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Impact of the pharmacist-led intervention on the control of medical cardiovascular risk factors for the primary prevention of cardiovascular disease in general practice

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i. Title

Impact of the Pharmacist-Led Intervention on the Control of Medical Cardiovascular Risk Factors for the Primary Prevention of Cardiovascular Disease in General Practice: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

ii. Short running title of less than 40 characters

Impact of Pharmacist-Led Intervention on the Main Cardiovascular Risk Factors for the Primary Prevention of Cardiovascular Disease Events

iii. The full names of all authors (**including the principal investigator (PI)'s name**).

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iv. PI statement: 'The authors confirm that the Principal Investigator for this paper is Abdullah A. Alshehri and that he had direct clinical responsibility for patients.')

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1. Structured Abstract

Aims

To conduct a systematic review and meta-analysis of the effectiveness of general practice based pharmacists' interventions in reducing the medical risk factors for the primary prevention of cardiovascular events.

Methods

A systemic search was undertaken in eight databases: PubMed, MEDLINE, EMBAS, PsycINFO, Cochrane Library, CINAHL Plus, SCOPUS and Science Citation Index, with no start date up to 27th March 2019. Randomised controlled trials assessing the effectiveness of pharmacists-led interventions delivered in the general practice in reducing the medical risk factors of cardiovascular events were included in the review. The risk of bias in the studies was assessed using the Cochrane risk of bias tool.

Results

A total of 1,604 studies were identified, with 21 RCTs (8,933 patients) meeting the inclusion criteria. 14 studies were conducted in patients with diabetes, seven in hypertension, two involving dyslipidaemia and two with hypertension and diabetes together. The most frequently used interventions were medication review and medication management. The quality of the included studies was variable. Patients receiving pharmacists-led interventions were associated with a statistically significant reduction in their systolic blood pressure -9.33 mmHg [95% CI -13.36 to -5.30]), HbA1c -0.76% [95% CI -1.15 to -0.37]) and LDL-Cholesterol -15.19 mg/dl [95% CI -24.05 to -6.33]). Moreover, practice-based pharmacists' interventions were also reported to have a positive impact on patient adherence to medications.

Conclusions

The findings of this review suggest that Pharmacists-led interventions in general practice can significantly reduce the medical risk factors of CVD events. These findings support the involvement of pharmacists as healthcare providers in managing patients with hypertension, diabetes and dyslipidaemia.

2. Statement1: What is already known about this subject (up to three bullet points)

- Hypertension, diabetes and dyslipidaemia are significant medical risk factors that can lead to CVD, which continues to be a leading cause of death and disability-adjusted life years worldwide
- Evidence suggests that pharmacists play an important role in the management of chronic diseases such as CVD

3. Statement 2: What this study adds (up to three bullet points)

- This systematic review and meta-analysis limited to randomised controlled trials provides evidence that pharmacists-led interventions can make a clinically important contribution in the primary prevention of CVD in the general practice
- The pharmacists-led interventions not only improved patients medicine adherence but were also reported to be cost-effective

4. Introduction

Cardiovascular disease (CVD) continues to be a leading cause of death and disability-adjusted life years (DALY) worldwide accounting for nearly 18 million deaths per year (31% mortality rate) [1] with an estimated 150 million DALYs by the year 2020 [2]. For example, in the year 2015 alone , CVD was responsible for around 3.9 million deaths (45%) of all reported deaths in Europe and around 65 million DALYs [4]. The European Heart Network estimates that the total cost attributable to CVD in Europe is € 210 billion per year, while the cost attributed to the United Kingdom (UK) economy is around € 22 billion per year [4].

Numerus studies including Framingham heart study [5] and the INTERHEART study [6] identified the modifiable and non-modifiable risk factors of CVDs. The INTERHEART study conducted in the year 2004 outlined the effects of modifiable risk factors of CVD including hypertension (HTN), diabetes mellitus (DM), hyperlipidaemia, smoking, alcohol consumption, high body mass index (BMI), psychosocial conditions, unhealthy diet and irregular exercise [6]. These nine modifiable risk factors can potentially reduce the risk of acute myocardial infarction by 90%. Early detection, intervention and management of these risk factors, are among some of the primary prevention strategies that can reduce the burden of CVD worldwide.

The Alma-Ata Declaration (1978) mentioned the primary health care as the key to achieve the goal of "Health for All" [7]. General practice (GP) is the primary and most common point of contact for individuals with health care needs especially in the developed countries. For example, in the UK, GP has been considered as the jewel in the crown of the National Health Service (NHS). "Save it. Build it …." Berwick [8]. However, over the past few years, GP has faced increased workload due to multiple reasons including the increase in population and average lifespan, increased prevalence of long-term medical conditions, frequency of diseases and complexity of treatment regimen [9]. Pharmacists by virtue of patient education, medicine reconciliation and management of CVD risk factors can play an important role in the primary prevention of CVD [10] that can help ease the burden on primary care physicians (PCP).

Several systematic reviews and meta-analysis have assessed the effectiveness of pharmacists' led interventions in reducing the risks associated with CVD across a range of healthcare settings [11-15]. However, these reviews were largely limited to interventions by community or hospital pharmacists with no assessment of pharmacists interventions in general practice. A systematic review and meta-analysis that assessed the impact of pharmacist's services on patients with primary and secondary prevention diseases in general practice conducted in the year 2014 [16]. However, this review included services provided by pharmacists' alone or in collaboration with the PCP and

other health care providers. Furthermore, several RCTs have been conducted to assess the pharmacists-led interventions since the publication of that review. This review therefore, aims to assess the impact of pharmacists' interventions focusing on the medical risk factors for the primary prevention of cardiovascular events in general practice by limiting the analysis to randomised controlled trials (RCTs) and by standardizing the type of interventions used by pharmacists.

5. Methods

The protocol was registered prospectively on PROSPERO (registration no CRD42018107132). The review supports the PRISMA statement [18] as well as the Joanna Briggs Institute (JBI) methods [19].

Search Strategy

A systemic search of the literature was undertaken by AA using eight electronic databases: PubMed (NCBI), Ovid MEDLINE (1946), EMBASE (1974), PsycINFO (OVID) (1967), Cochrane Library (Wiley), CINAHL Plus (EBSCO) (1937), SCOPUS (ELSEVIER) and Science Citation Index Expanded (Web of Science Core Collection) (1900) from inception to 27th March 2019 Some of the key words included: "pharmacist", "general practice", "cardiovascular diseases", "hypertension", "diabetes" and "dyslipidaemia". All terms in each database combined with Boolean operators (AND, OR and/or NOT). Searches were restricted to the English language and randomised controlled trials or cluster randomised controlled trials (See Appendix S1 for Search strategy). In addition, reference lists of included studies were screened to identify any additional relevant studies.

Types of studies

Studies were included in this review if they were RCTs or cluster RCTs that assessed the effectiveness of pharmacists' interventions delivered in general practice. Studies were included if they had compared pharmacists' interventions with usual care. Studies were excluded if they assessed pharmacists' interventions for cardiovascular disease prevention including post-stroke, myocardial infarction or heart failure. Studies were also excluded if they were delivered in community pharmacies, ambulatory units, secondary or tertiary care settings. Furthermore, studies that assessed pharmacists' interventions in collaboration with other healthcare were also excluded.

Types of participants

Studies of adult patients (≥18 years) with at least one of the medical risk factors for the primary prevention of cardiovascular disease, mainly HTN, type 2 diabetes mellitus (T2 DM) and dyslipidaemia were eligible for inclusion.

Types of interventions

Patient education, medication review and counselling, physical assessment, assessing adherence, lifestyle modification, and medication management such as prescribing, adjusting, monitoring and administering therapy and identifying drug related problems.

Outcomes assessed

Primary outcomes

The primary outcomes assessed included changes in Systolic-Diastolic blood pressure (SBP, DBP), haemoglobin A1C (HbA1c), fasting blood glucose (FBG), lipid profiles and cardiovascular risk score.

Secondary outcomes

The secondary outcomes assessed medicine adherence and cost effectiveness of pharmacists' interventions in general practice.

Study Selection and Data Extraction

All the initially identified studies were uploaded to Rayyan QCRI (a web and mobile app for a systematic review screening that facilitates collaboration between different reviewers for inclusion and exclusion of studies) [20]. Using this app, two reviewers (AA and AY) independently screened titles and abstracts of all potentially relevant papers based on the selection criteria. Then the full text of eligible studies was screened for inclusion by each reviewer. Any disagreement about study inclusion were resolved by the involvement of a third reviewer (ZJ). Reviewer AA independently extracted data from included studies using a data extraction sheet (See Appendix S2 for characteristics of included studies). Reviewer AY checked all data extracted in the sheets. The data extracted included; study design, country and setting, primary outcomes, assessed population size, patient age and gender, duration of intervention and follow up, and study results.

Risk of Bias Assessment

The risk of bias in the included studies was assessed by two independent reviewers (AA and AY) using the Cochrane Handbook risk of bias assessment tool [21]. Each study was assessed according to the following criteria: method of randomisation, concealment of allocation, blinding of outcome assessors, addressing of incomplete outcome data, selective outcome reporting and other sources of bias. Each risk of bias item was rated as “low risk”, “unclear” or “high risk”. A risk of bias graph and risk of bias summary was produced to report the quality of included studies. (See Appendix S3 for the risk of bias assessment tool).

Statistical analysis

A meta-analysis was conducted using Review Manager (RevMan, Version 5.3) for all primary outcome measures except cardiovascular risk score and FBG due to no enough studies assessing these outcomes. For continuous outcomes, data extracted from these studies included sample size, means and standard deviations (SDs). If these were not reported, SDs from confidence intervals (CIs) were obtained where possible. We included final score data, in the absence of final score data, difference in the baseline and follow up score was used in the meta-analyses, following the advice of the *Cochrane Handbook9.4.5.2* [21]. Secondary outcomes were not included in the meta-analysis due to variations in the measurement of study outcomes including patient medication adherence and the cost-effectiveness tools. These outcomes were included in the narrative review.

A Random-effects model was used to synthesise the data due to the expected heterogeneity between included studies. To further minimise heterogeneity, studies using similar interventions (medication review and medication management) were included in meta-analysis. Heterogeneity was measured using Chi-square tests and the I^2 statistic. A heterogeneity above 50% was considered ’substantial’ heterogeneity and above 75% was considered as considerable heterogeneity [21]. The effect size was calculated as the Mean Difference (MD) with 95% Confidence Interval (CI). A meta-regression was used to examine relationship between the magnitude of the difference for all the outcome measures and the duration of studies. The Statistical package (STATA, Version 16) was used for this part of the analysis.

6. Results

Search and Study Selection

The initial search produced 1,604 studies (Figure 1 shows the PRISMA flow diagram for this study [18]). After removal of duplicates and studies that did not match the inclusion criteria, 1,173 were searched at title and abstract level. Of these studies, 1,086 were excluded, 87 studies were deemed eligible for full-text screening. Sixty six studies were subsequently excluded because of study design, interventions not located in general practice setting, study protocol, conference abstract, no relevant outcome, interventions provided to primary healthcare physician and/or the pharmacist involved in collaboration with other healthcare providers. Finally, twenty-one RCTs contributed to the systematic review [22-42]. Of these, eleven studies were included in the meta-analysis.

[Insert Figure 1 here]

Study Characteristics

All 21 studies included involved 8,933 participants aged from 49 to 65. The included studies were either cluster randomised controlled trials [25,28,29] or were randomised controlled trials [22-24,26,27,30-42] conducted in general practice. These studies were conducted in different countries including: ten in USA [23,25,26,28,29,33-36,42], four in Canada [24,27,37,38], three in Brazil [30-32] and one each in Jordan [40], Chile [41], Malaysia [22] and Thailand [39]. Appendix S2, presents further characteristics of the studies included in this systematic review. Of the 21 included studies, 14 were included patients with diabetes [22-27,30-32,34-38], seven with hypertension [28,29,31-33,39,42] and two with dyslipidaemia [40,41]. Pharmacists used multi-faceted interventions including patient education, medication review and counselling, physical assessment (e.g. BP), assessing adherence, lifestyle modification, and medication management such as prescribing, adjusting, monitoring and administering therapy and identifying drug related problems. The duration of the interventions ranged from 3 months [36]to 36 months [31].

Study quality

The quality of the included studies was variable (see figure 2 for risk of bias graph). Five studies (25%) did not report blinding of outcome assessed and two studies (10%) had attrition bias. Appendix S3, presents the risk of bias summary for each study.

[Insert Figure 2 here]

Meta-analysis

Eleven RCTs included in the meta-analysis (2,253 patients) used two similar interventions, medication review and medication management [22,23,28,30,31,33,34,37,39,41,42]. Only one trial [36] that measured clinical endpoints was excluded, as appropriate data were not available.

Impact of Pharmacists-led Interventions on Blood Pressure

Of the 11 RCTs included in the meta-analysis, nine studies (1,841 patients) reported both systolic and diastolic blood pressure [22,28,30,31,33,34,37,39,42].

Systolic blood pressure: Meta-analysis of data from the nine studies reported a significant reduction in favour of intervention participants, with a pooled effect of 9.33 mmHg reduction in systolic blood pressure (95% CI -5.30 to -13.36, Z = 4.54 (P < 0.00001)) using the random effect model. There was considerable heterogeneity among studies assessing SBP (Chi^2 = 56.04, df = 8 (P < 0.00001); I^2 = 86%, figure 3A). The major heterogeneity could be attributed to the inclusion of a study with a longer duration of follow-up (3 years) [31] compared to the other studies that used between 6-12 months of follow-up period.

Diastolic blood pressure: Meta-analysis of data from the nine studies showed statistical significant reduction in favour of practice pharmacist interventions, with a pooled effect of 3.71 mmHg reduction in diastolic blood pressure (95% CI -1.43 to -6.00, Z = 3.18 (P = 0.001)) using the random effect model. Statistical heterogeneity across the studies assessing DBP was considerable (Heterogeneity: Chi^2 = 38.41, df = 8 (P < 0.0001); I^2 = 79%, figure 3B).

[Insert Figure 3 A&B here]

Impact of Pharmacists-led Interventions on Blood Glucose

Of the 11 RCTs included in the meta-analysis, five studies (694 patients) reported HbA1c [22,23,30,31,37]. Meta-analysis of data from the five studies showed statistical significant reduction in favour of practice pharmacist interventions, with a pooled effect of 0.76% greater reduction in HbA1c (95% CI -0.37 to -1.15, Z = 3.81 (P = 0.0001)) when compared to usual care. There was considerable heterogeneity among studies assessing HbA1c (Chi^2 = 13.97, df = 4 (P = 0.007); I^2 = 71%, figure 4). Only two RCTs in this review measured FBG (441 patients) [30,31] were demonstrated statistical significant reduction in favour of pharmacist care.

[Insert Figure 4 here]

Impact of Pharmacists-led Interventions on Lipid Profiles

Five RCTs reported data on clinical outcomes of dyslipidaemia were included in the meta-analysis [22,30,31,37,41].

Total cholesterol: Meta-analysis of these five studies assessing TC (752 patients) indicated statistically significant reductions in favour of the practice pharmacist care, and the pool estimate showed a significant reduction in TC (-20.24 mg/dl [-33.53, -6.95], Z = 2.99 (P = 0.003)). There was considerable heterogeneity among studies assessing TC (Chi^2 = 22.36, df = 4 (P = 0.0002); I^2 = 82%, figure 5A).

LDL-C: Meta-analysis of the five RCTs assessing LDL-C (738 patients) showed statistical significant reduction in favour of pharmacist care, with a pooled effect of 15.19 mg/dl reduction in LDL-C (95% CI -6.33 to -24.05, Z = 3.94 (P = 0.0008)). Statistical heterogeneity across the studies assessing LDL-C was substantial (Chi^2 = 11.79, df = 4 (P = 0.003); I^2 = 66%, figure 5B).

HDL-C: Meta-analysis of five studies that reported HDL-C (742 patients, see figure 5C), the pooled estimate did not show a statistically significant change in HDL-C (4.56 mg/dl [-0.62, 9.75], Z = 1.73 (P = 0.08)). There was considerable heterogeneity among studies assessing HDL-C (Chi^2 = 72.32, df = 4 (P < 0.00001); I^2 = 94%).

Triglyceride: Five studies reporting changes in triglyceride levels (753 patients) demonstrated statistically significant reduction in favour of pharmacist care. Pooled analyses of pharmacist interventions indicated a -37.90 mg/dl greater reduction in triglyceride (95% CI -16.98 to 58.81, Z = 3.55 (P = 0.0004)) when compared to usual care. There was substantial heterogeneity (Chi^2 = 8.08, df = 4 (P = 0.09); I^2 = 50%, figure 5D) among studies assessing triglyceride in the meta-analysis.

[Insert Figure 5 A,B,C&Dhere]

Sensitivity analysis

Two approaches were used to measure the robustness of the results. Firstly, studies with fewer than six months of follow-up were excluded from the meta-analysis. Secondly, as recommended by Tobias [43], studies were excluded step-wise to assess the overall input on Z-statistic and P value. Both approaches did not make any significant difference in the results of any outcomes of meta-analysis.

Meta-regression

The meta-regression reported a statistically significant negative relationship between the magnitude of the difference in both systolic and diastolic blood pressure ($p<0.001$) with the duration of studies. This means that the longer the duration of the study the smaller is the difference. All other outcome measures did not reveal any statistically significant association with the duration of studies.

Cardiovascular Risk Score

Cardiovascular risk score was estimated in two studies [27,31]. The Framingham Risk Score (FRS) was used in both studies to predict CHD risk. There was a significant reduction in mean FRS in the intervention group and a significant difference in the change in comparison to the control group [31]. Ladhani et al. [27] demonstrated a significant decrease in median change of FRS in intervention patients, but no significant difference in median change comparison with the control group.

Medication Adherence

Nine RCTs assessed patient's adherence to their medication [22,25,26,28,30,31,39,40,42]. Due to the variations in methods of measuring adherence, meta-analysis was not conducted. Methods of adherence measurement included: prescription refill, the validated Morisky-Green test (four items scale), tablet counting and filling in self-reported questionnaires by patients were used. Three studies reported a significant increase in medication adherence in the intervention compared to the control group [28,31,39]. Two studies [30,42] reported non-statistical significant improvement in the intervention group compared to control group. The remaining four studies provided no quantitative data about adherence.

Cost-effectiveness analysis

Three studies analysed the cost effectiveness of the pharmacists' interventions [32,33,38]. All these three studies indicated that the cost-effectiveness ratio was lower in the intervention group than in the control group. Furthermore, these studies identified no significant difference in total direct healthcare related costs between the intervention and control groups that was associated with a statistical significant improvement on clinical outcomes.

7. Discussion

To author's knowledge, this is the first comprehensive systematic review and meta-analysis of RCTs that has focused on pharmacists' interventions on the medical risk factors for primary prevention of cardiovascular disease solely in the general practice setting. The findings of this review suggest that pharmacist's interventions directed to patients with HTN, T2 DM or dyslipidaemia could significantly improve their clinical outcomes compared to patients without pharmacists' interventions.

The improvement in the clinical outcomes reported in this review are consistent with the findings of a previous systematic review and meta-analysis that assessed the impact of hospital and community pharmacists' interventions on CVD risk factors in diabetic patients [44]. Moreover, a recent review conducted by pharmacist across range of healthcare settings including general practice and reported a positive effect on blood pressure, HbA1c, lipid profiles and the prediction for CV risk score for diabetic patients [45]. These two reviews support the findings of this review were conducted in other settings besides general practice. A systematic review conducted in general practice reported a statistically significant improvement in BP, HbA1c, TC and FRS [16]. However, these interventions were delivered by pharmacists alone or in collaboration with the PCP for a range of chronic diseases. Furthermore, this review identified an additional four studies that was not included by Tan et al. [16] besides assessing clinical outcomes not assessed previously.

Studies included in this review reported improvement in medication adherence. These finding is also consistent with results from a previous systematic review [46] which described the role of hospital and community pharmacists in management of patients with CVDs and showed statistical significant results improving adherence to prescribed medication. There was limited evidence regarding the cost effectiveness as only three studies conducted an economic analysis. These findings show that pharmacists' interventions greatly cost effective and; limited effect on total cost between intervention and usual care groups. Future work including economic and clinical outcomes, along with humanistic outcomes (ECHO approach) should be considered in order to reach a

comprehensive evaluation of pharmaceutical services [47]. A recent review of many systematic reviews assessed the impact of pharmacists' interventions on both cardiovascular medical risk factors and diseases across settings and supports findings from our review as it, indicated that both humanistic outcomes such as adherence and economic outcomes are poorly assessed in the current available literature [10].

Implications for practice and policy

The evidence presented in this review, together with previous reviews, provide an important message to health organisation systems and policy makers regarding the effectiveness of GP practice-based pharmacists' interventions. The review demonstrates that pharmacists have an important role in contributing to the management of chronic diseases such as diabetes and hypertension. The significant reductions in SBP, DBP, HbA1c, FBG, TC, LDL and Triglyceride reported in this meta-analysis, if sustained in clinical practice, could have significant implications for managing HTN, DM and dyslipidaemia that could prevent cardiovascular morbidity and mortality. For example, evidence from a meta-analysis involving one million adults informed that every 1 mmHg reduction in SBP could prevent about 10,000 deaths related to CHD in the US each year [48]. In addition, evidence from an epidemiological analysis of the United Kingdom Prospective Diabetes Study (UKPDS) presented that every percentage point reduction in HbA1c reduced about 25% of diabetes-related deaths and 18% of myocardial infarction [49]. Additionally, the findings of the humanistic and economic cost of pharmacist's interventions would have important implication on saving the economic resources and easing the burden and financial on healthcare services.

Strengths and limitations

The review has some limitations. Although, all the relevant studies were identified by a broad search strategy and manual checking reference lists, non-RCTs and studies published in language other than English were not included. This review did not include non-medical risk factors of CVD such as smoking, alcohol consumption and physical activities. Although this review addressed patient adherence to medication, other humanistic outcomes such as patient satisfaction and health related quality of life were not included.

Additionally, while most of the studies favoured pharmacists' interventions compared with usual care, there was a considerable heterogeneity between the identified studies. Nevertheless, this review minimised the risk of heterogeneity by limiting the meta-analysis to studies using similar pharmacists' interventions (medication review and medication management) and by using two approaches to measure the robustness of the results.

Conclusions

This systematic review suggest that pharmacists-led interventions in general practice have a significant impact on reducing the medical risk factors for primary prevention of CVD events. In addition, pharmacists' interventions were effective in improving medication adherence and were cost effective. These findings support a greater involvement of the pharmacist in the general practice in the management all of HTN, DM and dyslipidaemia. Future work is needed to address the effectiveness of pharmacist's interventions on non-medical risk factors of cardiovascular disease such as obesity, smoking and alcohol consumption. More sustained RCTs to present the clinical, economical and humanistic outcomes on long duration of interventions would be recommended.

8. Conflict of interest

The authors report no conflict of interest

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Figure legends

Figure 1 *Flow diagram of study selection process*

Figure 2 *Risk of bias graph: the review authors' judgments about each risk-of-bias item presented as percentages across all included studies.*

Figure 3 Forest plots show the effect of pharmacist intervention on the mean difference in systolic BP (A) and in diastolic BP (B). Mean differences of less than 0 pharmacist and usual care groups show an effect in favour of pharmacist intervention.

Figure 4 Forest plots show the effect of pharmacist intervention on the mean difference in HbA1c. Mean differences of less than 0 pharmacist and usual care groups show an effect in favour of pharmacist intervention.

Figure 5 Forest plots show the effect of pharmacist intervention on the mean difference in Total Cholesterol (A), LDL-C (B), HDL-C (C) and in Triglyceride (D). Mean differences of less than 0 pharmacist and usual care groups show an effect in favour of pharmacist intervention.

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