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Evaluation of the association between admission systolic blood pressure and the choice of initial antiplatelet therapy for minor ischemic stroke in real-world

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Abstract

To evaluate whether admission systolic blood pressure (SBP) is associated with the choice of initial antiplatelet therapy for minor stroke. Eligible patients retrospectively gathered from 2010 to 2018. Finally, 1312 of 1494 patients were divided into three groups: aspirin monotherapy (AM, n = 538, 41.0%), dual antiplatelet therapy with aspirin and load-clopidogrel (clopidogrel loading dose of 300 mg on the first day, DAPT-ALC, n = 474, 35.6%), and dual antiplatelet therapy with aspirin and unload-clopidogrel (clopidogrel 75 mg daily with no loading dose, DAPT-AUC, n = 300, 22.9%). The mean ± SD age of final patients was 62.0 ± 12.7 years old; 903 (70.9%) participants were male. Patients in the DAPT-ALC group were more likely to be younger, to arrive earlier, and to have a lower proportion of intracerebral hemorrhage than those in the AM group. DAPT-AUC group patients were more like to have a history of acute myocardial infarction and less likely to have a history of ICH than the AM group (4.7% vs. 1.7% and .3% vs. 2.6%, $p < .05$). Overall, there was a likely "S-shaped" association between the selection of the DAPT-ALC or DAPT-AUC scheme and admission systolic blood pressure (P for nonlinearity = .012). Compared with the SBP < 140 mmHg group, the SBP ≥ 180 mmHg group was more likely to be given DAPT-AUC (OR = 2.92 [1.62–5.26], $p < .001$) than DAPT-ALC. Our findings support that admission SBP is associated with the choice of initial antiplatelet, especially when the SBP was greater than or equal to 180 mmHg.

KEYWORDS
antiplatelet therapy, minor ischemic stroke, systolic blood pressure

1 | INTRODUCTION

Stroke is the leading cause of death and the most burdensome disease in China.[1,2] Antiplatelet therapy plays a vital role in the secondary prevention of ischemic stroke.[3] The Clopidogrel with Aspirin in Acute Minor Stroke or Transient Ischemic Attack (CHANCE) and Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT) trials showed that early initiation of dual antiplatelet therapy (DAPT) with aspirin and clopidogrel significantly reduced the rate of stroke events during follow-up compared with aspirin monotherapy.[4,5] In clinical practice, physician decision-making should follow a rational and algorithmic process in which physicians consciously process the clinical data and apply the best evidence from the findings of clinical trials.[6,7] The analysis of data from observational studies also follows an intention-to-treat approach based on patients in real-world settings.[8] The selection of a treatment for acute ischemic stroke is based on patient and physician factors. Physicians sometimes prescribe drugs outside of guideline recommendations in clinical practice. This phenomenon is rooted in differences between the patient populations enrolled in clinical trials and real-world observational registries, and it involves issues of comparability between clinical trials themselves.[9] Doctors often consider the patient's age, sex, ethnicity, alcohol and tobacco use, blood pressure, and whether they have diabetes, anemia, renal insufficiency, or a history of intracranial hemorrhage (ICH) or gastrointestinal bleeding.

Elevated blood pressure (BP) is common in the acute phase of ischemic stroke and occurs in approximately 80% of patients.[10,11] The function of dynamic cerebral autoregulation is suggested to be impaired in the affected hemisphere after ischemic stroke, which makes early BP management more challenging.[10,11] Thus, the patient's overall propensity for bleeding should be evaluated when choosing an antiplatelet regimen. Post hoc analyses of the CHANCE and POINT trials reported associations between baseline systolic blood pressure (SBP) and DAPT and a lower risk of recurrent stroke.[12,13]

Whether the admission SBP level affects the choice of the antiplatelet regimen in clinical practice is unclear. Therefore, we further evaluated the relationship between admission SBP and the choice of an initial antiplatelet scheme for secondary prevention of minor ischemic stroke.

2 | METHODS

2.1 | Population and study design

This study is a multicenter retrospective observational cohort study based on real-world research conducted at three advanced stroke centers in Shanxi Province (First Hospital of Shanxi Medical University, Bethune Hospital of Shanxi Province, Taiyuan Iron and Steel Group Co., Ltd.). The study included patients with acute minor ischemic stroke (National Institutes of Health Stroke Scale (NIHSS) score $\leq$ 5) treated with an antiplatelet drug within 72 h of symptom onset. We screened the electronic medical records of all patients hospitalized for minor ischemic stroke in four months (March, June, September, December) in 2010, 2012, 2014, 2016, and 2018.

Patients were ineligible for the study if they had a diagnosis of hemorrhage or other pathologies, such as vascular malformation, tumor, abscess, or other major nonischemic brain diseases (e.g., multiple sclerosis), on baseline head computed tomography (CT) or magnetic resonance imaging (MRI). The inclusion criteria were (1) ischemic stroke patients within 72 h of onset and (2) NIHSS score $\leq$5 points at onset or NIHSS score >5 points at onset, but symptoms were alleviated before receiving an antiplatelet drug. The exclusion criteria were (1) a modified Rankin Scale (mRS) score >2, (2) transient ischemic attack (TIA), (3) treatment with recombinant tissue plasminogen activator (rt-PA), or (4) participation in other clinical trials.

Ethics approval and consent to participate: Informed consent was waived because of study subject anonymity and minimal risk to the participants. The Ethics Committee of First Hospital of Shanxi Medical University approved the procedure (No. 2021-K044). The study was performed according to the ethical guidelines of the Declaration of Helsinki.

Clinical Trial Registration: http://www.chictr.org.cn; Identifier: ChiCTR2100046958.

2.2 | Data collection

Clinical information was collected from three advanced stroke centers in Shanxi Province. Three trained neurologists collected the data from the electronic medical records system. Demographic, clinical, imaging, and laboratory data were retrospectively collected. Baseline data, including NIHSS scores, were collected for all patients. The stroke subtypes were classified according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria after complete diagnostic profiling.[14] The following data were directly obtained from the registry database: (1) demographics, including age, sex, body mass index, initial SBP, and diastolic blood pressure (DBP), (2) medical history, including previous TIA, previous stroke, previous coronary artery disease (CAD), previous peripheral artery disease (PAD), hypertension (HTN), diabetes mellitus, dyslipidemia, smoking, and atrial fibrillation, (3) medication, including previous antiplatelet medication and previous antihypertensive medication, (4) stroke characteristics and acute treatment, including the time from onset to arrival, initial NIHSS scores, prestroke mRS score, and ischemic stroke subtype according to the TOAST criteria, (5) laboratory data, including white blood cell counts, creatinine serum levels, glucose at presentation, platelet counts, and fasting low-density lipoprotein cholesterol (LDL-C), and (6) in-hospital treatment, including statin therapy. The BP record from the first hospital where the patient presented after the onset of the stroke was used. We retrospectively collected all data described above from the hospital's electronic medical record system.

The study subjects were divided into three groups according to the antiplatelet regimen used at admission: aspirin monotherapy (AM), dual antiplatelet therapy with aspirin and loading clopidogrel (DAPT-ALC; clopidogrel loading dose of 300 mg on the first day), and dual

antiplatelet therapy with aspirin and no loading clopidogrel (DAPT-AUC; clopidogrel 75 mg daily with no loading dose). We trichotomized SBP levels (<140 mmHg, 140–180 mmHg, and ≥180 mmHg) according to the examination of patients at admission.

2.3 | Study outcomes

The clinical outcome of the subjects was observed during hospitalization, and the follow-up time was the number of days in the hospital. The effect endpoint events were determined by three neurologists using data from a study outcome visit, medical records, and neuroimaging review. The primary outcome was stroke recurrence, which included new ischemic stroke, hemorrhagic stroke, and TIA. Recurrence of ischemic stroke was defined as acute focal cerebral or retinal infarction: an increase in the NIHSS score of four or more, new infarction or enlargement of the original focus on MRI or CT. Hemorrhagic stroke was defined as acute infiltration of blood into the brain parenchyma or subarachnoid space with associated neurological symptoms and imaging findings. TIA was defined as a transient episode of neurological dysfunction without acute cerebral infarction, as described previously.[15] Safety endpoints included any bleeding incidence (Global Use of Strategies to Open Occluded Coronary Arteries definition),[16] including any bleeding events (intracranial hemorrhage, skin bleeding, mucous membrane bleeding, gastrointestinal bleeding, and other visceral organ bleeding) during hospitalization.

2.4 | Statistical analysis

Statistical analysis was performed using the intention-to-treat (ITT) population. Patient characteristics by group were summarized after stratification by different antiplatelet therapies. The frequency (percentage), mean ± SD, or median (interquartile range, IQR) were reported depending on the variable type. We tested for intergroup differences with a *t*-test for continuous variables and the χ^2 test for categorical variables. Categorical variables were analyzed using Pearson's chi-squared test or Fisher's exact test, and continuous variables were analyzed using Student's *t*-test or the Wilcoxon rank-sum test, as appropriate. The missing values were substituted with median values. We also used restricted cubic splines to express the potentially nonlinear relationship of admission SBP level and choice of initial antiplatelet regimen. We fit multinomial and multivariate logistic regression analysis models to antiplatelet therapy and reported the unadjusted and adjusted odds ratios. To test our hypothesis regarding the association between the admission blood pressure level and antiplatelet therapy, we included a cross-grouped term (SBP × HTN), which assigns subgroups based on admission SBP levels and history of HTN, in logistic regression analysis models. We fit Logistic models to our outcomes and reported crude and adjusted odds ratios. All analyses were performed with the statistical software packages R (http://www.R-project.org, The R Foundation) and Free Statistics software version 1.3.

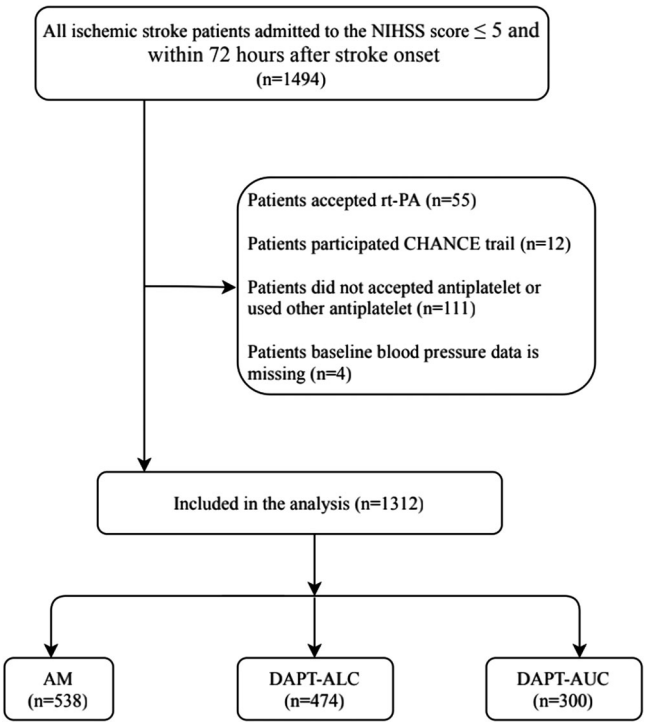

FIGURE 1 Flowchat of participant selection

3 | RESULTS

3.1 | Study participants and baseline characteristics

We included 1312 of the original 1494 patients (Figure 1). Baseline demographic characteristics are shown in Table 1. Of the 1312 patients included in the study, the mean (SD) age was 62.0 (12.7) years; 903 (70.9%) patients were male. The general characteristics of the patients who received AM ($n = 538$, 41.0%) versus DAPT-ALC ($n = 474$, 35.6%) and DAPT-AUC ($n = 300$, 22.9%) are shown in Table 1. Compared with those in the AM group, patients in the DAPT-ALC group were more likely to be younger; to arrive earlier; to have a history of smoking, CAD, and dyslipidemia; to have a large artery atherosclerosis stroke subtype and moderate to severe steno-occlusion of the relevant artery; to have a lower proportion of ICH and shorter hospitalization days; and to be taking statin medication at stroke onset. Moreover, the baseline characteristics of the DAPT-AUC and AM groups were similar regarding mean age, history of smoking, and coronary heart disease (CHD). However, DAPT-AUC group patients were more likely to have a history of acute myocardial infarction (AMI) and less likely to have a history of ICH than those in the AM group (4.7% vs. 1.7% and .3% vs. 2.6%, $p < .05$). Also, the proportion of patients who received antihypertensive drugs within 24 h of admission was higher in the DAPT-AUC group than in the AM group or the DAPT-ALC group (12.0%, 9.3%, and 9.3%, respectively). There were no significant differences in laboratory data among the three groups.

TABLE 1 Comparison of clinical characteristics according to different antiplatelet therapies

N (%)	Total *n* = 1312	AM *n* = 538	DAPT-ALC *n* = 474	DAPT-AUC *n* = 300	*p*-Value
Clinical items					
Sex (Male)	930 (70.9)	359 (66.7)	349 (73.6)	222 (74.0)	.02
Age, y	62.0 ± 12.7	63.7 ± 13.8	59.6 ± 11.5	61.4 ± 12.0	.000
SBP, mmHg	149.5 ± 22.1	148.0 ± 22.2	148.0 ± 20.2	152.5 ± 23.8	.003
DBP, mmHg	87.0 ± 13.6	86.0 ± 13.3	87.0 ± 13.3	88.0 ± 14.6	.08
Medical history					
Smoking	580 (44.2)	215 (40.0)	245 (51.7)	120 (40.0)	.000
HTN	772 (58.8)	310 (57.6)	268 (56.5)	194 (64.7)	.06
DM	277 (21.1)	101 (18.8)	114 (24.1)	62 (20.7)	.12
Dyslipidemia	60 (4.6)	23 (4.3)	29 (6.1)	8 (2.7)	.07
AF	42 (3.1)	14 (2.6)	14 (3.0)	12 (4.0)	.73
TIA	20 (1.5)	8 (1.5)	9 (1.9)	3 (1.0)	.64
Stroke	305 (23.2)	134 (24.9)	106 (22.4)	65 (21.7)	.48
CHD	70 (5.3)	23 (4.3)	35 (7.4)	12 (4.0)	.000
AMI	40 (3.0)	9 (1.7)	17 (3.6)	14 (4.7)	.038
PAD	2 (.2)	0 (0)	2 (.4)	0 (0)	.19
Gastric ulcer	16 (1.2)	6 (1.1)	6 (1.3)	4 (1.3)	.95
ICH	21 (1.6)	14 (2.6)	6 (1.3)	1 (.3)	.03
Previous treatment					
Antiplatelet use	122 (9.3)	53 (9.9)	50 (10.5)	19 (6.3)	.12
Antihypertensive use	486 (37.0)	210 (39.0)	182 (38.4)	94 (31.3)	.065
Drug use at admission					
Statin	477 (36.4)	116 (21.6)	280 (59.1)	81 (27.0)	.000
Antihypertension[a]	130 (9.9)	50 (9.3)	44 (9.3)	36 (12.0)	.000
Clinical examination					
TOAST, *n* (%)					.002
SVO	605 (46.1)	167 (38.7)	377 (50.1)	61 (48.0)	
LAA	519 (39.6)	184 (42.6)	284 (37.7)	51 (40.2)	
CA	32 (2.4)	8 (1.9)	20 (2.7)	4 (3.1)	
OE	78 (5.9)	34 (7.9)	38 (5.0)	6 (4.7)	
UD	78 (5.9)	39 (9)	34 (4.5)	5 (3.9)	
ICAS, *n* (%)					.001
0	692 (53.5)	245 (57.2)	386 (52.1)	61 (46.8)	
1	553 (42.7)	169 (40.4)	327 (44.1)	57 (45.4)	
mRS *n* (%)					.781
0	1037 (79.0)	342 (79.2)	595 (79)	100 (78.7)	
1	255 (19.4)	81 (18.8)	149 (19.8)	25 (19.7)	
2	20 (1.5)	9 (2.1)	9 (1.2)	2 (1.6)	
Onset to arrival time					.000
≤24 h	801 (56.1)	257 (47.5)	299 (63.1)	191 (63.5)	
24–72 h	568 (43.3)	283 (52.6)	175 (36.9)	110 (36.7)	

(Continues)

TABLE 1 (Continued)

N (%)	Total *n* = 1312	AM *n* = 538	DAPT-ALC *n* = 474	DAPT-AUC *n* = 300	*p*-Value
Initial NIHSS score					.22
≤3	1064 (76.0)	423 (78.2)	348 (73.4)	230 (76.4)	
4–5	315 (24.0)	118 (21.9)	126 (26.6)	71 (23.7)	
Hospitalization days	13.0 (10.0, 15.0)	13.0 (10.0, 14.0)	12.0 (10.0, 14.0)	14.0 (11.0, 15.0)	.000
Onset year					
Before recommended	560 (40.7)	295 (54.5)	106 (22.4)	123 (40.9)	
After recommended	817 (59.3)	246 (45.5)	368 (77.6)	178 (59.1)	.000
Laboratory data, median (IQR)					
WBC, 10^9/L	7.6 (6.7, 7.7)	7.6 (6.8, 7.8)	7.6 (6.2, 8.0)	7.6 (7.6, 7.6)	.064
Platelet counts, 10^9/L	209.8 (185.4, 222.0	209.8 (183.0, 222.5	209.8 (179.0, 225.2	209.8 (208.0, 212.4	.087
LDL-C, mmol/L	2.5 (2.1, 2.7)	2.5 (2.1, 2.6)	2.5 (2.0, 2.9)	2.5 (2.3, 2.5)	.078
Creatinine, μmol/L	71.9 (64.3, 75.0)	71.9 (65.2, 75.0)	71.9 (62.2, 78.0)	71.9 (69.8, 71.9)	.251
Glucose, mmol/L	6.4 (5.1, 6.4)	6.3 (5.0, 6.4)	6.2 (5.1, 6.5)	6.4 (5.2, 6.4)	.315

Abbreviations: AF, atrial fibrillation; After recommended: after 2015. AM indicates aspirin monotherapy; AMI, acute myocardial infarction; Before recommended: before 2015; CE, cardioembolic; CHD, coronary artery disease; CM, indicates clopidogrel monotherapy; DAPT-ALC, dual antiplatelet therapy with aspirin and load-clopidogrel (clopidogrel loading dose of 300 mg on the first day; DAPT-AUC, dual antiplatelet therapy with aspirin and unload-clopidogrel (clopidogrel 75 mg daily with no loading dose); DBP, diastolic blood pressure; DM, diabetes mellitus; HTN, hypertension; ICAS, intracranial cerebral atherosclerosis; ICH, intracranial hemorrhage; LAA, large artery atherosclerosis; LDL-C, low-density lipoprotein cholesterol; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OE, other etiology; PAD, peripheral artery disease; SBP, systolic blood pressure; SVO, small vessel occlusion; TIA, transient ischemic attack; TOAST, Trial of ORG 10172 in Acute Stroke Treatment; UD, undetermined etiology; WBC, White blood cell counts.

[a]Use antihypertension medicine within 24 h postadmission. Data are shown as *n* (%), mean ± SD or median (IQR)

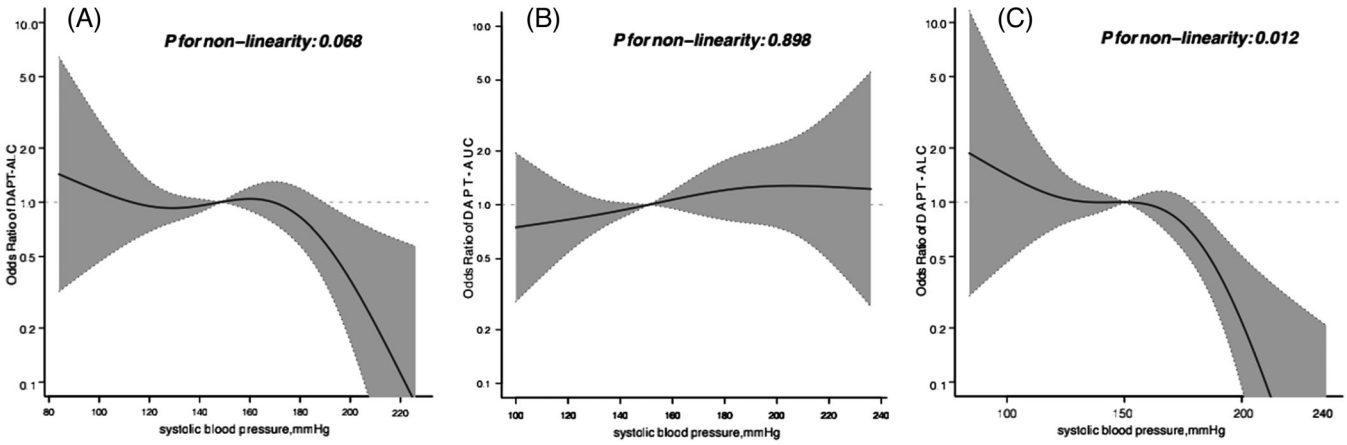

FIGURE 2 Relationship of admission systolic blood pressure with initial antiplatelet schemes

A indicates AM and DAPT-ALC schemes, B indicates AM and DAPT-AUC schemes, and C indicates DAPT-ALC and DAPT-AUC schemes. *Adjusted for sex, age, onset to arrival time, GC, ICH, baseline NIHSS, onset year, history of TIA, stroke, AMI, and used antiplatelet; OR indicates odds ratio

3.2 | Association between SBP and different antiplatelet regimens

Figure 2 shows the restricted cubic spline analysis, which indicated a likely "S-shaped" association between the selection of the DAPT-ALC or the DAPT-AUC scheme and admission SBP (P for nonlinearity = .012), with an increased likelihood of using DAPT-AUC for participants with higher SBP. There was a significant curve relationship between the DAPT-ALC and DAPT-AUC groups; at the same time, the inflection point of blood pressure was 188.5 mmHg (186.9, 190.1) ($p = .029$).

3.3 | Multivariate logistic regression analysis of intention-to-treat therapy and admission SBP

The relationship between SBP level and different drug groups was analyzed by multiclassification logistic regression using the AM group as

TABLE 2 OR and 95% CI of DAPT-ALC and DAPT-AUC in multinomial logistic regression analysis of intention-to-treat therapy and admission SBP level

	SBP, mmHg	Crude OR (95%CI)	*p*-Value	Model 1 OR (95%CI)	*p*-Value	Model 2 OR (95%CI)	*p*-Value	Model 3 OR (95%CI)	*p*-Value
DAPT-ALC	<140	1 (Ref)		1 (Ref)		1 (Ref)		1 (Ref)	
	140–180	.17 (.37–1.02)	.06	.56 (.33–.96)	.033	.56 (.32–.95)	.03	.55 (.32–.96)	.036
	≥180	1.05 (.80–1.37)	.77	.98 (.73–1.31)	.885	.98 (.73–1.32)	.90	.99 (.73–1.34)	.964
DAPT-AUC	<140	1 (Ref)		1 (Ref)		1 (Ref)		1 (Ref)	
	140–180	1.91 (1.19–3.53)	.007	1.81 (1.12–2.94)	.016	1.77 (1.09–2.90)	.02	1.49 (.89–2.47)	.128
	≥180	1.12 (.82–1.54)	.47	1.11 (.80–1.54)	.54	1.09 (.78–1.52)	.61	1.00 (.71–1.41)	.99

Note: AM as the reference group; Model 1 adjusted for sex, age, onset to arrival time, GC, ICH, baseline NIHSS, and onset year; Model 2 adjusted for sex, age, onset to arrival time, GC, ICH, baseline NIHSS, onset year, history of TIA, stroke, AMI, and antiplatelet use; Model 3 adjusted for all factors.

TABLE 3 OR and 95% CI of DAPT-AUC in multivariate logistic regression analysis of intention-to-treat therapy and admission SBP

= Variables	SBP, mmHg	Crude OR (95%CI)	*p*-Value	Model 1 OR (95%CI)	*p*-Value	Model 2 OR (95%CI)	*p*-Value	Model 3 OR (95%CI)	*p*-Value
DAPT-AUC	<140	1 (Ref)		1 (Ref)		1 (Ref)		1 (Ref)	
	140–180	1.07 (.77–1.48)	.68	1.11 (.8–1.55)	.54	1.11 (.79–1.55)	.55	.97 (.68–1.39)	.88
	≥180	3.09 (1.81–5.28)	<.001	3.25 (1.88–5.63)	.001	3.28 (1.89–5.69)	<.001	2.92 (1.62–5.26)	<.001
Trend test		1.49 (1.17–1.9)	.001	1.52 (1.20–1.97)	.001	1.54 (1.20–1.97)	.001	1.42 (1.09–1.86)	.001

Note: DAPT-ALC as the reference group; Model 1 adjusted for sex, age, onset to arrival time, GC, ICH, baseline NIHSS, and onset year; Model 2 adjusted for sex, age, onset to arrival time, GC, ICH, baseline NIHSS, onset year, history of TIA, stroke, AMI, and antiplatelet use; Model 3 adjusted for all factors.

a reference (Table 2). Compared with the SBP less than 140 mmHg group, patients with blood pressure at the level of 140–180 mmHg were more likely to be given AM (OR = .56 [.32–.95], p = .03) and DAPT-AUC (OR = 1.77 [1.09–1.52], p = .02) in the crude and adjusted models. Among patients with blood pressure greater than or equal to 180 mmHg, the admission choices of antiplatelet therapy were not significantly different. Compared with the SBP less than 140 mmHg group, the patients with SBP greater than or equal to 180 mmHg were more likely to be given DAPT-AUC (OR = 2.92 [1.62–5.26], p < .001) than DAPT-ALC in all models (Table 3). In addition, the trend test was statistically significant (OR = 1.42 [1.09–1.86], p = .001).

To verify the interaction between pre-HTN and admission SBP levels, we introduced a cross-grouped item consisting of SBP and previous HTN history (SBP × HTN) into logistic regression models (Table 4). In the crude model, compared with patients with SBP less than 140 mmHg who did not have a history of HTN, patients with SBP greater than or equal to 180 mmHg who did not have a history of HTN were given DAPT-AUC rather than DAPT-ALC (OR = 9.23 [2.51~33.99], p = .001; OR = 2.9 [1.55~5.41], p = .001). Similar results were found after adjusting for sex, age, onset to arrival time, history of GC and ICH, admission NIHSS score, and onset year in Model 1. When adjusting for all factors in Model 3, there were similar results in patients with SBP greater than or equal to 180 mmHg who did not have a history of HTN (OR = 8.2 [2.11~31.92], p = .002; OR = 4.55 [2.2~9.4], p < .001). However, patients with SBP less than 180 mmHg who did not have a history of HTN were also treated with DAPT-AUC rather than DAPT-ALC (OR = 2.33 [1.23~4.41], p = .009; OR = 2.08 [1.25~3.48], p = .005). The trend test was significant (OR = 1.27 [1.13~1.43], <.001).

3.4 | Primary and safety outcomes in SBP subgroups

To compare the primary and safety outcomes between DAPT-AUC and DAPT-ALC at different SBP levels, we trichotomized SBP levels into less than 140 mmHg, 140–180 mmHg, and equal to or greater than 180 mmHg. The primary outcome, a composite event consisting of ischemic stroke, TIA, and hemorrhagic stroke, occurred in 34 patients (7.2%) in the DAPT-ALC group compared with 18 patients (6.0%) in the DAPT-AUC group (OR = .83 [.46–1.49], p = .53) (Table 5). There were no significant differences between the DAPT-AUC and DAPT-ALC groups, regardless of whether the blood pressure level was less than 180 mmHg or more than or equal to 180 mmHg. In the SBP <180 mmHg subgroup, ischemic stroke occurred in 21 patients (4.7%) in the DAPT-ALC group and in 17 (6.7%) in the DAPT-AUC group (OR = .90 [.44–1.94], p = .83). Hemorrhagic stroke occurred in 7 patients in each of the two study groups (1.3% vs. .4%, p = .254). The rate of any bleeding event was 1.9% in the DAPT-AUC group

TABLE 4 OR and 95% CI of DAPT-AUC stratified by admission SBP levels and hypertension (SBP × HTN)

		Crude		Model 1		Model 2		Model 3	
SBP×HTN	*n* (%)	OR (95%CI)	*p*-Value	OR (95%CI)	*p*-Value	OR (95%CI)	*p*-Value	OR (95%CI)	*p*-Value
S1×H0	46 (31.9)	1 (Ref)		1 (Ref)		1 (Ref)		1 (Ref)	
S1×H1	42 (39.6)	1.4 (.83~2.36)	.21	1.36 (.79~2.36)	.27	1.37 (.8~2.36)	.25	2.33 (1.23~4.41)	.009
S2×H0	47 (30.9)	.95 (.58~1.56)	.85	.95 (.57~1.58)	.84	.97 (.59~1.61)	.90	.95 (.56~1.62)	.86
S2×H1	118 (39.7)	1.4 (.92~2.14)	.11	1.45 (.93~2.25)	.1	1.46 (.94~2.26)	.09	2.08 (1.25~3.48)	.005
S3×H0	13 (81.2)	9.23 (2.51~33.99)	.001	10.41 (2.78~39.02)	.001	10.66 (2.85~39.94)	<.001	8.20 (2.11~31.92)	.002
S3×H1	34 (57.6)	2.9 (1.55~5.41)	.001	2.95 (1.55~5.61)	.001	2.92 (1.54~5.55)	.001	4.55 (2.2~9.4)	<.001
Trend. test	300 (38.8)	1.21 (1.09~1.34)	<.001	1.22 (1.1~1.36)	<.001	1.22 (1.1~1.36)	<.001	1.27 (1.13~1.43)	<.001

Note: DAPT-ALC as the reference group; S1×H0 indicates SBP less than 140 mmHg and no history of HTN; S1×H1 indicates SBP less than 140 mmHg and history of HTN; S2×H0 indicates SBP between 140 mmHg and less than 180 mmHg and no history of HTN; S2×H1 indicates SBP between 140 mmHg and less than 180 mmHg and history of HTN; S3×H0 indicates SBP more than or equal to 180 mmHg and no history of HTN; S3×H1 indicates SBP more than or equal to 180 mmHg and history of HTN. **DAPT-ALC** as the reference group; Model 1 adjusted for sex, age, onset to arrival time, GC, ICH, baseline NIHSS, and onset year; Model 2 adjusted for sex, age, onset to arrival time, GC, ICH, baseline NIHSS, onset year, history of TIA, stroke, AMI, and antiplatelet use; Model 3 adjusted for all factors.

TABLE 5 OR and 95% CI of hospitalization outcomes stratified by admission SBP in the DAPT-ALC and DAPT-AUC groups

Outcome	DAPT-ALC[#] event rate,	DAPT-AUC event rate,	Crude		Adjusted model	
SBP level, mmHg	No./total No. (%)	No./total No. (%)	OR (95%CI)	*p*-Value	OR (95%CI)	*p*-Value
Primary outcome						
Composite event[a]						
All	34/474 (7.2)	18/300 (6.0)	.83 (.46–1.49)	.53	.82 (.45–1.51)	.53
<140 mmHg	11/162 (6.8)	7/88 (8.0)	1.19 (.44–3.18)	.73	.92 (.3–2.76)	.88
140–180 mmHg	22/284 (7.7)	10/165 (6.1)	.77 (.35–1.67)	.50	.80 (.36–1.76)	.57
≥180 mmHg	1/28 (3.6)	1/47 (2.1)	.59 (.04–9.77)	.71	.30 (0–84.1)	.68
Ischemic stroke						
<140 mmHg	6/162 (3.7)	5/88 (5.7)	1.57 (.46–5.29)	.47	1.14 (.23–5.57)	.87
140–180 mmHg	15/284 (5.3)	6/165 (3.6)	.68 (.26–1.78)	.43	.74 (.27–2.0)	.55
≥180 mmHg	0/28 (.0)	1/47 (2.1)	Inf (0-Inf)	.99	Inf (0–Inf)	1.00
Transient ischemic attack						
<140 mmHg	4/162 (2.5)	2/88 (2.3)	.92 (.16–5.12)	.92	1.4 (.22–9.07)	.72
140–180 mmHg	2/284 (.7)	3/165 (1.8)	2.61 (.43–15.79)	.30	2.89 (.44–19.1)	.27
≥180 mmHg	1/28 (3.6)	0/47 (.0)	0 (0–Inf)	.99	0 (0–Inf)	1.00
Hemorrhagic stroke						
<140 mmHg	1/162 (.6)	0/88 (.0)	0 (0–Inf)	1.0	0 (0–Inf)	1.0
140–180 mmHg	5/284 (1.8)	1/165 (.6)	.34 (.04~2.94)	.33	.30 (.03–2.8)	.29
≥180 mmHg	0/28 (0)	0/47 (0)	1.0 (0–Inf)	1.0	1.0 (0–Inf)	1.0
Safety outcomes						
Any bleeding						
All	10/474 (2.1)	4/300 (1.3)	.63 (.19–2.02)	.43	.52 (.15–1.8)	.30
<140 mmHg	2/162 (1.2)	2/88 (2.3)	1.86 (.26–13.4)	.54	6.14 (.26–146)	.26
140–180 mmHg	8/284 (2.8)	2/165 (1.2)	.42 (.09–2.02)	.28	.25 (.04–1.37)	.11
≥180 mmHg	0/28	0/47	0 (0–Inf)	1.00	0 (0–Inf)	1.00

[a]The composite event consisted of ischemic stroke, TIA, and hemorrhagic stroke. The model adjusted for age, sex, history of ischemic stroke, TIA, MI, HTN, diabetes mellitus, hypercholesterolemia, smoking, NIHSS score, interval from onset to arrival time, onset year, white blood cell counts, serum creatinine levels, glucose, platelet counts, and LDL-C.

[#]The DAPT-ALC group served as the reference group.

compared with 1.6% in the DAPT-ALC group (OR = .63 [.19–2.02], $p = .43$) (Table 5). There were no significant interactions in the two SBP subgroups ($p > .10$ for all comparisons).

4 | DISCUSSION

This is a retrospective study conducted in China, and approximately one-third of patients received treatment with DAPT-AUC at admission in real-world clinical practice. We first found that a higher admission SBP level was associated with the choice of initial antiplatelet therapy for minor ischemic stroke. Moreover, we found a likely S-shaped association between the admission SBP level and the selection of DAPT-AUC. More importantly, patients with an admission SBP greater than or equal to 180 mmHg were 4.55–8.20 times more likely to be treated with DAPT-AUC, regardless of whether there was a reported history of HTN.

Our study included patients with NIHSS scores less than or equal to 5 points who received treatment within 72 h of onset, which is inconsistent with the current guidelines. The definition of minor stroke is not uniform at present, even though it was divided into three categories in the CHANCE and POINT trials. However, in most studies of intravascular therapy for ischemic stroke, the definition of minor ischemic stroke is an NIHSS score less than or equal to five points. China's treatment guidelines for high-risk nondisabling cerebrovascular events (HR-NICE) have also proposed classifying an NIHSS score ≤3 or an NIHSS score ≤5 as minor ischemic stroke.[17]

This study showed that the proportion of males was significantly higher than that of females, which may cause bias. However, in a real-world study in South Korea, they also enrolled a significantly higher proportion of men, possibly because minor stroke patients are more likely to be men.[18] Males were more likely to be younger and to have a status (or history) of smoking than females, while females were more likely to have a history of HTN, diabetes, and antihypertensive drug use (Table S1). Chinese studies in recent years have found that men have significantly higher rates of stroke than women.[19]

There was a significant increase in the proportion of DAPT-ALC use since 2015 and a significant decrease in the proportion of AM use, but there was no significant change in the use of DAPT-AUC. However, DAPT-AUC did not appear in the guidelines for acute ischemic stroke or the latest randomized controlled trials (RCTs),[5,20,21] and it is not known whether this therapy maintains a similar effect to standard double antiplatelet therapy in preventing stroke recurrence. The endpoint events were not significantly different between the DAPT-ALC and DAPT-AUC groups (Table 5). However, the results may not be accurate due to the sample size and need further validation.

Our study found an interesting phenomenon of the relationship between admission SBP level and the choice of DAPT-AUC, with a blood pressure inflection point of 188 mmHg. The SBP levels in the DAPT-AUC group were higher than those in the other treatment groups, and the differences were statistically significant (Table 1). This coincides with the result of the curve fitting. Several studies have shown that 75%–80% of patients with acute cerebral infarction experience elevated blood pressure, especially within 72 h of onset.[10,22] Therefore, whether high blood pressure levels in acute periods tend to increase the risk of intracranial bleeding is the most critical consideration for clinicians when choosing antiplatelet drugs and is also an important factor affecting their decision-making. In Table S1, the proportion of cerebral hemorrhage in the group with blood pressure greater than or equal to 180 mmHg was significantly higher than that in the other blood pressure groups. On the other hand, many studies have shown that increased blood pressure during acute periods of ischemic stroke is clearly associated with poor prognoses, such as high short-term mortality and long-term disability.[13,23] In the acute stage of stroke, the incidence of stroke recurrence, hemorrhage conversion, and cerebral edema increased significantly in patients with HTN. For ischemic risk, bleeding events, especially intracranial bleeding, may require discontinuation of antiplatelet therapy, and thus, patients do not benefit from ongoing antiplatelet therapy.

The multivariate logistic regression model showed that patients with higher blood pressure between 140–180 mmHg were treated with the DAPT-AUC scheme but not the AM regimen. The post hoc analysis of the POINT trial reported that patients with baseline SBP lower than 140 mmHg could benefit from DAPT and have a lower risk of recurrent stroke, while the CHANCE trial reported inconsistent results. For people with blood pressure greater than 180 mmHg, the difference in the likelihood of selecting standard or nonstandard dual antiplatelet therapy was not statistically significant compared to the control group. However, for patients with blood pressure greater than 180 mmHg, there were significant differences in whether the blood pressure level affected the type of dual antiplatelet therapy. Such patients were more likely to have intracranial atherosclerosis given the higher rates in Asian patients with stroke.[24] Patients with intracranial atherosclerotic stenosis may require higher blood pressure in the subacute period after stroke to prevent recurrent stroke or extend the initial stroke from hypoperfusion.[25]

The prevalence of HTN in this population was close to 60% (Table 1). A history of HTN impacts the decision-making for the entire population (Table 4). Nevertheless, in patients with SBP greater than or equal to 180 mmHg, there was a greater possibility of being treated with DAPT-AUC regardless of whether there was a history of HTN. BP is an important determinant of the risk of initial stroke among individuals with HTN and those without HTN.[26,27] Following ischemic stroke, the early BP increase often reflects uncontrolled or undiagnosed chronic HTN. However, an early hypertensive response to physical and psychological stresses from brain ischemia is an important contributing factor to elevated BP in acute ischemic stroke.[28] In clinical decision-making, safety and efficacy are more important than effectiveness in physician decision-making regarding drugs, as bleeding events can lead to the termination of antiplatelet therapy, which can lead to more fatal outcomes for patients, especially those excluded from an RCT.

Our study found that the proportion of DAPT-AUC treatment in clinical practice is approximately 25%, although the guidelines do not recommend it. Whether patients could benefit is unclear. Our study performed additional prognostic analysis and found no significant difference in the risk of in-hospital stroke recurrence between

DAPT-AUC and DAPT-ALC. However, further validation is required for the assessment of the long-term prognosis. The effect of high blood pressure on stroke outcomes in the real world needs further verification. On the one hand, BP-lowering treatment may reduce vascular damage, cerebral edema, and hemorrhagic transformation of cerebral infarction. It may then help prevent secondary injury and hasten the transition to long-term antihypertensive therapy.

4.1 | Study limitations

Our study has some limitations. First, many complicated factors in making clinical decisions include indications, physician factors, practice environment, and policy. Second, for incomplete and missing record data of first blood pressure at the emergency room, our analysis mainly focused on the SBP level measured at the time of admission, and there may be a bias. We collected data of antiplatelet drugs used within 24 h of admission. The proportion was highest in the DAPT-AUC group, which is consistent with the main result that when SBP was ≥180 mmHg, patients were more likely to be given DAPT-AUC. It also indirectly reflects that the blood pressure level in the DAPT-AUC group was likely higher than 180 mmHg at the first visit. Third, we had a small sample size, and our results should be verified in a large-scale trial.

5 | CONCLUSION

There are many factors associated with antiplatelet regimens in clinical practice, including blood pressure levels. Our findings suggest that admission SBP is associated with the choice of initial antiplatelet therapy, especially when the SBP level is greater than or equal to 180 mmHg.

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CONFLICTS OF INTEREST

None of the authors has any conflicts of interest.

AUTHORS' CONTRIBUTIONS

TL was a major contributor to the writing of the manuscript; YW performed the formal analysis; XN supervised the study and performed data visualization; YL, KZ, HF, JR and JL performed data collection; LM, XL and XW supervised each stroke center.

REFERENCES

1. Collaborators GBDCoD. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet*. 2017;390(10100):1151-1210.
2. Wang W, Jiang B, Sun H, et al. Prevalence, incidence, and mortality of stroke in china: results from a Nationwide Population-Based Survey of 480 687 adults. *Circulation*. 2017;135(8):759-771.
3. Kleindorfer DO, Towfighi A, Chaturvedi S, et al. 2021 Guideline for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline from the American Heart Association/American Stroke Association. *Stroke*. 2021;52(7):e364-e467.
4. Pan Y, Li Z, Li J, et al. Residual risk and its risk factors for ischemic stroke with adherence to guideline-based secondary stroke prevention. *J Stroke*. 2021;23(1):51-60.
5. Wang Y, Wang Y, Zhao X, et al. Clopidogrel with aspirin in acute minor stroke or transient ischemic attack. *N Engl J Med*. 2013;369(1):11-19.
6. Shamy MC, Jaigobin CS. The complexities of acute stroke decision-making: a survey of neurologists. *Neurology*. 2013;81(13):1130-1133.
7. Saposnik G, Johnston SC. Decision making in acute stroke care: learning from neuroeconomics, neuromarketing, and poker players. *Stroke*. 2014;45(7):2144-2150.
8. Kim D, Park JM, Kang K, et al. Dual versus mono antiplatelet therapy in large atherosclerotic stroke. *Stroke*. 2019;50(5):1184-1192.
9. King PK, Fosnight SM, Bishop JR. Consensus clinical decision-making factors driving anticoagulation in atrial fibrillation. *Am J Cardiol*. 2019;124(7):1038-1043.
10. Qureshi AI, Ezzeddine MA, Nasar A, et al. Prevalence of elevated blood pressure in 563,704 adult patients with stroke presenting to the ED in the United States. *Am J Emerg Med*. 2007;25(1):32-38.
11. Wang Y, Xu J, Zhao X, et al. Association of hypertension with stroke recurrence depends on ischemic stroke subtype. *Stroke*. 2013;44(5):1232-1237.
12. de Havenon A, Johnston SC, Easton JD, et al. Evaluation of systolic blood pressure, use of aspirin and clopidogrel, and stroke recurrence in the platelet-oriented inhibition in new TIA and minor ischemic stroke trial. *JAMA Netw Open*. 2021;4(6):e2112551.
13. Xu J, Tao Y, Li H, et al. Different levels of blood pressure, different benefit from dual antiplatelet therapy in minor stroke or TIA patients. *Sci Rep*. 2017;7(1):3884.
14. Adams HP Jr, Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke*. 1993;24(1):35-41.
15. Wong KS, Chen C, Fu J, et al. Clopidogrel plus aspirin versus aspirin alone for reducing embolisation in patients with acute symptomatic cerebral or carotid artery stenosis (CLAIR study): a randomised, open-label, blinded-endpoint trial. *Lancet Neurol*. 2010;9(5):489-497.
16. GUSTO investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. *N Engl J Med*. 1993;329(10):673-682.
17. Wang Y. High-risk non-disabling ischemic cerebrovascular events: a window of opportunity for stroke control. *Zhonghua Nei Ke Za Zhi*. 2015;54(9):745-746.
18. Kim JT, Park MS, Choi KH, et al. Comparative effectiveness of dual antiplatelet therapy with aspirin and clopidogrel versus aspirin monotherapy in acute, nonminor stroke: a nationwide, multicenter registry-based study. *Stroke*. 2019;50(11):3147-3155.
19. Li Z, Jiang Y, Li H, Xian Y, Wang Y. China's response to the rising stroke burden. *BMJ*. 2019;364:l879.
20. Wang Y, Liu M, Pu C. 2014 Chinese guidelines for secondary prevention of ischemic stroke and transient ischemic attack. *Int J Stroke*. 2017;12(3):302-320.
21. Johnston SC, Easton JD, Farrant M, et al. Clopidogrel and aspirin in acute ischemic stroke and high-risk TIA. *N Engl J Med*. 2018;379(3):215-225.

22. Wong KS, Wang Y, Leng X, et al. Early dual versus mono antiplatelet therapy for acute non-cardioembolic ischemic stroke or transient ischemic attack: an updated systematic review and meta-analysis. *Circulation*. 2013;128(15):1656-1666.
23. Leitao L, Soares-Dos-Reis R, Neves JS, Baptista RB, Bigotte Vieira M, Mc Causland FR. Intensive blood pressure treatment reduced stroke risk in patients with albuminuria in the SPRINT trial. *Stroke*. 2019;50(12):3639-3642.
24. Bang OY. Intracranial atherosclerosis: current understanding and perspectives. *J Stroke*. 2014;16(1):27-35.
25. Wong LK. Global burden of intracranial atherosclerosis. *Int J Stroke*. 2006;1(3):158-159.
26. Blood pressure, cholesterol, and stroke in eastern Asia. Eastern stroke and coronary heart disease collaborative research group. *Lancet*. 1998;352(9143):1801-1807.
27. Greenlund KJ, Croft JB, Mensah GA. Prevalence of heart disease and stroke risk factors in persons with prehypertension in the United States, 1999–2000. *Arch Intern Med*. 2004;164(19):2113-2118.
28. Carlberg B, Asplund K, Hägg E. Factors influencing admission blood pressure levels in patients with acute stroke. *Stroke*. 1991;22(4):527-530.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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