

abnormalities, and albuminuria [7,8]. However, it remains unclear how to practically stratify this residual risk of developing ASCVD in medicated hypertensive patients. Urinary albumin excretion (UAE) is relatively easy and inexpensive to measure and is a powerful predictor of the development of ASCVD in hypertensive patients [12,13]. UAE may, therefore, be useful as an index for stratifying the residual risk of developing ASCVD in medicated hypertensive patients in comparison to nonhypertensive individuals with optimal risk levels; however, the community-based studies have not clearly validated this hypothesis. Thus, we conducted the present study among community-dwelling people in order to validate this hypothesis.

METHODS

Study participants

The Iwate-Kenpoku cohort (Iwate-KENCO) study is a population-based prospective study that was conducted among residents of the Ninohe, Kuji, and Miyako districts in northern Iwate prefecture, which is located in the northeast area of Honshu, Japan. The study participants were recruited from a government-regulated health checkup program that was conducted between April 2002 and January 2005 [14]. A total of 15 927 individuals who resided in the Ninohe and Kuji districts, where cardiovascular events were completely followed, agreed to participate in this cohort study. After applying the exclusion criteria [<40 years of age ($n = 583$), past history of ASCVD (myocardial infarction or stroke; $n = 500$), SBP at least 160 mmHg or DBP at least 100 mmHg ($n = 1044$), urinary albumin-to-creatinine ratio (UACR) at least 300 mg/g ($n = 304$), or missing covariates ($n = 775$)], 13 082 individuals were included in the analysis. The present study was approved by our institutional ethics committee. Informed consent was obtained from all participants.

Measurements

The BMI was calculated by dividing the weight (in kilograms) by the square of the height (in meters). Participants completed a self-reported questionnaire to document their medical history, including current medications and lifestyle factors, such as smoking habit. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations modified by a Japanese coefficient [15]. A single-void urine sample was collected during the daytime and was used to measure the UACR. Urinary albumin was quantitatively assessed using an immunonephelometric method (N antiserum albumin, Dade Behring) and urinary creatinine was quantitatively measured by an enzymatic colorimetric test [16]. The between-assay coefficient of variation for urinary albumin and creatinine was within 5% throughout the range of concentrations. The sensitivity limit for the urinary albumin concentration was 6 mg/l. Urinary albumin levels below this limit were regarded as no albumin excretion, irrespective of the urinary creatinine concentration.

Risk factor definition

Participants were classified into the following four groups according to the BP levels at baseline: normal BP (BP1), defined as SBP less than 120 mmHg and DBP less than

80 mmHg; high normal BP (BP2), defined as SBP at least 120 mmHg but less than 130 mmHg and DBP less than 80 mmHg; elevated BP (BP3), defined as SBP at least 130 mmHg but less than 140 mmHg and/or DBP at least 80 mmHg but less than 90 mmHg; and grade 1 hypertension (BP4), defined as SBP at least 140 mmHg but less than 160 mmHg and/or DBP at least 90 mmHg but less than 100 mmHg, based on the Japanese Society Hypertension guidelines for the management of hypertension 2019 [17]. Furthermore, participants receiving treatment with antihypertensive agents were categorized into two groups according to sex-specific median level of the UACR, which was 15.4 mg/g in men and 19.0 mg/g in women. Diabetes mellitus was defined as a random blood glucose level of at least 200 mg/dl, a fasting blood glucose level of at least 126 mg/dl, a glycosylated hemoglobin (NGSP equivalent value) level of at least 6.5%, and/or current antidiabetic therapy. Dyslipidemia was defined as a total cholesterol level of at least 240 mg/dl, a high-density lipoprotein cholesterol (HDL-C) level of less than 40 mg/dl, and/or current lipid-lowering therapy. A smoking habit was defined as currently smoking. Atrial fibrillation was diagnosed using standard supine 12-lead electrocardiogram at baseline by two trained research nurses and one cardiologist.

Outcomes

Patients with newly diagnosed stroke, acute myocardial infarction, sudden cardiac and unexpected death (SCUD), or heart failure were registered through December 2012. Registration was initially performed by attending physicians at each hospital. To ensure the complete capture of all registrations, investigators (who included physicians and trained research nurses) visited and reviewed medical charts and/or discharge summaries at referral hospitals within the study area.

The endpoint of the study was the time of the onset of the first composite ASCVD event (stroke, acute myocardial infarction, SCUD, or heart failure). Stroke was identified from local stroke registry data [18]. Acute myocardial infarction and heart failure were identified according to the MONItoring of trends and determinants in CArdiovascular Disease (MONICA) criteria [19] and the Framingham criteria [20], respectively. According to the WHO criteria for sudden death, SCUD was defined as sudden unexpected death within 24 h of having been observed alive and symptom-free [21].

Statistical analyses

The baseline data of study participants according to their BP category and antihypertensive medication status were presented as the mean \pm standard deviation (SD) or percentage, with the exception of the UACR, which was presented as the median with interquartile range. To estimate the effect of the BP category at baseline on the incidence of ASCVD events, a multivariable Cox model was constructed, which included age, sex, BMI, eGFR, diabetes mellitus (yes or no), dyslipidemia (yes or no), smoking habit (yes or no), atrial fibrillation (yes or no), and the BP category stratified by the antihypertensive medication status (model 1) or the combined category of the BP category and the antihypertensive medication status (model 2). After confirming the assumption of proportional hazards, we calculated hazard

TABLE 2. Association of blood pressure category with the incidence of cardiovascular events according to the antihypertensive agent treatment status

Blood pressure category	Number of individuals	Number of events	Number/1000 person-years	Model 1 ^a				Model 2 ^b			
				HR	95%CI	P value	P for trend	HR	95%CI	P value	P for trend
Untreated											
Normal blood pressure	4736	189	3.7	1.00			<0.001	1.00			<0.001
High normal blood pressure	1541	101	6.2	1.26	0.99–1.61	0.066		1.27	0.99–1.62	0.056	
Elevated blood pressure	2060	138	6.3	1.30	1.04–1.62	0.021		1.31	1.05–1.63	0.017	
Grade 1 hypertension	1815	207	11.0	2.05	1.67–2.51	<0.001		2.07	1.69–2.53	<0.001	
Treated											
Normal blood pressure	589	62	10.4	1.00			0.141	1.69	1.26–2.27	<0.001	
High normal blood pressure	512	62	11.9	1.15	0.81–1.64	0.440		1.95	1.45–2.61	<0.001	
Elevated blood pressure	828	93	11.1	1.14	0.83–1.58	0.415		1.94	1.50–2.51	<0.001	
Grade 1 hypertension	1001	142	14.2	1.39	1.03–1.88	0.030		2.37	1.89–2.97	<0.001	

CI, confidence interval; HR, hazard ratio.

^aModel 1 was constructed for age, sex, BMI, estimated glomerular filtration rate, diabetes mellitus (yes or no), dyslipidemia (yes or no), smoking habit (yes or no), atrial fibrillation (yes or no), and the blood pressure category, stratified by the antihypertensive medication status.

^bModel 2 was constructed for age, sex, BMI, estimated glomerular filtration rate, diabetes mellitus (yes or no), dyslipidemia (yes or no), smoking habit (yes or no), atrial fibrillation (yes or no), and the combined category of the blood pressure category and the antihypertensive medication status.

antihypertensive medication status on the outcome. In medicated hypertensive patients with lower UAE, the multivariable-adjusted hazard ratio for the development of ASCVD in individuals with BP1–BP3 was not different from that in untreated individuals with BP1. On the other hand, this hazard ratio in medicated hypertensive patients with higher UAE was significantly increased in comparison to that in untreated

individuals with BP1 (all $P < 0.001$) and was comparable to that in untreated individuals with BP4 (Fig. 2). This tendency, in which the risk of ASCVD in medicated hypertensive patients was separated between the UAE groups, was similarly observed in the sub-analyses of individuals grouped according to age (< 70 years of age or ≥ 70 years of age) or sex, and in a sub-analysis of individuals without diabetes mellitus (Fig. 3).

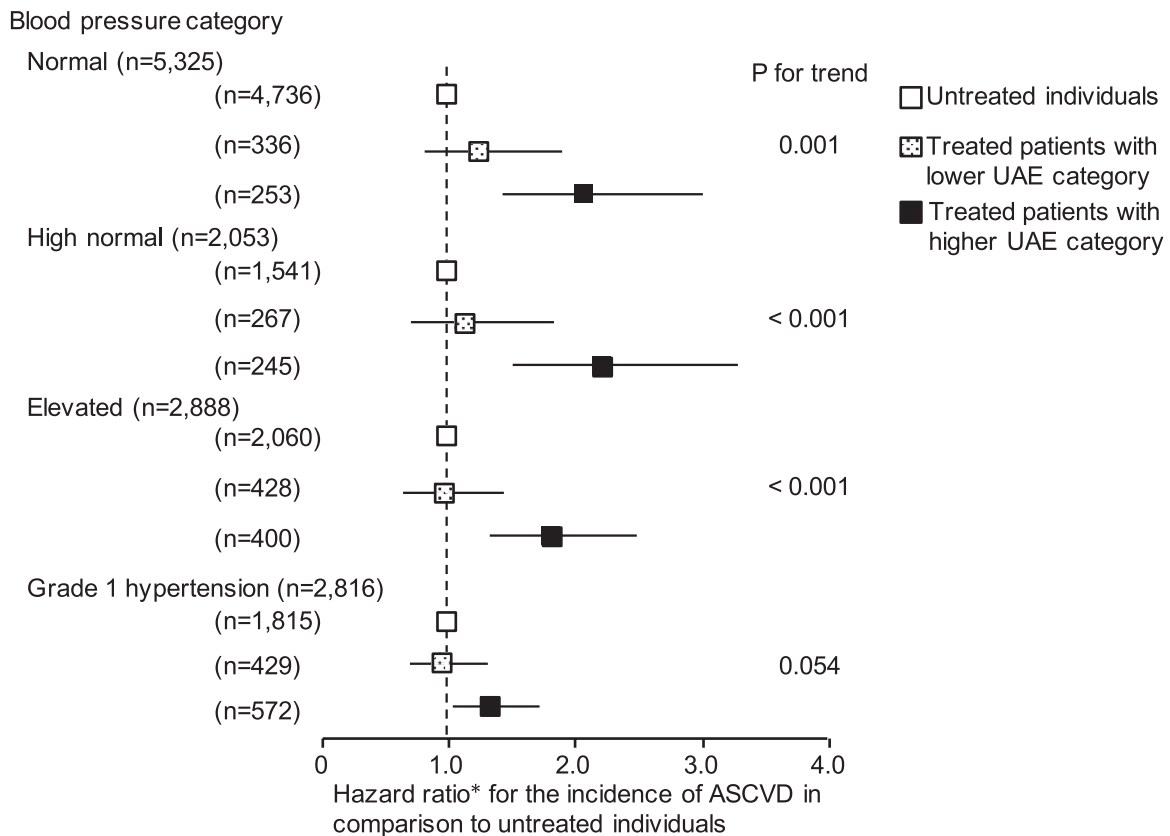


FIGURE 1 The multivariable-adjusted hazard ratios for the incidence of cardiovascular events in the combination group, which consisted of the urinary albumin excretion category and antihypertensive treatment status, according to the blood pressure category. Urinary albumin excretion (UAE) was categorized into two groups according to the median urinary albumin-to-creatinine ratio, which was 15.4 mg/g for men and 19.0 mg/g for women. *Hazard ratios were adjusted for age, sex, BMI, estimated glomerular filtration rate, diabetes mellitus (yes or no), dyslipidemia (yes or no), smoking habit (yes or no), atrial fibrillation (yes or no). ASCVD, atherosclerotic cardiovascular disease.

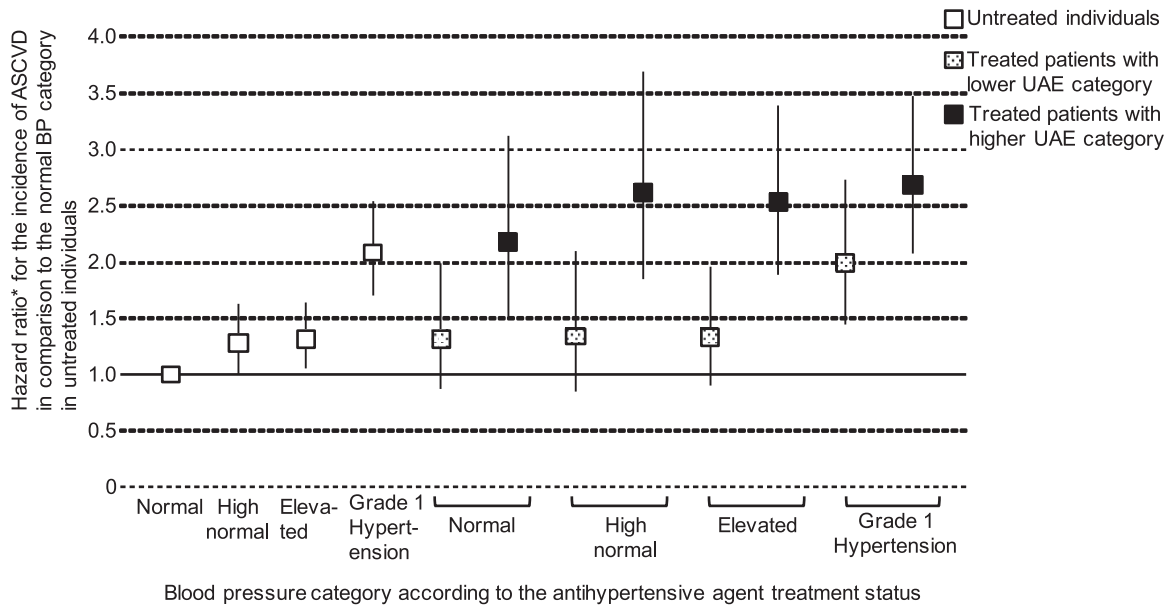


FIGURE 2 The multivariable-adjusted hazard ratios for the incidence of cardiovascular events in the combination group, which consisted of the blood pressure category in untreated individuals and the blood pressure and urinary albumin excretion categories in treated patients with antihypertensive medication. *Hazard ratios were adjusted for age, sex, BMI, estimated glomerular filtration rate, diabetes mellitus (yes or no), dyslipidemia (yes or no), smoking habit (yes or no), atrial fibrillation (yes or no). Urinary albumin excretion (UAE) was categorized into two groups according to the median urinary albumin-to-creatinine ratio, which was 15.4 mg/g for men and 19.0 mg/g for women. ASCVD, atherosclerotic cardiovascular disease.

DISCUSSION

The present study showed several important findings. First, in patients treated with antihypertensive medication, the risk of developing ASCVD showed little stratification among the BP categories at baseline. In addition, categorization based on the BP measured at baseline showed a residual risk of developing ASCVD in treated hypertensive patients, as patients with BP1 already had a higher risk of developing

ASCVD in comparison with untreated individuals with BP1. Second, the risk of developing ASCVD in medicated hypertensive patients in comparison with that in untreated individuals was stratified by UAE, which was classified based on a UACR at a threshold that was lower than that considered to be clinically significant, especially in the BP1–BP3 categories. Third, if treated individuals were within the BP1–BP3 categories, the risk of developing ASCVD in those

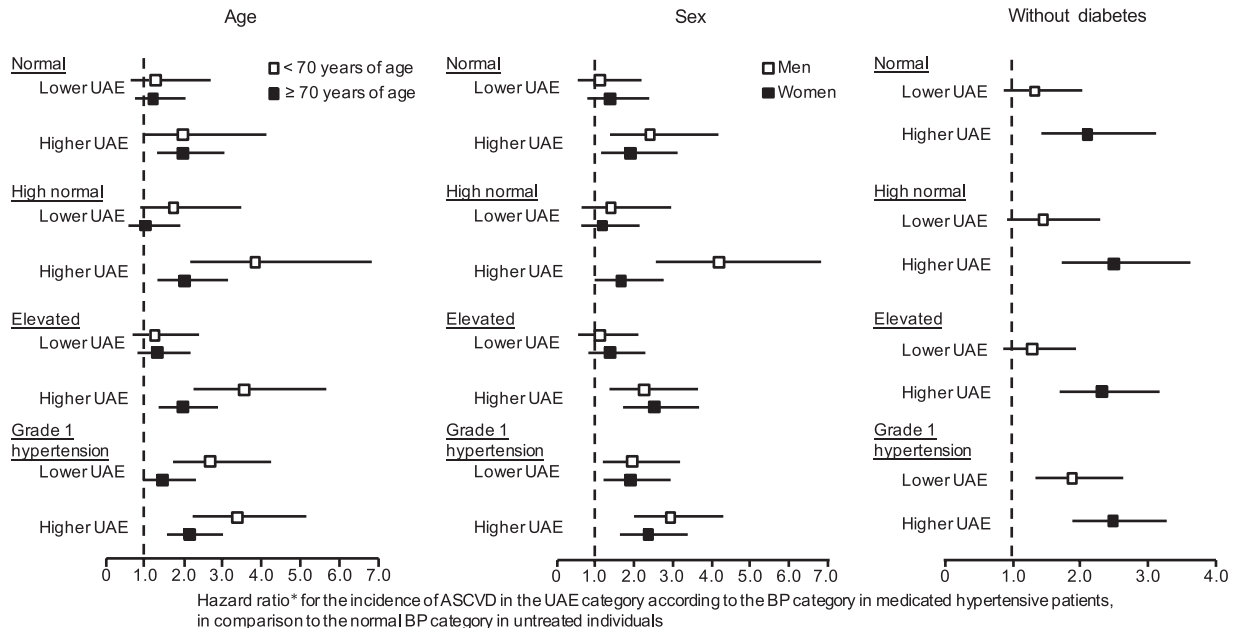


FIGURE 3 The multivariable-adjusted hazard ratios for the incidence of atherosclerotic cardiovascular disease in each urinary albumin excretion category according to the blood pressure category in medicated hypertensive patients, in comparison to the normal blood pressure category in untreated individuals as a reference group, in the subgroups according to age and sex, and in patients without diabetes mellitus. *Hazard ratios were adjusted for age, sex, BMI, estimated glomerular filtration rate, diabetes mellitus (yes or no), dyslipidemia (yes or no), smoking habit (yes or no), atrial fibrillation (yes or no). UAE was categorized into two groups according to the median urinary albumin-to-creatinine ratio, which was 15.4 mg/g for men and 19.0 mg/g for women. ASCVD, atherosclerotic cardiovascular disease; UAE, atherosclerotic cardiovascular disease.

with lower UAE values was comparable with that in untreated individuals with BP1. In contrast, the risk of developing ASCVD in those with higher UAE values was comparable with that in untreated individuals with BP4. To our knowledge, this is the first community-based study to clarify the utility of UAE as an index for stratifying the residual risk of developing ASCVD in medicated patients with well controlled hypertension in comparison to non-hypertensive individuals with optimal risk levels.

Previous observational studies have reported various findings regarding the relationship between BP values and the risk of developing ASCVD in medicated hypertensive patients [9–11,22,23]. In a multicenter observational study in the United Kingdom, the risk of mortality from ischemic heart disease and stroke in medicated hypertensive patients with SBP values of at least 155–170 mmHg was higher than that with SBP values of less than 134 mmHg [22]. In Japanese multicenter studies, the BP category in medicated hypertensive patients had a weak association with mortality from ischemic heart disease and heart failure but not from stroke [9]. On the other hand, the Japan Collaborative Cohort study showed a U-shaped association between the BP category and the risk of ASCVD-related mortality in medicated hypertensive patients, suggesting that individuals with low BP values had comorbidities, such as atrial fibrillation and heart failure [11]. In a longitudinal cohort study with a follow-up period of 25–28 years, BP achieved during the first 15 years of follow-up was not associated with the risk of ASCVD in medicated hypertensive patients [24]. The Ohasama study revealed a linear association between the stroke risk of medicated hypertensive patients and the self-measured home BP, but not the casual-screening BP, suggesting that a certain proportion of treated individuals with masked hypertension who were assigned to the optimal BP category overwhelmed the relationship between the conventional BP and the risk of stroke [25]. This report bears some relation to the findings of the present study in which the risk of developing ASCVD in medicated hypertensive patients did not differ to a statistically significant extent among the BP categories.

It has been known that medicated hypertensive patients, even those in the optimal BP range, have a residual risk of developing ASCVD in comparison to nonhypertensive individuals. This is – to a certain extent – related to the presence of subclinical disease, such as left ventricular hypertrophy and microalbuminuria [7,8]. Even in medicated hypertensive patients under well controlled BP management, the UAE is suggested to represent insufficient control of the actual BP (e.g. 24-h ambulatory BP) [26], the intrarenal activation of the renin–angiotensin–aldosterone system [26], and end-organ damage because of long-term exposure to higher BP levels [8], linking to the increased risk of clinical ASCVD events. A meta-regression analysis of clinical trials showed that, in hypertensive patients with albuminuria, a risk reduction in clinical ASCVD during BP-lowering treatment was evident in the subgroup with a reduction of UAE greater than 20% but not in that with a reduction 20% or less, independently of the achieved BP [27]. Given this finding, in the present study, the UAE category in medicated hypertensive patients may partly reflect the degree of changes in UAE during BP-lowering

treatment, leading to the risk stratification of developed ASCVD in categories BP1 to BP3. On the other hand, the ASCVD risk in medicated hypertensive patients in the BP4 category has not been clearly stratified by the UAE category. In general, a reduction in albuminuria has a parallel association with that in BP under antihypertensive treatment. Given this, treated patients with lower UAE values in the BP4 category may thus have had some underlying renal pathologic condition, such as ischemic injury, different from those with lower UAE values in the BP1–BP3 category. As a result, such patients may have been at a higher cardiovascular risk, thus resulting in the small difference in the risk of ASCVD incidence between the UAE category for the treated patients in the BP4 category. In our observational study, UAE categorized according to the UACR at a lower threshold than that used to define microalbuminuria, stratified the residual risk of developing ASCVD in medicated hypertensive patients. This finding is in line with that of a meta-analysis that reported that the association between UAE and cardiovascular outcomes was continuous, without threshold effects [28]. Furthermore, it may be notable that stroke mainly accounted for the ASCVD events in the present study (70.3%). The kidney and brain are hemodynamically similar in that their small blood vessels are branched off directly from large high-pressure arteries and are vulnerable to vascular damage when exposed to high arterial pressure under common risk factors [29]. Cho *et al.* revealed that UAE which was categorized according to the UACR levels (≥ 17 mg/g for men and ≥ 25 mg/g for women) was associated with burdens of white matter hyperintensities in individuals who underwent medical checkups and suggested a link between the kidney and brain through vascular endothelial damage as a shared pathophysiology [30]. This may account for the link between UAE and the risk of clinical ASCVD, which mainly consisted of stroke in the present study.

The present study has some important clinical implications. Medicated hypertensive patients in whom SBP and DBP are controlled within 140 mmHg and 90 mmHg, respectively, may still have a higher risk of developing ASCVD in comparison to nonhypertensive individuals with optimal risk levels. This residual risk of developing ASCVD should be evaluated by the combination of the UAE with the BP, rather than by the BP alone. If medicated hypertensive patients fail to achieve a sufficient reduction in UAE, even when their BP is within the optimal range, their risk of developing ASCVD would remain. Liu *et al.* [8] suggested that delaying the initiation of antihypertensive therapy results in increased cumulative exposure to BP and leads to increased end-organ damage, thereby making it difficult to reverse to the risk levels of individuals who have never had hypertension. Thus, early interventions for individuals with BP over an optimal level (e.g. lifestyle modification and pharmacotherapy) may help to reduce the cardiovascular risk of those individuals who later require the antihypertensive agent treatment; however, this hypothesis should be validated in further studies.

The present study was associated with some limitations. First, given the relatively long-term follow-up period in the present study, significant changes in BP, UAE, and other risk factors which would have occurred during the study

period and the induction of medication, such as antihypertensive and lipid-lowering agents could have affected the outcomes and altered the difference of the risk of ASCVD between untreated and treated participants. In addition, the effect on changes in UAE for patients receiving BP-lowering treatment differs according to the type of antihypertensive agent to be administered [31]. This effect may have modified the categorization of UAE during the study period and led to alter the relationship between the UAE category and the risk of ASCVD development in medicated hypertensive patients [27]. However, these details during follow-up were not obtained in the present study. Second, the participants in the present study tended to be relatively older than those in the other previous studies; thus, the treatment period of patients who received antihypertensive medication would have been relatively prolonged. This tendency may have reduced the strength of the association between the measured BP at baseline and the risk of developing ASCVD in medicated hypertensive patients [32]. Third, UAE was estimated from a single measurement. This raises the possibility that individuals with UAE, which was occasionally found as physiological reaction, were classified into a higher UAE category. However, this possibility would have led to the underestimation of the true association between UAE and the risk of developing ASCVD in the present study. Finally, in the present study, which was conducted in a Japanese population, the cumulative incidence of stroke was much higher than that of acute myocardial infarction/SCUD, which is consistent with reports from previous Japanese epidemiological studies [33,34]. Thus, it may not be possible to simply extrapolate our results to other populations.

In conclusion, UAE is useful for stratifying the residual risk of developing ASCVD in medicated hypertensive patients with well controlled hypertension in comparison to nonhypertensive individuals with optimal risk levels.

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Conflicts of interest

There are no conflicts of interest.

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