Nighttime ambulatory pulse pressure predicts cardiovascular and all-cause mortality among middle-aged participants in the 21-year follow-up

Päivi A. Lempiäinen MD1 | Antti Ylitalo MDPhD2 | Heikki Huikuri MDPhD1 | Y. Antero Kesäniemi MDPhD1 | Olavi H. Ukkola MDPhD1

1 Research Unit of Internal Medicine, Medical Research Center Oulu, Oulu University Hospital, University of Oulu, Oulu, Finland
2 Heart Center, Turku University Hospital and University of Turku, Turku, Finland

Correspondence Olavi H. Ukkola, Faculty of Medicine and Medical Research Center Oulu, University of Oulu / Oulu University Hospital, Kajaanintie 50, FIN-90220 Oulu, Finland. Email: olavi.ukkola@oulu.fi

Abstract
Office pulse pressure (PP) is a predictor for cardiovascular (CV) events and mortality. Our aim was to evaluate ambulatory PP as a long-term risk factor in a random cohort of middle-aged participants. The Opera study took place in years 1991–1993, with a 24-h ambulatory blood pressure measurement (ABPM) performed to 900 participants. The end-points were non-fatal and fatal CV events, and deaths of all-causes. Follow-up period, until the first event or until the end of the year 2014, was 21.1 years (mean). Of 900 participants, 22.6% died (29.6% of men/15.6% of women, p<.001). A CV event was experienced by 208 participants (23.1%), 68.3% of them were male (p<.001). High nighttime ambulatory PP predicted independently CV mortality (hazard ratio [HR] 2.60; 95% confidence interval [CI 95%] 1.08–6.31, p=.034) and all-cause mortality in the whole population (HR 1.72; CI 95% 1.06–2.78, p=.028). In males, both 24-h PP and nighttime PP associated with CV mortality and all-cause mortality (24-h PP HR for CV mortality 2.98; CI 95% 1.11–8.04, p=.031 and all-cause mortality HR 2.40; CI 95% 1.32–4.37, p=.004). Accordingly, nighttime PP; HR for CV mortality 3.13; CI 95% 1.14–8.56, p=.026, and for all-cause mortality HR 2.26; CI 95% 1.29–3.96, p=.004. Cox regression analyses were adjusted by sex, CV risk factors, and appropriate ambulatory mean systolic BP. In our study, high ambulatory nighttime PP was detected as a long-term risk factor for CV and all-cause mortality in middle-aged individuals.

KEYWORDS
ambulatory pulse pressure, all-cause mortality, cardiovascular mortality, follow-up, nighttime pulse pressure
Pulse pressure (PP) is defined as the difference between systolic blood pressure (SBP) and diastolic blood pressure (DBP) and it is considered as a surrogate marker for arterial stiffening (viite). PP increases with ageing, as SBP increases, and DBP decreases.1,2 High office PP is a known independent risk factor for cardiovascular (CV) events and CV mortality2–7 especially in individuals over 60 years of age,2,7 but also in the middle-aged participants.4–6,8 Increased office PP is also associated with all-cause mortality in a middle-aged male population,4 and in young adults.9 A rising trend in PP over a period of time was discovered to increase the risk for all-cause mortality in a large population study with a wide age group.10 In the very elderly however, PP may not be a CV risk factor.11

There is evidence that ambulatory PP could be an even better method in predicting the risk of CV events and mortality than office PP,8,12 or ambulatory systolic blood pressure (BP).8,13 Increased ambulatory PP has been found as a CV risk factor in different specific patient groups: it predicts CV events in patients with peripheral artery disease,14 CV mortality in hemodialysis patients,15 and also a variety of adverse CV outcomes and all-cause mortality in participants with hypertension.16 In a population study, daytime and 24-h PP had a predictive value in the general population, whereas the nighttime PP was a risk factor for men.17 In a large study consisting of 11 different populations, all individuals within the highest 24-h PP distribution had an elevated risk for CV events, and those over 60 years had the higher all-cause mortality than those below.18 In some studies, however, there has been controversy over significance of ambulatory PP as a predictor for CV and all-cause mortality.19

In the present study, our aim was to investigate ambulatory PP (24-h, daytime, and nighttime) as a predictor for long-term cardiovascular events and all-cause mortality in a middle-aged population as a whole, and also separately in both sexes, because sex differences have been reported earlier.17,20 To our knowledge, population based studies targeting ambulatory PP as a predictive factor for CV events or mortality with such a long follow-up period as ours do not exist.

**METHODS**

**Study population**

This study is part of the OPERA (Oulu Project Elucidating Risk of Atherosclerosis) project, a prospective, population-based cohort study designed to evaluate the risk factors of atherosclerotic cardiovascular diseases. The details have been published earlier.21 In short, a cohort of 600 hypertensive (300 women and 300 men) inhabitants of city of Oulu (106,500 inhabitants) in Northern Finland was randomly selected from the register for the reimbursement of antihypertensive medication maintained by the Social Insurance Institute. An age- and sex-matched control cohort consisting of 600 participants was randomly sampled from the social insurance register of the area. Study participants were 40–62 years of age at the time of recruitment. Out of the 1200 invited, 1045 individuals (87.1%, 525 women, 520 men) participated in the baseline study which was carried out between years 1990 and 1993, and ABPM was recorded in 903 participants. In our analyses we included those, whose ABPM was available, a total of 900 participants. Three participants were excluded because of missing nighttime values of ABPM (Figure 1). Further details of the baseline study can be found elsewhere.22 Our study was approved by the Ethics Committee of the Faculty of Medicine, University of Oulu, and was conducted by the principles of the Declaration of Helsinki. All study participants gave an informed consent.

**Baseline study**

The participants of the study underwent a clinical examination, including height and weight measurements. A questionnaire covering the past medical history, medication use, alcohol consumption, and smoking habits was completed by two trained nurses. The laboratory tests, including a 2-h oral glucose tolerance test, were obtained after an overnight fast, and analyzed in the Central Laboratory of the Oulu University Hospital.21 The estimated glomerular filtration rate (eGFR) was calculated by using CKD-EPI equation.23 Body mass index was calculated as weight (kg) divided by height squared (m). Type 2 diabetes was
determined by the WHO criteria: diabetes was diagnosed if fasting plasma glucose was ≥7.0 mmol/L and/or 2-h plasma glucose was ≥11.1 mmol/L in a 2-h oral glucose tolerance test, or if a person was on medication for diabetes. Hypertension was defined as blood pressure over 140/90 mmHg or current use of antihypertensive medication. A comprehensive report of the baseline study has been published earlier.

2.3 Blood pressure measurements

The office BP was measured by a specially trained registered nurse, using an appropriately fitted cuff size and automatic oscillometric device (Dinamap Procare 100, Criticon, Tampa, FL, USA) when the participants were seated for the minimum of 5 min. BP was then measured at 1 min intervals three times. The mean of the second and the third measurement was used for the analyses.

ABPM was recorded by a noninvasive fully automatic SpaceLabs90207 oscillometric unit (SpaceLabs Inc., Redmond, WA, USA). The measurements were taken every 15 min from 04:00 AM to 12:00 PM and every 20 min between 12:00 PM and 04:00 AM. The British Hypertension Society and the US Association for the Advancement of Medical Instrumentation have previously confirmed the accuracy and reproducibility of the BP readings acquired with this device. The proper positioning of the cuff was ensured in each individual by means of the similarity (difference <5 mmHg) between four SpaceLabs BP measurements and four auscultatory readings using a Y-connector and the patients were instructed to relax their arm during the measurement. Values were automatically excluded from the analysis if systolic BP (SBP) was less than 70 or more than 250 mmHg, diastolic BP (DBP) less than 40 or more than 150 mmHg, and heart rate less than 40 or more than 150 beats per minute. Less than 3% of the BP readings were rejected as artifacts based on these criteria. Three recordings were excluded because of missing nighttime variables. Pulse pressure was calculated as a difference between systolic BP and diastolic BP.

2.4 Follow-up of cardiovascular events and mortality

Follow-up time was defined as the time from the date of the baseline examination to the first end-point event (CV event or death), or, if event free, until December 31, 2014. The mean follow-up time was 21.1 years (median 22.5 years, range 18.0–23.2 years).

The primary end-point was CV event—a major coronary heart disease (CHD) event or stroke, non-fatal or fatal, whichever occurred first. The secondary end-point was death of all-causes. Information on events leading to hospitalization was obtained from the Care register for health care of the Finnish institute for health and welfare. Data on fatal outcome and causes of death were obtained from death certificates from the Archive of death certificates of Statistics Finland. Each study participant was identified and followed with a personal social security number. The diagnoses were classified according to the International Classification of Diseases, Ninth Revision (ICD-9) before 1994 and the Tenth Revision (ICD-10) thereafter. CHD was based on the following diagnosis: I20, I21, I22 (ICD-10) / 410, 4110 (ICD-9) as the main diagnosis, and I21, I22 (ICD-10) / 410 (ICD-9) as a first or second side diagnosis or third diagnosis (ICD-9 only), or coronary artery bypass grafting, or coronary angioplasty. CHD as a cause of death included I20–I25, I46, R96, R98 (ICD-10) / 410–414, 798 (not 7980A) (ICD-9) as the underlying or immediate cause of death and I21 or I22 (ICD-10) / 410 (ICD-9) as the first to the third contributing cause of death. Stroke as an end-point included I61, I63 (not I63.6), I64 (ICD-10), and 431, 4330A, 4331A, 4339A, 4340A, 4341A, 4349A, 436 (ICD-9) as the main diagnosis or as a side diagnosis, or as a cause of immediate or contributing cause of death.

2.5 Statistical methods

Data analyses were performed with IBM SPSS Statistics for Windows (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0 Armonk, NY: IBM Corp.). Data are expressed as mean ± standard deviation for continuous variables, or median with 25th and 75th quartiles for skewed variables. Continuous variables were tested for differences between the groups with Student’s t test or with Mann–Whitney’s test, when appropriate. Pearson’s Chi-square test was used to test differences between categorical variables. Log transformation was made for fasting insulin and triglycerides. Hazard curves were estimated by using the Kaplan–Meier method and tested by log-rank test. We used Cox regression analysis to estimate the pulse pressure tertiles as a predictor for cardiovascular events and all-cause mortality in multivariate models adjusted by variables with significance in univariate analyses. 24-h PP range was 32–44 mmHg in the lowest tertile (T1), 45–51 mmHg in the middle (T2), and 52–89 mmHg in the highest tertile (T3). Daytime PP was 24–45 mmHg in T1, 46–52 mmHg in T2, and 53–93 mmHg in T3. Nighttime PP range was 24–42 mmHg in T1, 43–48 mmHg in T2, and 49–88 mmHg in T3. All of the fully-adjusted regression analyses in this study also included the corresponding ambulatory mean SBP as a cofactor: either 24-h SBP for models assessing 24-h PP, or daytime SBP for models with daytime PP, or nighttime SBP for models evaluating nighttime PP. p values <.05 were considered as statistically significant.

3 RESULTS

Originally 1045 participants attended the OPERA study. All those (n=900, 50.4% women, and 49.6% men) who underwent a qualified 24-h ABPM recording in the baseline study were included in the analyses. Only three recordings were disqualified on the basis of missing nighttime readings.

The characteristics of the study population at baseline are presented in Table 1. Those who died, were older, their BMI was higher, smoking was more frequent, and alcohol consumption was higher among them compared with those who survived. Coronary artery disease (CAD), diabetes, and previous stroke or TIA were more prevalent.
among those who died. Pulse pressure (PP) was higher, including office, 24-h PP, daytime, and nighttime PP in those who did not survive compared with those who did. Office blood pressure was higher in those who deceased compared with the survivors. Also baseline ambulatory 24-h mean systolic and diastolic BP, 24-h daytime systolic and diastolic BP and nighttime systolic and diastolic BP blood pressure were all higher among those who died compared with those staying alive.

In laboratory measures, fasting glucose, insulin, and triglyceride levels were higher, and HDL cholesterol was lower among those who died, but there were no differences in total cholesterol or LDL levels.

During the follow-up time of 21 years, 208 (23.1%) CV events (a major coronary incident, stroke, or cardiovascular death) occurred, and the majority (n=83, 39.9 %) of them in the highest 24-h PP tertile. Men experienced 68.3 % of the CV events. Total number of deaths was 203 (22.6% of the study population). All-cause mortality was the highest in the highest 24-h PP tertile (30.5 % vs the lowest tertile 16.2%). All-cause mortality among men (29.6%) was almost two-fold compared with women (15.6%). There were 68 (33.5%, 51 men, 17 women) CV deaths, and 75% of those occurred in men.

### TABLE 1  Baseline characteristics of the study population by CV events and all-cause mortality during follow-up

|                              | CV event n=208 | No CV event n=692 | p value | Deceased n=203 | Alive n=697 | p value | All n=900 |
|------------------------------|----------------|-------------------|---------|----------------|-------------|---------|-----------|
| Females/Males (%)            | 66 (31.7)/142 (68.3) | 388 (56.1)/304 (43.9) | <.001 | 71 (35.0)/132 (65.0) | 383 (54.9)/314 (45.1) | <.001 | 454 (49.6)/446 (50.4) |
| Age (y)                      | 53.0 ± 5.7 | 50.9 ± 5.9 | <.001 | 53.0 ± 5.8 | 50.9 ± 5.9 | <.001 | 51.4 ± 5.9 |
| Body mass index (kg/m²)      | 28.4 ± 4.3 | 27.4 ± 4.6 | .006 | 28.5 ± 4.7 | 27.3 ± 4.5 | .001 | 27.6 ± 4.6 |
| Smoking (%)                  | 67 (32.2) | 188 (27.2) | .157 | 81 (39.9) | 174 (25.0) | <.001 | 255 (28.3) |
| Alcohol consumption (g/w)    | 33 (3 - 122) | 24 (2 - 72) | <.001 | 36 (3-120) | 24 (2-72) | <.001 | 24 (2-84) |
| CAD (%)                      | 45 (21.6) | 57 (8.2) | <.001 | 31 (15.3) | 43 (6.2) | <.001 | 74 (8.2) |
| Hypertension (%)             | 118 (56.7) | 340 (49.1) | .055 | 112 (55.2) | 346 (49.6) | .165 | 458 (50.9) |
| Diabetes (%)                 | 35 (16.8) | 56 (8.1) | <.001 | 37 (18.2) | 54 (7.7) | <.001 | 91 (10.1) |
| Stroke/TIA (%)               | 9 (4.3) | 8 (1.2) | .007 | 8 (3.9) | 9 (1.3) | .015 | 17 (1.9) |
| eGFR (mL/min/1.73 m²)        | 84.8 ± 14.3 | 83.9 ± 15.0 | .441 | 84.8 ± 15.7 | 83.9 ± 14.5 | .433 | 84.1 ± 14.8 |
| Antihypertensive medication (%) | 126 (60.6) | 334 (48.3) | .002 | 112 (55.2) | 348 (49.9) | .188 | 460 (51.1) |

**Office blood pressure (mmHg)**

|                              | Mean SBP | Mean DBP | Daytime SBP | Daytime DBP | Nighttime SBP | Nighttime DBP | Mean PP | Daytime PP | Nighttime PP | Fasting glucose (mmol/L) | Fasting insulin (mU/L) | Total cholesterol (mmol/L) | HDL-c (mmol/L) | LDL-c (mmol/L) | Triglycerides (mmol/L) |
|------------------------------|----------|----------|-------------|-------------|---------------|---------------|---------|------------|--------------|-------------------------|----------------------|--------------------------|--------------|--------------|---------------------|
| CV event n=208               | 154 ± 22 | 83 ± 9   | 139 ± 16    | 87 ± 9      | 121 ± 15      | 72 ± 9        | 51 ± 10 | 52 ± 11    | 49 ± 10      | 5.9 ± 1.2               | 12.3 (8.3 - 20.2) | 5.8 ± 1.2                 | 1.2 ± 0.4      | 3.7 ± 1.0    | 1.5 ± 1.1 - 2.3       |
| No CV event n=692            | 147 ± 22 | 80 ± 8   | 134 ± 13    | 85 ± 9      | 116 ± 14      | 70 ± 9        | 48 ± 9  | 49 ± 9     | 46 ± 9       | 5.6 ± 1.0               | 10.1 (7.1 - 15.5) | 5.7 ± 1.0                 | 1.4 ± 0.4      | 3.5 ± 0.9    | 1.2 ± 0.9 - 1.7       |
| p value                      | <.001    | .01      | <.001       | .002        | <.001         | .001          | <.001   | <.001      | <.001        | <.001                   | <.001               | <.001                    | <.001         | <.001        | <.001               |
| p value (Deceased n=203)     | 155 ± 24 | 82 ± 9   | 139 ± 16    | 87 ± 9      | 120 ± 16      | 72 ± 10       | 51 ± 10 | 52 ± 11    | 49 ± 10      | 5.0 ± 1.6               | 12.6 (8.2 - 20.0) | 5.8 ± 1.2                 | 1.3 ± 0.4      | 3.6 ± 1.0    | 1.5 ± 1.1 - 2.1       |
| p value (Alive n=697)        | 146 ± 21 | 88 ± 12  | 134 ± 13    | 85 ± 9      | 116 ± 14      | 70 ± 9        | 48 ± 9  | 49 ± 9     | 46 ± 9       | 4.6 ± 1.3               | 10.2 (7.1 - 15.5) | 5.7 ± 1.0                 | 1.4 ± 0.4      | 3.5 ± 0.9    | 1.2 ± 1.0 - 1.7       |
| p value (All n=900)          | <.001    | .001     | <.001       | .008        | <.001         | .023          | <.001   | <.001      | <.001        | <.001                   | <.001               | <.001                    | <.001         | <.001        | <.001               |

**Note:** Data as mean ± SD, mean (25th–75th percentiles) or number (percentages). Statistical testing by ANOVA or chi-square test between the groups. Abbreviations: ABPM, ambulatory blood pressure measurement; CAD, coronary artery disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate (CKD-EPI); HDL-c, HDL cholesterol; LDL-c, LDL cholesterol; PP pulse pressure; SBP, systolic blood pressure.


TABLE 2  Baseline characteristics according to 24-h pulse pressure tertiles

|                              | 1<sup>st</sup> tertile=309 | 2<sup>nd</sup> tertile=322 | 3<sup>rd</sup> Tertile=269 | p value |
|------------------------------|-----------------------------|-----------------------------|-----------------------------|---------|
| Pulse pressure range         | 32 – 44                     | 45 – 51                     | 52 – 89                     |         |
| Deceased (%)                 | 50 (16.2)                   | 71 (22.0)                   | 82 (31.5)                   | <.001   |
| CV event (%)                 | 57 (18.4)                   | 68 (21.1)                   | 83 (30.9)                   | .001    |
| Females (%)                  | 149 (48.2%)                 | 150 (46.6 %)                | 155 (57.6%)                 | .018    |
| Age (y)                      | 50.0 ± 5.6                  | 51.0 ± 5.9                  | 53.4 ± 5.9                  | <.001   |
| Body mass index (kg/m²)      | 26.6 ± 4.0                  | 27.6 ± 4.4                  | 28.8 ± 5.1                  | <.001   |
| Smoking (%)                  | 79 (26 %)                   | 95 (30 %)                   | 81 (30%)                    | .406    |
| Alcohol consumption (g/w)    | 30 (3 – 84)                 | 24 (3 – 84)                 | 17 (1 – 72)                 | .976    |
| CAD (%)                      | 21 (6.8)                    | 23 (7.1)                    | 30 (11.2)                   | .279    |
| Hypertension (%)             | 136 (44.0)                  | 158 (49.1)                  | 164 (61.0)                  | <.001   |
| Diabetes (%)                 | 20 (6.5)                    | 25 (7.8)                    | 46 (17.1)                   | <.001   |
| Stroke (%)                   | 7 (2.3)                     | 3 (0.9)                     | 7 (2.6)                     | .225    |
| eGFR (mL/min/1.73m²)         | 84 ± 15                     | 85 ± 15                     | 82 ± 15                     | .038    |
| Antihypertensive medication (%) | 138 (44.7)          | 160 (49.7)                   | 162 (60.2)                  | .001    |
| Office BP (mmHg)             |                             |                             |                             |         |
| Office SBP                   | 139 ± 19                    | 146 ± 19                    | 161 ± 22                    | <.001   |
| Office DBP                   | 89 ± 12                     | 87 ± 12                     | 91 ± 12                     | .001    |
| Office PP                    | 50 ± 11                     | 59 ± 12                     | 70 ± 15                     | <.001   |
| 24-h ABPM                    |                             |                             |                             |         |
| Mean SBP                     | 120 ± 8                     | 128 ± 8                     | 143 ± 13                    | <.001   |
| Mean DBP                     | 79 ± 7                      | 80 ± 8                      | 84 ± 9                      | <.001   |
| Daytime SBP                  | 125 ± 9                     | 133 ± 9                     | 148 ± 13                    | <.001   |
| Daytime DBP                  | 84 ± 7                      | 84 ± 8                      | 88 ± 10                     | <.001   |
| Nighttime SBP                | 108 ± 10                    | 115 ± 10                    | 129 ± 14                    | <.001   |
| Nighttime DBP                | 69 ± 9                      | 69 ± 9                      | 73 ± 10                     | <.001   |
| Mean PP                      | 40 ± 3                      | 48 ± 2                      | 60 ± 7                      | <.001   |
| Daytime PP                   | 41 ± 3                      | 49 ± 2                      | 61 ± 9                      | <.001   |
| Nighttime PP                 | 39 ± 4                      | 45 ± 4                      | 56 ± 10                     | <.001   |
| Fasting glucose (mmol/L)     | 4.5 ± 0.9                   | 4.6 ± 1.2                   | 5.1 ± 1.9                   | <.001   |
| Fasting insulin (mU/L)       | 9.5 (6.7 – 14.9)            | 10.8 (7.6 – 15.6)           | 11.9 (7.9 – 19.6)           | <.001   |
| Total cholesterol (mmol/L)   | 5.7 ± 1.0                   | 5.7 ± 1.1                   | 5.8 ± 1.0                   | .313    |
| HDL-c (mmol/L)               | 1.3 ± 0.4                   | 1.4 ± 0.4                   | 1.3 ± 0.4                   | .366    |
| LDL-c (mmol/L)               | 3.5 ± 0.9                   | 3.5 ± 1.0                   | 3.6 ± 0.9                   | .207    |
| Triglycerides (mmol/L)       | 1.2 (0.9 – 1.7)             | 1.3 (1.0 – 1.8)             | 1.4 (1.1 – 1.9)             | .001    |

Note: Data as mean± SD, mean (25th–75th percentiles) or number (percentages). Statistical testing by ANOVA or chi-square test between the groups. Abbreviations: ABPM, ambulatory blood pressure measurement; BP, blood pressure; CAD, coronary artery disease; CV, cardiovascular; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate (CKD-EPI); HDL-c, HDL cholesterol; LDL-c, LDL cholesterol; PP, pulse pressure; SBP, systolic blood pressure.

Regarding CV events, those who experienced a CV event in comparison with those who were event-free, the differences in above mentioned variables were quite similar (Table 1). However, total cholesterol and LDL levels were higher in CV event group, in which also antihypertensive medication was more frequent. Overall prevalence of use of antihypertensive agents in the whole study population was 51.1% (beta blocker 27.2%, ACE inhibitor 19.0%, thiazide 14.3%, calcium channel blocker 12.1%, loop diuretic 1.9%, and other agents 2.7%).

The baseline population was divided into tertiles according to 24-h mean PP (Table 2). During the follow-up time of 21 years, 208 (23.1%) CV events (a major coronary incident, stroke, or cardiovascular death) occurred, and the majority (n=83, 39.9 %) of them in the highest 24-h PP tertile (Table 2). Men experienced 68.3% of the CV events.
### Risk for cardiovascular mortality during 21 years of follow-up by 24-h pulse pressure tertiles

|                | Males                              | Females                           | All                                |
|----------------|------------------------------------|-----------------------------------|------------------------------------|
|                | HR (95% CI)                        | p value                           | HR (95% CI)                        | p value                           |
| 24-h mean PP   |                                    |                                   |                                    |                                   |
| T1             | .080                               | .976                              | .488                               |
| T2             | 1.51 (0.63–3.56)                   | .355                              | 1.22 (0.21–7.26)                   | .826                              | 1.48 (0.71–3.08) | .295 |
| T3             | 2.98 (1.11–8.04)                   | .031                              | 1.18 (0.16–8.95)                   | .872                              | 1.68 (0.68–4.10) | .259 |
| Daytime PP     |                                    |                                   |                                    |                                   |
| T1             | .284                               | .779                              | .560                               |
| T2             | 1.45 (0.62–3.37)                   | .391                              | 0.99 (0.21–4.79)                   | .994                              | 1.27 (0.62–2.60) | .522 |
| T3             | 2.17 (0.83–5.69)                   | .115                              | 0.56 (0.08–3.92)                   | .561                              | 1.60 (0.68–3.77) | .282 |
| Nighttime PP   |                                    |                                   |                                    |                                   |
| T1             | .020                               | .987                              | .073                               |
| T2             | 3.37 (1.42–7.99)                   | .006                              | 1.04 (0.22–5.02)                   | .957                              | 2.18 (1.04–4.60) | .040 |
| T3             | 3.13 (1.14–8.56)                   | .026                              | 1.15 (0.19–6.78)                   | .880                              | 2.60 (1.08–6.31) | .034 |

Cox regression models were adjusted for appropriate mean systolic pressure, age, body mass index, hypertension, diabetes, previous stroke, coronary artery disease, smoking, alcohol consumption, use of antihypertensive medication, triglycerides levels, and sex for analyses for all. Abbreviations: CI, confidence interval; HR, hazard ratio; PP, pulse pressure; T, tertile. 

P value <.05 considered as statistically significant.

Total number of deaths was 203 (22.6% of the study population). All-cause mortality was the highest in the highest 24-h PP tertile (30.5% vs the lowest tertile 16.2%). All-cause mortality among men (29.6%) was almost two-fold compared with women (15.6%). There were 68 (33.5%, 51 men, 17 women) CV deaths, and 75% of those occurred in men.

There were differences in incidence of CV mortality, CV events, and total mortality between the PP tertiles, and the linear associations were significant. All systolic and diastolic BP measurements, office, daytime and nighttime ambulatory, and pulse pressure, differed between the PP tertile groups. Prevalence of hypertension and diabetes increased by tertiles, but there were no statistically significant differences in prevalence of CAD nor previous stroke. In laboratory measurements, there were significant differences in fasting glucose, insulin, and triglycerides levels, and in estimated GFR between the tertiles. Prevalence of antihypertensive medication increased towards the highest PP tertile. There were statistically significant differences in thiazide and calcium blocker use, but not in other agents.

### 3.2 Pulse pressure and cardiovascular events

We assessed the association of 24-h, daytime, and nighttime ambulatory PP with CV events by multivariate Cox regression. The model was controlled by the same set of variables as in the Cox regression models presented before. When systolic mean ambulatory BP (24-h, daytime, or nighttime, where applicable according the model) was added to Cox regression models, the statistical significance of high PP as a risk factor for CV events was lost in the whole study population (HR 1.12; 95% CI 0.69–1.84 for 24-h PP, HR 1.45; 95% CI 0.89–2.35 for the daytime PP, and HR 1.33; 95% CI 0.82–2.14 for the nighttime PP). When the analyses were performed by sex, PP did not appear as a significant factor either. The result of the analyses is available as a supplemental material.

### 3.3 Pulse pressure and all-cause mortality

Figures 2–4 show the cumulative Kaplan–Meier curves for hazards for all-cause mortality in 24-h, daytime, and nighttime PP tertiles. Ambulatory PP was assessed as a predictor for all-cause mortality in multivariate Cox regression analyses separately for 24-h, daytime, nighttime (Table 4), and for both sexes. Adjustments for sex, age, BMI, diabetes, hypertension, antihypertensive medication use, CAD, previous stroke, alcohol consumption, smoking, and triglycerides levels were made. The
### Table 4: Risk for all-cause mortality during 21 years of follow-up by 24-h pulse pressure tertiles

|                | Males HR (95% CI) | p value | Females HR (95% CI) | p value | All HR (95% CI) | p value |
|----------------|-------------------|---------|---------------------|---------|----------------|---------|
| **24-h mean PP** |                   |         |                     |         |                |         |
| T1             | 1.25 (0.76 - 2.04) | .009    | 0.82 (0.45 - 1.60)  | .566    | 1.23 (0.83 - 1.81) | .456    |
| T2             | 2.40 (1.32 - 4.37) | .004    | 0.62 (0.26 - 1.49)  | .287    | 1.36 (0.82 - 2.26) | .230    |

| **Daytime PP** |       |         |                     |         |                |         |
| T1             | 1.68 (1.04 - 2.71) | .015    | 1.20 (0.62 - 2.29)  | .592    | 1.49 (1.02 - 2.19) | .060    |
| T2             | 2.26 (1.29 - 3.96) | .004    | 0.87 (0.37 - 2.03)  | .742    | 1.72 (1.06 - 2.78) | .028    |

| **Nighttime PP** |       |         |                     |         |                |         |
| T1             | 1.25 (0.76 - 2.04) | .009    | 0.82 (0.45 - 1.60)  | .566    | 1.23 (0.83 - 1.81) | .302    |
| T2             | 2.40 (1.32 - 4.37) | .004    | 0.62 (0.26 - 1.49)  | .287    | 1.36 (0.82 - 2.26) | .230    |

Cox regression models were adjusted for appropriate mean systolic pressure, age, body mass index, hypertension, diabetes, previous stroke, coronary artery disease, smoking, alcohol consumption, use of antihypertensive medication, triglycerides levels, and sex for analyses for all.

Abbreviations: CI, confidence interval; HR, hazard ratio; PP, pulse pressure; T, tertile.
P value < 0.05 considered as statistically significant.

**Figure 2** Kaplan–Meier all-cause mortality survival curves by tertiles (T1, T2, T3) of 24-h pulse pressure. T1, where PP ≤44 mmHg; T2, PP 45–51 mmHg; T3, PP > 51 mmHg. Log Rank Test p<.001.

**Figure 3** Kaplan–Meier all-cause mortality survival curves by tertiles (T1, T2, T3) of daytime pulse pressure. T1, where PP ≤45 mmHg; T2, PP 46–52 mmHg; T3, PP > 52 mmHg. Rank Test p=.001.

In our 21-year follow-up study higher nighttime PP in all participants, and higher 24-h PP in men were associated with the risk of CV and all-cause mortality in a random cohort of middle-aged population. The latter associations were evident after extensive adjustments including mean systolic ambulatory BP measurements.

The increasing of PP is a phenomenon usually seen with aging as SBP rises with age, while DBP begins to gradually decline after a plateau.
phase between 50 and 60 years.\textsuperscript{1} There is a sex difference,\textsuperscript{27} since women’s earlier lower BP catches up with men’s BP by the end of the sixth decade.\textsuperscript{1} The widening of PP is mostly due to reduced arterial stiffness. Our study participants were middle-aged when investigated in the early 1990’s—over 90% of them were under the age of 60, but still a significant independent association between nighttime PP and CV as well as all-cause mortality was detected.

Recently, Tadic and coworkers\textsuperscript{17} found out that 24-h PP and daytime PP predicted CV events and mortality in a general population of wide age range, but nighttime PP was significant only in men. Earlier, 24-h, daytime and nighttime PP were recognized as better prognostic factors for CV events in a group of 60 years of age or older, compared with a younger group.\textsuperscript{28} In a recent comparative outcome trial, with previously untreated elderly hypertensive patients, nighttime ambulatory PP was the most consistent pretreatment BP predictor of all-cause and CV mortality during 11-year follow-up,\textsuperscript{29} which is in accordance with our 21-year follow-up study. Staessen and coworkers\textsuperscript{12} reported that high nighttime PP increased the risk of all-cause and CV mortality in hypertensive patients over 60 years of age attending the placebo group. Antihypertensive medication was controlled by adjustments in the initial data with ABPM and a follow-up of 21-years is almost unique in the scientific world.

In conclusion, nighttime ambulatory pulse pressure showed a significant and independent association with CV and all-cause mortality in a random cohort of middle-aged normotensive and hypertensive participants in the long-term follow-up. Also 24-h PP was detected as a prognostic factor in male participants. Wide PP, especially nighttime PP, may identify individuals with an increased risk for mortality, and therefore ambulatory BPM should be in use, together with office BP measurements.

**ACKNOWLEDGMENTS**

We would like to thank the study nurses for the assistance with data collection, and all participants of this study.

**REFERENCES**

1. Franklin SS, Gustin W, 4th, Wong ND, et al. Hemodynamic patterns of age-related changes in blood pressure. The Framingham heart study. *Circulation*. 1997;96(1):308-315. https://doi.org/10.1161/01.cir.96.1.308

2. Franklin SS, Larson MG, Khan SA, et al. Does the relation of blood pressure to coronary heart disease risk change with aging? The Framingham heart study. *Circulation*. 2001;103(9):1245-1249. https://doi.org/10.1161/01.cir.103.9.1245

3. Madhavan S, Ooi WL, Cohen H, Alderman MH. Relation of pulse pressure and blood pressure reduction to the incidence of myocardial infarction. *Hypertension*. 1994;23(3):395-401. https://doi.org/10.1161/01.hyp.23.3.395

4. Benetos A, Safar M, Rudnichi A, et al. Pulse pressure: a predictor of long-term cardiovascular mortality in a French male population.
5. Franklin SS, Khan SA, Wong ND, Larson MG, Levy D. Is pulse pressure useful in predicting risk for coronary heart disease? The Framingham heart study. Circulation. 1999;100(4):354-360. https://doi.org/10.1161/01.hyp.30.6.1410

6. Thomas F, Blacher J, Benetos A, Safar ME, Pannier B. Cardiovascular risk as defined in the 2003 european blood pressure classification: the assessment of an additional predictive value of pulse pressure on mortality. J Hypertens. 2008;26(6):1072-1077. https://doi.org/10.1097/1HJH.b013e3282fc22b

7. Selvaraj S, Steg PG, Elbezy Y, et al. Pulse pressure and risk for cardiovascular events in patients with atherothrombosis: From the REACH registry. J Am Coll Cardiol. 2016;67(4):392-403. S0735-1075(15)07492-6 [pii]. https://doi.org/10.1016/j.jacc.2015.10.084

8. Verdecchia P, Schillaci G, Bortolini C, Ciucci A, Pede S, Porcellati C. Ambulatory pulse pressure: A potent predictor of total cardiovascular risk in hypertension. Hypertension. 1998;32(6):983-988. https://doi.org/10.1161/01.hyp.32.6.983

9. Li J, Huang JY, Lo K, Zhang B, Huang YQ, Feng YQ. Association of pulse pressure with all-cause mortality in young adults. Postgrad Med J. 2020;96(1138):461-466. https://doi.org/10.1136/postgradmedj-2019-137070

10. Protogerou AD, Vlachopoulos C, Thomas F, et al. Longitudinal changes in mean and pulse pressure, and all-cause mortality: data from 71,629 untreated normotensive individuals. Am J Hypertens. 2017;30(11):1093-1099. https://doi.org/10.1093/ajh/hpx110

11. Benetos A, Gautier S, Labat C, et al. Mortality and cardiovascular events are best predicted by low central/peripheral pulse pressure amplification but not by high blood pressure levels in elderly nursing home subjects: the PARTAGE (predictive values of blood pressure and arterial stiffness in institutionalized very aged population) study, J Am Coll Cardiol. 2012;60(16):1503-1511. https://doi.org/10.1016/j.jacc.2012.04.055

12. Staessen JA, Thijs L, O’Brien ET, et al. Ambulatory pulse pressure as predictor of outcome in older patients with systolic hypertension. Am J Hypertens. 2002;15(10 Pt 1):835-843. S0895-7061(02)02987-4 [pii]. https://doi.org/10.1016/s0895-7061(02)02987-4

13. Baillei F, Spenalla F, Giuliatti F, et al. Ten-year changes in ambulatory blood pressure: the prognostic value of ambulatory pulse pressure. J Clin Hypertens (Greenwich). 2018;20(9):1230-1237. https://doi.org/10.10111/jch.13344

14. Skoglund PH, Ostergren J, Svensson P. Ambulatory pulse pressure predicts cardiovascular events in patients with peripheral arterial disease. Blood Press. 2012;21(4):227-232. https://doi.org/10.3109/00034819.2012.676755

15. Amar J, Vernieri I, Rossignol E, et al. Nocturnal blood pressure and 24-hour pulse pressure are potent indicators of mortality in hemodialysis patients. Kidney Int. 2000;57(6):2485-2491. S0085-2538(15)70003-0 [pii]. https://doi.org/10.1046/j.1523-1755.2000.00107.x

16. Kao YT, Huang CC, Leu HB, et al. Ambulatory pulse pressure as a novel predictor for long-term prognosis in essential hypertensive patients. J Hum Hypertens. 2011;25(7):444-450. https://doi.org/10.1038/jhh.2010.80

17. Tadic M, Quarti-Trevano F, Bombelli M, et al. The importance of pulse pressure on cardiovascular risk and total mortality in the general population: is sex relevant? J Clin Hypertens (Greenwich). 2018;20(6):1001-1007. https://doi.org/10.1111/jch.13300

18. Gu YM, Thijs L, Li Y, et al. Outcome-driven thresholds for ambulatory pulse pressure in 9938 participants recruited from 11 populations. Hypertension. 2014;63(2):229-237. https://doi.org/10.1161/HYPERTENSIONAHA.113.02179

19. Kikuya M, Staessen JA, Ohkubo T, et al. Ambulatory arterial stiffness index and 24-hour ambulatory pulse pressure as predictors of mortality in ohasama, Japan. Stroke. 2007;38(4):1161-1166.

01.STR.0000259604.67283.69 [pii]. https://doi.org/10.1161/01.STR.0000259604.67283.69

20. Miura K, Dyer AR, Greenland P, et al. Pulse pressure compared with other blood pressure indexes in the prediction of 25-year cardiovascular and all-cause mortality rates: The Chicago Heart Association Detection Project in Industry Study. Hypertension. 2001;38(2):232-237. https://doi.org/10.1161/01.hyp.38.2.232

21. Rantala AO, Kauma H, Liija M, Savolainen MI, Reunanen A, Kesäniemi YA. Prevalence of the metabolic syndrome in drug-treated hypertensive patients and control subjects. J Intern Med. 1999;245(2):163-174. https://doi.org/10.1046/j.1365-2796.1999.00429.x

22. Perkólmájí JK, Nortamo S, Ylitalo A, Kesániemi A, Ukkola O, Huiuki HV. Ambulatory blood pressure characteristics and long-term risk for atrial fibrillation. Am J Hypertens. 2017;30(3):264-270. https://doi.org/10.1039/ajh/hpw149

23. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604-612. doi: 150/9/604 [pii]. https://doi.org/10.7326/0003-4819-150-9-200909050-00006

24. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med. 1998;15(7):539-553. doi: AID-DIA668-3.0.CO;2-S [doi]

25. Reinders A, Reggiori F, Shennan AH. Validation of the DINAMAP ProCare blood pressure device according to the international protocol in an adult population. Blood Press Monit. 2006;11(5):293-296. https://doi.org/10.1093/ambhpa.2000217998.96967.fb

26. Ylitalo A. Cardiovascular Autonomic Regulation in Systemic Hypertension. University of Oulu; 1999.

27. Coutinho T. Arterial stiffness and its clinical implications in women. Can J Cardiol. 2014;30(7):756-764. doi: S0828-28X(14)00166-4 [pii].

28. Khattar RS, Swales JD, Dore C, Senior R, Lahiri A. Effect of aging on the prognostic significance of ambulatory systolic, diastolic, and pulse pressure in essential hypertension. Circulation. 2001;104(7):783-789. https://doi.org/10.1161/hc3201.094227

29. Wing LMH, Chowdhury EK, Reid CM, Beilin LJ, Brown MA, ANBP2 Management Committee. Night-time ambulatory blood pressure is the best pretreatment blood pressure predictor of 11-year mortality in treated older hypertensives. Blood Press Monit. 2018;23(5):237-243. https://doi.org/10.1097/MBP.0000000000000331

30. Sabbatini AR, Karagias G. Estrogen-related mechanisms in sex differences of hypertension and target organ damage. Biol Sex Differ. 2020;11(1):31-37. https://doi.org/10.1186/s13293-020-00306-7

31. Regnault V, Thomas F, Safar ME, et al. Sex difference in cardiovascular risk: Role of pulse pressure amplification. J Am Coll Cardiol. 2012;59(20):1771-1777. https://doi.org/10.1016/j.jacc.2012.01.044

32. Van Ryswyk E, Mukherjee S, Chai-Coetzer CL, Vakulin A, McEvoy RD. Sleep disorders, including sleep apnea and hypertension. Am J Hypertens. 2018;31(8):857-864. https://doi.org/10.1039/ajh/hpy082

SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Lempiäinen PA, Ylitalo A, Huiuki H, Kesäniemi YA, Ukkola OH. Nighttime ambulatory pulse pressure predicts cardiovascular and all-cause mortality among middle-aged participants in the 21-year follow-up. J Clin Hypertens. 2021;23:1547-1555. https://doi.org/10.1111/jch.14317