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Scientific Update™

New Insights on Combination Therapy for Arterial Hypertension

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Despite recent advances in the management of arterial hypertension, the incidence of cardiovascular complications in treated hypertensive patients is higher than that of matched normotensive individuals. Compliance with therapy is undoubtedly an important factor, but even in patients who adhere strictly to their therapy, the optimum target blood pressure is unknown although recent national and international guidelines are recommending increasingly aggressive targets. It is unlikely, at least in a significant proportion of patients, that such ambitious targets can be achieved with monotherapy. Indeed, most patients are likely to require combination therapy to achieve adequate control. This *Update* reviews some of the most recent reports on combination antihypertensive therapy.

The Hypertension Optimal Treatment (HOT) Study

The recently published study set out to investigate the hypothesis that the persistently elevated cardiovascular morbidity and mortality levels observed in treated hypertensive patients were due to blood pressure (BP) levels that were not lowered to near normotensive levels.[1] This contrasts with the so-called J-curve concept that postulates that vigorous BP lowering may be associated with increased cardiovascular risk. Therefore, the HOT study, in a randomized and prospective trial, addressed the important question of whether there was a benefit of lowering BP to fully normotensive levels, or whether there was little benefit in lowering diastolic blood pressure (DBP) below 90 mm Hg. The main goals of the study were: 1) to evaluate the association between major cardiovascular events (non-fatal myocardial infarction [MI], non-fatal stroke, and cardiovascular death) and DBP targets of ≤90 mm Hg, ≤85 mm Hg, and ≤80 mm Hg during antihypertensive treatment, and 2) to evaluate the association between major cardiovascular events and the DBP achieved during treatment. A third goal, to assess the effects of low dose aspirin in addition to antihypertensive treatment, is beyond the scope of this *Update*.

The patient population in the HOT study included 18,790 patients from 26 countries in Europe, North and South America, and Asia with a mean age of 61.5 years (range 50-80 years), with hypertension and a DBP between 100-115 mm Hg (mean 105 mm Hg). The patients were randomized to one of the three target blood pressures and aspirin or placebo. The study was conducted according to the Prospective, Randomized, Open with Blinded Endpoint evaluation (PROBE) design. The randomization resulted in three practically identical groups in terms of numbers of patients, as well as baseline characteristics of BP, age, sex distribution, previous morbidity, and previous antihypertensive treatment. The patients were followed for an average of 3.8 years (range 3.3-4.9 years) and the total observation amounted to 71,051 patient-years.

Treatment

Antihypertensive therapy was initiated in all patients with the long-acting calcium antagonist felodipine at a dose of 5 mg once daily. Additional therapy was allowed in 4 further steps pre-defined in the protocol to reach the randomized target BP.

Angiotensin-converting enzyme (ACE) inhibitors or ß-blockers were added to felodipine 5 mg at step 2, and dosage titrations were used at step 3 (increasing felodipine to 10 mg once daily), or step 4 (doubling of the dose of either the ACE

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Table 1: Treatment at the end of the HOT study[1]

	Diastolic blood pressure target group		
	≤90 mm Hg	≤85 mm Hg	≤80 mm Hg
Felodipine (%)	77	78	79
ACE inhibitors (%)	35	42	45
ß-blockers (%)	25	28	32
Diuretics (%)	19	22	24

ACE = angiotensin-converting enzyme

inhibitor or the ß-blocker). A final step 5 consisted of the possibility of adding a diuretic.

Results

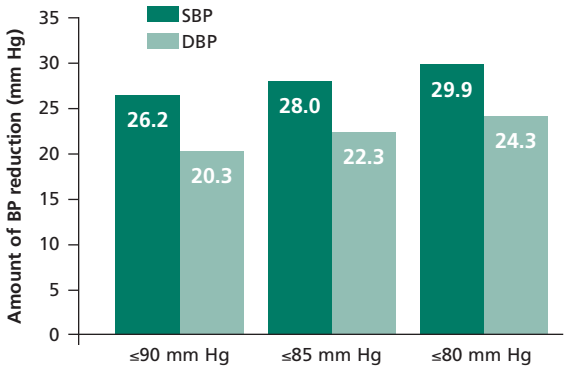
At the conclusion of the study, 78% of patients were still taking felodipine as baseline therapy, often in combination with an ACE inhibitor (41%) or a ß-blocker (28%) (Table 1). The proportions of patients taking these additional medications as well as diuretics increased, as one would expect, with the more aggressive BP target. Of note, the aggressive felodipine-based combination therapy utilized in the study was well-tolerated, with the proportion of patients reporting side-effects actually decreasing during the trial to 2.2% at the final visit.

When compared with BP at the time of randomization, the average DBP was reduced by 20.3 mm Hg, 22.3 mm Hg, and 24.3 mm Hg; the systolic blood pressure (SBP) was reduced by 26.2 mm Hg, 28.0 mm Hg, and 29.9 mm Hg in the target groups ≤90 mm Hg, ≤85 mm Hg, and ≤80 mm Hg, respectively. These very impressive reductions provide convincing evidence that combination therapy can effectively reduce BP to targets that are more aggressive than what had been attempted in previous trials. The magnitudes of the reductions in BP, however, must be interpreted with some caution because, since there was no placebo-controlled group in this study, they are not corrected for the effect of placebo. Nevertheless, as placebo usually accounts for a BP reduction of only 3-4 mm Hg, these are still substantial and impressive reductions.

The fact that over 91% of patients in the HOT study achieved DBP ≤90 mm Hg demonstrates that it is possible in the majority of the patients – frequently with the use of combination therapy – to reduce BP well below 140/90 mm Hg.

A key aspect of the HOT study is that it was conducted in community practice offices and clinics, not in large academic research centers. Arguably, the main lesson of this study is that it is possible for family physicians to lower BP to less than 90 mm Hg with good tolerability, using combination therapy, when specific guidelines or protocols are followed. Family physicians should be encouraged, therefore, to manage blood pressure with the BP targets or guidelines in mind and use combination therapy as necessary to achieve those targets.

Figure 1: Differences between baseline and achieved blood pressure in the HOT Study[1]



Interestingly, the investigators examined the estimated incidence of cardiovascular events in relation to achieved mean DBP and SBP. The results of the HOT study demonstrated that the lowest incidence of major cardiovascular events occurred at a mean achieved DBP of 82.6 mm Hg and a mean achieved SBP of 138.5 mm Hg. Further reduction below these levels was safe, although it did not result in any additional benefit.

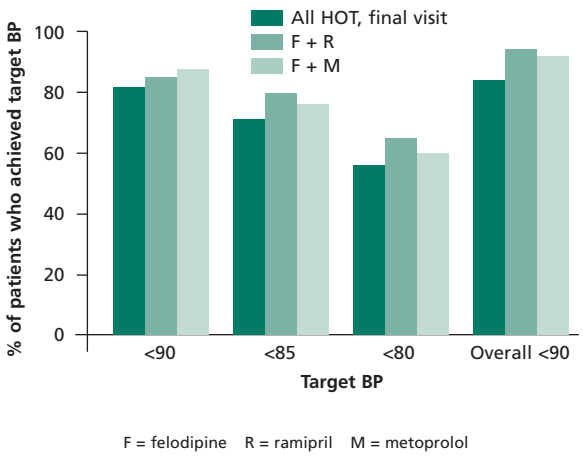
Benefits are amplified in diabetic patients

An analysis of the HOT study in diabetic patients yielded reassuring results on the efficacy and safety of felodipine-based treatment. This is particularly important in view of recent reports suggesting that the dihydropyridine CCBs are associated with a higher incidence of cardiovascular events in diabetic hypertensive patients. This was not observed in the 1,501 diabetics included in the HOT study. In fact, in what is arguably the most important finding of the study, in patients with diabetes mellitus there was a 51% reduction in major cardiovascular events in target group ≤80 mm Hg compared with target group ≤90 mm Hg (p=0.005).

Efficacy and tolerability of combination therapy in intensive BP lowering: Experience from the HOT Study

One of the substudies from the HOT Study further analyzed the BP-lowering effects and tolerability of the combination of felodipine and the ACE inhibitor ramipril versus the combination of felodipine and the ß-blocker, metoprolol.[2] In the HOT study, there were 929 patients on felodipine and ramipril, and 1015 patients on felodipine and metoprolol. In both groups, patients were comparable in terms of their age, gender distribution, smoking history, and previous antihypertensive therapy. In the entire population of the HOT study, the proportions of patients achieving their target DBP at the final visit were 85.8%, 72.7%, and 55.2% for targets ≤90, ≤85, and ≤80 mm Hg, respectively. The combination of felodipine and the ACE inhibitor compared very

Figure 2: Comparison of BP lowering effects: final visit – all HOT vs. F+R vs. F+M



F = felodipine R = ramipril M = metoprolol

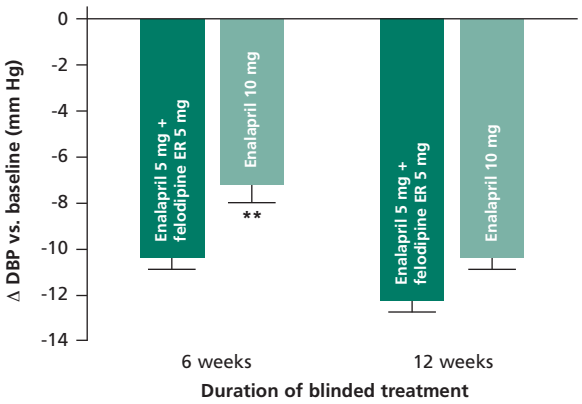
favorably with the overall results of the study as the targets were achieved in 88.8%, 81.3%, and 63.7% of patients, respectively. A very impressive 93.5% on this combination achieved a DBP of ≤90 mm Hg. The combination of felodipine and the ß-blocker also performed quite well in the study as the target BP was achieved in 89.5%, 74.9%, and 63.7% of the patients for target BPs of ≤90, ≤85 and ≤80 mm Hg, respectively (Figure 2). Overall, 92% of patients on this combination achieved a DBP of ≤90 mm Hg.

Of note, the rates of adverse events were similar between the two combination treatment groups and, as in the overall study; they declined between the initial and the final visits to a modest 1.2% for felodipine plus the ACE inhibitor, and 1.6% for felodipine plus the ß-blocker. In conclusion, the use of felodipine, in combination with the ACE inhibitor or the ß-blocker, was extremely effective and well-tolerated in the HOT study population.

Combination of calcium antagonists and ACE inhibitors: The incidence of vasodilatory edema

Vasodilatory edema is one of the most common adverse effects associated with the use of calcium antagonists. It occurs more frequently with the dihydropyridine class of calcium antagonists than with the other classes. As well, it is more common in women than in men, and because it is dose-dependent, it often limits the tolerability of higher doses of these agents. A recent study evaluated the incidence of all forms of edema in a cohort of 1,189 patients with arterial hypertension who were treated either with placebo, a dihydropyridine calcium antagonist alone (amlodipine or felodipine, 5 mg or 10 mg once daily), or with the combination of an ACE inhibitor (benazapril or enalapril) with the 5 mg dose of the calcium antagonist.

Figure 3: Changes in DBP, from baseline, after 6 weeks of randomized treatment (first two bars), and after 6 further weeks (second two bars)



ER = extended release
**p <.01 between groups

Note: During the second 6-week period, all patients took 5 mg enalapril + 5 mg felodipine ER once daily; the labels on the bars indicate the initial treatment assignment

A significantly higher incidence of edema (24.5%) was observed in patients taking the 10 mg dose of the calcium antagonist, than in those assigned to placebo (2.6%, p<0.001). No significant increase in edema was observed in patients taking the 5 mg dose of the calcium antagonist (5.3%, p = ns versus placebo). Interestingly, combination ACE inhibitor and calcium antagonist resulted in an even lower incidence of edema (3.4%, p<0.0001 versus 10 mg of calcium antagonist). Indeed, for a given decrease of 10 mm Hg in SBP with 10 mg of either felodipine or amlodipine, 27% of the patients experienced edema. In contrast, similar antihypertensive efficacy and an incidence of vasodilatory edema not different from placebo can be achieved by the addition of an ACE inhibitor to the 5 mg dose of either felodipine or amlodipine, which in this study, were used interchangeably.[3]

Low-dose combination therapy versus increased dose of monotherapy

A recent study compared two strategies for intensifying antihypertensive treatment, a low-dose combination of enalapril and felodipine versus an increased dose of enalapril.[4] This was a randomized, double-blind study in which 217 patients received 5 mg of enalapril for 3 weeks before being randomized to 6 weeks of treatment with either a low-dose combination therapy (5 mg enalapril + 5 mg felodipine once daily), or a higher dose of monotherapy with enalapril 10 mg once daily. In a subsequent crossover stage, the patients taking 10 mg of enalapril were switched to the combination therapy for an additional 6 weeks. The patients randomized to the combination achieved significantly greater reductions at 6

weeks in sitting SBP (-14.2 mm Hg) and DBP (-10.6 mm Hg) than the group randomized to increased monotherapy with enalapril (SBP –9.7 mm Hg, DBP –7.4 mm Hg; p<0.05 and <0.01 respectively) (Figure 3). As well, a higher percentage of patients responded to the combination (defined as DBP < 90 mm Hg or a decrease of at least 10 mm Hg): 59% versus 41% with monotherapy (p<0.01). Furthermore, when the patients originally randomized to 10 mg of enalapril were crossed over to the combination therapy for a further 6 weeks there was a significant additional BP reduction and an increase in response rates equivalent to those seen in the patients on the low-dose combination. The greater antihypertensive efficacy of the low-dose combination was achieved without sacrificing tolerability, and independent of age, gender and race. These results are consistent with the hypothesis that when the target BP reduction is not achieved with a low dose antihypertensive agent, a combination of two drugs, eg, felodipine and an ACE inhibitor, can offer complementary mechanisms of action is often more effective than increasing the dose of the first agent.

Effects of combination antihypertensive therapy on baroreflex sensitivity and heart rate variability in systemic hypertension

Arterial hypertension is associated with multiple manifestations of impaired cardiovascular autonomic regulation such as reduced baroreflex sensitivity (BRS) and heart rate variability (HRV). These phenomena have been linked to increased cardiac mortality after acute MI and there is also increasing evidence that impaired cardiovascular autonomic regulation may be predictive of mortality and adverse outcomes in patients without documented coronary artery disease. As well, previous population-based studies show that BRS and HRV decrease in middle-aged hypertensive patients despite long-term antihypertensive treatment. It is not clear whether the autonomic impairment is a primary feature characteristic of arterial hypertension which precedes its onset and whether these abnormalities can be reversed by intensive combination antihypertensive therapy. A recent study evaluated BRS and HRV in 33 hypertensive patients with poor BP control randomized to either enalapril or metoprolol. Following a period of monotherapy, treatment was intensified in both groups for an additional 10 weeks by adding felodipine to the metoprolol therapy, or hydrochlorothiazide to the enalapril group. The addition of the second drugs resulted in a significant further decline in 24-hour SBP and DBP, from an average of 139/86 to 126/80 mm Hg (p<0.0001). BRS improved from 6.2±3.2 mm Hg to 8.9±4.1 ms/mm Hg (p<0.0001) and the measurements of HRV also improved significantly during the combination therapy (the standard deviation of all RR intervals increased from 128±45 ms to 145±46 ms, p<0.0001). Abnormal cardiovascular autonomic regulation in patients with poor BP control is not, therefore, an irreversible phenomenon, but it can be significantly improved by intensive combination antihypertensive therapy as seen here when felodipine was added to a ß-blocker. These findings may provide an additional mechanism to explain the observed cardiovascular benefits associated with improved BP control.[5]

Conclusion

This issue of *Cardiology Scientific Update* has reviewed recent reports on the safety and efficacy of felodipine-based combination antihypertensive therapy. The HOT study demonstrated that aggressive BP-lowering is not only feasible, but can also be achieved safely. Aggressive BP control was of great benefit, in particular, in the diabetic population. The use of the combination of felodipine plus an ACE inhibitor or ß-blocker was highly effective and well-tolerated in the HOT study and resulted in a DBP ≤90 mm Hg in over 91% of the patients. In separate studies, the addition of an ACE inhibitor to a calcium antagonist like felodipine or amlodipine not only resulted in improved blood pressure control, but also in an incidence of vasodilatory edema that was significantly decreased and no different than placebo. An additional recent study demonstrated that adding low dose felodipine to enalapril was more effective in lowering blood pressure than doubling the dose of enalapril.

The effects of intensive BP control on the abnormalities of autonomic cardiovascular regulation associated with poorly controlled hypertension were also examined by a recent study. Combination therapy, including felodipine plus metoprolol, resulted in significant improvements in autonomic regulation as measured by parameters such as BRS and HRV. Impaired autonomic cardiovascular regulation is a significant predictor of risk and its improvement could be one of the mechanisms explaining the beneficial effects of intensive antihypertensive therapy on major cardiovascular events.

Physicians should be aware that combination therapy can increase cost to the patient and thus, it is important to keep in mind the differences in cost among various agents, even within certain drug classes.

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