



Incident cerebral microbleeds and hypertension defined by the 2017 ACC/AHA Guidelines

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Background: The cut-off for hypertension was lowered to blood pressure (BP) over 130/80 mmHg in the 2017 American College of Cardiology/American Heart Association (ACC/AHA) guideline. Whether the new definition of hypertension remains a potent risk factor of cerebral microbleeds (CMBs) is uncertain. We aimed to analyze the relationship between the new definition of hypertension and incident CMBs in a 7-year longitudinal community study.

Methods: This study is a sub-study of the Shanghai Aging Study (SAS). A total of 317 participants without stroke or dementia were included at baseline (2009–2011), and were invited to repeated clinical examinations and cerebral magnetic resonance imaging (MRI) at follow-up (2016–2018). CMBs at baseline and follow-up were evaluated on T2*-weighted gradient recalled echo (GRE) and susceptibility-weighted angiography (SWAN) sequence of MRI. We classified baseline BP into four categories: normal BP, elevated systolic BP, stage 1 hypertension and stage 2 hypertension according to the ACC/AHA guideline. We assessed the associations between BP categories and incident CMBs by generalized linear models.

Results: A total of 159 participants (median age, 67 years) completed follow-up examinations with a mean interval of 6.9 years. Both stage 1 and stage 2 hypertension at baseline were significantly related with a higher risk of incident CMBs (IRR 2.77, 95% CI, 1.11–6.91, P=0.028; IRR 3.04, 95% CI, 1.29–7.16, P=0.011, respectively), indicating dose-response effects across BP categories. Participants with ≥ 5 incident CMBs or incident CMBs in the deep locations all had baseline stage 1 and 2 hypertension.

Conclusions: Participants with baseline stage 1 and stage 2 hypertension had a significantly higher risk of incident CMBs in this 7-year longitudinal community cohort.

Keywords: Cerebral microbleeds (CMBs); blood pressure (BP); ACC/AHA guidelines; longitudinal studies; cerebral small vessel disease

Submitted Jul 05, 2020. Accepted for publication Nov 15, 2020.

doi: 10.21037/atm-20-5142

View this article at: <http://dx.doi.org/10.21037/atm-20-5142>

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Introduction

Cerebral microbleeds (CMBs), an imaging marker of cerebral small vessel diseases, are visualized as small rounded hypointense lesions on blood-sensitive magnetic resonance imaging (MRI) sequences (1), and are associated with recurrent stroke, dementia and mortality (2-4).

Cross-sectional (5,6) and longitudinal studies (7,8) revealed that blood pressure (BP) over 140/90 mmHg was a crucial risk factor of CMBs in the general population. Since the Systolic Blood Pressure Intervention Trial (SPRINT) showed that aggressive control of BP resulted in lower rates of major cardiovascular events and mortality (9), cut-off for hypertension was lowered from 140/90 to 130/80 mmHg in the 2017 American College of Cardiology/American Heart Association (ACC/AHA) guideline (10). While several randomized clinical trials supported a target of BP lower than 130/80 mmHg in secondary stroke prevention (11,12), one study pointed out that there would be an increase in serious adverse events if the SPRINT intensive systolic blood pressure (SBP) treatment goal was fully implemented (13). The clinical value of this new definition of hypertension remains controversial (14-16).

Few studies have examined the significance of this new definition of hypertension in the prevalence and progression of CMBs. One cross-sectional study demonstrated that stage 1 hypertension (SBP: 130–139 mmHg, DBP: 80–89 mmHg) was independently associated with the prevalence of CMBs in a healthy population (17). However, to our knowledge, the relationship between baseline stage 1 hypertension and incident CMBs in longitudinal studies remains unclear.

In our study, we aimed to investigate the relationship between the new definition of hypertension and incident CMBs in a 7-year longitudinal community cohort study.

We present the following article in accordance with the STROBE reporting checklist (available at <http://dx.doi.org/10.21037/atm-20-5142>).

Methods

Study population

This study is a sub-study of the Shanghai Aging Study (SAS), which was a cohort study on the elderly community residents in Jing'an Temple, an urban community in Shanghai, China. We have published the detailed study protocol previously (18). A total of 350 adults over 60 years of age without dementia or stroke underwent baseline

clinical examinations and cerebral MRI including T2*-weighted gradient recall echo (GRE) sequence from 2009 to 2011. Of the 350 MRI examinations, 33 were excluded because of the missing of GRE sequence. Therefore, 317 participants were considered as baseline participants for this study. Exclusion criteria were listed as follows: (I) more than 50% stenosis of cerebral large vessels; (II) brain tumors or hydrocephalus; (III) MRI contraindications; (IV) incorporative or inability to complete the examination. All eligible participants were invited to repeated clinical examinations and cerebral MRI at follow-up (2016–2018), as described in our previous study (19).

MRI

From 2009 to 2011 at baseline, all eligible participants took cerebral MRI scans on a 1.5-Tesla GE scanner. The sequences were as follows: T2*-weighted gradient recalled echo (GRE), T1-weighted, T2-weighted, axial fluid-attenuated inversion recovery (FLAIR), and magnetic resonance angiogram (MRA) sequence. We have described full acquisition details previously (20).

From 2016 to 2018 at follow-up, all eligible participants underwent repeated MRI scans on a 3.0-Tesla GE scanner with following sequences: Susceptibility Weighted ANgiography (SWAN) (slice thickness 2.0 mm, flip angle 15 degree, TR/TE minimum/45 ms), 3D T1 BRAVO (slice thickness 1.2 mm, flip angle 12 degrees), T2 PROPELLER (slice thickness 6.0 mm, slice spacing 2.0 mm, flip angle 140 degree, TR/TE = 7.586 s/93.76 ms), Cor CUBE FLAIR (slice thickness 2.0 mm, TR/TE 6,000/90 ms), and MRA (slice thickness 1.4 mm, flip angle 20 degree, TR/TE minimum/minimum).

CMBs were defined on T2*-weighted GRE at baseline or SWAN at follow-up as rounded areas of signal void with associated blooming, 2 to 10 mm in diameter (1). Signal voids were excluded in case of sulcal vessels, choroid plexus and pineal calcifications, symmetrical calcifications in the basal ganglia, and signal averaging from bone (21). Two neurologists with certification and registration assessed the number and location of CMBs at baseline and follow-up according to the Microbleed Anatomical Rating Scale (MARS) without knowing the clinical data of the participants (22). CMBs were assessed with good inter-rater reliability ($k=0.75$) and excellent intra-rater reliability ($k=0.90$). Results were confirmed by a senior neurologist if any disagreements exist. The participants were categorized into two groups according to CMBs location (i.e., strictly

deep CMBs *vs.* lobar or infratentorial CMBs [with or without additional deep CMBs]). Incident CMBs were defined as any new CMBs from baseline.

Clinical assessment

We evaluated baseline demographics, vascular risk factors and medication use, including age, sex, education, body mass index, current smoking, apolipoprotein E (APOE) genotypes, history of hypertension, diabetes mellitus, hyperlipidemia, cardiogenic disease, and use of antihypertensive, antidiabetic, lipid lowering, and antiplatelet or anticoagulation medication. Cardiogenic disease was defined as atrial fibrillation or coronary artery disease. APOE genotypes were assessed via DNA samples from blood or saliva (20). The presence of at least one $\epsilon 4$ (or $\epsilon 2$) allele was treated as being APOE $\epsilon 4$ (or $\epsilon 2$) positive. History of hypertension was defined by a self-reported medical history of hypertension, and was confirmed in medical records (SBP ≥ 140 or DBP ≥ 90 mmHg). Details of clinical assessment were previously published elsewhere (20).

After the participants rested on a comfortable ordinary chair for at least 5 minutes, baseline BP was measured by using a mercury sphygmomanometer with a cuff of appropriate size, following standard recommended procedures (23). Two readings of SBP and DBP were taken at 5-minute intervals, and SBP and DBP data were obtained by averaging each 2 readings (17). According to the 2017 ACC/AHA hypertension guidelines (10), participants' BP at baseline were categorized into 4 groups: (I) normal BP, SBP < 120 mmHg and DBP < 80 mmHg; (II) elevated systolic BP, SBP of 120 to 129 mmHg and DBP < 80 mmHg; (III) stage 1 hypertension, SBP of 130 to 139 mmHg or DBP of 80 to 89 mmHg; and (IV) stage 2 hypertension, SBP ≥ 140 mmHg or DBP ≥ 90 mmHg. Mean arterial pressure (MAP) was estimated using a formula in which the DBP was doubled and added to the SBP and that composite sum then was divided by 3 to estimate MAP. Pulse pressure (PP) was the SBP minus the DBP.

Statistical analysis

We performed statistical analysis on Stata v14.0 (StataCorp, College Station, Texas, USA). Graphs were drawn using Prism v7.0 (GraphPad Software, San Diego, CA). Median and interquartile range (IQR) were used to describe continuous variables because of the non-normal distribution. Categorical variables were described

using number and percentage. Continuous variables were compared using Mann-Whitney U test or Kruskal-Wallis test. Categorical variables were compared using Chi-square test or Fisher's exact test.

The associations between incident CMBs and baseline risk factors including BP categories were evaluated using univariable and multivariable generalized linear models (Poisson regression). Covariables were selected from univariable analyses with $P < 0.05$ or with known potential clinical significance (7,17,24,25). 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.

All incident rate ratios, 95% confidence intervals and P values were estimated in a two-tailed fashion. $P < 0.05$ was considered statistically significant.

Ethical statements

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by the medical ethics committee of Huashan Hospital, Fudan University, Shanghai, China (ID: 2016-359), and conducted in accordance with Chinese Good Clinical Practice of Pharmaceutical Products and the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from all participants or their legally acceptable representative.

Results

Of the 317 subjects, 28 people were deceased, 60 refused to be followed, 32 could not be reached, 11 moved to other communities, 9 could not participate actively due to dementia and tumor, and 18 had MRI contraindications. As a result, we were able to prospectively study 159 subjects with a mean interval of 6.9 years (*Figure 1*).

Table S1 showed the characteristics of the 159 participants at baseline and follow-up. Baseline median age was 67 years, and 44.7% were male. Mean follow-up interval was 6.9 ± 0.4 years (5.7 to 8.0 years). Compared to those followed participants, those lost to follow-up were significantly older with more baseline vascular risk factors and prevalence of microbleeds (*Table S2*).

The overall prevalence of CMBs at baseline and follow-

up were 16 (10.1%) and 53 (33.3%) respectively. The number and location of CMBs at baseline and follow-up in the four BP groups were shown in Table S3. The prevalence of any microbleeds at baseline was higher in those with stage 1 hypertension (11.4%) and stage 2 hypertension (11.4%) than those with normal BP (4.8%). 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%).

Forty-six (28.9%) participants developed incident CMBs during the follow-up period. The percentages of participants with incident CMBs in the four BP groups were shown in Figure 2. Participants with ≥ 5 incident CMBs all

had baseline stage 1 and 2 hypertension (Figure 2A). With respect to CMBs location (Figure 2B), participants with incident strictly deep CMBs all had baseline stage 1 and 2 hypertension. No difference was found in the distribution of incident lobar or infratentorial CMBs.

The relationships between baseline predictors and incident CMBs were demonstrated in Table 1. In the univariable model, baseline stage 1 hypertension and stage 2 hypertension were significantly related with a higher incidence rate of CMBs (IRR 2.7, 95% CI, 1.11–6.54, $P=0.028$; IRR 3.22, 95% CI, 1.41–7.38, $P=0.006$, respectively). After multivariable adjustment, baseline stage 1 hypertension and stage 2 hypertension were also significantly associated with a higher incidence rate of CMBs (IRR 2.77, 95% CI, 1.11–6.91, $P=0.028$; IRR 3.04, 95% CI, 1.29–7.16, $P=0.011$, respectively), showing dose-response effects across BP categories.

Participants with incident CMBs had significantly higher baseline SBP than those without incident CMBs ($P=0.024$, Figure 3). Participants who developed incident CMBs had a trend toward higher baseline DBP, MAP and PP; this association almost reached statistical significance for PP ($P=0.057$).

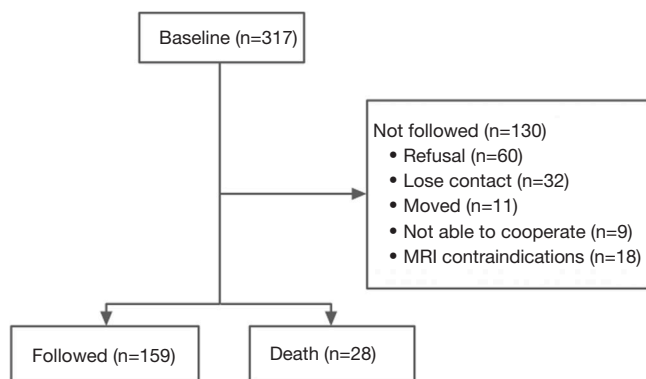


Figure 1 Flowchart of subject recruitment in Jing'an Temple Community.

Discussion

In this 7-year longitudinal relatively healthy community cohort study, we found that 28.9% of participants developed incident CMBs. Participants with baseline stage 1 and stage

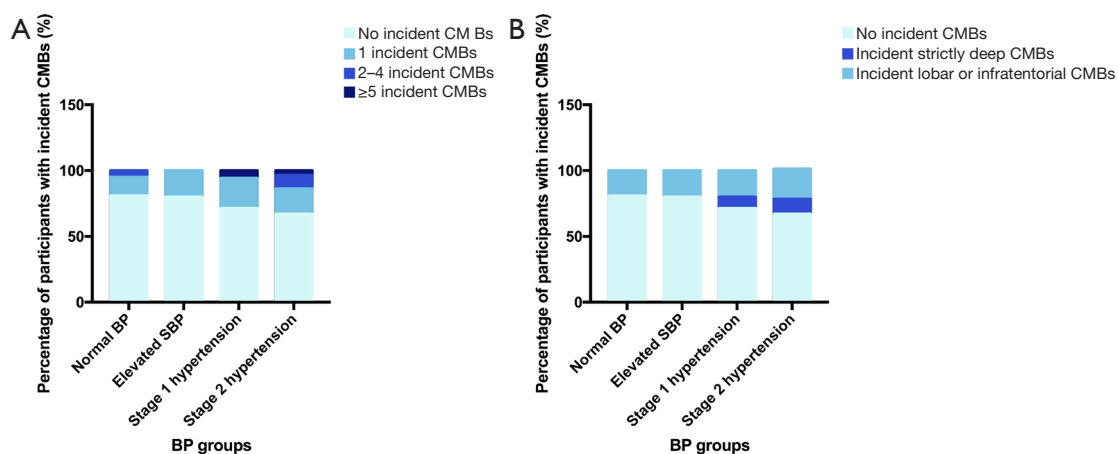


Figure 2 Percentage of participants with incident CMBs in each BP group. All participants ($n=159$) were categorized into four groups by baseline BP levels. Each column represents the distribution of participants with incident CMBs in each BP group. (A) Columns were assigned different colors in terms of number of incident CMBs; (B) columns were assigned different colors in terms of location of incident CMBs. CMBs, cerebral microbleeds; BP, blood pressure; SBP, systolic blood pressure.

Table 1 Univariable and multivariable analyses between possible predictors and the incidence of 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	0.93,5.75	0.070
ApoE ϵ 4 carriers	1.20	0.74,1.94	0.467	1.70	1.00,2.87	0.049
ApoE ϵ 2 carriers	0.63	0.35,1.11	0.112	0.57	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	2.77	1.11,6.91	0.028
Stage 2 hypertension	3.22	1.41,7.38	0.006	3.04	1.29,7.16	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	0.33	0.21,0.54	<0.001
Cardiogenic diseases	0.53	0.25,1.14	0.105	0.52	0.24,1.14	0.103
Antiplatelet/ anticoagulation	0.76	0.46,1.27	0.300	0.71	0.41,1.23	0.225

*, P values were calculated after adjusting for age, sex, body mass index, current smoking, ApoE ϵ 4 carriers, ApoE ϵ 2 carriers, BP categories, diabetes, hyperlipidemia, cardiogenic diseases, and antiplatelet or anticoagulation medication. BP categories: (I) normal BP, SBP <120 mmHg and DBP <80 mmHg; (II) elevated systolic BP, SBP of 120 to 129 mmHg and DBP <80 mmHg; (III) stage 1 hypertension, SBP of 130 to 139 mmHg or DBP of 80 to 89 mmHg; (IV) stage 2 hypertension, SBP \geq 140 mmHg or DBP \geq 90 mmHg. BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; IRR, incident rate ratio; CI, confidence interval.

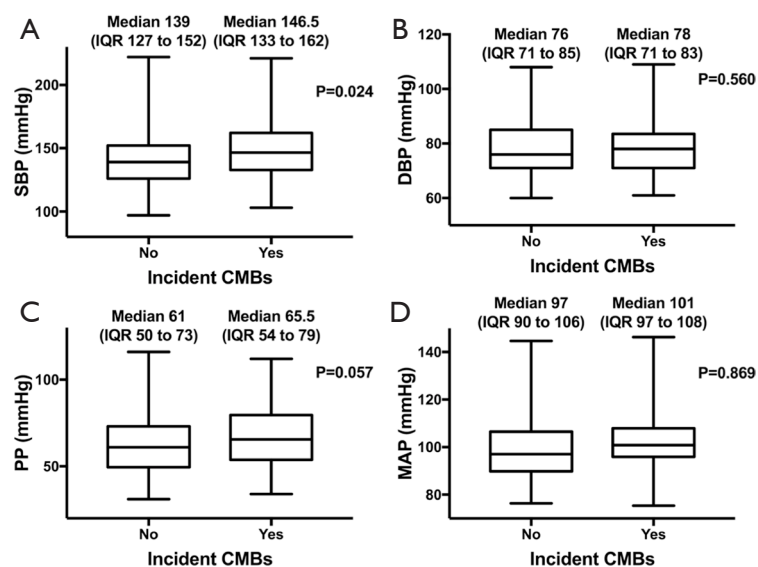


Figure 3 Baseline BP in participants with and without incident CMBs. Box and whisker plots show baseline BP in participants with no incident CMBs (n=113) and with incident CMBs (n=46). Boxes show 25–75th percentile of BP, lines show median, and whiskers show range of BP. CMBs, cerebral microbleeds; BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; MAP, mean arterial pressure; IQR, interquartile range

2 hypertension defined by the 2017 ACC/AHA guidelines were approximately 3 times more likely to develop incident CMBs compared with normal BP in this elderly healthy population.

Hypertension defined as BP over 140/90 mmHg was considered a crucial risk factor of CMBs in the general population. In the middle-aged and elderly individuals in Rotterdam Scan Study (5), hypertension was associated with the presence of CMBs. One Swedish study found that hypertension was the major risk factor for CMBs in the general population (6). Longitudinal community studies (7,8) also demonstrated that baseline hypertension was associated with development of new CMBs.

However, studies on the relationship between hypertension defined by the ACC/AHA guideline and CMBs are lacking. One cross-sectional study in routine health checkups (17) found that middle-aged participants with stage 1 hypertension had a higher prevalence of CMBs than those with normal BP, suggesting the clinical significance of this new definition of hypertension in predicting CMBs. Since cross-sectional studies proved only the association but not the causality, longitudinal studies were needed. Our 7-year longitudinal study in the elderly population indicated that participants with baseline stage 1 hypertension were significantly more likely to have incident CMBs, especially numerous and strictly deep CMBs. This implied that a new, stricter BP control might help prevent CMBs.

The SPRINT Memory and Cognition IN Decreased Hypertension (SPRINT MIND) study (26) found intensive BP lowering to a SBP target <120 mmHg slowed the development of white matter lesions (another marker of CSVD). In our study, we found no association between the group with slightly elevated SBP (120 to 129 mmHg) and a higher incidence rate of CMBs.

Consistent with previous longitudinal studies (7,8), we found that higher SBP rather than DBP at baseline was associated with incident CMBs, suggesting that an aggressive anti-hypertensive treatment with a strict long-term control of SBP under 130 mmHg might alleviate the progression of CMBs in the general population. This needs to be validated in randomized clinical trials.

A previous study found that cerebral small vessels were vulnerable to a wide pulse pressure (PP) because elevated PP could promote severe vascular dysfunction and lead to disruption of the neurovascular unit (27). Another study pointed out that aortic stiffness resulted in consequential increases in the amplitude of SBP and amplification of PP in the elderly population (28,29), and eventually led to

thinned-walled distal portion and cerebrovascular injury, an important contributing factor to the pathogenesis of CMBs (30,31). Our results supported the associations between elevated SBP, PP and incident CMBs in an elderly population over 60 years of age.

ApoE gene encodes a protein involved in lipid and cholesterol metabolism and plays an important role in β -amyloid ($A\beta$) deposition and clearance (32). Pathology studies suggested that the $\epsilon 2$ allele contributed to vascular ruptures and the $\epsilon 4$ allele either contributed to increased $A\beta$ deposition or decreased $A\beta$ clearance in the vessels (33). Previous studies demonstrated that APOE $\epsilon 4$ allele carriers possessed more prevalence of CMBs in the community-dwelling population (5,34), while the associations between APOE $\epsilon 2$ allele and CMBs remain uncertain (5,35-37). In this longitudinal study, we found APOE $\epsilon 4$ associated with incident CMBs. No association was found between APOE $\epsilon 2$ and incident CMBs.

The major strengths of this study are its population-based design, long follow-up duration up to 7 years, and repeated imaging. We collected detailed and comprehensive characteristics of participants that enabled us to examine a variety of risk factors and to adjust for potential confounders. Our study has several limitations. First, T2*-GRE sequence was applied for detecting CMBs at baseline, while SWAN was applied at follow-up. Theoretically, more CMBs could be detected on SWAN sequence compared to T2*-GRE, which might lead to an overestimation of the incidence rate of CMBs. However, since all participants underwent the same MRI sequence at the same time point, the variation of MRI sequence could be considered as a systematic error with limited impact when examining the associations between BP and incident CMBs. Second, BP was measured in a single day in the office. With regard to white coat effect, this might lead to misclassification. However, previous epidemiological studies revealed that BP measurements at a single visit were adequate for determining hypertensive status (38). 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. Third, we did not observe any impact of the BP control at follow-up on the incidence rate of CMBs (Table S4). This result needed to be further reexamined in the future community studies with repeated BP measurements throughout the follow-up period, since BP data at follow-up could not fully determine the status of BP control throughout the 7 years. Finally, there was an

attrition bias during the follow-up period. People included in the analysis were younger and healthier than those lost to follow-up, leading to a probable bias in analyzing risk factors. However, even in this relatively healthy cohort, we found stage 1 hypertension associated with incident CMBs.

Conclusions

In conclusion, participants with baseline stage 1 and stage 2 hypertension had a significantly higher risk of incident CMBs in this 7-year longitudinal community cohort.

Acknowledgments

Funding: This study is funded by the National Key R&D Program of China (2016YFC1300503, 2017YFC1308201), the National Natural Science Foundation of China (81971123), the Shanghai Municipal Science and Technology Major Project (No.2018SHZDZX01) and ZJLab, and the Research Center on Aging and Medicine, Fudan University.

Footnotes

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at <http://dx.doi.org/10.21037/atm-20-5142>

Data Sharing Statement: Available at <http://dx.doi.org/10.21037/atm-20-5142>

Peer Review File: Available at <http://dx.doi.org/10.21037/atm-20-5142>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/atm-20-5142>). All authors report grants from the National Key R&D Program of China (2016YFC1300503, 2017YFC1308201), the National Natural Science Foundation of China (81971123), the Shanghai Municipal Science and Technology Major Project (No.2018SHZDZX03) and Zhangjiang Lab, and the Research Center on Aging and Medicine, Fudan University, during the conduct of the study. The authors have no other conflicts of interest to declare.

Ethical Statements: The authors are accountable for all aspects of the work in ensuring that questions related

to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by the medical ethics committee of Huashan Hospital, Fudan University, Shanghai, China (ID: 2016-359), and conducted in accordance with Chinese Good Clinical Practice of Pharmaceutical Products and the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from all participants or their legally acceptable representative.

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Cite this article as: Xia Y, Wang Y, Yang L, Wang Y, Liang X, Zhao Q, Wu J, Chu S, Liang Z, Ding H, Ding D, Cheng X, Dong Q. Incident cerebral microbleeds and hypertension defined by the 2017 ACC/AHA Guidelines. *Ann Transl Med* 2021;9(4):314. doi: 10.21037/atm-20-5142