CME CREDIT

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THE HYPERTENSION OPTIMAL TREATMENT TRIAL

Aggressive blood pressure lowering is safe, but benefit is still hard to prove

ABSTRACT

In the Hypertension Optimal Treatment (HOT) study, hypertensive patients who were randomly assigned to undergo antihypertensive treatment to achieve a goal diastolic blood pressure of 80 mm Hg or lower did not experience fewer cardiovascular events than did patients who received treatment with goal pressures of 85 or 90 mm Hg. Such aggressive antihypertensive treatment was safe and well tolerated, and did result in fewer cardiovascular events in the subset of patients with diabetes. All patients were randomly assigned to take aspirin 75 mg/day or placebo, and patients in the aspirin group had a 15% lower rate of major cardiovascular events and myocardial infarctions than did patients who received placebo. This finding establishes the efficacy of aspirin in preventing strokes and myocardial infarctions in hypertensive patients.

FOR THE LAST FIVE YEARS, 1,904 physicians in 26 countries have been investigating one of the fundamental questions of medicine: How far should blood pressure be lowered?

The results of that trial, the Hypertension Optimal Treatment (HOT) study,[1] are now in. Although the study did not answer that question with certainty, we can now state with assurance that:

- Blood pressure can safely be lowered to levels substantially lower than in previous clinical trials.
- Previous fears of a J-shaped relationship between diastolic blood pressure and coronary events were not verified in this trial, at least with diastolic blood pressure levels of 80 mm Hg. In other words, aggressive antihypertensive treatment seems unlikely to be harmful.
- Hypertensive patients with diabetes benefit from having their diastolic blood pressure reduced to 80 mm Hg or lower.
- Aspirin in a low dose is safe and effective as primary prevention of coronary artery disease in hypertensive patients.

BACKGROUND: "THE LOWER THE BETTER" VS THE J-CURVE

Although most physicians today accept that treating high blood pressure is beneficial, this was not always so. The term "essential hypertension," coined by Richard Bright in the early 19th century, reflected the theory that a higher blood pressure was a physiologic response essential to maintain blood flow to vital organs. And although actuarial statistics and observational studies clearly showed that higher blood pressure meant a shorter life expectancy,[2] nobody knew if treating it might not actually be harmful.

The question was moot until the early 1960s, when safe and effective drugs to treat high blood pressure became available and a triumphant series of studies seemed to settle the case that blood pressure lowering was beneficial.[3] Or did they?

In the mid-1980s, analyses of observational studies and post hoc analyses of studies conducted for other purposes suggested that lowering the diastolic blood pressure

*The Hypertension Optimal Treatment trial was sponsored by Astra AB, Sweden; Astra Merck Inc., USA; and Hoechst, Argentina.

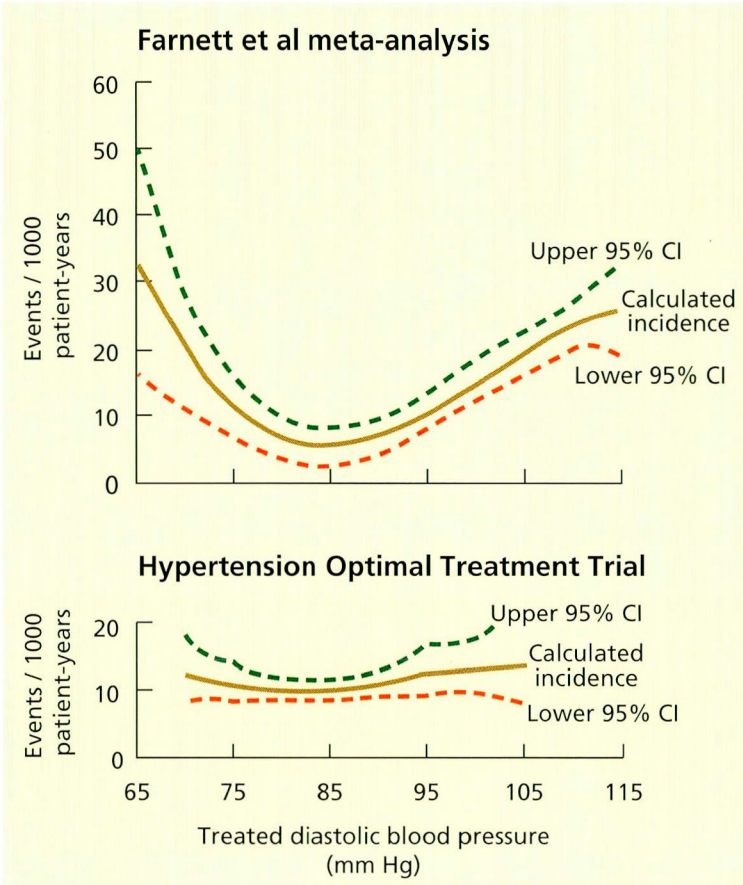

FIGURE 1. Top, the relationship between ischemic heart disease events and treated diastolic blood pressure, derived by Farnett et al from a meta-analysis of 48,000 patients in 13 clinical trials. Bottom, the relationship between major cardiovascular events and treated diastolic blood pressure in the 18,790 patients in the Hypertension Optimal Treatment (HOT) trial.

SOURCE: ADAPTED FROM FARNETT L, MULROW CD, LINN WD, LUCEY CR, TULEY MR. THE J-CURVE PHENOMENON AND THE TREATMENT OF HYPERTENSION. IS THERE A POINT BEYOND WHICH PRESSURE REDUCTION IS DANGEROUS? JAMA 1991; 265:489–495; and HANSSON L, ZANCHETTI A, CARRUTHERS SG, ET AL FOR THE HOT STUDY GROUP. EFFECTS OF INTENSIVE BLOOD-PRESSURE LOWERING AND LOW-DOSE ASPIRIN IN PATIENTS WITH HYPERTENSION: PRINCIPAL RESULTS OF THE HYPERTENSION OPTIMAL TREATMENT (HOT) RANDOMISED TRIAL. LANCET 1998; 351:1755–1762.

past a certain point might result in an increase in adverse cardiovascular endpoints in patients with coronary artery disease.[4] This was referred to as a J-shaped (or U-shaped) relationship. As for systolic blood pressure, a strategy of the lower the better seemed to hold true, but not in all reports.

In 1991, Farnett et al[4] conducted a meta-analysis of available studies, and estimated that the optimal treated diastolic blood pressure with respect to heart disease events was approximately 84 mm Hg (FIGURE 1). With regard to stroke, the lower the blood pressure, the better.

ASPIRIN AND HYPERTENSION: MI PREVENTION VS STROKE RISK

Aspirin, by inhibiting cyclooxygenase-dependent platelet enzymes, inhibits platelet aggregation, a key process in thrombosis. Previous studies such as the Physicians' Health Study[5] found that low doses of aspirin decreased the risk of myocardial infarction in healthy volunteers. However, no study had yet been conducted in persons with hypertension, in whom there was concern that long-term aspirin treatment would increase the risk of hemorrhagic stroke and other bleeding events.

STUDY DESIGN

The HOT study investigated whether diastolic blood pressure levels lower than the 90 mm Hg currently recommended as the goal for most patients would be optimal for reducing cardiovascular events, stroke, and death. In addition, another arm of the study examined whether low-dose aspirin reduced the cardiovascular endpoints.

Patient characteristics

In all, the study included 18,790 patients, aged 50 to 80 years, with diastolic blood pressure between 100 mm Hg and 115 mm Hg. The mean blood pressure at entry (off antihypertensive medications) was 170/105 mm Hg, and the mean age was 61.5 years. Fifty-three percent of the patients were men. The mean serum creatinine level was 1.0 mg/dL, and the mean serum cholesterol level was 236 mg/dL. The prevalence rates of other cardiovascular risk factors were:

- Smoking: 15.9%
- Previous myocardial infarction: 1.5%
- Other previous coronary heart disease 5.9%
- Previous stroke: 1.2%
- Diabetes mellitus: 8.0%.

Blood pressure treatment: Stepped care starting with a calcium blocker

Patients were randomly assigned to have their diastolic blood pressure reduced to one of three target levels: 90 mm Hg or less, 85 mm Hg or less, or 80 mm Hg or less. To achieve this blood pressure, the study used a stepped-care protocol.

- Step one: Felodipine (a dihydropyridine calcium antagonist) 5 mg/day
- Step two: Add an angiotensin-converting enzyme (ACE) inhibitor or a beta-blocker
- Step three: Double the dose of felodipine to 10 mg/day and continue the ACE inhibitor or beta-blocker
- Step four: Double the dose of the ACE inhibitor or the beta-blocker and continue felodipine at 10 mg/day
- Step five: Add a diuretic to the above regimen.

Patients returned for follow-up at 3 months, 6 months, and every 6 months thereafter. Each patient's achieved blood pressure was calculated as the mean of his or her blood pressure measurements while on treatment.

Aspirin as primary prevention of MI

All patients received, in a randomized, double-blind fashion, either aspirin 75 mg/day or placebo.

STUDY FINDINGS

After an average follow-up of 3.8 years, blood pressure was considerably lower than at baseline in all three treatment groups. Starting from a mean of 170/105 mm Hg, the blood pressure had dropped to 144/85 in the ≤ 90-mm Hg target group, to 141/83 in the ≤ 85-mm Hg group, and to 140/81 in the ≤ 80-mm Hg group. However the three groups overlapped to a great extent in their achieved blood pressures (FIGURE 2).

This degree of blood-pressure reduction—more than 20 mm Hg diastolic—deserves comment in itself. In an earlier meta-analysis, Collins et al[3] calculated that the average reduction in diastolic blood pressure was only 5 to 6 mm Hg in trials performed up to 1990. In addition, systolic blood pressure was reduced more than 25 mm Hg.

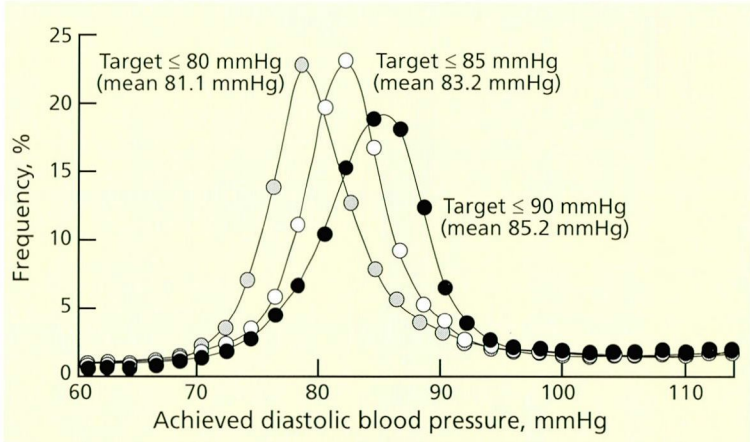

FIGURE 2. Distribution of mean diastolic blood pressure from 6 months' follow-up to the end of the study in the Hypertension Optimal Treatment (HOT) trial.

SOURCE: HANSSON L, ZANCHETTI A, CARRUTHERS SG, ET AL FOR THE HOT STUDY GROUP. EFFECTS OF INTENSIVE BLOOD-PRESSURE LOWERING AND LOW-DOSE ASPIRIN IN PATIENTS WITH HYPERTENSION: PRINCIPAL RESULTS OF THE HYPERTENSION OPTIMAL TREATMENT (HOT) RANDOMISED TRIAL. LANCET 1998; 351:1755–1762.

Endpoints were lower than expected

The investigators originally estimated that the trial would need to run for 2.5 years to demonstrate a difference in outcomes among the three target blood pressure groups. However, even at 3.8 years of follow-up, the incidence of endpoints—major cardiovascular events, myocardial infarctions, strokes, cardiovascular deaths, and all deaths—still did not differ among the groups, except for a slightly lower number of myocardial infarctions in the ≤ 80-mm Hg group compared with the ≤ 90-mm Hg group, which achieved borderline statistical significance ($P = .05$).

The incidence of cardiovascular events did not differ among the treatment groups

Two factors may account for this failure to demonstrate a difference:

- The number of events was lower than expected.
- The treatment groups overlapped in their blood pressures (FIGURE 2).

Aggressive treatment beneficial in patients with diabetes

One subgroup did enjoy a significant reduction in major cardiovascular events and other endpoints when a lower goal blood pressure was attempted: the 1,501 patients with diabetes (FIGURE 3). In this group the incidence of

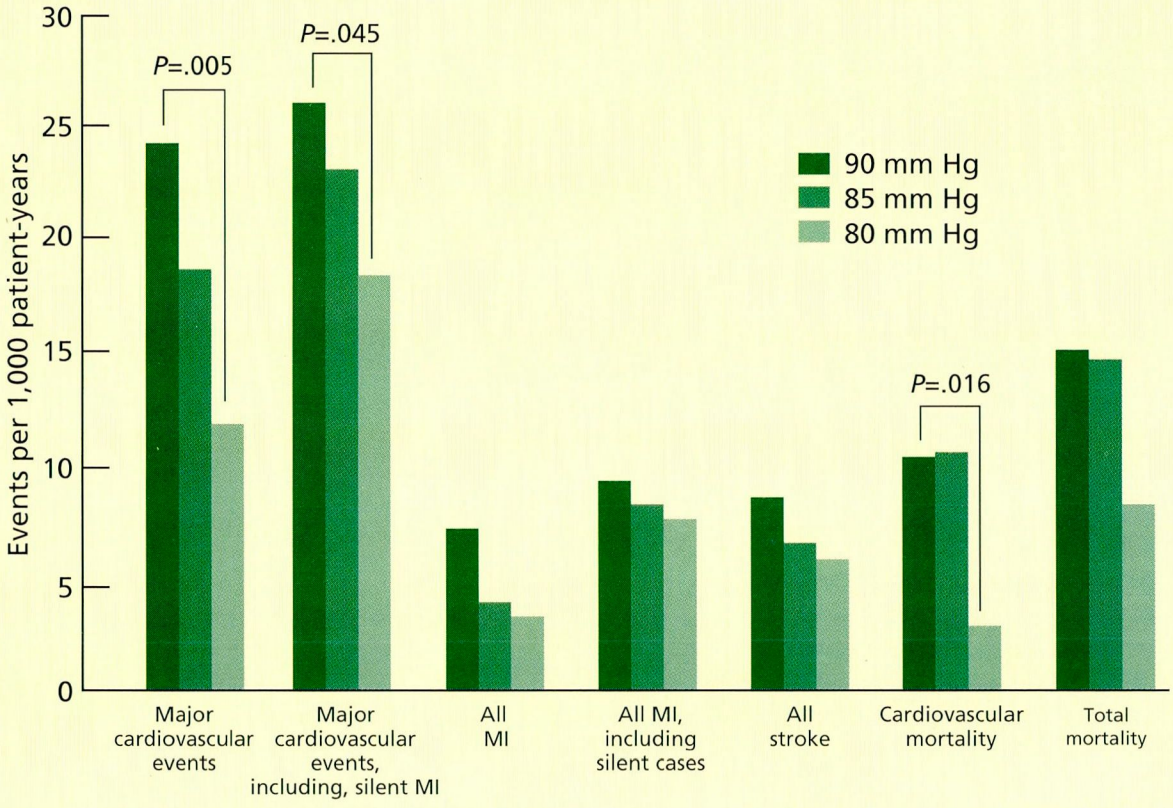

FIGURE 3. Events in patients with diabetes mellitus at baseline, according to treatment group in the Hypertension Optimal Treatment (HOT) trial.

SOURCE: DATA FROM HANSSON L, ZANCHETTI A, CARRUTHERS SG, ET AL FOR THE HOT STUDY GROUP. EFFECTS OF INTENSIVE BLOOD-PRESSURE LOWERING AND LOW-DOSE ASPIRIN IN PATIENTS WITH HYPERTENSION: PRINCIPAL RESULTS OF THE HYPERTENSION OPTIMAL TREATMENT (HOT) RANDOMISED TRIAL. LANCET 1998; 351:1755–1762.

cardiovascular mortality was 3.7 per 1,000 patient-years in the ≤ 80 mm Hg target group, compared with 11.1 in the ≤ 90 mm Hg target group—a 67% lower incidence (P =.016).

Achieved blood pressure and cardiovascular events: A very flat J-curve

The investigators also pooled the results and analyzed the endpoints on the basis of each patient's achieved blood pressure. The graph for major cardiovascular events looked somewhat like a J-curve, but much flatter than in the analysis by Farnett et al[4] for ischemic heart disease events (FIGURE 1).

Of note, the nadir of the curve—the diastolic blood pressure at which the fewest major cardiovascular events occurred—was at 82.6 mm Hg, which was remarkably close to the nadir of 84 mm Hg calculated by Farnett et al. For systolic blood pressure, the lowest point of risk was at 138.5 mm Hg.

Side effects and quality of life

At 3 months, 16.9% of the patients reported some side effects, but at the final visit, only 2.2% did.[1,6,7] The principal side effects were dizziness, headache, leg edema, and flushing (which were attributable to the use of felodipine) and coughing (which was attributable to the use of an ACE inhibitor). Nevertheless, at the end of the study, 78% of the patients were still taking felodipine, 41% were taking an ACE inhibitor, and 28% were taking a beta-blocker.

In a substudy of 922 patients in the HOT study, Wiklund et al[8] concluded that patients in the lowest target blood pressure group actually enjoyed a better quality of life at 6 months than at baseline, as reflected by higher scores

on two standardized tests—the Psychological General Well-Being (PGWB) index and the Subjective Symptoms Assessment Profile (SSA-P). In comparison, patients in the highest target blood pressure group did not show any improvement.

Endpoints according to aspirin use

Aspirin significantly reduced the number of major cardiovascular events by 15%, and the number of myocardial infarctions by 36%. These numbers declined to 9% and 15%, respectively, when silent myocardial infarctions were included in the analysis.

This benefit did come at the price of increased bleeding: 129 major episodes in the group receiving aspirin compared with 70 in the group receiving placebo ($P < .001$), and 156 minor bleeding episodes in the group receiving aspirin compared with 87 in the group receiving placebo. Fatal bleeding episodes, however, were equally rare in both groups: 7 deaths in 9,399 patients taking aspirin, vs 8 deaths in 9,391 patients taking placebo.

LESSONS FROM THE HOT STUDY

There is little to fear from the J-curve effect

A primary goal of the HOT study was to verify the validity of the J-curve hypothesis, that is, the theory that reducing the blood pressure too vigorously may increase cardiovascular risk. While the study did not entirely disprove the existence of a J-curve,[9] additional lowering of diastolic blood pressure below 85 mm Hg did not prove harmful.

The investigators stated, "There was no evidence of a J-shaped curve for the relation of major cardiovascular events, all myocardial infarctions, all stroke, and cardiovascular mortality with achieved blood pressures, at least in the ranges observed in our study (down to 70 mm Hg diastolic and 120 mm Hg systolic). This was also true in the subgroup of more than 3,000 patients with a history or clinical evidence of ischemic heart disease at randomization."

However, the investigators *did* calculate the blood pressures at which the risk was lowest. They found that the lowest risk of major cardiovascular events was at 138.5/82.6 mm Hg, the lowest risk of all myocardial infarctions was at 142.2 mm Hg systolic, for all strokes at 142.2 mm Hg systolic, and for cardiovascular mortality at 138.8/86.5 mm Hg. These values seem to contradict the statement that there is no J-curve risk, since they are higher than the 120/70 mm Hg cited above.

Moreover, few study patients had diastolic pressures in the 70-to-80 mm Hg range. Therefore the confidence intervals in this range were wide, precluding any definitive conclusion about the safety of blood pressures in this range. To err on the cautious side, we would say that the HOT study showed that lowering diastolic blood pressure was safe down to approximately 80 mm Hg, not 70.

Is lower better? The answer is still uncertain

The study did not prove the opposite theory either, that lower blood pressure is better. Several factors conspired to obscure any possible differences in benefit. The differences in blood pressure achieved among the three treatment groups randomly assigned to reach diastolic levels of 80, 85, or 90 mm Hg were less than half of those intended. Moreover, far fewer patients suffered cardiac events in this study than predicted from event rates in earlier controlled clinical trials, even considering that the HOT study patients were older (61.5 years vs 56 years, respectively).

Recent fears about calcium antagonists seem unwarranted

The low event rate in the HOT study, in turn, was likely due to the effectiveness of both systolic and diastolic blood pressure control throughout the trial. The proportion of patients reaching the randomized target blood pressures increased gradually up to the final study visit, at which time a diastolic blood pressure greater than 90 was found in only 12% of the patients in the target group ≤ 90 mm Hg, in only 7% in the target group ≤ 85 mm Hg, and in 6% of patients randomized to the target group ≤ 80 mm Hg. The diastolic blood pressure was reduced by over 20 mm Hg in the majority of patients enrolled in the HOT study. The mean reduction in systolic blood pressure was over 25 mm Hg. This degree of both systolic and diastolic blood pressure reduction in the HOT study appears to translate into low rates of cardiovascular morbidity and mortality.

Are newer drugs better?

One could also consider attributing the low rate of cardiovascular events to the use of newer antihypertensive agents (a calcium antagonist, ACE inhibitors, and beta-blockers, compared with diuretics and beta-blockers in older studies), and it is tempting to do so. The study did not analyze the effects of specific drugs on cardiovascular events, but does provide some assurance that recent fears of higher rates of coronary events in hypertensive patients taking long-acting calcium antagonists[10] seem unwarranted.

Calcium antagonists and diabetic patients. Two recent clinical trials in diabetic patients (the ABCD trial[11] and the FACET trial[12]) reported higher rates of coronary events in diabetic hypertensive patients receiving a calcium antagonist compared with patients on an ACE inhibitor. Among the 1,500 diabetic patients in the HOT study, the calcium antagonist-based regimen provided striking protection from cardiovascular events. In particular, the risk of major cardiovascular events in the group randomized to ≤ 80 mm Hg was half that of the target group ≤ 90 mm Hg. As a result, cardiovascular mortality was significantly lower in the ≤ 80 mm Hg target group than in the higher target groups.

The lower the blood pressure, the higher the quality of life

Lowering blood pressure improves quality of life

In the quality-of-life substudy, Wiklund and colleagues[8] examined the widely held view that hypertension is an asymptomatic condition by investigating the relationship between the three target diastolic blood pressure groups and quality of life. They also examined whether side effects compromised quality of life in those patients receiving added antihypertensive treatment.

Using two self-administered, validated questionnaires, completed at baseline and after 6 months, the investigators found that the lower the diastolic blood pressure achieved, the greater the improvement in well-being. Although more intensive antihypertensive therapy was associated with a slight increase in subjective symptoms, patients still noted improvement in well-being.

These observations tend to negate long-standing concerns that intensive antihypertensive treatment is associated with more side effects and an increase in patient nonadherence to therapy.

Systolic pressure not studied

Like nearly all treatment trials to date, the HOT study concentrated on diastolic blood pressure. Yet we are coming to realize that systolic pressure predicts cardiovascular risk more accurately than does diastolic pressure.

Epidemiologic studies show that risk increases with systolic pressures higher than 110 mm Hg. Surprisingly, the HOT investigators found values of approximately 140 mm Hg for the optimal systolic pressure. One would think that the optimal systolic pressure would be lower. Two explanations may account for this discrepancy. Conceivably, hypertensive persons suffer some diathesis such that decreasing the systolic pressure back into the normal range (ie, < 140 mm Hg) does not reduce their risk. A more likely interpretation, however, is that the HOT study was simply not designed to analyze the effect of systolic blood pressure, and that these findings, like those of all post hoc analyses, must therefore be viewed with skepticism and interpreted with caution.

What we need is a "HOST" trial—Hypertension Optimal *Systolic* Treatment.

Aspirin beneficial in hypertensive patients

Finally, the HOT study showed that a small dose of acetylsalicylic acid reduced the risk of acute myocardial infarction without exaggerating the risk of cerebral bleeding. This observation supports the use of acetylsalicylic acid with antihypertensive therapy, provided that the blood pressure is well controlled and patients are assessed regarding the risk of gastrointestinal and nasal bleeding.

MOST HYPERTENSIVE PERSONS DO NOT HAVE ADEQUATE CONTROL

An estimated 50 million adult Americans have hypertension. Data from the National Health and Nutrition Examination Survey (NHANES),[13] reported in the sixth report of

the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI),[14] suggested that only 68.4% of persons with hypertension are aware of it. Of those aware, 53.6% are receiving treatment for it, and of those treated, 27.4% actually have their blood pressures controlled to below 140/90 mm Hg. Conversely, almost 90% of persons with hypertension—45 million Americans—do *not* have their blood pressure controlled to even 140/90 mm Hg.

The JNC VI report made it clear that we must intensify our hypertension treatment and control efforts. The HOT study showed that we can provide intensive antihypertensive therapy to large numbers of persons to achieve lower goal levels of blood pressure, and that these lower levels of blood pressure can be achieved and maintained without compromising patient safety or quality of life.

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