ORIGINAL ARTICLE

Feasibility of Treating Prehypertension with an Angiotensin-Receptor Blocker

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ABSTRACT

BACKGROUND

Prehypertension is considered a precursor of stage 1 hypertension and a predictor of excessive cardiovascular risk. We investigated whether pharmacologic treatment of prehypertension prevents or postpones stage 1 hypertension.

METHODS

Participants with repeated measurements of systolic pressure of 130 to 139 mm Hg and diastolic pressure of 89 mm Hg or lower, or systolic pressure of 139 mm Hg or lower and diastolic pressure of 85 to 89 mm Hg, were randomly assigned to receive two years of candesartan (Atacand, AstraZeneca) or placebo, followed by two years of placebo for all. When a participant reached the study end point of stage 1 hypertension, treatment with antihypertensive agents was initiated. Both the candesartan group and the placebo group were instructed to make changes in lifestyle to reduce blood pressure throughout the trial.

RESULTS

A total of 409 participants were randomly assigned to candesartan, and 400 to placebo. Data on 772 participants (391 in the candesartan group and 381 in the placebo group; mean age, 48.5 years; 59.6 percent men) were available for analysis. During the first two years, hypertension developed in 154 participants in the placebo group and 53 of those in the candesartan group (relative risk reduction, 66.3 percent; P<0.001). After four years, hypertension had developed in 240 participants in the placebo group and 208 of those in the candesartan group (relative risk reduction, 15.6 percent; P<0.007). Serious adverse events occurred in 3.5 percent of the participants assigned to candesartan and 5.9 percent of those receiving placebo.

CONCLUSIONS

Over a period of four years, stage 1 hypertension developed in nearly two thirds of patients with untreated prehypertension (the placebo group). Treatment of prehypertension with candesartan appeared to be well tolerated and reduced the risk of incident hypertension during the study period. Thus, treatment of prehypertension appears to be feasible. (ClinicalTrials.gov number, NCT00227318.)

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THE NAME OF THE RANGE OF BLOOD PRESsures between what is clearly normal and what is definitely hypertensive changed from "transient hypertension" in the 1940s[1] to "borderline hypertension" in the 1970s,[2] "high-normal blood pressure" in the 1990s,[3] and most recently, "prehypertension" in 2003.[4] Regardless of terminology, this condition is a precursor of hypertension[1,2,5,6] and is associated with excess morbidity and deaths from cardiovascular causes.[1,2,7-10] Furthermore, an association of prehypertension with other cardiovascular risk factors has been established.[11-14]

The Trial of Preventing Hypertension (TROPHY)[15] was an investigator-initiated study to examine whether early treatment of prehypertension, defined for this study as systolic pressure of 130 to 139 mm Hg and diastolic pressure of 89 mm Hg or lower and systolic pressure of 139 mm Hg or lower and diastolic pressure of 85 to 89 mm Hg, might prevent or delay the development of subsequent incident hypertension. We justified our study of pharmacologic intervention with the use of an angiotensin-receptor blocker in prehypertension on three grounds. First, in prehypertension, blood pressure remains a strong predictor of cardiovascular events after a statistical adjustment for other risk factors,[10,14,16] suggesting that lowering blood pressure might be beneficial. Hypertension is a self-accelerating condition. The transition from prehypertension to established hypertension reflects, in part, ongoing changes such as arteriolar hypertrophy[17] and endothelial dysfunction.[18] Increased vasoconstriction and diminished vasodilatation, consistent with these structural and functional findings, have been described in prehypertension.[19]

Second, growth factors mediated by stimulation of the sympathetic nervous system[20] and excess activity of the renin–angiotensin system[21] tend to promote vascular hypertrophy by direct as well as hemodynamic effects. Elevations in plasma norepinephrine and plasma renin concentrations[22,23] have been described in prehypertension. In humans, antihypertension treatment with angiotensin-converting–enzyme (ACE) inhibitors or angiotensin-receptor blockers, but not with beta-blockers, has been reported to cause regression of arteriolar hypertrophy.[24,25] In studies in rats, brief treatment with ACE inhibitors during the early life of rats with spontaneous hypertension attenuates the development of hypertension.[26,27] Third, present guidelines recommend that prehypertension be managed with changes in the participant's lifestyle.[3,4] Weight loss,[28] salt restriction,[29] exercise,[30,31] and dietary modifications[32] have been shown to reduce blood pressure in clinics specializing in lifestyle modification. Despite intensive community efforts to promote healthful lifestyles, however, the prevalence of prehypertension[33] in the United States is increasing. In the absence of evidence of the long-term efficacy of lifestyle approaches to preventing hypertension, our study assessed the safety, tolerability, and efficacy of two years of treatment in participants with prehypertension.

METHODS

OBJECTIVE

The primary objective of the study was to determine whether in patients with prehypertension two years of treatment with candesartan (at a dose of 16 mg daily) reduces the incidence of hypertension for up to two years after the discontinuation of active treatment. A secondary objective was to evaluate the incidence of hypertension during two years of treatment with candesartan or placebo. These objectives were analyzed first according to the cumulative incidence of events at two and four years (unadjusted). They were then analyzed according to the time-to-event distribution during two and four years (adjusted).

DESIGN

This four-year, multicenter, randomized study involved untreated participants 30 to 65 years of age with blood pressure on study entry in the high-normal range, according to the classification developed by the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI).[3] The design of the study is shown in Figure 1. Blood pressure was measured with the use of an automated reading and recording device (HEM-705CP, Omron Healthcare) or with a standard measuring tool (usual device) while participants were seated after five minutes of rest. Only automated readings of blood pressure were taken into consideration for enrollment and follow-up. The run-in period consisted of three consecutive weekly clinic visits during each of which blood-pressure readings were obtained. Participants were eligible for the trial if they were not being treated for hypertension, if at the first

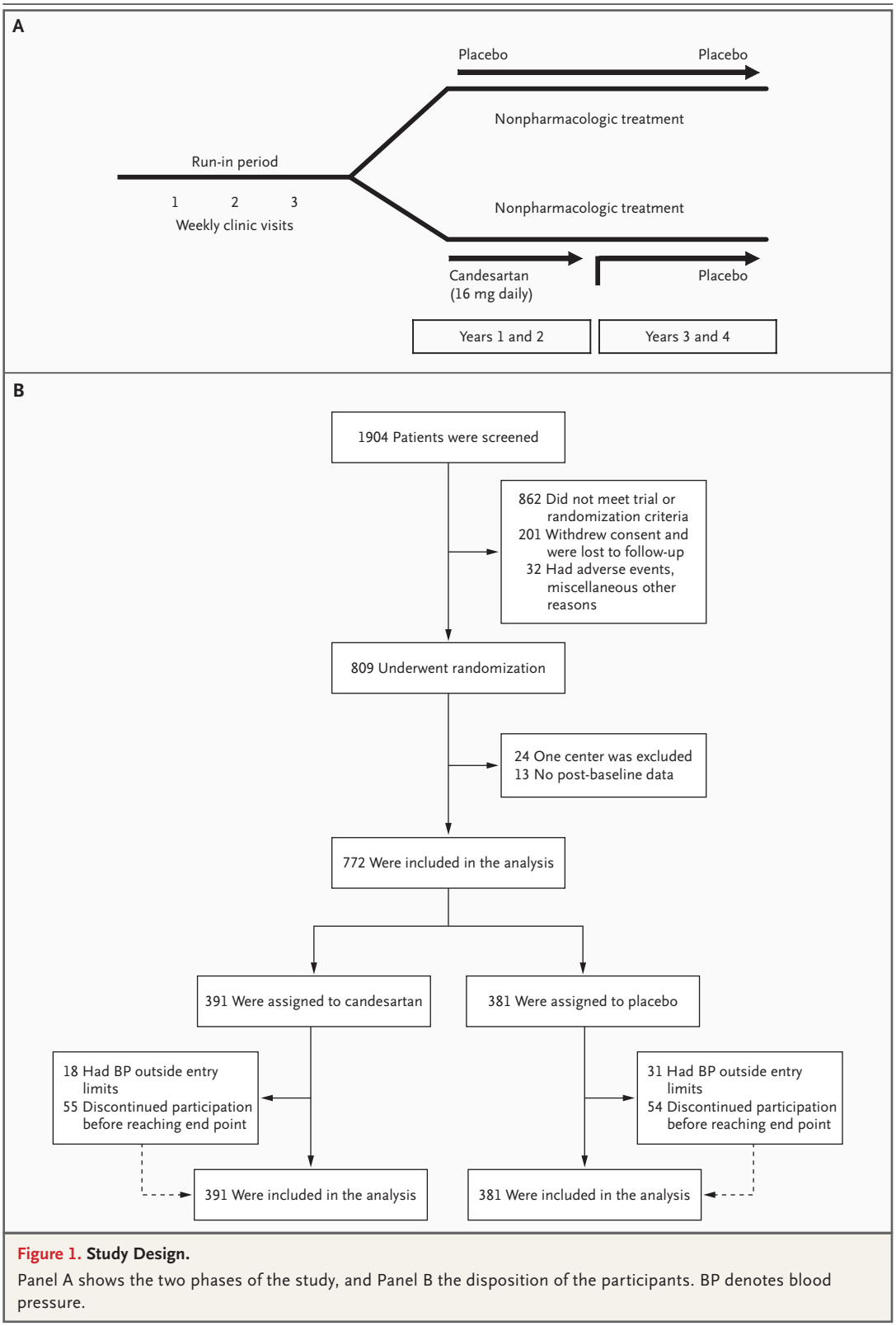


Figure 1. Study Design.

Panel A shows the two phases of the study, and Panel B the disposition of the participants. BP denotes blood pressure.

clinic visit the blood pressure was lower than 160/100 mm Hg, and if the average of the three blood-pressure readings at the three visits was a systolic pressure of 130 to 139 mm Hg and a diastolic pressure of 89 mm Hg or lower or a systolic pressure of 139 mm Hg or lower and a diastolic pressure of 85 to 89 mm Hg.

Participants who met these criteria underwent randomization to double-blind treatment with candesartan (at a dose of 16 mg daily) or matching placebo. Return visits were scheduled at month 1 and month 3 and every three months thereafter until the visit at month 24. In year 3 of the study, clinic visits were at months 25 and 27 and every third month thereafter to month 48. Patients also measured their blood pressure at home twice a day for seven days using the automated device before undergoing randomization and before the clinic visits at months 12, 24, 36, and 48.

The study consisted of a two-year, double-blind, placebo-controlled phase that was followed by a two-year phase in which all study patients received placebo. Throughout the second two-year phase, study investigators remained blinded to each patient's initial treatment assignment. No goal for blood pressure was set, and the participant's treatment regimen could be changed only if hypertension developed. Randomization was performed according to study site in blocks of four. The sites called an automated randomization system, which assigned the number of the bottle containing either candesartan tablets or matching placebo. On entry and throughout the study, all participants received printed materials about lifestyle modification. Participants' adherence to this diet and exercise regimen was reviewed and reinforced at all subsequent visits. Evaluation was performed at study entry and at annual intervals or at the endpoint visit and included a physical examination and taking of blood and urine samples for routine studies.

The study was managed by a clinical research organization (Omnicare Clinical Research). Biochemical testing was performed by Covance Laboratories (Indianapolis). The protocol was approved by the institutional review boards of the participating institutions, and all participants provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki.

The investigators submitted a proposal to Astra Merck (subsequently AstraZeneca). The protocol was revised by a group of experts (subsequently called the TROPHY executive committee) and the sponsor. The sponsor provided funding and organized the study. After completion of the study, statisticians at AstraZeneca implemented the prespecified data-analysis plan. Thereafter, the raw data were transferred to the senior authors of the study for verification and further analyses. The manuscript was prepared and submitted for publication by Drs. Julius, Nesbitt, and Egan, who attest to its veracity and completeness.

END POINTS

The main study end point was the development of clinical hypertension, defined as the first appearance of one of the following outcomes: an averaged reading at a clinic visit of systolic pressure of 140 mm Hg or higher or diastolic pressure of 90 mm Hg or higher, or both, at any three visits during the four years of the study (not necessarily consecutive); an average reading during a clinic visit of systolic pressure of 160 mm Hg or higher or diastolic pressure of 100 mm Hg or higher at any visit during the four study years; a finding by the clinical investigator of target-organ damage or other reasons to initiate pharmacologic treatment; or an average reading of systolic pressure of 140 mm Hg or higher or diastolic pressure of 90 mm Hg or higher at the visit at month 48.

After an end point was reached, antihypertension treatment with metoprolol (Toprol XL, AstraZeneca), at a dose of 50 mg daily, or hydrochlorothiazide (Microzide, Watson), at a dose of 12.5 mg daily, was offered at no cost. However, study physicians could prescribe other antihypertension medications, with the exception of angiotensin-receptor blockers. Further follow-up of participants in the study clinic was also offered. The study was monitored by a data and safety monitoring board that reviewed the safety data annually.

STATISTICAL ANALYSIS

The sample size was calculated assuming an incidence of new-onset hypertension of 40 percent over the four-year study period, as was also observed in the Trials of Hypertension Prevention[28] over a period of four years. On the basis of Fisher's exact test with 95 percent power and a two-sided alpha level of 0.05, 420 patients were required in each of the two study groups. The actual incidence of hypertension during the first two years was higher than anticipated.[15]

Results are reported as means ±SD. To test the incidence of hypertension after two and four years, the two-tailed Fisher's exact test was used first, then logistic-regression analysis adjusted for significant baseline predictors of hypertension. To analyze the end points throughout the trial,[15] the difference in Kaplan–Meier curves for the two groups was tested by the log-rank test and also adjusted by Cox proportional-hazards analysis. As in similar trials,[28,29,34] to minimize the distortion resulting from active antihypertension treatment, we imputed missing values by using the last-observation-carried-forward method, carrying forward the last blood pressure recorded before the initiation of antihypertension treatment. If a participant discontinued in the study, the blood pressure recorded at the last clinic visit was also carried forward.

RESULTS

The first patient underwent randomization in June 1999, and the last participant completed the study in June 2005. We screened 1904 candidates,

Table 1. Baseline Characteristics of the Study Participants.*

	Candesartan Group (N=391)	Placebo Group (N=381)
Age — yr	48.6±7.9	48.3±8.2
Male sex — no. (%)	231 (59.1)	229 (60.1)
Race — no. (%)†		
White	312 (79.8)	321 (84.3)
Black	48 (12.3)	31 (8.1)
Other	31 (7.9)	29 (7.6)
Weight — kg	89.0±17	88.8±17.7
Body-mass index‡	29.9±5.1	30.0±5.5
Blood pressure — mm Hg		
Measured at clinic visit with automated device§	133.9±4.3/84.8±3.8	134.1±4.2/84.8±4.1
Measured at clinic visit with usual device	130.9±7.2/85.0±4.8	131.5±7.1/84.9±5.6
Measured at home with automated device	133.9±8.5/82.7±5.9	133.9±8.5/82.7±5.9
Cholesterol — mg/dl	202.9±34.9	205.7±39.1
≥200 mg/dl — %	53.6	57.5
Triglycerides — mg/dl	145.8±86.1	159.8±110.8
≥150 mg/dl — %	34.9	41.2
HDL cholesterol — mg/dl	48.9±13.7	49.2±14.5
Lower than normal range — %¶	36.3	36.8
Glucose — mg/dl	95.5±11.2	95.9±18.2
Insulin — IU	11.7±16	11.2±7.9
Insulin:glucose ratio	15.4±16.7	15.1±10.3
Creatinine — mg/dl	0.84±0.2	0.85±0.2

* Plus–minus values are means ±SD. To convert values for cholesterol to millimoles per liter, multiply by 0.026. To convert values for triglycerides to millimoles per liter, multiply by 0.011. To convert values for glucose to millimoles per liter, multiply by 0.056. To convert values for insulin to picomoles per liter, multiply by 6. HDL denotes high-density lipoprotein.
† Race was self-reported.
‡ Body-mass index is the weight in kilograms divided by the square of the height in meters.
§ The automated reading and recording device used to measure blood pressure was the HEM-705CP model (Omron Healthcare).
¶ HDL cholesterol levels lower than the normal range were defined as <40 mg per deciliter for men and <50 mg per deciliter for women.

and 809 participants (409 assigned to candesartan and 400 assigned to placebo) were eligible for enrollment at 71 study centers in the United States. In the second year of the study, one center at which 24 participants had undergone randomization was excluded from the study because of inadequate record keeping. Of those included in the safety population, data on blood pressure beyond the baseline measurements were not available for 13 participants. Consequently, data on 772 participants (391 in the candesartan group and 381 in the placebo group) were available for further analysis.

Of the 772 participants included in the analysis, 49 (6 percent) had blood-pressure values outside the limits required for entry (mean values, 137.8±5.1 mm Hg systolic and 87.2±4.8 mm Hg diastolic); and 109 (14 percent; 55 participants in the candesartan group and 54 in the placebo group) who had mean values of 133.0±4.9 mm Hg systolic and 84.4±4.6 mm Hg diastolic discontinued participation in the study before reaching an end point. The mean follow-up time was 3.56±1.11 years (3.68±0.95 in the candesartan group and 3.44±1.24 in the placebo group). A total of 2749 participant-years of observation were accumulated.

Table 1 shows the baseline characteristics of

Table 2. Incident Hypertension and Incidence of Serious Adverse Events.*

	Candesartan Group (N=391)	Placebo Group (N=381)	P Value	Relative Risk (95% CI)
New-onset hypertension				
No. of participants in whom hypertension developed	208	240		
Hypertension at year 2 visit — %	13.6	40.4	<0.001†	0.34 (0.25–0.44)
Hypertension at year 4 visit — %	53.2	63.0	0.007†	0.84 (0.75–0.95)
Hypertension during study period			<0.001‡	0.58 (0.49–0.70)
Clinical criteria for end-point determination				
BP at three clinic visits, ≥140 mm Hg systolic, ≥90 mm Hg diastolic, or both — no. (%)	142 (36)	168 (44)	0.03†	0.82 (0.69–0.98)
BP at any clinic visit ≥160 mm Hg systolic, ≥100 mm Hg diastolic, or both — no. (%)	15 (3.8)	19 (5.0)	0.49†	0.77 (0.40–1.49)
BP requiring pharmacologic treatment — no. (%)	45 (12)	48 (13)	0.66†	0.91 (0.62–1.34)
BP at month 48 clinic visit ≥140 mm Hg systolic, ≥90 mm Hg diastolic, or both — no. (%)	6 (1.5)	5 (1.3)	>0.99†	1.17 (0.36–3.80)

	Candesartan Group (N=396)	Placebo Group (N=391)
	no. (%)	
Incidence of adverse events		
Participants with any serious adverse event	14 (3.5)	23 (5.9)
Organ system		
Cardiovascular	1 (0.3)	6 (1.5)
Gastrointestinal	4 (1.0)	2 (0.5)
Cancer	4 (1.0)	3 (0.8)
Endocrine disorders	2 (0.5)	0
Infections	2 (0.5)	4 (1.0)
Peripheral-nerve disorders	2 (0.5)	0
Abnormal liver-function tests	1 (0.3)	1 (0.3)
Musculoskeletal and connective-tissue disorders	1 (0.3)	3 (0.8)
Psychiatric disorders	1 (0.3)	0
Vascular disorders	1 (0.3)	0
Ear and labyrinth disorders	0	1 (0.3)

the two study groups, which were well matched. In the two groups, participants were overweight and had a high incidence of dyslipidemia. The main results of the study are summarized in Table 2 and Figure 2. New onset of hypertension was suppressed in the candesartan group at two years ($P<0.001$) and four years ($P<0.001$), as calculated by Fisher's exact test. This result was further tested with the use of logistic-regression analysis, with adjustment for the following significant baseline predictors: diastolic pressure as measured by the participant using the automatic device at home, systolic pressure as measured at clinic visits with the use of the automated device, hematocrit, plasma insulin:glucose ratio, and age. Throughout the study period a P value of less than 0.05 was considered to indicate statistical significance. There was an absolute difference of 26.8 percent between the two groups and a relative risk reduction of 66.3 percent in the candesartan group at year 2. At year 4, two years after discontinuation of candesartan, there was an absolute difference of 9.8 percent between the two groups and a relative reduction in the risk of new-onset hypertension of 15.6 percent in participants in the candesartan group.

In these analyses, we assumed that hypertension did not develop in patients who discontinued

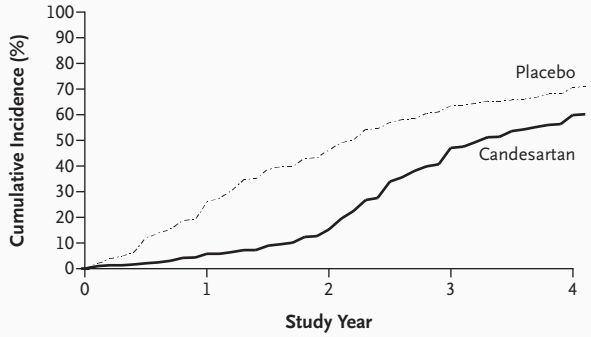
Table 2. (Continued.)

	Candesartan Group (N=396)	Placebo Group (N=391)
	no. (%)	
Hepatobiliary disorders	0	2 (0.5)
Reproductive system and breast disorders	0	1 (0.3)
General disorders	3 (0.8)	2 (0.5)
Other adverse events	352 (88.9)	346 (88.5)
Headache	85 (21.5)	74 (18.9)
Upper respiratory tract infection	57 (14.4)	52 (13.3)
Arthralgia	38 (9.6)	44 (11.3)
Nasopharyngitis	40 (10.1)	38 (9.7)
Back pain	37 (9.3)	40 (10.2)
Sinusitis	34 (8.6)	41 (10.5)
Dizziness	41 (10.4)	33 (8.4)
Bronchitis	21 (5.3)	34 (8.7)
Fatigue	32 (8.1)	21 (5.4)
Pain in an extremity	30 (7.6)	18 (4.6)
Depression	21 (5.3)	23 (5.9)
Gastroesophageal reflux	22 (5.6)	21 (5.4)
Insomnia	22 (5.6)	21 (5.4)
Nausea	16 (4.0)	27 (6.9)
Diarrhea	22 (5.6)	17 (4.3)
Anxiety	20 (5.1)	17 (4.3)
Hypotension	4 (1.0)	2 (0.5)
Syncope	2 (0.5)	1 (0.3)
Angioedema	0	1 (0.3)

* Participants were grouped according to the treatment actually received. One participant in the placebo group and five in the candesartan group received the incorrect study medication at one or more clinic visits during the first phase of the study, and these participants were therefore included in the analyses for the two groups. Participants may have had more than one adverse event. Adverse events included are those with a frequency ≥5 percent overall or ≥5 percent in the candesartan group. Other adverse events occurring with a frequency of less than 5 percent that were of potential relevance to the treatment of elevated blood pressure are also listed. CI denotes confidence interval, and BP blood pressure.

† The P value was calculated by Fisher's exact test.

‡ The P value was calculated by the log-rank test or Cox proportional-hazards analysis.



No. of Patients without Hypertension					
Candesartan group	391	356	309	191	127
Placebo group	381	269	184	118	85

Figure 2. Kaplan–Meier Analysis of New-Onset Clinical Hypertension.

participation in the study early. A sensitivity analysis assuming that hypertension developed in all participants who dropped out did not change the results. Exclusion of the 49 participants in violation of the entry criteria did not alter the results ($P<0.001$ at year 2 and $P<0.001$ at year 4 [data not shown], by Fisher's exact test). The median time to the development of hypertension was 2.2 years (95 percent confidence interval, 2.0 to 2.5) in the placebo group and 3.3 years (95 percent confidence interval, 3.0 to 3.8) in the candesartan group.

The Kaplan–Meier curves for the study end point (new-onset hypertension) (Fig. 2) were significantly different throughout the four years of the study ($P<0.001$ by log-rank test and $P<0.001$ by Cox proportional-hazards regression analysis, after adjustment for predictors). After discontinuation of the study medication in the candesartan group, when all participants in the two groups were receiving placebo, the incidence of hypertension in the candesartan group increased but the Kaplan–Meier curves remained separated until the end of the study. Hazard ratios for new-onset hypertension in various subgroups (Fig. 3) were lower in the candesartan group.

Trends in blood pressure during the study period are shown in Figure 4. Blood pressure decreased more rapidly in the candesartan group than in the placebo group in the first two years, but in the third year, after discontinuation of the study medication in the candesartan group and when all participants were receiving placebo, blood pressure increased more rapidly in the candesartan group. At the end of the study, systolic pressure was 2.0 mm Hg lower in the candesartan group ($P=0.037$) and diastolic pressure 1.1 mm Hg lower ($P=0.073$).

Rates of serious adverse events during the first two years were low and were similar in the two groups (Table 2). Serious adverse events occurred in 3.5 percent of the participants in the candesartan group and in 5.9 percent of those in the placebo group. The incidence of other adverse events was similar in the two groups (88.9 percent in the candesartan group, and 88.5 percent in the placebo group) (Table 2). Laboratory values in the two groups were similar during the first two years (Table 1 in the Supplementary Appendix, available with the full text of this article at www.nejm.org).

DISCUSSION

Untreated hypertension is a self-accelerating condition. Evolving arteriolar hypertrophy[17] and endothelial dysfunction[18] facilitate the later increase of blood pressure and contribute to the transition from prehypertension to established hypertension. Abnormalities in cardiovascular structure and function and in neuroendocrine control occur in young adults with a predisposition to hypertension.[11,23,35,36] In rats with spontaneous hypertension, brief treatment of young animals with a renin–angiotensin antagonist has lifelong effects in reducing blood pressure.[26,27] Therefore, we hypothesized that an intervention in humans with prehypertension might alter the natural history and prevent or delay the onset of established hypertension.

The results of the study support our primary

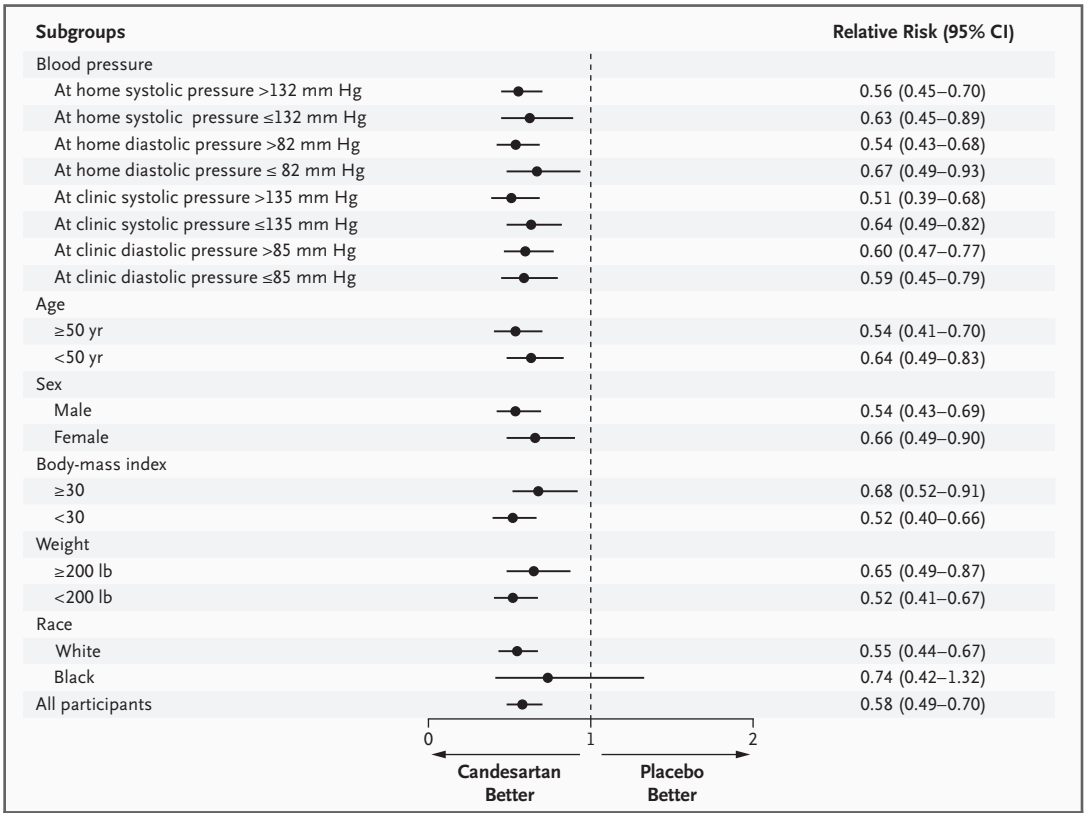


Figure 3. Hazard Ratios for New-Onset Hypertension in Various Subgroups.

Hazard ratios of time to event throughout the four years of the study were calculated by Cox proportional-hazards regression analysis. BMI denotes body-mass index (defined as the weight in kilograms divided by the square of the height in meters), and CI confidence interval. To convert pounds to kilograms, multiply by 0.45. Race was self-reported.

hypothesis[15] that pharmacologic treatment of prehypertension may prevent or postpone the development of hypertension. At four years — two years after discontinuation of candesartan — there was a significant reduction in incident hypertension in participants with prehypertension who had received candesartan. The relative proportion of participants who were hypertension-free was 26.5 percent greater in the candesartan group.

The results of two years of candesartan treatment support our secondary hypothesis that pharmacologic treatment of prehypertension may suppress the development of hypertension. During the active treatment phase, we did not set a specific blood-pressure goal, and dose adjustment was not permitted. Nevertheless, there was a relative reduction of 66.3 percent in new-onset hypertension and an absolute reduction of 26.8 percent in new-onset hypertension in the candesartan group. Using the absolute difference between the two groups, we calculated that four participants with prehypertension needed to be treated for a set period (two years in the present study) to prevent one case of new-onset hypertension during that two-year period. Treatment with candesartan appeared to be safe; in a comparison between active treatment with candesartan and placebo for two years, serious adverse events and other side effects were infrequent, and the rates of each were similar in the two groups.

Current guidelines[4] recommend lifestyle modification for the management of prehypertension. The results of our study can be compared with findings of the Trials of Hypertension Prevention,[28] the only trial of lifestyle modification with a similar duration: the absolute reduction in the incidence of new-onset hypertension at two years with candesartan was 26.8 percent, as compared with 8 percent with the most successful lifestyle intervention in the Trials of Hypertension Prevention.

During the study, hypertension developed in

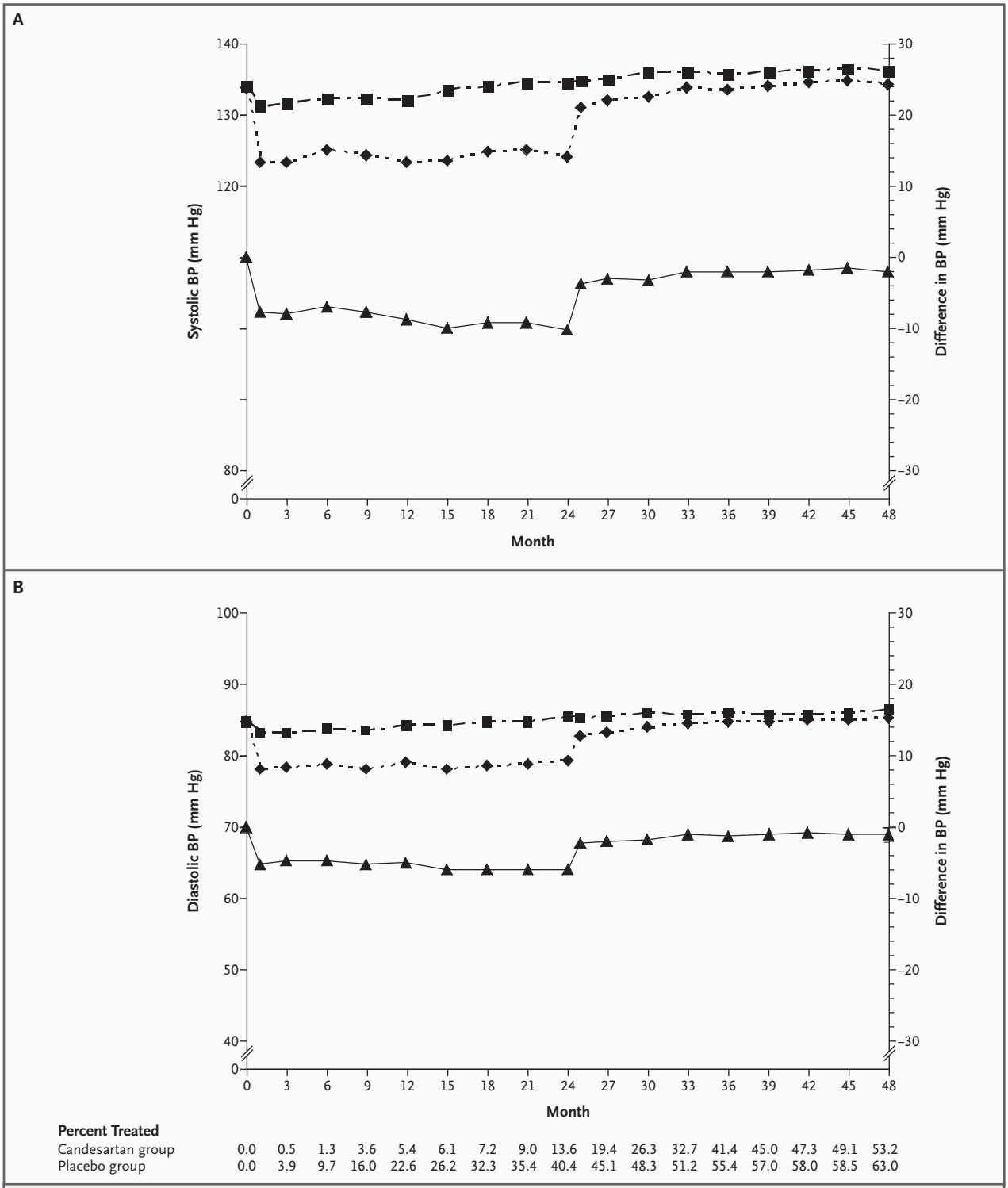


Figure 4. Blood Pressure in the Two Study Groups.

Squares represent the placebo group, and diamonds the candesartan group; triangles represent the difference between the two groups. Below the graphs are the cumulative percentages of participants in the two groups receiving antihypertension treatment at each clinic visit. Blood-pressure readings were obtained in the clinic with the use of an automated device. BP denotes blood pressure.

63 percent of those in the placebo group. Among an estimated 65 million persons in the United States with prehypertension,[14,33,37] approximately 25 million have blood-pressure readings similar to those of the participants in our study. Hypertension will develop in almost 16 million of these persons in the next four years, given the results in the placebo group in our study. In the follow-up of the large-scale Multiple Risk Factor Intervention Trial (MRFIT) involving young and middle-age men,[9] 22.2 percent of the cohort had blood pressures of 130 to 139 mm Hg systolic and 85 to 89 mm Hg diastolic. As compared with members of that cohort with optimal blood pressure, the men in this group had age-adjusted relative risks of 1.61 and 2.14 for fatal coronary events and strokes, respectively. Death from cardiovascular causes among persons with prehypertension increased steeply over 16 years of observation.[9] A successful intervention in this large population might potentially have a substantial public health effect. The recommended lifestyle measures for blood-pressure control in prehypertension[3] have had no demonstrable effect on public health to date.[33] Consequently, we believe it was appropriate to evaluate whether pharmacologic treatment of prehypertension is feasible. In our study, candesartan suppressed the onset of hypertension. In the first phase of the study, new-onset stage 1 hypertension developed in 13.6 percent of the participants in the candesartan group, as compared with 40.4 percent of those in the placebo group. We did not test the long-term safety and efficacy of this form of pharmacotherapy for prehypertension.

Our study also indicates that the effect of active treatment on delaying the onset of hypertension can extend to up to two years after the discontinuation of treatment. However, the absolute reduction of 9.8 percent in incident hypertension in the study at four years was modest.

Although the observations in this study indicate that candesartan may ameliorate blood pressure in persons with prehypertension, we do not advocate treatment of the 25 million people with prehypertension. We are unaware of any ongoing prospective trials in prehypertension, and hope that the present results will stimulate further research. The public health implications of such research are potentially large. Further studies are needed to answer a number of questions.

The mean age of 48.5 years among participants in our study is younger than that in other recent studies of hypertension. Whether treatment in even younger persons could maximize the prevention of hypertension is unknown. It is also not known whether longer periods of treatment than in our study or a larger degree of blood-pressure lowering than was achieved in the study would yield different results. Whether the results of our study reflect only the blood-pressure–lowering actions of the study drug or other effects of angiotensin blockade has not been resolved. Potentially, the largest effect would come from a study of clinical outcomes with pharmacologic intervention in prehypertension. Finally, the issue of cost-effectiveness has not been resolved. A head-to-head comparison of the cost-effectiveness of lifestyle modification and pharmacologic treatment of prehypertension would of great interest.

Treatment of prehypertension with candesartan monotherapy decreased incident hypertension in participants in this study. Additional studies will be needed to ascertain whether this or other strategies involving early pharmacologic treatment of prehypertension would positively affect clinical outcomes.

Dr. Julius reports having served as a consultant to Novartis and Servier, and having received lecture fees from Novartis and Merck and grant support from AstraZeneca and Novartis. Dr. Nesbitt reports having served as a consultant to AstraZeneca, Novartis, and Pfizer, and having received lecture fees from Boehringer Ingelheim, Pfizer, and Novartis and grant support from AstraZeneca. Dr. Egan reports having served as a consultant to AstraZeneca, Novartis, Pfizer, and Merck; having received lecture fees from Boehringer Ingelheim, Novartis, and Pfizer and grant support from Pfizer, Novartis, and AstraZeneca; and having received royalties from Elsevier. Dr. Weber reports having served as a consultant to Novartis, Pfizer, Merck, and Sankyo, and having received lecture fees from Novartis, Sankyo, Bristol-Myers Squibb, Pfizer, Merck, and Sanofi-Aventis. Dr. Grimm reports having served as a consultant to Pfizer and Merck, and having received lecture fees from Merck, Pfizer, and Novartis. Dr. Michelson is an employee of AstraZeneca. Dr. Black reports having served as a consultant to MSD, Myogen, Pfizer, Novartis, and BMS/Sanofi, and having received lecture fees from Pfizer, BMS/Sanofi, Boehringer Ingelheim, and Novartis and grant support from Pfizer. Dr. Oparil reports having served as a consultant to Merck, Novartis, Pfizer, Salt Institute, and Sankyo Pharma; having received lecture fees from Bristol-Myers Squibb, Merck, Pfizer, and Sankyo Pharma; having received grant support from Abbott Laboratories, AstraZeneca, Aventis, Biovail, Boehringer Ingelheim, Bristol-Myers Squibb, Forest Laboratories, GlaxoSmithKline, Novartis, Merck, Pfizer, Sankyo Pharma, Sanofi-Synthelabo, and Schering-Plough; and reports being a member of the board of directors of Encysive Pharmaceuticals. No other potential conflict of interest relevant to this article was reported.

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APPENDIX

The following investigators participated in the Trial of Preventing Hypertension (TROPHY) Study: **Executive Committee:** S. Julius, B. Egan, S. Nesbitt, H. Black, R. Grimm, F.H. Messerli, S. Oparil, M.A. Schork, M. Weber; **Data and Safety Monitoring Board:** M. Weinberger, J. Izzo, B. Katz; **Investigators other than the authors are as follows (those listed within parentheses left the study before completion):** N. Abate, University of Texas Southwestern Medical Center, Dallas; R. Abbott, Rochester, N.Y.; T. Adamson, Sharp Rees-Stealy Medical Group, San Diego, Calif.; S. Ahmad, (R. Davidson), Scribner Kidney Center, Seattle; B. Akpunonu, Medical College of Ohio, Toledo; S. Arnold, T. Au, Honolulu; J. Brose, Ohio University Osteopathic Medical Center, Athens; D. Calhoun, University of Alabama at Birmingham, Birmingham; R.S. Castaldo, Buffalo, N.Y.; C. Cervera, California Clinical Research Center, Baldwin Park, Calif.; J. Chinn, Las Vegas Veterans Affairs (VA) Medical Center, Las Vegas; J. Cohen, Saint Louis University Health Science Center, St. Louis; J.N. Cohn, University of Minnesota Medical Center, Minneapolis; C.N. Corder, COR Clinical Research, Oklahoma City; R. Cronin, VA North Texas Health Care Systems, Dallas; L. Crouse Kramer, Crouse Cardiology, Shawnee Mission, Kans.; W. Cushman, VA Medical Center, Memphis, Tenn.; V. Davila-Roman, Washington University, St. Louis; V.L. DeQuattro, University of Southern California School of Medicine, Los Angeles; D. Edmundowicz, (G. Ziady), Cardiovascular Institute at University Center, Pittsburgh; W. Elliott, Rush–Presbyterian–St. Luke's Medical Center, Chicago; H. Carlton Palmer, (D.M. Elnicki), West Virginia University School of Medicine, Morgantown; D.S. Estock, Wilmington, Del.; D.B. Feller, A.H. Gradman, Western Pennsylvania Hospital, Pittsburgh; S. Franklin, University of California at Irvine Heart Disease Prevention Program, Irvine; D.L. Fried, Omega Medical Research, Warwick, R.I.; M. Galler, Williamsville, N.Y.; C.G. Govantes, Ocala, Fla.; D.S. Charba, (C. Grimm), Medical College of Wisconsin, Milwaukee; J. Guntapalli, (N. Rahman), University of Texas Health Science Center at Houston, Houston; T. Hart, Muscle Shoals, Ala.; A. Hinderliter, University of North Carolina at Chapel Hill, Chapel Hill; R.K. Hippert, Fleetwood Medical Associates, Fleetwood, Pa.; B.K. Jackson, ARI [Arroyo Research] Clinical Trials, Redondo Beach, Calif.; J. Torchia, (J.D. Kearney), Conner Research Group, Camp Hill, Pa.; M.S. Kipnes, Diabetes and Glandular Research Associates, San Antonio, Tex.; L. Kirchner, (F. Whittier, R. Crock), Mercy Medical Center, Canton, Ohio; M. Kozinn, Amherst Cardiology and Internal Medicine, Williamsville, N.Y.; N. Kopyt, Northeast Clinical Research Centers, Allentown, Pa.; P. Kushner, Long Beach, Calif.; L. Hebert, (S. Ladson-Wofford), Ohio State University Medical Center, Columbus; D. Lichtinger, Leesburg, Fla.; M. Lillestol, Internal Medicine Associates, Fargo, N.D.; M. Lucas, Patterson Medical Clinic, Florissant, Mo.; D. MacPherson (J. Whittle), Pittsburgh VA Medical Center, Pittsburgh; H. Malik, Cedarwood Medical Center, St. Joseph, Mich.; M. Mirani, Hamburg, N.Y.; J. Asher, (A. Naftilan), Dial Research Associates, Nashville; J. Neutel, Orange County Research Center, Tustin, Calif.; W.B. Olney, Cardiology and Internal Medicine, Rochester, N.H.; V. Papademetriou, Georgetown University Medical Center, Washington, D.C.; F.S. Pettyjohn, University of South Alabama, Mobile; L. Rice, Biltmore Medical Associates, Asheville, N.C.; B. Rogers, (N. Winer), University of Missouri at Kansas City School of Medicine, Kansas City; R. Settipane, Providence, R.I.; J.G. Shanes, Consultants in Cardiovascular Medicine, Melrose Park, Ill.; U.R. Shettigar, Bay Pines VA Medical Center, Bay Pines, Fla.; D. Sica, Virginia Commonwealth University, Richmond; H.T. Smith, Berman Center for Outcomes and Clinical Research, Minneapolis; R. Smith, Wake Forest University Health Sciences, Winston-Salem, N.C.; A. Stahl, (T. Bowers), Heart Institute of Nevada, Las Vegas; S. Steigerwalt, St. Clair Specialty Physicians, Detroit; M. Tonkon, Apex Research Institute, Santa Ana, Calif.; D.G. Vidt, Cleveland Clinic Foundation, Cleveland; J.G. Wahhwani, Erie County Medical Center, Buffalo, N.Y.; M. Weerasinghe, Rochester Clinical Research, Rochester, N.Y.; M.S. Weinberg, Hypertension and Nephrology, Providence, R.I.; M. Wofford, University of Mississippi Medical Center, Jackson; S. Yarows, Chelsea Medical Center, Chelsea, Mich.

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