Fixed Low-Dose Drug Combination for the Treatment of Hypertension

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The goal of treating hypertension is to maximize therapeutic efficacy without untoward side effects. The accepted approach is to start treatment with a low dose of a single drug and then titrate it upward as needed to achieve a better therapeutic effect. However, higher doses of administered individual drugs increase the frequency and severity of side effects. A rational combination of individual drugs administered in low doses is preferable because it is associated with a high degree of efficacy, low incidence or severity of side effects, and high patient compliance. The most commonly used drug combinations are as follows: (1) diuretics with potassium-sparing agents; (2) β-adrenergic blockers with diuretics; (3) angiotensin-converting enzyme inhibitors with diuretics; (4) angiotensin II receptor blockers with diuretics; and (5) angiotensin-converting enzyme inhibitors with calcium-channel blockers. *Arch Fam Med. 1998;7:370-376*

The goal of antihypertensive treatment is to maximize therapeutic efficacy without significant side effects. The accepted approach is to initiate treatment with a low dose of a single drug and titrate its dose upward as needed to achieve a better therapeutic effect.[1] However, this approach may not necessarily lead to higher efficacy, since most drugs reach an early plateau phase of their dose-response effect, and further increase in dose leads to higher incidence and severity of side effects. Recent studies have shown that monotherapy for hypertension was successful in only 50% to 60% of the cases.[2] This is because hypertension is a multifactorial disease with more than 1 pathophysiological mechanism operating and thus cannot be effectively controlled by 1 drug. Also, the administration of a single drug sets in motion several counterregulatory mechanisms that can interfere with its effectiveness. The rationale for combining drugs is to counterbalance these regulatory mechanisms and thus increase their antihypertensive effectiveness. To accomplish this, drugs that are combined should belong to different classes and have mechanisms of action that are complementary to each other.

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Drug combinations have the following advantages: they allow the use of lower doses of the component drugs, decrease the incidence and magnitude of clinical and metabolic side effects, often have a longer duration of action than the individual drugs, are often suitable for once-daily administration, increase patient compliance, and frequently lower the cost of care.[3-9]

The intent of this article is not to substitute combination therapy of hypertension for monotherapy, but to offer low-dose drug combinations as an alternative to high-dose monotherapy. In addition, the treatment of hypertension will be viewed in the context of existing concomitant cardiovascular risk factors and their favorable modification by the antihypertensive treatment. Below, I will describe the most commonly used drug combinations and explain the rationale for their use.

DIURETIC–POTASSIUM-SPARING DRUG COMBINATIONS

This is the oldest drug combination for the treatment of hypertension. The rationale for this combination is to spare potassium and magnesium losses through the kidneys from the diuretics[10,11] and to enhance their antihypertensive effective-

Table 1. Marketed Fixed-Dose Drug Combinations*

Preparation	Dose, mg
Diuretics/potassium sparing	
HCTZ/triamterene (Dyazide, Maxzide)	25/37.5, 50/75
HCTZ/amiloride (Moduretic)	50/5
HCTZ/spironolactone (Aldactazide)	25/25, 50/50
β-Blocker/diuretic	
Atenolol/chlorthalidone (Tenoretic)	50/25, 100/25
Bisoprolol fumarate/HCTZ (Ziac)	2.5/6.25, 5/6.25, 10/6.25
Metoprolol tartrate/HCTZ (Lopressor HCT)	50/25, 100/25
Nadolol/bendroflumethiazide (Corzide)†	40/5, 80/5
Propranolol/HCTZ (Inderide)	40/25, 80/25
Propranolol LA/HCTZ (Inderide LA)	80/50, 120/50, 160/50
Timolol maleate/HCTZ (Timolide)	10/25
ACE inhibitor/diuretic	
Benazepril/HCTZ (Lotensin HCT)	5/6.25, 10/12.5, 20/12.5, 20/25
Captopril/HCTZ (Capozide)	25/15, 25/25, 50/15, 50/25
Enalapril maleate/HCTZ (Vaseretic)	5/12.5, 10/25
Lisinopril/HCTZ (Prinzide, Zestoretic)	10/12.5, 20/12.5, 20/25
ACE inhibitor/calcium-channel blocker	
Benazepril/amlodipine besylate (Lotrel)	10/2.5, 10/5, 20/5
Enalapril maleate/felodipine ER (Lexxel)	5/5
Enalapril maleate/diltiazem ER (Teczm)	5/180
Trandolapril/verapamil SR (Tarka)	2/180,1/240, 2/240, 4/240
A_{II} receptor blocker/diuretic	
Losartan potassium/HCTZ (Hyzaar)	50/12.5
Valsartan/HCTZ (Diovan/HCT)	80/12.5, 160/12.5
α_2-Agonist/diuretic	
Clonidine/chlorthalidone (Combipres)	0.1/15, 0.2/15, 0.3/15
Methyldopa/HCTZ (Aldoril)	250/15, 250/25, 500/30, 500/50
α_1-Blocker/HCTZ	
Prazosin/polythiazide (Minizide)	1/0.5, 2/0.5, 5/0.5

*HCTZ indicates hydrochlorothiazide; LA, long acting; ACE, angiotensin-converting enzyme; A_{II}, angiotensin II; ER, extended release; and SR, slow release.
†No longer available in the United States.

ness.[10] Potassium and magnesium, both intracellular ions, have membrane-stabilizing and vasodilating properties, and their depletion may lead to vasoconstriction,[12,13] which in turn may decrease their hypotensive action.[14,15] Low-dose thiazide or chlorthalidone administration has been shown, in large clinical trials, to be safe and effective, reverse left ventricular hypertrophy,[16,17] improve the quality of life,[18] and decrease the cardiovascular morbidity and mortality of hypertensive patients.[19-21] The incidence of metabolic abnormalities is lower with low-dose thiazide diuretics,[19-22] in contrast to larger doses, which were frequently associated with significant metabolic side effects.[23,24] The combination of low-dose thiazide diuretics with potassium-sparing drugs by preventing potassium losses through the kidneys[25,26] does not disturb glucose metabolism, since insulin secretion is potassium dependent.[27] However, low-dose thiazide diuretics are not completely innocuous, since some investigators have reported significant lipid increases with hydrochlorothiazide, 12.5 mg/d,[28] and studies by my coworkers and me[10,29] showed that, when 25 mg of hydrochlorothiazide was combined with 50 mg of triamterene or 5 mg of amiloride hydrochloride, no evidence of hypokalemia or hyperglycemia was noted, but there was a mild, statistically significant, increase in serum urea nitrogen, triglyceride, and uric acid levels.[10,29]

In a recent report of elderly hypertensive, non–insulin-dependent diabetic patients treated with low doses of chlorthalidone alone or in combination with atenolol, diabetes did not worsen in the majority of cases[30]; however, increased serum glucose levels (11.1 mmol/L [200 mg/dL]) were noted in 32.9% of these patients during treatment compared with 19.3% at baseline. These findings indicate that thiazide diuretics should be used with caution in such patients, and if a diuretic is necessary, indapamide, an indolin diuretic, could be tried first. Several studies have shown that indapamide, given in low daily doses of 1.25 to 2.5 mg, is an effective antihypertensive agent, and at the same time does not cause any significant disturbances in glucose, lipids, or potassium metabolism.[31-33]

Prime candidates for an initial treatment with a diuretic–potassium-sparing combination are older, black, and obese hypertensive patients. When such preparations are used, careful consideration should be given to watch for signs of worsening uremia and hyperkalemia. Currently available fixed diuretic–potassium-sparing agents are listed in **Table 1**.

β-BLOCKER–DIURETIC COMBINATIONS

β-Adrenergic receptor blockers are effective agents for the treatment of hypertension, and their use has been associated with reduced cardiovascular morbidity and mortality in large clinical trials[19-21] and in large case-control studies.[34] Proposed mechanisms for the antihypertensive action of β-blockers include suppression of plasma renin activity,[35] inhibition of the central sympathetic nervous system,[36] and reduction of the cardiac output through a decrease in myocardial contractility and heart rate.[36] β-Blockers, in low doses, can be effectively combined with low-dose diuretics for an additive antihypertensive effect.[3-9,29,37-39] This low-dose combination is effective in lowering the blood pressure and decreasing the incidence and magnitude of clinical and metabolic side effects. My coworkers and I[29] showed that combining hydrochlorothiazide/triamterene, 25/50 mg, with atenolol, 25 or 50 mg once daily, resulted in greater reduction of blood pressure than either component alone. Similar results were reported by Frishman[9] with the combination of low doses of hydrochlorothiazide, 6.25, 12.5, and 25 mg/d, and low doses of bisoprolol fumarate, 2.5, 10, and 40 mg/d.[9] This combination produces a greater antihypertensive effect, since the decrease in sodium excretion caused by the β-blocker is reversed by the diuretic,[40] and the stimulation of renin release by the

kidneys induced by the diuretic is suppressed by the β-blocker.[35,41] Thus, the combination of β-blockers with a diuretic makes them effective in the treatment of hypertension of black patients, who are usually resistant to β-blocker monotherapy.[42,43] The additional postulated benefit that the combination of β-blockers with a diuretic spares potassium losses has not been substantiated by all studies.[44-46] When a fixed combination is used, preferably the diuretic dose should not exceed 25 mg/d. All the fixed-dose, β-blocker–diuretic combinations are listed in Table 1.

Combinations of β-blockers with vasodilators or calcium-channel blockers have not been successful for the treatment of hypertension. A fixed combination (Tenif) of atenolol, 50 mg/d, and nifedipine slow release, 20 mg/d, was tested for the treatment of hypertension vs enalapril maleate, 20 mg/d, or atenolol, 100 mg/d, and was found to be slightly better than enalapril or atenolol given separately.[47] No such fixed drug combination is available in the United States at present.

CERTAIN CONSIDERATIONS WHEN β-BLOCKERS ARE USED

Although β-blockers are effective and overall safe agents for the treatment of hypertension, they also possess certain characteristics that may make them undesirable under some unique clinical circumstances (**Table 2**). β-Blockers, especially nonselective ones, are not routinely recommended for the treatment of hypertension in the presence of diabetes mellitus, peripheral vascular disease, chronic obstructive pulmonary disease, bronchial asthma, or allergic bronchitis, unless absolutely necessary.[36] In such cases, a low dose of a cardioselective β-blocker with a low-dose diuretic may be used. Examples of such low doses of cardioselective β-blockers include acebutolol, 200 mg/d; atenolol, 25 to 50 mg/d; betaxolol hydrochloride, 10 mg/d; bisoprolol fumarate, 2.5 to 5 mg/d; and metoprolol tartrate, 50 to 100 mg/d. In patients with hypertension and resting bradycardia, the combination should include, preferably, a β-blocker with intrinsic sympathomimetic activity. In other hypertensive patients with either cardiac arrhythmias or insomnia, the β-blocker–diuretic combination should include a β-blocker with a membrane stabilizing action or a water-soluble one.[46] However, lipid or water solubility does not always predict the outcome.

Table 2. β-Adrenergic Blocker Classification*

Agent	β_1	β_2	LS†	WS†	ISA	MSA†
Acebutolol	+	0	0	+	+	0
Atenolol	+	0	0	+	0	0
Betaxolol hydrochloride	+	0	+	0	0	0
Bisoprolol fumarate	+	0	+	+	0	0
Carteolol hydrochloride	+	+	0	+	+	0
Metoprolol tartrate	+	0	+	0	0	+
Nadolol	+	+	0	+	0	0
Penbutolol sulfate	+	+	0	+	+	0
Pindolol	+	+	0	+	+	0
Propranolol hydrochloride	+	+	+	0	0	+
Timolol maleate	+	+	0	+	0	0

**LS indicates lipid soluble; WS, water soluble; ISA, intrinsic sympathomimetic activity; MSA, membrane stabilizing activity; plus sign, present; and 0, absent.*
†Clinical significance is questionable.

ANGIOTENSIN-CONVERTING ENZYME INHIBITOR–DIURETIC COMBINATIONS

The combination of angiotensin-converting enzyme (ACE) inhibitors with diuretics is widely used for the treatment of hypertension. The ACE inhibitors lower blood pressure through several mechanisms: (1) inhibition of conversion of angiotensin I to angiotensin II, a very potent vasoconstrictor peptide; (2) suppression of aldosterone release from the adrenal glands; (3) inhibition of kinin degradation through inhibition of kininase II, a substance identical with ACE; and (4) inhibition of central sympathetic nervous system. A combination of an ACE inhibitor with a diuretic is a logical one, because the ACE inhibitor will enhance the natriuretic effect of the diuretic and will also block the renin stimulation and potassium loss from the diuretic.

Several studies have demonstrated the antihypertensive effectiveness of such combinations given in low doses.[48-57] Black hypertensive patients having low-renin hypertension[56] do not respond well to monotherapy with ACE inhibitors, but the addition of a diuretic stimulates plasma renin activity through volume depletion, and these patients become responsive to ACE inhibitors combined with diuretics, like white hypertensive patients. Also, the combination of ACE inhibitors with diuretics prevents or reverses the latter's adverse effects on serum glucose, lipids, and potassium.[48-51,57-59] There are 12 ACE inhibitors approved in the United States and Europe, and several of them are marketed in fixed combinations with diuretics (Table 1). The most common adverse effects of the ACE inhibitor–diuretic combinations are dry cough (15% to 20%), rashes, angioedema, and de novo or worsening uremia and hyperkalemia, especially in patients with compromised renal function. However, recent studies have shown that these drugs have a protective effect toward progression of chronic renal disease, proteinuria, and renal damage from diabetes mellitus and should be used in these conditions under close supervision.[60-62] Another major benefit from the use of ACE inhibitors is the so-called reverse cardiovascular remodeling, ie, the regression of cardiac and vascular structural changes induced by chronic sustained hypertension and angiotensin II.[63-65]

ACE INHIBITOR–CALCIUM-CHANNEL BLOCKER COMBINATIONS

The ACE inhibitors have recently been combined with calcium-channel blockers and found to

be more effective in lowering the blood pressure than the component drugs.[66-68] The ACE inhibitors suppress angiotensin II generation and aldosterone release and inhibit the sympathetic system. Calcium-channel blockers are potent arteriolar dilators and cause a further reduction in peripheral vascular resistance. This combination allows for the use of smaller doses of the component drugs, leading to better tolerance by the patients and amelioration of adverse effects,[69] and has been found effective in patients with hypertension and renal failure for lowering blood pressure without further aggravating renal function.[70,71] They are also good drugs for the treatment of hypertension associated with non–insulin dependent diabetes mellitus because both drugs are metabolically neutral.[69] In addition, the incidence of peripheral edema is lower with combined therapy than with monotherapy with calcium-channel blockers.[66,72-78]

In a long-term multicenter study, my coworkers and I[79] showed that a fixed combination of enalapril with diltiazem malate extended release in 4 fixed combinations (enalapril/diltiazem malate, 5/120 mg, 5/180 mg, 10/240 mg, and 10/360 mg given once daily) produced sustained blood pressure control in patients with stage 3 to 4 essential hypertension. However, the majority of the patients with more severe hypertension required the addition of another drug. The incidence of ankle edema in the patients treated with enalapril-diltiazem was 2.2%.[79] On the basis of these beneficial effects of an ACE inhibitor–calcium-channel blocker combination, the Food and Drug Administration has approved 4 such combinations for the treatment of hypertension. Their trade names and formulations are listed in Table 1. All of these preparations are recommended for once-daily administration.

ANGIOTENSIN II RECEPTOR BLOCKER–DIURETIC COMBINATIONS

Angiotensin II receptor blockers exert their antihypertensive effects by blocking the action of angiotensin II at the receptor level, thus causing peripheral vasodilation and a decrease in peripheral vascular resistance.[80] The concept of angiotensin II receptor blockade was first introduced 18 years ago with the angiotensin II competitive receptor antagonist saralasin acetate.[81] However, this drug was a peptide and had to be given intravenously; its administration was associated with an initial rise of blood pressure, followed by a fall that was of short duration.[81,82] For these reasons it was abandoned as an antihypertensive drug. The new class of drugs are synthetic oral agents with prolonged duration of action and are specific for the AT_1 receptor subtype of angiotensin II.[80] Losartan potassium (Cozaar), a member of this class of drugs, has been approved by the Food and Drug Administration for the treatment of hypertension. This drug is effective as monotherapy in doses of 50 to 100 mg/d.[83] The antihypertensive effect of losartan is potentiated when it is combined with a diuretic, and the combination can be used effectively for the treatment of mild to severe hypertension.[84-86] A combination of losartan potassium, 50 mg, with hydrochlorothiazide, 12.5 mg (Hyzaar), has been approved by the Food and Drug Administration for the treatment of hypertension given once daily. Other members of this class of drugs are valsartan (Diovan) and irbesartan (Avapro), which were recently approved by the Food and Drug Administration and are marketed in doses of 80 and 160 mg for valsartan and 75, 150, and 300 mg for irbesartan given once daily. These drugs are also selective AT_1 receptor blockers and are effective in the treatment of hypertension when given in single daily doses.[87,88] A fixed combination of valsartan with low-dose hydrochlorothiazide in daily doses of 80/12.5 and 160/12.5 mg has been marketed recently.[89]

OTHER CALCIUM-CHANNEL BLOCKER COMBINATIONS

The only combinations of calcium-channel blockers are those with the ACE inhibitors discussed previously. No combinations of calcium-channel blockers with diuretics are available at present, although some investigators have reported an additive effect,[90,91] whereas others have not found any additional antihypertensive effect.[92]

α_1-ADRENERGIC BLOCKER–DIURETIC COMBINATIONS

Selective α_1-adrenergic blockers were reserved in the past as add-on agents to preexisting antihypertensive drugs.[93] However, recently they have become a preferred therapy in patients with hypertension and benign prostatic hypertrophy, since they block the α_1-receptors on prostatic smooth muscle and bladder neck, causing relaxation of the muscle with relief of obstruction to the flow of urine.[94] There are 3 members of this class marketed in the United States: doxazosin mesylate, prazosin hydrochloride, and terazosin hydrochloride. These drugs have a good cardiovascular risk profile because they also lower levels of total cholesterol, low-density lipoprotein cholesterol, and triglycerides and increase levels of high-density lipoprotein cholesterol.[95] Only 1, prazosin, is marketed in fixed combination with a diuretic. This preparation (Minizide) is a combination of prazosin hydrochloride, 1, 2, or 5 mg, and polythiazide, 0.5 mg (Table 1). The combination with low-dose thiazide diuretics minimizes the latter's adverse effects on lipids while enhancing the antihypertensive effectiveness. Doxazosin and terazosin are long-acting, whereas prazosin is short-acting. However, the combination of prazosin with polythiazide makes it a long-acting drug.[96]

α_2-ADRENERGIC AGONIST–DIURETIC COMBINATIONS

The members of this class of antihypertensive drugs are clonidine hydrochloride, guanabenz acetate, guanfacine hydrochloride, and methyldopa. Although they are recommended by the JNC-V (Joint National Committee) as first-line therapy for hypertension, they are infrequently used at present, primarily because of their central ner-

Table 3. Blood Pressure Effects of Combination Therapy Compared With Monotherapy*

Source	Monotherapy	Combination Therapy
β-Blocker/diuretic		
Frishman[9]	Bisoprolol, HCTZ	Better
Chrysant et al[29]	Atenolol, HCTZ	Better
Kubik et al[37]	Metoprolol, chlorthalidone	Better
Chrysant et al[38]	Timolol, HCTZ	Better
Prisant et al[39]	Bisoprolol, HCTZ	Better
Veterans Administration[42]	Nadolol, bendroflumethiazide	Better
Veterans Administration[43]	Propranolol HCl, HCTZ	Better
ACE inhibitor/diuretic		
Chrysant[48]	Lisinopril, HCTZ	Better
Chrysant et al[49]	Moexipril, HCTZ	Better
Chrysant et al[50]	Benazepril HCl, HCTZ	Better
Chrysant[51]	Perindopril, HCTZ	Better
Ambrosioni et al[52]	Captopril, HCTZ	Better
Pool et al[53]	Lisinopril, HCTZ	Better
Brown et al[54]	Perindopril, HCTZ	Better
Holland et al[55]	Captopril, HCTZ	Better
ACE inhibitor/calcium-channel blocker		
Frishman et al[66]	Benazepril, amlodipine	Better
Cappuccio et al[67]	Lisinopril, amlodipine	Better
Morgan et al[68]	Enalapril, nifedipine	Better
Gradman et al[72]	Enalapril, felodipine	Better
Applegate et al[73]	Enalapril, diltiazem ER	Better
White et al[74]	Captopril, nifedipine	Better
Eggersten et al[75]	Captopril, isradipine	Better
Viskoper et al[76]	Trandolapril, verapamil SR	Better
Maclean[77]	Captopril, amlodipine	Better
Jensen et al[78]	Enalapril, amlodipine	Better
Chrysant et al[79]	Enalapril, diltiazem ER	Better
A_{II} receptor blocker/diuretic		
Soffer et al[84]	Losartan potassium, HCTZ	Better
Mackay et al[85]	Losartan, HCTZ	Better
Dunlay et el[86]	Losartan, HCTZ	Better
Black et al[89]	Valsartan, HCTZ	Better
Calcium-channel blocker/diuretic		
Chrysant et al[90]	Amlodipine, HCTZ	Better
Chrysant and Stimpel[91]	Verapamil, HCTZ	Better
Nicholson et al[92]	Verapamil, HCTZ	No better
α_1-Blocker/diuretic		
Gordon and Woeltjen[96]	Prazosin HCl/polythiazide	Good
α-Agonist/diuretic		
Mroczek et al[99]	Clonidine HCl/chlorthalidone	Better
McMahon[100]	Methyldopa, HCTZ	Better

HCTZ indicates hydrochlorothiazide; HCl, hydrochloride; ACE, angiotensin-converting enzyme; A_{II}, angiotensin II; ER, extended release; and SR, slow release.

vous system side effects. The rebound hypertension, which has been reported mostly for clonidine, has not always been reproduced[97] but should be considered for patients not accustomed to taking their medications on a regular basis. This rebound effect may be exaggerated if clonidine is taken together with a nonselective β-blocker because of the unopposed sympathetic stimulation through blockade of β_2 receptors.[98] Fixed once-daily combinations of clonidine with chlorthalidone, 15 mg (Combipres), and of methyldopa with hydrochlorothiazide (Aldoril) have been shown to be more effective than the individual drugs.[99,100] The different combinations are listed in Table 1. However, these drugs and their combinations are rarely used today. **Table 3** lists all the marketed fixed drug combinations with selected literature references.

CONCLUSIONS

The advantages of fixed-dose combinations include simplicity, convenience, patient compliance, low-dose administration, blood pressure control, lack of side effects, and cost-effectiveness. Disadvantages include loss of separate titration of component drugs, loss of component drug modification, and suitability of a component drug.

The most effective fixed-dose drug combinations are as follows: (1) ACE inhibitors in combination with diuretics; (2) angiotensin II receptor blockers in combination with diuretics; (3) β-blockers in combination with diuretics; (4) diuretics in combination with potassium-sparing agents; (5) ACE inhibitors in combination with calcium-channel blockers; (6) α_2-agonists in combination with diuretics; and (7) α_1-blockers in combination with diuretics.

In most cases, the disadvantages of fixed-dose drug combinations are more theoretical than practical, and a fixed low-dose drug combination can be given safely for the treatment of hypertension unresponsive to low-dose monotherapy.

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