Peer Review File

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Reviewer A

Dr. Xia and colleagues performed a longitudinal study in a part of the Shanghai Aging Study (SAS), described as a prospective, population-based cohort study in old people in Jing'an Temple Community, an urban community in Shanghai, China.

In this sample, the authors show that incident cerebral microbleeds (CMBs) increase according to the newer AHA-ACC definition of stages of hypertension. The study is of interest and add important information about subclinical damages secondary to elevated BP values. The presentation of the results is good and the discussion is fair.

I think the major weaknesses in the study are the great loss of participants at follow-up and the change in the MRI methods (T2-GRE vs SWAN) to identify CMBs.

I have other comments to improve the manuscript:

Comment 1: Page 6 lines 11-12: I don't agree with the sentence "While several randomized clinical trials supported a target of BP lower than 130/80 mm Hg in secondary stroke prevention (11,12)". There are also several trials that show that to decrease too much BP after a stroke is deleterious.

Reply 1: We agree it is deleterious to decrease too much BP because it might cause an increase in serious adverse events. Therefore, we added some arguments in the introduction section ((Page 7, Line 11~15).

Changes in the text: While several randomized clinical trials supported a target of BP lower than 130/80 mm Hg in secondary stroke prevention (1,2), one study pointed out that there would be an increase in serious adverse events if the SPRINT intensive SBP treatment goal were fully implemented (3). The clinical value of this new definition of hypertension remains controversial (4-6).

Comment 2: It is not perfectly clear what covariates were put in the final linear model: each of the variables mentioned in the legend of table 1 or a selection with $p<0.05$? All the subgroups of BP categories were put together or one at a time? Please clarify (also in the manuscript).

Reply 2: Covariables were selected from univariable analyses with $P<0.05$ or with known potential clinical significance. We clarified the selection process in the methods section (Page 13, Line 7-9). All the subgroups of BP categories were put together in the models by using dummy variable categories. Normal BP was considered as the reference category. We clarified this in the methods section (Page 13, Line 9-11).

Changes in the text: Covariables were selected from univariable analyses with $P<0.05$ or with known potential clinical significance (7-10). These covariables were adjusted in multivariable models. All the subgroups of BP categories were put together in the

models by using dummy variable categories. Normal BP was considered as the reference category.

Comment 3: The sentence at page 10 lines 3-4 “The characteristics of the study population at baseline and follow-up were compared by Mann-Whitney U test in continuous variables, and Chi-square test or Fisher’s exact test in categorical variables.” Seems a repetition.

Reply 3: Thank you for the suggestion. We deleted this sentence in the methods section (Page 13, Line 2~4).

Changes in the text: ~~The characteristics of the study population at baseline and follow-up were compared by Mann-Whitney U test in continuous variables, and Chi-square test or Fisher’s exact test in categorical variables.~~

Comment 4: A careful English editing by a native English speaker is needed. Just to mention some typos:

- Page 11 line 11: groups were “demonstrated” (please substitute with a more appropriate term like shown).

- Page 11 lines 14: “The” (A not the) similar trend was observed in the prevalence of…

- For sake of clarity: page 13 lines 13-14: In our study, we found no association between (please add: the group with slightly) elevated SBP (120 to 129 mmHg) and higher “incident” (please substitute with “incidence”) rate of CMBs.

Reply 4: Thank you for the suggestion. We corrected the typos mentioned above in the manuscript (Page 15, Line 6; Page 15, Line 8; Page 18, Line 7~9). The manuscript was also edited by a native English speaker.

Changes in the text:

- The number and location of CMBs at baseline and follow-up in the four BP groups were shown in Table e-3.

- A similar trend was observed in the prevalence of any microbleeds at follow-up (normal BP: 19.0%, elevated systolic BP: 26.7%, stage 1 hypertension: 31.4%, stage 2 hypertension: 38.6%).

- In our study, we found no association between the group with slightly elevated SBP (120 to 129 mmHg) and higher incidence rate of CMBs.

Reviewer B

Aim of the study is to examine the relationship between the new definition of hypertension following the ACC/AHA 2017 Us Guidelines and incident Cerebral Microbleeds (CMBs) in a 7-year longitudinal community cohort study, in consideration of their prognostic significance.

Major issues

Comment 1: According to the authors, the assessment of blood pressure levels was carried out exclusively at the time of enrolment. No information is provided regarding the degree of blood pressure control achieved by the patients during the follow-up period. This data could influence the development of CMBs even more than the initial blood pressure level. The lack of this data reduces the reliability of the results.

The authors themselves in the discussion section suggest that a closer control of SBP could be useful in reducing the risk of new CMBs, demonstrating the importance of the achieved level of pressure control within the follow-up, which they do not provide and recognize this as a limitation of their study; in my opinion, unfortunately it is such a limitation that it severely limits the validity of the results.

Reply 1: We agree that the degree of blood pressure (BP) control during the follow-up period might influence the development of CMBs. Therefore, we made some analyses to examine the impact of BP control within the follow-up on the development of CMBs. BP data at follow-up (2016-2018) were collected the same way as they were collected at baseline, and were categorized into two groups: 1) well controlled BP: SBP <130 mmHg and DBP <80 mmHg; 2) uncontrolled BP: SBP ≥130 mm Hg or DBP ≥80 mmHg. Thus, the BP data at follow-up were transformed into a binary variable and were then adjusted in the multivariable analyses between possible predictors and incident CMBs. The results were shown in Table e-4. The relationships between baseline BP categories and incident CMBs remained the same after adjusting the BP control data at follow-up.

However, since we only had data of BP control at one point during the follow-up period and failed to measure the BP regularly at intervals throughout the 7 years, the data of BP control might not be precise enough. We discussed this limitation in the discussion section (Page 20~21, Line 16~5).

Changes in the text: Third, we only had data of BP at baseline (2009-2011) and follow-up (2016-2018), and failed to measure the BP regularly at intervals throughout the 7 years. Therefore, although we didn't observe any impact of the BP control at follow-up on the incidence rate of CMBs (Table e-4), this needed to be further examined in the future community studies with repeated BP measurements throughout the follow-up period.

Table e-4. Univariable and multivariable analyses between possible predictors and incident cerebral microbleeds

Possible predictors	Univariable			Multivariable		
	IRR	95%CI	P	IRR	95%CI	P*
Age	1.07	1.03,1.10	<0.001	1.11	1.07,1.15	<0.001
Sex	0.37	0.24,0.57	<0.001	0.17	0.10,0.29	<0.001
Body mass index	1.04	0.99,1.09	0.101	1.04	0.99,1.10	0.140
Current smoking	0.53	0.25,1.14	0.105	2.32	0.93,5.76	0.070
ApoE ε4 carriers	1.20	0.74,1.94	0.467	1.70	1.00,2.87	0.049
ApoE ε2 carriers	0.63	0.35,1.11	0.112	0.56	0.31,1.03	0.063
BP categories						

Normal BP	Ref	Ref	Ref	Ref	Ref	Ref
Elevated systolic BP	0.7	0.17,2.80	0.614	0.96	0.24,3.94	0.958
Stage 1 hypertension	**2.7**	**1.11,6.54**	**0.028**	**2.79**	**1.11,7.00**	**0.029**
Stage 2 hypertension	**3.22**	**1.41,7.38**	**0.006**	**3.05**	**1.29,7.24**	**0.011**
Diabetes	2.54	1.68,3.85	<0.001	2.75	1.76,4.31	<0.001
Hyperlipidemia	0.46	0.30,0.71	<0.001	0.34	0.21,0.54	<0.001
Cardiogenic diseases	0.53	0.25,1.14	0.105	0.52	0.24,1.15	0.105
Antiplatelet/ anticoagulation	0.76	0.46,1.27	0.300	0.71	0.41,1.23	0.224
Uncontrolled BP at follow-up	1.16	0.76,1.77	0.486	0.99	0.64,1.53	0.949

*P values were calculated after adjusting for age, sex, body mass index, current smoking, ApoE ε4 carriers, ApoE ε2 carriers, BP categories, diabetes, hyperlipidemia, cardiogenic diseases, antiplatelet or anticoagulation medication and uncontrolled BP at follow-up. BP categories: (1) normal BP, SBP <120 mmHg and DBP <80 mmHg; (2) elevated systolic BP, SBP of 120 to 129 mmHg and DBP <80 mm Hg; (3) stage 1 hypertension, SBP of 130 to 139 mm Hg or DBP of 80 to 89 mm Hg; (4) stage 2 hypertension, SBP ≥140 mm Hg or DBP ≥90 mmHg. Uncontrolled BP at follow-up: SBP ≥130 mm Hg or DBP ≥80 mmHg.

Abbreviations: BP = blood pressure; SBP = systolic blood pressure; DBP = diastolic blood pressure; IRR = incident rate ratio; CI = confidence interval

Comment 2: The other point that the authors recognize as a limitation of the study is also a severe limitation, since all major international guidelines recognize that only with appropriate out-of-office monitoring is it possible to accurately identify a truly hypertensive subject avoiding the risk of white-coat effect or masked hypertension.

Reply 2: We agree that white-coat effect might lead to misclassification of hypertensive status. However, we consider the effect as a limited systematic error because BP was measured under the same circumstances for all the participants at baseline. We added this part in the discussion section (Page 20, Line 14~16).

Changes in the text: Moreover, since BP was measured under the same circumstances for all the participants at baseline, the misclassification of BP categories due to white coat effect could be regarded as a limited systematic error.

Comment 3: In addition, the authors' attribution to the different ACC AHA 2017 categories of BP is further distorted by the fact that about 48% of patients enrolled were already hypertensive and possibly already taking one or more anti-hypertensive drugs (45.9 % according to table e-1). Therefore, it is conceivable that a subject categorized as normal was a subject with stage 2 hypertension well controlled by therapy.

Reply 3: We agree that a subject categorized as normal BP might be a subject with stage 2 hypertension well controlled by therapy. However, the objective of this study was to examine the impact of baseline BP level on the progression of CMBs, no matter anti-hypertensive drugs were taken or not. In other words, as long as the subjects had normal BP, they were categorized into the normal BP group regardless of their medication

history. In our future study, we will explore the impact of anti-hypertensive drugs on the progression of CMBs in subjects with same baseline BP level.

Minor changes

Comment 4: Introduction Line 5 and foll - correct the indication of references: (8,9) or (8-10) and not (8) (9)

Reply 4: Thank you for the suggestion. We have modified the references as advised (Page 7, Line 5~6).

Changes in the text: Cross-sectional (11,12) and longitudinal studies (9,13) revealed that blood pressure (BP) over 140/90 mmHg was a crucial risk factor of CMBs in the general population.

Comment 5: Methods pag 9 Line 1: please better define “cardiogenic disease”

Reply 5: Thank you for the suggestion. We defined “cardiogenic disease” in the methods section (Page 11, Line 9~10).

Changes in the text: Cardiogenic disease was defined as atrial fibrillation or coronary artery disease

References

1. Kitagawa K, Yamamoto Y, Arima H, et al. Effect of Standard vs Intensive Blood Pressure Control on the Risk of Recurrent Stroke: A Randomized Clinical Trial and Meta-analysis. JAMA Neurol 2019.

2. Group SPSS, Benavente OR, Coffey CS, et al. Blood-pressure targets in patients with recent lacunar stroke: the SPS3 randomised trial. Lancet 2013;382:507-15.

3. Bress AP, Kramer H, Khatib R, et al. Potential Deaths Averted and Serious Adverse Events Incurred From Adoption of the SPRINT (Systolic Blood Pressure Intervention Trial) Intensive Blood Pressure Regimen in the United States: Projections From NHANES (National Health and Nutrition Examination Survey). Circulation 2017;135:1617-28.

4. Schiffrin EL. New blood pressure cut-offs, prevalence of hypertension and control, and mood disorders: are patients benefitting from lower cut-offs for defining hypertension? Eur Heart J 2019;40:739-42.

5. Brunstrom M, Carlberg B. Association of Blood Pressure Lowering With Mortality and Cardiovascular Disease Across Blood Pressure Levels: A Systematic Review and Meta-analysis. JAMA Intern Med 2018;178:28-36.

6. Atasoy S, Johar H, Peters A, et al. Association of hypertension cut-off values with 10-year cardiovascular mortality and clinical consequences: a real-world perspective from the prospective MONICA/KORA study. Eur Heart J 2019;40:732-8.

7. Nam KW, Kwon HM, Jeong HY, et al. Cerebral Small Vessel Disease and Stage 1 Hypertension Defined by the 2017 American College of Cardiology/American Heart Association Guidelines. Hypertension 2019;73:1210-6.

8. Vernooij MW, van der Lugt A, Ikram MA, et al. Prevalence and risk factors of cerebral microbleeds: the Rotterdam Scan Study. Neurology 2008;70:1208-14.

9. Ding J, Sigurdsson S, Garcia M, et al. Risk Factors Associated With Incident Cerebral Microbleeds According to Location in Older People: The Age, Gene/Environment Susceptibility (AGES)-Reykjavik Study. JAMA Neurol 2015;72:682-8.

10. Loehrer E, Ikram MA, Akoudad S, et al. Apolipoprotein E genotype influences spatial distribution of cerebral microbleeds. Neurobiol Aging 2014;35:899-905.

11. Poels MM, Vernooij MW, Ikram MA, et al. Prevalence and risk factors of cerebral microbleeds: an update of the Rotterdam scan study. Stroke 2010;41:S103-6.
12. Elmstahl S, Ellstrom K, Siennicki-Lantz A, et al. Association between cerebral microbleeds and hypertension in the Swedish general population "Good Aging in Skane" study. J Clin Hypertens (Greenwich) 2019;21:1099-107.
13. Poels MM, Ikram MA, van der Lugt A, et al. Incidence of cerebral microbleeds in the general population: the Rotterdam Scan Study. Stroke 2011;42:656-61.