Rational approaches to the treatment of hypertension: drug therapy—monotherapy, combination, or fixed-dose combination?

Başol Canbakan

1Ankara Numune Training and Research Hospital, Ankara, Turkey

Blood pressure (BP) control is inadequate worldwide. Many clinical trials suggest that BP is not satisfactorily controlled using monotherapy in most patients. Free drug or fixed-dose combinations are other therapeutic options. The advantages and disadvantages for different treatment approaches are discussed in this review.

According to the World Health Organization, hypertension is the most common cause of preventable death worldwide. Relationship between blood pressure (BP) and mortality is dramatic. Death from ischemic heart disease or stroke increases progressively as BP increases. For every 20 mm Hg systolic or 10 mm Hg diastolic increase in BP above 115/75 mm Hg, the mortality rate for both ischemic heart disease and stroke doubles.

The aim of antihypertensive therapy is to maximally reduce cardiovascular risk without compromising quality of life. The current BP goal is less than 140/90 mm Hg for all patients and less than 130/80 mm Hg for patients at high risk, i.e., those with diabetes mellitus or chronic kidney disease. Unfortunately, BP control is poor worldwide. According to the Prevalence, awareness, treatment and control of hypertension in Turkey (PatenT) Study, the proportion of patients in those with blood pressure targets of below 140/90 mm Hg was only achieved in 20.7% of patients.

The first step to achieve BP control is lifestyle changes. A 3-month trial is recommended in compliant patients willing to make therapeutic lifestyle changes, prior to determining that drug therapy is necessary. Despite lifestyle changes, if BP is still 140/90 mm Hg or above, drug therapy should be initiated.

As it is well known, blood pressure is determined by cardiac output and systemic vascular resistance. Furthermore, cardiac output is the product of stroke volume and heart rate. Finally, the hemodynamic determinants of BP are stroke volume, heart rate, and systemic vascular resistance. Antihypertensive drugs control BP via these factors: renin-angiotensin-aldosterone system (RAAS) inhibitors by reducing angiotensin II-mediated effects, calcium antagonists by causing vascular smooth muscle relaxation and decreasing systemic vascular resistance, diuretics by blocking NaCl reabsorption and decreasing blood volume, and beta blockers by reducing the heart rate and myocardial contractility. These medications are extensively used as a monotherapy or in combination in blood pressure control.

Monotherapy is the widespread form of initial antihypertensive therapy, but most patients will require more than one antihypertensive medicine to reach their treatment target. In the Antihypertensive and Lipid-Lowering Treatment to
Prevent Heart Attack Trial (ALLHAT), although 36% of patients had diabetes mellitus, the BP target was set at less than 140/90 mm Hg for all patients including the diabetics. Nevertheless, BP was controlled only in 26% of patients after 5 years with monotherapy. In the Losartan Intervention for Endpoint Study (LIFE), more than 90% required at least two antihypertensive drugs. In addition, a meta-analysis of 42 clinical trials involving nearly 11,000 patients found that combining any two drugs decreased blood pressure more than doubling of standard dose. The reduction in BP with combined drugs is approximately 5 times greater than doubling the dose of one drug.

Combination therapy will be necessary in the majority of hypertensive patients to achieve the target blood pressure. The average number of drugs required to reach blood pressure goals is 3.2, in trials focusing on cardiovascular morbidity and mortality. It is expected that the combination should increase the desired therapeutic effect but not the side effects. The combination must block counter-regulatory system activation, have additive effects on BP reduction, and be compatible pharmacokinetically. Another aim of the combination therapy is that of increasing tolerability.

One of the most preferred specific drug regimens is RAAS inhibitor/diuretic combination. Diuretics lead to RAAS activation by reducing intravascular volume. RAAS inhibitors block this counter-regulatory activation. Additionally, the RAAS inhibitors improve the hypokalemic effects of diuretics. Another preferred combination is RAAS inhibitors and calcium channel blockers (CCBs). One of the most common dose-dependent adverse effects of CCBs is peripheral edema due to arteriolar dilatation. This effect is partially neutralized by RAAS inhibitor-induced venodilation. Additionally, RAAS inhibitors prevent tachycardia due to dihydropyridine CCBs. Preferred, acceptable, and less effective drug combinations are shown in Table 1.

The Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial compared the ACEI benazepril plus the diuretic hydrochlorothiazide and benazepril plus CCB amlodipine. ACEI/diuretic is equally effective as ACEI/CCBs on BP levels. However, the ACCOMPLISH trial showed that the amlodipine-based combination was more effective than a thiazide-based combination in reducing cardiovascular events. Acceptable regimens are mainly BB/diuretic, CCB/diuretic, and BB/CCB combinations. However, in the ONTARGET Trial, combining an ACEI with ARB increased the risk of renal complications and death compared to monotherapy. Thus, the ACEI/ARB combination is less effective and not recommended.6

In addition to adequate BP control, the length of the time to achieve this goal is also important. Rapid BP reduction also leads to a reduction in the associated CV events. BP control was achieved more rapidly using combination therapy from the outset. In the International Verapamil Trandolapril Study (INVEST) Trial, in most patients the speed of improved primary and secondary outcome correlated with BP control.7 A meta-analysis of 9 double-blind placebo controlled trials showed that goal BP was achieved by 50% of patients in 14 days with Valsartan + HCTZ. Goal BP was achieved in 72% of patients with the angiotensin receptor blocker valsartan 160 mg monotherapy versus in 92% of patients given the same-dose valsartan in combination with HCTZ. BP control correlated with all outcomes independent of the drug type. Moreover, when the patients were re-evaluated 6 months after achieving goal BP, it was determined that the patients' risk was correlated with BP regardless of drug therapy.8

Gradman et al. retrospectively evaluated 1762 adult patients with hypertension using electronic medical charts between 2005–2009. Patients initiated on combination therapy at the outset were compared to those initiated on monotherapy and later switched to combination therapy as two groups. After 6 months of therapy, 40.3% and 32.6% of patients with initial versus delayed combination treatment reached BP control, respectively. Cardiovascular events were significantly reduced with initial combination therapy. More rapid BP control was found to be important in reducing cardiovascular risk.9

A meta-analysis of 15 clinical trials involving nearly 33,000 patients showed that fixed-dose combinations improved adherence to treatment significantly with potential advantages in BP control and adverse effects.10

Fixed-dose combinations should be used in hypertensive patients who are inadequately controlled on monotherapy or require multiple drugs initially. Combination therapy is strongly recommended for BP 20/10 mm Hg or above target. BP control is achieved more rapidly with combinations, and they are found safe, effective, and well tolerated. Agents should be selected from among preferred or acceptable combinations. Additionally, comorbidities, individual characteristics, and cost should also be considered.

In conclusion, in stage 1 patients who are using monotherapy but do not have their BP controlled, additional therapy is required. To minimize side effects, a second drug must be preferred instead of the maximum dose of initial drug. Because monotherapy is usually inadequate, combination therapy could be used routinely. Especially, combination therapy is strongly recommended if BP is 20/10 mm Hg or above target. The selection of specific drug combinations should be made from preferred or acceptable combinations. Fixed-dose combination should be preferred instead of multiple single drugs.

Table 1 | Recommended drug combinations in antihypertensive therapy

| Preferred       | Acceptable | Less effective |
|-----------------|------------|----------------|
| ACEI/diuretic   | BB/diuretic| ACEI/ARB       |
| ARB/diuretic    | CCB(diuretic) | ACEI/BB    |
| ACEI/CCB       | CCB/diuretic | ARB/BB     |
| ARB/CCB        | Renin inhibitor/diuretic | CCB(non-diuretic)/BB |
|                | Renin inhibitor/ARB  | Centrally acting agent/BB |
|                | Thiazide diuretic/k-sparing diuretic | |

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta blocker; CCB, calcium channel blocker.
DISCLOSURE
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REFERENCES
1. Altun B, Ari M, Nergizoglu G et al. Prevalence, awareness, treatment and control of hypertension in Turkey (the PatenT study) in 2003. *J Hypertens* 2005; 23: 1817–1823.
2. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: the Antihypertensive and Lipid-lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002; 288: 2981–2997.
3. Dahlof B, Devereux RB, Kjeldsen SE et al. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomized trial against atenolol. *Lancet* 2002; 359: 995–1003.
4. Wald DS, Law M, Morris JK et al. Combination therapy versus monotherapy in reducing blood pressure: meta-analysis on 11,000 participants from 42 trials. *Am J Med* 2009; 122: 290–300.
5. Jamerson K, Weber MA, Bakris GL et al. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. *N Engl J Med* 2008; 359: 2417–2428.
6. Yusuf S, Teo KK, Pogue J et al. Telmisartan, ramipril or both in patients at high risk for vascular events. *N Engl J Med* 2008; 358: 1547–1559.
7. Mancia G, Messerli F, Bakris G et al. Blood pressure control and improved cardiovascular outcomes in the International Verapamil SR-Trandolapril Study. *Hypertension* 2007; 50: 299–305.
8. Weir MR, Levy D, Crickelair N et al. Time to achieve blood pressure goal: influence of dose of valsartan monotherapy and valsartan and hydrochlorothiazide combination therapy. *Am J Hypertens* 2007; 20: 807–815.
9. Gradman AH, Parisé H, Lefebvre P et al. Cardiovascular events in hypertensive patients: a matched cohort study. *Hypertension* 2013; 61: 309–318.
10. Gupta AK, Arshad S, Poulter NR. Compliance, safety and effectiveness of fixed dose combinations of antihypertensive agents: a meta-analysis. *Hypertension* 2010; 55: 399–407.