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## Review

# A promising choice in hypertension treatment: Fixed-dose combinations

Xinhuan Wan<sup>a</sup>, Panqin Ma<sup>b</sup>, Xiangrong Zhang<sup>a,\*</sup><sup>a</sup> Shenyang Pharmaceutical University, No. 103, Wenhua Road, Shenyang 110016, China<sup>b</sup> Ningxia Kangya Pharmaceutical Co., Ltd, No. 6 Road, Yinchuang 750002, China

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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  $\geq 20$  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

\* Corresponding author. Tel./fax: +86 24 23986522.

E-mail addresses: [wanxinhuan20073212@163.com](mailto:wanxinhuan20073212@163.com) (X. Wan), [zhangxr@vip.sina.com](mailto:zhangxr@vip.sina.com) (X. Zhang).

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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.

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## 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.

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## 3. Common combinations

There are several common drug classes can be used in tackling hypertension: thiazide diuretics, calcium channel blockers (CCB's), beta( $\beta$ )-blockers, alpha( $\alpha$ )-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.

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