HbA_{1c}) between 0.46% and 1%.⁶⁻¹⁰

Some systematic reviews and meta-analyses reveal high inconsistencies and heterogeneity on the impact of MR. Possible causes of this problem are the lack of control of confounding factors such as age and other demographic data,

months of follow-up, control groups without usual care or dummy interventions, variability, and fidelity of the intervention including different settings.⁵⁻¹⁰ These specific setting elements could include access to care teams for proposed action plans, proximity and relationship with prescribers, the physical place of the intervention, and other related factors.⁶⁻¹⁰ How these differences in ambulatory settings could influence the clinical impact of the pharmacist's provision of MR has not been reported.

The main objective of this meta-analysis was to analyze the impact of pharmacist-led MRs on CVD risk factors overall and in different ambulatory settings while exploring the effects of different components of MRs.

Methods

Data Sources and Searches

A systematic review was performed using the PRISMA statement and Cochrane Collaboration recommendations.¹²⁻¹⁴ Two reviewers (F.M.-M., A.A.-C.) performed all of the steps individually, and any discrepancies were decided by a third author (V.G.-C.). Searches were conducted in PubMed, Web of Science, Embase (through Ovid), the Cumulative Index to Nursing and Allied Health Literature, and the Cochrane Library Central Register of Controlled Trials database, without any time limit (up to May 2019). A manual search in the reference lists of included studies was performed, and grey literature (eg, Google) was also searched. The complete search strategy for each database is available in Table S1.

Eligibility Criteria

Table 1 describes inclusion and exclusion criteria. The Pharmaceutical Care Network Europe (PCNE) categories of MR conducted by pharmacists were used to classify interventions as¹¹: type 1: a basic review of medicines and health problems based on the available medication history in the pharmacy; type 2: an intermediate review with the available medication history in the pharmacy and clinical records or information obtained directly from the patient; and type 3: an advanced review using medication history, clinical records, and information obtained directly from the patient.

During the screening phase (title and abstract reading), articles were excluded if considered irrelevant to the study goals. The full-text eligibility phase excluded articles that did not fulfill all of the inclusion criteria.

Data Extraction

Standardized data collection forms were used to extract data on the studies' metadata (eg, author names and year), patients' characteristics (eg, sample size, mean age, sex, and diseases), type of interventions and its components, setting of intervention,

Table 1. Inclusion and Exclusion Criteria

Category	Inclusion Criteria
Population	Patients older than 18 years with hypertension, T2DM, or dyslipidemia as CVD risk factors
Setting	Ambulatory care settings as ACs or CPs
Study design	RCT or cluster RCT
Intervention	Medication reviews provided by pharmacists describing the components of the intervention
Comparator	Usual care
Outcomes	Studies that include at least 1 of the outcomes of study. Outcomes were dichotomous as the control of hypertension; T2DM and dyslipidemia as achievement of clinical targets defined in each study; and continuous as systolic blood pressure, diastolic blood pressure, glycated hemoglobin, fasting glucose, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides
Language of publication	English or Spanish
Category	Exclusion criteria
Missing data	Studies that report incomplete values (as lacking uncertainty) when the authors could not provide this information when requested

ACs indicates ambulatory clinics; CPs, community pharmacies; CVD, cardiovascular disease; RCT, randomized controlled trial; T2DM, type 2 diabetes mellitus.

number of visits, PCNE MR category, method of communication with patients and physicians, and clinical outcomes.

Nonpharmacological interventions included education in lifestyle changes, medication use and disease; self-monitoring of parameters; vitals assessment such as BP, capillary glycemia, or cholesterol measurements; and adherence interventions. Pharmacological interventions consisted of pharmacists suggesting modifications to treatment in detected drug-related problems or only in CVD risk problems.^{5–10}

Two ambulatory settings were included. An ambulatory clinic (AC) is defined as a primary care center where health care is mostly provided by general practitioners but could also include specialized outpatient clinics.¹⁵ Community pharmacies (CPs) are legally approved establishments that supply prescription and nonprescription medicines and may provide professional pharmacy services and patient counselling while dispensing.¹⁶

Quality Assessment

The revised Cochrane risk-of-bias tool for randomized controlled trials was used to identify the risk of bias. Studies were classified as having low risk, high risk, or some concerns of bias.¹⁷

Statistical Analyses

Pairwise meta-analyses of the studies were performed for the outcome measures whenever possible. These analyses were conducted using the software Comprehensive Meta-Analysis version 3 (Biostat).

The random effect model was used with the inverse of the variance to obtain pooled effect sizes, and results were reported with a 95% CI and $P < 0.05$. The calculation of 95% prediction intervals (PIs) was performed in preformatted sheets in Excel

with the method described by Borenstein and Higgins using mean effect size and its variance (random effect weights), degrees of freedom, and τ^2 (estimation measure of the true effect size distribution) in log units (normal approximation).^{18,19} PIs allow more informative inferences in meta-analyses (eg, true treatment effects that can be expected in future settings), especially when there is large variation in the strength of the effect (high heterogeneity between studies).^{14,18,19}

For the meta-analyses of dichotomous data (therapeutic goals), the odds ratio (OR) was calculated. For the meta-analyses of continuous outcomes, the differences between baseline and final values with the corresponding SDs reported by the individual studies (pre-post correlation of 0.999) were used.¹⁴

For articles that reported 95% CI as a measure of uncertainty, SD was calculated using the size of the samples, the length of the CI, and the value from Student *t* distribution. When numeric data were insufficient to conduct the pooled analysis, a request was sent to the author by email. If the authors responded negatively or not at all, we excluded the article from the analyses.^{18,19}

The between-trial heterogeneity was assessed using the inconsistency index value (I² statistic) with ranges of <25% (low), 25–50% (moderate), 50–75% (high) and >75% (very high) heterogeneity. Sensitivity analyses were conducted together with analyses for publication and other bias (funnel and scatter plots, Failsafe N) to test the robustness of the results. Subgroup analyses considering setting and components of interventions were performed when possible.¹⁴

Results

Sixty-nine studies reported data that could be included in the meta-analyses (Figure 1). One study was excluded from these

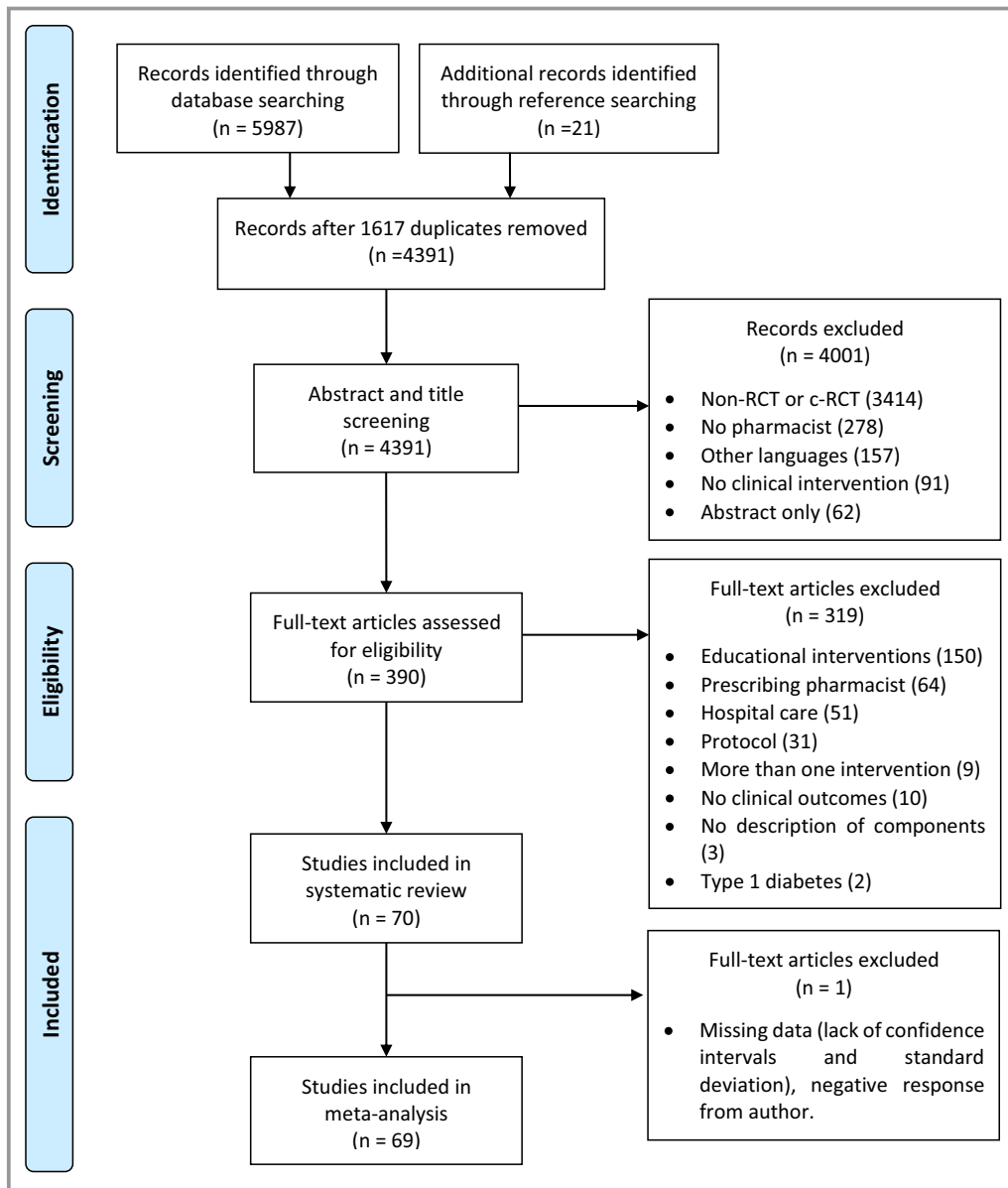


Figure 1. PRISMA flowchart for systematic review and meta-analysis.^{12,13}. c-RCT indicates cluster randomized controlled trial; RCT, randomized controlled trial.

analyses because it lacked uncertainty data (and the author responded negatively). Forty-five of these studies were undertaken in ACs and 24 in CPs. The total number of patients was 11 743, with 11 644 included in the meta-analyses. Of these, 8014 patients were in ACs and 3630 in CPs, with a mean age of 60 ± 7.2 years, and the percentage of men in the included studies was $43 \pm 8.8\%$, without differences between subgroups (Table 2). The mean follow-up time was 8.35 ± 4.44 months, and there were 5.21 ± 2.52 contacts with patients in average. Most studies provided lifestyle and disease education, and 23 studies considered the opinion of each patient before changing pharmacotherapy. In 39 studies, pharmacists only implemented changes in medications for

CVD risk (ignoring other medical conditions). In 48 studies, pharmacists assessed vitals during the interviews and provided self-monitoring education in 38 studies.

Risk of Bias

Sixty-one of the 69 studies included in the meta-analysis presented low risk or some concerns about bias. The main issues were the impossibility to blind patients to the intervention and the lack of details in the randomization process. Eight studies had a high risk of bias, mostly because of indefinite randomization and the lack of blinded process in the assessment of clinical outcomes. The effect of excluding

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Table 2. Continued

Lead Study Author and Date	Age (SD), y	No. of IG (% of Men)	No. of CG (% of Men)	MR	Goal Included	Continuous Outcomes										Contact						Components					Risk of Bias						
						SBP	DBP	HbA _{1c}	FG	TC	LDL	HDL	Triglyceride	Visits	Mo	Physician	Specialist	Disease Education	Self-Monitoring	Lifestyle Education	All DRP	Patient	Vitals										
Milnevene 2010 ⁴¹	61 (11)	108 (64)	117 (61)	2	TC	X	X	X	X	X	X	X	X	X	6	12	I	I							X							C	
Wang 2011 ⁴²	48 (9)	29 (62)	30 (47)	2		X	X								6	12	W	I					X		X		X				L		
Zillich 2005 ⁴³	65 (7)	64 (36)	61 (42)	2	BP	X	X								4	3	W/P	IP					X		X		X				C		
ACs																																	
Abulohia 2016 ⁴⁴	55 (10)	45 (42)	43 (42)	3				X							3	3	I	I	X				X		X		X					L	
Aguilar 2016 ⁴⁵	62 (8)	36 (31)	37 (35)	3	BP, T2DM	X	X	X			X				3	12	I	IP	X				X		X		X		X			L	
Al Mazroui 2009 ⁴⁶	49 (8)	117 (71)	117 (68)	3	T2DM	X	X	X	X	X	X	X	X		4	12	I	I	X				X		X		X					C	
Allsoul-Younes 2011 ⁴⁷	57 (10)	130 (47)	123 (48)	3	BP	X	X								9	9	I	I					X		X		X					L	
Azevedo 2017 ⁴⁸	63 (11)	33 (21)	30 (27)	3		X	X	X	X	X	X	X	X		8	6	W/I	IP					X		X		X					H	
Bogden 1997 ⁴⁹	57 (12)	47 (34)	47 (19)	3	TC					X					12	6	I	I														C	
Bogden 1998 ⁵⁰	55 (8)	49 (41)	46 (43)	3	BP	X	X								6	6	I	IP										X				H	
Borenstein 2003 ⁵¹	62 (5)	98 (37)	99 (41)	3	BP	X	X								12	12	P	I	X								X				H		
Carber 2008 ⁵²	61 (12)	101 (42)	78 (46)	3	BP	X	X								6	9	I	I														C	
Carber 2009 ⁵³	59 (14)	192 (38)	210 (44)	3	BP	X	X								3	6	I	I														L	
Chan 2012 ⁵⁴	63 (10)	51 (59)	54 (52)	3	BP, T2DM, TC	X	X	X	X	X	X	X	X		4	9	W	I					X		X		X					L	
Chen 2016 ⁵⁵	72 (6)	50 (51)	50 (49)	3				X							2	6	I	IP														L	
Choe 2005 ⁵⁶	52 (10)	36 (49)	29 (46)	3				X							6	12	I	IP					X		X		X					L	
Clifford 2002 ⁵⁷	60 (12)	48 (48)	25 (58)	3				X							4	6	I	I	X				X		X		X					C	
Clifford 2005 ⁵⁸	70 (8)	92 (48)	88 (57)	2		X	X	X	X	X	X	X	X		3	12	W	IP					X		X		X					L	
de Castro 2015 ⁵⁹	61 (10)	30 (31)	34 (38)	3		X	X								5	6	I	I	X				X		X		X					C	
Ehid 2014 ⁶⁰	54 (13)	140 (51)	140 (48)	3	BP	X	X								3	3	I	I	X				X		X		X					L	
Firmihho 2015 ⁶¹	60 (9)	26 (24)	30 (24)	3		X	X								6	9	W	I					X		X		X					L	
Green 2008 ⁶²	59 (9)	237 (56)	247 (55)	3	BP	X	X								1	12	W	W					X		X		X					C	
	57 (10)	110 (36)	89 (39)	3		X	X		X						6	6	I	I					X		X		X					L	

Continued

Table 2. Continued

Lead Study Author and Date	Age (SD), y	No. of IG (% of Men)	No. of CG (% of Men)	MR	Goal Included	Continuous Outcomes							Components						Risk of Bias														
						SBP	DBP	HbA _{1c}	FG	TC	LDL	HDL	Triglyceride	Visits	Mo	Physician	IP	Specialist		Disease Education	Self-Monitoring	Lifestyle Education	All DRP	Patient	Vitals								
Wal 2013 ⁸⁷	60 (9)	54 (47)	48 (52)	3		X	X										X			X												C	
Wishah 2014 ⁸⁸	53 (6)	52 (39)	54 (46)	3				X	X	X	X	X																					C
Oparah 2009 ⁸⁹	55 (9)	50 (46)	49 (47)	3		X	X	X	X																								H

ACs indicates ambulatory clinics; BP, blood pressure; C, some concerns; CG, control group; CPs, community pharmacies; DRPs, intervention in all drug-related problems found; H, high risk; HbA_{1c}, glycated hemoglobin; HDL, high-density lipoprotein cholesterol; I, face-to-face interview; IG, intervention group; L, low risk; LDL, low-density lipoprotein cholesterol; MR, Pharmaceutical Care Network Europe medication review category; NI, not informed; P, phone interview; T2DM, type 2 diabetes mellitus; TC, total cholesterol; W, written message (email or letter).
 *Excluded from meta-analysis for lacking baseline values.

high-risk articles from the analyses was explored for each outcome.^{20–27} Table S2 presents individual risk-of-bias analysis.

Clinical Outcomes and Components

Figures 2 through 4 and Tables 3 through 5 present clinical outcomes overall and by individual setting. Figures S1 through S8 contain additional forest plots for each clinical outcome and Table S3 shows the effect of each individual component and type of MR.

Hypertension

Table 3 presents pooled size effects for hypertension outcomes. Mean follow-up time of the MR service was 8.49±4.99 months, with 5.28±2.59 patient visits. The meta-analysis for overall BP control (31 studies; n=7031 patients) showed a statistically significant pooled OR of 2.73 (95% PI, 1.05–7.08) (Figure 2). Heterogeneity was high (I²=71%) and the AC subgroup also had a significant PI.

Fifty-two studies (n=9935 patients) were included in the analysis of systolic BP (SBP) (Figure S1). Heterogeneity was very high (I²=99%) and resulted in significant PIs for the CP subgroup but not for the AC subgroup or overall.

For diastolic BP (DBP) (49 studies; n=9526 patients) heterogeneity was very high (I²=99%), and PIs were not significant overall or in subgroups (Figure S2).

Excluding studies with a high risk of bias, small studies or outliers resulted in similar results for hypertension outcomes (Table 3).

Type 2 Diabetes Mellitus

For diabetes mellitus studies, mean follow-up time was 9.96±6.22 months, with 4.88±2.57 patient visits. The overall OR for achievement of T2DM control (12 studies; n=1805 patients) was 3.11 (95% PI, 1.48–6.52) (Figure 3). Only 1 CP article reported this outcome, and the AC subgroup showed a significant PI. Heterogeneity was moderate (I²=30%). No article had a high risk of bias. Table 4 presents effect sizes for T2DM outcomes.

A total of 3452 patients with T2DM from 25 studies were included in the analysis of the differences in HbA_{1c} levels (Figure S3). There was very high heterogeneity (I²=99%), which resulted in a nonsignificant PI. Subgroup analysis also showed no significant PI. No study had a high risk of bias.

In the fasting glucose analysis (17 studies; n=2505 patients) there was very high heterogeneity (I²=99%) with nonsignificant PI (Figure S4).

Sensitivity analyses showed no differences except for the exclusion of 3 outliers in diabetes mellitus control, which

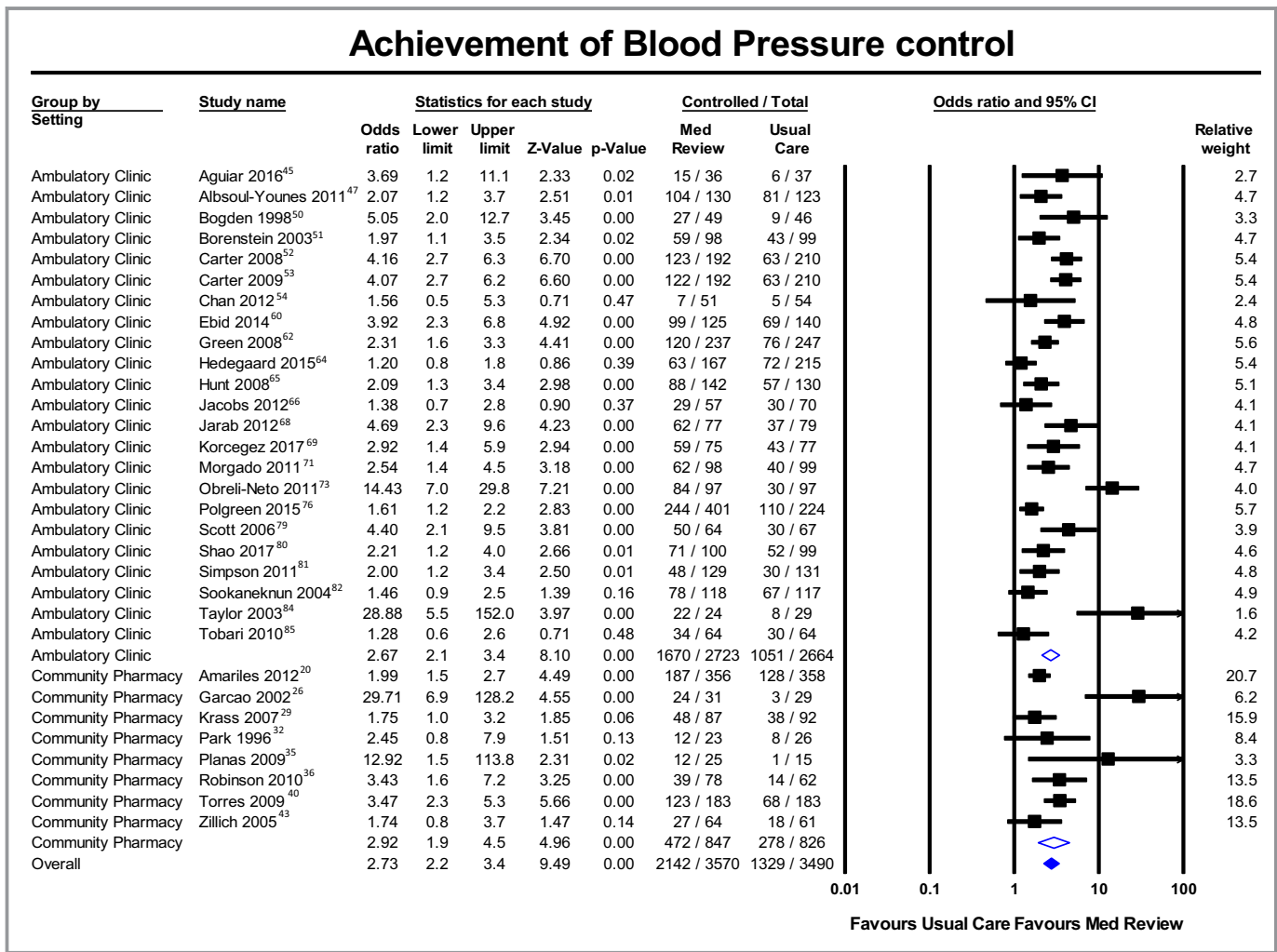


Figure 2. Meta-analysis of patients reaching blood pressure control with medication reviews or usual care. Values in odds ratios with 95% CIs.

reduced heterogeneity to 0%, and 1 outlier in HbA_{1c}, which resulted in a significant PI overall (Table 4).

Dyslipidemias

Table 5 presents dyslipidemia outcomes. Mean follow-up time was 9.01±6.31 months, with 5.58±2.87 patient visits. Eleven studies (n=2012 patients) reported cholesterol goals (Figure 4), finding a significant OR of 1.91 (95% PI, 1.05–3.46), with moderate heterogeneity (*I*²=31%). AC had a significant PI. There were no studies with a high risk of bias.

The analysis of total cholesterol had very high heterogeneity (*I*²=99%) resulting in a nonsignificant PI (Figure S5). There was a significant difference between subgroups (Q=7.91, *P*=0.005), with ACs having a larger reduction in TC levels than CPs.

Very high heterogeneity (*I*²=99%) was found in the low-density lipoprotein cholesterol analysis, with a significant PI in the CP subgroup only (Figure S6). A statistical difference was observed between subgroups (Q=9.62, *P*=0.002) with a larger

effect in ACs. CP analysis included 5 studies versus 15 in the AC subgroup.

For high-density lipoprotein cholesterol (20 studies; n=2804 patients), there was very high heterogeneity (*I*²=99%), which led to a nonsignificant PI (Figure S7). There was a significant difference between subgroups (Q=5.25, *P*=0.022), with a larger effect in ACs versus CPs, but none had statistical significance.

For triglyceride levels (23 studies; n=3185), a nonsignificant PI was observed with very high heterogeneity (*I*²=99%) (Figure S8).

Excluding small studies or an outlier reduced heterogeneity to 0% and produced significant PI in the control of total cholesterol (Table 5).

Discussion

To our knowledge, this is the first meta-analysis for MRs that includes a high number of CVD outcomes and uses PIs to account for high heterogeneity. The inclusion of control of

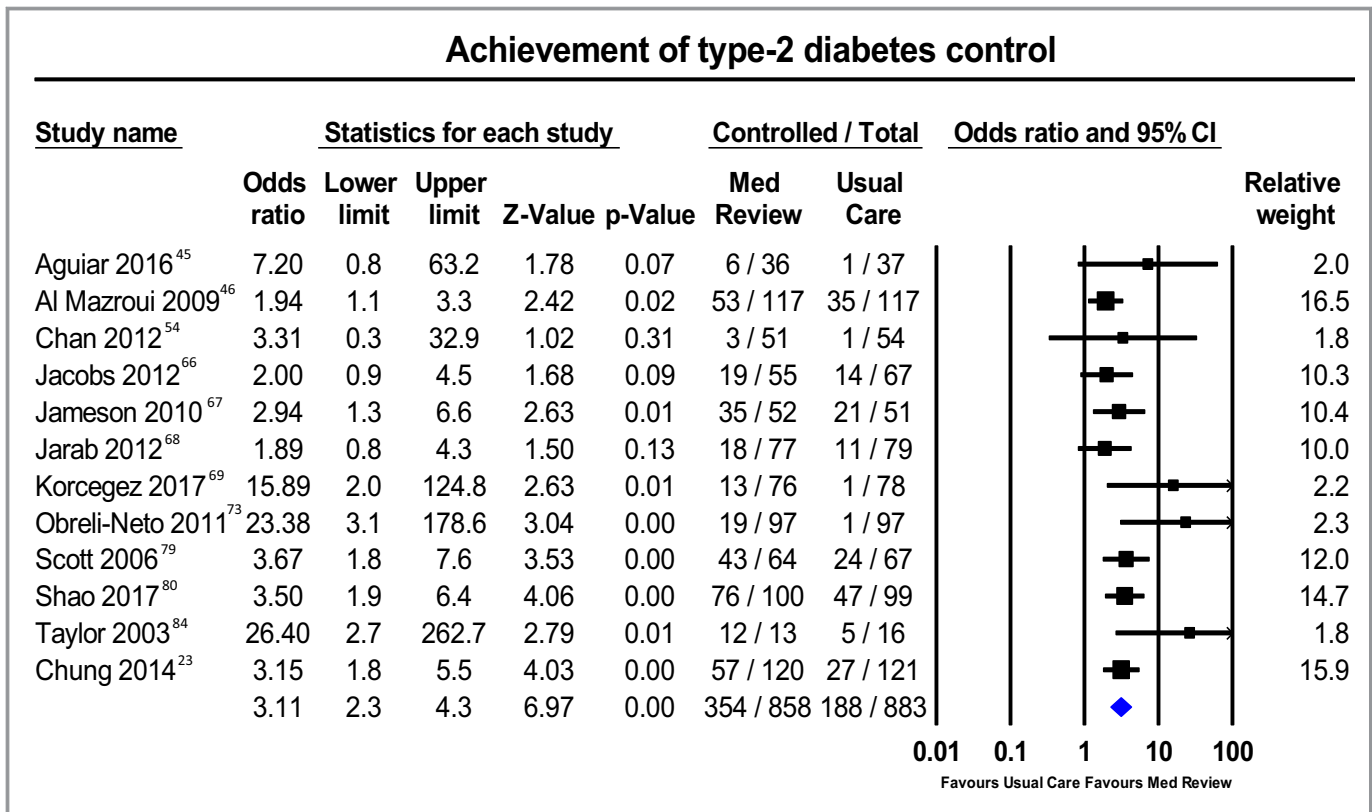


Figure 3. Meta-analysis of patients with type 2 diabetes mellitus reaching glycated hemoglobin <7% with medication reviews or usual care. Values in odds ratios with 95% CIs.

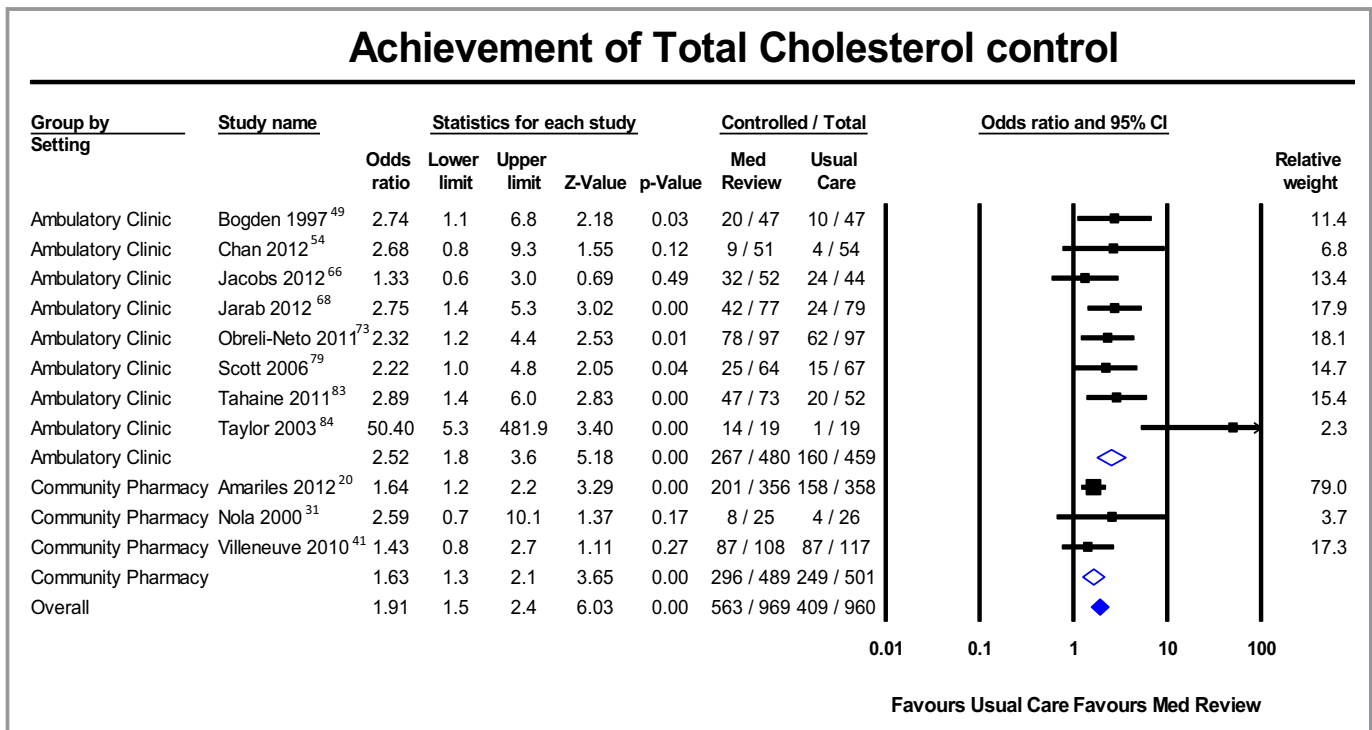


Figure 4. Meta-analysis of patients reaching cholesterol control with medication reviews or usual care. Values in odds ratios with 95% CIs.

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Table 3. Pooled Analysis of Hypertension Outcomes

Outcome	Analysis		Studies (No. of Patients)	Effect Size	95% CI	<i>I</i> ² , %	95% PI
BP control (OR)	Overall		31 (7031)	2.73	2.20–3.36*	71	1.05–7.08*
	Setting	AC	23 (5332)	2.67	2.11–3.39*	74	0.97–7.49
		CP	8 (1699)	2.92	1.91–4.46*	66	0.86–9.92
	Sample size	Excluding N <100 ^{26,32,35,45,50,84}	25 (6635)	2.43	2.02–2.93*	70	1.04–5.69*
	RoB	Excluding high ^{35,36,50,51,82}	26 (6324)	2.74	2.18–3.44*	73	1.02–7.39*
	Outliers	Excluding OR>20 ^{26,84}	29 (6896)	2.51	2.11–3.07*	67	1.08–5.82*
SBP, mm Hg	Overall		52 (9935)	−8.50	−9.66 to −7.34*	99	−19.0 to 1.68
	Setting	AC	33 (6816)	−8.34	−10.1 to −6.61*	99	−18.8 to 2.02
		CP	19 (3119)	−8.64	−10.2 to −7.07*	99	−16.0 to −1.26*
	Sample size	Excluding N <100 ^{21,26,27,30,32,33,35,37}	36 (8887)	−7.53	−9.17 to −5.89*	99	−17.8 to 2.76
	RoB	Excluding high ^{21,35,36,39,48,50,51}	45 (9144)	−7.94	−9.45 to −6.42*	99	−18.5 to 2.57
	Outliers	Excluding >20 mm Hg decrease in SBP ^{30,35,73}	49 (9640)	−7.54	−8.72 to −6.54*	99	−15.3 to −0.27*
DBP, mm Hg	Overall		49 (9526)	−3.68	−4.45 to −2.92*	99	−9.56 to 2.20
	Setting	AC	32 (6619)	−4.53	−5.75 to −3.32*	99	−11.8 to 2.74
		CP	17 (2907)	−3.13	−4.11 to −2.14*	99	−7.60, 1.34
	Sample size	Excluding N <100 ^{21,26,27,30,32,33,37,42}	34 (8518)	−3.85	−4.85 to −2.85*	99	−9.98 to 2.28
	RoB	Excluding high ^{21,36,48,50,82}	44 (8972)	−3.78	−4.65 to −2.91*	99	−9.74 to 2.18
	Outliers	Excluding >10 mm Hg decrease in DBP ^{50,73}	47 (9237)	−3.72	−4.50 to −2.94*	99	−9.24 to 1.80

AC indicates ambulatory clinic; BP, blood pressure; CP, community pharmacy; DBP, diastolic blood pressure; N, total number of patients; OR, odds ratio; PI, prediction interval; RoB, risk of bias; SBP, systolic blood pressure.

*Statistical significance.

hypertension, T2DM, and dyslipidemia and continuous clinical outcomes allowed exploration of a multidimensional effect of the provision of MR by pharmacists. We included a high number of studies and accounted for multiple components of the intervention, exploring the effect of possible bias.

Settings presented significant differences in some outcomes, with the AC subgroup having larger effect sizes in cholesterol values and DBP. This subgroup had significant increases in the achievement of T2DM and TC goals with moderate heterogeneity. Continuous outcomes had high heterogeneity and nonsignificant PIs.

In contrast with community pharmacists, AC pharmacists could directly be part of clinical teams, which may help to increase the acceptance of interventions from physicians, thus increasing the impact of MR.⁹ This assumption could not be tested since only a small number of studies included acceptance rate. The AC group included more patients (almost twice), longer follow-up times (3±7.3 months difference), and more studies in all outcomes than the CP subgroup. All of these elements could increase effects sizes and heterogeneity at the same time.¹⁴ More studies were

undertaken in the AC setting, some with high effects (outliers); however, we found no differences in magnitude and significance of effects when removed from the analyses.

In CPs there were significant decreases in low-density lipoprotein and SBP values. CP studies tended to be shorter and smaller than AC studies. All CP effects were more affected than ACs when accounting for a high risk of bias and publication bias, with fewer reporting the number of outcomes per study. The lower number of patients within each study could have lowered heterogeneity (increasing statistical significance) and effect sizes in almost all outcomes.^{10,14}

MR classification had significant differences between types 2 and 3, with advanced MRs providing larger effects in DBP, HbA_{1c}, and lipids, but this significance is limited because of a small number of pairwise comparisons, and no study with type 1 MR classification resulted from the inclusion criteria (Table S3).^{11,14} Most of the individual components of the MR service did not have significant effects on outcomes (Table S3). Assessment of BP during visits increased the effect in control of BP and SBP, as patients tend to improve compliance when they are tightly monitored.^{1–3}

Table 4. Pooled Analysis of T2DM Outcomes

Outcome	Analysis	Studies (Patients)	Effect Size	95% CI	I ² , %	95% PI	
T2DM control (OR)	Overall	12 (1805)	3.11	2.26–4.27*	30	1.48–6.52*	
	Setting	Excluding CP	11 (1564)	3.18	2.18–4.65*	36	1.27–8.00*
	Sample size	Excluding N <100 ^{45,84}	10 (1679)	2.89	2.16–3.87*	22	1.58–5.27*
	Outliers	Excluding OR >15 ^{69,73,84}	9 (1406)	2.71	2.11–3.47*	0	2.01–3.65*
HbA _{1c} , %	Overall	25 (3452)	−0.81	−0.99 to −0.64*	99	−1.78 to 0.15	
	Setting	AC	18 (2569)	−0.93	−1.17 to −0.69*	99	−2.05 to 0.19
		CP	7 (833)	−0.69	−0.94 to −0.45*	99	−1.57 to 0.19
	Sample size	Excluding N <100 ^{24,27,33,39,44,45,56,57}	17 (2802)	−0.99	−1.25 to −0.74*	99	−2.16 to 0.18
	Outliers	Excluding >1.5% decrease ⁴⁶	24 (3218)	−0.84	−0.97 to −0.70*	99	−1.51 to −0.13*
Fasting glucose, mg/dL	Overall	17 (2505)	−28.8	−38.1, −19.6*	99	−70.9, 13.2	
	Setting	AC	13 (1790)	−30.9	−41.0 to −20.9*	99	−73.0 to 11.2
		CP	4 (715)	−18.2	−41.1 to 4.50	99	−13.0 to 94.0
	Sample size	Excluding N <100 ^{33,44,48,61,75}	12 (2146)	−27.8	−37.1 to −18.5*	99	−65.8 to 10.2
	RoB	Excluding high ⁴⁸	16 (2442)	−28.3	−37.8 to −18.8*	99	−70.7 to 14.1
	Outliers	Excluding >50 mg/dL decrease ^{23,68,75,88}	13 (1939)	−20.3	−27.9 to −12.7*	99	−51.8 to 11.2

AC indicates ambulatory clinic; CP, community pharmacy; HbA_{1c}, glycated hemoglobin; OR, odds ratio; PI, prediction interval; RoB, risk of bias; T2DM, type 2 diabetes mellitus.
*Statistical significance.

Decreasing cholesterol or BP values would be expected to happen faster and to require fewer visits than improving diabetes mellitus outcomes, but we found no differences in follow-up times or the number of visits for the included studies or in regard to the observed effects.^{1–3} In hypertension, a significant increase overall in achievement of BP goals was found. Analyses show nonsignificant decreases in SBP and DBP (only CP achieved PI significance in SBP) but with high heterogeneity. Excluding small studies in the SBP analysis had no effect in the AC subgroup but decreased the effect in CPs and prevented significant PIs, which, together with an asymmetric funnel plot, suggested that there was a risk of publication bias in the CP subgroup (excluding outliers produced the same effect as they were mostly in CPs).¹⁴ The small effect in DBP could be explained by the fact that most included patients were older adults, who often have isolated systolic hypertension.^{2,3}

In T2DM, an overall significant increase in achieving HbA_{1c} goals was observed. Only 1 CP study reported this outcome despite most studies reporting HbA_{1c} percentages and being a key outcome, which prevented subgroup analysis.⁹ In dyslipidemia outcomes, the control of total cholesterol increased significantly overall and in ACs even while removing outliers or small studies, but not in continuous variables (except for low-density lipoprotein cholesterol in CP with a low number of studies) as heterogeneity was high.

Previous reviews reported significant reductions in SBP, DBP, HbA_{1c}, and cholesterol values, and our analysis reported

a similar magnitude in clinical changes.^{6–10} However, we found that at a larger number of studies and when accounting for heterogeneity, statistical significance was lost in most continuous outcomes (as shown by nonsignificant PI). Nevertheless, our results support a significant effect in the control of these cardiovascular risk diseases by pharmacist-led MRs, even when accounting for high heterogeneity.

There are only a limited number of studies that measure the impact of MR services by other health professionals. Nurses generally show lower effects than pharmacist-led MRs in similar outcomes, but interventions that included both pharmacists and nurses seemed to provide better outcomes.^{6–10,90–95}

Previous evidence has suggested that heterogeneity in pharmaceutical care studies could be accounted for by some major causes such as differences in sampling, patient demographic and clinical characteristics, differences in intervention components, and fidelity of the intervention.^{9,10,96,97} We found that most studies had similar patient characteristics such as age, sex percentage, and baseline health conditions of patients. Interestingly, excluding outliers had no effect on the magnitude of point estimate or heterogeneity.

The effects of individual components of the MR service were examined, but the description of interventions was both vague and varied greatly. Most studies did not include key points such as acceptance rate for interventions and fidelity of the pharmacists to provide MR, which could have effects on outcomes.^{96,97} The interaction between physicians and pharmacists was poorly described in many studies, therefore

Table 5. Pooled Analysis of Dyslipidemia Outcomes

Outcome	Analysis	Studies (Patients)	Effect Size	95% CI	I ² , %	95% PI	
TC control (OR)	Overall	11 (2012)	1.91	1.55–2.35*	31	1.05–3.46*	
	Setting	AC	8 (1022)	2.52	1.78–3.58*	26	1.18–5.40*
		CP	3 (990)	1.63	1.25–2.12*	0	0.29–8.97
	Sample size	Excluding N <100 ^{31,49,84}	8 (1814)	1.87	1.68–2.90*	0	1.01–3.50*
	Outliers	Excluding OR >10 ⁸⁴	10 (1959)	1.92	1.58–2.34*	0	1.53–2.42*
TC, mg/dL	Overall	24 (3851)	−14.3	−18.2 to −10.5*	99	−36.3 to 7.63	
	Setting	AC	17 (2439)	−18.1	−23.2 to −12.9*	99	−41.6 to 5.52
		CP	7 (1412)	−9.73	−15.5 to −3.99*	99	−29.2 to 9.79
	Sample size	Excluding N <100 ^{31,33,34,48,49,61,75}	17 (3393)	−14.7	−19.3 to −10.1*	99	−35.9 to 6.42
	RoB	Excluding high ⁴⁸	23 (3788)	−14.4	−18.3 to −10.5*	99	−36.1 to 7.28
	Outliers	Excluding >30 mg/dL decrease ^{46,49,68}	21 (3367)	−13.3	−16.7 to −10.0*	99	−29.7 to 3.06
LDL-C, mg/dL	Overall	20 (2576)	−10.3	−12.1 to −8.57*	99	−23.9 to 3.31	
	Setting	AC	15 (2021)	−15.3	−18.9 to −11.7*	99	−31.0 to 0.40
		CP	5 (555)	−8.80	−10.8 to −6.82*	96	−16.4 to −1.17*
	Sample size	Excluding N <100 ^{24,31,33,45,48,61,75}	13 (2103)	−15.6	−18.7 to −12.4*	99	−28.6 to −2.52*
	RoB	Excluding high ⁴⁸	19 (2513)	−13.7	−16.6 to −10.7*	99	−27.7 to 0.38
	Outliers	Excluding >25 mg/dL decrease ^{46,75}	18 (2279)	−12.1	−14.9 to −9.37*	99	−24.9 to 0.64
HDL-C, mg/dL	Overall	20 (2804)	0.90	0.40–1.40*	99	−10.2 to 12.0	
	Setting	AC	16 (2327)	4.07	1.66–6.49*	99	−6.80 to 15.0
		CP	4 (477)	0.76	0.26–1.27*	99	−1.49 to 3.02
	Sample size	Excluding N <100 ^{31,33,48,61,75}	15 (2483)	2.87	0.58–5.17*	99	−7.21 to 13.0
	RoB	Excluding high ⁴⁸	19 (2741)	3.26	0.85–5.66*	99	−8.30 to 14.8
	Outliers	Excluding >10 mg/dL increase ^{73,75}	18 (2376)	2.72	1.65–3.78*	99	−2.26 to 7.70
Triglycerides, mg/dL	Overall	23 (3185)	−29.7	−36.4 to −23.0*	99	−64.2 to 4.78	
	Setting	AC	16 (2327)	−34.8	−43.8 to −25.8*	99	−74.4 to 4.83
		CP	7 (858)	−23.4	−33.4 to −13.4*	99	−57.7 to 11.0
	Sample size	Excluding N <100 ^{31,33,34,48,61,75}	17 (2821)	−30.2	−38.3 to −22.1*	99	−66.8 to 6.40
	RoB	Excluding high ⁴⁸	22 (3122)	−30.5	−37.5 to −23.5*	99	−65.1 to 4.08
	Outliers	Excluding >60 mg/dL decrease ^{34,48,68,86}	19 (2782)	−24.3	−31.1 to −17.5*	99	−56.1 to 7.48

AC indicates ambulatory clinic; CP, community pharmacy; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; OR, odds ratio; PI, prediction interval; RoB, risk of bias; TC, total cholesterol.

*Statistical significance.

sensitivity analysis could not be performed. It would be optimal when generating evidence to have and use a standardized intervention that clearly defines the components and characteristics of the intervention, ie, dose and fidelity so that this source of heterogeneity could be ameliorated.^{96,97}

Intermediate and advanced MR services seem to provide benefits in controlling cardiovascular risk diseases as a result of many factors such as resolution of drug-related problems, increase in medication adherence, simplification of therapies, and reduction of clinical inertia (common in cardiovascular conditions).^{5–11} We believe that the increase in control of hypertension, T2DM, and dyslipidemias of pharmacist-led MR

and its positive effects in most clinical outcomes support the implementation of this service, but more evidence is necessary regarding the in-depth description of components to optimize its effects.

Study Limitations

This study has several limitations. Moderate to high heterogeneity was observed, which represented a difficulty in establishing the true impact of MR. Individual effects of components of the MR interventions could not be adequately compared. Because of large variability in the number of

reported components in many studies, combined effects meta-regressions could not be performed, therefore paired analyses using means and *P* values for significance had to be used. These results could be biased by the combined accumulation of type I errors for the large number of studies, thus its results should be interpreted with caution.¹⁴ There could be some risk of bias as a result of the exclusion of languages other than English and Spanish, with differences in cultural and healthcare system organization.

Conclusions

There is evidence to conclude that MRs provided by pharmacists may improve control of BP, cholesterol, and T2DM as significant effects sizes and PIs were found overall. We could not conclude that MR was better than usual care in most continuous clinical outcomes. Although effect sizes were positive with significant CIs for all analyses and settings, PI lacked significance in these outcomes. ACs had significant effects in the achievement of control of diabetes mellitus and high cholesterol, while CPs had significant decreases in SBP and low-density lipoprotein cholesterol values, but larger studies are needed to further explore these differences. Advanced MRs in ACs could have larger effects in diabetes mellitus and cholesterol outcomes, but more evidence is needed. To ensure that there is optimization of research resources and for healthcare systems to adopt MR as usual practice, international standards should be set for the evaluation of MR services including defining in detail the target population and the MR intervention.

Disclosures

None.

References

- Benjamin EJ, Blaha MJ, Chiuve SE, Cushman M, Das SR, Deo R, de Ferranti SD, Floyd J, Fornage M, Gillespie C, Isasi CR, Jiménez MC, Jordan LC, Judd SE, Lackland D, Lichtman JH, Lisabeth L, Liu S, Longenecker CT, Mackey RH, Matsushita K, Mozaffarian D, Mussolino ME, Nasir K, Neumar RW, Palaniappan L, Pandey DK, Thiagarajan RR, Reeves MJ, Ritchey M, Rodriguez CJ, Roth GA, Rosamond WD, Sasson C, Towfighi A, Tsao CW, Turner MB, Virani SS, Voeks JH, Willey JZ, Wilkins JT, Wu JHY, Alger HM, Wong SS, Muntner P. Heart disease and stroke statistics—2017 update: a report from the American Heart Association. *Circulation*. 2017;135:e146–e603.
- Violán C, Bejarano-Rivera N, Foguet-Boreu Q, Roso Llorach A, Pons-Vigués M, Martín Mateo M, Pujol-Ribera E. The burden of cardiovascular morbidity in a European Mediterranean population with multimorbidity: a cross-sectional study. *BMC Fam Pract*. 2016;17:150.
- World Health Organization. *Noncommunicable Diseases Progress Monitor, 2017*. Geneva, Switzerland: World Health Organization; 2017.
- World Health Organization. *Noncommunicable Diseases: Country profiles 2018*. Geneva, Switzerland: World Health Organization; 2018.
- Jalal ZS, Smith F, Taylor D, Patel H, Finlay K, Antoniou S. Pharmacy care and adherence to primary and secondary prevention cardiovascular medication: a systematic review of studies. *Eur J Hosp Pharm*. 2014;21:238–244.
- Omran D, Guirguis LM, Simpson SH. Systematic review of pharmacist interventions to improve adherence to oral antidiabetic medications in people with type 2 diabetes. *Can J Diabetes*. 2012;36:292–299.
- Morgado MP, Morgado SR, Mendes LC, Pereira LJ, Castelo-Branco M. Pharmacist interventions to enhance blood pressure control and adherence to antihypertensive therapy: review and meta-analysis. *Am J Health Syst Pharm*. 2011;68:241–253.
- Babar ZU, Kousar R, Murtaza G, Azhar S, Khan SA, Curley L. Randomized controlled trials covering pharmaceutical care and medicines management: a systematic review of literature. *Res Social Adm Pharm*. 2018;14:521–539.
- Omboni S, Caserini M. Effectiveness of pharmacist's intervention in the management of cardiovascular diseases. *Open Heart*. 2018;5:e000687.
- Sabater-Hernández D, Sabater-Galindo M, Fernandez-Llimos F, Rotta I, Hossain LN, Durks D, Franco-Trigo L, Lopes LA, Correr CJ, Benrimoj SJ. A systematic review of evidence-based community pharmacy services aimed at the prevention of cardiovascular disease. *J Manag Care Spec Pharm*. 2016;22:699–713.
- Allemann S, van Mil JWF, Botermann L, Berger K, Griese N, Hersberger K. Pharmaceutical Care: the PCNE definition 2013. *Int J Clin Pharm*. 2014;36:544–555.
- Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009;6:e1000097.
- Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med*. 2009;6:e1000100.
- Higgins JP, Green S. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0* [updated March 2011]. The Cochrane Collaboration. 2011.
- Kunders GD. *Hospitals: facilities planning and management*.
- World Health Organization. *The role of the pharmacist in the health care system*. 1994.
- Sterne JA, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, Cates CJ, Cheng HY, Corbet MS, Eldridge S, Emberson JR, Hernan MA, Hopewell S, Hróbjartsson A, Junqueira DR, Jüni P, Kirkham JJ, Lasserson T, Li T, McAleenan A, Reeves BC, Shepperd S, Shrier I, Stewart LA, Tilling K, White IR, Whiting PF, Higgins JP. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019;366:l4989.
- Int'Hout J, Ioannidis JP, Rovers MM, Goeman JJ. Plea for routinely presenting prediction intervals in meta-analysis. *BMJ Open*. 2016;6:e010247.
- Borenstein M, Hedges LV, Higgins JP, Rothstein HR. *Prediction Intervals—Chapter 17. Introduction to Meta-Analysis*. Hoboken: NJ; John Wiley & Sons. 2007:127–133.
- Amariles P, Sabater-Hernández D, García-Jiménez E, Rodríguez-Chamorro MA, Prats-Más R, Marín-Magán F, Galán-Ceballos JA, Jiménez-Martín J, Faus MJ. Effectiveness of Dader method for pharmaceutical care on control of blood pressure and total cholesterol in outpatients with cardiovascular disease or cardiovascular risk: EMDADER-CV randomized controlled trial. *J Manag Care Pharm*. 2012;18:311–323.
- Bajorek B, Lemay KS, Magin P, Roberts C, Krass I, Armour CL. Implementation and evaluation of a pharmacist-led hypertension management service in primary care: outcomes and methodological challenges. *Pharmacy Pract*. 2016;14:723.
- Basheti IA, Tadros OK, Aburuz S. Value of a community-based medication management review service in Jordan: a prospective randomized controlled study. *Pharmacotherapy*. 2016;36:1075–1086.
- Chung WW, Chua SS, Lai PS, Chan SP. Effects of a pharmaceutical care model on medication adherence and glycemic control of people with type 2 diabetes. *Patient Prefer Adher*. 2014;8:1185–1194.
- Doucette WR, Witry MJ, Farris KB, McDonough RP. Community pharmacist-provided extended diabetes care. *Ann Pharmacother*. 2009;43:882–889.
- Fornos JA, Andres NF, Andres JC, Guerra MM, Egea B. A pharmacotherapy follow-up program in patients with type-2 diabetes in community pharmacies in Spain. *Pharm World Sci*. 2006;28:65–72.
- Garcao JA, Cabrita J. Evaluation of a pharmaceutical care program for hypertensive patients in rural Portugal. *J Am Pharm Assoc*. 2002;42:858–864.
- Jahangard-Rafsanjani Z, Sarayani A, Nosrati M, Saadat N, Rashidian A, Hadjibabaie M, Ashouri A, Radfar M, Javadi M, Gholami K. Effect of a community pharmacist-delivered diabetes support program for patients receiving specialty medical care: a randomized controlled trial. *Diabetes Educ*. 2015;41:127–135.

28. Kjeldsen LJ, Bjerrum L, Dam P, Larsen BO, Rossing C, Søndergaard B, Herborg H. Safe and effective use of medicines for patients with type 2 diabetes—a randomized controlled trial of two interventions delivered by local pharmacies. *Res Social Adm Pharm*. 2015;11:47–62.
29. Krass I, Armour CL, Mitchell B, Brilliant M, Dienaar R, Hughes J, Lau P, Peterson G, Stewart K, Taylor S, Wilkinson J. The Pharmacy Diabetes Care Program: assessment of a community pharmacy diabetes service model in Australia. *Diabet Med*. 2007;24:677–683.
30. Lugo De Ortellado G, De Bittner MR, Chavez GH, Perez S. Implementación de un programa de atención farmacéutica en farmacias comunitarias para la detección de la hipertensión arterial y su seguimiento farmacoterapéutico. *Lat Am J Pharm*. 2007;4:590–595.
31. Nola KM, Gourley DR, Portner TS, Gourley GK, Solomon DK, Elam M, Regel B. Clinical and humanistic outcomes of a lipid management program in the community pharmacy setting. *J Am Pharm Assoc*. 2000;40:166–173.
32. Park JJ, Kelly P, Carter BL, Burgess PP. Comprehensive pharmaceutical care in the chain setting. *J Am Pharm Assoc*. 1996;36:443–451.
33. Paulo PT, Medeiros PA. A randomised clinical trial of the impact of pharmaceutical care on the health of type 2 diabetic patients. *Lat Am J Pharm*. 2016;35:1361–1368.
34. Paulos CP, Akesson Nygren CE, Celedon C, Carcamo CA. Impact of a pharmaceutical care program in a community pharmacy on patients with dyslipidemia. *Ann Pharmacother*. 2005;39:939–943.
35. Planas LG, Crosby KM, Mitchell KD, Farmer KC. Evaluation of a hypertension medication therapy management program in patients with diabetes. *J Am Pharm Assoc*. 2009;49:164–170.
36. Robinson JD, Segal R, Lopez LM, Doty RE. Impact of a pharmaceutical care intervention on blood pressure control in a chain pharmacy practice. *Ann Pharmacother*. 2010;44:88–96.
37. Skowron A, Polak S, Brandys J. The impact of pharmaceutical care on patients with hypertension and their pharmacists. *Pharmacy Pract*. 2011;9:110–115.
38. Stewart K, George J, Mc Namara KP, Jackson SL, Peterson GM, Bereznicki LR, Gee PR, Hughes JD, Bailey MJ, Hsueh YA, McDowell JM, Bortoletto DA, Lau R. A multifaceted pharmacist intervention to improve antihypertensive adherence: a cluster-randomized, controlled trial (HAPPY trial). *J Clin Pharm Ther*. 2014;39:527–534.
39. Taylor SJ, Milanova T, Hourihan F, Krass I, Coleman C, Armour CL. A cost-effectiveness analysis of a community pharmacist-initiated disease state management service for type 2 diabetes mellitus. *Int J Pharm Pract*. 2005;13:33–40.
40. Torres A, Fité B, Gascón P, Barau R, Guayta-Escobies M, Estrada-Campmany C, Rodríguez C. Efectividad de un programa de atención farmacéutica en la mejora del control de la presión arterial en pacientes hipertensos mal controlados. Estudio PressFarm. *Hipertens Riesgo Vasc*. 2010;27:13–22.
41. Villeneuve J, Genest J, Blais L, Vanier MC, Lamarre D, Fredette M, Lussier MT, Perreault S, Hudon E, Berbiche D, Lalonde L. A cluster randomized controlled Trial to Evaluate an Ambulatory primary care Management program for patients with dyslipidemia: the TEAM study. *CMAJ*. 2010;182:447–455.
42. Wang J, Wu J, Yang J, Zhuang Y, Chen J, Qian W, Tian J, Chen X, She D, Peng F. Effects of pharmaceutical care interventions on blood pressure and medication adherence of patients with primary hypertension in China. *Clin Res Regul Aff*. 2010;28:1–6.
43. Zillich AJ, Sutherland JM, Kumbera PA. Hypertension outcomes through blood pressure monitoring and evaluation by pharmacists (HOME Study). *J Gen Intern Med*. 2005;20:1091–1096.
44. Abuloha S, Alabbadi I, Albsoul-Younes A, Younes N, Zayed A. The role of clinical pharmacist in initiation and/or dose adjustment of insulin therapy in diabetic patients in outpatient clinic in Jordan. *JJPS*. 2016;9:33–50.
45. Aguiar PM, da Silva CHP, Chiann C, Dórea EL, Lyra DP, Storpirtis S. Pharmacist–physician collaborative care model for patients with uncontrolled type 2 diabetes in Brazil: results from a randomized controlled trial. *J Eval Clin Pract*. 2018;24:22–30.
46. Al Mazroui NR, Kamal MM, Ghabash NM, Yacout TA, Kole PL, McElnay JC. Influence of pharmaceutical care on health outcomes in patients with type 2 diabetes mellitus. *Brit J Clin Pharmaco*. 2009;67:547–557.
47. Albsoul-Younes AM, Hammad EA, Yasein NA, Tahaineh LM. Pharmacist-physician collaboration improves blood pressure control. *Saudi Med J*. 2011;32:288–292.
48. Azevedo MG, Pedrosa RS, Aوقي CM, Martins RR, Junior TN. Effectiveness of home pharmaceutical interventions in metabolic syndrome: a randomized controlled trial. *Braz J Pharm Sci*. 2017;53:e16089.
49. Bogden PE, Koontz LM, Williamson P, Abbott RD. The physician and pharmacist team. An effective approach to cholesterol reduction. *J Gen Intern Med*. 1997;12:158–164.
50. Bogden PE, Abbott RD, Williamson P, Onopa JK, Koontz LM. Comparing standard care with a physician and pharmacist team approach for uncontrolled hypertension. *J Gen Intern Med*. 1998;13:740–745.
51. Borenstein JE, Graber G, Saltiel E, Wallace J, Ryu S, Jackson A, Deutsch S, Weingarten SR. Physician-pharmacist comanagement of hypertension: a randomized, comparative trial. *Pharmacotherapy*. 2003;23:209–216.
52. Carter BL, Bergus GR, Dawson JD, Farris KB, Doucette WR, Chrischilles EA, Hartz AJ. A cluster-randomized trial to evaluate physician/pharmacist collaboration to improve blood pressure control. *J Clin Hypertens* (Greenwich). 2008;10:260–271.
53. Carter BL, Ardery G, Dawson JD, James PA, Bergus GR, Doucette WR, Chrischilles EA, Franciscus CL, Xu Y. Physician/pharmacist collaboration to improve blood pressure control. *Arch Intern Med*. 2009;169:1996–2002.
54. Chan CW, Siu SC, Wong CK, Lee VW. A pharmacist care program: positive impact on cardiac risk in patients with type 2 diabetes. *J Cardiovasc Pharmacol Ther*. 2012;17:57–64.
55. Chen JH, Ou HT, Lin TC, Lai EC, Kao YH. Pharmaceutical care of elderly patients with poorly controlled type 2 diabetes mellitus: a randomized controlled trial. *Int J Clin Pharm*. 2016;38:88–95.
56. Choe HM, Mitrovich S, Dubay D, Hayward RA, Krein SL, Vijan S. Proactive case management of high-risk patients with type 2 diabetes mellitus by a clinical pharmacist: a randomised controlled trial. *Am J Manag Care*. 2005;11:253–260.
57. Clifford RM, Batty KT, Davis TM, Davis W, Stein G, Stewart G, Plumridge RJ. A randomised controlled trial of a pharmaceutical care programme in high-risk diabetic patients in an outpatient clinic. *Int J Pharm Pract*. 2002;10:85–89.
58. Clifford RM, Davis WA, Batty KT, Davis TM. Effect of a pharmaceutical care program on vascular risk factors in type 2 diabetes: the Fremantle Diabetes Study. *Diabetes Care*. 2005;28:771–776.
59. de Castro MS, Fuchs FD, Santos MC, Maximiliano P, Gus M, Moreira LB, Ferreira MB. Pharmaceutical care program for patients with uncontrolled hypertension. Report of a double-blind clinical trial with ambulatory blood pressure monitoring. *Am J Hypertens*. 2006;19:528–533.
60. Ebid AH, Ali ZT, Ghobary MA. Blood pressure control in hypertensive patients: impact of an Egyptian pharmaceutical care model. *J App Pharm Sci*. 2014;4:093–101.
61. Firminho PY, Vasconcelos TO, Ferreira CC, Moreira LM, Romero NR, Dias LA, de Queiroz MG, Lopes MV, Fonteles MM. Cardiovascular risk rate in hypertensive patients attended in primary health care units: the influence of pharmaceutical care. *Braz J Pharm Sci*. 2015;51:617–627.
62. Green BB, Cook AJ, Ralston JD, Fishman PA, Catz SL, Carlson J, Thompson RS. Effectiveness of home blood pressure monitoring, web communication, and pharmacist care on hypertension control: the E-BP randomized controlled trial. *JAMA*. 2008;299:2857–2867.
63. Hammad EA, Yasein N, Tahaineh L, Albsoul-Younes AM. A randomized controlled trial to assess pharmacist-physician collaborative practice in the management of metabolic syndrome in a university medical clinic in Jordan. *J Manag Care Pharm*. 2011;17:295–303.
64. Hedegaard U, Kjeldsen LJ, Pottegård A, Henriksen JE, Lambrechtsen J, Hangaard J, Hallas J. Improving medication adherence in patients with hypertension: a randomized trial. *Am J Med*. 2015;128:1351–1361.
65. Hunt JS, Siemenczuk J, Pape G, Rozenfeld Y, Mackay J, LeBlanc BH, Touchette D. A randomized controlled trial of team-based care: impact of physician-pharmacist collaboration on uncontrolled hypertension. *J Gen Intern Med*. 2008;23:1966–1972.
66. Jacobs M, Sherry PS, Taylor LM, Amato M, Tataronis GR, Cushing G. Pharmacist Assisted Medication Program Enhancing the Regulation of Diabetes (PAMPERED) study. *J Am Pharm Assoc*. 2012;52:613–621.
67. Jameson JP, Baty PJ. Pharmacist collaborative management of poorly controlled diabetes mellitus: a randomized controlled trial. *Am J Manag Care*. 2010;16:250–255.
68. Jarab AS, Alqudah SG, Mukattash TL, Shattat G, Al-Oirim T. Randomized controlled trial of clinical pharmacy management of patients with type 2 diabetes in an outpatient diabetes clinic in Jordan. *J Manag Care Pharm*. 2012;18:516–526.
69. Korcegeç EI, Sancar M, Demirkan K. Effect of a pharmacist-led program on improving outcomes in patients with type 2 diabetes mellitus from Northern Cyprus: a randomized controlled trial. *J Manag Care Spec Pharm*. 2017;23:573–582.
70. Lee VW, Fan CS, Li AW, Chau AC. Clinical impact of a pharmacist-physician managed programme on hyperlipidaemia management in Hong Kong. *J Clin Pharm Ther*. 2009;34:407–414.

71. Morgado M, Rolo S, Castelo-Branco M. Pharmacist intervention program to enhance hypertension control: a randomised controlled trial. *Int J Clin Pharm*. 2011;33:132–140.
72. Mourao AO, Ferreira WR, Martins MA, Reis AM, Carrillo MR, Guimaraes AG, Ev LS. Pharmaceutical care program for type 2 diabetes patients in Brazil: a randomised controlled trial. *Int J Clin Pharm*. 2013;35:79–86.
73. Obreli-Neto PR, Marusic S, de Lyra Junior DP, Pilger D, Cruciol-Souza JM, Gaeti WP, Cuman RK. Effect of a 36-month pharmaceutical care program on the coronary heart disease risk in elderly diabetic and hypertensive patients. *J Pharm Pharmac Sci*. 2011;14:249–263.
74. Okamoto MP, Nakahiro RK. Pharmacoeconomic evaluation of a pharmacist-managed hypertension clinic. *Pharmacotherapy*. 2001;21:1337–1344.
75. Plaster CP, Melo DT, Boldt V, Cassaro KO, Lessa FC, Boëchat GA, Bissoli NS, de Andrade TU. Reduction of cardiovascular risk in patients with metabolic syndrome in a community health center after a pharmaceutical care program of pharmacotherapy follow-up. *Braz J Pharm Sci*. 2012;48:435–446.
76. Polgreen LA, Han J, Carter BL, Ardery GP, Coffey CS, Chrischilles EA, James PA. Cost effectiveness of a physician-pharmacist collaboration intervention to improve blood pressure control. *Hypertension*. 2015;66:1145–1151.
77. Rothman RL, Malone R, Bryant B, Shintani AK, Crigler B, Dewalt DA, Dittus RS, Weinberger M, Pignone MP. A randomized trial of a primary care-based disease management program to improve cardiovascular risk factors and glycated hemoglobin levels in patients with diabetes. *Am J Med*. 2005;118:276–284.
78. Sanchez-Guerra J, Lopez Y LOPEZ G, García-Jiménez S, Ávila-Jiménez L, Gómez-Galicia D, Carreras-Olivares B, Toledano-Jaimes C. Impact of a pilot program of medication review with follow-up on the blood pressure control in hypertension ambulatory patients with metabolic syndrome in Mexico. *Pharm Care Esp*. 2018;20:3–26.
79. Scott DM, Boyd ST, Stephan M, Augustine SC, Reardon TP. Outcomes of pharmacist-managed diabetes care services in a community health center. *Am J Health Syst Pharm*. 2006;63:2116–2122.
80. Shao H, Chen G, Zhu C, Chen Y, Liu Y, He Y, Jin H. Effect of pharmaceutical care on clinical outcomes of outpatients with type 2 diabetes mellitus. *Patient Prefer Adher*. 2017;11:897–903.
81. Simpson SH, Majumdar SR, Tsuyuki RT, Lewanczuk RZ, Spooner R, Johnson JA. Effect of adding pharmacists to primary care teams on blood pressure control in patients with type 2 diabetes: a randomized controlled trial. *Diabetes Care*. 2011;34:20–26.
82. Sookaneknun P, Richards RM, Sanguansermisri J, Teerasut C. Pharmacist involvement in primary care improves hypertensive patient clinical outcomes. *Ann Pharmacother*. 2004;38:2023–2028.
83. Tahaine L, Albsoul-Younes A, Al-Ashqar E, Habeb A. The role of clinical pharmacist on lipid control in dyslipidemic patients in North of Jordan. *Int J Clin Pharm*. 2011;33:229.
84. Taylor CT, Byrd DC, Krueger K. Improving primary care in rural Alabama with a pharmacy initiative. *Am J Health Syst Pharm*. 2003;60:1123–1129.
85. Tobarí H, Arimoto T, Shimojo N, Yuhara K, Noda H, Yamagishi K, Iso H. Physician-pharmacist cooperation program for blood pressure control in patients with hypertension: a randomized-controlled trial. *Am J Hypertens*. 2010;23:1144–1152.
86. Villa LA, Von Chrismar AM, Oyarzun C, Eujenin P, Fernandez ME, Quezada M. Pharmaceutical Care Program for dyslipidemic patients at three primary health care centers: impacts and outcomes. *Latin Am J Pharm*. 2009;28:415–420.
87. Wal P, Wal A, Bhandari A, Pandey U, Rai AK. Pharmacist involvement in the patient care improves outcome in hypertension patients. *J Res Pharm Pract*. 2013;2:123–129.
88. Wishah RA, Al-Khawaldeh OA, Albsoul AM. Impact of pharmaceutical care interventions on glycemic control and other health-related clinical outcomes in patients with type 2 diabetes: randomized controlled trial. *Diabetes Metab Syndr*. 2015;9:271–276.
89. Oparah AC, Famakinde AJ, Adebaya OJ. Outcomes of pharmacists' interventions in the collaborative care of patients with diabetes. *Pharmacy Education*. 2015;15:1477–2701.
90. Carter BL, Rogers M, Daly J, Zheng S, James PA. The potency of team-based care interventions for hypertension: a meta-analysis. *Arch Intern Med*. 2009;169:1748–1755.
91. Loveman E, Royle P, Waugh N. Specialist nurses in diabetes mellitus. *Cochrane Database Syst Rev*. 2003;2:CD003286.
92. Clark CE. Nurse led interventions to improve control of blood pressure in people with hypertension: systematic review and meta-analysis. *BMJ*. 2010;341:c3995.
93. Proia KK, Thota AB, Njie GJ, Finnie RK, Hopkins TE, Mukhtar Q, Pronk NP, Zeigler D, Kottke TE, Rask KJ, Lackland DT, Brooks JF, Braun LT, Cooksey T. Team-based care and improved blood pressure control: a community guide systematic review. *Am J Prev Med*. 2014;47:86–99.
94. Holland R, Desborough J, Goodyer L, Hall S, Wright D, Loke YK. Does pharmacist-led medication review help to reduce hospital admissions and deaths in older people? A systematic review and meta-analysis. *Br J Clin Pharmacol*. 2008;65:303–316.
95. Zermansky AG, Alldred DP, Petty DR, Raynor DK, Freemantle N, Eastaugh J, Bowie P. Clinical medication review by a pharmacist of elderly people living in care homes—randomised controlled trial. *Age Ageing*. 2006;35:586–591.
96. Crespo-Gonzalez C, Fernandez-Llimos F, Rotta I, Correr CJ, Benrimoj SJ, Garcia-Cardenas V. Characterization of pharmacists' interventions in asthma management: a systematic review. *J Am Pharm Assoc*. 2018;58:210–219.
97. Garcia-Cardenas V, Armour C, Benrimoj SJ, Martinez-Martinez F, Rotta I, Fernandez-Llimos F. Pharmacists' interventions on clinical asthma outcomes: a systematic review. *Eur Respir J*. 2016;47:1134–1143.

Supplemental Material

Table S1. Complete search strategies.

Database	Search details	Results
MEDLINE (PubMed)	((((pharmaceutical services[MeSH Terms]) OR (pharmacists) OR "medication review" OR "pharmaceutical care") AND ((hypertension[MeSH Terms]) OR (diabetes mellitus, Type 2[MeSH Terms]) OR (cardiovascular) OR (cholesterol, LDL[MeSH Terms]) OR "blood pressure" OR diabetes OR hypertension))) AND ((primary OR ambulatory OR clinic OR outpatient OR pharmacies OR community))	3161
Web of Science (without MEDLINE)	TI= ((pharmacists OR "pharmaceutical care" OR "medication review" OR "pharmaceutical services") AND (community OR ambulatory OR primary OR clinic) AND (cardiovascular OR hypertension OR diabetes OR cholesterol))	257
Embase (Ovid) (without MEDLINE)	((pharmacist or "medication review" or "pharmaceutical services" or "pharmaceutical care" or "pharmacy care" or pharmacists) and (community or clinic or primary) and (cardiovascular or hypertension or diabetes or cholesterol)).mp.	331
Cochrane CENTRAL Library	((pharmacists OR "pharmaceutical care" OR "medication review" OR "pharmaceutical services") AND (community OR ambulatory OR primary OR clinic) AND (cardiovascular OR hypertension OR diabetes OR cholesterol))	1091
The Cumulative Index to Nursing and Allied Health Literature (CINAHL)	((pharmacists OR "pharmaceutical care" OR "medication review" OR "pharmaceutical services")) AND ((community OR ambulatory OR primary OR clinic) AND ((cardiovascular OR hypertension OR diabetes OR cholesterol))	327

Table S2. Results of the revised Cochrane risk of bias tool for randomized controlled trials and cluster randomized trials.

Study Name	Random	Individual allocation (clusters)	Deviations from the intervention	Missing data	Measure of outcome	Selection report	Others	Bias
Abuloha et al 2016 ¹	L		L	L	L	L	L	LOW
Aguiar et al 2016 ²	L		L	L	L	L	C	LOW
Al Mazroui et al 2009 ³	C		L	L	C	L	L	CONCERNS
Albsoul-Younes et al 2011 ⁴	L		L	L	L	L	L	LOW
Amariles et al 2012 ⁵	L	L	L	L	L	L	L	LOW
Azevedo et al 2017 ⁶	C		L	L	H	L	L	HIGH
Bajorek et al 2016 ⁷	C	C	H	L	C	L	L	HIGH
Basheti et al 2016 ⁸	L		L	L	C	L	L	CONCERNS
Bogden et al 1997 ⁹	C	L	L	L	C	L	L	CONCERNS
Bogden et al 1998 ¹⁰	H	L	L	L	L	L	L	HIGH
Borenstein et al 2003 ¹¹	C		L	L	H	L	L	HIGH
Carter et al 2008 ¹²	L	C	L	L	C	L	L	CONCERNS
Carter et al 2009 ¹³	L	L	L	L	L	L	L	LOW
Chan et al 2012 ¹⁴	L		L	L	L	L	L	LOW
Chen et al 2016 ¹⁵	L		L	L	L	L	L	LOW
Choe et al 2005 ¹⁶	C		L	L	L	C	L	CONCERNS
Chung et al 2014 ¹⁷	C		L	L	C	L	L	CONCERNS
Clifford et al 2002 ¹⁸	L		L	L	C	L	L	LOW
Clifford et al 2005 ¹⁹	C		L	L	C	L	L	CONCERNS
de Castro et al 2015 ²⁰	L		L	L	C	L	L	LOW
Doucette et al 2009 ²¹	C		L	L	C	L	L	CONCERNS
Ebid et al 2014 ²²	C		L	L	L	L	L	LOW
Firminho et al 2015 ²³	L		L	L	C	L	L	CONCERNS
Fornos et al 2006 ²⁴	L		L	L	C	L	L	CONCERNS
Garcao et al 2002 ²⁵	C		L	L	C	L	L	CONCERNS
Green et al 2008 ²⁶	L		L	L	L	L	L	LOW
Hammad et al 2011 ²⁷	L		L	L	L	L	L	LOW

Hedegaard et al 2015 ²⁸	L		L	L	L	L	L	LOW
Hunt et al 2008 ²⁹	L		L	L	L	L	C	LOW
Jacobs et al 2012 ³⁰	L		L	L	L	L	L	LOW
Jahangard-Rafsanjani et al 2014 ³¹	L		L	L	L	L	L	LOW
Jameson et al 2010 ³²	L		L	L	L	L	L	LOW
Jarab et al 2012 ³³	L		L	L	C	C	L	CONCERNS
Kjeldsen et al 2014 ³⁴	C		L	L	C	L	L	CONCERNS
Korcegez et al 2017 ³⁵	L		L	L	L	L	L	LOW
Krass et al 2007 ³⁶	C	C	L	L	C	L	L	CONCERNS
Lee et al 2009 ³⁷	L		L	L	L	L	L	LOW
Lugo De Ortellado et al 2008 ³⁸	C		L	L	C	L	L	CONCERNS
Morgado et al 2011 ³⁹	L		L	L	L	L	L	LOW
Mourao et al 2013 ⁴⁰	L		L	L	C	L	L	CONCERNS
Nola et al 2000 ⁴¹	L		L	L	L	L	L	LOW
Obreli-Neto et al 2011 ⁴²	L		L	L	L	L	L	LOW
Okamoto et al 2001 ⁴³	L		L	L	C	L	C	CONCERNS
Oparah 2009 ⁴⁴	L		L	H	U	H	L	HIGH
Park et al 1996 ⁴⁵	C		L	L	C	L	L	CONCERNS
Paulo et al 2016 ⁴⁶	C		L	L	C	L	L	CONCERNS
Paulos et al 2005 ⁴⁷	C		L	L	C	L	L	CONCERNS
Planas et al 2009 ⁴⁸	L		L	L	C	H	L	HIGH
Plaster et al 2012 ⁴⁹	L		L	L	L	L	L	LOW
Polgreen et al 2015 ⁵⁰	L		L	L	L	L	L	LOW
Robinson et al 2010 ⁵¹	C	C	L	L	L	L	L	HIGH
Rothman et al 2005 ⁵²	L		L	L	L	L	L	LOW
Sanchez-Guerra et al 2018 ⁵³	L		L	L	L	L	L	LOW
Scott et al 2006 ⁵⁴	L		L	L	C	L	L	CONCERNS
Shao et al 2017 ⁵⁵	L		L	L	L	L	L	LOW
Simpson et al 2011 ⁵⁶	L		L	L	L	L	L	LOW
Skowron et al 2010 ⁵⁷	C	C	L	L	C	L	L	CONCERNS

Sookaneknun et al 2004 ⁵⁸	L		L	L	H	L	L	HIGH
Stewart et al 2014 ⁵⁹	L	C	L	L	C	L	L	CONCERNS
Tahaine et al 2011 ⁶⁰	L		L	L	L	L	L	LOW
Taylor et al 2003 ⁶¹	C		L	L	C	L	L	CONCERNS
Taylor et al 2016 ⁶²	C	C	L	L	L	L	L	HIGH
Tobari et al 2010 ⁶³	L		L	L	C	L	L	CONCERNS
Torres et al 2009 ⁶⁴	L	L	L	L	C	L	L	CONCERNS
Villa et al 2009 ⁶⁵	C		L	L	L	L	L	CONCERNS
Villeneuve et al 2010 ⁶⁶	L	L	L	L	C	L	L	CONCERNS
Wal et al 2013 ⁶⁷	L		L	L	C	C	L	CONCERNS
Wang et al 2011 ⁶⁸	L		L	L	L	L	L	LOW
Wishah et al 2014 ⁶⁹	L		L	L	L	L	L	LOW
Zillich et al 2005 ⁷⁰	L	C	L	L	C	L	L	CONCERNS

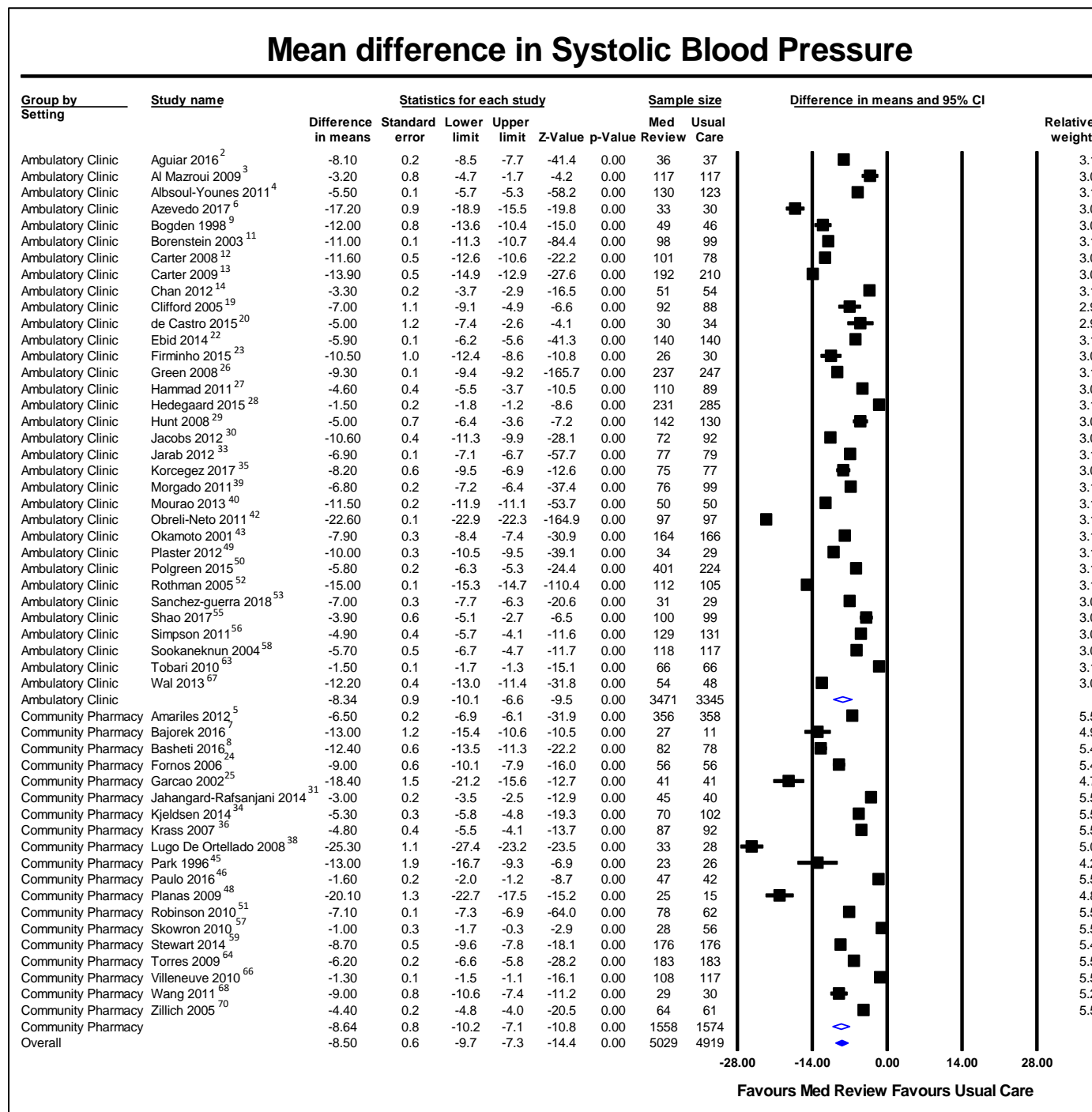
C: some concerns; H: high risk; L: low risk.

Table S3. Analysis of the impact of settings, type of MR and components in all outcomes.

Components		BP Goal	T2D Goal	TC Goal	SBP	DBP	HbA1c	FG	TC	LDL-C	HDL-C	TG
Type of MR	2	2.92	N/A	2.12	-8.52	-2.68	-0.62	-10.7	-8.1	-9.15	1.19	-23.4
	3	2.68	N/A	2.52	-8.41	-4.65	-0.94	-31.6	-19	-14.8	4.21	-34.8
p value		0.73	N/A	0.58	0.92	0.01*	0.03*	0.04*	0.01*	0.01*	0.02*	0.11
Specialist Phys	Y	2.23	2.71	N/A	-6.38	-4.24	-0.82	-35.9	-25	-15.7	3.09	-22.4
	N	2.82	3.67	N/A	-8.97	-4.61	-0.97	-29.4	-17	-15.2	4.3	-34.3
p value		0.40	0.44	N/A	0.15	0.81	0.62	0.42	0.12	0.94	0.48	0.62
Follow-up time	≤ 6 mo	2.84	3.5	2.82	-8.35	-3.97	-0.79	-32.5	-15	-15.3	4.24	-29.5
	> 6 mo	2.62	3.05	1.84	-8.62	-4.16	-0.18	-21.5	-15	-12	2.64	-36.1
p value		0.70	0.78	0.12	0.84	0.83	0.50	0.30	0.96	0.32	0.50	0.50
Number of visits	≤ 1v/mo	2.32	3.15	3.32	-8.42	-3.93	-0.94	-32.2	-15	-16.7	6.64	-34.7
	> 1v/mo	2.96	3.18	2.11	-8.56	-4.31	-0.84	-25	-15	-12.7	2.49	-28.6
p value		0.23	0.98	0.04*	0.92	0.68	0.56	0.55	0.94	0.42	0.06	0.45
Disease Ed	Y	2.63	3.09	2.24	-8.03	-3.89	-0.86	-29.6	-15	-14.5	3.85	-34.4
	N	2.97	3.67	2.57	-10.3	-4.75	-0.84	-2	-15	-6.89	0.6	-22.4
p value		0.57	0.67†	0.62	0.25	0.27	0.98†	0.01†	0.95	0.01†	0.01†	0.01†
Self	Y	2.88	3.09	1.84	-8.22	-4.12	-0.86	-29.3	-15	-14	4.25	-34.2
	N	2.54	3.67	2.85	-8.93	-3.96	-0.89	-23.5	-15	-13.2	2.41	-8
p value		0.63	0.67†	0.09	0.63	0.85	0.86	0.58	0.93	0.81	0.29	0.72
Lifestyle Ed	Y	2.66	N/A	2.33	-8.43	-3.97	-0.86	N/A	-15	-14.2	3.7	-32.4
	N	3.3	N/A	2.74	-9.43	-5.01	-0.85	N/A	-18	-5	0.2	-30
p value		0.48†	N/A	0.74†	0.65	0.43	0.98†	N/A	0.80†	0.01†	0.01†	0.01†
All DRP	Y	3.93	4.98	2.25	-9.58	-4.16	-0.82	-27.5	-16	-13.3	3.76	-32.6
	N	2.22	2.87	2.63	-7.19	-3.91	-0.9	-28.3	-15	-14.1	3.28	-16
p value		0.01*	0.23	0.58	0.10	0.78	0.69	0.91	0.86	0.78	0.81	0.87
Pat goals	Y	2.93	5.85	1.7	-9.49	-4.09	-0.7	-22.5	-13	-12.1	4.3	-31.6
	N	2.62	2.91	2.73	-7.77	-4.03	-0.94	-31.9	-17	-14.9	2.88	-30.2
p value		0.62	0.31	0.02*	0.24	0.94	0.12	0.31	0.23	0.40	0.44	0.18
Vitals assess	Y	2.76	5.85	2.3	-9.49	-4.15	-0.75	-23.5	-13	-13.1	3.64	-39.5
	N	2.65	2.91	2.62	-4.92	-3.74	-0.98	-33	-22	-14.9	3.3	-26.8
p value		0.97	0.31	0.71	0.01*	0.72	0.21	0.31	0.01*	0.64	0.85	0.65

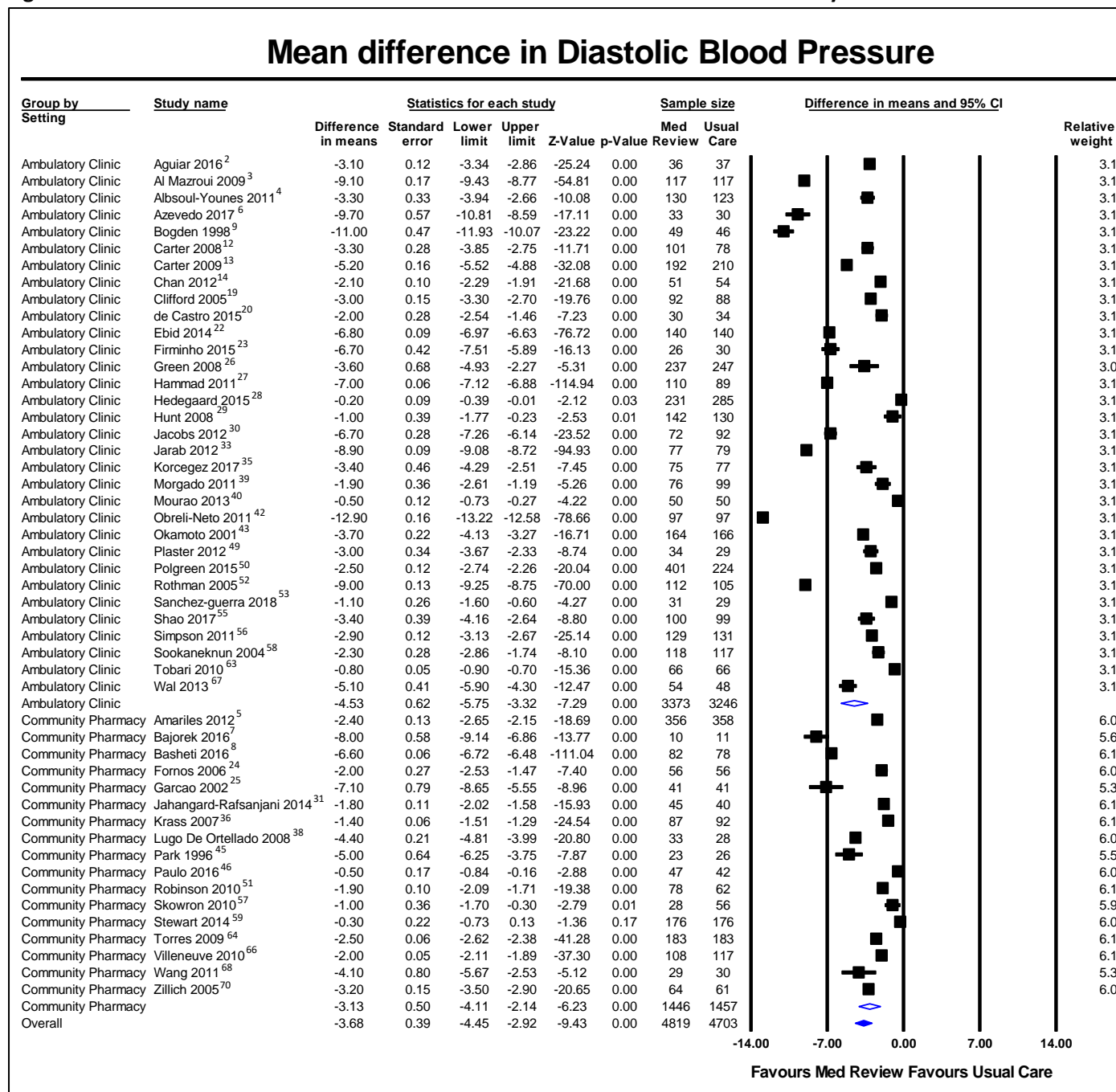
*: statistical significance; †: comparison made with 1 or 2 studies; All DRP: intervention in all drug related problems found; BP: blood pressure; Ed: education; HbA1c: glycated hemoglobin; HDL: high-density lipoprotein cholesterol; LDL: Low-density lipoprotein cholesterol; MR: Pharmaceutical Care Network Europe Medication review category; N/A: no studies to compare; Pat: patient; Phys: physician; Self: self-monitoring; T2D: type 2 diabetes; TC: total cholesterol; TG: triglycerides; v/mo: visits per month.

Figure S1. Raw mean difference on Systolic Blood Pressure in millimetres of mercury.



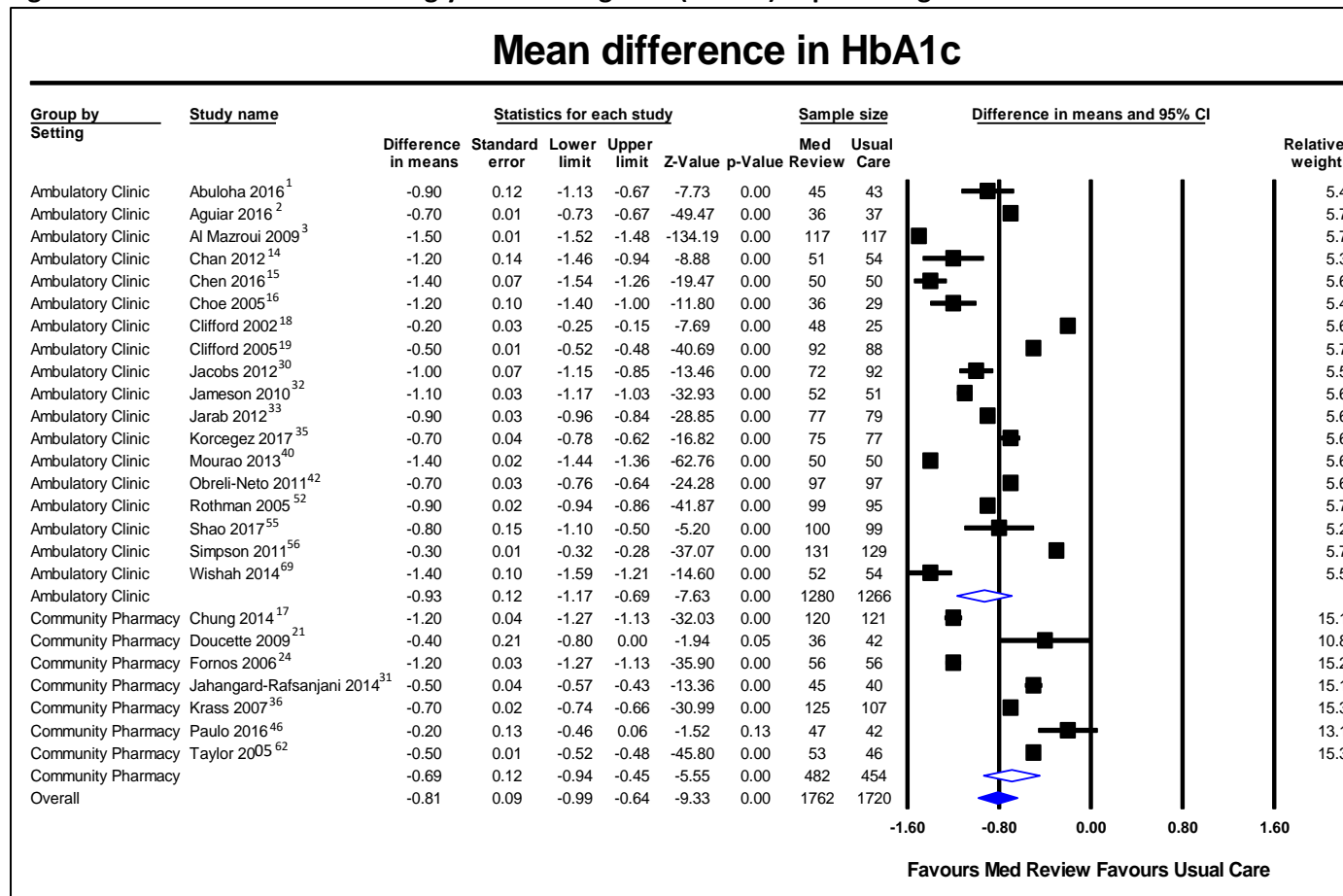
CI: confidence interval.

Figure S2. Raw mean difference on Diastolic Blood Pressure in millimetres of mercury.



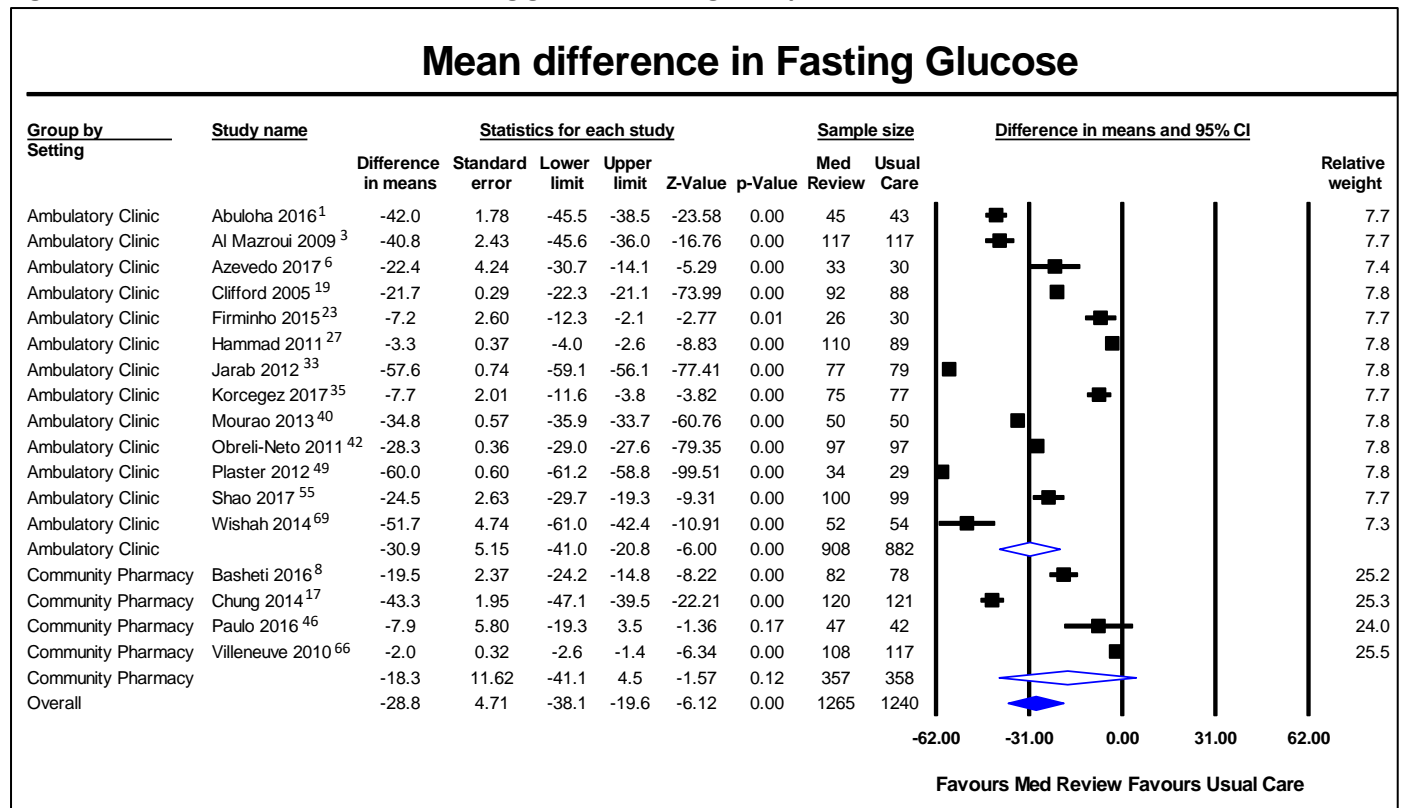
CI: confidence interval.

Figure S3. Raw mean difference on glycated hemoglobin (HbA1C) in percentage.



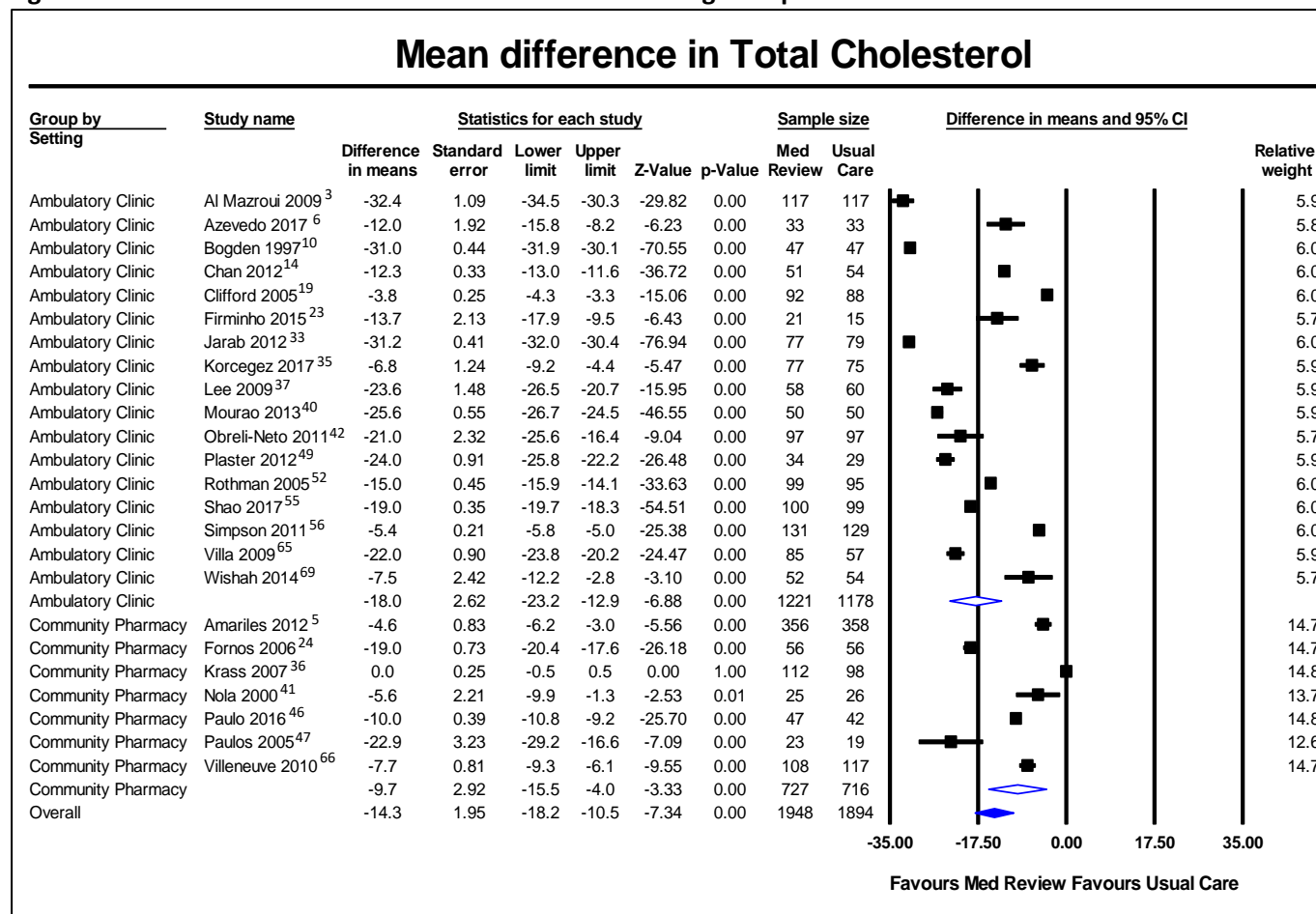
CI: confidence interval.

Figure S4. Raw mean difference on fasting glucose in milligrams per decilitre.



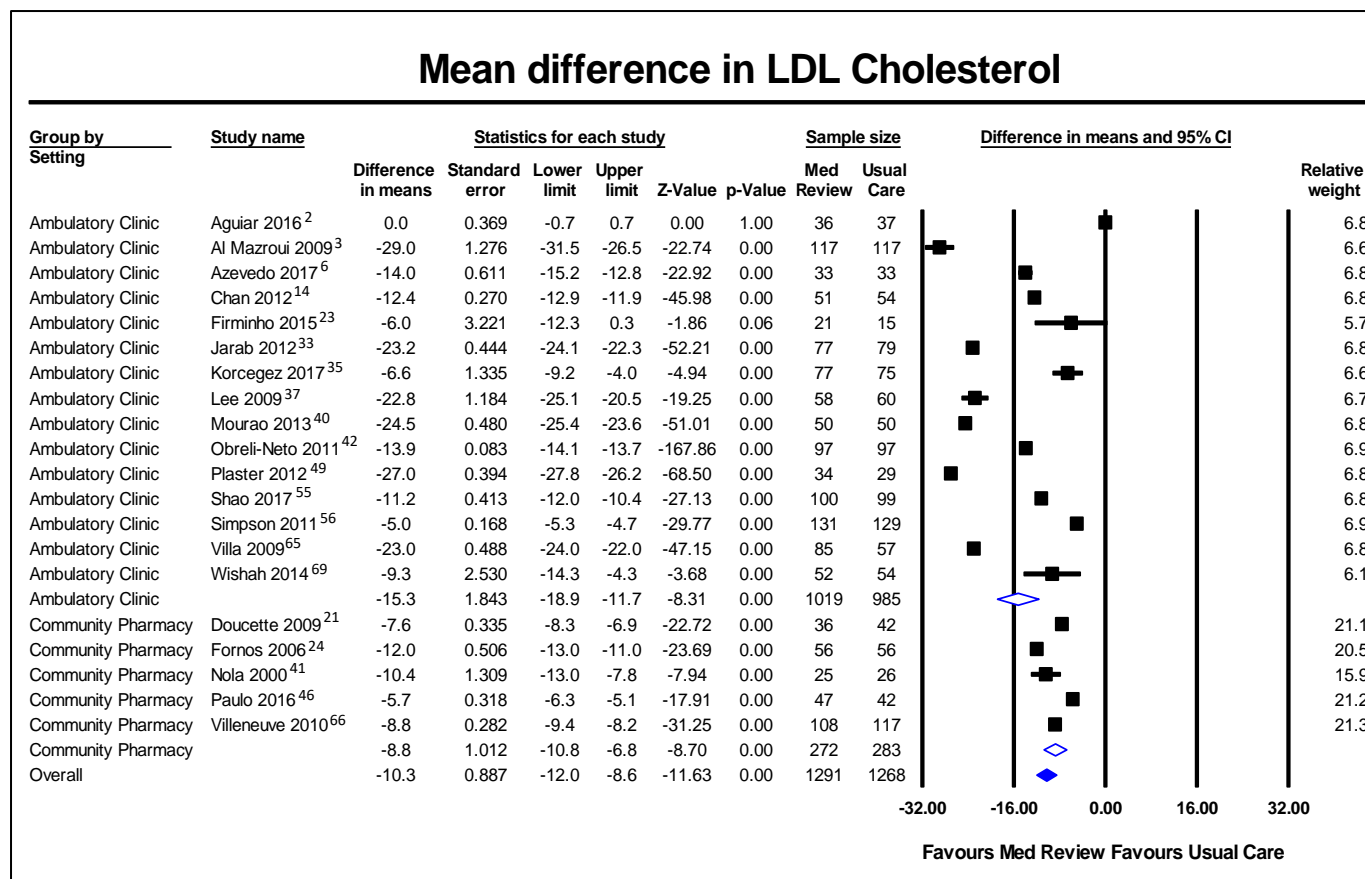
CI: confidence interval.

Figure S5. Raw mean difference on total cholesterol in milligrams per decilitre.



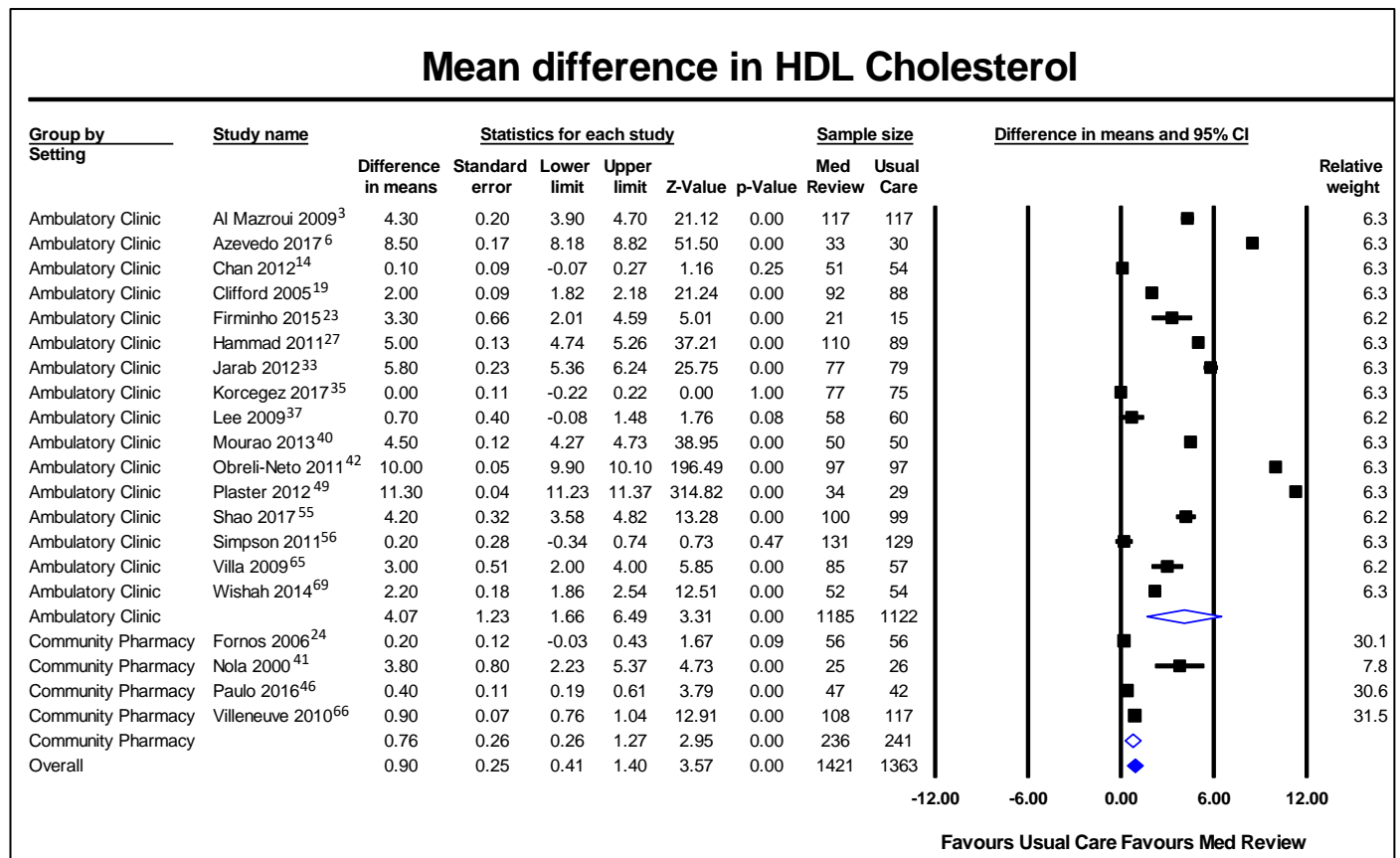
CI: confidence interval.

Figure S6. Raw mean difference on Low Density Lipoprotein (LDL) cholesterol in milligrams per decilitre.



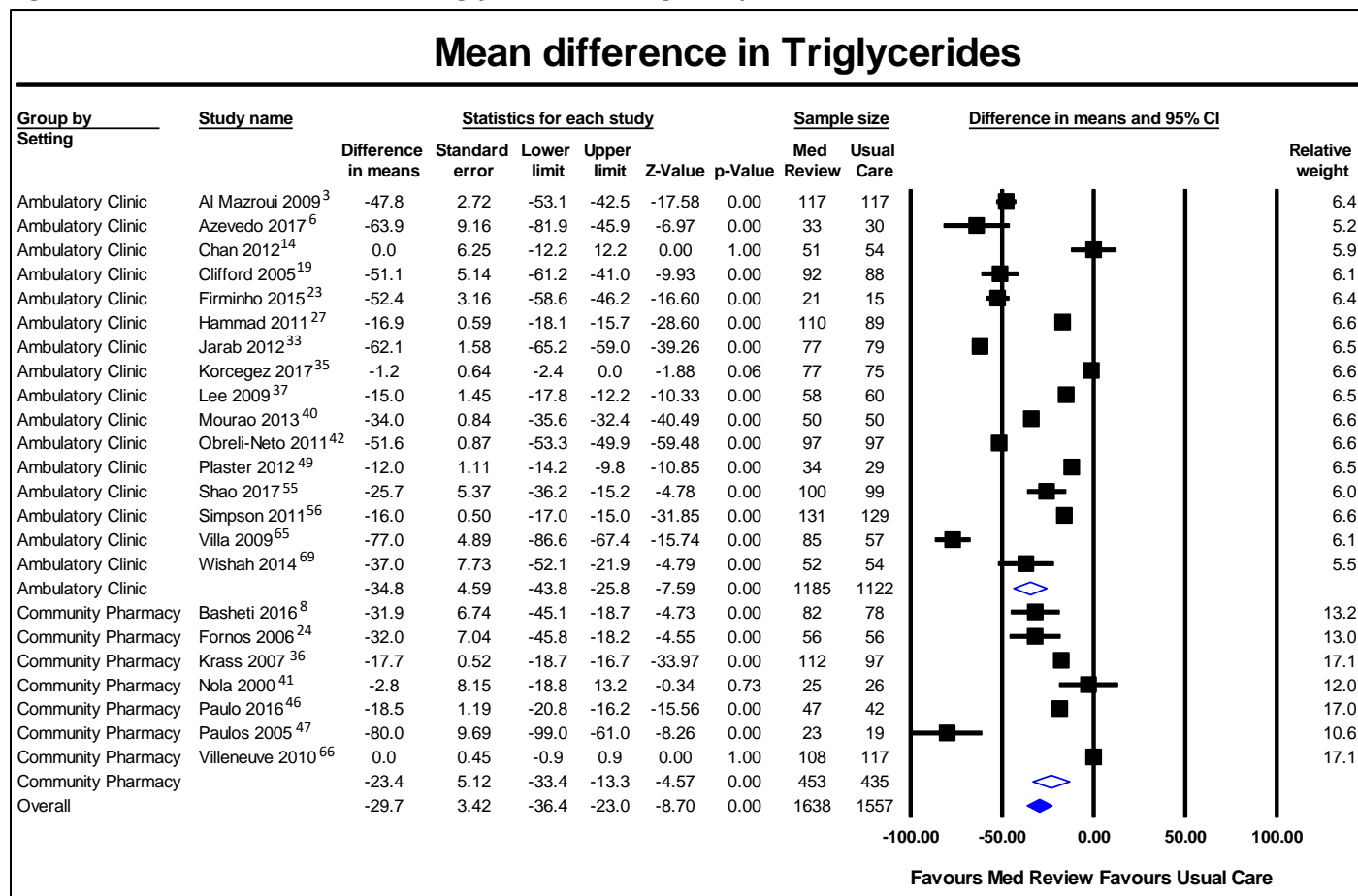
CI: confidence interval.

Figure S7. Raw mean difference on High Density Lipoprotein (HDL) cholesterol in milligrams per decilitre.



CI: confidence interval.

Figure S8. Raw mean difference on Triglycerides in milligrams per decilitre.



CI: confidence interval.

Supplemental References:

1. Abuloha S, Alabbadi I, Albsoul-Younes A, Younes N, Zayed A. The role of clinical pharmacist in initiation and/or dose adjustment of insulin therapy in diabetic patients in outpatient clinic in Jordan. *JJPS*. 2016; 9:33-50.
2. Aguiar PM, da Silva CHP, Chiann C, Dórea EL, Lyra DP, Storpirtis S. Pharmacist–physician collaborative care model for patients with uncontrolled type 2 diabetes in Brazil: results from a randomized controlled trial. *J Eval Clin Pract*. 2018; 24:22–30.
3. Al Mazroui NR, Kamal MM, Ghabash NM, Yacout TA, Kole PL, McElnay JC. Influence of pharmaceutical care on health outcomes in patients with Type 2 diabetes mellitus. *Brit J Clin Pharmacol*. 2009; 67:547–557.
4. Albsoul-Younes AM, Hammad EA, Yasein NA, Tahaine LM. Pharmacist-physician collaboration improves blood pressure control. *Saudi Med J*. 2011; 32:288–292.
5. Amariles P, Sabater-Hernández D, García-Jiménez E, Rodríguez-Chamorro MA, Prats-Más R, Marín-Magán F, Galán-Ceballos JA, Jiménez-Martín J, Faus MJ. Effectiveness of Dader method for pharmaceutical care on control of blood pressure and total cholesterol in outpatients with cardiovascular disease or cardiovascular risk: EMDADER-CV randomized controlled trial. *J Manag Care Pharm*. 2012; 18:311–23.
6. Azevedo, MGB, Pedrosa RS, Aoqui CM, Martins RR, Junior TN. Effectiveness of home pharmaceutical interventions in metabolic syndrome: a randomized controlled trial. *Braz J Pharm Sci*. 2017; 53:e16089.
7. Bajorek B, Lemay, KS, Magin P, Roberts C, Krass I, Armour CL. Implementation and evaluation of a pharmacist-led hypertension management service in primary care: outcomes and methodological challenges. *Pharmacy Pract*. 2016; 14: 723.
8. Basheti IA, Tadros OK, Aburuz S. Value of a Community-Based Medication Management Review Service in Jordan: A Prospective Randomized Controlled Study. *Pharmacotherapy*. 2016; 36:1075-1086.
9. Bogden PE, Abbott RD, Williamson P, Onopa JK, Koontz LM. Comparing standard care with a physician and pharmacist team approach for uncontrolled hypertension. *J Gen Intern Med*. 1998; 13:740-745.
10. Bogden PE, Koontz LM, Williamson P, Abbott RD. The physician and pharmacist team. An effective approach to cholesterol reduction. *J Gen Intern Med*. 1997; 12:158-164.
11. Borenstein JE, Graber G, Saltiel E, Wallace J, Ryu S, Jackson A, Deutsch S, Weingarten SR. Physician-Pharmacist Comanagement of Hypertension: A Randomized, Comparative Trial. *Pharmacotherapy*. 2003; 23:209-216.
12. Carter BL, Bergus GR, Dawson JD, Farris KB, Doucette WR, Chrischilles EA, Hartz AJ. A Cluster-Randomized Trial to Evaluate Physician/Pharmacist Collaboration to Improve Blood Pressure Control. *J Clin Hypertens*. 2008; 10:260–271.
13. Carter BL, Ardery G, Dawson JD, James PA, Bergus GR, Doucette WR, Chrischilles EA, Franciscus CL, Xu Y. Physician/Pharmacist Collaboration to Improve Blood Pressure Control. *Arch Intern Med*. 2009; 169:1996–2002.
14. Chan CW, Siu SC, Wong CK, Lee VW. A pharmacist care program: positive impact on cardiac risk in patients with type 2 diabetes. *J Cardiovasc Pharmacol Ther*. 2012; 17:57–64.

15. Chen JH, Ou HT, Lin TC, Lai EC, Kao YH. Pharmaceutical care of elderly patients with poorly controlled type 2 diabetes mellitus: a randomized controlled trial. *Int J Clin Pharm.* 2016; 38:88-95.
16. Choe HM, Mitrovich S, Dubay D, Hayward RA, Krein SL, Vijan S. Proactive case management of high-risk patients with type 2 diabetes mellitus by a clinical pharmacist: a randomised controlled trial. *Am J Manag Care.* 2005; 11:253–260.
17. Chung WW, Chua SS, Lai PSM, Chan SP. Effects of a pharmaceutical care model on medication adherence and glycemic control of people with type 2 diabetes. *Patient Prefer Adher.* 2014; 8:1185–1194.
18. Clifford RM, Batty KT, Davis TM, Davis W, Stein G, Stewart G, Plumridge RJ. A randomised controlled trial of a pharmaceutical care programme in high-risk diabetic patients in an outpatient clinic. *Int J Pharm Pract.* 2002; 10:85-89.
19. Clifford RM, Davis WA, Batty KT, Davis TM. Effect of a pharmaceutical care program on vascular risk factors in type 2 diabetes: the Fremantle Diabetes Study. *Diabetes Care.* 2005; 28:771-776
20. de Castro MS, Fuchs FD, Santos MC, Maximiliano P, Gus M, Moreira LB, Ferreira MB. Pharmaceutical care program for patients with uncontrolled hypertension. Report of a double-blind clinical trial with ambulatory blood pressure monitoring. *Am J Hypertens.* 2006; 19:528–533.
21. Doucette WR, Witry MJ, Farris KB, McDonough RP. Community pharmacist-provided extended diabetes care. *Ann Pharmacother.* 2009; 43:882–889.
22. Ebid AHIM, Ali ZT, Ghobary MAF. Blood pressure control in hypertensive patients: Impact of an Egyptian pharmaceutical care model. *J App Pharm Sci.* 2014; 4:093-101.
23. Firminho PYM, Vasconcelos TO, Ferreira CC, Moreira LM, Romero NR, Dias LA, de Queiroz MGR, Lopes MVO, Fonteles MMF. Cardiovascular risk rate in hypertensive patients attended in primary health care units: the influence of pharmaceutical care. *Braz J Pharm Sci.* 2015; 51:617-627
24. Fornos JA, Andres NF, Andres JC, Guerra MM, Egea B. A pharmacotherapy follow-up program in patients with type-2 diabetes in community pharmacies in Spain. *Pharm World Sci.* 2006; 28:65–72.
25. Garcao JA, Cabrita J. Evaluation of a pharmaceutical care program for hypertensive patients in rural Portugal. *J Am Pharm Assoc.* 2002; 42:858–864.
26. Green BB, Cook AJ, Ralston JD, Fishman PA, Catz SL, Carlson J, Thompson RS. Effectiveness of Home Blood Pressure Monitoring, Web Communication, and Pharmacist Care on Hypertension Control: The e-BP Randomized Controlled Trial. *JAMA.* 2008; 299:2857–2867.
27. Hammad EA, Yasein N, Tahaineh L, Albsoul-Younes AM. A randomized controlled trial to assess pharmacist-physician collaborative practice in the management of metabolic syndrome in a university medical clinic in Jordan. *J Manag Care Pharm,* 2011; 17:295-303.
28. Hedegaard U, Kjeldsen LJ, Pottegård A, Henriksen JE, Lambrechtsen J, Hangaard J, Hallas J. Improving Medication Adherence in Patients with Hypertension: A Randomized Trial. *Am J Med.* 2015; 128:1351-1361.
29. Hunt JS, Siemieniczuk J, Pape G, Rozenfeld Y, Mackay J, LeBlanc BH, Touchette D. A Randomized Controlled Trial of Team-Based Care: Impact of Physician-Pharmacist Collaboration on Uncontrolled Hypertension. *J Gen Intern Med.* 2008; 23:1966-1972.

30. Jacobs M, Sherry PS, Taylor LM, Amato M, Tataronis GR, Cushing G. Pharmacist Assisted Medication Program Enhancing the Regulation of Diabetes (PAMPERED) study. *J Am Pharm Assoc.* 2012; 52:613–621.
31. Jahangard-Rafsanjani Z, Sarayani A, Nosrati M, Saadat N, Rashidian A, Hadjibabaie M, Ashouri A, Radfar M, Javadi M, Gholami K. Effect of a community pharmacist-delivered diabetes support program for patients receiving specialty medical care: a randomized controlled trial. *Diabetes Educ.* 2015; 41:127-135.
32. Jameson JP, Baty PJ. Pharmacist collaborative management of poorly controlled diabetes mellitus: a randomized controlled trial. *Am J Manag Care.* 2010; 16:250–255
33. Jarab AS, Alqudah SG, Mukattash TL, Shattat G, Al-Qirim T. Randomized controlled trial of clinical pharmacy management of patients with type 2 diabetes in an outpatient diabetes clinic in Jordan. *J Manag Care Pharm.* 2012; 18:516–526.
34. Kjeldsen LJ, Bjerrum L, Dam P, Larsen BO, Rossing C, Søndergaard B, Herborg H. Safe and effective use of medicines for patients with type 2 diabetes – a randomized controlled trial of two interventions delivered by local pharmacies. *Res Social Adm Pharm.* 2015; 11:47–62
35. Korcegez EI, Sancar M, Demirkan K. Effect of a pharmacist-led program on improving outcomes in patients with type 2 diabetes mellitus from Northern Cyprus: a randomized controlled trial. *J Manag Care Spec Pharm.* 2017; 23:573–582.
36. Krass, I, Armour, CL, Mitchell B, Brilliant M, Dienaar R, Hughes J, Lau P, Peterson G, Stewart K, Taylor S, Wilkinson J. The Pharmacy Diabetes Care Program: assessment of a community pharmacy diabetes service model in Australia. *Diabetic Medicine.* 2007; 24:677-683.
37. Lee VW, Fan CS, Li AW, Chau AC. Clinical impact of a pharmacist-physician co-managed programme on hyperlipidaemia management in Hong Kong. *J Clin Pharm Ther.* 2009; 34:407–414.
38. Lugo De Ortellado G, De Bittner MR, Chavez GH, Perez S. Implementación de un programa de atención farmacéutica en farmacias comunitarias para la detección de la hipertensión arterial y su seguimiento farmacoterapéutico. *Lat Am J Pharm.* 2007; 4:590-595.
39. Morgado M, Rolo S, Castelo-Branco M. Pharmacist intervention program to enhance hypertension control: a randomised controlled trial. *Int J Clin Pharm.* 2011; 33:132-140.
40. Mourao AO, Ferreira WR, Martins MA, Reis AM, Carrillo MR, Guimaraes AG, Ev LS. Pharmaceutical care program for type 2 diabetes patients in Brazil: a randomised controlled trial. *Int J Clin Pharm.* 2013; 35:79-86
41. Nola KM, Gourley DR, Portner TS, Gourley GK, Solomon DK, Elam M, Regel B. Clinical and humanistic outcomes of a lipid management program in the community pharmacy setting. *J Am Pharm Assoc.* 2000; 40:166–173.
42. Obreli-Neto PR, Marusic S, de Lyra Junior DP, Pilger D, Cruciol-Souza JM, Gaeti WP, Cuman RK. Effect of a 36-month pharmaceutical care program on the coronary heart disease risk in elderly diabetic and hypertensive patients. *J Pharm Pharmac Sci.* 2011; 14:249-263.
43. Okamoto MP, Nakahiro RK. Pharmacoeconomic evaluation of a pharmacist-managed hypertension clinic. *Pharmacotherapy.* 2001; 21:1337–1344.
44. Oparah AC, Famakinde AJ, Adebaya OJ2. Outcomes of pharmacists' interventions in the collaborative care of patients with diabetes. *Pharmacy Education.* 2015; 15:1477-2701.
45. Park JJ, Kelly P, Carter BL, Burgess PP. Comprehensive pharmaceutical care in the chain setting. *J Am Pharm Assoc.* 1996; 36:443–451.

46. Paulo PT, Medeiros PA. A randomised clinical trial of the impact of pharmaceutical care on the health of type 2 diabetic patients. *Lat Am J Pharm.* 2016; 35: 1361-1368.
47. Paulos CP, Akesson Nygren CE, Celedon C, Carcamo CA. Impact of a pharmaceutical care program in a community pharmacy on patients with dyslipidemia. *Ann Pharmacother.* 2005; 39:939–943
48. Planas LG, Crosby KM, Mitchell KD, Farmer KC. Evaluation of a hypertension medication therapy management program in patients with diabetes. *JAPhA.* 2009; 49:164–170.
49. Plaster CP, Melo DT, Boldt V, Cassaro KOS, Lessa FCR, Boëchat GAP, Bissoli NS, de Andrade TU. Reduction of cardiovascular risk in patients with metabolic syndrome in a community health center after a pharmaceutical care program of pharmacotherapy follow-up. *Braz J Pharm Sci.* 2012; 48:435-446.
50. Polgreen LA, Han J, Carter BL, Ardery GP, Coffey CS, Chrischilles EA, James PA. Cost effectiveness of a physician-pharmacist collaboration intervention to improve blood pressure control. *Hypertension.* 2015; 66:1145–1151.
51. Robinson JD, Segal R, Lopez LM, Doty RE. Impact of a pharmaceutical care intervention on blood pressure control in a chain pharmacy practice. *Ann Pharmacother.* 2010; 44:88–96.
52. Rothman RL, Malone R, Bryant B, Shintani AK, Crigler B, Dewalt DA, Dittus RS, Weinberger M, Pignone MP. A randomized trial of a primary care-based disease management program to improve cardiovascular risk factors and glycated hemoglobin levels in patients with diabetes. *Am J Med.* 2005; 118:276–284.
53. Sanchez-Guerra J, Lopez y Lopez G, García-Jiménez S, Ávila-Jiménez L, Gómez-Galicia D, Carreras-Olivares B, Toledano-Jaimes C. Impact of a pilot program of medication review with follow-up on the blood pressure control in hypertension ambulatory patients with metabolic syndrome in Mexico. *Pharm Care Esp.* 2018; 20: 3-26
54. Scott DM, Boyd ST, Stephan M, Augustine SC, Reardon TP. Outcomes of pharmacist-managed diabetes care services in a community health center. *Am J Health Syst Pharm.* 2006; 63:2116–2122.
55. Shao H, Chen G, Zhu C, Chen Y, Liu Y, He Y, Jin H. Effect of pharmaceutical care on clinical outcomes of outpatients with type 2 diabetes mellitus. *Patient Prefer Adher.* 2017; 11:897–903.
56. Simpson SH, Majumdar SR, Tsuyuki RT, Lewanczuk RZ, Spooner R, Johnson JA. Effect of Adding Pharmacists to Primary Care Teams on Blood Pressure Control in Patients with Type 2 Diabetes: A randomized controlled trial. *Diabetes Care.* 2011; 34:20–26.
57. Skowron A, Polak S, Brandys J. The impact of pharmaceutical care on patients with hypertension and their pharmacists. *Pharmacy Pract.* 2011; 9:110-115.
58. Sookaneknun P, Richards RME, Sanguansermsri J, Teerasut C. Pharmacist involvement in primary care improves hypertensive patient clinical outcomes. *Ann Pharmacother.* 2004; 38:2023–2028.
59. Stewart K, George J, Mc Namara KP, Jackson SL, Peterson GM, Bereznicki LR, Gee PR, Hughes JD, Bailey MJ, Hsueh YA, McDowell JM, Bortoletto DA, Lau R. A multifaceted pharmacist intervention to improve antihypertensive adherence: a cluster-randomized, controlled trial (HAPPY trial). *J Clin Pharm Ther.* 2014; 39: 527–534.
60. Tahaineh L, Albsoul-Younes A, Al-Ashqar E, Habeb A. The role of clinical pharmacist on lipid control in dyslipidemic patients in North of Jordan. *Int J Clin Pharm.* 2011; 33: 229.

61. Taylor CT, Byrd DC, Krueger K. Improving primary care in rural Alabama with a pharmacy initiative. *Am J Health Syst Pharm.* 2003; 60:1123–1129.
62. Taylor SJ, Milanova T, Hourihan F, Krass I, Coleman C, Armour CL. A cost-effectiveness analysis of a community pharmacist-initiated disease state management service for type 2 diabetes mellitus. *Int J Pharm Pract.* 2005; 13: 33-40.
63. Tobari H, Arimoto T, Shimojo N, Yuhara K, Noda H, Yamagishi K, Iso H. Physician-pharmacist cooperation program for blood pressure control in patients with hypertension: a randomized-controlled trial. *Am J Hypertens.* 2010; 23:1144–1152.
64. Torres A, Fité B, Gascón P, Barau R, Guayta-Escolies M, Estrada-Campmany C, Rodríguez, C. Efectividad de un programa de atención farmacéutica en la mejora del control de la presión arterial en pacientes hipertensos mal controlados. *Estudio PressFarm. Hipertens Riesgo Vasc.* 2010; 27: 13–22.
65. Villa LA, Von Chrismar AM, Oyarzun C, Eujenin P, Fernandez ME, Quezada M. Pharmaceutical Care Program for dyslipidemic patients at three primary health care centers: impacts and outcomes. *Latin Am J Pharm.* 2009; 28:415-420.
66. Villeneuve J, Genest J, Blais L, Vanier MC, Lamarre D, Fredette M, Lussier MT, Perreault S, Hudon E, Berbiche D, Lalonde L. A cluster randomized controlled Trial to Evaluate an Ambulatory primary care Management program for patients with dyslipidemia: the TEAM study. *CMAJ.* 2010; 182:447–455.
67. Wal P, Wal A, Bhandari A, Pandey U, Rai AK. Pharmacist involvement in the patient care improves outcome in hypertension patients. *J Res Pharm Pract.* 2013; 2:123-129.
68. Wang J, Wu J, Yang J, Zhuang Y, Chen J, Qian W, Tian J, Chen X, She D, Peng F. Effects of pharmaceutical care interventions on blood pressure and medication adherence of patients with primary hypertension in China. *Clin Res Regul Aff.* 2010; 28:1-6
69. Wishah RA, Al-Khawaldeh OA, Albsoul AM. Impact of pharmaceutical care interventions on glycemic control and other health-related clinical outcomes in patients with type 2 diabetes: randomized controlled trial. *Diabetes Metab Syndr.* 2015; 9:271–276.
70. Zillich AJ, Sutherland JM, Kumbera PA. Hypertension outcomes through blood pressure monitoring and evaluation by pharmacists (HOME Study). *J Gen Intern Med.* 2005; 20:1091-1096.