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Triple Antihypertensive Medication Prediction Score After Intracerebral Hemorrhage (the TRICH Score)

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Abstract

Background and Objectives

Poor long-term blood pressure (BP) control due to undertreatment of hypertension is not uncommon after intracerebral hemorrhage (ICH). It heightens the risk of ICH recurrence and subsequent stroke, which is the highest within the first year. Promptly achieving BP targets would significantly reduce these risks. To accomplish this, upfront triple antihypertensive medications could be prescribed soon after ICH because many ICH survivors require ≥3 antihypertensives. However, not all would suit this approach, particularly those with cerebral amyloid angiopathy (CAA), where elevated admission BP may be due to acute hypertensive response rather than underlying hypertension. In addition, overtreatment and excessive BP lowering would cause more side effects and have been associated with increased mortality in older patients. Hence, to facilitate individualized treatment, we aimed to develop a score (TRICH) to predict the need for ≥3 antihypertensives at 3 months after ICH.

Methods

We developed the score using data from the University of Hong Kong prospective ICH registry (2011–2022) and validated it in 3 hospitals (2020–2022) locally. Consecutive patients with spontaneous ICH who survived >90 days and had follow-up BP 3 months after ICH were included. Predictors for needing ≥3 antihypertensive medications at 3 months were identified using multivariate logistic regression, and the score was created using the β-coefficients.

Results

The TRICH score was developed from 462 patients (mean age 66.6 ± 14.3 years, 60% male) and validated in 203 patients (mean age 66.3 ± 14.6 years, 62% male). The 9-point score (age younger than 60 years = 1, male = 1, ischemic heart disease = 1, admission estimated glomerular filtration rate <60 mL/min/1.73 m^2 = 2, admission systolic BP 190–230 mm Hg = 2 while >230 mm Hg = 4) has a *c*-statistic (95% CI) of 0.79 (0.75–0.83) in the development cohort and 0.76 (0.69–0.82) in validation. A dichotomized score (≥3 points) predicted the need for ≥3 antihypertensives with 0.73 (95% CI 0.67–0.80) sensitivity and 0.76 (95% CI 0.70–0.81) specificity. The score performed better in patients with untreated/uncontrolled hypertension before ICH than in controlled patients (*c*-statistic [95% CI] 0.81 [0.77–0.86] vs 0.74 [0.69–0.80], $p = 0.037$) but showed no difference between patients with CAA and non-CAA patients.

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Supplementary Material

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Glossary

ACEI = angiotensin-converting enzyme inhibitor; **ARB** = angiotensin receptor blocker; **BP** = blood pressure; **CAA** = cerebral amyloid angiopathy; **CCB** = calcium channel blocker; **eGFR** = estimated glomerular filtrate rate; **FNR** = false-negative rate; **FPR** = false-positive rate; **HKU** = University of Hong Kong; **ICH** = intracerebral hemorrhage; **IQR** = interquartile range; **MACCE** = major adverse cardiac and cerebrovascular event; **PRA** = plasma renin activity; **SBP** = systolic BP; **TIS** = therapeutic intensity score.

Discussion

The TRICH score identifies patients with ICH who need ≥3 antihypertensive medications 3 months after ICH with good discrimination ability. It may guide upfront triple antihypertensive prescription, but further research is warranted, particularly in non–Han Chinese populations.

Introduction

Intracerebral hemorrhage (ICH) is the most severe form of stroke, and uncontrolled hypertension is the main cause of this devastating disease.[1] For those who survive their ICH, achieving adequate blood pressure (BP) control is the single most crucial factor in reducing the risk of ICH recurrence and major adverse cardiac and cerebrovascular events (MACCEs).[2,3] However, only a minority of ICH survivors were able to achieve adequate BP control in real-world data,[4,5] which predisposes these patients to ICH recurrence and MACCEs. Hence, improving BP control after ICH is the highest priority if we are to lessen the health care and social burden of the disease.

Uncontrolled hypertension, in general, is caused by clinician-related factors, such as undertreatment of hypertension, or patient-related factors, which include resistant hypertension and drug compliance.[6,7] Resistant hypertension is defined when BP remains above goal despite the use of ≥3 antihypertensive medication classes at maximally tolerated doses or BP at goal while on ≥4 antihypertensives.[8] Because ICH survivors have more severe hypertension, the rate of resistant hypertension after ICH is up to 30%,[7] which is much higher than the 10%–15% in the general hypertensive population.[9,10] Intuitively, owing to the high rate of resistant hypertension, approximately half of the ICH survivors require ≥3 antihypertensive medications for BP control.[7,11] Hence, frequent up-titration of antihypertensives is necessary after ICH. However, therapeutic inertia, where clinicians fail to intensify antihypertensive therapy when BP goals are not met, is frequently encountered in clinical practice. Studies have shown that clinicians are often willing to accept higher BP measurements in their patients,[12,13] and that medication intensification only occurred in 14%–32% of uncontrolled hypertension encounters.[14] Therapeutic inertia leads to the undertreatment of hypertension, which is one of the leading causes of uncontrolled hypertension,[15] and underlies up to two-thirds of uncontrolled hypertension in ICH survivors.[7] Therefore, addressing therapeutic inertia is pivotal for improving hypertension control among ICH survivors.

In addition to achieving BP control, prompt BP lowering to the treatment goal is also particularly crucial. BP control at 3 months after ICH correlates with long-term BP control and, importantly, recurrent stroke and mortality risk.[7] Of note, the risk of recurrent ICH and stroke is highest shortly after the initial ICH event, with one-third of all subsequent events within 5 years, occurring in the first year.[7] Hence, because most ICH survivors required ≥3 antihypertensive medications, upfront prescription of triple antihypertensive regimen soon after ICH could both address therapeutic inertia and enable prompt BP control. A triple combination antihypertensive pill (triple pill) is preferred to improve adherence.[16,17] The benefits of triple pills after ICH are currently being evaluated in the ongoing Triple Therapy Prevention of Recurrent Intracerebral Disease Events Trial study (ClinicalTrial.gov identifier NCT02699645). However, upfront triple antihypertensive regimen may not be suitable for all patients, particularly in patients with cerebral amyloid angiopathy (CAA),[18] in which the elevated admission BP may be due to acute hypertensive response rather than underlying hypertension.[19] It is also important to consider the risk of overtreatment and excessive BP lowering with triple therapy, which would result in more side effects and had been linked to increased mortality especially in older patients.[20,21] In addition, the general use of triple pills in all patients with ICH may have cost implications, especially in low-income or middle-income countries where ICH is also more prevalent,[1] because triple pills are more expensive when compared with conventional antihypertensive medications.

Thus, having a predictive tool to identify patients with ICH who require ≥3 antihypertensive medications for BP control will facilitate individualized treatment for upfront triple antihypertensive medication prescription. This approach would enable clinicians to achieve BP targets in their patients safely and promptly through informed prescribing practices, while also mitigating the risk of overtreating hypertension and

reducing treatment-related complications. Therefore, we aimed to develop and validate a score (the TRICH score) to predict the need for ≥3 antihypertensive medications for BP control at 3 months after ICH.

Methods

Study Population

We developed the TRICH score using data from the University of Hong Kong (HKU) stroke registry. The HKU stroke registry is an ongoing, prospective stroke registry that recruits consecutive patients with spontaneous ICH admitted to Queen Mary Hospital, Hong Kong. Patients enrolled in the registry from 2011 to 2022 were included in the developmental cohort. The validation cohort comprised consecutive patients with ICH admitted to 3 other hospitals in Hong Kong from 2020 to 2022: Ruttonjee, Yan Chai, and Princess Margaret Hospitals. The diagnosis of ICH was confirmed by CT scan of the brain. Patients with ICH aged 18 years and older with acute spontaneous ICH who survived beyond 90 days after the index event were included. Secondary ICHs including ICH resulting from hemorrhagic cerebral infarct, head trauma, brain tumor, aneurysm, or vascular malformation were excluded.

Standard Protocol Approvals, Registrations, and Patient Consents

The study protocol was approved by the institutional review boards of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (UW12-177/UW18-361), Hong Kong East Cluster (HKECREC-2020-084), and Kowloon West Cluster (KWEX20120). Written informed consent was obtained from the patient or a proxy during enrollment into the HKU stroke registry from 2011 to 2019. However, owing to the coronavirus disease 2019 pandemic and ward access restrictions for research staff, consent was waived by relevant institutional review boards for all 4 centers for patients enrolled between 2020 and 2022. During the period of 2020–2022, study participants were identified through admission records of stroke units of respective hospitals and data were accessed remotely through the electronic patient record system. If additional information was required, in-person interview would be performed by the designated site principal investigator.

Data Collection

Demographic data, medical history, cardiovascular risk factors, and details of the hospitalization during the index ICH were collected by trained study staff through in-person interviews of patients (and/or reliable informants) and/or a review of electronic medical records at the time of enrollment. All patients discharged from participating hospitals were followed up under a single government-funded health care system, the Hospital Authority. Patients were regularly followed up by their respective clinicians for around 2–4 months after index ICH. All clinical records, including BP during follow-up and medication prescriptions, were entered into a territory-wide electronic medical record system. The 3-month (±2 weeks) office BP recorded during follow-up and the antihypertensive medications prescribed were retrieved by dedicated study staff who were blinded to patients' clinical and imaging information.

Definition of Variables

Controlled hypertension was defined as systolic BP (SBP) of ≤130 mm Hg, based on the recommendation of the 2022 American Heart Association/American Stroke Association ICH guideline.[22] Only the SBP was considered for this definition because it is more indicative of the risk of recurrent ICH and MACCE after ICH[2] and is the primary parameter for BP targets according to local guidelines.[23] We considered patients with uncontrolled hypertension while on ≤2 antihypertensive medications as undertreated because these patients should have had their antihypertensive medications intensified. Patients with undertreated hypertension were excluded because they may, in theory, require ≥3 antihypertensive medications for hypertensive management. We also excluded patients with white-coat effect, where office SBP was >130 mm Hg but home SBPs were consistently ≤130 mm Hg,[24] as well as those with missing 3-month BP. Patients with missing 3-month BP record but were prescribed ≥3 antihypertensives were still included in this study.

The primary outcome of this study was the need for ≥3 antihypertensive medications at 3 months after ICH based on the number of antihypertensive medications prescribed. This included patients who were prescribed ≥3 antihypertensives despite not being on at least 2 maximally tolerated doses of antihypertensive medications.

The total dose of antihypertensive medications for each patient was represented using the therapeutic intensity score (TIS).[25] The TIS of each patient was formulated as the summative representation of the total dose of antihypertensive medication prescribed based on the maximum US Food and Drug Administration recommended dose. The therapeutic intensity of each drug was determined using the prescribed daily dose as the numerator and the corresponding maximum dose as the denominator. The TIS is the sum of the therapeutic intensity of all drugs prescribed. For instance, if a patient was prescribed 3 antihypertensive medications, with 1 at 25% of the maximum recommended dose and the other 2 at 50%, the TIS would be 1.25 (0.25+0.5+0.5).

The etiology of the ICH was classified as either hypertensive arteriopathy or CAA. Locations of ICH were first identified as lobar (cerebral cortex or cortical-subcortical regions), deep (basal ganglia, thalamus, or brainstem), or cerebellum. Cerebellar ICH was categorized separately because it can be caused by either hypertensive arteriopathy or CAA.[26] We classified patients as having CAA if they met the criteria for possible/probable CAA of the Modified Boston Criteria.[18] Probable CAA was defined as patients aged 55 years and older with MRI or CT demonstrating multiple lobar hemorrhages

(ICH or microbleeds) while those with single hemorrhage were identified as possible CAA. The Boston Criteria version 2.0 were not used because most patients,[27] particularly those with deep-seated ICH, did not have MRI scans. Hypertensive arteriopathy was considered the cause of ICH in patients who were not diagnosed as CAA.[28]

Statistical Methods

Statistical analyses were performed using SPSS Statistics software (version 29.0; IBM Corp., Armonk, NY) and Prism version 6.0. All significance tests were 2-tailed, and p value <0.05 was considered statistically significant. The clinical characteristics of patients in the development and validation cohorts were compared. Differences between groups for continuous variables were compared using the independent-samples t-test or Mann-Whitney U test as appropriate. Categorical variables were compared using the χ^2 test. Continuous variables were expressed as mean and SD or median with interquartile range (IQR) and categorical variables as numbers and percentages. The admission estimated glomerular filtrate rate (eGFR) was calculated using the CKD-EPI formula (2021).

From the development cohort, factors associated with the need for ≥3 antihypertensive medications after ICH were determined using logistic regression. The cutoff for continuous variables, such as age and admission SBP, was determined using the receiver operating characteristic analysis. In addition, because the degree of BP elevation at admission is likely indicative of the severity of underlying hypertension and, consequently, the intensity of antihypertensive medication, we established an additional SBP cutoff at the highest decile of admission SBP, rounding to the nearest multiple of 10 (SBP >230 mm Hg). This was performed to further explore the association between extreme hypertension and antihypertensive needs. The admission eGFR was stratified into <60 and ≥60 mL/min/1.73 m^2. Multivariate logistic regression was performed by entering all variables with $p < 0.20$ in the univariate analysis. The TRICH score was derived based on the β-coefficients from the final regression model. The assigned scores for each item were determined by summing the β-coefficients (B), calculating the point for each risk factor as $10 \times (\beta i/B)$ rounded to the closest point. Model performance of the score was calculated for both the development and validation cohorts, including c-index for discrimination and the Hosmer-Lemeshow goodness-of-fit statistic for calibration. The optimal cutoff for the TRICH score was determined using the Youden index, and the test characteristics (sensitivity, specificity, false-negative rate [FNR], false-positive rate [FPR], and positive and negative predictive values) were calculated based on the dichotomized categories.

To assess the potential clinical implication of a false-positive or false-negative result of the TRICH score, we compared the clinical characteristics and antihypertensive medication prescriptions of these falsely classified patients with true positives from both cohorts.

Subgroup Analysis

Because ICH population consists of a diverse group of patients, specific subgroup analyses were conducted to assess the performance of the TRICH score for different subgroups of patients. Using data from both development and validation cohorts, we categorized patients based on whether they had controlled or untreated/uncontrolled hypertension before ICH and ICH etiology (CAA vs hypertensive arteriopathy).

The performance of the TRICH score in each subgroup was analyzed using the receiver operating characteristic curves and compared using the DeLong test to determine whether the score's performance differed significantly between the groups. In addition, a similar analysis on a smaller subset of patients from the development cohort with MRI for CAA diagnosis was conducted, to evaluate any performance differences of the score compared with the main result, where CAA was diagnosed using CT scans only.

Data Availability

Anonymized data pertaining to the research presented will be made available from the corresponding authors on reasonable request by any qualified investigator.

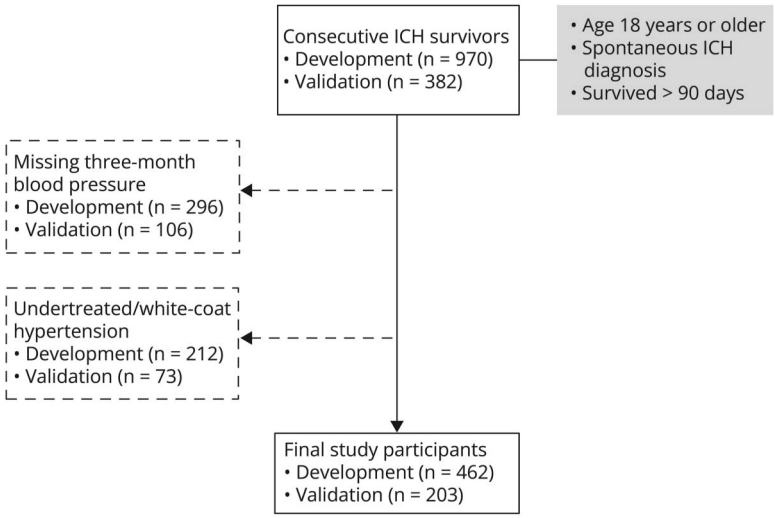
Results

Study Participants

During the study period, 1,352 spontaneous ICH survivors were enrolled (development cohort: 970; validation cohort: 382). After excluding patients with missing 3-month BP, who were undertreated, and with white-coat hypertension, 665 patients (development: 462; validation: 203) were included in this analysis (Figure). The clinical characteristics of the study participants are given in Table 1. In the development cohort, the mean age was 66.6 ± 14.3 years and 60.0% were men. A total of 449 patients (97.2%) had hypertension, of whom 209 (45.2%) had controlled hypertension before ICH. The mean admission SBP was 187.2 ± 31.7 mm Hg. Deep-seated ICH accounted for 69.0% of ICH while 22.7% of patients were diagnosed with CAA. The mean admission eGFR was 79.3 ± 22.4 mL/min/1.73 m^2. At 3 months after ICH, controlled hypertension was achieved in 346 patients (74.9%) and 117 (25.5%) had resistant hypertension. The median number of antihypertensive medications prescribed was 2 (IQR 2) while 196 (42.4%) were on ≥3 antihypertensive medications. The median antihypertensive medication TIS for patients on 3 drugs was 1.6 (IQR 0.8) and increased to 1.8 (IQR 0.9) if including only patients with ≥3 antihypertensive medications.

There were no significant differences in clinical characteristics between the development and validation cohorts, except for a higher rate of antiplatelet prescription in the validation cohort. The rate of controlled hypertension and the number of antihypertensive medications prescribed did not differ significantly (Table 1).

Figure Flow Diagram of Study Inclusion and Exclusion Criteria



ICH = intracerebral hemorrhage.

TRICH Score Development

eTable 1 provides the univariate analysis of factors associated with the need for ≥3 antihypertensive medications at 3 months after ICH, which include age younger than 60 years, male sex, history of ischemic heart disease, eGFR <60 mL/min/1.73 m^2, and higher admission SBP.

In the multivariate regression analysis, these factors remained independently associated with the need for ≥3 antihypertensive medications after ICH (Table 2). The 5-item TRICH score was created with a total score ranging from 0 to 9, using the β-coefficients obtained from the regression model (Table 3).

Validation of the TRICH Score

Table 4 provides the *c*-statistics, sensitivity, specificity, and distribution of the TRICH score. The *c*-statistic for the TRICH score was 0.79 (95% CI 0.75–0.83) in the development cohort and 0.76 (95% CI 0.69–0.82) in the validation cohort. The Hosmer-Lemeshow test indicated that the score had satisfactory calibration in both cohorts (p = 0.53 for development; p = 0.13 for validation).

The optimal cutoff of the TRICH score was <3 and ≥3 based on the Youden index, with 0.73 (95% CI 0.67–0.80) sensitivity, 0.76 (95% CI 0.70–0.81) specificity, 0.27 (95% CI 0.20–0.33) FNR, and 0.24 (95% CI 0.19–0.30) FPR in the development cohort, and 0.73 (95% CI 0.63–0.82) sensitivity, 0.68 (95% CI 0.58–0.77) specificity, 0.27 (95% CI 0.18–0.37) FNR, and 0.32 (95% CI 0.23–0.42) FPR in the validation cohort. The test characteristics of the score at different cutoffs are presented in eTable 2.

Clinical Characteristics and Antihypertensive Medication Prescriptions of Falsely Classified Patients Based on a Cutoff of TRICH Score ≥3

eTable 3 provides the characteristics and antihypertensive medication prescriptions of false-positive patients. Compared with true positives, patients who were false positive were older (69.7 vs 60.0 years, p < 0.001), had lower admission SBP (199.0 vs 214.8 mm Hg, p < 0.001), and had lower median TRICH scores (3 vs 4, p < 0.001). The median number of antihypertensive medications was 2 (IQR 1), with a median antihypertensive medication TIS of 0.8 (IQR 0.9).

As for patients who were false negative based on the TRICH score (eTable 4), similarly, they were also older (67.0 vs 60.0 years, p < 0.001) but had much lower admission SBP (173.9 vs 214.8 mm Hg, p < 0.001) and were more frequently women (51.3% vs 25.6%, p < 0.001), with higher rates of controlled hypertension before ICH (59.0% vs 35.3%, p < 0.001). Although the median TRICH score was only 1, the median number of antihypertensive medications was 3 (IQR 1), with a median TIS of 1.6 (IQR 1.0).

Performance and Test Characteristics of the TRICH Score for Different Subgroups

The performance and test characteristics of the TRICH score for patients who had controlled hypertension or untreated/uncontrolled hypertension before ICH and with CAA or hypertensive arteriopathy are provided in Tables 5 and 6, respectively. The *c*-statistics were >0.70 for all the subgroups, with the highest among patients with untreated/uncontrolled hypertension before ICH (0.81, 95% CI 0.77–0.86). There was satisfactory calibration for the score in all subgroups (all p for the Hosmer-Lemeshow test >0.05). The score performed

Table 1 Study Participant Characteristics of Development and Validation Cohorts

Variables	Development cohort (N = 462)	Validation cohort (N = 203)	*p* Value
Demographics			
Age, y, mean ± SD	66.6 ± 14.3	66.3 ± 14.6	0.85
Male sex	277 (60.0)	125 (61.6)	0.69
Race/ethnicity			
Han Chinese	449 (97.2)	196 (96.6)	0.91
White	2 (0.4)	1 (0.5)	
Others	11 (2.4)	6 (3.0)	
Medical and drug history			
Controlled hypertension	209 (45.2)	87 (42.9)	0.57
History of diabetes mellitus	80 (17.3)	46 (22.7)	0.11
History of ischemic stroke	48 (10.4)	32 (15.8)	0.05
History of ICH	25 (5.4)	14 (6.9)	0.45
History of ischemic heart disease	32 (6.9)	22 (10.8)	0.09
Antiplatelet use	76 (16.5)	48 (23.6)	0.03
Anticoagulation use	38 (8.2)	18 (8.9)	0.78
Admission and imaging data			
Admission systolic BP, mm Hg, mean ± SD	187.2 ± 31.7	187.8 ± 40.0	0.83
Admission diastolic BP, mm Hg, mean ± SD	104.7 ± 22.4	106.4 ± 25.6	0.40
Admission systolic BP			
<190 mm Hg	246 (53.2)	106 (52.2)	0.08
190–230 mm Hg	172 (37.2)	66 (32.5)	
>230 mm Hg	44 (9.5)	31 (15.3)	
eGFR, mL/min/1.73 m^2, mean ± SD	79.3 ± 22.4	80.1 ± 25.5	0.70
ICH volume, mL, median (IQR)	12.6 (22.8)	12.6 (24.6)	1.00
ICH location			
Deep	319 (69.0)	144 (70.9)	0.86
Lobar	114 (24.7)	46 (22.7)	
Cerebellum	29 (6.3)	13 (6.4)	
Cerebral amyloid angiopathy	105 (22.7)	40 (19.7)	0.39
3-mo BP and antihypertensive medications			
Systolic BP, mean ± SD[a]	122.7 ± 14.0	122.3 ± 14.6	0.77
Diastolic BP, mean ± SD[a]	72.8 ± 11.4	71.3 ± 11.5	0.16
Controlled hypertension[a]	346 (74.9)	142 (70.0)	0.18
Resistant hypertension[b]	117 (25.5)	62 (32.5)	0.07
No. of antihypertensive medications, median (IQR)	2 (2)	2 (2)	0.30
≥3 antihypertensive medications	196 (42.4)	97 (47.8)	0.20
Antihypertensive medication TIS, median (IQR)	1.1 (1.2)	1.2 (1.5)	0.98
Types of antihypertensive medication			

Continued

Table 1 Study Participant Characteristics of Development and Validation Cohorts *(continued)*

Variables	Development cohort (N = 462)	Validation cohort (N = 203)	*p* Value
Calcium channel blockers	383 (82.9)	158 (77.8)	0.12
ARB/ACEI	264 (57.1)	115 (56.7)	0.91
Diuretics	33 (7.1)	13 (6.4)	0.73
Alpha blockers	95 (20.6)	60 (29.6)	0.01
Beta blockers	202 (43.7)	103 (50.7)	0.10
Others	80 (17.3)	28 (13.8)	0.26

Abbreviations: ACEI = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker; BP = blood pressure; eGFR = estimated glomerular filtration rate; ICH = intracerebral hemorrhage; IQR = interquartile range; TIS = therapeutic intensity score.
[a] Thirty-one missing data.
[b] Sixteen missing data.

better in patients with untreated/uncontrolled hypertension before ICH compared with those with controlled hypertension ($p = 0.037$ for the DeLong test) but did not differ for ICH etiology ($p = 0.96$ for the DeLong test).

In the subset of 192 patients with MRI from the development cohort, the distribution of cerebral microbleeds is presented in eTable 5. Among them, 22.9% with deep and 27.3% with cerebellar ICH subsequently met the diagnostic criteria for CAA, contributing to an additional 50% of CAA diagnosis compared with using CT alone. Nonetheless, the test performance of the TRICH score remained good for both hypertensive arteriopathy and CAA and still did not differ between groups ($p = 0.63$ for the DeLong test) (eTable 6).

Analysis of Excluded Patients With Missing Follow-Up BP

Compared with the patients included in the analysis, those with missing BP at 3 months were younger, were more likely to belong to a race/ethnicity other than Han Chinese or White, had lower rates of controlled hypertension, and had higher mean admission eGFR. Despite these differences, the median TRICH score did not significantly differ between the 2 groups (eTable 7).

Discussion

We developed and validated a predictive score for the need for ≥3 antihypertensive medications at 3 months after ICH. The component of TRICH score includes 5 common clinical parameters: age, sex, history of ischemic heart disease, admission SBP, and eGFR. The score had an acceptable discriminant value with an optimal cutoff of 3 and performed better in patients with untreated/uncontrolled hypertension before ICH. Because ICH survivors have high recurrent ICH, stroke, and MACCE risk, especially in the first year of ICH, timely BP control is vital to reduce these risks. The TRICH score can guide clinicians to adopt early prescription of triple antihypertensive regimen. Applying this score facilitates individualized treatment, enabling prompt BP control after ICH and mitigating the potential risk of overtreating patients who do not have severe underlying hypertension.

Table 2 Multivariable Analysis of Factors Associated With the Need for ≥3 Antihypertensive Medications 3 Months After ICH

Variables	β-coefficient	aOR (95% CI)	*p* Value
Age younger than 60 years	1.16	3.19 (2.03–5.02)	<0.001
Male sex	0.59	1.81 (1.15–2.85)	0.011
History of ischemic heart disease	0.98	2.65 (1.15–6.14)	0.023
Admission eGFR <60 mL/min/1.73 m^2	1.25	3.49 (1.93–6.32)	<0.001
Admission systolic blood pressure			<0.001
<190 mm Hg	—	Ref	Ref
190–230 mm Hg	1.32	3.75 (2.39–5.89)	<0.001
>230 mm Hg	2.99	19.76 (7.10–54.98)	<0.001

Abbreviations: aOR = adjusted odds ratio; eGFR = estimated glomerular filtration rate; ICH = intracerebral hemorrhage.

Table 3 TRICH Scores

Variable	Points
Age	
Younger than 60 years	1
60 years and older	0
Sex	
Male	1
Female	0
History of ischemic heart disease	
Yes	1
No	0
eGFR	
eGFR <60 mL/min/1.73 m^2	2
eGFR ≥60 mL/min/1.73 m^2	0
Admission systolic blood pressure	
>230 mm Hg	4
190–230 mm Hg	2
<190 mm Hg	0

Abbreviation: eGFR = estimated glomerular filtration rate.

The TRICH score comprised well-known factors of resistant hypertension, namely sex, renal impairment, and age. Hypertension is not only more prevalent in men but also more difficult to control.[29-31] This is because androgens activate the sympathetic nervous system and renal-angiotensin system, leading to higher levels of angiotensin II that consequently increase sodium and water reabsorption.[29] Along the same discussion, patients with chronic renal impairment also have higher levels of angiotensin II.[32] Other hormonal factors that lead to hypertension in chronic renal impairment include excess aldosterone,[32] nitric oxide deficiency,[33] and hyperuricemia,[34] which further contribute to high BP through sodium/water retention and arterial vasoconstriction. As for age, there are conflicting reports on the relationship between age and resistant hypertension, which is probably due to regional and ethnic differences.[30,35] However, it is no surprise that age younger than 60 years is a component of the TRICH score because younger age has been associated with resistant hypertension in Han Chinese,[35] and ICH in older patients is more commonly due to CAA,[18] where hypertensive arteriopathy may not be the predominant contributing pathology.

The TRICH score also demonstrated that the prediction of the need for ≥3 antihypertensive medications after ICH cannot solely depend on admission BP, except for extreme SBP of >230 mm Hg. Admission BPs are often higher than the "true" underlying BPs because of the acute hypertensive response in ICH. Hence, admission SBP of <190 mm Hg does

Table 4 Test Characteristics of the TRICH Score

Variables	Development cohort (n = 462)	Validation cohort (n = 203)
***c*-Statistics (95% CI)**	0.79 (0.75–0.83)	0.76 (0.69–0.82)
Score	≥3 antihypertensive medications, n (%)	
0–2	52/254 (20.5)	26/98 (26.5)
3–4	92/150 (61.3)	39/66 (59.1)
5–6	42/48 (87.5)	26/32 (81.3)
7–9	10/10 (100.0)	6/7 (85.7)
Dichotomized score		
<3	52/254 (20.5)	26/98 (26.5)
≥3	144/208 (69.2)	71/105 (67.6)
Dichotomized test characteristics (95% CI)		
Sensitivity	0.73 (0.67–0.80)	0.73 (0.63–0.82)
Specificity	0.76 (0.70–0.81)	0.68 (0.58–0.77)
False-negative rate	0.27 (0.20–0.33)	0.27 (0.18–0.37)
False-positive rate	0.24 (0.19–0.30)	0.32 (0.23–0.42)
Positive predictive value	0.69 (0.63–0.75)	0.68 (0.58–0.76)
Negative predictive value	0.80 (0.74–0.84)	0.73 (0.64–0.82)

Abbreviation: ICH = intracerebral hemorrhage.

Table 5 Performance of the TRICH Score for Controlled and Untreated/Uncontrolled Hypertension Before ICH

Variables	Controlled hypertension (n = 296)	Untreated/uncontrolled hypertension (n = 369)
***c*-Statistics (95% CI)**	0.74 (0.69–0.80)	0.81 (0.77–0.86)
Score	≥3 antihypertensive medications, n (%)	
0–2	46/178 (25.8)	32/174 (18.4)
3–4	49/85 (57.6)	82/131 (62.6)
5–6	23/28 (82.1)	45/52 (86.5)
7–9	4/5 (80.0)	12/12 (100.0)
Dichotomized score		
<3	46/178 (25.8)	32/174 (18.4)
≥3	76/118 (64.4)	139/195 (71.3)
Dichotomized test characteristics (95% CI)		
Sensitivity	0.62 (0.53–0.71)	0.81 (0.75–0.87)
Specificity	0.76 (0.69–0.82)	0.72 (0.65–0.78)
False-negative rate	0.38 (0.29–0.47)	0.19 (0.13–0.25)
False-positive rate	0.24 (0.18–0.31)	0.28 (0.22–0.35)
Positive predictive value	0.64 (0.55–0.73)	0.71 (0.64–0.78)
Negative predictive value	0.74 (0.67–0.80)	0.82 (0.75–0.87)

Abbreviation: ICH = intracerebral hemorrhage.

Table 6 Performance of the TRICH Score for ICH Due to Hypertensive Arteriopathy or Cerebral Amyloid Angiopathy

Variables	Hypertensive arteriopathy (n = 520)	Cerebral amyloid angiopathy (n = 145)
***c*-Statistics (95% CI)**	0.78 (0.74–0.82)	0.78 (0.70–0.86)
Score	≥3 antihypertensive medications, n (%)	
0–2	61/258 (23.6)	17/94 (18.1)
3–4	108/176 (61.4)	23/40 (57.5)
5–6	60/70 (85.7)	8/10 (80.0)
7–9	15/16 (93.8)	1/1 (100.0)
Dichotomized score		
<3	61/258 (23.6)	17/94 (18.1)
≥3	183/262 (69.8)	32/51 (62.7)
Dichotomized test characteristics (95% CI)		
Sensitivity	0.75 (0.69–0.80)	0.65 (0.50–0.78)
Specificity	0.71 (0.66–0.77)	0.80 (0.71–0.88)
False-negative rate	0.25 (0.20–0.31)	0.35 (0.22–0.50)
False-positive rate	0.29 (0.23–0.34)	0.20 (0.12–0.29)
Positive predictive value	0.70 (0.64–0.75)	0.63 (0.48–0.76)
Negative predictive value	0.76 (0.71–0.83)	0.82 (0.73–0.89)

Abbreviation: ICH = intracerebral hemorrhage.

not contribute to any points in the TRICH score while an additional component is required for SBP 190–230 mm Hg to increase the specificity of the score. This, along with the age criteria, will mitigate the risk of overtreating older patients and those with CAA who do not have or have less severe underlying hypertension.

The TRICH score is designed to tackle the issue of therapeutic inertia, which is one of the leading causes of uncontrolled hypertension after ICH.[7] Patients with a TRICH score of ≥3 should start a triple antihypertensive regimen within the first few days to ensure prompt BP lowering, instead of gradual inpatient/outpatient titration of antihypertensive medications. Combining multiple antihypertensive agents has an additive effect on lowering BP because multiple pathophysiologic pathways contribute to hypertension.[36] Considering that the median TIS of antihypertensive medications in the true-positive group was 1.9, a reasonable starting TIS for the triple antihypertensive regime should be around 1, with the option of a triple pill. Trials involving hypertensive populations have illustrated the beneficial effect of a combination antihypertensive pill on BP reduction, by minimizing side effects and enhancing adherence compared with multiple single-agent regimens.[17,37,38]

Like all predictive scores, there were false classifications by the TRICH score. False-positive patients have a marginal positive TRICH score (median of 3), and the false classification is likely contributed by the high admission SBP due to acute hypertensive response. Nevertheless, the risk of overtreating these patients should not be high because the median TIS of antihypertensive medication was 0.8. Given that the minimum antihypertensive medication TIS for a triple pill in the market is 1.25, the use of the lowest dose triple pill may be appropriate for this group of patients, but overtreatment remains a concern. On the contrary, false-negative patients were typically older women with higher rates of controlled hypertension before ICH and a significantly lower admission SBP. The low admission SBP that results in lower scores likely contributed to the false classification. This could be due to their state of controlled hypertension before ICH or a smaller hypertensive response during ICH. Clinicians should be aware of this specific group of patients who require higher intensities of antihypertensive medications but with low TRICH scores, in whom early review for up-titration of antihypertensive medications would be warranted.

In the subgroup analyses, the performance of the TRICH score was more robust in patients with untreated/uncontrolled hypertension before ICH. This is likely because the admission BPs of these patients are higher and not affected by preexisting use of antihypertensive medications. The *c*-statistic of the score was around 0.80 for both ICHs due to hypertensive arteriopathy or CAA, indicating that the TRICH score is applicable regardless of ICH etiology. Hence, the score can effectively identify patients with CAA who also have underlying severe hypertension, which necessitates the use of triple antihypertensive regime. Identifying these patients and achieving prompt BP control are essential because uncontrolled hypertension also heightens the risk of recurrent ICH and MACCE in lobar ICH.[2,39]

As shown in our study, patients with ICH have high rates of resistant hypertension. Therefore, in addition to triple pill, further tailoring of therapy could enhance BP control. One effective approach involves the use of stimulated plasma renin activity (PRA) and aldosterone phenotyping.[40-43] PRA and aldosterone need to be measured in stimulated conditions, either by administering furosemide or while the patient is taking angiotensin receptor blockers (ARBs) or angiotensin-converting enzyme inhibitors (ACEIs). Patients with low PRA/low aldosterone exhibit a Liddle phenotype and respond best to amiloride. ARBs are most effective in those with high PRA/high aldosterone (renal phenotype) while patients with low PRA/high aldosterone have inappropriate aldosterone secretion and, hence, aldosterone antagonists work best.[40,41] Although these data are not collected in our ICH cohort, the TRICH score can be potentially used in conjunction with renin/aldosterone phenotyping. Further studies on using the TRICH score to identify patients who require ≥3 antihypertensive medications, combined with renin/aldosterone phenotyping to facilitate further individualized treatment approach, could greatly benefit this high-risk population. Furthermore, responses to the type of antihypertensive medication may vary based on race and ethnicity. While ARBs and ACEIs are generally the first-line treatment choice, calcium channel blockers (CCBs) or thiazide-like diuretics are preferred for patients of African descent[44] while those of Eastern Asian descent generally respond better to CCBs.[45] Choosing the most appropriate antihypertensive medication is particularly important in ICH survivors because they have elevated risks of cardiovascular events, stroke, and recurrent ICH.[2,3]

Our study has several limitations. First, the TRICH score was developed and validated in a population predominantly consisting of Han Chinese patients. The generalizability of the score to other populations is a significant limitation, and further studies are necessary. Second, approximately 30% of enrolled patients were excluded because of missing 3 months of follow-up BP. These patients were younger and had a lower rate of controlled hypertension before ICH, both of which are known factors associated with therapeutic noncompliance.[46] However, the median TRICH score for those excluded was not significantly different from that of included patients. Hence, the TRICH score should be applicable to most patients who adhere to treatment and follow-up. Next, we could not determine medication compliance among study participants because it was not routinely recorded during follow-ups. Fourth, patients were not followed up under a standardized protocol, and antihypertensive medications were prescribed at the treating clinician's discretion. However, all patients were treated under a single health care system where the clinical practice was mostly consistent among

clinicians. Furthermore, we defined the need for ≥3 antihypertensive medications based on the number of prescribed drugs without accounting for the dosage. Nevertheless, the median antihypertensive medication TIS of those prescribed 3 drugs was 1.6, indicating that most patients are prescribed at least 2 drugs at near-maximally tolerated doses. Because the lowest TIS of triple pills is 1.25, the TRICH score could select patients for upfront prescription of triple pill or triple antihypertensive regime, beginning at lower doses, which would also help minimize side effects. In addition, the TRICH score, which is meant to predict antihypertensive medication requirements 3 months after ICH, may not account for changes in BP control and medication needs beyond 3 months. Hence, further medication titration, including down-titration, may be necessary after this initial period. Nevertheless, the TRICH score can help clinicians ensure timely BP control after ICH through early and appropriate medication prescriptions, which is crucial in reducing early recurrent ICH and stroke risk. Finally, the definition of controlled hypertension and the TRICH score derived in this study were based solely on SBP. This limitation may affect the application of the TRICH score in ICH survivors because patients may still have isolated diastolic hypertension despite treatment. Isolated diastolic hypertension is particularly important in younger patients because it is more prevalent and associated with increased cardiovascular risk in this age group.[47-49] However, it is often overlooked, and the significance of isolated diastolic hypertension among ICH survivors is also not well studied.

In conclusion, the TRICH score identifies patients with ICH who need ≥3 antihypertensive medications 3 months after ICH for BP control with good discrimination ability. Using the TRICH score for upfront prescription of triple antihypertensive medications within days after ICH could potentially change clinical practice, by facilitating individualized treatment, addressing therapeutic inertia, and enabling prompt BP control. It is important to note that this score will mitigate the risk of overtreatment and excessive BP lowering, especially in older patients and those with CAA. A randomized controlled trial based on the dichotomized cutoff of TRICH score <3 and ≥3 would help prove the benefit of the TRICH score in clinical practice.

Author Contributions

C.H. So: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data. C. Yeung: major role in the acquisition of data. R.W.-H. Ho: major role in the acquisition of data. Q.H. Hou: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. C.H.F. Sum: major role in the acquisition of data. W. Leung: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. Y.K. Wong: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. K.C.R. Liu: major role in the acquisition of data. H.H. Kwan: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. J. Fok: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. E.K.-K. Yip: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. B. Sheng: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. D.Y.-H. Yap: drafting/revision of the manuscript for content, including medical writing for content. G.K.K. Leung: drafting/revision of the manuscript for content, including medical writing for content. K.H. Chan: drafting/revision of the manuscript for content, including medical writing for content. G.K.K. Lau: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. K.C. Teo: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data.

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References

1. Feigin VL, Stark BA, Johnson CO, et al. Global, regional, and national burden of stroke and its risk factors, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet Neurol*. 2021;20(10):795-820. doi:10.1016/s1474-4422(21)00252-0
2. Teo KC, Keins S, Abramson JR, et al. Blood pressure control targets and risk of cardiovascular and cerebrovascular events after intracerebral hemorrhage. *Stroke*. 2023;54(1):78-86. doi:10.1161/STROKEAHA.122.039709
3. Li L, Poon MTC, Samarasekera NE, et al. Risks of recurrent stroke and all serious vascular events after spontaneous intracerebral haemorrhage: pooled analyses of two population-based studies. *Lancet Neurol*. 2021;20(6):437-447. doi:10.1016/S1474-4422(21)00075-2
4. Rodriguez-Torres A, Murphy M, Kourkoulis C, et al. Hypertension and intracerebral hemorrhage recurrence among white, black, and Hispanic individuals. *Neurology*. 2018;91(1):e37-e44. doi:10.1212/WNL.0000000000005729
5. Zahuranec DB, Wing JJ, Edwards DF, et al. Poor long-term blood pressure control after intracerebral hemorrhage. *Stroke*. 2012;43(10):2580-2585. doi:10.1161/STROKEAHA.112.663047
6. Wang TJ, Vasan RS. Epidemiology of uncontrolled hypertension in the United States. *Circulation*. 2005;112(11):1651-1662. doi:10.1161/CIRCULATIONAHA.104.490599

7. Biffi A, Teo KC, Castello JP, et al. Impact of uncontrolled hypertension at 3 months after intracerebral hemorrhage. *J Am Heart Assoc*. 2021;10(11):e020392. doi:10.1161/JAHA.120.020392
8. Carey RM, Calhoun DA, Bakris GL, et al. Resistant hypertension: detection, evaluation, and management: a scientific statement from the American Heart Association. *Hypertension*. 2018;72(5):e53-e90. doi:10.1161/HYP.0000000000000084
9. Persell SD. Prevalence of resistant hypertension in the United States, 2003-2008. *Hypertension*. 2011;57(6):1076-1080. doi:10.1161/HYPERTENSIONAHA.111.170308
10. Egan BM, Zhao Y, Axon RN, Brzezinski WA, Ferdinand KC. Uncontrolled and apparent treatment resistant hypertension in the United States, 1988 to 2008. *Circulation*. 2011;124(9):1046-1058. doi:10.1161/CIRCULATIONAHA.111.030189
11. Khawaja AM, Shiue H, Boehme AK, et al. Admission systolic blood pressure predicts the number of blood pressure medications at discharge in patients with primary intracerebral hemorrhage. *Neurologist*. 2018;23(2):60-64. doi:10.1097/NRL.0000000000000173
12. Ali DH, Kiliç B, Hart HE, et al. Therapeutic inertia in the management of hypertension in primary care. *J Hypertens*. 2021;39(6):1238-1245. doi:10.1097/HJH.0000000000002783
13. Shawahna R, Khalaily S, Abu Saleh D. Promoters of therapeutic inertia in managing hypertension: a consensus-based study. *Am J Manag Care*. 2021;27(11):480-486. doi:10.37765/ajmc.2021.88775
14. Salanitro AH, Funkhouser E, Agee BS, et al. Multiple uncontrolled conditions and blood pressure medication intensification: an observational study. *Implement Sci*. 2010;5:55. doi:10.1186/1748-5908-5-55
15. Guthrie B, Inkster M, Fahey T. Tackling therapeutic inertia: role of treatment data in quality indicators. *BMJ*. 2007;335(7619):542-544. doi:10.1136/bmj.39259.400069.AD
16. Tsioufis K, Douma S, Kallistratos MS, Manolis AJ. Effectiveness and adherence to treatment with perindopril/indapamide/amlodipine single-pill combination in a Greek population with hypertension. *Clin Drug Invest*. 2019;39(4):385-393. doi:10.1007/s40261-019-00761-0
17. Webster R, Salam A, de Silva HA, et al. Fixed low-dose triple combination antihypertensive medication vs usual care for blood pressure control in patients with mild to moderate hypertension in Sri Lanka: a randomized clinical trial. *JAMA*. 2018;320(6):566-579. doi:10.1001/jama.2018.10359
18. Greenberg SM, Charidimou A. Diagnosis of cerebral amyloid angiopathy: evolution of the Boston criteria. *Stroke*. 2018;49(2):491-497. doi:10.1161/STROKEAHA.117.016990
19. Qureshi AI, Qureshi MH. Acute hypertensive response in patients with intracerebral hemorrhage pathophysiology and treatment. *J Cereb Blood Flow Metab*. 2018;38(9):1551-1563. doi:10.1177/0271678X17725431
20. Masoli JAH, Delgado J, Pilling L, Strain D, Melzer D. Blood pressure in frail older adults: associations with cardiovascular outcomes and all-cause mortality. *Age Ageing*. 2020;49(5):807-813. doi:10.1093/ageing/afaa028
21. Bohm M, Schumacher H, Teo KK, et al. Achieved blood pressure and cardiovascular outcomes in high-risk patients: results from ONTARGET and TRANSCEND trials. *Lancet*. 2017;389(10085):2226-2237. doi:10.1016/S0140-6736(17)30754-7
22. Greenberg SM, Ziai WC, Cordonnier C, et al. 2022 guideline for the management of patients with spontaneous intracerebral hemorrhage: a guideline from the American Heart Association/American Stroke Association. *Stroke*. 2022;53(7):e282-e361. doi:10.1161/STR.0000000000000407
23. Chan KK, Szeto CC, Lum CCM, et al. Hong Kong College of Physicians position statement and recommendations on the 2017 American College of Cardiology/American Heart Association and 2018 European Society of Cardiology/European Society of Hypertension Guidelines for the Management of Arterial Hypertension. *Hong Kong Med J*. 2020;26(5):432-437. doi:10.12809/hkmj198330
24. Muntner P, Shimbo D, Carey RM, et al. Measurement of blood pressure in humans: a scientific statement from the American heart association. *Hypertension*. 2019;73(5):e35-e66. doi:10.1161/HYP.0000000000000087
25. Levy PD, Willock RJ, Burla M, et al. Total antihypertensive therapeutic intensity score and its relationship to blood pressure reduction. *J Am Soc Hypertens*. 2016;10(12):906-916. doi:10.1016/j.jash.2016.10.005
26. Incontri D, Marchina S, Andreev A, et al. Etiology of primary cerebellar intracerebral hemorrhage based on topographic localization. *Stroke*. 2023;54(12):3074-3080. doi:10.1161/STROKEAHA.123.044271
27. Charidimou A, Boulouis G, Frosch MP, et al. The Boston criteria version 2.0 for cerebral amyloid angiopathy: a multicentre, retrospective, MRI-neuropathology diagnostic accuracy study. *Lancet Neurol*. 2022;21(8):714-725. doi:10.1016/S1474-4422(22)00208-3
28. Puy L, Parry-Jones AR, Sandset EC, Dowlatshahi D, Ziai W, Cordonnier C. Intracerebral haemorrhage. *Nat Rev Dis Primers*. 2023;9(1):14. doi:10.1038/s41572-023-00424-7
29. Maranon R, Reckelhoff JF. Sex and gender differences in control of blood pressure. *Clin Sci (Lond)*. 2013;125(7):311-318. doi:10.1042/CS20130140
30. Sim JJ, Bhandari SK, Shi J, et al. Characteristics of resistant hypertension in a large, ethnically diverse hypertension population of an integrated health system. *Mayo Clin Proc*. 2013;88(10):1099-1107. doi:10.1016/j.mayocp.2013.06.017
31. Connelly PJ, Currie G, Delles C. Sex differences in the prevalence, outcomes and management of hypertension. *Curr Hypertens Rep*. 2022;24(6):185-192. doi:10.1007/s11906-022-01183-8
32. Sica DA. The kidney and hypertension: causes and treatment. *J Clin Hypertens (Greenwich)*. 2008;10(7):541-548. doi:10.1111/j.1751-7176.2008.08189.x
33. Modlinger PS, Wilcox CS, Aslam S. Nitric oxide, oxidative stress, and progression of chronic renal failure. *Semin Nephrol*. 2004;24(4):354-365. doi:10.1016/j.semnephrol.2004.04.007
34. Johnson RJ, Feig DI, Herrera-Acosta J, Kang DH. Resurrection of uric acid as a causal risk factor in essential hypertension. *Hypertension*. 2005;45(1):18-20. doi:10.1161/01.HYP.0000150785.39055.e8
35. Ma W, Zhang Y; HOT-CHINA working group. Low rate of resistant hypertension in Chinese patients with hypertension: an analysis of the HOT-CHINA study. *J Hypertens*. 2013;31(12):2386-2390. doi:10.1097/HJH.0b013e32836586a1
36. Neutel JM, Smith DH. Hypertension management: rationale for triple therapy based on mechanisms of action. *Cardiovasc Ther*. 2013;31(5):251-258. doi:10.1111/1755-5922.12015
37. Salam A, Atkins ER, Hsu B, Webster R, Patel A, Rodgers A. Efficacy and safety of triple versus dual combination blood pressure-lowering drug therapy: a systematic review and meta-analysis of randomized controlled trials. *J Hypertens*. 2019;37(8):1567-1573. doi:10.1097/HJH.0000000000002089
38. Parati G, Kjeldsen S, Coca A, Cushman WC, Wang J. Adherence to single-pill versus free-equivalent combination therapy in hypertension: a systematic review and meta-analysis. *Hypertension*. 2021;77(2):692-705. doi:10.1161/HYPERTENSIONAHA.120.15781
39. Biffi A, Anderson CD, Battey TW, et al. Association between blood pressure control and risk of recurrent intracerebral hemorrhage. *JAMA*. 2015;314(9):904-912. doi:10.1001/jama.2015.10082
40. Spence JD. Physiologic tailoring of treatment in resistant hypertension. *Curr Cardiol Rev*. 2010;6(2):119-123. doi:10.2174/157340310791162695
41. Huang X, Li J, Liu L, et al. Interpreting stimulated plasma renin and aldosterone to select physiologically individualized therapy for resistant hypertension: importance of the class of stimulating drugs. *Hypertens Res*. 2019;42(12):1971-1978. doi:10.1038/s41440-019-0327-2
42. Spence JD, Rayner BL. Hypertension in blacks: individualized therapy based on renin/aldosterone phenotyping. *Hypertension*. 2018;72(2):263-269. doi:10.1161/HYPERTENSIONAHA.118.11064
43. Akintunde A, Nondi J, Gogo K, et al. Physiological phenotyping for personalized therapy of uncontrolled hypertension in Africa. *Am J Hypertens*. 2017;30(9):923-930. doi:10.1093/ajh/hpx066
44. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2018;71(19):e127-e248. doi:10.1016/j.jacc.2017.11.006
45. Wang JG, Kario K, Lau T, et al. Use of dihydropyridine calcium channel blockers in the management of hypertension in Eastern Asians: a scientific statement from the Asian Pacific Heart Association. *Hypertens Res*. 2011;34(4):423-430. doi:10.1038/hr.2010.259
46. Jin J, Sklar GE, Min Sen Oh V, Chuen Li S. Factors affecting therapeutic compliance: a review from the patient's perspective. *Ther Clin Risk Manag*. 2008;4(1):269-286. doi:10.2147/tcrm.s1458
47. Franklin SS, Jacobs MJ, Wong ND, L'Italien GJ, Lapuerta P. Predominance of isolated systolic hypertension among middle-aged and elderly US hypertensives: analysis based on National Health and Nutrition Examination Survey (NHANES) III. *Hypertension*. 2001;37(3):869-874. doi:10.1161/01.hyp.37.3.869
48. Lee H, Yano Y, Cho SMJ, et al. Cardiovascular risk of isolated systolic or diastolic hypertension in young adults. *Circulation*. 2020;141(22):1778-1786. doi:10.1161/CIRCULATIONAHA.119.044838
49. Yano Y, Kim HC, Lee H, et al. Isolated diastolic hypertension and risk of cardiovascular disease: controversies in hypertension: pro side of the argument. *Hypertension*. 2022;79(8):1563-1570. doi:10.1161/HYPERTENSIONAHA.122.18459