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Review

Impact of intervention of community pharmacists on cardiovascular outcomes in Spain: A systematic review

[Impacto de la intervención de los farmacéuticos comunitarios en los resultados cardiovasculares en España: una revisión sistemática]

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Abstract

Context: Cardiovascular disease (CVD) is one of the leading causes of morbidity and premature mortality across Spain. According to the World Health Organization (WHO), 80% of these premature deaths are preventable by controlling cardiovascular risk factors. Community pharmacists (CPs) are well situated to provide professional educational advice and implement interventions for the reduction of CVD.

Aims: To analyze the impact of community pharmacists' interventions on cardiovascular risk factors and CVD prevention in Spain.

Methods: Two independent reviewers searched PubMed/MEDLINE; SCOPUS; Cochrane Central Register of Controlled Trials (CENTRAL); EMBASE; National Regional Database (LILACS BIREME); CINAHL; Pharm-line; ClinicalTrials.gov; ISRCTN; DOAJ (Directory of Open Access Journals), International Pharmaceutical Abstracts (IPA), the Spanish National Research Council (CSIC), WHO ICTRP, SCIELO and opengrey.eu and Google Scholar and considered research published between January 2000 and August 2020. The Cochrane risk of bias (RoB2) and ROBINS-I tools were used to evaluate the randomised/quasi-randomised controlled trials and the nonrandomised studies of interventions (NRSI), respectively.

Results: The database search resulted in 457 items from which fourteen met our inclusion criteria. A total of 4,250 participants, aged 18 to 85, were included in the pharmacists' interventions offered in the form of medication reconciliation and patient education. Studies showed a beneficial effect of CPs intervention on medication reconciliation and the control of hypertension, dyslipidaemias, obesity, and diabetes. However, evidence on smoking cessation and alcohol advice services is meager.

Conclusions: This study suggests that community pharmacist counselling and personalized intervention could contribute to improving cardiovascular outcomes in Spain.

Keywords: Community pharmacy cardiovascular interventions; systematic review; Cochrane risk of bias; PRISMA-S; Spanish cohort.

Resumen

Contexto: La enfermedad cardiovascular (ECV) es una de las principales causas de morbilidad y mortalidad prematura en España. Según la Organización Mundial de la Salud (OMS), el 80% de estas muertes prematuras se pueden prevenir controlando los factores de riesgo cardiovasculares. Los farmacéuticos comunitarios (FC) están bien situados para proporcionar asesoramiento educativo profesional e implementar intervenciones para la reducción de las ECV.

Objetivos: Analizar el impacto de las intervenciones de los FC sobre los factores de riesgo cardiovascular y la prevención de las ECV en España.

Métodos: Dos revisores independientes realizaron búsquedas en PubMed/MEDLINE; SCOPUS; Registro Cochrane Central de Ensayos Controlados (CENTRAL); EMBASE; Base de Datos Regional Nacional (LILACS BIREME); CINAHL; Pharm-line; ClinicalTrials.gov; ISRCTN; DOAJ (Directory of Open Access Journals), International Pharmaceutical Abstracts (IPA), Consejo Superior de Investigaciones Científicas (CSIC), WHO ICTRP, SCIELO y opengrey.eu y Google Scholar. Los revisores consideraron investigaciones publicadas entre enero de 2000 y agosto de 2020. Se utilizaron las herramientas Cochrane de riesgo de sesgo (RoB2) y ROBINS-I para evaluar los ensayos controlados aleatorios/cuasialeatorios y los no aleatorios de intervenciones (NRSI), respectivamente.

Resultados: La búsqueda en la base de datos dio como resultado 457 artículos, de los cuales catorce cumplieron con nuestros criterios de inclusión. Un total de 4.250 participantes, con edades comprendidas entre 18 y 85 años, fueron incluidos en las intervenciones de los farmacéuticos ofrecidas en forma de conciliación de la medicación y educación del paciente. Los estudios mostraron un efecto beneficioso de la intervención de los farmacéuticos en la conciliación de la medicación y el control de la hipertensión, las dislipidemias, la obesidad y la diabetes. Sin embargo, las evidencias sobre los servicios de asesoramiento para dejar de fumar y el alcohol son escasas.

Conclusiones: Este estudio sugiere que el asesoramiento del farmacéutico comunitario y la intervención personalizada podrían contribuir a mejorar los resultados cardiovasculares en España.

Palabras Clave: Intervenciones cardiovasculares en farmacia comunitaria; revisión sistemática; herramienta Cochrane de riesgo de sesgo; PRISMA-S; cohorte española.

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Abbreviations: BMI: Body mass index; BP: Blood pressure; CP: Community pharmacist; CV: Cardiovascular; CVD: Cardiovascular disease; DM: Diabetes mellitus; DRPs: Drug-related problems; FBG: Fasting blood glucose; HbA1c: Glycated haemoglobin; HDL: High-density lipoproteins; LDL: Low-density lipoproteins; M: Months; NHS: National Health System; NRSI: Nonrandomised studies of intervention; PICO: Patient, Intervention, Comparison group and Outcome; RCT: Randomised controlled trials; SC: Smoking cessation; SR: Systematic review; TC: Total cholesterol; WHO: World Health Organisation.

INTRODUCTION

Cardiovascular disease (CVD) accounts for an estimated 17.3 million deaths per year worldwide, with 14.6% of all deaths in Spain caused by CVD (Soriano et al., 2018; World Health Organization, 2014). Spanish community pharmacists (CPs) non-commissioned services extended the spectrum of patient detection at an early stage of CVD progression and have reduced pressure on the healthcare system over the years. Moreover, several groups, like the Research Group on Pharmaceutical Care at the University of Granada (GIAFUGR), have significantly contributed to promoting the CP's interventions and enhancing research in Spain. Indeed, they developed "The Pharmacotherapy Monitoring Dáder Method", a useful tool that allows pharmacists to follow clear and straightforward guidelines to carry out pharmacotherapy monitoring in a systematic way (Gastelurrutia et al., 2013). Many CPs have also focused their efforts on reducing modifiable CV risk factors (e.g., hypertension, hypercholesterolemia, diabetes, smoking, alcohol consumption or unhealthy diet, among others) (World Health Organization, 2011). According to the WHO, 80% of CVD can be eliminated by reducing patient risk factors (World Health Organization, 2014).

In 2018, a total of 74,043 pharmaceutical professionals were registered in Spain, with a professional profile of 71.6% women and 45.5% under 44 years of age. The latest reports show that in Spain, there is a ratio of 4.7 pharmacies per 10,000 inhabitants. Out of all the practising registered pharmacists, 87.1% (51,959 pharmacists) worked in community pharmacies (Portalfarma, 2016). The strategic locations, extended operating hours, and accessibility place the pharmacies at the heart of the community for the elderly, social minorities, and immigrants (Beaglehole and Bonita, 2008; Hernando et al., 2018). Furthermore, they are a well-suited avenue for implementing public health services in resource-poor locations with disproportionately high rates of CVD (Beaglehole and Bonita, 2008). Therefore, Spanish CPs have an unlocked potential to provide professional clinical care to reduce patient's CV risk. Research has shown the potential benefits of pharmacy services in other countries through many years of interventional practice (Blenkinsopp et al., 2003). A multidisciplinary approach involving pharmacists along with other healthcare professionals may improve cardiovascular outcomes in Spain (Chaudhri et al., 2019; Gastelurrutia et al., 2009). The main goal of this study is to ascertain the health promotional impact of community pharmacy services targeting CVD reduction, including primary prevention of dyslipidaemia, hypertension, metabolic syndrome, and diabetes, as well as smoking cessation (SC), alcohol intake advice, diet recommendations, body weight reduction counselling and medication compliance in the reduction of the CV risk among the Spanish population.

MATERIAL AND METHODS

Literature search

The research strategy is reported by using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA-S) 14 item protocol as a guide (for further information, see Annex 1). Electronic bibliographic databases and grey literature were searched, including PubMed (via https://pubmed.ncbi.nlm.nih.gov/), SCOPUS (via biblioguias.ucm.es), Cochrane Central Register of Controlled Trials (CENTRAL; via https://www.cochranelibrary.com/), MEDLINE & Embase (via OvidSP), National Regional Database (LILACS BIREME, via https://lilacs.bvsalud.org/es/), CINAHL (via EBSCO), Pharm-line (via worldcat.org), ClinicalTrials.gov (via clinicaltrials.gov), ISRCTN (via isrctn.com), DOAJ (Directory of Open Access Journals; via doaj.org), opengrey.eu International Pharmaceutical Abstracts (IPA; via ebsco.com), the Spanish National Research Council (CSIC; via digita.csic.es), the WHO ICTRP (via www.who.int/clinical-trials-registry-platform), SciELO (via https://scielo.org/es) and Google Scholar. A comprehensive systematic search was performed by using keywords (e.g., cardiovascular disease, ischemic heart disease, diabetes, community pharmacist(s)/pharmacy(ies) or pharmaceutical services). The specific keywords, search terms and combination of index terms used with the Boolean search operators can be found in Annex 2. The search was not limited by publication type. In Google Scholar only the first 20 pages were considered. In the search bar, appropriate limits for human studies, Spanish/English language and published from 2000 onwards and no cross-sectional study design were applied. The literature search started on 24th March 2020. An auto-alert on PubMed, OVID, Scopus, and EBSCO was created to notify the researcher about the new data published after the original search date. The new references identified were included in the review till the 30th of August 2020. Also, the authors searched through the citations of previous systematic reviews (SR). Refer-

ence lists of articles were also examined for relevant studies. The articles were imported in the Mendeley data manager and duplicates were removed from the list. The OVID de-duplication tool was used to remove duplicates as part of a simultaneous search in MEDLINE and Embase.

Selection process and criteria

The eligibility criteria used for abstract selection process were Spanish/English studies of intervention of community pharmacists in the primary prevention of CVD presented in form of measurable outcomes in patients within the Spanish community setting. Studies that include at least 1 of the outcomes of synthesis were included. The outcomes considered as a result of the community pharmacy services were the control of hypertension, type 2 diabetes mellitus, clinical targets of dyslipidaemia, increase adherence to CVD medicines, abstinence from smoking and reduction in alcohol consumption. The authors conducted a SR of articles evaluating the effectiveness of intervention of community pharmacists in the primary prevention of CVD within the Spanish population. Two reviewers assessed studies independently before coming together to discuss disagreements and with a third person if needed. The research question was defined by using the PICO (patient, intervention, comparison group and outcome) technique (Institute of Medicine et al., 2011; Higgins et al., 2019). Eligible studies were set as all full-text English and Spanish articles on Spanish population from January 2000 onwards for all services performed by Spanish pharmacists in community pharmacies settings based in Spain compared with the provision of usual pharmaceutical care designed to improve the CVD via vascular risk reduction. To increase comprehensiveness in ascertaining relevant studies, the authors did an extensive search to identify all published research. Also, randomised controlled trials, being the gold standard in the hierarchy of the quality assessment framework, were preferably chosen (Higgins et al., 2019; Institute of Medicine, 2011).

However, only a few RCTs on this theme existed. Therefore, randomised/quasi-randomised controlled trials and observational studies were also considered.

Risk of bias assessment

The bias domains included in the version 2 template of the Cochrane risk-of-bias tool for randomised trials (RoB 2) was used to assess the risk of bias (RoB) demonstrated in Fig. 1A-B. On the other hand, the bias domains in NRSIs were assessed using the ROBINS-I template (Fig. 2A-B) (Sterne et al., 2016). The author used the Robvis tool to create risk-of-bias plots (McGuinness and Higgins, 2020).

Data assessment

The selected articles were used to extract the name of the author, location of the study, time of publication, name of institution, study design, duration, sample size, type of community pharmacy services being assessed, controlled group and the type of treatment, primary and secondary outcome measures, conclusion, source of funding and conflict of interest. Additional information, on the recruitment process, interventions implementation, the economic impact of the services, equity issues for patient and users' experiences were also obtained if available. The data synthesis used was a mixture of quantitative (e.g., grouping of similar articles and tabulating the results) and qualitative (content analysis) method. Studies with similar design (e.g., RCTs) and interventional services were grouped together. Detailed information about the data assessment process can be found in Table 1.

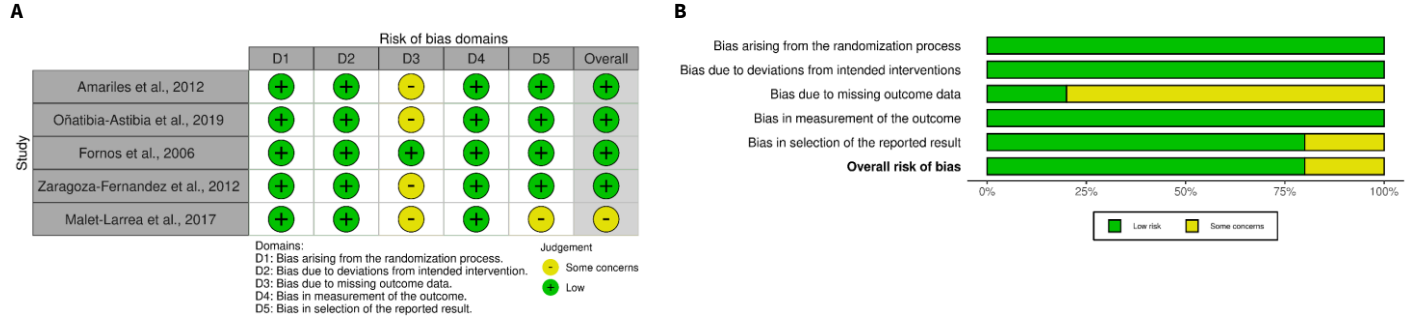
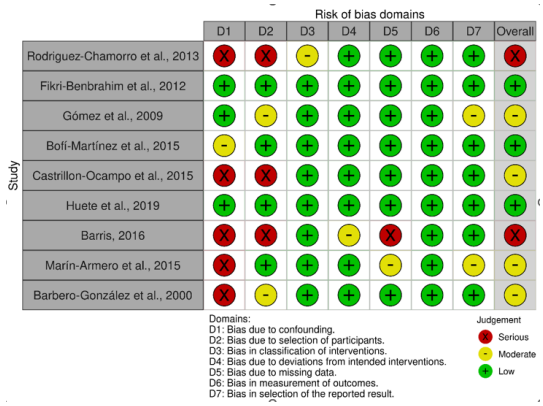


Figure 1. (A) Risk of bias assessment across randomised controlled trials (RCT) studies in the systematic review (McGuinness et al., 2020). **(B)** Visual illustration of the risk of bias among community pharmacists' intervention for cardiovascular risk reduction for RCTs (based on the risk of bias visualisation tool (McGuinness and Higgins, 2020).



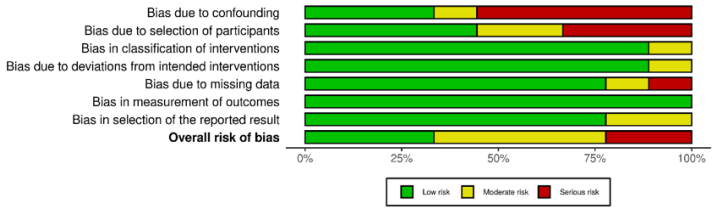


Figure 2. (A) Risk of bias assessment across non-randomize studies interventions (NRSIs) studies in the systematic review (McGuinness et al., 2020). **(B)** Visual illustration of the risk of bias among community pharmacists' intervention for cardiovascular risk reduction for NRSIs (based on the risk of bias visualisation tool (McGuinness and Higgins, 2020).

RESULTS

The PRISMA-S tool has been used to report the number of records identified by searching the available electronic databases; articles included and excluded. The reasons for exclusions are shown in Fig. 3 (Moher et al., 2009). The search of the electronic databases resulted in 1225 items (1193 after the removal of the 32 duplicates) both in English and Spanish, as shown in Fig. 3. After an initial screening of the title and abstract, those articles not meeting the inclusion criteria were excluded for the following reasons, e.g., not performed in Spain (Al Haqan et al., 2017; Bajorek et al., 2017), interventions targeting a different disease (Alacreu et al., 2019), pharmacists not included in the interventions (Estruch et al., 2006), investigating pharmaceutical services in the hospital setting (López Cabezas et al., 2006), pharmaceutical interventions exploring the stakeholders but not patients' benefit (Sabater-Hernández et al., 2018) and ongoing studies with no published results yet (Gómez-Martínez et al., 2020). Thereafter, full text assessment of articles resulted in the further exclusion of 268 papers. Reasons for exclusion in this stage were not meeting the eligibility criterion for study design, providing insufficient information for outcome evaluation or trials still ongoing with no published data to be used in the SR. A total of 14 studies were included.

Table 1 provides a summary of the studies included in this SR. The intervention setting was community pharmacies across Spain. A total of 11,262 participants were included in the CPs' intervention, with the patients' age ranging from 18 to 85. In terms of study design, four studies were RCTs (Amariles et al., 2012; Fornos et al., 2006; Oñatibia-Astibia et al., 2019; Zaragoza-Fernandez et al., 2012), one was a cluster randomised trial (Malet-Larrea et al., 2017), one was an effectiveness implementation hybrid study (Castrillon-Ocampo et al., 2015), one was a descriptive prospective study (Barbero-González et al., 2000), two were nonrandomised controlled before-after design (Marín-Armero et al., 2015; Rodriguez-Chamorro et al., 2013), two were nonrandomised uncontrolled before-after (Huete et al., 2019; Narjis et al., 2012), one was a randomised experimental study (Bofí-Martínez et al., 2015), one was a controlled observational study (Gómez et al., 2009) and one was an uncontrolled observational (Barris, 2016). Study duration varied from 2 to 24 months. The sample size varied from 25 to 1,403 patients in some studies. Ethical approval was not obtained or not mentioned in 3 studies (Fornos et al., 2006; Marín-Armero et al., 2015; Zaragoza-Fernandez et al., 2012).

Risk of bias

Sources of bias may wrongly illustrate a positive outcome as a result of CPs' interventions effects (Gluud, 2006). Figs. 1 and 2 describe the risk of bias in individual studies. The Cochrane risk of bias tool considers factors such as randomisation, allocation concealment, blinding of treatment, intention to treat analysis or complete follow-up as potential biases that may occur during the study (Higgins et al., 2019). Randomised controlled studies performed randomisation of the participants which increased the internal validity of their studies.

Impact of community pharmacists' intervention on the management of cardiovascular risk factors

Table 3 shows various interventions performed by Spanish CPs. Considering the five studies that investigated the impact of CPs' intervention on BP prevention and control, four investigated a drop in systolic (SBP) and diastolic blood pressure (DBP) (Amariles et al., 2012; Narjis et al., 2012; Rodriguez-Chamorro et al., 2013; Zaragoza-Fernandez et al., 2012) and one looked at nocturnal BP using an ambulatory blood pressure monitoring (ABPM) (Barris et al., 2016). They employed mixed methodologies of interventions, from medication reconciliation to patient education. Three employed the Dáder method to ensure uniformity among service providers (Amariles et al., 2012; Barris, 2016; Rodriguez-Chamorro et al., 2013).

Table 1. General information about the selected studies.

Study	Journal (Impact Factor)	Study design	Study follow up in months (M)	Ethical approval	Final sample size
Amariles et al., 2012 In English	Journal of Managed Care Pharmacy (IF* = 2.713)	RCT*. ITT* = Yes	Eight months	Yes	714 patients (IG* =356; CG * =358)
Oñatibia-Astibia et al., 2019 In English	Health Services Research (IF* = 2.706)	RCT* ITT* = Yes	Six months	Yes	746 patients (IG*)
Rodriguez-Chamorro et al., 2013 In English	Latin American Journal of Pharmacy (IF* = 0.155)	Quasi-experimental UBAS* carried out in 18 CP* in Spain. Multicentral ITT* = No	Six months (24 weeks)	Yes	117 patients (IG*)
Fornos et al., 2006 In English	Pharmacy World Science (IF* = 1.265)	RCT*; patients with diabetes type 2 ITT* = No	13 months	No	112 patients (IG* =58; CG* =56)
Fikri-Benbrahim et al., 2012 In English	American Journal of Health-System Pharmacy (IF = 1.882 (2014))	Non-randomised CBAS*; patients with hypertension ITT*= Yes	Five months	Yes	176 patients (IG* = 87; CG* = 89)
Gómez et al., 2009 In English	The Annals of Pharmacotherapy (IF* = 2.059)	Uncontrolled prospective longitudinal (observational) study. ITT* = NR*	Six months	Yes	422 patients (IG*)
Zaragoza-Fernandez et al., 2012 In English	Latin American Journal of Pharmacy (IF* = 0.37)	RCT* ITT* = No	2 months	NR*	150 patients (IG*)
Bofí-Martínez et al., 2015 (FISFTES-PM Study) In Spanish	Atención Primaria (IF* = 0.34)	RCT* ITT* = No	6 months	Yes	100 patients (IG*)
Malet-Larrea et al., 2017 In English	European Journal of Health Economics (IF* = 2.601)	RCT* ITT* = Not applicable	6 months	Yes,	1403 patients (IG* = 688; CG* = 715)
Castrillon-Ocampo et al., 2015 In English	International Journal of Clinical Pharmacy (IF* = 2.054)	Effectiveness-implementation hybrid design ITT* = NR*	18 months	Yes	132 patients (IG*)

Table 1. General information about the selected studies (continued...)

Study	Journal (Impact Factor)	Study design	Study follow up in months (M)	Ethical approval	Final sample size
Huete et al., 2019 In English	International Journal of Clinical Pharmacy (IF* = 2.054)	CBAS ITT* = No	24 months follow up	Yes,	40 patients (IG*)
Barris, 2016 In English	Pharmaceutical Care España (IF* = 0.04)	Observational study, uncontrolled, nonrandomised pharmacy in Benalmádena (Málaga) ITT* = NR*	24 months	NR*	38 patients (IG*)
Marín-Armero et al., 2015 In English	Patient Preference and Adherence (IF* = 1.49)	Open, analytical, UBAS, quasi-experimental clinical study ITT* = NR*	4 months	NR*	23 patients (IG*)
Barbero-González et al., 2000 In Spanish	Atención Primaria (IF* = 1.087)	A descriptive prospective study ITT* = Not applicable	1-year follow up	NR*	77 patients (IG*)
Characteristics of ongoing studies' according to Cochrane guide (12)					
Gómez-Martínez et al., 2020 In Spanish	Farmacia Comunitaria	Observational pre-post interventional	Ongoing	Yes,	>1000 patients (recruitment ongoing)

*BAS: Before and after study, BMI: Body mass index; CG: Control group; CBAS: Controlled before and after study; CP: Community pharmacy/ies; CPS: Community pharmacy services; DRP: Drug-related problems; GP: General practitioner; IG: Intervention group; ITT: Intention to treat; PC: Pharmaceutical care; PFU: Pharmacotherapy follow-up; RCT: Randomized controlled trial; SC: Standard counselling; SD: Standard deviation; UBAS: Uncontrolled before and after study; NR: Not reported.

Table 2. General characteristics of the patients, intervention, inclusion, exclusion criteria and final results obtained.

Study title	Population age (years)	Inclusion and exclusion criteria	Intervention	Primary and secondary outcome	Main finding
Effectiveness of Dader Method for Pharmaceutical Care on Control of BP and TC in Outpatients with CVD or Cardiovascular Risk: EMDADER-CV Randomized Controlled Trial by **Amariles et al. (2012)**	25-74	Patients attending CP* with 1 CVD* (hypertension, hypercholesterolemia, cardiovascular prophylaxis, and type 2 diabetes) or CV* risk factors.	Intervention group (IG*) received Dáder pharmaceutical care protocol *versus* control group that received usual routine dispensing counselling.	Primary outcome: Patients achieving therapeutic goals on BP*, TC* and BP/TC based on presence of comorbidities such as diabetes. Secondary outcome: reduction in Mean BP* and TC* values.	Statistically significant differences in favour of pharmaceutical care in numbers of patients who achieved goals for BP (52.5% *vs*. 43% p=0.017), TC (56.5% *vs*. 44.1%, p=0.001) and BP/TC (37.1% *vs*. 21.8%, p<0.001) therapeutically.
Tailored interventions by CP* and general practitioners improve adherence to statins in a Spanish randomised controlled trial by **Oñatibia-Astibia et al. (2019)**	>18	Patients with a prescription of at least one statin within the last three previous months. Patients who had participated in other adherence-promotion or cardiac-rehabilitation programs, those who were not able to communicate with the health professionals, those who could not self-administer statins, those who were dependent or living in long-term care facilities, or those who had suffered a stroke in the previous six months were excluded from this study.	Patients were split into ADH* or NADH* groups to statin. Nonadherent patients were randomly assigned to the intervention (INT) or non-intervention (NOINT) group. Patients enrolled in the IG* received a specific intervention depending on the cause of nonadherence to statins. Patients in the ADH* and NOINT groups received usual care.	Primary outcome: Adherence to statin therapy assessed by Morisky-Green Levine test as well as by cholesterol test done by Reflotron Plus (Roche). Secondary outcome: Adherence to diet and exercise to reduce cholesterol.	The CP* intervention group demonstrated a higher adherence (OR = 2.34; 95% CI: 1.81-3.03; p<0.001). Adherent patients showed lower values of TC compared with nonadherent patients at baseline (ADH*: 200.3 mg/dL *vs.* NADH*: 216.7 mg/dL; p<0.001) and at the endpoint (ADH: 197.3 mg/dL *vs.* NOADH: 212.2 mg/dL; p<0.001).
A pharmacotherapy follow-up program in patients with type-2 diabetes in community pharmacies in Spain by **Fornos et al. (2006)**	NR*, mean age was 62.4 +-10.5 (32 women and 24 men) and in the control group, 64.9 +-10.9 (32 women and 24 men).	Inclusion: Patients under treatment with oral antidiabetics for ≤2 M, volunteered to take part Exclusion: Patients involved in another PFU*. Cognitively impaired patients.	-IG* = Dáder methodology. Assessment of **Metabolic control** HbA1c every three months, Fasting Blood Glucose M. Lipid parameters (TC, HDLc, LDLc, Triglycerides) every 6 M (**beginning**, six months and end; albumin/creatinine ratio measured beginning – final; **BP =** 1M. **WT* and BMI** 1M **Knowledge of disease and medication. DRPs*, necessity effectiveness and safety** -CG = Non.	Primary outcome: improvement in metabolic control (HbA1c), the resolution of DRPs by pharmacist's intervention and the increase in patient awareness of diabetes. Secondary outcome: FBG*, lipids, BP*, BMI, Albumin-to-creatinine ratio, cholesterol, triglycerides, drug-related problems.	Significant difference from baseline between IG* - CG* in DRPs (1.7 ± 1.2 *versus* 3.1 ± 1.2 p<0.0001), knowledge (17.9 ± 3.7 *versus* 11.4 ± 6.7 points p<0.0001), HbA(1c) (7.9 ± 1.7 *versus* 8.5 ± 1.9% p<0.0001), FBG (154 ± 61.3 *versus* 168 ± 57.8 mg/dL p=0.0004), TC (202 ± 41.5 *versus* 217 ± 43.5 mg/dL p=0.0054) and SBP (135 ± 16.4 *versus* 150 ± 19.9 mmHg p=0.0006).

Table 2. General characteristics of the patients, intervention, inclusion, exclusion criteria and final results obtained (continued...)

Study title	Population age (years)	Inclusion and exclusion criteria	Intervention	Primary and secondary outcome	Main finding
Intensive Two-Month Intervention on Diet and Lifestyle in Uncontrolled Hypertensive Patients in a Community Pharmacy by **Zaragoza-Fernandez et al. (2012)**	>18	Inclusion patients ≥18 who taking medication for hypertension, were treatment-compliant and had a BP ≥ 140/90 mm Hg, or ≥ 130/80 mmHg in the case of patients with other risk factors such as smokers, diabetes, or hypercholesterolemia, had a cardiovascular accident or stroke. Exclusion criteria were children under the age of 18, pregnant women, lack of consent, and non- compliant patients in the intervention group who remained non-compliant after the pharmacist's intervention.	-IG* = Participants had their BP taken and given a sheet with a list of changes to be made in their diet and lifestyle. Participants were called on the same day for three consecutive weeks and week 4 for a personal interview. In the interview, they were asked about the changes they had made, problems they had, BP measurement, Participants were telephoned for the next three weeks and had an interview, and BP measured in week 8.	Primary outcomes BP*, BMI, lifestyle behaviours (modification of diet, salt restriction, alcohol intake reduction, regular physical exercise), weight reduction. Secondary outcome NR*.	The intervention group's systolic and DBP levels fell by 16.08- and 9.95-mm Hg, and the control group by 1.79- and 0.95-mm Hg, (p<0.001). By implementing an intensive, short-term intervention on diet and lifestyle, CP* can achieve a significant BP reduction in hypertensive patients who are not controlled with antihypertensive agents.
Cost analysis and cost-benefit analysis of a medication review with follow-up service in aged polypharmacy patients by **Malet-Larrea et al. (2017)**	>65 years	Inclusion patients aged >65 years and taking ≥ five medications for at least 6M.	IG * = Medication review with follow-up (MRF). Pharmacists collect information about health problems, clinical and biological parameters, medication use, lifestyle habits, and patient concerns about diseases and medications. Pharmacists identify drug-related problems (DRP) and unfavourable clinical outcomes related to medicines (NCOM) and solve them. CG* = Received usual care. Direct medical costs were expressed in euros at 2014 prices for 6M.	Primary outcome cost reduction for the healthcare system, pharmacies and patients. In patient's quality-adjusted life years (QALY) was measured to demonstrate the impact of the services. Secondary outcome NR.	The cost analysis showed that the MRF saved 97 € per patient in 6 months and 273 € per patient per year. The cost-benefit ratio revealed that for every 1 € invested in MRF, a benefit of 3.3 € to 6.2 € would be obtained. The QALYs obtained were 0.3721 (0.12) in the IG and 0.3488 (0.15) in the CG* (p=0.002).

Table 2. General characteristics of the patients, intervention, inclusion, exclusion criteria and final results obtained (continued...)

Study title	Population age (years)	Inclusion and exclusion criteria	Intervention	Primary and secondary outcome	Main finding
Non-randomized studies interventions (NRSIs) and observational studies					
Effectiveness of Pharmacotherapy Follow-Up for the Control of Hypertensive Patients in Community Pharmacies: EMDADER-HTA Study by **Rodriguez-Chamorro et al. (2013)**	35- 74	Included Patients with HTN* that attended the CP during the study period with a prescription for at least one drug for HTN*. Excluded People with prescriptions for others, pregnant patients, BP >180/110 mm Hg, history of MI <3 months before, attending a cardiac rehabilitation program, or terminal illness.	-IG* = pharmacotherapy follow-up (PFU) with BP and TC measured at the start, at 4-6, 12, and 24W. -CG* = non. PFU* = Patients educating on the disease and drugs, treatment adherence and lifestyle changes, and conducting interventions related to the need for, effectiveness and safety of drugs, with Dr. collaboration.	Primary outcome: Reaching adequate therapeutic targets for HTN*, Wilson-Grundy (W-G) CVR*, quantitative CVR *SCORE, SBP, DBP and TC Secondary outcome: NR.	After 6 M of PFU*, achieved therapeutic targets for HTN * (23.9%, p<0.001) and TC* (15.4%, p=0.004). The initial quantitative Wilson-Grundy (W-G) CVR*, quantitative CVR* SCORE, SBP*, DBP* and TC were 6.7%, 2.7%, 137.6 mm Hg, 80.8 mm Hg and 209.7 mg/dL, respectively (Table 3). statistically significant (p<0.05) data. Decreases in the average WG * CVR* (-1.5%, CI 95%: -2.43 to -0.69), CVR SCORE (-0.5%, CI 95%: -0.85 to -0.18), SBP (-7.6 mm Hg, CI 95%: -10.31 to -4.88), DBP (-3.3 mm Hg, CI 95%: -4.94 to -1.83) and TC (-14.6 mg/dL, CI 95%: -20.98 to -8.24).
Effect of pharmacist intervention in the Spanish community pharmacies on BP control in hypertensive patients **by Fikri-Benbrahim et al. (2012)**	**>18**	Inclusion: Hypertensive patients of both sexes ≤ 18 Exclusion: Patients living with a person taking the same antihypertensive - pregnant, had an average systolic BP (SBP)/diastolic BP (DBP*) of ≥200/110 mm Hg - a psychological disorder- had experienced a CV* event within the previous 6M, had changed their antihypertensive in the last 4W, were on the specific program, or already performed BP monitoring at least two days per month.	-IG* = Education regarding hypertension, lifestyle changes, self-monitoring of BP, and medication adherence support; detection of DRPs; and referral to patients' GP when appropriate –CG* = Non.	The primary outcome was the proportion of patients with controlled BP at the end of the study. Secondary outcome NR*.	Significant baseline-to-endpoint reductions in SBP and DBP in Intervention arm 71.3% compared with 52.9% at baseline. The odds of achieving BP control in the intervention group was 2.46 times higher than in the control group (95% confidence interval, 1.15–5.24; p=0.020).

Table 2. General characteristics of the patients, intervention, inclusion, exclusion criteria and final results obtained (continued...)

Study title	Population age (years)	Inclusion and exclusion criteria	Intervention	Primary and secondary outcome	Main finding
Promoting Appropriate Drug Use Through the Application of the Spanish Drug-Related Problem Classification System in the Primary Care Setting by **Gómez et al. (2009)**	**>18**	Inclusion polypharmacy (regularly took ≥five medications for the last six months before the study) who attended either of 2 primary healthcare centres in southern Spain (province of Badajoz). Excluded patients who refused to participate.	-IG* = Detect DRP* in three main categories, such as necessities, effectiveness, and safety. DPR was then resolved by communication with the GP*.	Primary outcome -Promote appropriate drug use in the ambulatory clinical setting by detection and evaluation of DRPs*. Secondary outcome Pharmacist intervention on ADR* prevention with GPs and patients.	422 patients, 80% > 65 years or older, each patient was taking a mean ± SD* of 8.1 ± 2.4 medications. 304 medications with 245 DRPs; medications. Most (60%) of the identified DRPs related to the effectiveness, 28.6%. To safety were most frequently reported DRP of the 215 interventions carried out to resolve these DRPs, 173 (80.5%) were addressed to GPs, who agreed to change therapy regimens on 90.2% of the occasions. Forty-two (19.5%) interventions were addressed to patients. Furthermore, the interventions accepted by GPs and patients resolved 176 (82%) DRPs.
Comparison of health education and pharmacotherapeutic follow-up interventions in patients with cardiovascular risk factors who go to a community pharmacy (FISFTES-PM Study) by **Bofí-Martínez et al. (2015) (FISFTES-PM Study)**	18- 85 who went to the pharmacy during the study period (March 2010-May 2011).	Inclusion was age 18- 85 with at least one medication for high BP, dyslipidaemia, diabetes and heart disease. Or patients whose consultation was related to the presence of any FRCV (request for a blood test, or advice to stop smoking. Exclusion pregnancy, disability, patients with pacemakers, congenital hypercholesterolemia, history of acute myocardial infarction or cerebral-vascular infarction.	To compare health education (HE) and drug therapy monitoring (DTM) interventions in patients with cardiovascular risk factors (CVRF).	Primary outcome regulation of hypertension, dyslipidaemia, diabetes, smoking, obesity, and an increase in physical activity. Secondary outcome Body mass index, waist measurement, waist-to-hip ratio, waist-to-height ratio, body fat, and treatment compliance.	The differences in the reduction percentages were statistically greater in DTMG* than in HEG* for the following variables: SBP 5.40% (p=0.001); heart rate 2.95%(p=0.015); weight 2.00% (p=0.002); BMI 2.24% (p=0.003); fasting glucose 8.65% (p=0.004); TC 6.45% (p=0.002); waist measurement 1.85% (p=0.010); and waist-to-height ratio 1.66% (p=0.002).

Table 2. General characteristics of the patients, intervention, inclusion, exclusion criteria and final results obtained (continued...)

Study title	Population age (years)	Inclusion and exclusion criteria	Intervention	Primary and secondary outcome	Main finding
Implementation of a medication review with follow-up in a Spanish community pharmacy and its achieved outcomes by **Castrillon-Ocampo et al. (2015)**	NR	All patients attending CP of the province of Gipuzkoa, Spain had been prescribed at least one medicine.	During the 18 months of follow-up, patients attended the pharmacy monthly and received the MRF service using the Dáder method.	The impact of the service on Improvement in Economic, clinical and humanistic measures were assessed.	In 18 M, 408 ADR* - detected, 393 were resolved. The average number of medicines used decreased to 3.3 (SD: 2.2). A significant decrease in hospitalizations (OR = 0.31 (IC 95 % = 0.10–0.99)) and in emergency department visits OR = 0.16 (IC 95 % = 0.05–0.55); p=0.001. Increase all quality of life. The higher increase was observed in the construct health transition (mean increase: 30.7 (SD: 25.4)), body pain mean increase: 22.3 (SD: 25.4), and general health mean increase: 20.7 (SD: 23.7). Medication knowledge increased from 8.9 (SD: 17.5) to 87.9 (SD: 25.0), and dose and frequency from 9.3 (SD: 17.9) to 92.5 (22.1).
Impact of pharmacist's intervention on reducing cardiovascular risk in obese patients by **Huete et al. (2019)**	>18	Inclusion were all subjects who were at least 18 years of age. Obese patients (BMI≥30 kg/m^2; waist circumference greater than 102 cm for men or 88 cm for women. Exclusion criteria were pregnancy, lactation, individuals under anticoagulant treatment, as well as geriatric patients with cognitive alterations.	-IG* = Obese patients (BMI≥30) with (group A, n = 30) and without (group B, n = 14) comorbidities were selected. anthropometric values (weight, height, waist circumference), BP, glycaemic (glucose, HbA1c) and lipid parameters (TC, HDL-c, LDL-c, triglycerides) were measured. The PharmaFit Protocol with 24-month follow-up focused on (i) M adherence to nutritional guidelines and modification of lifestyle habits, and (ii) bi-monthly on anthropometric variables, BP. Feedback was provided to PCT.	Primary outcome Reduction in body weight, waist circumference, BMI, total fat mass, glycaemic parameter, lipid parameters, BP, change in REGICOR risk estimate, Secondary outcome NR.	Bodyweight and BMI attributed to mass fat lost was observed (women A: 35.7 ± 0.8 *vs*. 31.1 ± 1.2, p<0.001; men A: 27.2 ± 0.5 *vs*. 23.5 ± 0.6, p<0.001; women B: 29.9±2.2 *vs*. 26.3 ± 1.4, p<0.001; men B 27.7 ± 0.3 *vs*. 24.4 ± 1.3, p<0.001). Plasma glucose levels were significantly reduced in the IG. Lipid parameters improved in IG, whereas HDL-c significantly raised. REGICOR score was significantly reduced in the IG* female (13.8 ± 1.6 *vs*. 5.8 ± 1, p<0.0001) and male (12.7 ± 1.7 *vs*. 4.4 ± 0.6, p<0.005) patients.
Results of the screening and the Ambulatory BP Monitoring (ABPM) services of hypertensive patients in a community pharmacy by **Barris (2016)**	>18	Inclusion >18 years old with and without pharmacological treatment. Exclusion patients with incomplete BP readings.	-IG* = BP was measured on at least three planned visits for 2-3 weeks, two measurements were made in each visit, separated by 1-2 minutes, and BP <140/90 mmHg were considered as the limit.	Ambulatory BP monitoring for 24-48 hours to Identify patients with raised nocturnal BP or BP >140/90 mmHg.	Forty-eight hypertensive patients were identified. 41.7% were sent to the doctor for evaluation. Among these, 60.0% went back to the pharmacy, 91.6% received antihypertensive drug therapy in contrast with the 8.4% to whom lifestyle measures to reduce the BP were given.

Table 2. General characteristics of the patients, intervention, inclusion, exclusion criteria and final results obtained (continued...)

Study title	Population age (years)	Inclusion and exclusion criteria	Intervention	Primary and secondary outcome	Main finding
Pharmaceutical care in smoking cessation by **Marín-Armero et al. (2015)**	>18	Inclusion >18 years old who were smokers and sought CP help to quit smoking and consented to participate in the study. Exclusion patients who did not want to participate in the study.	-IG* = Smoking cessation CP intervention in the form of a health campaign.	The primary outcome was described as an assessment of the efficacy of a smoking cessation campaign carried out at a CP; Secondary outcome effects of pharmaceutical care on patients who decide to try to stop smoking.	43.48% of the total number of patients achieved complete smoking cessation.
Smoking cessation program from community pharmacy by **Barbero-González et al. (2000)**	Mean age of the participants was 41.6 ± 10.8.	Inclusion Smokers who were seekers of CP advice on quitting. Exclusion All patients who did not keep their scheduled appointments and could not be reached by telephone on three occasions on different days were excluded from the study.	-IG* = Smoking cessation.	The primary outcome was abstinence from smoking. Patients who stated that they had not smoked a cigarette and obtained a measurement of exhaled CO ≤ 8 ppm. Secondary outcome NR.	The quitting rates of the smoking-cessation program were: 1st month 80.5%; 3rd month 54.5%; 6th month 45.5% and 1st year 42.8%. The patients who use the nicotine treatment for at least two months have more probability of quitting smoking successfully ($p<0,05$).

* ADH: Adherent; BMI: Body mass index; BP: Blood pressure; CG: Control group; CP: Community pharmacy/ies; CPS: Community pharmacy services; CVD: Cardiovascular disease; CVR: Cardiovascular risk; DBP: Diastolic blood pressure; DRP: Drug-related problems; DTM: Drug therapy monitoring; GP: General practitioner; HbA(1c): Glycated haemoglobin; HDL: High-density lipoprotein; HE: health education; HTN: Hypertension; IG: Intervention group; ITT: Intention to treat; PC: Pharmaceutical care; LDL: Low-density lipoprotein; NADH: Nonadherent; NR: Not reported; P: Probability; PFU: Pharmacotherapy follow-up; Pre-MetS: Premorbid metabolic syndrome; QALY: Quality-adjusted life years ; RCT: Randomized controlled trial; SBP: Systolic blood pressure; SC: Standard counselling; SD: Standard deviation; TC: Total cholesterol

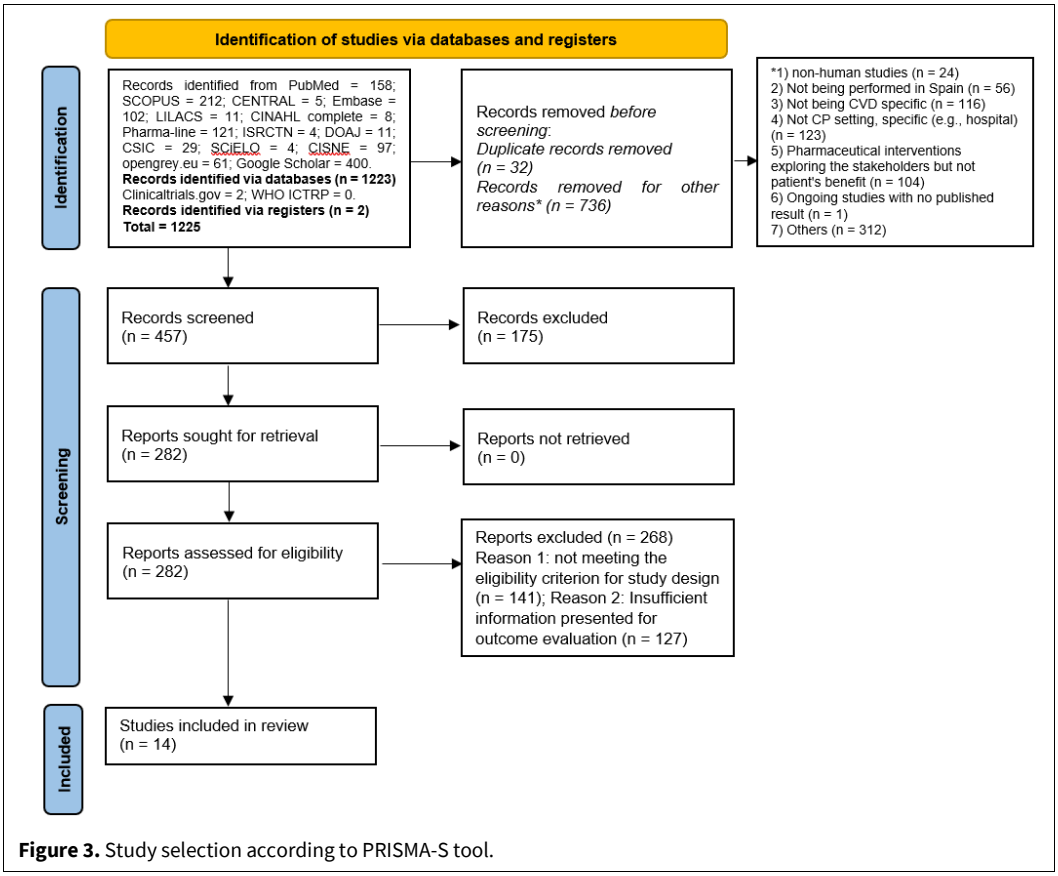


Figure 3. Study selection according to PRISMA-S tool.

One study reported 8 hours of training for pharmacists on the protocol (Amariles et al., 2012); one mentioned oral instruction given to community pharmacists for BP monitoring only (Narjis et al., 2012). In terms of results, two studies reported favourable outcomes in lowering both SBP and DBP (Amariles et al., 2012; Narjis et al., 2012). In this regard, one study using the Dáder method evidenced that 52% of the patients included in the intervention arm *versus* 43 % of controlled group (usual care), achieved BP therapeutic goals ($p<0.05$) (Amariles et al., 2012), whereas in another study using patient education and pharmacotherapeutic follow-up, only 24% of the subjects achieved the therapeutic goal at the end of a six-month study period (Rodriguez-Chamorro et al., 2013). In addition, while this study exhibited a reduction of SBP and DBP of 7 and 3 mmHg (CI 95%), respectively, other studies indicated an average reduction of 16 mmHg in SBP after CPs' intervention (Zaragoza-Fernandez et al., 2012).

All studies investigating lipid control (Table 2) reported favourable results (Amariles et al., 2012; Bofí-Martínez et al., 2015; Fornos et al., 2006; Huete et al., 2019; Oñatibia-Astibia et al., 2019). The use of calibrated devices to monitor biochemical values were reported in all studies for blood parameters. Two studies used the Dáder methodology. While the first one stated that 56% of patients who received CPs' intervention achieved their therapeutic goal (Amariles et al., 2012), the other one reported a significant reduction in TC of around 15 mg/dL ($p<0.05$) (Fornos et al., 2006). Similarly, in another investigation where health education and drug therapy monitoring were used as an intervention, a significant reduction in TC levels of 6.45% ($p<0.05$) (Bofí-Martínez et al., 2015) was described. In addition, an association between adherence to statins (95% CI: 1.81-3.03; $p<0.001$) and lower values of TC in the CP intervention arm has also been reported (Oñatibia-Astibia et al., 2019). Furthermore, one article investigated the effect of CPs' intervention on all CV risk factors (BP, total cholesterol (TC), diabetes mellitus (DM), smoking cessation, obesity, and physical activity). They used the patient education and drug monitoring intervention method and observed statistically significant improvement in all biochemical values (Bofí-Martínez et al., 2015).

Among the studies that investigated the impact of CPs' intervention on diabetes (Table 2), both had a long follow-up time of 13 months (M) (Fornos et al., 2006) and 24 M (Huete et al., 2019). One employed the Dáder method (Fornos et al., 2006), and another used the Pharmafit protocol (Huete et al., 2019). The Pharmafit protocol monitors patients monthly; the researcher observed the patient's body weight, body mass index (BMI), fat mass, TC, low-density lipoproteins (LDL), high-density lipoprotein (HDL), triglycerides, as well as glucose and glycated haemoglobin (HbA1c) (Huete et al., 2019). This protocol also meas-

ured Registre GIroní del COR (REGICOR) CV risk estimate (Bardají, 2013). This study reported clinically meaningful effects on patient outcomes (e.g., a fat mass reduction of around 5% in women and 4% in men ($p<0.001$) in all intervention groups and a glucose reduction of around 32 and 46 mg/dL in women and men, respectively after a 24-month follow-up). Another group measured five main variables monthly, namely metabolic control (HbA1c, fasting blood glucose (FBG), TC, HDL, LDL, albumin/creatinine), BP, weight and BMI, patients' knowledge and drug-related problems (DRPs) (Fornos et al., 2006). This article stated a significant reduction in HbA(1c) of 0.34 in women and 0.75 in men ($p<0.001$), together with an average reduction in FBG of 14 mg/dL ($p<001$) after the CP' intervention. Both studies collaborated closely with physicians to improve the patient's glycaemic control. One study reported the provision of foot care as well (Fornos et al., 2006). The complexity of diabetes calls for a multidisciplinary approach for preventing macrovascular and microvascular disease.

CP services on weight reduction (Table 2) focused on providing education, personalised nutritional advice and promoting regular physical exercise (Huete et al., 2019; Zaragoza-Fernandez et al., 2012). However, some of these studies relied on patients' reports for data collection. Those studies revealed that the adjustment in body weight together with the promotion of healthy diet and adherence to the pharmacists' lifestyle advice significantly reduced BP, TC and glycemia (Huete et al., 2019; Zaragoza-Fernandez et al., 2012).

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Impact of community pharmacists' intervention on smoking cessation and alcohol intake

SC services reported in two studies (Barbero-González et al., 2000; Marín-Armero et al., 2015) as a primary intervention showed improving CV health. Both studies used the Fagerström nicotine dependency test (Barbero-González et al., 2000; Marín-Armero et al., 2015). They also used motivational interviewing. One study used a CO oximeter to encourage patients to quit smoking (Marín-Armero et al., 2015). One research group provided smoking cessation advice as a secondary outcome to improve BP (Zaragoza-Fernandez et al., 2012) as part of health education and pharmacotherapeutic follow-up (Bofí-Martínez et al., 2015). Others reported that patients using nicotine therapy in the first two months of the intervention had a higher probability of quitting (Barbero-González et al., 2000). Only one article was identified as investigating the impact of patient education on alcohol consumption and its relation to BP (Zaragoza-Fernandez et al., 2012). The interventions were reported to be delivered directly by pharmacist-patient interactions. One stated intervention via phone (Zaragoza-Fernandez et al., 2012).

Medication reconciliation services and economic aspects of pharmaceutical care

All studies that identified and resolved drug-related problems by CPs mentioned favourable results (Fornos et al., 2006; Gómez et al., 2009; Malet-Larrea et al., 2017; Narjis et al., 2012; Castrillon-Ocampo et al., 2015; Oñatibia-Astibia et al., 2019). One of the studies that investigated the therapeutic compliance of patients used the Morisky-Green test (Oñatibia-Astibia et al., 2019). Only one study commented on the cost-effectiveness of CP's medication reconciliation by CPs by using cost-benefit analysis (Table 2). This was from the Spanish National Health System (NHS), with six months follow-up (Malet-Larrea et al., 2017). The same study reported favourable results of CP intervention on the quality-adjusted life years (QALY) as a direct result of community pharmacies medication reconciliation services (Malet-Larrea et al., 2017). The author reported a three-day training for a medication review with follow-up (MRF) (Malet-Larrea et al., 2017).

Table 3 illustrates the type of outcome measured in each intervention. To summarise BP control and medication reconciliation were the most measured outcomes, followed next by obesity prevention and SC, followed by DM or cholesterol control. One study reported telephone interactions of pharmacists with patients to encourage appointment attendance (Amariles et al., 2012).

Risk of bias of randomised controlled trials

The initial aspect considered in the narrative synthesis of the RCS is the bias rising from the randomization. By assessing the randomization domain for RCTs included in this SR, it was evident that one research group mentioned using a computer-generated randomisation schedule. One study used partial randomisation by the "coin toss" method to select the group assignment of the first recruited patient, and subsequent patients were assigned on an alternating

Table 3. Community Pharmacists' intervention categorized according to type of outcomes measured.

Category	BP control	Diabetes control	Cholesterol control	Obesity prevention	Smoking cessation	Medicine reconciliation	Alcohol advice
Cardiovascular risk factors interventional programs	Amariles et al., 2012; Zaragoza-Fernandez et al., 2012; Rodriguez-Chamorro et al., 2013; Narjis et al., 2012; 5. Barris, 2016)	Fornos et al., 2006; Huete et al., 2019)	Amariles et al., 2012; Oñatibia-Astibia et al., 2019; Fornos et al., 2006; Huete et al., 2019; Barris, 2016)	Barris, 2016; Zaragoza-Fernandez et al., 2012; Huete et al., 2019)	Gómez-Martínez et al., 2020; Barbero González et al., 2000; Marín-Armero et al., 2015)	Oñatibia-Astibia et al., 2019; Fornos et al., 2006; Castrillon-Ocampo et al., 2015; Narjis et al., 2012)	Zaragoza-Fernandez et al., 2012)
Cost						Malet-Larrea et al., 2017	

basis into two groups (Narjis et al., 2012). The author acknowledged this partially randomised selection as a potential source of bias (Narjis et al., 2012). Six studies used randomisation for selection of volunteer pharmacists and participants (Amariles et al., 2012; Bofí-Martínez et al., 2015; Fornos et al., 2006; Malet-Larrea et al., 2017; Oñatibia-Astibia et al., 2019; Zaragoza-Fernandez et al., 2012). Randomisation eliminates selection and confounding bias. Furthermore, the intervention group's baseline characteristics should be like the control group unless any imbalance derived from randomisation. This has been considered and mentioned in various studies.

It is debatable considering the ever-increasing certainty of the positive impact of CP intervention on reducing of CV risks (Sabater-Hernández et al., 2016), whether having a control group is ethical. However, from an epidemiological perspective it seems essential.

The second domain presented in the RoB 2 tool investigates deviations from intended intervention. To conclude this domain, the researchers looked at the additional interventions given in the form of non-protocol measures, failure in the implementation of interventions and non-adherence by the trial participants to the intervention (Amariles et al., 2012; Fornos et al., 2006; Huete et al., 2019; Malet-Larrea et al., 2017; Narjis et al., 2012; Oñatibia-Astibia et al., 2019; Zaragoza-Fernandez et al., 2012). Most of these studies did not specify what they meant by usual care. Blinding of trial participants and trial personnel can minimize the risk of bias in RCTs. CPs' interventions were not blind due to operational technicality. Patients in intervention or control groups were informed of the nature of the treatment. Noteworthy, RoB 2 does not consider unblind trials to be at high risk of bias. Allocation concealment is another domain to consider. Due to the nature of the pharmacists' interventions, allocation concealment was not performed. Awareness of treatment group assignment may influence the pharmacist's behaviour. However, some authors acknowledged and discussed this potential bias (Fornos et al., 2006).

Another domain to be considered in the RoB2 is missing outcome data. The reviewers looked for participants who withdrew from the studies, did not attend a study visit or did not report the outcome. Most studies reported these aspects. Details for this domain are shown in Table 2. Another factor to be considered is the appropriate sample size. This should be estimated before performing the interventional studies to detect clinically relevant differences between the intervention and control group. The formula to calculate the necessary sample size is different between continuous variables (BP, cholesterol, blood glucose levels) or categorical (smoker or non-smoker) ones (Pandis et al., 2011). Although some studies have mentioned the significance level and power of the study used to determine the appropriate sample size (Amariles et al., 2012; Fornos et al., 2006; Oñatibia-Astibia et al., 2019), they did not disclose the formula.

Only one study has mentioned the use of OpenEpi software (Oñatibia-Astibia et al., 2019). Most sample size calculators available have limited validity because they use a single formula (Faber and Fonseca, 2014). Small sample size was observed in some studies (Castrillon-Ocampo et al., 2015; Zaragoza-Fernandez et al., 2012). A short follow up period was also observed in some studies (Zaragoza-Fernandez et al., 2012). Intention to treat was another limitation seen in some reports (Amariles et al., 2012; Narjis et al., 2012; Oñatibia-Astibia et al., 2019). However, no specific issues were detected in the devices used in

the studies for measuring the anthropometric and biochemical values, although some studies relied on a self-report questionnaire for measuring outcomes, such as the use of a patient's report in determining lifestyle factors (Zaragoza-Fernandez et al., 2012). This may lead to poor validity of the measures. On the other hand, the outcome assessment was standardized across all trials. Although due to logistic issues, some multicentral studies used different outcome assessors, one study reported 8 hours of training for pharmacists on the protocol (Amariles et al., 2012), and another author reported a three-day training for a medication review with follow-up (MRF) for pharmacists (Malet-Larrea et al., 2017). The final domain assessed by the authors was the selection of the reported results. Most studies reported statistically significant clinical outcomes with adjusted models and the statistical method they used (Amariles et al., 2012; Oñatibia-Astibia et al., 2019). One study reported non-significant clinical results for triglycerides, albumin: creatinine ratio and HDLc measurements; still, it did not report the summary statistic for these non-significant results (Fornos et al., 2006). Prespecified and date-stamped analysis plan RCT registries were used to detect form a selection of the reporting bias, but nothing was detected. A high level of heterogeneity, variation in study characteristics and, lack of data to calculate standardized effect ruled out the meta-analysis performance.

Narrative synthesis of observational and nonrandomised studies of intervention

The observational and nonrandomised studies were assessed by the ROBINS-I tool. The initial aspect considered in the narrative synthesis of these studies was biased due to confounding. Only one of the studies adjusted their results to consider possible confounders (Huete et al., 2019). Random selection of patients in some studies might have reduced the impact of confounders (Bofí-Martínez et al., 2015). Another domain considered by the ROBINS-I tool is bias due to the selection of participants. Most studies did not clearly report precise details about recruitment. Only two studies mentioned that the recruitment process included displaying an announcement on a poster in a pharmacy setting (Barbero-González et al., 2000; Marín-Armero et al., 2015). One study provided a clear explanation of the participant process (Narjis et al., 2012). Selection bias might have occurred due to certain exclusion criteria imposed by the researchers. For instance, excluding participants with comorbidities from the study may have impacted the generalizability of the benefits of community pharmacy interventions (Gómez-Martínez et al., 2020; Rodriguez-Chamorro et al., 2013). Selection of the participants in some of the studies were related to intervention and outcome (Rodriguez-Chamorro et al., 2013). Two studies distinguished start of follow-up from start of intervention: others did not provide details (Huete et al., 2019; Narjis et al., 2012). The next signalling questions in ROBINS-I tool assess classification of intervention bias. One study collected the retrospective information (e.g., information about negative outcome associated with medication or drug related problems, which makes the study open to recall bias (Rodriguez-Chamorro et al., 2013). In relation to deviation from the intended intervention, although all researchers followed the intended interventions as initially laid out in their protocols, we must consider the effect of cointerventions in pharmaceutical care. For instance, if personalised advice was provided for a group of patients receiving medication for BP but standard care was given to others, lower rates of BP observed in patients receiving counselling might be attributable to relations built between the service provider and patients (reduced white coat syndrome) rather than to the CP intervention, which presents a potential for bias. Also, consideration should be given to the fidelity of implementation of the CP intervention. Provision of prior training to the service providers can standardize the service providers skills. Regarding multicentral investigations, only one study mentioned oral instruction or formal training given to CPs for pharmaceutical care provision (Narjis et al., 2012). The final ROBINS-I domains look at the missing data, measurement of outcomes and selection of the reported result. Although some studies did not provide information about the patient loss to follow-up, they all reported their findings clearly, as shown in Fig. 2 (Barris, 2016).

The studies included in this SR that evaluated the impact of CPs' interventions on the improvement of CV health reported statistically significant results in reducing CV risk, improved patients' understanding of the state of their disease and enhanced their medication compliance. Almost all previous SR that investigated the impact of CPs' intervention on CVD reported positive trends toward CV risk reduction and improvement in anthropometric and biochemical values (Ifeanyi et al., 2015; Tam-Tham et al., 2019). A critical finding of this SR was that CV risk factors are highly intangible; for instance, losing weight was shown to directly reduce TC, BP, and glucose levels (Huete et al., 2019). Healthy diet and adherence to pharmacist's lifestyle advice were shown to lower BP, TC, glycemia, weight, and waist circumference (Zaragoza-Fernandez et al., 2012).

Some of the studies were performed over a short period which may impact the generalizability of the final outcomes (Marín-Armero et al., 2015; Zaragoza-Fernandez et al., 2012. In this regard, some studies

argued that the short-term impact of CP interventional is not cost saving for healthcare nor beneficial to patients since most return to their destructive habits. They have recommended establishing a sustainable health system model to reduce CV risk potential and cut costs over the longer term (Tam-Tham et al., 2019). According to a framework suggested by the Robert Wood Johnson Foundation, on the management of population health, only 30% of patient's health outcomes is influenced by healthy behaviours at an individual level, and the rest is determined by a mixture of various socioeconomic factors beyond healthcare professionals' interventions (Chandra et al., 2017). The empirical evidence shown in this SR is decisive in terms of the impact of CP intervention on reducing of CV risk. However, further rigorous studies that fully incorporate the Cochrane standards to avoid RoBs are required.

Limitations

There was a limited body of evidence available with RCT design. Therefore, the authors selected a range of study designs on the effectiveness of the CPs interventions. Also, various studies included in the review presented inconsistent information, which makes it challenging to drawing conclusions. Therefore, some researchers were contacted by the author via email to find the missing information but the response rate over five months was 27% leaving the author reluctant to rely on the existing data in the articles.

CONCLUSION

There is some evidence demonstrating that the services provided by community pharmacies to reduce BP, TC as well as to control diabetes, weight reduction and medication reconciliation, could significantly reduce the rate of CVD across the Spanish cohort. Conclusions about SC and alcohol consumption services provided by CPs cannot be made due to a lack of well-designed studies such as RCT with longer duration and more participants. This article also attempted to identify the strength and weaknesses of interventional studies performed in Spain, inspecting the elements of CPs interventions and the real impact they had on their patients' CV health. Furthermore, community pharmacies are recognised worldwide as an integrated part of the healthcare system and in countries such as the United Kingdom, their services are commissioned. We look forward to the day that CPs' interventions are included in the Spanish healthcare agenda and are commissioned to benefit the Spanish population. Further, CPs can be acknowledged for their dedicated contributions and the positive impact they have on CVD eradication.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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AUTHOR CONTRIBUTION:

Contribution	Manouchehri M	Fernández-Alfonso MS	Gil-Ortega M
Concepts or ideas	x	x	x
Design	x	x	x
Definition of intellectual content	x	x	x
Literature search	x		x
Data acquisition	x		x
Data analysis	x	x	x
Manuscript preparation	x	x	x
Manuscript editing	x	x	x
Manuscript review	x	x	x

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Annex 1. PRISMA-S checklist.

Section/topic	#	Checklist item	Location(s) Reported
INFORMATION SOURCES AND METHODS			
Database name	1	Name each individual database searched, stating the platform for each.	Line 96-104
Multi-database searching	2	If databases were searched simultaneously on a single platform, state the name of the platform, listing all of the databases searched.	Line 117-118
Study registries	3	List any study registries searched.	Figure 3 Line 97, line 103
Online resources and browsing	4	Describe any online or print source purposefully searched or browsed (e.g., tables of contents, print conference proceedings, web sites), and how this was done.	The tables of contents of Spanish Pharmacy Deans Conference on Classification of Community Pharmacy services were reviewed.
Citation searching	5	Indicate whether cited references or citing references were examined, and describe any methods used for locating cited/citing references (e.g., browsing reference lists, using a citation index, setting up email alerts for references citing included studies).	Line 111-112;114-116 of article
Contacts	6	Indicate whether additional studies or data were sought by contacting authors, experts, manufacturers, or others.	Line 451-453 of article
Other methods	7	Describe any additional information sources or search methods used.	Full detail in Figure 3
SEARCH STRATEGIES			
Full search strategies	8	Include the search strategies for each database and information source, copied and pasted exactly as run.	Additional information File 2
Limits and restrictions	9	Specify that no limits were used, or describe any limits or restrictions applied to a search (e.g., date or time period, language, study design) and provide justification for their use.	Date limit used is described on line 110-111, Language limits describe on line 110. study design filter 110-111
Search filters	10	Indicate whether published search filters were used (as originally designed or modified), and if so, cite the filter(s) used.	Line 108 of article. Additional file 2
Prior work	11	Indicate when search strategies from other literature reviews were adapted or reused for a substantive part or all of the search, citing the previous review(s).	
Updates	12	Report the methods used to update the search(es) (e.g., rerunning searches, email alerts).	Line 111-112
Dates of searches	13	For each search strategy, provide the date when the last search occurred.	Line 114 Additional file 2

Annex 1. PRISMA-S checklist (continued...)

Section/topic	#	Checklist item	Location(s) Reported
PEER REVIEW			
Peer review	14	Describe any search peer review process.	
MANAGING RECORDS			
Total Records	15	Document the total number of records identified from each database and other information sources.	Figure 3
Deduplication	16	Describe the processes and any software used to deduplicate records from multiple database searches and other information sources.	Figure 3 Article, line 116-118

Rethlefsen ML, Kirtley S, Waffenschmidt S, Ayala AP, Moher D, Page MJ, Koffel JB, PRISMA-S Group (2021) PRISMA-S: An Extension to the PRISMA Statement for Reporting Literature Searches in Systematic Reviews. Syst Rev 10**:** 39. https://doi.org/10.1186/s13643-020-01542-z

Last updated February 27, 2020.

Annex 2. Structure search strategy:

A comprehensive systematic search was performed by using keywords: cardiovascular disease, ischemic heart disease, diabetes, community pharmacist(s)/pharmacy(ies), pharmaceutical services, health campaigns, Spain, Spanish, diet, (nutrition), body weight reduction, excess weight, (obesity), smoking cessation, tobacco dependence, (passive) smoking, (tobacco), comorbidities, elevated blood pressure, hypertension, cholesterol, hypertension, hypercholesterolemia, dyslipidaemia, metabolic syndrome, elevated TC, LDL, HDL (hyperlipidaemia), alcohol consumption, medication adverse drug reactions (ADRs), and medication reconciliation, physical activity (exercise) level, and polypharmacy. This is not an exhaustive list of patients' behavioural attributes for CVDs, but it refers to the closest scientifically known factors. Boolean search operators (and, or and not) were employed to create a more focused search. The risk factors were used as a keyword in combination with other words: community AND (pharmacy OR pharmacies OR pharmacist OR pharmaceutical) AND (care OR services) AND (cardiovascular OR heart) AND intervention. The following terms were also searched in Spanish. Also, special emphasis was given to keywords (women OR woman), geriatric AND elderly as neglected themes in cardiovascular care. The correlated words were kept in parentheses to specify the order in which they are interpreted by the database.

The search was not limited by publication type. In the search bar, appropriate limits for human studies, Spanish/English language and published from 2000 onwards were applied.

Also, the authors searched through the citations of previous SRs and used cite indexing to trace the impact of an article or author upon later publications. Title and abstract were assessed initially. Thereafter, full text screening of eligible selected articles was performed to ensure they meet the inclusion criteria. Disagreement on selected articles was resolved by discussion among the team until consensus was achieved. The articles were double screened by using abstrackr, an online systemic review tool.

Additional search strategy:

Example of strategies used:

PubMed/Medline (01/01/2000- 25/03/2020) search strategy was: (("community pharmacy services"[MeSH Terms] OR ("community"[All Fields] AND "pharmacy"[All Fields] AND "services"[All Fields]) OR "community pharmacy services"[All Fields]) AND ("Spain"[MeSH Terms] OR "Spain"[All Fields] OR "Spain s"[All Fields])) AND (2000/1/1:2020/3/25[pdat]). ("community pharmacy services"[MeSH Terms] OR ("community"[All Fields] AND "pharmacy"[All Fields] AND "services"[All Fields]) OR "community pharmacy services"[All Fields]) AND ("Spain"[MeSH Terms] OR "Spain"[All Fields] OR "Spain s"[All Fields]) AND ("hypertense"[All Fields] OR "hypertension"[MeSH Terms] OR "hypertension"[All Fields] OR "hypertension s"[All Fields] OR "hypertensions"[All Fields] OR "hypertensive"[All Fields] OR "hypertensive s"[All Fields] OR "hypertensives"[All Fields])

Literature review in PUBMED (01/01/2000- 25/03/2020) search strategy was: (("community pharmacy services"[MeSH Terms] OR ("community"[All Fields] AND "pharmacy"[All Fields] AND "services"[All Fields]) OR "community pharmacy services"[All Fields]) AND ("Spain"[MeSH Terms] OR "Spain"[All Fields] OR "Spain s"[All Fields])) AND (2000/1/1:2020/3/25)The limits were: studies published in the last twenty years and in Spanish and/or English.

("community pharmacy services"[MeSH Terms] OR ("community"[All Fields] AND "pharmacy"[All Fields] AND "services"[All Fields]) OR "community pharmacy services"[All Fields]) AND ("Spain"[MeSH Terms] OR "Spain"[All Fields] OR "Spain s"[All Fields]) AND ("hypertense"[All Fields] OR "hypertension"[MeSH Terms] OR "hypertension"[All Fields] OR "hypertension s"[All Fields] OR "hypertensions"[All Fields] OR "hypertensive"[All Fields] OR "hypertensive s"[All Fields] OR "hypertensives"[All Fields])"

SCOPUS with filter human, country of origin Spain, language English and Spanish, study type

TITLE-ABS-KEY (Community pharmacist AND Spain AND Cardiovascular)

Cochrane Central Register of Controlled Trials (CENTRAL)

TITLE-ABS-KEY, S icon was used to search for word variations, MeSH was used for (MeSH descriptor: Community Pharmacy Services; MeSH term matched Synonyms: Service, Community Pharmaceutic; Services, Community Pharmaceutic; Pharmaceutical Services, Community; Community Pharmaceutical Service; Community Pharmaceutic Services; Pharmacy Service, Community; Pharmaceutic Service, Community; Pharmaceutical Service, Community; Services, Community Pharmaceutical; Services, Community Pharmacy; Community Pharmacy Service; Pharmacy Services, Community; Service, Community Pharmacy; Community Pharmaceutical Services; Service, Community Pharmaceutical; Community Pharmaceutic Service; Pharmaceutic Services, Community; AND MeSH descriptor cardiovascular disease, Synonyms: Diseases, Cardiovascular; Disease, Cardiovascular; Cardiovascular Disease, Heart Disease Risk Factors

Synonyms: Risk Factors for Cardiovascular Disease; AND Spain, Spanish, Balearic Islands; Canary Islands …)

Embase

Database (s): Summaries and Abstracts All Ovid

Search Strategy:

#	Query	Results 1 Jul 2021
1	(((((AllFields:community and AllFields:pharmacy) or AllFields:pharmacist or AllFields:pharmacies or AllFields:pharmaceutic) and AllFields:Spain and AllFields:cardiovascular) or AllFields:heart) and AllFields:animal).mp. [mp=title, abstract, full text, caption text]	0
2	..nlp community AND (pharmacy OR pharmacists OR pharmacies OR pharmacuetic) AND Spain AND cardiovascular OR heart NOT animal {Sin términos relacionados}	5,342
3	limit 2 to yr="2000 - 2021"	5,058
4	(((((AllFields:community and AllFields:pharmacy) or AllFields:pharmacist or AllFields:pharmacies or AllFields:pharmaceutic) and AllFields:Spain and AllFields:cardiovascular) or AllFields:heart) and AllFields:animal).mp. [mp=title, abstract, full text, caption text]	0
5	from 3 keep 1	1

(((((AllFields:community and AllFields:pharmacy) or AllFields:pharmacist or AllFields:pharmacies or AllFields:pharmaceutic) and AllFields:Spain and AllFields:cardiovascular) or AllFields:heart) and AllFields:animal).mp. [mp=title, abstract, full text, caption text] ..nlpx "query=community AND (pharmacy OR pharmacists OR pharmacies OR pharmacuetic) AND Spain AND cardiovascular OR heart NOT animal","desiredResults=10000","minHitsDivisor=7","permitHyponyms=NO","lowestVocabularySearchLevel=none","phrasesBroken=NO","speedWanted=Fastest","comment=Sin términos relacionados","elimEnable=NO","constraintMinTerms=2" limit 2 to yr="2000 - 2021"

(((((AllFields:community and AllFields:pharmacy) or AllFields:pharmacist or AllFields:pharmacies or AllFields:pharmaceutic) and AllFields:Spain and AllFields:cardiovascular) or AllFields:heart) and AllFields:animal).mp. [mp=title, abstract, full text, caption text] from 3 keep 1

National Regional Database (LILACS BIREME) example of search:

TITLE-ABS-KEY (community) AND (pharmacy) AND (cardiovascular) AND (intervention) AND (Spain) AND (year_cluster:[2000 TO 2020]). The search was repeated with various keywords such as described before.

CINAHL, EBSCO full text database supported by the University of UCM was used.

pharmacy AND community AND cardiovascular AND (Spain or Spanish or España)

Interfaz - EBSCOhost Research Databases

Pantalla de búsqueda - Búsqueda avanzada

Base de datos -CINAHL Complete

Pharma-line

Search results for 'kw:"community pharmacy*"AND"Spain"AND"cardiovascular"' > '2000..2020'

Clinicaltrials.gov

Top of Form

2 Studies found for: community pharmacy intervention Spain | Cardiovascular Diseases | Spain | First posted from 01/01/2000 to 08/01/2020

Bottom of Form

ISRCTN e.g., community pharmacy Spain Remove filter within Date applied: from: 01/01/2000 Remove filter Date applied: to: 30/08/2020 Remove filter

DOAJ

https://bit.ly/3AbX7Cx

<script type="text/javascript">

var SEARCH_CONFIGURED_OPTIONS={"query":{"filtered":{"filter":{"bool":{"must":[{"terms":{"index.schema_codes_tree.exact":["LCC:R"]}},{"term":{"_type":"article"}}]}},"query":{"query_string":{"query":"community pharmacy AND Spain AND cardiovascular ","default_operator":"AND"}}}}}

</script>

<script src="https://doaj.org/static/widget/fixed_query.js" type="text/javascript"></script>

International Pharmaceutical Abstracts (IPA)

Search Results for "community AND (pharmacy OR pharmacists OR pharmacies OR pharmaceutic) AND Spain AND cardiovascular OR heart NOT animal"

WHO ICTRP, Trial registration data sets in this database were available on the ICTRP Search Portal only in English. Only Cuba and Peru had a registry, but Spain didn't. Same keywords explained above was used here too but no research was found.

SCiELO

e.g., farmacia Y comunitaria Y intervención Y cardiovascular Y España

community OR pharmacy OR cardiovascular OR Spain

community AND pharmacy AND cardiovascular AND Spain

Opengrey.eu

e.g., "community pharmacists"AND"Cardiovascular"

keyword:(Pharmacologie) keyword:(PHARMACIE) year:(2000)

Google Scholar

e.g., community pharmacies+Spain+cost+services

allintitle: pharmaceutical care in community pharmacies in Spain