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Combination Antihypertensive Therapy: Does It Have a Role in Rational Therapy?

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The pharmacological treatment of hypertension allows one to reduce substantially the risk of developing a cardiovascular complication. It appears more and more important to bring blood pressure to normal values in order to get the maximal benefit from antihypertensive therapy. Blood pressure lowering drugs make it possible to control blood pressure in about half of the patients when administered as monotherapy. The fraction of patients with a normal blood pressure can be markedly increased by combining drugs acting by different mechanisms. Low doses of antihypertensive agents are generally enough when coadministered. This helps to keep the incidence of side effects minimal and facilitates the patient's compliance with long-term treatment. Low-dose, fixed-dose combination therapy may therefore represent a valuable option not only to treat hypertensive patients unresponsive to drugs given as monotherapy, but also to initiate the treatment. Am J Hypertens 1997;10:131S–137S

KEY WORDS: **Blood pressure, antihypertensive drugs, tolerability, compliance, fixed-dose combination therapy, sequential monotherapy.**

Essential hypertension is a common and highly heterogenous disease.[1,2] A complex interplay exists among genetic and environmental factors so that predisposed persons tend to become hypertensive under certain conditions. The pathogenetic mechanisms involved in the abnormal blood pressure elevation are multiple and may differ considerably from patient to patient. Not surprisingly, therefore, not every patient responds to every antihypertensive drug in the same fashion. Some patients normalize their blood pressure when given a compound acting by a given specific mechanism whereas others do not. This means that the treatment has to be individualized for each patient.

Five major classes of antihypertensive agents are now available to treat hypertensive patients: diuretics, β-blockers, angiotensin converting enzyme (ACE) inhibitors, calcium antagonists, and α_1-adrenoceptor blockers.[3] These drugs with different modes of action can be used as first-line therapy and, when required, might be combined. Most likely angiotensin II receptor antagonists will also be recommended soon as an acceptable option to initiate antihypertensive therapy.

Despite the availability of an increasing number of antihypertensive drugs, the management of hypertension in everyday practice remains a difficult task. This is reflected by the results of a recent analysis performed in 10,222 hypertensive patients, which has shown a high rate of discontinuation of antihypertensive drugs in general practice.[4] Only 40% to 50% of patients having had a new course of treatment initiated with a diuretic, a β-blocker, an ACE inhibitor, or a calcium antagonist were still on the same drug 6 months later. Whether the treatments were terminated because of insufficient efficacy or poor tolerability could not be decided from this investigation, which was based on the analysis of prescriptions. Conceivably, this high rate of treatment changes might have

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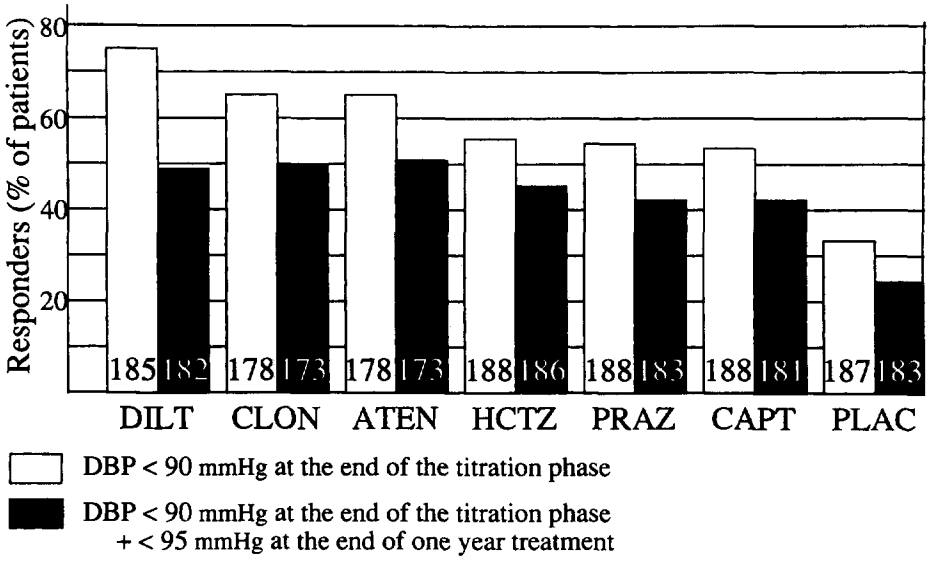


FIGURE 1. *Response rate to long-term treatment with diltiazem (DILT), atenolol (ATEN), clonidine (CLON), hydrochlorothiazide (HCTZ), captopril (CAPT), prazosine (PRAZ), and placebo (PLAC). The open columns correspond to the results obtained at the end of the titration period and show the percentage of patients with a diastolic blood pressure <90 mm Hg. The hatched columns depict the data observed at the end of the 1 year treatment. Responders were defined at that time as patients with a diastolic blood pressure <90 mm Hg at the end of the titration period and <95 mm Hg at the end of the 1 year follow-up. The numbers at the bottom of the bars indicate the number of patients included in each group (adapted from Materson BJ et al[5]).*

had an adverse impact on the patients' compliance and, consequently, on the long-term quality of blood pressure control.

The question now arises of how the available antihypertensive drugs should be used to get the greatest benefit, ie, to achieve optimal blood pressure control without altering the patient's quality of life, the ultimate goal of lifelong treatment being to prevent as much as possible the occurrence of cardiovascular complications. Different approaches can be advocated to initiate treatment. One is to try to find for each patient a drug that is at the same time effective and well tolerated when administered as monotherapy (sequential monotherapy). Another is to associate a priori low doses of drugs lowering blood pressure by different mechanisms (combined therapy). Both ways of treating hypertension have advantages and limitations. The present paper is aimed at reviewing a few clinical trials illustrating the rationale for single and combined antihypertensive therapy.

TAILORED THERAPY USING MONOSUBSTANCES

In general, any antihypertensive drug might be expected to control blood pressure in about 40% to 50% of hypertensive patients. This is illustrated by the results of a large trial having compared recently the five standard, first-choice treatments recommended nowadays, as well as a centrally acting antihypertensive agent (clonidine).[5] In this study 1,292 hypertensive men (diastolic blood pressure of 95 to 109 mm Hg) were randomized to receive for 1 year either placebo or the diuretic hydrochlorothiazide (12.5 to 50 mg per day), the β-blocker atenolol (25 to 100 mg/day), the ACE inhibitor captopril (25 to 100 mg/day), a sustained-release preparation of the calcium antagonist diltiazem (120 to 360 mg/day), the α_1-blocker prazosin (4 to 20 mg/day) or the centrally acting sympatholytic clonidine (0.2 to 0.6 mg/day). The drug doses were titrated to reach a target diastolic blood pressure of less than 90 mm Hg. What were the main messages derived from this study? First, as anticipated, all test drugs provided significantly greater blood pressure reductions than placebo. Second and most important, each of the therapeutic classes allowed the control of blood pressure in a substantial number of patients. This is shown in Figure 1. At the end of the titration phase, diastolic blood pressure was <90 mm Hg in more than half of the patients having received an active treatment. At 1 year, unfortunately, the results were less impressive, even if the criteria used to calculate the response rate were less severe (diastolic blood pressure <90 mm Hg at the end of the titration phase and <95 mm Hg at the end of the study) than those used at the end of the titration phase. Thus, the antihypertensive efficacy of drugs given as monotherapy tended to wear off with time though a decreasing compliance over time could have been the cause of the seemingly reduced efficacy. Of note is that the dose increase was not associated in this trial with a decreased tolerability, at least as estimated by the withdrawal rate observed during administration of low, medium, and high doses of the various agents. This is rather surprising considering the fact that a number of adverse drug reactions have a clear dose-dependent character.[6] This is the case for diuretics (metabolic side effects), for β-blockers (mainly bradycardia, cardiac depression, and central side effects),

for ACE inhibitors (possibly cough), for calcium antagonists (vasodilatation-induced side effects, ie, edema, flushing, headaches, palpitations), for α_1-blockers (especially orthostatic hypotension), as well as for clonidine (central side effects, dry mouth).

The study described above was carried out according to a parallel group design. It allows comparisons between groups of patients, but does not tell anything about the differential blood pressure responses to the test compounds in a given patient. This is a key issue for the clinician who would like to know which type of antihypertensive agent he or she should prescribe preferentially in a given patient in order to get the highest probability of normalizing the patient's blood pressure. Cross-over studies can provide the answer to this question, as each patient receives consecutively all treatments. Several crossover trials have been conducted to compare the efficacy of drugs acting by different mechanisms, for example a β-blocker (betaxolol) and a calcium antagonist (verapamil),[7] an ACE inhibitor (enalapril) and a calcium antagonist (diltiazem),[8] a diuretic (hydrochlorothiazide), or an ACE inhibitor (lisinopril) and a calcium antagonist (nifedipine).[9] In all these trials, the blood pressure responses were assessed by noninvasive ambulatory blood pressure monitoring. A constant finding was that it is impossible to predict if a given patient will be a good responder or not. Some patients normalized their blood pressure whatever the drug used, some responded exclusively to one drug, whereas others remained hypertensive irrespective of the drug used. On this basis, one can conclude that sequential monotherapy is indeed a rational therapeutic approach as it offers the opportunity to identify the most suitable drug and to normalize blood pressure in many patients. One has to admit, however, that the search for an effective and well tolerated antihypertensive agent may take a lot of time, as several 4 to 6 week treatment periods may be needed to find the most appropriate drug.

THE RATIONALE FOR COMBINED THERAPY

The combination of two drugs lowering blood pressure by different mechanisms is known to increase the fraction of hypertensive patients having their blood pressure controlled.[1,10] The enhanced antihypertensive efficacy is probably related to the simultaneous attack on several regulatory systems involved in the abnormal blood pressure elevation. Also, all the vasoconstrictor systems are intimately interacting. It means that a blood pressure reduction resulting from the specific blockade of one system almost always triggers compensatory activation of other systems, with an ensuing attenuation of the overall antihypertensive efficacy. Another important point is that hopefully lower doses are needed when two drugs are co-administered than when they are given as single agents, although this is not always evident. Lower doses are important in terms of tolerability as the incidence of many side effects is dose dependent.[6] Theoretically, the most logical combinations consist of diuretics and ACE inhibitors, diuretics and β-blockers, calcium antagonists and β-blockers (particularly the dihydropyridines), and calcium antagonists and ACE inhibitors.[10]

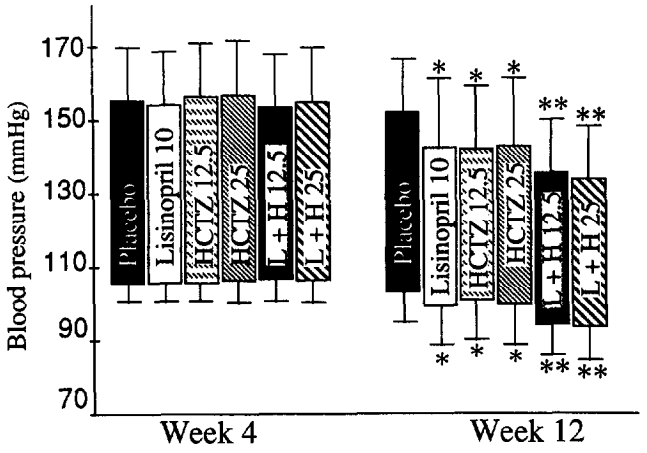


FIGURE 2. *Blood pressure effect of various treatments administered for 8 weeks after a 4 week run-in placebo period. L, lisinopril; HCTZ, hydrochlorothiazide (adapted from Chrysant SG[13].*

Diuretics and ACE Inhibitors The salt depletion induced by diuretics triggers the release of renin from juxtaglomerular cells. This reactive hyperreninemia renders blood pressure maintenance dependent on angiotensin II, blunting thereby the antihypertensive efficacy of diuretics.[11] The addition of an ACE inhibitor to a diuretic makes it possible to block the increased production of angiotensin II and, in this way, to enhance greatly the blood pressure lowering effect of salt depletion. Such a combination of drugs provides advantages not only from the point of view of antihypertensive effectiveness, but also from that of tolerability. It is indeed well established that ACE inhibitors prevent or attenuate the metabolic side effects of thiazide diuretics such as hypokalemia, hyperglycemia, hypercholesterolemia, and hyperuricemia.[12]

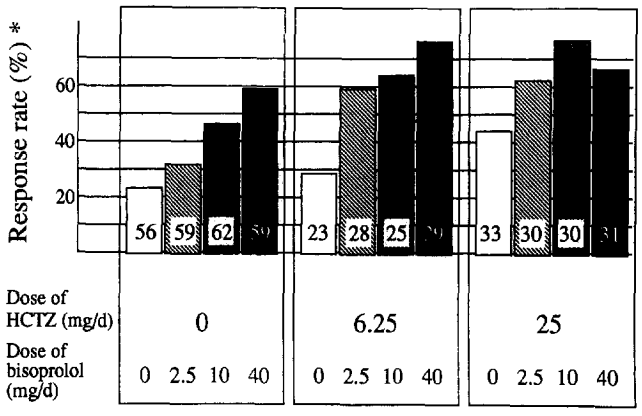
An example of a study involving an ACE inhibitor and a diuretic is given in Figure 2.[13] In this trial, carried out in double-blind fashion, 505 patients whose diastolic blood pressure was 100 to 114 mm Hg were randomly assigned to an 8-week treatment with either the ACE inhibitor lisinopril, 10 mg/day, hydrochlorothiazide, 12.5 or 25 mg/day, the combination of lisinopril, 10 mg/day and hydrochlorothiazide, 12.5 or 25 mg/day, or placebo. It appeared that all active treatments significantly lowered blood pressure in comparison with placebo. The fall in blood pressure was of similar magnitude with the drugs used as monotherapy, but was more pronounced with the combined treatment. A key observation was that 12.5

and 25 mg hydrochlorothiazide were equally effective when administered together with lisinopril. In this study, cough was the only side effect encountered with an increased incidence in lisinopril-treated patients. The 12.5 mg dose of hydrochlorothiazide, whether given alone or in association with lisinopril, was free of metabolic side effects, whereas the 25 mg dose caused a significant increase in serum glucose levels in both the presence and absence of simultaneous ACE inhibition. The 25 mg dose of hydrochlorothiazide alone decreased significantly serum potassium levels, but this effect was not present anymore with concurrent lisinopril treatment. Based on these observations, a fixed-dose combination containing 10 mg lisinopril and 12.5 mg hydrochlorothiazide is therefore appealing.

Considering the use of a fixed-dose combination of an ACE inhibitor and a diuretic as first-choice antihypertensive treatment, one might be concerned by the potential risk of reducing blood pressure too much. Hypotensive episodes, however, do not represent a problem, as indicated by observations made in 263 hypertensive patients aged 15 to 60 years and 276 hypertensive patients older than 65, the latter being probably more prone than the former to develop orthostatic hypotension.[14] All these patients exhibited a diastolic blood pressure in the range of 95 to 115 mm Hg when they entered the study and received once a day for 4 months a fixed-dose combination of 50 mg captopril plus 25 mg hydrochlorothiazide. Only one elderly patient had to interrupt the treatment because of hypotension. Of note is that a high rate of blood pressure normalization (defined as a diastolic blood pressure below 90 mm Hg) was obtained after 4 months, at 83% and 86% in the younger and older patients, respectively.

Diuretics and β-Blockers The combination of a diuretic and a β-blocker has proved to be very effective in primary prevention drug trials and now represents a cornerstone for the treatment of hypertension. β-Blockers tend to suppress renin secretion and thereby attenuate the hyperreninemia induced by diuretics.

A recently reported trial has provided convincing evidence that a low-dose combination of a diuretic and a β-blocker is indeed efficacious and well tolerated.[15] In this trial, a total of 512 hypertensive patients with a diastolic blood pressure ranging from 95 to 115 mm Hg at the end of a 4 to 6 week wash-out period were allocated to a 12 week double-blind treatment with bisoprolol (0, 2.5, 10, or 40 mg/day) plus placebo, bisoprolol (0, 2.5, 10 or 40 mg/day) plus hydrochlorothiazide, 6.25 mg/day, or bisoprolol (0, 2.5, 10, or 40 mg/day) plus hydrochlorothiazide, 25 mg/day. Figure 3 shows the response rate in the different groups of patients. Bisoprolol given alone had a



* Sitting DBP ≤ 90 mmHg at week 12

FIGURE 3. *Response rate after a 12 week treatment with various doses of bisoprolol and hydrochlorothiazide (HCTZ) given in combination (adapted from Frishman WH et al[15]).*

dose-dependent blood pressure lowering effect. This was also true for the diuretic, the blood pressure control being better with the 25 mg than with the 6.25 mg dose of hydrochlorothiazide. The major finding however was that the association of 6.25 mg hydrochlorothiazide with the β-blocker gave results very similar to that of 25 mg hydrochlorothiazide with the β-blocker. Of note also is that there was no clear-cut advantage to increase the dose of bisoprolol from 2.5 to 40 mg when the β-blocker was administered together with the diuretic. Another issue to take into account is the tolerability. For instance, the 25 mg dose of hydrochlorothiazide significantly lowered serum potassium levels, which was not the case with the 6.25 mg dose. It was concluded from this study that a fixed low-dose combination of bisoprolol and hydrochlorothiazide may be used in place of monotherapy as first-line treatment. This view was even supported by the US Food and Drug Administration, which approved that fixed low-dose combination for the initiation of antihypertensive therapy.[16] It is worth quoting here the justification that led to the approval: "The pivotal consideration is that each of these agents (bisoprolol and hydrochlorothiazide) has both dose-dependent and dose-independent adverse drug reactions. In a given patient, the dose-independent risks of the combination of low-dose bisoprolol and low-dose hydrochlorothiazide might, therefore, be preferable to the dose-dependent risks associated with monotherapy that employed a higher dose of either agent."[16]

The usefulness of a fixed-dose combination of bisoprolol and hydrochlorothiazide for the initial treatment of hypertension has been directly compared with that of traditional monotherapies in a randomized, double-blind, parallel group study.[17] After a 4- to 5-week placebo period, 218 hypertensive patients with diastolic blood pressures between 95 and 114 mm Hg were randomly allocated to take for 12 weeks either

the calcium antagonist amlodipine (2.5 to 10 mg/day), enalapril (5 to 20 mg/day), or the combination of bisoprolol (2.5 to 10 mg) with 6.25 mg hydrochlorothiazide. The response rates (either a diastolic pressure ≤90 mm Hg or a decrease of diastolic pressure ≥10 mm Hg) were 71% for the β-blocker–diuretic combination, 69% for amlodipine, and 45% for enalapril. The overall incidence of adverse experiences was 29%, 42%, and 47% for the drug combination, amlodipine, and enalapril, respectively. The corresponding values for the drug-related adverse events were 16%, 21%, and 23%. Thus the low-dose combination of bisoprolol and hydrochlorothiazide can indeed be regarded as a first-line option to replace single-agent therapies.

β-Blockers and Calcium Antagonists β-Blockers and dihydropyridine calcium antagonists complement each other when administered in combination. This is true not only in terms of antihypertensive efficacy, but also from the point of view of tolerability. Thus, β-blockers prevent the baroreceptor-reflex–mediated increase in heart rate observed in some patients during calcium entry blockade. On the other hand, the dihydropyridine-induced vasodilatation may attenuate the unwanted effects of β-blockade on the peripheral circulation. β-blockers should not be associated with a phenylalkylamine such as verapamil, as there exists the risk of precipitating an atrioventricular block or a myocardial depression. For the same reason, caution must also be exerted when considering the association of a β-blocker with a benzothiazepine such as diltiazem.

The usefulness of a β-blocker–calcium antagonist combination can be exemplified by the results of a double-blind, randomized, parallel group study aimed to compare extended-release formulations of either felodipine (10 mg/day) plus metoprolol (100 mg/day), metoprolol (100 mg/day), or felodipine (10 mg/day).[18] The drugs were administered once daily for 12 weeks in a total of 159 hypertensive patients with a diastolic blood pressure >95 mm Hg. The reductions in blood pressure achieved during the course of the study were 20/14 mm Hg with the drug combination, 13/10 mm Hg with the calcium antagonist, and 11/8 mm Hg with the β-blocker. The blood pressure control, as defined by a diastolic blood pressure <90 mm Hg after 12 weeks, was significantly better with the combination (71%) than with felodipine (49%) or metoprolol (34%). The three treatments were equally well tolerated.

Further relevant findings have been reported from a double-blind, randomized, crossover trial in which 58 hypertensive patients were treated for consecutive 12 week periods with 5 to 10 mg/day of felodipine, 50 to 100 mg/day of metoprolol, and a once-a-day fixed-dose combination of 5 to 10 mg felodipine plus 50 to 100 mg metoprolol.[19] Responders were defined by a diastolic blood pressure ≤90 mm Hg and/or a decrease in diastolic blood pressure of ≥10 mm Hg at the end of the study. Figure 4 depicts the number of responders observed with the various treatments. It also shows the large heterogeneity in blood pressure responses, some patients being responders whatever the treatment used whereas some were responders during administration of two or even one drug only. The increased efficacy of the felodipine–metoprolol combination was obtained without compromising the tolerability, as compared with the component monotherapies.

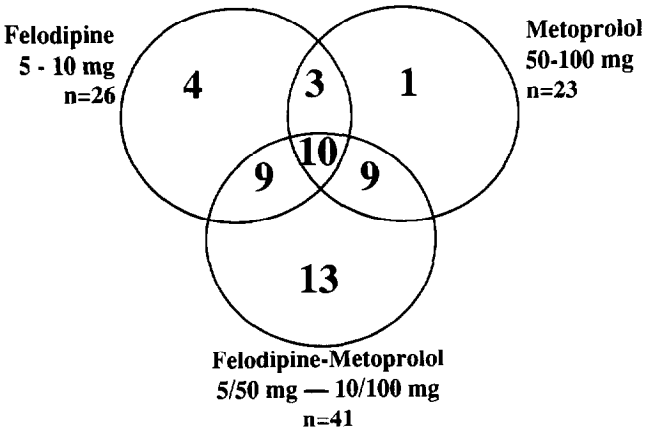


FIGURE 4. *Number of patients having normalized their diastolic blood pressure (≤90 mm Hg) after a 12 week treatment with felodipine and metoprolol given alone or in combination. The overlap between circles shows the patients who were good responders to two or more of the treatments (adapted from Dahlöf B et al[19]).*

Calcium Antagonists and ACE Inhibitors Calcium antagonists and ACE inhibitors exhibit additive antihypertensive efficacy when combined, and their safety profile is, if anything, improved. For example, captopril co-administered with nifedipine decreases the incidence of ankle edema resulting from calcium entry blockade.[20] More importantly, ACE inhibition blunts the reflex increase in sympathetic nerve activity mediated by dihydropyridines. This is illustrated in Figure 5. In this study, 24 hypertensive patients with a diastolic blood pressure of 95 to 115 mm Hg at the end of a 3 to 4 week wash-out period were randomized to receive in single-blind fashion for 4 weeks either captopril, 50 mg twice a day, or nitrendipine, 20 mg once a day. For the following 4 weeks half of the patients were treated with placebo and half with nitrendipine, 10 mg once a day, plus captopril, 25 mg twice a day.[21] In the panel A of Figure 5 are shown the patients treated initially with captopril. The ACE inhibitor produced a significant fall in diastolic blood pressure with no concomitant change in heart rate. The patients randomized to placebo returned again to pretreatment blood pressure values whereas the association of captopril and nitrendipine led to an additional fall in

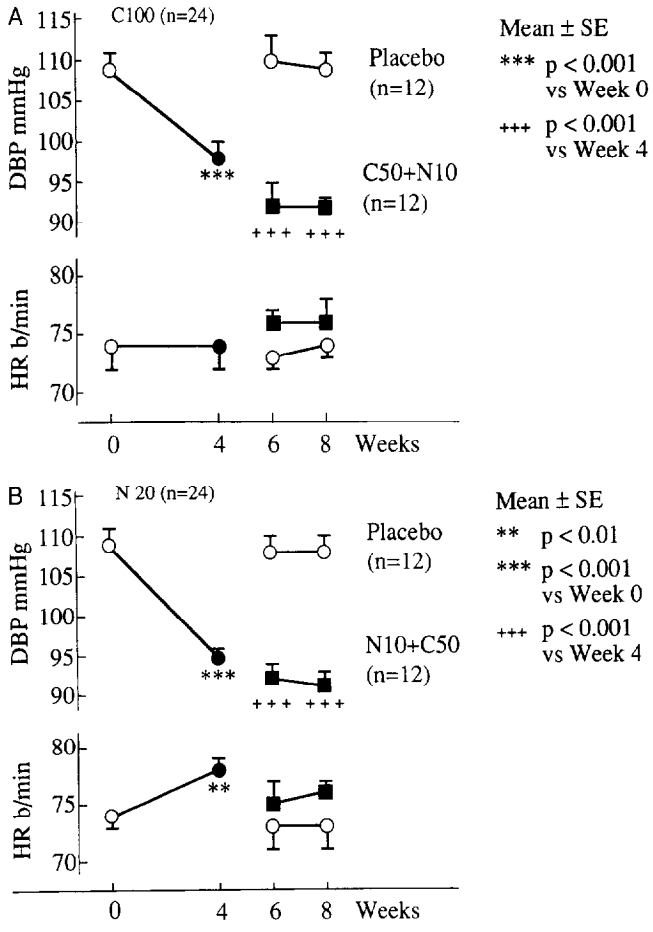


FIGURE 5. *Blood pressure and heart rate response to captopril (C) and nitrendipine (N) administered alone or in combination.* **Panel A:** *patients initially treated with captopril.* **Panel B:** *patients initially treated with nitrendipine. (Adapted from Gennari C et al[21]).*

blood pressure, which was significant when compared with the ACE inhibitor alone, whereas heart rate remained stable. The panel B of Figure 5 depicts the patients treated with nitrendipine first. This calcium antagonist caused a significant blood pressure decrease that was associated with a significant heart rate acceleration. Baseline values were reached again by those patients allocated to placebo during the last 4 weeks of the study. In the remaining patients treated by the combination of nitrendipine, 10 mg/day, and captopril, 50 mg/day, a further significant fall in blood pressure was observed in comparison with the nitrendipine monotherapy phase. During combined treatment, however, there was no evidence anymore for a reflex increase in heart rate. Other studies have confirmed the effectiveness of combined treatment with an ACE inhibitor and a calcium antagonist. For example, isradipine (1.25 to 2.5 mg twice daily) as monotherapy, was found to normalize blood pressure after 6 months in 49% of hypertensive patients compared with 56% with captopril as monotherapy (12.5 to 25 mg twice daily).[22] Combining both drugs resulted in an increased rate of blood pressure control, but not at the expense of a reduced tolerability. A potentially important advantage of this type of combination is that both calcium antagonists and ACE inhibitors are devoid of untoward metabolic effects.

Other Potentially Useful Drug Combinations

β-Blockers may well be combined with α_1-blockers.[10] Labetalol is a racemic compound offering simultaneously both types of adrenoceptor blockade. β-Blockers might also be associated with ACE inhibitors resulting in a better control blood pressure in a number of patients.[23] Diuretics may also increase the antihypertensive efficacy of calcium antagonists,[24,25] although such evidence has not been found.[26] Actually, it has been suggested that the coadministration of a diuretic and a calcium antagonist may be as effective in lowering blood pressure as the combination of a diuretic with an ACE inhibitor.[27] A rational and widely accepted combination is that of a thiazide with a potassium-sparing diuretic. In the future, one might also consider to associate an ACE inhibitor with an angiotensin II receptor antagonist with the goal of rendering more complete the blockade of the renin-angiotensin system.

THE NEED FOR FIXED-DOSE COMBINATIONS

Already several years ago it has been recognized that fixed-dose combinations might be useful for the treatment of hypertension.[28] At that time, most of the experience was based on the association of a diuretic with a centrally acting drug, mainly reserpine or methyldopa. Later on it was felt, however, that the use of fixed-ratio drug combinations should not be generalized, principally because of the lack of flexibility in adjusting the doses of the individual components. Fixed-dose combinations elicit nowadays a growing interest.[29–32] One realizes more and more that it is very difficult to find the most appropriate dose of two antihypertensive agents if one wishes to combine them in an attempt to normalize blood pressure of a given hypertensive patient. Frequently the dose titration ends with the choice of too high doses, with the risk of favoring the occurrence of dose-related adverse reactions. The use of fixed-dose combinations greatly facilitates the therapeutic approach. The doctor knows that the doses of the two components were established on the basis of large clinical trials and that the primary aim was to develop a simple drug regimen that is at the same time efficacious and well tolerated. Fixed-dose combinations of antihypertensive agents are expected to increase the patient's compliance to therapy, as they enable to control blood pressure in many patients with a once-a-day administration. It is therefore not really surprising that a highly respected regulatory authority like the US Food and Drug Administration has already approved a fixed-dose combina-

tion as a first-line antihypertensive therapy. No doubt this will encourage many physicians to adopt this meaningful therapeutic approach.

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