Ambulatory Blood Pressure and Prognosis

Daytime and Nighttime Blood Pressure as Predictors of Death and Cause-Specific Cardiovascular Events in Hypertension

Robert H. Fagard, Hilde Celis, Lutgarde Thijs, Jan A. Staessen, Denis L. Clement, Marc L. De Buyzere, Dirk A. De Bacquer

Abstract—Our aim was to assess the prognostic significance of nighttime and daytime ambulatory blood pressure and their ratio for mortality and cause-specific cardiovascular events in hypertensive patients without major cardiovascular disease at baseline. We performed a meta-analysis on individual data of 3468 patients from 4 prospective studies performed in Europe. Age of the subjects averaged 61 ± 13 years, 45% were men, 13.7% smoked, 8.4% had diabetes, and 61% were under antihypertensive treatment at the time of ambulatory blood pressure monitoring. Office, daytime, and nighttime blood pressure averaged 159 ± 20/91 ± 12, 143 ± 17/87 ± 12, and 130 ± 18/75 ± 12 mm Hg. Total follow-up amounted to 23 164 patient-years. We used multivariable Cox regression analysis to assess the hazard ratios associated with 1 standard deviation higher blood pressure. Daytime and nighttime systolic blood pressure predicted all-cause and cardiovascular mortality, coronary heart disease, and stroke, independently from office blood pressure and confounding variables. When these blood pressures were entered simultaneously into the models, nighttime blood pressure predicted all outcomes, whereas daytime blood pressure did not add prognostic precision to nighttime pressure. Appropriate interaction terms indicated that the results were similar in men and women, in younger and older patients, and in treated and untreated patients. The systolic night–day blood pressure ratio predicted all outcomes, which only persisted for all-cause mortality after adjustment for 24-hour blood pressure. In conclusion, nighttime blood pressure is in general a better predictor of outcome than daytime pressure in hypertensive patients, and the night–day blood pressure ratio predicts mortality, even after adjustment for 24-hour blood pressure. (Hypertension. 2008;51:55-61.)

Key Words: ambulatory blood pressure ■ coronary heart disease ■ daytime blood pressure ■ mortality ■ nighttime blood pressure ■ stroke

Ambulatory blood pressure (ABP) monitoring (ABPM) has become increasingly important for the management of patients with hypertension.1-3 Most studies have shown that mean 24-hour ABP is a better predictor of morbidity and mortality than office BP (OBP).4 However, there is still debate on the relative importance of daytime and nighttime ABP and on the prognostic significance of the night–day BP ratio. Studies that reported on daytime and nighttime ABP separately found that both BPs carried significant prognostic information in patients with hypertension.4-9 Whereas the prognostic value of daytime and nighttime ABP was about similar in 2 studies,5,7 others directly compared the prognostic value of the 2 BPs and found that nighttime ABP was a significantly better predictor than daytime ABP.6,8,9 Also results on the night–day BP ratio are not consistent in hypertension. Some studies observed a significantly better prognosis in patients with a greater decline in nighttime ABPs,10 but this was not confirmed by others.7,11

Divergent results among studies may be attributable to differences in methodology, study population, sample size, and end points. To better appreciate the prognostic significance of daytime and nighttime ABP and the night–day BP ratio in hypertension, and to assess whether the results would differ for mortality and various types of cardiovascular (CV) events, we pooled the individual data of hypertensive patients from 4 prospective studies, performed in Europe and coordinated in Belgium.6,7,12,13 Common features of the 4 studies were that both fatal and nonfatal events were registered during prospective follow-up and that end point committees used the same criteria for validation of the events. We report on the prognostic value of daytime and nighttime ABP and their ratio for all-cause, noncardiovas-
cular (NCV), and CV mortality, and for fatal and nonfatal coronary heart disease (CHD), stroke, and an aggregate of major CV events.

Methods

We used individual data of hypertensive patients from 4 studies performed in Europe and coordinated at the universities of Ghent or Leuven. Three of the studies were performed in close collaboration of the 2 groups. The studies were approved by the appropriate institutional review committees and all subjects gave informed consent. Inclusion and exclusion criteria and results on the prognostic significance of various aspects of ABP in these studies have been reported previously. Patients with severe coexisting disease, debilitating illness, dementia, and impairment of renal function were usually excluded from these studies, and for the current meta-analysis we also excluded patients with a history of major CV disease at baseline, namely myocardial infarction, stroke, and congestive heart failure.

The Ambulatory blood pressure Monitoring and Treatment of Hypertension (APTH) trial included 419 patients who were 18 years old and whose diastolic OBP measured off active treatment and on placebo was 95 through 114 mm Hg. During the 6-month trial, patients were randomized to antihypertensive therapy on the basis of ABP or OBP, whereas after follow-up was continued for 5 more years. The Office versus Ambulatory blood pressure (OvA) study included patients who had been treated with antihypertensive drugs for 3 months by the time of the inclusion visit. Prerequisite for inclusion was documented hypertension, defined as diastolic BP >90 mm Hg under treatment or >95 mm Hg without treatment, at 2 separate visits before the enrollment visit. The total number of recruited patients amounted to 1963. After exclusion of 41 patients from the APTH trial who were also included in the OvA study and 115 patients with a history of CV disease at inclusion, 1807 patients remained for the current analyses. Follow-up amounted to 6.5 years after the end of the study inclusion period. The Systolic Hypertension in Europe (Syst-Eur) trial randomized 4695 patients who were ≥60 years old and had a systolic BP of 160 to 219 mm Hg with a diastolic BP <95 mm Hg during the placebo run-in period. ABPM was performed in 1108 patients, that is during the run-in period in 695 patients, and, shortly after randomisation, during placebo in 187 patients and during active treatment in 226 patients. After the end of the double-blind phase of the trial, all patients received active study drugs and follow-up was extended by 5 years. After exclusion of 27 patients whose OBP was normal when ABPM was performed after randomization into the placebo group, and 61 patients with a history of CV disease, 1020 patients remained for the current meta-analysis. The fourth study was performed in >60-year-old patients, registered in one primary care (I Care) practice in Flanders, Belgium, irrespective of blood pressure. The study included 462 patients of whom 12 were bedridden, demented, or admitted in a home for sick elderly people. ABPM was performed in 383 of the remaining patients, of whom 251 were hypertensive based on clinic systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg or taking antihypertensive therapy. After exclusion of 29 patients with prior CV disease, 222 hypertensive patients remained for the analysis. Follow-up amounted to 10 years after the end of the baseline examination period.

Blood Pressure

Office BP was the average of 2 or 3 BP measurements in the sitting position by the auscultatory technique using the 5th Korotkoff sound for diastolic BP, during the baseline visit, closest to ABPM. ABPM was monitored during 24 hours, by use of validated devices. BP was measured every 15 minutes or at intervals of not more than 30 minutes during daytime and every 30 minutes or at intervals of not more than 60 minutes during the night. In the current analysis daytime ABP was the average BP from 10 AM to 8 PM and nighttime ABP was the average BP from midnight to 6 AM, which corresponds well with the actual awake and asleep ABP. The night–day BP ratio was calculated from these values.

Outcomes

Outcome variables were: (1) all-cause mortality; (2) CV mortality, including all fatal CV events; (3) NCV mortality; (4) Coronary heart disease (CHD) including sudden death and fatal and nonfatal myocardial infarction. Sudden death included any death of unknown origin occurring immediately or within 24 hours of the onset of acute symptoms, as well as unattended death for which no likely cause could be established. Myocardial infarction was defined as 2 of the following 3 disorders: typical chest pain, electrocardiographic changes and increased cardiac enzymes; cardiac enzymes included creatine kinase (CK), CK-MB or aspartate aminotransferase (AST), which had to be higher than 2 times the upper limit of normality; (5) Fatal and nonfatal stroke, defined as a neurological deficit with symptoms continuing for >24 hours or leading to death with no apparent cause other than vascular; transient ischemic attack was not an end point; (6) Major CV disease (CVD) including CV mortality and nonfatal myocardial infarction and stroke. All events that occurred during follow-up were corroborated by the study end point committees, using the same diagnostic criteria. One of the authors took part in the 4 committees.

Statistical Analysis

Database management and statistical analyses were performed using SAS software, version 8.2 (SAS Institute Inc). Individual patient data from the 4 studies were pooled for the meta-analysis. Data are reported as mean±SD or as percentages. We used Cox proportional hazards regression analysis to assess the prognostic significance of the various BPs, after testing the proportional hazards assumption. All analyses were stratified by study. For patients who experienced multiple events, analysis was restricted to the first event under study. The hazard ratio (HR) represents the risk associated with a 1 SD increment in BP. In multivariable Cox regression analysis, we adjusted for age, gender, smoking, serum total cholesterol, diabetes, and antihypertensive treatment at the time of ABPM. To assess whether the effect was independent from other BP measurements, we performed additional adjustments for other BPs. We tested whether the effect of BP on outcome differed (1) among the studies, and (2) by treatment status, by inclusion of the appropriate interaction terms in the Cox models. Sensitivity analyses were performed for the models which included both daytime and nighttime ABP; analyses were done (1) with consecutive exclusion of each study, and (2) separately in men and women, older and younger patients, and treated and untreated patients, with tests of heterogeneity by use of appropriate interaction terms. A 2-tailed probability value ≤0.05 was considered significant.

Results

Patient Characteristics at Baseline

Age of the 3468 included participants averaged 60.8±13.1 years (range: 18 to 96; median: 62.8); 44.8% were men, 13.7% were current smokers, 8.4% had diabetes and 61.4% were under antihypertensive treatment at the time of ABPM. BMI averaged 27.7±4.5 kg/m². OBP averaged 159.0±19.9/91.0±11.7 mm Hg, daytime ABP 143.5±17.0/87.1±11.7 mm Hg, nighttime ABP 129.8±17.6/75.4±12.3 mm Hg, and the night–day BP ratio 0.907±0.085/0.866±0.095. Please see Table S1 at http://hyper.ahajournals.org for separate data of the 4 studies.

Follow-Up

Median follow-up time was 6.57 years (range: 0.08 to 13.1), and total follow-up time amounted to 23 164 patient-years. The total number of events during follow-up, including first and subsequent events, consisted of 324 deaths (145 from a CV cause: CHD: 68; CHF: 29; stroke: 31; other: 17) and 72
nonfatal myocardial infarctions and 93 nonfatal strokes. Please see Table S2 for separate data of the 4 studies.

Prognostic Significance of Daytime and Nighttime Blood Pressure

Table 1 gives the HRs of the relationships of daytime, nighttime, and 24-hour ABP with the study end points, with adjustment for OBP and the other covariates. Systolic daytime and nighttime ABP significantly and independently predicted all outcomes, except NCV mortality which was only predicted by nighttime ABP. Diastolic daytime and nighttime ABP predicted CVD, CHD, and stroke, but mortality was only significantly predicted by nighttime ABP. Among the other covariates age, male gender, smoking, total cholesterol, and diabetes at baseline predicted outcome to various extents in the different models. However, antihypertensive treatment at the time of ABPM was never a significant predictor of events. The interaction terms of the various ABPs with studies and with treatment were never significant.

Table 2 summarizes the HRs when both daytime and nighttime ABP were included in the models, together with the other covariates. Systolic nighttime ABP significantly predicted death, CVD, CHD, and stroke, and diastolic nighttime ABP predicted all-cause and CV mortality and CVD. Daytime ABP did not add prognostic precision to nighttime ABP (P > 0.05). Figures 1 and 2 summarize the adjusted HRs according to gender, age below or above median age and treatment status, with inclusion of systolic daytime and nighttime ABP in the same models. Whereas the HR was not significant for daytime ABP (except for stroke in the older patients), nighttime ABP was a significant predictor of all-cause mortality and CVD (largest number of events) in all subgroups, and for most subgroups for the other end points. None of the interaction terms of BP with, respectively, gender, age, and treatment status, reached statistical significance. In addition, the interaction terms were not significant for diastolic ABP, except for nighttime ABP and CVD (P = 0.04; data not shown).

The analyses on all-cause mortality and major CVD were also repeated with consecutive exclusion of each study. Whereas the HR was never significant for daytime ABP, systolic and diastolic nighttime ABP remained significant predictors of outcome in all analyses, except for diastolic ABP and all-cause mortality when the Syst-Eur trial was excluded (P = 0.09).

Prognostic Significance of the Night–Day Blood Pressure Ratio

Table 3 gives the adjusted HRs of the relationships of the night–day blood pressure ratio with outcome. Before adjustment for gender, smoking, total cholesterol, diabetes, antihypertensive treatment, and office blood pressure.

Data are hazard ratios (95% confidence intervals) for each 1 standard deviation higher blood pressure, stratified for study and adjusted for age, gender, smoking, total cholesterol, diabetes, antihypertensive treatment, and office blood pressure.

Significance of hazard ratios: * P < 0.05; † P < 0.01; ‡ P < 0.001.

BP indicates blood pressure; CHD, coronary heart disease; CV, cardiovascular; CVD, cardiovascular disease; NCV, noncardiovascular.
24-hour ABP, the systolic night–day BP predicted all end points, but the relationship persisted only for all-cause mortality after additional adjustment for 24-hour ABP. The diastolic night–day ratio predicted all-cause and CV death before and after adjustment for 24-hour ABP.

Discussion
The main findings of the present meta-analysis of individual patient data on the prognostic significance of ABP in hypertensive patients without major cardiovascular disease at baseline are as follows for systolic BP. (1) Daytime and nighttime ABP significantly predict all-cause and CV mortality, CHD, stroke and an aggregate of major CVD, independently from OBP and confounding factors. Only nighttime ABP predicts NCV mortality. (2) Nighttime ABP adds to the prognostic significance of daytime ABP for all end points; daytime ABP does not add prognostic precision to nighttime ABP. (3) The prognostic significance of the night–day BP ratio for death, CVD, CHD, and stroke only persists for all-cause mortality after adjustment for 24-hour ABP. Similar but less consistent results were observed for diastolic ABP.

Apart from studies included in the current meta-analysis, few other studies investigated the prognostic significance of daytime and nighttime ABP in hypertensive patients, with adjustment for OBP and other covariates. Daytime ABP significantly and independently predicted all-cause mortality, CV, and stroke mortality in patients referred for ABPM, all strokes in older hypertensive patients, and an aggregate of CV events in refractory hypertension. Nighttime ABP independently predicted all-cause, CV, and stroke mortality but not total stroke. When daytime and nighttime ABP were included in the same model for the prediction of death, nighttime ABP was
superior to daytime ABP for all-cause, CV, cardiac, and stroke mortality. Our results confirm these observations for all-cause and CV mortality for both systolic and diastolic ABP. In addition, we observed that systolic nighttime ABP was the better predictor for NCV death and fatal and nonfatal CVD, CHD, and stroke. These results were consistent in men and women, in young and old, and in treated and untreated patients for most of the outcomes. There is currently no clear explanation why nighttime ABP would be a better predictor of outcome than daytime ABP, but several factors could be involved. BP is more variable during the day than during the night because of physical and mental activity so that it is possible that intermittent BP measurements may not completely capture the true average daytime ABP. It is of note that Khattar et al., who used continuous intraarterial ABP recordings, reported that the prognostic value of daytime and nighttime ABP for CV events was about similar, but the 2 BPs were not included in the same model. Nighttime BP is likely to be more stable so that intermittent BP measurements may be more representative of the true nighttime average BP. Moreover, BP during sleep is more closely related to basal BP which has been shown to predict life expectancy better than casual BP. Finally, nighttime ABP may be influenced by sleep apnoea in some patients, which is associated with a worse prognosis.

The relative importance of daytime and nighttime ABP has also been assessed in population-based studies but the results have not been quite consistent. Nighttime ABP appeared to be superior to daytime ABP for mortality, but others found that nighttime and daytime ABP were of similar importance. In addition, Hansen et al observed that daytime and nighttime ABP both predicted an aggregate of CV events for diastolic BP but that only daytime ABP, rather than nighttime ABP, was significant for systolic BP.
We assessed the effect of the nocturnal decline of BP on prognosis by using the night–day BP ratio as a continuous variable. We observed that the systolic night–day BP ratio was significantly associated with mortality, which persisted for all-cause mortality after adjustment for 24-hour ABP. The significant associations of CVD, CHD, and stroke with the systolic night–day BP ratio did not persist after adjustment for 24-hour BP. The diastolic night–day BP ratio predicted all-cause and cardiovascular mortality, both before and after adjustment for 24-hour ABP. Few other studies reported on the prognostic significance of the night–day BP ratio in hypertension. Khattar et al.\textsuperscript{5,11} found that this ratio did not carry any prognostic information for CV events, and this was also observed in a population-based study of elderly men.\textsuperscript{28}

The current meta-analysis has strengths and limitations. To achieve our aim to assess the prognostic significance of daytime and nighttime ABP for mortality and cause-specific CV events in a large sample of patients with hypertension and no history of major CV disease at baseline, we pooled the individual patient data of 4 European studies which were performed or coordinated in Belgium.\textsuperscript{6,7,12–17} Common features of these studies are: the prospective design; follow-up for fatal and nonfatal events; and evaluation of events by blinded end point committees, which used the same definitions of events. The different selection criteria of the various studies are a potential limitation of the current meta-analysis. On the other hand, the database represents a wide and comprehensive spectrum of hypertensive patients with regard to age, gender, type of hypertension, antihypertensive treatment, and type of care (primary care and specialist care). In addition, use of appropriate interaction terms and sensitivity analyses indicates that the predictive power of daytime and nighttime ABP did not differ among the 4 studies and that the results were roughly similar in men and women, in younger and older patients, and in treated and untreated patients. However, because the studies included only Caucasians, our findings cannot be extrapolated to hypertensive patients of other ethnic origin.

In conclusion, we observed that both daytime and nighttime ABP carry prognostic information for mortality and fatal and nonfatal CHD and stroke in hypertensive patients, which is independent from OBP and a number of confounders; that nighttime ABP is in general a better predictor of outcome than daytime ABP, and that the night–day BP ratio predicts mortality, even after adjustment for 24-hour ABP.

**Perspectives**

ABPM is an important adjunct in the management of hypertension, because it is, in general, a better predictor of outcome than OBP. Daytime ABP carries independent prognostic information and this could be an argument to limit ABPM to the daytime period. It appears however that nighttime ABP is a better predictor than daytime ABP, so that ABPM over the full 24 hours with separate analyses of daytime and nighttime ABP is warranted. Nocturnal BP may be a target to reduce CV morbidity and mortality in hypertensive patients.

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**Disclosures**

None.

**References**


**Table 3. Adjusted Hazard Ratios for Death and Cardiovascular Events With the Night-Day Blood Pressure Ratio, Before and After Additional Adjustment for 24-Hour Blood Pressure**

<table>
<thead>
<tr>
<th>Blood pressure</th>
<th>Death</th>
<th>NCV Death</th>
<th>CV Death</th>
<th>CVD</th>
<th>CHD</th>
<th>Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Unadjusted for 24-hour BP</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP</td>
<td>1.18$\ddagger$ (1.07–1.30)</td>
<td>1.18$^*$ (1.03–1.35)</td>
<td>1.18$^*$ (1.03–1.37)</td>
<td>1.20$\ddagger$ (1.07–1.34)</td>
<td>1.21* (1.03–1.43)</td>
<td>1.21* (1.02–1.43)</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>1.15$\dagger$ (1.04–1.28)</td>
<td>1.11 (0.96–1.28)</td>
<td>1.21 (1.04–1.40)</td>
<td>1.12 (0.99–1.25)</td>
<td>1.09 (0.91–1.30)</td>
<td>1.11 (0.93–1.32)</td>
</tr>
<tr>
<td><strong>Adjusted for 24-hour BP</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP</td>
<td>1.13$^*$ (1.02–1.24)</td>
<td>1.14 (0.99–1.30)</td>
<td>1.11 (0.96–1.28)</td>
<td>1.11 (0.99–1.25)</td>
<td>1.14 (0.96–1.35)</td>
<td>1.10 (0.93–1.30)</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>1.14$^*$ (1.02–1.26)</td>
<td>1.09 (0.94–1.26)</td>
<td>1.20$^*$ (1.03–1.39)</td>
<td>1.09 (0.97–1.23)</td>
<td>1.07 (0.89–1.28)</td>
<td>1.07 (0.89–1.28)</td>
</tr>
</tbody>
</table>

Data are hazard ratios (95% confidence intervals) for each 1 standard deviation higher night-day blood pressure ratio, stratified for study and adjusted for age, gender, smoking, total cholesterol, diabetes, and antihypertensive treatment, and, in addition, for 24-hour ABP. Significance of hazard ratios: *$P$<0.05; †$P$<0.01; ‡$P$<0.001.

BP indicates blood pressure; CHD, coronary heart disease; CV, cardiovascular; CVD, cardiovascular disease; NCV, noncardiovascular.


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