

Blood Pressure Level and Outcomes in Adults Aged 65 and Older with Prior Ischemic Stroke

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OBJECTIVES: To examine the association between blood pressure (BP) levels and long-term stroke outcomes in elderly stroke survivors.

DESIGN: Observational study.

SETTING: The Cardiovascular Health Study (CHS) of 5,888 community-dwelling adults.

PARTICIPANTS: Two hundred fifty-four adults aged 65 and older (mean age 78.6) who sustained a nonfatal first ischemic stroke.

MEASUREMENTS: BP levels assessed at prestroke and poststroke CHS visits were examined as predictors of stroke recurrence, coronary heart disease (CHD), combined vascular events (CVEs), and mortality.

RESULTS: Higher poststroke BP level, assessed 261.6 days (mean) after stroke, was associated with higher risk of stroke recurrence over 5.4 years (mean) of follow-up. The multivariate-adjusted hazard ratio for stroke recurrence was 1.42 (95% confidence interval (CI) = 1.03–1.99) per standard deviation (SD) of systolic BP ($P = .04$) and 1.39 (95% CI = 1.01–1.91) per SD of diastolic BP ($P = .04$). Mortality was significantly greater in patients with low or high poststroke BP than in those with intermediate BP. Poststroke BP was not associated with risk of CHD or CVE, although further analyses suggested that high systolic BP predicted CHD and CVE in younger but not older subjects. Prestroke BP did not predict poststroke outcomes.

CONCLUSION: In this observational study of adults aged 65 and older assessed approximately 8 months after stroke,

low BP was associated with favorable risk of recurrent stroke, although high and low poststroke BP levels were associated with greater mortality. Long-term antihypertensive trials in older stroke survivors would increase knowledge about the benefits of lowering BP in this population. *J Am Geriatr Soc* 54:1309–1316, 2006.

Key words: stroke; blood pressure; prognosis

In the U.S. population, more than 6% of individuals aged 65 to 74 and more than 11% of those aged 75 and older have a history of stroke.¹ The optimal approach to managing high blood pressure (BP) levels in older people during long-term follow-up after stroke is unclear. Randomized placebo-controlled trials support the use of antihypertensive drug therapy in patients with prior stroke or transient ischemic attack (TIA).^{2–8} In the Perindopril Protection Against Recurrent Stroke Study (PROGRESS), antihypertensive therapy that included a low-dose diuretic reduced risk of stroke recurrence and major vascular events in 6,105 patients with a history of stroke or TIA.⁸ As in most such trials of lowering BP in stroke survivors,⁷ patients studied in PROGRESS were relatively young, with mean age of 64. Thus, uncertainty remains regarding the potential risks and benefits of lowering BP levels in older adults who have had a prior stroke. In the acute phase of stroke⁹ and during the initial months of recovery,¹⁰ patients with intermediate BP levels appear to have the most favorable prognosis, whereas those with low or high BP levels have greater risk of stroke recurrence and poor outcomes. These observations have led many clinicians to exercise caution when lowering BP in elderly individuals with prior cerebrovascular events, which may explain in part why high BP is common in this population.¹¹

An analysis of BP level and outcomes was conducted during 5-year follow-up of adults aged 65 and older enrolled in the Cardiovascular Health Study (CHS) cohort who sustained an incident ischemic stroke and survived until their next study visit.

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DOI: 10.1111/j.1532-5415.2006.00838.x

METHODS

Study Population and Setting

CHS is a prospective, population-based cohort study of stroke and other cardiovascular disease (CVD) in adults aged 65 and older living in four U.S. communities.¹² The present analyses include the original cohort of 5,201 participants recruited in 1989/90 and 687 additional participants recruited in 1992/93 to enhance the racial/ethnic diversity of the cohort. Individuals from Medicare eligibility lists and other adults living in their household were invited to participate in CHS.¹²

Study Visits

CHS participants completed standardized clinical examinations and questionnaires at study baseline and at nine annual follow-up visits.¹² Medical history, behaviors, and demographic factors were assessed. Research staff who received central BP measurement training measured repeat right-arm seated BP levels annually, except at the sixth CHS visit, using standardized procedures.

Events Collection

All deaths and incident CVD events during follow-up were identified through semiannual participant contacts, notification of events by participants, and periodic searches of national administrative databases including the Medicare Utilization database and National Death Index. Medical records for all deaths, strokes, congestive heart failure (CHF), myocardial infarctions (MIs), and other CVD events were centrally reviewed and classified.^{13,14}

Inception Cohort of Ischemic Stroke Patients

For the analyses presented in this report, an inception cohort of CHS participants who sustained a first ischemic stroke between study baseline and 1999 was identified (Figure 1). It was required that subjects have had at least one CHS study visit with BP measurements completed after their stroke. Subjects were excluded if they experienced death, recurrence, or MI before completion of poststroke visits. Because the focus was on incident strokes, subjects with a history of stroke at CHS study baseline and those with strokes that were not confirmed after review, hemorrhagic strokes, and TIAs were excluded.

Definition of CVD Risk Factors

Clinical risk factors were defined according to data collected at the most recent CHS visit before the incident stroke (prestroke visits) and at the next CHS visit after stroke (poststroke visits). Hypertension was defined as physician diagnosis (treated or untreated), systolic BP (SBP) of 140 mmHg or greater, or diastolic BP (DBP) of 90 mmHg or greater. BP level was not assessed at the sixth CHS visit. Therefore, subjects whose poststroke visit was CHS visit six were excluded, and earlier visits were used to define prestroke BP levels for subjects with incident stroke between CHS visits six and seven. Prior coronary heart disease (CHD) was defined as history of MI, angina pectoris, or coronary revascularization. Diabetes mellitus was defined as fasting glucose of 7 mmol/L or greater or physician diagnosis. Functional impairment was quantified as self-re-

ported number of difficulties with activities of daily living (ADLs) and instrumental activities of daily living (IADLs); scores ranged from 0 to 6, with higher levels indicating a greater degree of impairment.

Analyses of BP and Events after Ischemic Stroke

Whether prestroke BP levels, poststroke BP levels, and change in BP levels (poststroke BP—prestroke BP) predicted subsequent events was examined. Events that were examined were recurrent strokes (ischemic or hemorrhagic); CHD events (MI or fatal CHD); CVD mortality (due to stroke, CHD, or other vascular causes); non-CVD mortality; all-cause mortality; and combined vascular events (CVEs), including CHD, recurrent stroke, and CVD mortality.

Cox proportional hazards models were used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) associated with BP variables modeled as categorical and continuous variables. Category cutpoints were 130, 150, and 160 mmHg for SBP, and 65, 75, and 85 mmHg for DBP. For continuous analyses, linear variables were defined in units of standard deviations (SDs), with SD of 24.4 for prestroke SBP, 11.7 for prestroke DBP, 23.3 for poststroke SBP, and 11.8 for poststroke DBP. HRs associated with a 9-mmHg change in SBP and a 4-mmHg change in DBP, which were the BP reductions produced by antihypertensive drug therapy in the PROGRESS trial,⁸ were also computed. To evaluate U- or J-shaped associations, the significance of quadratic terms when added to models containing linear terms for BP level was examined. Models were adjusted for age, sex, stroke subtype, race, prior CHD, hypertension, antihypertensive medications (beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, calcium channel blockers, diuretics, and others), total cholesterol, smoking, diabetes mellitus, study clinic, and year of stroke. In analyses of BP change, the means of prestroke and poststroke BP levels were also included as adjustment variables. To examine whether associations between BP and each outcome differed by age, sex, and hypertension status, stratified analyses were conducted, and interaction terms between SBP, DBP, age, sex, and hypertension status were screened to identify significant effect modification at $P \leq .01$. To assess the association between BP level and frailty, Spearman rank correlations between BP level and number of difficulties with ADLs and IADLs were computed.

RESULTS

Subject Characteristics

Of the 5,888 men and women participating in CHS, 559 had an incident ischemic stroke while under observation. Of those with incident ischemic stroke, 254 subjects who completed a poststroke visit with valid BP measurements before recurrence or MI were included in analyses (Figure 1). Poststroke visits were completed a mean of 261.6 days (75th percentile, 298 days; 90th percentile, 405 days) after the occurrence of stroke. Subjects who did not complete poststroke visits had similar BP levels as subjects who completed poststroke visits but were significantly older ($P < .01$), less likely to have diabetes mellitus ($P < .01$),

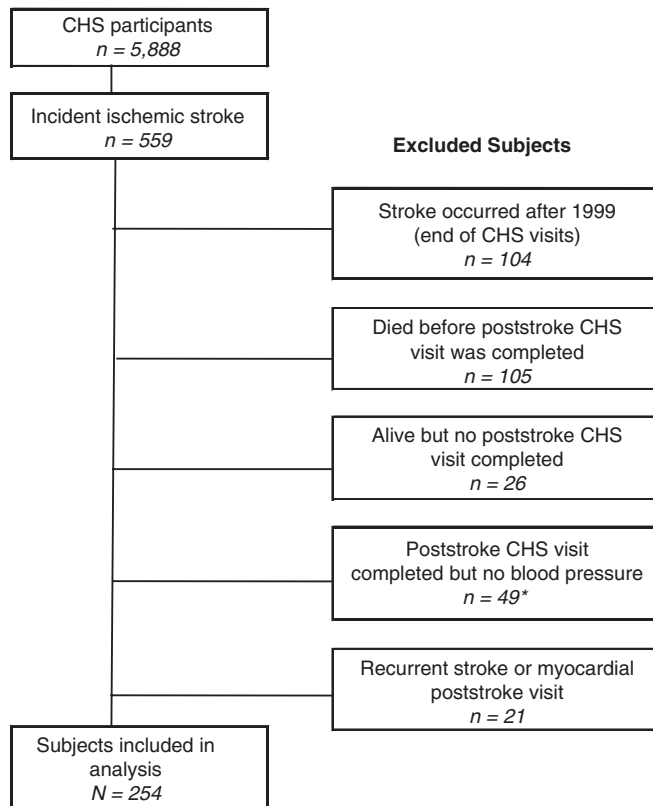


Figure 1. Identification of Cardiovascular Health Study (CHS) participants with incident ischemic stroke. *For 44 of 49 subjects, the reason for missing poststroke blood pressure (BP) measurements was because BP was not measured at CHS Visit 6.

and more likely to have unknown etiology of ischemic stroke ($P < .01$).¹¹

Among ischemic stroke subjects who were included in the analyses, mean age was 78.6 (Table 1). One hundred ninety-seven (77.6%) of the 254 stroke subjects were hospitalized for their incident stroke. Two hundred three subjects were hypertensive at the most-recent visit before stroke, 75% of whom were drug-treated, and 51 were non-hypertensive. The most commonly used antihypertensive medications were thiazide diuretics (used by 33% of hypertensives), ACE inhibitors (21%), beta-blockers (25%), and calcium channel blockers (31%). Five percent of subjects were using lipid-lowering therapy, and 35% were taking aspirin at the time of stroke. During 5.4 years (mean) of follow-up, 51 subjects had a recurrent stroke (including 37 ischemic strokes, 10 hemorrhagic strokes, and 4 indeterminate strokes), 53 had a CHD event, and 145 died (including 54 CVD deaths and 91 non-CVD deaths).

BP Levels and Recurrent Stroke

Prestroke BP level was not associated with risk of recurrent stroke, whereas higher poststroke BP level was associated with higher risk of recurrent stroke (Figure 2 and Tables 2 and 3). In multivariate analyses adjusted for age, sex, etiologic subtype of initial ischemic stroke, race, prior CHD, hypertension, antihypertensive medications, total cholesterol, smoking, diabetes mellitus, study clinic, and year, the HR for recurrent stroke was 1.42 per SD of poststroke SBP (95%

Table 1. Characteristics of 254 Subjects Aged 65 and Older with Incident Ischemic Stroke

Characteristic	Value
Lacunar stroke, %	15
Cardioembolic stroke, %	25
Large-artery/atherosclerotic stroke, %	4
Other etiologic subtype, %	56
Age, mean \pm SD	78.6 \pm 6.0
Female, %	56
Male, %	44
Prior coronary heart disease, %	43
Diabetes mellitus, %	29
Current smoking, %	9
Cholesterol, mmol/L, mean \pm SD	
Total	5.7 \pm 1.3
Low-density lipoprotein	3.5 \pm 1.0
High-density lipoprotein	1.3 \pm 0.4
Hypertension, %	80
BP, mmHg, mean \pm SD	
Prestroke	
Systolic	142.8 \pm 24.2
Diastolic	71.4 \pm 11.7
Poststroke	
Systolic	138.8 \pm 23.2
Diastolic	70.3 \pm 11.8
Change (poststroke–prestroke)	
Systolic	– 4.0 \pm 24.5
Diastolic	– 1.2 \pm 12.1
Days from prestroke visit to stroke, mean \pm SD	228.6 \pm 220.8
Days from stroke to poststroke BP levels, mean \pm SD	261.6 \pm 277.4
Follow-up, years, mean \pm SD	5.4 \pm 2.8
Events, n, incidence/1,000 person-years (95% confidence interval)	
Recurrent stroke	51, 40.8 (31.0–53.7)
Coronary heart disease	53, 41.0 (31.3–53.7)
Combined vascular events	100, 66.2 (54.4–80.5)
All-cause mortality	145, 106.7 (90.7–125.5)
CVD mortality	54, 39.7 (30.4–51.9)
Non-CVD mortality	91, 67.0 (54.5–82.2)

SD = standard deviation; BP = blood pressure; CVD = cardiovascular disease.

CI = 1.03–1.99, linear $P = .04$) and 1.39 per SD of poststroke DBP (95% CI = 1.01–1.91, linear $P = .04$). These HRs translated into a 13% relative risk reduction for a 9-mmHg decrease in SBP and an 11% relative risk reduction for a 4-mmHg decrease in DBP. Across categories of SBP and higher risk of recurrent stroke. The association between DBP level and risk of recurrent stroke suggested a possible threshold effect, with similar risk in categories 1 (<65 mmHg) and 2 (65–74 mmHg) and a gradient of increasing risk across the upper two categories (75–84 mmHg and ≥ 85 mmHg).

BP Levels and Other Vascular Events

Risk of CHD events was not associated with prestroke or poststroke BP levels. Higher poststroke SBP level tended to

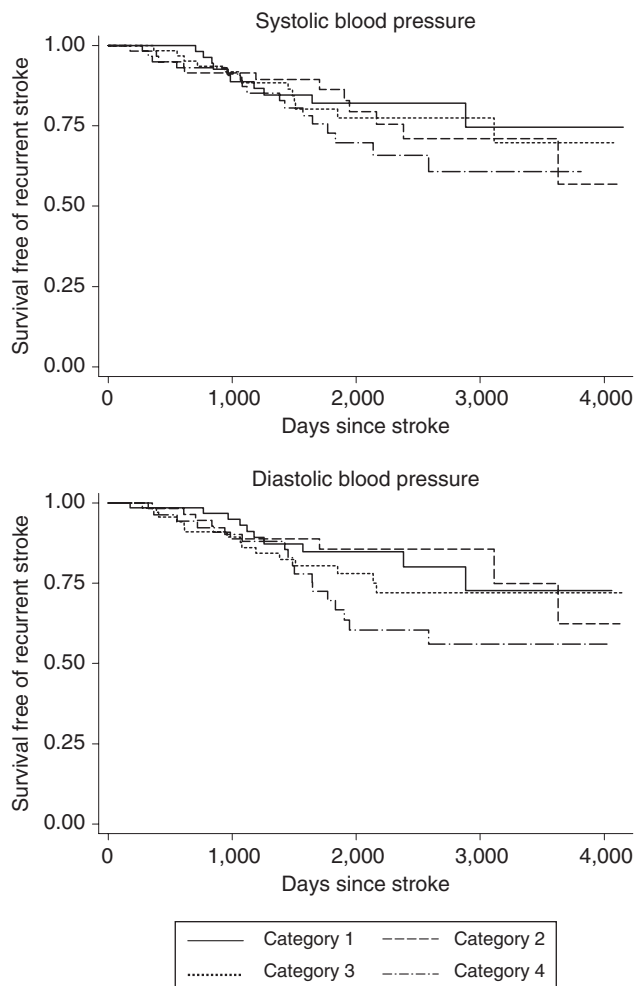


Figure 2. Survival curves for recurrent stroke, by poststroke systolic blood pressure (SBP) and diastolic blood pressure (DBP) level. Category cutpoints for SBP are 130 mmHg, 150 mmHg, and 160 mmHg. Category cutpoints for DBP are 65 mmHg, 75 mmHg, and 85 mmHg.

be associated with higher risk of CVE, but this finding did not reach statistical significance (linear $P = .12$) (Table 2).

BP Levels and Mortality

Prestroke BP level was not a risk factor for mortality after stroke. Poststroke SBP level had a reverse J-shaped association (quadratic plus linear $P < .001$) with all-cause mortality (Table 2). Greater all-cause mortality was observed in subjects in the lowest SBP category (< 130 mmHg). DBP levels had a U-shaped association (quadratic plus linear $P < .01$) with all-cause mortality (Table 3). The lowest overall mortality was observed in subjects in the second category of DBP (75–84 mmHg), and greater mortality was observed in those in the lowest (< 65 mmHg) and highest (≥ 85 mmHg) DBP categories. In analyses of cause-specific mortality, significant associations were observed between BP level and non-CVD mortality but not CVD mortality, although the number of CVD deaths was small ($n = 54$).

Changes in BP Levels After Stroke

Between the prestroke and poststroke visits, SBP decreased by an average of 4 mmHg and DBP by an average of 1 mmHg. One-quarter of subjects had SBP decreases of 17 mmHg or more, and one-quarter had DBP decreases of 9 mmHg or more. Subjects with the largest BP decreases had significantly higher prestroke BP levels ($P < .001$), but the magnitude and direction of BP changes were not associated with the presence of other vascular risk factors.

Changes in BP Levels and Outcomes

In multivariate-adjusted analyses, subjects whose SBP level decreased between the prestroke and poststroke visits tended to have lower risk of recurrent stroke than subjects whose SBP increased ($P = .07$). Compared with subjects who had SBP decreases of 17 mmHg or more after stroke, the adjusted HR was 1.26 (95% CI = 0.50–3.17) for those with SBP changes of -17 to -4 mmHg, 1.77 (95%

Table 2. Poststroke Systolic Blood Pressure (SBP) Level and Risk of Subsequent Events in Adults Aged 65 and Older with Ischemic Stroke

Event	SBP, mmHg			<i>P</i> -value [†]	
	130–149 (<i>n</i> = 89)	150–159 (<i>n</i> = 26)	≥ 160 (<i>n</i> = 44)	Linear	Quadratic
Recurrent stroke	1.23 (0.49–3.10)	1.51 (0.62–3.68)	1.86 (0.76–4.59)	.04	.10
CHD	1.17 (0.57–2.38)	1.43 (0.71–2.88)	1.22 (0.58–2.57)	.44	.57
Combined vascular events	1.22 (0.66–2.26)	1.35 (0.73–2.51)	1.27 (0.67–2.42)	.12	.11
Mortality					
All-cause	0.67 (0.40–1.09)	0.67 (0.41–1.10)	0.74 (0.45–1.21)	.91	$< .001$
CVD	1.22 (0.52–2.85)	1.31 (0.56–3.03)	1.11 (0.47–2.66)	.87	.99
Non-CVD	0.43 (0.23–0.82)	0.46 (0.25–0.87)	0.55 (0.29–1.01)	.92	$< .001$

SBP < 130 ($n = 95$) was the reference category.

* Adjusted for age, sex, stroke subtype, race, prior coronary heart disease (CHD), hypertension, antihypertensive medications, total cholesterol, smoking, diabetes mellitus, clinic, and year.

[†] *P*-values were computed based on linear term for blood pressure level or omnibus test for linear and quadratic terms entered simultaneously into model. Models in which linear term is nonsignificant but test of quadratic plus linear terms is significant suggest a nonlinear relationship.

Table 3. Poststroke Diastolic Blood Pressure (DBP) Level and Risk of Subsequent Events in Adults Aged 65 and Older with Ischemic Stroke

Event	DBP, mmHg						<i>P</i> -value [†]	
	65–74 (n = 83)		75–84 (n = 65)		≥85 (n = 26)			
	Adjusted Hazard Ratio* (95% Confidence Interval)						Linear	Quadratic
Recurrent stroke	0.91	(0.34–2.44)	1.22	(0.53–2.84)	1.75	(0.72–4.27)	.04	.03
CHD	0.75	(0.37–1.50)	1.09	(0.59–2.02)	0.80	(0.38–1.68)	.88	.94
Combined vascular events	0.93	(0.49–1.73)	1.14	(0.64–2.01)	1.18	(0.63–2.20)	.22	.03
Mortality								
All-cause	0.76	(0.46–1.23)	0.69	(0.43–1.10)	1.20	(0.72–2.01)	.30	<.01
CVD	0.62	(0.27–1.42)	0.62	(0.29–1.22)	0.66	(0.27–1.61)	.56	.35
Non-CVD	0.76	(0.41–1.42)	0.74	(0.41–1.35)	1.54	(0.81–2.91)	.10	<.01

Note: DBP < 65 (n = 80) was the reference category.

* Adjusted for age, sex, stroke subtype, race, prior coronary heart disease (CHD), hypertension, antihypertensive medications, total cholesterol, smoking, diabetes mellitus, clinic, and year.

† *P*-values were computed based on linear term for blood pressure level or omnibus test for linear and quadratic terms entered simultaneously into model. Models in which linear term is nonsignificant but test of quadratic plus linear terms is significant suggest a nonlinear relationship.

CVD = cardiovascular disease.

CI = 0.73–4.30) for those with SBP changes of –4 to +13 mmHg, and 1.81 (95% CI = 0.74–4.42) for those with SBP increases of 13 mmHg or more. Although change in DBP level after stroke was not significantly associated with stroke recurrence (*P* = .26), there was a nonsignificant trend suggesting that the lowest recurrence risk occurred in subjects in the lowest quartile of DBP change (decrease of ≥9 mmHg). There was no association between change in BP level and risk of CHD, CVE, or mortality.

Age Subgroups

Age had a significant interaction with poststroke SBP in relation to the outcomes of recurrent stroke (*P* for interaction < .001) and combined vascular events (*P* for interaction < .01) (Figure 3). For these outcomes, the interactions suggested the presence of an association between higher SBP and greater risk in younger subjects but a weakening of this relationship with advancing age. A similar pattern of results was seen for coronary events, with the *P*-value for interaction indicating borderline statistical significance (*P* = .06). For mortality, a significant (*P* = .01) interaction between age and poststroke SBP was also found. In older subjects, there was a more-pronounced reverse J shape to the association between SBP and mortality (greater mortality in lowest category). In contrast to the results for SBP, associations with poststroke DBP did not differ by age for any outcome. Thus, higher DBP predicted higher risk of stroke recurrence in younger and older members of the study population.

Sex Subgroups

No interactions between BP and sex were significant at the prespecified *P* ≤ .01 level. For analyses of mortality, the *P* for interaction with sex was .03 for DBP and SBP. There tended to be a U-shaped association between BP and mortality in women (greater mortality in lowest and highest categories),

whereas results in men tended to have a reverse J shape (greater mortality in lowest category).

Hypertensive and Nonhypertensive Subgroups

No interactions between hypertension and BP levels were statistically significant. For analyses of poststroke DBP and recurrent stroke, the HR per SD was 1.56 in nonhypertensive subjects and 1.37 in hypertensive subjects. For poststroke SBP and recurrence, a HR per SD of 1.42 was observed in both hypertensive and nonhypertensive subgroup. The small number of events in nonhypertensive subjects (9 recurrent strokes, 15 coronary events, and 34 deaths in 51 subjects) limited the ability to assess interactions between BP level and hypertension.

BP Levels and Functional Limitation

Lower poststroke DBP levels tended to be associated with worse functional status after stroke. The mean number of difficulties with ADLs was 1.5 in the lowest DBP category (<65 mmHg), 1.1 in the middle two DBP categories, and 0.8 in the highest DBP category (≥85 mmHg). Analyses of IADLs also suggested a higher number of functional limitations in subjects in the lowest DBP category (2.0) than in those in the upper three categories (1.4). These associations between low DBP level and greater functional limitation were of borderline statistical significance (*P* = .07–.08). The associations between DBP and mortality were unchanged after further adjustment of models for ADLs and IADLs. Subjects with high and low poststroke DBP tended to have greater prevalence of CHF (DBP Category 1, 25%; Category 2, 14%; Category 3, 19%; Category 4, 23%; not significant according to chi-square test). No evidence was found for associations between SBP and functional limitation or prevalent CHF.

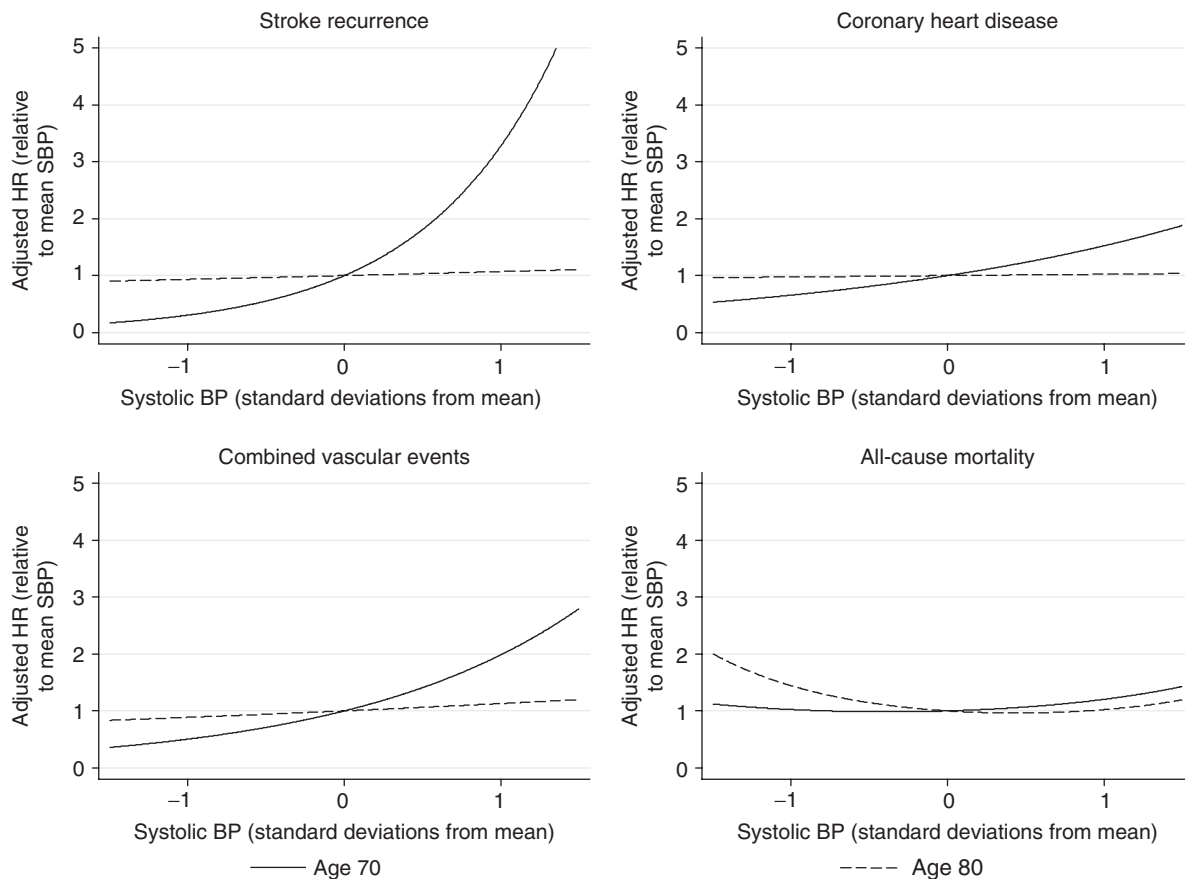


Figure 3. Poststroke systolic blood pressure (SBP) level and outcomes for older adults with ischemic stroke: interaction with age. Associations between poststroke SBP level and outcomes for subgroups defined by age were derived using interaction terms between age and SBP in multivariate Cox proportional hazards models. Age and SBP were parameterized as linear predictor variables, except for mortality, which had a nonlinear relationship with SBP. (For mortality, SBP was parameterized using linear-plus-quadratic terms.) The figures describe the association between SBP level and outcomes at two representative levels of age: 70 and 80. The mean SBP level serves as the reference group. Hazard ratios (HRs) are indicated for SBP levels ranging from 1.5 standard deviations (SDs) below the mean to 1.5 SDs above the mean. SD = 23.3 for poststroke SBP. *P* for interaction between SBP and age <.001 for recurrent stroke; .06 for coronary events; <.01 for combined vascular events; and .01 for all-cause mortality. In contrast to results for SBP, no significant interaction was detected between age and poststroke diastolic blood pressure (DBP) for any outcome. Thus, the relationships between DBP and outcomes described in Table 3 did not vary significantly between age groups.

DISCUSSION

In this observational study of older adults (mean age 78.6) with incident ischemic stroke, subjects with the highest BP levels, measured approximately 8 months after stroke, had the highest risk of stroke recurrence during 5-year follow-up. It was also found that patients who had decreases in SBP between prestroke and poststroke visits tended to have lower risk of recurrence than those with increases. Poststroke BP levels were not associated with risk of CHD or CVE, although further analyses suggested that high SBP predicted CHD and CVE in younger but not older subjects. Paradoxically, greater mortality was observed in subjects at the low and high ends of the spectrum of poststroke SBP and DBP levels.

Adults aged 70 and older have not been well represented in prior clinical trials of antihypertensive therapy in stroke survivors, and in all major trials, the average age of participants has been younger than 70.^{2–8} In the PROGRESS trial, active antihypertensive treatment reduced SBP level by 9 mmHg and DBP level by 4 mmHg and produced a 28%

relative risk reduction in stroke recurrence.⁸ This is consistent with a recent metaanalysis estimate that, in patients with prior stroke, BP-lowering therapy significantly lowers risk of recurrent stroke by 24% (95% CI = 8–37% relative risk reduction compared with placebo).⁷ The current study confirmed that high poststroke BP is a risk factor for recurrent stroke in an elderly stroke survivor population with mean age near 80. Evidence was found of interaction between SBP and age, such that elevated SBP had a stronger association with recurrence risk in younger members of the study population, although the relationship between DBP levels and recurrence was similar regardless of age. Based on the findings from this observational cohort study, it was estimated that a 9-mmHg decrease in SBP would produce a 13% relative risk reduction in stroke recurrence and a 4-mmHg decrease in DBP would produce an 11% relative risk reduction in stroke recurrence. These projected risk reductions are substantially lower than the actual risk reductions associated with similar BP decrements in PROGRESS and other antihypertensive treatment trials.^{2–8} Thus, these

data raise questions about whether the expected magnitude of benefit associated with BP lowering may differ in elderly stroke survivors and in younger populations. It is also possible that the specific types of antihypertensive medications used may have accounted for this discrepancy. In PROGRESS, the combination of a low-dose diuretic (indapamide) and perindopril was associated with significant benefit, but perindopril alone was not.⁸ In the current study, 33% of hypertensive patients were receiving low-dose diuretics, and 21% were receiving ACE inhibitors.

This study showed that subjects with low and high BP levels measured at poststroke visits had greater mortality than those with intermediate BP levels. Mortality was relatively high in subjects with poststroke BP levels below 130 mmHg SBP and below 75 mmHg DBP. Therefore, the results suggest that elderly stroke survivors with low BP may have less risk of stroke recurrence but greater risk of death over long-term follow-up. Further analyses suggested that an excess in non-CVD mortality rather than CVD mortality may have explained this; small numbers of events limited statistical power for these subgroup analyses. The data suggested that low DBP level was associated with functional limitations and CHF. This may in part account for the greater mortality in subjects with low BP. Adjustment for these variables did not eliminate the association between low BP and mortality. In previous clinical trials, antihypertensive therapy in stroke survivors tended to reduce vascular mortality, although wide confidence intervals the aggregate results characterized, which did not reach statistical significance.⁷ However, elderly subjects who are frail and have serious systemic illness are likely to be excluded from clinical trials.

Prior clinical trials suggest that antihypertensive therapy significantly reduces CHD events by 21% (95% CI = 2–37% relative risk reduction) in stroke survivors.⁷ It was not found that high BP levels predicted greater risk of CHD after stroke in this cohort of adults aged 65 and older, but further analyses suggested that higher SBP level tended to predict greater risk of CHD in younger study subjects. The lack of a strong and consistent association between high BP and coronary events is notable, because during long-term follow-up in this population, incident CHD events were nearly as common as recurrent strokes.¹¹ In contrast to these results in older stroke survivors, prior analyses have found that high SBP and DBP predicted risk of incident MI in CHS subjects without a prior history of vascular events.¹⁵ Thus, the high prevalence of vascular disease may have explained the lack of association between BP and CHD in this poststroke population. Alternatively, the data did not indicate the “J-curve” phenomenon of higher coronary risk at low levels of BP. This has particularly been shown for DBP¹⁶ and may reflect reduced epicardial perfusion at low DBP.

BP level measured before stroke did not predict long-term stroke outcomes. The analyses presented here were limited to CHS subjects with stroke who had poststroke BP levels available, although the results are consistent with previous analyses conducted in all CHS stroke patients (who were included regardless of availability of follow-up BPs), which suggested that prestroke BP levels or preexisting hypertension were unassociated or only weakly associated with case fatality¹⁴ and with long-term mortality, recurrence, or CHD events.¹¹

The observational design of this study limits the ability to draw definitive conclusions about the relationship between BP levels and outcomes in elderly stroke survivors. Other, unmeasured patient characteristics that were associated with high or low BP levels and prognosis may explain the findings. It was not possible to determine whether antihypertensive medications, stroke, or other comorbidities induced changes in BP level after stroke. Only information in available medical records was used when reviewing events, and as a result, information on diagnostic evaluation for stroke may have been incomplete. Lowering of BP may harm patients with severe bilateral large-artery stenoses.¹⁷ Standardized assessments of carotid artery stenosis were obtained in CHS, but there were too few subjects with severe stenoses to permit valid analyses in the present investigation (at baseline, ~2% had >75% carotid stenosis).¹⁸ Similarly, because of inadequate sample size, this study was unable to assess the importance of BP level in etiological subtypes of ischemic stroke.

The population was limited to ischemic stroke patients from a volunteer population (the CHS) who were alive and healthy enough to complete study visits approximately 8 months after their stroke. The results of this study may only be generalized to similar patient populations assessed at a comparable point in time after their stroke. The exclusion of stroke patients who died, had recurrence or MI before poststroke visits, or were too ill to participate is a limitation of the study. Alternatively, because all subjects completed CHS study visits before and after stroke, this presented an opportunity to examine prestroke BP, poststroke BP, and BP change in relation to stroke prognosis. The design of the CHS study also offered other strengths, including a geographically diverse sample, standardized BP measurements, and examination of several outcomes, including stroke, CHD, CVD mortality, and non-CVD mortality over long-term follow-up. These data captured BP levels during long-term follow-up after stroke, and the relationship between BP and outcomes may differ in the acute setting. In the acute phase of stroke, current recommendations advise against the use of antihypertensive therapy unless BP levels rise above SBP 220 mmHg or DBP 120 mmHg.¹⁹

In conclusion, in this study of stroke patients with mean age of 78.6 assessed approximately 8 months after stroke, higher BP levels were associated with higher recurrent stroke risk over long-term follow-up. High (≥ 85 mmHg DBP) and low (< 130 mmHg SBP or < 65 mmHg DBP) BP levels were associated with higher mortality. Overall, BP levels were not associated with other types of vascular events, although analyses of age-by-BP interactions suggested that high SBP predicted greater risk of CHD and CVE in younger members of the population. When considered in combination with the available clinical trial evidence, the data support normalizing high BP in elderly patients with prior stroke, although the finding of higher mortality in patients at low BP levels raises questions about whether aggressive BP lowering is appropriate in elderly patients who have survived an ischemic stroke. Long-term clinical trials of antihypertensive therapy in this population would help to fill a major gap in the knowledge about the net risks and benefits of lowering BP in older stroke survivors.

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A full list of participating CHS investigators and institutions can be found at <http://www.chs-nhlbi.org>.

ACKNOWLEDGMENTS

Financial Disclosure: The research reported in this article was supported by Contracts N01-HC-85079 through N01-HC-85086, N01-HC-35129, and N01 HC-15103 and Grant R01 HL43201 from the National Heart, Lung, and Blood Institute and Grant 5R01AG009556-08 from the National Institute on Aging.

Author Contributions: Dr. Kaplan had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors contributed to collection, analysis, and interpretation of data, and all meet criteria for authorship.

Sponsor's Role: None.

REFERENCES

- Heart Disease, Stroke Statistics—2005 Update. Dallas, TX: American Heart Association, 2005
- Sleight P, Yusuf S, Pogue J et al. Blood-pressure reduction and cardiovascular risk in HOPE study. *Lancet* 2001;358:2130–2131.
- Eriksson S, Olofsson BO, Wester PO. Atenolol in secondary prevention after stroke. *Cerebrovasc Dis* 1995;5:21–25.
- Carter AB. Hypotensive therapy in stroke survivors. *Lancet* 1970;1:485–489.
- Post-stroke antihypertensive treatment study. A preliminary result. PATS Collaborating Group. *Chin Med J (Engl)* 1995;108:710–717.
- Trial of secondary prevention with atenolol after transient ischemic attack or nondisabling ischemic stroke. The Dutch TIA Trial Study Group. *Stroke* 1993;24:543–548.
- Rashid P, Leonardi-Bee J, Bath P. Blood pressure reduction and secondary prevention of stroke and other vascular events: A systematic review. *Stroke* 2003;34:2741–2748.
- Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. *Lancet* 2001;358:1033–1041.
- Oliveira-Filho J, Silva SC, Trabuco C et al. Detrimental effect of blood pressure reduction in the first 24 hours of acute stroke onset. *Neurology* 2003;61:1047–1051.
- Irie K, Yamaguchi T, Minematsu K et al. The J-curve phenomenon in stroke recurrence. *Stroke* 1993;24:1844–1849.
- Kaplan RC, Tirschwell DL, Longstreth WT et al. Vascular events, mortality, and preventive therapy following ischemic stroke in the elderly. *Neurology* 2005;65:835–842.
- Fried LP, Borhani NO, Enright P et al. The Cardiovascular Health Study: Design and rationale. *Ann Epidemiol* 1991;1:263–276.
- Ives DG, Fitzpatrick AL, Bild DE et al. Surveillance and ascertainment of cardiovascular events. The Cardiovascular Health Study. *Ann Epidemiol* 1995;5:278–285.
- Longstreth WT Jr, Bernick C, Fitzpatrick A et al. Frequency and predictors of stroke death in 5,888 participants in the Cardiovascular Health Study. *Neurology* 2001;56:368–375.
- Psaty BM, Furberg CD, Kuller LH et al. Association between blood pressure level and the risk of myocardial infarction, stroke, and total mortality: The Cardiovascular Health Study. *Arch Intern Med* 2001;161:1183–1192.
- Somes GW, Pahor M, Shorr RI et al. The role of diastolic blood pressure when treating isolated systolic hypertension. *Arch Intern Med* 1999;159:2004–2009.
- Rothwell PM, Howard SC, Spence JD. Relationship between blood pressure and stroke risk in patients with symptomatic carotid occlusive disease. *Stroke* 2003;34:2583–2590.
- Johnston SC, O'Meara ES, Manolio TA et al. Cognitive impairment and decline are associated with carotid artery disease in patients without clinically evident cerebrovascular disease. *Ann Intern Med* 2004;140:237–247.
- Adams HP Jr, Adams RJ, Brott T et al. Guidelines for the early management of patients with ischemic stroke: A scientific statement from the Stroke Council of the American Stroke Association. *Stroke* 2003;34:1056–1083.