# Consistency of Blood Pressure Control After Ischemic Stroke: Prevalence and Prognosis

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Original Contribution

# Consistency of Blood Pressure Control After Ischemic Stroke
## Prevalence and Prognosis

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***Background and Purpose***—Blood pressure (BP) reduction lowers vascular risk after stroke; however, little is known about the relationship between consistency of BP control and risk of subsequent vascular events.

***Methods***—In this post hoc analysis of the Vitamin Intervention for Stroke Prevention trial (n=3680), individuals with recent (<120 days) stroke, followed up for 2 years, were divided according to proportion of visits in which BP was controlled (<140/90 mm Hg): <25%, 25% to 49%, 50% to 74%, and ≥75%. Multivariable models adjusting for demographic and clinical variables determined the association between consistency of BP control versus primary (stroke) and secondary (stroke, myocardial infarction, or vascular death) outcomes.

***Results***—Only 30% of participants had BP controlled ≥75% of the time. Consistency of BP control affected outcomes in individuals with baseline systolic BP >132 mm Hg. Among individuals with baseline systolic BP >75th percentile (>153 mm Hg), risks of primary and secondary outcomes were lower in those with BP controlled ≥75% versus <25% of visits (adjusted hazard ratio, 0.46; 95% confidence interval, 0.26–0.84 and adjusted hazard ratio, 0.51; 95% confidence interval, 0.32–0.82). Individuals with mean follow-up BP <140/90 mm Hg had lower risk of primary and secondary outcomes than those with BP ≥140/90 mm Hg (adjusted hazard ratio, 0.76; 95% confidence interval, 0.59–0.98 and adjusted hazard ratio, 0.76; 95% confidence interval, 0.62–0.92).

***Conclusions***—In this rigorous clinical trial, fewer than one third of patients with stroke had BP controlled ≥75% of the time for 2 years. Furthermore, consistency of BP control among those with elevated baseline systolic BP was linked to reduction in risk of recurrent stroke and stroke, myocardial infarction, and vascular death. **(*Stroke*. 2014;45:00-00.)**

**Key Words:** blood pressure ■ hypertension ■ mortality ■ prevention and control ■ stroke

Hypertension is the leading modifiable risk factor for stroke.[1] Lowering systolic blood pressure (SBP) by 10 mm Hg or diastolic BP (DBP) by 5 mm Hg reduces coronary heart disease events by 25% and stroke by 36%.[2] Among stroke survivors, BP reduction lowers risk of recurrent stroke, myocardial infarction (MI), and other vascular events.[3] Although most clinical trials assess BP control using mean BP during the course of the study, the use of mean follow-up BP may not necessarily provide a complete picture of BP control because of the variability in BP from visit to visit. Indeed, a post hoc analysis of individuals with hypertension and coronary artery disease enrolled in the INternational VErapamil SR-Trandolapril (INVEST) trial revealed that both proportion of visits with BP control and mean follow-up SBP were independently related to the risk of death, nonfatal MI, or nonfatal stroke.[4] Whether consistency of BP control is also important among stroke survivors remains unknown.

## Methods

### Patient Population

We conducted a post hoc analysis of the Vitamin Intervention for Stroke Prevention (VISP) trial, a double-blind, randomized, controlled trial assessing whether best medical therapy and high-dose folic acid, pyridoxine, and cobalamin given to lower homocysteine levels would reduce the incidence of recurrent stroke in patients with a nondisabling ischemic stroke within the preceding 120 days.[5] Details of the trial protocol and main results have been published previously.[5,6] In brief, from September 1996 to May 2003, VISP enrolled 3680 recent ischemic stroke patients ≥35 years of age from centers across the United States (n=45), Canada (n=10), and Scotland (n=1). Ischemic stroke was defined as brain infarction characterized by the sudden onset of a neurological deficit lasting ≥24 hours or evident on computed tomography or MRI. Infarcts attributable to cardioembolism (atrial fibrillation within 30 days of stroke, prosthetic cardiac valve, intracardiac thrombus or neoplasm, or valvular vegetation) were excluded.[5,6] At 1 month after randomization, at 6 months, and every 6 months thereafter (≤24 months), participants returned for evaluation including interview, examination, medication use assessment, stroke symptom questionnaire, stroke scales, and medical follow-up questionnaire.

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**Table 1. Baseline Characteristics of VISP Study Participants (n=3680)**

| | Proportion of Visits With BP Controlled (<140/90 mm Hg) | | | | |
|---|---|---|---|---|---|
| Baseline Characteristics | <25% (n=1289) | 25%–49% (n=590) | 50%–74% (n=693) | ≥75% (n=1108) | *P* Value |
| Age, y, mean (SD) | 67.9 (10.5) | 66.4 (10.2) | 66.1 (10.6) | 64.4 (11.2) | <0.001 |
| Sex, % | | | | | |
| Men | 60.3 | 62.7 | 62.2 | 65.3 | 0.10 |
| Women | 39.7 | 37.3 | 37.8 | 34.7 | |
| Race, % | | | | | |
| White | 77.8 | 77.6 | 78.9 | 82.8 | <0.001 |
| Black | 16.7 | 18.1 | 13.4 | 11.7 | |
| Other | 5.5 | 4.2 | 7.6 | 5.5 | |
| Current smoker, % | 15.1 | 19.2 | 16.7 | 17.9 | 0.11 |
| BMI, % | | | | | 0.004 |
| <25 kg/m$^2$ | 24.5 | 27.5 | 29.9 | 32.0 | |
| 25–30 kg/m$^2$ | 42.7 | 41.4 | 39.0 | 39.9 | |
| >30 kg/m$^2$ | 32.8 | 31.1 | 31.1 | 28.2 | |
| Stroke severity, % | | | | | |
| NIHSS 0 | 31.3 | 34.2 | 30.7 | 37.8 | 0.02 |
| NIHSS 1–4 | 60.5 | 57.6 | 60.6 | 54.4 | |
| NIHSS ≥5 | 8.1 | 8.1 | 8.7 | 7.8 | |
| Total cholesterol, mg/dL, mean (SD) | 206.3 (44.4) | 201.4 (43.7) | 200.5 (47.5) | 198.0 (49.8) | <0.001 |
| LDL, mg/dL, mean (SD) | 126.5 (39.9) | 121.8 (38.9) | 121.1 (41.6) | 119.3 (39.9) | <0.001 |
| Triglycerides, mg/dL, median (IQR) | 149.0 (108.0–215.0) | 147.0 (106.0–212.0) | 149.0 (106.0–220.0) | 138 (100.0–199.0) | 0.002 |
| Alcohol use in prior year, % | 57.6 | 59.0 | 57.4 | 63.0 | 0.04 |
| History of stroke >90 days before randomization, % | 23.0 | 25.1 | 22.8 | 22.9 | 0.72 |
| History of hypertension, % | 83.8 | 80.8 | 75.0 | 57.9 | <0.001 |
| History of diabetes mellitus, % | 30.3 | 31.6 | 30.9 | 25.4 | 0.01 |
| History of myocardial infarction, % | 14.9 | 14.1 | 17.7 | 18.4 | 0.03 |
| History of congestive heart failure, % | 5.2 | 3.1 | 6.6 | 5.6. | 0.03 |
| History of carotid endarterectomy, % | 6.9 | 6.9 | 7.2 | 6.0 | 0.75 |
| Any antithrombotic use during trial, % | 47.1 | 52.7 | 54.1 | 55.4 | <0.001 |
| Any statin use during trial, % | 40.9 | 40.5 | 47.2 | 46.0 | 0.006 |

BMI indicates body mass index; BP, blood pressure; IQR, interquartile range; LDL, low-density lipoprotein; NIHSS, National Institutes of Health Stroke Scale; and VISP, Vitamin Intervention for Stroke Prevention.

All subjects received the best available medical and surgical management as determined by their primary physician, including risk factor modification and often aspirin 325 mg daily. A cardiovascular end point review committee adjudicated coronary heart disease end points. MI was defined by new ECG changes, including Q waves or marked ST-T changes plus abnormal cardiac enzymes, cardiac symptoms plus abnormal enzymes, or symptoms plus hyperacute ECG changes resolving with thrombolysis. A Cerebrovascular End point Review Committee adjudicated recurrent stroke end points. Recurrent stroke was defined by sudden onset of neurological symptoms lasting ≥24 hours, with an increase in the National Institutes of Health Stroke Scale on a section that was normal in the previous examination.

**Table 2. Baseline and Mean Follow-Up Blood Pressure in the 4 Groups of Patients With Different Proportions of Visits With Blood Pressure Under Control**

| | Proportion of Visits With BP Controlled (<140/90 mm Hg) | | | | |
|---|---|---|---|---|---|
| Variable | <25% (n=1289) | 25%–49% (n=590) | 50%–74% (n=693) | ≥75% (n=1108) | *P* Value |
| Baseline SBP, mm Hg, mean (SD) | 154.8 (14.5) | 144.0 (15.8) | 136.9 (15.5) | 125.3 (12.4) | <0.001 |
| Baseline DBP, mm Hg, mean (SD) | 81.6 (9.9) | 79.8 (10.0) | 76.9 (9.4) | 73.3 (8.7) | <0.001 |
| Follow-up SBP, mm Hg, mean (SD) | 155.7 (12.1) | 143.3 (8.8) | 136.0 (8.7) | 124.0 (8.8) | <0.001 |
| Follow-up DBP, mm Hg, mean (SD) | 82.1 (8.7) | 79.3 (7.5) | 76.7 (7.8) | 72.6 (6.8) | <0.001 |
| SBP change, mm Hg, mean (SD) | 1.0 (14.9) | −0.8 (18.7) | −0.9 (19.7) | −1.4 (12.9) | 0.03 |
| DBP change, mm Hg, mean (SD) | 0.5 (8.8) | −0.4 (9.9) | −0.2 (9.7) | −0.7 (4.7) | 0.004 |

BP indicates blood pressure; DBP, diastolic blood pressure; and SBP, systolic blood pressure.

If symptoms that occurred suddenly and lasted ≥24 hours were not accompanied by an increased National Institutes of Health Stroke Scale score in an area that was previously normal, then recurrent stroke was diagnosed if cranial computed tomography or MRI revealed evidence of new infarction consistent with the clinical presentation. The ethics committee or institutional review board at each site approved the trial, and all participants provided written informed consent. VISP did not find high-dose vitamin therapy superior to the low-dose regimen in recurrent stroke prevention; hence, data for all enrolled patients were combined and included in these analyses.[5]

## Statistical Analysis

BP control was defined as SBP <140 mm Hg and DBP <90 mm Hg. For the purpose of the analysis, subjects were divided into 4 groups according to the proportion of visits in which BP was in control: <25%, 25% to 49%, 50% to 74%, and ≥75%. Primary outcome was time to stroke. Secondary outcome was time to stroke, MI, or vascular death.

Cox competing risks regression models were used to examine the association between each group, with vascular outcomes before and after adjusting for baseline covariates. The following 6 prespecified covariates were included in each of the models: age, sex, history of previous stroke, history of congestive heart failure, history of coronary heart disease (MI, coronary bypass surgery, or coronary angioplasty), and history of diabetes mellitus. The remaining covariates, including history of hypertension, alcohol use in previous year, history of endarterectomy, current smoking, stroke severity (National Institutes of Health Stroke Scale), medication use, race, and body mass index were selected into the final model using the backward stepwise procedure with a liberal $P<0.15$ as the retention criteria. Covariates were also include in the model if the adjusted hazard ratios (HRs) were >1.2 in the appropriate direction, regardless of the $P$ value.

The models allowed for interactions between groups with the following prespecified baseline factors: age, sex, race, history of hypertension, history of diabetes mellitus, and baseline BP. Baseline SBP and DBP were modeled as linear predictors after confirming linearity.

**Table 3. Cox Models for Predicting Vascular Outcomes After Stroke**

| | I. Stroke | | | | II. Stroke, MI, Vascular Death | | | |
|---|---|---|---|---|---|---|---|---|
| | 3576 Subjects, 290 Events | | | | 3575 Subjects, 456 Events | | | |
| Predictor | HR | Lower CI | Upper CI | *P* Value | HR | Lower CI | Upper CI | *P* Value |
| Age/y | 1.01 | 1.00 | 1.02 | 0.088 | 1.03 | 1.02 | 1.04 | <0.001 |
| Female sex | 0.98 | 0.77 | 1.25 | 0.890 | 0.88 | 0.72 | 1.07 | 0.198 |
| Baseline SBP, per mm Hg | 1.01 | 1.00 | 1.02 | 0.034 | 1.02 | 1.01 | 1.03 | 0.001 |
| History of diabetes mellitus | 1.29 | 1.00 | 1.67 | 0.048 | 1.53 | 1.26 | 1.87 | <0.001 |
| History of prior stroke | 1.83 | 1.44 | 2.34 | <0.001 | 1.78 | 1.46 | 2.17 | <0.001 |
| History of coronary heart disease | 0.92 | 0.71 | 1.21 | 0.562 | 1.25 | 1.02 | 1.53 | 0.030 |
| History of congestive heart failure | 1.40 | 0.90 | 2.17 | 0.131 | 1.69 | 1.23 | 2.33 | 0.001 |
| History of hypertension | 1.24 | 0.91 | 1.70 | 0.179 | … | … | … | … |
| Alcohol use in prior year | 0.70 | 0.55 | 0.89 | 0.004 | 0.82 | 0.67 | 0.99 | 0.043 |
| History of carotid endarterectomy | 1.24 | 0.83 | 1.87 | 0.298 | 1.42 | 1.05 | 1.92 | 0.022 |
| Current smoking | 1.24 | 0.91 | 1.68 | 0.173 | 1.31 | 1.02 | 1.68 | 0.033 |
| NIHSS 1–4, vs 0 | 1.17 | 0.89 | 1.53 | 0.256 | 1.19 | 0.96 | 1.47 | 0.110 |
| NIHSS >4, vs 0 | 1.51 | 0.99 | 2.29 | 0.056 | 1.43 | 1.02 | 2.01 | 0.039 |
| Any antithrombotic use during trial | 0.78 | 0.61 | 0.99 | 0.043 | 0.76 | 0.63 | 0.92 | 0.005 |
| Percentage of visits with BP control | | | | | | | | |
| Baseline SBP=25th percentile (130 mm Hg) | | | | | | | | |
| <25% | Ref | … | … | … | Ref | … | … | … |
| 25%–49% | 1.02 | 0.59 | 1.76 | 0.953 | 1.23 | 0.79 | 1.93 | 0.357 |
| 50%–74% | 1.05 | 0.66 | 1.69 | 0.827 | 1.54 | 1.06 | 2.23 | 0.025 |
| ≥75% | 1.03 | 0.66 | 1.62 | 0.891 | 1.24 | 0.86 | 1.79 | 0.246 |
| Baseline SBP=median/mean (141 mm Hg) | | | | | | | | |
| <25% | Ref | … | … | … | Ref | … | … | … |
| 25%–49% | 0.93 | 0.62 | 1.38 | 0.712 | 1.10 | 0.80 | 1.53 | 0.550 |
| 50%–74% | 0.95 | 0.64 | 1.39 | 0.779 | 1.27 | 0.93 | 1.73 | 0.130 |
| ≥75% | 0.70 | 0.44 | 1.13 | 0.144 | 0.81 | 0.56 | 1.19 | 0.286 |
| Baseline SBP=75th percentile (153 mm Hg) | | | | | | | | |
| <25% | Ref | … | … | … | Ref | … | … | … |
| 25%–49% | 0.84 | 0.57 | 1.23 | 0.365 | 0.98 | 0.72 | 1.32 | 0.887 |
| 50%–74% | 0.84 | 0.54 | 1.30 | 0.437 | 1.03 | 0.73 | 1.45 | 0.863 |
| ≥75% | 0.46 | 0.26 | 0.84 | 0.011 | 0.51 | 0.32 | 0.82 | 0.006 |
| Interaction: baseline SBP x % visits with BP control | | | *P*=0.0083 | | | | *P*=0.0001 | |

Coronary heart disease=myocardial infarction, coronary bypass surgery, or coronary angioplasty. BP indicates blood pressure; CI, confidence interval; HR, hazard ratios; MI, myocardial infarction; NIHSS, National Institutes of Health Stroke Scale; and SBP, systolic blood pressure.

For modeling of time to stroke, all-cause mortality was considered a competing event using the Fine and Gray model.[7] For modeling of time to stroke, MI, or vascular death, nonvascular mortality was considered a competing event. Persons who did not experience the event of interest or the specified competing event were censored at the time of last follow-up. All statistical analyses were performed using the statistical software STATA (version 11.2; StataCorp).

## Results

Of 3680 participants in the trial, 1289 (35%) had BP controlled <25% of the time, 590 (16%) had BP controlled 25% to 49% of the time, 693 (19%) had BP controlled 50% to 74% of the time, and 1108 (30%) had BP controlled ≥75% of the time. Individuals with higher proportion of visits with target BP control were younger, more likely to have a history of MI and to use statins and antithrombotics, and had lower body mass index, total cholesterol, low-density lipoprotein, and triglycerides levels (Table 1). They were less likely to be black or to have a history of hypertension or diabetes mellitus (Table 1). Persons with a higher proportion of visits with well-controlled BP had lower baseline SBP and DBP, lower mean follow-up SBP and DBP, and greater mean reduction in SBP and DBP (Table 2).

There was a significant interaction between proportion of visits with BP control and baseline SBP for predicting recurrent stroke ($P$=0.0083) and for predicting stroke, MI, or vascular death ($P$=0.0001; Table 3). Allowing for interaction between the groups with age, sex, race, history of hypertension, history of diabetes mellitus, and baseline BP revealed that the effect of group on vascular events differed according to baseline SBP (but there were no other significant interactions). The association between higher number of visits with BP in control and lower rate of adverse vascular events was stronger at higher levels of baseline SBP (Table 3; Figures I and II in the online-only Data Supplement). The consistency of BP control did not affect outcomes in individuals with baseline SBP <132 mm Hg.

Separate HR estimates were computed at 3 different values of baseline SBP, including 25th percentile, median, and 75th percentile of the observed SBP distribution, under the Cox model (Table 3). The model predicted that a higher number of visits with BP in control was associated with a lower rate of adverse vascular events at the higher end of baseline SBP distribution, but not at the lower end of the distribution. Among individuals with baseline SBP in the 75th percentile (>153 mm Hg), having BP controlled ≥75% of the time conferred a lower risk of stroke (HR, 0.46; 95% confidence interval [CI], 0.26–0.84), and stroke, MI, or vascular death (HR, 0.51; 95% CI, 0.32–0.82), compared with having BP controlled <25% of the time, after adjustment for covariates (Table 3; Figures 1 and 2).

Consistency of BP control and mean follow-up BP under control were highly correlated ($r$=0.80; $P$<0.0001). Individuals whose mean BP was in control for the trial had a lower risk of stroke (HR, 0.68; 95% CI, 0.54–0.85), and stroke, MI, or vascular death (HR, 0.70; 95% CI, 0.59–0.84), even after adjusting for sociodemographic and clinical variables (adjusted HR, 0.76; 95% CI, 0.59–0.98 and adjusted HR, 0.76; 95% CI, 0.62–0.92; Table 4).

## Discussion

This post hoc analysis of the VISP trial shows that fewer than one third of individuals with stroke enrolled in the trial had BP controlled ≥75% of the time. Both achieving mean follow-up BP within target range and consistency of BP control among those with high baseline SBP were linked to reduction in recurrent stroke and other vascular events. The relationship between higher proportion of visits with target BP control and lower risk of vascular events among patients with recent ischemic stroke started from a baseline SBP of ≈132 mm Hg. These findings highlight the importance of ensuring BP is controlled at each poststroke clinical encounter, particularly among patients with elevated baseline SBP.

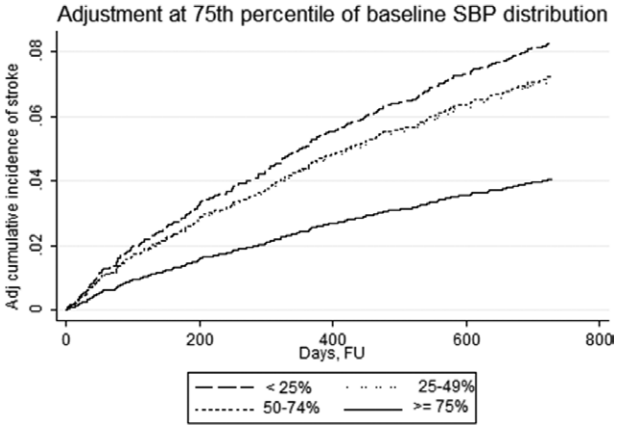


**Figure 1.** Cumulative probability of stroke by blood pressure control category (<25%, 25% to 49%, 50% to 74%, and ≥75%) in patients with recent ischemic stroke. FU indicates follow-up; and SBP, systolic blood pressure.

Our data confirm results from previous studies showing that BP reduction protects individuals with stroke from subsequent stroke, MI, and vascular death.[3] However, a novel finding is that higher consistency of BP control may reduce subsequent events in those with baseline hypertension. These findings are consistent with the post hoc analysis of data from the INVEST trial, which revealed that as the proportion of visits with BP control increased, there was an associated steep reduction in cardiovascular risk, independent of baseline characteristics and mean on-treatment BP.[4] Consistency of BP control offers information above and beyond mean BP. The visits in which BP is >140/90 reflect periods of absence of BP control: conceivably settings in which individuals are at higher cardiovascular risk.

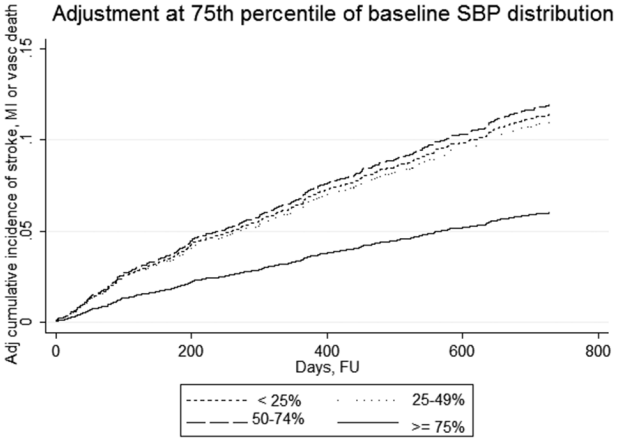


**Figure 2.** Cumulative probability of stroke, myocardial infarction (MI), or death by blood pressure control category (<25%, 25% to 49%, 50% to 74%, and ≥75%) in patients with recent ischemic stroke. FU indicates follow-up; and SBP, systolic blood pressure.

**Table 4. Association Between Mean Follow-Up BP in Control and Vascular Outcomes**

| Outcome | Mean Follow-Up BP in Control | n | Unadjusted | | Adjusted | |
|---|---|---|---|---|---|---|
| | | | HR (95% CI) | *P* Value | HR (95% CI) | *P* Value |
| Stroke | No | 1845 | Ref | … | Ref | … |
| | Yes | 1835 | 0.68 (0.54–0.85) | 0.001 | 0.76 (0.59–0.98) | 0.034 |
| Stroke, myocardial infarction, and vascular death | No | 1845 | Ref | … | Ref | … |
| | Yes | 1835 | 0.70 (0.59–0.84) | <0.001 | 0.76 (0.62–0.92) | 0.006 |

BP indicates blood pressure; CI, confidence interval; and HR, hazard ratios.

Several other findings in our study deserve mention. First, individuals with a history of MI were more likely to have more consistent BP control than those without a history of MI. This may reflect the more aggressive management in individuals with coronary heart disease. Perhaps both healthcare practitioners and patients are aware of the importance of controlling BP after MI, but less knowledgeable, or less diligent, about BP control after stroke. Second, individuals with higher proportion of visits with target BP control had lower body mass index, total cholesterol, low-density lipoprotein, and triglyceride levels, suggesting better baseline vascular health, healthier lifestyle, or more aggressive medical management. The more frequent use of statins and antithrombotics among those with more consistent BP control supports the latter. The lower frequency of consistent BP control among blacks is consistent with numerous studies, which have found that hypertension in blacks is more prevalent,[8] less frequently controlled,[9] and more difficult to control.[10] Finally, the consistency of BP control was poor in this trial, with fewer than one third of patients with BP within target range ≥75% of the time. This finding has important implications: if BP is so inconsistently controlled in a randomized controlled trial with close follow-up, one can imagine that in the overall stroke population, a small minority of individuals have consistent BP control. However, single BP measurements are imprecise as they are prone to considerable background day-to-day variability (noise). This can make it difficult to interpret measurements as reflecting noise versus true signal.[11] A post hoc analysis of the Perindopril Protection Against Recurrent Stroke Study (PROGRESS) trial suggested that usual clinical approaches to monitoring the effect of medications on lowering BP have a low probability of yielding reliable information about true changes in BP given BP variability.[11] Methods to account for the natural variability of BP will likely be required in routine clinical practice to make more informed decisions on titrating BP medications. With the combination of home BP monitors and mobile health technology, healthcare teams will be able to use home measurements to more reliably determine adequacy of BP control and to make subsequent treatment decisions.

This study has limitations. First, individuals with BP controlled >75% of the time had overall better cardiovascular profiles (lower body mass index, total cholesterol, low-density lipoprotein, and triglycerides levels) than those with BP controlled less often. Although we adjusted for these factors and numerous other covariates in our multivariable models, there is a possibility of unmeasured confounding. Second, because of the relatively short time frame for follow-up (2 years), this study may have missed the effect of consistency of BP control on outcomes in individuals with less severe baseline BP elevation. In addition, this study only assessed BP every 6 months. More frequent BP assessments may have provided a more accurate portrayal of consistency of BP control, particularly given the variability in BP measurements discussed previously. Finally, this is a post hoc analysis of a clinical trial. The patient population in the trial is not representative of the overall stroke population, limiting generalizability. Nevertheless, this is the first study to our knowledge that shows the importance of consistency of BP control among individuals with previous stroke. Future prospective studies are necessary to determine effective methods for ensuring that BP is consistently controlled.

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## Disclosures

None.

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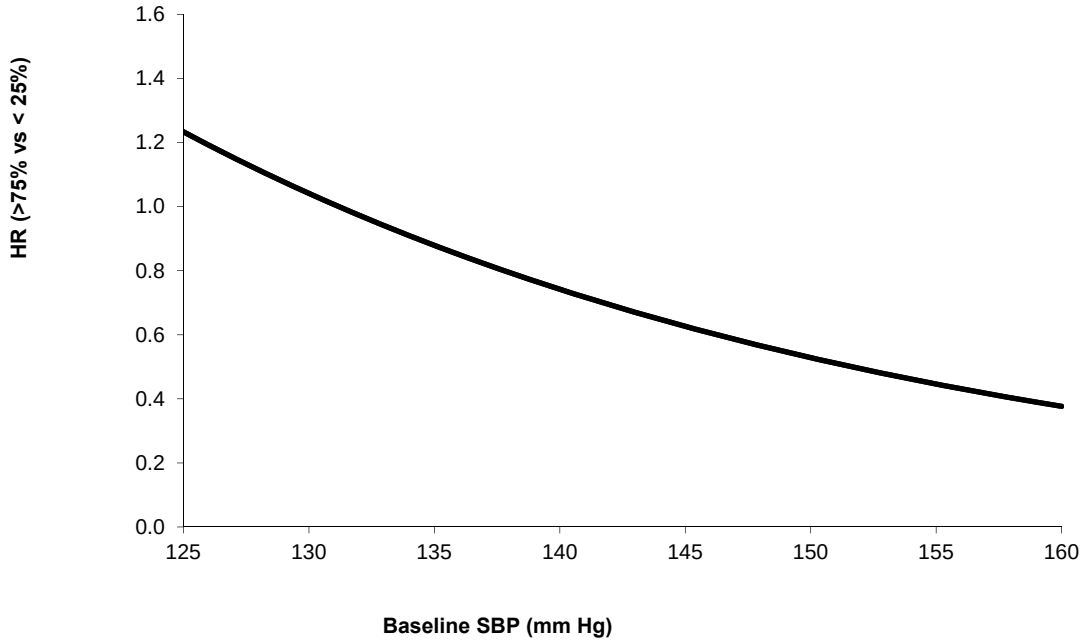
**SUPPLEMENTAL MATERIAL**

**Supplementary Figure Legends**

**Supplementary Figure I.** HR for the relation between percent of visits with target BP control vs. primary outcome (stroke) as a function of baseline SBP

**Supplementary Figure II.** HR for the relation between percent of visits with target BP control vs. secondary outcome (stroke, MI or vascular death) as a function of baseline SBP

## Supplementary Figure I



## Supplementary Figure II