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Correlation of polypill and blood pressure level: A systematic review of clinical trials

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Abstract:

BACKGROUND: High blood pressure (BP) is considered as the most important risk factor for cardiovascular disease (CVD). The main aim of this study was to investigate the effect of polypill on BP by reviewing clinical trial studies.

MATERIALS AND METHODS: In this systematic review study, online databases such as PubMed, Scopus, and Web of Science databases with no limited time were systematically searched until July 10, 2020. Clinical trial studies published in English that examined the effect of polypill on BP were included. BP was the main outcome investigated.

RESULTS: Eleven original articles with a population of 17,042 people were reviewed. The polypill drugs studied in this study had different compounds. Compared to conventional care, treatment with polypill compounds has a positive and significant effect on lowering BP ($P < 0.05$).

CONCLUSION: Our finding confirmed that polypills could reduce BP in patients. It seems that changing routine care and replacing it with a polypill strategy could facilitate the achievement of BP control goals.

Keywords:

Blood pressure, clinical trial, polypill, systematic review

Introduction

Cardiovascular disease (CVD) is one of the most important causes of disability and mortality worldwide.[1,2] It is estimated that 17.9 million people die each year from CVD, accounting for about 31% of all deaths worldwide.[1] Reports indicate that cardiovascular risk factors (such as hypertension, hypercholesterolemia, diabetes, and obesity) are increasing worldwide.[3] Therefore, the incidence of disabilities and deaths due to CVD will increase significantly,[2] so it is estimated that by 2025, 50% of global deaths will be due to CVDs.[4] This disease is defined as a condition in which a person's systolic pressure is >140 mm Hg, and diastolic pressure is >90 mm Hg.[5]

High blood pressure (BP) can lead to heart attack, enlargement of the heart, and eventually heart failure.[6] High BP can also lead to kidney failure, blindness, ruptured blood vessels, and cognitive impairment.[7] High BP in the brain can cause cerebral hemorrhage and small vessel disease leading to stroke, transient ischemic attacks, or dementia.[8] BP control has two main goals: (i) to achieve optimal BP levels and (ii) to reduce cardiovascular events and mortality.[9]

Numerous controlled and double-blind studies have shown that lowering BP prevents strokes, heart attacks, and heart failure.[10] Thiazide diuretics effectively lower BP and are the most common antihypertensive drugs.[10] Due to the

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prescription of various drugs, disease management faces many problems so that only 20% of people follow their treatment completely,[11-13] and a small number of people have controlled BP.[14,15]

Polypill is a combination of drugs in pill form. In other words, the term polypill means that this drug is made of a combination of several elements and substances, which usually have a fixed-dose[16] with proven benefits for the prevention of CVD. A type of polypill that consists of several medicines components and each of which is one of the main factors reducing cardiovascular risk is "multifunctional polypill" or "cardiovascular polypill."[17] Another type is a combination of several low-dose medicines to control a single risk factor (high BP, high blood glucose, or high cholesterol), called single-purpose polyps.[17] These compounds were originally invented to prevent CVD and have since gained considerable acceptance[18,19] in a way that today, these drugs are used to treat chronic diseases.[16] These medicines are also used to prevent or treat pathophysiological conditions.[20]

Polypill reduces the number of pills taken by the patient, so they are helpful for patients.[20] These compounds also increase patients' adherence to drug use.[20,21] Consumption of polypills is also involved in controlling cardiovascular risk factors.[22] Accordingly, a combination of several antihypertensive drugs (polypill) has recently been used as a primary treatment in patients with hypertension.[23]

It has been observed that the use of polypill, which is a combination of several low-dose drugs, reduces dose-dependent side effects compared to the use of one or two higher-dose drugs. Also, these compounds improve adherence to treatment and control of BP.[21] The results of Law *et al.*'s[24] study of combination therapy with low-dose antihypertensive drugs showed a significant reduction in BP. In a study by Patel *et al.*,[25] polypill did not reduce BP.

Purpose of this study

To the best of our knowledge, no general results and no systematic review have been reported regarding the use of polypill drugs and their effect on BP. This systematic review study was conducted to provide a general and unified result regarding the consumption of polypills and their effects.

Materials and Methods

Search strategy and ethics statement

In this systematic review study, Scopus (https://www.scopus.com/), PubMed (https://www.ncbi.nlm.nih.gov/pubmed/), and Web of Science (https://www.webofknowledge.com/) databases were investigated to access related documentation. For this search, we used the keywords "Polypill," "Blood pressure," "Hypertension," "High Blood Pressures," "Diastolic Pressure," "Pulse Pressure," "Systolic Pressure" and their synonyms. There was no time limit for the search, and all published articles were retrieved by July 10, 2020. The main criteria for entering the articles in this structured review were clinical trial studies published in English that examined the effect of polypill on BP. To select studies and extract the data: first, all articles were reviewed by two persons by the titles and the duplicates were removed, then the remaining articles were carefully studied by their titles and abstracts, and articles without inclusion criteria were removed.

Finally, the full text of possible related articles was reviewed, qualified articles were selected, and irrelevant items were removed. Articles were extracted and evaluated by two independent researchers to prevent bias. If articles are not entered, the reason for their rejection is mentioned. In cases of disagreement between the two researchers, the article was reviewed by a third person. In the next step, information about the selected article including the name of the first author, year and place of the study, year of publication of the article, sample size, general characteristics of the samples, design methodology, BP measurement tool, and the results reported in the study were recorded in a pre-designed form. To evaluate the quality of the studies entered in the systematic review in terms of selection bias (production of random sequence and concealment of allocation); execution (blinding of participants and evaluators), diagnosis (blinding of statistical analyst), sample loss (exclusion after randomization) and reporting (selective outcome report) were examined, for this purpose, the Cochrane Collaboration Risk of bias tool was used.[26] The Kermanshah University of Medical Sciences Institutional Re-view Board approved this study and systematic review (IR.KUMS.REC.1399.179).

Results

In this study, the studies performed on the effect of polypill drugs on BP were systematically evaluated according to PRISMA(Preferred Reporting Items for Systematic Reviews and Meta-Analysis) instructions. Based on the initial search in the database, 412 possible related articles were identified and transferred to the information management software (EndNote). Then, of the 412 studies identified, 78 were duplicate studies and were excluded. Of the remaining 434 articles in the competency assessment stage, 365 articles were removed by studying the title and abstract of the article based on inclusion and exclusion criteria due to irrelevance. Also, of the remaining 69 studies, 58 studies were excluded by studying the full

text of the article. In the qualitative evaluation stage, by studying the full text of the article and based on the score obtained from the STROBE checklist, out of the remaining 11 studies, no study was deleted. Finally, 11 articles were entered in the final analysis [Figure 1].

The quality of the articles entered in the systematic review study was evaluated using Cochran's risk of bias tool. In terms of random sequence bias, six studies due to the use of random production software,[25,27] random number table,[19] block randomization,[18] choose a chance card[20,28] were considered for assigning individuals to control or intervention groups with low bias, five studies were in the vague range due to lack of explanation of how randomization was performed.[21,22,29-31] Regarding allocation concealment bias, three studies were evaluated as low bias due to the use of methods such as choosing a chance card by study participants.[18,27,28] Other studies were vague due to a lack of sufficient information to judge.[21,22,25,29-31]

In terms of performance bias, two studies were evaluated using a single capsule for participants with low bias.[27,31] Other studies were in a vague range due to insufficient information to judge.[21,22,28-30] In both studies, both participants and evaluators were unaware of the type of intervention of the study groups.[18,19] Two studies were considered highly biased due to the physician's knowledge of how to assign participants to the intervention group.[20,25]

In terms of detection bias, other studies were considered with a high bias due to the analyst's knowledge about the placement of individuals in the intervention and control groups.[18,19,22,27,28,31] In five studies[18,19,21,27,31] the number and cause of sample loss were reported. In other studies, participants were present from the time of randomization to analyze the results in the study, so they were assessed as low bias in terms of sample fall bias. In the review of reporting bias, by comparing the methodology section and the results of the studies, it seems that all the reviewed articles have all the expected consequences, so they were considered without bias.

Of the 11 studies entered in a systematic review, studies in Mexico[22] (1 case) with a sample size of 572 people and age range >18 years, Canada[31] (1 case) with a sample size of 2,053 people and age range 45–80 years, India[27] (1 case) with a sample size of 518 people and an average age of 57 years, Iran[18] (1 case) with a sample size of 475 people and age range 50–79 years, USA[19,21] (2 cases) with a sample size of 84 people and age range >50 years and a sample size of 303 people

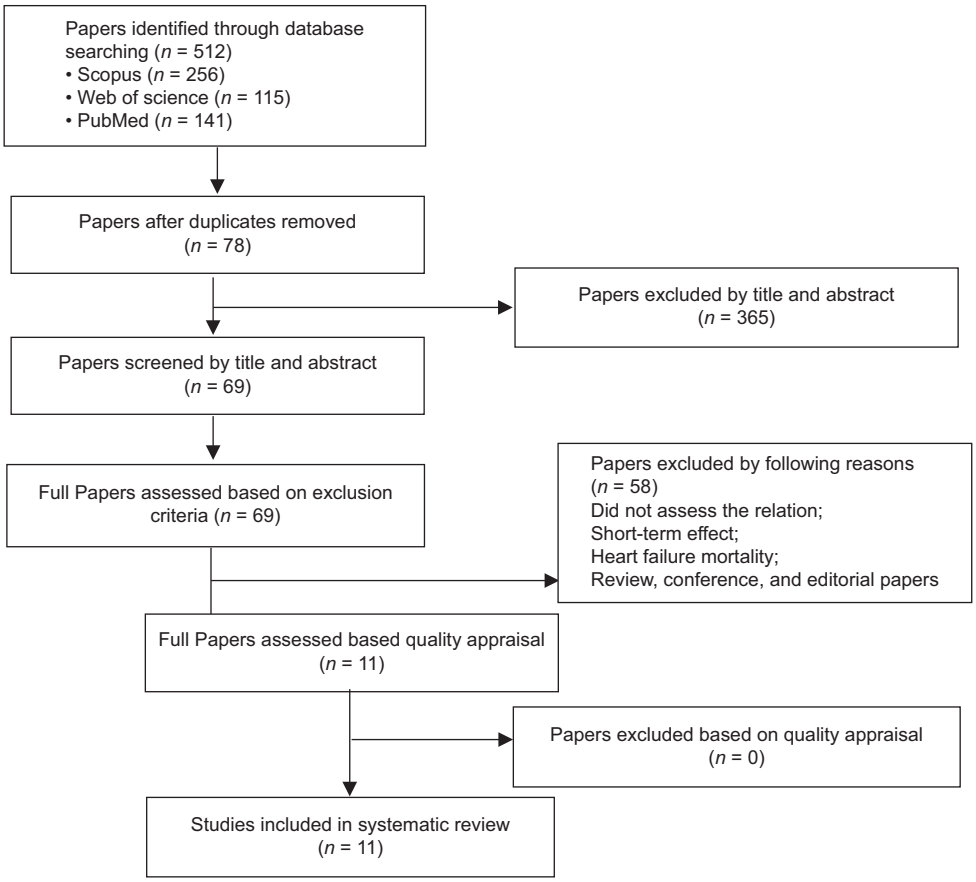

Figure 1: PRISMA flow diagram

and an age range 45–75 years, England[28] (1 case) with a sample size of 303 people and age range 45–75 years, Australia[25] (1 case) with a sample size of 623 people and age range >18 years, Spain[20] (1 case) with a sample size of 695 people and age range >40 years, the Netherlands[29,30] (2 cases) with a sample size of 5,702 people and age range 18–80 years [Table 1].

Articles were published between 2009 and 2019. The total sample size was 17,042 people. To measure BP, the average of two measures of sitting BP was used.[19,21,27-31] In the study of Malekzadeh *et al*.,[18] Standing and sitting BP were measured. In the study of Thom *et al*.[28] and Patel *et al*.,[25] BP was measured with an (Omron705CPII) device. The results of four studies showed that in the polypill treatment group, systolic and diastolic BP was significantly reduced compared to the groups that did not receive antihypertensive drugs ($P < 0.05$).[18,22,27,31]

The results of a study by Wald *et al*.[19] and Lafeber *et al*.[29] showed that polypill reduced BP. In the study conducted by Thom *et al*.[28] and the study of Muñoz *et al*.,[21] the results showed that systolic BP in the intervention group was significantly lower than the control group ($P < 0.001$). In the three studies by Patel *et al*.,[25] Castellano *et al*.,[20] Lafeber *et al*.,[30] there was no significant difference between the routine care group and the polypill group in terms of the effect of treatment on diastolic and systolic BP ($P > 0.05$). The studies reviewed are summarized in Table 1.

Discussion

This systematic review study aimed to evaluate and summarize the results of clinical trials performed on the effect of polypill on BP lowering. According to the Cochrane risk of bias tool criteria, most studies had a suitable methodology. The components and the number of people recruited in these studies were not the same in all clinical trials, which may increase heterogeneity and bias. Due to the heterogeneity in the studies (differences in method and implementation and time of intervention), meta-analysis was not possible. Therefore, the results were reported qualitatively.

High BP is a major global problem associated with an increased risk of coronary heart disease (CHD), stroke, heart failure, and kidney disease.[32] Treatment of hypertension reduces stroke by 30–35% and myocardial infarction by 20%.[33] In addition, other complications of hypertension such as CHD, heart failure, atrial fibrillation, and ventricular arrhythmias are reduced by controlling BP. Therefore, to prevent the complications of major CVD, it is important to identify, treat, and control the rate of BP increase.[34] Patients at risk for CVD use a combination of aspirin, antihypertensive drugs, fat-lowering drugs, and possibly folic acid. By increasing the number of medications, the patient needs, adherence, and success in treatment decrease.[35] In this study, almost all clinical trials had the same duration (>9 months), except for the clinical trials of Wald *et al*.[19] and Yusuf *et al*.,[27] which lasted 3 months and 2 months, respectively. If the duration of the clinical trial is long, the impact of the intervention can be measured and compared in different periods, which increases the accuracy of the results. Based on the results of some studies, there was no statistically significant difference between the polypill drug group and the control group.[20,25,30] This result is due to the high adherence to the usual treatment in the control group.[20] The study by Patel *et al*.[25] failed to use the number of participants it had originally planned and therefore did not have sufficient power to demonstrate a significant reduction in BP and cholesterol.

Most of the articles reviewed in the present study stated that using the polypill drug has a positive and significant effect on reducing diastolic and systolic BP in the intervention group ($P < 0.05$). In other words, the BP of people treated with polypill had a greater decrease than the control group.[18,19,21,22,27-29,31] Based on the results of a meta-analysis, polypill-based therapy significantly improved the achievement of all three ESC targets for control of BP, LDL, and antiplatelet therapy compared with routine care.[36] The results of a study by Roshandel *et al*.[2] showed a significant reduction in systolic BP in the polypill group in 24 months (mean difference −3.05 mm Hg, 95% CI (−4.19 up to −1.91). In a randomized crossover clinical trial, the effect of capsules (containing four antihypertensive drugs) compared with the placebo group was evaluated in 55 patients with a mean age of 58 years. These people had not previously received antihypertensive therapy; the study results showed that in the group receiving four pills, the reduction of systolic BP during 24 h was 19 mm Hg.[37] The results of a study by Eva Lonn *et al*.[38] showed that polypill reduces systolic and diastolic BP by 7.4 and 5.6 mm Hg, respectively. In general, polypills are cost-effective and multipurpose. Maintaining a consistent composition that prevents increasing the dosage of the pill and reducing the risk of side effects are other benefits of these compounds. In general, polypill improves the management of CV risk factors, including BP.[39] This systematic review has limitations. There are few clinical studies in this study. One possible reason is the lack of clinical trials in the field of polypill. The clinical trials in the present systematic review were performed for a relatively short time.

Conclusion

Based on the available clinical trials, polypill reduces BP in patients, and this analysis showed that shifting routine

Table 1: Characteristics of studies

Author/year/place of trial/ type of trial	Participants	Intervention	Duration of study (months)	Outcome
Gómez-Álvarez (2019, Mexico)[22] A multicenter, observational, one cohort	572 patients >18 years with CVD, polypill group (*n*=341), Placebo group (*n*=231)	Polypill group: acetylsalicylic acid 100 mg, ramipril 5/10 mg, simvastatin 40 mg Placebo group: polypill + concomitant antihypertensive treatment	12	Decrease in systolic and diastolic BP In the polypill group compared to placebo group
Yusuf (2009, Canada)[31] a double-blind trial	2,053 people without CVD between 45 and 80 years. Polypill group (*n*=412), Placebo group (*n*=1600)	Polypill group: thiazide (12·5 mg), atenolol (50 mg), ramipril (5 mg), simvastatin (20 mg), aspirin (100 mg) Placebo group: aspirin alone, simvastatin alone, Hydrochlorothiazide alone, three combinations of the two blood-pressure-lowering drugs, three blood-pressure-lowering	March 5, 2007, and August 5, 2008 (10 months)	Decrease in systolic and diastolic BP In the polypill group compared to placebo group
Yusuf (2012, India)[27] randomized clinical trial	518 people with previous vascular disease or diabetes mellitus from 27 centers, Polypill group (*n*=257), Placebo group (*n*=261)	Polypill group: hydrochlorothiazide, 12.5 mg atenolol, 50 mg ramipril, 5 mg) simvastatin (20 mg), aspirin (100 mg) Placebo group: polycap (plus K + supplementation)	2	Decrease in systolic and diastolic BP In the polypill group compared to placebo group
Malekzade (2010, Iran)[18] Double blind placebo controlled parallel group trial	475 participants, 50-79 years, without CVD, hypertension or hyperlipidemia, Polypill: (*n*=241) Placebo (*n*=234)	Polypill group: hydrochlorothiazide 12.5 mg, aspirin 81 mg, enalapril 2.5 mg, and atorvastatin 20 mg Placebo group:	12	Decrease in systolic and diastolic BP In the polypill group compared to placebo group
Wald (2012, United Kingdom)[19] a randomized double-blind placebo-controlled crossover trial	84 people >50 years with no history of CVD, Polypill group (*n*=41) Placebo (*n*=43)	Polypill group: amlodipine 2.5 mg, losartan 25 mg, hydrochlorothiazide 12.5 mg simvastatin 40 mg Placebo group: usual care	3	Decrease in BP In the polypill group compared to placebo group
Thom (2013, England)[28] The UMPIRE trial, a randomized, open-label, blinded-end-point trial	2,004 men and women aged 18 years or older with high cardiovascular risk, defined as either established CVD (history of CHD, ischemic cerebrovascular disease (CVD), or peripheral vascular disease, Polypill group (*n*=1002), Placebo (*n*=1002)	Polypill group: (1) 75 mg aspirin, 40 mg simvastatin, 10 mg lisinopril, and 50 mg atenolol or (2) 75 mg aspirin, 40 mg simvastatin, 10 mg lisinopril, and 12.5 mg hydrochlorothiazide Placebo group: usual care	12	Decrease in systolic BP In the polypill group compared to placebo group
Patel (2015, Australia)[25] a randomized, open-label trial	623 men and women aged ≥18 years at high CVD risk. Polypill group (*n*=311), Placebo (*n*=312)	Polypill group: polypills - version 1 (containing aspirin 75 mg, simvastatin 40 mg, lisinopril 10 mg, atenolol 50 mg) or version 2 (containing aspirin 75 mg, simvastatin 40 mg, lisinopril 10 mg, hydrochlorothiazide 12.5 mg Placebo group: usual care	36	No decrease in systolic and diastolic BP In the polypill group compared to placebo group
Castellano (2014, Spain)[20] The cross-sectional FOCUS study (Phase 1) randomized into a controlled trial (Phase 2)	695 men and women >40 with a history of acute MI in the past 2 years. Polypill group (*n*=350), Placebo (*n*=345)	Polypill group: containing aspirin 100 mg, simvastatin 40 mg, and ramipril 2.5, 5, or 10 mg Placebo group: ASA or ramipril or simvastatin	9	No decrease in systolic and diastolic BP In the polypill group compared to placebo group
Lafeber (2012, the Netherlands)[29] prospective cohort	In total, 5,702 patients aged 18-80 years with CAD, CVD, peripheral arterial occlusion disease (PAOD), abdominal aortic aneurysm (AAA) or, DM2 in the period 1996-2009	Polypill group: aspirin, statin, and ≥1 BP-lowering Polypill group Placebo group: aspirin or statins or β-blockers Placebo	in the period 1996-2009	Decrease in BP In the polypill group compared to placebo group

Contd...

Table 1: Contd...

Author/year/place of trial/ type of trial	Participants	Intervention	Duration of study (months)	Outcome
Lafeber (2012, the Netherlands)[30] prospective cohort	2,706 patient with CAD with a mean age of 60 years	Polypill group: aspirin, statin, and BP-lowering Polypill group Placebo group: absence of combination therapy Placebo	between January 1996 and February 2010	No decrease in systolic and diastolic BP In the polypill group compared to placebo group
Muñoz (2019, United States)[21] a randomized, controlled trial	303 people 45-75 years without CHD, stroke, cancer, liver disease or insulin-dependent, Polypill group (*n*=148), Placebo (*n*=155)	Polypill group: atorvastatin (at a dose of 10 mg), amlodipine (2.5 mg), losartan (25 mg), and hydrochlorothiazide (12.5 mg) Placebo group: usual care	12	Decrease in systolic BP In the polypill group compared to placebo group

care to a polypill strategy could facilitate the achievement of BP control goals.

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Conflicts of interest
There are no conflicts of interest.

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