## Increasing adherence: is that enough?

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 ${f H}$  ypertension is the most common and important risk factor for cardiovascular morbidity and mortality in both developed and developing countries. Analysis of worldwide data indicates that 26.4% of the adult population had hypertension in 2000 and 29.2% will have hypertension in 2025. In terms of absolute numbers, there were 972 million subjects with hypertension in 2000, and this number is predicted to increase by 60% to approximately 1.56 billion people with high blood pressure (BP) in 2025.<sup>1</sup> China is the world's most populous nation and, as a result, had the largest hypertensive population (>180 million people) in the world in 2000. The number of individuals with hypertension in China will increase by 65% and will reach almost 300 million in 2025.1 This figure represents the entire current population of the United States.

Data from the National Health and Nutrition Examination Survey 1999-2004 in the United States demonstrate that BP control (<140/90 mm Hg), among all patients with hypertension, has significantly improved from 29.2% in 1999-2000 to 36.8% in 2003–2004. The BP control rate was 56.6% among those individuals receiving antihypertensive treatment in 2003-2004.<sup>2</sup> However, data from the China National Nutrition and Health Survey 2002 showed that only 5% of patients with hypertension in China had their BP < 140/90 mm Hg, with significantly higher levels of BP control in urban than in rural areas (6% vs. 3%, respectively). Among treated hypertensive patients, BP was controlled in 24%, with a similar discrepancy between rural and urban areas (men, 28% in urban and 23% in rural areas; women, 27% in urban and 20% in rural areas). In absolute numbers, 153 million Chinese adults had hypertension, 38 million were aware of their condition, 31 million were on antihypertensive treatment, but <7 million were adequately controlled.<sup>3</sup>

Achievement of optimal BP control is the single most important issue in the management of hypertension, and in most individuals with high BP it is difficult or impossible to control their BP levels with one drug. The current guidelines recommend the use of combination therapy as first-line treatment or early in the management of complicated hypertension that requires prompt BP reduction.

Poor adherence to medication regimens contributes to the practice-outcome gap in which clinical guidelines are implemented but expected results are not achieved. For example, in one study, non-adherence to medication was (by far) the leading cause of hospitalization among 179 patients admitted to hospitals with acute decompensation of pre-existing congestive heart failure, which was implicated in 42% of hospital admissions.<sup>4</sup> In another study, self-reported nonadherence to medication was associated with a >2-fold increased rate of subsequent cardiovascular events, such as coronary heart disease death, myocardial infarction and stroke, in outpatients with stable coronary heart disease.5

Adherence to antihypertensive treatment is inversely related to BP levels, that is, nonadherent patients tend to have higher BP than adherents. Fixed-dose combination therapy is an efficacious, relatively safe and cost-effective method of reducing BP in most patients with hypertension.<sup>6</sup> Starting antihypertensive treatment with more than one agent offers the potential advantages of achieving BP control more rapidly and avoiding the doserelated side effects of individual drugs by producing greater BP reductions at lower doses of the component agents.<sup>6</sup>

In this issue of Hypertension Research, Wong et al.7 evaluated the discontinuation rates of antihypertensive drugs among Chinese patients who received fixed-dose combination therapy and factors related to noncompliance. Using an electronic patient record database with more than seven million patient records, they analyzed 29 253 patients with hypertension who were treated with fixed-dose combination therapy. After 180 days from the first prescription, 93% were considered as still taking their medications. Similar to previous studies, Wong et al. demonstrated lower adherence among the young (<50 years) compared with the elderly, males compared with females, and uncomplicated hypertensive patients compared with patients with  $\geq 2$  co-morbidities. Follow-up patients were also more compliant than new patients.

This article is relevant due to two particular aspects: (1) China is the most populous country in the world, and interventions to improve BP control may cause a profound impact in the global prevalence/incidence of cardiovascular diseases; and (2) the identification of factors associated with treatment discontinuation can guide health strategies to improve compliance among specific groups.

As indicated by the authors, their study reported a significantly higher adherence rate than previous studies. A longitudinal database study with 4783 patients from 21 clinical trials evaluated adherence to antihypertensive treatment among patients who participated in the studies.8 The discontinuation rate was approximately 50% within 1 year. In the study presented by Wong et al., only 7% of patients stopped medication after 180 days. The increased tolerability of combination therapies among Chinese patients and the greater convenience of combination therapies perceived by the Chinese culture were hypothesized as the reasons for the disparity from previous studies.

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Figure 1 Factors related to BP control.

Different methods, such as self-reporting, treatment response, drug levels in body fluids and pill counts can be used to measure adherence to treatment, but most of them have low accuracy. In this study, discontinuation was defined by the absence of a refill prescription from subsequent clinic visits. However, prescription refills are an indirect measure of adherence. As acknowledged by the authors, prescription refills do not necessarily indicate 'real medication-taking behavior'.

High BP control rates would be expected in a population with high adherence rates. One may wonder how a 93% adherence rate for antihypertensive treatment and only 28% (the highest rate in China: men among the treated hypertensive patients in urban areas) of BP control can be explained. In addition, how are high control rates among patients with low adherence rates explained?

Contrary to what most people think, hypertension management is not a simple task. It is almost an art. It is a laborious job in which many factors have to be considered to achieve good results (that is, BP control). Lifestyle, appropriate drug choice, adherence, and medical and patient education are just some of the factors that interfere with BP control (Figure 1).

Appropriate combination therapy at optimal doses is essential to achieve BP goals. As hypertension is multifactorial, and many pathophysiological factors contribute to high BP, the combination of medications with different (and complementary) mechanisms of action provides more complete blockage of pressor mechanisms with less activation of counter-regulatory mechanisms. Combination therapy also reduces dose-dependent adverse side effects (clinical or metabolic) of the individual components and, consequently, improves tolerability and adherence.

In this study, 98% of the prescriptions consisted of diuretic combinations (triamterene-hydrochlorothiazide and amiloridehydrochlorothiazide). Combinations with agents of different classes putatively provide greater BP reduction than combinations of agents among the same class. The renin-angiotensin-aldosterone system is an important modulator of BP and volume regulation. Angiotensin-converting enzyme inhibitor-diuretic or angiotensin receptor blocker-diuretic combinations are the most commonly used fixed-dose combinations. These combinations have an additive effect on BP reduction and the favorable vascular, metabolic, cardiac and renoprotective effects of the angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. In the present study, only 0.2% of the prescriptions were filled for the angiotensin receptor blockers-thiazide combination. Owing to the design of the study, which included patients with co-morbidities such as diabetes mellitus, lipid disorders, kidney diseases and previous cardiovascular events, a larger number of prescriptions of the angiotensin receptor blocker-based combination would be expected.

A combination of diuretics (thiazidespotassium-sparing) effectively reduces thiazide-related adverse events such as hypokalemia. The correction of potassium by a diuretics combination could also reduce the incidence of thiazide-induced dysglycemia.<sup>9</sup> Combinations of thiazide and amiloride or mineralocorticoid receptor antagonists are recommended for patients with resistant hypertension, as they often have inappropriate volume expansion and aldosterone excess.<sup>10</sup> However, these combinations are recommended after appropriate treatment with optimized doses of angiotensin-converting enzyme inhibitors (or angiotensin receptor blockers), calcium channel blockers and hydrochlorothiazide (or chlorthalidone).<sup>10</sup> Furthermore, the dose of amiloride used in fixed-dose combinations is enough to reduce hypokalemia (2.5–5.0 mg) but is lower than that recommended (5.0–10.0 mg) for appropriate BP treatment.

In conclusion, Wong *et al.* present important data regarding adherence to combination therapy in China and characterization of non-adherent patients. Their study is important to create strategies to improve the compliance of these groups. However, many other factors are related to BP control and must be considered by health professionals. Adherence to antihypertensive treatment is an essential (but not the only) factor to improve BP control.

## CONFLICT OF INTEREST

The author declares no conflict of interest.

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