CLINICAL RESEARCH STUDY

THE AMERICAN JOURNAL of MEDICINE®

Blood Pressure Trajectories and Outcomes for Veterans Presenting at VA Medical Centers with a Stroke or Transient Ischemic Attack

Greg Arling, PhD,[a,b] Anthony Perkins, MS,[a,c] Laura J. Myers, PhD,[a,d,e,f] Jason J. Sico, MD, MHS,[g,h] Dawn M. Bravata, MD[a,d,e,f,i]

[a]Department of Veterans Affairs (VA) Health Services Research and Development (HSR&D) Precision Monitoring to Transform Care (PRISM) Quality Enhancement Research Initiative (QUERI), Washington, DC; [b]School of Nursing, Purdue University, West Lafayette, Indianapolis, IN; [c]Biostatistics, Indiana University School of Medicine, Indianapolis, IN; [d]VA HSR&D Center for Health Information and Communication (CHIC), Richard L. Roudebush VA Medical Center, Indianapolis, IN; [e]Department of Internal Medicine, Indiana University School of Medicine, Indianapolis, IN; [f]Health Services Research, Regenstrief Institute, Indianapolis, IN; [g]Neurology Service, VA Connecticut Healthcare System, West Haven, Conn; [h]Department of Neurology, Yale School of Medicine, New Haven, Conn; [i]Medicine Service, Richard L. Roudebush VA Medical Center, Indianapolis, IN.

ABSTRACT

BACKGROUND: Blood pressure control has been shown to reduce risk of vascular events and mortality after an ischemic stroke or transient ischemic attack (TIA). Yet, questions remain about effectiveness, timing, and targeted blood pressure reduction.

METHODS: We analyzed data from a retrospective cohort of 18,837 veterans cared for 12 months prior and up to 12 months after an emergency department visit or inpatient admission for stroke or TIA. Latent class growth analysis was used to classify patients into systolic blood pressure trajectories. With Cox proportional hazard models, we examined relationships between blood pressure trajectories, intensification of antihypertensive medication, and stroke (fatal or non-fatal) and all-cause mortality in 12 months following the index event.

RESULTS: The cohort was classified into 4 systolic blood pressure trajectories: 19% with a low systolic blood pressure trajectory (mean systolic blood pressure = 116 mm Hg); 65% with a medium systolic blood pressure trajectory (mean systolic blood pressure = 136 mm Hg); 15% with a high systolic blood pressure trajectory (mean systolic blood pressure = 158 mm Hg), and 1% with a very high trajectory (mean systolic blood pressure = 183 mm Hg). After the stroke or TIA, individuals in the high and very high systolic blood pressure trajectories experienced a substantial decrease in systolic blood pressure that coincided with intensification of antihypertensive medication. Patients with very low and very high systolic blood pressure trajectories had a significantly greater ($P < .05$) hazard of mortality, while medication intensification was related significantly ($P < .05$) to lower hazard of mortality.

CONCLUSIONS: These findings point to the importance of monitoring blood pressure over multiple time points and of instituting enhanced hypertension management after stroke or TIA, particularly for individuals with high or very high blood pressure trajectories.

 • The American Journal of Medicine (2022) 135:889–896

KEYWORDS: Antihypertensive agent; Blood pressure; Cohort studies; Hypertension; Stroke

Funding: This work was supported by the US Department of Veterans Affairs Health Services Research and Development (HSR&D) grants HX001388-01A1 (to JJS) and HSR&D Precision Monitoring to Transform Care (PRISM) Quality Enhancement Research Initiative (QUERI) (QUE 15-280). The funding agencies had no role in the design of the study, data collection, analysis, interpretation, or in the writing of this manuscript.

Conflicts of Interest: GA, AP, LJM, JJS, and DMB report grant support from the Department of Veterans Affairs during the conduct of the study. The views expressed in this article are those of the authors and do not necessarily represent the view of the Department of Veterans Affairs.

Authorship: Each author participated in the writing of the manuscript, saw and approved the submitted version, had access to the data, and was involved in the conception and design of the study, or the analysis of the data.

Requests for reprints should be addressed to Greg Arling, PhD, School of Nursing, Purdue University, 502 N University Street, West Lafayette, IN 47907-2069.

E-mail address: garling@purdue.edu

https://doi.org/10.1016/j.amjmed.2022.02.012

INTRODUCTION

Hypertension is the leading risk factor for stroke and transient ischemic attack (TIA).[1] Providing high quality, guideline-concordant management of cerebrovascular risk factors, especially hypertension, is therefore an essential prevention strategy.[2-7] Patients who have experienced a stroke or TIA are at greatly elevated risk for a subsequent stroke, other vascular events, and mortality.[8,9] Blood pressure control and intensification of antihypertensive medications after stroke or TIA have been associated with a reduced risk of recurrent stroke.[10,11] Yet, questions remain about the overall effectiveness, timing, and targeted level of blood pressure reduction.[12,13] Most observational, population-based studies of blood pressure and vascular events or mortality have measured blood pressure or antihypertensive medication at single time points prior to an index cardiovascular event, at discharge from an index hospitalization, or during a limited follow-up period, for example, 90 days after the event.

CLINICAL SIGNIFICANCE

- Prior to their ischemic stroke or transient ischemic attack (TIA), about one-sixth of patients had high systolic blood pressure (SBP) trajectories.
- Intensification of hypertension medication after the index stroke or TIA was associated with lowered blood pressure and reduced the risk of mortality.
- Clinicians should exercise caution in medication intensification for patients with very low SBP trajectories because of their heightened risk of mortality.

Only a handful of observational studies have classified individuals into blood pressure trajectories. Three studies modeled blood pressure trajectories over multiple years in the general population and examined the association of these trajectories with cardiovascular disease, stroke, or mortality.[14-16] Only one study modeled blood pressure trajectories after stroke, but only for a 24-hour period in the hospital.[17] None of the studies examined the relationships between blood pressure trajectories over extended periods, prior to and after a stroke or TIA.

The aims of our study were to model blood pressure trajectories for a cohort of patients in the 12 months prior to their index stroke or TIA; and to examine relationships between blood trajectories, intensification of antihypertensive medication, and recurrent stroke or mortality in the 12 months after the index event.

METHODS

Data Sources

The Department of Veterans Affairs (VA) Corporate Data Warehouse was used to identify veterans with TIA or ischemic stroke who were cared for in the emergency department (ED) or inpatient setting from October 2014 to September 2018.[2,5,18,19] Primary diagnosis codes (International Classification of Diseases, Ninth Revision and Tenth Revision [ICD-9 and ICD-10]) were used to identify patients with ischemic stroke (ICD-9 433.X1, 434.00, 434.X1, and 436; ICD-10 I63, I66, I67.89, I97.81, I97.82) and TIA (ICD-9 435.0, 435.1, 435.3, 435.8, and 435.9; ICD-10 G45.0, G45.1, G45.8, G45.9, I67.848) during the index ED visit or inpatient admission.[2,19,20] Mortality was obtained from the VA Vital Status File.[21] Recurrent stroke events were identified using a combination of both VA and fee-basis data (ie, covering services paid for by the VA but obtained in non-VA facilities). The study was approved by the human subjects committee at the Indiana University Institutional Review Board and the Roudebush VAMC Research and Development Committee.

Study Cohort

The patient sample consisted initially of 32,950 patients who experienced an index cerebrovascular event, defined as presenting at the ED or having an inpatient admission after a stroke or TIA, from October 1, 2014 to September 30, 2018. A total of 5976 patients were excluded because they did not meet study criteria: 327 died at discharge; 1199 left against medical advice; 2614 transferred to another non-VA inpatient facility; 473 had a history of dialysis; and 1363 were hospice/palliative care patients.

Data for the cohort ranged from up to 12 months prior to and 12 months after the index event. For purposes of the trajectories analysis, the date range was divided into 4 90-day periods prior to the index event (Q1-Q4), the index event (Q5), and 4 periods after the index event (Q6-Q9). The modeling required blood pressure readings in at least 2 90-day periods in the 12 months leading up to the index event. A total of 8137 patients were excluded because they did not meet this criterion. This left 18,837 patients in the analysis cohort.

Measures

Systolic blood pressure readings were obtained from VA outpatient NEXUS+ clinics (eg, Primary Care, Cardiology, Endocrinology, Neurology). Aside from the index event, we excluded blood pressure readings during ED visits, inpatient stays, or visits to specialty clinics. If a patient had multiple blood pressure readings recorded during a visit, then we used the last reading for the analysis. If a patient had blood pressure readings from multiple visits during the 90-day period, then we took the mean of the blood pressure recorded during the multiple visits. The coefficient of variation (CV) for all systolic blood pressure readings during the 4 quarters leading up to the index event served as an indicator of systolic blood pressure variability; the larger the CV, the greater the variability.

The measure of antihypertensive medication was based on filled prescriptions from VA pharmacy records for each of 6 medication classes (beta-blockers, α_1-adrenergic

receptor antagonists, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, loop diuretics, and other diuretics) commonly prescribed in the VA.[22,23] We determined the span of days for prescriptions in a class, and then we allocated the days for that class to 90-day periods. If a span ran between 2 or more 90-day periods, the days were assigned proportionately to each period.

Intensification of the antihypertensive medication regimen was measured by calculating the day-weighted number of classes in the 90 days after the stroke or TIA (Q6) minus the number of classes in the 90 days prior to the event (Q4). In addition to intensification, we included a variable for the number of antihypertensive medication classes in the 90-day period following discharge (Q6).

The study's outcomes were all-cause mortality and recurrent fatal and non-fatal stroke over the 12 months following discharge from the index stroke or TIA, with death served as a competing risk for recurrent stroke.

Statistics

We identified systolic blood pressure trajectories with latent class growth analysis, a person-centered approach that identifies distinct classes or sub-populations of individuals.[24-26] The observed distribution of outcomes (ie, change in systolic blood pressure) in the overall sample is assumed to be a mixture of subpopulation distributions, representing different latent trajectories not directly observable empirically.

We modeled systolic blood pressure trajectories leading up to the index event. Each individual patient could have systolic blood pressure readings in up to 4 90-day periods (Q1-Q4). A total of 7664 patients had systolic blood pressure values in 2 periods, 6704 patients had 3 periods with values, and 4469 patients had 4 periods with values. Missing blood pressure measurements were assumed to be at random. This simplifying assumption restricts generalizability of the findings to individuals with regular primary care visits, which we note as a study limitation.

This latent class growth analysis model assumes that within each latent class, outcomes are independent Bernoulli random variables, and associations between outcomes are incorporated into the model as the probability of belonging to the latent class variable.[27] We began by specifying a 2-class model and then expanded the model with additional classes until achieving the best fit and arriving at classes that were most meaningful clinically. We evaluated model fit with Bayesian Information Criteria, entropy and overall model interpretability, and parsimony. The modeling software was Mplus Version 8.[27]

RESULTS

Study Sample

A very high percentage of this 18,837-veteran sample was male (96%), 24% was African American, and the mean age was 71 years (Table 1). Over half of the sample (57%) had a stroke as their index event and the remainder had a TIA. About half (52%) of patients had a history of stroke and 31% had a history of TIA, both occurring in >12 months prior to the index stroke or TIA. Most individuals (83%) were admitted as inpatients; the remainder was discharged from the ED. The mean systolic blood pressure in the pre-index event period (Q1-Q4) ranged from 135.8 to 136.0 mm Hg (SDs, 18.2 to 18.5).

Systolic Blood Pressure Trajectories

The latent class growth analysis of systolic blood pressure yielded 4 trajectories (classes) that were distinctly different in their patterns over the 4 90-day periods prior to their index stroke or TIA. The Vuong-Lo-Mendell-Rubin likelihood ratio test for testing 4 classes (null hypothesis) vs 5 classes had a P value of 0.2691, indicating that the 5-class model was not significantly different from the 4-class model. All prior testing 1 vs 2, 2 vs 3, and 3 vs 4 were significant ($P < .05$).

Nineteen percent of the sample followed a low systolic blood pressure trajectory (T1), 65% a medium systolic blood pressure trajectory (T2), 15% a high systolic blood pressure trajectory (T3), and 1% a very high systolic blood pressure trajectory (T4). Over the 4 90-day periods leading up to the index event, the majority of the sample had mean systolic blood pressure meeting a goal of <140 mm Hg. Individuals in T1 had the lowest average systolic blood pressure (mean 115.0-117.8 mm Hg, SD 10.2-12.) T2 had a higher average systolic blood pressure but still within goal (mean 135.7-136.0 mm Hg, SD 11.2-14.0); T3 had elevated systolic blood pressure (mean 154.1-159.8 mm Hg, SD 12.6-15.5); and the small number of individuals (266) in T4 had highly elevated systolic blood pressure (mean 180.5-186.4 mm Hg, SD 15.5-18.7).

Characteristics of Individuals with Different Trajectories

Individuals in the 4 trajectories differed significantly in several respects. The low systolic blood pressure trajectory (T1) had the lowest percentage, and the very high trajectory (T4) had the highest percentage of individuals with an index stroke, inpatient admission, and history of hypertension, stroke, and chronic kidney disease. In contrast, the low systolic blood pressure trajectory (T1) had the highest percentage with a history of TIA, dementia, myocardial infarction, chronic heart failure, peripheral vascular disease, and obstructive sleep apnea. These patterns were confirmed in a multiple variable generalized logit model comparing the medium trajectory (T2) to each of the other trajectories (Supplementary Table 1, available online).

Mean Systolic Blood Pressure and Medication Patterns Over Time

The mean systolic blood pressures in each 90-day period are reported in Table 1 and displayed graphically in

Table 1 Demographic Distributions by Each Class — At Least 2 Prior, Only 4 Prior Quarters (n = 18,837)

	Total Sample 100% (n = 18,837)	T1 (Low) 19% (n = 3546)	T2 (Medium) 65% (n = 12,213)	T3 (High) 15% (n = 2812)	T4 (Very High) 1% (n = 266)	*P* Value
Mean (SD) systolic (Q1-Q4)	136.1 (15.3)	115.9 (6.4)	135.9 (7.6)	158.0 (6.8)	183.3 (9.3)	< .001
% with mean systolic <140 mm Hg	63.0 (11,870)	100.0 (3546)	68.2 (8323)	0.0 (1)	0.0 (0)	< .001
Systolic coefficient of variation	9.6 (4.8)	10.1 (5.4)	9.2 (4.7)	10.6 (4.5)	10.4 (4.8)	< .001
Mean age (SD)	70.6 (10.6)	70.0 (11.2)	70.8 (10.5)	70.9 (10.3)	69.0 (10.3)	< .001
% Male (n)	95.7 (18,031)	94.5 (3350)	96.0 (11,726)	95.8 (2695)	97.7 (260)	< .001
% African-American	24.4 (4593)	19.3 (686)	24.2 (2955)	30.6 (860)	34.6 (92)	< .001
% Index stroke (n)	56.8 (10,698)	48.4 (1716)	56.8 (6933)	65.5 (1842)	77.8 (207)	< .001
% Admitted (n)	83.4 (15,711)	81.5 (2891)	82.9 (10,130)	86.9 (2444)	92.5 (246)	< .001
% Current smoker (n)	32.5 (6113)	33.2 (1178)	32.2 (3936)	32.4 (912)	32.7 (87)	.743
% History of TIA (n)	30.6 (5763)	36.7 (1302)	30.6 (3739)	24.0 (675)	17.7 (47)	< .001
% History of stroke (n)	52.0 (9794)	46.1 (1636)	51.6 (6305)	59.4 (1670)	68.8 (183)	< .001
% History of diabetes (n)	50.4 (9500)	45.7 (1620)	50.1 (6119)	57.1 (1606)	58.3 (155)	< .001
% History of heart failure (n)	17.4 (3280)	25.8 (914)	15.9 (1938)	14.1 (397)	11.7 (31)	< .001
% History of hypertension (n)	85.5 (16,108)	74.3 (2635)	86.3 (10,536)	95.2 (2678)	97.4 (259)	< .001
History of hyperlipidemia	69.9 (186)	70.4 (2495)	69.9 (8533)	69.7 (1961)	69.9 (186)	.945
% History of chronic kidney disease (n)	20.8 (3925)	19.7 (698)	19.9 (2427)	25.5 (717)	31.2 (83)	< .001
% History of dementia (n)	7.9 (1496)	9.0 (320)	7.8 (947)	7.5 (211)	6.8 (18)	.057
% History of myocardial infarction (n)	8.2 (1547)	11.7 (416)	7.4 (907)	7.2 (202)	8.3 (22)	< .001
% History of peripheral vascular disease (n)	15.9 (2996)	19.4 (688)	15.0 (1835)	15.2 (428)	16.9 (45)	< .001
% History of obstructive sleep apnea (n)	20.5 (3856)	22.6 (803)	20.3 (2481)	19.0 (533)	14.7 (39)	< .001
Systolic blood pressures, mm Hg						
Mean systolic (SD) Q1	135.8 (18.2)	115.1 (10.2)	135.7 (11.2)	159.8 (12.6)	186.4 (15.5)	< .001
Mean systolic (SD) Q2	135.8 (18.4)	115.0 (10.8)	135.8 (11.6)	159.4 (13.3)	181.4 (16.6)	< .001
Mean systolic (SD) Q3	136.0 (18.5)	116.6 (11.7)	136.0 (12.9)	157.3 (15.3)	183.0 (17.6)	< .001
Mean systolic (SD) Q4	135.8 (18.4)	117.8 (12.8)	136.0 (14.0)	154.1 (15.5)	180.5 (18.7)	< .001
Mean systolic (SD) - index	148.8 (25.0)	133.5 (21.3)	149.3 (23.1)	163.3 (25.8)	175.2 (27.8)	< .001
Mean systolic (SD) Q5	132.7 (16.7)	120.5 (13.9)	133.0 (14.5)	144.2 (17.1)	155.7 (22.4)	< .001
Mean systolic (SD) Q6	133.0 (17.5)	120.9 (14.6)	133.5 (15.5)	144.2 (18.5)	154.3 (22.2)	< .001
Mean systolic (SD) Q7	133.2 (17.3)	122.6 (15.3)	133.5 (15.6)	143.8 (18.0)	150.9 (22.2)	< .001
Mean systolic (SD) Q8	133.2 (17.7)	121.9 (15.1)	133.7 (16.0)	143.9 (18.8)	151.5 (24.2)	< .001
Mean # classes weighted						
Mean # classes (SD) Q1	1.5 (1.2)	1.4 (1.2)	1.5 (1.2)	1.6 (1.2)	1.5 (1.3)	< .001
Mean # classes (SD) Q2	1.5 (1.2)	1.4 (1.2)	1.5 (1.2)	1.7 (1.1)	1.7 (1.3)	< .001
Mean # classes (SD) Q3	1.5 (1.2)	1.4 (1.2)	1.5 (1.1)	1.7 (1.1)	1.7 (1.2)	< .001
Mean # classes (SD) Q4	1.5 (1.2)	1.4 (1.2)	1.5 (1.1)	1.7 (1.1)	1.8 (1.3)	< .001
Mean # classes (SD) - Index	1.6 (1.2)	1.4 (1.2)	1.6 (1.2)	1.9 (1.3)	2.1 (1.4)	< .001
Mean # classes (SD) Q5	1.7 (1.1)	1.4 (1.1)	1.6 (1.1)	2.0 (1.1)	2.4 (1.2)	< .001
Mean # classes (SD) Q6	1.5 (1.1)	1.3 (1.1)	1.5 (1.1)	1.9 (1.1)	2.0 (1.2)	< .001
Mean # classes (SD) Q7	1.5 (1.2)	1.2 (1.1)	1.5 (1.1)	1.8 (1.2)	2.0 (1.3)	< .001
Mean # classes (SD) Q8	1.5 (1.2)	1.2 (1.1)	1.5 (1.1)	1.8 (1.2)	2.0 (1.3)	< .001
Outcomes						
% Death 365 days	8.4 (1581)	10.9 (388)	7.6 (934)	8.1 (229)	11.3 (30)	< .001
% Stroke 365 days	7.8 (1460)	6.3 (225)	7.4 (908)	10.7 (301)	9.8 (26)	< .001
% Death 365 days no stroke	7.4 (1393)	10.1 (357)	6.7 (815)	6.9 (194)	10.2 (27)	< .001
% Stroke no death 365 days	6.8 (1272)	5.5 (194)	6.5 (789)	9.5 (266)	8.7 (23)	< .001
% Death 365 days with stroke	1.0 (188)	0.9 (31)	1.0 (119)	1.2 (35)	1.1 (3)	0.494

Note: *P*-values represent Kruskal-Wallis Test for continuous measures and Chi-squared tests for categorical variables.
SD = standard deviation.

Figure 1. The mean systolic blood pressures for the 4 trajectories showed a consistent pattern of separation prior to the index stroke or TIA (Figure 1). The 3 lower systolic blood pressure trajectories (T1-T3) spiked during the index ED visit or inpatient admission (Q5). The trajectories converged after the index event with a sharp decrease in systolic blood pressure for the 2 highest trajectories (T3 and T4). It is noteworthy that T4 with the highly elevated systolic blood pressure prior to the index event had the greatest decrease after the index event.

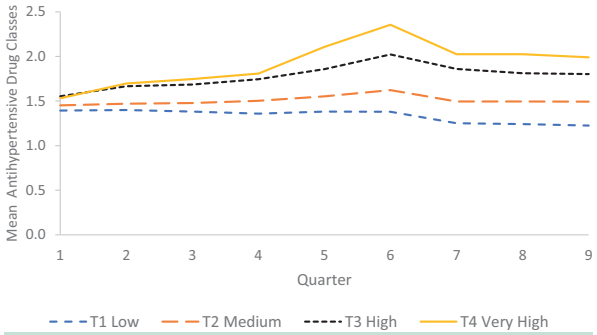

Figure 1 Mean number of day-weighted antihypertensive drug classes for systolic blood pressure trajectories by 90-day periods prior to (Quarter 1-4) and after (Quarter 6-9) the index event (Quarter 5).

The weighted mean number of antihypertensive medication classes for the 4 trajectories are also reported in Table 1 and shown in Figure 2. The pattern of intensification corresponds directly with the pattern of systolic blood pressure reduction for the 2 highest trajectories. Individuals in the 2 highest trajectories (T3 and T4) had a sharp increase in the number of medication classes during the index inpatient admission or ED visit and in the subsequent 90-day periods. For example, patients within the T4 trajectory (green dashed lines in Figures 1 and 2) had the highest mean systolic blood pressure but lowest mean number of medication classes in Q1, indicating either possible undertreatment of hypertension or severe hypertension in the pre-event period, and then a marked increase in antihypertensive medication classes during the index event (Q5), with a sharp decrease in systolic blood pressure immediately after the index event.

To confirm the patterns of intensification, we estimated multiple regression models for hypertensive medication intensification (number of Q6 classes − number of Q4 classes) by systolic blood pressure trajectories while controlling statistically for covariates (Table 2). The table shows results for models without trajectory variables (first two colums) and with trajectory variables included (last 2 columns).

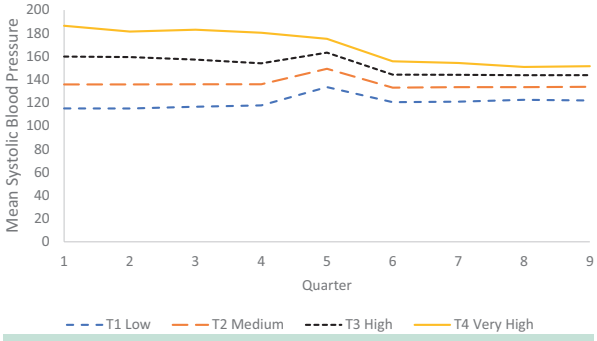

Figure 2 Mean systolic blood pressure for systolic blood pressure trajectories by 90-day periods prior to (Quarter 1-4) and after (Quarter 6-9) the index event (Quarter 5).

When we compared intensification for each of the other trajectories to the medium trajectory (T2), we found a negative coefficient for the low trajectory (T1), indicating a decrease in number of drug classes. In contrast, intensification increased significantly for the high and very high trajectories (T3 and T4).

Mortality and Recurrent Stroke

Results from Cox-proportional hazard models for 365-day mortality and recurrent stroke are presented in Table 3. Among covariates, the hazard ratios (HR) for mortality were significantly higher with: advancing age, an index stroke (vs TIA), a history of diabetes, chronic kidney disease, dementia, myocardial infarction, peripheral vascular disease, and congestive heart failure, and current smoking. The hazard ratios for a recurrent stroke were significantly higher with a history of stroke or an index stroke, current smoking, or a history of diabetes, hypertension, chronic kidney disease, or myocardial infarction.

The HRs for the 4 trajectories displayed a J-curve pattern in predicting 365-day mortality. In comparison with the medium trajectory (HR 1.00), the low systolic blood pressure trajectory (T1) had an HR of 1.37 (95% confidence interval [CI], 1.21-1.54); the high trajectory had an HR of 1.08 (CI, 0.93-1.25); and the very high trajectory had an HR of 1.59 (CI,1.10-2.29). Hypertensive medication intensification had a significant HR of 0.92 (CI, 0.86-0.98); although the number of medication classes was not significant. Finally, the greater the variability of systolic blood pressure readings (% CV) in the 90-day periods prior to the index event, the greater the hazard of mortality (HR 1.02; CI, 1.01-1.03).

In the model for a recurrent stroke (Table 3), individuals in the high systolic blood pressure trajectory (T3) had a significantly higher HR than the medium systolic blood pressure trajectory (T2 reference category). Unlike the mortality outcome, we found no evidence of a J-curve. The HR for T1 trajectory was not significantly different from the HR for T2. Nor was medication intensification significantly related to a recurrent stroke. Also, the HR for T4 trajectory (very high systolic blood pressure) was not significantly different from the T2 HR. This finding could have been due to insufficient statistical power; the number of people with the T4 trajectory was relatively small (n = 266). The 365-day recurrent stroke rate for the T4 trajectory was 9.8%, compared with 6.3% for T1, 7.4% for T2, and 10.7% for T3 (Table 1). In a model duplicating the analysis in Table 3, but combining T3 and T4, we found a significant positive HR of 1.29 for the T3/T4 combined trajectories (Supplementary Table 2).

DISCUSSION

Earlier research with a 2007 cohort of stroke patients in VA Medical Centers documented inadequate blood pressure control despite numerous opportunities to improve control through better management of hypertensives and adherence

Table 2 Linear Model Results for Medication Intensification

	Estimate (SE)	*P* Value	Estimate (SE)	*P* Value
Age	−0.003 (0.001)	< .001	−0.003 (0.001)	< .001
Male	0.052 (0.029)	.073	0.047 (0.029)	.101
African-American	0.059 (0.014)	< .001	0.047 (0.014)	.001
Admitted	0.085 (0.019)	< .001	0.079 (0.019)	< .001
Index stroke	0.060 (0.021)	.004	0.050 (0.021)	.015
History of TIA	−0.020 (0.020)	.309	−0.008 (0.020)	.697
History of stroke	−0.068 (0.017)	< .001	−0.066 (0.017)	< .001
History of diabetes	−0.033 (0.012)	.006	−0.039 (0.012)	.001
History of hypertension	0.015 (0.018)	.410	−0.025 (0.018)	.168
History of chronic kidney disease	−0.040 (0.015)	.008	−0.049 (0.015)	.001
History of dementia	−0.054 (0.022)	.014	−0.046 (0.022)	.035
History of myocardial infarction	−0.021 (0.022)	.338	−0.011 (0.022)	.597
History of peripheral vascular disease	−0.037 (0.016)	.023	−0.033 (0.016)	.046
History of heart failure	−0.037 (0.016)	.023	−0.014 (0.016)	.401
Current smoker	0.038 (0.013)	.004	0.040 (0.013)	.002
Trajectory				
Low (mean systolic = 116 mm Hg)			−0.098 (0.015)	< .001
Medium (mean systolic = 136 mm Hg)			0.00	
High (mean systolic = 158 mm Hg)			0.160 (0.017)	< .001
Very high (mean systolic = 183 mm Hg)			0.418 (0.049)	< .001

Notes: Mean Systolic is average of systolic blood pressure readings in the 12 months prior to the index event. Difference in medications is number of classes in the 90-day period prior to the index event minus the number of classes in the 90-day period prior to the event.

SE = standard error; TIA = transient ischemic attack.

Table 3 Proportional Hazards Models for Mortality or a Recurrent Stroke within 12 Months After Discharge

	Mortality Within 12 Months		Recurrent Stroke Death as Competing Risk	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age	1.06 (1.05-1.06)	< .001	0.99 (0.98-0.99)	< .001
Male	1.02 (0.75-1.37)	.922	0.99 (0.76-1.28)	.942
African-American	0.94 (0.83-1.06)	.314	1.13 (1.01-1.27)	.039
Admitted	1.05 (0.88-1.25)	.610	0.70 (0.58-0.83)	< .001
Index stroke	1.47 (1.21-1.78)	< .001	2.11 (1.71-2.61)	< .001
History of TIA	1.09 (0.91-1.30)	.338	1.10 (0.91-1.33)	.328
History of stroke	1.16 (1.00-1.35)	.052	1.34 (1.13-1.61)	.001
History of diabetes	1.18 (1.07-1.31)	.002	1.24 (1.11-1.39)	< .001
History of hypertension	0.98 (0.83-1.17)	.850	1.29 (1.06-1.56)	.011
History of chronic kidney disease	1.35 (1.21-1.51)	< .001	1.15 (1.01-1.30)	.032
History of hyperlipidemia	0.71 (0.63-0.80)	< .001	0.97 (0.86-1.10)	.626
History of dementia	1.90 (1.68-2.16)	< .001	0.88 (0.72-1.09)	.240
History of myocardial infarction	1.29 (1.11-1.50)	.001	1.22 (1.02-1.45)	.026
History of peripheral vascular disease	1.25 (1.11-1.41)	< .001	1.09 (0.94-1.25)	.250
History of heart failure	1.70 (1.52-1.91)	< .001	0.98 (0.85-1.12)	.731
Current smoker	1.29 (1.15-1.44)	< .001	1.15 (1.03-1.29)	.012
Trajectory				
Low (mean systolic = 116 mmm Hg)	1.36 (1.21-1.54)	< .001	0.92 (0.79-1.06)	.244
Medium (mean systolic = 136 mm Hg)	1.00		1.00	
High (mean systolic = 158 mm Hg)	1.04 (0.90-1.21)	.561	1.32 (1.15-1.51)	< .001
Very high (mean systolic = 183 mm Hg)	1.56 (1.08-2.25)	.017	1.05 (0.71-1.56)	.797
Increase in medications	0.92 (0.86-0.97)	.005	0.98 (0.92-1.05)	.616
Greater systolic variability	1.02 (1.01-1.03)	< .001	1.00 (0.99-1.01)	.978

Notes: Mean systolic is average of systolic blood pressure readings in the 12 months prior to the index event. Increase in medications is number of classes in the 90-day period after the index event minus the number of classes in the 90-day period prior to the event.

CI = confidence interval; HR = hazard ratio; TIA = transient ischemic attack.

counseling.[22,23] Our findings from 10 years later suggest substantial improvement in blood pressure control. After their index stroke or TIA, individuals in our study with high and very high systolic blood pressure trajectories experienced substantial decrease in systolic blood pressure. The post-discharge decrease in systolic blood pressure coincided with the intensification of antihypertensive medication. Medication intensification was, in turn, related significantly to lower all-cause mortality.

An important finding from our study was the J-curve pattern of significantly higher mortality for individuals in both the lowest and very highest systolic blood pressure trajectories, a pattern observed in some prior research.[1,10,13,28-31] The higher all-cause mortality for individuals with a low systolic blood pressure trajectory may have been due to their greater prevalence of dementia and cardiovascular disease, for example, myocardial infarction, chronic heart failure, and peripheral vascular disease.

We also found that inpatient admission (compared with discharge directly from the ED) was more likely for patients with higher systolic blood pressure trajectories, and it was associated with greater medication intensification and lower hazard of recurrent stroke. In earlier studies, we found inpatient admission to be associated with expeditious stroke/TIA evaluation, increased likelihood of receiving preventive measures, and improved care coordination with outpatient providers and services.[5,20]

Finally, the relationship between greater variability in blood pressure readings and increased hazard of mortality is noteworthy clinically. Prior studies have found that variability in systolic blood pressure between visits was a strong predictor of stroke.[32-35] Although we did not find the association between systolic blood pressure variability and recurrent stroke, its relationship to mortality offers evidence for its prognostic value and in targeting for hypertension treatment.

Limitations

The study findings have limited generalizability because they are based on a population of largely male veterans in the VA health care system. Our sample was restricted further to patients with at least 2 systolic blood pressure readings, and thus, these individuals could have better managed blood pressure and antihypertensive medications than the average patient in the VA or other settings. In addition, our sample included individuals with either stroke or TIA and with either an ED visit only or with an inpatient admission. Prior research on outcomes after a vascular event has focused on inpatient admissions after stroke, a narrower population at higher risk for a subsequent stroke or mortality. The very highest systolic blood pressure trajectory (T4) was small (1% of the sample), with relatively high systolic blood pressure variance. Thus, we have difficulty inferring about mortality or recurrent stroke for this group of patients. Finally, although we observed significant decreases, many individuals with high or very high trajectories (T3 and T4) still had mean systolic blood pressures above goals of 140 or 130 mm Hg.

CONCLUSIONS

Individuals in our study could be successfully classified into 4 relatively stable systolic blood pressure trajectories. Those with a high or very high pre-event systolic blood pressure trajectory had significantly increased medication intensity, a substantial decrease in systolic blood pressure, and a significantly reduced risk of mortality after their stroke or TIA. These findings point to the importance clinically of monitoring blood pressure over multiple time points and of instituting enhanced hypertension management.

References

1. Benjamin EJ, Muntner P, Alonso A, et al. Heart Disease and Stroke Statistics−2019 Update: a report from the American Heart Association. *Circulation* 2019;139:e56–e528.
2. Bravata DM, Myers LJ, Homoya B, et al. The protocol-guided rapid evaluation of veterans experiencing new transient neurological symptoms (PREVENT) quality improvement program: rationale and methods. *BMC Neurol* 2019;19(1):294.
3. Fletcher RD, Amdur RL, Kolodner R, et al. Blood pressure control among US veterans: a large multiyear analysis of blood pressure data from the Veterans Administration health data repository. *Circulation* 2012;125(20):2462–8.
4. Mouradian MS, Majumdar SR, Senthilselvan A, Khan K, Shuaib A. How well are hypertension, hyperlipidemia, diabetes, and smoking managed after a stroke or transient ischemic attack? *Stroke* 2002;33:1656–9.
5. Bravata DM, Myers LJ, Reeves M, et al. Processes of care associated with risk of mortality and recurrent stroke among patients with transient ischemic attack and nonsevere ischemic stroke. *JAMA Netw Open* 2019;2(7):e196716.
6. Cushman WC, Ford CE, Cutler JA, et al. Success and predictors of blood pressure control in diverse North American settings: the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT). *J Clin Hypertens (Greenwich)* 2002;4(6):393–404.
7. Kernan WN, Ovbiagele B, Black HR, et al. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2014;45(7):2160–236.
8. Brønnum-Hansen H, Davidsen M, Thorvaldsen P, Danish MONICA Study Group. Long-term survival and causes of death after stroke. *Stroke* 2001;32(9):2131–6.
9. Weiss A, Beloosesky Y, Kenett RS, Grossman E. Systolic blood pressure during acute stroke is associated with functional status and long-term mortality in the elderly. *Stroke* 2013;44(9):2434–40.
10. Ovbiagele B, Diener HC, Yusuf S, et al. Level of systolic blood pressure within the normal range and risk of recurrent stroke. *JAMA* 2011;306(19):2137–44.
11. Kitagawa K, Yamamoto Y, Arima H, et al. Effect of standard vs intensive blood pressure control on the risk of recurrent stroke: a randomized clinical trial and meta-analysis. *JAMA Neurol* 2019;76(11):1309–18.
12. Zonneveld TP, Richard E, Vergouwen MD, et al. Blood pressure-lowering treatment for preventing recurrent stroke, major vascular events, and dementia in patients with a history of stroke or transient ischaemic attack. *Cochrane Database Syst Rev* 2018;7(7):CD007858.
13. Boan AD, Lackland DT, Ovbiagele B. Lowering of blood pressure for recurrent stroke prevention. *Stroke* 2014;45(8):2506–13.
14. Portegies ML, Mirza SS, Verlinden VJ, et al. Mid- to-late-life trajectories of blood pressure and the risk of stroke: the Rotterdam Study. *Hypertension* 2016;67(6):1126–32.

15. Wills AK, Lawlor DA, Muniz-Terrera G, et al. Population heterogeneity in trajectories of midlife blood pressure. *Epidemiology* 2012;23(2):203–11.
16. Tielemans SM, Geleijnse JM, Menotti A, et al. Ten-year blood pressure trajectories, cardiovascular mortality, and life years lost in 2 extinction cohorts: the Minnesota Business and Professional Men Study and the Zutphen Study. *J Am Heart Assoc* 2015;4(3):e001378.
17. Kim BJ, Cho YJ, Hong KS, et al. Trajectory groups of 24-hour systolic blood pressure after acute ischemic stroke and recurrent vascular events. *Stroke* 2018;49(8):1836–42.
18. Bravata DM, Myers LJ, Perkins AJ, et al. Assessment of the protocol-guided rapid evaluation of veterans experiencing new transient neurological symptoms (PREVENT) program for improving quality of care for transient ischemic attack: a nonrandomized cluster trial. *JAMA Netw Open* 2020;3(9):e2015920.
19. Bravata DM, Myers LJ, Cheng E, et al. Development and validation of electronic quality measures to assess care for patients with transient ischemic attack and minor ischemic stroke. *Circ Cardiovasc Qual Outcomes* 2017;10(9):e003157.
20. Arling G, Sico JJ, Reeves MJ, Myers L, Baye F, Bravata DM. Modelling care quality for patients after a transient ischaemic attack within the US Veterans Health Administration. *BMJ Open Qual* 2019;8(4):e000641.
21. Sohn MW, Arnold N, Maynard C, Hynes DM. Accuracy and completeness of mortality data in the Department of Veterans Affairs. *Popul Health Metr* 2006;4:2.
22. Roumie CL, Ofner S, Ross JS, et al. Prevalence of inadequate blood pressure control among veterans after acute ischemic stroke hospitalization: a retrospective cohort. *Circ Cardiovasc Qual Outcomes* 2011;4(4):399–407.
23. Roumie CL, Zillich AJ, Bravata DM, et al. Hypertension treatment intensification among stroke survivors with uncontrolled blood pressure. *Stroke* 2015;46(2):465–70.
24. Jung T, Wickrama KA. An introduction to latent class growth analysis and growth mixture modeling. *Soc Personal Psychol Compass* 2008;2(1):302–17.
25. Muthén B, Muthén LK. Integrating person-centered and variable-centered analyses: Growth mixture modeling with latent trajectory classes. *Alcohol Clin Exp Res* 2000;24(6):882–91.
26. van der Nest G, Passos VL, MJ Candel, van Breukelen GJ. An overview of mixture modelling for latent evolutions in longitudinal data: modelling approaches, fit statistics and software. *Adv Life Course Res* 2020;43:100323.
27. Muthén LK, Muthen BO. *Mplus Statistical Analysis with Latent Variables: User's Guide*. Los Angeles: Muthén & Muthén; 2017.
28. Irie K, Yamaguchi T, Minematsu K, Omae T. The J-curve phenomenon in stroke recurrence. *Stroke* 1993;24(12):1844–9.
29. Leonardi-Bee J, Bath PM, Phillips SJ, Sandercock PA, IST Collaborative Group. Blood pressure and clinical outcomes in the International Stroke Trial. *Stroke* 2002;33(5):1315–20.
30. Rothwell PM, Coull AJ, Giles MF, et al. Change in stroke incidence, mortality, case-fatality, severity, and risk factors in Oxfordshire, UK from 1981 to 2004 (Oxford Vascular Study). *Lancet* 2004;363(9425):1925–33.
31. Xie X, Xu J, Gu H, et al. The J-curve association between systolic blood pressure and clinical outcomes in ischemic stroke or TIA: the BOSS Study. *Sci Rep* 2017;7(1):14023.
32. Rothwell PM, Howard SC, Dolan E, et al. Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. *Lancet* 2010;375(9718):895–905.
33. de Havenon A, Fino NF, Johnson B, et al. Blood pressure variability and cardiovascular outcomes in patients with prior stroke: a secondary analysis of PRoFESS. *Stroke* 2019;50(11):3170–6.
34. Manning LS, Mistri AK, Potter J, Rothwell PM, Robinson TG. Short-term blood pressure variability in acute stroke: post hoc analysis of the controlling hypertension and hypotension immediately post stroke and continue or stop post-stroke antihypertensives collaborative study trials. *Stroke* 2015;46(6):1518–24.
35. Manning LS, Rothwell PM, Potter JF, Robinson TG. Prognostic significance of short-term blood pressure variability in acute stroke: systematic review. *Stroke* 2015;46(9):2482–90.

SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amjmed.2022.02.012.

Supplementary Table 1 Generalized Logit Model with Trajectories as Outcomes

	T1 vs T2		T3 vs T2		T4 vs T2	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Age	0.99 (0.99-1.00)	< .001	1.00 (1.00-1.01)	.419	0.98 (0.97-0.99)	.002
Male	0.77 (0.65-0.93)	0.005	0.87 (0.70-1.07)	.194	1.70 (0.75-3.87)	.204
African-American	0.79 (0.71-0.87)	< .001	1.28 (1.16-1.40)	< .001	1.32 (1.01-1.72)	.042
Admitted	1.02 (0.90-1.15)	0.798	1.24 (1.07-1.43)	.003	1.95 (1.17-3.24)	.010
Index stroke	0.77 (0.67-0.88)	0.000	1.07 (0.92-1.25)	.376	1.93 (1.15-3.24)	.013
History of TIA	1.18 (1.04-1.34)	0.010	0.71 (0.61-0.82)	< .001	0.69 (0.42-1.14)	.150
History of stroke	1.11 (0.99-1.24)	0.069	0.97 (0.85-1.09)	.573	0.87 (0.60-1.25)	.436
History of diabetes	0.91 (0.84-0.99)	0.028	1.17 (1.08-1.28)	< .001	1.07 (0.83-1.38)	.596
History of hypertension	0.41 (0.37-0.46)	< .001	2.91 (2.41-3.51)	< .001	4.81 (2.24-10.34)	< .001
History of chronic kidney disease	1.00 (0.91-1.11)	0.938	1.25 (1.13-1.39)	< .001	1.73 (1.31-2.28)	< .001
History of dementia	1.29 (1.12-1.48)	< .001	0.90 (0.76-1.05)	.175	0.87 (0.53-1.43)	.575
History of myocardial infarction	1.45 (1.27-1.66)	< .001	0.93 (0.79-1.10)	0.398	1.06 (0.67-1.67)	.797
History of peripheral vascular disease	1.28 (1.16-1.42)	< .001	0.98 (0.87-1.10)	0.746	1.14 (0.82-1.60)	.439
History of CHF	1.96 (1.78-2.16)	< .001	0.76 (0.67-0.85)	< .001	0.53 (0.36-0.79)	.002
Current smoker	1.02 (0.93-1.11)	0.692	0.98 (0.90-1.08)	0.734	0.83 (0.63-1.09)	.183

CHF = congestive heart failure; CI = confidence interval; OR = odds ratio; TIA = transient ischemic attack.

Supplementary Table 2 Proportional Hazards Models for Mortality or a Recurrent Stroke within 12 Months After Discharge — High and Very High Systolic Blood Pressure Trajectories (T3 and T4) Combined

	Mortality within 12 Months		Recurrent Stroke Death as Competing Risk	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age	1.06 (1.05-1.06)	< .001	0.99 (0.98-0.99)	< .001
Male	1.02 (0.76-1.37)	.907	0.99 (0.76-1.28)	.928
African-American	0.94 (0.83-1.06)	.326	1.13 (1.01-1.27)	.039
Admitted	1.05 (0.88-1.25)	.594	0.70 (0.58-0.83)	< .001
Index stroke	1.47 (1.22-1.78)	< .001	2.11 (1.71-2.60)	< .001
History of TIA	1.09 (0.91-1.30)	.344	1.10 (0.91-1.34)	.324
History of stroke	1.16 (1.00-1.34)	.055	1.34 (1.13-1.61)	.001
History of diabetes	1.18 (1.07-1.31)	.002	1.24 (1.11-1.39)	< .001
History of hypertension	0.99 (0.83-1.17)	.863	1.29 (1.06-1.56)	.011
History of chronic kidney disease	1.36 (1.21-1.51)	< .001	1.15 (1.01-1.30)	.034
History of hyperlipidemia	0.71 (0.63-0.80)	< .001	0.97 (0.86-1.10)	.627
History of dementia	1.90 (1.67-2.16)	< .001	0.88 (0.72-1.09)	.243
History of myocardial infarction	1.29 (1.11-1.50)	.001	1.22 (1.02-1.44)	.026
History of peripheral vascular disease	1.25 (1.11-1.41)	< .001	1.09 (0.94-1.25)	.253
History of CHF	1.70 (1.51-1.90)	< .001	0.98 (0.85-1.12)	.740
Current smoker	1.29 (1.15-1.44)	< .001	1.15 (1.03-1.29)	.011
Trajectory				
Low (mean systolic = 116 mm Hg)	1.36 (1.21-1.54)	< .001	0.92 (0.79-1.06)	.242
Medium (mean systolic = 136 mm Hg)	1.00		1.00	
High andvery high (mean systolic = 160 mm Hg)	1.09 (0.94-1.25)	.249	1.29 (1.14-1.47)	< .001
Difference in medications	0.92 (0.86-0.98)	.005	0.98 (0.92-1.05)	.587
Systolic coefficient of variation	1.02 (1.01-1.03)	< .001	1.00 (0.99-1.01)	.971

Notes: Mean Systolic is average of blood pressure readings in the 12 months prior to the index event. Difference in medications is number of classes in the 90-day period prior to the index event minus the number of classes in the 90-day period prior to the event.

CHF = congestive heart failure; CI = confidence interval; HR = hazard ratio; OR = odds ratio; TIA = transient ischemic attack.