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Scientific Update™

What target blood pressure?

The Hypertension Optimal Treatment (HOT) study: an update

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The field of hypertension research finds itself in an excellent position to start providing answers to a number of questions of crucial importance to the clinician, and of course the hypertensive patient, such as whether the newer agents like calcium antagonists, angiotensin converting enzyme (ACE) inhibitors or angiotensin II receptor antagonists are equivalent, or better, than the more traditional agents such as ß-blockers and diuretics, which have been demonstrated in prospective randomized trials to reduce the incidence of important cardiovascular events such as stroke and myocardial infarction in the hypertensive patient. Other equally important, yet unresolved questions, relate to the optimal level of diastolic blood pressure control and the need for a better understanding of preservation of cognitive function and quality of life. We are beginning to see the completion of large, prospective, randomized trials like the Hypertension Optimal Treatment Study (HOT) which will provide the necessary tools for dealing with these issues.

Introduction

The field of cardiovascular medicine, particularly hypertension, was recently shaken by a controversy in the medical and lay media about the safety of calcium antagonists. This controversy was fueled by reports based on observational studies, such as case-control and cohort studies, that putatively indicated that calcium antagonists increased the risk of coronary heart disease,[1,2] cancer,[3,4] and bleeding[4-9]. After this controversy, the Liaison Committee of the World Health Organization (WHO) and the International Society of Hypertension (ISH) formed an ad hoc subcommittee to review the relevant available evidence linking calcium antagonists to those risks. The subcommittee has recently issued its conclusions.

WHO/IHS subcommittee report

Highlights of the subcommittee report can be summarized as follows[10]:

1. *"The available evidence does not prove the existence of either beneficial or harmful effects of calcium antagonists on the risks of major coronary heart disease events, including fatal or non-fatal myocardial infarctions and other deaths from coronary heart disease. This applies to the evidence on all calcium antagonists considered collectively; and to that on subgroups of these agents."*
2. *"...the available evidence from observational studies does not provide good evidence of an adverse effect of calcium antagonists on cancer risk..."*
3. *"...the available evidence from observational studies and randomized trials does not provide clear evidence of an adverse effect of calcium antagonists on bleeding risk."*

Now that this controversy has been laid to rest, investigators are in an excellent position to find answers to several questions of crucial importance to clinicians and hypertensive patients in the field of hypertension research.

The unfortunate controversy over the safety of calcium antagonists serves to underscore the importance of large-scale, prospective, randomized trials, and the inappropriate role that observational studies played in generating public concerns, despite their serious limitations.

Ongoing trials

Within the next few years, data will be available from clinical trials of about 100,000 hypertensive patients ran-

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domized to either calcium antagonist or traditional β-blocker/diuretic therapy. About half of these patients are in prospective trials of newer slow-release or long-acting dihydropyridines; the remainder, in clinical trials of other types of calcium antagonists. These prospective studies should provide additional, reliable data on the long-term safety of calcium antagonists. Of note, most studies had been planned or initiated – in some cases, recruitment had been completed – prior to the controversy.

At least five trials outside North America are addressing one of two crucial issues. The first, whether clinicians should aim for an optimal level of BP to minimize the risk of cardiovascular disease, will be addressed by the Swedish Behandla Blodtryck Battre (BBB) Trial and Hypertension Optimal Treatment (HOT) study. The BBB trial has revealed interesting trends but no definitive conclusions. The ongoing HOT study, on completion within a few months, should adequately assess this issue.

The second important issue – the question of whether traditional antihypertensive agents, such as diuretics and β-blockers, are more effective than newer agents, such as calcium antagonists and ACE inhibitors, in reducing cardiovascular risk – is the current focus of three ongoing trials; the Captopril Prevention Project, the Nordic Diltiazem Study (NORDIL), the Swedish Trial in Old Patients with Hypertension-2 (STOP Hypertension-2) was designed to compare the conventional therapy with β-blockers and diuretics, proven effective in STOP-Hypertension.[11] All of these ongoing trials should be completed in the near future and are expected to yield valuable information that will significantly improve our approach to the management of hypertension.[12]

The Hypertension Optimal Treatment (HOT) study

What target blood pressure? This major question in the management of arterial hypertension is still unanswered. When treating arterial hypertension, the optimal BP reduction is one that yields the maximum achievable prevention of hypertension-associated cardiovascular morbidity and mortality. It is quite clear that this goal has not yet been reached by our present approach to hypertension management.

Several large interventional trials have shown that treated hypertensive patients still have an increased risk of cardiovascular morbidity and mortality. One possible explanation for this finding is that treated BP is rarely, if ever, reduced to completely normotensive levels. Another explanation, favored by proponents of the "J-curve" argument, is that excessive BP lowering may increase cardiovascular risks. Regrettably, hypertension research has not directly investigated this dispute. Consequently, due to the lack of reliable data, it has continued to persist for some time. The problem has finally been tackled by the design and initiation of an appropriately large international trial: the Hypertension Optimal Treatment (HOT) study.

The HOT study is a prospective, randomized, multicenter clinical trial in 26 countries, including Canada and the United States.[13] Two major issues are being investigated:

1. What is the optimal target diastolic blood pressure during antihypertensive treatment with respect to the reduction in cardiovascular morbidity and mortality?
2. What is the effect of low-dose aspirin (75 mg daily) vs placebo on cardiovascular morbidity and mortality?

To address these questions, patients were randomized to three different therapeutic goals: a diastolic BP of <90 mm Hg, <85 mm Hg, or <80 mm Hg. The first aim is being investigated according to PROBE design (Prospective Randomized Open Blinded Endpoint evaluation), whereas the evaluation of aspirin versus placebo is a double-blinded trial. Therefore, patients were first randomized to one of the three diastolic BP targets, then to aspirin or placebo.

All patients were given the calcium antagonist felodipine at a dose of 5 mg daily as basic antihypertensive therapy. If target BP was not reached, additional antihypertensive therapy with either an ACE inhibitor or β-blocker was prescribed. Further dosage adjustments were made, if required, according to a well-defined protocol to achieve the randomized therapeutic goal. As a final step, a diuretic could be added.

Recruitment was completed on April 30, 1994. In total, 19,196 patients have been randomized: 9,055 women (47%) and 10,141 men (53%) with an average age of 61.5±7.5 years (mean±standard deviation). The average prerandomization BP in untreated patients was 169±14/106±3 mm Hg; in treated patients, 170±14/105±3 mm Hg.

In August 1994, BP data were available for 14,710 and 10,275 patients who had completed 3 and 6 months of treatment, respectively. The average reduction in diastolic BP was 22 mm Hg after 6 months.[14]

For the purpose of data analysis and testing the relevance of therapy in patients of different ages, predefined age groups were established (<65 years, n=13,080 patients; >65 years, n=6,116 patients).

At 12 months, on average, the <90 mm Hg target group had reached a diastolic BP of 86 mm Hg, the <85 mm Hg target group had reached 83 mm Hg, and <80 mm Hg target group had reached 81 mm Hg.

The percentage of patients who had reached their target diastolic BP at 12 months was 84% in the <90 mm Hg group, 72% in the <85 mm Hg group, and 57% in the <80 mm Hg group. Interestingly, in the >65 age group, the percentage of patients at target at 12 months was higher in all BP groups at 86%, 76%, and 61%, respectively.

Significantly, in terms of side effects, in young and elderly patients, only ankle edema (2.6% and 3%) and

coughing (1.3% and 0.8%) exceeded a frequency of 1%. At 12 months, 88% of patients were still on baseline therapy with felodipine.[15]

These 12-month results have shown the excellent efficacy and tolerability profile of felodipine and fueled the optimism that it may be possible to fulfill the primary aims of the HOT Study.

The HOT Study at 36 months

The HOT study reached 36 months in May 1997. At 36 months, there has clearly been a steady, gradual improvement in diastolic BP control over the course of the trial. In fact, an impressive and steadily higher number of patients have achieved the target BP during the scheduled follow-up. This finding is best illustrated by comparing the 6- and 36-month results: in the <80 mm Hg target group, 50% and 60% of patients reached BP targets at 6 and 36 months, respectively; in the <85 mm Hg group, 65% and 75%; in the <90 mm Hg group, 80% and 90%.

Similar results were observed in the elderly and young subgroups. As with previous analyses at earlier time-points, more patients in the elderly group (>65 years) achieved their diastolic BP goals in the three target groups. It appears that, in the majority of patients, diastolic BP ranged from 75-90 mm Hg.

Most patients had systolic BPs between 115-160 mm Hg. In fact, a decline in systolic BP was closely correlated with a decrease in diastolic BP. For example, when the diastolic BP decreased by <10 mm Hg, only 9.7% of patients achieved a systolic BP of <140 mm Hg. In contrast, when the diastolic BP decreased by 11-20 mm Hg, the number of patients with a systolic BP of <140 mm Hg rose to 36.8%. As illustrated in Table 1, the data may be interpreted as indicating that when the target diastolic BP is <80 mm Hg, more patients achieve a systolic BP of <140 mm Hg.

Table 1: Systolic BP at 36 months (% patients)

Target group	<140 mm Hg	140-150 mm Hg	>150 mm Hg
≤80 mm Hg	51.3	29.1	19.6
≤85 mm Hg	47.6	28.8	23.6
≤90 mm Hg	40.6	31.2	28.2

In terms of side effects at 36 months, the HOT Study had good news. Overall, the frequency of all side effects decreased with time. A possible explanation for this result is that patients who do not tolerate the trial medication are removed from the study. However, the patient dropout ratio is extremely low, so this explanation seems unlikely. A more positive and more likely interpretation is that, over time, patients tolerate the medications better and experience fewer side effects.

Table 2: Frequency of side effects (%)

	6 months	12 months	24 months	36 months
all side effects	10.5	8.5	5.7	3.6
edema	4.0	2.8	1.4	1.0
headache	0.9	0.3	0.2	0.1
cough	1.1	1.2	0.5	0.3

A more detailed analysis of the most common side effects over time appears in Table 2. The percentage of patients remaining on felodipine at the different time points is illustrated in Table 3. As seen from these tables, effective and safe long-term control of hypertension can be achieved with felodipine in large numbers of patients with minimal side effects.

Table 3: Patients on felodipine (%)

Target group	6 months	12 months	24 months	36 months
≤80 mm Hg	90	88	84	82
≤85 mm Hg	91	88	84	83
≤90 mm Hg	91	88	84	83

The data on dose titration after inadequate BP control with felodipine was similar at 12 and 36 months. The most common adjunctive therapies were an ACE inhibitor, then β-blocker. Both additions were shown to be equally effective when added to felodipine. Interestingly, the previously treated patients had a BP of 161±18/99±9 mm Hg (mean±standard deviation) on their original medications before the washout period (n=5,907). BP had decreased in this group to 141±15/83±7 mm Hg at 36 months. These patients had a marked improvement in BP control when the study protocol was followed.

The reason for this finding is probably that, at enrollment, most of these patients were on monotherapy, whereas at 3 years, the majority of HOT patients were on double-drug therapy. Therefore, by starting with felodipine then adding other antihypertensive agents in a stepwise progression, a dramatic improvement in BP control may be achieved.

To emphasize the importance of these data, meta-analysis has determined that a 5-6 mm Hg reduction in diastolic BP corresponds to about a 40% reduction in stroke.

In late 1995, the HOT study reached the initial target follow-up of 40,000 patient-years. However, the study had to be continued and, when it terminates in August 1997, the follow-up is expected to reach 75,000 patient-years.

Why are additional patient-years of follow-up necessary? The answer lies in the observed clinical events in relation to time of study. At 6 and 12 months, the clinical event rate was

12 events/1,000 patient-years. Contrary to what was expected in this high-risk population, the event rate did not increase with the passage of time. In fact, the opposite effect was observed. The event rate actually declined to 9.5 events/1,000 patient-years at 36 months. The reason for this finding is unknown at this time, but the most logical explanation is that treatment is protecting against clinical events. Whether this beneficial effect is due to BP control *per se*, the addition of aspirin, or both is unclear presently.

The decline in event rate is the reason that the study had to be extended to obtain a higher number of patient-years of follow-up. The HOT study is expected to end in August 1997, when the target of 1,100 major cardiovascular events is likely to be reached.

Effects of Baseline BP, age, and body weight on BP response

The HOT study database includes tens of thousands of patient-years of follow-up. HOT investigators have access to an excellent center for data analysis to evaluate the tremendous wealth of information that the study is generating.

One interesting, important question that the HOT database has enabled investigators to explore is the effect of baseline BP (prior to treatment) on BP response to antihypertensive therapy. There is marked confusion in clinical medicine over this issue, which is often underscored by the belief that severe hypertension is hardest to treat, whereas mild or moderate hypertension is easier to treat. This concept is based on older studies that used older, traditional medications. A HOT database analysis at 36 months revealed that precisely the opposite is true, i.e., the higher the baseline BP, the easier it is to treat – and the greater the decrease with felodipine therapy. A HOT data analysis for the effect of monotherapy with felodipine showed a similar finding: a greater decline in BP occurred in patients with higher baseline BPs. In fact, a much higher percentage of patients with baseline diastolic BP of 110-115 mm Hg had a decline in diastolic BP with felodipine of at least 30 mm Hg, compared with patients who had lower BPs before treatment.

Analysis of the effect of age on BP response also yielded surprising results. There is an old belief in clinical medicine that, in the elderly, hypertension is "fixed", due to atherosclerosis and "vessel stiffness", and much more difficult to treat. Again, HOT results contradicted this old axiom. In fact, the elderly group (>65 years) actually responded to therapy much better than the younger group. Moreover, the older the patient, the greater the drop in BP with antihypertensive therapy. The only exception to this finding were patients who, due to protocol-sanctioned changes, were on β-blocker monotherapy. In this subset of patients, as age increased, response to β-blockers decreased. In contrast, monotherapy with other agents conformed to the described pattern. ACE inhibitors worked better as age increased, but felodipine produced the best results in the elderly. Whether this phenomenon is due to differences in etiology is not clear, but it appears that lowering BP in the elderly is easier than in the younger population.

The effect of body weight on BP control was also evaluated. HOT patients with lower body weights had the best BP responses. This pattern was maintained in all target groups. However, when the decline in diastolic BP was correlated with body mass index, an indicator of obesity, the relationship disappeared. This result may be due to the fact that plasma volume correlates better with body weight. It raises the issue of whether optimal antihypertensive therapy should be adjusted on the basis of body weight – something not presently done in adults. Of interest, the response to monotherapy also correlated closely with body weight. In patients with body weights <70 kg, the response to monotherapy was about 60%, whereas in patients over 90 kg, it was significantly lower.

Another important issue is the correlation of a decline in systolic BP with diastolic-BP response to treatment. This issue is crucial in view of the importance of systolic BP as an independent risk factor for cardiovascular events. A HOT database analysis showed a practically linear relationship between systolic and diastolic BP declines. Consequently, when the target diastolic BP is <80 mm Hg, only 20% of patients had a systolic BP >150 mm Hg. Thus, if the aim of therapy is to lower diastolic BP more aggressively, there is a much better chance of reducing the systolic BP to levels that are considered acceptable and associated with lower risk.

Renal failure does not preclude an adequate BP control

A renal function substudy was included in HOT to assess whether the presence of renal dysfunction precluded the attainment of adequate BP control in patients with essential arterial hypertension. Another substudy goal was to investigate whether lower levels of diastolic BP correlate with better preservation of renal function.

Serum creatinine and creatinine clearance were measured initially in all 19,193 patients enrolled in HOT. Patients were divided into those achieving and those not achieving the target BP at 12 and 24 months of follow-up, then renal function of the two groups was compared. Patients were also divided into groups depending on baseline serum creatinine levels: >1.5 mg/dl (133 µmol/L) and <1.5 mg/dl.

At 1 and 2 years, no significant difference in renal function was found between patients who achieved

target BPs and those who did not. The decline in diastolic BP was similar when patients were divided according to baseline creatinine levels. However, to achieve an equal level of BP control, therapeutic needs were significantly higher in patients with serum creatinine levels >1.5 mg/dl.

The HOT renal function substudy has shown that impaired renal function does not preclude adequate BP control when a stepwise approach to therapy is used. An adequate response to the antihypertensive therapy may be achieved by increasing the dosage or adding other medications.

Quality of life: Does lowering BP improve mood?

Epidemiological data suggest that a strong correlation exists between low systolic BP and minor psychological dysfunction, depression, psychosomatic symptoms, or fatigue – as based on basal rather pharmacologically lowered BP. Nevertheless, the HOT study included a quality of life (QOL) substudy designed with two aims: to investigate whether lowering BP had any impact on well-being and to compare the three target groups in this respect; second, to investigate whether side effects, as a consequence of more aggressive antihypertensive therapy, affected QOL.

A total of 610 male and female patients were entered into the QOL substudy. The target groups had no differences in baseline characteristics, diastolic or systolic BPs, clinical data, or baseline QOL scores.

QOL assessment was performed at entry and at 6 months. QOL was evaluated by two self-administered questionnaires that corresponded to two well-validated methods: the psychological general well-being index (PGWB) and the subjective symptom assessment profile (SSAP). The PGWB evaluates multiple psychological parameters, including anxiety, depression, vitality, and overall sense of well-being. The SSAP evaluates symptoms, including cardiac complaints, aspects of sex life, peripheral circulation, edema, cough, headaches, and dizziness.

Well-being, as measured by PGWB, was unchanged in the <90 mm Hg target group. In contrast, there was a slight improvement in the <85 mm Hg target group ($p<0.05$) and considerable improvement in the <80 mm Hg target group ($p<0.01$). In fact, improvement correlated with the actual BP achieved ($p<0.05$). The most marked improvement was observed in patients who achieved a diastolic BP of <80 mm Hg, whereas patients whose achieved BP was >91 mm Hg actually suffered a deterioration in their scores. Improvements of 4 points in PGWB score within the <80 mm Hg target group have been shown to be highly relevant when this method was applied to other populations. All domains of the test contributed to the improvement but, in particular, there was a marked decrease in anxiety.

Significant improvements occurred in most areas assessed by the SSAP. For example, a comparison between baseline and 6-month scores shows improvements in cardiac symptoms ($p<0.05$), dizziness ($p<0.01$), and headaches ($p<0.001$) in all three BP target groups.

Analysis of adverse effects revealed that all target groups had an increased incidence of ankle edema ($p<0.001$). Dry cough increased in the <80 mm Hg target group ($p<0.001$). A slight deterioration in parameters of sex life occurred in the <80 and <85 mm Hg. The magnitude of adverse change was only 0.25 points on a scale of 1-7, but it reached statistical significance ($p<0.05$). This change affected only male patients, as scores in women were unchanged, and related only to sexual capacity, as interest and other parameters were unaffected. It is possibly due to the increased use of β-blockers in patients with more aggressive BP targets.

The QOL Substudy demonstrated that, lowering BP to a greater extent improved patient mood and well-being, as measured by the PGWB index. Therefore, in contrast to epidemiological observations related to systolic BP, there was no evidence that a more aggressive approach to BP lowering had deleterious effects.

Compliance: Lessons from the HOT Study

HOT is a large, well-designed trial that has challenged many old and unsubstantiated myths about antihypertensive therapy. The critical issue and implications of patient noncompliance with antihypertensive therapy were also examined in this trial. Many surveys in Europe and North America have shown that hypertension is often not well-controlled. The proportion of patients of any age with diastolic BPs of 90 mm Hg or less rarely exceeds 40%.[16] This finding contrasts with the 90% of patients who achieved their BP target at 36 months in the <90 mm Hg group.

Interestingly, these studies have also determined that nearly 75% of physicians consider that poor patient compliance with therapy is the principal reason for the failure to achieve BP control as opposed to other potential explanations, such as ineffective therapy or side effects.

The HOT Study included a compliance substudy, that monitored patient compliance to aspirin or placebo for one year with a sophisticated electronic device placed in the lid of the medication container. Each time that patients opened the container, the electronic system recorded the time and date of access. This approach, while superior to past methods, is still limited, because there is no way to monitor whether the patient actually took the medication or placebo after opening the container.

Over 500 patients were enrolled in the substudy in Italy, Switzerland, Germany, and the United Kingdom. Baseline characteristics of the substudy sample were identical to those of the entire HOT study population, thus, the substudy population was highly representative, both at baseline and at 12 months.

At 6 months, patients opened the medication container once daily on 82% of days. This figure declined slightly to 78% at 12 months. Compliance was remarkably high, identical in men and women, in younger (50-65 years) and older age groups (>65 years), and similar in all four participating countries.

Perhaps the most interesting finding is that compliance was identical (78% at 12 months) for the three target diastolic BP groups – whether or not the target BP had actually been achieved. This finding suggests that, if the target BP was not achieved, it was not because patients were non-compliant with the treatment protocol – a contradiction to the widely held notion that poor compliance is the main reason for inadequate BP control. It is possible that, for most patients, this problem is due to the limits of antihypertensive therapy rather than poor compliance.

Nevertheless, the compliance substudy demonstrated that, when an effective therapy is used and a multidisciplinary team of physicians, nurses, and other personnel works hard to keep patients motivated and aware of the importance of treatment, BP can be normalized in most patients. When BP cannot be normalized, it is not necessarily a problem of compliance and other factors, such as ineffective therapy, should be considered.

This substudy showed, as well, that a stepwise protocol can normalize BP in most patients with minimal side effects and an excellent compliance profile. These results shift some responsibility for compliance from patient to physician.

Summary

The HOT Study is expected to end in late August 1997, when the follow-up of 75,000 patient-years and 1,100 cardiovascular events will be completed. At that time, the crucial question of the optimal level of diastolic BP needed to prevent the highest number of major cardiovascular events will be answered.

The HOT Study is expected to refute, if its hypothesis is correct, the "J-curve" hypothesis, which postulates that an excessive reduction of diastolic BP is detrimental. This landmark trial will also provide important additional information, obtained prospectively, about the safety of calcium antagonists.

Regardless of final results, the HOT Study has already made remarkable contributions to our understanding of the optimal management of essential arterial hypertension. It has already shown that a stepwise approach to therapy, based on newer antihypertensive agents, such as the calcium antagonist felodipine, can normalize BP in most patients safely and with minimal side effects, while improving significantly important parameters of quality of life. This finding appears to hold true independently of age, gender, severity of hypertension, and baseline renal function.

The HOT Study is destined to become a landmark trial in the history of cardiovascular medicine and appears to be poised to have a significant impact on daily clinical practice.

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