Hypertension Optimal Treatment (HOT) Study
Home Blood Pressure in Treated Hypertensive Subjects

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Abstract—The Hypertension Optimal Treatment Study is a prospective trial conducted in 26 countries. The aims are to (1) evaluate the relationship between three levels of target office diastolic blood pressure (BP) (≤80, ≤85, or ≤90 mm Hg) and cardiovascular morbidity and mortality in hypertensive patients and (2) examine the effects on cardiovascular morbidity and mortality of 75 mg aspirin daily versus placebo. A total of 19,193 patients between 50 and 80 years of age had been randomized by the end of April 1994. Treatment was initiated with felodipine 5 mg daily, and additional therapy was given in accordance with a set protocol. The present substudy of 926 patients performed in nine countries aimed to (1) compare home with office BP in a representative subsample of the HOT Study population after the titration of treatment was completed and (2) clarify whether the separation into the target groups could be expanded into the out-of-office setting. The differences between office and home measurements in diastolic BP of 0.2 mm Hg (SD, 9; 95% confidence interval, −0.36 to 0.81; P=.40) and systolic BP of 0.5 mm Hg (SD, 15; 95% confidence interval, −0.53 to 1.46; P=.21) were not significant. The group differences in home BP were 1.9 mm Hg (≤80 versus ≤85) and 1.2 mm Hg (≤85 versus ≤90) for diastolic BP (F=11.69; ANOVA, P<.0001) and 2.6 and 2.1 mm Hg for systolic BP (F=8.44, P=.0002). Thus, office and home BPs measured with the same semiautomatic device are comparable in treated hypertensive subjects in the HOT Study, and the separation into the target groups based on office readings prevails at home. (Hypertension. 1998;31:1014-1020.)

Key Words: antihypertensive agents ■ blood pressure monitoring ■ cardiovascular diseases ■ clinical trials ■ hypertension, white coat

The Hypertension Optimal Treatment (HOT) Study is a multicenter trial being conducted in 26 countries. The rationale and background have been described in detail previously.1 The HOT Study is conducted in accordance with the PROBE design.2 The main aim is to evaluate the relationship between three levels of target diastolic BP (≤80, ≤85, or ≤90 mm Hg) and cardiovascular morbidity and mortality in hypertensive patients. In addition, the study will examine the effects on morbidity and mortality of a low dose (75 mg daily) of acetylsalicylic acid or double-blind placebo.1 When the inclusion of patients was stopped on April 30, 1994, 19,193 patients between 50 and 80 years of age had been randomized. Basic antihypertensive treatment was initiated with the calcium channel blocker felodipine (5 mg daily). If target blood pressure was not reached, additional antihypertensive therapy was given in accordance with a set protocol.1 Details of the patient characteristics at randomization, cardiovascular risk profiles, and early BP results have previously been published.3,4

Home BP monitoring can easily be taught and learned, and it has a high reproducibility and sensitivity of measurement.5,6 Because of the lack of prospective mortality/morbidity data, home BP monitoring cannot be used alone to decide whether treatment is indicated,7 and treatment decisions must still be based on repeated standard clinic BP readings. Home BP has been investigated in a large study of normotensive and untreated hypertensive subjects.8 However, large studies of home BP in treated hypertensive patients have not been done. This is particularly feasible in the HOT Study because of the standardization of measurements of BP with a semiautomatic device and the subsequent possibility to train subjects at every office visit. Therefore, the aim of the present study was to compare home BP with office BP in a large and representative subsample of the HOT Study population after the titration of antihypertensive treatment. The study also aimed to clarify whether the separation of subjects into the three main groups (≤80, ≤85, or ≤90 mm Hg) based on office readings could be expanded into the out-of-office setting.

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Methods

Subjects
In the main study, a total of 19193 hypertensive patients of any race aged 50 to 80 years were randomized in 26 countries. Details of their characteristics at randomization have previously been published.1 The average mean ± SD randomization BP in patients untreated at enrollment was 169±14/106±3 mm Hg; in the treated patients, after at least 2 weeks of washout, the mean ± SD BP was 170±14/105±3 mm Hg. The three target BP groups were well matched at the outset of the study.2

There were no additional criteria for participation in the home BP substudy except for patient willingness. For practical reasons, the study was limited to 88 centers from a total of 1921 participating centers in the HOT Study. The sample (n = 926) that participated in the substudy contained a higher percentage of previously treated subjects (66% versus 52%); otherwise, characteristics were comparable with those of the subjects in the main study (Table 1). The distribution of the 926 patients between countries was as follows: Canada 72, Greece 34, Hungary 36, Israel 10, The Netherlands 19, Norway 109, Spain 124, Sweden 82, and United States 440 patients.

Protocol
Patients in the HOT Study were recruited after giving informed consent provided that the substudy had been approved by the local ethics committee in the respective country. BP was measured at enrollment and then at two qualifying visits at least 7 days apart. The diastolic BP had to be in the range of ≥100 to ≤115 mm Hg at both qualifying visits. A number of exclusion criteria were specified.1 All patients started active antihypertensive treatment with felodipine, 5 mg once daily. In treated patients, this was preceded by a washout period of at least 2 weeks. If the target BP was not reached, additional antihypertensive therapy with either an angiotensin-converting enzyme inhibitor or a β-adrenergic blocking agent was given. Further dosage adjustments were made in accordance with a set protocol.3 As a fifth and final step, a diuretic could be added. After 6 months,1 the percentages of patients who had achieved their randomized target clinic diastolic BP were 57%, 71%, and 83% for the target groups at ≤80, ≤85, or ≤90 mm Hg, respectively, and after 12 months they were 57%, 72%, and 84%, respectively.2 The distribution of the dose steps in the three target groups was fairly similar.3,4

BP and HR have been measured in the sitting position with a newly calibrated semiautomatic oscillometric device with a digital readout (Visomat OZ, D2 International, Hestia Pharma GmbH). The accuracy of this device has been extensively validated (in 407 normotensive and hypertensive subjects) against standard sphygmomanometer readings according to the recommendations of the British Hypertension Society,9 with the conclusion that this device provides accurate and reliable measurements of BP.9 Measurements were done in the same arm each time and with a cuff of appropriate size relative to the patient’s arm. The cuff was kept at the heart level, and the arm was supported at the time of the measurement. In the office, three measurements were made at least 15 seconds apart, after 5 minutes of rest, and the averages were calculated for statistical analysis. Visits took place at the same time of the day, usually in the morning, and the measurements were performed at the end of the dosing interval by the same person.

Home assessments were performed over 7 consecutive days with the same kind of semiautomatic device after appropriate training of the participating patients. After the subjects sat for 5 minutes, both in the morning before leaving home and in the afternoon after returning home, BPs and HR were taken three times, and the measurements were registered on special case record forms. Conditions for measurements were thus comparable at home and in the investigator’s office; however, measurements were not standardized for intake of antihypertensive medication. The averages of all measurements at home have been used for comparisons with the respective office measurements. The averages of the morning measurements have also been compared with the averages of the afternoon measurements.

Assessments of BP and HR at home were performed at a time when the titration of antihypertensive medication in the study had been finalized, ie, at least 6 months after randomization. An automatic device was given to the patient after a scheduled visit for the majority of patients at 6 (n = 168), 12 (n = 462), 18 (n = 191), or 24 (n = 67) months; the home measurements were then performed shortly thereafter (on average 4 days later) and in most subjects (n = 890) on consecutive days. In each patient, the data from the home assessments were compared with BP and HR taken at the regular scheduled visit to the office of the investigator that was nearest in time to, and usually preceded, the home measurements. Nine patients were excluded from the home-office comparison because the exact time for home measurements had not been written on the registration form. One patient had not written the diastolic BPs on the form, and four had not registered HRs.

The home BP data was edited by one of the investigators (S.E.K.) according to an a priori protocol for the purpose of cleaning the data for clearly erroneous recordings. This was done before any statistical analysis. Approximately 3% of all recordings were considered erroneous (single numbers incompatible with life or way out of range with all others in the same patient, diastolic BP almost identical to systolic BP or higher, HRs compatible with a paroxysmal tachycardia); the accompanying BPs and HRs taken simultaneously were deleted. Not all patients had all measurements taken at all 14 occasions, leaving nearly 34000 measurements of both BPs and HR for analysis.

Statistics
To study the repeatability of the method, the within-individual SD both in mm Hg and as a percentage of the total mean was calculated. The average bias of one method relative to the other was estimated.
by the mean difference and a 95% CI of the mean difference between the two methods. To study how well the two methods were likely to agree for an individual, the limit of agreement (mean±2·SDlo) was calculated.12 For comparison between home and office BP, Wilcoxon’s signed rank test for matched pairs was used. Pearson correlation coefficients (r) were calculated. Methods of BP measurement were also compared by plotting the difference between two methods for each subject against the average of BP measured by the two techniques. A one-way ANOVA was used for the overall test between target groups. Tukey-Kramer studentized range test12 was used for pairwise post hoc comparisons between target groups.

### Results

Within-individual SD for home BP for all patients (n=926) was as follows for (1) calculations between all days: diastolic BP 4.7 mm Hg (5.7%), systolic BP 7.3 mm Hg (5.3%), and HR 4.5 bpm (6.0%); (2) calculations between morning and afternoon on the same day: diastolic BP 6.5 mm Hg (7.9%), systolic BP 9.8 mm Hg (7.1%), and HR 6.6 bpm (8.8%); and (3) calculations between three measurements at the same occasion: diastolic BP 4.8 mm Hg (5.8%), systolic BP 7.8 mm Hg (5.7%), and HR 3.5 bpm (4.7%).

The difference found in diastolic BP of 0.2±0.9 mm Hg between home and office measurements was not statistically significant (Table 2); neither could any significant difference between home and office be related to previous treatment status (treated versus untreated), age, race, or level of serum cholesterol or serum creatinine at randomization (data not shown). However, for the target group randomized to clinic diastolic BP ≤90, there was a slightly lower diastolic BP measured at home. This difference between office and home readings was significant (Table 2), as was the case for readings taken by female subjects (Δ1.16 mm Hg; 95% CI, 0.26 to 2.06 mm Hg; P=.003; n=418) and patients with body mass index <28.1 kg/m² (Δ0.85 mm Hg; 95% CI, 0.00 to 1.70; P=.047; n=395).

One-way ANOVA between the target groups showed differences for diastolic BP measured in the office (F=30.93, P<.0001), as well as at home (F=11.69, P=.0001). For the three diastolic BP target groups, the differences in office measurements between the groups were 3.0 mm Hg (≤80 versus ≤85, P<.05), 1.8 mm Hg (≤85 versus ≤90, P<.05), and 4.8 mm Hg (≤80 versus ≤90, P<.05). These differences were fairly comparable to the differences between the groups obtained during home BP measurements: 1.9 mm Hg (≤80 versus ≤85, P<.05), 1.2 mm Hg (≤85 versus ≤90, NS), and 3.1 mm Hg (≤80 versus ≤90, P<.05), respectively.

The difference in systolic BP measured in the office compared with at home averaged 0.5±15.3 mm Hg for all patients and was not statistically significant (Table 2). There were minimal differences between office and home systolic BP measurements with respect to previous treatment status, age, race, or level of serum creatinine at randomization (data not shown). For the treatment group targeted at ≤90 mm Hg, the lower systolic BP at home compared with office was significant (Table 2), which was also the case for women (Δ1.69 mm Hg; 95% CI, 0.13 to 3.25; P=.012; n=419), patients with body mass index <28.1 kg/m² (Δ2.08 mm Hg; 95% CI, 0.58 to 3.58; P=.007; n=395), and patients with serum cholesterol ≥6.1 mmol/L (Δ1.58 mm Hg; 95% CI, 0.09 to 3.26; P=.015; n=376).

One-way ANOVA between target groups showed differences for systolic BP in the office (F=19.49, P<.0001) and at home (F=8.44, P=.0002). For the three diastolic BP target groups, the differences between the groups during office measurements were 4.2 mm Hg (≤80 versus ≤85, P<.05), 3.3 mm Hg (≤85 versus ≤90, P<.05), and 7.5 mm Hg (≤80 versus ≤90, P<.05), which is fairly comparable to the differences between the groups during home BP measurements: 2.6 mm Hg (≤80 versus ≤85, P<.05), 2.1 mm Hg (≤85 versus ≤90, NS), and 4.7 mm Hg (≤80 versus ≤90, P<.05), respectively.

### Table 2. Comparison of BP and HR Taken in the Office and by Self-Assessment at Home

<table>
<thead>
<tr>
<th>Variable and Target Group</th>
<th>Office</th>
<th>Home</th>
<th>Difference, Office-Home</th>
<th>95% CI</th>
<th>P†</th>
<th>95% Limits of Agreement</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diastolic BP, mm Hg</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All (n=914)</td>
<td>82.7±7.9</td>
<td>82.5±7.9</td>
<td>0.2±9.0</td>
<td>−0.36 to 0.81</td>
<td>NS</td>
<td>−17.4 to 17.9</td>
</tr>
<tr>
<td>≤90 (n=302)</td>
<td>84.9±8.2</td>
<td>83.9±7.5</td>
<td>1.0±9.0</td>
<td>0.03 to 2.05</td>
<td>.025</td>
<td>−16.6 to 18.6</td>
</tr>
<tr>
<td>≤85 (n=313)</td>
<td>83.1±7.3</td>
<td>82.7±8.1</td>
<td>0.4±8.7</td>
<td>−0.55 to 1.37</td>
<td>NS</td>
<td>−16.5 to 17.4</td>
</tr>
<tr>
<td>≤80 (n=299)</td>
<td>80.1±7.5</td>
<td>80.8±7.7</td>
<td>−0.8±9.3</td>
<td>−1.84 to 0.26</td>
<td>NS</td>
<td>−19.0 to 17.4</td>
</tr>
<tr>
<td><strong>Systolic BP, mm Hg</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All (n=915)</td>
<td>137.5±15.1</td>
<td>137.0±14.2</td>
<td>0.5±15.3</td>
<td>−0.53 to 1.46</td>
<td>NS</td>
<td>−29.5 to 30.5</td>
</tr>
<tr>
<td>≤90 (n=302)</td>
<td>141.1±15.7</td>
<td>139.3±14.2</td>
<td>1.8±15.0</td>
<td>0.09 to 3.48</td>
<td>.024</td>
<td>−27.7 to 31.3</td>
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<tr>
<td>≤85 (n=313)</td>
<td>137.8±15.3</td>
<td>137.2±14.0</td>
<td>0.6±15.0</td>
<td>−1.07 to 2.27</td>
<td>NS</td>
<td>−28.9 to 30.1</td>
</tr>
<tr>
<td>≤80 (n=299)</td>
<td>133.6±13.1</td>
<td>134.6±14.0</td>
<td>−1.0±15.8</td>
<td>−2.80 to 0.77</td>
<td>NS</td>
<td>−31.9 to 29.9</td>
</tr>
<tr>
<td><strong>HR, bpm</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All (n=911)</td>
<td>76.7±12.3</td>
<td>75.0±10.6</td>
<td>1.7±8.6</td>
<td>1.09 to 2.21</td>
<td>.0001</td>
<td>−15.2 to 18.5</td>
</tr>
<tr>
<td>≤90 (n=302)</td>
<td>77.6±11.8</td>
<td>75.8±10.9</td>
<td>1.8±8.4</td>
<td>0.84 to 2.73</td>
<td>.0007</td>
<td>−14.7 to 18.2</td>
</tr>
<tr>
<td>≤85 (n=313)</td>
<td>77.1±12.7</td>
<td>75.5±10.6</td>
<td>1.6±9.2</td>
<td>0.54 to 2.58</td>
<td>.017</td>
<td>−16.4 to 19.5</td>
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<tr>
<td>≤80 (n=299)</td>
<td>75.4±12.3</td>
<td>73.7±10.4</td>
<td>1.6±8.2</td>
<td>0.68 to 2.54</td>
<td>.005</td>
<td>−14.4 to 17.7</td>
</tr>
</tbody>
</table>

Values are mean±SD.

†Test of systematic changes.

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HR averaged 1.7 bpm higher in the office compared with at home (SD 8.6), and this difference, although rather small, was statistically significant (Table 2). This office-home difference in HR was stable among the three different BP target groups and in relation to the various demographic variables at randomization (data not shown). For the three diastolic BP target groups, the differences in HR between the groups during office measurements were 1.7 bpm (≤80 versus ≥85, NS) and 0.5 bpm (≤85 versus ≥90, NS). These differences were largely comparable to the differences between the groups during home measurements: 1.8 bpm (≤80 versus ≥85, P<.05) and 0.3 bpm (≤85 versus ≥90, NS), respectively.

For all patients there were statistically significant correlations (P<.0001 for all) between office and home measurements for diastolic BP (r=.35), systolic BP (r=.45), and for HR (r=.73). These correlations are shown in Fig 1, whereas the plots of the differences between office-home against the means of office and home for each patient are shown in Fig 2. The coefficients of regression for systolic BP (P<.05) and for HR (P<.001) between differences in office-home and mean (office-home) are significant. The variance explained is 0.4% for systolic BP and 4% for HR.

There was a significant (P<.0001) mean±SD decrease of 1.2±5.5 mm Hg in diastolic BP from morning (83.1±8.4 mm Hg) to afternoon (81.9±8.2 mm Hg). Corresponding values for systolic BP were 137.5±14.6 and 136.6±15.0 mm Hg (P<.001) and for HR 73.9±10.9 and 76.2±11.1 bpm (P<.0001). There were significant correlations (P<.0001 for all) between average measurements in the morning and in the afternoon for diastolic BP (r=.78), systolic BP (r=.84), and HR (r=.87) (Fig 3). Fig 4 shows the plots of the differences between afternoon-morning against the means of afternoon and morning for each patient. There are not any significant coefficients of regression for BPs or HR between differences in afternoon-morning and mean (afternoon-morning).

The numbers of patients who had home and office BPs within ±10 mm Hg, home BP ≥10 mm Hg higher than office BP, and office BP >10 mm Hg higher than home BP were 700, 98, and 116 for diastolic BP and 477, 207, and 231 for systolic BP, respectively.

**Discussion**

The present substudy to the HOT trial of 926 patients in nine countries aimed to compare home BP with office BP in a representative subsample after the titration of treatment and to clarify whether the separation in main BP target groups (≤80, ≥85, or ≥90 mm Hg) observed in the office could be expanded into the out-of-office setting. Small office-home differences in measured diastolic and systolic BPs were not significant. However, HR was significantly higher in the office compared with at home. For the three BP target groups, the differences between the groups during office BP measurements were 1.9 mm Hg (≤80 versus ≥85) and 1.2 mm Hg (≥85 versus ≥90) for diastolic BP and 2.6 and 2.1 mm Hg for systolic BP, respectively.

Some previous large-scale trials in mild-to-moderate hypertension have undoubtedly included substantial numbers of borderline and white coat hypertensive subjects with low risk. Our results show that the patients in the HOT Study have comparable treated (“target”) BPs in the doctor’s office and at home (r=.45), for diastolic BP in the office and at home (r=.35), and similarly for HR (r=.73).

![Figure 1. For all patients (n=914) these plots show significant correlations (P<.0001 for all) between systolic BP in the office and at home (r=.45), for diastolic BP in the office and at home (r=.35), and similarly for HR (r=.73).](http://hyper.ahajournals.org/DownloadedFromKjeldsen)
three BP target groups based on office readings prevails in the out-of-office setting, which increases the likelihood of detecting differences between the groups in cardiovascular events in the main HOT Study.

Ambulatory BPs over 24 hours may be somewhat lower than self-measured BP at home. The reason for this difference seems to be that the former technique includes nighttime BP, which is lower than daytime BP in most subjects. Awake ambulatory BP, however, compares rather well to self-assessed home BP in a large study, suggesting that the home BPs measured in the present study, although not directly compared, are representative for daytime BP.

Devices for home BP monitoring have been extensively tested. The National High Blood Pressure Education Program of the United States concluded that all three types of devices (mercury, aneroid, and electronic) are reasonably accurate for home use, provided they are properly calibrated and individuals using them appropriately trained. However, Evans et al, who also tested a range of equipment types (mercury, aneroid, and electronic), found that 11 (48%) of the 23 devices they tested were inconsistent with duplicates of the same devices and failed the standards for automated devices of the Association for the Advancement of Medical Instrumentation. Fewer than 25% of the devices were considered suitable for home use on the basis of accuracy, reliability, and ease of use. Thus, care must be taken in the choice of device, and training is required for all devices.

Figure 2. For all patients (n=914) these plots show the differences between office-home against the means of office and home for each patient. The standard deviations are drawn in.

Figure 3. For all patients (n=926) these plots show significant correlations (P<.0001 for all) between average measurements in the morning and in the afternoon for systolic BP (r=.84), diastolic BP (r=.78), and HR (r=.87).
that patients had any white coat effect or alerting reaction with at home, there was no clear evidence in the HOT Study of strong correlations between morning and afternoon registrations taken by the patients themselves. The accuracy of the home measurements could be noted by (1) the low SDs compared with the office readings, and (2) the consistency of the rather small variation of the home findings and within-individual SDs for home BP, (3) the rather accuracy in the office readings. To achieve acceptable readings, patients went through the measurement procedure repeatedly at the clinic visits before taking home measurements. The accuracy of the home measurements could be noted by (1) the very low within-individual SDs for home BP, (2) the consistency of the main results with small variation of the home findings and SDs compared with the office readings, and (3) the rather strong correlations between morning and afternoon registrations taken by the patients themselves.

Despite the higher HR measured in the office compared with at home, there was no clear evidence in the HOT Study that the patients had any white coat effect or alerting reaction on BP when in the treated state. It may be possible that with treatment of more established hypertension, as in the HOT Study, the difference between home and office measurements decreases compared with other groups of hypertensive patients. Thus, it would be expected that the proportion of patients with white coat hypertension and even white coat effect would be low. There is also a stability factor of several months or years of evaluation that may have excluded borderline or white coat individuals, and there may be a habituation to office BP measurements with time. However, it may also be speculated whether the use of a semiautomatic device with digital readout by itself dampens the white coat effect and makes it insignificant. If this is the case, this technique for measurement of BP could preferentially be used in the screening for subjects in future large-scale clinical hypertension trials.

In conclusion, office and home BPs are comparable in treated hypertensive subjects in the HOT Study, and the separation into target groups based on office readings prevails in the out-of-office setting.

Appendix


Acknowledgments

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