

Available online at www.sciencedirect.com**ScienceDirect**journal homepage: <http://ees.elsevier.com/ajps/default.asp>**Review****A promising choice in hypertension treatment:
Fixed-dose combinations****Xinhuan Wan^a, Panqin Ma^b, Xiangrong Zhang^{a,*}**^a Shenyang Pharmaceutical University, No. 103, Wenhua Road, Shenyang 110016, China^b Ningxia Kangya Pharmaceutical Co., Ltd, No. 6 Road, Yinchuang 750002, China**ARTICLE INFO****Article history:**

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ABSTRACT

Obtaining the target blood pressure level by monotherapy can be challenging currently, especially for the patients who are suffering from other diseases meanwhile. It is demonstrated that a majority of hypertensive patients need two or more antihypertensive drugs to lower their blood pressure effectively. Consequently, fixed-dose which can be defined as that several active agents were combined in single pharmaceutical formulations appears to be a novel and underlying power in overcoming the cardiovascular disease. Based on the analysis of some literature and relative data from FDA, the advantages of fixed-dose combination are elucidated and formulations of common dual, triple-combinations were summarized. Clinical practices proved that fixed-dose combinations had many benefits comparing with single drug and separate agents in terms of effects, convenience, compliance, and costs to a certain extent. From the patients' perspective, the fixed-dose combination therapy will be increasingly utilized in blood pressure control in the future.

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1. Introduction

Hypertension, a common cardiovascular disease, should take the most responsibility for the morbidity and mortality caused by disease in the world every year. Hypertension is the primary cause of cardiovascular disease (CVD) and deaths globally [1]. Report from the American Heart Association showed

that based on 2007–2010 data, 33.0% of US adults ≥ 20 years of age were in hypertension [2]. According to an incomplete statistics in the year of 2001, the mortality induced by hypertension takes the proportions of 12.5%–14.2% in the total fatalities in the world [3]. Although people have made substantial efforts in blood pressure control and got great achievement accordingly, we also have a long way on the path

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to optimized blood pressure control in the view of clinical practice. As early as 1999, WHO/ISH guidelines [4] have recommended the monotherapy from six classes and fixed-dose with the definition of combining two or more active agents in a single pharmaceutical formulation for the initial treatment of hypertension. Statistics shows that only a minority of hypertension patients can obtain rational blood pressure by monotherapy, that is to say, most patients need combination therapy to control their disease. A survey on the trends in the use of antihypertensive agents in France from 2002 to 2012 supported the view mentioned above with the result that the prescriptions of fixed-dose combinations increased from 19% to 30% [5]. Combination therapy can be two or more agents administered separately or in a fixed-dose combination dosing, and the latter seems to be more popular in clinical practice based on its advantages in terms of convenience, cost, compliance, efficacy and aggressive effects.

2. Advantages of fixed-dose combinations

2.1. Monotherapy versus combination therapy

A number of clinical trials show that most hypertensive patients were unlikely to achieve a normal blood pressure by taking single drug for a quite long term. Hence, doctors tend to give a higher dose at the first time, however, high dose therapy usually only bring a modest antihypertensive effect stepped with some severe side effects [6], supporting the perspective that patients may not obtain more at a higher dose when a drug can't meet their needs at a recommended dose [7].

2.2. Combination therapy with separate agents versus fixed-dose combinations

Combination therapy rises as an alternative for the patients who fail to lower their blood pressure by monotherapy or who are in co-morbidities conditions. Combination therapy was classified into two kinds: one is various drugs were prescribed separately; the other is drugs in fixed-dose combinations. Undoubtedly, the former brought much trouble for the patients especially the elders who were tired of taking a series of pills every day. But the fixed-dose combination can solve this problem well by offering a relative simple regimen with fewer pills or once-daily dosing. Anyway, patients suffering a chronic disease like hypertension prefer simple prescribing program. Although fixed-dose formulations are still in suspicious by physicians in some areas, it should be acknowledged that fixed-dose in combination is a natural trend in the history of improving the blood pressure control. Some rational fixed-dose formulations have been widely practiced in treating other disease such as type 2 diabetes mellitus (sitagliptin and metformin) [8] and so on.

2.3. Fixed-dose combinations

When monotherapy was replaced by fixed-dose combination pills, one may ask whether fixed-dose formulations can offer enough advantages to defeat traditional monotherapy. Fixed-

dose combination pill as a promising choice to hypertensive patients may have some potential superiorities as follows:

Firstly, fixed-dose formulations usually can give patients some surprising effects comparing with only taking anyone ingredient of the combinations. Fixed-dose combinations sometimes may provide a synergistic effect in a perfect combination except the usual additive effect. Since drugs in formulations from different classes exert their effects based on individual mechanism with different action sites and action time, fixed-dose combinations in hypertension have a potential for a modest and long term action. Clinical trials demonstrated that angiotensin II receptor blockers (ARB) such as valsartan can minimize the peripheral edema caused by a calcium channel blocker such as amlodipine [9], which is in concert with the notion that combining two antihypertensive agents from different classes in a formulation in many cases may partly offset the adverse effects from each other. Besides, all the side effects from drugs in combination can also be decreased because of the low dose. In summary, for rational fixed-dose combinations, they may control hypertension well without additional side effects. Matthew R. Weir et al. [10] conducted a titrate-to-goal study by switching patients who can't obtain target blood pressure level on monotherapy to fixed-dose combinations of amlodipine and olmesartan medoxomil \pm hydrochlorothiazide with a satisfying result that the majority of subjects achieved blood pressure goals without suffering severe adverse effects.

Next, there is a psychological problem must be taken into consideration in treating the chronic disease. Since most hypertension patients are elders who have poor memory and can't act easily, the convenience and compliance brought by therapy are especially important. A meta-analysis based on a certain number of database demonstrated that fixed-dose combinations brought a tremendous improvement in compliance and persistence for the treatment of hypertension [11]. Combination therapy with fixed-dose usually can exhibit its effects with fewer pills or once-daily dosing formulation, then improve patients compliance and psychological state largely.

At last, cost may also be an obstacle in blood pressure control for part patients. Combination therapy with fixed-dose may be less costly than the drugs administered separately, what's more, combination therapy may reduce the prescribing cost with fewer medications and offer the poor patients a lower overall health care costs. Statistical analysis shows that the cost of angiotensin-converting enzyme inhibitors (ACEI)/ARB and thiazide diuretics administered in single combination products can bring a cost-saving about \$27–45 million per year for the Canadian health care system than drugs administered separately [12]. Fig. 1 showed advantages of fixed-dose combinations versus monotherapy and separate agents.

3. Common combinations

There are several common drug classes can be used in tackling hypertension: thiazide diuretics, calcium channel blockers (CCB's), beta(β)-blockers, alpha(α)-blockers, ACEI, ARB and some centrally acting drugs. Table 1 showed fixed-dose combination products approved by FDA from 2003 to 2013 including dual combinations and triple-combination.

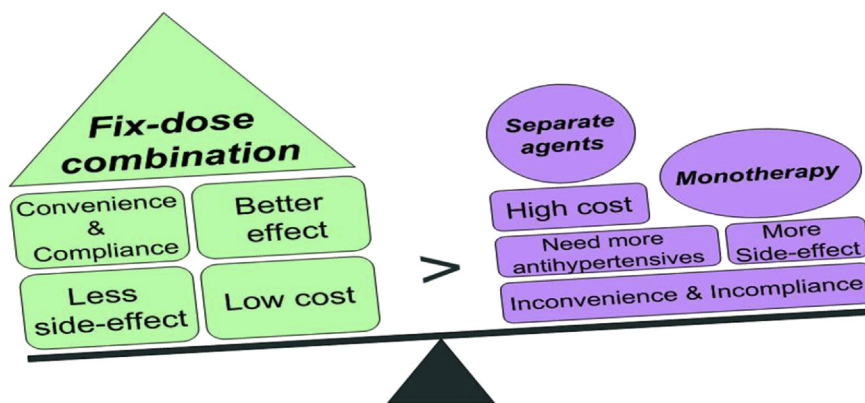


Fig. 1 – Advantages of fixed-dose combinations versus monotherapy and separate agents.

3.1. Thiazide diuretics plus ACEI/ARB

Since the use of fixed-dose combinations in hypertension is being a new trend and method in clinical practice, more and more combination products were developed especially the drugs comprising of thiazide diuretics and ACEI/ARB. When elderly patients treated with ACEI alone fail to achieve ideal blood pressure, fixed-dose combinations consist of thiazide diuretics and ACEI can often perform a favorable effect demonstrating that thiazide diuretics and ACEI can make up an almost ideal group. Diuretics would induce increased sodium loss and intravascular volume depletion when exerting their effects which can lead to an activation of renin–angiotensin–aldosterone system (RAAS) thus boosting the antihypertensive effect of ACEI. Study in uncontrolled hypertensive patients with a fixed-dose combination of ramipril/hydrochlorothiazide certified the powerful effects of combinations mentioned above [13]. Based almost the same mechanism, the combination of thiazide diuretics and ARB shows an additive antihypertensive effect. Stepped with the selective inhibition of ARB on angiotensin II, the antihypertensive effect of thiazide diuretics was enhanced greatly. ARB also can reduce the potassium loss and hyperuricemia caused by thiazide diuretics owing to the interdiction of aldosterone secretion. The combination of losartan with hydrochlorothiazide has been widely used in China since 2008, and studies attested that this combination has a stable long-term antihypertensive effect in patients whose blood pressure can't be controlled with ARB or combinations with a CCB [14]. The combination of candesartan and hydrochlorothiazide was also demonstrated to be an excellent alternative in treating hypertension for its outstanding efficacy and tolerability [15]. Fixed-dose combinations of ARB and thiazide diuretics not only exerted a superior efficacy but also maintained the outstanding tolerability profile of the ARB in clinical practice.

3.2. Thiazide diuretics plus β -blockers

As the based antihypertensive drugs, thiazide diuretics also can be combined with β -blockers. It is known that β -blockers can reduce cardiac output, inhibit the secretion of renin and weaken the function of peripheral sympathetic and thus

obtain antihypertensive effects. Owing to the inhibition of the production of renin and angiotensin II brought by β -blockers, combinations of these two agents exhibit a significant reduction in side effects caused by thiazide diuretics such as intravascular volume depletion and total body sodium loss. The first fixed-dose formulation consists of bisoprolol and hydrochlorothiazide was marketed in china in April 2007, and it was recommended by JVC V and JVC VI as the first-line drug for treating hypertension. Recent trial results showed that fixed-dose combination of nebivolol and hydrochlorothiazide was effective in controlling blood-pressure levels without a side effect on glucose and lipid profile during the study period [16].

3.3. β -blockers plus CCB's

Calcium channel blockers as an important class of antihypertensive drugs can selectively block voltage-dependent calcium channels, relax the vascular smooth muscle, reduce peripheral vascular resistance, and so get blood pressure drops. According to the different chemical structures, CCB's are categorized into two classes namely dihydropyridine and non-dihydropyridine. It is reported that the non-dihydropyridine CCB's including verapamil and diltiazem cannot combine with β -blockers because of the occurrence of symptomatic bradycardia and atrioventricular block [7]. However, the integration of β -blockers and dihydropyridine CCB's can be ideal combinations. The control of renin level due to β -blockers will reinforce the vasodilatory properties, thus achieving synergistic antihypertensive effects.

3.4. β -blockers plus ACEI/ARB

Early trials have attested that adding a β -blocker to an ACEI did not offer more superiority in lowering blood pressure than single therapy with ACEI [17]. The result may be explained by their antihypertensive mechanism. ACEI can be applied to all types of hypertension especially in normal or high-renin state, which may conflict with the inhibition of renin level induced by β -blockers. Literature also reported that combinations of renin–angiotensin–aldosterone system blockers and beta-

Table 1 – Fixed-dose combination products approved by FDA from 2003 to 2013.

Trade name	Active ingredients	Formulations	Specifications (mg)	Approval date	Applicants
Benicar HCT	Hydrochlorothiazide/olmesartan medoxomil	Tablet	12.5/20 12.5/40 25/40	2003-6-5	Daiichi Sankyo Inc
Exforge	Amlodipine besylate/valsartan	Tablet	5/160 5/320 10/160 10/320	2007-6-20	Novartis Pharmaceuticals Corp
Azor	Amlodipine besylate/olmesartan medoxomil	Tablet	5/20 5/40 10/20 10/40	2007-9-26	Daiichi Sankyo Inc
Tekturna HCT	Aliskiren hemifumarate/hydrochlorothiazide	Tablet	150/12.5 150/25 300/12.5 300/25	2008-1-18	Novartis Pharmaceuticals Corp
Valturna	Aliskiren hemifumarate/valsartan	Tablet	150/160 300/320	2009-9-16	Novartis Pharmaceuticals Corp
Exforge HCT	Amlodipine/hydrochlorothiazide/valsartan	Tablet	5/12.5/160 5/25/160 10/12.5/160 10/25/160 10/25/320	2009-4-30	Novartis Pharmaceuticals Corp
Twynsta	Amlodipine besylate/telmisartan	Tablet	5/40 5/80 10/40 10/80	2009-10-16	Boehringer Ingelheim Pharmaceuticals Inc
Losartan potassium and hydrochlorothiazide	Hydrochlorothiazide/losartan potassium	Tablet	12.5/100 12.5/50 25/100	2010-4-6	Teva Pharms
Tribenzor	Amlodipine besylate/hydrochlorothiazide/olmesartan medoxomil	Tablet	10/12.5/40 10/25/40 5/12.5/20 5/12.5/40 5/25/40	2010-7-23	Daiichi Sankyo
Tekamlo	Aliskiren hemifumarate/amlodipine besylate	Tablet	150/10 150/5 300/10 300/5	2010-8-26	Novartis
Trandolapril and verapamil hydrochloride	Trandolapril/verapamil hydrochloride	Tablet, extended release	1/240 2/180 2/240 4/240	2010-8-30	Glenmark Generics
Amturnide	Aliskiren hemifumarate/amlodipine besylate/hydrochlorothiazide	Tablet	150/5/12.5 300/10/12.5 300/10/25 300/5/12.5 300/5/25	2010-12-21	Novartis
Irbesartan; hydrochlorothiazide	Irbesartan/hydrochlorothiazide	Tablet	150/12.5 300/12.5 300/25	2011-2-16	Zydus Pharms USA Inc
Amlodipine besylate; olmesartan medoxomil	Amlodipine besylate/olmesartan medoxomil	Tablet	10/20 10/40 5/20 5/40	2011-3-7	Matrix Labs Ltd
Olmesartan medoxomil; hydrochlorothiazide	Olmesartan medoxomil/hydrochlorothiazide	Tablet	20/12.5 40/12.5 40/25	2011-4-15	Mylan Pharma
Amlodipine besylate; benazepril hydrochloride	Amlodipine besylate/benazepril hydrochloride	Capsule	10/40	2011-7-5	Lupin Pharms
Telmisartan; hydrochlorothiazide	Telmisartan/hydrochlorothiazide	Tablet	40/12.5 80/12.5 80/25	2011-9-15	Watson Labs Florida

Table 1 – (continued)

Trade name	Active ingredients	Formulations	Specifications (mg)	Approval date	Applicants
Edarbyclor	Azilsartan kamedoxomil/ chlorthalidone	Tablet	40/12.5 40/25	2011-12-20	Takeda Pharms USA
Irbesartan and hydrochlorothiazide	Hydrochlorothiazide/irbesartan	Tablet	12.5/150 12.5/150 12.5/300 12.5/300 25/300	2012-3-30	Teva
Valsartan; hydrochlorothiazide	Valsartan/hydrochlorothiazide	Tablet	160/12.5 160/25 320/12.5 320/25 80/12.5	2012-4-10	Torrent Pharms Ltd
Valsartan and hydrochlorothiazide	Hydrochlorothiazide/valsartan	Tablet	12.5/160 12.5/320 12.5/80 25/160 25/320	2012-9-21	Mylan Pharms Inc
Amlodipine, valsartan and hydrochlorothiazide	Amlodipine/hydrochlorothiazide/ valsartan	Tablet	10/12.5/160 10/25; /60 10/25/320 5/12.5/160 5/25/160	2012-9-25	Teva Pharms
Hydrochlorothiazide; Irbesartan	Hydrochlorothiazide/irbesartan	Tablet	12.5/150 12.5/300	2012-9-28	Cipla Limited
Irbesartan hydrochlorothiazide	Hydrochlorothiazide/irbesartan	Tablet	25/300	2012-10-15	Apotex Inc
Candesartan cilexetil and hydrochlorothiazide	Candesartan cilexetil/ hydrochlorothiazide	Tablet	16/12.5 32/12.5 32/25	2012-12-4	Mylan Labs
Candesartan cilexetil; hydrochlorothiazide	Candesartan cilexetil/ hydrochlorothiazide	Tablet	16/12.5 32/12.5 32/25	2012-12-11	Teva Pharms USA
Amlodipine besylate and valsartan	Amlodipine besylate/valsartan	Tablet	10/160 10/320 5/160 5/320	2013-3-28	Par Pharm Inc
Amlodipine; valsartan; hydrochlorothiazide	Amlodipine/valsartan/ hydrochlorothiazide	Tablet	10/160/12.5 10/160/25 10/320/25 5/160/12.5 5/160/25	2013-4-18	Par Pharm Inc
Amlodipine besylate; valsartan	Amlodipine besylate/valsartan	Tablet	10/160 10/320 5/160 5/320	2013-4-29	Lupin Ltd
Telmisartan; amlodipine	Telmisartan/amlodipine	Tablet	40/10 40/5 80/10 80/5	2013-5-28	Lupin Ltd

blockers provided little additional antihypertensive effects compared with either single therapy [18].

3.5. CCB's plus ACEI/ARB

ACEI and ARB belong to the inhibitors of renin-angiotensin-aldosterone system (RAAS). Calcium channel blockers as potent antihypertensive agents will sensitize the renin-angiotensin-aldosterone system (RAAS) and therefore lead to an improvement of renin state, which will enhance the antihypertensive effects of ACEI/ARB

without doubt. In addition to their improvement in effects, many combinations of CCB's and ACEI also applied to patients with comorbid conditions. Previous study on the fixed-dose combinations of lercanidipine plus enalapril demonstrated that this combination provide an encouraging renal protection for patients with chronic renal failure [19]. Additionally, research on trandolapril/verapamil combination showed that this formulation may be an optimal alternative for the treatment of hypertensive patients with diabetes [20]. Combinations of agents from CCB's and ARB respectively also brought much surprise for patients with elevated blood pressure, this

theory can be supported by an uncontrolled study on combination of olmesartan and amlodipine with the conclusion that the formulation was effective and well-tolerated in initial treatment [21]. Study on the initial therapy effect of fixed-dose product amlodipine/valsartan and single drug amlodipine in black patients with stage 2 hypertension demonstrated that the former exhibited a greater and faster blood-pressure reduction [22].

3.6. Triple fixed-dose combinations

When patients can't obtain target blood pressure with two drugs in combination, there are triple fixed-dose combinations to choose. Three-in-one fixed-dose combination of reserpine, apresoline and hydrochlorothiazide was the first triple fixed-dose formulation to be marketed in US, which exhibit obvious advantages over placebo in trial. Tribenzor[®], a triple fixed-dose combination consisting of amlodipine, olmesartan medoxomil and hydrochlorothiazide, was approved by FDA in July 2010, and trial certificated that the formulation can provide an effective and safe hypertension control in obese patients [23] except the normal hypertensive patients. Researches on the triple therapy exhibit that this prescription with less pills may improve adherence and clinical outcomes without increasing cost [24]. There are also other triple fixed-dose combinations arising such as Exforge HCT[®] (amlodipine + valsartan + hydrochlorothiazide; Novartis Pharmaceuticals, East Hanover, NJ), and Amturnide[®] (amlodipine + aliskiren + hydrochlorothiazide; Novartis), thus three-in-one combinations with fixed-dose seem to have a huge market prospect in the near future.

4. Dosage form of fixed dose combination

There are many types of fixed dose combinations comprising oral, inhalation and parental on market in many medical field [25]. Among the common types, oral dosage forms of tablet and capsule provide simplified treatment regimens, greater patient convenience and compliance. Formulation technologies such as multi-layer tablets, multiparticulate systems, active film coating, and hot-melt granulation are developed in the design of formulation. Reviews of the Physicians' Desk Reference (PDR) show that infections, cardiovascular, hormone, allergies and pain are the top five medical areas for fixed dose combinations of oral dosage forms, nevertheless hypertension treatment takes 80% in cardiovascular [26].

5. Precautions of the applications of fixed-dose combinations

In spite of proven benefits of fixed-dose combinations in treating hypertension, there are some problems should be considered in applying them. Practically, some products of fixed-dose combinations are widely used in the area of hypertension, however some others are unnecessary and even brought negative effects in some cases [27]. Firstly, rational combinations of different agents should be chose based on the complementary pharmaceutical mechanisms or the

effective prohibition of the counter-regulatory response [28]. Next, safety can be a key point to consider during the application of fixed-dose combinations. The prescription of combination products consisting of aliskiren (ALI) ACEI and ARB was warned of possible drawbacks by the FDA when using then in patients with complications of diabetes or renal impairment [29].

6. Conclusion

When monotherapy encountered bottlenecks in treating hypertension, fixed-dose combinations were recommended as an effective and safe regimen for initiating therapy especially for the patients with complications. Each drug in perfect combination will exert its best effectiveness with fewer side effects. Additionally, fixed-dose combinations also brought economical benefits for patients with fewer medications compared with several drugs administered separately. Based on the clinical practice and market research, fixed-dose formulations are becoming a promising choice for hypertensive patients gradually.

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