One-Year Systolic Blood Pressure Trajectory After Acute Ischemic Stroke

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Abstract

Although the effect of blood pressure on post-stroke outcome is well-recognized, the long-term trajectory of blood pressure after acute ischemic stroke and its influence on outcomes have not yet been fully elucidated. From a multicenter prospective registry of acute ischemic stroke patients, 5,514 patients with measurements of systolic blood pressure (SBP) at more than 2 of 7 prespecified time-points, up to 1-year after stroke onset, were analyzed. Outcome measures, a composite of stroke recurrence, myocardial infarction and mortality, and each stroke recurrence and mortality, were prospectively collected up to 1-year after stroke onset. The study subjects were categorized into 4 groups according to their SBP trajectories: *Low* (27.0%), *Moderate* (59.5%), *Persistently high* (1.2%), and *Slowly dropping* (12.4%). After adjustments for pre-determined covariates, the *Slowly dropping SBP Group* was at higher risk of the composite outcome (hazard ratio, 1.32; 95% confidence interval, 1.05—1.65), and mortality (1.35; 1.03—1.78) compared to the *Moderate SBP Group*. Four main 1-year longitudinal SBP trajectories were identified after acute ischemic stroke. One trajectory, slowly dropping SBP, was particularly prone to adverse outcomes after stroke. These findings provide possible leads for future investigations of SBP control targets after stroke.

Introduction

Clinicians are accustomed to managing blood pressure (BP) according to single measurements with limited attention to longitudinal changes in BP over time. Analysis of BP data based on trajectories is another option, although this approach is often not explored by practitioners in routine office practice [1]. Studies adopting group-based approaches according to BP trajectory patterns are primarily population-based studies of the effect of longitudinal BP changes over a lifetime. These studies have shown that individuals with sustained, poorly controlled high BP have a higher risk of cardiovascular events or mortality [2–6].

Whereas an elevation or early surge of BP after acute stroke is well known [7], some recent studies on BP trajectory after acute ischemic stroke show that BP changes during the acute period have distinct patterns that are associated with prognosis [8–10]. Specifically, individuals with distinguishable BP trajectory patterns, whose BP does not drop or remains elevated during the first few hours after stroke onset, may be at higher risk of a poor prognosis [8]. However, the dynamics of BP beyond the acute stroke time period are unknown, as there is a paucity of studies on the prognostic impact of the long-term time course of BP changes after ischemic stroke. Such knowledge may be important as it may facilitate more appropriate BP management after stroke.

In this study, we describe the patterns of BP changes up to 1-year after ischemic stroke using group-based trajectory models to categorize BP and to explore the associations between BP trajectory groups and stroke outcomes.

Methods

Study subjects

Patients with acute ischemic stroke, who were admitted to the 10 participating centers of the Clinical Research Collaboration for Stroke in Korea (CRCS-K) registry [27,28] between January 2010 and December 2011 and who met the study's eligibility criteria, i.e., 1) hospitalization within 7 days of symptom onset (N = 6,547) and 2) documentation of ischemic lesions relevant to stroke symptoms on diffusion-weighted images (DWI) (N = 5,791), were identified in the CRCS-K registry database. Those who died during hospitalization due to the index stroke were excluded from this study (N = 158).

Informed consent was waived for collection of clinical information in the CRCS-K registry with approval by the Institutional Review Board (IRB) of all participating centers (Seoul National University Bundang Hospital, Nowon Eulji Medical Center, Inje University Ilsan Paik Hospital, Soonchunhyang University Hospital, Eulji University Hospital, Seoul Medical Center, Yeungnam University Medical Center, Dong-A University Hospital, Chonnam National University Hospital, Hallym University Sacred Heart Hospital) as the data was collected under the purpose of quality of stroke care monitoring and improvement and the data was provided to the researchers after de-identification. In addition, analysis of the registry database with additional collection of data for this study was approved by all local ethics committees mentioned above. All methods were carried out in accordance with relevant guidelines and regulations.

Blood pressure and clinical data collection

For the 5,633 eligible patients, BP data were collected at 7 time-points after onset (day 0, day 3, day 7, day 30, day 90, day 180, and day 365) by medical record review. BP data obtained after outcome events were excluded from the analysis. BP was measured during hospitalization or at outpatient clinic during routine practice, following the institutional protocols of each hospital. It was recommended to use a standard mercury sphygmomanometer or a non-invasive BP monitoring device on the non-paralytic arm. A total of 452,654 systolic BP (SBP) measurements were collected, along with the date and time of measurement. The measured SBP was allocated to one of the aforementioned 7 time-points that was closest to the measured date or time. The number of patients with allocated SBP data at each time-point and median duration from the measured time-points to the allocated time-points are described in Supplemental Table 1.

Basic demographics and clinical information on vascular risk factors (hypertension, diabetes, hyperlipidemia, atrial fibrillation, coronary heart disease, current smoking, and previous history of stroke or transient ischemia attack); stroke characteristics, including initial stroke severity according to the National Institute of Health stroke scale (NIHSS) and stroke subtypes according to the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification, with some modification [29]; premorbid functional status, as recorded in the modified Rankin scale; symptomatic steno-occlusion (more than 50% of stenosis or occlusion) of relevant major cerebral arteries; acute treatment modalities; and medications at discharge were obtained directly from the CRCS-K registry database.

Information on antihypertensive agents used during hospitalization and in outpatient clinics was collected from the reimbursement claims database of each hospital. The number of antihypertensive agents, date of their prescription, and number of days of treatment were extracted and used for analysis in this study.

Outcome measures

The primary outcome measure was a composite of stroke recurrence, myocardial infarction, and all-cause mortality. The secondary outcome measures were stroke recurrence and mortality. All outcome events were captured prospectively up to 1 year after the index stroke, based on structured telephone interview or during routine follow-up visits in the outpatient clinics. Detailed definitions of outcomes and the protocols of the CRCS-K registry are published elsewhere [27,28].

Statistical analysis

We applied a group-based trajectory model approach using the TRAJ procedure of SAS software to determine the SBP trajectories during 1 year after the index stroke and categorizes patients according to the trajectory groups [8,30]. Briefly, this approach is an application of a finite mixture model, in which the longitudinal SBP data were fitted and grouped by a maximum likelihood method as a mixture of multiple latent trajectories in a censored normal model with a polynomial function of time [1]. Patients with 2 or more SBP data entries at the aforementioned 7 time-points were eligible for this analysis. The optimal number of groups were determined using the Bayesian information criterion (BIC) comparing $2 \times \Delta BIC$ between each number of groups and polynomial orders for time function (Supplemental Tables 2 and 3). Each group was named according to the visual description of the SBP trajectory.

In each group of patients, parameters were described as mean ± SD for interval variables, frequency (%) for categorical variables, and median with interquartile range (IQR) for ordinal variables. Comparisons among groups were made by chi-square tests, one-way analysis of variance, or the Kruskal–Wallis test according to the type of data. The cumulative incidence of the primary and secondary outcomes in each SBP trajectory group was estimated using the Kaplan–Meier (product-limit) method, and crude cumulative incidence was compared among groups using the log-rank test.

For multivariable analysis, a shared frailty model with the participating centers as a random effect was used along with predetermined covariates. Hazard ratios for each outcome among groups were provided by: 1) unadjusted models, 2) model 1 adjusting for age, sex, time interval from onset to hospital arrival stroke subtype, and initial NIHSS score, and 3) model 2 with further adjustments for pre-stroke mRS score; history of hypertension, diabetes, hyperlipidemia, TIA, or stroke; atrial fibrillation; coronary heart disease; current smoking; intravenous thrombolysis; endovascular thrombectomy; and prescription of antiplatelet, anticoagulant, statin, and/or antihypertensive agents (angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, beta-blocker, calcium channel blocker, diuretics) at discharge. Information on the symptomatic steno-occlusion of a relevant artery was provided.

As a sensitivity analysis, the group-based trajectory modeling approach was restricted to patients who had 3 or more SBP data entries at the 7 time-points, to prove the robustness of the study results.

All statistical analyses were conducted using SAS software version 9.4. (SAS Institute Inc. Cary, NC, USA), and R software version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria). A p-value < 0.05 was considered as statistically significant.

Results

A total of 5,514 patients who had at least 2 SBP data entries at the 7 time-points were included in the final analysis. Using the group-based trajectory model, the patients were grouped into 4 SBP trajectory categories (Fig. 1 and Supplemental Table 2). Based on the visual depiction of the SBP curves over time, the SBP trajectory groups were named the "*Low SBP*" (N = 1,487), "*Moderate SBP*" (N = 3,280), "*Persistently high SBP*" (N = 66), and "*Slowly dropping SBP*" (N = 681) groups. In the first 3 groups, SBP decreased in the first 3–7 days and remained steady thereafter. The mean SBP in these groups was in the range of approximately 114–116 mmHg in the *Low SBP Group*, 130–135 mmHg in the *Moderate SBP Group*, and 147–171 mmHg in the *Persistently high SBP Group*. In the *Slowly dropping SBP Group*, the SBP trajectory decreased more slowly over the first month, from 182 mmHg to 135 mmHg, and then paralleled the SBP trajectory of the *Moderate SBP Group.*

The patient characteristics differed among the SBP trajectory groups (Table 1). The *Persistently high SBP Group* were younger than the other groups and were more likely to have vascular risk factors, such as hypertension or diabetes, whereas the *Low SBP Group* were more likely to have atrial fibrillation. Nearly 90% of individuals in the *Slowly dropping SBP Group* and *Persistently high SBP Group* had hypertension. More than 70% of individuals in these two groups were on antihypertensive medications at discharge. In terms of antihypertensive drug class, renin–angiotensin–aldosterone system inhibitors were most frequently prescribed at discharge, followed by calcium channel blockers. Beta-blockers or diuretics were prescribed infrequently. The proportion of individuals diagnosed with hypertension before the index stroke was markedly higher in the *Slowly dropping SBP Group* and in the *Persistently high SBP Group* than in the other two groups. The antihypertensive prescription rate among those diagnosed with hypertension was 78% at stroke onset in the *Slowly dropping SBP Group* and exceeded 85% in the other 3 groups. In terms of stroke subtypes, large artery atherosclerosis was most common in the *Persistently high SBP Group* (59%), while cardioembolic stroke was most common in the *Low SBP Group* (30%).

Table 1
Comparison of baseline characteristics among systolic blood pressure trajectory groups

	Low SBP (N = 1,487)	Moderate SBP (N = 3,280)	Persistently high SBP (N = 66)	Slowly dropping SBP (N = 681)	P-value
Age, mean ± SD	66.04 ± 13.55	67.96 ± 12.45	63.00 ± 10.78	67.31 ± 12.43	< 0.001
Male	889 (59.8)	1946 (59.3)	38 (57.6)	384 (56.4)	0.477
Body-mass index, mean ± SD	23.14 ± 3.25	23.72 ± 3.09	25.67 ± 3.31	23.91 ± 3.27	< 0.001
Onset to arrival time, hour, median (IQR)	7.15 (1.88–30.23)	9.42 (2.57–35.19)	21.81 (6.45–52.38)	9.00 (2.52–27.50)	< 0.001
Hypertension	805 (54.1)	2444 (74.5)	59 (89.4)	602 (88.4)	< 0.001
Diagnosed before hospitalization	708 (47.6)	2161 (65.9)	55 (83.3)	488 (71.7)	< 0.001
On antihypertensive agents before hospitalization	636 (42.8)	1869 (57.0)	49 (74.2)	382 (56.1)	< 0.001
Diagnosed after hospitalization	97 (6.5)	283 (8.6)	4 (6.1)	114 (16.7)	< 0.001
Diabetes	454 (30.5)	1148 (35.0)	41 (62.1)	258 (37.9)	< 0.001
Hyperlipidemia	531 (35.7)	1162 (35.4)	31 (47.0)	223 (32.7)	0.111
Atrial fibrillation	389 (26.2)	569 (17.3)	4 (6.1)	96 (14.1)	< 0.001
Coronary heart disease	159 (10.7)	295 (9.0)	6 (9.1)	51 (7.5)	0.092
Stroke or TIA	338 (22.7)	792 (24.1)	22 (33.3)	147 (21.6)	0.104
Current smoker	398 (26.8)	850 (25.9)	20 (30.3)	192 (28.2)	0.547
Pre-stroke mRS score					0.865

Values are numbers of patients (%) if not otherwise indicated.

SBP, systolic blood pressure; SD, standard deviation; IQR, interquartile range; TIA, transient ischemic attack; NIHSS, National Institute of Health Stroke Scale; mRS, modified Rankin scale; ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers

	Low SBP (N = 1,487)	Moderate SBP (N = 3,280)	Persistently high SBP (N = 66)	Slowly dropping SBP (N = 681)	P-value
0	1222 (82.2)	2696 (82.2)	51 (77.3)	560 (82.2)	
1	87 (5.9)	216 (6.6)	5 (7.6)	42 (6.2)	
2 or more	178 (12.0)	368 (11.2)	10 (15.2)	79 (11.6)	
Initial NIHSS score, median (IQR)	4 (2–9)	3 (2–7)	2.5 (1–4)	4 (2–8)	< 0.001
Stroke subtype					< 0.001
Large artery atherosclerosis	465 (31.3)	1345 (41.0)	39 (59.1)	289 (42.4)	
Small vessel occlusion	192 (12.9)	633 (19.3)	12 (18.2)	142 (20.9)	
Cardioembolism	439 (29.5)	601 (18.3)	4 (6.1)	107 (15.7)	
Other determined	45 (3.0)	63 (1.9)	1 (1.5)	13 (1.9)	
Undetermined	346 (23.3)	638 (19.5)	10 (15.2)	130 (19.1)	
Symptomatic steno-occlusion of the relevant arteries	712 (47.9)	1508 (46.0)	34 (51.5)	312 (45.8)	0.513
Intravenous thrombolysis	225 (15.1)	361 (11.0)	2 (3.0)	75 (11.0)	< 0.001
Endovascular reperfusion therapy	127 (8.5)	155 (4.7)	0 (0.0)	25 (3.7)	< 0.001
Antiplatelet at discharge	1104 (74.2)	2777 (84.7)	62 (93.9)	589 (86.5)	< 0.001
Anticoagulation at discharge	445 (29.9)	554 (16.9)	4 (6.1)	105 (15.4)	< 0.001
Statin at discharge	1163 (78.2)	2677 (81.6)	57 (86.4)	597 (87.7)	< 0.001
Antihypertensive agents at discharge	547 (36.8)	1645 (50.2)	49 (74.2)	485 (71.2)	< 0.001

Values are numbers of patients (%) if not otherwise indicated.

SBP, systolic blood pressure; SD, standard deviation; IQR, interquartile range; TIA, transient ischemic attack; NIHSS, National Institute of Health Stroke Scale; mRS, modified Rankin scale; ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers

	Low SBP (N = 1,487)	Moderate SBP (N = 3,280)	Persistently high SBP (N = 66)	Slowly dropping SBP (N = 681)	P-value
ACEI or ARB	345 (63.1)	1121 (68.1)	38 (77.6)	308 (63.5)	
Beta-blockers	117 (21.4)	281 (17.1)	11 (22.4)	86 (17.7)	
Calcium channel blockers	212 (38.8)	769 (46.7)	27 (55.1)	317 (65.4)	
Diuretics	109 (19.9)	268 (16.3)	7 (14.3)	87 (17.9)	
Values are numbers of patients (%) if not otherwise indicated.					
SBP, systolic blood pressure; SD, standard deviation; IQR, interquartile range; TIA, transient ischemic attack; NIHSS, National Institute of Health Stroke Scale; mRS, modified Rankin scale; ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers					

The median follow-up duration was 373 (IQR, 363–399) days. Overall, the 1-year cumulative incidence was 11.9% for the primary outcome, 5.0% for stroke recurrence, and 8.2% for all-cause mortality. The *Slowly dropping SBP Group* showed the highest cumulative incidence for the primary outcome during most of the 1-year follow-up period, but the final 1-year cumulative incidence was comparable in both the *Slowly dropping SBP Group* and the *Persistently high SBP Group* (15.7% vs. 15.8%). The 1-year cumulative incidence of mortality was highest in the *Slowly dropping SBP Group* (11.1%). Interestingly, the 1-year cumulative incidence for all outcomes in the *Low SBP Group* was comparable with that of the *Moderate SBP Group*, although numerically, the value was higher in the *Moderate SBP Group* than in the *Low SBP Group* (Fig. 2 and Supplemental Table 4).

In both adjusted models 1 and 2, only the *Slowly dropping SBP Group* had a significantly higher hazard ratio, of 1.3, for the primary outcome than the *Moderate SBP Group*, which had the lowest 1-year cumulative incidence for the primary outcome. The hazard ratio for all-cause mortality was also increased significantly in the *Slowly dropping SBP Group*, but the hazard ratio for stroke recurrence was not. The hazard ratio for all outcomes was not increased significantly in the *Low SBP Group* or the *Persistently high SBP Group* as compared to the *Moderate SBP Group* (Table 2).

Table 2
Unadjusted and adjusted hazard ratios according the systolic blood pressures trajectory groups for outcome events

	Unadjusted model		Adjusted Model 1†		Adjusted Model 2‡	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Composite outcome						
Low SBP	0.91 (0.76–1.10)	0.34	0.86 (0.71–1.04)	0.12	0.86 (0.71–1.04)	0.13
Moderate SBP	1		1		1	
Persistently high SBP	1.23 (0.65–2.30)	0.53	1.93 (1.03–3.64)	0.04	1.71 (0.90–3.23)	0.10
Slowly dropping SBP	1.30 (1.04–1.62)	0.02	1.35 (1.08–1.68)	0.009	1.32 (1.05–1.65)	0.01
Stroke recurrence						
Low SBP	0.81 (0.60–1.09)	0.16	0.77 (0.57–1.03)	0.08	0.76 (0.56–1.03)	0.07
Moderate SBP	1		1		1	
Persistently high SBP	1.85 (0.87–3.96)	0.11	2.09 (0.97–4.48)	0.06	1.74 (0.80–3.77)	0.16
Slowly dropping SBP	1.07 (0.76–1.53)	0.69	1.08 (0.76–1.54)	0.66	1.08 (0.76–1.55)	0.66
Mortality						
Low SBP	0.98 (0.78–1.22)	0.83	0.92 (0.74–1.15)	0.48	0.91 (0.73–1.14)	0.42
Moderate SBP	1		1		1	
Persistently high SBP	0.92 (0.38–2.23)	0.85	1.90 (0.78–4.62)	0.16	1.77 (0.72–4.33)	0.21
Slowly dropping SBP	1.36 (1.04–1.78)	0.02	1.40 (1.07–1.83)	0.01	1.35 (1.03–1.78)	0.03

† Adjusted for age, sex, onset to arrival time, stroke subtype, and initial National Institute of Health Stroke Scale score

‡ Adjusted for covariates for model 2 and premorbid modified Rankin's scale score, history of hypertension (diagnosed before and after admission), diabetes, hyperlipidemia, stroke or transient ischemia attack, atrial fibrillation, coronary heart disease, current smoking, intravenous thrombolysis, endovascular reperfusion therapy, discharge antiplatelet, discharge anticoagulant, discharge statin, discharge antihypertensive agent (angiotensin converting enzyme inhibitors or angiotensin receptor blockers, beta-blocker, calcium channel blocker, diuretics), and symptomatic steno-occlusion of relevant artery

	Unadjusted model	Adjusted Model 1†	Adjusted Model 2‡
HR (95%CI) and P-value by Shared Frailty Model for considering the center effect			
HR, hazard ratio; CI, confidence interval; SBP, systolic blood pressure			

Information on the antihypertensive agent prescription during the 1-year follow-up period was available for 3,627 patients. The overall rate of prescription of antihypertensive agents increased to approximately 70% during the first 2 months post-stroke and then decreased slightly (Fig. 3). The proportion of those receiving multiple antihypertensive agents reached about 40% at 2 months after stroke onset. The antihypertensive prescription rate was markedly higher in the *Persistently High SBP Group* and in the *Slowly dropping SBP Group* than in the other 2 groups, and more than 50% of participants in these groups were on multiple agents after day 30 (Fig. 4).

The sensitivity analysis, which was restricted to subjects who had more than 3 SBP data entries among the 7 possible time-points (N = 4,603), showed similar results for the 4 SBP trajectory groups, with a higher risk for the primary outcome in the *Persistently high SBP Group* and the *Slowly dropping SBP Group* (Supplemental Tables 5 and 6, Supplemental Figure).

Discussion

We identified 4 distinctive categories of SBP trajectory: the *Low SBP, Moderate SBP, Persistently high SBP*, and *Slowly dropping SBP* groups. Longitudinal changes in the mean SBP in the study subjects overall were similar to that of previous findings, in that more than 80% of patients with acute ischemic stroke had elevated SBP above 140 mmHg early after ischemic stroke;[15] this largely stabilized by 24 hours after stroke onset [7,11]. Using the BP trajectory model, we were able to find distinguishable patterns that could not be detected by observing the overall group mean of SBP. Furthermore, we observed that distinct patterns were associated with differences in clinical outcomes.

The most noteworthy category among the 4 SBP trajectory groups was the *Slowly dropping SBP Group*. Compared to the *Moderate SBP Group*, the *Slowly dropping SBP Group* had markedly higher SBP (approximately 180 mmHg at stroke onset), which decreased slowly during the first month, and finally reached a level of 120–130 mmHg; the SBP level at 30 days after the index stroke was similar to that in the *Moderate SBP Group*. However, the risk of the primary outcome was higher in the *Slowly dropping SBP Group* than in the *Moderate SBP Group*, despite the similarity in SBP levels after the first month. This result is concordant with the findings from previous studies focusing on BP trajectories in a more acute stroke time period. Our prior study showed that SBP during the first 24 hours after stroke onset had distinct trajectory groups, and patients who were classified by categories as having SBP above 150 mmHg at 24 hours had a higher risk of adverse events, including mortality [8]. Additionally, a secondary analysis of the CATIS trial about the SBP trajectories during the first week after stroke onset showed a similar result, in that patients with SBP above 160 mmHg had the highest risk of adverse events.[9]

Interestingly, in the latter study, patients who initially had a high SBP (approximately 180 mmHg), but which rapidly dropped to 140 mmHg (within 3 days), had a lower risk of mortality than those whose SBP remained high. In our study, the *Slowly dropping SBP Group* and *Persistently high SBP Group* may have been comparable to those with high early SBPs in these prior studies.

One possible explanation for the poor outcome in ischemic stroke patients with higher SBP at baseline is that high SBP is a marker of elevated sympathetic activity, which may lead to subsequent cardiovascular complications, and consequently makes an individual more prone to comorbidities, such as infection [12,13]. However, in the *Slowly dropping SBP Group*, more than one-third of the patients who were diagnosed with hypertension before the index stroke were not on antihypertensive medications at stroke onset. This implies undertreatment of hypertension in this patient group. Uncontrolled and sustained high BP throughout the lifetime is also known to result in poor outcomes. Previous studies analyzing the long-term BP trajectory in the general population consistently showed that those with higher BP have a higher risk of adverse events than those who are normotensive. BP trajectory groups with a high BP level show a higher risk of mortality [2,5,6,14]; cardiovascular events, such as stroke [4,6], myocardial infarction [4], heart failure [14], and atrial fibrillation [15]; and also subclinical markers, such as increased carotid intima-media thickness or left ventricular mass index [3].

BP drop during the early stage of ischemic stroke is known to result in subsequent neurological deterioration by decreasing cerebral perfusion [16], and current practice guidelines mention that initiating BP-lowering therapy within the first 48 or 72 hours of onset may have no benefit [17]. However, eventually lowering SBP to guideline-based levels (e.g., < 140 mmHg or < 130 mmHg) in patients with stroke or transient ischemic attack is recommended to prevent subsequent cardiovascular events [18]. It is not clear when to begin lowering of BP or how quickly target BP levels should be reached in patients with acute ischemic stroke. There have been several clinical trials, such as the CATIS, ENOS, and SCAST trial, all of which failed to show a benefit in the primary outcome endpoint with more intensive BP-lowering therapy in patients with acute stroke [19–21]. Our study results imply that the BP trajectory immediately after the acute stage of ischemic stroke is a potential target for BP-lowering interventions. More than half of the *Slowly dropping SBP Group* received no antihypertensive medication or only one medication at 30 days after stroke onset (Fig. 4). Intense treatment, particularly during the first 30 days after stroke onset, might improve outcomes in these patients. This area of research needs to be explored further, as physicians may feel that clinical equipoise exists in relation to when and how much to lower BP after stroke; this may explain, at least in part, the finding of no or only 1 antihypertensive medication being prescribed at 30 days in our *Slowly dropping SBP Group*.

It is interesting to note that the *Low SBP Group* did not have an evidently lower risk of mortality than the *Moderate SBP Group* (Table 2 and Supplemental Table 4). This result supports the findings from previous observational studies that there may be a “J-shaped” association between BP and outcomes [22,23]. About 30% of the *Low SBP Group* were classified as having cardioembolic stroke and about 25% had atrial fibrillation (Table 1). These findings might explain both the low SBP and poor outcome in these patients,

as atrial fibrillation results in decreased cardiac contractility and is associated with cardiovascular comorbidities, such as myocardial infarction and heart failure [24,25]. Our data showed that the *Low SBP Group* were more likely to have atrial fibrillation and coronary heart disease and to present with more severe neurologic deficits at arrival, all of which could increase mortality (Supplemental Table 7).

Our study had several limitations. First, as we included patients who had SBP measurements taken at no fewer than 2 of 7 time-points, there might be a potential selection bias. On the other hand, only 2 measurements are not adequate for estimating BP trajectories. We intended to maximize the inclusion of such patients to minimize possible selection bias and performed a sensitivity analysis with subjects with 3 or more SBP measurements, which demonstrated the robustness of our study results. Second, although we were able to find associations between 1-year SBP trajectories and outcomes, we cannot conclude that there is a causal relationship between our main outcome findings and SBP trajectory results. However, we analyzed SBP data that were obtained before outcome events, in order to maintain the temporal relationships between SBP measurements and outcome events. Third, all the centers participating in the CRCS-K registry are academic hospitals, and therefore the generalizability of the study results to the entire stroke population might be limited. However, the age and sex distributions of the CRCS-K registry subjects are similar to those of the ischemic stroke population in South Korea [26]. Forth, BP measurement protocol and device were not standardized between centers. Although we tried to consider the center effect using the Shared Frailty Model, this heterogeneity should be noted.

In conclusion, SBP trajectory in acute ischemic stroke patients were categorized into four distinct groups and patients in the *Slowly dropping SBP* group had poor outcome after index stroke event. While only small proportion of patients used antihypertensive agents despite high SBP during the early period in this group, meticulous BP management in these patients might be a potential target for improving outcome.

Declarations

Data availability: The data on which the findings of this study are based are available from the corresponding author upon reasonable request.

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Author contributions

Study concept and design: K.J.L., H.J.B. - Acquisition of data: B.J.K., M.K.H, J.T.K., K.H.C., D.I.S., J.K.C., D.H.K., D.E.K., W.S.R., J.M.P., K.K., S.J.L., M.S.O., K.H.Y., B.C.L., K.S.H., Y.J.C., J.C.C., T.H.P., S.S.P., J.H.K., W.J.K., K.B.L., Jun Lee, S.I.S., J.H.H. - Analysis and interpretation of data: K.J.L., H.J.B., L.S.L. - Drafting of

the manuscript: K.J.L., H.J.B. - Critical revision of the manuscript for important intellectual content: B.J., Juneyoung Lee; P.B.G., H.J.B. - Statistical analysis: J.S.L., K.J.L..

Competing interests:

Dr. Gorelick serves on a Data Monitoring Board for a clinical trial study of LCZ 696 in the treatment of heart failure for cognitive maintenance sponsored by Novartis. Dr. Bae is involved in the principal investigator, a member of steering committee, and/or a site investigator of multicenter clinical trials or clinical studies sponsored by Bayer, Boehringer Ingelheim, ESAI-Korea, Daichi Sankyo, AstraZeneca Korea, Dong-A Pharmaceutical, Yuhan Corporation, BMS Korea, Korean Drug Co., Ltd, Servier, Shire Korea Ltd., and Shin Poong Pharm. Co. Ltd.; served as the scientific advisory board for Amgen Asia Holding Limited. The remaining authors have no conflicts of interest to report.

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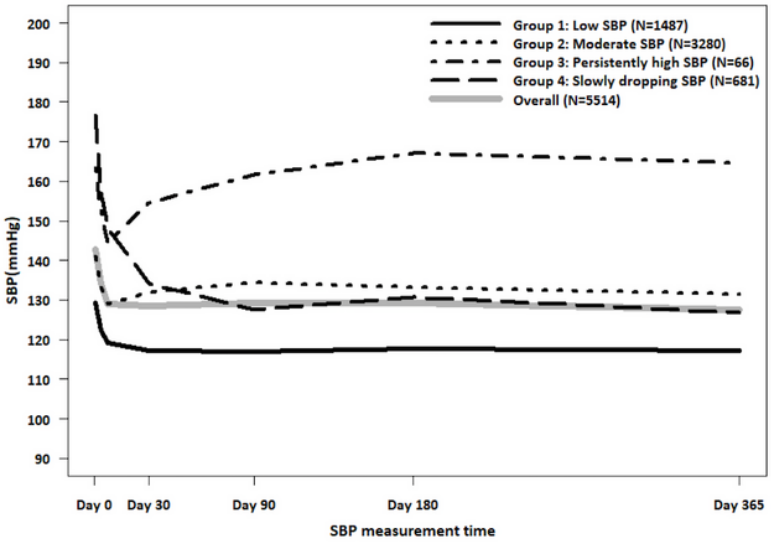
Figures



	Day 0	Day 3	Day 7	Day 30	Day 90	Day 180	Day 365
Low SBP, mmHg (mean ±SD)	124.68±17.42	118.56±13.99	116.00±13.29	113.79±13.98	113.52±13.51	114.66±13.06	114.17±13.95
Moderate SBP, mmHg (mean ±SD)	142.28±18.76	134.23±16.29	130.07±15.17	132.60±16.08	135.19±15.29	133.90±14.79	131.97±15.42
Persistently high SBP, (mean ±SD)	167.77±22.83	154.53±19.93	146.65±20.27	157.92±19.70	164.67±17.24	171.02±18.96	168.51±24.34
Slowly dropping SBP, (mean ±SD)	181.70±22.10	160.41±18.89	150.49±17.34	134.98±19.07	126.73±16.24	130.42±17.01	125.92±14.95
Overall, mmHg (mean ±SD)	142.82±25.49	134.24±20.78	129.09±18.33	128.57±18.52	129.14±18.27	129.30±17.81	127.81±17.94

Figure 1

Systolic blood pressure trajectory patterns until 1 year after index stroke event

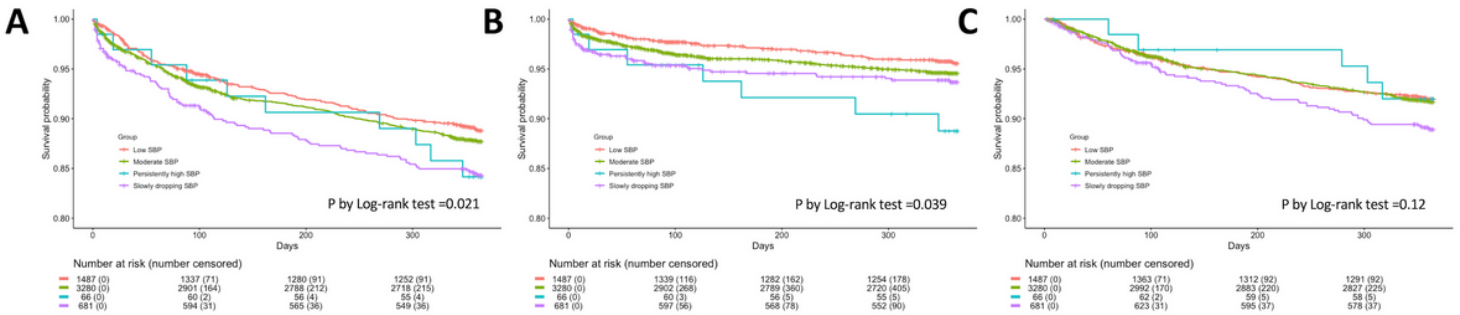


Figure 2

Survival curve of outcome events by systolic blood pressure trajectory group (A) Primary outcome (composite of stroke, myocardial infarction, and mortality) (B) Stroke recurrence (C) Mortality

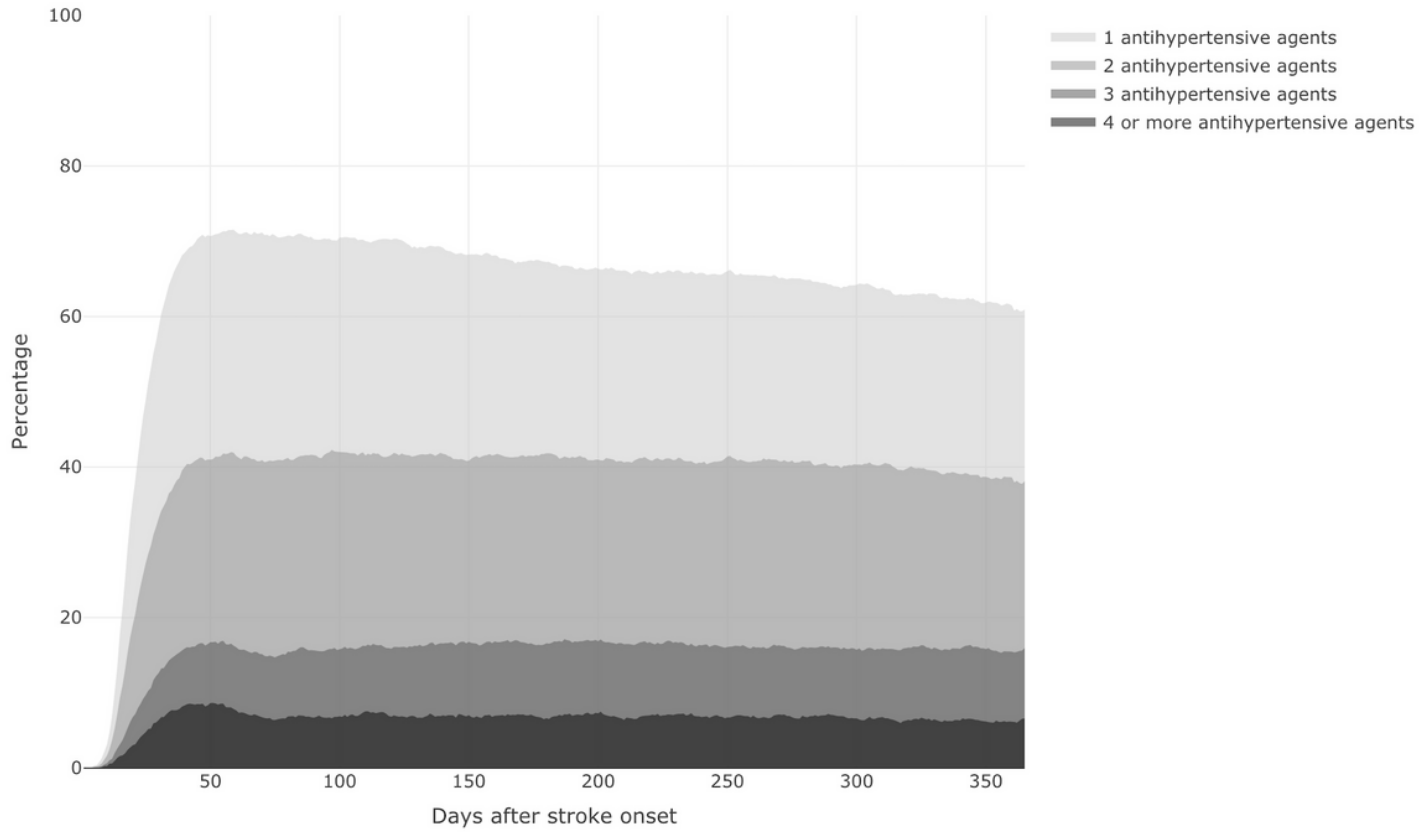


Figure 3

Number of prescribed antihypertensive agents according to day after stroke onset

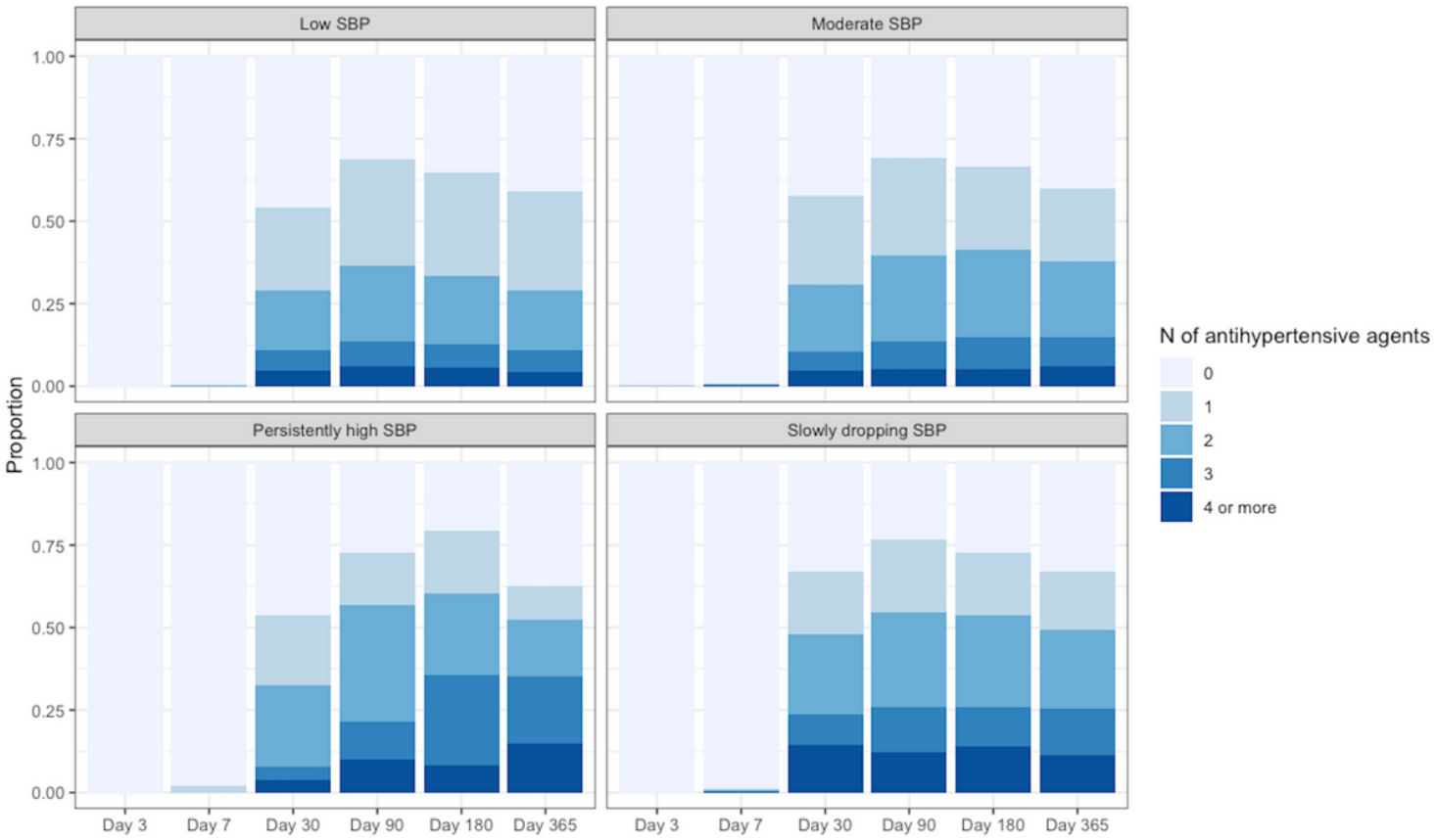


Figure 4

Number of prescribed antihypertensive agents according to day after stroke onset by systolic blood pressure trajectory group

Supplementary Files

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