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ORIGINAL RESEARCH

Treatment Intensification for Elevated Blood Pressure and Risk of Recurrent Stroke

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BACKGROUND: It remains unclear whether physicians' attitudes toward timely management of elevated blood pressure affect the risk of stroke recurrence.

METHODS AND RESULTS: From a multicenter stroke registry database, we identified 2933 patients with acute ischemic stroke who were admitted to participating centers in 2011, survived at the 1-year follow-up period, and returned to outpatient clinics ≥2 times after discharge. As a surrogate measure of physicians' attitude, individual treatment intensification (TI) scores were calculated by dividing the difference between the frequencies of observed and expected medication changes by the frequency of clinic visits and categorizing them into 5 groups. The association between TI groups and the recurrence of stroke within 1 year was analyzed using hierarchical frailty models, with adjustment for clustering within each hospital and relevant covariates. Mean±SD of the TI score was −0.13±0.28. The TI score groups were significantly associated with increased risk of recurrent stroke compared with Group 3 (TI score range, −0.25 to 0); Group 1 (range, −1 to −0.5), adjusted hazard ratio (HR) 13.43 (95% CI, 5.95–30.35); Group 2 (range, −0.5 to −0.25), adjusted HR 4.59 (95% CI, 2.01–10.46); and Group 4 (TI score 0), adjusted HR 6.60 (95% CI, 3.02–14.45); but not with Group 5 (range, 0–1), adjusted HR 1.68 (95% CI, 0.62–4.56). This elevated risk in the lowest TI score groups persisted when confining analysis to those with hypertension, history of blood pressure-lowering medication, no atrial fibrillation, and regular clinic visits and stratifying the subjects by functional capacity at discharge.

CONCLUSIONS: A low TI score, which implies physicians' therapeutic inertia in blood pressure management, was associated with a higher risk of recurrent stroke. The TI score may be a useful performance indicator in the outpatient clinic setting to prevent recurrent stroke.

Key Words: clinical inertia ■ hypertension ■ prevention ■ stroke ■ treatment intensification

Vascular events after ischemic stroke can be prevented by management of risk factors and administration of the appropriate antithrombotic.[1] Blood pressure (BP) control has been a mainstay in the prevention of recurrent stroke.[2] Although lowering BP is an effective therapy for reducing the risk of recurrent stroke, the best time for starting antihypertensive drugs or how quickly BP should be reduced is not clear in patients with acute stroke.[3] Clinicians may find themselves in a state of clinical equipoise concerning

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CLINICAL PERSPECTIVE

What Is New?

- Treatment intensification score, calculated by dividing the difference between observed and predicted blood pressure-lowering medication changes by the number of the clinic visit, can be generated and evaluated among patients with ischemic stroke.
- Treatment intensification score, which represents physicians' attentiveness toward abnormal blood pressure measurements, was associated with an increased risk of recurrent events among patients with ischemic stroke.

What Are the Clinical Implications?

- Treatment intensification score may be used as a performance measure of physicians' attentiveness in the secondary prevention after ischemic stroke.

Nonstandard Abbreviations and Acronyms

CRCS-K	Clinical Research Collaboration for Stroke in Korea
TI	treatment intensification

the best timing and rate of BP-lowering treatment after stroke,[3] and this uncertainty may lead to poor BP control in real-world practice.

Elevated BP is frequently encountered in a stroke prevention clinic, and adequate BP control after stroke may not be easily achieved.[4] Only 30% to 40% of survivors of stroke had their BP reasonably controlled during the 1-year follow-up at veterans hospitals.[5,6] A quarter of patients with hypertension discontinued antihypertensive medications within 2 years after index stroke.[7] Medication nonadherence may only partially explain the failure to control BP successfully, and thus a better understanding of the reasons for such failure is needed. Physicians' attentiveness toward elevated BP may be an underlying factor.[8] However, it has not been well studied at least in terms of secondary prevention of stroke.

Among the various measures of physicians' attitudes, the treatment intensification (TI) score has been widely applied.[8] The TI score, which ranges from –1 to +1, is obtained by dividing the difference between the frequencies of observed medication changes and expected medication changes (according to given standards) by the frequency of clinic visits. A 0 score implies perfect responsiveness, –1 implies complete negligence, and +1 indicates excessive aggression. Studies on the TI score have been reported in various clinical settings as its median or mean values ranging from –0.43 to –0.25,[8–10] but there has been no study in a stroke population.

In this context, using a prospective multicenter stroke registry database, this study aimed to describe physicians' attitudes toward BP control, quantified by the TI score, and its effect on the risk of recurrent stroke in patients with acute ischemic stroke.

METHODS

Data Availability

Anonymized data used in the current study can be obtained through an appropriate request to the corresponding author.

Study Design and Subjects

This retrospective, observational study was conducted among consecutive patients with acute ischemic stroke who were registered into CRCS-K (Clinical Research Collaboration for Stroke in Korea), a nationwide, prospective, multicenter clinical stroke registry database.[11] Data on eligible patients' BP, clinic visits, and prescription of BP-lowering medications were extracted retrospectively from medical records. Information on other clinical data and clinical outcomes after index stroke, available for up to 1 year after the stroke, were directly obtained from the registry database. The local institutional review boards approved data collection for the CRCS-K registry in order to monitor and improve the quality of stroke care in all participating centers with a waiver of patient consent. Additional data collection and analysis for this study were approved further at the study centers (institutional review board approval number, B-1103/124-111).

During the year 2011, 5528 patients with acute ischemic stroke were admitted to the participating centers and entered into the registry database. Among these patients, we selected the study subjects by applying the following algorithm: (1) the availability of clinical outcomes (n=4279), (2) the availability of BP data at clinic visits after discharge (n=3470), (3) ≥2 visits during the follow-up (n=2946), and (4) exclusion of those who had died during the 1-year follow-up period (n=2933; for baseline characteristics of 2715 excluded cases, see Table S1).

BP and Prescription Data Collection and TI Score Calculation

Physicians at clinics prescribe antihypertensive medications at their discretion and according to current guidelines,[12,13] but their dosage and types depend on

patient characteristics, including expected medication adherence and functional status, comorbidities, and stroke mechanisms. We collected all outpatient blood pressure measurements for all study subjects, measured by means of an automated oscillometric blood-pressure cuff.

BP measurements and prescription of antihypertensive medications were collected retrospectively by review of medical records. The BP-lowering medications were defined in the current study as oral drugs given to patients to lower BP and were classified as renin-angiotensin receptor antagonists, angiotensin-converting-enzyme inhibitors, beta blockers, calcium channel blockers, and diuretics. Some alpha blockers and vasodilators approved as antihypertensive drugs by the Korean Food and Drug Administration were also regarded as BP-lowering medications.

The TI score during the follow-up period was calculated for each patient using the following formula[8]:

$$\frac{(\text{Frequency of observed medication changes} - \text{Frequency of predicted medication changes based on given standards})}{\text{Frequency of clinic visits}}$$

For those who had a recurrent stroke during the follow-up, BP and prescription data before the recurrent event were used to generate the individual TI score.

Observed medication changes included the changes in the regimen of BP-lowering medications, such as dose increment, alteration in a drug class, and addition of a new compound. Joint National Committee VII was used as the standard for predicted medication changes.[14] In brief, a medication change was predicted in case systolic BP was ≥130 mm Hg or diastolic BP was ≥80 mm Hg in patients with diabetes mellitus or chronic kidney disease or systolic BP was ≥140 mm Hg or diastolic BP was ≥90 mm Hg without such comorbidities.

Clinical Data Collection

We retrieved demographic data, stroke characteristics, and other clinical data of the study participants from the CRCS-K registry database. Recurrent stroke events and mortality were prospectively captured through telephone interviews by experienced and trained study coordinators or direct interviews by clinicians during clinic visits. We collected data on recurrent stroke within 1 year after the index stroke, permitting a 2-month grace period (ie, 12±2 months). Details of definitions used in the CRCS-K registry have been published elsewhere.[11]

Statistical Analysis

Descriptive analyses were summarized as mean±SD or medians (interquartile range) for continuous variables or frequencies with percentages for categorical variables. Study subjects were categorized into 5 groups: group 1 (TI score range, –1 to –0.5), group 2 (–0.5 to –0.25), group 3 (–0.25 to 0), group 4 (0), and group 5 (0–1), as the number of subjects with TI score 0 was 1209 (41.2%). Baseline characteristics were summarized and compared according to those groups using the chi-square test or 1-way ANOVA, as appropriate. To estimate associations between the TI score groups and recurrent stroke, we used a multivariable log-normal frailty model to adjust for clustering within each hospital.[15] Hospitals were incorporated as a random effect in the frailty models. The following multivariable models were constructed: (1) model 1 with no covariates; (2) model 2 with age, sex, and National Institutes of Health Stroke Scale score at arrival; and (3) model 3 with covariates of model 2 and other clinically relevant variables such as stroke mechanism, hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, and prestroke disability (modified Rankin Scale score ≥1 before the index stroke). Group 3, which incorporated the mean of TI score, was taken as a reference category to compare both ends of the TI score strata.

The formula for the TI score inherently implies that subjects with a TI score of 0 are heterogeneous, including patients with perfect BP control, nonhypertensives, or debilitated patients who could not return to outpatient clinics. To assess the robustness of our findings, we performed several post hoc sensitivity analyses, as follows: restricting analysis subsets to those who were diagnosed with hypertension before or during the stroke admission; were prescribed BP-lowering medications; did not have atrial fibrillation because patients with atrial fibrillation tended to have a lower BP trajectory[16]; visited outpatient clinics for ≥3, ≥4, and ≥5 times; and stratifying the study subjects according to functional capacity at the time of discharge (modified Rankin Scale score 0–2 versus 3–5).

A significance level was set as a 2-tailed *P* value of <0.05. Frailty models were fitted using the *frailtyHL* package version 2.3.[17] Statistical analyses were performed using R for statistical computing version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Of 2933 patients eligible for this study, the mean age was 67±13 years, and 61% were men. The median

Table 1. Baseline Characteristics of the Included Patients (n=2933)

Category	Variable	Value
TI score	TI score	−0.13±0.28 0 [−0.30, 0]
	Observed medication changes	0.71±1.38 0 [0–1]
	Predicted medication changes	1.52±2.20 1 [0–2]
	Number of clinic visits	6.40±4.26 6 [3–9]
Demographic information	Male sex	1788 (61.0%)
	Age, y	66.8±12.5
	Prestroke disability (mRS score ≥1 before the stroke)	483 (16.5%)
Stroke information	Onset to arrival, h	8.8 [2.5–33.7]
	Baseline National Institutes of Health Stroke score	3 [1–6]
	Stroke mechanism	
	Large artery atherosclerosis	1110 (37.8%)
	Small-vessel occlusion	590 (20.1%)
	Cardioembolism	601 (20.5%)
	Other determined etiology	56 (1.9%)
	Undetermined etiology	576 (19.6%)
	Recanalization treatment	397 (13.5%)
Vascular risk factors	History of stroke	623 (21.2%)
	Hypertension	2155 (73.5%)
	Diabetes mellitus	1042 (35.5%)
	Dyslipidemia	1203 (41.0%)
	Habitual smoking	1204 (41.1%)
	Atrial fibrillation	547 (18.6%)
Laboratory information	Hemoglobin, mg/dL	13.7±2.0
	Total cholesterol, mg/dL	176.2±41.1
	Blood urea nitrogen, mg/dL	16.8±7.9
	Creatinine, mg/dL	1.00±0.91
	Fasting blood glucose, mg/dL	113±47
	Systolic blood pressure, mm Hg	148±27
	Diastolic blood pressure, mm Hg	86±16
Stroke outcomes	mRS score at discharge	
	0	741 (25.3%)
	1	662 (22.6%)
	2	521 (17.8%)
	3	496 (16.9%)
	4	363 (12.4%)
	5	150 (5.1%)
	mRS score at 3 mo after stroke (N=2765)	
	0	851 (30.8%)
	1	684 (24.7%)
	2	473 (17.1%)
	3	344 (12.4%)
	4	277 (10.0%)
	5	136 (4.9%)
	6	0
	mRS score at 1 y after stroke (N=2768)	
	0	1036 (37.4%)
	1	639 (23.1%)
	2	404 (14.6%)
	3	314 (11.3%)
	4	224 (8.1%)
	5	151 (5.5%)
	Recurrent stroke within 1 y after stroke	175 (6.0%)
	F/U for stroke, d	350±66

Values are presented as means±SDs, medians [interquartile ranges], or frequencies (percentages), respectively. mRS indicates modified Rankin Scale; and TI, treatment intensification.

baseline National Institutes of Health Stroke Scale score was 3 (interquartile range, 1–6), and 17% were functionally disabled (modified Rankin Scale score ≥1) before the index stroke. Hypertension was diagnosed in 74% (Table 1).

During a mean follow-up period of 350±66 days, the mean frequency of clinic visits was 6.4±4.3. Medication changes were observed 2086 times in 1063 patients (36.2%); the mean was 0.71±1.38 times per patient, and the median was 0. Medication changes were expected 4472 times in 1654 patients (56.4%); the expected mean was 1.52±2.20 times per patient, and the median was 1. The mean TI score of the entire study population was −0.13±0.28, and the median was 0 (for a histogram of TI score, see Figure S1). The TI score was 0 in 41.2% of the study subjects (n=1209). Recurrent stroke occurred in 175 patients (6.0%).

We categorized the study subjects into 5 groups by their TI scores to explore associations of TI scores with baseline profiles and the risk of recurrent stroke. Compared with the middle TI score group (group 3), the lowest TI score group (group 1) was more likely to have a prestroke disability, diabetes mellitus, and a higher mean systolic BP at arrival. The proportion of cardioembolic stroke was greater in groups 4 and 5. Recurrent stroke occurred most frequently in group 1 (G1; Figure 1; Table 2). The multivariable analyses considering clustering within hospitals and adjusted for relevant covariates showed that the G1 (adjusted hazard ratio [HR], 13.43; 95% CI, 5.95–30.35), group 2 (adjusted HR, 4.59; 95% CI, 2.01–10.46), and G4 (adjusted HR, 6.60; 95% CI, 3.02–14.45) had a significantly

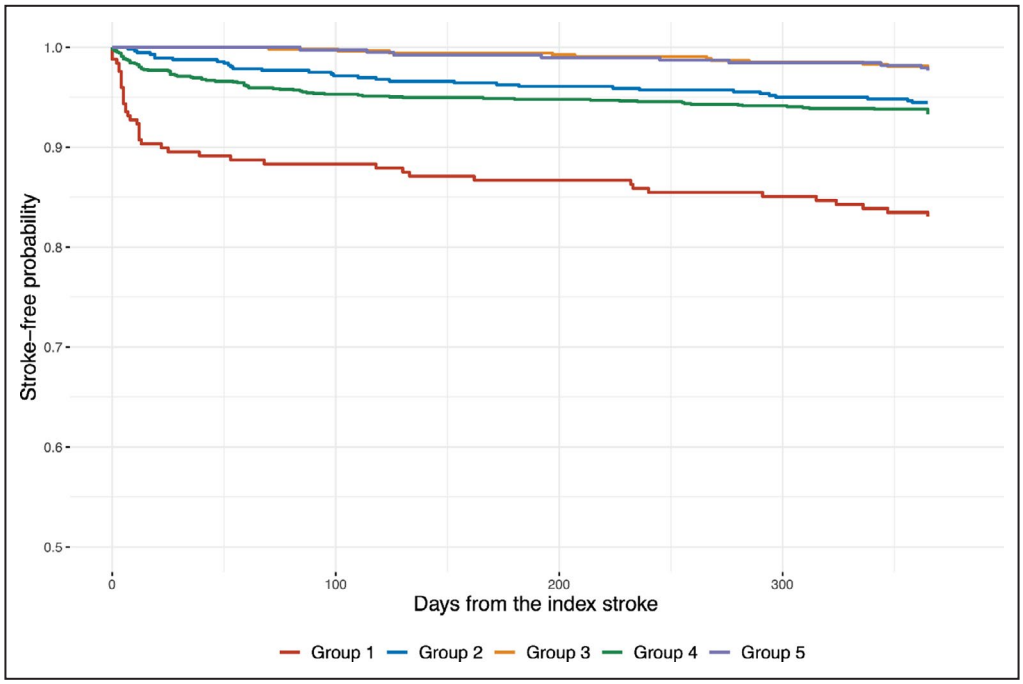

Figure 1. Stroke-free survival by the quintile groups of TI score.
Hazard ratios and 95% CIs were calculated using frailty models that considered the clustering effect of the treating hospitals and adjusted for age, sex, baseline National Institutes of Health Stroke Scale score, stroke mechanism, hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, and prestroke disability. TI indicates treatment intensification.

elevated risk of recurrent stroke during the first year after stroke when compared with group 3, but not with group 5 (adjusted HR, 1.68; 95% CI, 0.62–4.56; Table 3).

We performed several sensitivity analyses to demonstrate the robustness of our results (Figure 2). The increased risk of recurrent stroke of G1 persisted in the subgroups who were diagnosed with hypertension, who were prescribed on BP-lowering medications, and who did not have atrial fibrillation. We further repeated the main frailty models in those with the frequency of clinic visits of ≥3, ≥4, and ≥5 times after discharge to address attrition bias. The point estimates and statistical significance of G1 and G4 diminished after focusing on the subjects who return to the clinic regularly. When stratified by functional capacity at the time of discharge, HRs from the G1 and G4 remained significant (Table S2).

DISCUSSION

Among the 2933 patients with ischemic stroke who visited outpatient clinics more than 2 times during the 1 year of follow-up, we observed a mean TI score of −0.13±0.28. Furthermore, patients who belonged to the lowest group of TI scores had a 13.4-fold elevated risk of recurrent stroke compared with those in the middle range of TI score. The deleterious effect of the lower TI score on the risk of recurrent stroke was carried forward in several sensitivity analyses.

The concept of TI for elevated BP was first proposed in 2006, counting the medication changes only, and TI was reported to occur in 64% of patients during the first 6 months of treatment in a primary care setting.[18] A higher TI score was shown to be associated with better BP control in a follow-up study of patients with coronary artery disease.[19] Rose et al pointed out the inherent limitation in the precedent definition of a raw change[4,19–21] and demonstrated the better performance of the standard-based method compared with other methods for measuring TI.[8,22] The TI score, rather than medication adherence, was more predictive of the systolic BP trajectory among 9569 patients with newly diagnosed coronary artery disease during a mean follow-up period of 1.8 years.[23] In a 1-year follow-up study of patients with resistant hypertension, TI occurred in 22% of the study population and increased the odds of adequate BP control at 1 year by 64%.[9]

Lower TI scores, implying physician's hesitancy in increasing the dose of BP-lowering medications for patients with high BP recordings, are not uncommon in clinical practice.[24] How might we explain such a clinical contradiction? First, in modern practice, it is known that physicians' attention may be diverted

Table 2. Clinical Profiles by TI Score Quintile Groups

Variable	Five Groups of TI Score					*P*-for-Difference
	G1 (n, 248) [−1 to −0.5]	G2 (n, 560) (−0.5 to −0.25)	G3 (n, 529) [−0.25 to 0]	G4 (n, 1209) [0]	G5 (n, 387) [0 to 1]	
TI score	−0.78±0.17	−0.41±0.08	−0.17±0.06	0	0.24±0.15	
Observed medication changes	0.41±0.82	0.48±0.95	0.78±1.24	0.21±0.64	2.39±2.14	<0.01
Predicted medication changes	4.44±3.35	2.78±2.07	2.19±1.59	0.21±0.64	0.60±1.32	<0.01
Number of clinic visits	5.73±4.29	5.92±3.86	8.76±3.58	4.49±3.39	8.46±4.99	<0.01
Male sex	165 (67%)	349 (62%)	318 (60%)	736 (61%)	220 (57%)	0.16
Age, y	65.4±12.0	68.8±11.6	66.7±11.7	66.2±13.4	67.1±11.4	<0.01
Pre-stroke disability	49 (20%)	114 (20%)	86 (16%)	173 (14%)	61 (16%)	0.01
Baseline National Institutes of Health Stroke score	3 [1–5]	3 [2–6]	3 [1–5]	3 [1–7]	3 [1–7]	<0.01
Stroke mechanisms						<0.01
Large artery atherosclerosis	104 (42%)	237 (42%)	213 (40%)	427 (35%)	129 (33%)	
Small-vessel occlusion	63 (25%)	128 (23%)	115 (22%)	235 (19%)	49 (13%)	
Cardioembolism	30 (12%)	85 (15%)	97 (18%)	269 (22%)	120 (31%)	
Other determined etiology	2 (0.1%)	7 (0.1%)	9 (0.2%)	31 (0.3%)	7 (0.2%)	
Undetermined etiology	49 (19%)	103 (18%)	95 (18%)	247 (20%)	82 (21%)	
Recanalization treatment	22 (9%)	63 (11%)	63 (12%)	187 (16%)	62 (16%)	<0.01
History of stroke	59 (24%)	127 (23%)	121 (23%)	234 (19%)	82 (21%)	0.28
Hypertension	213 (86%)	453 (81%)	433 (82%)	725 (60%)	331 (86%)	<0.01
Diabetes mellitus	172 (71%)	283 (51%)	180 (34%)	312 (26%)	92 (24%)	<0.01
Dyslipidemia	112 (45%)	238 (43%)	224 (42%)	495 (41%)	134 (35%)	0.06
Habitual smoking	113 (46%)	239 (43%)	223 (42%)	487 (40%)	142 (37%)	0.18
Atrial fibrillation	28 (11%)	85 (15%)	87 (16%)	239 (20%)	108 (28%)	<0.01
Hemoglobin	13.8±2.1	13.6±2.1	13.9±1.7	13.6±1.9	13.6±2.0	0.11
Total cholesterol	180±45	177±42	177±41	175±41	175±39	0.56
Blood urea nitrogen	18.7±10.5	17.2±7.2	16.9±8.3	16.2±7.6	16.4±7.4	<0.01
Creatinine	1.31±1.81	1.05±0.85	0.98±0.79	0.95±0.73	0.97±0.79	<0.01
Fasting blood glucose	126±55	120±55	111±39	110±45	109±41	<0.01
SBPe	160±29	153±29	151±27	142±24	148±27	<0.01
DBP	90±17	87±16	86±16	85±16	86±16	<0.01
mRS score 0–1 at discharge	122 (49%)	242 (43%)	273 (52%)	575 (48%)	191 (49%)	0.08
SBP during the follow-up period	141.7±10.3	136.2±10.4	133.0±10.9	124.6±9.7	128.9±114.4	<0.01
DBP during the follow-up period	80.7±7.6	78.7±8.1	77.4±9.5	74.6±6.6	75.7±7.1	<0.01
Recurrent stroke	42 (17%)	31 (6%)	12 (2%)	81 (7%)	9 (2%)	<0.01

Values are presented as means±SDs, medians [interquartile ranges], or frequencies (percentages), respectively. DBP indicates diastolic blood pressure; mRS, modified Rankin Scale; SBP, systolic blood pressure; and TI, treatment intensification.

away from patients as only 33% of practice time may include direct physician–patient interaction.[25] At a clinic visit, mild elevation of BP is usually asymptomatic, and it may be overlooked as a physician is distracted by the time pressure of practice and the endless demand for documentation.[26] Second, physicians may be subject to clinical inertia, that is, they fail to initiate or intensify appropriate therapies or diagnostic tests despite abnormal findings on laboratory tests or clinical exams.[27] The clinical inertia has been observed in primary care settings in the management of hypertension, diabetes mellitus, and dyslipidemia.[4,28] It may reflect physicians' overestimation of the amount of care that they had already provided, lack of motivation, nihilism, or lack of proper training for treating some conditions.[9] Finally, BP measurement may often be inaccurate. Clinicians may not feel obligated to treat BP when it seems to be measured falsely.[29,30] Considering the TI score formula and the potential clinical inertia that may underlie low TI scores, the TI score may be interpreted as a surrogate of physicians' attentiveness to treat elevated BP.[31] Physicians who have lower TI scores may also be less watchful of several other subtle

Table 3. TI Score Quintile Groups and the Risk of Recurrent Stroke

	Quintile Groups of TI Score				
	G1	G2	G3	G4	G5
Number of cases	248	560	529	1209	387
TI score (mean±SD and range)	−0.78±0.17 [−1 to −0.5)	−0.41±0.08 [−0.5 to −0.25)	−0.17±0.06 [−0.25 to 0)	0	0.24±0.15 (0–1]
Crude model	13.50 [6.04 to 30.15]	4.51 [1.98 to 10.26]	Reference	5.80 [2.67–12.62]	1.70 [0.63–4.61]
Multivariable model #1	13.95 [6.24 to 31.16]	4.48 [1.97 to 10.20]	Reference	5.97 [2.74–13.01]	1.72 [0.64–4.67]
Multivariable model #2	13.43 [5.95 to 30.35]	4.59 [2.01 to 10.46]	Reference	6.60 [3.02–14.45]	1.68 [0.62–4.56]

Hazard ratios and 95% CIs were calculated using frailty models that considered the clustering effect of the treating hospitals. Multivariable model #1 was adjusted for age, sex, and baseline National Institutes of Health Stroke Scale score. Multivariable model #2 was adjusted for age, sex, baseline National Institutes of Health Stroke Scale score, stroke mechanism, hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, and prestroke disability. TI indicates treatment intensification.

abnormal signals in patients' complaints, laboratory tests, or clinical examinations. As BP is an easily measurable and manageable target for intervention, the TI score can be used as a performance indicator in outpatient clinic settings. However, this contention needs to be verified and validated in a prospective study.

We observed a higher risk of future events in tG4 whose TI score was 0. Subjects with a TI score of 0 may be a heterogeneous group of patients. Specifically, the TI score will be 0 when there is perfect antihypertensive prescription when encountering abnormal BP measurements, patients with no hypertension or no BP-lowering medication prescription, or patients' failure to return for follow-up to stroke clinics possibly because of functional dependency or other reasons.

In the subset of study subjects who regularly returned to the clinic, the HRs and statistical significance diminished altogether in the whole groups (Figure 2D through 2F). Most of the recurrent strokes in groups 1, 2, and 4 occurred in their clinical courses after stroke. Therefore, the validity of our study results cannot be applied to the long-term follow-up of stroke survivors.

A few points in this study need further clarification. We applied the Joint National Committee VII criteria, as the study subjects were managed between 2011 and 2013. Patients' adherence to medications was neither recorded nor analyzed, and the TI score for drugs other

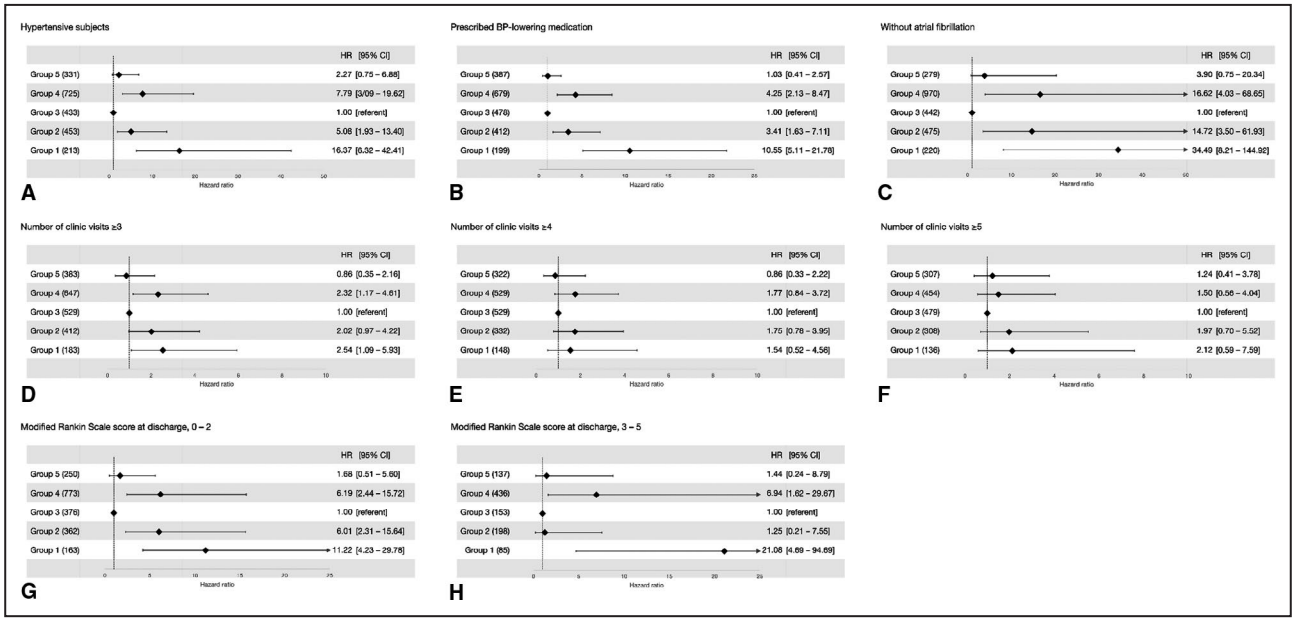

Figure 2. Sensitivity analyses.
The frailty models adjusted for the clustering effect and for the relevant covariates were repeated with subsets of patients: subjects with hypertension (**A**), subjects who had prescribed BP-lowering medication (**B**), subjects without atrial fibrillation (**C**), those who returned to the outpatient clinic ≥3 (**D**), ≥4 (**E**) and ≥5 (**F**) times, and those who had mRS score 0 to 2 (**G**) and 3 to 5 (**H**) at the time of discharge. BP indicates blood pressure; HR, hazard ratio; and mRS, modified Rankin Scale.

than BP-lowering medications was not examined. We do not have information on adverse events possibly related to antihypertensive medications. All the BP measurements were performed at outpatient clinics as routine clinical practice. We focused on patients who visited ≥2 times after discharge, and the follow-up duration was limited to 1 year. Overt imbalances in BP levels and other vascular risk factors according to the TI score groups could not be controlled completely despite adjustments. Residual confounding may still exist. The TI score for each physician may be estimated, but this was not possible in our study. Finally, the study subjects were managed by stroke neurologists at specialized academic centers for control of their vascular risk factors, including hypertension. Thus, the generalization of our findings to other primary care settings may be limited.

CONCLUSIONS

Using a TI score, a surrogate for physicians' attitudes toward abnormal BP measurements, our study showed that inadequate treatment intensification of elevated BP might be associated with a higher risk of recurrent stroke. With previous studies emphasizing the importance of TI score compared with medication adherence, our study suggests that the TI score can measure the physician's performance or attentiveness. However, the validity of our study for the long-term clinical courses after stroke was not demonstrated in the study. Therefore, this concept should be examined in well-designed prospective studies and clinical trials with a sufficient number of clinic visits for a sufficient length of time.

ARTICLE INFORMATION

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Supplementary Material

Tables S1–S2
Figure S1

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SUPPLEMENTAL MATERIAL

Table S1. Baseline characteristics of excluded patients (n, 2715).

Category	Variable	Value
Demographic information	Male sex	1485 (54.7%)
	Age (years)	67.5 ± 13.3
	Pre-stroke disability	480 (17.7%)
Stroke information	Onset to arrival (hour)	6.8 [2.0 - 34.3]
	Baseline NIHSS score	3 [1 - 9]
	Stroke mechanism	
	Large artery atherosclerosis	823 (37.8%)
	Small-vessel occlusion	273 (12.5%)
	Cardioembolism	512 (23.5%)
	Other determined etiology	50 (2.3%)
	Undetermined etiology	522 (23.9%)
	Recanalization treatment	359 (13.2%)
Vascular risk factors	History of stroke	567 (20.9%)
	Hypertension	1782 (65.6%)
	Diabetes	850 (31.3%)
	Dyslipidemia	998 (36.8%)
	Habitual smoking	979 (36.1%)
	Atrial fibrillation	557 (20.5%)
Laboratory information	Hemoglobin (mg/dL)	13.4 ± 2.0
	Total cholesterol (mg/dL)	179 ± 43
	Blood urea nitrogen (mg/dL)	17.4 ± 10.5
	Creatinine (mg/dL)	1.01 ± 1.08
	Fasting blood glucose (mg/dL)	119 ± 47
	Systolic blood pressure (mm Hg)	144 ± 27
	Diastolic blood pressure	85 ± 16
Stroke outcomes	mRS score at discharge (n, 2710)	
	0	820 (30.3%)
	1	474 (17.5%)
	2	296 (10.9%)
	3	321 (11.8%)
	4	282 (10.4%)
	5	383 (14.1%)
	6	134 (4.9%)
	mRS score at three months after stroke (N = 2563)	

	0	777 (30.3%)
	1	446 (17.4%)
	2	266 (10.4%)
	3	296 (11.5%)
	4	228 (8.9%)
	5	229 (8.9%)
	6	321 (12.5%)
	mRS score at one year after stroke (N = 2367)	
	0	829 (35.0%)
	1	400 (16.9%)
	2	199 (8.4%)
	3	226 (9.6%)
	4	153 (6.5%)
	5	103 (4.4%)
	6	457 (19.3%)
	Recurrent stroke until one year	181 (6.7%)

Table S2. Full models for main and sensitivity analyses.

The effect of TI score quintile groups on recurrent stroke; multivariable model #1

	Adjusted HR [95% CI]
G1 of TI score	13.95 [6.24 - 31.16]
G2 of TI score	4.48 [1.97 - 10.20]
G3 of TI score	reference
G4 of TI score	5.97 [2.74 - 13.01]
G5 of TI score	1.72 [0.64 - 4.67]
Age (per 1-year increase)	1.02 [1.00 - 1.03]
Male sex	0.93 [0.68 - 1.27]
Baseline NIHSS score (per 1-point increase)	0.99 [0.96 - 1.02]

The effect of TI score quintile groups on recurrent stroke; multivariable model #2

	Adjusted HR [95% CI]
G1 of TI score	13.43 [5.95 - 30.35]
G2 of TI score	4.59 [2.01 - 10.46]
G3 of TI score	reference
G4 of TI score	6.60 [3.02 - 14.45]
G5 of TI score	1.68 [0.62 - 4.56]
Age (per 1-year increase)	1.01 [1.00 - 1.03]
Male sex	0.93 [0.67 - 1.28]
Baseline NIHSS score (per 1-point increase)	0.98 [0.94 - 1.01]
Stroke mechanism, large artery atherosclerosis	reference
Stroke mechanism, small vessel occlusion	0.72 [0.45 - 1.14]
Stroke mechanism, cardioembolism	1.08 [0.61 - 1.90]
Stroke mechanism, others	0.83 [0.53 - 1.28]
Hypertension	1.39 [0.93 - 2.07]
Diabetes	1.27 [0.91 - 1.78]
Dyslipidemia	1.13 [0.81 - 1.57]
Atrial fibrillation	1.49 [0.87 - 2.57]
Prestroke dependency	0.82 [0.53 - 1.24]

Sensitivity analysis; diagnosed of hypertension (n, 2155)

	Adjusted HR [95% CI]
G1 of TI score	16.37 [6.32 - 42.41]

G2 of TI score	5.08 [1.93 - 13.40]
G3 of TI score	reference
G4 of TI score	7.79 [3.09 - 19.62]
G5 of TI score	2.27 [0.75 - 6.88]
Age (per 1-year increase)	1.02 [1.00 - 1.04]
Male sex	0.94 [0.65 - 1.35]
Baseline NIHSS score (per 1-point increase)	0.97 [0.94 - 1.01]
Stroke mechanism, large artery atherosclerosis	reference
Stroke mechanism, small vessel occlusion	0.93 [0.55 - 1.56]
Stroke mechanism, cardioembolism	1.50 [0.79 - 2.87]
Stroke mechanism, others	0.88 [0.52 - 1.48]
Hypertension	Not included in the model
Diabetes	1.29 [0.88 - 1.88]
Dyslipidemia	1.09 [0.75 - 1.57]
Atrial fibrillation	1.28 [0.69 - 2.38]
Prestroke dependency	0.84 [0.54 - 1.31]

Sensitivity analysis; Prescribed BP-lowering drugs (n, 2155)

	Adjusted HR [95% CI]
G1 of TI score	10.55 [5.11 - 21.78]
G2 of TI score	3.41 [1.63 - 7.11]
G3 of TI score	reference
G4 of TI score	4.25 [2.13 - 8.47]
G5 of TI score	1.03 [0.41 - 2.57]
Age (per 1-year increase)	1.01 [0.99 - 1.03]
Male sex	0.89 [0.62 - 1.27]
Baseline NIHSS score (per 1-point increase)	0.99 [0.96 - 1.03]
Stroke mechanism, large artery atherosclerosis	reference
Stroke mechanism, small vessel occlusion	0.65 [0.38 - 1.11]
Stroke mechanism, cardioembolism	1.00 [0.51 - 1.96]
Stroke mechanism, others	0.76 [0.46 - 1.27]
Hypertension	1.15 [0.68 - 1.94]
Diabetes	1.29 [0.89 - 1.87]
Dyslipidemia	1.10 [0.76 - 1.60]
Atrial fibrillation	2.02 [1.07 - 3.82]
Prestroke dependency	1.12 [0.72 - 1.74]

N.B. Identical numbers of sensitivity analysis datasets from diagnosed of

hypertension and prescribed BP-lowering drugs are coincidental.

Sensitivity analysis; No atrial fibrillation (n, 2386)

	Adjusted HR [95% CI]
G1 of TI score	34.49 [8.21 - 144.92]
G2 of TI score	14.72 [3.50 - 61.93]
G3 of TI score	reference
G4 of TI score	16.62 [4.03 - 68.65]
G5 of TI score	3.90 [0.75 - 20.34]
Age (per 1-year increase)	1.01 [1.00 - 1.03]
Male sex	0.96 [0.66 - 1.38]
Baseline NIHSS score (per 1-point increase)	0.98 [0.94 - 1.02]
Stroke mechanism, large artery atherosclerosis	reference
Stroke mechanism, small vessel occlusion	0.70 [0.44 - 1.11]
Stroke mechanism, cardioembolism	1.16 [0.60 - 2.23]
Stroke mechanism, others	0.82 [0.51 - 1.31]
Hypertension	1.38 [0.87 - 2.18]
Diabetes	1.18 [0.80 - 1.73]
Dyslipidemia	1.12 [0.76 - 1.63]
Atrial fibrillation	Not included in the model
Prestroke dependency	0.87 [0.53 - 1.41]

Sensitivity analysis; Number of visits ≥3 (n, 2154)

	Adjusted HR [95% CI]
G1 of TI score	2.54 [1.09 - 5.93]
G2 of TI score	2.02 [0.97 - 4.22]
G3 of TI score	reference
G4 of TI score	2.32 [1.17 - 4.61]
G5 of TI score	0.86 [0.35 - 2.16]
Age (per 1-year increase)	1.00 [0.98 - 1.02]
Male sex	1.37 [0.84 - 2.25]
Baseline NIHSS score (per 1-point increase)	1.01 [0.96 - 1.05]
Stroke mechanism, large artery atherosclerosis	reference
Stroke mechanism, small vessel occlusion	0.81 [0.40 - 1.63]
Stroke mechanism, cardioembolism	1.93 [0.88 - 4.22]

Stroke mechanism, others	1.03 [0.54 - 1.97]
Hypertension	1.57 [0.82 - 3.01]
Diabetes	1.43 [0.88 - 2.34]
Dyslipidemia	1.10 [0.68 - 1.78]
Atrial fibrillation	1.11 [0.51 - 2.41]
Prestroke dependency	0.91 [0.49 - 1.69]

Sensitivity analysis; Number of visits ≥4 (n, 1860)

	Adjusted HR [95% CI]
G1 of TI score	1.54 [0.52 - 4.56]
G2 of TI score	1.75 [0.78 - 3.95]
G3 of TI score	reference
G4 of TI score	1.77 [0.84 - 3.72]
G5 of TI score	0.86 [0.33 - 2.22]
Age (per 1-year increase)	1.00 [0.97 - 1.02]
Male sex	1.26 [0.71 - 2.25]
Baseline NIHSS score (per 1-point increase)	1.02 [0.96 - 1.07]
Stroke mechanism, large artery atherosclerosis	reference
Stroke mechanism, small vessel occlusion	0.85 [0.36 - 2.00]
Stroke mechanism, cardioembolism	1.82 [0.70 - 4.74]
Stroke mechanism, others	0.91 [0.40 - 2.08]
Hypertension	1.30 [0.61 - 2.77]
Diabetes	1.22 [0.68 - 2.20]
Dyslipidemia	1.34 [0.77 - 2.35]
Atrial fibrillation	1.39 [0.55 - 3.48]
Prestroke dependency	1.41 [0.72 - 2.77]

Sensitivity analysis; Number of visits ≥5 (n, 1684)

	Adjusted HR [95% CI]
G1 of TI score	2.12 [0.59 - 7.59]
G2 of TI score	1.97 [0.70 - 5.52]
G3 of TI score	reference
G4 of TI score	1.50 [0.56 - 4.04]
G5 of TI score	1.24 [0.41 - 3.78]

Age (per 1-year increase)	0.99 [0.96 - 1.02]
Male sex	1.24 [0.60 - 2.57]
Baseline NIHSS score (per 1-point increase)	1.05 [0.99 - 1.11]
Stroke mechanism, large artery atherosclerosis	reference
Stroke mechanism, small vessel occlusion	1.72 [0.65 - 4.57]
Stroke mechanism, cardioembolism	2.62 [0.80 - 8.57]
Stroke mechanism, others	0.98 [0.32 - 2.99]
Hypertension	0.93 [0.39 - 2.25]
Diabetes	1.26 [0.60 - 2.64]
Dyslipidemia	1.32 [0.66 - 2.67]
Atrial fibrillation	1.04 [0.33 - 3.28]
Prestroke dependency	1.65 [0.71 - 3.82]

Sensitivity analysis; mRS score at discharge, 0 - 2 (n, 1924)

	Adjusted HR [95% CI]
G1 of TI score	11.22 [4.23 - 29.78]
G2 of TI score	6.01 [2.31 - 15.64]
G3 of TI score	reference
G4 of TI score	6.19 [2.44 - 15.72]
G5 of TI score	1.68 [0.51 - 5.60]
Age (per 1-year increase)	1.00 [0.99 - 1.02]
Male sex	0.90 [0.61 - 1.32]
Baseline NIHSS score (per 1-point increase)	0.97 [0.92 - 1.02]
Stroke mechanism, large artery atherosclerosis	reference
Stroke mechanism, small vessel occlusion	0.64 [0.38 - 1.09]
Stroke mechanism, cardioembolism	0.83 [0.41 - 1.67]
Stroke mechanism, others	0.64 [0.36 - 1.13]
Hypertension	1.35 [0.84 - 2.18]
Diabetes	1.45 [0.96 - 2.18]
Dyslipidemia	1.13 [0.75 - 1.70]
Atrial fibrillation	1.86 [0.93 - 3.74]
Prestroke dependency	0.95 [0.52 - 1.73]

Sensitivity analysis; mRS score at discharge, 3 - 5 (n, 1009)

	Adjusted HR [95% CI]

G1 of TI score	21.08 [4.69 - 94.69]
G2 of TI score	1.25 [0.21 - 7.55]
G3 of TI score	reference
G4 of TI score	6.94 [1.62 - 29.67]
G5 of TI score	1.44 [0.24 - 8.79]
Age (per 1-year increase)	1.03 [1.00 - 1.06]
Male sex	0.97 [0.55 - 1.72]
Baseline NIHSS score (per 1-point increase)	0.98 [0.93 - 1.03]
Stroke mechanism, large artery atherosclerosis	reference
Stroke mechanism, small vessel occlusion	0.85 [0.33 - 2.20]
Stroke mechanism, cardioembolism	2.33 [0.85 - 6.39]
Stroke mechanism, others	1.39 [0.66 - 2.93]
Hypertension	1.53 [0.72 - 3.23]
Diabetes	0.98 [0.54 - 1.78]
Dyslipidemia	0.84 [0.48 - 1.48]
Atrial fibrillation	0.85 [0.36 - 2.02]
Prestroke dependency	0.81 [0.44 - 1.51]

Figure S1. Histogram and density plot for the distribution of TI score.