Treatment of Young Subjects at High Familial Risk of Future Hypertension With an Angiotensin-Receptor Blocker

Karin Skov, Hans Eiskjær, Hans Erik Hansen, Jens Kristian Madsen, Stinne Kvist, Michael John Mulvany

Abstract—Offspring of hypertensive parents are at high risk of future hypertension and subsequent cardiovascular diseases. We investigated whether early treatment with an angiotensin-receptor blocker in young normotensive offspring of hypertensive parents persistently lowered blood pressure after treatment withdrawal, a possibility supported by animal studies. The study is an investigator-initiated, double-blind study of 110 healthy normotensive subjects aged 18 to 36 years where both parents have essential hypertension randomly assigned to 1 of 2 treatment groups: candesartan (Atacand, Astra Zeneca), 16 mg o.d. or placebo. The intervention period was 12 months, with 24 months of follow-up. Primary outcome was mean 24-hour ambulatory blood pressure recordings (mean AMBP) after 12 and 24 months follow-up and was based on intention to treat (n=110). Secondary outcomes were changes during treatment in mean AMBP, left ventricular mass, renal hemodynamics, and adverse events during intervention and were based on those completing the intervention period (n=105). Primary outcome: At 12 and 24 months follow-up, mean AMBP was not different to placebo. Secondary outcomes: After 12 months of intervention, mean AMBP was reduced: −3.9/−3.4 mm Hg for candesartan versus 0.3/0.6 mm Hg for placebo, P<0.0001. Renal vascular resistance and left ventricular mass were also reduced (P=0.0007, P=0.019, respectively). There were no significant differences in adverse advents between the 2 groups. In conclusion, temporary treatment of subjects at high familial risk of future hypertension with an angiotensin receptor blocker is feasible, but the treatment had no persistent effect on blood pressure when treatment was withdrawn. (Hypertension. 2007;50:89-95.)

Key Words: familial hypertension ■ prophylactic treatment ■ angiotensin II receptor blocker ■ randomized clinical trial ■ renal vascular resistance ■ left ventricular mass

Human essential hypertension remains the most common risk factor for cardiovascular morbidity and mortality.1 Preventing or delaying the onset of the disease may therefore have large impact on public health. Such treatment should be directed toward normotensive persons likely to develop hypertension, for which at least 2 major populations can be identified: those who have blood pressures in the upper part of the normotensive range and those who have hypertensive parents. Both these populations have at least a 50% chance of developing hypertension, and each (not mutually exclusive) constitute 10 to 20% of most Western societies.2 The recently published Trial Of Prevention HYpertension (TROPHY) study3 has studied this question in the first population, and reported that treatment of subjects with high-normal blood pressure (prehypertensives, eg, blood pressure 130 to 139/85 to 89 mm Hg) with an angiotensin-receptor blocker, candesartan, can delay the onset of hypertension. The result is remarkable,4 but has also been criticized.5,6

The present study (Danish Hypertension Prevention Project [DHyPP]) concerns the second population.7 The study is based on the consistent reports from genetic rat models of essential hypertension that short-term inhibition of the renin-angiotensin system has persistent effects on blood pressure when treatment is withdrawn.8,9 Starting with the work of Giudicelli8 numerous studies have shown that short-term treatment of young, still normotensive spontaneously hypertensive rats9 and Lyon hypertensive rats10 with angiotensin-converting-enzyme inhibitors or angiotensin receptor antagonists has a long-term antihypertensive effect, so that blood pressure remains low even after withdrawal of treatment.8,9 The effect appears to be mediated by the kidney.9 Transfer of this finding to the clinic would have important therapeutic implications. We have therefore investigated if such treatment has a persistent effect in a similar human population by choosing young subjects at high risk of future hypertension. We have included young normotensive persons for whom both parents had essential hypertension, and these were treated with candesartan or placebo for 1 year with 2-year follow-up. As we11 and others12,13 have shown, these individuals have early markers of cardiovascular disease including

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higher blood pressure, increased body mass index, increased left ventricular mass index (LVMI), and increased renal vascular resistance. Because we wanted the subjects to remain in the study throughout the intervention period, we included only subjects with diastolic blood pressure below 85 mm Hg at baseline.

Patients and Methods

Study Design

DHyPP is a monocenter, investigator-initiated, double-blind, randomized, placebo-controlled study. Interim analyses were made at conclusion of intervention, and at 6 and 12 months follow-up by the independent data committee (K.L.C., M.V., see Acknowledgments), which had exclusive access to the randomization schedule. The trial was approved by the local ethics committee (20000114) and the Danish Medicines Agency (2612-1332). Trial registration: ClinicalTrials.gov, number NCT00150631.

Patient Recruitment

Data from hospital electronic discharge registers of 3 counties in Denmark were used to identify cases of essential hypertension over the previous 5 years, and from these we traced 12,462 adults aged 36 to 75 years. By mail the persons were asked if their spouse also had hypertension and if they had shared children of age 18 to 36 years. Those who responded (1,896) were sent further information and a questionnaire regarding their blood pressure status, and of these 698 couples were prepared to participate. Participation involved acceptance that we could (1) contact their general practitioners/hospitals where their blood pressure was being controlled and (2) contact their children, whose contact details they had provided. This enabled us to obtain confirmation that both parents did indeed have essential hypertension which had been present for more than 1 year, information about the last measured blood pressure (measured maximally 6 months previously), and their antihypertensive treatment. 216 couples fulfilled all criteria and their 382 children aged 18 to 36 years were invited to participate by letter and telephone. After further questioning, 115 were screened at the hospital, and 110 healthy persons aged 18 to 36 years were included by K.S. (Figure 1). These were of mixed social classes. Exclusion criteria were: non-white, daily medication, clinic diastolic blood pressure >85 mm Hg over 2 visits during the run-in period, or if there were any clinical or biochemical signs of disease in heart, kidney, liver, or endocrine organs. Informed written consent was obtained from all participants; 105 completed the whole protocol (Figure 1).

Randomization

The randomization schedule was generated centrally by AstraZeneca, Mölndal, Sweden, and concealed from the investigators. The randomization was in a one-to-one ratio. Patients were randomized to candesartan (Atacand, Astra Zeneca) or placebo sequentially, starting from the lowest allocation number, according to the randomization schedule.

Intervention

During the first 2 weeks of intervention, the subjects were given a daily dose of oral candesartan cilexetil, 8 mg or matching placebo. Thereafter patients received a daily dose of oral candesartan 16 mg or matching placebo for 12 months. During intervention, subjects were evaluated at month 0, 0.5, 1, 2, 4, 6, 10, and 12 by a trained research assistant at Aarhus University Hospital (Skejby) to ensure compliance, record adverse events, and measure clinic blood pressure.

Outcome Measures

The primary outcome measure was mean 24-hour ambulatory blood pressure recordings (mean AMBP) at 12- and 24-month follow-up. AMBP and heart rate measurements were obtained with Spacelabs monitor model 90217 and a proper cuff size placed on the left arm of the subject. The recordings were performed every 20 minutes for 24 hours on regular work days when possible. Awake and asleep AMBP were calculated according to individual records of time for retiring and rising. Each AMBP report had to include at least 24 hours of data with at least 75% of readings being valid. If these criteria were not met (6 out of 516 measurements), subjects were asked to repeat AMBP within 2 weeks. At baseline and at month 12, the AMBP equipment was demonstrated in the clinic preceded by at least 2 oscillometric blood pressure measurements taken for familiarization. The oscillometric measurements were then confirmed by
comparing with auscultatory measurements (Hawksley random zero mercury sphygmomanometer) with the subjects in the sitting position and the left arm supported.16 3 measurements each. During the intervention period, auscultatory clinic blood pressure was measured under identical circumstances. Two trained research assistants performed all the clinic blood pressure measurements. AMBP was determined before inclusion, at the end of treatment (month 12), and after 6, 12, and 24 months of follow-up. Subjects were taken out of the study if treatment was started.

Secondary outcomes were changes during intervention in mean AMBP, renal hemodynamics (determined using 51Cr-EDTA and 125I-hippuran as previously described11; at month 12, 24-hour after last dose, with successful measurements in 89 subjects at both baseline and month 12), and LVMI (determined by 2-dimensional echocardiography17,18); adverse events during intervention; plasma renin activity (determined by a double-sided immunoradiometric method, using two monoclonal antibodies against human-active renin linked to biotin and 125I [Nichols Institute, Geneva, Switzerland]); angiotensin II (Ang II rabbit-antibody kindly provided by Prof Jan Danser, Rotterdam, Holland); aldosterone (measured in plasma by radioimmunoassay using DSL-8600 active aldosterone Coated-Tube Ria Kit, Diagnostics Systems Laboratories Inc, Webster, Tex).11

Statistical Analysis

Analysis of the primary end point was by intention-to-treat (n=110). The last measured mean AMBP was carried forward in the calculation of later group mean AMBPs. Analysis of secondary end points was on those completing intervention (n=105). Unless otherwise indicated, results are presented as mean±SD or as mean change from baseline (95% confidence interval). Effects of treatment within individuals were examined by paired 2-tail t test. Linear multivariable regression analysis was made to determine whether change in left ventricular mass during treatment was a predictor of blood pressure at 1 or 2 years of follow-up. Adverse event distributions were tested by χ²-test. The criterion for statistical significance was set at α=0.05.

A sample size of 96 subjects (48 in each arm) was required to detect a 4 mm Hg difference in mean AMBP between groups (the expected difference if a persistent fall was achieved), with an α-error of 5% and a β-error of 80%. This was based on variance in AMBP measurements in a similar Dutch population (age 23 years and with 2 hypertensive parents).11 To compensate for possible discontinuations during follow-up, we aimed to have 100 subjects completing the first year of intervention. Achieved variance was smaller, such

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TABLE 1. Baseline Characteristics of Study Subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>Candesartan</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, n (%)</td>
<td>27 (53)</td>
<td>25 (46)</td>
</tr>
<tr>
<td>Age, year</td>
<td>28.9±5.5</td>
<td>29.9±5.4</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>77.7±15.3</td>
<td>81.2±18.4</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25.4±4.4</td>
<td>26.0±5.1</td>
</tr>
<tr>
<td>Arm circumference, cm</td>
<td>29.9±3.3</td>
<td>30.3±3.9</td>
</tr>
<tr>
<td>Current smokers, n (%)</td>
<td>12 (24)</td>
<td>15 (28)</td>
</tr>
<tr>
<td>Physical activity, hour/week</td>
<td>4.8±3.6</td>
<td>5.2±5.6</td>
</tr>
<tr>
<td>Clinic systolic blood pressure, mm Hg</td>
<td>129±12</td>
<td>129±11</td>
</tr>
<tr>
<td>Clinic diastolic blood pressure, mm Hg</td>
<td>78±9</td>
<td>79±8</td>
</tr>
</tbody>
</table>

Data are mean±SD. n indicates numbers of individuals; BMI, body mass index. Clinic blood pressure was measured by Spacelab equipment.

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that our study had the power to detect a 3 mm Hg difference in mean AMBP between groups.

Ethics and Safety

The local ethical committee approved the study protocol in accordance with the Helsinki Declaration. An independent Data Safety Monitoring Board (GCP-unit, Aarhus University Hospital) monitored the study.

At baseline and at intervention month 12, electrocardiography was obtained and fasting blood and urine samples were taken for laboratory analyses. Additionally, serum potassium and creatinine were controlled after 1 month intervention. For female participants, a urine test for pregnancy was performed prior to the renal function tests. It was a requirement that all female participants used contraceptives (oral or intrauterine device) throughout the intervention period.

Adverse events data were obtained throughout the study by observation and indirect questioning and were defined as any unintended adverse finding with no attempt to assess whether or not it was related to the study treatment. Events of special interest in the trial included dizziness, headache, and cough.

Results

Between November 2000 and February 2003, 110 subjects were enrolled in the study (Figure 1). The parent population consisted of 84 couples, mean age 58.4±6.9 years, systolic blood pressure 147.7±13.6 mm Hg and diastolic blood pressure 86.7±8.1 mm Hg, average number of used drugs 2.0±1.0, and duration of hypertension 9.4 (range 1 to 34) years. Baseline characteristics of the two groups of study subjects were balanced (Table 1). Descriptive laboratory values at baseline and end of treatment (month 12) are reported (Table S2, available in a data supplement online at http://hyper.ahajournals.org.).
Intervention
From month 1, clinic systolic and diastolic BP were significantly lower in the candesartan treated group (Figure 2). Mean AMBP was lower in the candesartan group at month 12 (Figure 3). Similar reduction was seen for all other pressures measured (systolic, diastolic, mean, awake, asleep; Table S1). At baseline, LVMI was positively correlated to mean AMBP \((P=0.0002)\). Twelve months candesartan treatment caused a decrease in LVMI (Table 2), mainly due to a reduction in the interventricular septum (Table S4).

Baseline renal hemodynamics were balanced in the 2 groups (Table 2). Twelve months of candesartan treatment reduced both renal vascular resistance and filtration fraction. There was no effect on renal blood flow or glomerular filtration rate.

Plasma renin activity and angiotensin II plasma concentrations increased during candesartan treatment (Table 2). Plasma aldosterone was not decreased.\(^{19,20}\) Treatment did not affect 24-hour sodium excretion, clearance of sodium, or renal tubular sodium handling measured by lithium clearance (Table S2). Hematocrit and hemoglobin were decreased by about 5% in the candesartan treated group at month 12\(^{21}\) (Table S2).

Outcomes
There was no difference in mean AMBP between the 2 groups during follow-up (months 6, 12, 24; Figure 3). Change in LVMI during intervention was not a predictor of mean AMBP at follow-up. During follow-up, 2 subjects in the candesartan group (follow-up months 7 and 14) and one subject in placebo group (follow-up month 16) had begun antihypertensive treatment.

Adverse Events
Overall, 91% of the study subjects reported at least 1 adverse event during intervention. There was no significant difference between the 2 groups for any of the recorded adverse events (Table S3). No subjects developed a significant rise in serum potassium or creatinine. Four candesartan treated subjects suffered mild dizziness for more than 50 days compared with 1 placebo treated subject \((P=0.3)\). There were no events of syncope and no serious adverse events during the 12 months of intervention.

### TABLE 2. Effects on Secondary and Related Outcome Parameters at End of Treatment (Month 12)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Candesartan</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure, mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AMBP systolic</td>
<td>123.3±9.6</td>
<td>123.4±8.5</td>
</tr>
<tr>
<td>AMBP diastolic</td>
<td>74.6±5.9</td>
<td>74.3±4.9</td>
</tr>
<tr>
<td>24-hour pulse, min(^{-1})</td>
<td>71.1±8.3</td>
<td>72.4±8.6</td>
</tr>
<tr>
<td>LVMI, g/m(^2)</td>
<td>84.2±18.7</td>
<td>81.6±19.3</td>
</tr>
<tr>
<td>ERPF, mL/min per 1.73 m(^2)</td>
<td>464.6±62.6</td>
<td>474.5±80.6</td>
</tr>
<tr>
<td>RBF, mL/min per 1.73 m(^2)</td>
<td>776.5±121.4</td>
<td>806.7±164.7</td>
</tr>
<tr>
<td>FF, %</td>
<td>22.2±2.3</td>
<td>21.7±2.2</td>
</tr>
<tr>
<td>GFR, mL/min per 1.73 m(^2)</td>
<td>102.2±11.1</td>
<td>101.8±13.0</td>
</tr>
<tr>
<td>RVR, mm Hg/dL per min/1.73 m(^2)</td>
<td>12.1±2.5</td>
<td>12.0±2.7</td>
</tr>
<tr>
<td>p-renin activity, mU/L</td>
<td>16.0±8.1</td>
<td>20.2±24.4</td>
</tr>
<tr>
<td>p-aldosterone, pmol/L</td>
<td>191.0±95.9</td>
<td>247.7±180.1</td>
</tr>
<tr>
<td>p-angiotensin II, pmol/L*</td>
<td>7.4±3.2</td>
<td>11.0±16.3</td>
</tr>
</tbody>
</table>

Data are mean±SD and mean change from baseline (95% confidence interval). There is no significant difference between the 2 groups at baseline. LVMI indicates left ventricular mass index; ERPF, effective renal plasma flow; RBF, renal blood flow; FF, filtration fraction; GFR, glomerular filtration rate; RVR, renal vascular resistance. Mean blood pressure (MBP) was calculated as diastolic blood pressure plus one third of the pulse amplitude. RBF was estimated by dividing ERPF by 1 minus the hematocrit. FF was calculated by dividing GFR by ERPF. RVR was estimated by dividing MBP by RBF. \(P\) value indicates significance of difference between changes in baseline in the 2 groups.

\(^*\)n=49 in candesartan group and n=52 in placebo group.


**Discussion**

The study shows that treatment with an angiotensin-receptor blocker had no persistent effect on blood pressure after the treatment was withdrawn in normotensive offspring of hypertensive parents. During intervention, blood pressure, renal vascular resistance, and left ventricular mass were lowered. The treatment was well tolerated.

The mean AMBP measurements showed small variance, allowing the solid conclusion that it is very unlikely that candesartan treatment has a persistent effect on blood pressure in this population of young persons at familial risk of hypertension. The result contrasts with the strong animal data, and comparison with these suggests that the discrepancy could be attributable to our subjects being too old (mean age 29 years) or that treatment duration was too short. The animal evidence on which the study is based shows that the persistent effect is most pronounced if the inhibition of the renin–angiotensin system is made in prepubertal animals; for ethical reasons such studies are hardly feasible in humans. Another possible reason for the lack of persistent effect is that the animal studies show that the effect is related to renal mechanisms. In the present study, the reduction in renal vascular resistance corresponded to the reduction in blood pressure, and renal vascular resistance was still higher than that which we have measured in a parallel study in offspring of normotensive parents. This suggests that the intervention did not have a specific effect on renal hemodynamics, as confirmed in other long-term studies on hypertensives.

A third possible reason is that the dose of candesartan (16 mg o.d.) used was insufficient for full inhibition of the renin–angiotensin system, in that doses up to 32 mg o.d. are now recommended. The trial thus indicates that the data obtained from spontaneously hypertensive and Lyon hypertensive rats cannot easily be transferred to the clinic. In this connection it may be relevant that the only other strain of hypertensive rat studied in this respect, the Milan hypertensive rat, did not show a persistent effect on blood pressure after 20 weeks treatment with an angiotensin converting enzyme inhibitor. AMBP was chosen for monitoring our primary effect parameter during follow-up, because of its higher reproducibility compared with clinic blood pressure. During the intervention period, clinic blood pressures were made, mainly to ensure compliance, and these measurements showed that the antihypertensive effect of treatment was similar to that obtained in the TROPHY study (ca. 8/5 mm Hg) and substantially greater than the effect measured with 24-hour AMBP (ca. 4/3.5 mm Hg at month 12). Such differences in the effect of treatment on clinic blood pressures and on 24-hour AMBP have been reported previously and are likely attributable to treatment causing a reduction of white-coat effect.

The blood pressure of the placebo group remained in our study stable over the 3-year period of observation, even though the blood pressure in this group was already elevated at inclusion. We suggest that the lack of rise could be attributable to the placebo-effect of the subjects, which can reduce blood pressure by a significant amount, as for example in the SYSTolic hypertension in EURope (SYS-EUR) trial or to the natural history of blood pressure in these young study subjects.

Candesartan treatment caused reduction in LVMI. A multivariate analysis has indicated that 1 of the main factors for the redevelopment rate of both systolic and diastolic blood pressure after withdrawal of treatment is left ventricular mass. However, in the present study the reduction in LVMI did not predict future blood pressure, in accordance with findings in patients with established hypertension. However, given that the values measured were in the high-normal range and that left ventricular hypertrophy is an independent predictor of cardiovascular risk, it cannot be excluded that this effect of candesartan could be advantageous.

Candesartan had adverse event profiles similar to those of placebo. Comparable findings have been reported in the TROPHY study. Our findings are thus in accordance with the general opinion of the placebo-like tolerability of angiotensin-receptor blockers, and extends the similar results of TROPHY (mean age 48.5 years) to a younger population. The results show that treatment of this normotensive but high-risk group is feasible, analogous to the conclusion of TROPHY.

The lack of persistent effect of blood pressure reduction after withdrawal of treatment is in contrast to that of the TROPHY trial even though the effect on clinic blood pressure during intervention was similar. TROPHY reported that in persons with high-normal blood pressure the risk of hypertension was slightly reduced (by 15.6%), and that there was a small persistent reduction in clinic systolic blood pressure (of 2 mm Hg), but not diastolic blood pressure, at the end of the 4-year study. Although the clinical significance of these small reductions is perhaps marginal, they have given exciting encouragement to the possibility that antihypertensive treatment could have long term effects. The contrast with our findings could be attributable to the smaller number of subjects (105 subjects) compared with TROPHY (772 subjects), although as indicated our negative results have reasonable statistical strength. The difference could also be attributable to the difference in study populations, although our study population was based on firm animal studies, indicating that the younger the subject the better is the chance of a persistent effect. Another possibility is the rather liberal definition of hypertension used in the TROPHY study, which was defined as systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg at any 3 of the 24 visits over the 4-year study period. This definition is in contrast to current guidelines, where hypertension is defined as maintained hypertension over a period (eg, hypertensive measurements on at least 2 or 3 successive visits). The TROPHY definition gives a substantial chance of being occasionally hypertensive at a particular consultation even if the underlying 24-hour blood pressure is unchanged. Thus the hypertension reported in TROPHY may be overestimated, and indeed 63% were reported to develop hypertension in the placebo group, which is high compared with other studies on the incidence of hypertension, and might account for some of the apparent persistent effect of the candesartan treatment. Lastly the difference may be because our subjects were on average far from being hypertensive (diastolic blood pressure
<85 mm Hg on entry), a deliberate decision to ensure that there would be few drop-outs because of onset of hypertension, but possibly also reducing the chances of obtaining a persistent effect.

**Perspectives**

The main conclusion from the present study as well as the previous TROPHY study appears to be that although both studies have demonstrated the feasibility of treating prehypertension with an angiotensin receptor antagonist, neither study has demonstrated a convincing clinical argument that short-term treatment of high-risk subjects can have useful persistent effects. Thus if the clear animal data are to be transferred to the clinic, other approaches must be sought. The rat data suggest that the persistent effect is although it might be possible in children with multiple risk factors. The rat data also suggest that the persistent effect is mediated through structural outward remodeling of the afferent arterioles, and thus treatments which specifically dilate the renal vasculature might be effective.

**Conclusions**

The study shows that temporary treatment of subjects at high familial risk of future hypertension is feasible, but the protocol used did not delay the onset of hypertension when treatment was withdrawn. Other approaches are needed if the animal findings are to be transferred to the clinic.

**Acknowledgments**

We thank the study subjects, technicians, nurses, and the Data Safety Monitoring Board members. The Independent Data Committee, Dr. Kent Lodberg Christensen and Prof Michael Væth, are thanked for making interim analysis and for statistical advice. None of the sponsors had any role in study design, data collection, data analysis, data interpretation, or writing of the report. The main sponsor (AstraZeneca) made suggestions during the planning phase. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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**Disclosures**

None.

**References**


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