

## Fixed dosed combinations in the treatment of hypertension

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### Abstract

Currently cardiovascular disease is the leading cause of mortality worldwide, resulting in approximately one third of all deaths globally. In order to address the role that hypertension plays in the morbidity and mortality of cardiovascular diseases, there is an urgent need for a paradigm shift in global hypertension management and treatment. Obtaining target pressure levels using monotherapy can be a difficult task especially in the case of patients with other associated diseases; consequently modern therapeutic guides recommend combinations of two or more antihypertensives. Fixed dose combinations associate two or more pharmaceutical substances in a single pharmaceutical formulation; each drug typically working at a separate site, blocking different effector pathways. Compounds that struggle to be efficient in the monotherapy of patients with hypertension often become more effective if combined with another drug; associating drugs with different but complementary mechanism of action often leads to increased therapeutic efficacy. The current review presents the advantages of fixed dose combination and summarizes formulations of common dual, triple combinations used in therapy.

*Keywords:* Antihypertensives, Hypertension Treatment, Fixed-dose Combinations.

### 1. Introduction

Cardiovascular diseases are the leading cause of mortality and a major cause of disability worldwide which substantially contributes to the increased costs of the healthcare systems. There are multiple factors that influence and increase the occurrence of cardiovascular diseases: high blood pressure (HBP), diabetes, obesity, dyslipidaemia, smoking, sedentary lifestyle; but if we want to highlight a factor that plays the major role in triggering cardiac pathological phenomena this would be HBP (1).

HBP is a chronic disease that is characterized by high blood pressure levels over a long

period of time; this medical condition causes the heart to pump blood at a much faster rate than normal, which will lead to the development of associated pathologies that will alter the patient's health. If left untreated, HBP can affect the blood vessels in the organs, which could lead to complications, such as: myocardial infarction, heart or kidney failure, stroke or blindness. Usually, the symptoms of HBP are not present before the blood vessels deteriorate. Hypertension is classified into two categories: essential hypertension (with no identified cause) and secondary hypertension (due to kidney, heart, endocrine or arterial diseases); most diagnosed cases of HBP falling into the first category (>90%) (2).

With a multifactorial etiology, hypertension is often resistant to monotherapy, thus it is necessary to combine two or more antihyper-

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tensives as treatment. The increasing prevalence of HBP and the reduced compliance of patients with antihypertensive treatment, especially with treatments involving co-administration of several drugs, has led to the need to develop combinations that ensure a better control of blood pressure and increase the patients' compliance with therapy (3).

Currently, according to therapeutic guides, five main pharmacological classes are recommended for the treatment of HBP: angiotensin enzyme converting inhibitors (AECIs), angiotensin II receptor blockers (ARBs - sartans), calcium channel blockers (CCB), beta-blockers ( $\beta$ -blockers), and diuretics (thiazide and thiazide-like) (4).

Combinations of antihypertensive medication associates drugs with different but complementary mechanism of action - combined to achieve increased therapeutic efficacy. At the same time, combinations have a better tolerability because smaller doses of each drug component are used and there is the possibility to compensate possible side effects. Thus, in modern medical practice we can find more and more fixed combinations of two or even three active substances used in the treatment of HBP (5, 6).

The current review discusses the role of fixed dose combination therapy in the modern treatment of hypertension, highlighting the importance of incorporating the strategic use of fixed dose combination therapy to improve control rates and outcomes in hypertension.

## **2. Fixed dose combinations versus mono dose administration**

Hypertensive patients often have other associated medical conditions (dyslipidemia, heart failure, ischemic coronary artery disease, hypertensive nephropathy, diabetes, hyperuricemia), which is why the number of pills they have to take daily can easily exceed five, if we think of an antihypertensive, a diuretic, a statin, an antiaggregant or an oral antidiabetic (and there are situations in which several antihypertensives are needed and also possibly a fibrate or a hypouricemic agent).

Thus, therapeutic schemes can become quite thick and can be neglected by patients, especially if they must be used for life. Because the hypertensive patient is often asymptomatic, he is less

inclined to take a chronic treatment that slightly improve his condition but may even disturb him by its adverse effects (7).

Currently it is considered that about 75% of hypertensive patients require at least two drugs for proper control of blood pressure. In fact, the current trend is to start antihypertensive treatment with a combination of two drugs (7).

Fixed dose combinations bring several benefits in antihypertensive treatment, including increased patient compliance (two or more pills turn into one), elimination of some adverse reactions (CCBs peripheral edema can be eliminated in combination with AECIs, because arteriolar dilatation caused by blockage of calcium channels is compensated by the venodilation produced by the AECI), and the simultaneous blocking of several pathogenic links of hypertension - making it possible to combine the synergistic / additive effects of the drugs and the use of lower doses of each drug (7, 8).

Drug combinations target several mechanisms, such as renin-angiotensin system blockade and induction of vasodilation and / or diuresis, reducing the heterogeneity of the hypertension response to the initial treatment and providing a more efficient response to the dose administered than was observed by the progressive increase of the single drug dose (8).

In addition, initiating therapy with a combination of two antihypertensive drugs ensures faster control of blood pressure (recent studies have shown that there is a close correlation between the time required to obtain blood pressure control and the clinical prognosis) (7).

According to the guidelines, around 15-20% of hypertensive patients require the administration of three or more drugs to control blood pressure. Triple combinations significantly increase patient compliance, reducing by two the number of pills in the treatment schedule of a patient with severe hypertension, who most likely has also other medical conditions (heart failure, diabetes, peripheral arteriopathy) that require drug therapy (9).

Currently, triple combination of antihypertensive is not recommended as an initial treatment in any category of patients; and their use is limited

only to hypertensive patients difficult to treat.

Cohort studies in large populations from current clinical practice have shown that initiation of combination therapy is associated with a lower rate of interruptions and patients are at lower risk of cardiovascular events than in the case of initial administration of monotherapy, followed by the gradual increase in administered drugs number (9).

Also fixed dose combinations may be in some cases less expensive than the same drugs administered separately; combination therapy may reduce the prescribing cost with fewer medications and offer patients a lower overall health care cost (10).

### 3. Fixed dose combination used in therapy

Antihypertensive drugs from different classes can be combined if: their mechanisms of action are different and complementary; it is shown that the antihypertensive effect of the combination is better than that of each component taken individually.

The administration of fixed dose combinations are associated with: the administration of smaller doses of both drugs compared to monotherapy; avoidance of frustration of repeatedly and vainly seeking effective monotherapy in patients

Fixed dosed combinations in the treatment of hypertension with very high blood pressure or organ damage; simplified treatment and compliance optimization; starting treatment with a combination of two drugs may allow blood pressure targets to be reached more frequently than in monotherapy (11).

Possible combinations of classes of antihypertensive drugs are presented in Figure 1.

Most combinations available on the market contain an antihypertensive drug (ARB, ACEI, CCB) combined with the diuretic drug, hydrochlorothiazide (7). Hydrochlorothiazide reduce sodium reabsorption in the distal convoluted tube, inducing natriuresis, concomitant water loss and intravascular volume depletion which can lead to an activation of renin-angiotensin-aldosterone system thus boosting the antihypertensive effect of ACEI (12). Based on an almost similar mechanism, the combination of hydrochlorothiazide and ARB shows a potentiated antihypertensive effect. The use of an ARB in combination with a thiazide diuretic has been observed to blunt metabolic derangements, such as hypokalaemia, hyperglycaemia, hypercholesterolaemia and hyperuricaemia; which are a common feature of high-dose diuretic therapy (13). Low doses of hydrochlorothiazide are enough when administered in fixed dose combinations with ARB, enabling the preservation of an excellent safety and tolerability profile, even

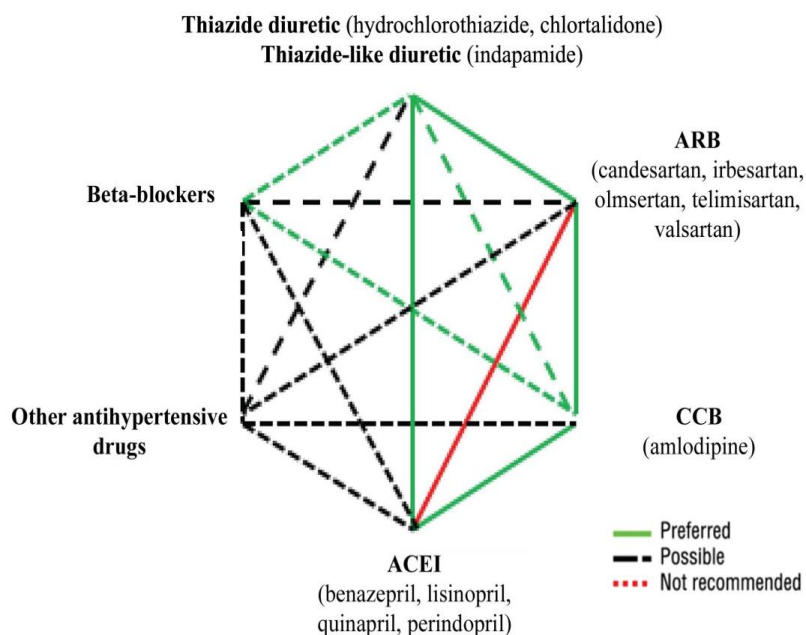


Figure 1. Possible combinations of classes of antihypertensive drugs.

regarding the unwanted metabolic effects of these agents (14).

All ARB have their combination with hydrochlorothiazide that is used in therapy, also hydrochlorothiazide is the first-choice diuretic for the combinations with ACEI. As exception, indapamide, a thiazide-like diuretic is used in combination with an ACEI, perindopril while the chlortalidone, a thiazide diuretic is used in combination with an ARB, azilsartan (7, 15).

The most effective combinations are considered those between a CCB and a renin-angiotensin system blocker (ARB) and between a CCB and a thiazide diuretic. CCB will sensitize the renin-angiotensin-aldosterone system and therefore lead to an improvement of renin state, which will enhance the antihypertensive effects of ACEI and ARB. ACEI decreases side effects of CCB, for example, decreased peripheral oedema and reflex increase in heart rate due to blunting of sympathetic tone (16, 17).

The combination of CCB and thiazide or

thiazide-like diuretics are less preferred by comparison with CCB and ARB or ACEI; and is usually used only in patients for whom renin-angiotensin system inhibition is not indicated (18).

Amlodipine is the first choice CCB used in fixed dose combinations with ARB and ACEI.

Fixed-dosed combination used in therapy are presented in Table 1.

In comparison with the large number of studies evaluating antihypertensive therapy, only a few compared directly the use of different fixed dose combinations. In most studies, the treatment was initiated using a monotherapy, subsequently with the addition of another drug, usually in a non-randomized manner, according to a predetermined treatment algorithm (19).

However, there are some clinical studies which compare directly two different combinations, each using a renin-angiotensin system blocker (ACEI, ARB) and a CCB with other combinations. In the study Avoiding Cardiovascular Events Through Combination Therapy in Patients Living

**Table 1.** Fixed dosed combination used in therapy.

Fixed dose combination	Drugs	Doses
ARB + thiazide diuretic	Candesartan cilexetil + Hydrochlorothiazide	16/12.5 mg
		32/12.5 mg
		32/25 mg
	Irbesartan + Hydrochlorothiazide	150/12.5 mg
		300/12.5 mg
		300/25 mg
	Losartan + Hydrochlorothiazide	50/12.5 mg
		100/12.5 mg
		100/25 mg
	Olmesartan medoxomil Hydrochlorothiazide	20/12.5 mg
		40/12.5 mg
		40/25 mg
Telmisartan + Hydrochlorothiazide	40/12.5 mg	
	80/12.5 mg	
	80/25 mg	
Valsartan + Hydrochlorothiazide	80/12.5 mg	
	160/12.5 mg	
	320/12.5 mg	
	160/25 mg	
Azilsartan medoxomil + Chlortalidone	40/12.5 mg	
	40/25 mg	

## Continued Table 1.

ACEI + thiazide/thiazide like diuretic	Benazepril + Hydrochlorothiazide	10/12.5 mg
		20/12.5 mg
		20/25 mg
		40/25 mg
	Fosinopril + Hydrochlorothiazide	10/12.5 mg
		20/12.5 mg
	Lisinopril + Hydrochlorothiazide	10/12.5 mg
		20/12.5 mg
		20/25 mg
Quinapril + Hydrochlorothiazide	10/12.5 mg	
	20/12.5 mg	
	20/25 mg	
ARB + CCB	Perindopril + Indapamide	2.5/0.625 mg
		5/1.25 mg
	Candesartan cilexetil + Amlodipine	10/2.5 mg
		8/5 mg
		16/5 mg
		16/10 mg
	Olmesartan medoxomil+ Amlodipine	20/5 mg
		40/5 mg
		40/10 mg
Telmisartan + Amlodipine	40/5 mg	
	80/5 mg	
	40/10 mg	
	80/10 mg	
Valsartan + Amlodipine	160/5 mg	
	320/5 mg	
	160/10 mg	
	320/10 mg	
ACEI + CCB	Benazepril + Amlodipine	10/5 mg
		20/5 mg
		40/5 mg
		20/10 mg
		40/10 mg
	Perindopril + Amlodipine	3.5/2.5 mg
		7/5 mg
		14/10 mg
	Trandolapril + Verapamil	2/180 mg
		4/240 mg
ARB + CCB + thiazide diuretic	Olmesartan + Amlodipine + Hydrochlorothiazide	20/5/12.5 mg
		40/5/12.5 mg
		40/10/12.5 mg
		40/10/25 mg

**Continued Table 1.**

	Valsartan + Amlodipine + Hydrochlorothiazide	160/5/12.5 mg 160/5/25 mg 160/10/12.5 mg 160/10/25 mg
ACEI + CCB + thiazide/thiazide like diuretic	Perindopril + Amlodipine + Indapamide	5/5/1.25 mg 5/10/1.25 mg 10/5/2.5 mg 10/10/2.5 mg
direct renin inhibitors + thiazide diuretic	Aliskiren hemifumarate + Hydrochlorothiazide	150/12.5 mg 150/25 mg 300/12.5 mg 300/25 mg
direct renin inhibitors + CCB	Aliskiren hemifumarate + Amlodipine	150/5 mg 150/10 mg 300/5 mg 300/10 mg

With Systolic Hypertension (ACCOMPLISH) (20), the ACEI-CCB combination proved to be superior to the combination containing ACEI-thiazide diuretic in the prevention of major cardiovascular events. The results was not confirmed in the Combination of Olmesartan and a CCB or diuretic studies in Japanese older hypertensive patients (COLM) (21) and in the Combination Therapy of Hypertension to Prevent Cardiovascular Events (COPE) (22) studies, which did not report significant differences in cardiovascular events when the ACEI-CCB combination was compared with the ACEI-thiazide diuretic combination.

#### 4. Conclusion

There is clinical evidence which shows that, compared to patients who were initially given monotherapy, patients who received fixed dose combinations of two drugs had better blood pressure control; this can be related to the fact that administration of fixed dose combinations is probably associated with better adherence to long-term therapy and because initial administration of two drugs prevents therapeutic inertia (hesitation or failure to increase treatment from one to multiple drugs when hypertension is not controlled) (7, 15).

These studies have undoubtedly shown that there is an inversely proportional relationship between the number of pills and the treatment ad-

herence. The recommended approach is now facilitated by the existence of several fixed dose combinations with a variety of doses, which eliminates the often-mentioned disadvantage of this therapy (the impossibility of increasing the dose of one drug independent of the other) (23).

Although currently the availability of fixed dose combinations containing two drugs is largely limited to an renin-angiotensin system blocker (ACEI, ARB) combined with a calcium CCB and /or a diuretic, it is desirable to develop as wide a range of low-cost pills containing various combinations according to the clinical needs of the patients (23).

Antihypertensive fixed dose therapy combines drugs with different but complementary mechanisms of action - so they have a higher efficacy; at the same time, they have a better tolerability - because smaller doses of each drug are used and there is the possibility to compensate some side effects.

The increasing role of fixed-dose therapy in the treatment of hypertension, including in the initial treatment, is a new and key strategy of modern medicine.

#### Conflict of Interest

None declared.

## 5. References

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