Pulse Pressure and Mortality in Older People

Robert J. Glynn, ScD; Claudia U. Chae, MD; Jack M. Guralnik, MD, PhD; James O. Taylor, MD; Charles H. Hennekens, MD, DrPH

Background: In older people, observational data are unclear concerning the relationships of systolic and diastolic blood pressure with cardiovascular and total mortality. We examined which combinations of systolic, diastolic, pulse, and mean arterial pressure best predict total and cardiovascular mortality in older adults.

Methods: In 1981, the National Institute on Aging initiated its population-based Established Populations for Epidemiologic Studies of the Elderly in 3 communities. At baseline, 9431 participants, aged 65 to 102 years, had blood pressure measurements, along with measures of medical history, use of medications, disability, and physical function. During an average follow-up of 10.6 years among survivors, 4528 participants died, 2304 of cardiovascular causes.

Results: In age- and sex-adjusted survival analyses, the lowest overall death rate occurred among those with systolic pressure less than 130 mm Hg and diastolic pressure 80 to 89 mm Hg; relative to this group, the highest death rate occurred in those with systolic pressure of 160 mm Hg or more and diastolic pressure less than 70 mm Hg (relative risk, 1.90; 95% confidence interval, 1.47-2.46). Both low diastolic pressure and elevated systolic pressure independently predicted increases in cardiovascular (P<.001) and total (P<.001) mortality. Pulse pressure correlated strongly with systolic pressure (R=0.82) but was a slightly stronger predictor of both cardiovascular and total mortality. In a model containing pulse pressure and other potentially confounding variables, diastolic pressure (P=.88) and mean arterial pressure (P=.11) had no significant association with mortality.

Conclusions: Pulse pressure appears to be the best single measure of blood pressure in predicting mortality in older people and helps explain apparently discrepant results for low diastolic blood pressure.

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In middle-aged populations, both systolic and diastolic blood pressure have strong, linear relationships with cardiovascular and total mortality.1-3 Because of the high correlation between systolic and diastolic pressure, studies examining cardiovascular risk in this age group commonly find that diastolic pressure provides little additional prognostic information after consideration of systolic pressure.1-4 In older people, however, observational studies have been less consistent6-13 and have commonly found U- or J-shaped relationships of blood pressure with mortality, especially for diastolic pressure. In some studies, individuals with the lowest blood pressure had the highest mortality.14,15 Treatment implications of these relationships remain controversial.16-20 With the loss of aortic compliance, systolic pressure rises with age in industrialized countries, while diastolic pressure declines after about age 60 years, leading to increased pulse pressure and a diminished association between systolic and diastolic pressure.21 This may lead to differing relationships of systolic and diastolic pressure with mortality in older people.

It is also possible that pulse pressure is the measure of blood pressure most strongly related to cardiovascular risk in older people, and that consideration of pulse pressure may explain the apparent increased risk associated with low diastolic pressure. Several prospective studies have found that elevated pulse pressure, which reflects increased arterial stiffness with age, is associated with risk of myocardial infarction, congestive heart failure, and cardiovascular and total mortality.22-27 However, pulse pressure is strongly correlated with systolic pressure, and it remains unclear whether it provides independent prognostic information or is useful in clarifying J-curves.28

Using data from 3 population-based cohorts of the Established Popu-
SUBJECTS AND METHODS
SUBJECTS AND MEASURES
In 1981, the National Institute on Aging initiated its Established Populations for Epidemiologic Studies of the Elderly studies of community-dwelling persons aged 65 years and older in 3 locations: East Boston, Mass; Washington and Iowa counties, Iowa; and New Haven, Conn. During 1982 and 1983, surveys were conducted in the entire populations of persons aged 65 years and older in East Boston and Iowa and in a stratified sample of residents of New Haven. To maximize participation, trained interviewers visited the homes of all eligible participants. Participation rates ranged from 80% to 85%, with 3809 participants in East Boston, 3673 participants in Iowa, and 2812 participants in New Haven, for a total population of 10,294 community-dwelling elderly subjects. Because some individuals participated through a proxy, 9431 participants had baseline blood pressure measurements, and they constitute the cohort for the current study.

In East Boston and New Haven, the trained interviewer took 3 blood pressure measurements at 30-second intervals by means of a standard mercury sphygmomanometer, after the participant had been seated for at least 5 minutes, according to the protocol used in the Hypertension Detection and Follow-up Program. Two measurements were taken in Iowa. For this study, systolic pressure was the average of all systolic measures; diastolic pressure was the average of all diastolic measures; pulse pressure was systolic minus diastolic pressure; and mean arterial pressure was \((\text{systolic} + 2 \times \text{diastolic pressure})/3\).

The interviewer also collected information about other characteristics potentially related to both blood pressure and mortality. Participants reported their height and weight, present and past use of cigarettes and alcohol, and whether they were ever told by a physician that they had myocardial infarction, stroke, or cancer. Angina was identified by the Rose questionnaire. All medications used in the 2 weeks before the interview were identified by direct inspection. Disability was identified through reports of problems with activities of daily living and problems with physical function by a 3-item scale. We classified participants as low in physical activity when they reported not exercising vigorously at least once a week, rarely or never taking walks, and not working frequently around the house or garden. Further information about demographic characteristics of the population and quality control of blood pressure measurements has been published elsewhere.

Participants were contacted yearly during the first 6 years after baseline, with in-home interviews at the 3- and 6-year follow-up and telephone interviews in the interim years. Thereafter, mortality follow-up continued through the end of 1992 through local surveillance supplemented by linkage to the National Death Index. These sources yielded complete follow-up of the cohort for mortality up to 1992, giving an average follow-up of 10.6 years (range, 9.1-11.1 years) among survivors. Of the 9431 participants, 4528 died, and death certificates were obtained for 4494. A single trained nosologist coded the underlying cause of death according to the International Classification of Diseases, Ninth Revision. We used these codes to classify deaths as being caused by cardiovascular disease including stroke (codes 401-459) or other causes.

STATISTICAL ANALYSIS
We first determined correlations among the measures of blood pressure to quantify their interrelationships. To examine the joint association of systolic and diastolic blood pressure with mortality, we classified participants according to categories of both variables. Categories used were the same as in a previous study of blood pressure in one of these populations, except that a priori we grouped individuals with systolic pressure between 140 and 159 mm Hg and also formed a single group among those with diastolic pressure between 70 and 79 mm Hg. Thus, we partitioned the population into 16 groups according to category of systolic pressure (<130, 130-139, 140-159, or ≥160 mm Hg) and category of diastolic pressure (<70, 70-79, 80-89, or ≥90 mm Hg). We used proportional hazards analyses to compare age- and sex-adjusted total and cardiovascular death rates across these 16 categories.

To examine whether simpler models might summarize these relationships, we compared the ability of both single measures and pairs of measures of blood pressure to predict total and cardiovascular mortality. We categorized pulse pressure and mean arterial pressure according to approximate quartiles in the population. We compared the ability of alternative models to predict mortality by means of the \(R^2\) statistic for survival analysis and the likelihood ratio–based discrimination index D (defined as the model likelihood ratio \(\chi^2\)–1 divided by the –2 log likelihood of the null model) described by Harrell and colleagues. We used likelihood ratio tests to determine whether adding variables to a model significantly improved the fit. Additional models included other variables that may affect both blood pressure and risk of death, but were restricted to the 4034 deaths in 8713 participants with complete data on these potential confounding variables.

We also examined whether associations of blood pressure with mortality differed in the following subgroups: women aged 65 to 74 years, women aged 75 years or more, men aged 65 to 74 years, men aged 75 years or more, users and nonusers of antihypertensive drugs, people with chronic disease (angina; history of myocardial infarction, stroke, or cancer; use of digoxin, loop diuretics, or hypoglycemic drugs), and those without these diseases. Because undetected diseases may affect blood pressure in those near death, we also examined deaths separately in the first 3 years and thereafter. Separate analyses in each site found comparable results.
RESULTS

INTERRELATIONSHIPS AMONG BLOOD PRESSURE MEASURES

Among the 9431 elderly subjects in these 3 communities, systolic blood pressure had a correlation of 0.50 with diastolic blood pressure. Although this correlation was large and highly significant (P<.001), it was substantially weaker than the correlation of nearly 0.80 between these measures found in studies of middle-aged populations.1,2

Overall, pulse pressure had a weak but slightly U-shaped relationship with diastolic pressure. On average, the lowest pulse pressures occurred among those with diastolic pressures between 70 and 89 mm Hg. Among those with diastolic pressure less than 80 mm Hg, the correlation with pulse pressure was −0.21 (P<.001), whereas above 80 mm Hg the correlation was 0.10 (P<.001). Conversely, pulse pressure and systolic pressure had a strong, almost linear association (Figure 1). The correlation of 0.82 between these measures further suggested that a straight line fits this relationship fairly well. Mean arterial pressure had strong correlations of 0.85 with systolic pressure and 0.89 with diastolic pressure but a weaker, although still highly significant (P<.001), correlation of 0.39 with pulse pressure.

JOINT RELATIONSHIPS WITH MORTALITY

The lowest risk of death occurred among the 321 participants with diastolic pressures between 80 and 89 mm Hg and systolic pressures less than 130 mm Hg, and we took this group as the referent (Table 1). The highest death rate occurred among the 173 participants with elevated systolic pressure (≥160 mm Hg) and low diastolic pressure (<70 mm Hg), who had a 90% higher death rate than the referent group (P<.001). The next highest death rates occurred among the individuals in the adjacent categories, with elevated systolic pressure and diastolic pressure of 70 to 79 mm Hg (relative risk [RR], 1.59; 95% confidence interval [CI], 1.28-1.99) or borderline high systolic pressure (140-159 mm Hg) and low diastolic pressure (RR, 1.56; 95% CI, 1.26-1.93). More than 100 deaths occurred in 14 of the 16 blood pressure groups, indicating the ability to estimate reliably the joint relationship of systolic and diastolic pressure with mortality in all groups except those with elevated diastolic pressure (≥90 mm Hg) and systolic pressure less than 140 mm Hg.

The data in Table 1 strongly support the importance of pulse pressure as a determinant of the risk of death in older people. The lowest death rates occurred among normotensive subjects with low pulse pressure (ie, systolic pressure <130 mm Hg and diastolic pressure 70-89 mm Hg, or systolic pressure 130-139 mm Hg and diastolic pressure 80-89 mm Hg). The 1880 individuals in these groups all had pulse pressure less than 60 mm Hg and their mean pulse pressure was 46.7 mm Hg (interquartile range, 42-52 mm Hg). None of the groups in the lower left portion of Table 1 had significant elevations in death rates. Conversely, the highest death rates occurred among groups with the highest pulse pressures (top right of Table 1). The 1130 individuals in the 3 groups with the highest death rates all had pulse pressures greater than 70 mm Hg, and their mean pulse pressure was 92.4 mm Hg (interquartile range, 84-99 mm Hg).

We observed a similar relationship between categories of systolic and diastolic blood pressure and cardiovascular mortality (Figure 2), suggesting that pulse pressure was an important determinant of cardiovascular mortality. The same 3 groups with the highest total mortality also had the highest cardiovascular death rates, and these elevations were significant (P<.01) for each of these groups compared with the referent.

BEST PREDICTIVE MODELS

For both total (Table 2) and cardiovascular (Table 3) mortality, an age- and sex-adjusted model including only pulse pressure had slightly better predictive ability than a model including only systolic pressure or only diastolic pressure, as indicated by higher R² and discrimination index statistics. Those in the third quartile of pulse pressure (63-76 mm Hg) had a 19% increased risk of cardiovascular death, and those in the highest quartile (≥77 mm Hg) had a 57% increased risk of cardiovascular death, compared with those in the lowest quartile. Adding diastolic pressure to the model including pulse pressure alone left these effects of pulse pressure virtually unchanged. Within each category of diastolic pressure, persons with higher levels of pulse pressure had higher rates of cardiovascular death (Figure 3). Mean arterial pressure had a weak association with both total (Table 2) and cardiovascular (Table 3) mortality. In analyses including both pulse pressure and mean arterial pressure, pulse pressure continued to have the same strong relationship with mortality, whereas mean arterial pressure had a nonsignificant relationship with these end points (data not shown).

Alternative models that included both systolic and diastolic pressure found independent and highly significant effects of both measures and were significantly better than models including only one of these measures
vascular death (P < .001). After adjusting for age, sex, and diastolic pressure, higher levels of systolic pressure were associated with increased risk of cardiovascular death, with a significant 25% higher cardiovascular death rate (P < .001) among those with borderline high systolic pressure (140-159 mm Hg), relative to those with systolic pressure less than 130 mm Hg, and a 59% higher cardiovascular death rate (P < .001) among those with high systolic pressure (≥160 mm Hg). After controlling for systolic pressure, low diastolic pressure (<70 mm Hg) was independently associated with a 38% increase in risk of cardiovascular death (P < .001), relative to those with diastolic pressure 80 to 89 mm Hg, and diastolic pressure of 70 to 79 mm Hg was associated with a 17% higher cardiovascular death rate (P = .006). If diastolic pressure was not included in the model, then the effects of systolic pressure on risk were substantially reduced, and, similarly, if the model did not include systolic pressure, then the effects of diastolic pressure were also reduced. This further indicates the importance of including both systolic and diastolic pressure in predictive models in older people.

For both total mortality and cardiovascular mortality, these models including independent effects of both systolic and diastolic pressure had comparable predictive ability, compared with the models that also included interactions between these variables summarized in Table 1 and Figure 2. However, the predictive ability of the simpler model including only pulse pressure was nearly equal to that of the model including both systolic and diastolic pressure.

Further control for potential confounding variables had little effect on relationships of systolic pressure or pulse pressure with either cardiovascular mortality (Figure 4) or total mortality (data not shown). However, control for confounding variables attenuated the apparent increased risk associated with low diastolic pressure. Adjusting for systolic pressure and confounders, the risk associated with low diastolic pressure remained statistically significant (P = .02 for both total and cardiovascular death). With adjustment for pulse pressure as well as confounding variables, diastolic pressure had no significant association with mortality (P = .88 for total mortality and P = .33 for cardiovascular mortality). This suggests that pulse pressure and comorbidity explain the apparent relationships between low diastolic pressure and mortality in aging adults. With control for potential confounding variables and pulse pressure, mean arterial pressure also had no association with mortality (P = .11 for total mortality and P = .21 for cardiovascular mortality).

**SUBGROUP ANALYSES**

We found little evidence that either use of antihypertensive drugs or presence of important chronic diseases modified the relationships of pulse pressure and diastolic pressure with cardiovascular mortality, summarized for the entire population in Table 3. We did observe some apparent differences in relationships by age. In analyses of women aged 65 to 74 years and in men aged 65 to 74 years, we found somewhat stronger relationships of pulse pressure with mortality, compared with the effects in the total population: relative to women in the lowest quartile of pulse pressure, those in the highest quartile had a 2.13 higher risk of cardiovascular death (95% CI, 1.58-
2.88) and men in the highest quartile had a 1.87 increased risk (95% CI, 1.43-2.44), relative to those with pulse pressure in the lowest quartile. Conversely, relationships were weaker among those aged 75 years or older at baseline. Older women in the highest quartile of pulse pressure had a 1.34 increased risk of cardiovascular death (95% CI, 1.07-1.68) relative to older women in the lowest quartile; in older men the comparable RR was 1.05

### Table 2. Comparison of Alternative Survival Analyses Predicting Total Mortality Based on 4528 Deaths in 9431 People

<table>
<thead>
<tr>
<th>Blood Pressure, mm Hg</th>
<th>Alternative Models, RR (95% CI)*</th>
<th>Pulse Only</th>
<th>Systolic Only</th>
<th>Diastolic Only</th>
<th>Mean Arterial Only</th>
<th>Diastolic and Pulse</th>
<th>Diastolic and Systolic</th>
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*All models are adjusted for age and sex and stratified by site. RR indicates relative risk; CI, confidence interval.

### Table 3. Comparison of Alternative Survival Analyses Predicting Cardiovascular Mortality Based on 2304 Cardiovascular Deaths in 9431 People

<table>
<thead>
<tr>
<th>Blood Pressure, mm Hg</th>
<th>Alternative Models, RR (95% CI)*</th>
<th>Pulse Only</th>
<th>Systolic Only</th>
<th>Diastolic Only</th>
<th>Mean Arterial Only</th>
<th>Diastolic and Pulse</th>
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</table>

*All models are adjusted for age and sex and stratified by site. RR indicates relative risk; CI, confidence interval.
ship with cardiovascular deaths observed during the first 3 years after baseline. In separate analysis of deaths occurring after this time, pulse pressure had a strong graded relationship with cardiovascular mortality, with an RR of 1.61 (95% CI, 1.38-1.88) comparing those in the highest and lowest quartiles of pulse pressure.

These prospective data indicate that, in older people, both systolic and diastolic blood pressure provide important and independent prognostic information about the risk of cardiovascular and total mortality. As in middle-aged populations, higher systolic pressure predicted linear increases in cardiovascular and total mortality, with little evidence of confounding by other comorbid conditions and a clear increase in risk among those with borderline high (140-159 mm Hg) systolic pressure. Low diastolic pressure is also a marker of increased risk of death, independent of systolic pressure, although this association is largely explained by the confounding effects of frailty and comorbid conditions. Pulse pressure, although highly correlated with systolic pressure, has the advantage of incorporating the effects of both high systolic and low diastolic pressure. Prognostic models including pulse pressure are simpler and have nearly the same predictive ability as models including both systolic and diastolic pressure. Furthermore, in these data, pulse pressure appears to be the best single blood pressure measure to predict mortality risk in the elderly.

In healthy, middle-aged populations, pulse pressure is not a consistent and independent risk factor for cardiovascular disease. In the Framingham, Western Collaborative Group, and 4 Chicago Ill.-area prospective studies, level of systolic and/or diastolic blood pressure had stronger relationships with cardiovascular risk than pulse pressure. Results in this area are not entirely consistent, though, as some studies have found increases in cardiovascular risk associated with higher systolic pressure after controlling for level of diastolic pressure. The Multiple Risk Factor Intervention Trial found high rates of death from coronary heart disease in men with elevated systolic pressure and low diastolic pressure, but in other categories of systolic pressure, those with lower diastolic pressure had decreased death rates.

Several studies have indicated that the prognostic significance of systolic pressure increases with increasing age, while that of diastolic pressure and mean arterial pressure decreases. After age 60 years, stiffening of the large arteries leads to decreased diastolic pressure and increased pulse pressure, and this changes the relationship between low diastolic pressure and cardiovascular disease. Recent data from long-term follow-up of those aged 50 years or older in the Framingham Collaborative Group, and 4 Chicago Ill.-area prospective studies, level of systolic and/or diastolic blood pressure had stronger relationships with cardiovascular risk than pulse pressure. Results in this area are not entirely consistent, though, as some studies have found increases in cardiovascular risk associated with higher systolic pressure after controlling for level of diastolic pressure. The Multiple Risk Factor Intervention Trial found high rates of death from coronary heart disease in men with elevated systolic pressure and low diastolic pressure, but in other categories of systolic pressure, those with lower diastolic pressure had decreased death rates.

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(95% CI, 0.81-1.39). It is unclear whether these results reflect the natural variability of subgroup estimates or a true modification of the impact of blood pressure in relation to age, which is supported by several previous studies. In none of these subgroup analyses were there any significant relationships of diastolic blood pressure with cardiovascular mortality after controlling for pulse pressure and other potential confounding variables.

We also observed some variability in results of separate analyses examining cardiovascular deaths in the first 3 years of follow-up and thereafter. Neither pulse pressure nor diastolic pressure had any significant relationship with cardiovascular deaths observed during the first 3 years of follow-up and thereafter. Neither pulse pressure nor diastolic pressure had any significant relationship with cardiovascular deaths observed during the first 3 years of follow-up and thereafter. Neither pulse pressure nor diastolic pressure had any significant relationship with cardiovascular deaths observed during the first 3 years of follow-up and thereafter.
Framingham analysis had only 9 subjects and observed only 1 event in the group of persons with the highest pulse pressure (systolic pressure ≥160 mm Hg and diastolic pressure <70 mm Hg), compared with the 123 deaths among 173 persons in this high-risk group in our study.

Studies in high-risk and diseased populations also support an important prognostic role for pulse pressure. In patients with newly diagnosed hypertension and in patients with left ventricular dysfunction after myocardial infarction, elevated pulse pressure is a major risk factor for myocardial infarction and death.23,24 Pulse pressure appears to be the best measure of blood pressure to predict congestive heart failure in the elderly.26

Several plausible mechanisms may explain the association between elevated pulse pressure and cardiovascular disease. Arterial stiffness increases afterload23,44 and myocardiawork,45 impairs ventricular relaxation,46,47 and causes ischemia.48-50 It is strongly correlated with left ventricular hypertrophy,51,52 a known risk factor for cardiovascular events.53 Arterial stiffness is also correlated with the presence of atherosclerosis.54,55 The associated increase in shear stress and pulsatile strain may promote primary atheroma development56,57 and may contribute to rupture of vulnerable plaques.58

Studies in middle-aged populations have generally found higher RRs associated with elevated blood pressure, compared with the magnitude of the observed effects noted in our data.7 Factors that could explain these reduced effects include greater variability of blood pressure in older persons and greater comorbidity, which is difficult to measure precisely. Correction of risk estimates for the variability of blood pressure measures identifies a much greater impact of blood pressure on risk,9 and such corrections have a greater effect on risk estimates in older adults.12 Similarly, our predictive models for 10-year mortality in the elderly, based on baseline characteristics, have only modest performance. However, this is also the case in younger populations,79 in whom the search for additional risk factors for cardiovascular events continues. Even if RRs associated with elevated blood pressure are lower in the older population, high blood pressure remains of great public health importance because absolute risks of cardiovascular death are far greater in older adults.12

These findings have implications for treatment as well as prognosis. They provide population-based evidence for the generalizability of the efficacy of treatment for hypertension in older patients, which has been unequivocally demonstrated in randomized trials.60-65 Higher levels of both systolic and pulse pressure had strong linear relationships with cardiovascular and total mortality. Borderline elevations in systolic pressure (140-159 mm Hg) were associated with significant elevations in risk, particularly among individuals who also had low diastolic pressures. Our data also shed light on the apparent J-shaped relationship between diastolic pressure and mortality. In older adults, low diastolic pressure commonly occurs in individuals with high pulse pressure and among those with substantial comorbidity.12,66,67 Control for these variables explains the apparent elevations in risk associated with low diastolic pressure. Therapies of potential value in improving arterial compliance include angiotensin-converting enzyme inhibitors,59 nitrates,60 and a low-salt diet.61 However, evidence from randomized trials with morbidity and mortality end points is needed to determine the relative value of these therapies and whether reduction of pulse pressure should be a specific treatment target. In evaluating cardiovascular risk in older persons, both systolic and diastolic blood pressure contribute independent information, but the best single measure of blood pressure to predict mortality appears to be pulse pressure.

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