Original Article

Cardiovascular Risk With and Without Antihypertensive Drug Treatment in the Japanese General Population Participant-Level Meta-Analysis

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Abstract—To evaluate the cardiovascular mortality risk in association with blood pressure level among people with and without antihypertensive treatment, we performed the participant-level meta-analysis that included 39,705 Japanese from 6 cohorts (58.4% women; mean age, 60.1 years; 20.4% treated). Multivariable-adjusted Cox models were used to analyze the risk of cardiovascular mortality and its subtypes among 6 blood pressure levels according to recent guidelines, optimal to Grade 3 hypertension, and the usage of antihypertensive medication at baseline. During median 10.0 years of follow-up, there were 2032 cardiovascular deaths (5.1 per 1000 person-years), of which 410 deaths were coronary heart disease, 371 were heart failure, and 903 deaths were stroke. Treated participants had significantly higher risk for cardiovascular mortality (hazard ratios, 1.50; 95% confidence intervals, 1.36–1.66), coronary heart disease (hazard ratios, 1.53; confidence intervals, 1.23–1.90), heart failure (hazard ratios, 1.39; confidence intervals, 1.09–1.76), and stroke (hazard ratios, 1.48; confidence intervals, 1.28–1.72) compared with untreated people. Among untreated participants, the risks increased linearly with an increment of blood pressure category ($P<0.011$). The risk increments per blood pressure category were higher in young participants (<60 years; 22% to 79%) than those in old people (≥60 years; 7% to 15%) with significant interaction for total cardiovascular, heart failure, and stroke mortality ($P=0.026$). Among treated participants, the significant linear association was also observed for cardiovascular mortality ($P=0.0003$), whereas no stepwise increase in stroke death was observed ($P=0.19$). The risks of cardiovascular mortality were 1.5-fold high in participants under antihypertensive medication. More attention should be paid to the residual cardiovascular risks in treated patients. (Hypertension. 2014;63:300–00.) • Online Data Supplement

Key Words: cardiovascular diseases • hypertension • meta-analysis

Blood pressure–lowering treatment reduces cardiovascular risk. However, individuals treated with antihypertensive medication had primarily worse prognosis for cardiovascular diseases than untreated hypertensive or normotensive population. Although the strong positive relationship between blood pressure level and cardiovascular disease risks were observed among general population, there is little argument as to the risk increase with elevation of blood pressure among treated participants. For instance, association between blood pressure level and stroke in treated participants was weak, not observed, or observed only based on self-measured home blood pressure. Furthermore, to our knowledge, no previous study compared the risk of different types of cardiovascular diseases, for example, coronary heart disease, heart failure, brush marks.

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*A list of all Evidence for Cardiovascular Prevention From Observational Cohorts in Japan (EPOCH-JAPAN) Research Group participants is given in the Appendix.

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or stroke, in association with their blood pressure level and treatment status. Accordingly, we addressed the issue in an individual-participant meta-analysis of 39,705 residents recruited from 6 populations and enrolled in the Evidence for Cardiovascular Prevention from Observational Cohorts in Japan (EPOCH-JAPAN).

Methods

Study Populations

The construction of the EPOCH-JAPAN database has been described previously.10–13 The inclusion criteria for the EPOCH-JAPAN project were as follows: collection of blood pressure, anthropometric indexes, and health examination measures; follow-up period >5 years and >1000 participants in principle; and nationwide as well as regional Japanese cohort study. All studies contributing to the EPOCH-JAPAN received ethical approval and have been described in detail in peer-reviewed publications.

At the time of writing this report, the EPOCH-JAPAN database included 13 eligible cohorts.6,9,14-24 Figure 1 describes the selection of cohorts and participants. In the present analysis, we excluded 7 cohorts with no data on cause of death.14–18 Information on antihypertensive medication unavailable (3 cohorts) or cardiovascular death was not reported among treated workers.20 Of those, 4,977 participants were excluded because their age was <40 years or ≥90 years (n=4504), because blood pressure was not fully measured (n=42), or because data on antihypertensive medication (n=181) or body mass index (n=250) were missing. Thus, the number of participants analyzed totaled 39,705 (Figure 1 and Table 1).6,9,21–24

Blood Pressure Measurement

Blood pressure was measured in the sitting position with a standard mercury sphygmomanometer or a validated automatic monitor (Ohasama).9 Participants rested before measurement without Ohasaki.22 Consecutive values of 2 (Ohasama) or 3 (Hisayama),24 otherwise 1 reading at the examination center were obtained and used in the analysis. By considering the current hypertension guidelines,25,26 we classified the participants into 6 categories according to their blood pressure levels: optimal (<120/<80 mmHg); normal (120–129/80–84 mmHg); high normal (130–139/85–89 mmHg); grade 1 hypertension (140–159/90–99 mmHg); grade 2 hypertension (160–179/100–109 mmHg); and grade 3 hypertension (≥180/≥110 mmHg). When a systolic or diastolic blood pressure was in a different level, the subject was assigned to the higher level. We further divided the participants according to whether they were being treated with antihypertensive medications or not. Thus, all participants were assigned to 1 of 12 blood pressure–based and treatment-based categories.

Risk Ascertainment and Follow-Up

In all cohorts, a questionnaire was used to obtain detailed information on each participant’s medical history, intake of medications, and drinking and smoking habits. Body mass index was body weight in kilograms divided by height in meters squared. Serum cholesterol and blood glucose were determined by automated enzymatic methods on venous blood samples. Diabetes mellitus was a self-reported diagnosis, a fasting or random blood glucose level of ≥7.0 mmol/L (126 mg/dL) or ≥11.1 mmol/L (200 mg/dL), respectively,27 or the use of antidiabetic drugs. Dyslipidemia was a serum total cholesterol ≥6.2 mmol/L (240 mg/dL)28 or use of lipid-lowering agents.

The National Vital statistics of the Ministry of Health, Labor, and Welfare, Japan, for determining causes of death were obtained in all cohorts.10–23–24 Death certificates were also used for the ascertainment and definition of fatal events in 2 cohorts (Hisayama and Ohasama).9 Other sources including autopsy, medical records,6,9 health examination,22 and questionnaires were also appropriately used. The underlying causes of death were coded according to the 9th International Classification of Disease (ICD-9) by the end of 1994 and according to the 10th International Classification of Disease (ICD-10) from the beginning of 1995. The cause of death used in the current study was defined as follows: cardiovascular disease (390–459 by ICD-9; 100–199 by ICD-10), total stroke (430–438, 430–438, coronary heart disease (410–414, 120–125), and heart failure (428, 150).

Table 1. Population Sampling Methods in Each EPOCH-JAPAN Cohort in the Present Study

<table>
<thead>
<tr>
<th>Cohort Name, Catchment Area</th>
<th>Recruitment Year(s)</th>
<th>No. in EPOCH-JAPAN Database With Cause of Death</th>
<th>No. Analyzed</th>
<th>Follow-Up, Y*</th>
<th>No. of Cardiovascular Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osaki, Miyagi22</td>
<td>1994</td>
<td>16,262</td>
<td>16,223</td>
<td>6.5 (1.8–6.7)</td>
<td>265</td>
</tr>
<tr>
<td>Ohasama, iwate8</td>
<td>1988–1995</td>
<td>3174</td>
<td>2766</td>
<td>11.7 (4.1–11.7)</td>
<td>121</td>
</tr>
<tr>
<td>RERF cohort, Hiroshima23</td>
<td>1986</td>
<td>4670</td>
<td>4431</td>
<td>16.5 (3.5–18.0)</td>
<td>523</td>
</tr>
<tr>
<td>Hisayama, Fukukoku24</td>
<td>1988</td>
<td>2736</td>
<td>2717</td>
<td>12.0 (3.9–12.0)</td>
<td>159</td>
</tr>
<tr>
<td>NIPPON DATA 80, Nationwide Japan21</td>
<td>1980</td>
<td>9638</td>
<td>7157</td>
<td>19.0 (5.3–19.0)</td>
<td>733</td>
</tr>
<tr>
<td>NIPPON DATA 90, Nationwide Japan21</td>
<td>1990</td>
<td>8202</td>
<td>6411</td>
<td>10.0 (4.9–10.0)</td>
<td>231</td>
</tr>
<tr>
<td>Total</td>
<td>1980–1995</td>
<td>44,682</td>
<td>39,705</td>
<td>10.0 (3.2–19.0)</td>
<td>2032</td>
</tr>
</tbody>
</table>

EPOCH-JAPAN indicates Evidence for Cardiovascular Prevention from Observational Cohorts in Japan; NIPPON DATA, National Integrated Project for Prospective Observation of Non-communicable Disease and Its Trends in the Aged; and RERF, Radiation Effects Research Foundation.

*Median (5th to 95th percentile interval).
Statistical Analysis
The SAS software, version 9.3 (SAS Institute, Cary, NC) was used in the present study. Standard summary statistics including t test, analysis of variance, and χ² test were used to illustrate results. We used the multivariable-adjusted Cox regression model to investigate the association between blood pressure level and cardiovascular disease mortality. The stratified Cox models were applied to account for the heterogeneity of baseline hazards among cohort29 and were adjusted for sex, age, body mass index, history of cardiovascular disease, total cholesterol (<160, 160–200, 200–240, ≥240 mg/dL), lipid-lowering medication, diabetes mellitus, smoking (current, past, never), and habitual drinking (current, past, never). In participants with unknown cardiovascular disease history (n=366), smoking (n=2675), or drinking habits (n=2637), or those with insufficient information to diagnose diabetes mellitus (n=1990) or dyslipidemia (n=1053), we included these factors using dummy variables to adjust confounding. We checked quadratic relationship between blood pressure level and outcomes by adding the quadratic term in the Cox model. We also assessed interactions by adding an interaction term to the Cox model. We tested heterogeneity in the hazard ratios among the 6 cohorts by testing an ordinal variable coding for these subgroups among participants. Statistical significance was an α-level of <0.05 on 2-sided tests.

Results
Table 2 lists the baseline characteristics of the 39705 participants by blood pressure category and treatment status. Among all participants, 23176 (58.4%) were women, 21099 (53.1%) were aged ≥60 years, 3966 (10.1%) experienced previous cardiovascular diseases, 14374 (38.8%) were current or ex-smokers, 16573 (44.7%) were current or ex-drinkers, 2982 (7.9%) had diabetes mellitus, and 6628 (17.2%) participants had dyslipidemia. Characteristics of participants by antihypertensive medication are summarized in Table S1 in the online-only Data Supplement. When compared with untreated participants, the rates of diabetes mellitus, dyslipidemia, and history of cardiovascular disease were significantly high in treated participants (P<0.0001) but significantly low rate for current or ex-smokers (P=0.0003). The systolic and diastolic blood pressure levels in

Table 2. Baseline Characteristics and Blood Pressure Definitions of Participants by Antihypertensive Medication

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Optimal</th>
<th>Normal</th>
<th>High Normal</th>
<th>Grade 1 Hypertension</th>
<th>Grade 2 Hypertension</th>
<th>Grade 3 Hypertension</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated participants (n=31 607)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number</td>
<td>6714</td>
<td>6588</td>
<td>7446</td>
<td>7606</td>
<td>2477</td>
<td>776</td>
<td></td>
</tr>
<tr>
<td>Women, %</td>
<td>4521 (67.3)</td>
<td>3897 (59.2)*</td>
<td>4162 (55.9)*</td>
<td>4017 (52.8)†</td>
<td>1291 (52.1)</td>
<td>374 (48.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>History of cardiovascular disease, %</td>
<td>256 (3.8)</td>
<td>278 (4.3)</td>
<td>335 (4.5)</td>
<td>386 (11.9)*</td>
<td>461 (19.0)*</td>
<td>190 (24.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>220 (3.5)</td>
<td>270 (4.3)†</td>
<td>401 (5.7)†</td>
<td>559 (7.6)*</td>
<td>267 (11.1)*</td>
<td>88 (11.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Dyslipidemia, %</td>
<td>864 (13.1)</td>
<td>901 (14.0)</td>
<td>1167 (16.0)*§</td>
<td>1288 (17.4)‡</td>
<td>446 (18.4)</td>
<td>135 (17.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Current or ex-smoker, %</td>
<td>2126 (34.0)</td>
<td>2640 (42.5)*</td>
<td>3228 (46.6)*</td>
<td>3424 (47.6)</td>
<td>1152 (49.5)</td>
<td>391 (54.0)§</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Current or ex-drinking habits, %</td>
<td>2418 (38.6)</td>
<td>2640 (42.5)*</td>
<td>3228 (46.6)*</td>
<td>3424 (47.6)</td>
<td>1152 (49.5)</td>
<td>391 (54.0)§</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age, y (SD)</td>
<td>56.2 (10.5)</td>
<td>58.6 (10.5)†</td>
<td>59.1 (10.5)*</td>
<td>60.5 (10.8)*</td>
<td>62.1 (11.1)*</td>
<td>63.4 (11.8)§</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Body mass index, kg/m² (SD)</td>
<td>22.3 (2.9)</td>
<td>22.9 (3.0)*</td>
<td>23.1 (3.1)*</td>
<td>23.6 (3.2)*</td>
<td>23.7 (3.5)‡</td>
<td>23.7 (3.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg (SD)</td>
<td>90.4 (7.7)</td>
<td>102.2 (4.6)*</td>
<td>112.2 (4.6)*</td>
<td>123.5 (4.8)*</td>
<td>144.4 (7.6)*</td>
<td>162.0 (8.5)*</td>
<td>185.3 (16.6)*</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg (SD)</td>
<td>67.4 (6.9)</td>
<td>75.2 (7.0)*</td>
<td>79.5 (7.3)*</td>
<td>85.3 (8.1)*</td>
<td>92.9 (9.5)*</td>
<td>102.0 (13.6)*</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Treated participants (n=8098)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number</td>
<td>514</td>
<td>795</td>
<td>1644</td>
<td>2817</td>
<td>1674</td>
<td>654</td>
<td></td>
</tr>
<tr>
<td>Women, %</td>
<td>336 (65.4)</td>
<td>511 (64.3)</td>
<td>1004 (61.1)</td>
<td>1700 (60.3)</td>
<td>978 (58.4)</td>
<td>385 (58.9)</td>
<td>0.017</td>
</tr>
<tr>
<td>History of cardiovascular disease, %</td>
<td>85 (16.5)</td>
<td>124 (15.6)</td>
<td>276 (16.8)</td>
<td>536 (19.1)</td>
<td>353 (21.3)</td>
<td>176 (27.2)§</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>120 (26.8)</td>
<td>123 (17.5)†</td>
<td>191 (12.7)§</td>
<td>379 (14.3)</td>
<td>238 (14.6)</td>
<td>126 (19.9)§</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Dyslipidemia, %</td>
<td>144 (30.8)</td>
<td>190 (25.6)§</td>
<td>367 (23.9)</td>
<td>581 (21.7)</td>
<td>364 (22.4)</td>
<td>181 (28.2)§</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Current or ex-smoker, %</td>
<td>163 (35.5)</td>
<td>244 (33.4)</td>
<td>536 (36.4)</td>
<td>966 (37.1)</td>
<td>610 (39.0)</td>
<td>236 (38.4)</td>
<td>0.15</td>
</tr>
<tr>
<td>Current or ex-drinking habits, %</td>
<td>205 (44.4)</td>
<td>302 (41.7)</td>
<td>665 (45.2)</td>
<td>1153 (44.2)</td>
<td>727 (46.4)</td>
<td>268 (44.4)</td>
<td>0.43</td>
</tr>
<tr>
<td>Age, y (SD)</td>
<td>65.0 (9.2)</td>
<td>65.2 (9.1)</td>
<td>65.4 (8.3)</td>
<td>65.5 (8.9)</td>
<td>65.2 (9.5)</td>
<td>65.6 (10.2)</td>
<td>0.73</td>
</tr>
<tr>
<td>Body mass index, kg/m² (SD)</td>
<td>23.4 (3.4)</td>
<td>23.9 (3.1)§</td>
<td>24.1 (3.3)</td>
<td>24.3 (3.3)</td>
<td>24.5 (3.3)</td>
<td>24.5 (3.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg (SD)</td>
<td>1104 (6.4)</td>
<td>1229 (4.4)*</td>
<td>1334 (4.5)*</td>
<td>1465 (7.1)*</td>
<td>1638 (8.3)*</td>
<td>1857 (16.1)*</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg (SD)</td>
<td>67.5 (7.3)</td>
<td>74.6 (7.8)*</td>
<td>78.8 (8.3)*</td>
<td>85.0 (8.6)*</td>
<td>92.1 (10.1)*</td>
<td>100.5 (13.5)*</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Values are number of participants (%) or arithmetic mean (SD). Blood pressure levels are defined from 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). Diabetes mellitus was a self-reported diagnosis, a fasting or random blood glucose level of ≥7.0 mmol/L (126 mg/dL) or ≥11.1 mmol/L (200 mg/dL), respectively, or the use of antidiabetic drugs. Dyslipidemia was a serum total cholesterol ≥6.2 mmol/L (240 mg/dL) or use of lipid-lowering agents. History of cardiovascular disease, diabetes mellitus, dyslipidemia, smoking, and drinking were unavailable in 366, 1990, 1053, 2675, and 2637 participants, respectively. P values were calculated using analysis of variance or χ² statistics.

*P<0.0001.
†P<0.001.
‡P<0.005.
§P<0.01 for significance of the difference with the adjacent lower category.
treated participants were 146.0 and 84.3 mm Hg, respectively, which were 14.1 mm Hg (95% CI, 13.6–14.6; \( P = 0.0001 \)) and 5.3 mm Hg (95% CI, 5.0–5.6; \( P = 0.0001 \)) higher than those in untreated participants.

The median follow-up of the overall study population was 10.0 years (5th to 95th percentile interval, 3.2–19.0 years), ranging from 6.5 years in Osaka to 19.0 years in NIPPON DATA 80 (Table 1). During 399,560 person-years of follow-up, there were 2032 cardiovascular deaths (5.1 per 1000 person-years), of which 410 were coronary heart disease, 371 were heart failure, and 903 deaths were stroke. The risks of cardiovascular mortality among treated participants in reference to the risk for untreated population were constantly higher (\( P \leq 0.0072 \)), ranging from 39% (95% CI, 9% to 76%) for coronary heart disease (Table 3). Results were confirmatory when we divided participants by sex (men versus women), age (<60 versus ≥60 years), and overweight (body mass index <25 versus ≥25 kg/m²) as shown in Table 3. There were no significant interactions between antihypertensive medication and subgroups for mortality (\( P \geq 0.30 \)) except the age group for total cardiovascular (\( P = 0.0011 \)), coronary heart disease (\( P = 0.043 \)), and stroke death (\( P = 0.029 \)). Similar results were observed when systolic blood pressure levels were excluded from the adjustment factor of the models (Table S2). The hypotheses of heterogeneity across 6 cohorts were rejected for cardiovascular mortality (heterogeneity \( P = 0.45 \)) as well as for subtypes of cardiovascular death (heterogeneity \( P \geq 0.14 \)).

Figure 2 indicates the risk in each 12 group according to the combination of 6 blood pressure levels and treatment status. Among untreated participants, the risks increased linearly with an increment of blood pressure category independent of the cause of death (\( P \leq 0.011 \)). The significant linear association between total cardiovascular mortality and blood pressure level was observed among treated participants (\( P = 0.0003 \)). Whereas, no stepwise increase in stroke risk was observed in treated participants (\( P = 0.19 \)). In this 8098 treated population, the association between blood pressure levels and risk of stroke death could be modeled using quadratic term of blood pressure (\( P = 0.024 \)). However, log likelihood tests indicated that the improvement of the Cox models including quadratic term was not significant for stroke mortality when compared with the models without quadratic term (\( P = 0.13 \)). When we excluded 3966 participants with history of cardiovascular diseases (Figure S1), the risk increased linearly with blood pressure category increase among 29,191 untreated participants irrespective of mortality subtypes (\( P \geq 0.0039 \)), although the risk increments among 6548 treated participants were not significant (\( P \geq 0.10 \)). Similar to the main analysis, the blood pressure level in treated patients was also curvilinearly associated with stroke mortality (\( P = 0.0076 \)); whereas, the improvement of the model was not significant (\( P = 0.094 \)). Stratifying participants by sex, age (<60 versus ≥60 years), and body mass index (<25 versus ≥25 kg/m²) confirmed the main analyses as reported in Tables S3 to S8.

The risk trends in each subgroup are shown in Table 4. Among untreated population, the risk increments per one blood pressure category were higher in young participants (<60 years; 22% to 79%) than those in old people (60 years; 7% to 15%), and significant interactions were observed for total cardiovascular, heart failure, and stroke mortality (Table 4; \( P \leq 0.026 \)). The interactions with blood pressure were also significant among treated patients for age on coronary heart disease death (\( P = 0.011 \)), for body mass index on cardiovascular (\( P = 0.054 \)), and for stroke (\( P = 0.016 \)) mortality among untreated participants. Interactions between blood pressure levels and sex were not reached to the significance (\( P \geq 0.078 \)).

**Discussion**

The present study is based on the 39,705 representative people with diverse blood pressure levels from 6 cohorts with 10-year

### Table 3. Risk of Cardiovascular Mortality in Treated Patients Compared with Untreated Participants

<table>
<thead>
<tr>
<th>Category</th>
<th>No. of Participants</th>
<th>No. of Events</th>
<th>Total Cardiovascular HR (95% CI)</th>
<th>Coronary Heart Disease HR (95% CI)</th>
<th>Heart Failure HR (95% CI)</th>
<th>Stroke HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All participants</td>
<td>39,705</td>
<td>2032</td>
<td>1.50 (1.36–1.66)†</td>
<td>410</td>
<td>1.53 (1.23–1.90)†</td>
<td>371</td>
</tr>
<tr>
<td>Women</td>
<td>23,176</td>
<td>1069</td>
<td>1.48 (1.30–1.70)†</td>
<td>188</td>
<td>1.59 (1.16–2.18)‡</td>
<td>229</td>
</tr>
<tr>
<td>Men</td>
<td>16,529</td>
<td>963</td>
<td>1.56 (1.35–1.80)§</td>
<td>222</td>
<td>1.51 (1.11–2.04)‡</td>
<td>142</td>
</tr>
<tr>
<td>Age &lt;60 y</td>
<td>18,060</td>
<td>292</td>
<td>1.66 (1.23–2.23)¶</td>
<td>59</td>
<td>2.17 (1.14–4.12)¶</td>
<td>49</td>
</tr>
<tr>
<td>Age ≥60 y</td>
<td>21,099</td>
<td>1740</td>
<td>1.48 (1.33–1.64)¶</td>
<td>351</td>
<td>1.45 (1.15–1.82)‡</td>
<td>322</td>
</tr>
<tr>
<td>Body mass index &lt;25 kg/m²</td>
<td>28,432</td>
<td>1574</td>
<td>1.52 (1.35–1.70)§</td>
<td>311</td>
<td>1.41 (1.09–1.83)‡</td>
<td>298</td>
</tr>
<tr>
<td>Body mass index ≥25 kg/m²</td>
<td>11,273</td>
<td>458</td>
<td>1.47 (1.21–1.76)†</td>
<td>99</td>
<td>1.75 (1.15–2.67)‡</td>
<td>73</td>
</tr>
</tbody>
</table>

Hazard ratios (HR), given with 95% confidence interval (CI), reflect the risk in patients with antihypertensive medication compared with untreated individuals as reference, and were adjusted for systolic blood pressure, sex (except sex-subgroup analysis), age, body mass index, history of cardiovascular disease, total cholesterol, diabetes mellitus, smoking, habitual drinking, and cohort.

† \( P = 0.0001 \).

‡ \( P = 0.001 \).

§ \( P = 0.01 \).

¶ \( P = 0.05 \).

‖Significant difference (\( P < 0.05 \)) in the hazard ratios between corresponding strata.
follow-up data. Individuals using antihypertensive medications had a higher cardiovascular risk compared with those without treatment for a given level of blood pressure at baseline. These results are consistent with those obtained in previous studies.3–5,7,30–32 Furthermore, we first demonstrated that the risk levels in participants under antihypertensive medication were different according to the subtypes of mortality.

Our participant-level meta-analysis of large sample size representing nationwide Japanese populations is clearly an advance over previous publications in the research field of blood pressure. We pooled data from prospective cohorts with a long follow-up period (median 10.0 years), and the results are likely to be generalizable to a wide age range of adult men and women. Meta-analyses based on individual-participant data, compared with meta-analyses of summary statistics, have unique advantages, including the possibility of computing survival curves and the ability to check whether the Cox proportional hazard assumption is fulfilled.33,34

Stroke risk and effect of antihypertensive medication in each blood pressure category were reported from 2 population-based studies in Japan.5,7 Izumi and colleagues collected health screening data with 142,989 untreated and 13,858 treated participants in Akita prefecture, Japan. During 3 years follow-up, they observed 1017 and 306 stroke events among untreated and treated participants, respectively. In multivariate-adjusting Poisson regression model, the stroke risk was amplified linearly with increasing blood pressure category, although they provided neither P values nor confidence intervals in each risk. The point estimates of hazard ratios in individuals with untreated and treated stage 3 hypertension were 10.6 and 5.6, respectively, compared with untreated optimal blood pressure category.

In the Japan Arteriosclerosis Longitudinal Study-Existing Cohorts Combined (JALS-ECC), which is a collaborative meta-analysis of individual-participant data, the study group analyzed 11,371 eligible participants from 4 cohorts; these cohorts were entirely different population from the present study. They were followed-up for a mean of 9.5 years, and 324 stroke incidences were observed.5 The stroke risk among 1913 treated participants was 1.72 times (CI, 1.34–2.21) higher than that among untreated participants. The stepwise increase in stroke risk was observed among untreated participants (P=0.0001) but not significant in treated participants (P=0.1),5 which is supported by our current findings.
for stroke mortality based on 8098 treated participants ($P=0.19$). In the present study, the blood pressure level might be curvilinearly associated with stroke mortality risk among treated participants (Figure 2 and Figure S1D), namely J- or U-shaped relationship. However, it should not be pushed too far because the quadratic model was not significantly superior to the linear trend model ($P_{20.079}$), and the phenomena are sometimes seen in the observational study.53

Our findings that treated individuals who had a higher cardiovascular risk compared with untreated participants do not indicate that antihypertensive therapy increases the risk. The importance of blood pressure control has been established based on intervention trials.1,2 As discussed in detail previously,5,9,35 treatment, per se, is a sort of marker in cohort studies with single baseline survey. Although hard to prove, doctors in the clinical practice that initiate antihypertensive treatment would comprehend and recognize an individual high risk sets a ceiling effect to the benefits of treatment and underlines the limitations of late interventions. In major- ity of patients with hypertension, antihypertensive treatment would be deferred until organ damage or even a cardiovascular event has occurred.35,38 Nevertheless, the importance to maintain low blood pressure in treated individual for preventing cardiovascular diseases was demonstrated by the current observational study for cardiovascular mortality ($P=0.0003$ for the trend risk in blood pressure categories; Figure 2A) and its subtypes except stroke mortality.

Similar to the previous reports,5–8 cardiovascular risks among untreated participants significantly increased as the increment of blood pressure (Figure 2). The significant interactions between age group and antihypertensive treatment (Table 3) as well as blood pressure category (Table 4) suggest that the impact of blood pressure and benefit of treatment would be deferred until organ damage or even a cardiovascular event has occurred.35,38 Nevertheless, the importance to maintain low blood pressure in treated individual for preventing cardiovascular diseases was demonstrated by the current observational study for cardiovascular mortality ($P=0.0003$ for the trend risk in blood pressure categories; Figure 2A) and its subtypes except stroke mortality.

Table 4. Trend and Interaction Among Strata by Usage of Antihypertensive Medication

<table>
<thead>
<tr>
<th>Strata</th>
<th>Untreated</th>
<th>Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cardiovascular</td>
<td>Coronary Heart Disease</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>1.12</td>
<td>1.09</td>
</tr>
<tr>
<td></td>
<td>(1.06–1.19)*</td>
<td>(0.95–1.26)</td>
</tr>
<tr>
<td>Men</td>
<td>1.24</td>
<td>1.23</td>
</tr>
<tr>
<td></td>
<td>(1.16–1.32)§</td>
<td>(1.08–1.40)†</td>
</tr>
<tr>
<td>Interaction $P$</td>
<td>0.17</td>
<td>0.97</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60</td>
<td>1.50</td>
<td>1.22</td>
</tr>
<tr>
<td></td>
<td>(1.35–1.68)§</td>
<td>(0.95–1.57)</td>
</tr>
<tr>
<td>≥60</td>
<td>1.11</td>
<td>1.13</td>
</tr>
<tr>
<td></td>
<td>(1.06–1.17)§</td>
<td>(1.02–1.26)§</td>
</tr>
<tr>
<td>Interaction $P$</td>
<td>&lt;0.0001</td>
<td>0.45</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25</td>
<td>1.15</td>
<td>1.12</td>
</tr>
<tr>
<td></td>
<td>(1.10–1.20)§</td>
<td>(1.00–1.24)†</td>
</tr>
<tr>
<td>≥25</td>
<td>1.29</td>
<td>1.32</td>
</tr>
<tr>
<td></td>
<td>(1.15–1.44)§</td>
<td>(1.03–1.69)‡</td>
</tr>
<tr>
<td>Interaction $P$</td>
<td>0.034</td>
<td>0.16</td>
</tr>
</tbody>
</table>

Hazard ratios (95% confidence interval) reflect the risk trend in each stratum associate with one category increase in six blood pressure categories, from optimal (<120/<80 mm Hg) to grade 3 hypertension (≥180/≥110 mm Hg). Interaction $P$ indicates a difference between women vs. men, age <60 vs. ≥60 yr, or body mass index <25 vs. ≥25 kg/m². Adjusted factors were systolic blood pressure, sex (except sex-subgroup analysis), age, body mass index, history of cardiovascular disease, total cholesterol, diabetes mellitus, smoking, habitual drinking, and cohort.

* $P<0.001$.
† $P<0.01$.
‡ $P<0.05$.
§ $P<0.0001$.
heat failure risk have generalizability for the current worldwide population.

In the Ohasama study,8 which is included to the current meta-analysis, the classification based on self-measured home blood pressure showed a significant linear increase in stroke risk even among treated participants (P=0.004), but not linear when based on conventional blood pressure (P=0.3). The blood pressures measured under outpatient settings or during health check-ups include biases known as white coat hypertension or masked hypertension.41,42 A certain proportion of treated patients would be masked hypertension, resulted to optimal or normal conventional blood pressure categories although their out-of-office blood pressure was high, although unverifiable because none of the other cohorts in the EPOCH-JAPAN project have longitudinal follow-up data based on home or ambulatory blood pressure recording. Meanwhile, previous publications had showed similar results on the risk of treated participants, suggesting that the present findings are mostly confirmatory.5,7,9

Our findings must be interpreted within the context of their potential limitations. First, our study population consists of residents in Japan, thus our current findings might not be generalizable to Western populations. Diuretics and β-blockers have been used less extensively in Japan, whereas not stroke but myocardial infarction is the overriding cardiovascular complication associated with blood pressure in European countries and the United States. Second, blood pressure was measured at the beginning of the follow-up period, and we could not take account for regression dilution bias.10 Participants might be reclassified when they were examined during the follow-up period. Third, caution is necessary when comparing or applying the results of this study to current patients because long-acting calcium channel blockers, angiotensin II receptor blockers, and direct renin inhibitors have been newly marketed. Fourth, we excluded cohorts without data on antihypertensive medication as shown in Figure 1. Furthermore, methods of blood pressure measurement and ascertainment of events were not identical among cohorts. However, we accounted for cohort as strata in the Cox proportional hazard models,20 and the heterogeneity was not significant in any of the pooled mortality results. Nevertheless, selection bias might be a concern because of the inclusion criteria of the EPOCH-JAPAN project,10-13 such as follow-up period >5 years and >1000 participants in principle. Finally, we evaluated the mortality outcome. The introduction of stroke units and the increasing availability of invasive coronary care and thrombolysis reduced during the past decades the case-fatality rate of most cardiovascular complications of hypertension.14 Taking account for nonfatal events is therefore needed for further investigation to generalize our findings.

Perspectives
Treated participants had significantly high cardiovascular risk compared with untreated participants. Meanwhile, the impacts of blood pressure level for risks of cardiovascular mortality and its subtypes were different in participants under antihypertensive medication. Based on the findings of the current EPOCH-JAPAN, the participant-level meta-analysis with 10-year follow-up data, more attention should be paid to the residual cardiovascular risks in treated patients with hypertension.

Appendix
The Evidence for Cardiovascular Prevention from Observational Cohorts in Japan (EPOCH-JAPAN) Research Group is composed of the following investigators. Chairperson: Hirotugu Ueshima (Shiga University of Medical Science); Co-Chairperson: Tomonori Okamura (Keio University); Executive committee: Hirotugu Ueshima (Shiga University of Medical Science), Yutaka Imai (Tohoku University Graduate School of Pharmaceutical Sciences), Takayoshi Ohkubo (Teikyo University School of Medicine), Fujiko Irie (Ibaraki Prefecture), Hiroyasu Ishi (Osaka University Graduate School of Medicine), Yutaka Kiyohara (Kyushu University Graduate School of Medicine), Katsuyuki Miura, Yoshitaka Murakami (Shiga University of Medical Science), Hideaki Nakagawa (Kanazawa Medical University), Takeo Nakayama (Kyoto University School of Public Health), Tomonori Okamura (Keio University), Akira Okayama (Japan Anti-Tuberculosis Association), Toshimi Sairenchi (Dokkyo Medical University), Shigeyuki Saitoh (Sapporo Medical University), Kiyomi Sakata (Iwate Medical University), Akiko Tamakoshi (Hokkaido University Graduate School of Medicine), Ichiro Tsuji (Tohoku University Graduate School of Medicine), Michiko Yamada (Radiation Effects Research Foundation), Akihiko Kitanura (Osaka Center for Cancer and Cardiovascular Disease Prevention), and Yoshihiro Miyamoto (National Cerebral and Cardiovascular Center).

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Disclosures
None.

References


Stewart LA, Parmar MK. Meta-analysis of the literature or of individual patient data: is there a difference? Lancet. 1993;341:418–422.


Stewart LA, Parmar MK. Meta-analysis of the literature or of individual patient data: is there a difference? Lancet. 1993;341:418–422.


Ohkubo T, Kikuya M, Metoki H, Asayama K, Obara T, Hashimoto J, Totsune K, Hoshi H, Satoh H, Imai Y. Prognosis of “masked” hypertension and “white-coat” hypertension detected by 24-h ambulatory blood
Novelty and Significance

What Is New?
- The risks of cardiovascular mortality were ≈1.5-fold higher in participants under antihypertensive medication than those without drug treatment.
- The impact of blood pressure level for risks of cardiovascular mortality differed according to its subtypes in participants under antihypertensive medication.

What Is Relevant?
- Individual using antihypertensive medication had a higher cardiovascular disk compared with those without treatment for a given level of blood pressure at baseline.
- The blood pressure level in treated patients was curvilinearly associated with stroke mortality, although the improvement of the model was not significant.

Summary
Based on the participant-level meta-analysis, which included 39,705 Japanese from 6 cohorts, treated participants had significantly high cardiovascular risk compared with untreated participants. Meanwhile, the association between blood pressure level and cardiovascular mortality risk in participants under antihypertensive drug treatment varied by mortality subtypes. More attention should be paid to the residual cardiovascular risks in treated patients with hypertension.
Cardiovascular Risk With and Without Antihypertensive Drug Treatment in the Japanese General Population: Participant-Level Meta-Analysis
Kei Asayama, Michihiro Satoh, Yoshitaka Murakami, Takayoshi Ohkubo, Sin-ya Nagasawa, Ichiro Tsuji, Takeo Nakayama, Akira Okayama, Katsuyuki Miura, Yutaka Imai, Hirotsugu Ueshima and Tomonori Okamura
on behalf of the Evidence for Cardiovascular Prevention From Observational Cohorts in Japan (EPOCH-JAPAN) Research Group

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SUPPLEMENTAL MATERIAL

This Online Data Supplement has been provided by the authors to give readers additional information about the work.

Supplement to:
Cardiovascular Risk With and Without Antihypertensive Drug Treatment in the Japanese General Population —Participant-Level Meta-Analysis
*Hypertension* 2014; published online.
http://dx.doi.org/10.1161/HYPERTENSIONAHA.113.03206.
Table S1. Baseline Characteristics of Participants by Antihypertensive Medication

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Participants (n=39705)</th>
<th>Untreated (n=31607)</th>
<th>Treated (n=8098)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of participants (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>23176 (58.4)</td>
<td>18262 (57.8)</td>
<td>4914 (60.7)</td>
</tr>
<tr>
<td>History of cardiovascular disease</td>
<td>3966 (10.1)</td>
<td>2416 (7.7)</td>
<td>1550 (19.2)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2982 (7.9)</td>
<td>1805 (6.0)</td>
<td>1177 (15.5)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>6628 (17.2)</td>
<td>4801 (15.5)</td>
<td>1827 (23.7)</td>
</tr>
<tr>
<td>Current or ex-smoker</td>
<td>14374 (38.8)</td>
<td>11619 (39.3)</td>
<td>2755 (37.0)</td>
</tr>
<tr>
<td>Current or ex-drinking habits</td>
<td>16573 (44.7)</td>
<td>13253 (44.7)</td>
<td>3320 (44.7)</td>
</tr>
<tr>
<td>Use of antihypertensive drug</td>
<td>8098 (20.4)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Mean (SD) of characteristic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>60.1 (10.9)</td>
<td>58.7 (10.9)</td>
<td>65.4 (9.0)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>23.4 (3.2)</td>
<td>23.1 (3.2)</td>
<td>24.2 (3.4)</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>134.7 (20.1)</td>
<td>131.8 (18.9)</td>
<td>146.0 (20.5)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>80.1 (11.8)</td>
<td>79.0 (11.4)</td>
<td>84.3 (12.3)</td>
</tr>
</tbody>
</table>

Values are number of participants (%) or arithmetic mean (SD). Diabetes mellitus was a self-reported diagnosis, a fasting or random blood glucose level of ≥7.0 mmol/L (126 mg/dL) or ≥11.1 mmol/L (200 mg/dL), respectively, or the use of antidiabetic drugs. Dyslipidemia was a serum total cholesterol ≥6.2 mmol/L (240 mg/dL) or use of lipid-lowering agents. History of cardiovascular disease, diabetes, dyslipidemia, smoking, and drinking were unavailable in 366, 1990, 1053, 2675, and 2637 participants, respectively. All test for differences between untreated and treated groups were significant (P≤0.0003) except for the prevalence of current or ex-drinking habits (P=0.92).
Table S2. Risk of Cardiovascular Mortality in Treated Patients Compared with Untreated Participants — Unadjusted by Blood Pressure Level

<table>
<thead>
<tr>
<th>Category</th>
<th>Nº of Participants</th>
<th>Nº of Events</th>
<th>HR (95% CI)</th>
<th>Nº of Events</th>
<th>HR (95% CI)</th>
<th>Nº of Events</th>
<th>HR (95% CI)</th>
<th>Nº of Events</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Participants</td>
<td>39705</td>
<td>2032</td>
<td>1.62 (1.46–1.78)§</td>
<td>410</td>
<td>1.63 (1.32–2.03)§</td>
<td>371</td>
<td>1.47 (1.16–1.87)†</td>
<td>903</td>
<td>1.63 (1.41–1.88)§</td>
</tr>
<tr>
<td>Subgroups</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>23176</td>
<td>1069</td>
<td>1.58 (1.38–1.81)§</td>
<td>188</td>
<td>1.70 (1.24–2.33)‡</td>
<td>229</td>
<td>1.50 (1.11–2.03)†</td>
<td>465</td>
<td>1.58 (1.29–1.93)§</td>
</tr>
<tr>
<td>Men</td>
<td>16529</td>
<td>963</td>
<td>1.71 (1.48–1.97)§</td>
<td>222</td>
<td>1.62 (1.20–2.19)†</td>
<td>142</td>
<td>1.50 (1.01–2.21)*</td>
<td>438</td>
<td>1.72 (1.39–2.13)§</td>
</tr>
<tr>
<td>Age &lt;60 years</td>
<td>18606</td>
<td>292</td>
<td>2.34 (1.75–3.14)¶</td>
<td>59</td>
<td>3.12 (1.66–5.87)¶</td>
<td>49</td>
<td>1.54 (0.69–3.46)</td>
<td>136</td>
<td>2.20 (1.44–3.38)¶</td>
</tr>
<tr>
<td>Age ≥60 years</td>
<td>21099</td>
<td>1740</td>
<td>1.55 (1.39–1.71)§</td>
<td>351</td>
<td>1.51 (1.20–1.89)†</td>
<td>322</td>
<td>1.47 (1.14–1.88)†</td>
<td>767</td>
<td>1.57 (1.34–1.83)§</td>
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<tr>
<td>Body mass index &lt;25 kg/m²</td>
<td>28432</td>
<td>1574</td>
<td>1.62 (1.45–1.82)§</td>
<td>311</td>
<td>1.50 (1.17–1.94)†</td>
<td>298</td>
<td>1.47 (1.12–1.93)†</td>
<td>695</td>
<td>1.69 (1.43–2.00)§</td>
</tr>
<tr>
<td>Body mass index ≥25 kg/m²</td>
<td>11273</td>
<td>458</td>
<td>1.60 (1.32–1.95)§</td>
<td>99</td>
<td>1.90 (1.25–2.89)†</td>
<td>73</td>
<td>1.62 (0.99–2.66)</td>
<td>208</td>
<td>1.50 (1.12–1.99)†</td>
</tr>
</tbody>
</table>

Hazard ratios (HR), given with 95% confidence interval (CI), reflect the risk in patients with antihypertensive medication compared with untreated individuals as reference, and were adjusted for sex (except sex-subgroup analysis), age, body mass index, history of cardiovascular disease, total cholesterol, diabetes mellitus, smoking, habitual drinking, and cohort. Significance of the hazard ratios: *, $P<0.05$; †, $P<0.01$; ‡, $P<0.001$; and §, $P<0.0001$. ¶ indicates a significant difference ($P<0.05$) in the hazard ratios between corresponding strata.
<table>
<thead>
<tr>
<th>Category</th>
<th>Nº of Participants</th>
<th>Nº of Events</th>
<th>HR (95% CI)</th>
<th>Nº of Events</th>
<th>HR (95% CI)</th>
<th>Nº of Events</th>
<th>HR (95% CI)</th>
<th>Nº of Events</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Cardiovascular</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Untreated</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Optimal</td>
<td>4521</td>
<td>61</td>
<td>1.00</td>
<td>9</td>
<td>1.00</td>
<td>21</td>
<td>1.00</td>
<td>20</td>
<td>1.00</td>
</tr>
<tr>
<td>Normal</td>
<td>3897</td>
<td>94</td>
<td>1.40</td>
<td>(1.02–1.94)*</td>
<td>17</td>
<td>1.65</td>
<td>(0.73–3.71)</td>
<td>19</td>
<td>0.82</td>
</tr>
<tr>
<td>High normal</td>
<td>4162</td>
<td>109</td>
<td>1.33</td>
<td>(0.97–1.83)</td>
<td>16</td>
<td>1.27</td>
<td>(0.56–2.88)</td>
<td>21</td>
<td>0.74</td>
</tr>
<tr>
<td>Grade 1 HT</td>
<td>4017</td>
<td>224</td>
<td>1.87</td>
<td>(1.40–2.49)§</td>
<td>37</td>
<td>1.89</td>
<td>(0.90–3.95)</td>
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Blood pressure levels are: optimal, <120/<80 mm Hg; normal, 120–129/80–84 mm Hg; high normal, 130–139/85–89 mm Hg; grade 1 HT, 140–159/90–99 mm Hg; grade 2 HT, 160–179/100–109 mm Hg; and grade 3 HT, ≥180/≥110 mm Hg. The reference category was untreated optimal level. Adjusted factors were age, body mass index, history of cardiovascular disease, total cholesterol, diabetes mellitus, smoking, habitual drinking, and cohort. Abbreviations: HR, hazard ratio; CI, confidence interval; HT, hypertension. Significance of the hazard ratios: *, P<0.05; †, P<0.01; §, P<0.001; and ‡, P<0.0001.
### Table S4. Adjusted HR of Each Mortality among 12 Categories in Men

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<th>Category</th>
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<th>Nº of Events</th>
<th>HR (95% CI)</th>
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Blood pressure levels are: optimal, <120/<80 mm Hg; normal, 120–129/80–84 mm Hg; high normal, 130–139/85–89 mm Hg; grade 1 HT, 140–159/90–99 mm Hg; grade 2 HT, 160–179/100–109 mm Hg; and grade 3 HT, ≥180/≥110 mm Hg. The reference category was untreated optimal level. Adjusted factors were age, body mass index, history of cardiovascular disease, total cholesterol, diabetes mellitus, smoking, habitual drinking, and cohort. Abbreviations: HR, hazard ratio; CI, confidence interval; HT, hypertension. Significance of the hazard ratios: * P<0.05; † P<0.01; ‡ P<0.001; and § P<0.0001.
Table S5. Adjusted HR of Each Mortality among 12 Categories in Aged <60 Years

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<th>Nº of Events</th>
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</table>

Blood pressure levels are: optimal, <120/<80 mm Hg; normal, 120–129/80–84 mm Hg; high normal, 130–139/85–89 mm Hg; grade 1 HT, 140–159/90–99 mm Hg; grade 2 HT, 160–179/100–109 mm Hg; and grade 3 HT, ≥180/≥110 mm Hg. The reference category was untreated optimal level. Adjusted factors were sex, age, body mass index, history of cardiovascular disease, total cholesterol, diabetes mellitus, smoking, habitual drinking, and cohort. Abbreviations: HR, hazard ratio; CI, confidence interval; HT, hypertension. Significance of the hazard ratios: *, P<0.05; †, P<0.01; ‡, P<0.001; and §, P<0.0001.
<table>
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<th>Category</th>
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<th>Nº of Events</th>
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Blood pressure levels are: optimal, <120/<80 mm Hg; normal, 120–129/80–84 mm Hg; high normal, 130–139/85–89 mm Hg; grade 1 HT, 140–159/90–99 mm Hg; grade 2 HT, 160–179/100–109 mm Hg; and grade 3 HT, ≥180/≥110 mm Hg. The reference category was untreated optimal level. Adjusted factors were sex, age, body mass index, history of cardiovascular disease, total cholesterol, diabetes mellitus, smoking, habitual drinking, and cohort. Abbreviations: HR, hazard ratio; CI, confidence interval; HT, hypertension. Significance of the hazard ratios: *, P<0.05; †, P<0.01; ‡, P<0.001; and §, P<0.0001.
Table S7. Adjusted HR of Each Mortality among 12 Categories in Body Mass Index <25 kg/m²

<table>
<thead>
<tr>
<th>Category</th>
<th>Nº of Participants</th>
<th>Nº of Events</th>
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<th>Nº of Events</th>
<th>HR (95% CI)</th>
<th>Nº of Events</th>
<th>HR (95% CI)</th>
<th>Nº of Events</th>
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<tr>
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<td>0.97 (0.57–1.68)</td>
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<td>1.37 (0.93–2.02)</td>
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<td>55</td>
<td>2.89 (1.60–5.21)‡</td>
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<td>0.95 (0.56–1.62)</td>
<td>68</td>
<td>1.22 (0.83–1.80)</td>
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<tr>
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<td>69</td>
<td>2.37 (1.33–4.25)†</td>
<td>74</td>
<td>1.55 (0.97–2.46)</td>
<td>154</td>
<td>1.87 (1.32–2.64)§</td>
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<td>1.79 (1.38–2.32)§</td>
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<td>1.94 (1.00–3.76)</td>
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<td>2.95 (1.22–7.15)†</td>
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<td>1.87 (0.95–3.68)</td>
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<td>177</td>
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<td>2.77 (1.45–5.29)†</td>
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<td>2.00 (1.16–3.45)*</td>
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<tr>
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<td>2.96 (1.97–4.45)$</td>
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<td>3.49 (2.20–5.54)$</td>
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</table>

Blood pressure levels are: optimal, <120/<80 mm Hg; normal, 120–129/80–84 mm Hg; high normal, 130–139/85–89 mm Hg; grade 1 HT, 140–159/90–99 mm Hg; grade 2 HT, 160–179/100–109 mm Hg; grade 3 HT, ≥180/≥110 mm Hg. The reference category was untreated optimal level. Adjusted factors were sex, age, body mass index, history of cardiovascular disease, total cholesterol, diabetes mellitus, smoking, habitual drinking, and cohort. Abbreviations: HR, hazard ratio; CI, confidence interval; HT, hypertension. Significance of the hazard ratios: *, P<0.05; †, P<0.01; ‡, P<0.001; and $, P<0.0001.
### Table S8. Adjusted HR of Each Mortality among 12 Categories in Body Mass Index ≥ 25 kg/m²

<table>
<thead>
<tr>
<th>Category</th>
<th>Nº of Participants</th>
<th>Nº of Events</th>
<th>Nº of Events</th>
<th>Nº of Events</th>
<th>Nº of Events</th>
<th>Nº of Events</th>
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<td></td>
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<td>Coronary</td>
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<td>Stroke</td>
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<td>Heart Disease</td>
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Blood pressure levels are: optimal, <120/<80 mm Hg; normal, 120–129/80–84 mm Hg; high normal, 130–139/85–89 mm Hg; grade 1 HT, 140–159/90–99 mm Hg; grade 2 HT, 160–179/100–109 mm Hg; and grade 3 HT, ≥180/≥110 mm Hg. The reference category was untreated optimal level. Adjusted factors were sex, age, body mass index, history of cardiovascular disease, total cholesterol, diabetes mellitus, smoking, habitual drinking, and cohort. Abbreviations: HR, hazard ratio; CI, confidence interval; HT, hypertension. Significance of the hazard ratios: *, P<0.05; †, P<0.01; ‡, P<0.001; and §, P<0.0001.
Figure S1. The Risk among 12 Categories Defined by Blood Pressure Levels and Usage of Antihypertensive Medication at Baseline in 38760 Participants without History of Cardiovascular Diseases for (A) Total Cardiovascular Mortality, Death from (B) Coronary Heart Disease, (C) Heart Failure, and (D) Stroke.

Filled squares express hazard ratios and are sized in proportion to the number of events observed, and vertical bars indicate 95% confidence intervals in each category compared with untreated optimal blood pressure category. Blood pressure levels are defined from 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). Trend P values denote the linearity among six categories when treated and untreated participants are separated. Adjusted factors are sex, age, body mass index, total cholesterol, diabetes mellitus, smoking, habitual drinking, and cohort.