

EDITORIAL

Fixed Combinations in Antihypertensive Therapy

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ABSTRACT

Several studies have now confirmed that optimal targets of blood pressure (BP) could rarely be reached by monotherapy and various drug combinations are required to do this more effectively. However, the best way to increase patient compliance may be fixed combinations of two or more drugs in a single pill. With further research into mechanisms of action and development of new drugs, it became evident that the most effective combinations were those whose mechanisms are complementary or synergistic. Thus, for the treatment of hypertension, the use of fixed combination therapy is gaining ground as a more practical and convenient approach for today's clinical practice.

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KEY WORDS: *hypertension;
antihypertensive therapy; diuretics;
angiotensin-converting enzyme
inhibitors; angiotensin receptor
blockers; calcium channel blockers;
combination therapy*

LIST OF ABBREVIATIONS:

ACE = angiotensin-converting enzyme
BP = blood pressure

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As we stand in the early years of the 21st century, with hundreds of antihypertensive drugs at our disposal, it is difficult to believe that 60 years ago there was absolutely nothing available for the treatment of hypertension. In fact, it was not even universally accepted that the “benign” or “essential” hypertension needed to be treated, unless it entered the malignant phase. At that point, it was treated with desperate measures, such as pyrogens or poisons causing circulatory shock or with radical surgical procedures, such as severance of sympathetic tracts or bilateral adrenalectomy.

Throughout the 1950s and 1960s several classes of antihypertensive agents became available and were tested in clinical trials.^{1,2} The results indicated not only that lowering elevated blood pressure (BP) was beneficial, but also that the optimal BP target was much lower than the initial target of 160/95 mmHg, which was later set at 140/90 and more recently at 130/80, whereas normal BP is now considered to be 120/80 or less. Indeed, several studies have now confirmed that average differences of 10/5 mmHg may translate into decreases of 20-40% in the rate of cardiovascular and cerebrovascular complications. However, it also became apparent that optimal targets could rarely be reached by monotherapy and indeed required multiple drugs in various combinations,³⁻¹⁴ leading patients to confusion, expense, denial. This led to the idea that the best way to overcome patient resistance may be fixed combinations of two or more drugs in a single pill or capsule.^{3,4,6-12} The earliest such two- or three-drug combinations appeared in the 1950s and consisted mostly of a diuretic, a sympatholytic and a vasodilator—whatever was available at the time.

With further research into mechanisms of action and development of new drugs,

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it became evident that the most effective combinations were those, whose mechanisms are complementary or synergistic.⁷⁻¹² An example of this is rendering the BP renin-dependent by removing salt with diuretics, so that angiotensin-inhibiting agents become greatly potentiated. Others have simply additive, or even less than additive effect, but may prevent each other's adverse effects, such as combination of a kaliuretic with a potassium-sparing diuretic. Others yet, have the capacity to treat frequently coexisting conditions, such as high BP and dyslipidemia, with a single pill. Thus, the pills containing a fixed drug combination have evolved from random (whatever happens to be available), to rational (complementary or synergistic) and expedient (concurrent treatment of co-morbidities). And the use of these combinations is gaining ground not only for treatment of hypertension, but also for related disorders, such as coronary artery disease, where initial treatment of acute coronary syndrome or chronic preventive treatment of coronary risk factors was proposed with the "tetrapill" or "polypill," i.e., various fixed combinations containing a diuretic, an ACE inhibitor, a beta-adrenoceptor blocker, a statin and low-dose aspirin.^{15,16} Even if the more distant future may promise personalized therapy based on pharmacogenetics, the current availability of rational fixed drug combinations is a practical and convenient approach for today's clinical practice.

REFERENCES

1. Hamdy RC. Hypertension: a turning point in the history of medicine...and mankind. *South Med J* 2001;94:1045-1047.
2. Freis ED. Effectiveness of drug therapy in hypertension: present status. *Circ Res* 1971;28:II-70.
3. Bakris GL, Berkwitz M. Trials that matter: the effect of a fixed-dose combination of an angiotensin-converting enzyme inhibitor and a diuretic on the complications of type 2 diabetes. *Ann Intern Med* 2008;148:400-401.
4. Dickson M, Plauschinat CA. Compliance with antihypertensive therapy in the elderly: a comparison of fixed-dose combination amlodipine/benazepril versus component-based free-combination therapy. *Am J Cardiovasc Drugs* 2008;8:45-50.
5. Bakris GL. Combined therapy with a calcium channel blocker and an angiotensin II type 1 receptor blocker. *J Clin Hypertens (Greenwich)* 2008;10(1 Suppl 1):27-32.
6. Smith DH. Fixed-dose combination antihypertensives and reduction in target organ damage: are they all the same? *Am J Cardiovasc Drugs* 2007;7:413-422.
7. Weir MR, Neutel JM, Bhaumik A, et al. The efficacy and safety of initial use of irbesartan/hydrochlorothiazide fixed-dose combination in hypertensive patients with and without high cardiovascular risk. *J Clin Hypertens (Greenwich)* 2007;9(12 Suppl 5):23-30.
8. Sharma SK, Ruggenti P, Remuzzi G. Managing hypertension in diabetic patients--focus on trandolapril/verapamil combination. *Vasc Health Risk Manag* 2007;3:453-465.
9. Patel A; ADVANCE Collaborative Group, MacMahon S, Chalmers J, Neal B, et al. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. *Lancet* 2007;370:829-840.
10. Struijker-Boudier HA, Ambrosioni E, Holzgreve H, et al. The need for combination antihypertensive therapy to reach target blood pressures: what has been learned from clinical practice and morbidity-mortality trials? *Int J Clin Pract* 2007;61:1592-1602.
11. Bangalore S, Kamalakkannan G, Parkar S, Messerli FH. Fixed-dose combinations improve medication compliance: a meta-analysis. *Am J Med* 2007;120:713-719.
12. Basile JN. Fixed-dose combination therapy in the treatment of hypertension: ready for prime time. *South Med J* 2007;100:343-344.
13. Gavras I, Gavras H. The debate goes on--what is your choice? *Am J Cardiol* 2005;95:53-54.
14. Ribeiro AB, Gavras H. Angiotensin II antagonists: clinical experience in the treatment of hypertension, prevention of cardiovascular outcomes and renal protection in diabetic nephropathy and proteinuria. *Arq Bras Endocrinol Metabol* 2006;50:327-333.
15. Fahey T, Brindle P, Ebrahim S. The polypill and cardiovascular disease. *BMJ* 2005; 330:1035
16. Reddy KS. The preventive polypill -- much promise, insufficient evidence. *N Engl J Med* 2007; 356:212.