ABSTRACT

Introduction Hypertension management remains a major public health challenge in primary care. Innovative interventions to improve blood pressure (BP) control are needed. One approach is through community-based models of care with the involvement of pharmacists and other non-physician healthcare professionals. Our objective is to systematically review the evidence of the impact of pharmacist care alone or in collaboration with other healthcare professionals on BP among hypertensive outpatients compared with usual care. Because these interventions can be complex, with various components, the effect size may differ between the type of interventions. One major focus of our study will be to assess carefully the heterogeneity in the effects of these interventions to identify which ones work best in a given healthcare setting.

Methods and analysis Systematic searches of the Medical Literature Analysis and Retrieval System Online (MEDLINE), Excerpta Medica (Embase) and Central Register of Controlled Trials (CENTRAL) databases will be conducted. Randomised controlled trials assessing the effect of pharmacist interventions on BP among outpatients will be included. Examples for pharmacist interventions are patient education, feedback to physician and medication management. The outcome will be the change in BP or BP at follow-up or BP control. Results will be synthesised descriptively and, if appropriate, will be pooled across studies to perform meta-analyses. If feasible, we will also perform a network meta-analysis to compare interventions that have not been compared directly head-to-head by using indirect evidence. Heterogeneity in the effect will be evaluated through prespecified subgroup and stratified analyses, accounting notably for the type and intensity of interventions, patients’ characteristics and healthcare setting.

Ethics and dissemination Ethical approval is not required as the results will be drawn from currently available published literature. Outcomes of the review will be shared through peer-reviewed journal and used for implementation policy.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This systematic review will provide updated evidence on the effect of pharmacist intervention on blood pressure management.
⇒ Heterogeneity in the effect of these interventions will be carefully evaluated which will help the implementation of effective interventions in various healthcare setting.
⇒ We will assess the comparative effectiveness of each intervention compared with each other by using direct and indirect evidence.
⇒ Due to the expected heterogeneity and complexity of both interventions and usual care, a sharp contrast between interventions might be difficult and the feasibility of the network meta-analysis might be limited.
⇒ The review methods were carefully planned according to current guidelines (Cochrane and Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) and prospectively submitted to the International Prospective Register of Systematic Reviews (PROSPERO) to minimise risk of bias related to study design and conduct and insure adequate reporting of results in the completed review.

INTRODUCTION

Rationale

Elevated blood pressure (BP) is the greatest single contributor to the global burden of disease and to global mortality.1 Although reduction of BP is a cornerstone of the prevention of cardiovascular diseases;2 numerous hypertensive patients do not achieve adequate BP control. Recent data that several healthcare jurisdictions might have reached a plateau in the percentage of treated and well-controlled hypertensive patients.3 Innovative interventions to improve BP control are therefore needed in primary care, where management of hypertension takes place.

One approach is a greater use of community-based models of care with the involvement of pharmacists and other non-physician
healthcare professionals. Pharmacists are highly accessible healthcare professionals and a valuable asset in the management of hypertension. The US Community Preventive Services Task Force has recommended team-based care, including pharmacists, to improve BP control. Further, recent hypertension guidelines, notably the 2017 guidelines from the American College of Cardiology and the American Heart Association as well as the 2018 guidelines of the European Society of Cardiology and the European Society of Hypertension, recommend the involvement of pharmacists for the team-based care management of hypertension.

A recent umbrella review (ie, a review of reviews) found that community pharmacists can improve clinical outcomes in a wide array of chronic diseases, including diabetes, hyperlipidaemia, HIV/AIDS, cardiovascular and respiratory diseases. The authors of this review concluded however that further studies were needed to assess the impact of specific interventions on given outcomes, and that is actually what we aim for in the current review that we will conduct. In 2014, we conducted a systematic review and meta-analysis of 39 randomised controlled trials (RCTs) with 14 224 patients and found that pharmacist interventions—alone or in collaboration with other healthcare professionals—improved BP management. Since then, new studies have been conducted to evaluate different types of interventions, notably using e-health and digital tools. Our review indicated also that pharmacist interventions had differential effects on BP, from very large to modest or no effect. Reasons for this large heterogeneity could not be clearly explained. It might be not surprising that the effect size may differ between the type of interventions, but it is key to try to identify what works best: is the intensity of intervention linked to the effect size? Are characteristics of the patients or specific setting associated with a large effect?

To address these questions, and toward the efficient implementation of this type of interventions in different healthcare setting and jurisdictions, updating evidence and explaining this heterogeneity is needed. In addition, with a view to identify what intervention works best, we will assess the feasibility of performing a network meta-analysis. This method allows estimate the comparative effectiveness of each intervention against each other by using direct and indirect evidence and rank interventions. One key element will be to determine the effect on BP according to the duration and intensity of interventions. Hence, we have shown previously that the effect on BP could be larger if the intervention was done at least monthly. Further, we will also assess whether there is an effect once the intervention is over. Hence, we have recently shown in a trial conducted in Switzerland that an effect on BP was seen 6 months after the end of a 6 months team-based care intervention involving pharmacists. This is one major element to assess the long-term effect of this type of interventions.

**Objectives**

The aim of this manuscript is to describe a protocol to systematically review, synthesise, and update the evidence of the impact of pharmacist care alone or in collaboration with other healthcare professionals on the control of elevated BP among outpatients when compared with those receiving usual care and to each other. The heterogeneity in the effect of these interventions will be closely evaluated notably to identify which interventions work best, for specific patients and in a given healthcare setting.

**METHODS AND ANALYSIS**

We will follow methods for conducting and reporting systematic reviews and meta-analyses according to Cochrane Collaboration and Center for Reviews and Dissemination guidance. We will report this protocol according the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols: elaboration and explanation paper. This updating protocol has been submitted to the International Prospective Register of Systematic Reviews (PROSPERO).

**Eligibility criteria**

**Study design**

The following criteria will be used to consider inclusion and exclusion of studies for this review. RCTs, cluster RCTs and cross-over RCTs will be eligible. Case reports, case series, non-randomised evaluations, reviews, meta-analyses, conference proceedings, policy papers, study protocols and expert opinions will be excluded.

**Setting**

Studies based in a community/ambulatory care setting will be included.

**Participants**

Studies will be considered if they include adult outpatients (18 years or over) with a diagnosis of hypertension, treated or not treated.

**Exposures/interventions**

We will include studies if they evaluate the effect of pharmacist interventions—alone or in collaborative care—in outpatients with hypertension compared with usual care. The pharmacist care must be delivered by a community or clinical pharmacist. We will classify pharmacist interventions using the following pre-defined categories: (1) pharmacist-directed care (pharmacist initiated and managed care) and (2) pharmacist collaborative care (pharmacist collaborating in interventions conducted by a multidisciplinary healthcare team according to the definition provided by Koshman and colleagues: the team can include physicians or nurses as well as physiotherapists, social workers or respiratory therapists).

Further, based on the Cochrane Effective Practice and Organization of Care (EPOC) taxonomy interventions, we will consider interventions targeted at patient level and at healthcare provider level as described in table 1.
We will exclude interventions targeted at healthcare organisation or regulatory level.

Comparators
Pharmacist intervention will be compared with usual care. We expect that usual care will encompass different situations between the included studies, ranging from regular visits by healthcare providers (planned or not) to no specific intervention. We also expect to have few information about usual care. We will however, if available, collect data systematically on usual care and describe it in detail in the final manuscript. We will try at least to collect information on the type of healthcare providers involved and the number of visits.

Outcome measures
Outcomes will be the systolic and diastolic BP at follow-up, the change in systolic and diastolic BP from last follow-up to baseline, or the BP control (BP below a predefined target level) at follow-up. We will extract outcomes in all data forms (continuous, dichotomous) as reported in included studies. Main results will be reported as mean difference in systolic and diastolic BP. We do no plan to impute missing data for the main outcome. If available, we will collect data on drug-related problems.

Time frame
There will be no restriction by duration of intervention or by length of follow-up. We will further identify studies in which the outcome was measured a period of time after the intervention is over to assess whether the intervention has an effect beyond the time of its application.

Language
We will consider publications in English, French and German.

### Search strategy

The search strategy aims to find both published and unpublished studies. The specific search strategies will be developed by an experienced medical librarian in systematic review searching (BK) in consultation with the project team. They are constructed to include the two main concepts of this systematic review: ‘hypertension’ and ‘pharmacist intervention’.

A three-step search strategy is used in this review. First, an initial limited search of MEDLINE (Ovid) is undertaken using the search terms ‘Pharmacist intervention’, ‘Pharmacists’, ‘Pharmaceutical Services’, ‘Pharmacy Service, Hospital’, ‘Pharmacies’, ‘Pharmacy’, ‘Hypertension’, ‘Blood pressure’. Second, an analysis of the text words contained in each article’s title, abstract and index terms is undertaken to expand the list of search terms. Based on the results of this analysis, a more thorough search is conducted in the chosen databases. The search strategy for MEDLINE (table 2) was created first and is then adapted for each database, including all identified keywords and index terms. Third, the reference lists of all included studies selected for critical appraisal is searched by hand and cited reference searches for all included studies will be conducted in Web of Science in order to find any additional studies not identified during the initial search processes.

The electronic databases to be searched include:

1. MEDLINE (Ovid) (1946 to DD Month YYYY).
2. Excerpta Medica database (Embase) (1947 to DD Month YYYY).
3. Cochrane Central Register of Controlled Trials (CENTRAL) (1947 to DD Month YYYY).
5. CINAHL (EBSCO) (1937 to DD Month YYYY).
6. Web of Science (1900 to DD Month YYYY).

### Table 1 Considered interventions based on the Cochrane Effective Practice and Organization of Care taxonomy

<table>
<thead>
<tr>
<th>Level</th>
<th>Type of intervention</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
<td>Education</td>
<td>Education and counselling about medications and medication adherence or patient educational workshop (individual or group).</td>
</tr>
<tr>
<td>Reminder</td>
<td>Telephone contact, websites, home visits or medication drug adherence aids (ie,</td>
<td>electronic monitors or weekly reminder to support medication intake.</td>
</tr>
<tr>
<td>Healthcare provider level</td>
<td>Educational material</td>
<td>Distribution of educational materials (published or printed recommendations for care including clinical practice guidelines, electronic publications delivered personally or through mass mailings).</td>
</tr>
<tr>
<td>Educational meetings</td>
<td>Educational meetings: participation of healthcare professionals in conferences,</td>
<td>lectures, workshops or training programmes.</td>
</tr>
<tr>
<td>Feedback</td>
<td>Clinical summary, medication review from medical records, monitoring of medication</td>
<td>therapy (assessment, adjustment or change of medication), recommendation to healthcare professionals (verbally/on paper), meeting with team to discuss care, reference to physician or observations from patients over a specified period of time.</td>
</tr>
<tr>
<td>Reminder</td>
<td>Patient-reminder or specific information, provided verbally, on paper or on a</td>
<td>computer screen, which is designed or intended to prompt a health professional to recall information, including computer-aided decision support and drug dosages.</td>
</tr>
</tbody>
</table>

**German.** We will consider publications in English, French and German. The intervention is over to assess whether the intervention has an effect beyond the time of its application. There will be no restriction by duration of intervention or by length of follow-up. We will further identify studies in which the outcome was measured a period of time after the intervention is over to assess whether the intervention has an effect beyond the time of its application.
**Table 2** Search strategy for Medical Literature Analysis and Retrieval System Online (MEDLINE)

<table>
<thead>
<tr>
<th>1</th>
<th>Pharmacists/ or Community Pharmacy Services/ or Pharmaceutical Services/ or Pharmaceutical Services, Online/ or Pharmacy Service, Hospital/ or Pharmacies/ or Pharmacy/ or Evidence-Based Pharmacy Practice/ or Pharmacy research/ or Drug Information Services/ or Medication Therapy Management/ or Patient Care Team/ or (“pharmacist” or “pharmaceutical intervention” or “pharmaceutical care” or “pharmacies” or “pharmacist-led” or “team-based care”).tw.</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Hypertension/ or essential hypertension/ or hypertension, malignant/ or Antihypertensive Agents/ or Blood Pressure/ or Blood Pressure Monitoring, Ambulatory/ or (hypertension or “high blood pressure” or “blood pressure management” or “blood pressure control” or “blood pressure monitoring” or “blood pressure telemonitoring” or “changes of blood pressure” or “hypertensive disease” or “antihypertensive” or “antihypertensive agents” or “high bp” or “bp raised” or “bp control”).tw. not (“pulmonary hypertension”).tw.</td>
</tr>
<tr>
<td>3</td>
<td>(randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or drug therapy.fs. or randomly.ab. or trial.ab. or groups.ab.) not (“trial registration number”).tw.</td>
</tr>
<tr>
<td>4</td>
<td>1 AND 2 AND 3</td>
</tr>
</tbody>
</table>

We will obtain full-text publications for all titles/abstracts that appear to meet inclusion criteria or where there is any uncertainty. Full-text publications will be independently examined to identify studies for inclusion (VG and BK) reasons for exclusion of ineligible studies will be recorded. Any disagreement will be resolved through discussion or, if required a third review author will be consulted (AC or VS). The selection process will be recorded in detail in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram.23

**Data extraction**

Study records retrieved by electronic searching will be uploaded to a reference management software (Covidence24) to enable importing citations, removing of duplicates, screening titles and abstracts and then full-texts publications. Data will be independently extracted by two reviewers (VG and BK) from each eligible study. To ensure consistency across reviewers, we will conduct calibration exercises before starting the review.

Using a structured data collection form, the two reviewers will independently extract the following data:

1. Study identification
   - Author(s), year of publication, study country.
2. Study characteristics
   - Setting and design.
   - Study duration, frequency of follow-up.
   - Randomisation, blinding.
   - Sample size (total and per arm).
3. Participants characteristics
   - Number of participants allocated to each group, number of patients analysed.
   - Mean age, age range and sex.
   - Diabetes, other comorbidities and cardiovascular risk factors (smoking, dyslipidaemia).
   - Drug intake.
4. Usual care (control group) characteristics
   - Healthcare providers involved.
   - Frequency of follow-up.
5. Intervention characteristics
   - Type of interventions (pharmacist alone or in collaboration).
   - Duration of intervention.
   - Description of interventions: key components, frequency, format (noting if the detail provided is enough for replication), healthcare providers involved.
   - Use of e-health or digital tools.
6. Outcomes
   - BP at baseline.
   - BP at follow-up, change in BP from baseline.
   - BP control (according to a pre-defined BP target).
   - BP as a primary or secondary outcome of the trial.
   - Method of BP measurement.

Discrepancies will be resolved through discussion. Where discrepancies remain, the abstract and retrieved information will be reviewed by a third author (AC or VS).

**Study selection**

Two independent reviews authors (VG and BK) will select studies at each phase of the review (screening, eligibility and inclusion in systematic review). After removing duplicate publications, titles and abstracts will be screened independently and in parallel for inclusion using the inclusion criteria (VG and BK). The citations (titles/abstracts) will be examined (electronically) independently by each reviewer who will indicate whether a citation is potentially relevant (meet inclusion criteria), is clearly not relevant, or if information is insufficient to make a judgement.


8. Tripdatabase (1997 to DD Month YYYY).

The search for unpublished studies will include:


The principal investigators of completed studies found on the trial registers will be contacted, via email, to access unpublished data. Supplementary searches for grey literature will be conducted through Google Scholar.

We will consider all publications in English, French and German and search all databases from inception to the date of search. The methodology search filter to limit retrieval to appropriate study designs, a modified version of the Cochrane Highly Sensitive Search Strategy, is used to identify randomised trials.19
Assessment of risk of bias in included studies—study quality

Two reviewers will independently assess the risk of bias (study quality) for each study using the ‘Cochrane Risk of Bias Tool’ for randomised trials. This tool assesses the risk of bias according to the following domains:

1. Random sequence generation.
2. Allocation concealment.
3. Blinding of participants and personnel.
5. Completeness of outcome data.
6. Selective outcome reporting (intention-to-treat and follow-up).
7. Other bias (eg, baseline imbalance inpatient characteristics).

We will classify the risk of bias for each domain as either ‘low’, ‘unclear’ or ‘high’ and provide information from each study together with the reasons for our evaluation in the risk of bias tables. Given the type of RCTs included in our review, blinding the participants and personnel is not feasible; only the outcome assessment can be blinded. In contrast, personnel blinding is impossible in cluster randomised trials. When blinding is not possible, evaluation is performed in each area; however, it will not be considered as an important domain when evaluating the entire RCT. We will resolve any disagreements through discussions. There is some consensus that these items can be applied for evaluation of studies across diverse clinical areas.

The quality of BP measurement will be also systematically assessed along three criteria: (1) use of clinically validated BP measurement devices; (2) training of outcome assessor; (3) measurement of BP out of the office. Criteria will be assessed as ‘low’, ‘unclear’ or ‘high’.

We will resolve any disagreement in quality assessment through discussions and involvement of an arbitrator where necessary.

The risk of bias for cluster randomised trials will be assessed according to the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions, which are as:

1. Recruitment bias
2. Baseline imbalance.
3. Loss of clusters.
4. Incorrect analysis.
5. Comparability with individually randomised trials.

We will derive an overall study risk of bias as follow. A judgement of high risk of bias in one or more domains will be considered as a ‘high risk’ study, a judgement of low risk of bias in most domains will be considered as a ‘low risk’ study, and a judgement of unclear risk of bias in most domains as an ‘unclear risk’ study. When considering treatment effects, we will take into account the risk of bias for the studies that contribute to that outcome.

Data analysis

Statistical analyses will be carried out using Stata (V.15.1) and R (V.4.1.0). Based on previous systematic reviews, we are confident that we will be able to pool data and run pairwise meta-analysis. Heterogeneity in the effect of interventions is expected across studies and random effect models will be used to estimate intervention effects and 95% CIs. If feasible, meaning that the network of the interventions included in our review is connected, we will also conduct a network meta-analysis. Further, we will conduct meta-regression analyses to assess the association of study characteristics with the outcome.

Measures of effect

For continuous outcomes, the effects will be calculated as weighted mean differences in BP between intervention and usual care group, with 95% CIs. For dichotomous outcomes, we will estimate pooled relative risk (RR) comparing intervention versus usual care group, respectively, with 95% CIs. Results from network meta-analysis will be reported as mean difference or RR for each pair of interventions included in the network.

Assessment of heterogeneity, subgroup analyses and sensitivity analyses

Reasons for heterogeneity in effect estimates have to be sought in meta-analyses. We will carefully list the elements that may potentially lead to heterogeneity between studies. Statistical heterogeneity between studies will be assessed by visual inspection of the forest plots and with the I² statistic and tested using the Cochran’s Q test. In network meta-analysis, we will assume a common parameter for heterogeneity variance across comparisons.

The main goal of the analyses is to identify which type of intervention has the largest effect on BP and if there are specific population or healthcare setting associated with a large effect. We will therefore conduct subgroup analyses according to specific characteristics: (1) country where the study was conducted (European vs North-American vs other countries); (2) setting (outpatient clinic vs community pharmacy); (3) including patients with diabetes or not; (4) including patients treated or not; (5) including old patients or not; (6) type of pharmacist care (pharmacist-led care vs collaborative care); (7) type of interventions (according to EPOC, see above); (8) including a nurse or not in the intervention; (9) frequency and duration of intervention (once a month vs less frequently); (10) use of e-health or digital tools; (11) level of BP at baseline; and (12) certain age categories and patient characteristics.

Finally, sensitivity analyses will be performed (1) excluding relatively small studies (with fewer than 50 participants per randomisation group), (2) restricting analyses to studies of high quality and (3) restricting analyses to studies having reported intention-to-treat effect size.

Assessment of publication bias

Publication bias will be assessed by visual inspection of funnel plots, and, if sufficient studies are available, funnel plot asymmetry will be examined using the Egger’s test.
Assessment of strength of evidence

The Grading of Recommendations Assessment, Development, and Evaluation framework will be applied in order to assess the strength of the body of evidence for this systematic review.30

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Contributors VS is the guarantor and developed the original idea of this project. VS, VG and AC drafted the manuscript. All authors (VG, BK, CDG, RT, GP, AC and VS) substantially contributed to the development of the selection criteria, the risk of bias assessment strategy and the data extraction list. BK developed the search strategy. VG and BK were in charge of acquisition of data. CDG and AC provided statistical expertise. VS and VG provided expertise on pharmacist care. All authors (VG, BK, CDG, RT, GP, AC and VS) read, provided feedback and approved the final version of the manuscript.

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