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New approach to blood pressure control: Triple combination pill ☆

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ABSTRACT

Blood pressure (BP) control remains insufficient worldwide, mostly due to poor adherence to treatments, clinical inertia, adverse effects and underuse of drug-combination strategies.

Monotherapy and its uptitration have been long considered the first-line strategy in the treatment of hypertension, often leading to ineffective, time consuming and frustrating results.

On the other hand, several studies have demonstrated that starting and continuing antihypertensive therapy based on a drug combination is associated with a greater reduction of BP, an earlier achievement of therapeutic goals and a higher proportion of patients achieving targets with favorable implications on cardiovascular events.

However, one-fourth to one-third of hypertensive patients fail to achieve BP control even with dual combination therapies, requiring three or more antihypertensive agents.

The aim of this review is to discuss the effects of triple-drug associations in terms of BP lowering and prevention of major cardiovascular events, also in high-risk patients.

We also discuss available data on side effects and tolerability of triple combination therapy, and the advantages to use a single-pill formulation to promote simplification and adherence to therapy. The findings reported have provided the background for most recent international guidelines on hypertension that support the use of dual and triple combination therapy for most patients.

Introduction

Although hypertension is the most common and probably the most intensively investigated cardiovascular (CV) risk factor, blood pressure (BP) control remains insufficient worldwide, since only 40–50% of treated hypertensive patients achieve the recommended targets, as shown by several epidemiological studies and meta-analyses [1]. In view of the more ambitious therapeutic targets recommended by the most recent 2018 European Society of Cardiology/European Society of Hypertension (ESC/ESH) [2] and 2017 American Heart Association/American College of Cardiology (AHA/ACC) [3] guidelines, which suggest achieving systolic BP (SBP) levels between 130 and 120 mmHg and diastolic BP (DBP) levels between 80 and 70 mmHg in most hypertensive subjects, the proportion of uncontrolled patients will unavoidably increase further.

Several factors contribute to poor control of BP. These include insufficient adherence to prescribed treatments, clinical inertia, adverse side effects and underuse of drug-combination strategies.

Monotherapy, in fact, is not sufficient to achieve an adequate BP control in most treated hypertensive patients, with little additional BP lowering obtained by uptitrating the doses of monotherapies and potentially increased risk of dose-related adverse events [4]. In addition, switching from one monotherapy to another, as suggested by previous sets of guidelines, is often ineffective, time consuming and frustrating, further reducing the adherence to the treatment and even the patient commitment and the patient-physician communication and trust [5].

Since it has been reported that the estimated expected BP lowering effect with a standard dose of one antihypertensive drug is [9.1 + 0.10 × (baseline SBP-154)] and [5.5 + 0.11 × (baseline DBP-97)] [6], it is intuitive that monotherapy cannot represent the optimal clinical choice for most individuals, especially for those with grade 2 (SBP between 160 and 179 mmHg, DBP between 100 and 109 mmHg), grade 3 (SBP ≥180 mmHg and DBP ≥110 mmHg) hypertension and grade 1 (SBP between 140 and 159 mmHg, DBP between 90 and 99 mmHg) hypertensives with high or very-high estimated CV risk, according to the ESC/ESH guidelines [2].

In addition, combining anti-hypertensive agents from two different classes has been shown to result in an approximately five-fold greater BP reduction with respect to doubling the dose

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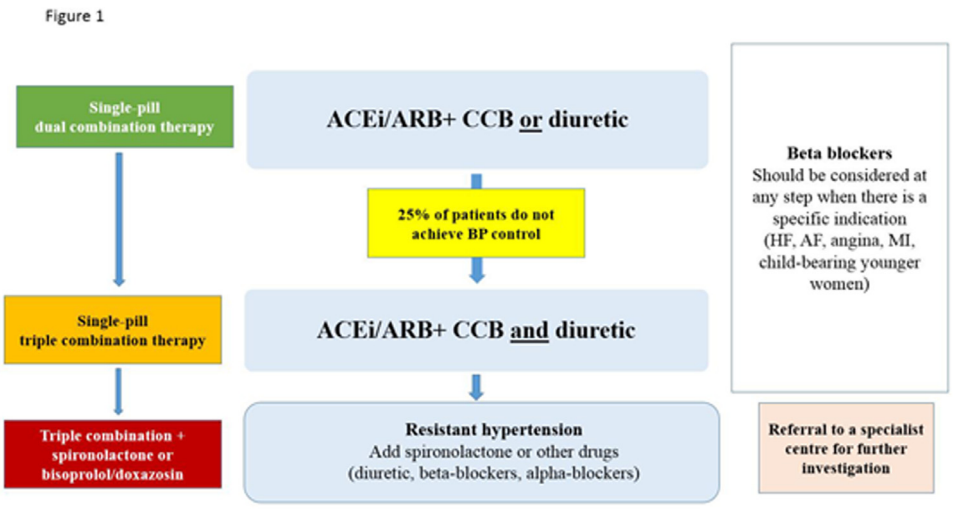

Fig. 1. Antihypertensive therapy management according to 2018 ESC/ESH guidelines.
Legend: ACEi: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; CCB: calcium-channel blocker; BP: blood pressure; HF: heart failure; AF: atrial fibrillation; MI: myocardial infarction.

of a single agent [5]. It is also frequently reported that the combination of antihypertensive agents at low doses, beside its higher efficacy, is associated with lesser incidence of adverse side-effects compared to either monotherapy [5].

Furthermore, starting and continuing antihypertensive therapy with a drug combination is associated with a 26% CV risk reduction compared to initiating with monotherapy and moving to a combination or returning to single-drug after an initial use of a combination [7].

The 2018 European guidelines also highlight the importance of an early BP response and recommend the achievement of BP therapeutic goals within 3 months from the initiation of a pharmacological treatment, particularly in high-risk grade 2 and 3 hypertensive patients [2]. Indeed, results from VALUE (Valsartan Antihypertensive Long Term Use Evaluation) trial [8], ASCOT-BPLA (Anglo-Scandinavian Cardiac Outcomes Trial—Blood Pressure Lowering Arm) [9] and ALLHAT (Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial) [10] suggest significant benefits in terms of reduction of myocardial infarction (MI), stroke, heart failure (HF) and CV mortality when BP control is achieved early as compared with a later control of BP [11]. On the basis of these data, combination therapies are today recommended as the first line strategy by European guidelines [2]. American guidelines also recommend combination therapy if initial BP is >20/10 mmHg higher than the suggested target [3].

However, even when treated with a dual combination, almost 25% of all treated hypertensive patients do not reach BP targets [12–14]. The most reasonable option in these subjects is to add another drug, adopting a triple combination strategy [13,15,16]. Both the dual and the triple drug combination therapy may be based on the single-pill approach (or with two pills) in order to reduce the pill burden and favor higher adherence. This is illustrated in Fig. 1 which is an adapted version of a simplified treatment algorithm recommended by the European Guidelines [2].

Rationale for choosing the right combination strategy

As aforementioned, one-fourth to one-third of hypertensive patients fail to achieve BP control with dual combination therapies, requiring three or more antihypertensive agents [12,13].

The 2018 ESC/ESH guidelines identify five classes of drugs, which have demonstrated comparable BP-lowering efficacy, when selected as a first choice strategy, including angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), thiazides (hydrochlorothiazide and bendroflumethiazide) and thiazide-like diuretics (chlorthalidone and indapamide), calcium channel blockers (CCBs) and beta-receptor blockers (BBs) [2].

Combining drugs from different classes, preferably with complementary mechanisms of action, may provide benefits beyond synergistic antihypertensive efficacy, improving their tolerability profile and rates of adherence.

For instance, the addition of an inhibitor of the renin–angiotensin–aldosterone system (RAS) (ACEi or ARBs) to a thiazide or a thiazide-like diuretic not only has an additive effect on BP reduction, but also counterbalances some of the diuretic-related adverse effects on electrolytes profile (hypokalaemia), uric acid and glucose metabolism [17].

With regard to the rationale of the combination of RAS blockers and CCBs, RAS blockers cause both arteriolar and venular capillary dilatation, with an increased reabsorption of the interstitial fluid, thus reducing the peripheral edema promoted by CCBs.

On the other hand, CCBs, as diuretics, provoke a counter-regulatory increased activation of RAS with consequent and synergistic BP-lowering effect due to an enhanced efficacy of ACEi and ARBs.

Based also on these considerations, European guidelines suggest that triple drug combinations should generally include an ACEi or an ARB, a dihydropyridinic CCB and a thiazide diuretic, except that in some specific clinical situations in which BBs have a compelling indication, such as coronary artery disease (CAD), HF and atrial fibrillation (HF) [2].

A practical platform, based on the best scientific evidence and clinical experience, has been recently proposed with the aim to provide physicians with the most appropriate individualized dual- or triple-drug, fixed-dose combination strategies, by taking into account the BP levels together with the clinical profile of the patient, that is the presence of concomitant risk factors, comorbidities and organ damage [18,19].

Physicians, however, may still have many difficulties in prescribing an appropriate single-pill triple combination, because not all potential formulations are commercially available (i.e. indapamide does not exist in combination with ARBs). In addition, the suggested triple-drug associations may not cover the needs of specific groups of patients, such as those affected by chronic kidney disease (CKD) or HF, who may require a loop diuretic rather than a thiazides or thiazide-like diuretics, or patients with history of CAD,

HF or AF, who may benefit from the use of BBs rather than dihydropyridinic CCBs. In these cases, the use of free three-drug association strategy rather than the single-pill three-drug combinations is mandatory. Moreover, in frail or very elderly patients a reasonable strategy may be represented by the use of triple-drug combinations composed of agents at minimal doses to limit side effects, especially hypotension associated to an increased risk of falls.

Efficacy of triple-combination therapy

Several studies have investigated the efficacy of triple combinations compared to dual strategies.

In Table 1, we report a series of representative studies, mostly based on the use of triple combinations of a RAS blocker, a CCB and a thiazide-like diuretic [20,22–27,30]

They systematically show that triple combination therapy is significantly superior to dual combination therapy in terms of office SBP and DBP, as well as in terms of percentage of responders or normalized patients.

As a representative, convincing example, a large, double-blind, parallel-design trial, which enrolled 2271 hypertensives with BP values >145/100 mmHg, demonstrated that triple therapy with Amlodipine/Valsartan/hydrochlorothiazide (Aml/Val/HCTZ) at a dosage of 10/320/25 mg lowered SBP by 39.7 mmHg, exceeding the BP reductions of 31.5–33.5 mmHg obtained with dual combinations Aml/Val 10/320 mg, Val/HCTZ 320/25 mg and Aml/HCTZ 10/25 mg. After 8 weeks, a significantly greater 70.8% percentage of patients achieved BP targets with triple therapy, compared with 48.3% for Val/HCTZ, 54.1% for Aml/Val and 44.8% for Aml/HCTZ [20].

The superiority of triple combination strategies has been demonstrated also in terms of reduction of out-of-office BP. For instance, in a study of 283 patients with grade 2 hypertension, the greatest 24-hour ambulatory BP reduction of 30.3/19.7 mmHg was observed in the group treated with Val/Aml/HCTZ, compared to the 18.8–24.1/11.7–15.5 mmHg reduction with the dual corresponding combinations [21].

In the PAINT (Perindopril-Amlodipine plus Indapamide Combination for Controlled Hypertension—Non-Intervention Trial) [28] and PIANIST (Perindopril-Indapamide plus Amlodipine in High Risk Hypertensive Patients) [29] trials, triple combination therapy with Aml/Per/Ind produced a significant reduction of office and ambulatory BP in hypertensive patients previously uncontrolled with monotherapy or dual-combination therapies.

Low-dose triple combination therapy has also been reported superior to usual care in the TRIUMPH (Triple Pill vs Usual Care Management for Patients With Mild-to-Moderate Hypertension) trial [30], which is shown in Table 1.

Apart from these trials, in which the long-term advantages of the triple combination at low dosages vs the dual combination were demonstrated, no further studies have investigated the benefits of low-dose triple combinations compared to usual doses of two-drug associations. Some additional information may be extrapolated from trials that have investigated the benefits of triple and quadruple low-dose associations compared to placebo or monotherapy.

In a trial by Mahmud and Feely, the quadruple quarter-dose combination based on amlodipine 1.25 mg, atenolol 12.5 mg, bendroflumethiazide 0.625 mg and captopril 12.5 mg twice daily has provided a significant greater SBP reduction (26 mmHg) compared to each monotherapy at standard dose (amlodipine 5 mg, atenolol 50 mg, bendroflumethiazide 2.5 mg, or captopril 50 mg twice daily) (SBP reductions 8 mmHg, 9.2 mmHg,11.4 mmHg and 7.1 mmHg with amlodipine, atenolol, bendroflumethiazide and captopril respectively) [31].

In another study, triple half-dose therapy demonstrated a significant larger BP reduction (18/10 mmHg) compared to placebo [32].

In a trial conducted by Chow et al., low-dose quadripill (irbesartan 37.5 mg, amlodipine 1.25 mg, hydrochlorothiazide 6.25 mg and atenolol 12.5 mg) provided a placebo-corrected reduction in systolic 24-hour BP of 19 mmHg and in office BP of 22/13 mmHg. In addition, during quadripill treatment all the patients achieved BP target <140/90 mmHg, compared to 33% of placebo-treated subjects [33].

These results are consistent with those reported by a meta-analysis of Bennett et al., which showed a 22.4/13.1 mmHg BP reduction with quadruple quarter-dose therapy compared to placebo and a 13.1/7.9 mmHg reduction compared to monotherapy [34].

Moreover, a meta-analysis of 11 studies including 7563 patients has demonstrated that triple combination therapy with CCB/ARB/HCTZ, at any dosage, provided a better BP control than dual combinations of these agents (5.8/3.5 mm Hg reduction in systolic/diastolic BP) [35].

Therefore, the studies discussed so far report a consistent superiority of triple (or quadruple) combination therapy, even at low doses, in terms of office or out-of-office BP reductions. Of course, it is important to document that a larger number of agents used in combination is not associated with a higher burden of side effects. In this regard, the benefits of a triple combination of ARBs/ACEIs, CCBs and diuretics are also supported by the evidence that the rates of the most common adverse events, such as mild-to-moderate and well tolerated dizziness, cough, peripheral edema and headache, are comparable to those related to the two-drug combinations used for comparisons [35]. These data are systematically confirmed by the aforementioned studies reported in Table 1. In other words, the added value of the triple combination single-pill therapy in terms of BP reduction is not hampered by any increase of adverse side effects, which may obviously represent a major downside for the use of this strategy.

Triple-combination therapy in high-risk patients

Triple-combination therapy with ACEis or ARBs associated to CCBs and diuretics is also recommended for the treatment in high-risk patients, such as those with CAD, CKD or stroke.

In a subgroup analysis of the TRINITY trial in individuals with diabetes, CKD or CAD, the triple combination of Aml/Olm/HCTZ has been demonstrated to be well tolerated, more efficacious in reducing BP as well as in terms of patients reaching BP goal compared to the corresponding dual regimens [36].

These results have been confirmed in other subgroup analyses of the TRINITY study which investigated the benefits of the triple combination in elderly patients aged >65 years [37] and in obese individuals (BMI>30 kg/m2) [38]. Again, in this study the triple combination was not associated with a higher burden of side effects.

In a post-hoc analysis of the ADVANCE (Action in Diabetes and Vascular Disease: PreterAx and Diamicron MI Controlled Evaluation) trial, the incidence of CV events was reduced in patients treated with a combination of indapamide, perindopril and CCBs compared to the corresponding monotherapies and two-drug combination [39].

Single-pill combination

Among the possible combination strategies, the 2018 ESC/ESH guidelines encourage to use single-pills rather than free-drug combinations, since there is strong evidence that the number of prescribed drugs is associated with higher rates of

Table 1
Representative trials comparing triple combination therapy with two-drug combinations.

Trial	Treatment groups	Baseline SBP (mmHg)	Baseline DBP (mmHg)	SBP Reduction (mmHg)		DBP Reduction (mmHg)		Patients reaching BP targets (%)		Side effects (%)
AML/VAL/HCTZ Vs dual-therapy recipients [17]	AML/VAL/HCTZ 10/320/25 mg ($n=583$)	169.6	106.4	39.7	P value <0.0001	24.7	P value <0.0001	70.8	P value <0.0001	45.2
	VAL/HCTZ 320/25 mg ($n=559$)	169.5	106.2	32.0		19.7		48.3		45.3
	AML/VAL 10/320 mg ($n=568$)	169.6	106.6	33.5		21.5		54.1		44.9
	AML/HCTZ 10/25 mg ($n=561$)	170.8	107.1	31.5		19.5		44.1		48.3
OLM/AML/HCTZ Vs OLM/AML [19]	OLM/AML/HCTZ 20/5/ 12.5 mg ($n=335$)	167.7	103.5	33.2	P value <0.001	22.5	P value <0.01	66.2	P value <0.0489	27.1
	OLM/AML 20/5 mg ($n=337$)	168.4	104.0	29.9		20.5		58.8		24.9
	OLM/AML/HCTZ 40/5/ 12.5 mg ($n=336$)	168.7	103.9	33.7	P value <0.001	22.5	P value <0.05	66.4	P value <0.0245	31.4
	OLM/AML/HCTZ 40/5/ 25 mg ($n=336$)	168.2	103.7	35.3	P value <0.0001	23.0	P value <0.01	72.8	P value <0.0001	28.1
	OLM/AML 40/5 mg ($n=337$)	168.4	103.8	30.4		21.2		57.8		30.4
	OLM/AML/ HCTZ 40/10/12.5 mg ($n=336$)	168.5	103.9	35.5	P value <0.01	23.9	P value <0.01	71.7	P value <0.0473	32.2
	OLM/AML/HCTZ 40/10/ 25 mg ($n=336$)	168.3	103.8	36.2	P value <0.001	23.8	P value <0.01	72.6	P value <0.0247	27.7
	OLM/AML 40/10 mg ($n=336$)	168.5	103.6	32.8		22.1		64.5		28.9
OLM/AML/HCTZ Vs OLM/HCTZ [20]	OLM/AML/ HCTZ 40/5/ 25 mg ($n=49$)	168.1	98.5		33.7		18.2		93.3	38.8
	OLM/AML/ HCTZ 40/10/ 25 mg ($n=22$)	170.7	100.9							
	OLM/HCTZ 40/12.5 mg ($n=123$)	164.6	97.6		29.3		16.1		83.2	39.0
	OLM/HCTZ 40/25 mg ($n=78$)	166.6	98.2							
TRINITY study [21]	OLM/AML/HCTZ 40/10/25 mg ($n=627$)	167.9	100.9	37.1	P value <0.001	21.8	P value <0.001	69.9	P value <0.001	28.2
	OLM/HCTZ 40/25 mg ($n=637$)	169.0	100.7	29.7		16.9		53.4		20.9
	AML/HCTZ 10/25 mg ($n=600$)	168.9	101.3	27.5		15.1		41.1		29.7
	OLM/AML 40/10 mg ($n=628$)	168.1	100.9	30		18.0		52.9		23.2
TELM/AML/HCTZ Vs TELM/HCTZ [22]	TELM/AML/HCTZ ($n=106$)	166.84	103.62		43.8		22.4			16.03
	TELM/HCTZ ($n=102$)	168.89	105.43		37.96		21.2			22.5
TELM/AML/HCTZ Vs TELM/AML [23]	TELM/AML/HCTZ 80/10/25 mg ($n=155$)	153.7	90.1	18.7	P value <0.001	9.3	P value <0.005	52.3	P value <0.001	29.0
	TELM/AML 80/10 mg ($n=155$)	152.6	88.8	12.2		7.0		24.8		16.3
TRIUMPH study [27]	Low-dose triple combination TELM/AML/CHLORTALIDONE 20/2,5/12,5 mg ($n=349$)	154.2	89.5	29.1	P value <0.001	13.9	P value <0.001	69.5	P value <0.001	38.1
	Usual Care ($n=351$)	154.2	90.0	20.3		9.3		55.3		34.8
EXCITE Study [24]	AML/VAL/HCTZ ($n=1191$)	165.8	97.7		36.6		17.8		69.9	6.1
	AML/VAL ($n=8603$)	160.9	97.1		31.0		16.6		69.9	11.2

AML, amlodipine; EXCITE, Experience of Amlodipine and Valsartan in Hypertension HCTZ, hydrochlorothiazide; OML, olmesartan; TRINITY, Triple Therapy with Olmesartan Medoxomil, Amlodipine, and Hydrochlorothiazide in Hypertensive Patients Study; TRIUMPH, Triple Pill vs Usual Care Management for Patients With Mild-to-Moderate Hypertension; VAL, valsartan.

therapy-discontinuation and reduced adherence to the treatment, resulting in a higher incidence of CV events [2].

In the TRIUMPH study, the use of single-pill was associated with a 21% increase in compliance compared to free-drug combination [30], these data being consistent with the 29% increased compliance and persistence with treatment demonstrated by a meta-analysis of 30,295 patients [40].

Moreover, Egan et al. have demonstrated that starting with single-pill strategies improves the achievement of BP control by 53% compared to corresponding free-drug association, in a large database of more than 100,000 hypertensive patients in 180 US centers [41]. Since a great number of hypertensive patients receive other medications for associated comorbidities, the administration of single-pill fixed-dose combinations may represent an important tool for improving compliance.

In this regard, the platform-based approach described above, or the development of other tools or apps, may help physicians to personalize the choice on the basis of the clinical profile as well as to adequate the intensity of the therapy to the grade of hypertension and to the individual risk profile, obtaining the optimal an effectiveness of the selected antihypertensive strategy [18,19].

Finally, the use of a single-pill formulation may simplify the treatment of truly resistant hypertensive patients, which often requires the addition of other drugs such as spironolactone or BBs or alpha-blockers to the three BP-lowering medications already administered.

Fixed-dose combinations, however, may have some downsides, such as the increased complexity of the prescribing/dispensing process and the enhanced risk of medication errors (e.g. therapeutic duplication) and drug–drug interactions [42].

Conclusions

A great number of hypertensive patients do not achieve an adequate BP control with monotherapy or dual therapy, with almost one-third of subjects requiring three or more drugs to reach therapeutic targets. Triple-combination therapy has been demonstrated to provide better results in terms of percentage of well-controlled subjects, office and 24-hour BP reduction and time to achieve BP goals compared to dual-combination therapy, without a significant increase in adverse events. The most rational, effective and safe combinations are based on ACEis or ARBs, CCBs and diuretics, due to their complementary mechanisms of action. Single-pill combinations should be preferred due to the improved adherence and higher persistence on treatment.

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