PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Antihypertensive drug effects according to the pretreatment self-measured home blood pressure: the HOMED-BP study
AUTHORS	Sano, Hikari; Hara, Azusa; Asayama, Kei; Miyazaki, Seiko; Kikuya, Masahiro; Imai, Yutaka; Ohkubo, Takayoshi

VERSION 1 – REVIEW

REVIEWER	KoKo Aung Paul L. Foster School of Medicine Texas Tech University Health Sciences Center at El Paso El Paso, Texas U.S.A.
REVIEW RETURNED	26-Jun-2020

GENERAL COMMENTS	MAJOR 1. This post-hoc analysis excluded about 30% of participants (1,095 of the randomised 3,518 patients) after randomization for various reasons. Please revise the manuscript to include the answers of the following questions: (a) To what extent did this affect the balances between the groups with respect to many known and unknown confounding or prognostic variables created by randomization? (b) How much assurance do we still have that this degree of exclusion after randomization is practically not converting the randomized trial to a non-randomized study? 2. This analysis found that self-measured HBP was minimally affected by regression to the mean. Please comment on biological and/or statistical plausibility of this finding. MINOR 3. Please re-pharase/reframe/revise some sentences to improve clarity: a. “HBP during pretreatment and monotherapy kept the almost identical level within each period, regardless of the pretreatment HBP value.” Needs revising/rephrasing to improve clarity. (page 3 of 36) b. “… … association between the pretreatment office blood pressure and the home blood pressure reduction was weakly observed.” (page 13 of 36) c. “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.” (page 16 of 36)

REVIEWER	ANTONELLA ZAMBON

	University of Milan-Bicocca Italy
REVIEW RETURNED	10-Jul-2020

GENERAL COMMENTS	This is an interesting paper but I have some doubts. 1095 patients were excluded from the analysis. About 700 of them were excluded because they obtained < 3 home readings at baseline or during monotherapy. Could this exclusion affect the findings? In the Statistical analyses section the authors wrote "home blood pressures during the five pretreatment days as well as those during the five monotherapy days were compared by a repeated measure mixed lineare model while taking missing values into account". More details are needed to verify the corretness of approach (e.g. type of variance-covariance matrix). In the Statistical analyses section the authors wrote "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...". It's not clear the model used. More details are needed In Results section, the authors wrote "Age, body mass index, and office blood pressure were signficantly and positively associted with baseline systolic blood pressure category" (page 11, lines 53-56). Perhaps, smoking is lacking In Results section, page 10 line 60, the authors reported the p-value of group 155-164 as the minimum p-value observed in table 2 for pretreatment group. It's not the most appropriate way to report these findings. In figure 4 the authors wrote "Figure 4. Reduction in the follow-up systolic home blood pressure...". I think that "home" is wrong.

REVIEWER	Woo Seok Choi Moon Soul Graduate School of Future Strategy, Korea Advanced Institute of Science and Technology (KAIST)
REVIEW RETURNED	29-Aug-2020

GENERAL COMMENTS	Dear Editor, This article focused on the relationship between pre-treatment office and home blood pressure (BP) level and home BP reduction level by antihypertensive monotherapy. The authors tried to demonstrate how much pre-treatment BP levels, as shown in the Wilder Law, affect post-treatment outcomes. Thank you for providing the opportunity to review an interesting and unusual study. As a whole, this paper did a good job in using relevant citations from existing literature and outlining the logical flow of the study. With that said, listed below are some minor issues that would need to be revised prior to publication in the BMJ Open. To Authors Methods Page 7, line 24 The authors mentioned that this research was in accordance with the ethical principles of the Declaration of Helsinki; The provision of citation for this would be helpful for readers. Page 11, line 17

	In the Statistical Analysis section, the authors defined the term 'white-coat hypertension' and identified the determinant of BP change by white-coat effect. It is advised for the authors to provide a rationale or citation for their use of the term.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1.

Thank you very much, Dr. Aung, for your valuable comments.

1. This post-hoc analysis excluded about 30% of participants (1,095 of the randomised 3,518 patients) after randomization for various reasons. Please revise the manuscript to include the answers of the following questions: (a) To what extent did this affect the balances between the groups with respect to many known and unknown confounding or prognostic variables created by randomization? (b) How much assurance do we still have that this degree of exclusion after randomization is practically not converting the randomized trial to a non-randomized study?

Response: The baseline characteristics of the 1,095 excluded patients and 2,423 study patients are shown in the new Supplemental Table 1. We combined other excluded populations in our response to Reviewer 2 and merged the findings with the characteristics of the total 2,423 patients from Table 1 to avoid showing redundant information. Although statistically significant differences were found in the age and systolic blood pressure because of the relatively large number of participants, other characteristics were similar. We therefore feel that there is little concern about the effect of the exclusion of 1,095 patients on the balance between groups. However, the questions raised by the Reviewer cannot be fully addressed under the current study design and remain major limitations. Please refer to our response to Reviewer 2 for further details.

In response to this comment, we have now added the following text along with a subheading "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 pressurespan style="font-family:Arial; font-weight:bold"> <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." (Page 9, line 23 running over page 10, line 6)

"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." (Page 15, lines 2–7)

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)

Characteristics	Analysed	Excluded			
		Any Reason	P	Insufficient Home Reading	P
No. 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 chi-squared test, with comparisons made between the 2,423 analysed patients and each excluded group.

2. This analysis found that self-measured HBP was minimally affected by regression to the mean. Please comment on biological and/or statistical plausibility of this finding.

Response: This conclusion was based on the statistical analysis, so the plausibility of this finding should be self-evident. The biological aspect of the minimal regression to the mean of the self-measured home blood pressure is currently based on the circumstantial evidences as cited in the present manuscript[1-4]. However, to our knowledge, 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 compared with that on ambulatory blood pressure monitoring[5].

We have now added the following text to clarify the current evidence level of this matter:

"Based on ambulatory blood pressure monitoring, regression to the mean was observed consistently among the five studies [5], and a portion of the reduction in blood pressure after initiating antihypertensive treatment can be explained by this phenomenon [5]. 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 …" (Page 13, lines 4–10)

3. Please re-pharase/reframe/revise some sentences to improve clarity:

a. "HBP during pretreatment and monotherapy kept the almost identical level within each period, regardless of the pretreatment HBP value." Needs revising/rephrasing to improve clarity. (page 3 of 36)

Response: We have now revised the text as follows:

"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." (Page 2, lines 12–14)

b. "… … association between the pretreatment office blood pressure and the home blood pressure reduction was weakly observed." (page 13 of 36)

Response: We have now revised the text as follows:

"…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…" (Page 12, lines 6–9)

c. "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." (page 16 of 36)

Response: We have now revised the text as follows:

“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.” (Page 15, lines 21–27)

Reviewer 2.
Thank you very much, Dr. Zambon, for your valuable comments.
This is an interesting paper but I have some doubts.
1095 patients were excluded from the analysis. About 700 of them were excluded because they obtained < 3 home readings at baseline or during monotherapy. Could this exclusion affect the findings?
Response: A total of 694 participants were excluded due to insufficient home blood pressure measurements at baseline or during monotherapy. As shown in the new Supplemental Table 1, the characteristics of the 694 excluded patients were similar to those of the 2,423 analysed participants, except for the drinking status and cardiovascular disease history, which was partly because of the relatively large number of participants. Nevertheless, the exclusion of study participants remains a major limitation.
We combined other excluded populations in our response to Reviewer 2 and merged the findings with the characteristics of the total 2,423 patients from Table 1 to avoid showing redundant information. We have also added the following text along with the subheading “Representativeness of the study patients” (page 9, line 23). Please refer to our response to Reviewer 1 for further details.
“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 for the comparison between analysed patients and patients who were excluded due to an insufficient number of home blood pressure measurements (P≤0.020), all other characteristics were similar.” (Page 9, line 24 running over page 10, line 6)
“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, so we should practice caution when applying the findings regarding antihypertensive drug effect to real-world clinical practice.” (Page 15, lines 2–7)
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)

Characteristics	Analysed	Excluded			
		Any Reason	P	Insufficient Home Reading	P
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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 chi-squared test, with comparisons made between the 2,423 analysed patients and each excluded group.

In the Statistical analyses section the authors wrote "home blood pressures during the five pretreatment days as well as those during the five monotherapy days were compared by a repeated measure mixed lineare model while taking missing values into account". More details are needed to verify the corretness of approach (e.g. type of variance-covariance matrix).

Response: We performed the comparison using the following SAS program, in which ID, Days, and BP denote the unique patient identifier, day 1–5 home blood pressure measurement, and home blood pressure value, respectively.

```
Proc mixed method=reml;
 class ID Days;
 model BP=Days /solution cl ddfm = kr;
 repeated Days /sub=ID type=cs;
 lsmeans Days /cl diffs;
run;
```

We believe that our addition of the text below should address your concerns. If this is insufficient, we would appreciate it if you would specificity what else should be added.

“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[6] for the degrees of freedom calculations.” (Page 8, line 23 running over page 9, line 1)

In the Statistical analyses section the authors wrote "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...". It's not clear the model used. More details are needed

Response: We apologize for the unclear expression. 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 listed variables were adjusted. We have revised the text to clarify the analysis as follows:

“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.” (Page 9, lines 1–6)

In Results section, the authors wrote "Age, body mass index, and office blood pressure were signficantly and positively associted with baseline systolic blood pressure category" (page 11, lines 53-56). Perhaps, smoking is lacking

Response: As suggested, we have revised the text as follows:

“The Age, body mass index, smoking habit, and office blood pressure were …” (Page 10, line 10)

In Results section, page 10 line 60, the authors reported the p-value of group 155-164 as the minimum p-value observed in table 2 for pretreatment group. It's not the most appropriate way to report these findings.
Response: We apologize for this length sentence muddling our message. We have now revised the sentence as follows:
“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).” (Page 10, lines 12–18)
In figure 4 the authors wrote "Figure 4. Reduction in the follow-up systolic home blood pressure...". I think that "home" is wrong.
Response: As suggested, we have corrected the Figure legend as follows:
“Figure 4. Reduction in the follow-up systolic blood pressure categorized by pretreatment office blood pressure.” (Page 22, lines 21–22)

Reviewer 3.
Thank you very much, Dr. Choi, for your valuable comments.
Methods
Page 7, line 24
The authors mentioned that this research was in accordance with the ethical principles of the Declaration of Helsinki; The provision of citation for this would be helpful for readers.
Response: As suggested, we have revised this sentence with the citation (World Medical Association 2013)[7] to reflect the philosophy of the Declaration of Helsinki, as described in the article 1, as shown below. Please understand that the current version of the Declaration of Helsinki consists of 37 articles, and to explain one by one is outside of the scope of the present manuscript.
“The HOMED-BP protocol complies with the Declaration of Helsinki with respect to the ethical principles for medical research involving human subjects [7], …” (Page 5, lines 8–10)
Page 11, line 17
In the Statistical Analysis section, the authors defined the term ‘white-coat hypertension’ and identified the determinant of BP change by white-coat effect. It is advised for the authors to provide a rationale or citation for their use of the term.
Response: We used the definition for the white-coat effect (not hypertension) described in previous reports[8-10]. We have now cited these references accordingly (page 9, line 13). Whereas, we would like to note that home blood pressure is free from white-coat ‘phenomenon’. To distinguish the analysed difference (white-coat effect) and the phenomenon observed in blood pressure, we have changed the word ‘effect’ to ‘phenomenon’ at appropriate points (page 4, line 6; page 4, line 12; and page 13, line 26).

References used in the Responses.
1) Imai Y, Hosaka M, Elnagar N, et al. Clinical significance of home blood pressure measurements for the prevention and management of high blood pressure. Clin Exp Pharmacol Physiol 2014;41:37-45 PubMed .
2) Vaur L, Dubroca II, Dutrey-Dupagne C, et al. Superiority of home blood pressure measurements over office measurements for testing antihypertensive drugs. Blood Press Monit 1998;3:107-114 PubMed .
3) Imai Y, Ohkubo T, Hozawa A, et al. Usefulness of home blood pressure measurements in assessing the effect of treatment in a single-blind placebo-controlled open trial. J Hypertens 2001;19:179-185 PubMed .

4) Ohkubo T, Asayama K, Kikuya M, et al. How many times should blood pressure be measured at home for better prediction of stroke risk? Ten-year follow-up results from the Ohasama study. J Hypertens 2004;22:1099-1104 PubMed .
5) Moore MN, Atkins ER, Salam A, et al. Regression to the mean of repeated ambulatory blood pressure monitoring in five studies. J Hypertens 2019;37:24-29 PubMed .
6) Kenward MG, Roger JH. Small sample inference for fixed effects from restricted maximum likelihood. Biometrics 1997;53:983-997 PubMed .
7) World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 2013;310:2191-2194 PubMed .
8) Asayama K, Ohkubo T, Rakugi H, et al. Comparison of blood pressure values-self-measured at home, measured at an unattended office, and measured at a conventional attended office. Hypertens Res 2019;42:1726-1737 PubMed .
9) Schmieder RE, Schmidt ST, Riemer T, et al. Disproportional decrease in office blood pressure compared with 24-hour ambulatory blood pressure with antihypertensive treatment: dependency on pretreatment blood pressure levels. Hypertension 2014;64:1067-1072 PubMed .
10) Ogata S, Kamide K, Asayama K, et al. Genome-wide association study for white coat effect in Japanese middle-aged to elderly people: The HOMED-BP study. Clin Exp Hypertens 2018;40:363-369 PubMed .

VERSION 2 – REVIEW

REVIEWER	KoKo Aung Paul L. Foster School of Medicine Texas Tech University Health Sciences Center at El Paso El Paso, Texas U.S.A.
REVIEW RETURNED	05-Oct-2020

GENERAL COMMENTS	Strengths and limitations section (after the abstract) can be further strengthened by stating how each bullet is a strength or a limitation instead of merely recounting the method and number of participants enrolled. In addition, it should also address the potential implication of large number of excluded participants in this post-hoc analysis after randomization (responses to reviewers #1 and #2 on this topic).

VERSION 2 – AUTHOR RESPONSE

Reviewer 1.
Thank you very much again, Dr. Aung, for your valuable comment.

Strengths and limitations section (after the abstract) can be further strengthened by stating how each bullet is a strength or a limitation instead of merely recounting the method and number of participants enrolled. In addition, it should also address the potential implication of large number of excluded participants in this post-hoc analysis after randomization (responses to reviewers #1 and #2 on this topic).

Response: As suggested, we have revised the ‘Strengths and limitations’ section to clarify these points as follows.

- 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 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.

Since we further emphasized one strength of the study, we have added the corresponding information in Study design section as follows:

"…; they were recruited from 457 general practices throughout Japan. [1,2]" (Page 5, lines 15–16)

References used in the Response.

1) Asayama K, Ohkubo T, Metoki H, et al. Cardiovascular outcomes in the first trial of antihypertensive therapy guided by self-measured home blood pressure. Hypertens Res 2012;35:1102-1110 PubMed .

2) Watabe D, Asayama K, Hanazawa T, et al. Predictive power of home blood pressure indices at baseline and during follow-up in hypertensive patients: HOMED-BP study. Hypertens Res 2018;41:622-628 PubMed .

VERSION 3 – REVIEW

REVIEWER	KoKo Aung Paul L. Foster School of Medicine Texas Tech University Health Sciences Center at El Paso U.S.A.
REVIEW RETURNED	17-Nov-2020

GENERAL COMMENTS	All the concerns of the reviewers have been adequately addressed. I have no additional comments.