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Antihypertensive drug effect according to the pretreatment self-measured home blood pressure level: the HOMED-BP study

Short title: Wilder Law on Home Blood Pressure

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on behalf of

Hypertension Objective Treatment Based on Measurement by Electrical Devices of Blood Pressure (HOMED-BP) investigators

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Abstract

Objectives—To clarify whether antihypertensive drug effect would be proportional to the baseline pretreatment self-measured home blood pressure (HBP) level in accordance with the law of initial value (Wilder law).

Design—Post-hoc analysis of a multicentre clinical trial.

Setting—Outpatients in nationwide Japan with mild-to-moderate essential hypertension.

Participants—Among 3,518 randomised participants, 2,423 who self-measured HBP during a pretreatment drug-free period, 10–28 days after starting fixed-dose antihypertensive monotherapy, and for mean 7.0 years' follow-up were eligible.

Main outcome measures— We analysed individual HBP readings during pretreatment and monotherapy.

Results—HBP during pretreatment and monotherapy kept the almost identical level within each period, regardless of the pretreatment HBP value. By the monotherapy, the reduction in the HBP increased by 2.2 mmHg (95% confidence interval [CI], 1.8–2.5) per 10-mmHg pretreatment HBP increase, up to 11.0 mmHg (CI, 9.9–12.0) among those with a HBP ≥165 mmHg during pretreatment. Among the 1,005 patients with a low dose monotherapy (defined daily doses=0.5 units), the reduction peaked at 8.9–9.1 mmHg in the pretreatment HBP 155–164 and ≥165 mmHg groups (*P*=0.88).

Conclusions— Following Wilder law, the HBP reduction by the fixed-dose monotherapy was proportional to the pretreatment HBP, but without any regression to the mean phenomenon. With low-dose antihypertensive drugs, however, the HBP reduction peaked in the patients with a high pretreatment HBP, indicating the need for patients with a high HBP to receive a sufficient amount of antihypertensive drug medication at the initial treatment.

Trial registration—UMIN Clinical Trial Registry (http://www.umin.ac.jp/ctr), Unique identifier: C000000137.

Keywords: ■ blood pressure reduction ■ antihypertensive treatment ■ home blood pressure ■ self-measurement ■ Wilder law ■ regression to the mean

Article summary

Strengths and limitations of this study

- In the present study, we enrolled 2,423 patients with mild-to-moderate essential hypertension who measured their daily self-measurement of blood pressure at home during the pretreatment period, after antihypertensive monotherapy, and for mean 7.0 years' follow-up.
- This is the first study to demonstrate that the reduction in the home blood pressure by antihypertensive drug monotherapy was proportional to the home blood pressure during pretreatment drug-free period, in accordance with the law of initial value (Wilder law).
- The findings also supported reports that self-measured home blood pressure was minimally affected by regression to the mean phenomenon.
- We were unable to assess the placebo effect, which is also a major influencing factor in the administration of antihypertensive medication, because all patients received antihypertensive medication.

Introduction

Hypertension is a foremost risk factor for cardiovascular disease.[1 2] A meta-analysis showed that a 10/5 mmHg reduction in conventional office systolic/diastolic blood pressure reduces the stroke risk by ≈40% and the coronary artery disease risk by ≈20%.[3] However, office blood pressure has major limitations including being affected by the white-coat effect, i.e. a warning response wherein the office blood pressure unexpectedly rises in an examination room in front of medical staff.[4] In contrast, self-measured home blood pressure assessed using automated devices in a non-medical setting can obtain a plurality of readings over a long period under relatively uniform conditions, resulting in highly reproducible values without observer bias when patients apply a standardised protocol.[2 4 5] Home monitoring is free from white-coat effect, and is suitable for the evaluation of drug efficacy.[2 5 6] Given its greater prognostic ability for cardiovascular complications than office blood pressure,[1 2 7-9] home blood pressure-based antihypertensive treatment is highly recommended.[2 9]

Recent studies[10 11] reported that the higher the pretreatment blood pressure, the greater the reduction in the blood pressure by antihypertensive drug treatment, according to the law of initial value (Wilder law[12]). However, the reduction in the 24-h ambulatory blood pressure corresponding to the pretreatment office blood pressure was relatively small.[10] Such disproportionality can be attributed to changes in the white-coat effect, which depends on pretreatment office blood pressure.[10] Although ambulatory and home blood pressures are both categorised as out-of-office blood pressure, the characteristics and usefulness of home blood pressure differ from those of ambulatory recordings,[1 2 9] and no report has described the difference in the antihypertensive drug effect according to the pretreatment blood pressure level.

We therefore investigated the association between the pretreatment home and office blood pressures levels and home blood pressure reduction by antihypertensive

monotherapy as well as long-term blood pressure changes in patients participating in a home blood pressure-based clinical trial.

Methods

Study design

This is a post-hoc analysis of the Hypertension Objective Treatment based on Measurement by Electrical Device of Blood Pressure (HOMED-BP) study[13-15] which was a multicentre clinical trial with a prospective, randomised, open-label, blinded end point, evaluation (PROBE)[16] design. The HOMED-BP protocol complies with the Declaration of Helsinki for the investigation of human subjects and is registered with the UMIN Clinical Trial Registry, number C000000137 (http://www.umin.ac.jp/ctr). The institutional review board of the Teikyo University School of Medicine approved the study (17-044-2), and all study participants gave their written informed consent.

We included patients with mild-to-moderate essential hypertension based on home blood pressure (135–179/85–119 mmHg) with a minimum age of 40 years old. The exclusion criteria were patients with severe hypertension (home blood pressure ≥180/≥120 mmHg or office blood pressure ≥220/≥125 mmHg), met the systolic criteria for the home blood pressure (≥135 mmHg) but diastolic home blood pressure was <65 mmHg, met the diastolic home blood pressure criteria (≥85 mmHg) but systolic home blood pressure was <110 mmHg, or those with contraindications to either calcium channel blockers, angiotensin converting enzyme inhibitors, or angiotensin receptor blockers.

Selection of patients

After the 1st visit on initial registration, the 5,211 enrolled patients were followed-up for at least two weeks without any antihypertensive drugs. At the 2nd visit, 3,518 (67.5%) eligible patients were randomised in a 2 × 3 design, to monotherapy with the first-line drug (calcium channel blockers, angiotensin-converting enzyme inhibitors, or angiotensin

receptor blockers) and target home blood pressure-based antihypertensive levels (usual control, ranging from 125 to 134 mmHg systolic and 80 to 84 mmHg diastolic; tight control, <125 mmHg systolic and <80 mmHg diastolic). Reasons for excluding the other 1,693 patients before the randomisation were described elsewhere[14] and listed in Supplemental Figure 1.

In the present analysis, we excluded 1,095 of the randomised 3,518 patients because they had obtained <3 home readings at baseline (pretreatment period; *n*=102) or during fixed-dose monotherapy with the first-line drug (*n*=592), they had isolated diastolic hypertension (home blood pressure ≤135/≥85 mmHg; *n*=143), they did not actually receive an antihypertensive drug or had been treated with ≥2 drug classes simultaneously (*n*=37), or we were unable to assess the blood pressure or treatment status during follow-up (*n*=221). A total of 2,423 participants were analysed statistically (Supplemental Figure 1). Based on our previous report indicating that the risks of cardiovascular outcomes were similar in the randomised groups (tight versus usual blood pressure control, and a comparison of drug classes to initiate treatment) because of the small blood pressure difference between the groups,[14] we combined all 2,423 participants in the present analysis.

Measurements of blood pressure

Patients enrolled in HOMED-BP received spoken and written instructions on blood pressure self-measurement and the utilisation of a validated cuff-oscillometric OMRON HEM 747IC-N (Omron Healthcare Co., Ltd., Kyoto, Japan),[17] in which all measured data, including the measurement time, are automatically recorded. The standard upper-arm cuff which covered 22–32 cm of patients' arm circumference was attached to the device. The importance of using appropriate sized cuff was noted in the user's manual of the device, and we provided another cuff according to the request. Throughout the study period, patients were asked to self-measure their blood pressure at home once every

morning within one hour of awakening, after urination, before breakfast, before taking antihypertensive medication, and after two minutes' rest in a sitting position.

Office blood pressure was measured by doctors in the outpatient clinic using a validated cuff-oscillometric OMRON HEM-907 (Omron Healthcare Co., Ltd., Kyoto, Japan).[18] At each visit, the office blood pressure was measured twice consecutively in a sitting position after at least two minutes' rest.

The evaluation of the blood pressure

In this study, the baseline pretreatment home blood pressure was the average of the preceding blood pressure for five days before the 2nd visit on randomisation, and the blood pressure during the monotherapy was the average that for five days within 10–28 days after the initiation of the randomised first-line drugs (Figure 1).[19] We used this time window for home readings because (1) the home blood pressure used for determining eligibility and treatment adjustments at every visit in the HOMED-BP study was the average of the home readings available over 5 days immediately preceding the visit,[14] (2) the clinical investigators followed the patients at intervals of approximately 2 to 4 weeks in general practice and approximately 4 to 8 weeks at hospital outpatient clinics, and (3) the time interval needed to receive sufficient antihypertensive effects is reported to be approximately 7 to 23 days.[20] All these home blood pressure values evaluated in the present study were therefore captured before the 3rd visit when the drug titration might be performed. The home blood pressure at the end of follow-up (mean follow-up period, 7.0 years; interquartile range, 5.1–9.1 years) was defined as the average of the last available five days of home blood pressure values. The office blood pressure during pretreatment and follow-up were the averages of the two consecutive measurements at each visit. The reduction in the blood pressure was calculated as the change from the pretreatment blood pressure at baseline.

Definition of comorbidity and quantification of drugs

The body mass index was calculated as the body weight in kilograms divided by the height in meters squared. Diabetes mellitus was defined as a fasting plasma glucose level of ≥7.0 mmol/L (≥126 mg/dL), HbA1c of ≥6.5%, or treatment with oral antidiabetic drugs or insulin. Hypercholesterolemia was defined as a total serum cholesterol level of ≥5.69 mmol/L (≥220 mg/dL), a history of hypercholesterolemia, or taking lipid-lowering drugs.[14 19]

We used the World Health Organization's defined daily doses (DDD) to quantify the use of antihypertensive drugs[21]; DDD is the standard maintenance dose per day for a drug used for its main indication in adults.[21] The standard usage per day is defined as a DDD of 1 unit.

Statistical analyses

For database management and statistical analyses, we used the SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA). Statistical significance was set at $\alpha<0.05$ on two-sided tests. We focused on our analyses based on systolic blood pressure, as systolic pressure is the overriding risk factor in middle-aged and older people.[22]

Patients were divided into four groups (≤145, 145–154, 155–164, and ≥165 mmHg) according to the baseline pretreatment systolic home blood pressure, and the blood pressure reduction was compared among the groups. For office blood pressure assessments, patients were stratified into 10 mmHg groups according to the pretreatment systolic office blood pressure as in the report by Schmieder et al.[10] The chi-square test and analysis of variance (ANOVA) were used to compare the baseline characteristics between groups appropriately. Home blood pressures during the five pretreatment days as well as those during the five monotherapy days were compared by a repeated measure mixed linear model while taking missing values into account. A covariance analysis (ANCOVA) was used to compare each blood pressure reduction group, and the change in the blood pressure reduction accompanying the increase in the pretreatment

blood pressure was evaluated using a multiple regression model, both adjusted for sex, age, body mass index, current smoking and drinking, hypercholesterolemia, diabetes mellitus, and history of cardiovascular disease. The DDD during the initial antihypertensive monotherapy and at the end of follow-up were further used as the adjustment factor to compare the pressure reduction from pretreatment to the initial treatment and to the end of follow-up, respectively. For 40 patients without body mass index data, we interpolated the value based on the sex and age (continuous). The white-coat effect was defined as the office blood pressure minus the home blood pressure as a continuous variable (it can be negative value if home blood pressure was higher than office blood pressure), and changes in the white-coat effect were determined by subtracting the effect observed at the end of follow-up period from the effect captured during pretreatment.

Patient and public involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for recruitment, design, or implementation of the study. No patients were asked to advise on interpretation or writing up of results. There are no specific plans to disseminate the results of the research to study participants or the relevant patient community beyond the usual channels of publication.

Results

Patients' characteristics

Table 1 shows the baseline characteristics of 2,423 patients. The average age of all participants was 60.0 (standard deviation, 9.8) years, and the proportion of women was 51.0%. Age, body mass index, and office blood pressure were significantly and positively associated with baseline systolic blood pressure category. As shown in Table 2, the daily home blood pressures during pretreatment and during monotherapy were almost identical within each period ($P \geq 0.41$) except for in patients with a home blood pressure <145

mmHg at pretreatment days (*P*=0.032) and 145–154 mmHg during monotherapy period (*P*=0.035); even among those patients, the differences between adjacent days were not significant (*P*≥0.12). Relationship of the white-coat effect and office or home blood pressure levels during pretreatment period as a cross-sectional approach are shown in Supplemental Figure 2. The white-coat effect increased as the office blood pressure increase (7.5 mmHg [95% confidence limits, 7.3–7.8 mmHg] per 10-mmHg increment); whereas, the home blood pressure level was negatively related to the white-coat effect (-4.5 mmHg [95% confidence limits, -3.9 to -5.0 mmHg] per 10-mmHg home blood pressure increment).

Reduction in the home blood pressure by monotherapy according to the pretreatment blood pressure

During the initial fixed-dose monotherapy, the reduction in the systolic home blood pressure enhanced by 2.2 mmHg (95% confidence interval [CI], 1.8–2.5 mmHg) per 10-mmHg pretreatment home blood pressure increase. The reductions in each baseline pretreatment blood pressure group are shown in Figure 2. The slope of the home blood pressure reduction accompanying the increase in the pretreatment office blood pressure was shallower, and it increased by 0.6 mmHg (95% CI, 0.4–0.9 mmHg) per 10-mmHg pretreatment office blood pressure increase.

Stratification by DDD

Figure 3 demonstrates the results according to the DDD of the initial antihypertensive drugs. Among 1,005 patients who started monotherapy with antihypertensive drugs of 1 unit DDD, the pretreatment home blood pressure was linearly associated with the blood pressure reduction at the time of monotherapy; the enhancement of the home blood pressure reduction for each increase in the pretreatment home blood pressure category was 2.6 mmHg (95% CI, 1.9–3.2 mmHg). However, among those receiving 0.5 units DDD (*n*=1,005; occasionally the same number), significant enhancement in home blood pressure reductions was observed up to the 155–164 mmHg group (per 1 group increase,

2.1 mmHg; 95% CI, 1.2–2.9 mmHg), where it peaked; the reductions in the home blood pressure among patients with a pretreatment home blood pressure between 155–164 mmHg and that of ≥165 mmHg were 8.9 and 9.1 mmHg, respectively (*P*=0.88). The results were confirmed when we divided whole 2,423 patients according to DDD <1 or ≥1 unit, as shown in Supplemental Figure 3.

Reduction in the follow-up blood pressure according to the pretreatment blood pressure

According to the previous report based on ambulatory blood pressure monitoring,[10] we compared the home and office blood pressure reductions at the end of follow-up according to the baseline pretreatment office blood pressure. After the 7.0 years' follow-up with a mean DDD of 1.8 units (median 1.5; interquartile range, 1.0–2.5), the reduction in the office blood pressure was linearly associated with the office blood pressure during pretreatment (reduction in the home pressure from the office blood pressure category <140 to ≥180 mmHg: 7.5 to 50.7 mmHg; Figure 4). Furthermore, similar to the previous report based on ambulatory monitoring[10], an association between the pretreatment office blood pressure and the home blood pressure reduction was weakly observed (reduction in the home pressure: 18.6 to 30.7 mmHg). Finally, changes in the white-coat effect during the follow-up period significantly increased as the pretreatment office blood pressure increased (Supplemental Figure 4; category increment *P*<0.0001).

Discussion

The antihypertensive drug effect depends on the pretreatment blood pressure. In line with Wilder law,[12] the home blood pressure reduction after the initial drug treatment was proportional to the baseline pretreatment home blood pressure in the present study. The current findings emphasize the need to assess the home blood pressure before treatment when evaluating and initiating antihypertensive drug therapy.

Wilder indicated that the direction of the body function response depends to a large extent on the initial level of that function, regardless of the agent.[12] Wilder law predicts that in the most severe hypertensive patients, the decrease in blood pressure will be greater with the same medication than in those with less-severe hypertension. The statistical phenomenon of regression to the mean (regression toward the mean) is another major confounding factor hampering the accurate assessment of the effect of antihypertensive agents.[23] However, as shown in Table 2, there were no regression trends in the home blood pressure values from the first to the final measurement during the pretreatment or monotherapy periods, regardless of the pretreatment home blood pressure level. This finding indicates the strength of the self-measurement of home blood pressure, as home measurement is associated with minimal (if any during an initial few days after the measurement begins[24]) regression to the mean.[5 6 25] It is therefore likely that home blood pressure measurement is useful for estimating the efficacy of antihypertensive drugs.

Schmieder et al[10] reported that the higher the baseline office blood pressure, the greater the blood pressure reduction after 1 year of the treatment enhancement, and this was more obvious in the office blood pressure than in the ambulatory blood pressure.[10] A recent meta-analysis also demonstrated that overall treatment-induced reduction was greater for office blood pressure than for 24-h ambulatory blood pressure.[11] In the present study, the reduction in the office blood pressure at the end of follow-up, after a mean 7.0 years was also greater than that in the self-measured home blood pressure (Figure 4). Schmieder et al[10] attributed this discrepancy to the changes in the white-coat effect, i.e. the higher the baseline office blood pressure, the greater the decrease in the white-coat effect due to antihypertensive treatment. This assumption was also supported by the findings of the present study (Supplemental Figure 4); however, the white-coat effect may not be a main driver for the discrepancy because the home blood pressure reduction also followed Wilder law despite the negative correlation between home blood

pressure level and white-coat effect during the pretreatment period. Nevertheless, the out-of-office blood pressure is theoretically free from the white-coat effect,[4] and the reduction in the office blood pressure by antihypertensive treatment partially includes a reduction in the white-coat effect as well. We should therefore follow-up out-of-office-measured blood pressure carefully, since patients with a higher blood pressure tend to show a greater antihypertensive effect when their values are based on office-based measurements, while their out-of-office blood pressure reduction might be insufficient, resulting in a persistent high risk for cardiovascular complications.

Among 1,005 patients who were taking low-dose antihypertensive drugs, namely at a dose of DDD 0.5 units or lower, home blood pressure reduction during the monotherapy in the group with a pretreatment home blood pressure of ≥165 mmHg was almost identical to the reduction in the group with a pretreatment home blood pressure of 155–164 mmHg. A high home blood pressure is associated with a high cardiovascular disease risk over the long term, both before and during antihypertensive therapy.[14 15] Inadequate control of office blood pressure with antihypertensive drug therapy remains a critical issue in Japan[26] as well as in Europe[27] and the United States.[28]. Previous studies[29 30] have shown the importance of rapid blood pressure control, and the current findings suggest that a sufficient dosage of antihypertensive drug from the beginning of treatment is necessary, particularly among those with a high home blood pressure before starting treatment.

Although the need to strengthen antihypertensive drug treatment has been gradually accepted,[1 2 9] various factors associate with medical providers, patients, and healthcare systems have contributed to clinical inertia (non-compliant).[31 32] Clinical inertia is associated with inadequate blood pressure control, resulting in the increased risk of adverse cardiovascular effects. Medical services should help overcome clinical inertia as well as other hindrances in order to improve the blood pressure control of patients. Self-measurement of home blood pressure would ameliorate the status quo because it leads

an improved awareness among patients with high blood pressure, helping them adhere to antihypertensive lifestyle modification and drug treatment.[5]

Our current study must be interpreted within the context of several potential limitations. First, because the patients in HOMED-BP received home blood pressure-guided therapy,[14] their treatment was adjusted according to the self-measured home blood pressure, and the office blood pressure was used as complimentary information. Second, we excluded 1,095 (31.1%) from the randomised HOMED-BP patients in which their status could affect the findings of the antihypertensive drug effect. Third, we were unable to assess the placebo effect in the present study because all patients received antihypertensive medication. The placebo effect is a major influencing factor, in addition to Wilder law and the regression to the mean phenomenon, in the administration of antihypertensive medication.[23] Fourth, because we do not have readings of office blood pressure 3 or more at each visit, the regression to the mean on office blood pressure cannot be assessed nor compared with that on home blood pressure. Finally, although our results are representative of middle- to old-aged Japanese patients, they might not be applicable to other settings or ethnic groups with different distributions of risk factors.

In conclusion, the reduction in the home blood pressure by antihypertensive drug monotherapy was proportional to the home blood pressure during pretreatment drug-free period, in accordance with Wilder law.[12] However, the home blood pressure reduction peaked in the patients with a high pretreatment home blood pressure, ≥155 mmHg, when their treatment were initiated with low-dose antihypertensive drugs. Patients with more than this home blood pressure threshold might be categorized as resistant hypertension because Wilder law was no longer applied under the insufficient therapy, although we cannot say too much based on this findings derived from the HOMED-BP patients with mild-to-moderate hypertension. Whether Wilder law can be similarly applicable to high risk patients with severe hypertension remains to be proved. Meantime, home blood pressure measurement was minimally affected by regression to the mean, suggesting the

usefulness of home blood pressure measurement for estimating the efficacy of antihypertensive drugs. Patients with a high home blood pressure during pretreatment should receive a sufficient amount of antihypertensive medication from the initial treatment.

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Contributors

KA, YI, and TO conceived and designed the study, AH, KA, MK, and YI acquired the data, and KA and HS carried out statistical analysis. HS drafted the original manuscript with KA and AH. SM, YI, and TO provided intellectual input, and all authors critically revised the manuscript and approved the final manuscript. KA is the guarantor.

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Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; KA, YI, and TO has received research grants from Omron Healthcare. No other relationships or activities that could appear to have influenced the submitted work.

Ethical approval

Fully disclosed in the Study design section.

Data sharing

No additional data are available.

Statements

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Dissemination declaration

Dissemination the results to study participants is not possible.

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Figure legends

Figure 1: Time course of blood pressure measurement during the study period.

Home blood pressures were the average of 5 days before randomisation without any antihypertensive treatment, after 10 to 28 days of monotherapy initiation, and at the end of follow-up period. Patients with 3 to 4 days of home blood pressure data in each interval were also included. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker.

Figure 2. Reduction in the systolic home blood pressure during monotherapy categorized by pretreatment home (left panel) and office (right panel) blood pressure.

Error bars indicate 95% confidence interval. Data were adjusted for sex, age, body mass index, diabetes mellitus, current smoking and drinking, hypercholesterolemia, history of cardiovascular disease, and defined daily dose during monotherapy.

Figure 3. Reduction in the systolic home blood pressure during monotherapy categorized by pretreatment home blood pressure, stratified by defined daily dose (0.5 unit, left panel; 1 unit, right panel).

Error bars indicate 95% confidence interval. Data were adjusted for sex, age, body mass index, diabetes mellitus, current smoking and drinking, hypercholesterolemia, and history of cardiovascular disease.

Figure 4. Reduction in the follow-up systolic home blood pressure categorized by pretreatment office blood pressure.

Error bars indicate 95% confidence interval. Adjusted for sex, age, body mass index, diabetes mellitus, current smoking and drinking, hypercholesterolemia, history of cardiovascular disease, and defined daily dose at the end of follow-up period (mean, 7.0 years).

Table 1: Baseline characteristics of patients.

Characteristics	Total	Systolic home blood pressure at baseline, mmHg				
		<145	145–154	155–164	≥165	*P*
No. of participants	2423	763	699	544	417	
Women, n	1235 (51.0)	416 (54.5)	342 (48.9)*	275 (50.6)	202 (48.4)	0.11
Age, years	60.0 (9.8)	59.3 (10.0)	59.3 (9.7)	61.0 (9.8)†	61.3 (9.5)	0.0003
Body mass index, kg/m²	24.4 (3.3)	24.2 (3.5)	24.2 (3.2)	24.6 (3.4)	24.8 (3.2)	0.0017
Smoking, n	501 (20.7)	142 (18.6)	138 (19.7)	112 (20.6)	109 (26.1)*	0.019
Drinking, n	1172 (48.4)	347 (45.5)	344 (49.2)	270 (49.6)	211 (50.6)	0.27
Diabetes mellitus, n	378 (15.6)	122 (16.0)	101 (14.4)	85 (15.6)	70 (16.8)	0.74
Hypercholesterolemia, n	1261 (52.0)	399 (52.3)	372 (53.2)	287 (52.8)	203 (48.7)	0.49
Previous cardiovascular diseases, n	66 (2.7)	25 (3.3)	17 (2.4)	17 (3.1)	7 (1.7)	0.37
Home blood pressure						
Systolic, mmHg	152.5 (11.6)	139.8 (3.0)	149.6 (2.9)§	159.4 (2.8)§	171.3 (4.3)§	<0.0001
Diastolic, mmHg	89.8 (10.3)	84.4 (8.4)	89.8 (8.9)§	92.6 (10.0)§	95.9 (10.9)§	<0.0001
Office blood pressure						
Systolic, mmHg	154.7 (17.4)	147.7 (15.5)	153.7 (16.5)§	157.8 (16.5)§	165.4 (17.1)§	<0.0001
Diastolic, mmHg	90.1 (12.2)	87.1 (11.2)	90.4 (11.8)§	91.1 (12.3)	94.0 (13.1)‡	<0.0001

Values are expressed as the arithmetic mean (standard deviation) or number (%). *P* values are calculated by an analysis of variance or the chi-squared test among the four systolic home blood pressure groups at baseline during pretreatment. For missing values of body mass index (*n*=40), single imputation with regression on sex and age was conducted.
Significance of differences from the left adjacent column: **P*<0.05, †*P*<0.01, ‡*P*<0.001, and §*P*<0.0001.

Table 2: Home systolic blood pressure values according to the measurement days.

Baseline blood pressure category	Number of patients	Home blood pressure measurement days (times)					
		First	Second	Third	Forth	Fifth	*P*
Pretreatment, mmHg							
All	2423	152.5 (14.7)	152.5 (14.8)	152.2 (14.9)	152.4 (14.6)	152.6 (14.9)	0.48
<145	763	140.3 (9.1)	139.6 (8.4)	139.1 (8.8)	139.7 (8.2)	140.4 (9.6)	0.032
145–154	699	149.6 (9.9)	150.0 (9.4)	149.5 (9.7)	149.5 (9.2)	149.5 (9.5)	0.85
155–164	544	159.3 (10.3)	158.7 (10.3)	159.5 (9.6)	159.8 (9.7)	159.8 (10.5)	0.41
≥165	417	170.9 (11.3)	172.0 (10.3)	171.1 (10.4)	171.0 (11.2)	171.4 (11.5)	0.66
Monotherapy, mmHg							
All	2423	145.5 (17.0)	145.2 (16.9)	145.4 (16.5)	145.4 (16.5)	144.7 (16.6)	0.58
<145	763	135.3 (13.2)	135.1 (13.1)	135.5 (13.4)	135.8 (13.2)	135.1 (13.1)	0.56
145–154	699	143.8 (13.8)	143.1 (13.3)	143.3 (13.0)	142.9 (13.3)	141.9 (12.9)	0.035
155–164	544	150.2 (15.3)	150.5 (15.4)	150.5 (14.6)	151.2 (14.4)	150.5 (14.7)	0.67
≥165	417	161.1 (16.5)	160.0 (17.0)	160.3 (15.4)	160.1 (16.1)	160.5 (15.9)	0.65

Values are expressed as the arithmetic mean (standard deviation). The numbers of patients with missing blood pressure data on the fourth and fifth days were 38 and 84 at pretreatment and 87 and 286 during monotherapy, respectively, while *P* values are calculated by a repeated measure mixed linear model to take missing values into account and represent the differences among the five systolic home blood pressure values according to the measurement day at baseline during pretreatment.
Differences between the adjacent days were not significant during pretreatment ($P \geq 0.12$) or monotherapy ($P \geq 0.14$).

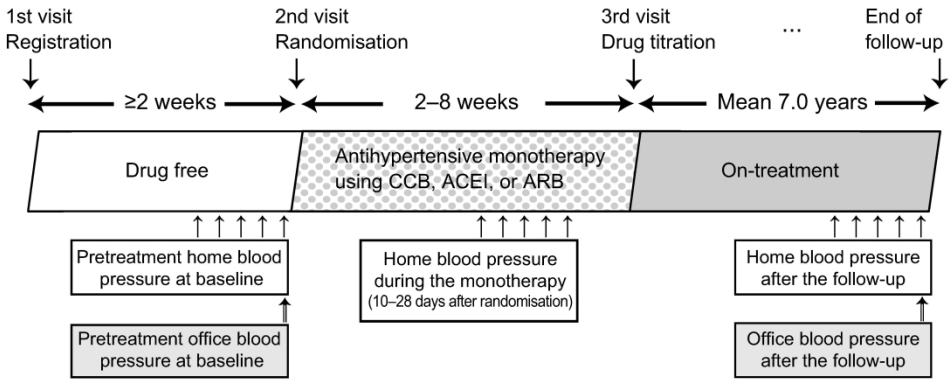

Figure 1: Time course of blood pressure measurement during the study period.
Home blood pressures were the average of 5 days before randomisation without any antihypertensive treatment, after 10 to 28 days of monotherapy initiation, and at the end of follow-up period. Patients with 3 to 4 days of home blood pressure data in each interval were also included. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker.

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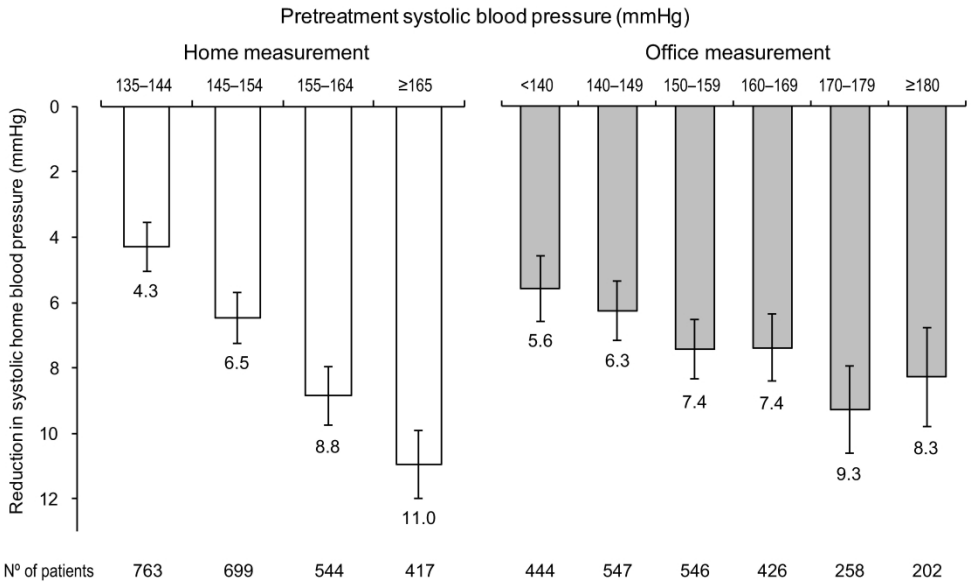

Figure 2. Reduction in the systolic home blood pressure during monotherapy categorized by pretreatment home (left panel) and office (right panel) blood pressure.
Error bars indicate 95% confidence interval. Data were adjusted for sex, age, body mass index, diabetes mellitus, current smoking and drinking, hypercholesterolemia, history of cardiovascular disease, and defined daily dose during monotherapy.

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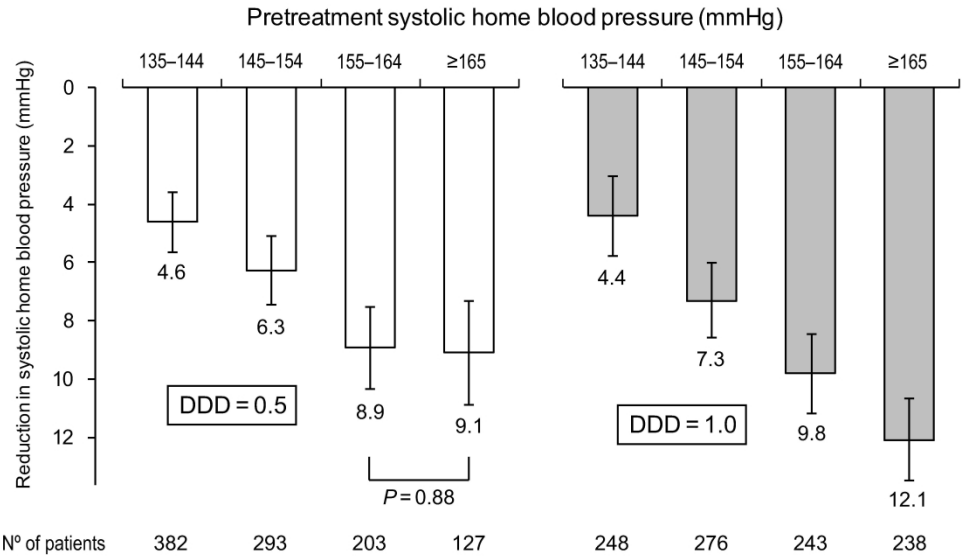

Figure 3. Reduction in the systolic home blood pressure during monotherapy categorized by pretreatment home blood pressure, stratified by defined daily dose (0.5 unit, left panel; 1 unit, right panel). Error bars indicate 95% confidence interval. Data were adjusted for sex, age, body mass index, diabetes mellitus, current smoking and drinking, hypercholesterolemia, and history of cardiovascular disease.

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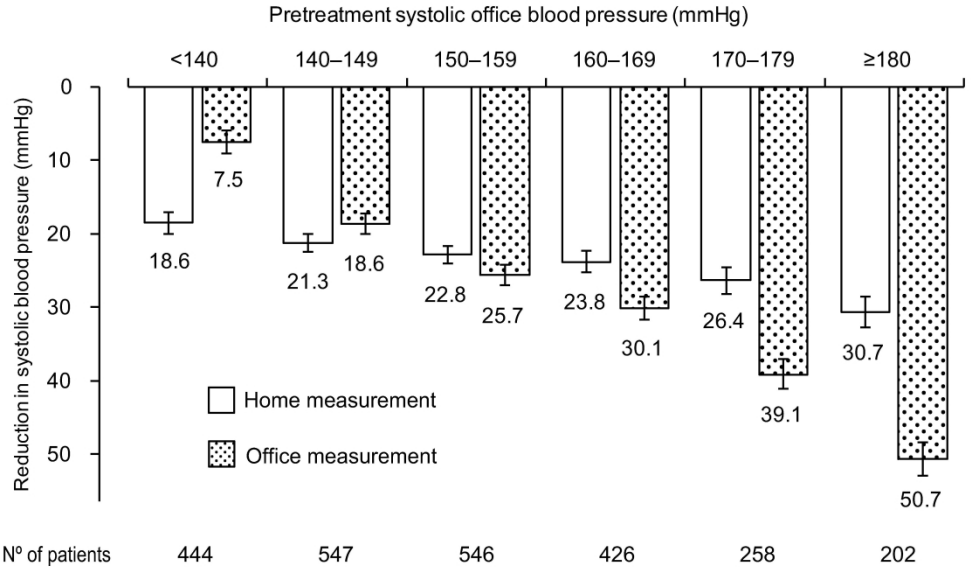

Figure 4. Reduction in the follow-up systolic home blood pressure categorized by pretreatment office blood pressure.
Error bars indicate 95% confidence interval. Adjusted for sex, age, body mass index, diabetes mellitus, current smoking and drinking, hypercholesterolemia, history of cardiovascular disease, and defined daily dose at the end of follow-up period (mean, 7.0 years).

196x115mm (600 x 600 DPI)

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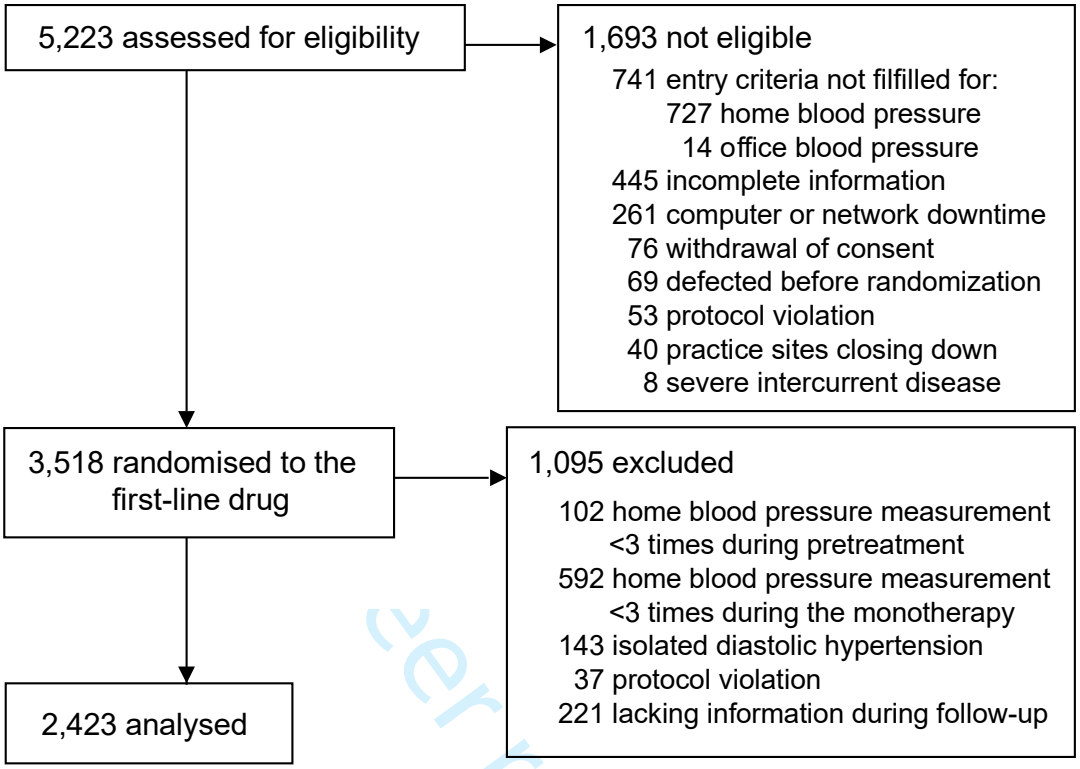
SUPPLEMENTARY INFORMATION

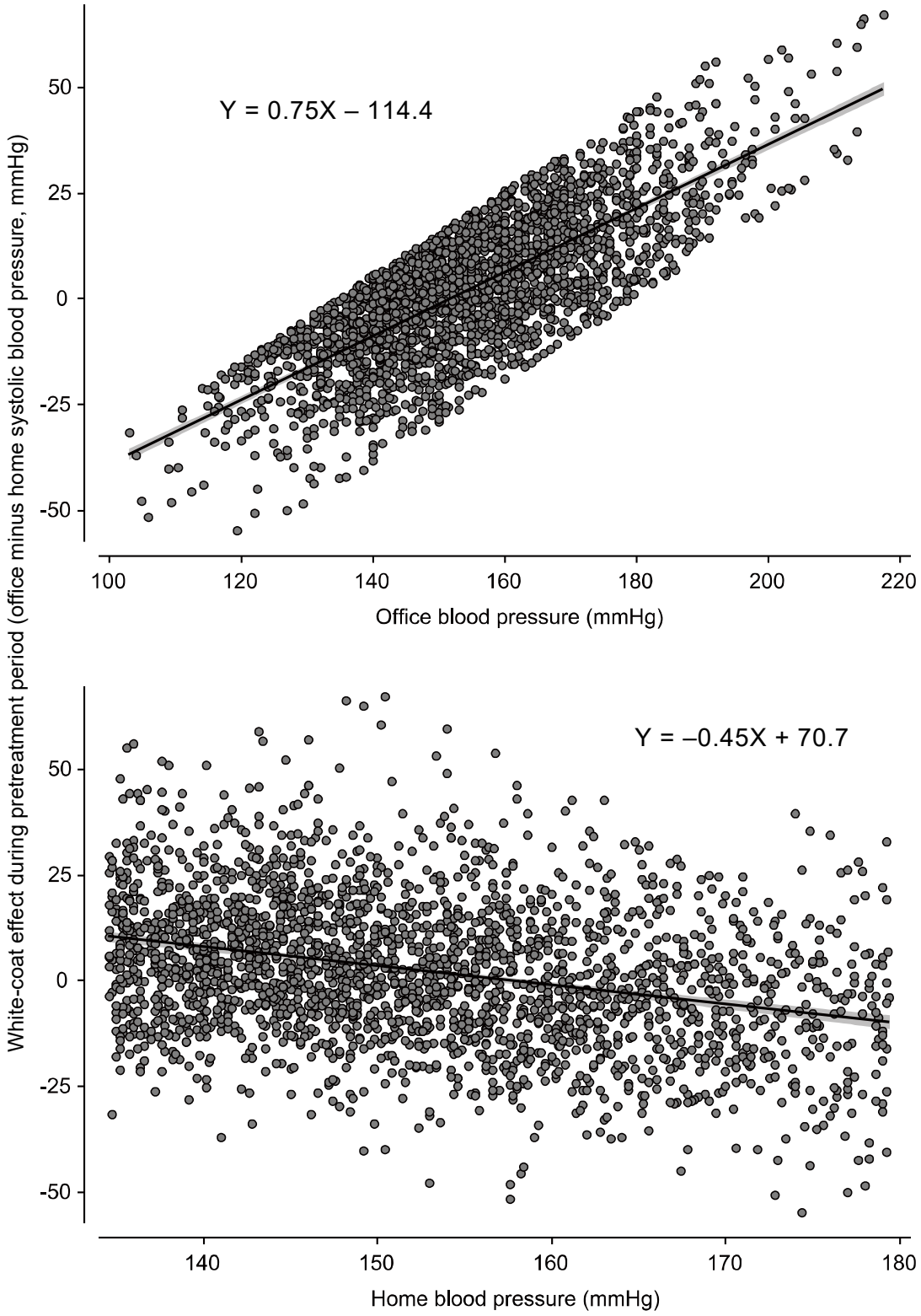
Antihypertensive drug effect according to the pretreatment self-measured home blood pressure: the HOMED-BP study

Short title: Wilder Law on Home Blood Pressure

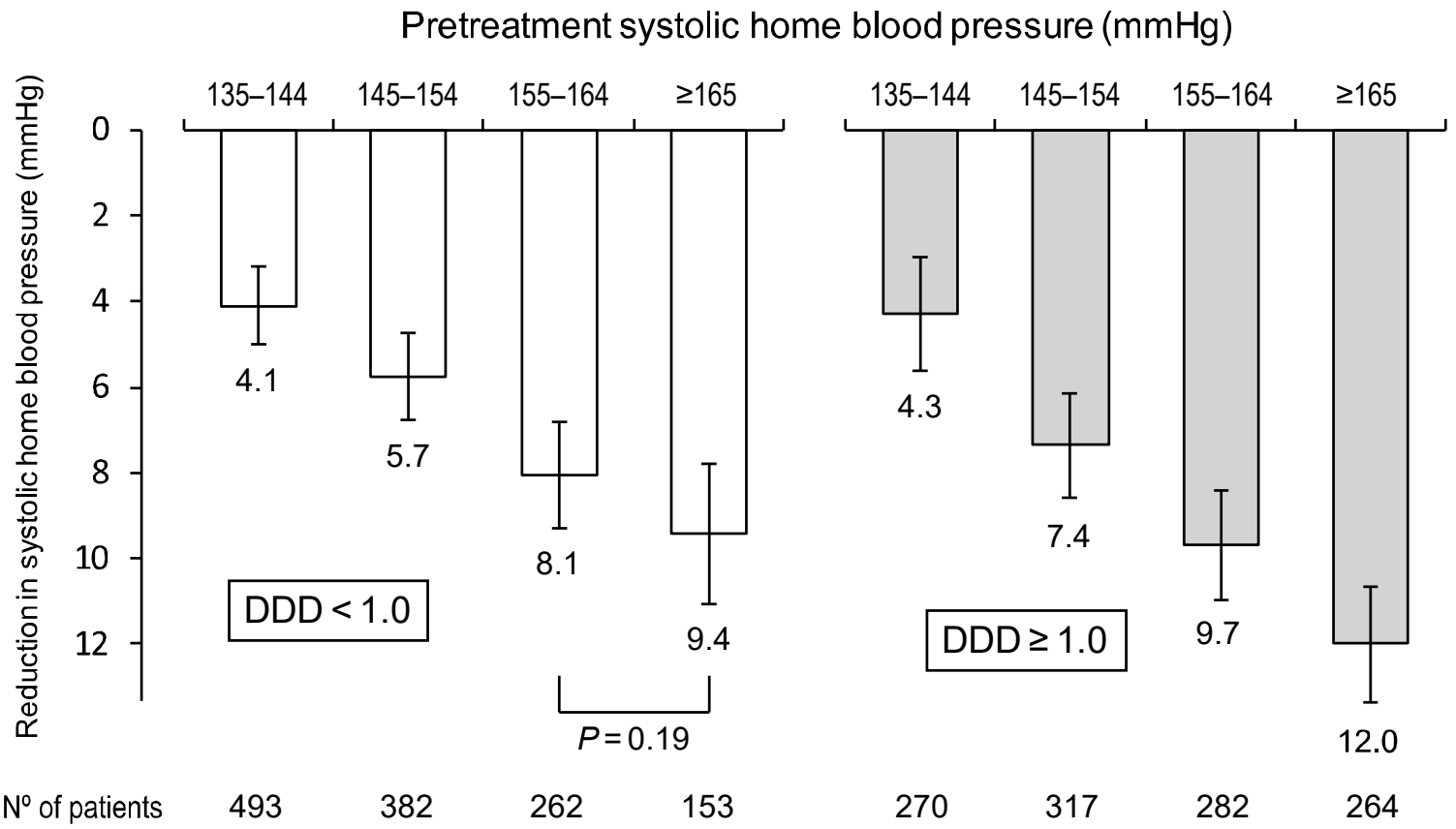
Hikari Sano, Azusa Hara, Kei Asayama, Seiko Miyazaki,
Masahiro Kikuya, Yutaka Imai, Takayoshi Ohkubo,
on behalf of
Hypertension Objective Treatment Based on Measurement
by Electrical Devices of Blood Pressure (HOMED-BP) investigators



Supplemental Figure 1: Flowchart of the study.

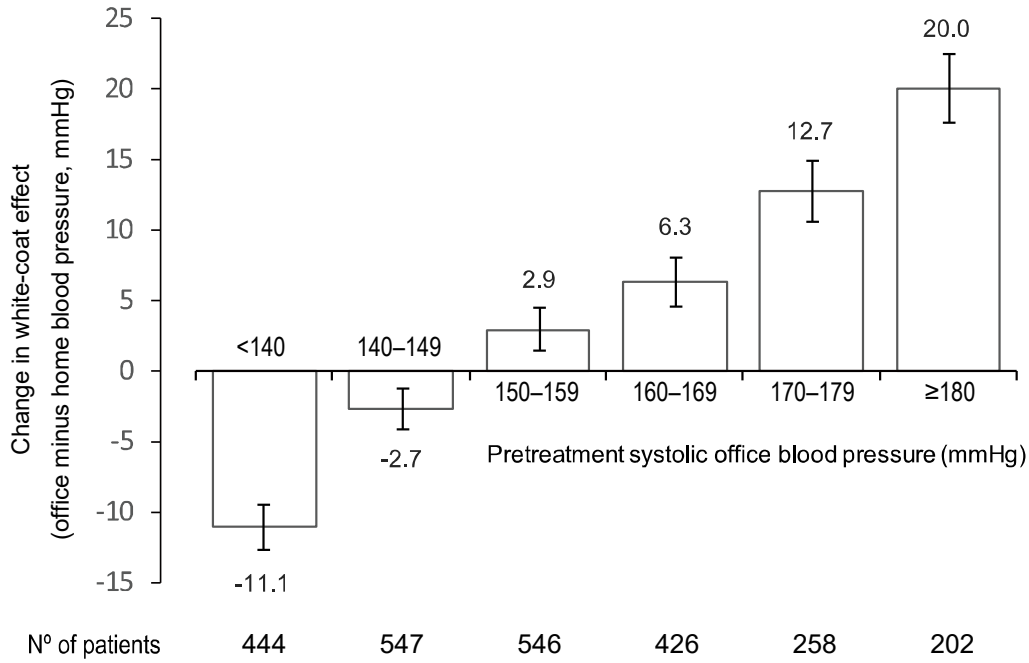


Supplemental Figure 2: Relationship between the white-coat effect and office systolic blood pressure (A) as well as home blood pressure (B) during pretreatment period.
The white-coat effect was defined as the office blood pressure minus the home blood pressure as a continuous variable. Regression line with 95% confidence limits were overlay on each scatter plot. Because systolic home blood pressure ranged 135–179 mmHg in this population, plots in panel A demonstrate as a band-like distribution which rises to the right.



Supplemental Figure 3: Reduction in the systolic home blood pressure during monotherapy categorized by pretreatment home blood pressure and stratified by defined daily dose (<1 unit, left panel; ≥1 unit, right panel).

Error bars indicate 95% confidence interval. Data were adjusted for sex, age, body mass index, diabetes mellitus, current smoking and drinking, hypercholesterolemia, history of cardiovascular disease, and defined daily dose during monotherapy.



Supplemental Figure 4: Changes in the white-coat effect during follow-up categorized by the pretreatment office blood pressure.

Error bars indicate 95% confidence interval. The white-coat effect was defined as the office blood pressure minus the home blood pressure, and changes in the white-coat effect were determined by subtracting the effect observed at the end of follow-up period from the effect during pretreatment.

Appendix

Hypertension Objective Treatment Based on Measurement by Electrical Devices of Blood Pressure (HOMED-BP) investigators:

Coordination and management

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Antihypertensive drug effects according to the pretreatment self-measured home blood pressure: the HOMED-BP study

Short title: Wilder's Law on Home Blood Pressure

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on behalf of
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Abstract

Objectives: To clarify whether or not the antihypertensive drug effect is proportional to the baseline pretreatment self-measured home blood pressure (HBP) in accordance with the law of initial value (Wilder's law).

Design: A Post-hoc analysis of a multicentre clinical trial.

Setting: Outpatients across Japan with mild-to-moderate essential hypertension.

Participants: Among 3,518 randomised participants, 2,423 who self-measured HBP during the pretreatment drug-free period (10–28 days after starting fixed-dose antihypertensive monotherapy) with a mean 7.0 years' follow-up were eligible.

Main outcome measures: We analysed individual HBP readings during pretreatment and monotherapy.

Results: The day-to-day HBP during both the pretreatment period and monotherapy period remains almost the same throughout each period; the results were consistent, regardless of the pretreatment HBP. Following monotherapy, the reduction in the HBP increased by 2.2 mmHg (95% confidence interval [CI], 1.8–2.5) per 10-mmHg pretreatment HBP increase, up to 11.0 mmHg (CI, 9.9–12.0) among patients with an HBP ≥165 mmHg during pretreatment. Among the 1,005 patients receiving low -dose monotherapy (defined daily dose: 0.5 units), the reduction peaked at 8.9–9.1 mmHg in those with pretreatment HBP 155–164 and ≥165 mmHg (P=0.88).

Conclusions: According to Wilder's law, the HBP reduction due to fixed-dose monotherapy was proportional to the pretreatment HBP without any regression to the mean phenomenon. With low-dose antihypertensive drugs, however, the HBP reduction peaked in patients with a high pretreatment HBP, indicating the need for such patients to receive a sufficient amount of antihypertensive drug medication at the initial treatment.

Trial registration: UMIN Clinical Trial Registry (http://www.umin.ac.jp/ctr), Unique identifier: C000000137.

Keywords: blood pressure reduction, antihypertensive treatment, home blood pressure, self-measurement, Wilder's law, regression to the mean

Article summary

Strengths and limitations of this study

- This is a post-hoc analysis of the Hypertension Objective Treatment based on Measurement by Electrical Device of Blood Pressure (HOMED-BP) study, which was a multicentre clinical trial with a prospective, randomised, open-label, blinded end point, evaluation (PROBE) design.
- We enrolled 2,423 patients with mild-to-moderate essential hypertension.
- Study patients measured their daily self-measurement of blood pressure at home during the pretreatment period, after antihypertensive monotherapy, and for a mean 7.0 years' follow-up.
- Home blood pressure was self-measured using a validated upper-arm cuff-oscillometric OMRON HEM 747IC-N device, in which all measured data, including the measurement time, were automatically recorded.
- We were unable to assess the placebo effect because all patients received antihypertensive medication.

Introduction

Hypertension is a major risk factor for cardiovascular disease.[1 2] A meta-analysis showed that a 10/5 mmHg reduction in conventional office systolic/diastolic blood pressure reduces the stroke risk by approximately 40% and the coronary artery disease risk by approximately 20%.[3] However, office blood pressure has major limitations including being affected by the white-coat phenomenon, i.e. a warning response wherein the office blood pressure unexpectedly rises when in an examination room in front of medical staff.[4] In contrast, self-measured home blood pressure assessed using automated devices in a non-medical setting can obtain a plurality of readings over a long period under relatively uniform conditions, resulting in highly reproducible values without observer bias when patients apply a standardised protocol.[2 4 5] Home monitoring is unaffected by the white-coat phenomenon and is suitable for the evaluation of drug efficacy.[2 5 6] Given its greater prognostic ability for cardiovascular complications than office blood pressure,[1 2 7-9] home blood pressure-based antihypertensive treatment is highly recommended.[2 9]

Recent studies[10 11] have reported that the higher the pretreatment blood pressure, the greater the reduction in the blood pressure by antihypertensive drug treatment, according to the law of initial value (Wilder's law[12]). However, the reduction in the 24-h ambulatory blood pressure corresponding to the pretreatment office blood pressure was shown to be relatively small.[10] Such disproportionality can be attributed to changes in the white-coat effect, which depends on pretreatment office blood pressure.[10] Although ambulatory and home blood pressures are both categorised as out-of-office blood pressure, the characteristics and usefulness of home blood pressure differ from those of ambulatory recordings,[1 2 9] and no report has described differences in antihypertensive drug effects according to the pretreatment blood pressure.

We therefore investigated the association between the pretreatment home and office blood pressures levels and home blood pressure reduction by antihypertensive

monotherapy as well as long-term blood pressure changes in patients participating in a home blood pressure-based clinical trial.

Methods

Study design

This was a post-hoc analysis of the Hypertension Objective Treatment based on Measurement by Electrical Device of Blood Pressure (HOMED-BP) study[13-15], which was a multicentre clinical trial with a prospective, randomised, open-label, blinded end point, evaluation (PROBE)[16] design. The HOMED-BP protocol complies with the Declaration of Helsinki with respect to the ethical principles for medical research involving human subjects[17] and is registered with the UMIN Clinical Trial Registry, number C000000137 (http://www.umin.ac.jp/ctr). The institutional review board of the Teikyo University School of Medicine approved the study (17-044-2), and all study participants gave their written informed consent.

We included patients with mild-to-moderate essential hypertension based on home blood pressure (135–179/85–119 mmHg) with a minimum age of 40 years old. The exclusion criteria were severe hypertension (home blood pressure ≥180/≥120 mmHg or office blood pressure ≥220/≥125 mmHg), meeting the systolic criteria for the home blood pressure (≥135 mmHg) but with a diastolic home blood pressure of <65 mmHg, meeting the diastolic home blood pressure criteria (≥85 mmHg) but with a systolic home blood pressure of <110 mmHg, or contraindications to either calcium channel blockers, angiotensin -converting enzyme inhibitors, or angiotensin receptor blockers.

Selection of patients

After the first visit at the initial registration, the 5,211 enrolled patients were followed-up for at least two weeks without any antihypertensive drugs. At the second visit, the 3,518 (67.5%) eligible patients were randomised in a 2 × 3 design to receive monotherapy with the first-line drug (calcium channel blockers, angiotensin-converting enzyme inhibitors, or

angiotensin receptor blockers) with target home blood pressure-based antihypertensive values (usual control, ranging from 125 to 134 mmHg systolic and 80 to 84 mmHg diastolic; tight control, <125 mmHg systolic and <80 mmHg diastolic). The reasons for excluding the other 1,693 patients before randomisation have been described elsewhere[14] and listed in Supplemental Figure 1.

In the present analysis, we excluded 1,095 of the randomised 3,518 patients because they had obtained <3 home readings at baseline (pretreatment period; *n*=102) or during fixed-dose monotherapy with the first-line drug (*n*=592), they had isolated diastolic hypertension (home blood pressure ≤135/≥85 mmHg; *n*=143), they did not actually receive an antihypertensive drug or had been treated with ≥2 drug classes simultaneously (*n*=37), or we were unable to assess the blood pressure or treatment status during follow-up (*n*=221). A total of 2,423 participants were analysed statistically (Supplemental Figure 1). Based on our previous report indicating that the risks of cardiovascular outcomes were similar in the randomised groups (tight vs. usual blood pressure control, and a comparison of drug classes to initiate treatment) because of the small blood pressure difference between the groups,[14] we combined all 2,423 participants in the present analysis.

Measurements of blood pressure

Patients enrolled in HOMED-BP received spoken and written instructions on blood pressure self-measurement and the utilisation of a validated cuff-oscillometric OMRON HEM 747IC-N (Omron Healthcare Co., Ltd., Kyoto, Japan),[18] in which all measured data, including the measurement time, are automatically recorded. The standard upper-arm cuff, which covered 22–32 cm of a patient's arm circumference, was attached to the device. The importance of using an appropriately sized cuff was noted in the user's manual of the device, and we provided another cuff upon request. Throughout the study period, patients were asked to self-measure their blood pressure at home once every

morning within one hour of awakening, after urination, before breakfast, before taking antihypertensive medication, and after two minutes' rest in a sitting position.

Office blood pressure was measured by doctors in the outpatient clinic using a validated cuff-oscillometric OMRON HEM-907 (Omron Healthcare Co., Ltd., Kyoto, Japan).[19] At each visit, the office blood pressure was measured twice consecutively in a sitting position after at least two minutes' rest.

The evaluation of the blood pressure

In this study, the baseline pretreatment home blood pressure was the average of all blood pressure measurements taken for five days before the second visit on randomisation, and the blood pressure during the monotherapy was the average of measurements taken for five days within the 10- to 28-day period after the initiation of randomised first-line drugs (Figure 1).[20] We used this time window for home readings because (1) the home blood pressure used for determining eligibility and treatment adjustments at every visit in the HOMED-BP study was the average of the home readings available over 5 days immediately preceding the visit,[14] (2) the clinical investigators followed the patients at intervals of approximately 2 to 4 weeks in general practice and approximately 4 to 8 weeks at hospital outpatient clinics, and (3) the time interval needed to receive sufficient antihypertensive effects is reported to be approximately 7 to 23 days.[21] All of the home blood pressure values evaluated in the present study were therefore captured before the third visit, when drug titration might have been performed. The home blood pressure at the end of follow-up (mean follow-up period, 7.0 years; interquartile range, 5.1–9.1 years) was defined as the average of the last available five days of home blood pressure values. The office blood pressure during pretreatment and follow-up were the averages of the two consecutive measurements at each visit. The reduction in the blood pressure was calculated as the change from the pretreatment blood pressure at baseline.

Definition of comorbidity and quantification of drugs

The body mass index was calculated as the body weight in kilograms divided by the height in meters squared. Diabetes mellitus was defined as a fasting plasma glucose level of ≥7.0 mmol/L (≥126 mg/dL), HbA1c of ≥6.5%, or treatment with oral antidiabetic drugs or insulin. Hypercholesterolemia was defined as a total serum cholesterol level of ≥5.69 mmol/L (≥220 mg/dL), a history of hypercholesterolemia, or taking lipid-lowering drugs.[14 20]

We used the World Health Organization's defined daily dose (DDD) to quantify the use of antihypertensive drugs[22]; the DDD is the standard maintenance dose per day for a drug used for its main indication in adults.[22] The standard usage per day is defined as a DDD of 1 unit.

Statistical analyses

For database management and statistical analyses, we used the SAS software package, version 9.4 (SAS Institute Inc., Cary, NC, USA). Statistical significance was set at an $\alpha<0.05$ on 2-sided tests. We focused on our analyses based on systolic blood pressure, as systolic pressure is the overriding risk factor in middle-aged and older people.[23]

Patients were divided into 4 groups (≤145, 145–154, 155–164, and ≥165 mmHg) according to the baseline pretreatment systolic home blood pressure, and the blood pressure reduction was compared among the groups. For office blood pressure assessments, patients were stratified into 10 -mmHg groups according to the pretreatment systolic office blood pressure, as in the report by Schmieder et al.[10] The chi-square test and an analysis of variance (ANOVA) were used to compare the baseline characteristics between groups appropriately. Home blood pressure values during the five pretreatment days as well as those during the five monotherapy days were compared by a repeated measure mixed linear model, as implemented in the PROC MIXED procedure of the SAS package with the residual maximum likelihood option as the estimation method for the covariance parameters and the Kenward and Roger

approximation[24] for the degrees of freedom calculations. The blood pressure reduction was compared among groups according to the pretreatment blood pressure using an analysis of covariance (ANCOVA), and the change in the blood pressure reduction per pretreatment blood pressure increase was calculated using a linear regression model. In both analyses, the sex, age, body mass index, current smoking and drinking habit, hypercholesterolemia, diabetes mellitus, and history of cardiovascular disease were used for adjustments. The DDD during the initial antihypertensive monotherapy and at the end of follow-up were further used as the adjustment factors to compare the pressure reduction from pretreatment to the initial treatment and to the end of follow-up, respectively. For the 40 patients without body mass index data, we interpolated the value based on the sex and age (continuous). The white-coat effect was defined as the office blood pressure minus the home blood pressure as a continuous variable (negative value if the home blood pressure was higher than the office blood pressure)[10 25 26], and changes in the white-coat effect were determined by subtracting the effect observed at the end of the follow-up period from the effect captured during pretreatment.

Patient and public involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing the plans for recruitment, design, or implementation of the study. No patients were asked to advise on the interpretation or writing up of the results. There are no specific plans to disseminate the results of the research to study participants or the relevant patient community beyond the usual channels of publication.

Results

Representativeness of the study patients

Supplemental Table 1 shows the baseline characteristics of the 2,423 patients included in the present analysis, along with the other 1,095 randomised patients excluded from the analysis and the 694 patients who were randomized but not included because they

measured their home blood pressure <3 times. Although statistically significant differences were found in the age (P≤0.030), systolic blood pressure (P≤0.0064) for the comparison between analysed patients and all excluded patients, and in the drinking habit and history of cardiovascular disease (P≤0.020) for the comparison between analysed patients and patients who were excluded due to an insufficient number of home blood pressure measurements, all other characteristics were similar.

Patients' characteristics

Table 1 shows the baseline characteristics of 2,423 patients. The average age of all participants was 60.0 (standard deviation, 9.8) years old, and the proportion of women was 51.0%. The Age, body mass index, smoking habit, and office blood pressure were significantly and positively associated with the baseline systolic blood pressure category. As shown in Table 2, the day-to-day home blood pressure measurements during both the pretreatment period and monotherapy period remains almost the same throughout each period. When patients were subdivided by the systolic home blood pressure at baseline, there were significant differences between the patients with a home blood pressure <145 mmHg during the pretreatment period (P=0.032) and 145–154 mmHg during the monotherapy period (P=0.035); however, the differences between adjacent days were not significant even among those patients (P≥0.12).

The Relationship of the white-coat effect and office or home blood pressure values during the pretreatment period as a cross-sectional approach is shown in Supplemental Figure 2. The white-coat effect increased along with the office blood pressure (7.5 mmHg [95% confidence limit, 7.3–7.8 mmHg] per 10-mmHg increment), whereas the home blood pressure was negatively related to the white-coat effect (-4.5 mmHg [95% confidence limit, -3.9 to -5.0 mmHg] per 10-mmHg home blood pressure increment).

Reduction in the home blood pressure by monotherapy according to the pretreatment blood pressure

During the initial fixed-dose monotherapy, the reduction in the systolic home blood pressure was increased by 2.2 mmHg (95% confidence interval [CI], 1.8–2.5 mmHg) per 10-mmHg pretreatment home blood pressure increase. The reductions in each baseline pretreatment blood pressure group are shown in Figure 2. The slope of the home blood pressure reduction accompanying the increase in the pretreatment office blood pressure was shallower, increasing by 0.6 mmHg (95% CI, 0.4–0.9 mmHg) per 10-mmHg pretreatment office blood pressure increase.

Stratification by the DDD

Figure 3 demonstrates the results according to the DDD of the initial antihypertensive drugs. Among 1,005 patients who started monotherapy with antihypertensive drugs of 1 unit DDD, the pretreatment home blood pressure was linearly associated with the blood pressure reduction at the time of monotherapy; the enhancement of the home blood pressure reduction for each increase in the pretreatment home blood pressure category was 2.6 mmHg (95% CI, 1.9–3.2 mmHg). However, among those receiving 0.5 units DDD (*n*=1,005; occasionally the same number), significant enhancement in home blood pressure reductions was observed up to the 155–164 mmHg group (per 1 group increase, 2.1 mmHg; 95% CI, 1.2–2.9 mmHg), where it peaked; the reductions in the home blood pressure among patients with a pretreatment home blood pressure of 155–164 mmHg and ≥165 mmHg were 8.9 and 9.1 mmHg, respectively (*P*=0.88). The results were confirmed when we divided the whole 2,423 patients according to a DDD of <1 or ≥1 unit, as shown in Supplemental Figure 3.

Reduction in the follow-up blood pressure according to the pretreatment blood pressure

According to the previous report based on ambulatory blood pressure monitoring,[10] we compared the home and office blood pressure reductions at the end of follow-up

according to the baseline pretreatment office blood pressure. After 7.0 years' follow-up with a mean DDD of 1.8 units (median 1.5; interquartile range, 1.0–2.5), the reduction in the office blood pressure was linearly associated with the office blood pressure during pretreatment (reduction in the home pressure from the office blood pressure category <140 to ≥180 mmHg: 7.5 to 50.7 mmHg; Figure 4). Furthermore, similar to the previous report based on ambulatory monitoring[10], the reduction in the home blood pressure was linearly associated with the office blood pressure during the pretreatment period; however, the degree of home blood pressure reduction per the pretreatment office blood pressure increase was weak (reduction in home pressure: 18.6 to 30.7 mmHg). Finally, changes in the white-coat effect during the follow-up period increased significantly as the pretreatment office blood pressure increased (Supplemental Figure 4; category increment $P<0.0001$).

Discussion

The antihypertensive drug effect depends on the pretreatment blood pressure. In line with Wilder's law,[12] the home blood pressure reduction after the initial drug treatment was proportional to the baseline pretreatment home blood pressure in the present study. The current findings emphasize the need to assess the home blood pressure before treatment when evaluating and initiating antihypertensive drug therapy.

Wilder indicated that the direction of the body function response depends to a large extent on the initial level of that function, regardless of the agent.[12] Wilder's law predicts that in the most severe hypertensive patients, the decrease in blood pressure will be greater with the same medication than in those with less-severe hypertension. The statistical phenomenon of regression to the mean (regression toward the mean) is another major confounding factor hampering the accurate assessment of the effect of antihypertensive agents.[27] However, as shown in Table 2, there were no regression trends in the home blood pressure values from the first to the final measurement during

the pretreatment or monotherapy periods, regardless of the pretreatment home blood pressure. This finding indicates the strength of the self-measurement of home blood pressure, as home measurement is associated with minimal (if any during an initial few days after the measurement begins[28]) regression to the mean.[5 6 29] Based on ambulatory blood pressure monitoring, regression to the mean was observed consistently among the five studies[30], and a portion of the reduction in blood pressure after initiating antihypertensive treatment can be explained by this phenomenon[30]. However, there have been no reports investigating the biological mechanism contributing to this reduced influence of the regression to the mean phenomenon on self-measured home blood pressure. Nevertheless, home blood pressure measurement is likely to be useful for estimating the efficacy of antihypertensive drugs.

Schmieder et al[10]. reported that the higher the baseline office blood pressure, the greater the blood pressure reduction after one year of treatment enhancement, and this was more obvious in the office blood pressure than in the ambulatory blood pressure.[10] A recent meta-analysis also showed that the overall treatment-induced reduction was greater for office blood pressure than for 24-h ambulatory blood pressure.[11] In the present study, the reduction in the office blood pressure at the end of a mean 7.0 years' follow-up was also greater than that in the self-measured home blood pressure (Figure 4). Schmieder et al[10]. attributed this discrepancy to the changes in the white-coat effect, i.e. the higher the baseline office blood pressure, the greater the decrease in the white-coat effect due to antihypertensive treatment. This assumption was also supported by the findings of the present study (Supplemental Figure 4); however, the white-coat effect may not be a main driver for the discrepancy because the home blood pressure reduction also followed Wilder's law despite the negative correlation between home blood pressure and white-coat effect during the pretreatment period. Nevertheless, the out-of-office blood pressure is theoretically free from the white-coat phenomenon,[4] and the reduction in the office blood pressure by antihypertensive treatment partially includes a reduction in the

white-coat effect as well. We should therefore follow-up out-of-office-measured blood pressure carefully, since patients with a higher blood pressure tend to show a greater antihypertensive effect when their values are based on office-based measurements, while their out-of-office blood pressure reduction might be insufficient, resulting in a persistent high risk for cardiovascular complications.

Among 1,005 patients who were taking low-dose antihypertensive drugs, namely at a DDD of 0.5 units, the reduction in home blood pressure during monotherapy in the group with a pretreatment home blood pressure of ≥165 mmHg was almost identical to that in the group with a pretreatment home blood pressure of 155–164 mmHg. A high home blood pressure is associated with a high cardiovascular disease risk over the long term, both before and during antihypertensive therapy.[14 15] Inadequate control of office blood pressure with antihypertensive drug therapy remains a critical issue in Japan[31] as well as in Europe[32] and the United States[33]. Previous studies[34 35] have shown the importance of rapid blood pressure control, and the current findings suggest that a sufficient dosage of antihypertensive drug from the beginning of treatment is necessary, particularly among those with a high home blood pressure before starting treatment.

Although the need to strengthen antihypertensive drug treatment has been gradually accepted,[1 2 9] various factors associated with medical providers, patients, and healthcare systems have contributed to clinical inertia (non-compliance).[36 37] Clinical inertia is associated with inadequate blood pressure control, resulting in the increased risk of adverse cardiovascular effects. Medical services should help overcome clinical inertia as well as other hindrances in order to improve the blood pressure control of patients. Self-measurement of home blood pressure is expected to ameliorate the status quo because it promotes an improved awareness among patients with high blood pressure, helping them adhere to antihypertensive lifestyle modifications and drug treatments.[5]

Our current study must be interpreted within the context of several potential limitations. First, because the patients in HOMED-BP received home blood pressure-guided

therapy,[14] their treatment was adjusted according to the self-measured home blood pressure, and the office blood pressure was used as complimentary information. Second, we excluded 1,095 (31.1%) of the randomised HOMED-BP patients, including 694 due to an insufficient number of home readings. According to Supplemental Table 1, there is likely little concern about the effect of exclusion on the balance between groups; however, this lack of an effect cannot be fully guaranteed, thus we should practice caution when applying the findings regarding antihypertensive drug effect to real-world clinical practice. Third, we were unable to assess the placebo effect in the present study because all patients received antihypertensive medication. The placebo effect is a major influencing factor, in addition to Wilder's law and the regression to the mean phenomenon, in the administration of antihypertensive medication.[27] Fourth, because office blood pressure was measured less than 3 times at each visit, the regression to the mean on office blood pressure cannot be assessed ~~or~~ compared with that on home blood pressure. Finally, although our results are representative of middle- to old-aged Japanese patients, they might not be applicable to other settings or ethnic groups with different distributions of risk factors.

In conclusion, the reduction in the home blood pressure by antihypertensive drug monotherapy was proportional to the home blood pressure during the pretreatment drug-free period, in accordance with Wilder's law.[12] However, the home blood pressure reduction peaked in the patients who had a high pretreatment home blood pressure (≥155 mmHg) when treatment was initiated with low-dose antihypertensive drugs. Patients with a systolic home blood pressure of ≥155 mmHg before treatment might be considered to have resistant hypertension because the effect of low-dose antihypertensive drug for the blood pressure reduction reached the plateau, which seems against Wilder's law; however, we cannot say too much about the issue because we enrolled patients with mild-to-moderate essential hypertension in the HOMED-BP study, and those with severe hypertension that tended to be resistant were not enrolled. Whether or not Wilder's law

can be similarly applied to high -risk patients with severe hypertension remains unclear. However, home blood pressure measurement was minimally affected by regression to the mean, suggesting the usefulness of home blood pressure measurement for estimating the efficacy of antihypertensive drugs. Patients with a high home blood pressure during pretreatment should receive a sufficient amount of antihypertensive medication starting from the very first treatment.

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Contributors

KA, YI, and TO conceived of and designed the study; AH, KA, MK, and YI acquired the data; and KA and HS carried out the statistical analyses. HS drafted the original manuscript with KA and AH. SM, YI, and TO provided the intellectual input, and all authors critically revised the manuscript and approved the final manuscript. KA is the guarantor.

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Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare no support from any organisation for the submitted work; KA, YI, and TO received research grants from Omron Healthcare. No other relationships or activities appear to have influenced the submitted work.

Ethical approval

Fully disclosed in the Study design section.

Data sharing

No additional data are available.

Statements

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Dissemination of the results to study participants is not possible.

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Figure legends

Figure 1: Time course of blood pressure measurement during the study period.

Home blood pressures were the average of 5 days before randomisation without any antihypertensive treatment, after 10 to 28 days of monotherapy, and at the end of the follow-up period. Patients with 3 to 4 days of home blood pressure data in each interval were also included. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker.

Figure 2. Reduction in the systolic home blood pressure during monotherapy categorized by pretreatment home (left panel) and office (right panel) blood pressure.

Error bars indicate the 95% confidence interval. Data were adjusted for sex, age, body mass index, diabetes mellitus, current smoking and drinking, hypercholesterolemia, history of cardiovascular disease, and defined daily dose during monotherapy.

Figure 3. Reduction in the systolic home blood pressure during monotherapy categorized by pretreatment home blood pressure, stratified by defined daily dose (0.5 units, left panel; 1 unit, right panel).

Error bars indicate 95% confidence intervals. Data were adjusted for sex, age, body mass index, diabetes mellitus, current smoking and drinking, hypercholesterolemia, and history of cardiovascular disease.

Figure 4. Reduction in the follow-up systolic blood pressure categorized by pretreatment office blood pressure.

Error bars indicate 95% confidence intervals. Data were Adjusted for sex, age, body mass index, diabetes mellitus, current smoking and drinking, hypercholesterolemia,

history of cardiovascular disease, and defined daily dose at the end of follow-up period (mean, 7.0 years).

Table 1: Baseline characteristics of patients.

Characteristics	Systolic home blood pressure at baseline, mmHg				
	<145	145–154	155–164	≥165	*P*
Number of participants	763	699	544	417	
Women, n	416 (54.5)	342 (48.9)*	275 (50.6)	202 (48.4)	0.11
Age, years	59.3 (10.0)	59.3 (9.7)	61.0 (9.8)†	61.3 (9.5)	0.0003
Body mass index, kg/m²	24.2 (3.5)	24.2 (3.2)	24.6 (3.4)	24.8 (3.2)	0.0017
Smoking, n	142 (18.6)	138 (19.7)	112 (20.6)	109 (26.1)*	0.019
Drinking, n	347 (45.5)	344 (49.2)	270 (49.6)	211 (50.6)	0.27
Diabetes mellitus, n	122 (16.0)	101 (14.4)	85 (15.6)	70 (16.8)	0.74
Hypercholesterolemia, n	399 (52.3)	372 (53.2)	287 (52.8)	203 (48.7)	0.49
Previous cardiovascular diseases, n	25 (3.3)	17 (2.4)	17 (3.1)	7 (1.7)	0.37
Home blood pressure					
Systolic, mmHg	139.8 (3.0)	149.6 (2.9)§	159.4 (2.8)§	171.3 (4.3)§	<0.0001
Diastolic, mmHg	84.4 (8.4)	89.8 (8.9)§	92.6 (10.0)§	95.9 (10.9)§	<0.0001
Office blood pressure					
Systolic, mmHg	147.7 (15.5)	153.7 (16.5)§	157.8 (16.5)§	165.4 (17.1)§	<0.0001
Diastolic, mmHg	87.1 (11.2)	90.4 (11.8)§	91.1 (12.3)	94.0 (13.1)‡	<0.0001

Values are expressed as the arithmetic mean (standard deviation) or number (%). *P* values were calculated by an analysis of variance or the chi-squared test among the four systolic home blood pressure groups at baseline during pretreatment. For missing values of body mass index (*n*=40), single imputation with regression on sex and age was conducted.
Significance of differences from the left adjacent column: **P*<0.05, †*P*<0.01, ‡*P*<0.001, and §*P*<0.0001.

Table 2: Home systolic blood pressure values according to the measurement days.

Baseline blood pressure category	Number of patients	Home blood pressure measurement days (times)					
		First	Second	Third	Forth	Fifth	*P*
Pretreatment, mmHg							
All	2423	152.5 (14.7)	152.5 (14.8)	152.2 (14.9)	152.4 (14.6)	152.6 (14.9)	0.48
<145	763	140.3 (9.1)	139.6 (8.4)	139.1 (8.8)	139.7 (8.2)	140.4 (9.6)	0.032
145–154	699	149.6 (9.9)	150.0 (9.4)	149.5 (9.7)	149.5 (9.2)	149.5 (9.5)	0.85
155–164	544	159.3 (10.3)	158.7 (10.3)	159.5 (9.6)	159.8 (9.7)	159.8 (10.5)	0.41
≥165	417	170.9 (11.3)	172.0 (10.3)	171.1 (10.4)	171.0 (11.2)	171.4 (11.5)	0.66
Monotherapy, mmHg							
All	2423	145.5 (17.0)	145.2 (16.9)	145.4 (16.5)	145.4 (16.5)	144.7 (16.6)	0.58
<145	763	135.3 (13.2)	135.1 (13.1)	135.5 (13.4)	135.8 (13.2)	135.1 (13.1)	0.56
145–154	699	143.8 (13.8)	143.1 (13.3)	143.3 (13.0)	142.9 (13.3)	141.9 (12.9)	0.035
155–164	544	150.2 (15.3)	150.5 (15.4)	150.5 (14.6)	151.2 (14.4)	150.5 (14.7)	0.67
≥165	417	161.1 (16.5)	160.0 (17.0)	160.3 (15.4)	160.1 (16.1)	160.5 (15.9)	0.65

Values are expressed as the arithmetic mean (standard deviation). The numbers of patients with missing blood pressure data on the fourth and fifth days were 38 and 84 at pretreatment and 87 and 286 during monotherapy, respectively, while *P* values were calculated by a repeated measure mixed linear model to take missing values into account and represent the differences among the five systolic home blood pressure values according to the measurement day at baseline during pretreatment.
Differences between the adjacent days were not significant during pretreatment ($P \geq 0.12$) or monotherapy ($P \geq 0.14$).

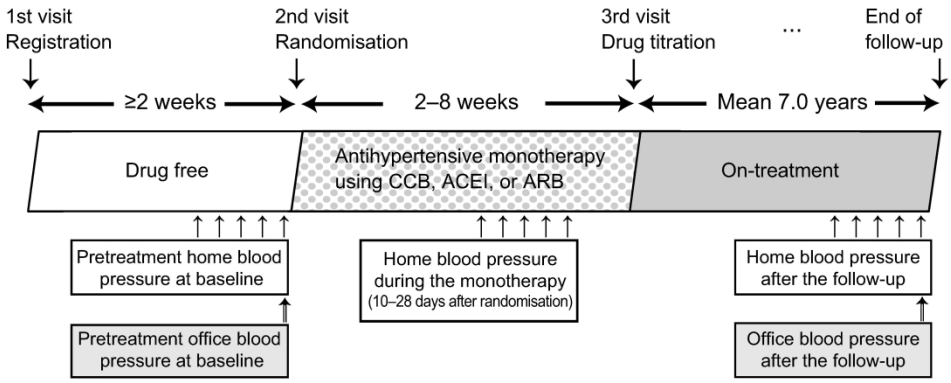

Figure 1: Time course of blood pressure measurement during the study period.
Home blood pressures were the average of 5 days before randomisation without any antihypertensive treatment, after 10 to 28 days of monotherapy initiation, and at the end of follow-up period. Patients with 3 to 4 days of home blood pressure data in each interval were also included. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker.

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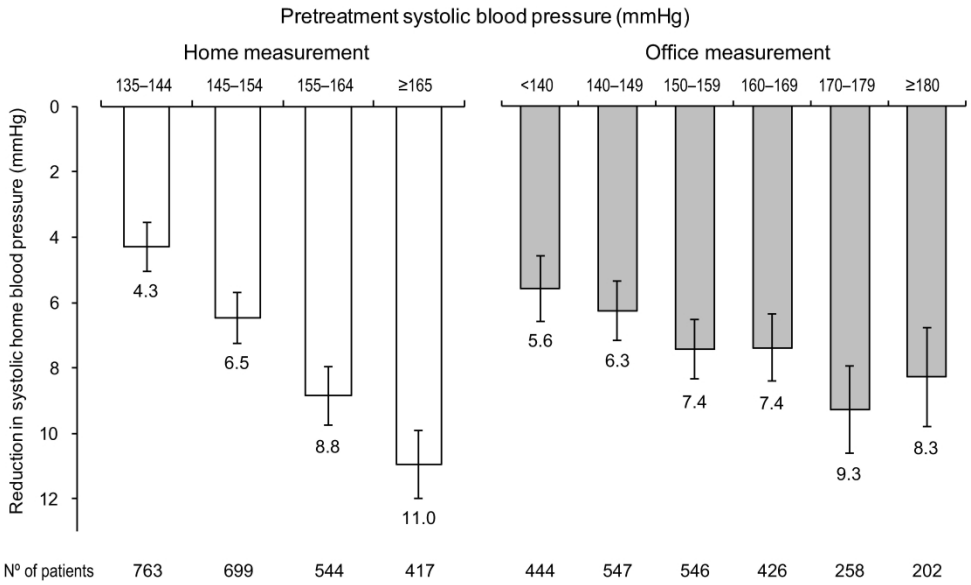

Figure 2. Reduction in the systolic home blood pressure during monotherapy categorized by pretreatment home (left panel) and office (right panel) blood pressure.
Error bars indicate 95% confidence interval. Data were adjusted for sex, age, body mass index, diabetes mellitus, current smoking and drinking, hypercholesterolemia, history of cardiovascular disease, and defined daily dose during monotherapy.

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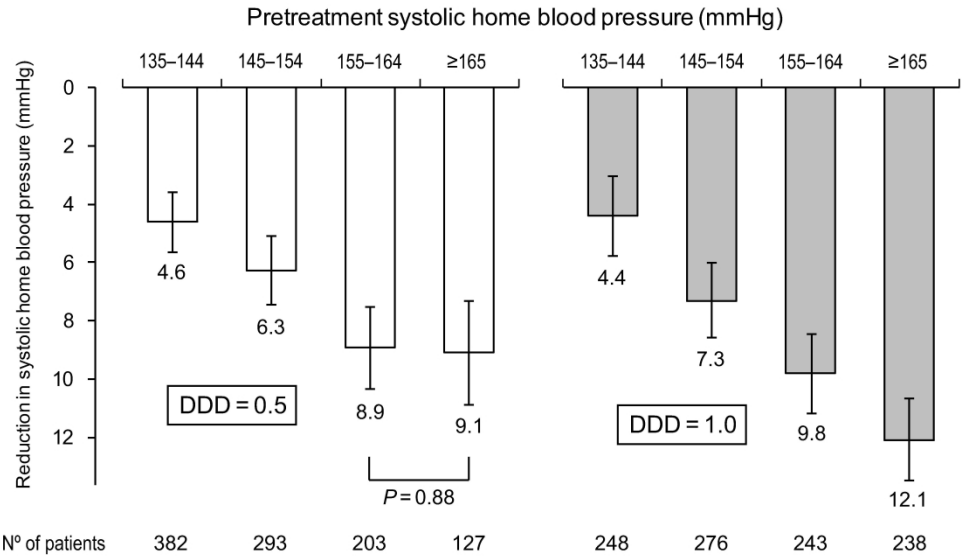

Figure 3. Reduction in the systolic home blood pressure during monotherapy categorized by pretreatment home blood pressure, stratified by defined daily dose (0.5 unit, left panel; 1 unit, right panel). Error bars indicate 95% confidence interval. Data were adjusted for sex, age, body mass index, diabetes mellitus, current smoking and drinking, hypercholesterolemia, and history of cardiovascular disease.

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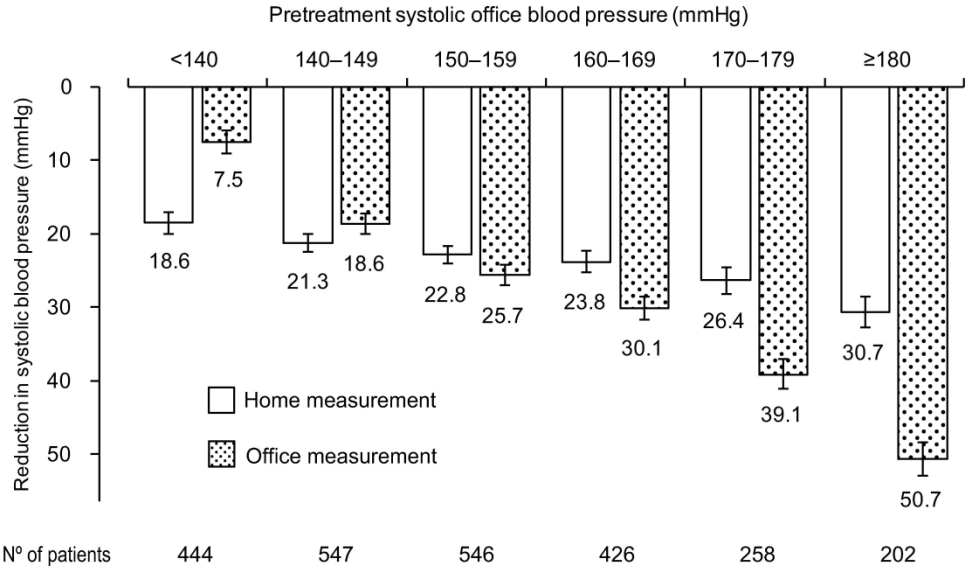

Figure 4. Reduction in the follow-up systolic blood pressure categorized by pretreatment office blood pressure.
Error bars indicate 95% confidence interval. Adjusted for sex, age, body mass index, diabetes mellitus, current smoking and drinking, hypercholesterolemia, history of cardiovascular disease, and defined daily dose at the end of follow-up period (mean, 7.0 years).

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SUPPLEMENTARY INFORMATION

Antihypertensive drug effects according to the pretreatment self-measured home blood pressure: the HOMED-BP study

Short title: Wilder's Law on Home Blood Pressure

Hikari Sano, Azusa Hara, Kei Asayama, Seiko Miyazaki, Masahiro Kikuya, Yutaka Imai, Takayoshi Ohkubo,

on behalf of

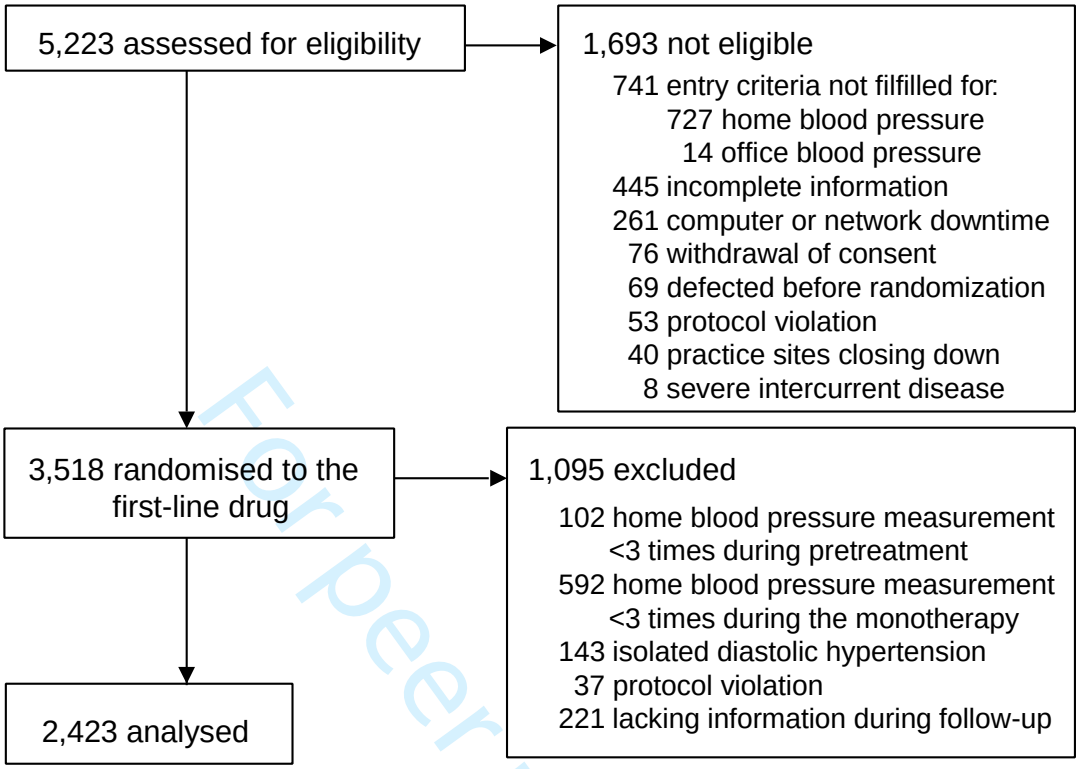
Hypertension Objective Treatment Based on Measurement by Electrical Devices of Blood Pressure (HOMED-BP) investigators

Supplemental Table 1: Baseline characteristics of the analysed patients (*n*=2,423), all excluded patients (*n*=1,095), and patients excluded due to an insufficient number of home blood pressure measurements (*n*=694).

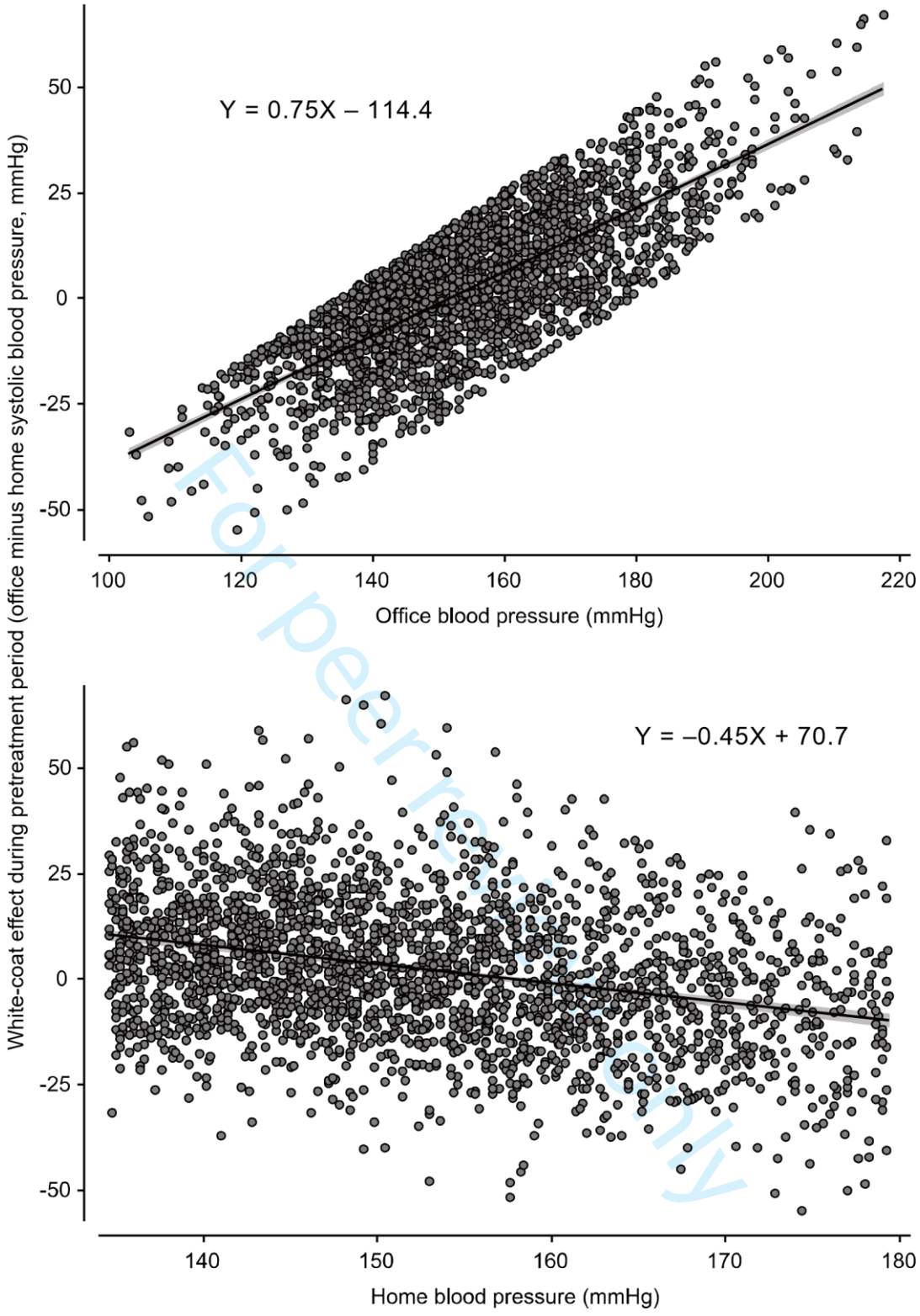
		Excluded			
Characteristics	**Analysed**	**Any Reason**	***P***	**Insufficient Home Reading**	***P***
Number of participants	2423	1095		694	
Women, n	1235 (51.0)	528 (48.2)	0.13	355 (51.2)	0.93
Age, years	60.0 (9.8)	58.6 (10.5)	<0.0001	59.1 (10.7)	0.030
Body mass index, kg/m²	24.4 (3.3)	24.4 (3.6)	>0.99	24.4 (3.6)	0.97
Smoking, n	501 (20.7)	242 (22.1)	0.34	149 (21.5)	0.65
Drinking, n	1172 (48.4)	499 (45.6)	0.12	299 (43.1)	0.014
Diabetes mellitus, n	378 (15.6)	160 (14.6)	0.45	105 (15.1)	0.76
Hypercholesterolemia, n	1261 (52.0)	542 (49.5)	0.16	347 (50.0)	0.34
Previous cardiovascular diseases, n	66 (2.7)	40 (3.7)	0.14	31 (4.5)	0.020
Home blood pressure					
Systolic, mmHg	152.5 (11.6)	149.7 (14.1)	<0.0001	152.6 (13.0)	0.83
Diastolic, mmHg	89.8 (10.3)	90.2 (9.5)	0.26	90.5 (9.8)	0.12

Office blood pressure					
Systolic, mmHg	154.7 (17.4)	153.0 (17.7)	0.0064	154.2 (17.2)	0.49
Diastolic, mmHg	90.1 (12.2)	90.3 (12.2)	0.71	90.0 (12.3)	0.85

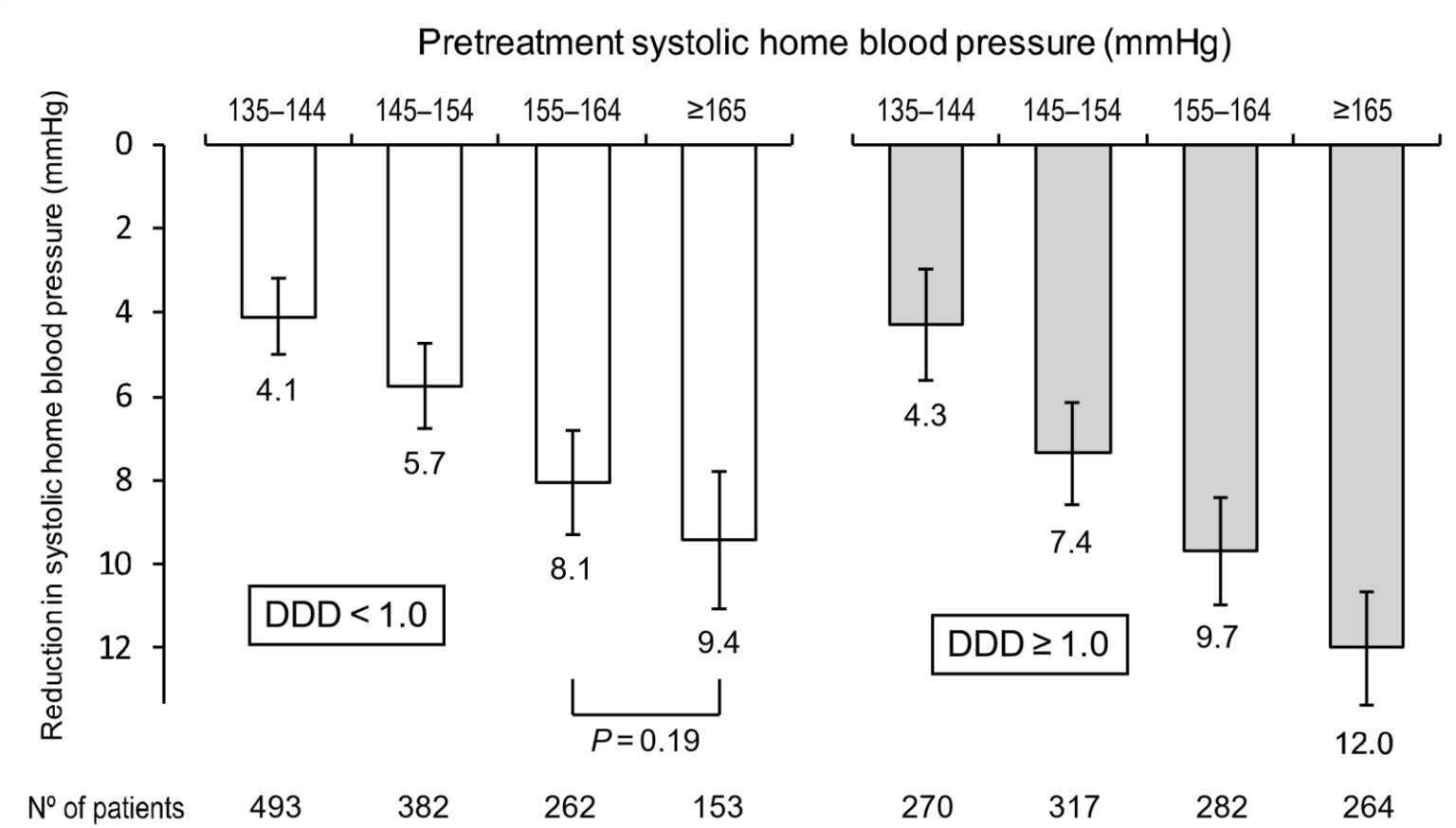
Values are expressed as the arithmetic mean (standard deviation) or number (%). *P* values were calculated by the t-test or the chisquared test, with comparisons made between the 2,423 analysed patients and each excluded group.



Supplemental Figure 1: Flowchart of the study.

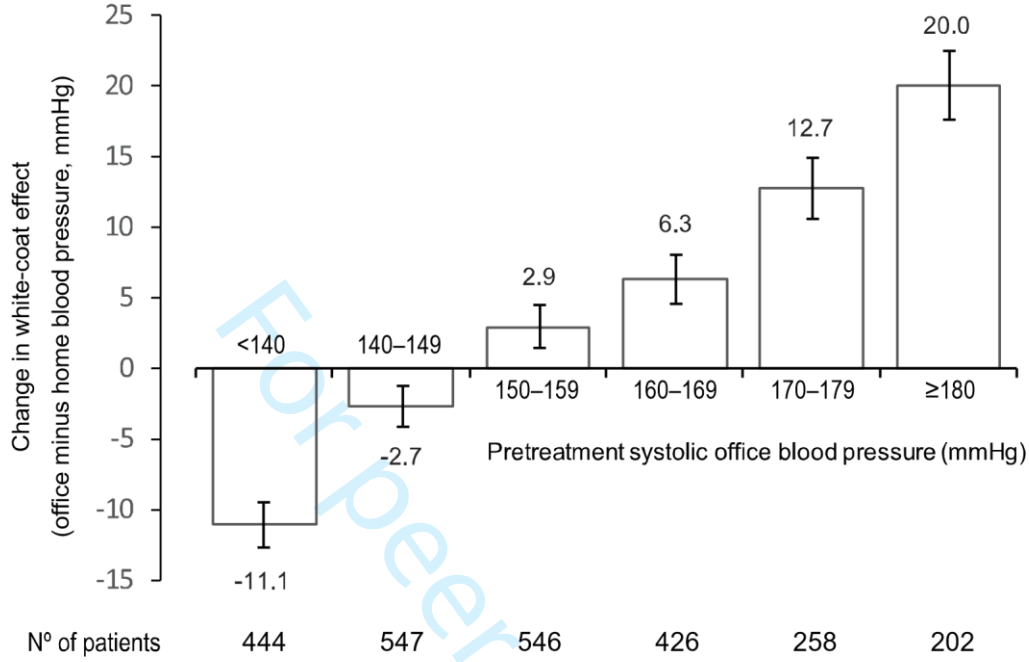


Supplemental Figure 2: Relationship between the white-coat effect and office systolic blood pressure (A) as well as home blood pressure (B) during pretreatment period. The white-coat effect was defined as the office blood pressure minus the home blood pressure as a continuous variable. Regression line with 95% confidence limits were overlay on each scatter plot. Because systolic home blood pressure ranged 135–179 mmHg in this population, plots in panel A demonstrate as a band-like distribution which rises to the right.



Supplemental Figure 3: Reduction in the systolic home blood pressure during monotherapy categorized by pretreatment home blood pressure and stratified by defined daily dose (<1 unit, left panel; ≥1 unit, right panel).

Error bars indicate 95% confidence interval. Data were adjusted for sex, age, body mass index, diabetes mellitus, current smoking and drinking, hypercholesterolemia, history of cardiovascular disease, and defined daily dose during monotherapy.



Supplemental Figure 4: Changes in the white-coat effect during follow-up categorized by the pretreatment office blood pressure.

Error bars indicate 95% confidence interval. The white-coat effect was defined as the office blood pressure minus the home blood pressure, and changes in the white-coat effect were determined by subtracting the effect observed at the end of follow-up period from the effect during pretreatment.

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Antihypertensive drug effects according to the pretreatment self-measured home blood pressure: the HOMED-BP study

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Keywords:	Hypertension < CARDIOLOGY, Cardiology < INTERNAL MEDICINE, EPIDEMIOLOGY

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Antihypertensive drug effects according to the pretreatment self-measured home blood pressure: the HOMED-BP study

Short title: Wilder's Law on Home Blood Pressure

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Tables 2, Figures 4

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Abstract

Objectives: To clarify whether or not the antihypertensive drug effect is proportional to the baseline pretreatment self-measured home blood pressure (HBP) in accordance with the law of initial value (Wilder's law).

Design: A Post-hoc analysis of a multicentre clinical trial.

Setting: Outpatients across Japan with mild-to-moderate essential hypertension.

Participants: Among 3,518 randomised participants, 2,423 who self-measured HBP during the pretreatment drug-free period (10–28 days after starting fixed-dose antihypertensive monotherapy) with a mean 7.0 years' follow-up were eligible.

Main outcome measures: We analysed individual HBP readings during pretreatment and monotherapy.

Results: The day-to-day HBP during both the pretreatment period and monotherapy period remains almost the same throughout each period; the results were consistent, regardless of the pretreatment HBP. Following monotherapy, the reduction in the HBP increased by 2.2 mmHg (95% confidence interval [CI], 1.8–2.5) per 10-mmHg pretreatment HBP increase, up to 11.0 mmHg (CI, 9.9–12.0) among patients with an HBP ≥165 mmHg during pretreatment. Among the 1,005 patients receiving low -dose monotherapy (defined daily dose: 0.5 units), the reduction peaked at 8.9–9.1 mmHg in those with pretreatment HBP 155–164 and ≥165 mmHg (P=0.88).

Conclusions: According to Wilder's law, the HBP reduction due to fixed-dose monotherapy was proportional to the pretreatment HBP without any regression to the mean phenomenon. With low-dose antihypertensive drugs, however, the HBP reduction peaked in patients with a high pretreatment HBP, indicating the need for such patients to receive a sufficient amount of antihypertensive drug medication at the initial treatment.

Trial registration: UMIN Clinical Trial Registry (http://www.umin.ac.jp/ctr), Unique identifier: C000000137.

Keywords: blood pressure reduction, antihypertensive treatment, home blood pressure, self-measurement, Wilder's law, regression to the mean

Article summary

Strengths and limitations of this study

- This is a post-hoc analysis of a multicentre clinical trial in which patients were recruited from 457 general practices throughout Japan.
- Enrolled 2,423 patients with mild-to-moderate essential hypertension measured their daily self-measurement of blood pressure at home during the pretreatment period, after antihypertensive monotherapy, and for a mean 7.0 years' follow-up.
- Home blood pressure was self-measured using a validated upper-arm cuff-oscillometric OMRON HEM 747IC-N device, in which all measured data, including the measurement time, were automatically recorded.
- We were unable to assess the placebo effect because all patients received antihypertensive medication.
- Limitations of the studies included large number of excluded participants (1,095 of the randomized 3,518 patients) by which we should practice caution when applying the findings regarding antihypertensive drug effect to real-world clinical practice.

Introduction

Hypertension is a major risk factor for cardiovascular disease.[1 2] A meta-analysis showed that a 10/5 mmHg reduction in conventional office systolic/diastolic blood pressure reduces the stroke risk by approximately 40% and the coronary artery disease risk by approximately 20%.[3] However, office blood pressure has major limitations including being affected by the white-coat phenomenon, i.e. a warning response wherein the office blood pressure unexpectedly rises when in an examination room in front of medical staff.[4] In contrast, self-measured home blood pressure assessed using automated devices in a non-medical setting can obtain a plurality of readings over a long period under relatively uniform conditions, resulting in highly reproducible values without observer bias when patients apply a standardised protocol.[2 4 5] Home monitoring is unaffected by the white-coat phenomenon and is suitable for the evaluation of drug efficacy.[2 5 6] Given its greater prognostic ability for cardiovascular complications than office blood pressure,[1 2 7-9] home blood pressure-based antihypertensive treatment is highly recommended.[2 9]

Recent studies[10 11] have reported that the higher the pretreatment blood pressure, the greater the reduction in the blood pressure by antihypertensive drug treatment, according to the law of initial value (Wilder's law[12]). However, the reduction in the 24-h ambulatory blood pressure corresponding to the pretreatment office blood pressure was shown to be relatively small.[10] Such disproportionality can be attributed to changes in the white-coat effect, which depends on pretreatment office blood pressure.[10] Although ambulatory and home blood pressures are both categorised as out-of-office blood pressure, the characteristics and usefulness of home blood pressure differ from those of ambulatory recordings,[1 2 9] and no report has described differences in antihypertensive drug effects according to the pretreatment blood pressure.

We therefore investigated the association between the pretreatment home and office blood pressures levels and home blood pressure reduction by antihypertensive

monotherapy as well as long-term blood pressure changes in patients participating in a home blood pressure-based clinical trial.

Methods

Study design

This was a post-hoc analysis of the Hypertension Objective Treatment based on Measurement by Electrical Device of Blood Pressure (HOMED-BP) study[13-15], which was a multicentre clinical trial with a prospective, randomised, open-label, blinded end point, evaluation (PROBE)[16] design. The HOMED-BP protocol complies with the Declaration of Helsinki with respect to the ethical principles for medical research involving human subjects[17] and is registered with the UMIN Clinical Trial Registry, number C000000137 (http://www.umin.ac.jp/ctr). The institutional review board of the Teikyo University School of Medicine approved the study (17-044-2), and all study participants gave their written informed consent.

We included patients with mild-to-moderate essential hypertension based on home blood pressure (135–179/85–119 mmHg) with a minimum age of 40 years old; they were recruited from 457 general practices throughout Japan[14 15]. The exclusion criteria were severe hypertension (home blood pressure ≥180/≥120 mmHg or office blood pressure ≥220/≥125 mmHg), meeting the systolic criteria for the home blood pressure (≥135 mmHg) but with a diastolic home blood pressure of <65 mmHg, meeting the diastolic home blood pressure criteria (≥85 mmHg) but with a systolic home blood pressure of <110 mmHg, or contraindications to either calcium channel blockers, angiotensin - converting enzyme inhibitors, or angiotensin receptor blockers.

Selection of patients

After the first visit at the initial registration, the 5,211 enrolled patients were followed-up for at least two weeks without any antihypertensive drugs. At the second visit, the 3,518 (67.5%) eligible patients were randomised in a 2 × 3 design to receive monotherapy with

the first-line drug (calcium channel blockers, angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers) with target home blood pressure-based antihypertensive values (usual control, ranging from 125 to 134 mmHg systolic and 80 to 84 mmHg diastolic; tight control, <125 mmHg systolic and <80 mmHg diastolic). The reasons for excluding the other 1,693 patients before randomisation have been described elsewhere[14] and listed in Supplemental Figure 1.

In the present analysis, we excluded 1,095 of the randomised 3,518 patients because they had obtained <3 home readings at baseline (pretreatment period; *n*=102) or during fixed-dose monotherapy with the first-line drug (*n*=592), they had isolated diastolic hypertension (home blood pressure ≤135/≥85 mmHg; *n*=143), they did not actually receive an antihypertensive drug or had been treated with ≥2 drug classes simultaneously (*n*=37), or we were unable to assess the blood pressure or treatment status during follow-up (*n*=221). A total of 2,423 participants were analysed statistically (Supplemental Figure 1). Based on our previous report indicating that the risks of cardiovascular outcomes were similar in the randomised groups (tight vs. usual blood pressure control, and a comparison of drug classes to initiate treatment) because of the small blood pressure difference between the groups,[14] we combined all 2,423 participants in the present analysis.

Measurements of blood pressure

Patients enrolled in HOMED-BP received spoken and written instructions on blood pressure self-measurement and the utilisation of a validated cuff-oscillometric OMRON HEM 747IC-N (Omron Healthcare Co., Ltd., Kyoto, Japan),[18] in which all measured data, including the measurement time, are automatically recorded. The standard upper-arm cuff, which covered 22–32 cm of a patient's arm circumference, was attached to the device. The importance of using an appropriately sized cuff was noted in the user's manual of the device, and we provided another cuff upon request. Throughout the study period, patients were asked to self-measure their blood pressure at home once every

morning within one hour of awakening, after urination, before breakfast, before taking antihypertensive medication, and after two minutes' rest in a sitting position.

Office blood pressure was measured by doctors in the outpatient clinic using a validated cuff-oscillometric OMRON HEM-907 (Omron Healthcare Co., Ltd., Kyoto, Japan).[19] At each visit, the office blood pressure was measured twice consecutively in a sitting position after at least two minutes' rest.

The evaluation of the blood pressure

In this study, the baseline pretreatment home blood pressure was the average of all blood pressure measurements taken for five days before the second visit on randomisation, and the blood pressure during the monotherapy was the average of measurements taken for five days within the 10- to 28-day period after the initiation of randomised first-line drugs (Figure 1).[20] We used this time window for home readings because (1) the home blood pressure used for determining eligibility and treatment adjustments at every visit in the HOMED-BP study was the average of the home readings available over 5 days immediately preceding the visit,[14] (2) the clinical investigators followed the patients at intervals of approximately 2 to 4 weeks in general practice and approximately 4 to 8 weeks at hospital outpatient clinics, and (3) the time interval needed to receive sufficient antihypertensive effects is reported to be approximately 7 to 23 days.[21] All of the home blood pressure values evaluated in the present study were therefore captured before the third visit, when drug titration might have been performed. The home blood pressure at the end of follow-up (mean follow-up period, 7.0 years; interquartile range, 5.1–9.1 years) was defined as the average of the last available five days of home blood pressure values. The office blood pressure during pretreatment and follow-up were the averages of the two consecutive measurements at each visit. The reduction in the blood pressure was calculated as the change from the pretreatment blood pressure at baseline.

Definition of comorbidity and quantification of drugs

The body mass index was calculated as the body weight in kilograms divided by the height in meters squared. Diabetes mellitus was defined as a fasting plasma glucose level of ≥7.0 mmol/L (≥126 mg/dL), HbA1c of ≥6.5%, or treatment with oral antidiabetic drugs or insulin. Hypercholesterolemia was defined as a total serum cholesterol level of ≥5.69 mmol/L (≥220 mg/dL), a history of hypercholesterolemia, or taking lipid-lowering drugs.[14 20]

We used the World Health Organization's defined daily dose (DDD) to quantify the use of antihypertensive drugs[22]; the DDD is the standard maintenance dose per day for a drug used for its main indication in adults.[22] The standard usage per day is defined as a DDD of 1 unit.

Statistical analyses

For database management and statistical analyses, we used the SAS software package, version 9.4 (SAS Institute Inc., Cary, NC, USA). Statistical significance was set at an $\alpha<0.05$ on 2-sided tests. We focused on our analyses based on systolic blood pressure, as systolic pressure is the overriding risk factor in middle-aged and older people.[23]

Patients were divided into 4 groups (≤145, 145–154, 155–164, and ≥165 mmHg) according to the baseline pretreatment systolic home blood pressure, and the blood pressure reduction was compared among the groups. For office blood pressure assessments, patients were stratified into 10 -mmHg groups according to the pretreatment systolic office blood pressure, as in the report by Schmieder et al.[10] The chi-square test and an analysis of variance (ANOVA) were used to compare the baseline characteristics between groups appropriately. Home blood pressure values during the five pretreatment days as well as those during the five monotherapy days were compared by a repeated measure mixed linear model, as implemented in the PROC MIXED procedure of the SAS package with the residual maximum likelihood option as the estimation method for the covariance parameters and the Kenward and Roger

approximation[24] for the degrees of freedom calculations. The blood pressure reduction was compared among groups according to the pretreatment blood pressure using an analysis of covariance (ANCOVA), and the change in the blood pressure reduction per pretreatment blood pressure increase was calculated using a linear regression model. In both analyses, the sex, age, body mass index, current smoking and drinking habit, hypercholesterolemia, diabetes mellitus, and history of cardiovascular disease were used for adjustments. The DDD during the initial antihypertensive monotherapy and at the end of follow-up were further used as the adjustment factors to compare the pressure reduction from pretreatment to the initial treatment and to the end of follow-up, respectively. For the 40 patients without body mass index data, we interpolated the value based on the sex and age (continuous). The white-coat effect was defined as the office blood pressure minus the home blood pressure as a continuous variable (negative value if the home blood pressure was higher than the office blood pressure)[10 25 26], and changes in the white-coat effect were determined by subtracting the effect observed at the end of the follow-up period from the effect captured during pretreatment.

Patient and public involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing the plans for recruitment, design, or implementation of the study. No patients were asked to advise on the interpretation or writing up of the results. There are no specific plans to disseminate the results of the research to study participants or the relevant patient community beyond the usual channels of publication.

Results

Representativeness of the study patients

Supplemental Table 1 shows the baseline characteristics of the 2,423 patients included in the present analysis, along with the other 1,095 randomised patients excluded from the analysis and the 694 patients who were randomized but not included because they

measured their home blood pressure <3 times. Although statistically significant differences were found in the age ($P \leq 0.030$), systolic blood pressure ($P \leq 0.0064$) for the comparison between analysed patients and all excluded patients, and in the drinking habit and history of cardiovascular disease ($P \leq 0.020$) for the comparison between analysed patients and patients who were excluded due to an insufficient number of home blood pressure measurements, all other characteristics were similar.

Patients' characteristics

Table 1 shows the baseline characteristics of 2,423 patients. The average age of all participants was 60.0 (standard deviation, 9.8) years old, and the proportion of women was 51.0%. The Age, body mass index, smoking habit, and office blood pressure were significantly and positively associated with the baseline systolic blood pressure category. As shown in Table 2, the day-to-day home blood pressure measurements during both the pretreatment period and monotherapy period remains almost the same throughout each period. When patients were subdivided by the systolic home blood pressure at baseline, there were significant differences between the patients with a home blood pressure <145 mmHg during the pretreatment period ($P=0.032$) and 145–154 mmHg during the monotherapy period ($P=0.035$); however, the differences between adjacent days were not significant even among those patients ($P \geq 0.12$).

The Relationship of the white-coat effect and office or home blood pressure values during the pretreatment period as a cross-sectional approach is shown in Supplemental Figure 2. The white-coat effect increased along with the office blood pressure (7.5 mmHg [95% confidence limit, 7.3–7.8 mmHg] per 10-mmHg increment), whereas the home blood pressure was negatively related to the white-coat effect (-4.5 mmHg [95% confidence limit, -3.9 to -5.0 mmHg] per 10-mmHg home blood pressure increment).

Reduction in the home blood pressure by monotherapy according to the pretreatment blood pressure

During the initial fixed-dose monotherapy, the reduction in the systolic home blood pressure was increased by 2.2 mmHg (95% confidence interval [CI], 1.8–2.5 mmHg) per 10-mmHg pretreatment home blood pressure increase. The reductions in each baseline pretreatment blood pressure group are shown in Figure 2. The slope of the home blood pressure reduction accompanying the increase in the pretreatment office blood pressure was shallower, increasing by 0.6 mmHg (95% CI, 0.4–0.9 mmHg) per 10-mmHg pretreatment office blood pressure increase.

Stratification by the DDD

Figure 3 demonstrates the results according to the DDD of the initial antihypertensive drugs. Among 1,005 patients who started monotherapy with antihypertensive drugs of 1 unit DDD, the pretreatment home blood pressure was linearly associated with the blood pressure reduction at the time of monotherapy; the enhancement of the home blood pressure reduction for each increase in the pretreatment home blood pressure category was 2.6 mmHg (95% CI, 1.9–3.2 mmHg). However, among those receiving 0.5 units DDD (*n*=1,005; occasionally the same number), significant enhancement in home blood pressure reductions was observed up to the 155–164 mmHg group (per 1 group increase, 2.1 mmHg; 95% CI, 1.2–2.9 mmHg), where it peaked; the reductions in the home blood pressure among patients with a pretreatment home blood pressure of 155–164 mmHg and ≥165 mmHg were 8.9 and 9.1 mmHg, respectively (*P*=0.88). The results were confirmed when we divided the whole 2,423 patients according to a DDD of <1 or ≥1 unit, as shown in Supplemental Figure 3.

Reduction in the follow-up blood pressure according to the pretreatment blood pressure

According to the previous report based on ambulatory blood pressure monitoring,[10] we compared the home and office blood pressure reductions at the end of follow-up

according to the baseline pretreatment office blood pressure. After 7.0 years' follow-up with a mean DDD of 1.8 units (median 1.5; interquartile range, 1.0–2.5), the reduction in the office blood pressure was linearly associated with the office blood pressure during pretreatment (reduction in the home pressure from the office blood pressure category <140 to ≥180 mmHg: 7.5 to 50.7 mmHg; Figure 4). Furthermore, similar to the previous report based on ambulatory monitoring[10], the reduction in the home blood pressure was linearly associated with the office blood pressure during the pretreatment period; however, the degree of home blood pressure reduction per the pretreatment office blood pressure increase was weak (reduction in home pressure: 18.6 to 30.7 mmHg). Finally, changes in the white-coat effect during the follow-up period increased significantly as the pretreatment office blood pressure increased (Supplemental Figure 4; category increment $P<0.0001$).

Discussion

The antihypertensive drug effect depends on the pretreatment blood pressure. In line with Wilder's law,[12] the home blood pressure reduction after the initial drug treatment was proportional to the baseline pretreatment home blood pressure in the present study. The current findings emphasize the need to assess the home blood pressure before treatment when evaluating and initiating antihypertensive drug therapy.

Wilder indicated that the direction of the body function response depends to a large extent on the initial level of that function, regardless of the agent.[12] Wilder's law predicts that in the most severe hypertensive patients, the decrease in blood pressure will be greater with the same medication than in those with less-severe hypertension. The statistical phenomenon of regression to the mean (regression toward the mean) is another major confounding factor hampering the accurate assessment of the effect of antihypertensive agents.[27] However, as shown in Table 2, there were no regression trends in the home blood pressure values from the first to the final measurement during

the pretreatment or monotherapy periods, regardless of the pretreatment home blood pressure. This finding indicates the strength of the self-measurement of home blood pressure, as home measurement is associated with minimal (if any during an initial few days after the measurement begins[28]) regression to the mean.[5 6 29] Based on ambulatory blood pressure monitoring, regression to the mean was observed consistently among the five studies[30], and a portion of the reduction in blood pressure after initiating antihypertensive treatment can be explained by this phenomenon[30]. However, there have been no reports investigating the biological mechanism contributing to this reduced influence of the regression to the mean phenomenon on self-measured home blood pressure. Nevertheless, home blood pressure measurement is likely to be useful for estimating the efficacy of antihypertensive drugs.

Schmieder et al[10]. reported that the higher the baseline office blood pressure, the greater the blood pressure reduction after one year of treatment enhancement, and this was more obvious in the office blood pressure than in the ambulatory blood pressure.[10] A recent meta-analysis also showed that the overall treatment-induced reduction was greater for office blood pressure than for 24-h ambulatory blood pressure.[11] In the present study, the reduction in the office blood pressure at the end of a mean 7.0 years' follow-up was also greater than that in the self-measured home blood pressure (Figure 4). Schmieder et al[10]. attributed this discrepancy to the changes in the white-coat effect, i.e. the higher the baseline office blood pressure, the greater the decrease in the white-coat effect due to antihypertensive treatment. This assumption was also supported by the findings of the present study (Supplemental Figure 4); however, the white-coat effect may not be a main driver for the discrepancy because the home blood pressure reduction also followed Wilder's law despite the negative correlation between home blood pressure and white-coat effect during the pretreatment period. Nevertheless, the out-of-office blood pressure is theoretically free from the white-coat phenomenon,[4] and the reduction in the office blood pressure by antihypertensive treatment partially includes a reduction in the

white-coat effect as well. We should therefore follow-up out-of-office-measured blood pressure carefully, since patients with a higher blood pressure tend to show a greater antihypertensive effect when their values are based on office-based measurements, while their out-of-office blood pressure reduction might be insufficient, resulting in a persistent high risk for cardiovascular complications.

Among 1,005 patients who were taking low-dose antihypertensive drugs, namely at a DDD of 0.5 units, the reduction in home blood pressure during monotherapy in the group with a pretreatment home blood pressure of ≥165 mmHg was almost identical to that in the group with a pretreatment home blood pressure of 155–164 mmHg. A high home blood pressure is associated with a high cardiovascular disease risk over the long term, both before and during antihypertensive therapy.[14 15] Inadequate control of office blood pressure with antihypertensive drug therapy remains a critical issue in Japan[31] as well as in Europe[32] and the United States[33]. Previous studies[34 35] have shown the importance of rapid blood pressure control, and the current findings suggest that a sufficient dosage of antihypertensive drug from the beginning of treatment is necessary, particularly among those with a high home blood pressure before starting treatment.

Although the need to strengthen antihypertensive drug treatment has been gradually accepted,[1 2 9] various factors associated with medical providers, patients, and healthcare systems have contributed to clinical inertia (non-compliance).[36 37] Clinical inertia is associated with inadequate blood pressure control, resulting in the increased risk of adverse cardiovascular effects. Medical services should help overcome clinical inertia as well as other hindrances in order to improve the blood pressure control of patients. Self-measurement of home blood pressure is expected to ameliorate the status quo because it promotes an improved awareness among patients with high blood pressure, helping them adhere to antihypertensive lifestyle modifications and drug treatments.[5]

Our current study must be interpreted within the context of several potential limitations. First, because the patients in HOMED-BP received home blood pressure-guided

therapy,[14] their treatment was adjusted according to the self-measured home blood pressure, and the office blood pressure was used as complimentary information. Second, we excluded 1,095 (31.1%) of the randomised HOMED-BP patients, including 694 due to an insufficient number of home readings. According to Supplemental Table 1, there is likely little concern about the effect of exclusion on the balance between groups; however, this lack of an effect cannot be fully guaranteed, thus we should practice caution when applying the findings regarding antihypertensive drug effect to real-world clinical practice. Third, we were unable to assess the placebo effect in the present study because all patients received antihypertensive medication. The placebo effect is a major influencing factor, in addition to Wilder's law and the regression to the mean phenomenon, in the administration of antihypertensive medication.[27] Fourth, because office blood pressure was measured less than 3 times at each visit, the regression to the mean on office blood pressure cannot be assessed ~~or~~ compared with that on home blood pressure. Finally, although our results are representative of middle- to old-aged Japanese patients, they might not be applicable to other settings or ethnic groups with different distributions of risk factors.

In conclusion, the reduction in the home blood pressure by antihypertensive drug monotherapy was proportional to the home blood pressure during the pretreatment drug-free period, in accordance with Wilder's law.[12] However, the home blood pressure reduction peaked in the patients who had a high pretreatment home blood pressure (≥155 mmHg) when treatment was initiated with low-dose antihypertensive drugs. Patients with a systolic home blood pressure of ≥155 mmHg before treatment might be considered to have resistant hypertension because the effect of low-dose antihypertensive drug for the blood pressure reduction reached the plateau, which seems against Wilder's law; however, we cannot say too much about the issue because we enrolled patients with mild-to-moderate essential hypertension in the HOMED-BP study, and those with severe hypertension that tended to be resistant were not enrolled. Whether or not Wilder's law

can be similarly applied to high -risk patients with severe hypertension remains unclear. However, home blood pressure measurement was minimally affected by regression to the mean, suggesting the usefulness of home blood pressure measurement for estimating the efficacy of antihypertensive drugs. Patients with a high home blood pressure during pretreatment should receive a sufficient amount of antihypertensive medication starting from the very first treatment.

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Contributors

KA, YI, and TO conceived of and designed the study; AH, KA, MK, and YI acquired the data; and KA and HS carried out the statistical analyses. HS drafted the original manuscript with KA and AH. SM, YI, and TO provided the intellectual input, and all authors critically revised the manuscript and approved the final manuscript. KA is the guarantor.

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Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare no support from any organisation for the submitted work; KA, YI, and TO received research grants from Omron Healthcare. No other relationships or activities appear to have influenced the submitted work.

Ethical approval

Fully disclosed in the Study design section.

Data sharing

No additional data are available.

Statements

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Dissemination declaration

Dissemination of the results to study participants is not possible.

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Figure legends

Figure 1: Time course of blood pressure measurement during the study period.

Home blood pressures were the average of 5 days before randomisation without any antihypertensive treatment, after 10 to 28 days of monotherapy, and at the end of the follow-up period. Patients with 3 to 4 days of home blood pressure data in each interval were also included. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker.

Figure 2. Reduction in the systolic home blood pressure during monotherapy categorized by pretreatment home (left panel) and office (right panel) blood pressure.

Error bars indicate the 95% confidence interval. Data were adjusted for sex, age, body mass index, diabetes mellitus, current smoking and drinking, hypercholesterolemia, history of cardiovascular disease, and defined daily dose during monotherapy.

Figure 3. Reduction in the systolic home blood pressure during monotherapy categorized by pretreatment home blood pressure, stratified by defined daily dose (0.5 units, left panel; 1 unit, right panel).

Error bars indicate 95% confidence intervals. Data were adjusted for sex, age, body mass index, diabetes mellitus, current smoking and drinking, hypercholesterolemia, and history of cardiovascular disease.

Figure 4. Reduction in the follow-up systolic blood pressure categorized by pretreatment office blood pressure.

Error bars indicate 95% confidence intervals. Data were Adjusted for sex, age, body mass index, diabetes mellitus, current smoking and drinking, hypercholesterolemia,

history of cardiovascular disease, and defined daily dose at the end of follow-up period (mean, 7.0 years).

Table 1: Baseline characteristics of patients.

Characteristics	Systolic home blood pressure at baseline, mmHg				
	<145	**145–154**	**155–164**	**≥165**	***P***
Number of participants	763	699	544	417	
Women, n	416 (54.5)	342 (48.9)*	275 (50.6)	202 (48.4)	0.11
Age, years	59.3 (10.0)	59.3 (9.7)	61.0 (9.8)†	61.3 (9.5)	0.0003
Body mass index, kg/m²	24.2 (3.5)	24.2 (3.2)	24.6 (3.4)	24.8 (3.2)	0.0017
Smoking, n	142 (18.6)	138 (19.7)	112 (20.6)	109 (26.1)*	0.019
Drinking, n	347 (45.5)	344 (49.2)	270 (49.6)	211 (50.6)	0.27
Diabetes mellitus, n	122 (16.0)	101 (14.4)	85 (15.6)	70 (16.8)	0.74
Hypercholesterolemia, n	399 (52.3)	372 (53.2)	287 (52.8)	203 (48.7)	0.49
Previous cardiovascular diseases, n	25 (3.3)	17 (2.4)	17 (3.1)	7 (1.7)	0.37
Home blood pressure					
Systolic, mmHg	139.8 (3.0)	149.6 (2.9)§	159.4 (2.8)§	171.3 (4.3)§	<0.0001
Diastolic, mmHg	84.4 (8.4)	89.8 (8.9)§	92.6 (10.0)§	95.9 (10.9)§	<0.0001
Office blood pressure					
Systolic, mmHg	147.7 (15.5)	153.7 (16.5)§	157.8 (16.5)§	165.4 (17.1)§	<0.0001
Diastolic, mmHg	87.1 (11.2)	90.4 (11.8)§	91.1 (12.3)	94.0 (13.1)‡	<0.0001

Values are expressed as the arithmetic mean (standard deviation) or number (%). *P* values were calculated by an analysis of variance or the chi-squared test among the four systolic home blood pressure groups at baseline during pretreatment. For missing values of body mass index (*n*=40), single imputation with regression on sex and age was conducted.
Significance of differences from the left adjacent column: **P*<0.05, †*P*<0.01, ‡*P*<0.001, and §*P*<0.0001.

Table 2: Home systolic blood pressure values according to the measurement days.

Baseline blood pressure category	Number of patients	Home blood pressure measurement days (times)					
		First	Second	Third	Forth	Fifth	*P*
Pretreatment, mmHg							
All	2423	152.5 (14.7)	152.5 (14.8)	152.2 (14.9)	152.4 (14.6)	152.6 (14.9)	0.48
<145	763	140.3 (9.1)	139.6 (8.4)	139.1 (8.8)	139.7 (8.2)	140.4 (9.6)	0.032
145–154	699	149.6 (9.9)	150.0 (9.4)	149.5 (9.7)	149.5 (9.2)	149.5 (9.5)	0.85
155–164	544	159.3 (10.3)	158.7 (10.3)	159.5 (9.6)	159.8 (9.7)	159.8 (10.5)	0.41
≥165	417	170.9 (11.3)	172.0 (10.3)	171.1 (10.4)	171.0 (11.2)	171.4 (11.5)	0.66
Monotherapy, mmHg							
All	2423	145.5 (17.0)	145.2 (16.9)	145.4 (16.5)	145.4 (16.5)	144.7 (16.6)	0.58
<145	763	135.3 (13.2)	135.1 (13.1)	135.5 (13.4)	135.8 (13.2)	135.1 (13.1)	0.56
145–154	699	143.8 (13.8)	143.1 (13.3)	143.3 (13.0)	142.9 (13.3)	141.9 (12.9)	0.035
155–164	544	150.2 (15.3)	150.5 (15.4)	150.5 (14.6)	151.2 (14.4)	150.5 (14.7)	0.67
≥165	417	161.1 (16.5)	160.0 (17.0)	160.3 (15.4)	160.1 (16.1)	160.5 (15.9)	0.65

Values are expressed as the arithmetic mean (standard deviation). The numbers of patients with missing blood pressure data on the fourth and fifth days were 38 and 84 at pretreatment and 87 and 286 during monotherapy, respectively, while *P* values were calculated by a repeated measure mixed linear model to take missing values into account and represent the differences among the five systolic home blood pressure values according to the measurement day at baseline during pretreatment.
Differences between the adjacent days were not significant during pretreatment ($P \geq 0.12$) or monotherapy ($P \geq 0.14$).

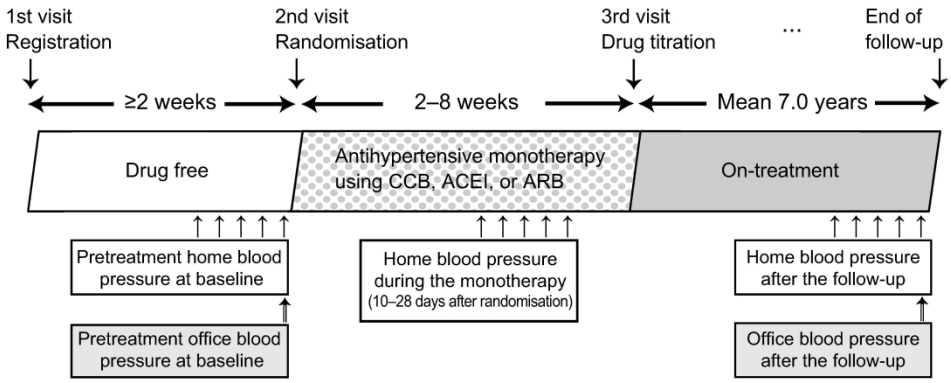

Figure 1: Time course of blood pressure measurement during the study period.
Home blood pressures were the average of 5 days before randomisation without any antihypertensive treatment, after 10 to 28 days of monotherapy initiation, and at the end of follow-up period. Patients with 3 to 4 days of home blood pressure data in each interval were also included. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker.

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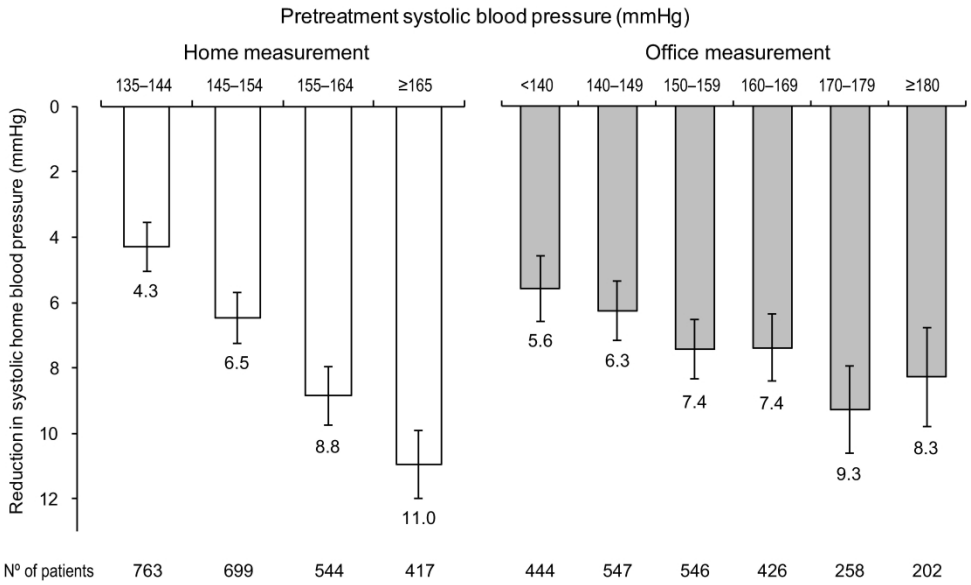

Figure 2. Reduction in the systolic home blood pressure during monotherapy categorized by pretreatment home (left panel) and office (right panel) blood pressure.
Error bars indicate 95% confidence interval. Data were adjusted for sex, age, body mass index, diabetes mellitus, current smoking and drinking, hypercholesterolemia, history of cardiovascular disease, and defined daily dose during monotherapy.

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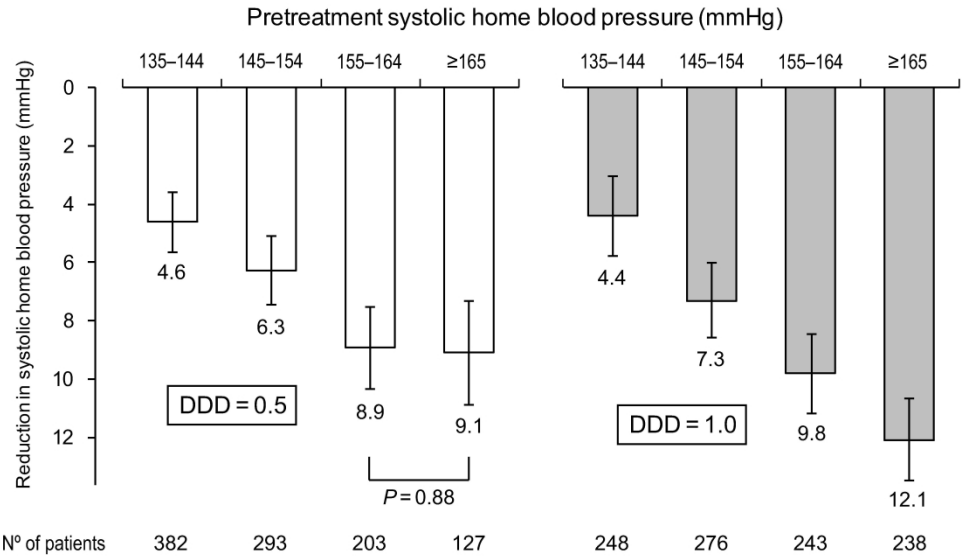

Figure 3. Reduction in the systolic home blood pressure during monotherapy categorized by pretreatment home blood pressure, stratified by defined daily dose (0.5 unit, left panel; 1 unit, right panel). Error bars indicate 95% confidence interval. Data were adjusted for sex, age, body mass index, diabetes mellitus, current smoking and drinking, hypercholesterolemia, and history of cardiovascular disease.

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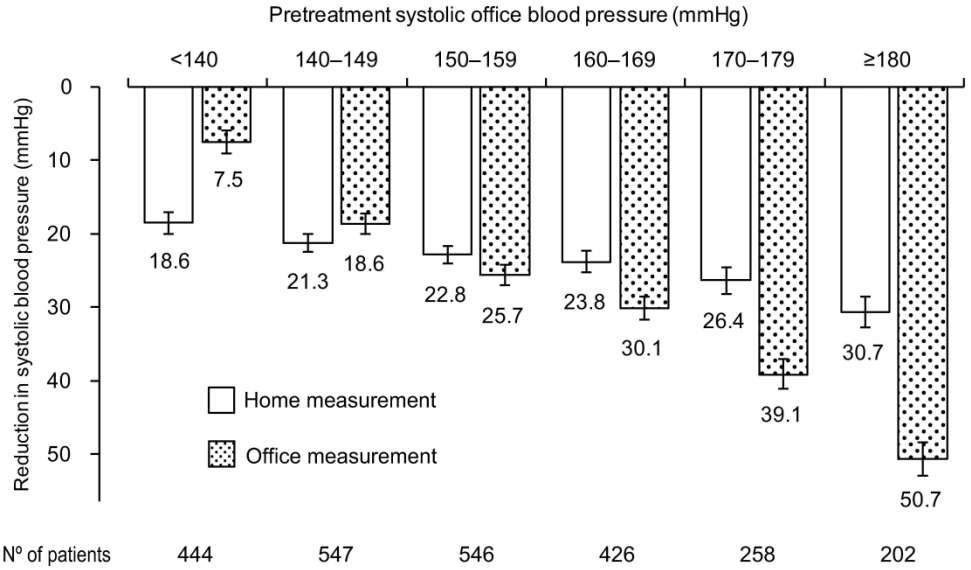

Figure 4. Reduction in the follow-up systolic blood pressure categorized by pretreatment office blood pressure.
Error bars indicate 95% confidence interval. Adjusted for sex, age, body mass index, diabetes mellitus, current smoking and drinking, hypercholesterolemia, history of cardiovascular disease, and defined daily dose at the end of follow-up period (mean, 7.0 years).

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SUPPLEMENTARY INFORMATION

Antihypertensive drug effects according to the pretreatment self-measured home blood pressure: the HOMED-BP study

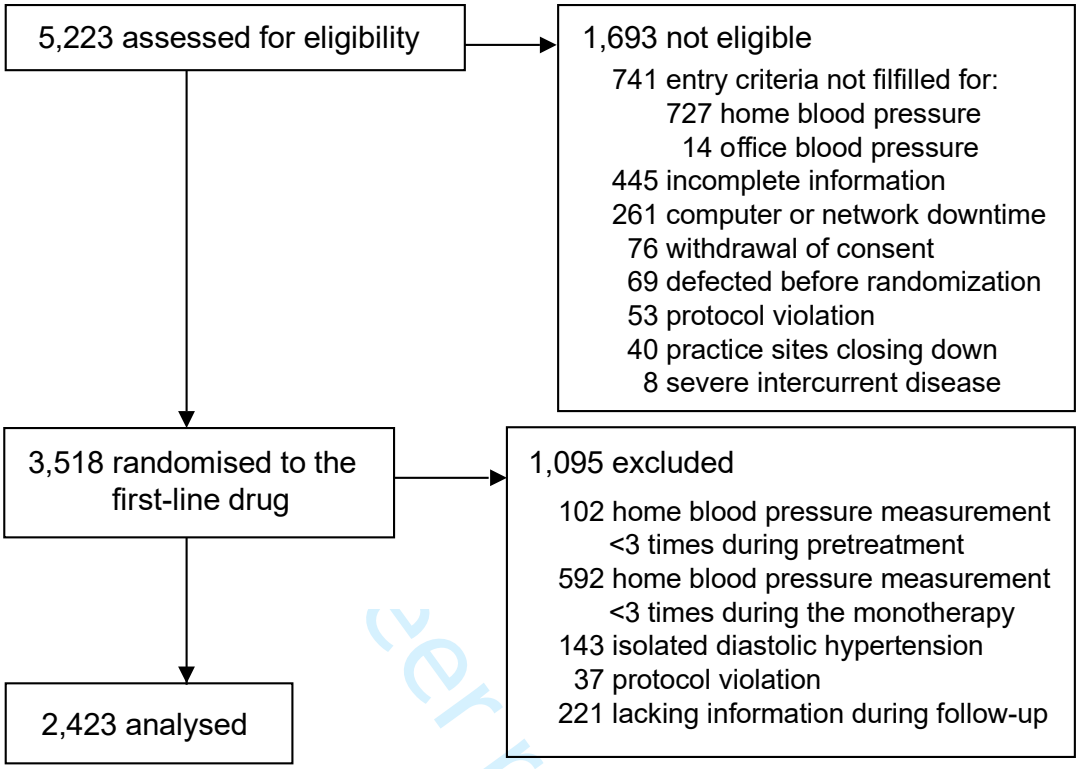
Short title: Wilder's Law on Home Blood Pressure

Hikari Sano, Azusa Hara, Kei Asayama, Seiko Miyazaki,
Masahiro Kikuya, Yutaka Imai, Takayoshi Ohkubo,
on behalf of
Hypertension Objective Treatment Based on Measurement
by Electrical Devices of Blood Pressure (HOMED-BP) investigators

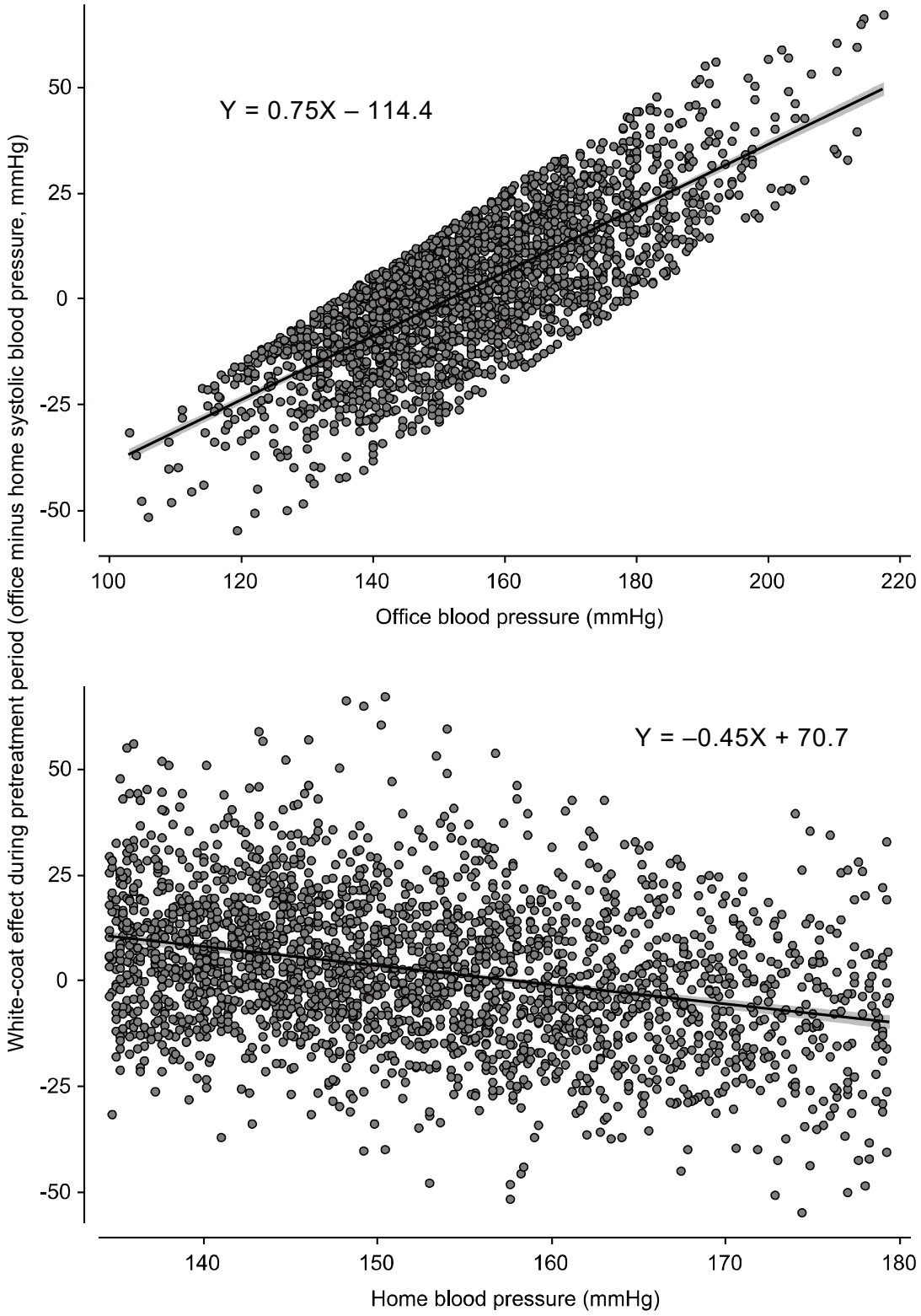
Supplemental Table 1: Baseline characteristics of the analysed patients (*n*=2,423), all excluded patients (*n*=1,095), and patients excluded due to an insufficient number of home blood pressure measurements (*n*=694).

		Excluded			
Characteristics	**Analysed**	**Any Reason**	***P***	**Insufficient Home Reading**	***P***
Number of participants	2423	1095		694	
Women, n	1235 (51.0)	528 (48.2)	0.13	355 (51.2)	0.93
Age, years	60.0 (9.8)	58.6 (10.5)	<0.0001	59.1 (10.7)	0.030
Body mass index, kg/m²	24.4 (3.3)	24.4 (3.6)	>0.99	24.4 (3.6)	0.97
Smoking, n	501 (20.7)	242 (22.1)	0.34	149 (21.5)	0.65
Drinking, n	1172 (48.4)	499 (45.6)	0.12	299 (43.1)	0.014
Diabetes mellitus, n	378 (15.6)	160 (14.6)	0.45	105 (15.1)	0.76
Hypercholesterolemia, n	1261 (52.0)	542 (49.5)	0.16	347 (50.0)	0.34
Previous cardiovascular diseases, n	66 (2.7)	40 (3.7)	0.14	31 (4.5)	0.020
Home blood pressure					
Systolic, mmHg	152.5 (11.6)	149.7 (14.1)	<0.0001	152.6 (13.0)	0.83
Diastolic, mmHg	89.8 (10.3)	90.2 (9.5)	0.26	90.5 (9.8)	0.12
Office blood pressure					
Systolic, mmHg	154.7 (17.4)	153.0 (17.7)	0.0064	154.2 (17.2)	0.49
Diastolic, mmHg	90.1 (12.2)	90.3 (12.2)	0.71	90.0 (12.3)	0.85

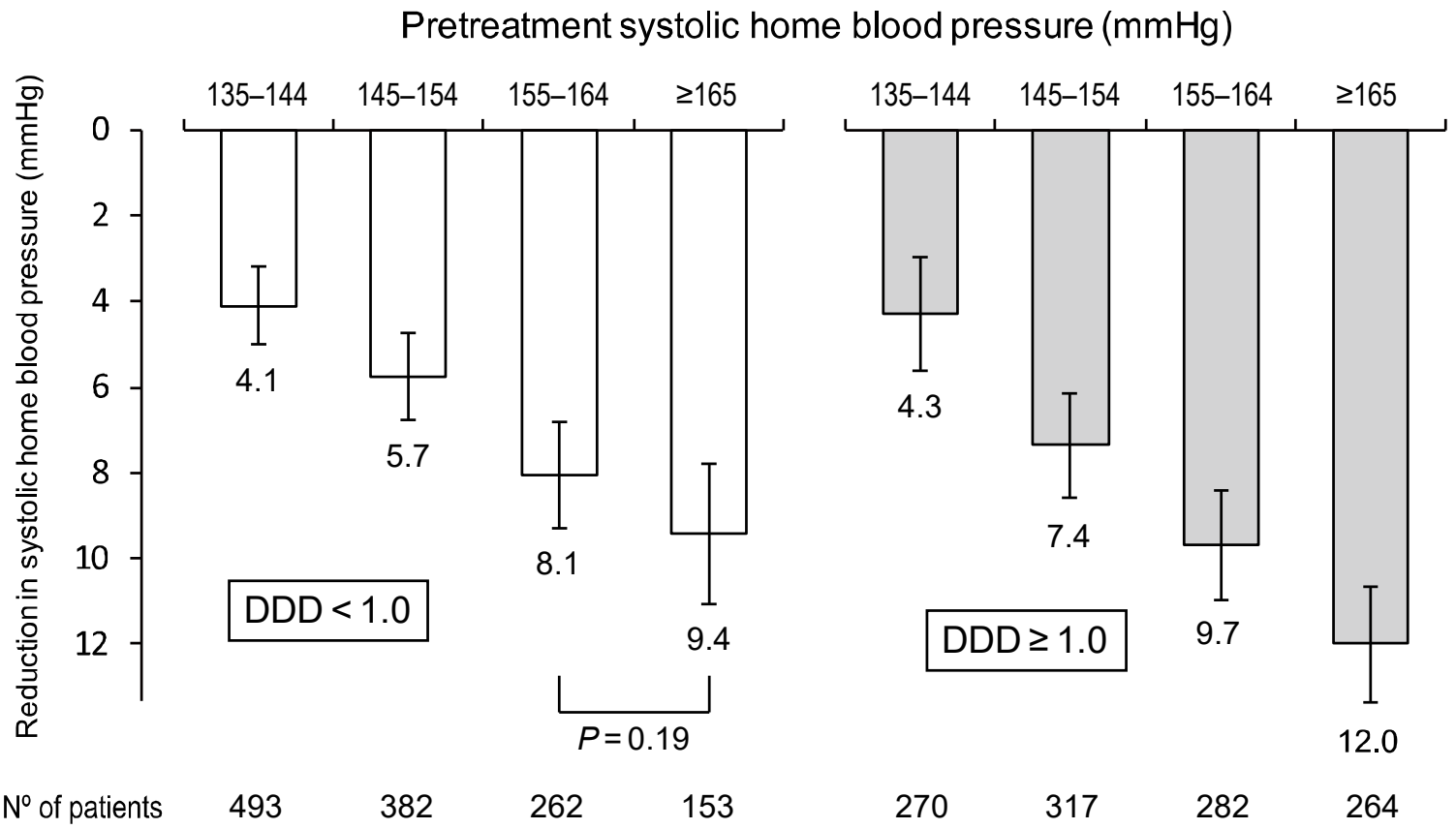
Values are expressed as the arithmetic mean (standard deviation) or number (%). *P* values were calculated by the t-test or the chi-squared test, with comparisons made between the 2,423 analysed patients and each excluded group.



Supplemental Figure 1: Flowchart of the study.

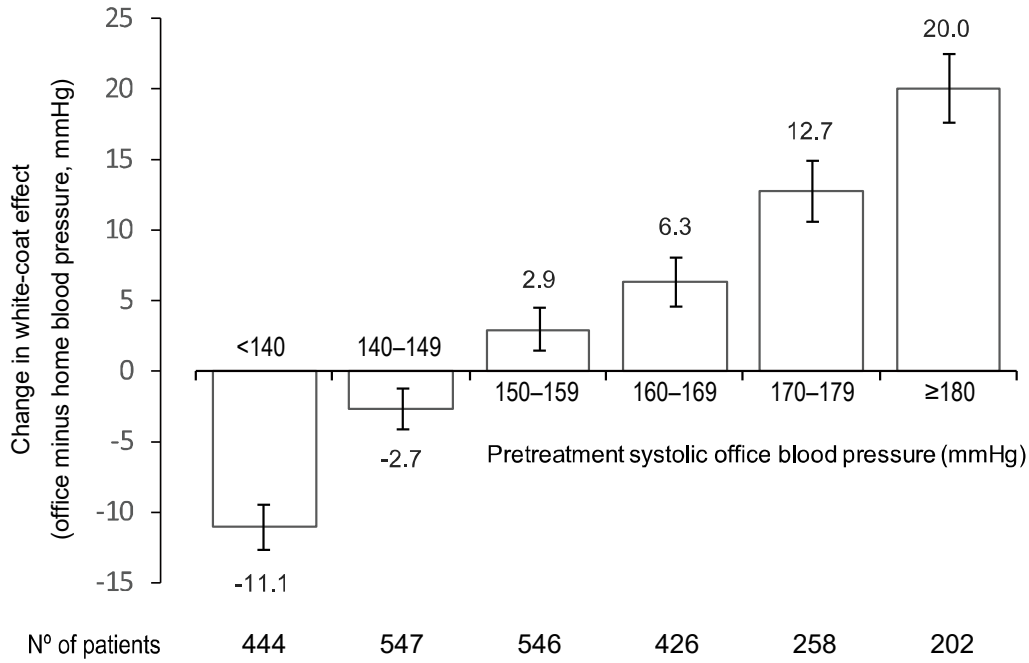


Supplemental Figure 2: Relationship between the white-coat effect and office systolic blood pressure (A) as well as home blood pressure (B) during pretreatment period.
The white-coat effect was defined as the office blood pressure minus the home blood pressure as a continuous variable. Regression line with 95% confidence limits were overlay on each scatter plot. Because systolic home blood pressure ranged 135–179 mmHg in this population, plots in panel A demonstrate as a band-like distribution which rises to the right.



Supplemental Figure 3: Reduction in the systolic home blood pressure during monotherapy categorized by pretreatment home blood pressure and stratified by defined daily dose (<1 unit, left panel; ≥1 unit, right panel).

Error bars indicate 95% confidence interval. Data were adjusted for sex, age, body mass index, diabetes mellitus, current smoking and drinking, hypercholesterolemia, history of cardiovascular disease, and defined daily dose during monotherapy.



Supplemental Figure 4: Changes in the white-coat effect during follow-up categorized by the pretreatment office blood pressure.

Error bars indicate 95% confidence interval. The white-coat effect was defined as the office blood pressure minus the home blood pressure, and changes in the white-coat effect were determined by subtracting the effect observed at the end of follow-up period from the effect during pretreatment.