GENERAL

A PHARMACIST CARE PROGRAM: THE POSITIVE IMPACT ON THE OUTCOMES OF LIPID-LOWERING THERAPY

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Abstract: Poor medication adherence is a major problem among patients with chronic diseases, and this is particularly commonly observed for lipid-lowering medications, including statins. A systematic review and meta-analysis were performed based on a search of two databases to identify relevant reports published by April 2021. The studies were controlled trials in which the community or clinical pharmacists conducted an intervention to improve patient adherence and clinical outcomes. Thirty-nine studies (34,137 participants) were included in the analyses. Participants in the intervention group had better adherence than those in the control group: odds ratio (OR) = 2.03; 95% confidence interval (CI) 1.63–2.61; $P=0.0001$; $I^2=79.44\%$; 66.23–87.49. This effect was accompanied by a significant improvement in clinical outcomes, i.e. a decrease in plasma lipid levels (TC, LDL-C, and triglycerides) and body mass index. These were influenced by the type and duration of intervention, the nature of the disorder, and the role of the pharmacist. Interventions delivered by both clinical and community pharmacists increase adherence for patients receiving lipid-lowering medication for dyslipidemia or cardiovascular disease and diabetes. The clinical pharmacist was found to have a more pronounced impact on the normalization of lipid profile.

Keywords: adherence, lipid-lowering medication, clinical pharmacist, community pharmacist

Poor medication adherence is one of the biggest challenges faced by health care. Non-adherent patients exhibit poor disease control, more incidents of hospitalization, and higher mortality. In recent studies, several interrelated factors that can determine patient adherence have been identified. These concern the patient (e.g., knowledge, attitudes, beliefs, socioeconomic status), medication (e.g., tolerability, cost), disease (e.g., symptoms, severity), and the health care system (e.g., trust in health care providers, organization of care) (1). Both community and clinical pharmacists can play an important role in achieving therapeutic goals in patients with chronic disorders by organizing pharmacotherapy follow-up programs. These can entail counseling the patient about the disease (e.g., arterial hypertension, hyperglycemia, dyslipidemia), recommending lifestyle changes, evaluating adherence to prescribed medications, and monitoring the impact of therapy, for example by measuring blood pressure, glucose, or total blood cholesterol levels. A recent systematic review found clinical pharmacy services targeting specific cardiovascular conditions, such as hypertension or diabetes mellitus have a positive impact on patient outcomes, including reduced blood pressure and hemoglobin A1c level (2). Similar works have also emphasized

the beneficial role of the community pharmacist in blood pressure management (3) and adherence to lipid-lowering medication; however, the results concerning such beneficial impacts on clinical outcomes, including lipid level control, remain inconclusive (4). Therefore, the purpose of the present survey was to conduct a systematic review and meta-analysis of the influence of the pharmacist on the clinical outcomes and patient adherence to lipid-lowering medication, based on data obtained by prospective and controlled clinical trials. The study also examines the influence of the type and duration of intervention, the nature of the disorder (diabetes, cardiovascular disease, dyslipidemia, etc.), and the role of the pharmacist (clinical, community pharmacists).

EXPERIMENTAL

Data source. The meta-analysis was reported in accordance with the PRISMA guidelines (5). The search corpus comprised Medline and Embase from January 1st 1990 to April 30th 2021. The databases were searched with no language restrictions using the following search terms in titles and abstracts: ('pharmacist intervention') OR ('pharmaceutical intervention') OR ('pharmacy service') AND (('lipid

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lowering therapy’) OR (‘hypercholesterolemia adherence’) OR (‘treatment adherence’) OR (‘non-adherence’) OR (‘dyslipidemia’) OR (‘hyperlipidemia’) OR (‘hypercholesterolemia’) OR (‘statin discontinuation’)) AND ‘clinical trials’.

Study selection. The inclusion criteria were defined *a priori*. Original studies were included if they met the following criteria: (i) being a clinical prospective, controlled trial assessing the effects of pharmacist-led interventions as an addition to the usual care that was addressed to adult patients, (ii) the recruited patients received lipid-lowering therapy (initiation or continuation), (iii) the effects of such interventions were demonstrated for ‘Intervention’ vs. control group as the difference between baseline and follow-up period in accordance with at least one plasma lipid parameter, or a parameter that described patient adherence to therapy.

The following exclusion criteria were applied.

1. Lack of original data
2. Lack of control group
3. Lack of baseline data (i.e., before particular intervention was begun)
4. Lack of plasma lipid or adherence parameter
5. Studies in which the interventions toward improvement of pharmacotherapy were led by other health care professionals (e.g., nurses)

Quality assessment. Methodological quality was determined; in particular, data on random sequence generation, blinding, or indications of incomplete outcome information according to the Jadad criteria (0-5 pts) was determined (6).

The outcomes involved: (i) adherence to pharmacotherapy, in particular, the percentage of patients that have achieved 75-80% of adherence according to medication-possession ratio (MPR) or patients that achieved the highest score in the Morisky-Green-Levine test; (ii) plasma lipid level, i.e. high-density lipoprotein (HDL-C), low-density lipoprotein (LDL-C), total cholesterol (TC) or triglycerides (TG). In addition, (iii) details concerning intervention performed by a pharmacist and its duration were recorded; as well as the medical history of the patient.

Statistical methods. The meta-analysis was conducted using STATISTICA 13.1 software and Module for Meta-analysis (StatSoft, Poland). The difference of dichotomous data between these groups was estimated based on the odds ratio (OR), with 95% two-tailed confidence intervals (CI), which compared event rates for the intervention and control groups (equation 1). The difference between an ‘Intervention’ group and a control group (usual care), regarding particular plasma lipid parameters or body mass index, was expressed as a difference in

means (D) with 95% two-tailed confidence intervals (CI) (equation 2). Due to variability in the quantification of particular parameters in the included studies, the data expressed in mg/dl or mg% were converted into mmol/L units according to the formula (equation 3). The standard deviation from the mean $\pm$ 95%CI was calculated according to Cochrane (7).

	Intervention	No intervention
Event happens	a	b
Event does not happen	c	d

$$(1) \frac{a/b}{c/d},$$

where a – d number of patients, and

$$(2) D = X_1 - X_2,$$

where X_1 – the difference between the end-study and baseline parameters (mean, $\pm$ standard deviation) for the Intervention group; X_2 – the difference between the end-study and baseline parameters (mean, $\pm$ standard deviation) for the control group (usual care)

$$(3) \text{mg/dl}_{TC,LDL-C,HDL-C} = 38.67 \times \text{mmol/L} \\ \text{and} \\ \text{mg/dl}_{TG} = 88.57 \times \text{mmol/L}$$

A DerSimonian and Laird random-effects model was used to compensate for the heterogeneity of studies.

Subgroup analyses

Heterogeneity was quantitatively assessed using Cochran’s Q, and I^2 statistics. $P < 0.05$ was regarded as statistically significant. To explore the potential sources of heterogeneity, particular subgroup analyses were conducted to determine the impact of particular type of intervention (e.g., activity focused on patient education, or motivation and monitoring, medication review, etc.) and its duration (i.e., 3, 6 or 12 months and more), the baseline diagnosis and target therapy (e.g., patient with dyslipidemia vs. diabetic patient, subjects with CVD that receive a number of drugs including lipid-lowering therapies), or the role of pharmacist (i.e., community vs. clinical pharmacist) The differences between the compared factors were confirmed based on the Q value ($P < 0.05$).

In order to examine the robustness of the results, a sensitivity analysis was conducted using the leave-one-out method, i.e. removing one study each time and recalculating the results.

Potential publication bias was examined using a visual inspection of Begg's funnel plot asymmetry, Begg's rank correlation, and Egger's weighted regression (8). Duval and Tweedie 'trim and fill' was used to adjust the analysis for the effects of publication bias (9).

RESULTS

Characteristics of included trials

In total, 7,500 articles were screened. Following the screening, 656 duplicates were excluded, followed by another 6,724 for the following reasons: they did not meet inclusion criteria, or they were not prospective controlled studies; they were not constructed to assess the role of the pharmacist in therapy; neither the plasma lipid levels or adherence parameters were reported. The studies in which the intervention group was categorized as non-adherent, if less than 90% of medication was available and it was not possible to re-calculate data, were also excluded. Following exclusion, 39 articles were included in the analysis (Fig. 1). The median Jadad score was three out of five.

All the analyzed studies (N = 39) were prospective and controlled trials, the majority of which were randomized (N = 38). The meta-analysis comprised 34,137 patients that were included to the particular clinical trials due to dyslipidaemias (n = 20,615), diabetes (n = 8,793), cardiovascular diseases incl. arterial hypertension, coronary heart disease and myocardial infarction or ischaemic stroke (n = 4,249), chronic kidney disease (n = 290) and other diseases

(n = 190). All patients received at least one lipid-lowering drug.

The median study period was six months (interquartile range, 6-12). In the majority of cases, the pharmacist-led intervention comprised patient education about the disease and its risk, current treatment, target goals, proper dosage, or storage of medications, as well as healthy lifestyle, e.g., advice on diet, physical activity, and smoking cessation. Other activities included follow-up monitoring, medication reviews, identification of drug-related problems (DRPs), and recommendations to physicians about the therapy, as well as motivational interviews to overcome patient barriers to adherence. In general, such interventions were led by community pharmacists (n = 13838 patients); however, a lower number was led by clinical pharmacists and these from ambulatory/primary care centers (n = 1,174) (Table 1).

Adherence to therapy

A wide spectrum of interventions was addressed to patients receiving lipid-lowering drugs, and these improved adherence to therapy, expressed as odds ratio. Overall adherence was increased two-fold as compared to subjects that received usual care (Fig. 2); the Intervention groups were twice as likely to achieve 75-80% adherence to therapy or highest score in the Morisky-Green-Levine test than the control group (Fig. 2A). Further subgroup analyses found that patients with cardiovascular diseases and (or) diabetes did not demonstrate any significant difference regarding the improvement of adherence to lipid-lowering therapy compared to those who were

Figure 1. Flow diagram of trial identification and selection.

Table 1. Characteristics of included studies.

Source	Study design	Study sample size#	Participants	Key components of pharmacist intervention	Intervention providers	Comparison	Outcomes
Al Hamarneh YN, 2018 (10)	RCT, 3 months	143/147	Patients with CKD and uncontrolled risk factors including high LDL-C levels	Treatment recommendations; control of individual CV risk; prescription adaptation and/or initiation as necessary; and regular monthly follow-up	Community pharmacist	Usual care	BP; HbA _{1c} ; LDL-C; smoking cessation
Al Mazroui NR, 2009 (11)	RCT, 4-12 months	117/117	Patients with diabetes	Education on the diabetes management, risk factors and pharmacotherapy, adherence (proper dosage, or storage of medications), healthy lifestyle	Community pharmacist	Usual care	BMI; BP; glucose; HbA _{1c} ; HDL-C; LDL-C; TC; TG
Ali M, 2012 (12)	RCT, 12 months	23/23	Patients with diabetes	Education about diabetes treatment and associated CVD factors; monitoring and counselling	Community pharmacist	Usual care	BMI; BP; glucose; HDL-C; LDL-C; TC; TG
Amariles P, 2012 (13)	RCT, 8 months	323/317	Patients with CVD or CVD risk factors (BP, diabetes, high LDL-C levels, heart failure, MI)	Provision of Dader method of Community Usual care; patient education about CVD; medications, identification of drug-related problems, advice on lifestyle changes, suggestions to physicians on treatment	Community pharmacist	Usual care	BP; HbA _{1c} ; LDL-C; TC
Aslani P, 2011 (14)	RCT, 9 months	179/178	Patients taking a lipid-lowering medicine	Serum TC measurements; patient education about proper adherence to pharmacotherapy; identification of drug-related problems (questionnaires: Brief Medication Questionnaire, Medication Adherence Report Scale)	Community pharmacist	Usual care	TC; exercise score
Blackburn DF, 2016 (15)	RCT, 12 months	999/907	Patients on statin therapy	Patient education about proper adherence to pharmacotherapy and side effects of statins	Community pharmacist	Usual care	Adherence
Bogden PE, 1997 (16)	RCT, 6 months	47/47	Patients with TC levels of 6.2 mmol/L or higher	Review of patient medication history and laboratory data; recommendations for physicians on dosage, drug selection and monitoring	Pharmacist from ambulatory care centres	Usual care	TC
Calvert SB, 2012 (17)	RCT, 6 months	55/55	Hospitalized patients with coronary artery disease discharged on aspirin, β -blocker, and statin	After in-hospital counseling, education about proper adherence to pharmacotherapy, and communication of discharge medications to community pharmacists and physicians, ongoing assessment of adherence by community pharmacists	Community pharmacist	Usual care	Adherence
Carter BL, 2018 (18)	RCT, 12 months	126/139	Patients on statin therapy	Counselling patients and preparing a treatment plan that included lifestyle changes and pharmacotherapy. Evaluation of lifestyle changes, patient tolerance and adherence with the pharmacotherapy	Community pharmacist	Usual care	BMI; BP; glucose; HDL-C; LDL-C; TC; TG

Table 1. Characteristics of included studies (cont.).

Source	Study design	Study sample size#	Participants	Key components of pharmacist intervention	Intervention providers	Comparison	Outcomes
Chan CW, 2012 (19)	RCT, 9 months	51/54	Patients with diabetes type 2	Regular drug-counseling sessions	Community pharmacist	Usual care	HbA _{1c} ; LDL-C
Doucette WR, 2009 (20)	RCT, 12 months	35/31	Patients with diabetes type 2	Patient education including specific advice on diet and physical activity; identification of drug related problems; recommendations to physicians	Community pharmacist	Usual care	BP; HbA _{1c} ; LDL-C
Eussen SR, 2010 (21)	RCT, 12 months	460/439	Patients on statin therapy	Patient counselling and education on adverse effects, dosage, and proper adherence to pharmacotherapy	Community pharmacist	Usual care	Adherence; LDL-C, TC
Faulkner MA, 2000 (22)	RCT, 6-12 months	15/15	Patients after cardiac surgery with baseline fasting LDL-C higher than 3.36 mmol/L	Telephone counselling – patients were questioned about when and where prescriptions were filled, potential side effects, overall well-being, and specific reasons for non-adherence	Community pharmacist	Usual care	HDL-C; LDL-C; TC; TG
Fornos JA, 2006 (23)	RCT, 13 months	56/56	Patients with diabetes type 2	Patient education including advice on diet, physical activity, smoking cessation and adherence to pharmacotherapy; identification of drug related problems; recommendations to physicians	Community pharmacist	Usual care	BMI; BP; HbA _{1c} ; HDL-C; LDL-C; TC; TG
Fretheim A, 2006 (24)	RCT, 12 months	7,771/7,815	Patients that started or continued the pharmacotherapy for hypertension or hypercholesterolemia	Within collaborative care, the pharmacist conducted educational outreach visit that included audit and feedback, and computerized reminders linked to the medical record system	Pharmacist*	Usual care	Achievement of treatment goals for cholesterol, BP and diabetes
Gulayin PE, 2019 (25)	RCT, 6 months	55/35	Patients with CVD, high CVD risk, LDL-C level ≥ 4.91 mmol/L or type 2 diabetes.	Patient counseling on medication adherence	Pharmacist from primary care centres	Usual care	LDL-C, adherence
Hedegaard U, 2015 (26)	RCT, 12 months	75/156	Patients with at least one antihypertensive agent prescribed	Within collaborative care – medication review and identification of drug related problems, patient interview, tailored adherence counseling (motivational interviewing and telephone follow-ups)	Clinical pharmacist	Usual care	Adherence to antihypertensive and lipid-lowering agents
Hirsch JD, 2014 (27)	RCT, 6 months	89/74	Patients with uncontrolled hypertension (recent blood pressure $\geq 140/90$ mmHg or blood pressure $\geq 130/80$ mmHg if patients also had diabetes mellitus), treated with at least one antihypertensive medication	Within collaborative care – education about hypertension and current treatment, review of medical and medication history, and current medications. Review of and/or order of laboratory tests, adjustments to hypertension medication regimen, medication adherence, or self-monitoring behavior	Clinical pharmacist	Usual care	BP, LDL-C

Table 1. Characteristics of included studies (cont.).

Source	Study design	Study sample size#	Participants	Key components of pharmacist intervention	Intervention providers	Comparison	Outcomes
Ho PM, 2014 (28)	RCT, 12 months	119/122	Patients admitted with ACS as the primary reason for hospital admission	Medication reconciliation (pre-hospital and post-hospital) and tailoring; patient education, and collaborative care (notification of the patient's primary care clinician and/or cardiologist that the patient was enrolled in the adherence intervention in the computerized medical record)	Clinical pharmacist	Usual care	BP; LDL-C; mortality; adherence
Hohmann C, 2014 (29)	RCT, 3 months	135/155	Ischaemic stroke patients admitted to hospital	Control and intervention group: medication reconciliation of patient admitted to the stroke unit, verification of the medication records during the hospital stay regularly, identification of drug-related problems, participation in ward rounds. Intervention group: additional medication report with detailed information in the discharge letter, approved by the neurologist	Clinical pharmacist	Usual care and clinical pharmacist	Adherence
Kooy MJ, 2016 (30)	RCT, 12 months	1345/268* (total: 3637/1054)	Patients initiating treatment with antidiuretics, bisphosphonates, RAS inhibitors, or statins	Counseling that included assessment of barriers and provision of information and motivation toward therapy	Community pharmacist	Usual care	Adherence
Kraemer DF, 2014 (31)	RCT, 12 months	31/36	Patients with diabetes type 2	Counseling for diabetes self-management	Community pharmacist	Usual care	Glucose; HbA _{1c} ; LDL-C; TC; TG
Krass I, 2007 (32)	RCT, 6 months	140/149	Patients with established type 2 diabetes and HbA _{1c} ≥ 7.5%, who were taking at least one oral glucose lowering medication or insulin; HbA _{1c} ≥ 7.0%, who were taking at least one oral glucose lowering medication or insulin and who were on at least one anti-hypertensive, angina or lipid-lowering drug.	Patient counseling according to SBGM, adherence to medications, lifestyle (physical activity, nutrition, alcohol consumption and smoking) and footcare issues; overview of medication history (drug/dose discrepancies and potential therapeutic problems)	Community pharmacist	Usual care	BMI; BP; HbA _{1c} ; TC; TG
Lee VW, 2009 (33)	RCT, 6 months	60/58	Patients taking one or more lipid-lowering agents	Consultation on the drug regimen and lifestyle modifications (educational leaflets included target LDL goals, importance of drug compliance, possible consequences of poor cholesterol control, side-effects of lipid lowering drugs, precautions of administrations); a telephone follow-up and follow-up interviews on the date of the physician visit	Community pharmacist	Usual care	HDL-C; LDL-C; TC; TG

Table 1. Characteristics of included studies (cont.).

Source	Study design	Study sample size#	Participants	Key components of pharmacist intervention	Intervention providers	Comparison	Outcomes
McAlister FA, 2014 (34)	RCT, 6 months	136/143	Ischaemic stroke patients or subjects with transient ischemic attack; systolic blood pressure > 140 mm Hg or fasting LDL-C > 2.0 mmol/L	Initiation or titration of antihypertensive and/or lipid-lowering therapy as appropriate according to treatment algorithms and current guidelines	Clinical pharmacist	Usual care	BMI; HDL-C; LDL-C; mortality
Oñativia-Astibia A, 2019 (35)	RCT, 6 months	94/89	Non-adherent hypercholesterolemic patients on statin therapy	Identification of the purpose on non-adherence to therapy. Dose/medication adjustment, information about treatment, adaptation the dose regimen to the patient's situation, providing such solutions as use dispensers, drug packaging, pictograms, use reminders (alarms)	Community pharmacist	Usual care	Adherence
Oñativia-Astibia A, 2020 (36)	RCT, 3-6 months	228/237	Patients on statin therapy	Identification of the cause of non-adherence and selection of the most appropriate intervention, monitoring at the subsequent visits adherence, and the effectiveness of pharmacotherapy	Community pharmacist	Usual care	Adherence
Pape GA, 2011 (37)	RCT, 24 months	4,916/2,047	Patients with diabetes	Review of the medical charts of patients with an elevated LDL-C level, proposal of treatment recommendations to include medication therapy and follow-up laboratory monitoring. Telephone contact with patient to confirm the medication history and previous adverse reactions, and to identify the barriers to adherence and patient education	Community pharmacist	Usual care	BP; HbA _{1c} ; LDL-C
Peterson GM, 2004 (38)	RCT, 6 months	42/39	Patients with a cardiovascular related diagnosis and discharged from hospital	Provision of educational and monitoring program, promotion of dietary and lifestyle modification and compliance with lipid-lowering therapy, assessment of drug-related problem during regular home visits	Community pharmacist	Usual care	TC
Phumipamorn S, 2008 (39)	RCT, 8 months	67/67	Ambulatory literate adult diabetic patients with HbA _{1c} >7%	A scheduled regular meetings with patients (refilling the prescriptions, counselling the uses of medication and verification of the pill count. Education (lifestyle, correct diet, antidiabetic medications).	Clinical pharmacist	Usual care	HbA _{1c} ; HDL-C; LDL-C; TC; TG
Planas LG, 2012 (40)	RCT, 9 months	22/30	Patients with diabetes, dyslipidaemia and hypertension who were enrolled in a managed care organization	Education and coaching on self-management skills such as diabetes goals, blood glucose monitoring, diet and lifestyle modifications, foot care, weight loss, sodium restriction, exercise, and dietary decreases in saturated fat, cholesterol and medication adherence. A comprehensive assessment of prescription and nonprescription medications to identify drug therapy problems at each visit.	Community pharmacist	Usual care	BP; HbA _{1c} ; LDL-C

Table 1. Characteristics of included studies (cont.).

Source	Study design	Study sample size#	Participants	Key components of pharmacist intervention	Intervention providers	Comparison	Outcomes
Renner HM, 2007 (41)	RCT, 3 months	221/199	40-75 year patients who had at least 2 prescription fills of a diabetes medication, and were not receiving statin therapy.	Pharmacist-to-prescriber intervention in the form of a phone call script and fax template to provide a prescription for an appropriate statin	Community pharmacist	Usual care	No of statins prescribed/dispensed
Rothman RL, 2005 (42)	RCT, 12 months	109/108	Patients with diabetes type 2	Diabetes education, applied algorithms for managing glucose control and decreasing cardiovascular risk factors; addressed barriers to care	Clinical pharmacist	Usual care	BP; HbA _{1c} ; TC
Straka RJ, 2005 (43)	Prospective, controlled study, 6.5 months	331/150	Patients with CHD and in whom LDL-C levels were out of guideline range	Provision of the physician-approved care plan according to management with lipid-lowering therapy and patient education on CV risk	Clinical pharmacist	Usual care	HDL-C; LDL-C; TC; TG
Suhadi R, 2018 (44)	RCT, 12 months	108/82	Low socioeconomic status Javanese population aged from 40 to 70 yrs	Patient education on topics of hypertension, hyperlipidemia, and diabetes. Promotion of lifestyle changes (physical activity)	Community pharmacist	No education	BP; glucose; HbA _{1c} ; HDL-C; LDL-C; TC; TG
Tahaine L, 2011 (45)	RCT, 6 months	52/73	Patients with dyslipidemia	Phone calls to remind patients about their visits, monitoring of medication efficacy, education on dyslipidemia management, lipid goals, and factors affecting dyslipidemia, compliance and its barriers, as well as nutrition counselling	Clinical pharmacist	Usual care	Achievement of treatment goals for cholesterol
Taveira TH, 2011 (46)	RCT, 6 months	44/44	Depressed patients with diabetes and HbA _{1c} >6.5%	Counseling and coaching sessions with patients including diabetes management and monitoring (visual acuity to use a glucometer, ability to prepare meals), physical activity and diet	Clinical pharmacist	Usual care	BP; HbA _{1c} ; n-HDL-C; LDL-C
Villeneuve J, 2010 (47)	RCT, 12 months	108/117	Inadequate lipids control (LDL-C, HDL-C)	Counseling about patient medications and providing a treatment plan, which included lifestyle changes and optimization of pharmacotherapy. Monitoring of the effectiveness and safety of medications and patients' adherence to therapy, and adjustment of medication dosage.	Community pharmacist	Usual care	BMI; BP; glucose; HbA _{1c} ; n-HDL-C; LDL-C; TC; TG; adherence
Vrijens B, 2006 (48)	RCT, 12 months	198/194	Hyperlipidemic patients taking statin for at least 3 months	Provision of electronically monitored pharmaceutical care package including education about disease treatment and associated CVD factors; monitoring and counselling	Community pharmacist	Usual care	BP; LDL-C; TC; adherence

= usual care/ intervention; * = Patients starting with statin; ACS = acute coronary syndrome; BP = blood pressure; BMI = body mass index; CHD = coronary heart disease; CKD = chronic kidney disease; CVD = cardiovascular disease; HbA_{1c} = glycosylated hemoglobin; HDL-C = high-density-lipoprotein; LDL = low-density-lipoprotein; MI = myocardial infarction; SBGM = self-blood glucose monitoring; TC = total cholesterol; QL = quality of life

treated for dyslipidemia alone (Fig. 2B). Similarly, the duration of interventions (3, 6, or 12 month-period) did not determine the overall adherence (Fig. 2C). Interventions delivered by both community and clinical pharmacists caused a significant improvement in overall adherence (Fig. 2D).

Clinical outcomes

Normalization of plasma lipids

Alterations in at least one plasma lipid parameter were reported for 3396 patients from the intervention and control groups. Patients that received an additional pharmacist-led intervention over the study period demonstrated a significant decline in plasma LDL-C, TC and triglyceride levels, but not in HDL-C, compared to those who received the usual care (Fig. 3A). The type of the disease did not determine the effectiveness of such interventions on the normalization of lipid parameters (Fig. 3B). Interventions delivered by both community and clinical pharmacists caused a significant decrease in TC and LDL-C parameters, with a more pronounced decrease in total cholesterol being observed among patients treated by clinical pharmacists (Fig. 3C).

However, no significant difference in the percentage of subjects that achieved the treatment goals for lipid therapy was observed between the intervention and control groups (OR = 1.53; 0.84-2.78; $P > 0.05$) ($n = 23,407$ patients). Another subgroup analysis found that the Intervention group was four times more likely to receive the appropriate statin at the relevant dose (OR = 4.23; 2.59-6.90; $P < 0.0001$) ($n = 1,341$ patients).

Body mass index

Patients that received pharmacist-led interventions demonstrated a significant decrease in BMI as compared to their counterparts from the control group ($D = -0.76 \text{ kg/m}^2$; -1.07 to -0.45 ; $P < 0.0001$) ($n = 867$). All subjects that belonged to this subgroup remained in contact with community pharmacists for 12 months.

Figure 4 demonstrates the results of publication bias. The result of Egger's test was significant for HDL-C measurements, and there is a suggestion of missing studies, making publication bias plausible. For most of the reported parameters, sensitivity analysis found the observed effect to be robust

Figure 2. Tree-plots demonstrating the effect of pharmacist-led care on the patient adherence to lipid-lowering therapy, expressed as odds ratio - OR (95% CI) in the intervention group vs. control. (A) - overall adherence was twofold greater compared to subjects that received usual care (OR = 2.06; 1.63-2.61; $P = 0.0001$; $I^2 = 79.44\%$; 66.23-87.49) ($n = 7427$ patients); in particular, the Intervention group was 1.96 (1.34-2.87; $P = 0.0006$) times more likely to achieve 75-80% adherence to therapy (MPR) than the control group; and was 2.13 (1.58-2.87; $P < 0.0001$) times more likely to achieve a better score based on the Morisky-Green-Levine test; (B) - patients with cardiovascular diseases and (or) diabetes, did not differ significantly ($P > 0.05$) from these subjects who were treated for dyslipidaemia only, regarding improvement of adherence to lipid-lowering therapy; (C) - the duration of intervention (3, 6 or 12 month-period) did not determine the overall adherence ($P > 0.05$); (D) - interventions delivered by both community and clinical pharmacists resulted in a significant improvement in overall adherence (OR = 2.15; 1.77-2.62; $P = 0.0001$, and OR = 1.94; 1.12-3.35; $P = 0.0182$, respectively).

Figure 3. Tree-plots demonstrate the effect of pharmacist-led care on the alterations in plasma lipid levels, expressed as difference in means – D (95% CI) in the intervention group vs. control. (A) – total cholesterol (TC); D = -0.33 mmol/L (-0.50; -0.15); P = 0.0003 (n = 2,977 patients); low-density lipoprotein cholesterol (LDL-C); D = -0.28 mmol/L (-0.41; -0.16); P < 0.0001 (n = 3,396); high-density lipoprotein cholesterol (HDL-C); D = -0.038 mmol/L (-0.089; 0.012); P > 0.05 (n = 1,247); triglyceride level (TG); D = -0.21 mmol/L (-0.29; -0.13); P < 0.0001 (n = 1,875); (B) – patients with cardiovascular diseases and (or) diabetes did not differ significantly (P > 0.05) from these subjects who were treated for dyslipidaemia alone regarding the effectiveness of such interventions on the normalization of plasma lipid levels; (C) – interventions delivered by both community and clinical pharmacists caused a significant decrease in TC (D = -0.24 mmol/L; -0.45–(-0.04); P = 0.0192; and D = -0.71 mmol/L; -0.88–(-0.54); P < 0.0001, respectively) and in LDL-C parameters (D = -0.34 mmol/L; -0.43–(-0.26); P < 0.0001; and D = -0.22 mmol/L; -0.44–(-0.01); P = 0.0384, respectively). The subgroup of patients under care of clinical pharmacists demonstrated a more pronounced decrease in TC (P = 0.0006).

and the statistical significance was not influenced by any single study included in the meta-analysis. This was found to be true for TC, LDL-C, HDL-C, triglyceride level, and body mass index, as well as the adherence parameter, and all trials were included in the analysis.

DISCUSSION

The current survey demonstrates the results of the quantitative meta-analysis of the effect of various pharmacist-led interventions on the improvement of clinical outcome, and the overall adherence to lipid-lowering agents, including statins, based on a corpus of prospective trials encompassing 34,137 participants.

A key novel finding of the present study is that the interventions delivered by pharmacists as an addition to the usual standard of care were not only associated with a significant reduction in total cholesterol (-0.33 mmol/L; 95% CI -0.50 to -0.15), low-density lipoprotein cholesterol (-0.28 mmol/L 95% CI -0.41 to -0.16) or triglyceride levels

(-0.21 mmol/L; 95% CI -0.29 to -0.13), but also by significant improvement in the overall adherence to therapy expressed as odds ratio (2.30; 95% CI 1.68 to 3.14). The additional study outcome was adherence that was related to the medication possession ratio (MPR), defined as the amount of drug available from refills during the follow-up period relative to the amount prescribed. For the purposes of the present survey, the number of non-adherent (composite MPR < 0.75–0.80) and adherent patients within the follow-up period was used as the binary outcome for the studies included in the analysis. Another measure of patient adherence was the result of the Morisky-Green-Levine scale. This contains questions about forgetting or stopping to take medicines, being careless about taking them, as well as the frequency of running out or missing doses (i.e. *stretching*) in the past 4 weeks (49). In both cases, the adherence to lipid-lowering therapy was found to be significantly better in the intervention group than in the control group. As no significant differences in patient adherence were identified by MPR ratio or Morisky-Green test, further analyses were

Figure 4. Funnel plots showing the distribution of published study outcomes (filled squares) vs. unpublished outcomes (open circles) estimated by Trim and Fill analysis. The dashed line represents the odds ratio – OR (95% CI) (A) or difference in means – D (95% CI) (B) – (E), with potentially-unpublished studies added in; the solid line represents published studies included in the meta-analysis. Vertical dashed line represents the global estimate of alterations in overall adherence to lipid-lowering therapy (A); TC (B); LDL-C (C); TG (D); HDL-C (E). No missing studies were added for (A) – (E). The result of Egger's test for (D) was significant, and there is a suggestion of missing studies, making publication bias plausible.

performed including these two subgroups of patients together.

The present observations are similar to the results obtained by Oñatibia-Astibia et al. (2020). The authors analyzed five studies according to the potential benefits from community pharmacist-led interventions towards the improvement of overall adherence (4).

The overall finding seems to be of clinical importance, as good adherence to cardiovascular medication can be associated with a 20% lower risk of cardiovascular events and a 35% decrease in mortality (50). The most popular pharmacological option for patients with dyslipidemias and cardiovascular diseases is the use of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor medications, otherwise known as statins. Lipid management is an important component of diabetes care and statins are commonly initiated with the diagnosis of diabetes and titrated soon after. However, statins have been associated with poor adherence, with several studies reporting that

most patients discontinue statin therapy during the first year. Poor adherence to statins has been found to be related to increased rates of adverse cardiovascular events, as noted in approximately 50% of patients with CVD and/or its major risk factors (51). It is nevertheless possible that certain aspects of such poor adherence, such as knowledge and attitudes to therapy, tolerability (muscle symptoms), and cost may be modifiable.

In addition, adherence to guideline-recommended statin therapy is often suboptimal, and it has been estimated that almost 80% of high-risk patients do not reach guideline-recommended LDL-C targets. While this could be due to insufficient prescription of high-intensity statins at the appropriate dosage by pharmacists, another reason could be the under-use of statins by patients (52). Only a few studies have examined the potential benefits of pharmacist-led interventions on increasing number of patients who continued statin at proper dose; however, our present findings confirm the significance of such intervention. This finding is also of clinical importance as

50% or more of patients have been found to discontinue statins within one year of treatment initiation; however, no increase in the percentage of patients who had achieved their lipid goals in line with Mann et al. (2010) (53) was identified in the present study. Lack of data prevented further analyses of the type of statin and dosage applied in particular trials, and very few studies reported a switch to another statin if LDL-C levels could not be controlled with the original prescription.

In the present study, only 20,615 patients of the total 34,137 were treated primarily for dyslipidemias; other patients were prescribed lipid-lowering medication due to diabetes, and cardiovascular diseases such as arterial hypertension, coronary heart disease, and myocardial infarction or ischaemic stroke. Therefore subgroup analyses were conducted to compare the effect of the enhanced pharmacist care program in patients with and without additional disorders, besides dyslipidemia; the results indicate no significant differences between the subgroups. Our findings indicate various means of intervention have been proposed in recent decades, including face-to-face meetings, telephone counseling, and e-mail reminders. Patient education has been found to be one of the main categories of interventions that can improve adherence (54). Such intervention was commonly provided by pharmacists in the included studies (87.8%), in which pharmacists frequently discussed diet, exercise, and medication adherence. In some studies (38.8%), pharmacists monitored patients according to the disease parameters or therapy, and in others (8.2%), they addressed motivation and the barriers to proper adherence. Due to the complexity of the care delivered by pharmacists, it was impossible to compare the effects of particular types of interventions based on 'head-to head' analyses.

A minority of interventions focused on changes in medication that followed identification of significant drug-related problems during medication reviews; this was primarily associated with clinical pharmacists (N = 12 per 39 of studies). Like the community group, the clinical pharmacists also performed consulting and coaching sessions with patients according to disease management, monitoring, medication adherence, or lifestyle changes. This might at least partially explain the similar improvements observed in patient adherence between community or clinical pharmacist groups.

On the other hand, a more positive improvement of clinical outcome was observed among the clinical pharmacists, with their subjects achieving more a pronounced decrease in plasma total

cholesterol. In this regard, the community pharmacy is increasingly regarded as very useful for patients to seek help with the management of chronic disease, as it is local and accessible. Although community pharmacists have immediate access to medication refill information, they are typically outside of closed health care systems, and do not usually have access to a patient's medical history; this is an important consideration when dealing with DRPs, which may limit the extent of service. A clinical pharmacist might carry out a targeted medicine use review and offer some recommendations to a general practitioner, but such activity is limited to hospitalized patients. The aim of the present study was not to demonstrate the differences, or weaknesses, of either profession but rather to explore the advantageous role of both in the health care system.

The current survey also examined the effect of study duration. Surprisingly, no significant differences in the enhancement of lipid profile or adherence were observed between subjects who received pharmacist-led intervention for three, six, or twelve months.

In conclusion, the present study shows that interventions by both community and clinical pharmacists can effectively improve medication adherence among patients with CV diseases or at risk of developing them. However, there is still a need for follow-up studies with longer study periods, and a greater focus on the type of medication received by patients to further evaluate the benefits of such pharmacist-provided care.

The present survey has some limitations. First, due to the nature of the intervention, participant blinding was not possible. There was no "placebo" treatment, and after randomization, patients could be informed of their group assignments. The second limitation was that the included studies differed methodologically, and a variety of forms of care were provided for subjects within the Intervention and control groups; similarly, the 'usual care' could be defined differently for the purposes of a particular study. This could account for the relatively high study heterogeneity, the sources of which were identified by subgroup analyses. Thirdly, some studies lacked detailed information about medication and dosage schedules, and these factors should be included in further analyses assessing the effectiveness of pharmacist-led interventions.

Conflict of interest

The authors declare no conflicts of interest.

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