Control of Hypertension and Risk of Stroke Recurrence

Gary Friday, MD, MPH; Milton Alter, MD, PhD; Sue-Min Lai, PhD, MS

Background and Purpose—We investigated whether low blood pressure increases the risk of stroke recurrence.

Methods—A cohort of 662 patients, obtaining care at the 8 acute care hospitals serving the Lehigh Valley in Pennsylvania, was enrolled within 1 month of an initial stroke and was followed twice annually for up to 4 years. Cox proportional hazard models were developed to examine the relationship between risk of recurrent stroke and blood pressure, controlling for other significant risk factors. Our analyses investigated both lowest follow-up and average follow-up blood pressures as predictors of stroke recurrence.

Results—There were 52 recurrent strokes among the 535 patients (mean age, 71 years; 51% men) with follow-up blood pressure. The risk ratio for stroke recurrence for diastolic blood pressure ≥80 mm Hg compared with <80 mm Hg was 2.4 (95% CI, 1.38 to 4.27) and for systolic blood pressure ≥140 mm Hg compared with <140 mm Hg was also 2.4 (95% CI, 1.39 to 4.15). For isolated systolic blood pressure (>140/<90 mm Hg), the risk ratio was 2.2 (95% CI, 1.23 to 3.79) relative to <140/<90 mm Hg. Using the Cox model, we also showed that patients who had at least 1 measured diastolic blood pressure <80 mm Hg during follow-up had a reduced risk of stroke recurrence compared with those with diastolic blood pressures 80 to 90 mm Hg (0.4 versus 1.0; 95% CI, 0.21 to 0.88) even after controlling for the possible confounding factors of hypertension and atrial fibrillation on ECG. Myocardial infarction on ECG, history of transient ischemic attack, and diabetes mellitus were not significant predictors of increased risk of recurrent stroke.

Conclusions—Our results imply that “lower is better” for blood pressure control as a goal in reducing stroke recurrence risk. (Stroke. 2002;33:2652-2657.)

Key Words: epidemiology ■ hypertension ■ recurrence

It is accepted by a broad consensus that a blood pressure (BP) in an adult ≤140 mm Hg systolic (SBP) and 90 mm Hg diastolic (DBP) is “normal” if not necessarily optimal. It is also accepted that consistent BPs above these levels constitute hypertension1 and are detrimental to the vascular system. Hypertension results in hyalin degeneration of smaller cerebral vessels2 and is associated with atherosclerosis in larger cerebral vessels.3 Hypertension also results in an increased frequency of ischemic and hemorrhagic stroke.4

A large body of evidence exists based on case series,5 population studies,6,7 and clinical trials8 demonstrating that control of hypertension reduces risk of initial stroke. It has also been demonstrated that treatment of isolated systolic hypertension in the elderly will reduce risk of stroke.9 Control of BP for reduction of risk of stroke recurrence has not been demonstrated consistently.10–12 Although lowering BP in hypertension appears to be beneficial in reducing stroke risk, the optimal level of reduction has also not been well studied. Perfusion of the brain is normally maintained within a wide range of SBP and DBP. Lowering BP, especially in older individuals who may well have vascular narrowing and less resilient vessels, may reduce perfusion of the brain, resulting in syncope or even stroke. It is well accepted that chronic hypertension impairs cerebrovascular autoregulation13 and, together with the pathological narrowing of cerebral vessels in individuals with chronic hypertension, provides a plausible basis for inquiring whether maintenance of BP below an optimal level may be detrimental. It has been postulated that a J-shaped relationship may exist between BP and stroke risk, with control below an “optimal” level resulting in increased stroke frequency14 and cardiac ischemia.15

An opportunity to study the relationship between level of BP over time and risk of stroke recurrence was afforded by the Lehigh Valley Stroke Study.16 This study included a population-based cohort of patients who had experienced an initial stroke and whose BP was followed prospectively and measured at regular intervals for up to 4 years.

Subjects and Methods

Patients in this study were enrolled from the Lehigh Valley, a region in northeastern Pennsylvania approximately 90 miles from Philadelphia and a similar distance from New York City. The quality of medical care in this region is very good, and therefore the inhabitants tend first to seek medical care locally. Approximately 600 000 individuals live in this region. Income and educational levels are above the mean for the United States as a whole, and the ethnic composition is 95% white, 3.3% Hispanic, and 1.7% black.

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From Thomas Jefferson Medical College, Philadelphia, Pa (G.F., M.A.); Medical College of Pennsylvania/Hahnemann University, Philadelphia, Pa (M.A.); and University of Kansas Medical Center, Kansas City, Kan (S-M.L.).

Reprint requests to Gary Friday, MD, MPH, 130 S Bryn Mawr Ave, H-Wing, 3rd Floor, Bryn Mawr, PA 19010. E-mail FridayG@mlhs.org

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All patients admitted to 1 of the 8 acute care hospitals in this region with a diagnosis of acute stroke were identified by monitoring hospital admission records. With their physician’s permission and after they signed an informed consent, they were interviewed, their medical records were reviewed, and they were examined to verify that they had an acute stroke. If they reported a prior stroke, had evidence of a stroke on examination, or their CT/MRI study showed a prior stroke, they were not enrolled in the present study. Approximately 4000 patients were screened, and 684 patients with an acute ischemic or hemorrhagic stroke were enrolled. The reasons for exclusion of the first 200 patients have been reported previously. In all patients enrolled, the stroke had occurred in the previous month; in 93%, the interval from onset was 2 weeks. Stroke type was diagnosed according to criteria that we have previously described and was a modification of the Stroke Data Bank criteria.

Of the 684 enrolled, 22 (3.2%) died from their initial stroke before discharge, and 127 (18.6%) were lost before the first scheduled follow-up visit that was at 4 months. Of those 127, 49 died, 35 withdrew consent for follow-up, 14 moved out of the study area, and 29 had a recurrent stroke that was a study end point precluding follow-up. The remaining 535 were followed first at 4 months after stroke onset and then every 6 months.

Trained study nurses obtained demographic data on the patients and information on 5 stroke risk factors: history of hypertension, diabetes mellitus, myocardial infarction, cardiac arrhythmia, and transient ischemic attacks (TIAs). The study nurses measured BP in a standardized way 3 times within 5 minutes, discarding the first reading and averaging the second and third readings. On each follow-up evaluation, they obtained an interim medical history emphasizing stroke symptoms and signs, performed a brief neurological examination, obtained an ECG, and again measured BP in a standardized way. If any history or signs of a recurrent stroke were found, the patient was examined by a study neurologist to determine whether a recurrent stroke had occurred. Medical records were reviewed if the patient had been hospitalized. If the patient died, the death certificate was obtained, the family and the patient’s physician were interviewed, and hospital records, if any, were reviewed.

Analysis

Investigators measured BP at enrollment and followed patients to determine whether those with elevated pressure initially had a different frequency of stroke recurrence than those with a “normal” baseline pressure. However, the stroke itself or hospitalization for the stroke may produce a reactive hypertension that does not accurately reflect the usual BP status of the patient. Nonetheless, measured BP at enrollment was used in the present study to determine the “hypertensive” group as 1 method of analysis. Most patients had been in the hospital at least several days, which allowed us to assume that the BP measured no longer reflected the reaction to the stroke itself or to the effects of admission to the hospital. Alternatively, one may rely on medical history and accept those already diagnosed as hypertensive before the stroke as representing the hypertensive group. We also did this in the present study.

However, using only history of hypertension and initial measurement of BP at enrollment would not take full advantage of a unique feature of the present study, ie, we were able to identify newly diagnosed hypertensive patients because we also followed patients at regular intervals. The measurements during follow-up visits reflected whether level of “control” of BP over time is associated with risk of stroke recurrence. The length of time that patients are followed must be sufficient to allow enough recurrent strokes to accrue to detect a statistically significant difference in relation to BP, or the cohort must be very large, because the recurrence rate often cited is only approximately 10% to 15% in 2 years. We evaluated patients twice annually over an average of 2 years and up to 4 years, whereas in the Framingham Study patients were reevaluated every 2 years to determine whether an effect exists between level of BP and risk of stroke. Thus, we were able to measure the level of BP control with more precision.

We “captured” the characteristic of variability by noting the standard deviation of BP measurement in each patient over time and analyzed stroke recurrence rates in those with smaller and larger standard deviations in BP (ie, less and more variability).

We chose somewhat arbitrary cutoff categories in the range of BP measurement and analyzed frequency of stroke recurrence in patients within each category. For diastolic pressures, the groups that we selected had mean follow-up values <60, 60 to 69, 70 to 79, 80 to 89, and ≥90 mm Hg; for systolic pressures, the groups analyzed had BPs <130, 130 to 139, 140 to 149, 150 to 159, and ≥160 mm Hg. To increase sample size, we analyzed the data after collapsing the middle categories and compared frequency of stroke recurrence in the lowest and highest categories. We also analyzed frequency of stroke recurrence in patients with isolated systolic hypertension, defined as SBP ≥140 mm Hg while DBP was <90 mm Hg. We also evaluated the lowest recorded BP during follow-up as a measure of level of BP control.

Patients who remain in follow-up longer have an increased chance of having a stroke recurrence. Because of this, a time-dependent Cox proportional hazards model was used to analyze stroke recurrence over time. The model incorporated possible confounding factors such as baseline BP, initial stroke type, demographic characteristics (age and sex), and medical risk factors (myocardial infarction, cardiac arrhythmia, diabetes mellitus, and TIA). We also examined goodness of fit with a linear and quadratic (J-shaped) model of BP on the one hand and stroke recurrence rate over time on the other hand.

Results

Among the 662 patients in this study discharged alive, those with a history of hypertension at enrollment (373; 56%) had a higher rate of stroke recurrence than patients without such a history (14.7% versus 9.7%; P = 0.01), confirming the accepted belief that there is an increase in risk of stroke recurrence in hypertensive patients. In the subset of 535 patients with at least 1 follow-up visit, those with a history of hypertension at enrollment also had an increased crude rate of stroke recurrence. The crude rate of stroke recurrence among the 535 was twice as high in the hypertensive group (12% versus 6%; P = 0.02) over a mean follow-up of 2 years (Table). All patients with a history of hypertension were being treated with antihypertensive medication at some point during follow-up.

In another analysis, patients whose baseline DBP at enrollment was in the hypertensive range (ie, >90 mm Hg) also showed an increased crude rate of stroke recurrence, with a similar trend for SBP (≥140 mm Hg) (Table).

To explore a possible J-shaped effect between BP and risk ratio (RR) for recurrent stroke, we analyzed patients whose mean BP during all follow-up visits was <60, 60 to 69, 70 to 79, 80 to 89, and ≥90 mm Hg. When we used those patients with DBP <60 mm Hg as the control group, the patients in the next 2 lowest categories of DBP (60 to 69 and 70 to 79 mm Hg) had a similar level of risk for stroke recurrence (RR = 2.8 and 2.8, respectively). and those patients in the highest levels of DBP had a similar level of risk for stroke recurrence (RR = 6.2 and 6.7, respectively) (Figure 1A). In view of the wide CIs for these subsets, the RR for stroke recurrence was recalculated for DBP ≥80 mm Hg (n = 101) compared with <80 mm Hg (n = 434) and found to be 2.4 (95% CI, 1.38 to 4.27; P = 0.00021). A similar analysis, in which we used mean SBP over the follow-up period among patients whose mean SBP was <130, 130 to 139, 140 to 149, 150 to 159, or ≥160 mm Hg, showed that patients with mean SBP ≥140 mm Hg had higher risk for stroke recurrence than
patients with SBP <140 mm Hg. When we used those patients with SBP <130 mm Hg as a control group, the RR for the group at the next highest BP level was essentially unchanged (RR=1.1; 95% CI, 0.48 to 2.52); however, the risk in the other successive BP groups was increased (RR=2.4, 2.6, and 2.5, respectively; Figure 1B). Because the RRs for the 2 lower groups and the 3 higher groups of BP were similar, those groups were collapsed, and the RR for stroke recurrence was recalculated for SBP <140 mm Hg (n=346) compared with ≥ 140 mm Hg (n=189) and found to be 2.4 (95% CI, 1.39 to 4.15; P=0.0017). As with SBP, patients with isolated elevated SBP (SBP ≥ 140 mm Hg and DBP <90 mm Hg; n=176) also showed increased risk of recurrent stroke compared with normotensive patients (SBP <140 mm Hg and DBP <90 mm Hg; n=344), with a RR of 2.3 (95% CI, 1.32 to 4.05; P=0.0035), suggesting that control of isolated SBP, which is more commonly found in the elderly, is beneficial.

Using the univariate time-dependent Cox proportional hazards model, we showed that history of hypertension and DBP <90 mm Hg were associated with increased risk of recurrent stroke (Table I). The RR for DBP <90 mm Hg was increased in the univariate model (RR=1.73; 95% CI, 0.78 to 3.84; P=0.010), which is consistent with previous studies reporting a gradient association between continuous blood pressure and risk of recurrent stroke.

### Table I

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. (%)</th>
<th>Recurrent Stroke, No. (%)</th>
<th>P*</th>
<th>RR Estimate</th>
<th>95% CI</th>
<th>P†</th>
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<td>&lt;80</td>
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<td>80–89</td>
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<td>≥90</td>
<td>42 (8)</td>
<td>9 (21)</td>
<td>&lt;0.001</td>
<td>1.73</td>
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<td>&lt;140</td>
<td>317 (59)</td>
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<td>≥140</td>
<td>218 (41)</td>
<td>28 (13)</td>
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<td>1.69</td>
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<td>Athero-occlusive‡</td>
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<td>Embolic</td>
<td>121 (23)</td>
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<td>Lacunar</td>
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<td>Nonspecific infarct</td>
<td>259 (48)</td>
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<td>&lt;65</td>
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<td>65–74</td>
<td>190 (36)</td>
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<td>75–84</td>
<td>169 (32)</td>
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<td>1.47</td>
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<td>≥85</td>
<td>51 (10)</td>
<td>6 (12)</td>
<td>0.76</td>
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<td>2.15</td>
<td>1.15–4.03</td>
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<td>Yes</td>
<td>148 (28)</td>
<td>17 (11)</td>
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<td>1.39</td>
<td>0.78–2.49</td>
<td>0.272</td>
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<td>Yes</td>
<td>89 (17)</td>
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<td>0.08</td>
<td>0.36</td>
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<td>30 (12)</td>
<td>0.11</td>
<td>1.78</td>
<td>1.03–3.09</td>
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<td>1.00</td>
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<td>125 (23)</td>
<td>10 (8)</td>
<td>0.61</td>
<td>0.85</td>
<td>0.43–1.69</td>
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</table>

*χ² test of association of recurrent stroke risk and characteristic. This analysis does not take into account period of follow-up.
†Significance of single predictor Cox proportional hazards model likelihood ratio test.
‡“Thrombotic” used in prior publications from Lehigh Valley cohort for this stroke type.
atrial fibrillation (among the various arrhythmias that were present) were associated with an increased rate of stroke recurrence. History of TIA before the initial stroke was associated with a decreased stroke recurrence rate. History of TIA before the initial stroke was associated with an increased rate of stroke recurrence.

For both DBP and SBP, we found a consistent increase in risk as the BP level increased, and therefore no J-curved relationship could be inferred. Inserting a quadratic term (ie, the square of the measured BP) in the time-dependent Cox proportional hazards model allowed us to test for a J-shaped relationship between BP and stroke recurrence even more precisely. As already mentioned, a J-shaped relationship would imply that stroke recurrence increased at the extremes of BP and that optimal reduction of stroke recurrence existed in the mid-range of BP control. The square of the lowest follow-up DBP as a continuous predictor variable was not a better predictor of stroke recurrence than a linear model in which the lowest DBP itself was used. Similar results were obtained with the use of the square of the lowest SBP in the analytic model. These results indicate that a J-shaped relationship between BP and stroke recurrence was not supported by our data. In other words, patients in the lowest BP category did not have a demonstrably greater risk of stroke recurrence than those with intermediate levels of BP control.

Variability of BP over time, as reflected by the standard deviation of the BP measurements for each patient, showed that patients with larger variability of DBP over time had higher risk for stroke recurrence compared with those with BPs 80 to 90 mm Hg (95% CI, 0.48 to 2.52, 1.13 to 5.26, 1.13 to 5.92, 0.95 to 6.58; P=0.81, 0.023, 0.023, 0.063, respectively). B, Univariate analysis of relationship between mean SBP and risk for stroke recurrence. SBP <130 mm Hg was set as reference and compared with SBP 130 to 139, 140 to 149, 150 to 159, and ≥160 mm Hg (95% CI, 0.37 to 21.46, 0.36 to 20.01, 0.83 to 46.96, 0.69 to 63.87; P=0.32, 0.33, 0.07, 0.10, respectively). B, Univariate analysis of relationship between mean SBP and risk for stroke recurrence. SBP <130 mm Hg was set as reference and compared with SBP 130 to 139, 140 to 149, 150 to 159, and ≥160 mm Hg (95% CI, 0.48 to 2.52, 1.13 to 5.26, 1.13 to 5.92, 0.95 to 6.58; P=0.81, 0.023, 0.023, 0.063, respectively).

A, Univariate analysis of relationship between mean DBP and risk of stroke recurrence. DBP <60 mm Hg was set as reference and compared with DBP 60 to 69, 70 to 79, 80 to 89, and ≥90 mm Hg (95% CI, 0.37 to 21.46, 0.36 to 20.01, 0.83 to 46.96, 0.69 to 63.87; P=0.32, 0.33, 0.07, 0.10, respectively). B, Univariate analysis of relationship between mean SBP and risk for stroke recurrence. SBP <130 mm Hg was set as reference and compared with SBP 130 to 139, 140 to 149, 150 to 159, and ≥160 mm Hg (95% CI, 0.48 to 2.52, 1.13 to 5.26, 1.13 to 5.92, 0.95 to 6.58; P=0.81, 0.023, 0.023, 0.063, respectively).

Discussion

It was previously reported from the Lehigh Valley that risk of recurrent stroke was reduced when DBP was controlled at <95 mm Hg.10 That study took into account variables such as age, sex, and comorbidities. Since publication of this earlier report, the recommended optimal level of BP reduction to achieve good control has been lowered to <120/80 mm Hg.1 However, Irie et al19 found that the risk of recurrent stroke actually increased below a diastolic level of 80 mm Hg. Vokó et al,14 in a study from Rotterdam, also found increased risk of stroke in elderly hypertensives with DBP <60 mm Hg. In the earlier study from the Lehigh Valley, whether BP in the lower end of the “controlled” range reduced stroke recurrence differently from BP near the higher end of this range was not investigated. Therefore, in the present analysis, we explored the effect of BP “control” over a wider range.

In the present study, having a DBP <80 mm Hg was a strong predictor of a decreased risk of recurrent stroke. This result was still present even at a level of DBP <60 mm Hg.

Our results are consistent with the meta-analysis of anti-hypertensive medication intervention trials by Gueyffier et al,12 who found that BP-lowering drug interventions reduced the risk of stroke recurrence. In contrast, Meissner et al,11 after taking age into account, did not find that treated hypertensives had fewer stroke recurrences than untreated hypertensives. In medication intervention clinical trials in which patients are randomized, confounding risk factors are usually balanced between treatment groups. However, because the inclusion and exclusion criteria applied in clinical trials may exclude many potential patients, the ability to generalize the results of clinical trials to the overall population could be limited. Therefore, population studies such as...
the one performed in the Lehigh Valley are useful in confirming the results of clinical trials.

Neither Meissner et al\(^1\) nor Gueyffier et al\(^2\) evaluated level of BP control in assessing risk of stroke recurrence.\(^1,2\) Therefore, our results are more appropriately compared with those of Rodgers et al.\(^20\) PROGRESS (Perindopril Protection Against Recurrent Stroke Study).\(^21\) and Irie et al.\(^19\) Rodgers et al\(^20\) used the data from the United Kingdom TIA aspirin trial. They reported a decreased risk of recurrent stroke with lower DBPs. However, only persons with TIA or minor stroke were included in that study. The Lehigh Valley study included strokes of varying severity but excluded TIA. The UK study also grouped patients by baseline BP to determine relative risk in each group. Mean follow-up BP 4 years after baseline was also used in the analysis of Rodgers et al\(^20\) and stratified by the baseline BP groups. Patients whose follow-up BP differed substantially from baseline during follow-up would have been included in a category different from their original group. This misclassification would not have been reflected in the analysis. In the Lehigh Valley study, we grouped patients by their follow-up BPs and based the calculation of risk of recurrent stroke on these actual follow-up BPs.

The PROGRESS study was a large clinical trial (n>6000) looking at the effect of BP lowering in hypertensive (defined as BP >160/90 mm Hg) and nonhypertensive patients on stroke recurrence rate.\(^21\) They found that lowering BP with antihypertensive medication even in those whose BP was <160/90 mm Hg led to decreased risk of stroke recurrence. Their study included only TIA and minor stroke, like the study of Rodgers et al,\(^20\) and raises the question of whether their results can be extrapolated to more severe strokes. Our study, which included mild and more severe strokes (but not TIA), suggests that the results of PROGRESS and Rodgers et al can, indeed, be generalized to more severe strokes. Although the PROGRESS results are consistent with ours, the BP cutoff of 160/90 mm Hg is higher than the currently recommended level of control and does not address the question of the level of BP control that would be optimal for prevention of stroke recurrence.

Our results did not confirm the observation of Irie et al\(^19\) that DBP <80 mm Hg was associated with an increased risk of recurrent stroke. However, there were differences in design and in types of patients that may have contributed to this disparity. Irie et al started follow-up at 4 weeks, whereas we started at 4 months; Irie et al studied Japanese patients, whereas in the Lehigh Valley study almost all were white; Irie et al performed a retrospective case series study, and ours was a population-based, prospective cohort study. Moreover, unlike Irie et al, we measured BPs prospectively in a standardized fashion using trained study personnel; Irie et al used BPs measured by many different health workers. Therefore, less intraobserver and interobserver variability of BP measurement in the Lehigh Valley study than in the study of Irie et al may reasonably be expected. Additionally, in the Lehigh Valley study, we took into account the variation over time of the follow-up BPs in the analysis of risk of stroke recurrence. The study of Irie et al looked at only the overall mean of the follow-up BPs and did not take into account in their analysis any variation in BP over time. The mean age of patients in the study of Irie et al was 62 years, whereas in the Lehigh Valley study patients were, on average, older; only 25% were younger than 65 years. However, when controlling for age in the Cox proportional hazards model, we still found a highly significant decreased risk of stroke recurrence in the lowest BP group, and therefore age differences between the 2 study cohorts may not explain the difference in results.

An additional finding in our study was that DBP variability was associated with an increased risk of stroke recurrence. This result suggests that BP variability should be considered when risk of stroke is assessed.

Although there are many strengths in our study design compared with other studies, there are some weaknesses. For example, we considered only a limited number of risk factors. Risk factors for initial stroke that were not evaluated in the present study include heart failure, lipids, smoking, alcohol use, illicit drug use, physical inactivity, elevated homocysteine, elevated fibrinogen, and carotid artery disease.\(^4\) It is not clear whether any of these risk factors for initial stroke are also risk factors for recurrent stroke, but it is possible that inclusion of these factors may have altered the conclusions of this study.

Because the patients in this study were almost entirely white, the results may not be applicable to other ethnic groups. The effect of BP control on other outcomes such as mortality not due to recurrent stroke or cardiac events was not assessed in this analysis. In addition, the effect of BP control immediately after onset and in the immediate poststroke interval was not assessed in this study. We assessed BP control only from 4 months after the initial stroke.

Approximately 9% of patients refused follow-up or moved out of the area. Stroke risk factor distribution at enrollment was similar for this subgroup compared with the overall group. If a recurrent stroke rate for this subgroup similar to that for the rest of the patients is assumed, it is not likely that they would have significantly affected our conclusions had they been included.

In summary, our results imply that, for BP, “lower is better” as a goal in reducing stroke recurrence risk.

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