Prognostic Value of Reading-to-Reading Blood Pressure Variability Over 24 Hours in 8938 Subjects From 11 Populations

Tine W. Hansen, Lutgarde Thijs, Yan Li, José Boggia, Masahiro Kikuya, Kristina Björklund-Bodegård, Tom Richart, Takayoshi Ohkubo, Jørgen Jeppesen, Christian Torp-Pedersen, Eamon Dolan, Tatiana Kuznetsova, Katarzyna Stolarz-Skrzypczak, Valérie Tikhonoff, Sofia Malysutina, Edoardo Casiglia, Yuri Nikitin, Lars Lind, Edgardo Sandoya, Kalina Kawecka-Jaszcz, Yutaka Imai, Jiguang Wang, Hans Ibsen, Eoin O’Brien, Jan A. Staessen, for the International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcomes Investigators

Abstract—In previous studies, of which several were underpowered, the relation between cardiovascular outcome and blood pressure (BP) variability was inconsistent. We followed health outcomes in 8938 subjects (mean age: 53.0 years; 46.8% women) randomly recruited from 11 populations. At baseline, we assessed BP variability from the SD and average real variability in 24-hour ambulatory BP recordings. We computed standardized hazard ratios (HRs) while stratifying by cohort and adjusting for 24-hour BP and other risk factors. Over 11.3 years (median), 1242 deaths (487 cardiovascular) occurred, and 1049, 577, 421, and 457 participants experienced a fatal or nonfatal cardiovascular, cardiac, or coronary event or a stroke. Higher diastolic average real variability in 24-hour ambulatory BP recordings predicted (P≤0.03) total (HR: 1.14) and cardiovascular (HR: 1.21) mortality and all types of fatal combined with nonfatal end points (HR: ≥1.07) with the exception of cardiac and coronary events (HR: ≥1.02; P≥0.58). Higher systolic average real variability in 24-hour ambulatory BP recordings predicted (P<0.05) total (HR: 1.11) and cardiovascular (HR: 1.16) mortality and all fatal combined with nonfatal end points (HR: ≥1.07), with the exception of cardiac and coronary events (HR: ≥1.03; P≥0.54). SD predicted only total and cardiovascular mortality. While accounting for the 24-hour BP level, average real variability in 24-hour ambulatory BP recordings added <1% to the prediction of a cardiovascular event. Sensitivity analyses considering ethnicity, sex, age, previous cardiovascular disease, antihypertensive treatment, number of BP readings per recording, or the night/day BP ratio were confirmatory. In conclusion, in a large population cohort, which provided sufficient statistical power, BP variability assessed from 24-hour ambulatory recordings did not contribute much to risk stratification over and beyond 24-hour BP. (Hypertension. 2010;55:1049-1057.)

Key Words: blood pressure variability ■ ambulatory blood pressure ■ population science ■ risk factors ■ epidemiology

Ambulatory blood pressure monitoring not only provides information on the blood pressure level but on the diurnal changes in blood pressure as well. Blood pressure variability includes both short-term and circadian components, which can be estimated by the SD of the blood pressure values over a defined period of the day or by the night/day blood pressure ratio, respectively. We recently reported in >7000 subjects recruited from 6 populations on the prognos-
tic accuracy of long-term blood pressure variability. Both daytime and nighttime blood pressure consistently predicted the composite end point of all cardiovascular events. Adjusted for the 24-hour blood pressure, the night/day blood pressure ratio predicted mortality but not fatal combined with nonfatal events.

Although the aforementioned analyses shed light on the association between outcome and long-term blood pressure variability, the predictive value of short-term reading-to-reading blood pressure variability remains uncertain. Possible limitations of previous studies were a lack of statistical power, selection of specific groups of patients, categorization of variability by arbitrary cutoff points, and sole reliance on fatal end points. Moreover, various parameters can capture short-term blood pressure variability over 24 hours, but most studies only considered the SD of systolic or diastolic blood pressure or both. To address the prognostic value of short-term blood pressure variability, we expanded, updated, and analyzed the International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcome.

Methods

Study Population

Previous publications described the construction of the International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcome. Studies were eligible for inclusion if they involved a random selection sample, if baseline information on ambulatory blood pressure and cardiovascular risk factors was available, and if the subsequent follow-up included fatal and nonfatal outcomes. At the time of writing this report, the International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcome included prospective studies from 11 centers (11 785 subjects). All studies received ethical approval and have been reported in peer-reviewed publications. In line with previous reports, we excluded 252 participants because they were <18 years of age and 1892 participants because they had <10 daytime or <5 nighttime blood pressure readings. For the analyses of the variability, we additionally disregarded 703 subjects because they had missing readings during 3 consecutive hours. The 8938 analyzed participants were 2018 residents from Copenhagen, Denmark; 1086 subjects from Noorderkempen, Belgium; 1069 older men from Uppsala, Sweden; 226 subjects from Novosibirsk, the Russian Federation; 1430 inhabitants from Ohasama, Japan; 346 villagers from the JingNing county, China; 1093 subjects from Montevideo, Uruguay; 161 subjects from Pilsen, the Czech Republic; 900 subjects from Dublin, Ireland; 303 subjects from Padova, Italy; and 306 subjects from Kraków, Poland. All participants gave informed written consent.

Blood Pressure Measurements

Conventional blood pressure was measured by trained observers with a mercury sphygmomanometer or oscillometric (OMRON HEM-705CP, Omron Corporation) devices, using the appropriate cuff size; and with participants in the sitting or supine position. Conventional blood pressure was the average of 2 consecutive readings obtained either at the person’s home or at an examination center. Hypertension was a conventional blood pressure of ≥140 mm Hg systolic or ≥90 mm Hg diastolic or the use of antihypertensive drugs.

We programmed portable monitors to obtain ambulatory blood pressure readings at 30-minute intervals throughout the whole day or at intervals ranging from 15 to 30 minutes during daytime and from 30 to 60 minutes at night. The devices implemented an auscultatory algorithm (Accutrace II) in Uppsala or an oscillometric technique (SpaceLabs 90202 and 90207, Nippon Colin, and ABPM-630) in the other cohorts. While accounting for the daily pattern of activities of the participants, we defined daytime as the interval from 10:00 AM to 8:00 PM in Europeans and South Americans and from 8:00 AM to 6:00 PM in Asians. The corresponding nighttime intervals ranged from 12:00 PM to 6:00 AM and from 10:00 PM to 4:00 AM, respectively. In dichotomous analyses, we defined systolic and diastolic nondipping as a nighttime to daytime blood pressure ratio of ≥0.90.

As measures of short-term reading-to-reading blood pressure variability, we used the SD over 24 hours weighted for the time interval between consecutive readings (SD_{dn}), the average of the daytime and nighttime SDs weighted for the duration of the daytime and nighttime interval (SD_{da}), and the average real variability weighted for the time interval between consecutive readings (average real variability in 24-hour ambulatory BP recordings; ARV_{24}). The SD_{dn} is the mean of day and night SD values corrected for the number of hours included in each of these 2 periods (Figure 1A), according to the following formula: SD_{dn}=(day SD×hours included in the daytime)+(night SD×hours included in the nighttime)/(hours included in daytime+nighttime). This method removes the influence of the day-night blood pressure difference from the estimate of blood pressure variability. The ARV_{24} averages the absolute differences between consecutive readings and thereby accounts for the order of the blood pressure readings. B illustrates that, for distinct blood pressure signals, SD can be the same, whereas ARV_{24} is not.
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Risk Associated With Blood Pressure Variability

Figure 2 shows the cohort-, sex-, and age-standardized rates for sex and baseline characteristics, including age (used as a continuous variable), 24-hour heart rate, body mass index, smoking (0 and 1) and drinking (0 and 1), serum cholesterol, history of cardiovascular disease (0 and 1), diabetes mellitus (0 and 1), and treatment with antihypertensive drugs (0 and 1). In fully adjusted models, we additionally adjusted for the 24-hour systolic or diastolic blood pressure. We used heterogeneity in the HRs across subgroups by introducing the appropriate interaction term in the Cox model. Finally, we applied the generalized $R^2$ statistic to assess the risks explained in Cox regression by consecutively entering the 24-hour blood pressure and ARV$_{24}$ as predictor variables into the models for the composite cardiovascular end point.

Results

Baseline Characteristics

The study population consisted of 6069 Europeans (67.9%), 1093 Asians (12.2%), and 1176 South Americans (19.9%). The 8938 participants included 4785 women (46.8%) and 3664 patients with hypertension (41.0%), of whom 1749 (47.7%) were taking blood pressure–lowering drugs. Mean (±SD) age was 53.0 ± 15.8 years. At enrollment, 2558 participants (28.7%) were current smokers, and 4351 (53.1%) reported intake of alcohol.

Table 1 shows the baseline characteristics by quartiles of diastolic ARV$_{24}$. Across quartiles, all characteristics were significantly different ($P < 0.05$). Participants with a higher blood pressure variability were older, had higher blood pressure, were more likely to be male, and were more likely to have diabetes mellitus (Table 1). The ARV$_{24}$, SD$_{24}$, and SD$_{dn}$ were highly correlated with one another; the correlation coefficients ranged from 0.75 to 0.81 ($P \leq 0.001$) for systolic blood pressure and from 0.71 to 0.79 ($P \leq 0.001$) for diastolic blood pressure.

Incidence of Events

In the overall study population, median follow-up was 11.3 years (fifth to 95th percentile interval: 2.5 to 17.6 years). Across cohorts, median follow-up ranged from 2.5 years (fifth to 95th percentile interval: 2.3 to 2.6) in JingNing to 17.6 years (fifth to 95th percentile interval: 16.4 to 18.2 years) in Dublin. During 96 041 person-years of follow-up, 1242 participants died (12.9 per 1000 person-years), and 1049 experienced a fatal or nonfatal cardiovascular complication (11.3 per 1000 person-years). Mortality included 487 cardiovascular and 713 noncardiovascular deaths and 42 deaths from unknown causes (Table 2). Considering cause-specific first cardiovascular events, the incidence of fatal and nonfatal stroke amounted to 138 and 371, respectively. Cardiovascular events consisted of 172 fatal and 405 nonfatal events, including 72 fatal and 204 nonfatal cases of acute myocardial infarction, 50 deaths from ischemic heart diseases, 13 sudden deaths, 37 fatal and 151 nonfatal cases of heart failure, and 50 cases of surgical or percutaneous coronary revascularization. For comparison, cohort-specific mortality data and country-specific mortality statistics published by the World Health Organization are presented in Table S2.
Diastolic blood pressure variability was predictive of all of the combined end points (P<0.03), with the exception of coronary events (P=0.15). In fully adjusted models, diastolic blood pressure variability only predicted all cardiovascular events combined (ARV24 and SDdn) and fatal plus nonfatal stroke (ARV24). Figure 3 shows the absolute risk of a combined cardiovascular event in relation to the ARV24 at different levels of systolic and diastolic 24-hour blood pressure (Figure 3A and 3B) and in relation to 24-hour blood pressure at different levels of the systolic and diastolic ARV24 (Figure 3C and 3D). The analyses were standardized to the distributions (mean or ratio) of cohort, sex, age, 24-hour heart rate, body mass index, smoking and drinking, serum cholesterol, history of cardiovascular disease, diabetes mellitus, and treatment with antihypertensive drugs. Absolute risk increased with both the 24-hour blood pressure (P<0.001) and ARV24 (P=0.04). However, with the 24-hour blood pressure in the model, ARV24 added only 0.1% to the explained risk of a composite cardiovascular event (Table 3).

### Sensitivity Analyses

In sensitivity analyses, we considered total mortality and all cardiovascular events combined in relation to diastolic and systolic ARV24 (Tables S3 and S4). We stratified the study population according to sex; median age (60 years); antihypertensive treatment; the presence or absence of hypertension; European, Asian, or South American origin; numbers of

### Fatal and Nonfatal Cardiovascular Events

In adjusted analyses not including the 24-hour blood pressure level, systolic blood pressure variability predicted all of the fatal combined with nonfatal cardiovascular events combined and stroke (Table 2).

### Table 1. Baseline Characteristics of Participants

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Quartiles of Diastolic Average Real Variability, Limits, mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤6.9</td>
</tr>
<tr>
<td>Subjects with characteristic</td>
<td></td>
</tr>
<tr>
<td>All subjects in quartile, n</td>
<td>2235</td>
</tr>
<tr>
<td>European, n (%)</td>
<td>1428 (63.9)</td>
</tr>
<tr>
<td>Asian, n (%)</td>
<td>666 (29.8)</td>
</tr>
<tr>
<td>South American, n (%)</td>
<td>141 (6.3)</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>1225 (54.8)</td>
</tr>
<tr>
<td>smokers, n (%)</td>
<td>644 (28.9)</td>
</tr>
<tr>
<td>All subjects in quartile, n</td>
<td>2235</td>
</tr>
<tr>
<td>Age, y</td>
<td>50.1±14.8</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>24.2±3.6</td>
</tr>
<tr>
<td>Ambulatory measurements</td>
<td></td>
</tr>
<tr>
<td>24-hour systolic, mm Hg</td>
<td>118.5±12.1</td>
</tr>
<tr>
<td>24-hour diastolic, mm Hg</td>
<td>71.8±8.0</td>
</tr>
<tr>
<td>Daytime systolic, mm Hg</td>
<td>124.6±13.1</td>
</tr>
<tr>
<td>Daytime diastolic, mm Hg</td>
<td>76.7±8.6</td>
</tr>
<tr>
<td>Nighttime systolic, mm Hg</td>
<td>107.9±12.6</td>
</tr>
<tr>
<td>Nighttime diastolic, mm Hg</td>
<td>63.1±8.6</td>
</tr>
<tr>
<td>24-hour heart rate, bpm</td>
<td>71.1±8.6</td>
</tr>
<tr>
<td>Serum cholesterol, mmol/L</td>
<td>5.4±1.1</td>
</tr>
</tbody>
</table>

Trends across quartiles were significant (P<0.05) for all characteristics.

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**Mortality**

In adjusted models not including the 24-hour blood pressure level, systolic blood pressure variability predicted both total and cardiovascular mortality (P≤0.04), with the exception of SD24 in relation to total mortality (P=0.17). We obtained similar results after additional adjustment for the 24-hour systolic blood pressure, with the exception of SD24 and SDdn, which no longer predicted cardiovascular mortality (P≥0.71). Diastolic blood pressure variability predicted total and cardiovascular mortality both in adjusted and fully adjusted models (P≤0.002; Table 2). Blood pressure variability did not predict noncardiovascular mortality (0.14≤P≤0.75).

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**Table 1. Baseline Characteristics of Participants**

- **Subjects with characteristic**: All subjects in quartile, n | 2235 | 2235 | 2234 | 2234
- **European, n (%)**: 1428 (63.9) | 1586 (71.0) | 1575 (70.5) | 1480 (66.3)
- **Asian, n (%)**: 666 (29.8) | 437 (19.6) | 347 (15.5) | 326 (14.6)
- **South American, n (%)**: 141 (6.3) | 212 (9.5) | 312 (14.0) | 428 (19.2)
- **Women, n (%)**: 1225 (54.8) | 1072 (48.0) | 983 (44.0) | 905 (40.5)
- **Smokers, n (%)**: 644 (28.9) | 675 (30.3) | 661 (29.7) | 578 (26.1)
- **All subjects in quartile, n**: 2235 | 2235 | 2234 | 2234
- **Age, y**: 50.1±14.8 | 51.4±15.2 | 53.4±16.1 | 57.0±16.2
- **Body mass index, kg/m²**: 24.2±3.6 | 25.1±4.1 | 25.9±4.0 | 26.4±4.4
- **Ambulatory measurements**: 24-hour systolic, mm Hg | 118.5±12.1 | 122.1±12.7 | 125.0±13.8 | 128.8±14.9
- **Daytime systolic, mm Hg**: 71.8±8.0 | 72.7±8.1 | 74.0±8.1 | 75.9±8.6
- **Nighttime systolic, mm Hg**: 124.6±13.1 | 128.5±13.6 | 131.9±15.2 | 135.0±15.7
- **24-hour diastolic, mm Hg**: 76.7±8.6 | 77.8±8.8 | 79.3±8.9 | 81.0±9.6
- **Daytime diastolic, mm Hg**: 107.9±12.6 | 110.6±13.7 | 112.8±14.5 | 116.9±16.9
- **Nighttime diastolic, mm Hg**: 63.1±8.6 | 63.6±8.8 | 64.5±8.9 | 66.3±9.8
- **24-hour heart rate, bpm**: 71.1±8.6 | 71.7±9.0 | 72.1±9.0 | 73.1±9.5
- **Serum cholesterol, mmol/L**: 5.4±1.1 | 5.6±1.2 | 5.8±1.2 | 5.7±1.2

Trends across quartiles were significant (P<0.05) for all characteristics.
Our current meta-analysis of individual data included >8000 people randomly recruited from 11 populations and covered, on average, 11 years of follow-up, during which 1242 people died and 1049 experienced a major cardiovascular complication. The key finding was that, while accounting for the 24-hour blood pressure level and other covariates, blood pressure variability was a significant and independent predictor of mortality and of cardiovascular and stroke events. However, the proportion of the risk explained by the variability index is low.

For most outcomes, ARV24 was a better predictor than SD24 and SDdn, probably because, as illustrated in Figure 1, subjects with different blood pressure profiles might have similar SDs but different ARV24s. Thus, ARV24 might be a more specific measure of blood pressure variability than SD.

Several prospective studies in populations and hypertensive patients searched for association between cardiovascular outcomes and blood pressure variability but reported inconsistent results. This might be because of insufficient sample size, too few events, varying definitions of the outcomes of interest, or the use of different indices of blood pressure variability. To assess blood pressure variability, most studies used ambulatory blood pressure monitoring with intermittent readings at intervals ranging from 15 to 30 minutes throughout 24 hours. In the Northwick Park Study, the investigators performed continuous intra-arterial recordings but did not fully exploit the potential of this recording technique. Instead of analyzing variability in the frequency

### Discussion

Our current meta-analysis of individual data included >8000 people randomly recruited from 11 populations and covered, on average, 11 years of follow-up, during which 1242 people died and 1049 experienced a major cardiovascular complication. The key finding was that, while accounting for the 24-hour blood pressure level and other covariates, blood pressure variability was a significant and independent predictor of mortality and of cardiovascular and stroke events. However, the proportion of the risk explained by the variability index is low.

For most outcomes, ARV24 was a better predictor than SD24 and SDdn, probably because, as illustrated in Figure 1, subjects with different blood pressure profiles might have similar SDs but different ARV24s. Thus, ARV24 might be a more specific measure of blood pressure variability than SD.

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### Table 2. Multivariable-Adjusted Standardized Hazard Ratios Relating Outcome to Blood Pressure Variability

<table>
<thead>
<tr>
<th>Outcome (No. of Events)</th>
<th>Systolic Blood Pressure</th>
<th>Diastolic Blood Pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SD24</td>
<td>SDdn</td>
</tr>
<tr>
<td>Mortality (n=1242)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>1.05 (0.98 to 1.13)§</td>
<td>1.13 (1.06 to 1.21)§</td>
</tr>
<tr>
<td>Adjusted</td>
<td>1.00 (0.94 to 1.07)†</td>
<td>1.08 (1.01 to 1.15)†</td>
</tr>
<tr>
<td>Fully adjusted*</td>
<td>1.11 (1.00 to 1.24)†</td>
<td>1.13 (1.02 to 1.26)†</td>
</tr>
<tr>
<td>Cardiovascular (n=487)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted</td>
<td>1.03 (0.93 to 1.13)†</td>
<td>1.05 (0.95 to 1.17)†</td>
</tr>
<tr>
<td>Fully adjusted*</td>
<td>1.13 (1.06 to 1.22)§</td>
<td>1.15 (1.07 to 1.24)§</td>
</tr>
<tr>
<td>Fatal and Nonfatal Events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular (n=1049)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted</td>
<td>1.02 (0.96 to 1.09)</td>
<td>1.04 (0.97 to 1.11)</td>
</tr>
<tr>
<td>Fully adjusted*</td>
<td>1.13 (1.02 to 1.24)†</td>
<td>1.11 (1.01 to 1.23)†</td>
</tr>
<tr>
<td>Coronary (n=421)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted</td>
<td>1.03 (0.94 to 1.12)</td>
<td>1.01 (0.92 to 1.11)</td>
</tr>
<tr>
<td>Fully adjusted*</td>
<td>1.11 (0.99 to 1.24)</td>
<td>1.09 (0.97 to 1.22)</td>
</tr>
<tr>
<td>Stroke (n=457)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted</td>
<td>1.07 (0.96 to 1.18)</td>
<td>1.04 (0.93 to 1.16)</td>
</tr>
<tr>
<td>Fully adjusted*</td>
<td>0.98 (0.88 to 1.09)</td>
<td>1.03 (0.92 to 1.14)</td>
</tr>
</tbody>
</table>

Values are standardized hazard ratios (HRs), which express the risk per SD increase in the predictor variables. All HRs (95% confidence interval) were computed by Cox regression stratified for cohort and adjusted for sex, age, 24-hour heart rate, body mass index, smoking and drinking, serum cholesterol, history of cardiovascular disease, diabetes mellitus, and treatment with antihypertensive drugs.

*Data were additionally adjusted for the corresponding 24-hour blood pressure level.
†P<0.05 HR significance.
‡P<0.01 HR significance.
§P<0.001 HR significance.
domain, they computed hourly means of blood pressure and the within-subject SD of the hourly means as a measure of each participant’s blood pressure variability. In the Ohasama Study, investigators used the self-measured blood pressure in addition to ambulatory blood pressure monitoring. In all but 2 studies, the researchers used the SD of daytime, nighttime, or 24-hour blood pressure as an index of variability. Four studies deliberately did not report on the predictive value of the variability in the 24-hour blood pressure, because the diurnal blood pressure profile also includes long-term variability, which is captured by the night:day blood pressure ratio. To address this potential concern, we computed SD\textsubscript{dn} and ARV\textsubscript{24} as measures of variability. Only 2 other prospective studies, one in a small general Venezuelan population (312 subjects with 31 composite cardiovascular end points), and one in a hypertensive population, implemented ARV\textsubscript{24}. Bilo et al were the first to propose SD\textsubscript{dn}, but to our knowledge there is no prospective study that has used this index of variability.

Diastolic blood pressure variability tended to be a stronger predictor of outcome than systolic blood pressure variability. We can only speculate about the mechanisms underlying this finding, but arterial stiffness might be involved. In normal conditions, systolic and diastolic blood pressures change in parallel in response to physiological stimuli, such as exercise or arousal. However, in subjects with stiff arteries, when systolic blood pressure increases, often diastolic blood pressure increases less or even falls, giving rise to larger variability. On the other hand, a chance finding cannot be excluded.

From a clinical point of view, our current findings suggest that, although statistically significant, the clinical applicability of blood pressure variability for risk stratification might be limited. First, antihypertensive drug treatment is bound to influence blood pressure variability. Second, the reproducibility of blood pressure variability is poor. In 97 normotensive subjects, the relative repeatability coefficient of the SD of the 24-hour blood pressure in individual recordings, expressed as a percentage of the fifth to 95th percentile interval in all recordings, was 13% systolic and 16% diastolic, whereas for the 24-hour blood pressure these coefficients were 4% and 5%, respectively, lower values, indicating better...
Finally, the added value in terms of absolute risk was modest in our population. For example, in adjusted analyses (Figure 3), the increase in the 10-year absolute risk of a composite cardiovascular event associated with an increase from the median to the 75th percentile was 0.21% for systolic ARV24 (1.5 mm Hg) and 1.23% for the 24-hour systolic blood pressure (9.8 mm Hg). The corresponding estimates for diastolic ARV24 and for 24-hour diastolic blood pressure were 0.16% (2.3 mm Hg) and 1.05% (5.8 mm Hg), respectively.

Notwithstanding the statistical power and the consideration of fatal and nonfatal events, our study has potential limitations. First, the International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcome is currently composed of 11 population-based cohorts from 3 continents, but our results might not yet be generally applicable, in particular to Africans of black ancestry or African Americans. Second, we and most other investigators applied intermittent techniques of ambulatory blood pressure monitoring, which compared with continuous blood pressure recording, is a less precise technique to capture short-term blood pressure variability. However, intra-arterial recordings or continuous recordings of the arterial signal at the finger are difficult, if not impossible, to implement in large epidemiological studies. Third, in the current meta-analysis of individual data, blood pressure variability turned out to provide independent risk information, and this finding was consistent in stratified sensitivity analyses. However, even in large cohort studies with numerous events, the power to detect heterogeneity across strata is generally low. For example, considering a 2-sided $\alpha$-level of 0.05, we had only 46% power to detect a 0.24 difference between normotensive and hypertensive subjects in the log-transformed HR of all cardiovascular events.

**Perspectives**

In line with several6–8,10,11 but not all7 previous studies, our current report established that short-term reading-to-reading blood pressure variability is an independent risk factor, but moreover it also highlighted that the level of the 24-hour blood pressure remains the primary blood pressure-related
Table 3. Risk of a Composite Cardiovascular Event Explained by Cox Regression

<table>
<thead>
<tr>
<th>Models</th>
<th>Systolic Blood Pressure</th>
<th>Diastolic Blood Pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Likelihood Ratio</td>
<td>P</td>
</tr>
<tr>
<td>Basic model</td>
<td>10 307.0</td>
<td>...</td>
</tr>
<tr>
<td>+24-hour blood pressure</td>
<td>10 213.4</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>+24-hour blood pressure and ARV</td>
<td>10 209.4</td>
<td>0.046</td>
</tr>
</tbody>
</table>

P values are for the improvement of the fit across nested models. ... indicates not applicable.

*The basic Cox model was stratified for cohort and included as covariables sex, age, 24-hour heart rate, body mass index, smoking and drinking, serum cholesterol, history of cardiovascular disease, diabetes mellitus, and treatment with antihypertensive drugs.

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In the *Hypertension* article by Hansen et al (Hansen TW, Thijs L, Li Y, Boggia J, Kikuya M, Björklund-Bodegård K, Richart T, Ohkubo T, Jeppesen J, Pedersen CT, Dolan E, Kuznetsova T, Stolarz-Skrzypek K, Tikhonoff V, Malyutina S, Casiglia E, Nikitin Y, Lind L, San-doya E, Kawecka-Jaszcz K, Imai Y, Wang J, Ibsen H, O’Brien E, Staessen JA, on behalf of the International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcomes Investigators. Prognostic Value of Reading-to-Reading Blood Pressure Variability Over 24 Hours in 8938 Subjects from 11 Populations. *Hypertension*. 2010;55:1049–1057.) a correction has been made to Figure 3A. The line labeled 17 has been deleted from the figure. The correct Figure appears below.

The authors regret the errors.
Data Supplement

Prognostic Value of Reading-to-Reading Blood Pressure Variability
over 24 Hours in 8938 Subjects from 11 Populations.

Short title: Blood Pressure Variability as Risk Predictor

Tine W. Hansen, Lutgarde Thijs, Yan Li, José Boggia, Masahiro Kikuya,
Kristina Björklund-Bodegård, Tom Richart, Takayoshi Ohkubo, Jørgen Jeppesen,
Christian Torp-Pedersen, Eamon Dolan, Tatiana Kuznetsova, Katarzyna Stolarz-Skrzypek,
Valérie Tikhonoff, Sofia Malyutina, Edoardo Casiglia, Yuri Nikitin, Lars Lind, Edgardo Sandoya,
Kalina Kawecka-Jaszcz, Yutaka Imai, Jiguang Wang, Hans Ibsen, Eoin O’Brien,
Jan A. Staessen, on behalf of the International Database on Ambulatory blood pressure
in relation to Cardiovascular Outcomes (IDACO) Investigators

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Facsimile: +32-16-34-7106 (office)
+32-15-41-4542 (home)
email: jan.staessen@med.kuleuven.be
       jan.staessen@epid.unimaas.nl
Research Center for Prevention and Health and Department of Clinical Physiology, Hvidovre University Hospital, Faculty of Health Sciences, Copenhagen, Denmark (T.W.H.); Studies Coordinating Centre, Division of Hypertension and Cardiovascular Rehabilitation, Department of Cardiovascular Diseases, University of Leuven, Belgium (Y.L., L.T., T.R., T.K., J.A.S.); Center for Epidemiological Studies and Clinical Trials (Y.L., J.W.), and Center for Vascular Evaluation, Shanghai Key Laboratory of Vascular Biology (Y.L.), Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China; Centro de Nefrología and Departamento de Fisiopatología, Hospital de Clínicas, Universidad de la República, Montevideo, Uruguay (J.B.); Tohoku University Graduate School of Pharmaceutical Science and Medicine, Sendai, Japan (M.K., T.O., Y.I.); Section of Geriatrics, Department of Public Health and Caring Sciences, Uppsala University, Uppsala, Sweden (K.B.-B., L.L.); Copenhagen University Hospital, Copenhagen, Denmark (J.J., C.T.-P.); Cambridge University Hospitals, Addenbrooke’s Hospital, Cambridge, United Kingdom (E.D.); First Department of Cardiology and Hypertension, Jagiellonian University Medical College, Kraków, Poland (K.S.-S., K.K.-J); Department of Clinical and Experimental Medicine, University of Padova, Padova, Italy (V.T., E.C.); Institute of Internal Medicine, Novosibirsk, Russian Federation (T.K., S.M., Y.N.); Asociación Española Primera de Socorros Mutuos, Montevideo, Uruguay (E.S.); Aarhus University and Division of Cardiology, Holbæk Hospital, Holbæk, Denmark (H.I.); Conway Institute of Biomolecular and Biomedical Research, University College Dublin, Dublin, Ireland (E.O’B.); and Department of Epidemiology, Maastricht University, Maastricht, the Netherlands (T.R., J.A.S.).

Correspondence to Jan A. Staessen, Studies Coordinating Centre, Division of Hypertension and Cardiovascular Rehabilitation, Department of Cardiovascular Diseases, University of Leuven, Campus Sint Rafaël, Kapucijnenvoer 35, Block d Level 00, B-3000 Leuven, Belgium. E-mail: jan.staessen@med.kuleuven.be or ja.staessen@epid.unimaas.nl
Appendix

IDACO Centers and Investigators:

Data Base Management and Coordination:
T. W. Hansen, M. Kikuya, Y.Li, T. Richart, J. A. Staessen (Project Coordinator), and L. Thijs (Supervisor Database Management) constructed the IDACO database at the Studies Coordinating Centre in Leuven, Belgium.
## Table S1. International Classification of Diseases (ICD) Codes Applied in each Cohort

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Stroke:</th>
<th>Myocardial infarction:</th>
<th>Angina pectoris:</th>
<th>Heart failure:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Copenhagen</td>
<td>ICD8 430-434 and 436, ICD10 I60-I64</td>
<td>ICD8 410, ICD10 I21-I22</td>
<td>ICD8 411-414, ICD10 I20 and I23-I25</td>
<td>ICD8 427.0, 427.1, 428.0, 429.0, 519.1 and 782.4, ICD10 I50 and J81</td>
</tr>
<tr>
<td>Noorderkempen</td>
<td>ICD8 430-434, 436 and 438</td>
<td>ICD8 410</td>
<td>ICD8 413</td>
<td>ICD8 427.0, 427.1, 428.0, 429.0, 519.1 and 782.4</td>
</tr>
<tr>
<td>Uppsala</td>
<td>ICD9 430-434 and 436, ICD10 I60-I64</td>
<td>ICD9 410, ICD10 I21</td>
<td>ICD9 413 and 411.1, ICD10 I20</td>
<td>ICD9 429, ICD10 I50</td>
</tr>
<tr>
<td>Dublin</td>
<td>ICD9 430-434 and 436</td>
<td>ICD9 410 and 412</td>
<td>ICD9 413, 411.1 and 414</td>
<td>ICD9 428</td>
</tr>
<tr>
<td>Novosibirsk</td>
<td>ICD9 430-434 and 436</td>
<td>ICD9 410 and 412</td>
<td>ICD9 413 and 411.1</td>
<td>ICD9 428</td>
</tr>
<tr>
<td>Pilsen</td>
<td>ICD9 430-434 and 436</td>
<td>ICD9 410 and 412</td>
<td>ICD9 413 and 411.1</td>
<td>ICD9 428</td>
</tr>
<tr>
<td>Padova</td>
<td>ICD9 430-434 and 436</td>
<td>ICD9 410 and 412</td>
<td>ICD9 413 and 411.1</td>
<td>ICD9 428</td>
</tr>
<tr>
<td>Kraków</td>
<td>ICD9 430-438</td>
<td>ICD9 410</td>
<td>ICD9 413</td>
<td>ICD9 428.0-428.4</td>
</tr>
<tr>
<td>Montevideo</td>
<td>ICD10 I60-I64</td>
<td>ICD10 I21-I22</td>
<td>ICD10 I20</td>
<td>ICD10 I50 and J81</td>
</tr>
<tr>
<td>Ohasama</td>
<td>ICD10 I60-I64</td>
<td>......</td>
<td>......</td>
<td>......</td>
</tr>
<tr>
<td>JingNing</td>
<td>ICD9 430-431 and 434</td>
<td>ICD9 410</td>
<td>ICD9 413</td>
<td>ICD9 428, 427.0 and 427.1</td>
</tr>
</tbody>
</table>

…… Not assessed, because of the low incidence in the Ohasama cohort.
Table S2. Cohort-Specific Mortality Data and Country-Specific Mortality Statistics as Published by the World Health Organization (WHO).

<table>
<thead>
<tr>
<th>Cohort</th>
<th>All-cause mortality</th>
<th>Cardiovascular mortality</th>
<th>Cardiovascular mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noorderkempen (n=2541)</td>
<td>170/2541 (7%)</td>
<td>59/170 (35%)</td>
<td>26%</td>
</tr>
<tr>
<td>Copenhagen (n=2311)</td>
<td>393/2311 (17%)</td>
<td>136/393 (35%)</td>
<td>26%</td>
</tr>
<tr>
<td>Uppsala (n=1143)</td>
<td>315/1143 (28%)</td>
<td>140/315 (44%)</td>
<td>33%</td>
</tr>
<tr>
<td>Dublin (n=981)</td>
<td>36/981 (4%)</td>
<td>19/36 (53%)</td>
<td>30%</td>
</tr>
<tr>
<td>EPOGH† (n=1055)</td>
<td>23/1055 (2%)</td>
<td>6/23 (26%)</td>
<td>37%</td>
</tr>
<tr>
<td>Kraków (n=321)</td>
<td>3/321 (1%)</td>
<td>2/3 (67%)</td>
<td>34%</td>
</tr>
<tr>
<td>Padova (n=310)</td>
<td>4/310 (1%)</td>
<td>0/4 (0%)</td>
<td>28%</td>
</tr>
<tr>
<td>Novosibirsk (n=250)</td>
<td>15/250 (6%)</td>
<td>4/15 (27%)</td>
<td>52%</td>
</tr>
<tr>
<td>Pilsen (n=174)</td>
<td>1/174 (1%)</td>
<td>0/1 (0%)</td>
<td>40%</td>
</tr>
<tr>
<td>Montevideo (n=1859)</td>
<td>124/1859 (7%)</td>
<td>46/124 (37%)</td>
<td>25%</td>
</tr>
<tr>
<td>Ohasama (n=1535)</td>
<td>345/1535 (22%)</td>
<td>127/345 (37%)</td>
<td>24%</td>
</tr>
<tr>
<td>JingNing (n=360)</td>
<td>14/360 (4%)</td>
<td>6/14 (43%)</td>
<td>26%</td>
</tr>
<tr>
<td>IDACO total (n=8938)§</td>
<td>1242/8938 (14%)</td>
<td>487/1242 (39%)</td>
<td>25.6%†</td>
</tr>
</tbody>
</table>

* Country-specific mortality due to ischemic heart disease and cerebrovascular disease, as reported by the World Health Organization (http://www.who.int/countries/en/).
† All 4 centers participating in the European Project on Genes in Hypertension combined.
§ Subjects included in the present analysis.
### Table S3. Multivariable-Adjusted Hazard Ratios for Total Mortality and for Fatal and Nonfatal Cardiovascular Events for Diastolic Average Real Variability According to Baseline Characteristics

<table>
<thead>
<tr>
<th>Strata</th>
<th>At risk (n)</th>
<th>Deaths (n)</th>
<th>Total mortality</th>
<th>Events (n)</th>
<th>Cardiovascular Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>All participants</td>
<td>8938</td>
<td>1242</td>
<td>1.13 (1.07-1.19)†</td>
<td>1049</td>
<td>1.07 (1.01-1.13)*</td>
</tr>
<tr>
<td>Women</td>
<td>4186</td>
<td>398</td>
<td>1.19 (1.04-1.36)†</td>
<td>319</td>
<td>1.11 (0.96-1.27)</td>
</tr>
<tr>
<td>Men</td>
<td>4752</td>
<td>844</td>
<td>1.10 (1.02-1.18)*</td>
<td>730</td>
<td>1.10 (1.02-1.19)†</td>
</tr>
<tr>
<td>&lt;60 years</td>
<td>5349</td>
<td>190</td>
<td>1.13 (0.92-1.37)</td>
<td>189</td>
<td>1.04 (0.85-1.24)</td>
</tr>
<tr>
<td>≥60 years</td>
<td>3589</td>
<td>1052</td>
<td>1.11 (1.04-1.19)†</td>
<td>860</td>
<td>1.12 (1.05-1.20)*</td>
</tr>
<tr>
<td>Normotension</td>
<td>5981</td>
<td>605</td>
<td>1.08 (0.97-1.20)</td>
<td>441</td>
<td>1.05 (0.93-1.18)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2957</td>
<td>637</td>
<td>1.13 (1.04-1.22)†</td>
<td>608</td>
<td>1.13 (1.05-1.22)†</td>
</tr>
<tr>
<td>Nº of readings ≤47</td>
<td>3045</td>
<td>408</td>
<td>1.23 (1.08-1.39)†</td>
<td>330</td>
<td>1.27 (1.12-1.44)†</td>
</tr>
<tr>
<td>Nº of readings 48-71</td>
<td>2891</td>
<td>378</td>
<td>1.13 (1.01-1.26)*</td>
<td>338</td>
<td>1.04 (0.93-1.16)</td>
</tr>
<tr>
<td>Nº of readings &gt;71</td>
<td>3002</td>
<td>456</td>
<td>1.09 (0.96-1.22)</td>
<td>381</td>
<td>1.06 (0.93-1.20)</td>
</tr>
<tr>
<td>Non-dippers</td>
<td>2794</td>
<td>539</td>
<td>1.18 (1.08-1.28)†</td>
<td>428</td>
<td>1.09 (0.99-1.19)</td>
</tr>
<tr>
<td>Dippers</td>
<td>6144</td>
<td>703</td>
<td>1.04 (0.93-1.15)</td>
<td>621</td>
<td>1.12 (1.01-1.24)*</td>
</tr>
<tr>
<td>Untreated</td>
<td>7183</td>
<td>753</td>
<td>1.04 (0.95-1.14)</td>
<td>586</td>
<td>1.04 (0.95-1.14)</td>
</tr>
<tr>
<td>Treated</td>
<td>1749</td>
<td>488</td>
<td>1.20 (1.10-1.32)†</td>
<td>463</td>
<td>1.16 (1.06-1.27)‡</td>
</tr>
<tr>
<td>Without β-blocker</td>
<td>1162</td>
<td>344</td>
<td>1.22 (1.05–1.41)*</td>
<td>321</td>
<td>1.18 (1.02-1.36)*</td>
</tr>
<tr>
<td>With β-blocker</td>
<td>587</td>
<td>144</td>
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<td>142</td>
<td>1.08 (0.92-1.27)</td>
</tr>
<tr>
<td>Asian</td>
<td>1776</td>
<td>331</td>
<td>1.21 (1.04-1.41)*</td>
<td>239</td>
<td>1.36 (1.15-1.62)‡</td>
</tr>
<tr>
<td>European</td>
<td>6069</td>
<td>840</td>
<td>1.08 (1.00-1.17)*</td>
<td>724</td>
<td>1.04 (0.96-1.13)</td>
</tr>
<tr>
<td>South American</td>
<td>1093</td>
<td>71</td>
<td>1.29 (1.01-1.63)*</td>
<td>86</td>
<td>1.19 (0.97-1.47)</td>
</tr>
</tbody>
</table>

Hypertension was a conventional blood pressure of at least 140 mm Hg systolic or 90 mm Hg diastolic or the use of antihypertensive medications. Nº of readings refers to the number of blood pressure measurements in a single ambulatory recording. Values are standardized hazard ratios (95% confidence interval), which express the risk per SD increase in the predictor variable. All hazard ratios were stratified for cohort and adjusted, as appropriate, for sex, age, 24-hour heart rate, body mass index, smoking and drinking, serum cholesterol, history of cardiovascular disease, diabetes mellitus, treatment with antihypertensive drugs, and the 24-hour diastolic blood pressure. Significance of the hazard ratios: * P<0.05; † P<0.01; and ‡ P<0.001. Braces point to heterogeneity between subgroups (P-value for difference between strata given).
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<td>3045</td>
<td>408</td>
<td>1.17 (1.03–1.34)*</td>
<td>330</td>
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<tr>
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</tr>
<tr>
<td>Untreated</td>
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<td>753</td>
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<td>586</td>
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<td>Treated</td>
<td>1749</td>
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<td>321</td>
<td>1.14 (0.94–1.27)</td>
</tr>
<tr>
<td>With β-blocker</td>
<td>587</td>
<td>144</td>
<td>1.25 (1.03–1.50)*</td>
<td>142</td>
<td>1.04 (0.88–1.23)</td>
</tr>
<tr>
<td>Asian</td>
<td>1776</td>
<td>331</td>
<td>1.12 (0.96–1.30)</td>
<td>239</td>
<td>1.20 (1.01–1.42)*</td>
</tr>
<tr>
<td>European</td>
<td>6069</td>
<td>840</td>
<td>1.10 (1.01–1.20)*</td>
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</tr>
<tr>
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<td>71</td>
<td>1.32 (0.99–1.73)</td>
<td>86</td>
<td>1.10 (0.85–1.42)</td>
</tr>
</tbody>
</table>

Hypertension was a conventional blood pressure of at least 140 mm Hg systolic or 90 mm Hg diastolic or the use of antihypertensive medications. N° of readings refers to the number of blood pressure measurements in a single ambulatory recording. Values are standardized hazard ratios (95% confidence interval), which express the risk per SD increase in the predictor variable. All hazard ratios were stratified for cohort and adjusted, as appropriate, for sex, age, 24-hour heart rate, body mass index, smoking and drinking, serum cholesterol, history of cardiovascular disease, diabetes mellitus, treatment with antihypertensive drugs, and the 24-hour systolic blood pressure. Significance of the hazard ratios: * P<0.05; † P <0.01; and ‡ P <0.001. There were no statistically significant differences across the strata according to baseline characteristics (P>0.07).