Ambulatory Blood Pressure and Mortality
A Population-Based Study

Tine Willum Hansen, Jørgen Jeppesen, Susanne Rasmussen, Hans Ibsen, Christian Torp-Pedersen

Abstract—The relationship between ambulatory blood pressure and mortality in a general Western population is unknown. Therefore, we conducted this prospective study of a random sample of 1700 Danish men and women, aged 41 to 72 years, without major cardiovascular diseases. At baseline, ambulatory blood pressure, office blood pressure, and other risk factors were recorded. After a mean period of 9.5 years, 174 had died: 63 were cardiovascular deaths. In multivariate proportional hazards models, adjusted for other risk factors of significance, the relative risk of cardiovascular mortality (95% confidence interval) associated with 10 mm Hg increments in systolic and 5 mm Hg increments in diastolic ambulatory blood pressure were 1.51 (1.28 to 1.77) and 1.43 (1.26 to 1.61). The corresponding figures for all cause mortality were 1.18 (1.06 to 1.31) and 1.18 (1.09 to 1.28). The relative risks of cardiovascular mortality were lower for office blood pressure, and office blood pressure did not predict all cause mortality. When ambulatory and office blood pressures were entered in the same multivariate models, only the ambulatory blood pressures were significant predictors of all cause mortality and cardiovascular mortality. The relationship between ambulatory blood pressures and risk of mortality was log-linear, with no indication of a threshold. The absolute risk of mortality was also dependent on age and smoking status, and an upper “acceptable” ambulatory blood pressure based on risk of mortality could only be defined when other risk factors were taken into account. In conclusion, ambulatory blood pressure provided prognostic information on mortality above and beyond that of office blood pressure. (Hypertension. 2005;45:499-504.)

Key Words: blood pressure monitoring ■ epidemiology ■ mortality ■ risk factors

Hypertension is a leading cause of death according to a recent World Health Organization survey.1 Numerous studies have defined hypertension as an important risk factor for cardiovascular disease.2,3 In general, these studies have been based on few blood pressure (BP) measurements in a clinical environment, and most outcome studies trying to distinguish normal from abnormal BP have also relied on office BP.2,3 Monitoring of ambulatory BP with multiple measurements recorded during usual daily activities would be expected to provide a better assessment of the risk for cardiovascular disease related to BP. This idea has been shown to hold true in patients with hypertension.4–6 So far, only 1 large study has examined the prognostic value of ambulatory BP in a general population, the Ohasama study, conducted in a Japanese population, found future cardiovascular deaths to be better predicted by ambulatory BP than office BP.7,8

In 1993 to 1994, we recorded ambulatory BP in a random sample of 1700 men and women from the general Danish population. Survival status was recorded until October 2003, allowing us to study the relationship between ambulatory BP and mortality in a general Western population for the first time. Because the recommendations from recent guidelines on cardiovascular disease prevention in clinical practice9 are based on 10-year risk of fatal cardiovascular disease, the relationship between ambulatory BP and 10-year risk of fatal cardiovascular disease was a matter of special interest in this study.

Methods

Study Population
In 1982 to 1984, a random sample of 4581 Danes from 11 municipalities in the southwestern part of Copenhagen county was invited to participate in the MONItoring of trends and determinants in CArdiovascular disease (MONICA 1) health survey.10 For the MONICA protocol, participants were selected to represent an equal number of men and women aged 30, 40, 50, and 60 years. Eventually, 3785 (83%) participated. In 1993 to 1994, the participants were re-invited to be examined again.11 Since the first examination, 428 subjects had died and 23 had moved or could not be reached. Of the remaining 4130 subjects, 2656 (64%) were willing to participate. The study was performed in the Research Center for Prevention and Health in Glostrup. All subjects completed a questionnaire about current and previous diseases, intake of medication, and risk factors. The study was conducted in accord with the Second Helsinki Declaration and approved by the ethics committee for Copenhagen County. Written informed consent was obtained from all subjects.

Received December 15, 2004; first decision December 30, 2004; revision accepted February 3, 2005.
From the Research Center for Prevention and Health (T.W.H.); Medical Department M (J.J., S.R., H.I.), Glostrup University Hospital; and Department of Cardiology (C.T.P., T.W.H.), Bispebjerg University Hospital, Copenhagen, Denmark.
Correspondence to Tine Willum Hansen, Bispebjerg Hospital, Y-forskning bygning 40, Bispebjerg Bakke, 2400 Copenhagen NV, Denmark. E-mail tw@heart.dk
© 2005 American Heart Association, Inc.
Hypertension is available at http://www.hypertensionaha.org
DOI: 10.1161/01.HYP.0000160402.39597.3b

Downloaded from http://hyper.ahajournals.org/ by guest on January 21, 2016
Criteria of Exclusion
For the present study, 956 subjects were initially excluded (574 because of technical problems or unwillingness to participate in the ambulatory BP monitoring, 240 with too few ambulatory BP readings [<14 readings of systolic and diastolic BP during the day or <7 readings of systolic and diastolic BP during the night]) according to recommendations,12 (13 with nighttime work and 129 with a previous diagnosis of myocardial infarction or stroke or using digoxin or nitrates), leaving 1700 (64%) men and women.

Data Collection
Office BP was measured with a random zero mercury sphygmomanometer with an appropriate cuff size in the sitting position after 5 minutes of rest. The mean of 2 measurements was reported. The ambulatory BP measurement was initiated immediately after recording of office BP using a Takeda TM-2421 (A&D, Tokyo, Japan) device. This device has passed validation tests.13 Oscillometric recordings were used in this study. BP recordings were made every 15 minutes between 7:00 AM and 11:00 PM, and every 30 minutes between 11:00 PM and 7:00 AM. Means of ambulatory BP were computed with weights according to the time interval between successive readings. The discrimination between daytime and nighttime was based on a diary, and when this information was inadequate (n=111) we defined daytime as the interval between 6:00 AM and 12:00 AM and nighttime from 12:00 AM to 6:00 AM.

Insulin, glucose, lipids, body mass index, waist to hip ratio, and subdivision of the population according to smoking status, low or high level of physical activity, and average daily intake ≥5 or <5 beverages was determined as described elsewhere.14

End Points
Complete follow-up regarding death was obtained through information from the Civil Registration System. Death certificates were collected and 2 independent investigators blinded to information on BP and other baseline data classified them. Coding decision was based on the underlying cause of death. All deaths were classified as cardiovascular unless a noncardiovascular cause was clearly described. The predefined endpoints for this study were all-cause mortality and cardiovascular mortality.

Statistical Analysis
All analyses were performed with the Statistical Analysis System (SAS), version 8.2. Survival was analyzed with Cox proportional hazard models. To identify variables listed in Table 1 that were significantly related to all-cause and cardiovascular mortality, all the variables were entered in Cox proportional hazard models with forward and backward selection. Both approaches gave the same results. The variables selected were then entered in our final Cox proportional hazard models that always included at least 1 BP variable. The assumption of linearity and the proportional hazard assumption were tested. Interaction was tested with a likelihood ratio test. Finally, we calculated the absolute risk of all-cause and cardiovascular mortality in subgroups stratified by other variables of interest using Cox proportional hazard models. All statistical tests were 2-sided and the significance level was chosen as P<0.05.

Results
Characteristics of the Population
Table 1 shows the baseline characteristics of the entire population. Of the participants, 160 (9%) were using antihypertensive medication.

Follow-Up and Mortality
The mean study duration—from baseline evaluation until October 1, 2003—was 9.5 years (SD, 0.41 years). A total of 174 participants died; 63 (36%) were classified as cardiovascular deaths: 18 (29%) as acute myocardial infarction, 13 (21%) as stroke, 4 (6%) as ischemic heart disease, 7 (11%) as other specified cardiovascular disease, and 21 (33%) as unspecified cardiovascular disease. A total of 5 death certificates were missing. The typical examples of unspecified cardiovascular death were sudden or unexpected death without autopsy. Of the 111 noncardiovascular deaths, 72 (65%) died of cancer.
BP and Risk

To study the overall relationship between ambulatory BP and mortality, we first examined the population divided into quintiles of BP for those who died (all-cause or cardiovascular). Figure 1 shows the univariate and multivariate hazard ratios for the overall relationship between ambulatory BP and mortality. The relationships were log-linear with no indication of a threshold.

The relationship between the various BPs and all-cause mortality are shown in Table 2. Of the variables listed in Table 1, only age, smoking, alcohol consumption, and physical activity were significantly related to all-cause mortality and thus entered with the various BPs in our final multivariate models. In these models, all the ambulatory BPs were significant predictors of all-cause mortality, whereas neither systolic nor diastolic office BP were significant predictors of all-cause mortality.

Table 3 shows the relationship between the various BPs and cardiovascular mortality. Of the variables listed in Table 1, only age and smoking were significantly related to cardiovascular mortality and thus entered with the various BPs in our final multivariate models. Considered separately, all BPs were significant predictors of cardiovascular mortality.

Table 2. Relative Risks (95% Confidence Interval) Per 10-mm Hg Increase in Systolic Blood Pressure and Per 5-mm Hg Increase in Diastolic Blood Pressure for All-Cause Mortality

<table>
<thead>
<tr>
<th>Variables</th>
<th>Univariate</th>
<th>Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ambulatory blood pressure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic 24-h</td>
<td>1.39 (1.26–1.54)‡</td>
<td>1.18 (1.06–1.31)†</td>
</tr>
<tr>
<td>Systolic daytime</td>
<td>1.36 (1.23–1.50)‡</td>
<td>1.15 (1.04–1.28)†</td>
</tr>
<tr>
<td>Systolic nighttime</td>
<td>1.36 (1.24–1.49)‡</td>
<td>1.19 (1.08–1.30)†</td>
</tr>
<tr>
<td>Diastolic 24-h</td>
<td>1.18 (1.09–1.28)‡</td>
<td>1.18 (1.09–1.28)‡</td>
</tr>
<tr>
<td>Diastolic daytime</td>
<td>1.16 (1.08–1.25)‡</td>
<td>1.16 (1.08–1.26)‡</td>
</tr>
<tr>
<td>Diastolic nighttime</td>
<td>1.18 (1.10–1.27)†</td>
<td>1.16 (1.08–1.25)‡</td>
</tr>
<tr>
<td>Office blood pressure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>1.24 (1.15–1.33)‡</td>
<td>1.05 (0.96–1.14)</td>
</tr>
<tr>
<td>Diastolic</td>
<td>1.08 (1.01–1.16)*</td>
<td>1.06 (0.99–1.14)</td>
</tr>
</tbody>
</table>

In multivariate analysis adjusted for age, smoking status, alcohol consumption, and physical activity.

*P<0.05.
†P<0.01.
‡P<0.0001.

Table 3. Relative Risks (95% Confidence Interval) Per 10 mm Hg Increase in Systolic Blood Pressure and Per 5-mm Hg Increase in Diastolic Blood Pressure for Cardiovascular Mortality

<table>
<thead>
<tr>
<th>Variables</th>
<th>Univariate</th>
<th>Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ambulatory blood pressure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic 24-hours</td>
<td>1.72 (1.48–2.01)‡</td>
<td>1.51 (1.28–1.77)‡</td>
</tr>
<tr>
<td>Systolic daytime</td>
<td>1.70 (1.46–1.99)‡</td>
<td>1.50 (1.27–1.76)‡</td>
</tr>
<tr>
<td>Systolic nighttime</td>
<td>1.61 (1.40–1.84)‡</td>
<td>1.41 (1.23–1.62)‡</td>
</tr>
<tr>
<td>Diastolic 24-hours</td>
<td>1.38 (1.23–1.55)‡</td>
<td>1.43 (1.26–1.61)‡</td>
</tr>
<tr>
<td>Diastolic daytime</td>
<td>1.35 (1.20–1.52)‡</td>
<td>1.40 (1.24–1.58)‡</td>
</tr>
<tr>
<td>Diastolic nighttime</td>
<td>1.35 (1.22–1.51)‡</td>
<td>1.36 (1.22–1.51)‡</td>
</tr>
<tr>
<td>Office blood pressure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>1.40 (1.25–1.57)‡</td>
<td>1.25 (1.10–1.42)‡</td>
</tr>
<tr>
<td>Diastolic</td>
<td>1.20 (1.07–1.34)*</td>
<td>1.21 (1.08–1.35)*</td>
</tr>
</tbody>
</table>

In multivariate analysis adjusted for age, and smoking status.

*P<0.01.
†P<0.001.
‡P<0.0001.

Notably, sex, total/high-density lipoprotein cholesterol ratio, and diabetes were not significant predictors of all-cause or cardiovascular mortality in this population along with ambulatory BP. Sex was a significant predictor for all-cause mortality and cardiovascular mortality if ambulatory BP was replaced with office BP.

As seen in Tables 2 and 3, the predictive value of daytime and nighttime BP was nearly identical and when they were both entered in models they had similar importance.

When systolic ambulatory BP and systolic office BP were entered in the same multivariate model, only systolic ambulatory BP was a significant predictor of all-cause mortality (P=0.001) and cardiovascular mortality (P=0.0003), whereas systolic office BP was not a significant predictor of all-cause mortality (P=0.23) or cardiovascular mortality (P=0.96). When entering diastolic ambulatory BP and diastolic office BP in the same model, a similar result was found, and only diastolic ambulatory BP was a significant predictor of all-cause mortality (P<0.0001) and cardiovascular mortality (P<0.0001), whereas diastolic office BP was not a significant predictor of all-cause mortality (P=0.17) or cardiovascular mortality (P=0.49).

Figure 1. Relationship between systolic ambulatory blood pressure and diastolic ambulatory blood pressure and all-cause mortality and cardiovascular mortality. The ordinate has a logarithmic scale.
When systolic ambulatory BP and diastolic ambulatory BP were entered in the same multivariate model, the results showed that only diastolic ambulatory BP was a significant predictor of all-cause mortality \((P=0.009)\) and cardiovascular mortality \((P=0.007)\), whereas systolic ambulatory BP did not give significant additional information about all-cause mortality \((P=0.97)\) or about cardiovascular mortality \((P=0.28)\). When both systolic office BP and diastolic office BP were entered in the same multivariate model, neither of the BPs were significant predictors of all-cause \((P=0.82/0.20 \text{ [systolic/diastolic]})\) and cardiovascular mortality \((P=0.19/0.21 \text{ [systolic/diastolic]})\).

Figure 2 shows the calculated 10-year absolute risk of all cause and cardiovascular mortality according to diastolic ambulatory BP and systolic ambulatory BP stratified by smoking status and age, the only other variables that were significant predictors of cardiovascular mortality. Diastolic BP is shown in the interval between 60 and 90 mm Hg and systolic BP in the interval between 110 and 155 mm Hg corresponding to the 5th and 95th percentiles of the respective BPs. The absolute risk related to ambulatory BP was strongly dependent on smoking status and age.

Additional Analysis
We repeated all analyses: (1) excluding the 160 participants using antihypertensive medication; (2) including the participants with too few observations of ambulatory BP or with nighttime work; (3) defining daytime between 10:00 AM and 8:00 PM and nighttime between 12:00 AM and 6:00 AM in subjects with inadequate information in the diary about sleeping time; (4) including all risk factors listed in Table 1 in one multivariate model; and (5) including participants with previous cardiovascular complications. The results of these analyses were basically identical to the results of our main analyses (data not shown). Finally, we examined the relationship between BP and cancer mortality, and no BPs were significant predictors of cancer mortality (data not shown).

Discussion
The present study showed that: (1) the relationship between ambulatory BP and risk of all-cause and cardiovascular mortality in a general Western population was log-linear without a threshold; (2) the absolute risk of all-cause and cardiovascular mortality related to ambulatory BP were strongly dependent on smoking status and age making it difficult to define an upper level of “acceptable” BP if these risk factors were not taken into account; and (3) ambulatory BP provided prognostic information about all-cause and cardiovascular mortality above and beyond that of office BP in a general Western population.

A major issue in hypertensive research is whether the relationships between both systolic and diastolic BP and risk of mortality are log-linearly increasing, or whether there is a threshold in this relation. Only 1 other large study has examined the relationship between ambulatory BP and mortality in a general population: the Ohasama study. In this study, there was a U-shaped relationship between ambulatory BP and cardiovascular mortality. The reason for this discrepancy between the Ohasama study and our study may rely on inclusion criteria. In the Ohasama study, subjects with cardiovascular diseases were included, whereas in our study subjects with major cardiovascular disease were excluded. Thus, in a relatively healthy population no threshold could be identified between risk of all-cause and cardiovascular mortality and ambulatory BP.

In the Ohasama study,7 systolic ambulatory BP was a significant predictor of cardiovascular mortality in a multivariate model including systolic office BP, whereas systolic office BP was not. This finding was confirmed in our study.

In this study, using the Cox proportional hazard models with systolic BP and diastolic BP entered in the same model, diastolic ambulatory BP provided more information on risk of all-cause and cardiovascular mortality than systolic ambulatory BP, whereas systolic and diastolic office BP failed to provide any independent information on risk of all-cause and cardiovascular mortality when entered in the same model. In the present study, diastolic ambulatory BP was positively related to risk of all-cause and cardiovascular mortality in all age groups, including the elderly, as seen in Figure 2. This was also the case for diastolic office BP (data not shown). These findings are in contrast with findings from the Framingham Heart Study, in which office diastolic BP was found to be negatively related to cardiovascular disease risk in the elderly. We have no obvious explanation for this discrepancy, but it should be noted that also in the Chicago Heart Association Study office diastolic BP was positively related to risk of all-cause and cardiovascular mortality.
Subjects with an absolute risk of 10%, whereas office BP overall only could identify sub-10-year absolute risk of cardiovascular mortality as high as ambulatory BP overall could identify subjects with a cardiovascular mortality for a 60-year-old person based on Figure shows the 10-year calculated absolute risk of compared with office BP is demonstrated in Figure 3. This predictor of risk of all-cause and cardiovascular mortality was low over the whole range of diastolic ambulatory BP and systolic ambulatory BP, regardless of smoking status. In contrast, for a 71-year-old smoker, the absolute risk of 10-year cardiovascular mortality increased from 17% to 30% when the diastolic ambulatory BP increased from 70 mm Hg to 80 mm Hg.

**Perspectives**

Our study points out that ambulatory BP provided prognostic information about mortality above and beyond that of office BP in a general population. In addition, this study shows that there is a continuous graded relationship between ambulatory BP and risk of mortality without a well-defined lower limit, but also that it is not meaningful to talk about a general upper acceptable ambulatory BP limit without considering the presence of other risk factors.

**Clinical Significance**

Our findings may have important clinical implications and point to an opportunity to refine risk stratification strategies. This study showed that ambulatory BP was a better predictor of risk of all-cause and cardiovascular mortality compared with office BP. A clinical relevant example of how much better ambulatory BP was to predict risk compared with office BP is demonstrated in Figure 3. This Figure shows the 10-year calculated absolute risk of cardiovascular mortality for a 60-year-old person based on ambulatory BP and office BP adjusted for smoking status. It is seen that the slope describing the relationship between BP and risk was much steeper for ambulatory BP, and that ambulatory BP overall could identify subjects with a 10-year absolute risk of cardiovascular mortality as high as 10%, whereas office BP overall only could identify subjects with an absolute risk of \( \approx 6\% \). It is also seen that subjects with low ambulatory BPs had an overall low risk of cardiovascular mortality.

What is an “acceptable” BP? The present study is the first to our knowledge to evaluate the prognostic value of ambulatory BP in a general Western population, and the conclusion seems to be that in general, it is not meaningful to evaluate only the level of BP, as illustrated in Figure 2. The curves in this Figure were calculated using Cox proportional hazard model and reflect the relative importance of significant risk factors. A given BP needs to be assessed in context with the overall risk profile. For example, in a 41-year-old person, the absolute 10-year risk of all-cause and cardiovascular mortality was low over the whole range of diastolic ambulatory BP and systolic ambulatory BP, regardless of smoking status.

**Study Limitations**

A total of 574 subjects had to be excluded because of technical problems or unwillingness to participate in the ambulatory BP recordings. This highlights an inherent limitation with ambulatory BP recordings. Nevertheless, this group of subjects did not differ significantly from the included group with respect to mortality; therefore, we believe that our results can be generalized.

**Perspectives**

Our study points out that ambulatory BP provided prognostic information about mortality above and beyond that of office BP in a general population. In addition, this study shows that there is a continuous graded relationship between ambulatory BP and risk of mortality without a well-defined lower limit, but also that it is not meaningful to talk about a general upper acceptable ambulatory BP limit without considering the presence of other risk factors.

**Clinical Significance**

Our findings may have important clinical implications and point to an opportunity to refine risk stratification strategies. This study showed that ambulatory BP was a better predictor of risk of all-cause and cardiovascular mortality compared with office BP. A clinical relevant example of how much better ambulatory BP was to predict risk compared with office BP is demonstrated in Figure 3. This Figure shows the 10-year calculated absolute risk of cardiovascular mortality for a 60-year-old person based on ambulatory BP and office BP adjusted for smoking status. It is seen that the slope describing the relationship between BP and risk was much steeper for ambulatory BP, and that ambulatory BP overall could identify subjects with a 10-year absolute risk of cardiovascular mortality as high as 10%, whereas office BP overall only could identify subjects with an absolute risk of \( \approx 6\% \). It is also seen that subjects with low ambulatory BPs had an overall low risk of cardiovascular mortality.

What is an “acceptable” BP? The present study is the first to our knowledge to evaluate the prognostic value of ambulatory BP in a general Western population, and the conclusion seems to be that in general, it is not meaningful to evaluate only the level of BP, as illustrated in Figure 2. The curves in this Figure were calculated using Cox proportional hazard model and reflect the relative importance of significant risk factors. A given BP needs to be assessed in context with the overall risk profile. For example, in a 41-year-old person, the absolute 10-year risk of all-cause and cardiovascular mortality was low over the whole range of diastolic ambulatory BP and systolic ambulatory BP, regardless of smoking status. In contrast, for a 71-year-old smoker, the absolute risk of 10-year cardiovascular mortality increased from 17% to 30% when the diastolic ambulatory BP increased from 70 mm Hg to 80 mm Hg.


