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REVIEW

Observational study and participant-level meta-analysis on antihypertensive drug treatment-related cardiovascular risk

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Although antihypertensive therapy reduces cardiovascular risk, individuals who are treated with antihypertensive medication generally have a worse prognosis for cardiovascular disease than untreated people. We recently evaluated the impact of conventional blood pressure level based on two Japanese individual participant databases and found that conventional blood pressure at baseline was not or was weakly associated with cardiovascular events among patients under antihypertensive drug medication. In the general population in Ohasama and the Hypertension Objective Treatment Based on Measurement by Electrical Devices of Blood Pressures study, self-measured home blood pressure significantly predicted cardiovascular outcomes in patients under antihypertensive treatment. Hypertension is a chronic disease, and blood pressure must be evaluated with repeated measurements over a long period of time. Therefore, although not proven by a randomized controlled trial, it is likely that the long-term management of hypertension by antihypertensive drug treatment should be based on self-measured home blood pressure. We should also pay careful attention to the residual cardiovascular risk in treated patients.
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Keywords: antihypertensive medication; blood pressure control; cardiovascular risk; home blood pressure; population science

INTRODUCTION

Blood pressure lowering treatment reduces cardiovascular risk,[1–4] and antihypertensive drug therapy for the management of hypertension is widely accepted in clinical practice. However, patients with hypertension are exposed to the progression of atherosclerosis and target organ damage for long periods of time both before and during therapy,[5] and therefore, people who are treated with antihypertensive medication generally have worse prognosis for cardiovascular diseases than untreated hypertensive individuals.[6–8]

Self-measurement of blood pressure at home was more likely to reflect the 'true' blood pressure in individuals and had a stronger predictive power for cardiovascular complications compared with conventional blood pressure that was measured at an office or at a screening setting.[9–11] However, little is known about the long-term implications of antihypertensive drug treatment based on home blood pressure. In this review, the prognostic significance of conventional blood pressure and home blood pressure in relation to antihypertensive treatment based on Japanese population studies is demonstrated, and perspectives on the application of home blood pressure for the management of hypertension with antihypertensive drugs are presented based on our recent findings.

CONVENTIONAL BLOOD PRESSURE

Japan Arteriosclerosis Longitudinal Study

On the basis of the Japan Arteriosclerosis Longitudinal Study-Existing Cohorts Combine,[12] a pooled project based on individual participant data from existing prospective cohort studies in Japan and a part of the Japan Arteriosclerosis Longitudinal Study (JALS), we collected data from 11 371 participants from the four population-based cohort studies (59.8% women; mean age, 55.1 years; 16.8% treated) who were followed-up for a mean of 9.5 years.[7] On the basis of conventional readings, participants were classified into six blood pressure-based categories according to the recent guidelines:[11,13] optimal ($<120/<80$ mm Hg); normal (120–129/80–84 mm Hg); high normal (130–139/85–89 mm Hg); grade 1 hypertension (mild hypertension, 140–159/90–99 mm Hg); grade 2 hypertension (moderate hypertension, 160–179/100–109 mm Hg); and grade 3 hypertension (severe hypertension, $\geqslant 180/\geqslant 110$ mm Hg). The risk of first stroke was assessed using the multivariable-adjusted Poisson regression model based on the cross-classification of the six blood pressure categories and the use of antihypertensive medication at baseline. As shown in Table 1, participants treated with antihypertensive medication had significantly higher stroke risk than those without treatment, independent of stroke subtypes. Among the untreated

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Table 1 Risk of first stroke and subtypes among treated patients compared with untreated participants—JALS

	All[a] (n = 11 371)		Women (n = 6801)		Men (n = 4570)	
Events	*HR*	*95% CI*	*HR*	*95% CI*	*HR*	*95% CI*
Total stroke ($n=324$)	1.73	1.35–2.22	1.39	0.97–2.00	2.14	1.52–3.01
Infarction ($n=198$)	1.63	1.19–2.23	1.00	0.61–1.66	2.31	1.53–3.47
Hemorrhage ($n=71$)	2.01	1.19–3.39	2.21	1.06–4.62	1.84	0.88–3.85
SAH ($n=53$)	1.94	1.01–3.74	1.76	0.81–3.82	2.26	0.65–7.83

Abbreviations: 95% CI, confidence interval; HR, hazard ratio; JALS, Japan Arteriosclerosis Longitudinal Study; SAH, subarachnoid hemorrhage.
HRs, given with 95% CIs, express the risk in treated patients compared with untreated individuals. Adjusted factors were age, overweight, smoking, drinking, diabetes mellitus, serum cholesterol level, lipid-lowering medication and systolic blood pressure level. Two stroke cases were unclassified.
[a]Sex was further used for covariates in the model. Reproduced from Asayama *et al.*[7]

population, the hazard ratio (HR) increased linearly with the elevation of blood pressure category ($P=0.0001$), and even people with normal blood pressure had a significantly higher stroke risk than those with optimal blood pressure (HR, 2.09; 95% confidence interval (95% CI), 1.09–4.01). The stroke risk among treated patients was significantly higher, even among those with optimal blood pressure (HR, 4.10; 95% CI, 1.17–14.4), compared with those in the untreated groups with the same blood pressure levels. There was, however, no stepwise increase in stroke risk observed among the treated groups ($P=0.1$).

Evidence for Cardiovascular Prevention from Observational Cohorts in Japan

The Evidence for Cardiovascular Prevention from Observational Cohorts in Japan (EPOCH-JAPAN) is a pooled analysis of Japanese cohort studies that is examining the relationships between health measures, that is, laboratory measurements and lifestyle and behavioral factors as well as diseases in the general population and the work-related population.[6,14] Both nationwide and single-site cohort studies were included. Eligible cohorts consisted of $\geqslant 1000$ participants with $\geqslant 10$ years of follow-up and provided health examination measurements. On the basis of this EPOCH-JAPAN database, 39 705 Japanese study participants from six cohorts (58.4% women; mean age, 60.1 years; 20.4% treated) were included for the analysis of cardiovascular mortality (2032 were observed) and its subtypes (410 coronary heart diseases, 371 heart failure and 903 stroke)[6] among six blood pressure levels according to the recent guidelines[11,13] and the usage of antihypertensive medication at baseline, which was the same as the aforementioned JALS report.[7] The event rates of this population were 5.1 per 1000 person-years for cardiovascular deaths. Multivariable-adjusted Cox models demonstrated that treated patients had a significantly higher risk for total cardiovascular mortality (HR, 1.50; 95% CI, 1.36–1.65), coronary heart disease (HR 1.52, 95% CI 1.23–1.89), heart failure (HR 1.38, 95% CI 1.09–1.74) and stroke (HR 1.48, 95% CI 1.28–1.71) compared with untreated people. Among participants without antihypertensive drug treatment at baseline, the risks increased linearly with the blood pressure category (Figure 1; $P\leqslant 0.011$). The risk increments per blood pressure category were higher in young participants (<60 years; 22–79%) than those in older participants ($\geqslant 60$ years; 7–15%), with a significant interaction for total cardiovascular, heart failure and stroke mortality ($P\leqslant 0.026$). Among treated participants, a significant linear association was also observed for cardiovascular mortality (Figure 1; $P=0.0003$), whereas a stepwise increase in stroke death was not observed ($P=0.19$). On the basis of the current EPOCH-JAPAN findings,[6] the impact of conventional blood pressure level on the risks of cardiovascular mortality and its subtypes was different in participants who were under antihypertensive medication.

HOME BLOOD PRESSURE

The ohasama study

Since 1987, our research group has been conducting the Ohasama study, a longitudinal observational study in a rural community in Hanamaki, Japan.[5,9,10] Home blood pressure was found to have a stronger predictive power for cardiovascular mortality[9] and stroke[10] than conventional blood pressure, and the predictive value increased progressively as the number of measurements increased and with no threshold within the range of 1–14 measurements.[10]

We assessed the prognostic significance of home blood pressure among the Ohasama residents with and without antihypertensive treatment.[5] During 11.9 years of follow-up, 242 cases of first stroke was observed among 2390 eligible participants (61.4% women; mean age, 59.3 years; 29.3% treated). Treated participants had significantly higher stroke risk than untreated residents when adjusted by either blood pressure information source (conventional blood pressure: HR 1.78, 95% CI 1.35–2.35; and home blood pressure: HR 1.48, 95% CI 1.11–1.97). When participants were cross-classified by the same six blood pressure levels as the JALS[7] and EPOCH-JAPAN,[6] stroke risk in the treated participants linearly increased based on home blood pressure ($P=0.004$), but a consistent association was not observed between conventional blood pressure level and stroke risk ($P=0.3$). Meanwhile, stroke risk was linearly increased in untreated people irrespective of blood pressure information ($P\leqslant 0.003$). The findings[5] suggest a strong association between elevated home blood pressure and the increased risk of stroke among patients under antihypertensive medication.

Hypertension Objective Treatment Based on Measurement by Electrical Devices of Blood Pressures study

The multicenter Hypertension Objective Treatment Based on Measurement by Electrical Devices of Blood Pressures (HOMED-BP) proved the feasibility of adjusting antihypertensive drug treatments based on home blood pressure.[15] Exploratory analyses of the whole 3518 study population (50.1% women; mean age, 59.6 years) showed that both the baseline systolic home blood pressure before the initiation of antihypertensive drug treatment and the achieved on-treatment home blood pressure during the follow-up period of the HOMED-BP study predicted major adverse cardiovascular events ($P\leqslant 0.0025$). In fully adjusted models with both baseline and on-treatment home blood pressure, the risk of major adverse cardiovascular events independently increased by 41% (95% CI, 6–89%) and by 47% (95% CI, 15–87%) for a 1 s.d. increment of baseline and follow-up systolic home blood pressure, respectively.

On the basis of the extended follow-up data of HOMED-BP, which included blood pressure data and ascertained outcomes until December 2012,[16] we assessed the risk of major adverse cardiovascular events according to the tertiles of baseline and follow-up home blood pressure. As shown in Figure 2, the risk increases across tertiles of systolic home blood pressure at baseline and during follow-up; the risk increases were both linear ($P\leqslant 0.0033$) and without evidence of a J- or U-curve. Notably, the mean blood pressure levels of the lowest tertile were 138.2 mm Hg at baseline and 116.8 mm Hg when under treatment with antihypertensive drugs, and the mean blood pressure level of the middle tertile, which was 123.4–133.5 mm Hg, was

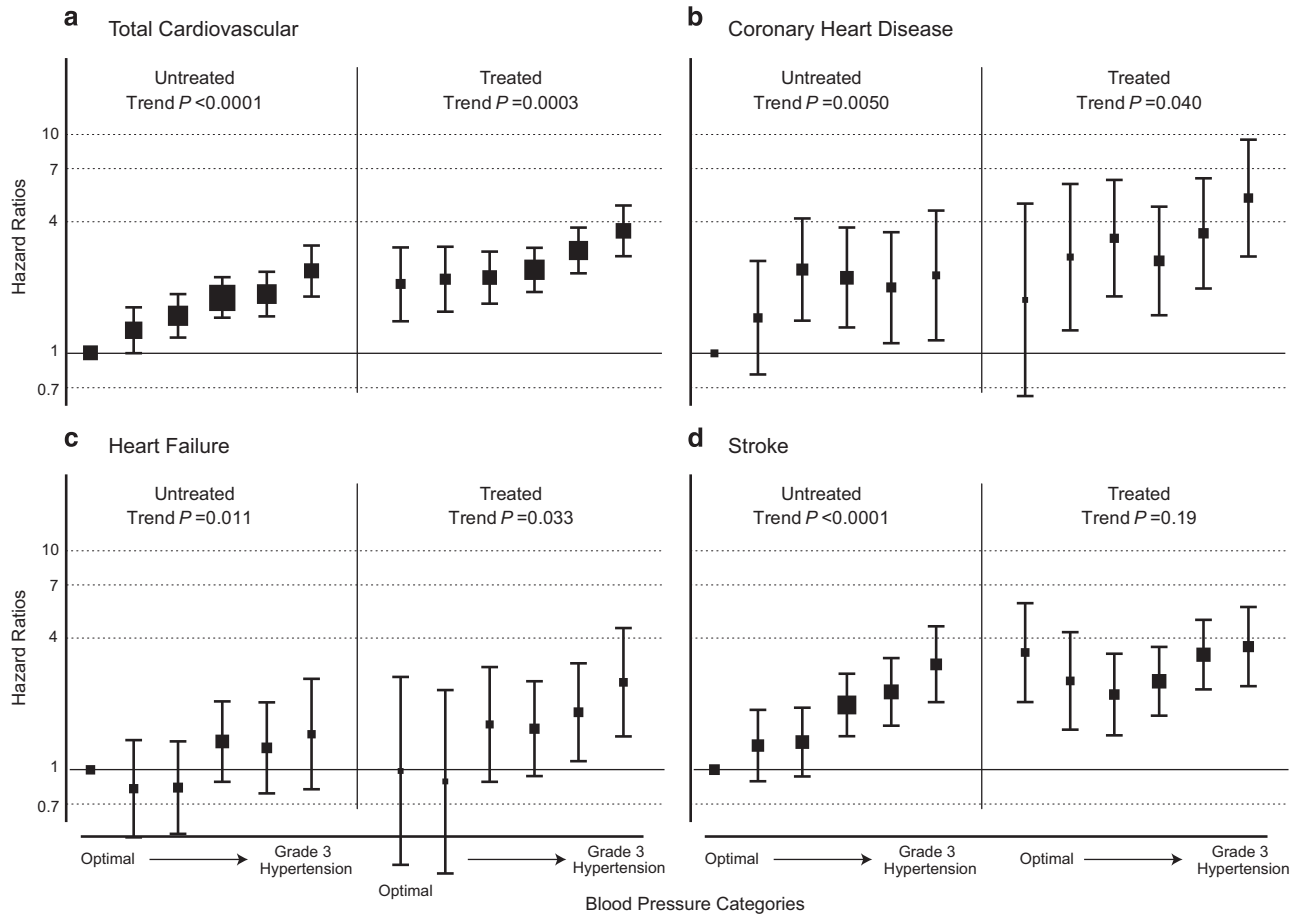

Figure 1 The risk among 12 categories of blood pressure levels and usage of antihypertensive medication at baseline for (**a**) total cardiovascular mortality, death from (**b**) coronary heart disease, (**c**) heart failure and (**d**) stroke—EPOCH-JAPAN. Filled squares indicate the hazard ratios and are sized in proportion to the number of events observed. Vertical bars indicate the 95% confidence intervals in each category compared with the untreated optimal blood pressure category. Blood pressure levels are defined as optimal (<120/<80 mm Hg), normal (120–129/80–84 mm Hg), high normal (130–139/85–89 mm Hg), grade 1 hypertension (140–159/90–99 mm Hg), grade 2 hypertension (160–179/100–109 mm Hg) and grade 3 hypertension (⩾180/⩾110 mm Hg) levels. Trend *P*-values denote the linearity among six categories when the treated and untreated participants are separated. Adjusted factors are sex, age, body mass index, history of cardiovascular disease, total cholesterol, diabetes mellitus, smoking, habitual drinking and cohort. Reproduced from Asayama *et al.*[6]

associated with a significantly higher major adverse cardiovascular event risk compared with the lowest tertile based on on-treatment systolic home blood pressure.

DISCUSSION

The advantage of home blood pressure measurements was also reported by Kario *et al.*[17] based on the Home blood pressure measurement with Olmesartan Naive patients to Establish Standard Target blood pressure (HONEST) study involving 21 591 patients receiving olmesartan (50.6% women; mean age, 64.9 years). Among the HONEST patients with conventional blood pressure <130 mm Hg, those with morning home systolic blood pressure ⩾145 mm Hg had a 2.47 times (95% CI, 1.20–5.08) higher cardiovascular risk compared with patients with morning home systolic blood pressure <125 mm Hg. Although they did not collect blood pressure measurements before antihypertensive treatment was initiated, their findings[17] are in line with ours, showing that a systolic home blood pressure <130 mm Hg is an achievable and safe target.[15]

Ambulatory blood pressure should be offered to those with elevated conventional blood pressure,[18,19] which has been a generally accepted strategy worldwide[13,20] except in Japan.[11] Hermida *et al.*[21] evaluated the achieved nighttime systolic blood pressure during sleep based on 24 h ambulatory monitoring and found that among 661 patients with chronic kidney disease and hypertension (40.1% women; mean age, 59.4 years), each 5 mm Hg decrease in mean nighttime systolic blood pressure was associated with a 14% reduction in the risk of cardiovascular events during follow-up ($P<0.001$). In contrast, a J-shaped relationship was found between achieved clinic systolic blood pressure and cardiovascular risk.[21] Ambulatory monitoring as a diagnostic strategy for hypertension after the initial raised reading in the clinic would reduce misdiagnosis and reduce costs.[22] Similarly, home blood pressure measurement that is incorporated for the treatment of hypertension would reduce medical costs.[23] Although the general validity of such a cost-saving advantage in home blood pressure monitoring still remains unclear, out-of-office blood pressure monitoring, including both home and ambulatory measurements, would be a better tool for the assessment of the risk of blood pressure level-associated cardiovascular complications, particularly among patients under antihypertensive drug treatment.

Masked hypertension and white-coat hypertension were each observed in ~20% of treated Japanese individuals.[24] The frequency of these phenomena depends on the information of out-of-office blood pressure, for example, ranging from 9.7 to 19.6% for masked hypertension and 6.3 to 12.5% for white-coat hypertension based on

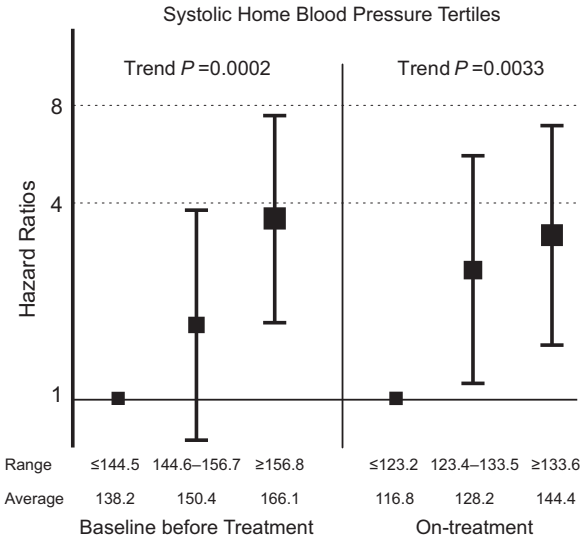

Figure 2 Risk of major adverse cardiovascular events among tertiles defined by systolic home blood pressure at baseline before treatment (left) and during follow-up (right)—HOMED-BP study. Filled squares indicate the hazard ratios and are sized in proportion to the number of events observed. Vertical bars indicate the 95% confidence intervals in each category compared with the lowest tertile. Range and average indicate the systolic home blood pressure range and the geometric mean in each tertile (mm Hg), respectively. Trend *P*-values express the linearity among the three categories. Multivariable adjustment was performed using sex, age, body mass index, history of cardiovascular disease, diabetes mellitus, hypercholesterolemia, smoking, habitual drinking and baseline systolic blood pressure in the on-treatment tertiles and on-treatment systolic blood pressure in the baseline tertiles.

daytime, nighttime and/or 24 h ambulatory monitoring intervals.[19] Masked hypertension was more frequently observed among the young population,[25] for example, 17.6% of healthy South Africans younger than 30 years old had masked hypertension.[26] The JALS[7] and EPOCH-JAPAN[6] participants with masked hypertension, although they could not be identified, were categorized into the optimal, normal and high-normal blood pressure groups based on the conventional measurement. In contrast, a certain proportion of participants that was categorized into grades 1–3 hypertension may have had white-coat hypertension, which is known as an essentially benign condition.[27] The white-coat effect was reported to be high among untreated individuals compared with treated patients.[28] Conventional blood pressure-based risk assessment accompanies such misclassifications, which may result in a lower or nonsignificant impact of conventional blood pressure level in predicting cardiovascular complications, particularly among treated patients.

Recently, automated office blood pressure (AOBP) techniques have been proposed to alter the conventional measurement method in an office setting.[29] AOBP is defined as multiple readings (three or more)[30] that are recorded automatically with the patient resting undisturbed in a quiet place in the absence of an observer.[29,30] The use of AOBP instead of conventional office blood pressure measurements can therefore refine the blood pressure information by eliminating the white-coat effect caused by being observed during blood pressure readings. Myers *et al.*[31] followed-up with 6183 community-dwelling residents in Ontario aged $\geqslant$66 years (58.0% women; mean age, 76.2 years) who had been undergoing antihypertensive drug therapy for a mean of 4.6 years. The composite fatal and nonfatal cardiovascular risk among participants with a systolic AOBP of 120–129 mm Hg was significantly higher compared with those with a systolic AOBP of 110–119 mm Hg (HR, 1.30; 95% CI, 1.01–1.66); however, the risks remained unchanged in participants with systolic AOBP of 130–139 mm Hg (HR, 1.23; 95% CI 0.96–1.58) and 140–149 mm Hg (HR, 1.18; 95% CI, 0.90–1.54), and the HR was relatively unchanged above 60 mm Hg in diastolic AOBP.[29] Although targeting a systolic AOBP of $<$120 mm Hg resulted in lower rates of cardiovascular complication in the Systolic Blood Pressure Intervention Trial when compared with a target systolic AOBP of $<$140 mm Hg,[4] findings by Myers *et al.*[31] imply the limitation of AOBP information for estimating future cardiovascular risk among treated patients as an observational study design. On the basis of the AOBP technique, we can eliminate only the part of the white-coat effect that is caused by an observer; the blood pressure in patients that is measured at clinic or screening settings must be monitored under different condition from that measured within their home as well as within ambulatory settings. Improvement of the predictive power by AOBP might, therefore, not be achieved to the level of the out-of-office measurements; however, relevant evidence has not been available.

Early introduction of antihypertensive medication has beneficial long-term effects for vascular events.[32] However, treatment is a type of marker, not only for greater severity of hypertension but also for other cardiovascular risk factors such as diabetes mellitus or hypercholesterolemia, which lead to a greater rate of events.[8] Because there are several types of undetectable residual confounding factors in addition to the classical risk factors,[33] cardiovascular risk, even after adjusting for classical risk factors, would still be high among treated participants.[34] Nevertheless, home blood pressure predicts cardiovascular risk better than conventional blood pressure,[9,10] and home blood pressure levels in patients under antihypertensive medication were linearly associated with cardiovascular risk.[5] Home and ambulatory blood pressure recordings have a natural advantage of entirely excluding the white-coat effect and of detecting masked hypertension.[35] Furthermore, hypertension is a chronic disease, and blood pressure must be evaluated with repeated measurement over a long period of time.[36] Records of daily home blood pressure measurements enable us to identify long-term factors such as seasonal variation.[37] Home blood pressure measurements require an active commitment by the patients themselves in medical care and health management, which results in a marked improvement in the adherence to medication.[38,39] Though not proven by a randomized controlled trial, it is likely that long-term management of hypertension in an individual should be based on home blood pressure self-measurement once he/she starts antihypertensive drug treatment. We should also pay careful attention to the residual cardiovascular risks in treated patients.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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