

The impact of interventions by pharmacists in community pharmacies on control of hypertension: a systematic review and meta-analysis of randomized controlled trials

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Hypertension is considered to be one of the most important treatable risk factors for cardiovascular disease.
- Research suggests that reduction of systolic or diastolic blood pressure is associated with a decreased risk of coronary heart disease and stroke.
- Recent systematic reviews and meta-analyses pooling observational studies and randomized controlled trials have suggested important contributions of community pharmacists in the management of hypertension in a range of healthcare settings.

WHAT THIS STUDY ADDS

- This systematic review and meta-analysis confined to randomized controlled trials provides evidence that community pharmacists can make a clinically important contribution to the management of hypertension in patients with or without associated cardiovascular co-morbidities.

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Keywords

hypertension, meta-analysis, pharmacists, randomized controlled trial

Received

30 April 2014

Accepted

21 June 2014

Accepted Article

Published Online

26 June 2014

AIMS

To undertake a systematic review and meta-analysis of randomized controlled trials concerned with the impact of community pharmacist-led interventions on blood pressure control in patients with hypertension.

METHODS

Eight electronic databases were searched up to 30 November 2013, with no start date (Web of Science, Embase, The Cochrane Library, Medline Ovid, Biomed Central, Biosis Citation Index, CINAHL, PsycINFO). All studies included were randomized controlled trials involving patients with hypertension, with or without cardiovascular-related co-morbidities, with difference in blood pressure as an outcome. Data collected included the study design, baseline characteristics of study populations, types of interventions and outcomes. The Cochrane tool was used to assess risk of bias.

RESULTS

From 340 articles identified on initial searching, 16 randomized controlled trials (3032 patients) were included. Pharmacist-led interventions were patient education on hypertension, management of prescribing and safety problems associated with medication, and advice on lifestyle. These interventions were associated with significant reductions in systolic [11 studies (2240 patients); -6.1 mmHg (95% confidence interval, -3.8 to -8.4 mmHg); $P < 0.00001$] and diastolic blood pressure [11 studies (2246 patients); -2.5 mmHg (95% confidence interval, -1.5 to -3.4 mmHg); $P < 0.00001$].

CONCLUSIONS

Community pharmacist-led interventions can significantly reduce systolic and diastolic blood pressure. These interventions could be useful for improving clinical management of hypertension.

Introduction

Despite benefits of blood pressure control for reducing risk of stroke and coronary heart disease [1–2] and other serious cardiovascular events [3], hypertension continues to be poorly controlled in the community [4]. It has been reported that pharmacist-led interventions can lead to significant reductions in blood pressure in patients seen in a range of healthcare settings [5, 6], including secondary care, community health clinics and community pharmacies [7, 8]. However, previous systematic reviews and meta-analysis of blood pressure control have been limited by including very short-term studies [5], by including observational studies [5, 6], largely confining outcomes to hypertensive patients with no reported cardiovascular problems including diabetes, kidney disease, stroke, atrial fibrillation, myocardial infarction and/or heart failure [5, 6] and by being unclear about the specific role of community pharmacists in improving the management of high blood pressure [8].

Increasingly in clinical practice, patients with hypertension have an associated range of cardiovascular co-morbidities. The aim of this systematic review and meta-analysis was to extend previous assessment of the impact of community pharmacist interventions on blood pressure control by limiting the analysis to randomized controlled trials (RCTs) and by evaluating studies in patients with hypertension with or without cardiovascular co-morbidities. Heterogeneity in pharmacist interventions was minimized by including data only from RCTs, by being specific about the setting for pharmacist intervention, i.e. community pharmacies, and by standardizing the nature of active pharmacist interventions considered as education about hypertension and its treatment, identifying prescribing and safety issues, and lifestyle advice.

Methods

Search strategy for identification of studies

A literature search of published articles, with no start date restrictions, was undertaken in November 2013 in eight electronic health-related databases: MEDLINE, Web of Science, the Cochrane library, EMBASE, Biosis Citation Index and Biomed Central, CINAHL and PsycINFO. Articles were retrieved up to 30 November 2013. Search terms included 'community pharmacy', 'essential hypertension', 'hypertension' OR 'blood pressure', 'randomized controlled trial' and 'intervention' (see Appendix S1 for complete search strategy).

In addition, reference lists were screened of all included articles retrieved at full paper and the first 100 results of this search strategy applied to Google Scholar. We also screened references in a further systematic review and meta-analysis published in April 2014 [8] for additional eligible RCTs.

Types of studies

Randomized controlled trials and systematic reviews of RCTs evaluating the clinical impact of community pharmacist interventions on patients with essential hypertension were included. Systematic reviews were searched to identify additional eligible RCTs. Studies that did not specify the types of hypertension were also considered for inclusion provided they met the inclusion criteria. Randomized controlled trials were included if they had a control group receiving standard or usual care, compared with the care in intervention groups.

Types of participants

All participants were adults (18 years or older) participating in an RCT of treatment for their hypertension in community pharmacies. A study was included if it had a minimum of 80% of the population meeting the inclusion criteria for study participants. Studies were also included which had participants with coexisting cardiovascular-related medical conditions (e.g. high cholesterol, diabetes, renal disease and clinical cardiovascular disease, including cerebrovascular disease and peripheral arterial disease).

Types of interventions

Pharmacological interventions were defined as interventions concerning education on drug treatment of blood pressure, advice to patients to improve medication adherence, identifying drug adverse effects and drug prescribing issues, and liaising with prescribers about concerns of drug treatment. Nonpharmacological interventions were defined as those concerning education about hypertension and education about lifestyle, such as advice to patients on healthy lifestyle, including diet, weight management, alcohol consumption and smoking cessation.

Types of outcome measures

Primary outcomes Reduction in systolic blood pressure and diastolic blood pressure measured in the community pharmacies or at home.

Secondary outcomes

- 1 Improvement in adherence to antihypertensive medications measured by tablet count, by pharmacy dispensing records, by use of the four-point Morisky questionnaire and by prescription claims data.
- 2 Identification and management of drug-related problems. Drug-related problems were defined as concerns about adverse drug effects expressed by the patient or the pharmacist. Methodology for assessing this was non-standard across included studies. Inappropriate drug selection or dose was based on pharmacist access to formularies and guidelines; sources for these were not clear across the studies.

3 Impact on cardiovascular risk factors, i.e. smoking, alcohol consumption, weight, cholesterol levels (in millimoles per litre) and glycated haemoglobin (HbA_{1c}, expressed as a percentage).

Exclusion criteria

The reviewers excluded studies with multidisciplinary interventions in which the pharmacist intervention within the team was not clearly defined, conference proceedings or abstracts only, systematic reviews of RCTs containing <50% of eligible studies, and articles published in languages other than English.

Data extraction, risk of bias and quality assessment

Two reviewers (EC and PS) independently reviewed titles and abstracts of all potentially relevant papers. Papers which met inclusion criteria were retrieved as full papers, and these two reviewers checked each paper for inclusion. Any differences were agreed through discussion or resolved by a third reviewer (DRJS). Reviewer EC independently extracted data, and PS checked all extraction sheets (see Appendix S2 for characteristics of included studies).

Criteria for quality assessment of included systematic reviews were based on those of the NHS Centre for Reviews and Dissemination (CRD) [9]. Two reviewers (EC and PS) rated each paper using the Cochrane Risk of Bias tool [10] to assess RCTs on their randomization procedure, allocation concealment, blinding of participants, reporting of incomplete outcome data, selective reporting or any other biases that did not fit into the above-mentioned categories. Other sources of bias explored in this review included the possibility of cross-contamination between study arms, recruitment of participants from a selected population and noncompliance of researchers to the study protocol. For each included study, a risk-of-bias graph and a risk-of-bias summary were generated [10]. The use of power calculations was recorded.

Statistical analysis

A narrative overview and analysis of included RCTs and systematic reviews was undertaken and supplemented with further meta-analyses. A cumulative meta-analysis of studies was used to identify changes in blood pressure control over time.

Meta-analyses were undertaken with random-effects models (Rev Man version 5.2; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). Mean difference [standard deviation] and 95% confidence intervals (CIs) were used to estimate effects. Because of differences in study population, sample size and methods of blood pressure measurement, a random-effects model was used, and τ^2 recorded. To minimize heterogeneity in the meta-analysis, studies using three similar interventions were used (patient education on disease

management, identification and management of prescribing and safety problems associated with antihypertensive medications, and advice on lifestyle). Heterogeneity was measured by Cochrane’s test. Statistical heterogeneity beyond that expected through chance was investigated using I^2 . Heterogeneity was further explored with sensitivity analysis by repeating meta-analysis after excluding a single outlying study and by using both random- and fixed-effect models.

Results

A total of 340 studies were identified (Figure 1), 330 from electronic databases and 10 from reference lists of previous reviews. Fifty-three duplicates were removed. Two hundred and eighty-seven records were screened at title level, with 143 irrelevant titles removed. The remaining

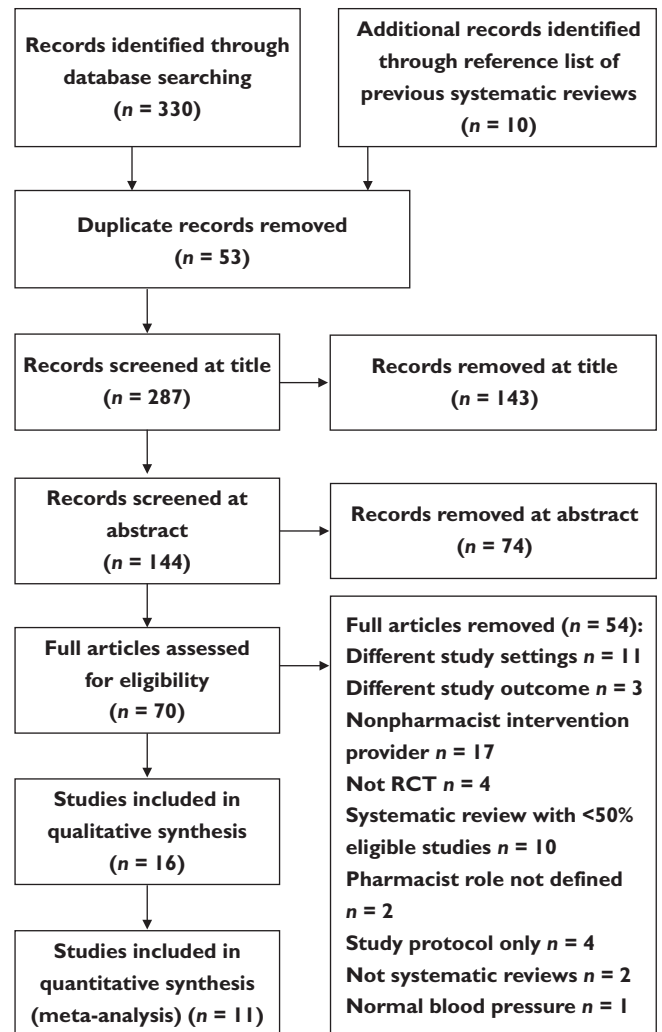


Figure 1
Prisma flow diagram

144 records were screened at abstract level. After eliminating abstracts not meeting inclusion criteria, 70 full-text studies were assessed for eligibility. Fifty-four studies did not meet inclusion criteria (Figure 1). Reasons for exclusion included the following: not RCTs; different study settings; systematic reviews containing <50% of eligible studies; intervention not provided by community pharmacists; <80% of study population hypertensive; blood pressure not a study outcome; studies not defining details of community pharmacist roles; and studies with published protocol only. Sixteen RCTs contributed to the systematic review [11–26]. Of these, 11 studies were included in the meta-analysis [11, 12, 14–17, 19, 21, 24–26].

Study characteristics

All 16 studies included were RCTs conducted in community pharmacies. These trials were conducted in Australia [17], Canada [20, 23], Portugal [16], Spain [12, 15], Thailand [24], the USA [14, 18, 19, 21, 22, 25, 26] and the UK [11, 13]. All 16 studies used intervention groups receiving a selection from the following interventions by community pharmacists: patient education on disease management; identification and management of prescribing and safety problems associated with antihypertensive medications; and advice on lifestyle, compared with a control group receiving usual care. No systematic reviews meeting the inclusion criteria were identified.

The duration of intervention ranged from 3 [26] to 13 months [15]). The studies included 3034 patients, with individual study size ranging from 50 [18] to 714 [12]. Mean age ranged from 53 [25] to 72 years [23]. Additional medical conditions included dyslipidaemia, diabetes mellitus, heart failure, angina pectoris and atrial fibrillation.

There was heterogeneity among studies for interventions, outcomes, population characteristics, study duration and methods for measuring outcomes. Only three of seven studies that measured adherence to antihypertensive medications reported using a similar assessment

method (pill count) [18, 21, 24]. Only four studies reported measuring the impact of pharmacists' interventions on other cardiovascular disease risk factors [12, 14, 15, 17].

Study quality

The quality of included studies assessed by Cochrane Risk of Bias tool is shown in Figure 2. Only three (18%) of 16 studies reported details of allocation concealment [12, 20, 25]. It was unclear in the remaining 13 studies whether they had used adequate allocation concealment. Only four (25%) studies reported using single blinding of participants [15, 16, 21, 25]. Only nine (56%) studies reported using power calculations [11, 12, 14–17, 21, 24, 25].

Impact of pharmacist interventions on outcome measures

All 16 studies included in this systematic review measured systolic and diastolic blood pressure at baseline and the end of the study. None measured ambulatory blood pressure. In 14 studies, measurements were in the community pharmacy, while in one study, home blood pressure recordings were used [26]. One study [13] reported improved blood pressure based on measurements in general practice, but did not report quantitative blood pressure results.

Of these 16 studies, 11 were included in the meta-analysis of effects on systolic (2240 patients) and diastolic blood pressure (2246 patients) [11, 12, 14–17, 19, 21, 24–26]. Absence of quantitative blood pressure data (one study) [13] and limitations in interventions were reasons to exclude the remaining four studies from meta-analysis [18, 20, 22, 23].

Meta-analysis

All 11 studies included in the meta-analysis used three similar interventions, namely patient education on hypertension and the importance of its treatment, identification of drug-related problems and lifestyle advice.

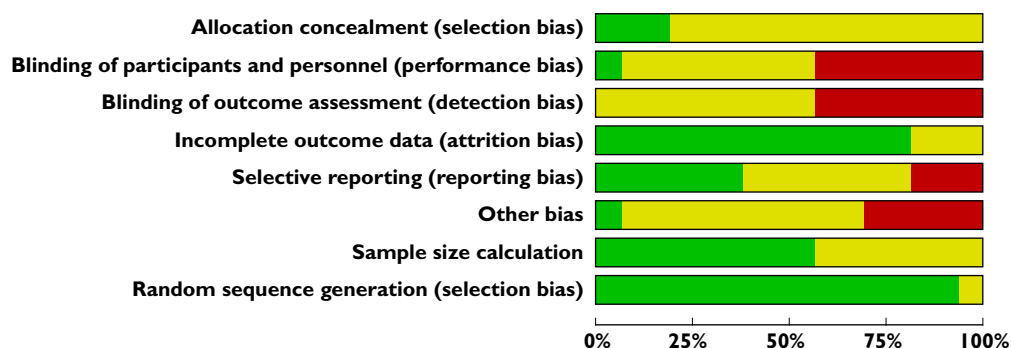


Figure 2

Cochrane risk-of-bias graph [10]. Authors' judgements about each risk-of-bias item are presented as percentages across all included studies. ■, low risk of bias; ■, unclear risk of bias; ■, high risk of bias

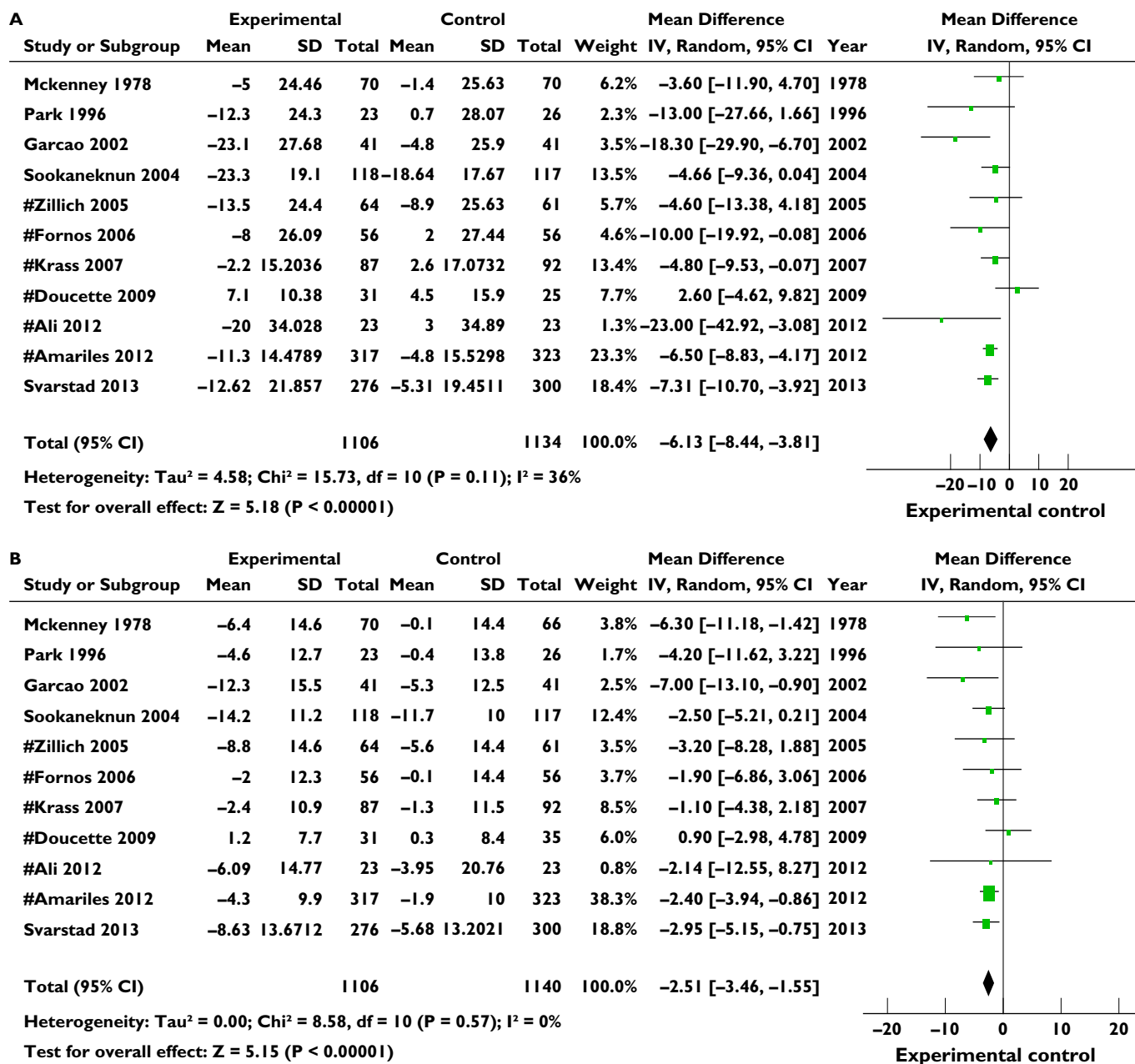


Figure 3

Forest plot comparisons of experimental (intervention) vs. control groups in 11 studies for systolic blood pressure (A) and diastolic blood pressure (B). #Indicates studies including patients with cardiovascular-related co-morbidities. Mckenney [19], Park [21], Garcao [16], Sookaneknun [24], Zillich [26], Fornos [15], Krass [17], Doucette [14], Ali [11], Amariles [12], Svarstad [25]

Systolic blood pressure: all subjects Meta-analysis of data from the 11 studies showed a significant benefit in favour of community pharmacist interventions, with a pooled effect of 6.1 mmHg reduction in systolic blood pressure (95% CI -3.8 to -8.4 mmHg, P < 0.00001) using a random-effect model. Heterogeneity among studies for differences in systolic blood pressure was low to moderate ($\chi^2 = 15.73$, d.f. = 10, P = 0.11, I² = 36%; Figure 3A).

Diastolic blood pressure: all subjects Meta-analysis of data from the 11 studies showed a significant benefit in favour of community pharmacist interventions, with a pooled effect of 2.5 mmHg reduction in diastolic blood pressure (95% CI -1.5 to -3.4 mmHg, P < 0.00001) using a random-effect model. There was no heterogeneity among the studies for differences in diastolic pressure ($\chi^2 = 8.58$, d.f. = 10, P = 0.57, I² = 0%; Figure 3B).

Sensitivity meta-analysis for blood pressure effects Two approaches were used to test the robustness of the results [10]. No significant difference was found between the results of fixed-effect model meta-analysis (systolic -6.2 mmHg, 95% CI -4.7 to -7.8 mmHg; diastolic -2.5 mmHg, 95% CI -1.6 to -3.5 mmHg) vs. the above random-effects model analysis. Results of random-effects model meta-analysis after removal of the outlier were similar for systolic (-6.6 mmHg, 95% CI -5.0 to -8.2 mmHg) and diastolic blood pressure (-2.7 mmHg, 95% CI -1.7 to -3.7 mmHg).

Cumulative meta-analysis identified no significant changes over time in the impact of pharmacist interventions on blood pressure control.

Blood pressure effects for five studies on hypertension without cardiovascular problems Pooled reduction in systolic blood pressure with active interventions in 528 patients without cardiovascular-related co-morbidities vs. 554 control subjects [16, 19, 21, 24, 25] was 7.2 mmHg (95% CI -3.6 to -10.8 mmHg, $P = 0.004$). Heterogeneity was low to moderate ($\chi^2 = 5.91$, d.f. = 4, $P = 0.21$, $I^2 = 32\%$).

Pooled reduction in diastolic blood pressure with active interventions in 528 patients without cardiovascular-related co-morbidities vs. 550 control subjects [16, 19, 21, 24, 25] was 3.4 mmHg (95% CI -1.9 to -5.0 mmHg, $P < 0.00001$). There was no significant heterogeneity ($\chi^2 = 3.32$, d.f. = 4, $P = 0.51$, $I^2 = 0\%$).

Blood pressure effects for six studies on hypertension with cardiovascular problems Pooled reduction in systolic blood pressure with active interventions in 578 patients with cardiovascular-related co-morbidities vs. 580 control subjects [11, 12, 14, 15, 17, 26] was 5.3 mmHg (95% CI -1.7 to -8.9 mmHg, $P < 0.0001$). Heterogeneity was moderate ($\chi^2 = 9.34$, d.f. = 5, $P = 0.10$, $I^2 = 46\%$).

The pooled reduction in diastolic blood pressure with active interventions in patients with cardiovascular-related co-morbidities was 1.9 mmHg (95% CI -0.7 to -3.1 mmHg, $n = 578$ intervention vs. 590 control subjects, $P = 0.002$). There was no significant heterogeneity ($\chi^2 = 2.88$, d.f. = 5, $P = 0.72$, $I^2 = 0\%$).

This trend for a smaller blood pressure reduction from community pharmacist interventions in patients with co-morbidities in comparison to those without co-morbidities was not significant (systolic difference 1.9 mmHg, 95% CI -3.1 to -6.9 mmHg, $P = 0.46$; and diastolic difference 1.5 mmHg, 95% CI -0.4 to -3.4 mmHg, $P = 0.127$).

Problems with blood pressure medications Pharmacists recorded drug-related problems in five studies. On entry to these studies, 822 medication-related problems were recorded in 337 patients; no medication-related data were recorded in 132 of the control patients. Categories of medication problems included patients not prescribed

a relevant antihypertensive medicine, patients not benefiting from effects of medicine(s) and patients experiencing adverse effects from antihypertensive medications [15, 16].

Within intervention groups (240 patients, five studies), pharmacists reported resolving 205 of 539 problems (38%) by advice to prescribers and patients.

Medication adherence Seven studies reported the impact of pharmacist interventions on adherence to antihypertensive medications [13, 18, 19, 22, 24–26]. Three studies used pill counting, one used pharmacy dispensing records, two used self-reported adherence questionnaires and one study used prescription claims data. One study [13] used a pharmacist-administered questionnaire based on a Medication Adherence Report Scale [27]. Another study used self-reported adherence [26] using the four-item Morisky questionnaire [28]. Three studies reported an increase in medication adherence in intervention compared with control groups [13, 22, 24]. One study reported increased adherence ($P < 0.005$) but provided no quantitative data. For the remaining six studies, adherence in intervention groups increased from 203 (56%) to 246 (68%) of 360 participants, and from 190 (59%) to 195 (61%) of 320 participants in the control group. Thus there was an increase in adherence of 43 from 158 poorly adherent subjects in intervention groups and four of 132 poorly adherent subjects in control groups (odds ratio 12.1, 95% CI 4.2–34.6; $P < 0.001$).

Reduction in cardiovascular risk factors Three studies reported results for total cholesterol levels [12, 15, 17]. One study [15] reported a reduction in total cholesterol levels by 0.52 mmol l⁻¹ ($P < 0.001$) in the intervention group. Two studies reported outcomes for low-density lipoprotein-cholesterol [14, 15]. All these studies reported a mean reduction in low-density lipoprotein-cholesterol for both intervention and control groups. Three studies measured HbA_{1c} % [14, 15, 17]. Two studies reported a mean reduction in HbA_{1c} % by 0.5 and 1.0% in patients in intervention groups [15, 17].

Discussion

These findings show that compared with usual blood pressure management, active interventions by pharmacists working in community pharmacies were associated with clinically important improvement in control of hypertension, whether or not associated with cardiovascular co-morbidities. In comparison to patients receiving usual care, both systolic and diastolic pressure decreased and adherence improved, as did control of other cardiovascular risk factors, including both diabetes mellitus and cholesterol.

Previous analyses have assessed the impact of community pharmacist interventions on blood pressure control in hypertensive patients without cardiovascular problems [5, 6] or of a wide range of clinical and other pharmacists working within inpatient and outpatient settings [7, 8]. The present study is the first meta-analysis to evaluate the specific impact of community pharmacist interventions delivered in community pharmacies both in hypertensive patients without cardiovascular problems and in patients with cardiovascular co-morbidities, including dyslipidaemia, diabetes mellitus, chronic kidney disease and clinical vascular disease. Of note, Santschi *et al.* [8] do not differentiate between the impact of different types of pharmacists working across a range of healthcare settings, including primary care health centres, hospitals, army medical centres, academic health centres, community pharmacies, community-based hypertension clinics and hospital outpatient clinics. Furthermore, in our meta-analysis of 11 community pharmacy-based RCTs, in addition to all four studies in community pharmacies identified by Santschi *et al.*, we include a further seven studies not referenced in that study [8].

The evidence presented in this review together with previous reviews [5–8] provides an important message to health professionals and policy makers about the potential for community pharmacists to ease the burden for physicians in primary and secondary care of chronic disease management in the context of hypertension. The results of this review show that interventions by community pharmacists were associated with clinically important reductions in both systolic and diastolic blood pressure within a wide range of international geographical regions from North America to Europe, South East Asia and Australia.

The improvement in blood pressure control appeared to occur irrespective of the length of intervention, across included studies whose duration ranged from 3 to 13 months. In the meta-analysis, in studies published from 1978 to 2013, there was also no obvious trend in degree of impact on blood pressure by year of publication. Community pharmacists appeared to be similarly effective in improving blood pressure control both for patients with high blood pressure alone [16, 19, 21, 24, 25] and for patients with hypertension coupled with serious cardiovascular problems [11, 12, 14, 15, 17, 26].

The largest category of preventable causes of poor blood pressure control across the studies included in this review appeared to be incorrect use of medicines by prescribers and patients. In the five studies which recorded this information, it was noteworthy that pharmacists reported being able to resolve only 38% of these problems by making suggestions to prescribers and patients, although expertise in resolving these problems is an expected core usual clinical activity of community pharmacists [29]. Further work is needed to investigate two major questions arising from this aspect of the meta-analysis.

First, how can the initial occurrence of medication-related problems, such as errors of omission and commission, be prevented when prescribing for hypertension and how can adverse effects from antihypertensive medications be prevented? Second, what would make interventions by community pharmacists more effective, when aiming to resolve medication-related problems? Possible reasons for the high proportion of unresolved medicine-associated problems include time pressure on community pharmacists providing clinical services within busy commercial settings [30] and challenges to effective inter-professional working arrangements between community pharmacists and other clinical practitioners [31].

There were limitations in this review. Although rigorous and systematic, the reviewers did not include unindexed and unpublished research. Studies were of variable quality, with low to moderate heterogeneity for systolic blood pressure. Home blood pressure monitoring was used in only one of studies in this systematic review [26]. There is however high-quality evidence from individual RCTs and robust meta-analysis that home blood pressure monitoring resulted in better blood pressure control and greater achievements of blood pressure targets than standard blood pressure monitoring in healthcare systems [32]. Furthermore, recent research suggests that home blood pressure monitoring is also a useful adjunct to pharmacist-supported management of hypertension within family doctor centres [33]. Further studies using home blood pressure monitoring are needed to discover whether this would have enhanced the already important reductions in blood pressure observed in this meta-analysis. There are well-established lifestyle approaches for improving control of hypertension [34]. However, details of lifestyle interventions were unclear in many of the studies in this systematic review, including whether specific advice was on reducing dietary salt, increasing fruit and vegetable intake and objective assessment of impact of this advice, e.g. from measurement of urinary electrolyte excretion. Future studies could, for example, evaluate formal use of established Dietary Approaches to Stop Hypertension Diet approaches [35] within community pharmacist interventions aimed at blood pressure control.

The reductions in systolic and diastolic blood pressure reported in this meta-analysis, if sustained in clinical practice, would have important implications for primary and secondary prevention of cardiovascular morbidity and mortality. For example, evidence from a meta-analysis involving 1 million adults in the USA reported that every 1 mmHg reduction in systolic blood pressure could prevent about 10 000 deaths related to coronary heart disease in the USA each year [3]. A further analysis suggests that a sustained 2 mmHg reduction in diastolic blood pressure would be expected to result in a 6% reduction in the risk of coronary heart disease and 15% decrease in stroke [36].

There are international differences in the extent to which community pharmacy services are embedded within usual clinical care of long-term medical conditions. In the National Health Service in the UK, a new contractual framework for community pharmacies was introduced in 2005, with the intention of moving pharmacists towards a more clinical service-oriented role [37]. For example, UK community pharmacies can provide Health Checks for people aged 40–74 years. Within these health checks, pharmacists can carry out a full vascular risk assessment and provide advice and support to help to reduce the risk of heart disease, strokes, diabetes and obesity [37].

However, such extensions in activities and services delivered by community pharmacists may conflict with the work of general practice and health professionals working in hospitals. There is a need for formal links to ensure coherence of treatment approaches and evidence-based integration of pharmacy-delivered services with other health services [38].

Conclusions

Effective blood pressure management requires a systematic multidisciplinary approach in the community. Provision of safe and effective medications to patients is a key role of community pharmacists. The findings of this meta-analysis highlight the significant potential benefits of community pharmacist-led interventions in the management of high blood pressure, whether or not associated with significant cardiovascular co-morbidity. These results support a greater involvement of the community pharmacist in the management of hypertension and its treatment.

Future work needed to address the policy implications of pharmacist-led interventions includes cost-effectiveness analysis of these approaches and their sustainability in the long term in clinical practice. Research is also needed into the type, mode and frequency of interventions in relation to differences in age, gender, ethnicity and other variables of potential importance in the selection and response to the management of hypertension.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

We thank Dr Peter Kimani for his statistical advice. In addition, we thank Samantha Johnson for her advice on search-

ing the electronic databases and Warwick University library for help in retrieving the studies evaluated in this review.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Appendix S1

Search strategies used in the major electronic databases

Appendix S2

Characteristics of included studies