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Single pill combination therapy for hypertension: New evidence and new challenges
Combination Therapy for Hypertension

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ABSTRACT

Hypertension (HTN) continues to be one of the most important risk factors for major cardiovascular events and mortality. The global prevalence of hypertension is approximately 30% among adults over 20 years old. Cardiovascular risk stratification is crucial to determine the most appropriate pharmacological therapeutic strategy for hypertensive patients. Despite the many scales to stratify risk, none is perfect and represents weighted mathematical models to determine risk at 10 years. Reports have identified numerous limitations, and the challenge persists. A practical way to determine CV risk is the clinical approach based on 1) the number of risk factors, 2) the degree of elevation of blood pressure, 3) the presence of target organ damage/DM/CKD, and 4) a history of major cardiovascular events. Currently, it is recommended to start with dual therapy in a single pill (either ACE inhibitors or ARB2 + dihydropyridine calcium channel blockers or thiazide/thiazide-like diuretic); however, many patients could need to start with triple therapy (low or standard doses) if they belong to the high- or very high-risk group with elevation grade 2 or 3 of blood pressure. This article discusses this topic and establishes some practical recommendations for the physician of first contact.

High blood pressure is the single most important cardiovascular (CV) risk factor worldwide because of its high prevalence in the population and its important impact on a large number of CV and renal consequences [1]. There is strong proof that treating high blood pressure with appropriate drugs significantly lowers the chances of heart attack, stroke, heart failure, kidney failure, problems with neurological blood flow, and memory issues [2]. Yet, hypertension remains today the first cause of death and burden of disease [3] because, despite progress in its diagnostic and treatment approaches, great challenges remain to be resolved. In a practical context, the most important challenges are that the detection and treatment of hypertension are far from optimal. Furthermore, the percentage of hypertensive patients in whom treatment achieves the blood pressure (BP) value at which CV protection is maximized (BP control) varies from country to country. A common denominator is an overall low rate, with the persistence of a CV risk greater than that of normotensive individuals [4].

Over the past decade, there has been a significant modification in the approach to pharmacological treatment of hypertension. Currently, most international guidelines suggest that most people with high blood pressure should use a combination of antihypertensive drugs because it is widely accepted that using only one drug is effective for only a few patients, and higher doses may increase adverse effects; therefore, most patients require two or three drugs to effectively control their blood pressure. There is also a common understanding that to improve unhealthy lifestyles, non-drug treatment strategies should be used at any blood pressure level because they can lower blood pressure, enhance the effects of antihypertensive drugs, and decrease the risk of cardiovascular issues and the chance of developing hypertension over

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a lifetime. However, there are some disagreements among guidelines regarding the BP values at which drug treatment should begin. In the 2023 ESH guidelines drug treatment initiation is recommended when systolic BP is ≥ 140 mmHg and/or diastolic BP is ≥ 90 mmHg, except for those patients with a very high cardiovascular risk (those with previous CV events), in whom the recommended treatment threshold is systolic BP ≥ 130 or diastolic BP ≥ 80. The 2024 ESC guidelines remarks [6], that antihypertensive drug treatment should be implemented within a BP range between 130-139/80-89 mmHg whenever CV risk (calculated by a score based on European data) is ≥ 10%, i.e., with established BP disease, diabetes, organ damage, or moderate to severe chronic kidney disease. The same criteria, albeit with greater caution, apply to old and very old (age > 80 years) subjects. Currently, these lower threshold values are the object of controversy because their support originates from a meta-analysis but not from evidence from any "ad hoc" individual trial. Additionally, when considering their acceptance for clinical practice, it is important to recognize that setting the threshold for drug treatment at 130/80 mmHg BP in adults with a 10-year risk of a cardiovascular event greater than -10% or even between 5% and 9% should significantly increase the number of candidates for antihypertensive medication. In most Western countries, virtually all males aged ≥ 70 years and females aged ≥ 75 years have a CV risk ≥ 10% [7].

Also, it is important to note that using a combination of two antihypertensive drugs is much more effective at lowering blood pressure than using just one and adding a third drug can lower it even more [9]. These findings can be explained by the fact that hypertension is a multifactorial condition, and BP is a multi-regulated variable. In simpler terms, combination therapy works better at lowering blood pressure because it can address the various underlying issues that cause high blood pressure [6–9]. Of course, the "corollary" dictates that the drugs combining should always have distinct mechanisms of action, not ones that overlap. This requirement does not limit the number of drug combinations available because studies show that antihypertensive treatment can be effective with various drugs that work in different ways, such as ACE inhibitors, ARBs, dihydropyridine calcium channel blockers (CCBs), and diuretics (thiazides and thiazide-like). Indeed, there are many protective drugs that work in different ways because, as noted by the 2023 ESH guidelines, beta-blockers also meet the key requirements for other major drug choices, such as showing they can lower blood pressure (since most of the treatment's protective effect relies on reducing blood pressure itself), providing cardiovascular protection compared to a placebo, and protecting against heart issues like coronary problems, strokes, and heart failure, with overall cardiovascular protection similar to other major drugs in studies [12]. It is also important to remember that, except for the ACEI/ARB combination, virtually all combinations between major antihypertensive drugs have shown the ability to effectively reduce BP, and that in most instances their combined use in outcome trials has resulted in CV protection (2018 ESC/ESHs) [5]. Thus, antihypertensive treatment with two drugs can offer physicians a choice between a large number of clinically validated combinations. The options are more limited when it comes to using three different types of drugs together, which usually include a diuretic, a renin-angiotensin system blocker, and a calcium channel blocker. Greater diversification, however, is possible, such as with the use of a beta-blocker in several specific conditions [12].

Other questions of great importance for clinical practice have emerged in the meantime. For instance, it is not well established whether: (i) the clinical effects differ for the association of a blocker of the renin-angiotensin system with a calcium antagonist or a diuretic. The former is perhaps a better choice for patients with dysmetabolic disorders, and the second when there is evidence of hypervolemia [13]. (ii) The association with a renin-angiotensin system blocker should favor an ACEi or an ARB., (iii) In a patient unresponsive to low doses of dual therapy, should up-titration or immediately go to triple therapy or to dose escalation of the double therapy component? (iv) Initial triple therapy should be considered in some patients (see below), and (v) in old patients who need deprescribing because of side effects and risk of hypotensive episodes, the preferred strategy should be reduction of drug doses or the number of drugs. On these and other issues, indisputable evidence is not available, i.e., data from controlled clinical trials are absent or controversial, which is why in guidelines the related treatment recommendations are not supported by the maximal level of evidence (IA) but by levels (IIa and IIb) that reflect the incomplete or controversial data availability. Unfortunately, this extends to several practical aspects of treatment. In several cases, the evidence is so limited that the treatment recommendations can only be based on unanimous or consensus among the expert group guidelines [3–12].

Initial two-drug treatment in a single-pill combination

An important element of novelty of the recent European guidelines (2023 ESH, 2024 ESC) [6,7] has been the recommendation to make use of double drug treatment as the initial treatment step in the majority of hypertensive patients and not just in those with a marked BP elevation, as recommended by past guidelines (2017 USA guidelines) [9]. Initial monotherapy has been reserved for very high-risk patients with BP in the 130-139/80-89 mmHg range because, at these initial BP values, only a few mmHg are required to reach the recommended BP target of <130/80 mmHg (although some authors recommend ideally 120/70 mmHg). Initial monotherapy is also recommended in those with a systolic BP slightly > 140/90 mmHg (provided that CV risk is only mildly increased) and in very old patients and frail patients, in this case, to avoid the risk of excessive BP reductions and injurious falls. Large use of initial combination treatment has been regarded as necessary because (i) the current lower BP target for treatment requires greater BP reductions, which are often only achievable with drug combinations. This is exemplified by the use of three drugs in most patients randomized to a systolic BP target of <120 mmHg in the SPRINT trial (14) and (ii) the evidence that in many countries monotherapy remains the most common treatment strategy because therapeutic inertia prevents up-titration of treatment to two or more prescribed drugs [5]. The advantages of initial dual combination treatment have not been tested by randomized outcome trials comparing the risk of outcomes in patients starting treatment with one or two drugs, but strong support for initial two-drug combination has been offered by large-scale real-life observational studies showing that initial use of two drugs improves long-term adherence to treatment, bypasses the problem of therapeutic inertia, favors long-term BP control, and reduces the risk of CV events [16], with only a small increase in the risk of an excessive BP reduction. The recommendation has been extended to the use of drug combinations in a single tablet because treatment simplification, such as a reduction in the daily number of pills, has been shown to markedly improve treatment adherence, favoring, as a result, BP control and CV protection [17]. In the 2023 ESH guidelines, it has been emphasized that while in the past the single pill, the two-drug combination, was almost entirely available only for a blocker of the renin-angiotensin system with a diuretic, the current choice is larger, and this larger choice is supported by evidence because, (i) except for the not recommended concomitant use of ACEIs and ARBs, all combinations of major antihypertensive drugs have been used in trials showing the protective effect of BP reduction [18], and (ii) many different combinations are now available as a single pill. For most dual combinations, current availability extends to lower and higher doses of the combination components, which

provides physicians with a good level of flexibility during the titration phase for BP control.

Triple-drug combined therapy

The European guidelines and other guidelines agree that if blood pressure (BP) isn't controlled after starting treatment with two drugs, the next step should be to increase the dose of one or both of those drugs and then consider adding a third drug, possibly in a single pill to keep treatment simple. The 2023 ES guidelines state that starting with three drugs should never be the first step to prevent the risk of too much BP lowering, which could lead to falls. However, the importance of three-drug therapy is still highlighted, as these guidelines note that while a two-drug combination can control BP in about 60% of patients, using three drugs can improve that control to over 90%, meaning that about one-third of patients may need three drugs. ISH guidelines mention that a three-drug administration should never be the initial treatment step to avoid the risk of an excessive and symptomatic BP reduction, with possible injury falls. The importance of the three-drug therapy, however, is not minimized because these guidelines also emphasized that while a double combination may control BP in about 60% of the patients, three-drug combinations raise this control to more than 90% of the patients, which means that three drugs may be needed in about one-third of treated individuals [7].

In general, however, information on the use of triple drug therapy as a first-line strategy remains limited, and more evidence on its advantages, disadvantages, and use in different treatment steps is needed. However, recently, several clinical trials using triple therapy have yielded encouraging results, even with low doses of triple therapy. This makes it clear that the more pathophysiological pathways are blocked, the greater the effect on hypertension. The analysis and descriptions of these trials are presented in the Table 1.

The rate of hypotensive episodes with a high dose of three-drug treatment is expected in nonselective patients. Nevertheless, as is shown in Table 1, the rate of hypotension using low, moderate, and standard doses of triple therapy is not significantly greater of dual therapy. In particular, the number of patients requiring three antihypertensive agents should be more precisely established because, with the current recommendation to pursue a target systolic BP $<$ 130 mmHg in most patients (achieving in many patients systolic values close to 120 mmHg), the use of three drugs may become more compelling. In the SPRINT trial, the arm randomized to a target systolic BP of $<$ 120 mmHg (actual on-treatment systolic BP 121-122 mmHg) almost always made use of three antihypertensive drugs [14,15]. Further arguments in favor of a larger use of triple therapy, possibly also as the first-line treatment step, are that (i) three drugs may be given at lower doses, and this may favor treatment tolerability because side effects are usually dose-related. (ii) three drugs may shorten the titration phase, with a potentially favorable effect on treatment inertia, an accepted major cause of failure to move from mono- to combination therapy (iii) the faster BP control guaranteed by initial three-drug use may add to the protective effect of treatment, particularly in people at high or very high CV risk [19]. In these patients, as well as in those with grade 3 or severe BP elevations, achieving the BP within a short time is perceived as necessary by many physicians, who for this reason may prefer to use low-dose triple therapy from the treatment initiation and work on their up-titration in the following steps. This may not be pathophysiologically inappropriate because a greater number of drugs may more successfully counteract the greater number of adverse mechanisms associated with high or very high CV risk (iv) because of the close relationship of adherence with the number of tablets to be taken daily [7], with the single-pill three-drug combinations, treatment adherence may be improved more clearly. A table containing the most relevant clinical trials, systematic reviews, meta-analyses, and real-world studies analyzing the triple combination is provided **in** Table 1.

Several studies have compared dual versus triple combination therapy as first-line treatment for moderate to severe hypertension [19]. Triple therapies have shown excellent tolerability, with adverse event profiles like dual regimen. In addition, in single-pill format, they have been associated with improved patient adherence to treatment, leading to better long-term BP control and reduced CV events. **The percentage of increase in adherence and persistence to treatment with SPC vs separate drugs has been fully demonstrated, and in general, it is increased by ∼30%. The consequence of improving adherence is reflected in better control and prognosis, and survival in the medium to long term** [19,20]. Better cost-effectiveness has also been reported. Finally, although currently triple therapies usually make use of a diuretic, a calcium channel blocker, and a blocker of the renin-angiotensin system (a mechanistically and clinically valid combination), in the future other combinations may expand the three-drug treatment potential. For example, a beta-blocker may replace one of the three drugs in several clinical conditions. A thiazide-like diuretic may be a more frequent alternative to the current large use of thiazide, particularly when there is kidney damage.

Finally, a very relevant aspect is to remove the wrong idea that treatment with SPC is more expensive; several recent studies have shown that, in addition to the improvement in adherence, persistence, and survival, the costs of QALY are favorable for the patient and the health system [21].

Cardiovascular risk stratification as a key to prescribing drugs in combination therapy

All guidelines agree that quantification of CV risk is important because identification of a high-risk level has several implications for the treatment strategy (lower BP threshold, faster achievement of BP control, use of specific antihypertensive drugs, more frequent visits, laboratory examinations, and assessment of organ damage during follow-up). This identification may be even more crucial in patients being evaluated for double or triple therapy, as they are more likely to have a greater degree of pathophysiological abnormalities. The indicator of a very high or high-risk level, such as a history of clinically overt CV events ($>$20% 10-year risk of an event or very high risk), subclinical organ damage, diabetes, severe hypertension, and three or more major CV risk factors together [9–12]. There is a huge number of calculators of CV risk, none is perfect and are based on mathematical algorithms with different determinant coefficients (R^2). Some of them are directed to specific groups, such as older adults, pregnant individuals, people of a certain race, and those of a certain gender [18,22–28]. In this sense, the table from ESH 2023 of risk stratification by degree and stage of blood pressure and associated risk factors is very helpful in clinical practice [7].

Monitoring using out-of-office BP

Monitoring using out-of-office BP, including ambulatory and home BP monitoring to detect masked hypertension and to avoid excessive BP lowering, is a keystone in the follow-up of hypertensive patients. One of the most common sources of adverse events or non-optimal control of BP is when using dual or triple therapy in SPC without out-of-office monitoring. The problem of the white coat or masked hypertension is very common even among patients with sustained hypertension. International guidelines, and we insist on this practice to avoid unnecessary opposing effects. Blood pressure variability is an additional risk factor to be considered, and in-depth knowledge of blood pressure behavior in and

Table 1
Principal recent clinical trials and meta-analysis on triple vs dual drug therapy for Hypertension.

Study	Sample Size	Characteristics of Patients	Comparison Groups	Follow-Up	BP Reduction	CV Effects
David A. Calhoun [29] CT	4285 patients enrolled, 583 Aml/Val/HCTZ 559 Val/HCTZ 568 Aml/Val 561 Aml/HCTZ	BP: ≥145 mm Hg; mean sitting diastolic BP: ≥100 mm Hg	Aml/Val/HCTZ 10/320/25 mg, Val/HCTZ 320/25 mg, Aml/Val 10/320 mg, or Aml/HCTZ 10/25 mg once daily.	8 weeks	Aml/Val/HCTZ -39 mmHg SBP -24 mmHg DBP Val/HCTZ -32 mmHg -19.7 (p>0.001)	Control Rate: Aml/Val/HCTZ 70.8% Val/HCTZ 48.3% Val/Aml 54.1% AEs leading to study discontinuation ~ 1% all similar
Kizilirmak et al [30] Metanalisis	11 studies (7563 Patients)	stage 1 or 2 hypertension	ARBs + Aml + HCTZ (dual or triple) at any dose	8 to 20 weeks	Dual Combination -25.5 mmHg SBP -14.0 mmHg DBP Triple Combination -32.9 mmHg SBP -18.7 mmHg DBP	Control Rate: Dual 49.8% Triple 67.7% AE risk was similar for dual and triple OR 0.96 p=0.43
Salam A. et al [31] PROSPERO TRIAL	Fourteen RCTs (11 457 pts)	sate 1 and 2 hypertension	ACEi/ARBs+Aml+BB or Diuretics (Dual or triple)	4 to 10 weeks	Dual Combination -32 mmHg SBP - 19 mmHg DBP Triple combination -36 mmHg SBP -16 mmHg DBP	AEs leading to study discontinuation 3.3% vs 3.4% Control Rate: Dual: 45% Triple: 58%
Oparil S. Et Al [32] TRINITY	2492 patients	stage ≥ 2 Hypertension	OM 40 mg/AML 10 mg (628 patients) OM 40 mg/HCTZ 25 mg (637 patients) AML 10 mg/HCTZ 25 mg (627 patients) **OM 40 mg/AML 10 mg/ HCTZ 25 mg** (600tients)	12 weeks	- 30.6 mmHg SBP - 17.5 mmHg DBP 30.0 mmHg SBP 16.0 mmHg DBP - 28.7 mmHg SBP - 14.7 mmHg DBP **- 37.5 mmHg SBP*** **- 21.0 mmHg DBP*** *p < 0.01 Triple vs dual combination	Control Rate average: Dual 46.1% Triple 63 % AEs leading to study discontinuation Triple 4% Dual 1-3%
Hong PJ et al [33]	N=340 patients Aml/Los/CTD, (N=171) Aml/Los (N=169)	Stage 2 HT	Aml 5 mg+ Los 50mg +CTD 12.5mg vs Aml 5 mg+Los 50mg After 2 weeks the doses were doubled	8 weeks	Triple -16.4 mmHg - 8.0 mmHg DBP Dual - 6.9 mmHg SBP -3.6 mmHg DBP	Control rate: SBP 55.7% 29.8% There were no serious AE
Webster R. TRIUMPH [34]	700 patients (349 Triple 351 Usual Care)	Stage 1 and 2 HT	Triple Combination: 20 mg of telmisartan, 2.5 mg of amlodipine, and 12.5 mg of chlorthalidone. Vs. Usual Care: Monotherapy or dual; Triple combination Was doubled at discretion of GP	6 months	Triple Combination -29 mmHg SBP -13 mmHg DBP Usual Care -20.3 mmHg SBP - 9.3 mmHg DBP	Control rate: Triple 69.5% Usual C. 55.3% AEs leading to study discontinuation Triple 6.6% Usual C. 6.8%
Mourad et al. [35]	449 patients Per/aml/ind (225 patients) Per/Ind (224 patients)	Stage ≥ 2 HT	Triple: Per/ind/aml 5/1.25/5 mg Per/Ind 5/1.25 mg Doses were doubled at discretion of GP (~25% in both) (144 in triple & 163 in dual)	3 months	Triple -20.8 mmHg SBP -12.9 mmHg DBP Dual -16.8 mmHg SBP -9.8 mmHg DBP p < 0.01	Control rate: Triple: 56% Dual 45% AEs leading to study discontinuation 3% in both
Nedogoda SV. et al [36]	148 patients 75 Per/Aml/ind(SPC) 73 Per/Ind+Aml	Stage 2 HT	Per/Aml/Ind SPC (5/5/1.25 mg) Per/Ind+Aml (5/1.25 + 5 mg)	12 weeks	SPC - 21.5 mmHg SBP -15.3 mmHg DBP Per/Ind+Aml -20.0 mmHg SBP -14.8 mmHg DBP	Control rate: SPC 87.8% Per/Ind+Aml 78.6% Simiar AE No serious

(continued on next page)

Table 1 (*continued*)

Study	Sample Size	Characteristics of Patients	Comparison Groups	Follow-Up	BP Reduction	CV Effects
Rodgers A. et al [37]	295 patients 63 Placebo 113 GMRx ¼ 119 GMRx ½	Home SBP basal 130 to 154 mmHg	GMRx1/4: Telmisartan 10mg Amlodipino 1.25 mg Indapamide 0.625 mg GMRx1/2: Telmisartan 20mg Amlodipino 2.50 mg Indapamide 1.25 mg	4 weeks	Placebo: Clinic 136±10 mmHg SBP 87± 9 mmHg DBP GMRx1/4 vs Placebo: Clinic -8.0 mmHg SBP -4.0 mmHg DBP Home BP -7.3 mmHg SBP -4.0 mmHg DBP GMRx1/2: Clinic: -9.5 mmHg SBP -4.9 mmHg SBP Home BP -8.2 mmHg SBP -5.5 mmHg DBP	Control rate: < 140/90 mmHg Placebo: 36% GMRx1/4: 65% GMRx1/2: 70% < 130/80 mmHg Placebo: 3% GMRx1/4: 20% GMRx1/2: 30% AEs leading to study discontinuation: Placebo 1.6% GMRx1/4: 0% GMRx1/2: 5.1%
Rodgers A. et al [38]	GMRx (N=551) Tel/ind (N=276) Tel/Aml (N=282) Aml/Ind (N=276)	All patients stage 1 and 2 ~1.6 antihypertensive drugs were taken previously in average. All randomly allocated (2:1:1:1) to continued GMRx2 half dose or dual half doses combinations; after 6 weeks all doses were doubled.	GMRx2, (telmisartan 20 mg, amlodipine 2•5 mg, and indapamide 1•25 mg); Tel/ind (20 mg/1.25mg) Tel/Aml(20 mg/2.5 mg) Aml/ind(2.5mg/1.25 mg) After 6 weeks all doses were doubled	4 weeks run in & switched to GMRx2 half dose. 6 weeks 4 groups Half doses. Then all doses were doubled	At screening All BP in Clinic ~ 142 mmHg SBP ~ 86 mmHg DBP 6 weeks: GMRx **-10 mmHg SBP** - 6 mmHg DBP Tel/ind -8 mm Hg SBP -4 mmHg DBP Tel/Aml -6 mmHg SBP -3 mmHg DBP Aml/Ind -4 mmHg SBP -2 mmHg DBP 12 Weeks: GMRx3 **-14 mmHg SBP** - 9 mmHg DBP Tel/ind -10 mmHg SBP - 4 mmHg DBP Tel/Aml -8 mmHg SBP -3 mmHg DBP Aml/Ind -7 mmHg SBP - 2 mmHg DBP	Control Rate in Clinic (< 140/90) GMRx: 74% All duals, 53 to 61%. AEs leading to study discontinuation, GMRx 2% Duals 1%

Aml, Amlodipine; ARBs, angiotensin receptor blockers; ACEi, Angiotensin-Converting Enzyme Inhibitors; BB, beta blockers; BP, blood pressure; HCTZ, hidrochlorotiazyde; OM, olmesartan, Val, Valsartan; GMRx2", Telmisartan 20 mg + Amlodipine 2.5 mg + Indapamide 1.25 mg; Tel, telmisartan; Ind, indapamide; CV, cardiovascular HT, Hypertension; Los, Losartan; CTD, chlortalidone; Per, perindopril; AE, adverse event; GMR, telmisartan+amlodipine+indapamide.

out of the office will help to adequately optimize treatment with SPC therapy (dual, triple, or more), and improve prognosis and survival [5–7].

Conclusions and trends in hypertension drug therapy

The rapid advancement in technologies, genetics, biology, and pathophysiology issues is having an impact on many diseases. Hypertension is no exception. New treatments using RNA silencers and new drugs with promising results are also under study. The initial results show a BP reduction lasting weeks or months for a single injection and thus a potential for successfully addressing to improve treatment adherence. However, there is little doubt that, due to the multifactorial nature of the high BP condition, even with new treatments, a combined pharmacological approach will maintain a central position among the treatment strategies against hypertension. In this context, dual therapy in SPC will continue to play a major role, but three-drug treatment as a single pill will probably be needed in more than the actual one-third of the patients to ensure optimal BP control. As mentioned above, triple combination therapy has been shown to lower BP noticeably more than dual therapy, and, although more evidence is needed, its use

Hypertension disease staging	Other risk factors, HMOD, CVD or CKD	BP (mmHg) grading			
		High-normal SBP 130–139 DBP 85–89	Grade 1 SBP 140–159 DBP 90–99	Grade 2 SBP 160–179 DBP 100–109	Grade 3 SBP ≥ 180 DBP ≥ 110
Stage 1	No other risk factors[a]	No Pharmacological Therapy	Monotherapy or low-dose dual	Dual	Triple
	1 or 2 risk factors	No Pharmacological Therapy	Dual	Dual/Triple	Triple
	≥3 risk factors	Monotherapy or Dual	Dual	Dual/Triple	Triple
Stage 2	HMOD, CKD grade 3, or diabetes mellitus	Low Dose Dual	Dual	Dual/Triple	Triple
Stage 3	Established CVD or CKD grade ≥4	Low Dose Dual	Dual	Dual or Triple	Triple

Fig. 1. Trends in selecting a combination therapy for hypertension. Each case must be individualized in its integral context, and the decision to start with low or standard doses.

does not appear to majorly affect treatment tolerability. Except for patients aged more than 80 years, the use of three antihypertensive drugs at lower doses may in the future also find a place as a first-step treatment for high- or very high-CV-risk patients, including those with grade 3 hypertension, ensuring wider and faster BP control (Fig. 1). Three drugs might also benefit these patients via their BP-independent CV and renal protective properties that have been suggested or demonstrated in many studies. Fig. 1 provides a general overview of where the combined therapeutic strategy to treat arterial hypertension might be heading. Using high- or low-dose triple therapy will depend on the baseline BP level as well as the high- or very high-risk level of CV risk. Perhaps, in the future, new combinations will be commercialized, such as therapy with 4 antihypertensive drugs plus statins or iSGLT2.

Declaration of competing interest

The authors declare that **they have no known** competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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CRediT authorship contribution statement

Martin Rosas-Peralta: Writing – original draft, Investigation, Conceptualization. **Giuseppe Mancia:** Writing – original draft, Investigation, Data curation, Conceptualization. **Miguel Camafort:** Writing – original draft, Conceptualization. **Héctor Galván-Oseguera:** Writing – review & editing, Supervision, Investigation. **Carlos M. Ferrario:** Writing – review & editing, Conceptualization. **Luis Alcocer:** Writing – review & editing, Supervision, Formal analysis, Conceptualization. **Ernesto Cardona-Muñoz:** Writing – review & editing, Formal analysis. **Humberto Álvarez-López:** Writing – review & editing, Conceptualization. **Silvia Palomo-Piñón:** Writing – review & editing, Conceptualization. **Adolfo Chávez-Mendoza:** Writing – review & editing, Conceptualization. **Enrique Díaz-Díaz:** Writing – review & editing, Conceptualization. **José M Enciso-Muñoz:** Writing – review & editing, Investigation, Conceptualization.

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