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Single-Pill Combination for Treatment of Hypertension: Only Better Adherence or Best Cardiovascular Prevention?

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Introduction

Cardiovascular disease (CVD) represents the leading cause of morbidity worldwide resulting in about one third of all deaths[1,2]. Despite significant advances in health care and access over the last 70 years, the global CVD burden continues increasing due to the maintained, even augmented, high prevalence of CVD risk factors. A large number of these CVD related deaths are driven by five modifiable CVD risk factors (hypertension, dyslipidaemia, type 2 diabetes, obesity and smoking), with elevated systolic blood pressure (SBP) being the largest contributor to population-attributable factors of incident CV events in all geographic areas[3-5].

Many international guidelines for screening, diagnosis and management of hypertension have been published in this period trying to convince caregivers of the urgent need for a better control of all CV risk factors, but a large proportion of patients remain undiagnosed or undertreated, being low adherence to either lifestyle changes and antihypertensive drug treatment some of the most important causes of poor BP control worldwide[6,7]. Although hypertension guidelines provide clear recommendations to overcome these problems, implementation is hampered by barriers at different levels: patient access to health care and best possible medications, suboptimal adherence to antihypertensive drug treatment, physician's inertia, and the huge disparities of health systems, either among high-income countries.

Underestimation of the impact of uncontrolled hypertension and limited health literacy lead to low adherence and persistence on treatment among patients, treatment inertia by physicians and lack of decisive healthcare system action. Causes of poor BP control rates are multifactorial, but a large body of evidence shows that one simple way to improve it is to use fixed-dose combination therapy, in which two or more classes of BP medications are present in a single pill or capsule (SPC). Unfortunately, this approach has been underutilized for many and complex reasons, where increasing use of SPC therapy could drastically improve hypertension control and reduce CV morbidity and mortality in both high- and low-income countries.

The most recent guidelines, i.e. 2020 ISH[8], 2021 WHO[9], 2023 ESH[10], 2024 ESC[11] and 2024 LASH[12] recommend the use of four major classes of antihypertensive agents in clinical practice: a) renin-angiotensin-aldosterone system (RAAS) blockers, including angiotensin receptor blockers (ARB) and angiotensin-converting

enzyme inhibitors (ACEi); b) calcium channel blockers (CCB), particularly dihydropyridine CCBs; c) thiazide and thiazide-like diuretics (DIU) such as hydrochlorothiazide, chlortalidone and indapamide; and d) long acting β-blockers with vasodilating properties[10,12]. However, some guidelines exclude β-blockers of the first line[8,9,11]. As summarized in Table 1, the majority of these guidelines recommend initiation of antihypertensive treatment with a SPC containing an ARB or ACEi (ensuring that the RAS is inhibited as part of the treatment strategy, which is important for many patient groups sucha as patients with diabetes, LVH, and CKD with or without proteinuria) plus a dihydropyrine CCB or a thiazide/thiazide-like diuretic for most patients. This approach is facilitated by the availability of many dual fixed-dose antihypertensive combinations in a SPC with a range of dosages, which eliminates the often-stated disadvantage of SPC therapy such as the inability to increase the dose of one drug independently of the other. In addition, the availability of three-drug SPC has also improved, although they are invariably based on a thiazide/thiazide-like diuretic, a RAS blocker (ACEi or ARB) and a DH-CCB.

Importantly, all these guidelines emphasize that monotherapy should be reserved for patients with low risk for atherosclerotic cardiovascular disease (ASCVD) and BP < 150/95 mmHg, or frail patients and/or advanced age[8-12]. Therefore, the current inertia for the initial use of monotherapy by most physicians worldwide should be reversed to the initial use of SPC therapy for most patients. In addition, all guidelines consider that β-blockers should be use in patients with specific clinical conditions such as heart failure with reduced ejection fraction (HFrEF), chronic coronary syndromes, post-myocardial infarction, and atrial fibrillation requiring heart rate control. Also in low risk hypertensive patients with elevated resting heart rate > 80 bpm, and younger hypertensive women planning pregnancy or already pregnant, BB should be considered in monotherapy or in combination[8-12].

Table 1. Recommendations of the most recent guidelines about the use of combination therapy of antihypertensive drugs in a single pill to start treatment in most patients.

2020 ISH hypertension practice guidelines[8].	2021 WHO hypertension guidelines[9].	2023 ESH hypertension guidelines[10].	2024 ESC hypertension guidelines[11].	2024 LASH hypertension guidelines[12].
• Initiation of therapy with two agents of different classes (ACEi or ARB plus a DH-CCB) • If BP not at target with full dose of dual therapy, add a T/TL diuretic.	• Initiation of therapy with two agents chosen from the following four drug classes: T/TL diuretic, ACEi/ARB, long-acting DH-CCBs. • If BP not at target with full dose of dual therapy, add a third drug.	• Dual combination as initial therapy for most hypertensive patients. • Preferred combinations are ACEi or ARB plus a DH-CCB or a T/TL diuretic. • All five major drug classes (ACEi, ARB, β-blockers, CCBs, T/TL diuretics) can be combined with one another, except for ACEi and ARB. • If BP not at target with full dose of dual therapy, add a third drug.	• Dual combination therapy at low dose to start treatment. • Preferred combinations are ACEi or ARB plus a DH-CCB or a T/TL diuretic. • The major four drug classes (ACEi, ARB, DH-CCBs, and thiazide or thiazide-like diuretics) are recommended as first- line BP-lowering medications, either alone or in combination	• Dual combination of ARB or ACEi plus DH-CCBs or T/TL diuretic at low dose as initial therapy in most patients. • If BP not at target with low dose dual combination increase to full dose or add a third drug in a triple low dose SPC. • If BP is not controlled with a dual combination at full-tolerated doses, add a third drug in a triple SPC
• Preferred use of SPC. • Use free combinations if SPCs are not available or unaffordable. • Reduce polypharmacy using SPC in once daily dosing over multiple times per day dosing.	• Preferred use of SPC of these four major drug classes to improve adherence and persistence.	• The use of SPCs should be preferred at any treatment step, i.e. during initiation of therapy with a two-drug combination and at any other step of treatment.	• A SPC initially containing two of these four major drug classes at low dose recommended for most.	• Fixed dose SPC of two or three drugs are preferred over free combinations with multiple drugs to increase adherence and persistence on treatment.

ACEi: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker; DH-CCB: dihydropyridine calcium channel blocker; T/TL: thiazide (hydrochlorothiazide)/thiazide-like (chlortalidone or indapamide) diuretic; SPC: fixed dose single pill combination; ISH: International Society of Hypertension; ESH: European Society of Hypertension; ESC: European Society of Cardiology; LASH: Latin American Society of Hypertension; WHO: World Health Organization.

The Importance of Adherence and Persistence on Treatment

The recommendation of the preferred use of SPC to start antihypertensive treatment is supported by robust evidence showing that this strategy induces greater BP reductions than monotherapy, may reduce side effects of the individual components (i.e. reducing the risk of hypokalemia due to diuretics, or the prevalence of peripheral oedema due to CCBs), improves therapeutic adherence and long-term persistence on treatment, and achieves earlier BP control. All these effects let to the reduction in cardiovascular events and mortality[8-13]. As mentioned before, all current data show that BP control is poor worldwide[6-8], being attributed to factors related to patient (the asymptomatic expression of hypertension, the lack of understanding the need persistent treatment, fear to possible or experienced adverse effects, perception of lack of treatment benefit, or treatment interference with patient's daily schedule, among others), some others related to physicians (physician's inertia, complexity of the prescribed regimen, lack of guidelines knowledge or training, time constraints and communications skills), and unsupportive healthcare systems (access to care, medication cost and affordability). Considering all these factors, low adherence to antihypertensive medication is recognized as a major contributor to poor BP control rates[8-13], and many studies confirm that poor adherence to medications is a crucial problem even in secondary prevention of patients in secondary prevention after a CV event[14-16].

When looking at adherence from the clinician's perspective, the patient-clinician relationship is a key element for both assessing adherence and selecting interventions tailored to the patient's profile. Evidence from clinical trials fully supports that the number of prescribed pills is inversely related to adherence to treatment, and the number of prescribed drugs is directly associated with an increased risk of non-adherence ranging from 74% (95% CI: 32-129) to 85% (95% CI: 58-116) in different studies[17-19]. A simple and easy measure such a simplification of treatment regimens by reducing the number of pills from two in a free equivalent combination (FEC) to one SPC may have an important positive impact improving 78% adherence and 87% persistence on medication[20], with the consequent reductions of CVD outcomes (about 11% to 17%) and healthcare costs[21,22].

We did recently a systematic review and meta-analysis of 44 studies assessing whether SPC therapy led to improved adherence, persistence, and better BP control compared with FEC therapy in adults aged ≥18 years with hypertension receiving SPC or FEC antihypertensive therapy[20]. Adherence, persistence, and reductions in systolic BP and/or diastolic BP were measured and compared. Most of the studies included in the analysis (18 of 23) showed that adherence was significantly improved in patients receiving SPC in comparison with those receiving FEC. Sixteen studies measured persistence, of which 14 (87%) showed that patients receiving SPC had significantly improved persistence, or were significantly less likely to discontinue therapy than patients receiving FEC. SBP (mean difference, −3.99 mmHg; 95% CI, −7.92 to −0.07; P=0.05) and DBP (−1.54 mmHg; 95% CI, −2.67 to −0.41; P=0.0076) were both significantly reduced with SPC therapy compared with FEC therapy at week 12. Figure 1 summarizes the results of 44 studies comparing adherence in patients treated with SPC vs FEC antihypertensive strategy[20].

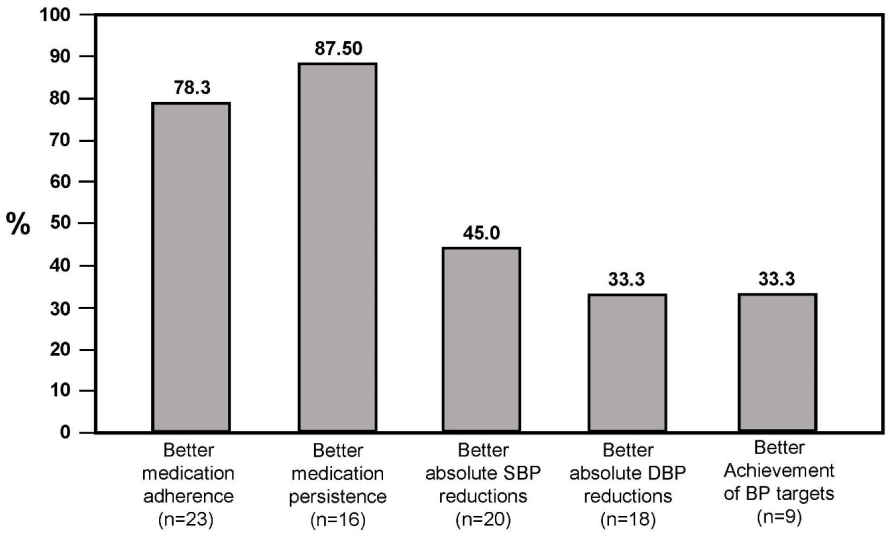

Figure 1: Percentage of patients improving adherence, persistence, absolute reductions of systolic (SBP) and diastolic (DBP) blood pressure, and better achievement of BP control under treatment with a single pill combination compared to free combination strategies in 44 studies. Parenthesis show the number of studies in which the parameter was reported. Data obtained from reference 20.

SPC therapy offers a number of potential advantages over FEC therapy, including improved tolerability, reduced pill burden, lower medical costs and resource utilization, reduced clinical inertia, and improved patient medication adherence, leading to improved BP control rates in hypertensive patients. However, several disadvantages and potential drawbacks of SPC compared to FEC therapy must be considered. Access to SPC may be hampered by problems related to cost and availability, not only in low-income countries but also in several high-income countries where fixed-dose combinations are not refunded. Presence of side effects of one of the components may limit its use, although the current availability of many dual and triple fixed-dose antihypertensive combinations in a SPC with a wide range of dosages eliminates this often-stated disadvantage. Finally, difficulties in the use of SPC in special groups of patients such as pregnant women, elderly patients with many associated comorbidities, or patients with CKD requiring a particular treatment approach must be mentioned.

In summary, all guidelines states that simplifying treatment regimens by using fixed-dose combinations of antihypertensive drugs in a SPC should be recommended[8-13]. The consequence of this recommendation is that local, regional, and national health authorities should increase efforts by placing SPC in drug formularies for the treatment of hypertension.

Only Better Adherence or Greater Cardiovascular Prevention?

The 2021 WHO Hypertension Guidelines[9] encouraged for new research studies on real-world experiences designed to determine if there is a difference in clinical outcomes, such as reduction in MACE, mortality, and serious adverse events between SPC versus FPC. The complexity and costs of prospective randomized clinical trials (RCTs) designed for this purpose partially explain the lack of these data. The most recent 2024 ESC Guidelines[11] insists on the fact that there are no outcomes data from prospective trials designed to prove superiority of upfront combination therapy (either as SPC or as FEC) over upfront monotherapy in the isolated treatment of hypertension. To my knowledge only two RCTs, the Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension (ACCOMPLISH) and the Combination Therapy of Hypertension to Prevent Cardiovascular Events (COPE) trials have directly compared this issue in hypertensive patients qualifying for dual combination therapy[23,24]. So, there is insufficient evidence from both RCTs and observational studies on how a narrowing of gaps in clinical practice relative to up-to-date guideline recommendations would translate to clinical benefit in hypertensive patients.

To expand insights into these gap we recently conducted a Monte Carlo simulation analysis to evaluate the 10-year clinical benefit, as measured by the absolute reduction in CV events, of optimal treatment with guideline-recommended dual agents in comparison to monotherapy in patients qualifying for dual BP-lowering therapy as per the 2018 ESC/ESH guidelines[25]. The data for this simulation came from a population of 1.1 million individuals with hypertension from the United Kingdom (UK) initiating

Table 2. Event Rates and absolute cardiovascular risk reduction for the primary endpoint: Overall population and atherosclerotic cardiovascular disease (ASCVD) or diabetes subgroups. Adapted from reference 25.

	All cohort (N=1,108,055)	ASCVD (N = 172,722)	No ASCVD (N = 935,333)	DM (N = 152,666)	No DM (N = 955,389)
Monotherapy or no treatment Event rates at 10 years (%)					
Untreated patients	22.4	47.6	17.8	32.6	20.7
Monotherapy: 100% Persistence	17.6	41.7	14.8	26.7	17.8
Observed Clinical Practice	17.8	42.7	13.3	28.3	16.1
% Risk reduction at 10 Years (Reference: Untreated)					
Monotherapy: 100% Persistence	4.8	5.9	3.0	5.9	2.9
Observed Clinical Practice	4.6	4.9	4.5	4.3	4.6
Dual SPC therapy (ARB + DH-CCB)					
Event Rate at 10 Years (%)					
Dual Therapy: 100% Persistence	13.6	31.8	11.2	21.0	13.0
Dual Therapy: 50% Persistence	22.2	47.0	17.4	31.8	20.6
% Risk reduction at 10 Years (Reference: Untreated)					
Dual Therapy: 100% Persistence	8.7	15.9	6.6	11.7	7.8
Dual Therapy: 50% Persistence	0.2	0.6	0.4	0.8	0.2

ASCVD: atherosclerotic cardiovascular disease; DM: type 2 diabetes mellitus; SPC: fixed-dose single pill combination; ARB: angiotensin II receptor blocker; DH-CCB: dihydropyridine calcium channel blocker.

antihypertensive therapy who were identified in the Clinical Practice Research Datalink (CPRD), Hospital Episode Statistics (HES) and Office for National Statistics (ONS) databases in the UK during 2005-2019. The primary endpoint represented a composite of non-fatal myocardial infarction (MI), non-fatal stroke (ischemic or haemorrhagic), non-fatal heart failure (HF) hospitalization or CV death.

In the overall population, the estimated 10-year event rates for the primary endpoint in patients with 100% persistence in monotherapy were 17.0 to 17.6 %, quite similar to the observed in clinical practice (17.8%). In patients with 100% persistence in dual therapy, estimated event rates were 13.6% for dual combinations of the ARB irbesartan plus the dihydropyridine CCB amlodipine (Table 2). Moreover, the absolute risk for the primary endpoint was reduced by 15.9% in patients with clinical (ASCVD) and by 6.6% in those without ASCVD. Similarly, the absolute risk was reduced by 11.7% in diabetics and 7.8% in those without diabetes, what is consistent with the fact that clinical benefit becomes higher with increasing baseline CV risk.

One interesting finding of this study was that in the scenario representing 50% persistence on dual therapy, the estimated 10-year event rates for the primary endpoint was close to the 0.6% observed in untreated patients and in those with 50% persistence in monotherapy, and even close to the observed 0.8% reduction in high risk subgroups with ASCVD or diabetes, indicating the lack of net clinical benefit with suboptimal persistence even in dual therapy. These findings reinforce and quantify a fundamental principle in achieving a good clinical outcome with antihypertensive therapy, which is to ensure adherence (i.e., following the prescribed regimen) and persistence (i.e., staying on therapy). In summary, the wide implementation of guidelines-based recommended treatment strategy in clinical practice, particularly in the form of SPC, with high persistence relative to monotherapy or free combinations, in hypertensive patients demonstrates the potential opportunity for a greater CV risk reduction[25].

The difficulty and cost in designing RCTs comparing therapeutic strategies, i.e. initial monotherapy vs. combination treatment on MACE and mortality, or comparing SPC vs. FPC strategies on hard endpoints, lead to new research approaches in the field. The transferability of the results of RCTs to clinical practice must be also a problem because RCTs are conducted in conditions of superior level of expertise, fewer errors in decisions, much better treatment adherence, and lower therapeutic inertia than in real-life practice. As stated in the 2023 ESH guidelines large local, regional or national registries and extensive biobank data, most covering long periods are now available and suitable data sources for addressing problems unaddressed by trials. These databases reflect the real-world patient heterogeneity, thereby offering better options for the development of precision or individualized medicine and their results can be obtained at reduced cost and much more quickly than in RCTS[10].

Disclosure

The author do not have any conflict of interest concerning this manuscript.

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