Optimizing antihypertensive care: exploring the therapeutic merits of single-pill combination therapy in antihypertensive management

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Abstract

Hypertension is a condition when the blood pressure in the arteries is too high. It is said to be hypertension if systolic blood pressure is ≥140 mmHg and diastolic blood pressure is ≥90 mmHg. There are two types of hypertension, namely, primary/essential and secondary/non-essential. Primary/essential hypertension is hypertension that is not related to other medical conditions. Meanwhile, secondary/non-essential hypertension is hypertension associated with other medical conditions that usually occur in the kidneys, arteries, heart or endocrine system. There are many types of antihypertensive drugs. These antihypertensive drugs are then formulated into various dosage forms or treatment patterns for use. Single-pill combination therapy is one of them. Of all the dosage forms or treatment patterns, single-pill combination therapy is often predicted to be the superior dosage form or treatment pattern because of its many advantages. The advantages of single-pill combination therapy are more effective in reducing blood pressure, lowering blood pressure more quickly to target, effective replacement in uncontrolled blood pressure, decreasing adverse effects, widely available, and improving adherence to medication. Adherence to medications itself has positive impacts on quality of life. Quality of life also has a relationship with adherence to medication. With increasing quality of life, the level of adherence to medication also increased. Single-pill combination therapy can improve adherence to medication, thus increasing the quality of life of hypertensive patients. Although it has many advantages, single-pill combination therapy also has some potential issues and disadvantages that must be taken into account when prescribing single-pill combination therapy as an antihypertensive treatment. Many guidelines recommend single-pill combination therapy as a treatment for hypertensive patients because of its advantages.

Keywords: single-pill combination therapy; adherence to mediation; quality of life; guidelines

1. Introduction

Hypertension is a condition when the blood pressure in the arteries is too high. Systolic blood pressure is the blood pressure when the heart contracts, while diastolic blood pressure is the blood pressure when the heart relaxes. Several sources provide a reference for the threshold number for normal blood pressure. It is said to be hypertension according to the World Health Organization and the American Heart Association if systolic blood pressure is ≥140 mmHg and diastolic blood pressure is ≥90 mmHg (WHO, 2021; Burnier & Egan, 2019).

There are two types of hypertension, namely, primary/essential and secondary/non-essential. Primary/essential hypertension is hypertension that is not related to other medical conditions. Meanwhile, secondary/non-essential hypertension is hypertension associated with other medical conditions that usually occur in the kidneys, arteries, heart or endocrine system (Carretero & Oparil, 2000). Based on the International Society of Hypertension in 2020, hypertension is classified into 4 categories based on blood pressure calculations, namely normal BP, high-normal BP, grade 1 hypertension, and grade 2 hypertension (AHA, 2020).

Many factors cause hypertension. Based on the Mosaic Theory put forward by Dr Irvine Page, the factors that cause hypertension can be depicted using an 8-sided plane whose corners are drawn, showing that interrelated factors cause hypertension. These factors are altered redox signaling/oxidative stress, innate and adaptive immunity, genetics, sodium intake/sodium storage, sympathetic activation, microbiome, renal mechanisms and vascular/endothelial dysfunction. The roles of the factors above vary for each individual and each research model. The Mosaic Theory that has been developed now can help further research (Harrison, 2021). Many impacts of hypertension can threaten a person's health. According to the American Heart Association, the diseases that are affected are heart attack, stroke, heart failure, kidney failure, loss of vision and sexual dysfunction (AHA, 2022).

There are many types of antihypertensive drugs, including diuretics, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), calcium channel blockers (CCBs), alpha-blockers, alpha-2 receptor agonists, combined alpha and beta blockers, central agonists, peripheral adrenergic inhibitors, and vasodilators (AHA, 2017). These antihypertensive drugs are then formulated into various dosage forms or treatment patterns for use. The dosage forms or treatment patterns can be classified into four categories: monotherapy, single-pill combination therapy, free combination, and combination therapy with three or more antihypertensive medications. Monotherapy refers to the administration of a solitary antihypertensive medication in the form of a single pill. A single-pill combination therapy refers to the administration of a single pill containing two substances, with at least one of them being an antihypertensive. The single-pill combination therapy was classified into two distinct categories: one consisting of two antihypertensive medications and the other consisting of an antihypertensive medication and a non-antihypertensive medication. Free combination refers to the administration of two distinct pills containing different substances. Combination therapy with three or more antihypertensive medications was defined as the use of at least three antihypertensive agents, which might be administered either as a single pill or multiple pill formulation (Lee et al., 2020). Furthermore, there is also the term fixed-dose drug combinations. Fixed dose drug combinations, or combination products, refer to the amalgamation of two or more active pharmaceuticals within a solitary dosage form (Gautam & Saha, 2008).

Of all the dosage forms or treatment patterns, single-pill combination therapy is often predicted to be the superior dosage form or treatment pattern. In fact, single-pill combination therapy has been included as a recommendation in many guidelines for the treatment of hypertension. Not without reason, but this single-pill combination therapy does have many advantages and benefits.

2. Advantages of single-pill combination therapy

Combining many drug types into a single-pill combination therapy can simplify things for patients, which can increase medication adherence and save drug costs, as recommended by WHO in 2002 (WHO, 2002). Based on a wealth of evidence, it was suggested that first-line combination treatment be taken into consideration for the majority of hypertensive patients (Wald et al., 2009). Single-pill combination therapy can be used in three ways: first, as first-line therapy for patients whose disease cannot be controlled with monotherapy; second, as second-line therapy for patients who cannot be controlled with monotherapy; and third, as a substitute for individual component doses that are treated separately (Gradman et al., 2013).

Combining 2 different antihypertensive drugs from the thiazides class, beta-blockers, angiotensin-converting enzyme inhibitors, and calcium channel blockers, is more effective in reducing blood pressure by 5 times compared to doubling the dose of monotherapy (Wald et al., 2009). Combination therapy also has the advantage of lowering blood pressure more quickly to target compared to monotherapy (Fogari et al., 2010). Previous research shows that combining two types of antihypertensive drugs which do not cause side effects when combined and are complementary is more effective in lowering blood pressure than increasing the dose of using one type of antihypertensive drug (Chrysant et al., 2008; Littlejohn et al., 2009). In patients whose blood pressure failed to be controlled with amlodipine monotherapy, replacement with single-pill combination therapy in the form of a combination of telmisartan and amlodipine showed a better reduction in blood pressure according to the target (Billecke & Marcovitz, 2013; Neldam et al., 2011). An 8-week long, placebo-controlled, double-blind, 4x4 factorial design trial study to assess the effects of telmisartan and amlodipine in the form of single-pill combination therapy with 562 patients participated found that combination of telmisartan and amlodipine has significant additive blood pressure lowering effects and also substantially greater response and control rates than only monotherapy with either telmisartan or amlodipine (White et al., 2010). Another study that was conducted to assess the effectiveness and safety of different combinations of medications in treating high blood pressure in Japanese patients and involved a randomized, double-blind, placebo-controlled, parallel-group design with participants who were given one of three fixed-dose combinations: losartan 50 mg plus hydrochlorothiazide 12.5 mg, losartan 50 mg plus hydrochlorothiazide 6.25 mg, or losartan 25 mg plus hydrochlorothiazide 6.25 mg and these combinations were compared to hydrochlorothiazide 12.5 mg alone, losartan 50 mg alone, or a placebo come up with results that showed the once-daily, fixed-dose combination therapy of losartan 50 mg and hydrochlorothiazide 12.5 mg is well tolerated and more effective in reducing diastolic and systolic blood pressure compared to using a single medication in Japanese patients with hypertension (Saruta et al., 2007). A QUARTET study, a phase 3 trial, examined patients with high blood pressure using a multicenter, parallel-group, active control, double-blind, randomized, controlled design and discovered that initiating hypertension management with a single-pill combination therapy containing ultra-low-dose quadruple drugs resulted in a greater and sustained reduction in blood pressure compared to the conventional approach of starting with monotherapy (Chow et al., 2021). Not only does switching from monotherapy to single-pill combination therapy show a significant reduction in blood pressure in uncontrolled hypertension, but replacing the previous single-pill combination therapy with another new single-pill combination therapy can also reduce blood pressure significantly in patients with uncontrolled hypertension (Karpov et al., 2017).

A quicker reduction in blood pressure by targeting blood pressure with combination therapy can also reduce the number of cardiovascular events (Gradman et al., 2013). Several studies also show the benefits of single-pill combination therapy for cardiovascular health better than free association. Single-pill combination therapy in the form of bisoprolol/perindopril has been proven to be effective in reducing both systolic and diastolic blood pressure significantly in patients with coronary artery disease, hypertension, and a history of myocardial infarction. Improvements in angina symptoms and reductions in heart rate also occurred in these patients (Kobalava et al., 2023). A retrospective cohort study comparing 18,665 patients receiving individual component therapy and 9929 hypertensive patients receiving single-pill combination therapy was conducted using a primary care database. The results showed that the individual component group experienced significantly more cardiovascular events than the single-pill combination therapy group (Belsey, 2012). When starting treatment with a single-pill combination therapy instead of a free association, blood pressure reductions were substantially bigger, and more individuals achieved blood pressure control within a median of six months, according to a review of primary care data from 1507 patients (Bronsert et al., 2013). In elderly patients with systolic hypertension, a combination of the calcium channel blocker felodipine (5 mg) and the angiotensin receptor antagonist candesartan (16 mg) significantly reduced mean 24-hour blood pressure more than either drug alone (11.0 / 11.2 mmHg) or felodipine or candesartan alone (11.9 / 5.7 mmHg or 12.2 / 7.5 mmHg, respectively) (Morgan & Anderson, 2002). Single-pill combination therapy of perindopril arginine/indapamide can reduce blood pressure significantly in overweight or obese patients (Glezer, 2020). The findings of a 12-week study involving 364 patients with stage 2 hypertension, conducted at multiple centers and using a double-blind methodology, revealed that fixed-dose combination therapy with amlodipine besylate/benazepril HCl was well tolerated. Furthermore, this combination therapy led to significantly greater reductions in blood pressure and a higher rate of achieving blood pressure goals compared to amlodipine besylate monotherapy. These results support the recommendation of using combination therapy as the initial treatment for stage 2 hypertension (Jamerson et al., 2004).

Drug therapy problems are unexpected events resulting from consuming drugs and interfere with the goals of drug therapy itself. Needing additional drug therapy is one of the drug therapy problems most frequently experienced by hypertensive patients. Taking many medications per day, namely ≥3 medications, is also a factor that is closely related to drug therapy problems (Bekele Daba & Hussen, 2017). Single-pill combination therapy can certainly be a solution that covers the problem of needing additional drug therapy and also related factors such as taking many medications per day. Blood pressure treatment with a combination of low-dose drugs increases efficacy and decreases adverse effects, excluding angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), which are mostly dose-related. For thiazide diuretics and calcium channel blockers, adverse effects were 80% fewer compared with standard doses (Law et al., 2003). Combination therapies offer a far lower risk of adverse events than two monotherapies, according to a meta-analysis of placebo-controlled randomized studies (Law et al., 2003). Combinations containing 25% of the recommended dose of two antihypertensive drugs were linked to considerably fewer adverse events than a conventional dose of monotherapy, according to a sizable systematic review and meta-analysis of randomized controlled trials (Bennett et al., 2017). Four of the five trials in the meta-analysis of cohort studies and clinical trials examining the safety and tolerability benefits of single-pill combination therapy over free associations reported a lower incidence of adverse events with single-pill combination therapies when compared to the corresponding free associations at equivalent doses. Consequently, there was a 20% drop in the likelihood of adverse outcomes (Gupta et al., 2010). In single-pill combination therapy, the negative effects of one component may be balanced out by the positive benefits of another in specific combinations. For example, simultaneous administration of a renin-angiotensin-aldosterone system (RAAS) inhibitor significantly reduces ankle edema, a common side effect of calcium channel blockers (CCBs) caused by precapillary vasodilation and increased hydrostatic pressure. This is because the RAAS inhibitor increases postcapillary dilation and attenuates pre-post-capillary pressure gradient and fluid exudation (Messerli, 2002). Angiotensin-converting-enzyme (ACE) Inhibitors or angiotensin receptor blockers (ARBs) in the form of single-pill combination therapy reduce the adverse effect, namely calcium channel blocker-associated peripheral edema (Makani et al., 2011).

For the availability of single-pill combination therapy, single-pill combination therapy is widely spread and available in all countries except Afghanistan (Bruyn et al., 2022). Up to twenty distinct forms of single-pill combination therapy combining two drugs to treat hypertension exist, each with a different dosage range (Campanaa et al., 2020). Treatment regimens may now be tailored based on patient characteristics thanks to the availability of a large variety of single-pill combination therapy (Mancia et al., 2019). It is now possible to up-titrate the various components of a single-pill combination therapy in the same manner as if the patient were taking a free association since a range of dosages is available. It is crucial to remember that dose availability differs by nation, whether it is for one or both components. It should be recalled that angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) have flatter dose-response curves than calcium channel blockers (CCBs), which may affect dosage adjustments (Campanaa et al., 2020).

A study using a Markov model analyzed the cost-effectiveness of lifetime antihypertensive therapy in Japan. The study considered large-scale clinical trials and epidemiological data. The results suggest that combining an angiotensin II receptor blocker (ARB) with a calcium channel blocker (CCB) may be a more cost-effective strategy for the lifelong treatment

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of hypertension compared to using either agent alone (Saito et al., 2008). In a Markov model study, the first available single-pill combination therapy of three drugs—valsartan, amlodipine, and hydrochlorothiazide—was compared to its dual combinations in terms of cost-utility in patients with moderate to severe hypertension. The results showed that the single-pill combination therapy of these three drugs is a more cost-effective antihypertensive option for treating moderate to severe hypertension than its dual components (Stafylas et al., 2015). A retrospective analysis was conducted using a database to evaluate medication adherence patterns in two groups of hypertensive patients. Group 1 consisted of subjects who were prescribed a single-capsule, fixed-dose combination of amlodipine besylate/benazepril HCl, while group 2 included subjects who were prescribed an angiotensin-converting enzyme (ACE) inhibitor and a dihydropyridine calcium channel blocker (CCB) as separate drugs. The analysis revealed that the average annual cost of cardiovascular-related care per subject was significantly lower in group 1 compared to group 2. Group 1 exhibited superior drug adherence and used fewer medical resources compared to group 2 (Taylor & Shoheiber, 2003).

Patients feel better psychologically when taking one or two medicines a day as opposed to three or four, which they could think is a symptom of illness (Ofili, 2006). Combination therapy can be given as a single pill to increase the patient's adherence to medication to antihypertensive medication (Unger et al., 2020). By using single-pill combination therapy, the pill burden of patients, especially hypertensive patients with other comorbidities, is reduced, thereby increasing their adherence to medication. (Mancia et al., 2019).

3. Single-pill combination therapy, adherence to medication, and quality of life

Long-term adherence to medication may be significantly impacted by the first medication selected and how easy the treatment regimen is to follow (Monane et al., 1997). It has been known that single-pill combination therapy is positively associated with adherence to medication (Lee et al., 2013). Increased patient adherence to medication may also contribute to improved therapeutic response (Cosin-Sales et al., 2021). The advantage of single-pill combination therapy is the comfort felt by the patient because they do not have to take much medication, so the patient's adherence to medication is maintained (Dezii, 2000). Single-pill combination therapy can be used as a strategy to reduce the pill burden, especially in elderly patients (Williams et al., 2018). The number of types of medication prescribed and the frequency of taking medication in a day both influence patient adherence to taking medication persistently (Coleman et al., 2012). Therefore, it is very useful to simplify antihypertensive therapy into single-pill combination therapy to increase patient adherence to medication (Gupta et al., 2010). Nowadays, the development of single-pill combination therapy in the pharmaceutical world is focused on increasing efficacy and simplifying treatment regimens so as to increase adherence to medication. (Burnier, 2017).

In a study with a microsimulation modelling approach, single-pill combination therapy has a better clinical outcome, such as reductions in mortality, incidence of clinical events, and disability-adjusted life years compared to current treatment practices, start low go slow, and free combination with multiple pills because single-pill therapy is associated with higher adherence to medication (Borghi & Granados, 2023). In a meta-analysis comparing free equivalent combination treatment and single-pill combination therapy in hypertensive patients, it was discovered that persistence was twice as probable and that drug adherence was 8% greater with single-pill combination therapy than with free association (Sherrill et al., 2011) When compared to an equivalent treatment with a free association, a meta-analysis of nine hypertension studies revealed that treatment with a single-pill combination therapy was associated with a 15% improvement in adherence to medication. Additionally, the single-pill combination therapy was associated with higher persistence (Du et al., 2018). Single-pill combination therapy was linked to a significant improvement in patient-doctor cooperation and increased patient adherence to medication schedules, according to a systematic review and meta-analysis conducted to evaluate the efficacy of fixed-dose combination or single-pill combination therapy and free equivalent combinations in antihypertensive therapy (Kawalec et al., 2018).

In a cross-sectional study with 120 hypertensive patients, adherence to medication was found to positively influence quality of life, where adherence to medication was measured with the Medication Adherence Self-Efficacy Scale (MASES) and quality of life was measured with SF-36 Quality of Life Scale (SF-36 QoL) (Mollaoğlu et al., 2015). In another cross-sectional study with 385 hypertensive patients, adherence to medication rather negatively and weakly correlates with quality of life, where adherence to medication was assessed with Drug Attitude Inventory quality of life measured with Euroqol EQ-5D (Saleem et al., 2012). Hierarchically higher research, namely a systematic review and meta-analysis that aim to verify the effects of adherence to medication on quality of life, found that adherence to medication has positive impacts on the mental and physical domain, as well as on the overall quality of life score (de Souza et al., 2016).

Hypertension is a disease with the highest health-related quality of life (HRQoL) impact compared to other diseases, such as diabetes, depression, ischemic heart disease, stroke, asthma, and low back pain (Burströ et al., 2001). Thus, individuals affected by hypertension experience relatively good overall well-being and functioning despite having the condition. However,

uncontrolled blood pressure, one of the causes being suboptimal adherence to medication, can lead to diseases such as vascular stiffness, left ventricular hypertrophy, myocardial infarction, and stroke (Burnier & Egan, 2019).

Transdermal clonidine could be an alternative solution to increase adherence to medication in hypertensive patients, especially those who are older. A double-blind, double-dummy, randomized clinical trial that involved elderly patients found that adherence to medication with transdermal clonidine was more consistent compared to oral verapamil. Moreover, 86% of patients were satisfied or highly satisfied with the convenience of transdermal clonidine. 87% of patients reported that the side effects of transdermal clonidine were much less or not at all bothersome. 65% of patients indicated that transdermal clonidine was more convenient than oral verapamil, and 60% of patients preferred transdermal clonidine over oral verapamil. Six out of ten indicators showed a minor improvement in quality of life scores for patients treated with verapamil and four out of ten parameters for patients treated with clonidine (Burris et al., 1991). Regarding the type of drugs, to determine the relative effects of cilazapril, atenolol, and nifedipine retard on quality of life, 540 hypertensive patients participated in a multicenter, randomized, double-blind study that lasted six months. The results showed that nifedipine retard was linked to a higher discontinuation rate and more symptomatic complaints than cilazapril and atenolol (Fletcher et al., 1992). Overall quality of life parameters did not differ between beta-blocker nebivolol and angiotensin receptor blocker losartan (Van Bortel et al., 2005).

In a longitudinal non-randomized cohort study, with 440 patients aged 60 or more with comorbidities, that aims to analyze the effects of antihypertensive on two groups, each given monotherapy and combined therapy on one of which is quality of life, found that both groups perceived better quality of life (Baptista et al., 2018). basically, based on this research, single-pill combination therapy and monotherapy can have the same impact on quality of life. However, this research only examined the quality of life aspect, and did not examine the adherence to medication aspect which could have a long-term effect on quality of life. Through a retrospective cohort study of 2006-2007 US MarketScan Medicare Supplemental and Coordination of Benefits administrative data, it was discovered that variations in the monthly number of non-antihypertensive pills did not influence the rates of adherence to antihypertensive medication. However, this study only concentrated on immediate reactions to alterations in pill burden and cannot exclude potential long-term effects. This study also fails to discover significant effects of pill load on medication adherence, partly due to physicians avoiding polypharmacy in patients whom they deem unlikely to comply with recommended instructions. Naturally, if physicians exclusively gave medications to individuals who consistently followed their prescribed treatment, researchers analyzing prescription claims databases would only discover high rates of adherence. However, this scenario is clearly not the reality (Zuckerman et al., 2012). A multicenter, non-interventional, prospective study was conducted to examine the psychosocial characteristics of patients with uncontrolled hypertension and identify factors that affect blood pressure control. The study found that patients with uncontrolled blood pressure had a significantly higher proportion of combination therapy involving three or more antihypertensive medications. The follow-up assessment of patients with uncontrolled blood pressure revealed a substantially worse quality of life, as assessed by the EuroQol 5D visual analogue scale (EQ-5D VAS), despite having identical baseline values. The multivariate logistic regression analysis demonstrated a substantial correlation between blood pressure management and quality of life at follow-up. Patients exhibiting a worse quality of life had a higher Charlson Comorbidity Index and a greater likelihood of using more than three antihypertensive medications. However, their adherence to treatment was comparable to that of patients with a higher quality of life. The results of this study indicate that in addition to using medication to treat hypertension, addressing comorbid diseases or providing psychological support may be beneficial in achieving optimal blood pressure control in individuals with uncontrolled hypertension (Lee et al., 2020). The Saga Challenge Antihypertensive Study (S-CATS) conducted in Japan aimed to assess the efficacy of combined antihypertensive therapy using losartan and hydrochlorothiazide (HCTZ) in 161 hypertensive patients, resulting in noteworthy reductions in both systolic and diastolic blood pressure, as well as heart rate. The patient's quality of life (QOL) score, as measured by the EuroQol 5 dimensions (EQ-5D) and the visual analogue scale (VAS), showed considerable improvement (Kamura et al., 2011). Quality of life also has a relationship with adherence to medication. In a prospective, cross-sectional, and analytical study with 186 hypertensive elderly patients, it was shown that with increasing quality of life, the level of adherence to recommended medication also increased, where the level of adherence to medication was negatively affected by older age, longer duration of disease, worse marital status, lower education, living alone, and using polytherapy (Uchmanowicz et al., 2018).

4. Potential issues and disadvantages caused by single-pill combination therapy

One of the disadvantages of single-pill combination therapy is the lack of a fixed dose that can be adjusted for each individual. This dosage determination is sometimes limited and difficult. Other factors related to things beyond the individual component still need to be understood (de Cates et al., 2014; Lonn et al., 2010; Viera et al., 2011). Before the widespread use of single-pill combination therapy, there was a perception that using single-pill combination therapy drugs made the dosage of the combined drugs inflexible and difficult to adjust. In fact, terms such as "fixed-dose combination" give the impression

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that single-pill combination therapy is not flexible. Drug regimens with single-pill combination therapy preparations are also limited. However, this can be overcome by the increasing availability of single-pill combination therapy, which combines various single drugs so that dosage settings can be adjusted flexibly and single-pill combination therapy can be adopted more widely (Bangalore & Ley, 2012).

Even though there have been many studies that state that single-pill combination therapy can reduce the number of cardiovascular events, as mentioned before, no robust direct data showing that single-pill combination therapy directly reduces cardiovascular morbidity and mortality rates. Apart from that, single-pill combination therapy is often perceived as expensive compared to ordinary generic drugs (Bangalore & Ley, 2012).

Some fixed drug combinations are formulated irrationally, so they can cause patients to experience adverse drug reactions (Gautam & Saha, 2008). A study examining the French National Health Insurance System found that the use of single-pill combination therapy was associated with a greater likelihood of hospitalization for hypotension, syncope, or collapse compared to the use of a free association of medications. Something to note is that patients without a history of hypertension therapy were not included in this data set; almost half of the patients were receiving a high-dose renin-angiotensin-aldosterone system (RAAS) inhibitor, and around 10% were taking a high-dose thiazide diuretic or calcium channel blocker (CCB). However, these results clearly show how critical it is to rule out orthostatic hypotension and think about other possible adverse effects. By combining antihypertensive drugs with varying rates of drug absorption, the danger of hypotension may be reduced as well (Nowak et al., 2015). Even though hypertension therapy using single-pill combination therapy can reduce adverse effects, as mentioned in some research before, caution must be exercised in prescribing it because it is very likely to cause adverse effects in certain people. Basically, drug prescribing must pay attention to personal aspects. Thus, before prescribing single-pill combination therapy, the possibility of adverse effects must be watched out for.

As was already mentioned, single-pill combination therapy can help patients take their medications more consistently, reducing the likelihood that they will forget to take them. Missing a single dose of a single-pill combination therapy, however, raises concerns because it means the patient will be missing multiple antihypertensive medications at once. It is necessary to conduct additional research to ascertain the consequences of missing a dose of single-pill combination therapy. Single-pill combination therapy management, when one medicine must be temporarily halted owing to intercurrent illnesses or surgery, has also worried physicians. In dehydration, a diuretic but not its combination may need to be stopped. Such conditions may need temporary monotherapy switches, and blood pressure and hydration status should dictate dosage titration. Sometimes, a team of specialists is needed to manage a clinical problem. Reviewing single-pill combination therapy approval procedures should reduce concerns about scientific legitimacy and possible conflicts of interest. First-line single-pill combination therapy were designed pursuant to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use criteria. WHO, the US FDA, and the European Medicines Agency have all established single-pill combination therapy development requirements. These recommendations also explain what local authorities in each nation should consider while registering and reimbursing single-pill combination therapy. Single-pill combination therapy is only allowed if its components are therapeutically recommended, clinical trial results support dose, effectiveness, safety, and acceptability, and a possible benefits and drawbacks analysis has been done (Campanaa et al., 2020; WHO, 2002).

It is simple to identify tolerability issues or adverse drug-related events when using the tiered care approach. The cardiovascular risks of postponing or failing to attain blood pressure objectives quickly outweigh the safety benefits of such a procedure because of poor adherence, persistence, and physician inertia in clinical practice. Combining treatments can actually raise risk, as evidenced by statistics that demonstrate increased benefits despite continued risks (Mancia et al., 2019). Therefore, single-pill combination therapy may be selected to specifically target issues such as the fluctuating pattern of blood pressure, the low levels of medication in the body at the end of dosing intervals, and the heightened likelihood of low blood pressure. Patients with a dipper profile, as determined by ambulatory blood pressure monitoring, may benefit from taking a mixture of medications in the morning. This combination should include amlodipine, indapamide, perindopril, and lisinopril, each with a duration of action of at least 24 hours. For those who do not experience a decrease in blood pressure throughout the night, taking a combination of an antihypertensive medicine that lasts for 24 hours and another antihypertensive medication with a shorter duration of action, such as ramipril and enalapril, in the evening may be useful (Bowles et al., 2018).

These potential issues and disadvantages must be taken into account when prescribing single-pill combination therapy as antihypertensive therapy. of the several issues and disadvantages that can be caused by treating hypertension using single-pill combination therapy above, this can open up opportunities for further research related to single-pill combination therapy. It is hoped that these studies will pave the way for establishing a more effective and safe strategy for using single-pill combination therapy as medicine. Collaboration by several parties, including health workers, health services, patients, and even the government, is also needed so that the implementation of the use of single-pill combination therapy can be regulated and systematic.

5. Guidelines and application of the single-pill combination therapy

Some specific drug combinations of single-pill combination therapy fall into the category of two drug combinations and are circulating on the market:

- renin-angiotensin-aldosterone system inhibitor and diuretic
- renin-angiotensin-aldosterone system inhibitor and calcium channel blocker
- renin inhibitors and angiotensin receptor blockers
- calcium channel blockers and diuretics,
- beta-blockers and diuretics
- thiazide diuretics and potassium-sparing diuretics,
- calcium channel blockers and beta-blockers

There are also less effective combinations:

- ACE Inhibitors and angiotensin receptor blockers
- renin-angiotensin-aldosterone system inhibitors + beta-blockers
- beta-blockers and centrally acting agents (Gradman et al., 2011).

Based on data, despite the fact that there is a combination of single-pill combination therapy available on the market and hypertension guidelines suggest starting treatment with single-pill combination therapy, only one-third of treated hypertensive individuals actually take single-pill combination therapy (Derington et al., 2020).

The American College of Cardiology, American Heart Association, European Society of Cardiology, and European Society of Hypertension, as guidelines, recommend single-pill combination therapy as a treatment strategy of antihypertensive drug therapy for the management of hypertension. There are similarities between the treatment strategies recommended by the guidelines of the American College of Cardiology and the American Heart Association. Likewise, there are similarities between the treatment strategies recommended by the guidelines of the European Society of Cardiology and the European Society of Hypertension. Therefore, treatment strategies can be divided into two groups of guidelines: the American College of Cardiology/American Heart Association and the European Society of Cardiology/European Society of Hypertension (Whelton et al., 2022).

In the recommended treatment strategy to the guidelines from the American College of Cardiology/American Heart Association, single-pill combination therapy can be used as a strategy to increase adherence to medication. However, it should be noted that although single-pill combination therapy can increase adherence to medication, it may involve lower-than-optimal doses of antihypertensive drugs from the thiazide diuretic group. Meanwhile, the recommended treatment strategy issued by the guidelines from the European Society of Cardiology/European Society of Hypertension uses single-pill combination therapy as initial therapy in the form of a combination of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blocker (ARB) plus calcium channel blocker (CCB) or diuretic is strongly favoured. In fact, the use of single-pill combination therapy is also recommended if blood pressure is still above the target determined by a combination of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers plus calcium channel blockers and diuretics (Whelton et al., 2022).

Thus, basically, both of these guidelines place a significant amount of emphasis on methods that can be utilized to enhance adherence to medication, with particular attention paid to the benefits of single-pill combination therapy as a means of overcoming therapeutic inertia and, in addition to the utilization of team-based care. However, there are subtle disparities between the two guidelines regarding the recommendation of using a single-pill combination therapy of antihypertensive medicines for specific purposes. The European Society of Cardiology/European Society of Hypertension guideline strongly advocates for the use of single-pill combination therapy. On the other hand, the American College of Cardiology/American Heart Association guideline supports the use of single-pill combination therapy whenever feasible. However, they acknowledge that many combination pills available in the United States contain hydrochlorothiazide instead of chlorthalidone and often have a lower dosage of diuretic compared to what has been used in significant treatment trials (Whelton et al., 2022).

The use of single-pill combination therapy is also included in the recommendations of the International Society of Hypertension guidelines. These recommendations are divided into two groups, namely essential recommendations and optimal recommendations. Single-pill combination therapy itself is included in the core drug-treatment strategy optimal group, where the ideal treatment strategy requires the use of single-pill combination therapy. The drug-treatment strategy based on optimal recommendations is divided into four steps. Step 1, using a dual low-dose combination of antihypertensives. Step 2, using a dual full-dose combination of antihypertensives. Step 3, using a triple combination of antihypertensives. Finally, in step 4, if resistant hypertension occurs, a triple combination of antihypertensive plus spironolactone or other drugs such as amiloride, doxazosin, eplerenone, clonidine, or beta blocker can be used. Single-pill combination therapy is also an essential

and optimal recommendation for adherence to antihypertensive drugs. It is hoped that the use of single-pill combination therapy can reduce polypharmacy can increase adherence to medication. Single-pill combination therapy in the form of a thiazide-like diuretic plus calcium channel blocker (CCB) or calcium channel blocker (CCB) plus angiotensin receptor blocker (ARB) is also recommended as management of hypertension in populations of African descent (Unger et al., 2020).

The Hypertension Canada Guidelines Committee, with their Hypertension Canada's 2017 guidelines for diagnosis, risk assessment, prevention, and treatment of hypertension in adults, recommends single-pill combination therapy as an initial treatment option for adults with diastolic and with or without systolic hypertension, besides monotherapy. The use of single-pill combination therapy is preferred over the use of monotherapy because the benefits obtained are much greater (Leung et al., 2017).

The Argentine Federation of Cardiology and the Argentine Society of Hypertension include single-pill combination therapy in their key therapy recommendations. The reason they do this:

- The majority of patients require a combination of therapies
- An accelerated decrease in blood pressure and an increased likelihood of attaining the desired blood pressure
- Eliminating the negative effects and increasing tolerability associated with the up-titration of single agents
- A simplified administration promotes adherence to medication,
- In contrast to increasing the dosage of a single drug administered as monotherapy, the administration of two (or even three) medications in modest concentrations concurrently offers the benefit of adverse effect reduction
- Combination therapies are justified on the grounds that the use of medications with complementary mechanisms of action results in a more effective reduction in blood pressure
- Specific populations that are at an elevated risk for cardiovascular complications may experience advantages when utilizing single-pill combination therapy. These populations include patients diagnosed with diabetes or those who have organ damage
- Specific populations that are at an elevated risk for cardiovascular complications may experience advantages when utilizing single-pill combination therapy. These populations include patients diagnosed with diabetes or those who have organ damage
- The cost-effectiveness of single-pill combination therapy is greater in Latin America,
- Potentially in the future, the polypill could offer a more substantial reduction in cardiovascular risk
- Promoting health policies that target the implementation of single-pill combination therapy is consistent with PAHO's HEARTS initiative (Renna et al., 2023).

6. Conclusion

Of all the advantages provided by single-pill combination therapy as a regimen for hypertension therapy, it can be concluded that single-pill combination therapy can be effective, productive, safe, widely available, more cost-effective, and increase adherence to medication options for patients. Hypertension. Adherence to medication itself has a positive impact on quality of life; thus, by increasing adherence to antihypertensive medication, the quality of life of hypertensive patients also increases. Quality of life also has a relationship with adherence to medication since, with improving quality of life, the level of adherence to recommended medication also increases. What should not be forgotten is that, despite its advantages, single-pill combination therapy also has several potential issues and disadvantages, such as the lack of a fixed dose that can be adjusted for each individual, no robust direct data showing that single-pill combination therapy directly reduces cardiovascular morbidity and mortality rates, perceived as expensive compared to ordinary generic drugs, irrationally formulated combinations, adverse effects that can occur, issues related to the need to stop one of the drugs for a while, the need for regulations governing the use of single-pill combination therapy, and the goal of single-pill combination therapy that must be more focused. These potential issues and disadvantages must be taken into account when prescribing single-pill combination therapy as antihypertensive therapy. Opportunities for further research related to single-pill therapy are also opened up and hoped to pave the way for establishing a more effective and safe strategy for using single-pill combination therapy as medicine. Guidelines from The American College of Cardiology, American Heart Association, European Society of Cardiology, European Society of Hypertension, International Society of Hypertension, The Hypertension Canada Guidelines Committee, Argentine Federation of Cardiology, and Argentine Society of Hypertension all include single-pill combination therapy as a recommendation for treatment using antihypertensive drugs. This is because there are many advantages that can be obtained if you use single-pill combination therapy as an option. Implementing these guidelines in an orderly manner can reduce blood pressure optimally for hypertensive patients.

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