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Short Communication

Single-Pill Combination versus Single-Agent Pills Treatment in Patients with Hypertension: An Overview of Reviews

***Corresponding author**
Reem A. Mustafa, Department of Internal Medicine, Division of Nephrology and Hypertension, University of Kansas Medical Center, Kansas City, Kansas, United States, Tel: 913–588–6048

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Abdallah El Alayli[1], Romina Brignardello-Petersen[2], Sara Jdiaa[3], Veena Manja[4,5], Razan Mansour[1], Paul K. Whelton[6], Brian Rayner[7], Nizal Sarrafzadegan[8,9], Andrew E. Moran[10,11], Akram Al-Makki[12], Velma Irazola[13], Unab I. Khan[24], Patricio Lopez-Jaramillo[14], Jing Yu[15], Hind Beheiry[16], Kenneth Connell[17], Marie Therese Cooney[18], Donald DiPette[19], Nnenna Ezeigwe[20], Thomas Andrew Gaziano[21], Agaba Gidio[22], Taskeen Khan[23], Vindya Kumarapeli[25], K. Srinath Reddy[26], M. Hassan Murad[27] and Reem A. Mustafa[1]*

[1]Department of Internal Medicine, Outcomes and Implementation Research Unit, University of Kansas Medical Center, USA

[2]Department of Health Research Methods, Evidence, and Impact, University of McMaster, Canada

[3]Department of Nephrology, University of Toronto, Canada

[4]Department of Surgery, University of California Davis, USA

[5]Department of Medicine, Department of Veterans Affairs, Northern California Health Care System, USA

[6]Department of Epidemiology School of Public Health and Tropical Medicine, University of Tulane, USA

[7]Division of Nephrology and Hypertension, Groote Schuur Hospital and University of Cape Town, South Africa

[8]Isfahan Cardiovascular Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Iran

[9]School of Population and Public Health, Faculty of Medicine, University of British Columbia, Canada

[10]Global Hypertension Control, Resolve to Save Lives, an initiative of Vital Strategies, USA.

[11]Division of General Medicine, Columbia University Irving Medical Centre, USA

[12]Indiana University Health Arnett, Lafayette, IN, USA

[13]Institute for Clinical Effectiveness and Health Policy, Buenos Aires, Argentina; South American Center of Excellence for Cardiovascular Health, Buenos Aires, Argentina

[14]Masira Research Institute, Medical School, Universidad de Santander, Colombia

[15]Hypertension Center, Department of Cardiology, Lanzhou University Second Hospital, China

[16]Faculty of Nursing Sciences, International University of Africa (IUA), Sudan

[17]Faculty of Medical Sciences, the University of the West Indies, Barbados

[18]Department of Cardiology, Adelaide Meath Hospital, Ireland

[19]Department Of Medicine, University Of South Carolina School of Medicine, USA

[20]Federal Ministry of Health, Nigeria

[21]Harvard Medical School, Boston, MA, USA; Brigham and Women's Hospital, USA

[22]Mulago National Referral Hospital Kampala Uganda

[23]Department of Non-Communicable Diseases, World Health Organization, Switzerland

[24]Department of Family Medicine, University of the Aga Khan, Pakistan

[25]Non-Communicable Disease Bureau, Ministry of Health, Sri Lanka

[26]Public Health Foundation of India, India

[27]Evidence-based Practice Center, Kern Center for the Science of Health Care Delivery, Mayo Clinic, USA

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Abstract

Introduction: Treatment with a single-pill combination (SPC) as compared to two or more single-agent pill (SAP) antihypertensive agents reduces pill burden potentially improving outcomes in patients with hypertension.

Aim: This overview of reviews summarized the evidence from systematic reviews (SRs) comparing SPC and SAP antihypertensive therapy to support the development of the World Health Organization guideline.

Methods: We searched Medline, Embase, and the Cochrane databases from January 1st, 2015, through May 29th, 2020, to identify SRs comparing SPC to SAP antihypertensive therapy. We screened eligible reviews and abstracted data, in duplicate. We assessed the quality of the reviews using the Assessing the Methodological Quality of Systematic Reviews (AMSTAR) tool and the certainty of the evidence using the Grading of Recommendations Assessments, Development, and Evaluation (GRADE) approach.

Results: We screened 3,229 records and included three SRs that summarized data from 31 studies. Antihypertensive pharmacotherapy with SPCs as compared to SAPs increased adherence to treatment as assessed by a medicine possession ratio (MPR) >0.8 (odds ratio [OR] 1.47, 95% confidence interval [CI] 1.23 to 1.74, and by the proportion of days covered (PDC) >0.80 (OR 2.25, 95% CI 1.09 to 4.64), increased treatment-related adverse events (risk ratio [RR] 1.13 (95%CI 0.85 to 1.50), and improved BP control (RR 1.11 (95%CI 0.92 to 1.33), all with low certainty. There was no evidence for other important patient outcomes.

Conclusion: While adherence and blood pressure control to antihypertensive medications may be better in patients treated with SPCs compared with SAPs, treatment-related adverse events may increase.

INTRODUCTION

Hypertension affects more than 1.4 billion adults worldwide [1]. Uncontrolled hypertension is the most common preventable risk factor for cardiovascular diseases (CVD) and can lead to heart failure, myocardial infarction, stroke, end stage kidney disease, and premature death [2-5]. although the effect of blood pressure (BP) control on preventing these complications is well established, achieving optimum BP control in most patients with hypertension is still challenging. One systematic analysis of population-based studies revealed that only 20% of patients with hypertension have good control of their blood pressure (BP) [1]. Additionally, sub-optimal adherence to treatment is associated with treatment failure and increased economic burden due to disease complications [6-9].

Pharmacological therapy of hypertension can be initiated as a monotherapy, with subsequent escalation to a combination of two or more medications if BP goals are not achieved. It is estimated that most patients with hypertension require combination therapy with two or more medications to reach their target for BP control [10]. Combination therapy can be administered in two forms; either as a single-pill combination (SPC) of multiple medications or as two or more drugs prescribed as a single-agent pill (SAP) combination. It is unclear whether single pill combinations of hypertensive agents provide greater benefit than the corresponding combination medications given separately. Retrospective observational studies suggest that SPC improves adherence to therapy potentially due to the decreased pill burden and simplicity of treatment [11, 12].

The European Society of Cardiology/European Society of Hypertension (ESC/ESH) recommends the initiation of treatment using a combination therapy (preferably using an SPC) in all patients with BP >140/90 mm Hg, with the exception of adults who are 65 years or older and those with stage 1 hypertension (SBP 140-150 mm Hg) who are at low risk of CVD [13]. The American College of Cardiology/ American Heart Association (ACC/AHA) encourages the use of combination antihypertensive drug therapy and specifically recommends the initiation of treatment using combination therapy with either an SPC or SAP in patients with BP ≥ 140/90 mm Hg who have a BP 20/10 mm Hg higher than their target BP, and in all black adults with hypertension [14].

The World Health Organization added multiple SPCs for hypertension treatment in the list of essential medicines [15]. In line with guideline treatment recommendations, the included SPCs consist of a combination of angiotensin-converting enzyme inhibitor (ACEI) or an angiotensin receptor blocker (ARB) and a calcium channel blocker (CCB) and/or a thiazide/thiazide-like diuretic (e.g. lisinopril or telmisartan with either amlodipine or hydrochlorothiazide).

In this overview of reviews, we summarize the evidence from published systematic reviews on the comparative outcomes of antihypertensive pharmacotherapy with SPCs and SAPs that was used to inform the World Health Organization Guideline for pharmacological treatment of hypertension in adults [16,17]. Long-term comparisons of monotherapy versus combination therapy, with hard clinical outcomes, was identified as one of several research gaps by the WHO Guideline Development Group (GDG).

METHODS

This overview was developed using a pre-specified registered protocol (PROSPERO ID: CRD42020203259) [18].

Eligibility criteria

Based on predetermined eligibility criteria, the review team included systematic reviews of observational studies and randomized clinical trials reporting on clinically important patient outcomes. The review was restricted to comparisons of an SPC with its corresponding SAP. Other comparisons such as SPC compared to monotherapy or a combination of medications other than the ones used in the SPC were excluded.

Reviewers excluded systematic reviews that targeted patients with secondary or drug induced hypertension, acute CVD events (e.g., myocardial infarction (MI) or stroke), end stage kidney disease on dialysis, organ transplant, pregnancy or breastfeeding, perioperative patients or patients being treated for hypertensive emergency or urgency.

Information source

An experienced information technologist conducted a search of English language publications identified in Ovid Medline, Ovid Embase, or the Cochrane Database of systematic reviews between January 1st, 2015 and May 29th, 2020. The search included a combination of key terms to capture all reports on hypertension management and filters to limit the results to systematic reviews and meta-analysis, health technology assessments and to capture studies targeting human subjects. The full search strategy can be found in the data supplement.

Study selection and data collection process

Reviewers (AE and RBP) assessed the eligibility of the systematic reviews identified and abstracted the following data from the included studies; population (general or specific), medications in the SPCs, medications in the SAPs, outcomes reported, types of studies included, and the date of the last search.

Quality and risk of bias assessment

The included systematic reviews were categorized as low, moderate or high quality using the Assessment of the methodological quality of systematic reviews (AMSTAR) tool [19]. In addition, we abstracted information to assess the risk of bias of the studies included in the systematic reviews.

Population

The population of interest was adult patients receiving hypertension treatment. Additional subgroups of interest include patients stratified by their estimated risk of CVD, age, sex, race/ethnicity, level of baseline BP, presence of pre-existing CVD, stroke, chronic kidney disease, and diabetes mellitus. [Table 1]

Outcomes

A predetermined outcomes list included: Death (all-cause mortality), major cardiovascular events, cardiovascular-related death (death from MI, sudden cardiac death, or stroke), stroke, myocardial infarction, end stage renal disease, dementia, heart failure events, adverse effects, patient satisfaction, medication adherence, BP control, BP level/change, and the number of antihypertensive medications. [Table 1].

Effect measures

The review team summarized all reported comparative outcomes comparing SPC to SAP. We abstracted the following effect estimates with their 95% confidence intervals (95%CI) in keeping with the statistical analysis tool in which they were reported in the respective systematic reviews; hazard ratio (HR), relative risk (RR), odds ratio (OR) for dichotomous outcomes and mean difference (MD) for continuous outcomes.

Adherence was measured by use of either medicine possession ratio (MPR), defined as the sum of the days' supply for all fills of a given drug in a particular time period divided by the number of days in the time period expressed as a percentage or the proportion of days covered (PDC), defined as ratio of number of days the patient is covered by the medication to the total number of days in the period expressed as a percentage. Both methods were calculated as the mean difference (MD) in days between both study arms and as an odds ratio (OR) in which a patient was considered adherent if he/she had an MPR or PDC >0.80. Treatment persistence was measured based on the prescription refill intervals. BP control was assessed as number of patients achieving BP target at the end of the trial.

Certainty of the evidence

The Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach [20] was used to assess the certainty in the evidence (also defined as confidence in the effect estimate). Based on this approach, the certainty level can be categorized as high, moderate, low or very low quality. By default, evidence from randomized clinical trials is considered high quality but the rating can be downgraded if risk of bias [21], indirectness [23], inconsistency [23], imprecision [24] and/or publication bias [25] exist. While evidence from observational studies is considered low quality, it can be downgraded for the same reasons or upgraded if there is a large magnitude of effect, residual cofounding after ruling out other cofounders, or dose-response gradient.

RESULTS

After screening 3,229 records, three relevant systematic reviews were identified that summarized the evidence from 31 studies [26-28]. These reviews compared SPC with equivalent SAP. [Figure 1] One systematic review included only randomized clinical trials and reported on adverse events, BP control, and mean systolic BP (SBP) [28]. Another systematic review included 20 observational studies and reported on adherence and treatment persistence [27], while the third review included all types of studies and reported on treatment persistence only [26] [Table 2].

Four additional reviews reported on SPC but were excluded for the following reasons; one summarized the results narratively [29],one was only published as an abstract [30],and two reported only on a specific combination and did not provide sufficient details in the methods and results sections [31,32].

Adherence

One systematic review reported on adherence in observational studies. Low certainty evidence suggested that SPC compared to SAP therapy may increase medication adherence, based on MPR >0.80 (OR 1.47, 95%CI 1.23 to 1.74), and PDC >0.80 (OR 2.25, 95%CI 1.09 to 4.64). [Table 3] It also reported that patients with SPC had a higher mean difference in MPR (MD 13.2 days higher, 95%CI 8.9 to 17.2)) and PDC (MD 29 days higher, 27.8 to 30.2) than patients treated with SAP. All the studies included were observational studies, thus the certainty of the evidence was low [27] [Table 3].

Table 1: PICO components

Population	Intervention	Comparison	Outcomes	Subgroup
Adult men and women with hypertension requiring pharmacological intervention	Single pill combination of antihypertensive drugs – 5 classes (any 2 or more from the 5)	Single agent pill	- Death (all-cause mortality) - Cardiovascular death (death from MI sudden cardiac death or stroke) - Stroke - Myocardial infarction - End stage renal disease - Heart failure events. - Adverse effects - Patient satisfaction - Adherence - Blood pressure level/change - Number of anti-hypertensive medications	Based on different effect modifiers such as: - Estimated cardiovascular risk (pre-existing CAD) - Stroke - Diabetes - Age - Sex - Chronic kidney disease - Race/ethnicity - level of baseline blood pressure

Table 2: Included systematic reviews characteristics

	Population		Intervention	Comparison	Outcomes reported					Studies	DS	Databases				T1	RoB	FP
	General	Special			AD	Pe	AE	BP	SY			MD	EM	Co	O			
Du 2018[26]	Yes	No	SPC	SAP	Yes	Yes				OS	June 2017	x	x			x	x	x
Kawalec 2016[27]	Yes	No	SPC	SAP	Yes	Yes	Yes	Yes	Yes	Any design	April 2015	x		x		x	x	x
Mallat 2016[28]	Yes	No	SPC	SAP	Yes		Yes	Yes		RCTs	May 2015	x	x	x	X	x	x	x

G: General (adults with hypertension), **AD**: adherence, **Pe**: Persistence, **AE**: adverse events, **BP**: blood pressure control, **SY**: safety, **MD**: Medline, **EM**: embase, **Co**: Cochrane, **O**: other, **DS**: date of last search, **T1**: table 1, **RoB**: risk of bias tool, **FP**: forest plots, **SPC**: single pill combination, **SAP**: single agent pill, **NR**: Not reported, **OS**: observational studies, **RCTs**: randomized clinical trials, **NA**: not applicable, **NR**: not reported

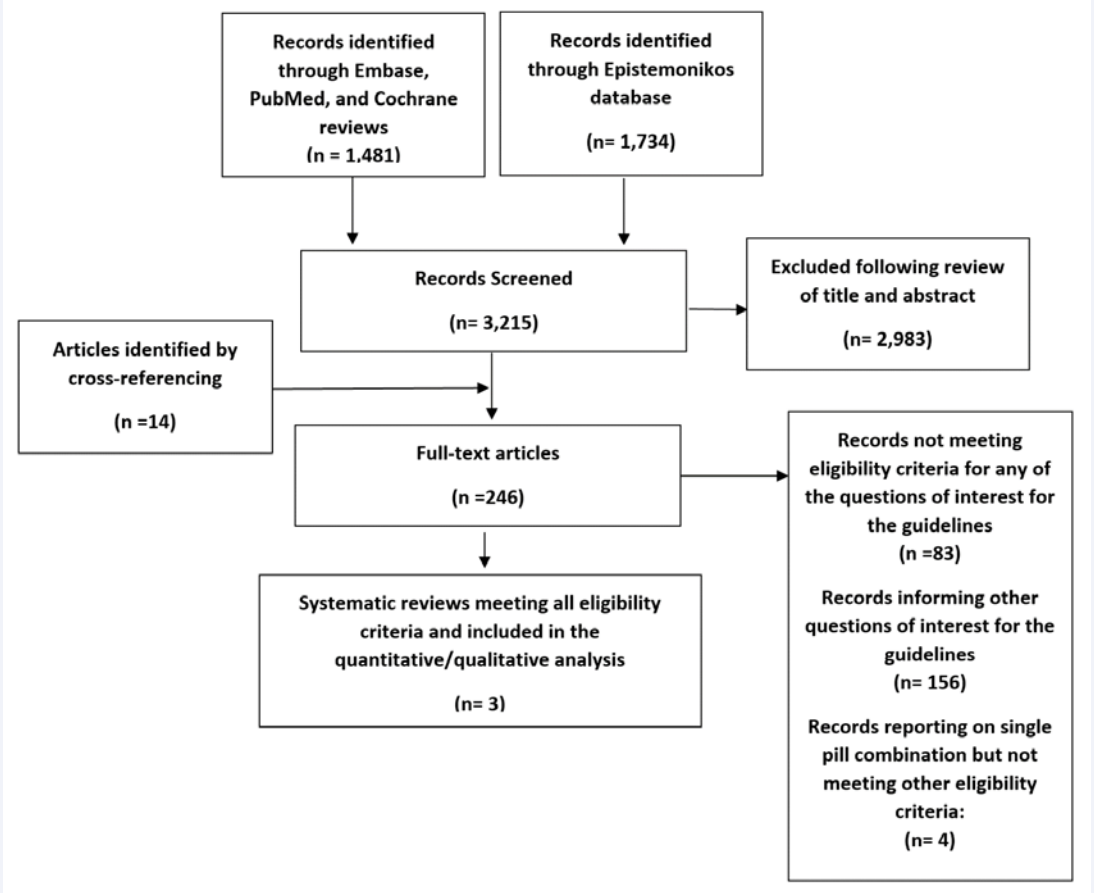

Figure 1 Flow Diagram.

Table 3: Summary of findings

Single pill combination compared to single agent pill in patients with hypertension					
Outcomes	**Anticipated absolute effects* (95% CI)**		**Relative effect (95% CI)**	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**
	Risk with no single pill combination	**Risk with single-pill combination**			
Adverse events assessed with: Mallat 2016 follow up: range 4 weeks to 4 months	408 per 1,000	461 per 1,000 (347 to 612)	RR 1.13 (0.85 to 1.50)	249 (4 RCTs)	⊕⊕◯◯ LOW [a,b]
Blood pressure control (number of patients achieving BP target at the end of the trial) assessed with: Mallat 2016 follow up: range 4 weeks to 12 weeks	731 per 1,000	811 per 1,000 (672 to 972)	RR 1.11 (0.92 to 1.33)	103 (3 RCTs)	⊕⊕◯◯ LOW [a,b]
Mean systolic blood pressure assessed with: Mallat 2016 follow up: range 4 weeks to 4 months	The mean systolic blood pressure was 0 mmHg	MD 0.81 mmHg lower (3.25 lower to 1.64 higher)	-	124 (3 RCTs)	⊕⊕⊕◯ MODERATE [a,c]
Adherence Medicine possession ratio (MPR): the number of days of medication supply within the prescription refill interval. A patient is adherent if MPR >0.8) assessed with: Kawalec 2018 follow up: range 6 months to 13 months	406 per 1,000	501 per 1,000 (456 to 543)	OR 1.47 (1.23 to 1.74)	2767 (2 observational studies)	⊕⊕◯◯ LOW [d]
Adherence MPR mean difference assessed with: Kawalec 2018 follow up: range 6 months to 5 years	0 days	MD 13.2 days higher (8.9 higher to 17.2 higher)	-	590294 (4 observational studies)	⊕⊕◯◯ LOW [d,f]
Adherence (Proportion of days covered (PDC): the percentage of days during which a medication was taken by patients, on the basis of the proportion of days covered. A patient is adherent if PDC>0.80) assessed with: Kawalec 2018 follow up: median 12 months	232 per 1,000	404 per 1,000 (247 to 583)	OR 2.25 (1.09 to 4.64)	17137 (2 observational studies)	⊕⊕◯◯ LOW [d,e]
Adherence PDC mean difference assessed with: Kawalec 2018 follow up: mean 12 months	0 days	MD 29 days higher (27.8 higher to 30.2 higher)	-	12612 (1 observational study)	⊕⊕◯◯ LOW [d]
Medication persistence (based on prescription refill interval) assessed with: Kawalec 2018 follow up: 6 months	407 per 1,000	724 per 1,000 (451 to 893)	OR 3.82 (1.20 to 12.21) [g]	582040 (2 observational studies)	⊕⊕◯◯ LOW [d,e]
Medication persistence (based on prescription refill interval) assessed with: Kawalec 2018 follow up: 12 months	214 per 1,000	469 per 1,000 (261 to 687)	OR 3.24 (1.30 to 8.08) [g]	20580 (4 observational studies)	⊕⊕◯◯ LOW [d]
All-cause mortality - not reported	-	-	-	-	-
Cardiovascular mortality - not reported	-	-	-	-	-
Stroke - not reported	-	-	-	-	-
Myocardial Infarction - not reported	-	-	-	-	-
End stage renal disease - not reported	-	-	-	-	-
Heart Failure - not reported	-	-	-	-	-
Patient satisfaction - not reported	-	-	-	-	-
Number of antihypertensive medications - not reported	-	-	-	-	-

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: Confidence interval; RR: Risk ratio; MD: Mean difference; OR: Odds ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Two systematic reviews reported on treatment persistence using prescription refill interval information. Based on low certainty evidence, SPC increased treatment persistence at six- and 12-months follow-up intervals when compared to SAP (OR 3.82, 95% CI 1.20 to 12.21, and OR 3.24, 95% CI 1.30 to 8.08, respectively) [27]. All of the reports included in this review were observational studies, thus the certainty of the evidence was low. Another systematic review reported on treatment persistence without a specific time point. The RR was 1.84, 95% CI, 1.00 to 3.39 [26] [Table 3].

BP control/level

One systematic review reported on BP control from three randomized trials. Low certainty evidence showed that SPC therapy may result in better BP control (RR 1.11, 95% CI 0.92 to 1.33) when compared to patients treated with SAP. The certainty of this evidence was low due to risk of bias and imprecision [28] [Table 3]. One systematic review reported on the SBP level from three randomized trials. Moderate certainty evidence showed that patients treated with SPCs probably attain an average level of SBP that is lower than the corresponding value in patients treated with SAP (MD - 0.81 mm Hg, 95% CI -3.25 lower to 1.64) [28] The certainty in the evidence was moderate due to risk of bias in the included studies.

Adverse events

One systematic review reported on adverse outcomes from seven randomized trials. The data suggested that SPC therapy may increase adverse events compared to treatment with SAP, including headache, edema and cough (RR 1.13, 95% CI 0.85 to 1.50). The certainty in the evidence was low due to risk of bias and imprecision [28] [Table 3].

DISCUSSION

Three published systematic reviews assessed the comparative outcomes for therapy with SPC and SAP. Evidence from observational studies suggested increased adherence, and improved treatment persistence in patients treated with SPC compared to SAP. Evidence from randomized clinical trials showed that SPC may improve BP control but increase adverse events when compared to SAP. The overall certainty of the evidence was deemed to be low due to the design of the included studies, risk of bias in primary studies, and the presence of imprecision.

This overview of review reports has many strengths. We conducted an extensive search of the English language literature to identify systematic reviews comparing treatment with SPC and SAP. We used predetermined eligibility criteria and relied on moderate to high quality reviews for evidence synthesis. We conducted all the review steps; screening of articles, abstracting data, assessing the reviews quality, and summarizing the evidence, in duplicate. The AMSTAR tool used for the assessment of the quality of the systematic reviews was previously validated [33]. The certainty of the evidence was assessed using the GRADE approach which is a leading approach in guidelines development and it is adopted by a multitude of national and international medical societies.

Our overview also has some limitations. Since our search focused on systematic reviews it is possible that we missed some primary studies that were not included in the reviews. Another shortcoming is the limited number of randomized trials that have addressed the topic. In addition, the availability of information detailing important patient outcomes such as all-cause mortality, cardiovascular mortality, and morbidity was insufficient to permit interpretation. Moreover, whether the reported improvement in BP control and adverse events in patients who used SPCs is a direct consequence of improved medication adherence is uncertain. However, our findings have clinical relevance because SPC therapy improved patient medication adherence and thus BP control compared with treatment with SAPs. One can reasonably expect therapy with SPCs compared with SAPs to provide a considerable reduction in CVD outcomes.

Many clinical practice guidelines include SPCs as part of their recommended management strategies. The 2018 (ESC/ESH) [13] hypertension guidelines recommended SPC when combination therapy is required based on evidence of increased adherence from systematic reviews. The ESC/ESH also recommends an escalation to a triple therapy SPC in patients whose BP is uncontrolled with dual therapy SPC [13,34]. The 2017 (ACC/AHA) BP guideline recommended combination therapy using either separate agents or a single pill combination in adults with stage 2 hypertension (average SBP ≥140 mm Hg or DBP ≥90 mm Hg) and an average SBP/DBP 20/10 mm Hg above their BP target. The writing committee stated that the use of SPCs compared to SAPs can improve patient adherence to antihypertensive treatments (class 2a recommendation) but had concerns related to the higher cost of SPCs compared with SAPs in the US and the choice of agents and doses in many of the single pill combinations available in the US [14].

Compared to previously published evidence, our results identify higher adverse events with SPCs as compared to SAPs, and consistent results for adherence to treatment. A meta-analysis of observational studies and randomized clinical trials was conducted in 2010 and reported that the use of SPCs in patients with hypertension when compared with SAPs was associated with a lower likelihood of adverse events (OR 0.80, 95% CI 0.58 to 1.11), reduction of 4 mmHg (95% CI 9.8 to1.5) in SBP, and improvement in medication adherence OR 1.21 (95% CI 1.03 to1.43) [34]. A randomized clinical trial including 148 patients reported that patients who received a triple therapy SPC had a lower mean sitting SBP compared with SAP therapy. The incidence of adverse events and adverse medication reactions were similar with SPC and SAP therapy [35]. However, to our knowledge this is the first overview of reviews to address the topic of SPC in the treatment of hypertension. It was conducted through a rigorous methodology and it expanded on earlier published evidence.

It is known that decreasing the number of pills improves treatment adherence in patients with hypertension. A meta-analysis report identified patients who received SPCs as having a mean MPR difference of 13.3% compared with SAPs [36]. One potential disadvantage of SPC therapy is the difficulty of titrating the dose of one component independently of other components, which does not allow for flexibility. However, many SPC formulations with a variety of component agent doses are now available, helping to overcome this potential disadvantage. Another challenge with SPC therapy is that when patients develop a side-effect from one component, it may be necessary to discontinue the SPC and shift to either another combination therapy or to SAP combination therapy.

In regards of cost, our analysis suggests SPC therapy is more cost effective than treatment with SAP [37, 38]. One cost-effectiveness analysis revealed that compared to olmesartan and amlodipine SAP therapy, treatment with an olmesartan/amlodipine SPC led to a decrease in cardiovascular events, and gained additional quality-adjusted life years (QALYs) of 0.052, and 0.037 per patient, respectively but resulted in an incremental cost of $791.3, and $148.2 [37]. Other challenging issues that can hinder the use of SPCs in patients with hypertension include the higher cost of the SPCs compared to SAPs, the insurance coverage of such medications, and the availability of the medications.

This overview of reviews highlights the lack of evidence on clinically important outcomes in patients treated with a SPC and the need for research related to this topic. Further clinical trials that compare SPC with SAP with longer intervals of follow-up are needed to better understand their effects on BP control and patient outcomes. Clinical trials comparing and evaluating different antihypertensive SPC regimes are also warranted to compare the efficacy of each combination. There is a need for research studies on real-world experiences, designed and statistically powered, to determine if there is a difference in clinical outcomes, such as reduction in major adverse cardiovascular events, mortality, and serious adverse events between single-pill combinations versus multiple-pill combinations. Health economic analyses are needed to quantify cost-effectiveness and budget implications of implementing incremental initial combination therapy compared with initial monotherapy.

Perspectives

In summary, we found that single-pill combination may improve treatment persistence and adherence and it may increase treatment adverse events. Hence, it might be reasonable to suggest the use of these combinations in clinical settings especially when in locations where the access to care is limited. However, in many regions and countries, especially economically underdeveloped countries, the availability of SAPs drugs is higher than that of SPCs

CONCLUSION

The benefits of SPC may result from a reduction in pill burden and a simpler treatment process. It is reasonable to recommend SPC in future hypertension guidelines. Several opportunities for future research include higher quality trials for surrogate outcomes that were previously reported: adherence, and BP control, in addition to randomized trials evaluating patient important outcomes like mortality or cardiovascular events in relation to SPC use, the use of SPC as initial BP lowering therapy, and the comparison different SPCs along with dual, triple, and quadruple regimens.

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Novelty and Significance

- What's newTo our knowledge, this is the first overview of reviews to answer the question on the effect of single pill combination in the treatment of hypertension.
- This overview provides a rigorous summary of published systematic reviews published since 2015.
- Single pill combinations likely improve blood pressure control and adherence to treatment compared with a combination of two or more single agent pills.
- Single pill combinations may increase treatment side effects compared with a combination of two or more single agent pills. This might be because. Single pill combinations are harder to titrate.

What's relevant

- The new World Health Organization 2021 guidelines will be implemented by clinicians globally
- Supply chain management become easier with a single pill combination, so this strategy is beneficial in areas of limited access to primary health care.
- Improved treatment adherence is an important factor in the prevention of long-term adverse health outcomes related to uncontrolled hypertension.
- The findings of this overview informed the new recommendation about single pill combination in the World Health Organization 2021 guidelines for the pharmacological management of hypertension in adults.

Summary

It is reasonable to suggest the use of single pill combination

for the treatment of hypertension requiring combination therapy. Additional research is needed to increase evidence certainty and subsequent strength of the recommendation in support of single pill combination antihypertensive medications.

EXPLANATIONS

a. All included trials had unclear or high risk of bias

b. The confidence interval suggests the possibility of important benefit and important harm

c. The confidence interval is precise around the line of no effect, suggesting the possibility of trivial benefit and trivial harm

d. According to the authors' analysis, risk of bias was not associated with study results

e. The CIs of the studies do not overlap; however, this is due to the very precise estimates, which are not qualitatively different

f. Although there is statistical heterogeneity, all studies are consistent with regards to the direction of the effect and thus we decided to not rate down further

g. Another systematic review (Du 2018) also reports this outcome, but without providing a specific time point. The RR was 1.84 (95% CI, 1.00 to 3.39)

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