Effectiveness of Interventions To Enable Hypertension Medication Adherence In Low-And Middle-Income Countries: A Systematic Review And Meta-analysis

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Abstract

Background: In recent decades low- and middle-income countries (LMICs) are witnessing an increase in hypertension and thus becoming a significant public health issue due to associated Cardiovascular disease (CVD) outcomes. Antihypertensive medication adherence is crucial to controlling blood pressure; therefore, this systematic review aimed to evaluate the effectiveness of non-pharmacological interventions on improving blood pressure control and medication adherence in patients with hypertension in LMICs.

Methods: We searched the following databases for relevant literature published between Jan 2005 – Dec 2020: PubMed, EBSCOhost included Academic Search; CINAHL and MEDLINE complete; PubMed; WEB of Science; Cochrane Central Register of Controlled Trials; Cochrane Database of Systematic Reviews and Google Scholar. Cochrane risk of bias tool (RoB 2) was used to appraise included studies critically, and the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) was used to measure the quality of evidence. We conducted a meta-analysis using DrSimonian-Laid's random-effect model at 95% confidence intervals (CIs). The secondary outcomes of interests were synthesised descriptively as changes in BP adherence outcomes.

Results: We identified 14 eligible randomised controlled trials that presented blood pressure (BP) effectiveness and medication adherence among BP patients aged between 18-75 years. The overall quality of evidence with the majority of trials was moderate. Meta weighed effect (SBP) for 12/14 studies was -4.74 (95% CI:-6.07 to -3.47) and $I^2 = 57\%$. Out of 14 eligible studies, (86%) suggested a significant improvement in the proportion of patients with controlled blood pressure (BP < 140/90mmHG) with a positive effect on secondary outcomes such as quality of life.

Conclusion: Non-pharmacological interventions could be effective in managing hypertension. In recommending the need to investigate the feasibility of non-pharmacological evidence in specific LMIC settings, focus should be on an intervention strategy consisting of an educational intervention directed toward the patients, health professionals and organisation. Considering heterogeneity, randomised trials that are well-designed with larger sample sizes are encouraged in LMICs` to help policymakers make well-informed decisions on hypertension management.

Systematic review Registration: PROSPERO registration number: CRD42020172954

Introduction

Hypertension is one of the leading risk factors for CVD worldwide [1–4]. Low- and middle-income countries have seen an increase in hypertension in recent decades, thus, making it a significant public health issue due to the associated adverse health outcomes such as the increased incidence of CVD accounting for 75% of the global deaths in LMICs (82% attributed to coronary heart disease (CHD), stroke and heart failure) [5–8]. Despite some LMICs offering universal access to hypertension medication, including Namibia, adherence to chronic medication remains a problem [6, 9–11]. Recent data shows that CVD in Namibia accounted for 21% of annual deaths and a reported prevalence of blood pressure (BP) among women and men aged 35–64 at between 44–57% [12, 13]. Thus, it would appear that the prevalence of hypertension in Namibia is high compared to the global and African regional prevalence of 22% and 27%, respectively[14]. Non-adherence to antihypertensive medication is common and contributes to poor BP control and adverse health outcomes [15]. While it is substantial to understand the barriers and enablers of non-adherence, it is equally important to explore different interventions' effectiveness on improving BP control and BP medication adherence [15–17].

Non-pharmacological interventions to encourage BP medication adherence include educational interventions directed towards the patients, educational interventions directed towards the health professional, appointment reminder systems/models, and Organisational interventions [10, 18–23]. These Interventions intentionally target non-adherence contributing factors at different levels: patients, health care workers, and the health care system[24, 25]. Many Higher-income countries have conducted extensive research on hypertension effective interventions [26, 27]. However, we cannot say the same about LMICs, especially in sub-Saharan Africa [28].

Due to the scarcity of evidence on effective interventions in LMIC's, thus far has caused a rise in CVD due to non-adherence despite pharmacological efforts [27, 29]. The contradictions around effective interventions for BP continue based on evidence conducted from several reviews such as Cochrane [20]. Henceforth it is essential to systematically review interventions that can effectively be beneficial to LMICs and help inform the feasibility of possible country-specific BP interventions that are effective.

Non-adherence, which usually occurs when BP patients fail to meet treatment goals [20], causes uncontrolled high blood pressure(Systolic blood pressure/SBP; Diastolic blood pressure/DBP) (above 120/80), which increases the risk of severe health problems, including heart attack and stroke [30]. Data regarding BP medication adherence in Namibia is minimal, with one study spanning a sample of public health facilities in the Khomas region (capital region) reporting suboptimal adherence in 2017 [17]. Effective, widely available, low-cost, and sustainable strategies are needed to prevent and manage hypertension [15]. Existing systematic reviews on interventions have recommended that adequate control of hypertension in developing countries could be achievable by community-based programs and by upgrading primary health systems [16, 17, 29]. A critical barrier to scaling up the literature suggests a greater need to identify the optimal and effective way to organise and deliver care to hypertensive patients in LMIC's in order to improve BP medication adherence [19, 20].

Benefits associated with blood pressure lowering include a reduction in many complications such as stroke (35–40%), heart attack (20–25%), and heart failure (over 50%) [22, 23]. Achieving the WHO global target of a 25% relative reduction in the risk of premature mortality from NCDs by 2025 and the SDG target of a one-third reduction in premature deaths from NCDs by 2030 requires hypertension management interventions. Therefore, this systematic review aims to evaluate the effectiveness of non-pharmacological interventions on improving blood pressure control (Primary Outcome) and medication adherence (Secondary Outcome) in patients with hypertension in LMICs. We anticipate that the results from this study will provide current evidence on effective hypertension strategies targeted at controlling hypertension and CVD in LMIC settings.

Methods

A study protocol was developed prior to the conduct of this review. The protocol is registered in the PROSPERO international prospective register of systematic reviews and is accessible via the link below: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020172954. The Centre for Reviews and Dissemination (CRD) guideline for systematic reviews in health care guided this study, following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines[31, 32]. Completed PRISMA checklist (see Additional file 1).

Identifying the research question

The identifying research question was the effectiveness of interventions to enable Hypertension Medication Adherence in LMICs.

Eligibility criteria

A Complete inclusion and exclusion criteria form part of this review protocol, registered with (PROSPERO; CRD42020172954).

We included studies published from 2005 which met the following criteria: Hypertensive patients over 18 years of age and above, regardless of sex and ethnicity with a diagnosis of primary hypertension in a specified geographically defined LMIC setting; randomised controlled trials (RCTs) of hypertensive patients which evaluated non- pharmacological effectiveness of the following interventions to improve BP medication adherence: educational interventions directed to the patient, educational interventions directed to the health professional, self-monitoring, models on appointment reminder systems, organisational interventions aimed at delivery care.

We excluded RCTs` not reporting evidence from LMIC settings published before 2005 and non-randomised controlled trials. Exclusion criteria also included studies reporting on other chronic illnesses, not reporting non-pharmacological effectiveness, and BP medication adherence outcome.

Search strategy for the identification of relevant studies and information sources

After consulting with an information scientist at the Department of Library Services, Faculty of Health Sciences, and the University of KwaZulu-Natal on literature search approaches, search strategies were developed based on the Cochrane Handbook of Intervention Guidelines and the Cochrane Central Register of Control Trials. To find relevant literature, we used the following keywords: hypertension or blood pressure, LMICs, adherence or compliance, control or monitoring, Educational, patient, Self-monitoring, health professional, reminder systems, organizational, delivery care. The Boolean search terms (AND OR) and MeSH terms were employed. A search of the following databases was performed in March 2019 and repeated in December 2020: PubMed, EBSCOhost included Academic Search; CINAHL and MEDLINE complete; PubMed; WEB of Science; Cochrane Central Register of Controlled Trials; Cochrane Database of Systematic Reviews and Google Scholar. Additionally, we searched Grey literature from university dissertations and theses from institutional repositories to retrieve relevant articles. We searched for randomised controlled trials conducted from January 2005 - December 2020 to capture the recent evidence on the effectiveness of hypertension interventions available in LMIC's. There was no language restrictions applied to the search.

The search management

After a rigorous, intensive search, we exported relevant articles to the Endnote X9 library. Following the import of relevant articles by title relevance, we removed duplicates before the abstract screening stage. We then conducted a selection of abstracts and full articles using eligibility criteria utilizing abstract and full title screening forms developed in Google (see Additional file 2) for identified articles and the date of each literature searching of each database. Independent reviewers (ON and PN) did the article screening. The third screener (SN) was involved in resolving discrepancies. Subsequently, we assessed disagreement using Cohen's Kappa coefficient (κ) statistic on Stata 13.0SE (StataCorp College Station, TX, USA (Additional file 3).

Data extraction and quality assessment

We used a data extraction tool developed in Google form based on a checklist provided in the Cochrane handbook for systematic review for intervention. The data extracted related to main study characteristics, including author, setting, type of randomised trial, intervention and control group details, and percentage of patients enrolled in intervention and control groups(see Table 1 at the end of manuscript for full characteristics of the studies). Meta-analysis data extracted included SBP/DBP changes from different non-pharmacological interventions (Additional file 4).

The methodological quality of included studies was assessed using the Cochrane risk of bias tool Current version RoB 2, which include aspects of randomisation process; deviations from intended interventions; missing outcome data; measurement of the outcome; selection of the reported result, and overall bias (reported as Low, Some concerns or High) (Figure 2) [33]. Data extraction and quality assessment were conducted by two reviewers' (ON and SN), and the third author resolved discrepancies through discussions and consensus. The quality of evidence was assessed according to the domains specified in the grading of recommendation, assessment, development, and evaluation (GRADE) guidelines [34].

Data synthesis and analysis

The primary outcome of this study was to determine the effectiveness of interventions to enable hypertension medication adherence in Low-and Middle-Income Countries. Based on the nature of our research question, we synthesised the data by presenting changes in mean systolic blood pressure (SBP) and mean diastolic blood pressure (DBP). Systolic and diastolic blood pressure was analysed and calculated as mean difference (MD) and pooled to produce an overall random effect size between intervention and control groups. Heterogeneity among trials was conducted using the χ^2 test at 95% confidence interval and I^2 statistic value. Forest and funnel plots were presented to show the results for the primary outcome

The secondary outcome aim was to determine hypertension medication adherence between intervention and control groups. We synthesized the data descriptively by showing the proportion of patients with medication adherence between intervention and control groups and effect sizes for medication adherence between the two groups. Medication adherence indicators synthesized include quality of life, and knowledge, beliefs, and retention in clinical care, number of hospitalisations, and cost-effectiveness of interventions. We adopted the definitions used by individual studies for anti-hypertension treatment and adequate control of blood pressure. [35].

Data was captured in Microsoft Excel and analysed in MetaXL version 5.3 (EpiGear International, Sunrise Beach, and Queensland, Australia).

Results

Literature search and study characteristics

The initial database search found 162 906 potentially eligible studies, of which 161 991 were excluded during title screening. Following title screening, 915 met eligibility criteria and were included in full title screening yielding 14 definitive studies and considered for meta-analysis (see Fig. 1 for the whole screening process). The inter-rater reliability score for full-article screening showed 61.34% agreement versus 92.00% expected by chance which constitutes a moderate agreement between the screeners (Kappa statistic = 0. 09 and p-value < 0.05). In addition, McNemar's chi-square statistic suggests that there is no statistically significant difference in the proportions of yes/no answers by reviewers with a p-value > 0.05 (Additional file 3).

All studies included and considered for meta-analysis are from LMICs conducted between 2005–2020 among patients diagnosed with hypertension ranging from 18 to 75 years. Additionally, most studies included parallel randomised controlled trials (n = 13) except one study, a 3-arm randomised trial conducted in a low resource setting in Cape -Town, South Africa. Studies recruited patients mostly from rural settings and low resource settings (n = 7), and five were conducted from government hospitals, including a community pharmacy (n = 1). The main reason for exclusion was non-randomised trials (n = 8), not LMIC's = 14; evaluated other chronic diseases apart from hypertension (n = 23) non-pharmacological (n = 5) and the rest were other reasons with studies which included older patients > 75 years and unclear methodology and outcome (n = 36). All studies included were published in English. Included articles all evaluated Educational intervention towards patients, however (7/14) articles evaluated more than one intervention of which it was either Educational intervention directed towards the health professional(2/14), Appointment reminder systems/models (7/14), or Organisational interventions (2/14). Appointment reminder systems encompassed principles of reminding patients when medicines were ready for collection or about scheduled clinic appointments information (2), organizational intervention aimed at delivery care- home BP monitoring and audit (2). Models on appointment reminder systems-reminder (3) box on taking medication.

The primary care providers were medical and nursing staff, community pharmacists and health workers, family support. Community interventions were delivered in community hospitals, community centres, or patients' homes (see Table 1).

Quality of included studies

Eleven (11) studies were graded to be Low risk, and three as having some concerns. All studies described randomisation methods; however, among the studies with some concerns, two had issues with the randomisation process where allocation sequence and concealment of participants enrolled and assigned to intervention was not indicated. The article with concerns of outcome measurement did not indicate whether the outcome assessment would have been influenced by the intervention received. The rest of the studies did not indicate any concerns with

deviations from intended interventions, missing outcome data, issues with measurement of the outcome, and selection of the reported results (Fig. 2). Overall, the GRADE quality of evidence was moderate (Additional file 10).

Effects of interventions

Primary outcomes (Meta-analysis results)

Data pooled from all 14 studies showed heterogeneity across studies for systolic and diastolic blood pressure. Random effects of meta-analysis results show that systolic blood pressure was reduced by -7.61(-10.47, -4.74), with four exceptions where systolic blood pressure was slightly lower in the intervention group. Heterogeneity across studies was statistically significant ($I^2 = 92\%$, $P = 0.00$) (Fig. 3). The pooled mean difference for diastolic blood pressure was -3.48(-5.52, -1.43). Heterogeneity for DBP was statistically significant ($I^2 = 89\%$, $P = 0.00$) (Fig. 4). When we excluded two studies (Alhalaiqa, 2012 and Mirniam, 2019) SBP random effect was -4.74 (95% CI:-6.07 to -3.47) and $I^2 = 57\%$. (Fig. 5) and DBP (-4.56-1.27) and $I^2 = 78\%$ (Fig. 6). Additional results showing funnel plots are included in the supplementary file material (Additional file 5-8).

Secondary outcome

Proportion (%) of patients with controlled BP (BP < 140/90mmHg)

Secondary outcome results indicating BP adherence outcome measures are presented as the proportion(%) of controlled hypertensive patients with corresponding effect differences between intervention and control group through OR (95% confidence interval). Additional secondary outcomes synthesised include quality of life, level of hypertension knowledge, beliefs on hypertension, retention to care, and the number of hospitalisations (Additional file 9). Out of 14 articles presented in this paper, 12 have shown a significant proportion of patients with controlled blood pressure (BP < 140/90mmHG).

Other secondary outcome results

In addition to the proportion of controlled hypertension reported from all 14 studies, a total number of BP medication adherence indicators from the included studies were synthesized as follows: articles that evaluated the quality of life(7); level of hypertension knowledge (2); beliefs on hypertension (2), retention to care (2); and the number of hospitalisations (2). Some studies reported more than one indicator. Results reporting on the quality of life display better overall health status in the intervention group(s) than those in the control group, similarly, with knowledge and beliefs. An increase in the knowledge level in the intervention groups was reported to modify patients' beliefs about medicines positively. Beliefs about medication in the intervention group have moved away from the view that medications are intrinsically harmful, towards one that recognises the benefits of medication. Retention in care, as well as hospital admissions, also improved. There was no significant difference in mean health care costs per patient between groups.

Discussion

Our systematic review findings reveal that Non-pharmacological interventions are effective in controlling blood pressure. We included studies from the following LMICs: Jordan, South Africa low resource settings, Turkey, India, Argentina, Bangladesh, Pakistan, Sri Lanka, Iran-Isfahan, Pakistan, China, and South Korea. We observed a statistically significant reduction in SBP and DBP among the following interventions: Educational intervention towards patients, Educational intervention directed towards the health professional, Appointment reminder systems/models, and Organisational interventions. Educational interventions directed to the patient and health professional and Organisational interventions showed the high-moderate quality of evidence. These interventions can be pilot tested in LMICs to establish suitable country specific BP strategies in anticipation to help meet Sustainable Development Goal (SDG) target 3.4 by reducing premature mortality from non-communicable diseases (NCDs) by a third by 2030. When we restricted analysis (12/14 studies), effects remained significant with low heterogeneity for SBP and DBP. Secondary outcomes, including quality of life, level of hypertension knowledge, beliefs on hypertension, retention to care, and the number of hospitalisations, showed a significant controlled blood pressure (BP < 140/90mmHG). The aforementioned secondary outcomes are well outlined in the WHO model of hypertension medication adherence as contributing factors of BP medication adherence.

We believe that this is the first study to estimate aggregate BP effects of randomised controlled trials conducted in LMICs only. Studies included in this systematic review were conducted between 2005-2020 from low resource settings providing recent evidence on the effectiveness of BP interventions and medication adherence. The variability in heterogeneity can be observed when two studies (Alhalaiqa, 2012 and Mirniam) are excluded showing a significant reduction in SBP and DBP (Fig. 5 & 6)). These studies had the weakest effect in the intervention groups, which could have been caused by high heterogeneity in random-effect analysis. Overall, we attribute heterogeneity across studies to different study periods, sample sizes, and pooling of multi-component interventions between studies. Though our findings had moderate evidence on average primarily because of inconsistency and publication bias, heterogeneity was expected because it is common in behavioral research [36]. Similar results on heterogeneity have been reported in several studies in High-income countries that evaluated the effectiveness of BP interventions [26, 27]. Considering the current burden on hypertension in LMICs, our results have heightened the need for scaling up interventions to improve hypertension outcomes and meet global SDG in achieving universal health coverage in LMICs [37].

Meta-analysis studies on the effectiveness of BP interventions have been conducted in developed countries [26, 27]. Interventions for hypertension show a more significant effect when administered in combination[36]. In agreement with significant effects of BP interventions when administered in combination is a Cochrane systematic review of 72 randomised trial studies which stated that educational interventions alone were unlikely to be effective[20]. Authors such as Anderson LJ et al. (2020) and Ampofo AG (2020) have stated that education interventions and reminders, including regular follow-ups, were found to be effective at improving patient adherence [38, 39]. Health care workers play an essential role in making sure that these interventions are effective. Results from our study have shown a significant controlled blood pressure among Educational interventions directed to the patient-led by health care workers, especially pharmacists or community health care workers. According to European and Canadian guidelines, Pharmacists should be the standard care of hypertension as they are valuable in team-based care (TBC) [40, 41]. The quality of our study findings was moderate on average, showing the reliability of our results. High-quality evidence was reported in a meta-analysis that evaluated non-pharmacological interventions, which concluded that Dietary Approach to Stop Hypertension (DASH) could be the most effective in hypertension management [27]. The high-quality evidence reported from DASH intervention could have been the result of evaluating more than 20 interventions from both High income and low-income countries included. The geographical settings of HIC and LMICs might have had an influence as well, in comparison to our study, which only focused on LMICs.

Our central findings that non-pharmacological interventions effectively control hypertension could positively impact non-adherence, subsequently reducing CVD's. Patients can get a better understand on hypertension management, which will eventually influence their awareness and behaviour towards BP medication adherence. More so, help clinicians make better decisions in clinical practice. The focus of this review was on RCT, which is the focused gold standard for evidence of the effectiveness of health [42]. In addition to the pooled change in systolic and diastolic blood pressure, the association between intervention and control group warrants health care workers to consider non-pharmacological interventions.

Hypertension management interventions are essential for achieving the global target of a 25% relative reduction in the risk of premature mortality from NCDs by 2025 and the SDG target of one-third reductions in premature deaths from NCDs by 2030. Thus, looking at our findings, non-pharmacological interventions for hypertension adherence could avoid over half of CVD events and complications in LMICs. Future research should focus more on evaluating the feasibility of BP non-pharmacological interventions in a specific LMIC setting. Specific LMIC interventions may enable the development of public policy measures required to establish, improve and upgrade community health services to cope with the increasing burden of chronic diseases [43]. More so, helping to identify the optimal and effective way to organise and deliver care to hypertensive patients in LMIC's [19, 20]

Conclusion

Our study findings conclude that non-pharmacological interventions are effective. Educational interventions directed to the patient and health professional and Organisational interventions could be the most effective in managing hypertension. There is compelling evidence that multi-component interventions delivered by pharmacists or health workers may be the most effective in hypertension management. The present and already stated interventions also positively affect outcomes of BP adherence which include quality of life, level of hypertension knowledge, beliefs, retention to care and number of hospitalisations.. Investigation of the feasibility of this evidence at a country level is necessary for LMIC to provide more reliable and effective interventions covering the country-specific needs having considered her health care system. A multi-component intervention involving patients, health professionals, and the health care system can be considered for future LMICs. Further well-designed randomised trials with larger sample sizes are encouraged to help policymakers make well-informed decisions on hypertension management.

Abbreviations

CVD: Cardio Vascular Diseases

LMICs: low- and Middle-Income Countries

HICs: Higher Income Countries

SBP/DBP: Systolic Blood Pressure/Diastolic Blood Pressure

WHO: World Health Organisation

NCDs: Non Communicable Diseases

BP: Blood Pressure

CHD: Coronary Heart Disease

SDG: Sustainable Development Goals RCT: Randomised Controlled Trials

GRADE: Grading Of Recommendation, Assessment, Development, and Evaluation

TBC: Team-Based Care

DASH: Dietary Approach to Stop Hypertension

UKZN: University of KwaZulu-Natal

Declarations

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Availability of data and materials

All data reported and analysed in this paper was only from the published literature; hence most of the data and study materials are available in the public domain. Other datasets generated and analysed are available in the article and appendix.

Authors' contributions

The study has been conceptualized and designed by ON, BS and TPM-T. The initial draft of the study has been prepared by ON and PN, SN contributed to the abstract screening and full title screening. ON, BS, SJ-N and TPM-T contributed to data analysis. All authors critically reviewed the draft. All authors approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable

There were no human participants

Consent for publication

Not applicable

Declaration of interest

We declare no interest

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Tables

Table 1
Characteristics of included studies

Author, Publication Year	Country, Geographical Setting	Type of RCT & Intervention type, Follow up period(months)	Intervention Group			Control Group		
			Population Details, Age (y)	Sample Size, Gender		Population Details, Age (y)	Sample Size, Gender	
Alhalaiqa,2012	Jordan, 3 government-run hospitals	Parallel group randomised trial Educational intervention directed to the patient- adherence therapy classes; 3 months	BP patients in the intervention group received Adherence Therapy (AT) in addition to Treatment As Usual (TAU). AT included seven one-to- one sessions of AT lasting 20 min over 7 weeks.AT sessions were delivered in the hospital outpatient by trained Field Assistants clinics (25% of all sessions) or at the patient's home (75% of all sessions) depending on the patient preference, ≥ 18 years	68	M = 37% F = 63%	BP patients in the control group received TAU, which consisted of monthly outpatient clinics where BP was measured, medication reviewed, laboratory investigations, and other care was delivered depending on individual needs. Consisted of a clinician-led team of medical and nursing staff based in the outpatient clinic, ≥ 18 years	68	M = 56% F = 44%
Bobrow,2016(A)	South Africa – Cape town, low resource setting	– 3-arm randomised trial(Bobrow A & B Educational intervention directed to the patients- written information about hypertension and healthy living, motivation on collecting and taking medicine Appointment reminder system- when medicines were ready for collection or about scheduled clinic appointments information 12 months	Informational SMS texting: All participants received written information about hypertension and healthy living and continued to receive care from the clinic. Personalized SMS text messages were sent to information-only. Adherence support groups were sent messages to motivate collecting and taking medicines and educating about hypertension and its treatment. Additional reminders were sent when medicines were ready for collection or about scheduled clinic appointments. ≥ 21 years	457	M = 28% F = 72%	Usual care: All participants received written information about hypertension and healthy living and continued to receive care from the clinic, ≥ 21 years	457	M = 28% F = 72%

Author, Publication Year	Country, Geographical Setting	Type of RCT & Intervention type, Follow up period(months)	Intervention Group			Control Group	
			Population Details, Age (y)	Sample Size, Gender		Population Details, Age (y)	Sample Size, Gender
Bobrow,2016(B)	South Africa- Cape town, low resource setting	Educational intervention directed to the patients- written information about hypertension and healthy living, interactive texts on healthy living, motivation on collecting and taking medicine Appointment reminder system- when medicines were ready for collection or about scheduled clinic appointments information 12 months	Interactive SMS texting: All BP participants received written information about hypertension and healthy living and continued to receive care from the clinic. Personalized SMS text messages were sent to interactive message group participants at weekly intervals. Messages were sent to motivate collecting and taking medicines and provide education about hypertension and its treatment. Additional reminders were sent when medicines were ready for collection or about scheduled clinic appointments. Participants allocated to the interactive adherence support received the same messages as the information-only group but could also respond to selected messages using free-to-user "Please-Call-Me" requests, ≥ 21 years	458	M = 28% F = 72%	Usual care: All BP participants received written information about hypertension and healthy living and continued to receive care from the clinic, ≥ 21 years	457 M = 28% F = 72%

Author, Publication Year	Country, Geographical Setting	Type of RCT & Intervention type, Follow up period(months)	Intervention Group			Control Group		
			Population Details, Age (y)	Sample Size, Gender		Population Details, Age (y)	Sample Size, Gender	
Cakir,2006	Turkey, University hospital in Istanbul	- Parallel group randomised trial Educational intervention directed to the patient- comprehensive lifestyle modification including DASH diet, weight reduction, sodium intake, reducing alcohol consumption, increasing physical exercise to a moderate degree, giving up cigarette smoking, and learning stress management. Classes were given by nurses on how to control hypertension to prevent heart diseases and stroke and included core knowledge and information on the behavioural skills necessary to manage hypertension 6 months	BP patients comprehensive lifestyle modification including DASH diet, reduce weight, sodium intake, reduce alcohol consumption, increase physical exercise to a moderate degree, give up cigarette smoking, Moreover, to learn stress management. Classes were given by nurses on how to control hypertension to prevent heart diseases and stroke and included core knowledge and information on the behavioural skills necessary to manage hypertension	30	M = 47% F = 63%	BP patients received usual lifestyles, including dietary and exercise habits, for 6 months	30	M = 40% F = 60%
Calvaho,2006	India-Mysore city, Rural community pharmacies	A parallel randomised controlled trial Educational intervention directed to the patient- education on BP, medication, and lifestyle modifications 3 months	BP patients without comorbidities were provided with education on BP, medication, and lifestyle modifications by a community pharmacist for 3 months, ≥ 18 years	26	M = 53.85% F = 46.15%	BP patients with or without comorbidities were provided with basic education on the correct way to take medication for three months, ≥ 18 years	21	M = 38.1% F = 61.9%

Author, Publication Year	Country, Geographical Setting	Type of RCT & Intervention type, Follow up period(months)	Intervention Group			Control Group		
			Population Details, Age (y)	Sample Size, Gender		Population Details, Age (y)	Sample Size, Gender	
Delavar,2019	Iran-Tehran, Fayyazbakhsh public hospital	Parallel group randomised trial Educational intervention directed to the patient- patients received SME tailored Patient Health Literacy, weekly face-to-face sessions, and telephone-based educational sessions twice weekly. Given educational materials 1 month	Elderly primary BP patients who received SME tailored Patient Health Literacy for 3 months (HL) face to face weekly sessions and telephone-based educational sessions twice weekly. Given educational materials by Four experts(one critical care and three health promotion specialists) Educational materials were related to hypertension definition and its risk factors, complications, medications, medication side effects, medication side effect management, medication adherence importance, and the importance of regular medical visits for blood pressure monitoring. Because of participants' old age and their inadequate HL, the teach-back method was used to provide educational materials in both face-to-face and telephone-based educational sessions, ≥60 years	54	M = 41.6% F = 57.4%	Elderly primary BP patients who received routine care services, including routine medical visits, medical prescriptions, and blood pressure management. ≥60 years	58	M = 55.2% F = 44.8%
He,2017	Argentina, poor urban primary health centres	Parallel group randomised trial Educational intervention directed to the patient-health coaching, physical education Educational intervention directed to the health professionals-physician training program,(online and onsite hypertension management organizational intervention aimed at delivery care-home BP monitoring and audit 18 months	BP patients received an 18-month multi-component intervention program including a community health worker-led home-based intervention (health coaching and home BP monitoring and audit), physical education, BP feedback, and weekly text messaging, ≥21 years.	743	M = 47.4% F = 52.6%	Neither physicians nor community health workers were trained to conduct study interventions. Additionally, participants did not receive home visits, home BP monitors, or text messages. Participants were encouraged to follow the clinical visit schedule of the Remediar + Redes Program, ≥ 21 years	689	M = 46.6% F = 53.4%

Author, Publication Year	Country, Geographical Setting	Type of RCT & Intervention type, Follow up period(months)	Intervention Group			Control Group		
			Population Details, Age (y)	Sample Size, Gender		Population Details, Age (y)	Sample Size, Gender	
Jafar,2020	Bangladesh, Pakistan, and Sri Lanka, rural districts	Parallel group randomised trial Educational intervention directed to the patient-home education Educational intervention directed at the health professional- physician training program on hypertension management Organizational interventions aimed at delivery care- Hypertension triage reception desk and hypertension care coordinator at the government clinics 24 months	BP patients received 24 months of Multi- component intervention: blood- pressure monitoring by physicians and the use of checklists to guide monitoring and referral to physicians. Involvement of Government community health workers to measure blood pressure; home health education by government community health workers. Hypertension triage reception desk and hypertension care coordinator at the government clinics. ,≥40years	1330	M = 34.1% F = 65.9%	BP patients received 24 months of Usual care consisted of existing services in the community, with routine home visits by community health workers for maternal and child care only. The clinics did not have designated triage reception desks or care coordinators for hypertension. ,≥40 years	1315	M = 37.3% F = 62.7%
Miriam,2019	Iran-Isfahan, Al Zahra hospital	Parallel group randomised trial Educational intervention directed to the patient- education on consequences of not taking HTN medication, methods of controlling the disease via appropriate lifestyle changes Models on appointment reminder systems- reminder box on taking medication through family support 3 months	BP patients who received Multifaceted interventions include motivational interviews and 90 minutes of training sessions, a drug reminder box, family support, and 4 phone call follow-ups. The content of the training sessions consisted of the nature and side effects of the disease, the consequences of not taking HTN medication, methods of controlling the disease via appropriate lifestyle changes, and etcetera, The content of the phone calls included question and answer sessions regarding the reinforcement of the content of the training sessions, techniques of strengthening family support, utilization of the medication reminder box, and answers to possible problems of the participants ≥ 18years	36	M = 47.2% F = 52.8%	BP patients who did not receive multifaceted intervention, only usual traditional care, ≥ 18years	36	M = 50.0% F = 50.0%

Author, Publication Year	Country, Geographical Setting	Type of RCT & Intervention type, Follow up period(months)	Intervention Group			Control Group		
			Population Details, Age (y)	Sample Size, Gender		Population Details, Age (y)	Sample Size, Gender	
Ramanath,2012	India –Medicine department of Adichnchanagiri hospital and research centre- B G Nagara, rural population	Parallel group randomised trial Educational intervention directed to the patients -patient counselling, patient information leaflets (PILS) Models on appointment reminder systems- frequent telephonic reminding 7 months	Clinical pharmacist intervention patient counselling, patient information leaflets (PILS), and frequent telephonic reminding. patients were counselled on various aspects such as drugs, lifestyle changes, and their disease management,≥18years	26	M = 61.5% F = 38.5%	Patients were not provided with any counselling and PILS at the baseline and in the first follow- up. However, They were provided with oral instruction and PIL at the end of the second follow- up. ,≥18years	26	M = 80.8% F = 19.2%
Saleem,2015	Pakistan- Northwest Balochistan, Cardiac units of Sandeman Provincial Hospital (SPH) and Bolan Medical Complex Hospital (BMCH) located in Quetta	Parallel group randomised trial Educational intervention directed to the patient- pocket- sized educational book on hypertension, information leaflets, and medication adherence cards 9 months	BP patients Who received pharmaceutical care, consisting of follow-up by the trained hospital pharmacist during 9 months. At each visit, the hospital pharmacist conducted a thorough interview with the patient, identified Problems leading to poor medication adherence and provided patient education. Patients in the IG were also provided with a pocket- sized educational book on hypertension, information leaflets, and medication adherence cards (all in Urdu) during the counseling process,≥18years	193	M = 64.8% F = 35.2%	BP patients who were not provided with pharmaceutical care, no hospital pharmacist involvement. Control patients received the traditional service provided by the hospitals (receiving prescription orders, counselling about medication use, and information about follow- up visits). ,≥18years	192	M = 72.9% F = 27.1%

Author, Publication Year	Country, Geographical Setting	Type of RCT & Intervention type, Follow up period(months)	Intervention Group			Control Group		
			Population Details, Age (y)	Sample Size, Gender		Population Details, Age (y)	Sample Size, Gender	
Zhai,2020	China-Xi'an city Shaanxi province, 8 community health care centres (CHCs)	Parallel group randomised trial Educational intervention directed to the patient- personal consultations by trained pharmacy students on BP medication adherence Models on appointment reminder systems- SMS text messages s regarding patients with poor knowledge on BP adherence and lifestyle modification 3 months	BP patients who receive intervention for 3 months program comprised 2 components. Personal consultations by trained pharmacy students. The second component was SMS text messages s Regarding patients with poor knowledge were given education on BP adherence and lifestyle modification ,≥18years	192	M = 35.4% F = 64.6%	BP patients who received a welcome SMS text message and an end-of-trial SMS text message but they did not receive a personal consultation. ,≥18years	192	M = 35.4% F = 64.6%
Park,2011	South Korea	Parallel group randomised trial Educational intervention directed to the patient- HABA program (health education, individual counselling, and tailored exercise program delivered by trained nurses and exercise program for 12 weeks) 3 months	BP patients who were given HABA program (education counselling delivered by trained nurses and exercise program for 12 weeks) ≥ 65years	18	M = 33.3% F = 66.7%	BP who received Usual care and did not receive HABA ≥ 65years	22	M = 31.8% F = 68.2%

Author, Publication Year	Country, Geographical Setting	Type of RCT & Intervention type, Follow up period(months)	Intervention Group			Control Group		
			Population Details, Age (y)	Sample Size, Gender		Population Details, Age (y)	Sample Size, Gender	
Wang,2011	China- Guangdong province, Shenzhen Second People's Hospital	Parallel group randomised trial Educational intervention directed to the patient- Individual education was performed to inform participants about drug names, indications, strengths, adverse effects, and usage instructions. Pharmacists also introduced accurate BP measurements), medication compliance, healthy lifestyle behaviours 12 months	BP patients were given pharmaceutical care for 12 months. Patients randomized to the intervention group met with clinical pharmacists every 2 months. Individual education was conducted to inform participants about drug names, indications, strengths, adverse effects, and usage instructions. Pharmacists also introduced accurate BP measurements (i.e., body position, arm position, cuff placement, and stethoscope, cuff size), medication compliance, healthy lifestyle behaviours (i.e., vegetarian diet, sodium intake, weight, and physical activity) to patients. ≥18years	29	M = 51.72% F = 48.2%	BP patients were given regular medicare, ≥ 18years	30	M = 46.67% F = 53.33%

Figures

Figure 1

Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow diagram of literature search and study selection process

Study ID	D1	D2	D3	D4	D5	Overall							
Alhalaiqa,2012	+	+	+	+	+	+	+	Low risk					
Bobrow(B),2016	+	+	+	+	+	+	!	Some concerns					
Bobrow,2016	+	+	+	+	+	+	-	High risk					
Cakir,2006	+	+	+	+	+	+							
carvalho,2020	!	+	+	+	+	!	D1	Randomisation process					
Delavar,2019	+	+	+	+	+	+	D2	Deviations from the intended interventions					
He Jiang,2017	+	+	+	+	+	+	D3	Missing outcome data					
Miriam,2019	+	+	+	+	+	+	D4	Measurement of the outcome					
Park,11	!	+	+	+	+	!	D5	Selection of the reported result					
Ramanath,2012	+	+	+	+	+	+							
Saleem,2015	+	+	+	!	+	!							
Wang,2011	+	+	+	+	+	+							
Zhai,2020	+	+	+	+	+	+							

Figure 2

The methodological quality of results

Figure 3

Forest plots of Systolic blood pressure of 14 included studies

Figure 4

Forest plots of Diastolic blood pressure of 14 included studies

Figure 5

Forest plots for Systolic blood pressure after exclusion of two articles

Figure 6

Forest plots for Diastolic blood pressure after exclusion of two articles

Supplementary Files

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