SVN Stroke & Vascular Neurology

Initial antihypertensive agent effects on acute blood pressure after intracerebral haemorrhage

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To cite: Ng Y, Qi W, King NKK, *et al*. Initial antihypertensive agent effects on acute blood pressure after intracerebral haemorrhage. *Stroke & Vascular Neurology* 2022;**7**: e001101. doi:10.1136/svn-2021-001101

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/svn-2021-001101).

Received 6 May 2021
Accepted 8 March 2022
Published Online First 20 April 2022

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ABSTRACT

Introduction Current guidelines recommend blood pressure (BP) lowering in patients after acute intracerebral haemorrhage (ICH) without guidance on initial choice of antihypertensive class. This study sought to determine if initial antihypertensive class differentially effects acute BP lowering in a large multiethnic ICH cohort.

Methods Subjects enrolled in the Ethnic/Racial Variations in ICH study between August 2010 and August 2017 with elevated admission BP and who received labetalol, nicardipine or hydralazine monotherapy as initial antihypertensive were analysed. Primary outcomes were systolic and diastolic BP changes from baseline to first BP measurement after initial antihypertensive treatment. Secondary outcomes included haematoma expansion (HE), hospital length of stay (LOS) and modified Rankin Score (mRS) up to 12 months after ICH. Exploratory outcomes assessed effects of race/ethnicity. Linear and logistic regression analyses, adjusted for relevant covariates, were performed to determine associations of antihypertensive class with outcomes.

Results In total, 1156 cases were used in analyses. Antihypertensive class was associated with diastolic BP change (p=0.003), but not systolic BP change (p=0.419). Initial dosing with nicardipine lowered acute diastolic BP than labetalol (least square mean difference (labetalol-nicardipine)=5.47 (2.37, 8.57), p<0.001). Initial antihypertensive class was also found to be associated with LOS (p=0.028), but not with HE (p=0.406), mortality (p=0.118), discharge disposition (p=0.083) or mRS score at discharge, 3, 6 and 12 months follow-up (p=0.262, 0.276, 0.152 and 0.36, respectively). Race/ethnicity variably affected multivariable models.

Conclusion In this large acute ICH cohort, initial antihypertensive class was associated with acute diastolic, but not systolic, BP-lowering suggesting differential effects of antihypertensive agents.

Trial registration number NCT01202864.

Key message

What is already known on this topic

⇒ For patients suffering from acute intracerebral haemorrhage (ICH) with initial systolic blood pressure greater than 150 mm Hg, the American Heart Association/American Stroke Association recommends reduction to below 140 mm Hg. However, no available data indicate which antihypertensive class might be most efficacious.

What this study adds

⇒ Initial choice of antihypertensive agent differentially effects immediate diastolic, but not systolic, blood pressure reduction in patients presenting with acute ICH, with nicardipine appearing to be more efficacious than labetalol.

How this study might affect research, practice or policy

⇒ While this study cannot advise on longer-term effects of initial antihypertensive choice after ICH, these results suggest that optimisation of patient-specific blood pressure therapy may be warranted through future real-world evidence or prospective clinical trials.

INTRODUCTION

Spontaneous, non-traumatic intracerebral haemorrhage (ICH) is a devastating neurological disease with no proven treatment, accounting only for 10%–15% of all strokes, but 50% of stroke-related mortality.[1 2] ICH prognosis remains poor with high mortality at 30 days[3] and 16-year cumulative survival of around 3% for men and 10% for women.[4] An effective treatment of ICH continues to be an important area of active research with promise for future successful therapeutic interventions.

For ICH patients with an initial systolic blood pressure (SBP) of 150–220 mm Hg, and without other contraindications to SBP lowering, the American Heart Association/American Stroke Association (AHA/ASA) guideline recommends that acute reduction of SBP to below 140 mm Hg.[5] High SBP is associated with early neurological deterioration, greater haematoma expansion (HE), worse clinical outcome, acute kidney injury[6]

and death.[7–9] The degree and speed of BP reduction may depend on antihypertensive class. However, no available data indicate which antihypertensive class might be most efficacious in treating acute ICH patients.

This study seeks to address this question using a large, multiethnic cohort of ICH patients. Our hypothesis was that class of antihypertensive agent differentially affects immediate BP reduction after acute ICH in a large, multiethnic cohort. The primary aim was to identify associations between antihypertensive medication class and differential immediate BP response after acute ICH. Secondary aims were to determine associations of antihypertensive class with clinical outcomes, including HE, survival and neurological recovery. Exploratory aims examined associations of antihypertensive class with outcomes in different race/ethnicity groups.

MATERIALS AND METHODS

Study population

Subjects were previously enrolled as part of the ERICH Study,[10 11] a multicentre, prospectively recruited ICH case–control study that enrolled 3000 ICH cases between August 2010 and August 2017. For this study, inclusion criteria included diagnosis of spontaneous, primary ICH and aged 18 years or older. Warfarin-associated ICH and peripartum ICH were included, but secondary aetiologies such as trauma, transformation of cerebral infarction, tumour-associated, dural venous sinus thrombosis, aneurysm, vascular malformation and malignancies leading to coagulopathy were excluded. Due to frequent use of labetalol, nicardipine and hydralazine as first-line intravenous agents in the ERICH study, individuals treated with other antihypertensive agents, treated with multiple antihypertensive agents, or with missing dose documentation were excluded. Only patients admitted through the enrolling hospital's emergency departments were included, thereby avoiding variability instilled by outside hospital transfers. Finally, all patients undergoing surgical procedure for haematoma evacuation or hemicraniectomy were excluded. Finally, the study did not proscribe an intervention strategy, so each site practised according to contemporary medical practice, following AHA guidelines at the time. Of the 3000 participants recruited into the original ERICH study, 1156 participants (figure 1) were identified who were administered an antihypertensive agent of interest in the emergency department with available premedication and post medication administration BP readings.

Collected variables

Demographic and baseline data from each subject were obtained via chart abstraction, including age, body mass index (BMI) at admission, sex, race/ethnicity, medical history and substance abuse (table 1). Heavy alcohol use was defined as consumption of more than 2 servings of alcohol per day. Information on previous cocaine use was obtained from subject/family interview. Clinical data

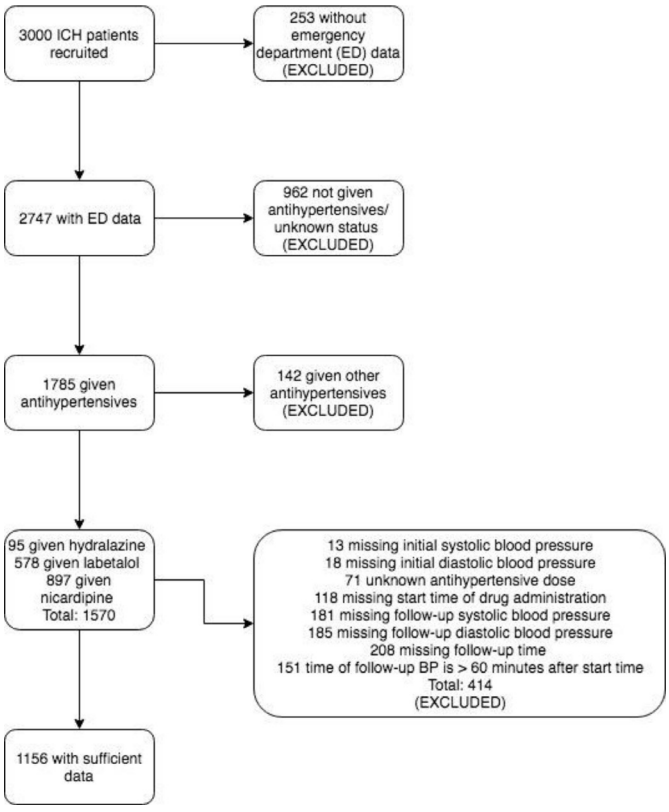

Figure 1 CONSORT diagram. CONSORT, Consolidated Standards of Reporting Trials; ICH, intracerebral haemorrhage.

related to the ICH event, namely, haematoma location, name and dose of first antihypertensive agent administered, BP immediately prior to and within an hour of antihypertensive administration, and time between antihypertensive administration and BP measurement. Following contemporary ICH guidelines and best practice, BP measurements were taken approximately 15 min after antihypertensive administration with automated entry into the electronic medical record.

Antihypertensive exposure

Labetalol, nicardipine and hydralazine were selected for analyses as the three the most common used intravenous agents in our sample population. The focus was on intravenous monotherapy because clinicians must choose a single intravenous agent to initiate BP reduction in the acute ICH setting; analyses of monotherapy provided clearly interpretable results; and cohorts of patients exposed to other antihypertensives or overlapping therapies became quite small. Antihypertensive agents were administered via intravenous bolus immediately after measurement of baseline BP. Cumulative dose of antihypertensive administered was calculated until the first subsequent BP reading after initial dosing.

Outcomes

The primary aim was to identify associations between antihypertensive medication class and differential immediate

Table 1 Subject demographics and baseline characteristics compared among three antihypertensive groups

Characteristics	Hydralazine (N=71)	Labetalol (N=415)	Nicardipine (N=670)	P value
Age (years), median (Q1, Q3)	59.0 (51, 76)	58.0 (50, 70)	58.0 (50, 69)	0.542
BMI, median (Q1, Q3)	28.3 (23.8, 34.0)	29.3 (24.7, 34.4)	28.3 (24.7, 32.9)	0.359
Dose (mg), median (Q1, Q3)	10.0 (10.0, 10.0)	17.5 (10.0, 20.0)	2.0 (0.7, 5)	------
Latency between antihypertensive administration and blood pressure measurement (minutes), median (Q1, Q3)	13.0 (8.0, 25.0)	13.0 (6.0, 25.0)	13.0 (5.0, 25.0)	0.555
Female gender, n (%)	24 (33.8)	171 (41.2)	283 (42.2)	0.389
Pre-ICH mRS >3, n (%)	0 (0)	7 (1.7)	17 (2.6)	0.281
History of stroke, n (%)	12 (16.9)	75 (18.3)	101 (15.2)	0.411
History of hypertension, n (%)	63 (88.7)	354 (86.1)	580 (87.5)	0.742
History of diabetes, n (%)	27 (38.6)	107 (26.4)	174 (26.4)	0.087
Cigarette use ever, n (%)	36 (54.5)	180 (47.8)	264 (45.1)	0.296
Heavy alcohol use, n (%)	15 (23.1)	64 (16.4)	97 (15.3)	0.265
Cocaine/crack use, n (%)	3 (4.4)	37 (9.9)	56 (9.1)	0.340
Race/ethnicity, n (%) ► Black ► Hispanic ► White	20 (28.2) 26 (36.6) 25 (35.2)	168 (40.5) 129 (31.1) 118 (28.4)	270 (40.3) 235 (35.1) 165 (24.6)	0.117
Lobar location, n (%)	21 (29.6)	107 (26.0)	155 (23.4)	0.382
Haematoma volume (mL) median (Q1, Q3)	17.8 (2.8, 32.8)	20.9 (6.2, 35.6)	15.3 (3.5, 27.1)	0.451
Prior antihypertensive use, n (%)	41 (57.8)	225 (54.2)	329 (49.1)	0.144
Initial SBP (mm Hg), mdian (Q1, Q3)	197.0 (181.0, 222.0)	200.0 (181.0, 222.0)	200.5 (178.0, 222.0)	0.730
Initial DBP (mm Hg), median (Q1, Q3)	105.0 (91.0, 120.0)	109.0 (94.0, 124.0)	108.0 (93.0, 125.0)	0.552

P value: Kruskal-Wallis test for continuous variables, χ^2 test for categorical variables with significance set to <0.05. Antihypertensive doses were not compared and are provided as a reference for amounts used in this cohort.
BMI, body mass index; DBP, diastolic blood pressure; ICH, intracerebral haemorrhage; mRS, modified Rankin Scale; Q1, lower quartile; Q3, upper quartile; SBP, systolic blood pressure.

BP response after acute ICH. The primary outcomes were change in SBP and diastolic BP (DBP) between initial BP measurement on hospital admission and first subsequent BP reading after initial administration of one of the three selected antihypertensive medication. Secondary outcomes included HE and 6 month mortality. Secondary aims were to determine associations of antihypertensive class with clinical outcomes, including HE, survival and neurological recovery. Secondary outcomes included hospital length of stay (LOS), modified Rankin Scale (mRS) at hospital discharge, 3, 6 and 12 months post-ICH and discharge disposition. Discharge disposition and mRS at discharge were obtained from discharge summaries. Surviving subjects were contacted at follow-up intervals by study personnel certified for administering outcome scales.[12] mRS was dichotomised for analyses, with mRS ≤3 representing favourable outcome and mRS >3 representing unfavourable outcome. Subject disposition was classified as discharge home (ie, to own home, care of relative or friend, or rehabilitation centre) or discharge to facility (ie, to skilled nursing home, assisted living, hospital or acute setting). Exploratory aims examined associations of antihypertensive class with primary and secondary outcomes in different race/ethnicity groups.

Imaging

The initial CT images for each subject was reviewed to confirm diagnosis of spontaneous ICH by site investigator and central imaging core neuroradiologist. Planimetric analysis using Alice software (Parexel, Waltham, Massachusetts, USA) was employed to measure haematoma volumes, previously reported to have exceptional inter-rater reliability.[13] HE was defined as >33% increase in haematoma volume from diagnostic CT to next subsequent CT imaging within 72 hours after ICH onset. Haematoma location was dichotomised into lobar and non-lobar.

Statistical analyses

Subjects were divided into three groups according to the initial antihypertensive agent administered on presentation to the emergency department. For comparisons of cohorts grouped by antihypertensive class without adjustment for covariates, Kruskal-Wallis test was used

to compare continuous variables and χ^2 test for the categorical variables. To estimate association of antihypertensives with outcomes, multivariable linear regression was performed for continuous outcomes (SBP, DBP, HE and LOS), while multiple logistic regression was performed for binary outcomes (mortality, mRS at specific time points, and disposition). Covariates adjusted in the above multiple linear/logistic regression models include race/ethnicity, age, BMI, dose of the first antihypertensive agent given, time difference between antihypertensive agent administration and measurement of BP, sex, prior history of stroke, hypertension, diabetes mellitus, cigarette use, heavy alcohol use or cocaine use, premorbid mRS, history of antihypertensive use and volume and location of ICH. To examine associations of outcomes and antihypertensive class depending on race/ethnicity, multiple linear/logistic regression models stratified by race/ethnicity was conducted in order to examine the associations of the outcomes and the antihypertensive class separately in each race/ethnicity group. For sensitivity analysis, we also fit the multiple linear/logistic regression models adjusted for the above set of covariates plus interaction term of antihypertensive class and race/ethnicity. Analyses for this study were performed using the SAS software V.9.4.

RESULTS

The antihypertensive agent administered acutely after ICH was hydralazine in 71 subjects (6.14%), labetalol in 415 subjects (35.90%), and nicardipine in 670 subjects (57.96%). Demographic characteristics of the study subjects are summarised in table 1, and crude outcomes, categorised by antihypertensive agent, are summarised in table 2. Time from ICH onset to administration of first antihypertensive agent was less than 6 hours in 72.75% of the cohort with 81.46% in total receiving initial antihypertensive therapy within 12 hours. The mean time difference between antihypertensive agent administration and BP measurement was 17.4±14.5 min across all three antihypertensive groups. The baseline characteristics of subjects in all three groups of antihypertensive agents were similar. SBP change was not different among three antihypertensive groups (p=0.730), but DBP change was significantly different (p=0.002). Secondary and exploratory outcomes were also not different among three antihypertensive groups except for LOS (p=0.004).

Linear regression models adjusted for covariates found no significant difference in antihypertensive medication class for the primary outcome of change in SBP. However, significant difference in DBP change (table 3) among antihypertensive medication classes was found, particularly between labetalol and nicardipine, where nicardipine could lower initial DBP to a greater extent than labetalol (figure 2). A sensitivity analysis for SBP and DBP using a cohort that excluded infratentorial haemorrhage cases was performed and did not alter the findings. Antihypertensive class was also found to be differentially associated with LOS (p=0.028; online supplemental table 1), particularly between labetalol and nicardipine (p=0.008; least square mean difference (labetalol-nicardipine)=−3.39 (−5.87, −0.90)), with nicardipine associated with shorter LOS. No association was found between antihypertensive class and other secondary outcomes including HE (p=0.406), mortality (p=0.118), mRS at time of discharge, 3, 6 and 12 months follow ups (p=0.262, 0.276, 0.152 and 0.36, respectively), or discharge disposition (p=0.083; online supplemental table 1).

The ERICH study was specifically designed to study racial/ethnic differences in ICH. In regression models for primary and secondary outcomes race/ethnicity was included as a covariate. Race/ethnicity had a statistically significant effect on SBP (p<0.001) and DBP (p=0.036) changes (table 4) but no associations with secondary outcomes. In exploratory analyses, regression models were stratified by race/ethnicity. In stratified models,

Table 2 Outcomes compared across three antihypertensive groups

Outcome	Hydralazine	Labetalol	Nicardipine	P value
SBP change, mm Hg, median (Q1, Q3)	−13 (−34, 0)	−18 (−36 to −5)	−19.5 (−41,−3)	0.353
DBP change, mm Hg, Median (Q1, Q3)	−9 (−25, 0)	−9 (−20, 0)	−12.5 (−27, 0)	**0.002**
HE, mL, median (Q1, Q3)	0.15 (−0.32, 2.83)	0.04 (−0.88, 1.37)	0.05 (−0.89, 1.55)	0.552
6 month mortality, n (%)	9 (13.9)	81 (22.7)	149 (26.4)	0.056
Length of stay, days, median (Q1, Q3)	8 (5, 16)	8 (4, 17.5)	10 (6, 18)	**0.004**
Discharge mRS=0–3, n (%)	28 (41.8)	153 (40.7)	210 (36.3)	0.322
90-day mRS=0–3, n (%)	34 (58.6)	186 (65.3)	272 (61.7)	0.494
6 month mRS=0–3, n (%)	35 (62.5)	200 (71.5)	272 (65.5)	0.109
12 month mRS=0–3, n (%)	33 (70.2)	183 (73.2)	262 (67.4)	0.291
Discharge to facility, n (%)	13 (21.3)	68 (18.8)	141 (25.4)	0.068

P value: Kruskal-Wallis test for continuous variables, χ^2 test for categorical variables with significance set at <0.05. Discharge to facility defined as discharge to skilled nursing home, assisted living, outside hospital or acute care setting.
DBP, diastolic blood pressure; HE, haematoma expansion; mRS, modified Rankin Scale; Q1, lower quartile; Q3, upper quartile; SBP, systolic blood pressure.

Table 3 Multiple linear regression models of primary outcomes of mean change in systolic or diastolic blood pressure (SBP/DBP) from antihypertensive administration to first subsequent blood pressure measurement, adjusted

Outcome	Predictor	Mean (95% CI)	P value
SBP change (mm Hg)	Antihypertensive used		0.419
	Hydralazine versus labetalol	4.50 (–4.46 to 13.46)	0.324
	Hydralazine versus nicardipine	5.71 (–2.97 to 14.39)	0.197
	Labetalol versus nicardipine	1.21 (–3.32 to 5.78)	0.601
DBP change (mm Hg)	Antihypertensive used		**0.003**
	Hydralazine versus labetalol	–3.41 (–9.54 to 2.72)	0.275
	Hydralazine versus nicardipine	2.06 (–3.88 to 8.00)	0.496
	Labetalol versus nicardipine	5.47 (2.37 to 8.57)	**<0.001**

P value, significance set to <0.05.

antihypertensive class was associated with DBP change in blacks (p=0.046), but not Hispanics (p=0.134) or whites (p=0.550), particularly between labetalol and nicardipine (p=0.013; least square mean difference (labetalol-nicardipine)=7.54 (1.58, 13.50)), where nicardipine lowered DBP more than labetalol. Associations were also found between antihypertensive class and LOS, disposition, 6-month mortality and mRS when stratified by race/ethnicity (online supplemental table 2). However, sensitivity analyses, using regression models with interaction term of antihypertensive class and race/ethnicity, found no association between the interaction term and any outcome.

DISCUSSION

In this large, multiethnic cohort, initial antihypertensive agent class is not associated with differences in initial SBP reduction after acute ICH or with subsequent clinical outcomes, but it is associated with initial DBP reduction. Physiologically, lowering BP may ameliorate acute ICH pathophysiology such as HE and perihaematomal oedema formation. AHA/ASA guidelines currently recommend SBP lowering to below 140 mm Hg.[5] Lack of

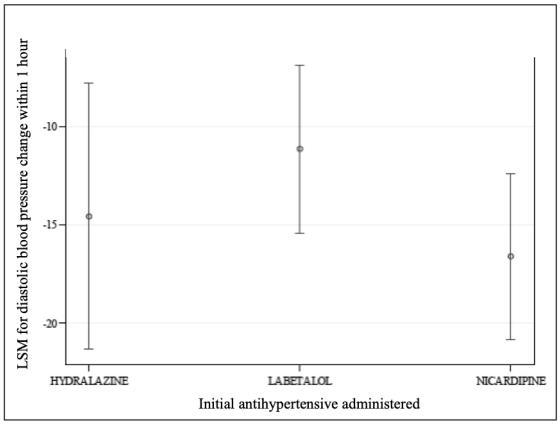

Figure 2 Least square means (LSM) diastolic blood pressure change within 1 hour of antihypertensive use, adjusted for covariates.

association with antihypertensive class and SBP reduction in acute ICH is consistent with these guidelines in which no specific antihypertensive agent is recommended. At present, antihypertensive medication after acute ICH should be selected by considering pharmacological profile, potential side effects, cost and practicability.

Clinical ICH trials have targeted SBP for treatment based on the evidence in the literature suggesting an association between SBP and HE.[14 15] However, our results demonstrated that the choice of initial antihypertensive agent was associated with a significant difference in DBP, not SBP. Effects on clinical outcome post-ICH for BP parameters other than SBP, such as DBP, pulse pressure and heart rate, remain mostly unstudied. Elevated DBP has been related to end-organ damage[16] and implicated as a strong predictor of cardiovascular disease in people under 50 years of age.[17] Recent research by Chang *et al*[18] found that widened pulse pressure, that is, the difference between SBP and DBP, was an independent predictor of increased mortality in ICH. Small vessels in the brain may be damaged by the elevated pressure pulse-wave, leading to cerebrovascular morbidity and mortality.[19 20] Failure of acute BP lowering to improve clinical outcome in ICH may be related to oversimplification of SBP as the primary variable of interest. As such, given the present investigation and related findings as discussed above, studies regarding the implication of DBP control after ICH might be considered.

The ERICH study was specifically designed to address racial/ethnic disparities and differences in ICH. Racial/ethnic differences in hypertension and the chronic effects of antihypertensive medications are well known.[21] However, differential antihypertensive effects after acute ICH have not been described. Thus, this study sought to explore possible associations between common antihypertensive agents, race/ethnicity and early effects after acute ICH. In this study, race/ethnicity affected associations between antihypertensive agents with SBP and DBP change but lacked associations with secondary clinical outcomes. To evaluate possible effects of race/ethnicity on antihypertensive therapy after acute ICH,

Table 4 Multiple linear regression models of different race/ethnicities for primary outcomes of mean change in systolic or diastolic blood pressure (SBP/DBP) from antihypertensive administration to first subsequent blood pressure measurement, adjusted for covariates

Outcome	Predictor	Mean (95% CI)	P value
SBP change (mm Hg)	Race/ethnicity		**<0.001**
	Black versus Hispanic	9.90 (4.91 to 14.89)	**<0.001**
	Black versus white	2.10 (–3.81 to 8.01)	0.486
	Hispanic versus white	–7.80 (–13.60 to 2.00)	**0.008**
DBP change (mm Hg)	Race/ethnicity		**0.036**
	Black versus Hispanic	3.60 (0.18 to 7.02)	**0.039**
	Black versus white	–0.97 (–5.01 to 3.07)	0.638
	Hispanic versus white	–4.57 (–8.53 to 0.61)	**0.024**

P value, significance set to <0.05. Bolded items highlight significant p-values.

not only was race-ethnicity included in multiple regression models, but also examined interaction effects of race-ethnicity and antihypertensive agent were examined, multiple regression models stratified by race-ethnicity were explored. Notably, associations of antihypertensive class and DBP was found in blacks, especially for labetalol versus nicardipine. Several other potentially significant associations were discovered, but these findings were highly exploratory and true relationships remain unclear, especially given the lack of significant interaction effect of race/ethnicity and antihypertensive agent for primary and secondary outcomes. Overall, race/ethnicity may be an important covariate for antihypertensive effects after acute ICH, but further research is required to evaluate these associations more fully.

As one of the largest acute ICH samples (N=1156), this study has adequate power to detect differences in HE among the antihypertensive agents, especially for nicardipine (N=670) and labetalol (N=415). Few missing data for secondary and exploratory outcomes and low lost to follow-up for mRS and survival-mortality provide further reassurance of validity of findings and avoidance of bias. However, the study cannot address effects of subsequent antihypertensive taken during and after hospitalisation[22] or changes in potentially relevant variables, such as creatinine or other serological profiles over time. Patient recruitment was similar across each race/ethnicity for the three antihypertensive agents allowing for exploratory analyses. However, route and dosing regimen of administration of antihypertensive medications across all subjects could not be standardised, which affects pharmacokinetics.[23] Thus, comparison of doses across subjects cannot be considered 1:1 equivalent.[24] Initial antihypertensive agents were analysed without including subsequent other antihypertensive agents, and despite the large sample, testing interactions beyond the three classes of agents was not possible. In particular, the sample size of subjects on hydralazine was relatively small, and clevidipine use was not in widespread use when this cohort was assembled. Further, initial National Institutes of Health Stroke Scale scores were not captured in the parent ERICH study and not available for inclusion in models. Thus, parsing out which specific antihypertensive class is most efficacious in each race/ethnicity or other patient-specific factors[25] is beyond the limits of this study, and would require a much larger sample from a prospectively collected cohort or specific clinical trial. Treatment of patients in this cohort with other antihypertensives in the prehospital setting remains a possible confounder. The baseline CT and initial dose of antihypertensive treatment was more than 3 hours after symptoms onset for some patients, but maximal HE may occur as early as the first 3 hours after ICH onset.[26] Also, HE was identified using imaging within the following 72 hours after ICH onset, though substantive clot retraction is unlikely during that time period. Finally, the present analyses may be confounded by BP changes that would naturally occur in the acute ICH setting.

CONCLUSION

Initial choice of antihypertensive agent differentially effects immediate DBP reduction, but not SBP reduction, in patients presenting with acute ICH, with nicardipine appearing to be more efficacious than labetalol. While this study cannot advise on longer-term effects of initial antihypertensive choice after ICH, future prospective, real-word evidence trials would be required, if warranted, to optimise patient-specific initial BP therapy.

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Funding This study was funded by the NIH/NINDS U01-NS069763-05 (D.W.).

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval The Ethnic/Racial Variations of Intracerebral Haemorrhage (principal investigator: DW, MD, Grant: U01-NS069763-05) data and analyses presented in this manuscript are based on the research files downloaded from the Archived Clinical Research web site.[11] Prior to commencement of study enrolment, Institutional Review Board approval at the contributing centres to the Ethnic/Racial Variations of Intracerebral Haemorrhage and informed consent from the patient or legal authorised representative were obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available in a public, open access repository. All de-identified subject data are available in a publicly accessible database maintained at Wake Forest University available through data access approval by the University of Cincinnati.

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Supplemental Table 1. Multiple linear/logistic regression models of secondary outcomes, adjusted for covariates. Note: %, percentage; CI, confidence interval; HE, hematoma expansion; mL, milliliters; mmHg, millimeters of mercury; mRS, modified Rankin Score; OR, odds ratio; vs, versus.

Outcome	Predictor	Mean/OR (95% CI)	p value
HE, mL*	**Antihypertensive used**		0.406
	Hydralazine vs Labetalol	0.262 (-3.862, 4.386)	0.901
	Hydralazine vs Nicardipine	-1.118 (-5.117, 2.881)	0.583
	Labetalol vs Nicardipine	-1.38 (-3.446, 0.687)	0.190
6-month mortality	**Antihypertensive used**		0.118
	Hydralazine vs Labetalol	0.358 (0.128, 1.001)	0.050
	Hydralazine vs Nicardipine	0.346 (0.126, 0.948)	**0.039**
	Labetalol vs Nicardipine	0.966 (0.64, 1.459)	0.869
Length of Stay, days	**Antihypertensive used**		**0.028**
	Hydralazine vs Labetalol	2.514 (-2.291, 7.319)	0.305
	Hydralazine vs Nicardipine	-0.872 (-5.529, 3.785)	0.713
	Labetalol vs Nicardipine	-3.386 (-5.87, -0.902)	**0.008**
Discharge mRS	**Antihypertensive used**		0.262
	Hydralazine vs Labetalol	1.128 (0.601, 2.114)	0.708
	Hydralazine vs Nicardipine	0.86 (0.466, 1.585)	0.628
	Labetalol vs Nicardipine	0.763 (0.55, 1.056)	0.103
90-day mRS	**Antihypertensive used**		0.276
	Hydralazine vs Labetalol	1.497 (0.753, 2.977)	0.250
	Hydralazine vs Nicardipine	1.115 (0.576, 2.16)	0.746
	Labetalol vs Nicardipine	0.745 (0.501, 1.108)	0.146
6-month mRS	**Antihypertensive used**		0.152
	Hydralazine vs Labetalol	1.542 (0.744, 3.196)	0.244
	Hydralazine vs Nicardipine	1.034 (0.514, 2.081)	0.925
	Labetalol vs Nicardipine	0.671 (0.441, 1.02)	0.062
12-month mRS	**Antihypertensive used**		0.360
	Hydralazine vs Labetalol	1.141 (0.503, 2.588)	0.752
	Hydralazine vs Nicardipine	0.827 (0.377, 1.813)	0.634
	Labetalol vs Nicardipine	0.724 (0.464, 1.131)	0.156
Discharge disposition	**Antihypertensive used**		0.083
	Hydralazine vs Labetalol	1.329 (0.613, 2.884)	0.471
	Hydralazine vs Nicardipine	0.83 (0.398, 1.729)	0.618
	Labetalol vs Nicardipine	0.624 (0.412, 0.945)	**0.026**

Supplemental Table 2. Multiple linear/logistic regression models of outcomes, adjusted for covariates, stratified by race/ethnicity. Note: %, percentage; BP, blood pressure; CI, confidence interval; HE, hematoma expansion; mL, milliliters; mmHg, millimeters of mercury; mRS, modified Rankin Score; OR, odds ratio; vs, versus.

Outcome	Race/ethnicity	Predictor	Mean/OR (95% CI)	p value
Systolic BP change, mmHg	**Black**	**Antihypertensive used**		0.401
		Hydralazine vs Labetalol	4.077 (-14.882, 23.036)	0.673
		Hydralazine vs Nicardipine	8.431 (-10.068, 26.93)	0.371
		Labetalol vs Nicardipine	4.354 (-3.219, 11.926)	0.259
	Hispanic	**Antihypertensive used**		0.663
		Hydralazine vs Labetalol	4.118 (-10.789, 19.026)	0.587
		Hydralazine vs Nicardipine	6.102 (-8.055, 20.26)	0.397
		Labetalol vs Nicardipine	1.984 (-6.174, 10.141)	0.633
	White	**Antihypertensive used**		0.495
		Hydralazine vs Labetalol	5.458 (-9.09, 20.005)	0.460
		Hydralazine vs Nicardipine	0.531 (-13.765, 14.828)	0.942
		Labetalol vs Nicardipine	-4.927 (-13.603, 3.75)	0.264
Diastolic BP change, mmHg	**Black**	**Antihypertensive used**		**0.046**
		Hydralazine vs Labetalol	-5.247 (-20.126, 9.631)	0.488
		Hydralazine vs Nicardipine	2.293 (-12.224, 16.809)	0.756
		Labetalol vs Nicardipine	7.54 (1.581, 13.499)	**0.013**
	Hispanic	**Antihypertensive used**		0.134
		Hydralazine vs Labetalol	-2.303 (-11.007, 6.402)	0.603
		Hydralazine vs Nicardipine	2.537 (-5.73, 10.803)	0.546
		Labetalol vs Nicardipine	4.839 (0.076, 9.602)	**0.047**
	White	**Antihypertensive used**		0.550
		Hydralazine vs Labetalol	-0.746 (-10.34, 8.849)	0.878
		Hydralazine vs Nicardipine	2.371 (-7.058, 11.8)	0.621
		Labetalol vs Nicardipine	3.117 (-2.606, 8.839)	0.284
HE, mL	**Black**	**Antihypertensive used**		0.464
		Hydralazine vs Labetalol	1.863 (-3.204, 6.93)	0.469
		Hydralazine vs Nicardipine	0.637 (-4.325, 5.599)	0.801
		Labetalol vs Nicardipine	-1.226 (-3.308, 0.856)	0.247
	Hispanic	**Antihypertensive used**		0.830
		Hydralazine vs Labetalol	1.167 (-7.651, 9.985)	0.794
		Hydralazine vs Nicardipine	-0.301 (-8.656, 8.054)	0.944
		Labetalol vs Nicardipine	-1.468 (-6.216, 3.28)	0.543
	White	**Antihypertensive used**		0.190
		Hydralazine vs Labetalol	0.986 (-5.873, 7.846)	0.777

		Hydralazine vs Nicardipine	-2.617 (-9.295, 4.062)	0.440
		Labetalol vs Nicardipine	-3.603 (-7.557, 0.35)	0.074
6-month mortality	**Black**	**Antihypertensive used**		0.585
		Hydralazine vs Labetalol	0 (-Inf, 0.980)	0.980
		Hydralazine vs Nicardipine	0 (-Inf, 0.980)	0.980
		Labetalol vs Nicardipine	0.678 (0.325, 1.415)	0.301
	Hispanic	**Antihypertensive used**		0.757
		Hydralazine vs Labetalol	0.596 (0.148, 2.392)	0.465
		Hydralazine vs Nicardipine	0.716 (0.198, 2.593)	0.611
		Labetalol vs Nicardipine	1.202 (0.533, 2.711)	0.658
	White	**Antihypertensive used**		0.053
		Hydralazine vs Labetalol	0.072 (0.008, 0.659)	**0.020**
		Hydralazine vs Nicardipine	0.117 (0.013, 1.044)	0.055
		Labetalol vs Nicardipine	1.62 (0.713, 3.682)	0.249
Length of Stay, days	**Black**	**Antihypertensive used**		0.183
		Hydralazine vs Labetalol	3.851 (-8.071, 15.772)	0.525
		Hydralazine vs Nicardipine	-0.724 (-12.339, 10.891)	0.902
		Labetalol vs Nicardipine	-4.575 (-9.465, 0.316)	0.067
	Hispanic	**Antihypertensive used**		0.085
		Hydralazine vs Labetalol	1.084 (-6.439, 8.608)	0.777
		Hydralazine vs Nicardipine	-3.545 (-10.655, 3.564)	0.327
		Labetalol vs Nicardipine	-4.63 (-8.856, -0.404)	**0.032**
	White	**Antihypertensive used**		0.396
		Hydralazine vs Labetalol	3.465 (-1.568, 8.498)	0.176
		Hydralazine vs Nicardipine	2.955 (-2.005, 7.916)	0.241
		Labetalol vs Nicardipine	-0.51 (-3.61, 2.59)	0.746
Discharge mRS	**Black**	**Antihypertensive used**		0.352
		Hydralazine vs Labetalol	1.494 (0.405, 5.503)	0.547
		Hydralazine vs Nicardipine	0.986 (0.275, 3.541)	0.983
		Labetalol vs Nicardipine	0.66 (0.373, 1.168)	0.154
	Hispanic	**Antihypertensive used**		**0.037**
		Hydralazine vs Labetalol	1.132 (0.423, 3.03)	0.805
		Hydralazine vs Nicardipine	0.556 (0.217, 1.426)	0.222
		Labetalol vs Nicardipine	0.491 (0.28, 0.864)	**0.014**
	White	**Antihypertensive used**		0.973
		Hydralazine vs Labetalol	0.915 (0.264, 3.172)	0.889
		Hydralazine vs Nicardipine	1.002 (0.299, 3.359)	0.997
		Labetalol vs Nicardipine	1.095 (0.496, 2.417)	0.822
90-day mRS	**Black**	**Antihypertensive used**		**0.032**
		Hydralazine vs Labetalol	7.811 (1.559, 39.141)	**0.012**
		Hydralazine vs Nicardipine	4.359 (0.908, 20.924)	0.066
		Labetalol vs Nicardipine	0.558 (0.26, 1.198)	0.135
	Hispanic	**Antihypertensive used**		0.124
		Hydralazine vs Labetalol	1.059 (0.338, 3.32)	0.922
		Hydralazine vs Nicardipine	0.535 (0.185, 1.552)	0.250

		Labetalol vs Nicardipine	0.506 (0.25, 1.022)	0.058
	White	**Antihypertensive used**		0.934
		Hydralazine vs Labetalol	0.769 (0.189, 3.135)	0.714
		Hydralazine vs Nicardipine	0.808 (0.2, 3.258)	0.764
		Labetalol vs Nicardipine	1.051 (0.376, 2.941)	0.924
6-month mRS	**Black**	**Antihypertensive used**		0.691
		Hydralazine vs Labetalol	1.296 (0.241, 6.967)	0.762
		Hydralazine vs Nicardipine	0.927 (0.181, 4.735)	0.927
		Labetalol vs Nicardipine	0.715 (0.332, 1.54)	0.391
	Hispanic	**Antihypertensive used**		0.053
		Hydralazine vs Labetalol	1.257 (0.365, 4.331)	0.717
		Hydralazine vs Nicardipine	0.533 (0.169, 1.685)	0.284
		Labetalol vs Nicardipine	0.424 (0.207, 0.871)	**0.020**
	White	**Antihypertensive used**		0.078
		Hydralazine vs Labetalol	6.505 (1.281, 33.032)	**0.024**
		Hydralazine vs Nicardipine	4.407 (0.913, 21.272)	0.065
		Labetalol vs Nicardipine	0.678 (0.245, 1.876)	0.454
12-month mRS	**Black**	**Antihypertensive used**		0.696
		Hydralazine vs Labetalol	1.82 (0.286, 11.6)	0.526
		Hydralazine vs Nicardipine	1.336 (0.222, 8.026)	0.752
		Labetalol vs Nicardipine	0.734 (0.319, 1.686)	0.466
	Hispanic	**Antihypertensive used**		0.091
		Hydralazine vs Labetalol	0.529 (0.1, 2.788)	0.452
		Hydralazine vs Nicardipine	0.272 (0.055, 1.346)	0.111
		Labetalol vs Nicardipine	0.515 (0.242, 1.098)	0.086
	White	**Antihypertensive used**		0.483
		Hydralazine vs Labetalol	2.483 (0.564, 10.925)	0.229
		Hydralazine vs Nicardipine	2.023 (0.494, 8.278)	0.327
		Labetalol vs Nicardipine	0.815 (0.3, 2.216)	0.688
Discharge disposition	**Black**	**Antihypertensive used**		0.882
		Hydralazine vs Labetalol	0.725 (0.127, 4.144)	0.718
		Hydralazine vs Nicardipine	0.841 (0.152, 4.666)	0.843
		Labetalol vs Nicardipine	1.16 (0.585, 2.298)	0.671
	Hispanic	**Antihypertensive used**		0.184
		Hydralazine vs Labetalol	1.552 (0.429, 5.611)	0.503
		Hydralazine vs Nicardipine	0.75 (0.238, 2.365)	0.623
		Labetalol vs Nicardipine	0.483 (0.221, 1.054)	0.068
	White	**Antihypertensive used**		**0.007**
		Hydralazine vs Labetalol	3.745 (0.767, 18.28)	0.103
		Hydralazine vs Nicardipine	0.765 (0.174, 3.368)	0.723
		Labetalol vs Nicardipine	0.204 (0.075, 0.555)	**0.002**