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COMBINATION THERAPY AS INITIAL TREATMENT FOR HYPERTENSION: A SYSTEMATIC REVIEW

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Abstract

Hypertension is a modifiable risk factor for cardiovascular disease, the leading cause of mortality in the world, and cardiovascular disease is a risk that may be minimized by managing hypertension. Even within the normal range, even a little elevation in blood pressure is associated with an increased risk. More than 70% of persons being treated for primary hypertension will eventually require the use of at least two antihypertensive drugs. Seventy percent or more of persons treated for primary hypertension will require at least two antihypertensive drugs, either initially as combination therapy or as add-on therapy if monotherapy and lifestyle modifications do not offer adequate blood pressure control. Combination therapy for the treatment of hypertension employs four key medication classes: thiazide diuretics, calcium channel blockers, angiotensin-converting enzyme inhibitors (ACEIs), and angiotensin receptor blockers (ARBs). Since 2003, individuals with hypertension have been prescribed two medications. Several people require dual antihypertensive medication treatment, which has been shown to be helpful, particularly for those with blood pressure >160/90 mmHg.

Keyword: *Combination therapy; Hypertension; Initial treatment; Monotherapy; Quadripills*

INTRODUCTION

Hypertension is a modifiable risk factor for cardiovascular disease, which is the world's largest cause of death, and cardiovascular disease is a risk that can be reduced by controlling hypertension. Even while remaining within the normal range, an increased risk is associated with even a little elevated blood pressure. More than seventy percent of adults who are being treated for primary hypertension will ultimately require the use of at least two antihypertensive medications.[1–3]

Angiotensin-converting enzyme inhibitors, but not angiotensin receptor blockers, reduced the incidence of serum creatinine level doubling in patients with diabetes, but had no effect on progression to end-stage renal disease, according to a meta-analysis.[4,5] An additional meta-analysis revealed that angiotensin-converting enzyme inhibitors are superior than angiotensin receptor blockers for lowering mortality from all causes and cardiovascular disease. Initial combination medication improves blood pressure control more rapidly than monotherapy, with comparable tolerability.[2,6]

In a randomized controlled trial, patients who began with monotherapy finally achieved blood pressure management comparable to those who began with combination medication. In 2017, the American College of Cardiology and American Heart Association (ACC / AHA) and in 2018, the European Society of Cardiology (ESC) announced updated hypertension recommendations.[7,8] The American Academy of Family Physicians continues to endorse the 2014 guidelines established by the Eighth Joint National Committee (JNC8).[9]

This study wants to assess the role of combination therapy as initial treatment for hypertension.

METHODS

Protocol

The author complied with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines to ensure that this research was conducted in compliance with the standards cited. This is done to assure the accuracy of the outcomes of this inquiry.

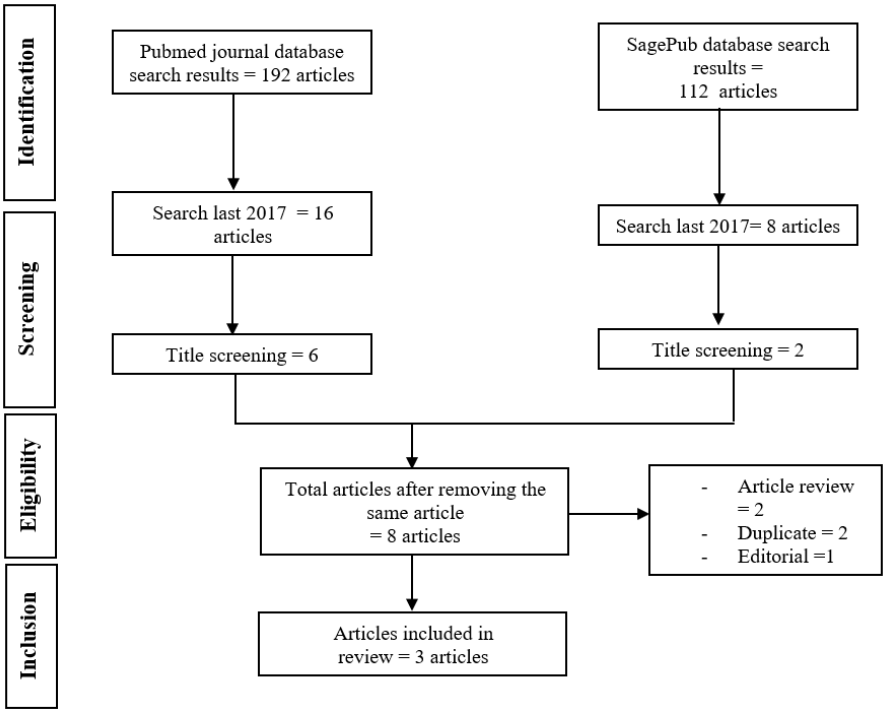

Figure 1. Article search flowchart

Criteria for Eligibility

This literature review seeks to analyze the role of combination therapy as initial treatment for hypertension by examining or analyzing prior research on the topic. The purpose of this article's theme is to demonstrate the significance of the issues highlighted. Researchers who participated in studies satisfied the following requirements: 1) In order to be selected for publication, the paper must be written in English and focus on the function of combination therapy as the initial treatment for hypertension. 2) This evaluation includes articles published after 2017 but before the time period covered by this systematic review. Examples of disallowed research include editorials, submissions without DOI, already published review articles, and entries significantly similar to those previously published in journals.

Search Strategy

We used "combination therapy"; "initial treatment", and "hypertension" as keywords.The search for studies to be included in the systematic review was carried out from February, 18th 2023 using the PubMed and SagePub databases by inputting

the words: *("combined modality therapy"[MeSH Terms] OR ("combined"[All Fields] AND "modality"[All Fields] AND "therapy"[All Fields]) OR "combined modality therapy"[All Fields] OR ("combination"[All Fields] AND "therapy"[All Fields]) OR "combination therapy"[All Fields]) AND ("initial"[All Fields] OR "initially"[All Fields] OR "initials"[All Fields] OR "initiate"[All Fields] OR "initiated"[All Fields] OR "initiates"[All Fields] OR "initiating"[All Fields] OR "initiation"[All Fields] OR "initiations"[All Fields] OR "initiator"[All Fields] OR "initiators"[All Fields]) AND ("therapeutics"[MeSH Terms] OR "therapeutics"[All Fields] OR "treatments"[All Fields] OR "therapy"[MeSH Subheading] OR "therapy"[All Fields] OR "treatment"[All Fields] OR "treatment s"[All Fields]) AND ("hypertense"[All Fields] OR "hypertension"[MeSH Terms] OR "hypertension"[All Fields] OR "hypertension s"[All Fields] OR "hypertensions"[All Fields] OR "hypertensive"[All Fields] OR "hypertensive s"[All Fields] OR "hypertensives"[All Fields])* used in searching the literature.

Data retrieval

After reading the abstract and title of the research, the authors analyzed the studies to determine if they met the inclusion criteria. The authors then select a selection of prior studies to cite as sources for this article. We have arrived at this conclusion after analyzing many studies that all followed the same pattern. All included research must be written in English and must not have been published before to 2017.

In the systematic review, we considered only those studies that satisfied all inclusion criteria. This confines the search to to relevant material. We do not examine any research results that do not meet our established standards. Following this phase is a comprehensive examination of the research. The following information was uncovered throughout the course of the inquiry of this study: names, authors, publication date, location, study activities, and parameters.

Quality Assessment and Data Synthesis

Each author did their own independent analysis of the individual studies supplied in the publication's title and abstract prior to selecting which papers to explore in greater depth. Thereafter, we will analyze all papers that meet the review's inclusion criteria and are suitable for inclusion. Then, based on our findings, we will choose which papers to include in the review. This criterion is used to select manuscripts for review. To simplify the method of selecting papers for review as much as possible. Which previous studies were conducted, and what elements of those investigations make them eligible for inclusion in the review?

RESULT

Chow, et al (2021)[10] conducted a study from June 8, 2017 to Aug 31, 2020 with 300 participants randomly assigned to intervention of initial quadpill treatment, and 291 to control of initial standard dose monotherapy treatment. The mean age of the 591 participants was 59 ± 12 years; 356 (60%) were male; 483 (82%) were White, 70 (12%) were Asian, and 38 (6%) reported as other ethnicity; and baseline mean unattended office blood pressure was 141 ± 13/85 ± 10 mmHg. By 12 weeks, 44 (15%) of 300 participants had additional blood pressure medications in the intervention group compared with 40% participants in the control group.

Systolic blood pressure was lower by 6,9 mm Hg (95% CI = 4,9-8,9; p<0·0001) and blood pressure control rates were higher in the intervention group (76%) versus control group (58%; relative risk [RR] = 1,30, 95% CI = 1,15-1,47; p<0·0001). There was no difference in adverse event-related treatment withdrawals at 12 weeks (intervention 4·0% vs control 2,4%; p = 0·27). Among the 417 patients who continued, uptitration occurred more frequently among control participants than intervention participants (p <0,0001).[10]

Table 1. The litelature include in this study

Author	Origin	Method	Sample Size	Agent Therapy	Result
Chow, 2021[10]	Australia	Multicentre, double-blind, parallel-group, randomised, phase 3 trial	591 untreated patients	Quadpill (containing irbesartan at 37·5 mg, amlodipine at 1·25 mg, indapamide at 0·625 mg, and bisoprolol at 2·5 mg) or an indistinguishable monotherapy control (irbesartan 150 mg)	A strategy with early treatment of a fixed-dose quadruple quarter-dose combination achieved and maintained greater blood pressure lowering compared with the common strategy of starting monotherapy. This trial demonstrated the efficacy, tolerability, and simplicity of a quadpill-based strategy.
McDonald, 2017[11]	United Kigndom	Double-blind, randomized controlled trial	605 untreated patients	Initial monotherapy (losartan 50-100 mg or hydrochlorothiazide 12.5-25 mg crossing over at 8 weeks), or initial combination (losartan 50-100 mg plus hydrochlorothiazide 12.5-25 mg)	Patients whose blood pressure is more than 150/95 mm Hg might be prescribed first combination medication.
Chow, 2017[12]	Australia	Randomised, placebo-controlled, double-blind, crossover trial	55 patients	Quarter-dose (irbesartan 37·5 mg, amlodipine 1·25 mg, hydrochlorothiazide 6·25 mg, and atenolol 12·5 mg)	The results of our modest trial, when placed in the context of existing randomised research, imply that the effects of quarter-dose treatment may be cumulative across classes and may give a drop in blood pressure that is clinically significant.

However, at 52 weeks mean unattended systolic blood pressure remained lower by 7,7 mm Hg (95% CI = 5,2-10,3) and blood pressure control rates higher in the intervention group (81%) versus control group (62%; RR 1,32, 95% CI = 1,16-1,50). In all randomly assigned participants up to 12 weeks, there were seven (3%) serious adverse events in the intervention group and three (1%) serious adverse events in the control group.[10]

Other study showed home systolic blood pressure dropped 4.9 mm Hg (range: 3.7–6.0 mm Hg) less over 32 weeks with initial monotherapy than with initial combination therapy (P0.001), but it caught up at 32 weeks (difference: 1.2 mm Hg [range: -0.4–2.8 mm Hg], P=0.13). In phase 1, the response of home systolic blood pressure to each monotherapy was very different between the three levels of renin. In contrast, the response to combination therapy was uniform and at least 5 mm Hg higher than the response to monotherapy. There was no difference in the number of withdrawals due to bad things happening.[11]

The placebo-corrected decrease in systolic blood pressure over 24 hours with the quadpill was 19 mm Hg (95% CI = 14-23), and office blood pressure was lowered by 22/13 mm Hg ($p < 0.001$). After quadpill therapy, 100% individuals attained office blood pressure below 140/90 mm Hg, compared to 33% participants during placebo treatment ($p = 0.0013$). There were no major adverse reactions, and all patients said that the quadpill was simple to swallow. They systematic evaluation found 36 trials (n = 4721 individuals) of one medication at a quarter-dose against placebo and six studies (n = 312) of two medicines at a quarter-dose versus placebo. The pooled placebo-corrected blood pressure-lowering effects were 5/2 mm Hg and 7/5 mm Hg, respectively (both $p < 0.0001$), and there were no adverse events associated with either regimen.[12]

DISCUSSION

Seventy percent or more of individuals treated for primary hypertension will eventually require at least two antihypertensive medications, either initially as combination therapy or as add-on therapy if monotherapy and lifestyle adjustments do not provide acceptable blood pressure control. In combination therapy for the treatment of hypertension, four major groups of drugs are employed: thiazide diuretics, calcium channel blockers, angiotensin-converting enzyme inhibitors (ACEIs), and angiotensin receptor blockers (ARBs).[10,13] Aspects of the pharmacoepidemiology of combination antihypertensive medication have been published in a number of studies that differ substantially from the present investigation.[14]

Quadpill approach is straightforward and efficient, according to the Chow study. Most intervention participants in this trial only need the quadpill to achieve blood pressure management. The control group began treatment with a standard dose of a widely prescribed, well-tolerated medicine, and uptitration was applied per recommended practice at each visit. Even though the control group saw uptitration more frequently than the intervention group did, blood pressure was not managed as well in the control group at either the 12-week or one-year mark. Between 12 weeks and 12 months, there was no apparent difference between the two groups, which might indicate lingering treatment inertia.[10]

Insufficient control with monotherapy is the clearest signal for adding a second medicine, which can be done either before or after titrating the initial agent to its maximum dose. If a patient does not obtain appropriate control with a modest initial dose of a single drug, it is reasonable to titrate or add a second agent. Initiating a second drug before titrating the first may result in a greater blood pressure drop than raising the first agent's dosage. Response to initial monotherapy varies greatly with plasma renin levels, therefore a second mode of action may be more suitable than raising the dosage of a somewhat unsuccessful first medication to address the patient's specific physiology.[9,12]

It is necessary for many individuals to take numerous medications that decrease blood pressure in order to attain their desired blood pressure levels, and the practice of beginning treatment with combination blood pressure lowering therapy is being more researched and encouraged. Combinations of blood pressure medications that decrease blood pressure at a low dose give more effective blood pressure reduction while also causing fewer unwanted effects.[15]

Recent developments include the addition of four dual combinations to the Essential Medicines List of the WHO, the completion of a triple half-dose combination trial as well as a pilot of a quadruple quarter-dose combination, and recent cardiovascular polypill trials have included two blood pressure lowering medications at low doses. All of these trials showed that low-dose combination treatment with a lower overall dosage was superior in terms of obtaining the desired blood pressure levels.[15]

The use of low-dose combination therapy as a first treatment for hypertension is an intriguing possibility that shows promise in terms of both its safety and its efficacy. Larger studies of triple and quadruple low-dose combination therapy are currently being conducted in different places, and these trials should give greater proof of the medication's effectiveness as well as information on the adverse effect profile.[15]

Since 2003, the usage of combination antihypertensive medications as first treatment has grown. Initial combination medication increases the average drop in blood pressure and achieves blood pressure control more quickly than monotherapy, with comparable tolerability.[14,16] Yet, individuals who begin with monotherapy ultimately achieve comparable blood pressure management to those who began with combination medication. There have been no

randomized controlled trials demonstrating a reduction in cardiac risk with first combination treatment, while some observational data have demonstrated a reduction in risk.[16,17]

Therapeutic inertia may explain why a considerable percentage of patients are not switched to combination treatment following monotherapy titration, as suggested by recommendations. In addition, therapeutic escalation delays of even a few months are linked with an increased risk of cardiac events or death (hazard ratio = 1.1). Regarding the lowest blood pressure that indicates the necessity for beginning combination treatment, experts differ. In patients with systolic blood pressure more than 160 mm Hg or larger than 20 mm Hg over target, or with diastolic blood pressure greater than 100 mm Hg or greater than 10 mm Hg above goal, there is consensus that initial combination treatment is safer and more successful than monotherapy.[18,19]

If necessary, therapy should be escalated within one month, regardless of the chosen treatment plan, in order to attain the goal blood pressure. Guidelines propose adding a third drug to dual treatment for individuals whose blood pressure is not controlled. In randomized controlled studies, individuals utilizing a combination of an angiotensin receptor blocker (ARB), calcium channel blocker (CCB), and thiazide diuretic had considerably better blood pressure management than those on a dual regimen of an ARB and a CCB.[20,21]

A new meta-analysis reveals that the addition of a third drug to dual therapy is more successful at reducing blood pressure than increasing doses of dual therapy, while posing no increased risk. Due to the dearth of mortality data from randomized controlled trials, it is fair to either titrate individual medications to maximal doses before adding an additional agent, or to administer an additional agent before the present agent reaches its highest dosage.[20,21] JNC8, ESC, and ACC/AHA recommendations concur that combination treatment should comprise a thiazide diuretic, a CCB, and an angiotensin-converting enzyme inhibitor (ACEI) or an angiotensin receptor blocker (ARB) for the majority of patients.

In addition, they concur that a patient should not take an ACEI and an ARB at the same time.[8,21] Randomized controlled trials (RCTs) have demonstrated that triple combinations of amlodipine / valsartan / hydrochlorothiazide, amlodipine / olmesartan / hydrochlorothiazide, and amlodipine / telmisartan / hydrochlorothiazide produce greater BP reductions, with a greater proportion of patients achieving BP control compared to dual therapies. Further data suggests that triple-combination treatment is effective for moderate to severe hypertension, resulting in a significant drop in BP over dual regimens.[22]

Both randomized controlled trials and post-marketing observational studies have demonstrated consistent and similar effectiveness in the general population and high-risk subsets of hypertension patients. Triple treatments are typically well tolerated, with profiles of side events comparable to those of dual therapy. Moreover, FDC administered as a single pill increase patient adherence, resulting in improved long-term blood pressure management. Depending on area conditions, they may also be economical. Consequently, single-pill triple combinations of distinct types of medications with complimentary modes of action increase the efficacy and adherence of therapy for patients.[22]

Activation of complementary pathophysiological pathways is required for successful BP reduction during combination therapy, while distinct medications can activate a similar mechanism of action more efficiently. Because the effects of each medication are mutually counterbalanced, the risk of adverse events during combination therapy may be decreased. Nevertheless, substantial BP reduction irrespective of the applied combination is related with an increase in treatment dropout.[23]

In the treatment of hypertension refractory to triple (diuretic-based) therapy, a fourth-line drug is only successful in controlling hypertension in 50% of patients. Nowadays, it is debatable whether combination therapy should replace monotherapy in newly-diagnosed hypertensive patients without significant BP increase or minimal cardiovascular risk. Each selection between free and fixed-dose combination therapy should be based on clinical factors.[23]

CONCLUSION

Initiation of dual drug use in patients with hypertension has been started since 2003. Many patients require dual antihypertensive drug therapy and this has proven effective, especially for those with blood pressure >160/90 mmHg.

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