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# Morning Home Blood Pressure Is a Strong Predictor of Coronary Artery Disease

## The HONEST Study

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## ABSTRACT

**BACKGROUND** Few studies have evaluated out-of-office blood pressure (BP) measurements as predictors of coronary artery disease (CAD) events.

**OBJECTIVES** The aim of this study was to determine morning home blood pressure (HBP) as a predictor of CAD events.

**METHODS** Using data from the HONEST (Home blood pressure measurement with Olmesartan Naive patients to Establish Standard Target blood pressure) study, we investigated the relationship between morning HBP and incidence of stroke and CAD events.

**RESULTS** In 21,591 treated hypertensive patients (mean age 64.9 years; mean follow-up 2.02 years), 127 stroke events (2.92 per 1,000 patient-years), and 121 CAD events (2.78 per 1,000 patient-years) occurred. The incidence of stroke events was significantly higher in patients with morning home systolic blood pressure (HSBP) ≥145 mm Hg compared with <125 mm Hg, and in patients with clinic systolic blood pressure (CSBP) ≥150 mm Hg compared with <130 mm Hg. Hazard ratios (HRs) were 6.01 (95% confidence interval [CI]: 2.85 to 12.68) between patients with morning HSBP ≥155 mm Hg and those with morning HSBP <125 mm Hg and 5.82 (95% CI: 3.17 to 10.67) between patients with CSBP ≥160 mm Hg and those with CSBP <130 mm Hg; morning HSBP predicted stroke events similarly to CSBP. Incidence of CAD events was significantly higher in patients with morning HSBP ≥145 mm Hg compared with <125 mm Hg and in patients with CSBP ≥160 mm Hg compared with <130 mm Hg. The HR for morning HSBP ≥155 mm Hg was 6.24 (95% CI: 2.82 to 13.84) and for CSBP ≥160 mm Hg was 3.51 (95% CI: 1.71 to 7.20); therefore, compared with morning HSBP, CSBP may underestimate CAD risk. Goodness-of-fit analysis showed that morning HSBP predicted CAD events more strongly than CSBP.

**CONCLUSIONS** Morning HBP is a strong predictor of future CAD and stroke events, and may be superior to clinic BP in this regard. There does not appear to be a J-curve in the relationship between morning HBP and stroke or CAD events. (Home blood pressure measurement with Olmesartan Naive patients to Establish Standard Target blood pressure Study [HONEST]; UMIN000002567) (J Am Coll Cardiol 2016;67:1519–27) © 2016 by the American College of Cardiology Foundation. Published by Elsevier. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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**ABBREVIATIONS AND ACRONYMS**

**ABPM** = ambulatory blood pressure monitoring

**BP** = blood pressure

**CAD** = coronary artery disease

**CBP** = clinic blood pressure

**CSBP** = clinic systolic blood pressure

**DBP** = diastolic blood pressure

**HBP** = home blood pressure

**HDBP** = home diastolic blood pressure

**HR** = hazard ratio

**HSBP** = home systolic blood pressure

Many studies have shown that clinic blood pressure (CBP) is a useful predictor of cardiovascular events, such as stroke and coronary artery disease (CAD) (1–4). In some of these studies, the relationship between CBP and stroke events and between CBP and CAD events was investigated separately. The results showed that although CBP is a strong predictor of stroke events, it might not be effective in predicting CAD events (4,5).

The relationship between out-of-office blood pressure (BP), such as ambulatory BP and home blood pressure (HBP), and cardiovascular events has been investigated in several studies (6–16). However, there is insufficient evidence as yet regarding which BP measurement predicts CAD events most strongly. IDACO (International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcomes) was a large-scale database study in which the relationship between ambulatory BP and CAD events was investigated (14). Its results showed that 24-h diastolic blood pressure (DBP) and isolated diastolic hypertension predict CAD in untreated people <50 years of age. The results of the Ohasama study (6,7) and the Finn-HOME study (8) showed that HBP correlates significantly with the hazard ratio (HR) for cardiovascular events, but the relationship between HBP and CAD events was not reported. Therefore, it is unclear which BP measurement predicts CAD events most strongly. Among out-of-office BP measurements, HBP has the advantage of being easy to measure, allowing multiple measurements and long-term monitoring.

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However, it remains unclear as to which time of day HBP should be measured to predict CAD events effectively. We have found that morning hypertension predicts cardiovascular events because both incidence of cardiovascular events and BP peak in the early morning (17). In 1 of our previous studies, the results of ambulatory blood pressure monitoring (ABPM) showed that ambulatory morning systolic BP (the 2-h average of systolic BP measurements recorded just after waking) is the strongest predictor of stroke events in elderly hypertensive patients (17). However, we were unable to determine which BP is the strongest predictor of CAD events because of the small number of such events that occurred in the study period.

Therefore, we investigated the relationship between morning HBP and the incidence of CAD events and stroke events using data from the largest real-world prospective study, the HONEST (Home blood pressure measurement with Olmesartan Naive patients to Establish Standard Target blood pressure) study (18,19). Previous analysis of the HONEST study focused on a composite cardiovascular endpoint (19); in contrast, the present analysis addresses the relationship between morning HBP and the separate components of the composite cardiovascular endpoint: CAD and stroke events.

## METHODS

**PATIENTS.** The inclusion and exclusion criteria for the HONEST study have already been reported (18). Briefly, olmesartan-naive outpatients with a physician-reported diagnosis of essential hypertension, who already owned a validated and approved electronic device for measuring HBP using the cuff-oscillometric principle, and who had recorded their morning HBP on 2 of the 28 days before starting olmesartan therapy, were eligible to participate. No BP range was specified as a criterion for eligibility. Patients were registered after being prescribed olmesartan in the period between October 1, 2009, and September 30, 2010.

**ETHICS COMMITTEE APPROVAL AND INFORMED CONSENT.** The ethical committee of Daiichi-Sankyo Co., Ltd., and the research ethics committees of the participating institutions approved the protocol of the HONEST study, at their discretion. The study was pre-approved by the Ministry of Health, Labour and Welfare of Japan and complied with Japanese Pharmaceutical Affairs Law. The study was carried out at registered medical institutions in compliance with Good Post-Marketing Study Practice and each institution's internal regulations for clinical studies. All study participants provided written informed consent.

**STUDY DESIGN.** The aim of this study was to investigate the relationship between morning HBP and incidence of stroke events and CAD events, using data from the HONEST study (18). It is registered at the UMIN Clinical Trials Registry with the unique trial number UMIN000002567.

**BP TARGETS AND ANTIHYPERTENSIVE DRUG THERAPY.** BP targets and olmesartan dose (administered orally, generally 10 or 20 mg once daily) were at the discretion of individual physicians. Regarding the use of antihypertensive drugs before the study, only prior olmesartan therapy was an exclusion criterion. No restrictions were placed on the use of combination antihypertensive drug therapy during the study period.

**DATA COLLECTION.** Data used in the present analysis were patient characteristics, HBP measurements,

clinical laboratory test values, and incidence of stroke, CAD, and adverse events during the study period. An Internet-based central data-capturing system (PostMaNet, Fujitsu FIP, Tokyo, Japan) was used. Data obtained from participating institutions were not cross-checked against medical records.

**HBP MEASUREMENT.** Patients were asked to measure their HBP twice in the morning and twice at bedtime, according to the guidelines of the Japanese Society of Hypertension (20). During the follow-up period, HBP was measured at 1, 4, and 16 weeks, and at 6, 12, 18, and 24 months. Patients measured their HBP twice in the morning and twice at bedtime on 2 different days for each measurement point. The average of the 2 HBP measurements at each time was calculated. For each measurement point, we used the average HBP over 2 days. Average HBP measurements during follow-up, excluding baseline values, were used in the analysis of their relationship with incidence of stroke and CAD events. For patients who had such events, we used the average of HBP measurements obtained until their first occurrence.

**CBP MEASUREMENT.** CBP was measured according to the usual methods of each institution. During the follow-up period, CBP was measured at 4 and 16 weeks, and at 6, 12, 18, and 24 months. For each measurement point, 1 measurement was reported. Average CBP measurements during follow-up, excluding baseline values, were used in the analysis. For patients who had stroke or CAD events, we used the average of CBP measurements obtained until their first occurrence.

**EVALUATION OF STROKE AND CAD EVENTS.** Event review committees evaluated events, precisely as described previously (18). All ischemic and hemorrhagic cerebrovascular events, except for transient ischemic attacks, were defined as stroke events. Myocardial infarction and angina pectoris with coronary revascularization procedure were defined as CAD events. The present analysis excluded sudden death events, 1 of the composite cardiovascular endpoints in the previous analysis of the HONEST study (19). Events were evaluated according to event definitions by 3 separate event review committees: 1 for stroke events; 1 for CAD events; and 1 for other events, including other vascular and renal diseases. Each event review committee consisted of 2 or more specialists who identified all events according to pre-determined event definitions. All well-validated clinical information on each stroke and CAD event is listed in a supplement to our previous paper (19).

**STATISTICAL ANALYSIS.** In the present analysis, we used data from eligible patients who had received olmesartan at least once. We used the Cox proportional hazards model to investigate the relationship between on-treatment HBP or CBP and incidence of stroke or CAD events. We also conducted the likelihood ratio test to assess whether the addition of HBP and/or CBP improved the goodness-of-fit of the model for stroke or CAD events. All statistical tests were 2-sided, and a significance level of 0.05 was used. SAS release 9.2 software (SAS Institute, Cary, North Carolina) was used for all statistical analyses.

## RESULTS

**STUDY PROFILE.** The study profile of the HONEST study has already been reported (19). Of the 22,373 patients who were registered, case report forms were collected from 22,298, and data from 21,591 were included in the analysis. The mean follow-up period was 2.02 ± 0.50 years (median and maximum follow-up periods were 2.08 and 3.4 years, respectively). Of the 21,591 patients whose data were used, 10,921 (51%) were women, and the mean age was 64.9 ± 11.9 years. During the follow-up period, 425 patients withdrew consent (but agreed to the use of data obtained until then), and 190 patients died. Of the patients who agreed to continue to participate in the study, contact was lost with 1,950 (9.0%), and their follow-up period was <21 months.

**CHANGE IN BP.** Online Figure 1 shows changes in morning HBP and CBP during the follow-up period. Morning HBP and CBP at baseline (systolic BP/DBP) were 151.2 ± 16.3/86.9 ± 11.7 mm Hg and 153.6 ± 19.0/87.1 ± 13.3 mm Hg, respectively. During follow-up, mean morning home systolic blood pressure (HSBP) and clinic systolic blood pressure (CSBP) were 135.2 ± 10.8/79.0 ± 8.4 mm Hg and 135.2 ± 11.5/77.4 ± 8.6 mm Hg, respectively.

**INCIDENCE OF STROKE AND CAD EVENTS.** Of the 21,591 patients whose data were included in the final analysis, the number of stroke events and CAD events were 127 (2.92 per 1,000 patient-years) and 121 (2.78 per 1,000 patient-years), respectively, and 21,345 patients experienced neither a stroke nor a CAD event. Subtypes of stroke and CAD events are shown in Online Table 1. One patient had 2 stroke events (lacunar infarction and unclassified stroke), and 1 patient had 2 CAD events (myocardial infarction and angina pectoris). Two patients developed both stroke and CAD events. In the analysis of stroke or CAD, we used the first occurrence as an event. **Table 1** shows the baseline characteristics of patients with stroke events, CAD events, and no events. The prevalence of diabetes mellitus and chronic kidney disease in patients with stroke events and of dyslipidemia, diabetes mellitus, chronic kidney disease, and cardiac

**TABLE 1 Baseline Characteristics of Patients With No Events, Stroke Events, or CAD Events**

| | No Events (n = 21,345) | Stroke Events (n = 127) | CAD Events (n = 121) |
|---|---|---|---|
| Women | 10,840 (51) | 52 (41)* | 30 (25)† |
| Age, yrs | 64.8 ± 11.9 | 69.6 ± 11.2† | 69.6 ± 10.5† |
| Body mass index, kg/m$^2$ | 24.3 ± 3.7 | 23.6 ± 3.5 | 23.4 ± 2.8* |
| Disease history | | | |
| Cerebrovascular disease or CAD | 2,192 (10) | 39 (31)† | 38 (31)† |
| Cerebrovascular disease | 1,389 (7) | 31 (24)† | 12 (10) |
| CAD | 939 (4) | 11 (9)* | 31 (26)† |
| Complications | | | |
| Dyslipidemia | 9,489 (45) | 55 (43) | 83 (69)† |
| Diabetes mellitus | 4,335 (20) | 36 (28)* | 56 (46)† |
| Chronic kidney disease | 4,273 (20) | 37 (29)‡ | 37 (31)‡ |
| Cardiac disease | 1,967 (9) | 17 (13) | 35 (29)† |
| Current smokers | 2,615 (12) | 18 (14) | 21 (17)† |
| Regular alcohol drinkers | 3,428 (16) | 20 (16) | 25 (21) |
| Previously used antihypertensive drugs | 10,717 (50) | 74 (58) | 82 (68)† |
| Calcium-channel blocker | 7,670 (36) | 56 (44) | 58 (48)‡ |
| Angiotensin II receptor blocker | 4,526 (21) | 20 (16) | 35 (29)* |
| Beta-blocker | 1,349 (6) | 12 (9) | 19 (16)† |
| Diuretic agent | 1,239 (6) | 9 (7) | 12 (10) |
| Angiotensin-converting enzyme inhibitor | 772 (4) | 4 (3) | 9 (7)* |
| Alpha-blocker | 465 (2) | 2 (2) | 3 (3) |
| Other | 97 (1) | 0 (0) | 0 (0) |
| Drugs used at study entry | | | |
| Lipid-lowering drugs | 6,045 (28) | 31 (24) | 51 (42)† |
| Antidiabetic drugs | 2,928 (14) | 21 (17) | 37 (31)† |
| Anticoagulant or antiplatelet drugs | 2,610 (12) | 35 (28)† | 40 (33)† |
| Lipid profile | | | |
| Total cholesterol, mg/dl | 202.6 ± 35.9 | 191.2 ± 35.6* | 193.0 ± 40.0* |
| Low-density lipoprotein cholesterol, mg/dl | 118.8 ± 30.9 | 113.1 ± 32.4 | 109.6 ± 32.4‡ |
| High-density lipoprotein cholesterol, mg/dl | 58.5 ± 15.7 | 57.0 ± 15.2 | 53.8 ± 15.9‡ |
| Triglycerides, mg/dl | 133.0 ± 84.3 | 132.6 ± 70.7 | 177.6 ± 251.5† |
| Fasting plasma glucose, mg/dl | 105.9 ± 29.6 | 114.3 ± 36.1 | 118.8 ± 45.8‡ |
| $HbA_{1c}$ (NGSP), % | 6.18 ± 1.09 | 6.55 ± 1.31‡ | 6.68 ± 1.28† |
| Creatinine, mg/dl | 0.79 ± 0.31 | 0.88 ± 0.46‡ | 0.91 ± 0.45† |
| Estimated glomerular filtration rate, ml/min/1.73 m$^2$ | 72.4 ± 20.2 | 70.4 ± 22.1 | 66.6 ± 18.9‡ |

Values are n (%) or mean ± SD. *p < 0.05, †p < 0.001, and ‡p < 0.01 vs. no events group.
CAD = coronary artery disease; HbA1c = glycosylated hemoglobin; NGSP = National Glycohemoglobin Standardization Program.

disease in patients with CAD events was higher than in patients with no events.

**RELATIONSHIP BETWEEN BP AND STROKE OR CAD EVENTS DURING FOLLOW-UP.** We investigated the incidence and HR of stroke and CAD events in 5 categories of morning HSBP and CSBP in relation to morning HSBP <125 mm Hg or CSBP <130 mm Hg.

The incidence and HR of stroke and CAD events in each category are shown in **Figure 1** and the **Central Illustration**, respectively. The incidence of stroke events was significantly higher in patients with morning HSBP 145 to <155 mm Hg (3.97 per 1,000 patient-years) or ≥155 mm Hg (12.57 per 1,000 patient-years) than in those with morning HSBP <125 mm Hg (**Figure 1A**), and in patients with CSBP 150 to <160 mm Hg (4.88 per 1,000 patient-years) or ≥160 mm Hg (14.17 per 1,000 patient-years) compared with <130 mm Hg (**Figure 1B**).

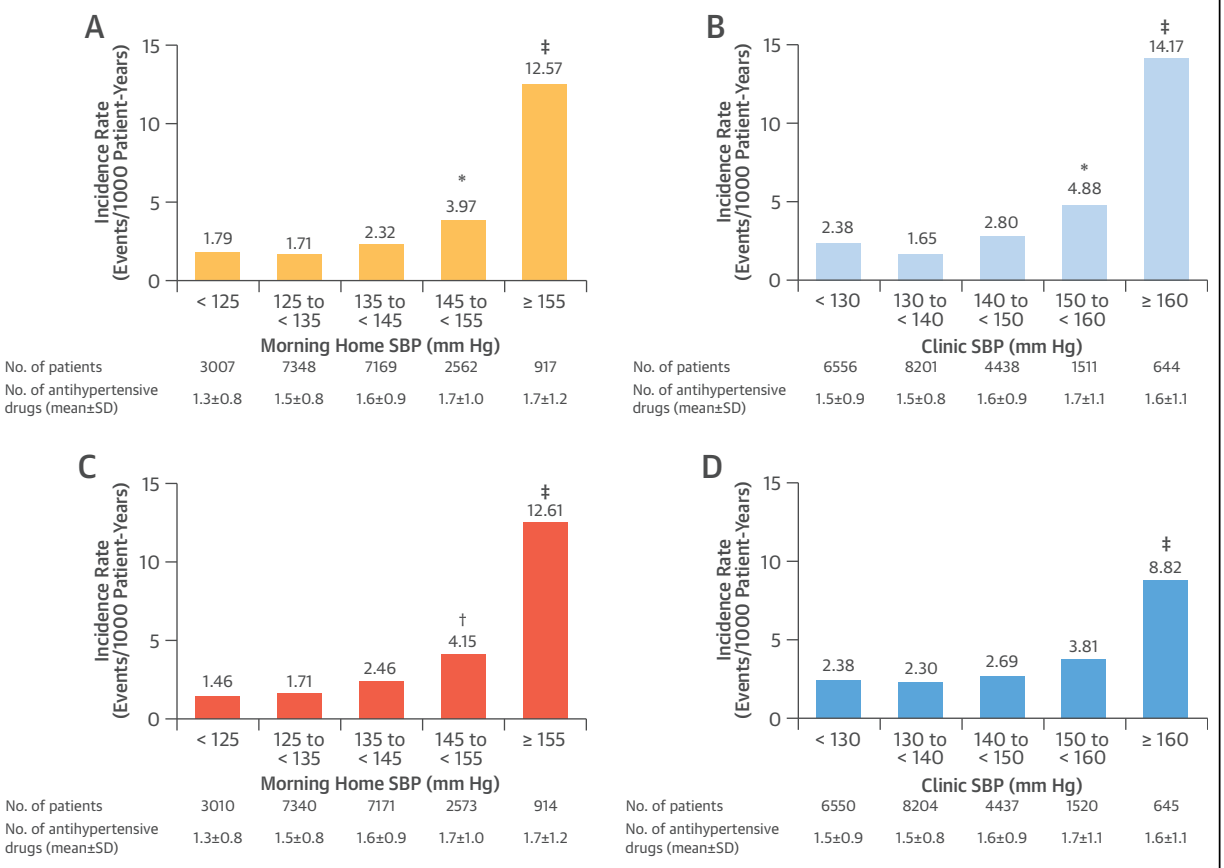
The HR for stroke events was significantly higher in patients with morning HSBP ≥155 mm Hg than in those with morning HSBP <125 mm Hg (HR: 6.01; 95% confidence interval [CI]: 2.85 to 12.68), and it tended to increase in patients with morning HSBP from 145 to <155 mm Hg compared with <125 mm Hg (HR: 1.90; 95% CI: 0.90 to 3.99; p = 0.091) (**Central Illustration**, panel A). The HRs for stroke events were significantly higher in patients with CSBP from 150 to <160 mm Hg (HR: 2.00; 95% CI: 1.06 to 3.76) or ≥160 mm Hg (HR: 5.82; 95% CI: 3.17 to 10.67) than in those with CSBP <130 mm Hg (**Central Illustration**, panel B). The incidence and HR of stroke events were significantly higher in patients with evening HSBP >145 mm Hg (Online Figures 2 and 3). These results showed that morning and evening HSBP predicted stroke events similarly to CSBP.

The incidence of CAD events was significantly higher in patients with morning HSBP 145 to <155 mm Hg (4.15 per 1,000 patient-years) or ≥155 mm Hg (12.61 per 1,000 patient-years) than in those with morning HSBP <125 mm Hg (**Figure 1C**), and in patients with CSBP ≥160 mm Hg compared with <130 mm Hg (8.82 per 1,000 patient-years) (**Figure 1D**). The HR for CAD events was significantly higher in patients with morning HSBP ≥155 mm Hg than in those with morning HSBP <125 mm Hg (HR: 6.24; 95% CI: 2.82 to 13.84), and it tended to increase in patients with morning HSBP 145 to <155 mm Hg compared with <125 mm Hg (HR: 2.15; 95% CI: 0.98 to 4.71; p = 0.056). In contrast, the HR for CAD was significantly higher only in patients with CSBP ≥160 mm Hg (HR: 3.51; 95% CI: 1.71 to 7.20). We also conducted Cox regression analysis using BP as a time-varying covariate; similar results were observed (Online Table 2).

As for evening HSBP, the incidence and HR of CAD events were significantly higher in patients with evening HSBP >155 mm Hg but not in those with evening HSBP from 145 to <155 mm Hg (Online Figures 2 and 3). These results showed that, compared with morning HSBP, CSBP and evening SBP may underestimate CAD risk.

There does not appear to be a J-curve phenomenon in the relationship between morning HBP and stroke or CAD events (**Central Illustration**). To further investigate the J-curve relationship, we subdivided the

**FIGURE 1** SBP and Incidence Rate of Stroke and CAD Events During Follow-Up

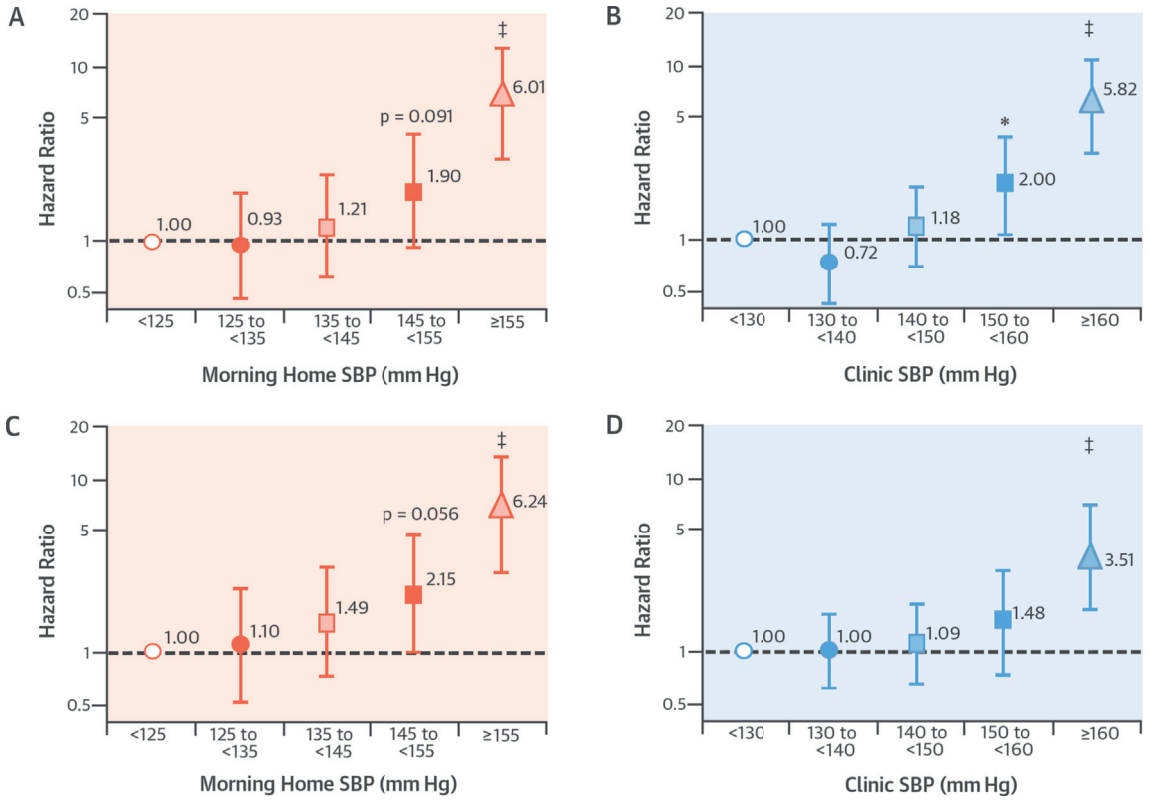



Relationship between mean morning HSBP **(A)** and CSBP **(B)** and incidence rate of stroke events, and between morning HSBP **(C)** and CSBP **(D)** and incidence rate of CAD events. *p < 0.05, †p < 0.01, and ‡p < 0.001 versus morning HSBP <125 mm Hg **(A and C)** or CSBP <130 mm Hg **(B and D)**. CAD = coronary artery disease; CSBP = clinic systolic blood pressure; HSBP = home systolic blood pressure; SBP = systolic blood pressure.

category of morning HSBP <125 mm Hg into <115 mm Hg and 115 to <125 mm Hg. The number of stroke events or CAD events per total number of patients (incidence rate) was 0 of 417 patients or 2 of 416 patients (2.49 per 1,000 patient-years) at morning HSBP <115 mm Hg, and 11 of 2,590 patients (2.06 per 1,000 patient-years) or 7 of 2,594 patients (1.31 per 1,000 patient-years) at morning HSBP 115 to <125 mm Hg, respectively. These methods have limitations because of the small numbers of stroke or CAD events at morning HSBP <125 mm Hg. Therefore, we conducted a spline regression analysis to investigate relative risks of stroke and CAD events in association with morning HSBP. As a result, relative risks of stroke and CAD events did not increase until morning HSBP <110 mm Hg (Online Figure 4).

**GOODNESS OF FIT ANALYSIS OF MORNING HBP VERSUS CBP FOR STROKE OR CAD EVENTS.** We investigated the goodness of fit of the models for stroke or CAD events by the likelihood ratio test (Table 2). Goodness-of-fit of the model for stroke or CAD events was improved by adding CSBP or morning HSBP to the model including only confounders. When morning HSBP was added to the CSBP model, the goodness-of-fit of the model for stroke or CAD events was significantly improved ($p < 0.001$ for stroke; $p < 0.001$ for CAD). In contrast, when CSBP was added to the morning HSBP model, the goodness-of-fit of the model for stroke events was significantly, but more weakly, improved ($p < 0.05$), and the goodness-of-fit of the model for CAD events was not significantly improved ($p = 0.434$).

**CENTRAL ILLUSTRATION** **Morning Home Blood Pressure and CAD: SBP and HR for Stroke and CAD Events During Follow-Up**

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Relationship between mean morning home systolic blood pressure (SBP) **(C)** and clinical SBP and hazard ratio (HR) for coronary artery disease (CAD) events. The Cox proportional hazards model was used, adjusting for sex, age, family history of cardiovascular disease, dyslipidemia, diabetes mellitus, chronic kidney disease, history of cardiovascular disease, and smoking status. *$p < 0.05$ and ‡$p < 0.001$ versus morning home SBP <125 mm Hg **(A and C)** or clinical SBP <130 mm Hg **(B and D)**. **Vertical lines** indicate 95% confidence intervals.

**DIASTOLIC BP.** We also investigated the relationship between DBP and stroke or CAD events (Online Figures 5 and 6). The HR for stroke events was significantly higher in patients with morning home diastolic blood pressure (HDBP) ≥90 mm Hg (HR: 3.59; 95% CI: 1.88 to 6.87) than in those with morning HDBP <75 mm Hg (Online Figure 6A), and in patients with clinic DBP ≥95 mm Hg (HR: 5.83; 95% CI: 2.71 to 12.55) compared with <80 mm Hg (Online Figure 6B). The HR for CAD events was significantly higher in patients with morning HDBP ≥90 mm Hg (HR: 3.11; 95% CI: 1.63 to 5.94) than in those with morning HDBP <75 mm Hg (Online Figure 6C), and in patients with clinic DBP ≥90 to <95 mm Hg (HR: 2.30; 95% CI: 1.07 to 4.92) and ≥95 mm Hg (HR: 3.01; 95% CI: 1.17 to 7.79) compared with <80 mm Hg (Online Figure 6D).

## DISCUSSION

The present analysis of the HONEST study, which included >20,000 Japanese hypertensive patients, shows that morning HBP is a strong predictor of future CAD events, as well as stroke events, and may be superior to CBP (**Central Illustration**). The analysis also shows that there does not appear to be a J-curve in the relationship between morning HBP and stroke or CAD events. The relationship between HBP, compared with CBP, and cardiovascular events has been investigated in several studies. In the Ohasama study (6,7), Finn-HOME study (8), and SHEAF study (12), HBP was found to be superior to CBP for the prediction of cardiovascular events. However, in the PAMELA (Pressioni Arteriose Monitorate e Loro Associazioni) study (11) and a

study by Niiranen et al. (16), HBP was found to be a useful predictor, but had a predictive ability similar to CBP. Although information regarding the relationship between HBP and cardiovascular events has been accumulating, few studies have investigated the relationship between HBP and CAD events. In particular, very few studies have investigated myocardial infarction separately (9,10), and no significant association has been found between HBP and myocardial infarction because of the small number of such events.

**RELATIONSHIP BETWEEN HSBP AND STROKE EVENTS.** This analysis of data from the HONEST study has shown that morning and evening HSBP, like CSBP, are strong predictors for stroke. The incidence of stroke events was 2.92 per 1,000 patient-years (127 events), similar to that found in previous studies: HOMED-BP (Multicenter Hypertension Objective Treatment Based on Measurement by Electrical Devices Blood Pressure) trial (usual control, 1.87; tight control, 2.30) (9) and J-HEALTH (Japan Hypertension Evaluation with Angiotensin II Antagonist Losartan Therapy) study (2.88 per 1,000 patient-years) (10). In previous studies, the relationship between stroke events and HBP or CBP has been investigated (7,10,17). In the Ohasama study, increased HBP, but not CBP, was found to significantly increase the HR for stroke and transient ischemic attack (7). In contrast, in the J-HEALTH study, stroke events increased with increases in both CBP and HBP. As for ABPM, our Jichi Medical University ABPM study (17) showed that morning SBP, evaluated by ABPM, has a stronger ability to predict stroke events than CSBP.

**RELATIONSHIP BETWEEN HSBP AND CAD EVENTS.** This analysis shows that morning HBP is a strong predictor of future CAD events and may be superior to CBP or evening HBP. The incidence of CAD events was similar to that for stroke events. The incidence of CAD events was significantly higher in patients with morning HSBP ≥145 mm Hg than in those with morning HSBP <125 mm Hg. However, for CSBP, the incidence of CAD events was higher only in patients with CSBP ≥160 mm Hg compared with <130 mm Hg. Furthermore, the HR for CAD events was significantly higher in patients with morning HSBP ≥155 mm Hg, and it tended to increase from 145 mm Hg. However, for CSBP, the HR for CAD events increased only in patients with CSBP ≥160 mm Hg. The finding in the present study that morning HSBP is superior to CSBP was obtained by analysis using 4 morning HBP measurements (2 measurements over 2 different days) for each measurement point, whereas there was only 1 measurement of CBP. Therefore, there is the possibility that fewer HBP measurements might not be more effective than CBP. Although the observed superiority of morning HBP may be a function of multiple measurements, HBP has an advantage over CBP in terms of the multiple measurements and being easy to measure.

**TABLE 2 Improvement in Goodness-of-Fit to Model for Stroke or CAD by Addition of CSBP and/or MHSBP***

| | Likelihood Ratio Chi-Square (p Value) | | | |
|---|---|---|---|---|
| | Stroke Events | | CAD Events | |
| | Vs. Model A | Vs. Model B | Vs. Model A | Vs. Model B |
| A: confounders only | – | | – | |
| B: confounders + CSBP | 26.38 (<0.001) | – | 10.81 (<0.05) | – |
| D: confounders + CSBP + MHSBP | 45.04 (<0.001) | 18.66 (<0.001) | 31.87 (<0.001) | 21.06 (<0.001) |
| | **Vs. Model A** | **Vs. Model C** | **Vs. Model A** | **Vs. Model C** |
| A: confounders only | – | | – | |
| C: confounders + MHSBP | 33.19 (<0.001) | – | 28.07 (<0.001) | – |
| D: confounders + MHSBP + CSBP | 45.04 (<0.001) | 11.85 (<0.05) | 31.87 (<0.001) | 3.80 (0.434) |

*Confounders included sex, age, family history of cardiovascular disease, dyslipidemia, diabetes mellitus, chronic kidney disease, history of cardiovascular disease, and smoking status.

CAD = coronary artery disease; CSBP = clinic systolic blood pressure; MHSBP = morning home systolic blood pressure.

To examine the significance of morning HSBP and CSBP in CAD risk prediction, we conducted a goodness-of-fit analysis. The goodness-of-fit of the model for stroke events was similar between morning HSBP and CSBP (increment of the likelihood ratio statistics: 33.19 vs. 26.38), indicating that both are important factors in the prediction of stroke events. In contrast, CSBP was significantly, but more weakly associated with CAD events than morning HSBP (increment of the likelihood ratio statistics: 10.81 vs. 28.07). The goodness-of-fit of the model for CAD events did not significantly improve when CSBP was entered into the model already including morning HSBP (increment of likelihood ratio statistics: 3.80; degrees of freedom: 4; $p = 0.434$). These results suggest that morning HSBP is much more important than CSBP for predicting CAD events. Moreover, the incidence and HR of CAD events increased significantly in patients with evening HSBP >155 mm Hg, but not in those with evening HSBP 145 to <155 mm Hg. Therefore, morning HSBP may be superior to evening HSBP in the prediction of CAD events. Regarding ambulatory BP, the results of the IDACO study showed that 24-h DBP and isolated diastolic hypertension could be considered as predictors of CAD in untreated people <50 years of age (14). Few reports have investigated the predictive ability of HBP for CAD events, and the present study is the first to show that morning HSBP may be superior to CSBP

for the prediction of CAD events. CAD events occur most frequently in the morning (21), and this phenomenon may be associated with an increase in BP and BP variability in the morning, resulting from increased activity of the renin-angiotensin system, as well as increased platelet function activity and a thrombotic tendency at this time of the day. Therefore, morning HBP can be a useful predictor of CAD events, providing assessment of BP at the time when CAD events are most likely to occur.

**J-CURVE PHENOMENON.** The J-curve phenomenon is the term used to describe the relationship between BP and cardiovascular risk when a plot of risk against BP assumes a J shape; this has been a finding in several studies. In the INVEST (International Verapamil SR-Trandolapril Study), in which patients with hypertension complicated with CAD were enrolled, risks for all-cause death and myocardial infarction increased at DBP <70 to 80 mm Hg (22). In the Systolic Hypertension in Europe trial, event risk increased at DBP <70 mm Hg in patients with systolic hypertension complicated with CAD (23). In the PATE (Practitioner's Trial on the Efficacy of Antihypertensive Treatment in the Elderly) Hypertension study, cardiac events increased at SBP <120 mm Hg, although the J-curve was not found with stroke events (24). In the present study, there does not appear to be a J-curve phenomenon in the relationship between morning HBP and stroke or CAD events. As for morning HSBP <125 mm Hg, no conclusion has been reached because of the small numbers of stroke or CAD events. However, the results of the subsequent spline regression analysis showed that there was no increase in relative risks of stroke and CAD events in patients with morning HSBP <125 mm Hg.

**HOME DBP.** In the HONEST study, we also investigated the relationship between morning HDBP or CDBP and CAD events. Both morning HDBP and CDBP may underestimate the risk of CAD events compared with morning HSBP or CSBP. No study has investigated the association between HDBP and CAD. The IDACO ABPM study showed that 24-h DBP and isolated diastolic hypertension predict CAD in untreated people <50 years of age (14).

**STUDY LIMITATIONS.** The findings of the present study are limited by the study design, which was intended to reflect real-world clinical practice; the BP target was at the discretion of the individual physician, combination therapy was unrestricted, and there was no control group. Therefore, this is a trial of achieved BP.

## CONCLUSIONS

Morning HBP is a strong predictor of future CAD events, as well as stroke events, and may be superior to CBP in this regard. Furthermore, there does not appear to be a J-curve in the relationship between morning HBP and stroke or CAD events.

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## PERSPECTIVES

**COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS:** Morning home blood pressure may be superior to clinic BP as a predictor of coronary events and stroke in patients with hypertension.

**TRANSLATIONAL OUTLOOK:** Randomized controlled trials are needed to confirm the relationship between morning HBP readings and future ischemic events and to determine whether therapy specifically targeted to lowing morning BP reduces the frequency of these events.

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**KEY WORDS** home blood pressure monitoring, hypertension, morning blood pressure, stroke

**APPENDIX** For supplemental figures and tables, please see the online version of this article.