Average Blood Pressure and Cardiovascular Disease–Related Mortality in Middle-Aged Women

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Background: The aim of this study was to assess which average blood pressure (BP) component (ie, systolic BP [SBP], diastolic BP [DBP], pulse pressure [PP], or mean arterial pressure [MAP]), is most strongly related to cardiovascular disease (CVD)–related mortality and to evaluate whether the strength of the relation varies with follow-up time.

Methods: This was a prospective cohort study. The studied cohort comprised a population of postmenopausal women ($n = 7813$) between the ages of 49 and 66 years of age, of whom four BP measurements were available, obtained at four different time points. Average BP, ie, the mean of the four measurements divided by the standard deviation, was entered in Cox proportional hazards models to facilitate direct comparison. Hazard ratios (HR) were calculated adjusted for age, body mass index, presence of diabetes mellitus, smoking habit, and use of BP-lowering medication. In addition analyses were repeated in strata of follow-up time (10, 15, and 20 years).

Results: During a mean follow-up of 13.1 years, 463 CVD-related deaths occurred. For SBP and MAP the highest HR for CVD mortality were found; however, the confidence intervals (CI) overlapped (SBP: HR = 1.43, 95% CI = 1.30 to 1.58; DBP: HR = 1.35, 95% CI = 1.23 to 1.50; PP: HR = 1.30, 95% CI = 1.19 to 1.42; MAP: HR = 1.43, 95% CI = 1.30 to 1.58). Analyses in strata of follow-up time did not show a difference in strength of the associations with increasing follow-up time.

Conclusions: In this prospective follow-up study of postmenopausal women, SBP and MAP seemed to be strongest related with CVD-related death; however the CI of the HR overlapped. Am J Hypertens 2005;18: 197–201 © 2005 American Journal of Hypertension, Ltd.

Key Words: Blood pressure, cardiovascular disease mortality.

Hypertension has long been known as an important modifiable risk factor for cardiovascular disease (CVD) and mortality. Recently, increasing attention has focused on the role of the different BP components as predictors of CVD and death. Several decades ago, elevated diastolic BP (DBP) was understood to relate to increased arteriolar tone and was therefore viewed as the most dangerous component of high BP.[1,2] Subsequently, elevated DBP became established as the main criterion to start pharmacotherapy. In the last several decades, attention has shifted to systolic BP (SBP) as an important predictor of cardiovascular events, as published data indicate that SBP is a better predictor than DBP.[3] Pulse pressure (PP) has recently been added, as it appears to be an important predictor of CVD and death, especially in middle-aged and elderly individuals.[4–6]

Few reports, however, have compared all BP components (ie, SBP, DBP, PP, and mean arterial pressure [MAP]) in the same analytic procedures.[7–16] Furthermore, in most published studies, only a single BP measurement obtained at baseline was available. This generally results in an underestimation of the association with cardiovascular events because of biological variability in BP. In addition, some studies indicated that age and follow-up time might modify the relation of BP to CVD and the magnitude of the association of the various BP components with cardiovascular events.[17] Consequently, differences in association with elevated BP between studies have been attributed to age and follow-up differences.

In this study, we examined 1) which BP component shows the strongest relationship with CVD-related mor-

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tality, and 2) whether follow-up time affects the strength of association.

Methods

Study Population

The study population is a subgroup of the participants of the *D*iagnostisch *O*nderzoek *M*ammacarcinoom (DOM) project. The DOM project started as a project for the early detection of breast cancer in Utrecht, The Netherlands. Study procedures have been described in more detail elsewhere.[18,19] Briefly, a total of 20,555 women living in the city of Utrecht who were born between 1911 and 1925 were invited to participate. Of these women 14,701 (72%) agreed to participate and were enrolled between December 1974 and September 1977. Information on smoking habits, use of medication, and medical and reproductive history was obtained from questionnaires. After a brief physical examination, BP was measured after 5 min of rest. This was done twice during a visit at the right arm of the subject using a standard mercury sphygmomanometer with a cuff size of 14 cm. The second measurement was recorded and truncated to 0 or 5. Hypertension was considered present when use of antihypertensive medication was reported. The BP measurements were first performed in spring 1975; therefore, no BP measurements of the first visit were available for the first 957 women of the cohort. Height, weight, and skin-fold thickness were measured. An overnight urine sample was taken and stored for future use. Women who reported use of medication or followed a special diet for diabetes mellitus were considered as having diabetes mellitus. Women were screened four times with an interval of 12 months between the first and the second visits, 18 months between the second and third visits, and 24 months between the third and fourth visits, respectively. On all occasions, BP was measured using the same procedure as at baseline.

To be able to correct for biological and within-subject variability of BP, the study population was restricted to those subjects with registered BP measurements at all four visits. This resulted in a total of 7813 subjects available for the analyses.

Cardiovascular Mortality

Each month, municipal authorities notified the staff of the DOM project of all deaths in the cohort. Participants' general practitioners provided data on causes of death, as detailed earlier.[19,20] Also, participants who moved out of the city of Utrecht were reported to the staff of the DOM project ($n = 657$). The follow-up period ended January 1, 1996. The outcome of interest for the present analyses was death from CVD (ICD-9 codes 390 to 459).[20,21]

Data Analysis

To correct for the phenomenon of regression to the mean, average SBP and DBP values were calculated (ie, the mean of four BP measurements at four different time points) instead of one baseline measurement. Subsequently, PP was calculated, defined as average SBP minus average DBP, and MAP was calculated as 1/3 average SBP + 2/3 average DBP. Spearman correlation coefficients were used to relate each pair of BP components. Cox proportional hazard regression models[18] were used to determine the hazard ratio (HR) for the risk of CVD mortality for each BP component separately. To facilitate the comparison of the various BP components, the BP component divided by its standard deviation was entered into the model. The data-analytic approach using Z-scores to compare BP parameters showed the same result; however, because Z-scores are more difficult for clinicians to interpret, we used the standard deviation approach. All analyses were adjusted for age at baseline and subsequently for body mass index (BMI), presence of diabetes mellitus, current smoking (yes or no), and use of BP-lowering medication (yes or no).

Using multiplicative interaction terms (BP component * age), we evaluated whether the relationship of BP to vascular death differed by age. As these interaction terms were not statistically significant (for interaction terms for SBP, DBP, MAP, and PP, $P = .13$, .24, .20, and .10, respectively), only the overall analyses were reported.

Because it has been described that the calculation of MAP at higher ages may be better reflected by MAP = (DBP + 1/2 PP) compared with (DBP + 1/3 PP), we performed additional analyses using the alternative MAP calculation for those patients >56 years of age (median of the study population). In theory, using the alternative approach would tend to lead to stronger associations than with the first calculation by reducing misclassification.

Using Cox proportional hazard regression models in the same manner as described earlier, we studied whether follow-up time affected the strength of association for CVD-related mortality. In addition, new censor variables were defined for follow-up periods of 10 years, 15 years, and 20 years from baseline, respectively.

Results

General characteristics of the 7813 participants are shown in Table 1. The mean age of the study population at enrollment was 56.3 years (SD 4.3), with a mean BMI of 25.9 kg/m^2 (SD 3.6). Approximately 25% of the participants were current cigarette smokers. Mean follow-up time from baseline was 17.6 years (SD 4.1), which was approximately 13.1 years from the fourth BP measurement onward. During follow-up, 463 CVD-related deaths occurred. Spearman correlation coefficients were as follows: for SBP and DBP, 0.81; for SBP and PP, 0.88; for DBP and PP, 0.45; for SBP and MAP, 0.95; and for DBP and MAP, 0.95. The relationship of BP to age is shown in Fig. 1.

Table 2 shows that average SBP and MAP seemed to be most strongly related to CVD mortality, followed by DBP and PP. As the 95% CI of the HR of all BP components

Table 1. General characteristics of the study population (n = 7813)

Characteristic	
Age (y)	56.3 (±4.3)
Average SBP (mm Hg)	156 (±21)
Average DBP (mm Hg)	93 (±11)
Average PP (mm Hg)	63 (±13)
Average MAP (mm Hg)	114 (±13)
Use of BP medication (%)	14.2
Current cigarette smoking (%)	25.8
BMI (kg/m^2)	25.9 (±3.6)
Diabetes mellitus (%)	2.0
Use of heart medication (%)	3.7
Follow-up time from baseline (y)	17.6 (±4.1)
CVD deaths (%)	5.9

BMI = body mass index; BP = blood pressure; CVD = cardiovascular disease; DBP = diastolic blood pressure; MAP = mean arterial pressure; PP = pulse pressure; SBP = systolic blood pressure.

Values are means with standard deviations in parentheses, or are percentages.

Table 2. Results of Cox proportional hazard regression models relating incidence of cardiovascular disease death to blood pressure components

	HR (95% CI)* (n = 7813)
SBP, crude†	1.50 (1.37–1.63)
SBP, adjusted‡	1.43 (1.30–1.58)
DBP, crude†	1.41 (1.29–1.54)
DBP, adjusted‡	1.35 (1.23–1.50)
PP, crude†	1.39 (1.27–1.51)
PP, adjusted‡	1.30 (1.19–1.42)
MAP, crude†	1.48 (1.36–1.61)
MAP, adjusted‡	1.43 (1.30–1.58)

CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 1.

* HR was associated with 1-SD increase in blood pressure (mm Hg).
† SBP, DBP, PP, and MAP were entered in separate models, adjusted for age. ‡ SBP, DBP, PP and MAP were entered in separate models, adjusted for age, body mass index, diabetes mellitus, smoking, and use of blood pressure–lowering medication.

overlapped, the differences in association with CVD mortality across BP components were not statistically significant. Table 3 shows the results of the Cox proportional hazard analyses of strength of association for CVD-related mortality at different lengths of follow-up from the baseline visit. For the study population, 96 events were registered after 10 years from baseline, 252 events after 15 years, and 461 events after 20 years. Analyses showed that the magnitude of the HR remained approximately the same with increasing follow-up time for all BP components. The association for SBP and MAP with risk for CVD mortality remained the strongest, although the CI overlapped.

When we used the alternative calculation of MAP, the mean was 128 mm Hg (SD 21.6). The age-adjusted hazard ratio was 1.57 (95% CI = 1.41 to 1.74), and the fully adjusted hazard ratio was 1.48 (95% CI = 1.31 to 1.67). Compared with findings in the Table 2, these hazard ratios were of a higher magnitude, although CI overlapped.

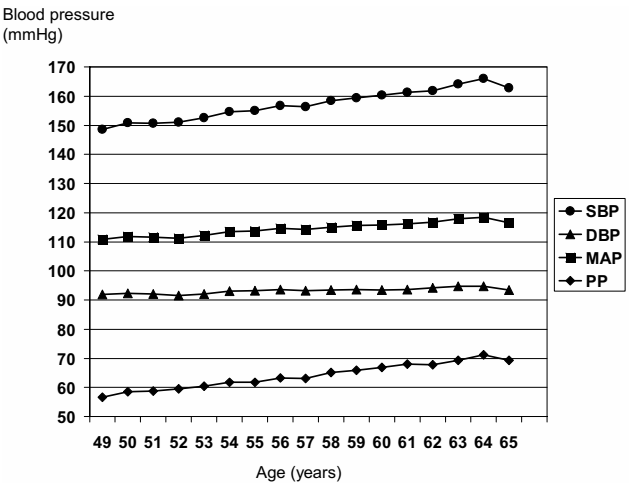

FIG. 1 Mean blood pressure of study subjects, by age.

We repeated the analyses excluding subjects on antihypertensive drugs (n = 1111). These results were similar to those of the overall analyses and thus only the latter are reported.

Discussion

Here we show that, in a cohort of postmenopausal women, SBP and MAP seemed to have the strongest relationship with CVD-related mortality, although the CI overlapped. The strength of the relationships remained approximately constant with follow-up time.

To appreciate the results, some limitations of the present study need to be discussed. First, to be able to correct for the phenomenon of regression to the mean, subjects were selected with four available BP measurements. This might have diluted the association with CVD-related death because women were selected who were able to visit the outpatient clinic four times in a period of 4.5 years and who might have been healthier in comparison with the other participants. Of the remaining 6888 subjects in the cohort, 615 (8.9%) died of CVD compared with 463 (5.9%) of the 7813 subjects presented in this report. It should be noted, however, that these are crude numbers and were not adjusted for risk factors for CVD-related death. Second, during data collection, BP was measured and truncated to a value below the original value ending in 0 or 5. This truncation influences the absolute numbers of BP but does not influence the strength of the associations. Third, the present study population comprised women only, which may limit generalization to men. However, results from the prospective studies collaboration indicated no difference in direction and magnitude of the relationship of BP to events between men and women.[11]

It has been described that the brachial measured BP may not accurately reflect aortic BP and that this error

Table 3. Relation of blood pressure components to cardiovascular disease–related death by follow-up time by means of Cox proportional hazard regression models (n = 7813)

	10-Year follow-up HR (95% CI)*	15-Year follow-up HR (95% CI)*	20-Year follow-up HR (95% CI)*
SBP, crude†	1.58 (1.31–1.90)	1.56 (1.39–1.76)	1.49 (1.37–1.63)
SBP, adjusted‡	1.41 (1.14–1.75)	1.48 (1.30–1.69)	1.43 (1.29–1.58)
DBP, crude†	1.43 (1.18–1.72)	1.44 (1.28–1.61)	1.41 (1.29–1.54)
DBP, adjusted‡	1.28 (1.03–1.59)	1.37 (1.20–1.57)	1.36 (1.23–1.50)
PP, crude†	1.48 (1.23–1.77)	1.45 (1.30–1.62)	1.38 (1.27–1.51)
PP, adjusted‡	1.32 (1.08–1.60)	1.35 (1.19–1.52)	1.30 (1.18–1.42)
MAP, crude†	1.53 (1.27–1.84)	1.53 (1.37–1.72)	1.48 (1.36–1.61)
MAP, adjusted‡	1.38 (1.11–1.72)	1.47 (1.28–1.68)	1.43 (1.30–1.58)

Abbreviations as in Tables 1 and 2.

* HR was associated with a 1-SD increase in BP (mm Hg). † SBP, DBP, PP, and MAP were entered in separate models, adjusted for age. ‡ SBP, DBP, PP, and MAP were entered in separate models, adjusted for age, body mass index, diabetes mellitus, smoking, and use of blood pressure–lowering medication.

declines with increasing age. It is assumed that MAP is constant across the arterial tree, so the estimates for MAP are likely to be valid. Also, DBP is relatively constant. Because SBP (and thus PP) is overestimated in younger compared with older women, and because the risk of CVD-related death is lower in younger compared with older women, both relationships may tend to underestimate the true relation. So, if we had relied on measurements of aortic BP, our final statement that SBP and MAP predict equally well might have been revised to the statement that SBP is superior to SBP.

Several studies have addressed the relation of BP components with CVD. However, the number of comparable articles is limited.[7–10,13–16] In addition, there are a few important differences across these studies, such as composition of the study population, type of BP measurement, duration of follow-up, and the studied endpoints. The type of BP measurement (single measurement, measurement in duplicate, measurements at different time points) affects the strength of association. With a single measurement on one occasion, misclassification in BP level can occur because of within-subject variability. This regression to the mean phenomenon results in an underestimation of the true strength of the associations. In our data, using average BP instead of one measurement at baseline, the HR for CVD death increased on average by 15% (eg, for SBP from 1.25 to 1.43, data not shown). With longer follow-up time periods, smaller relative risks are often found because of long-term fluctuations or changes within individuals. We were not able to show a clear effect of follow-up time on strength of relation with CVD events, although Clarke et al showed that with increasing follow-up time the underestimation of the associations increases.[23] Our lack of attenuation may be a consequence of having used average BP over a 4-year period.

Our data suggest that SBP and MAP play an important role in predicting CVD mortality. This finding is similar to a wealth of other data from observation and intervention research focusing on treatment of isolated systolic hypertension.[16,24] In our study, differences between the HR of the BP components were however small. This is likely due to the strong correlation between BP components, especially for SBP and PP and for SBP and MAP. Because the age range of our subjects was limited, the PP results should be generalized to those individuals <66 years of age, and may be different for older subjects.[13,15] The finding that SBP and MAP were most strongly associated with CVD death is in agreement with the results of a large meta-analysis.[11] In this analysis, individual patient data of 61 prospective follow-up studies were pooled and analyzed to investigate which BP component is the best predictor of ischemic heart disease–related death and stroke-related death with only one single measurement at baseline. Results indicated that SBP and MAP were the strongest predictors. Pulse pressure was a very weak predictor, although a trend toward a stronger association with increasing age was found.[11] In a pooled analysis, the Asia Pacific Cohort Studies Collaboration showed that SBP (based on a single measurement on one occasion) was the BP component that provided the best information in predicting risk for cardiovascular events.[25] It may be that, in our study, taking the average of measurements over a 4-year period may have resulted in comparable predictive capabilities of all BP components.

Implications for Clinical Practice

Blood pressure measurement forms a key element of cardiovascular risk management. The most important purpose of BP measurement is its role in overall cardiovascular risk profiling; that is, treatment starts based on the estimate of the absolute risk of an individual to experience a cardiovascular event in the next 10 years, rather than being based on BP level alone. There are substantial data, including the results of our own analyses, to suggest that the measurement of SBP conveys all of the risk information to be gained, with DBP levels adding little. For example, in most functions to estimate cardiovascular risk, only SBP is used. Furthermore,

SBP is generally the BP component that is measured most accurately and reproducibly,[26] both manually and with automated devices. In hypertension, both SBP and DBP are elevated to a largely similar extent or SBP is elevated in isolation, whereas isolated diastolic hypertension is a rare condition. We are aware that the term "hypertension" is defined on the basis of clear cut-off points, whereas for improving cardiovascular risk profile no true threshold exists. However, according to the Dutch hypertension guidelines,[27] thresholds are defined based on proven effectiveness of treatment in clinical trials and on age and comorbidity. About 96% of persons are correctly classified as hypertensive based on SBP alone,[28] and in our cohort 97.7% of hypertensive individuals, defined as those with an average SBP >140 mm Hg and DBP of >90 mm Hg, were correctly classified by SBP alone. As a consequence, in subjects with high BP who are <65 years of age and in whom risk factor modification is indicated, the presence of hypertension is very unlikely to be missed in the absence of a DBP measurement. Therefore we conclude that, in clinical practice, assessing cardiovascular risk profile and indications for treatment may be done on the basis of SBP measurement only.

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