Ischemic lesions, blood pressure dysregulation, and poor outcomes in intracerebral hemorrhage

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ABSTRACT

Objective: To evaluate the associations among diffusion-weighted imaging (DWI) lesions, blood pressure (BP) dysregulation, MRI markers of small vessel disease, and poor outcome in a large, prospective study of primary intracerebral hemorrhage (ICH).

Methods: The Ethnic/Racial Variations of Intracerebral Hemorrhage (ERICH) study is a multicenter, observational study of ICH among white, black, and Hispanic patients.

Results: Of 600 patients, mean ($\pm$ SD) age was 60.8 ± 13.6 years, median (interquartile range) ICH volume was 9.1 mL (3.5–20.8), and 79.6% had hypertension. Overall, 26.5% of cases had DWI lesions, and this frequency differed by race/ethnicity (black 33.8%, Hispanic 24.9%, white 20.2%, overall $p = 0.006$). A logistic regression model of variables associated with DWI lesions included lower age (odds ratio [OR] 0.721, $p = 0.002$), higher first recorded systolic BP (10-unit OR 1.12, $p = 0.002$), greater change in mean arterial pressure (MAP) prior to the MRI (10-unit OR 1.10, $p = 0.037$), microbleeds (OR 1.99, $p = 0.008$), and higher white matter hyperintensity (WMH) score (1-unit OR 1.16, $p = 0.002$) after controlling for race/ethnicity, leukocyte count, and acute in-hospital antihypertensive treatment. A second model of variables associated with poor 90-day functional outcome (modified Rankin Scale scores 4–6) included DWI lesion count (OR 1.085, $p = 0.034$) as well as age, ICH volume, intraventricular hemorrhage, Glasgow Coma Scale score, WMH score, race/ethnicity, acute in-hospital antihypertensive treatment, and ICH location.

Conclusions: These results support the hypotheses that acute BP dysregulation is associated with the development of DWI lesions in primary ICH and that DWI lesions are, in turn, associated with poor outcomes. *Neurology*® 2017;88:782–788

GLOSSARY

ADC = apparent diffusion coefficient; **BP** = blood pressure; **CAA** = cerebral amyloid angiopathy; **DWI** = diffusion-weighted imaging; **ERICH** = Ethnic/Racial Variations of Intracerebral Hemorrhage; **FLAIR** = fluid-attenuated inversion recovery; **GCS** = Glasgow Coma Scale; **GRE** = gradient recalled echo; **ICH** = intracerebral hemorrhage; **INTERACT2** = Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage 2; **IVH** = intraventricular hemorrhage; **MAP** = mean arterial pressure; **mRS** = modified Rankin Scale; **SBP** = systolic blood pressure; **SWI** = susceptibility-weighted imaging; **WMH** = white matter hyperintensity.

Primary intracerebral hemorrhage (ICH) is the second most common cause of stroke, affecting over 1 million people worldwide each year.^{1,2} ICH causes significantly greater morbidity and mortality than ischemic stroke. Hypertension is the most common risk factor for ICH. Elevated blood pressure (BP), often at extreme levels, frequently occurs in the hyperacute and acute phases of primary ICH and is associated with hemorrhage expansion and poor outcome.^{3,4} Several recent trials have sought to determine whether intensive lowering of BP acutely improves outcomes in patients with ICH.^{5–10}

Over the last several years, a growing number of studies have characterized the presence and frequency of ischemic lesions remote from the acute hematoma visualized on diffusion-weighted

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imaging (DWI) in patients with primary ICH undergoing MRI.^{11–19} Across these series, remote DWI lesions are visualized in 11%–41% of patients. There have been conflicting reports of an association between DWI lesions and large fluctuations in BP in the acute hospital setting.^{11,12,14,16,17} However, the mechanism and etiology of the lesions remains unclear, as does the potential association with poor outcomes. In these prior studies, the sample sizes were relatively small, with the majority being single-center retrospective case series.

The aim of the current analysis was to compare patient characteristics, imaging findings, and outcomes in patients with and without DWI lesions in the large, multicenter, prospective Ethnic/Racial Variations of Intracerebral Hemorrhage (ERICH) cohort of white, black, and Hispanic patients with ICH. We hypothesized that BP dysregulation would be associated with DWI lesion presence and that DWI lesions would be associated with poor outcomes.

METHODS The ERICH study is a multicenter, prospective, case-control study of primary ICH in non-Hispanic white, non-Hispanic black, and Hispanic participants, with the detailed design and methods of the study published previously.²⁰ The goal of the study is to recruit 3,000 patients with primary ICH and 3,000 matched controls from 19 centers in the United States. In addition to the overall goal of identifying genetic variations and other factors that affect ICH risk, ERICH was also designed to explore MRI characteristics of patients with primary ICH.

Overall the study aimed to have a baseline MRI performed on at least 20% of the cases. Since the ordering of MRIs in ICH may differ by physician or institution, an MRI was sought on every fifth case at each site to avoid bias. If clinical care did not include an MRI, a study-specific MRI was performed as long as deemed safe. If the fifth consecutive case was unable to have an MRI performed, each subsequent case was considered for MRI until one was completed. All MRIs were performed on 1.5T to 3.0T scanners with the following required sequences: gradient recalled echo (GRE), DWI with apparent diffusion coefficient (ADC) map, and fluid-attenuated inversion recovery (FLAIR). Sites were provided with recommended standardized sequences. In the absence of a GRE sequence, a susceptibility-weighted imaging (SWI) sequence was analyzed.

Neuroimaging studies were de-identified prior to interpretation. The core CT laboratory analyzed baseline noncontrast head CT scans to provide the baseline hemorrhage location, volume, and presence of intraventricular hemorrhage (IVH). A vascular neurologist (C.S.K.) with imaging expertise, and blinded to clinical data, performed MRI interpretations using Mango software.²¹ The following variables were measured for each case: planimetric assessment of ICH and IVH volumes (GRE; FLAIR or DWI if not accessible), ICH location, presence of microbleeds (GRE or SWI), number of microbleeds (GRE) and chronic hematomas by location (GRE or SWI), and presence and severity of white matter

disease employing a modified Fazekas scale (FLAIR).²² DWI and ADC sequences were evaluated for the presence, number, acuity (acute defined as hyperintense on DWI, hypointense on ADC; subacute defined as hyperintense on DWI, isointense or hyperintense on ADC), volume, and location of ischemic lesions remote from the hematoma. We excluded lesions immediately adjacent (typically a 10 mm rim) to the hematoma from the analysis. DWI lesions were not included in the assessment of white matter hyperintensity (WMH) severity. One rater (C.S.K.) scored 30 randomly selected scans twice for DWI lesion presence and number, blinded to the initial rating, with ratings separated by >6 months.

To qualify for the current analysis, participants had to have an MRI with a DWI sequence prior to any surgical intervention (i.e., no craniectomy or surgical hematoma evacuation). In order to assess baseline hematoma volumes at a standardized timepoint (hospital admission), hematoma volumes and presence of IVH measured on the first CT were included in the analyses since MRIs were obtained at more variable timepoints following the hospital admission. If no CT was obtained, an adjusted MRI volume was used.²³ Time intervals from ICH onset to MRI were calculated from last known well date and time. If the exact time of onset was not documented in the chart, then the time was estimated (table e-1 at Neurology.org).

All enrolled participants or designated proxies underwent a standardized data collection protocol including a personal (or proxy) interview and medical chart abstraction. Management of ICH proceeded in accordance with local medical practice and was not protocol-prescribed by the ERICH study. BP measurements in the dataset included the first recorded BP on arrival in the emergency department. In addition, sites recorded the highest and lowest BPs prior to the MRI. We calculated a δ mean arterial pressure (MAP) for each patient as the difference between the highest and lowest MAP. Medications used for treatment of ICH during the emergency department and intensive care unit stay were also recorded. We collected standardized functional outcomes (modified Rankin Scale [mRS]) at 3 and 6 months by telephone or in-person interviews. Poor outcome was defined as mRS of 4–6 at 3 and 6 months.

Standard protocol approvals, registrations, and patient consents. The protocol for the study received prior approval by the institutional review boards of all participating sites. Written informed consent was obtained from each participant or a legally authorized representative prior to study enrollment.

Statistical analyses. Baseline characteristics including neuroimaging variables were compared between participants with and without remote DWI lesions. Multivariable regression models were developed to identify variables associated with (1) the presence of DWI lesions and (2) poor functional outcome at 3 and 6 months. The associations between the DWI lesion count with δ MAP, microbleed count, and WMH score were tested using the Spearman rank correlation coefficient. For modeling, ICH volume was natural logarithm transformed to minimize overly influential observations in the tail of the volume distribution. Theory-driven variables as well as variables with $p < 0.1$ were entered into a logistic regression model and a backward elimination strategy was used to develop the multivariable model. The Box-Tidwell test was used to determine if all continuous variables were linear to the logit of the outcome. Multicollinearity diagnostics were performed for each model. Race/ethnicity and in-hospital BP treatment were included in the models as a priori hypotheses of the overall ERICH study design. Best and worst case scenario imputation was performed for participants with missing day 90 outcomes for the poor outcome model.

RESULTS Recruitment for the ERICh study officially began for cases on January 1, 2011. The current analysis included cases enrolled prior to January 1, 2014. Of the 2,400 cases enrolled at the time of analysis, a total of 600 qualified for the analysis (see figure e-1 for inclusion flow chart). Table 1 shows overall characteristics of the cohort as well as characteristics stratified by presence or absence of 1 or more ischemic DWI lesions (see figure 1 for representative case

example). Overall, 26.5% of patients had 1 or more DWI lesions (67% acute only, 15% subacute only, 18% both acute and subacute lesions—see table e-2 for group characteristics). Intrarater reliability for DWI lesion count for the 30 randomly selected scans was high (intraclass correlation coefficient 0.948, 95% confidence interval 0.894–0.975). At baseline, patients with DWI lesions were younger, more likely to be male, and more likely to have a history of a prior

Table 1 Clinical and imaging characteristics of patients with and without diffusion-weighted imaging (DWI) lesions

	Overall	DWI+ ^a	DWI–	p Value
No. (%)	600	159 (26.5)	441 (73.5)	
Age, y, mean (SD) (n = 600)	60.8 (13.6)	57.5 (13.2)	62.0 (13.5)	<0.0001
Race/ethnicity, n (%)				0.006
White	198	40 (20.2)	158 (79.8)	
Black	213	72 (33.8)	141 (66.2)	
Hispanic	189	47 (24.9)	142 (75.1)	
Female, n (%) (n = 600)	267 (44.5)	57 (35.9)	210 (47.6)	0.010
Hypertension, n (%) (n = 597)	475 (79.6)	130 (81.8)	345 (78.4)	0.241
First recorded SBP, ^b mm Hg, mean (SD) (n = 546)	184.8 (36.0)	203.1 (36.1)	178.7 (33.9)	<0.0001
Δ MAP mm Hg, mean (SD) (n = 600)	43.8 (35.4)	53.2 (28.6)	40.4 (23.3)	<0.0001
In-hospital antihypertensive treatment, n (%) (n = 600)	469 (78.2)	136 (85.5)	333 (75.5)	0.009
GCS, mean (SD) (n = 543)	13.3 (3.0)	12.8 (3.1)	13.4 (2.9)	0.046
Prior stroke, n (%) (n = 600)	98 (16.3)	35 (22.0)	63 (14.3)	0.024
Pre-ICH antihypertensive, n (%) (n = 600)	46.7	41.5	48.5	0.128
Pre-ICH antiplatelet, n (%) (n = 600)	243 (40.5)	70 (44.0)	173 (39.2)	0.291
Pre-ICH anticoagulant, n (%) (n = 600)	44 (7.3)	9 (5.7)	35 (7.9)	0.345
Pre-ICH illicit stimulant (cocaine or amphetamine) use, n (%) (n = 600)	44 (7.3)	12 (7.5)	32 (7.3)	0.904
Pre-ICH any illicit drug use, n (%) (n = 600)	81 (13.5)	22 (13.8)	59 (13.4)	0.885
Leukocyte count, mean × 10 ³ /μL, mean (SD) (n = 593)	9.5 (4.6)	10.3 (6.4)	9.2 (3.7)	0.010
Poor 90-d outcome, n (%) (n = 503)	181 (36.0)	61 (46.6)	120 (32.3)	0.003
Time (d) to MRI, median (IQR) (n = 591)	1.6 (0.8–3.4)	1.8 (1.1–3.9)	1.5 (0.8–3.1)	0.008
ICH location, n (%) (n = 600)				0.175
Lobar	216	53 (25)	163 (75.0)	
Deep	305	78 (26.0)	227 (74.0)	
Cerebellar	42	12 (29.0)	30 (71.0)	
Brainstem	31	14 (45.0)	17 (55.0)	
Pure IVH	6	2 (33.3)	4 (66.7)	
ICH volume (mL), median (IQR) (n = 591) ^{c,d}	9.1 (3.5–20.8)	9.3 (3.7–21.4)	9.1 (3.5–20.6)	0.887
Catheter angiography performed, n (%) (n = 600)	74 (12.3)	24 (15.1)	50 (11.3)	0.217
WMH score, median (IQR) (n = 588)	6 (4.0–8.0)	8 (4–10)	6 (4–8)	<0.0001
Presence of microbleeds, n (%) (n = 553)	297 (53.7)	106 (71.6)	191 (47.2)	<0.0001
IVH present, n (%) (n = 572)	197 (34.4)	58 (38.4)	139 (33.0)	0.231

Abbreviations: GCS = Glasgow Coma Scale; ICH = intracerebral hemorrhage; IQR = interquartile range; IVH = intraventricular hemorrhage; MAP = mean arterial pressure; SBP = systolic blood pressure; WMH = white matter hyperintensity.

^a See table e-2 for characteristics for key variables based on DWI lesion type (acute, subacute, or both).

^b First recorded emergency department systolic blood pressure.

^c p Value is based on the natural log (volume + 1).

^d Twenty-five cases without CT volumes had adjusted MRI volumes with median (IQR) time to MRI of 1.16 (0.74–2.53) days.

Figure 1 MRI

Left periventricular hemorrhage (gradient recalled echo [GRE], left panel) in a 45-year-old black man with hypertension. Middle panel (diffusion-weighted imaging [DWI]) shows multiple scattered ischemic lesions remote from the hematoma. Right panel (fluid-attenuated inversion recovery [FLAIR]) shows moderately severe white matter disease. The delta mean arterial pressure prior to the MRI was 106 mm Hg.

stroke, and had higher leukocyte counts and lower Glasgow Coma Scale (GCS) scores. In addition, patients with DWI lesions had higher MAPs and higher systolic BP (SBP) on the first emergency department recording, greater δ MAPs prior to their MRI, and were more likely to be treated with in-hospital antihypertensive medications. Compared to white and Hispanic participants, black participants were more likely to have DWI lesions (figure e-2). On univariable analysis, at 90 days, patients with 1 or more DWI lesions were more likely to have a poor outcome ($p = 0.003$).

Table 1 shows the imaging characteristics of the overall cohort as well as characteristics for patients with and without 1 or more DWI lesions. Of patients with DWI lesions, the median lesion count was 1 (interquartile range 1–4), mean count 5.4 (SD 12.4), range

1–99. DWI lesion count was modestly correlated with δ MAP (Spearman $\rho = 0.204$, $p < 0.0001$), as well as microbleed count (Spearman $\rho = 0.283$, $p < 0.0001$) and WMH score (Spearman $\rho = 0.181$, $p < 0.0001$). Patients with DWI lesions had a longer time interval from onset to MRI ($p = 0.008$). Patients with DWI lesions had a greater burden of white matter disease ($p < 0.0001$) and greater frequency of 1 or more microbleeds ($p < 0.0001$).

Of those cases with a microbleed interpretation, 82% had a GRE sequence, and 18% had an SWI sequence. There was no difference in the frequency of GRE sequences in cases with or without DWI lesions (75.5% vs 75.3%, $p = 0.962$), or those with or without microbleeds (79.5% vs 84.0%, $p = 0.171$). Magnet strength did not differ in patients with or without DWI lesions (1.5T in 73.0% vs 75.1% respectively, $p = 0.609$), or in patients with or without microbleeds (1.5T in 74.1% vs 76.2%, $p = 0.849$).

A multivariable logistic regression model of variables associated with the presence of 1 or more DWI lesions (table 2) included lower age ($p = 0.002$), higher delta MAP ($p = 0.037$), higher first recorded SBP ($p = 0.002$), presence of 1 or more microbleeds ($p = 0.008$), and higher WMH score ($p = 0.002$) after controlling for race/ethnicity, any in-hospital antihypertensive treatment, and leukocyte count. A second model (table 3) of variables associated with poor 90-day functional outcome (mRS scores 4–6) included DWI lesion count, age, ICH volume, GCS, WMH score, and ICH location. The same variables remained significant in the model following a sensitivity analysis exploring the best and worst case scenario imputation for participants with missing day 90 outcomes (table e-3). A model for 90-day outcomes based on DWI lesion presence yielded similar results, as did a model based on 6-month mRS (tables e-4 and e-5). Figure 2 shows ranked day 90 outcomes for patients with and without DWI lesions.

We also evaluated the frequency of DWI lesions in patients with and without possible or probable cerebral amyloid angiopathy (CAA) employing the Boston Criteria for diagnosis.²⁴ Nine of the 27 cases (33.3%) with probable CAA had DWI lesions compared to 117 of the 459 cases (25.5%) without probable CAA ($p = 0.538$). Eighteen of the 98 cases (18.4%) with either probable or possible CAA had DWI lesions compared to 108 of the 388 cases (27.8%) without possible or probable CAA ($p = 0.133$).

DISCUSSION In this prospective, multicenter study of 600 patients with primary ICH and baseline MRIs, approximately one-quarter of patients had one or more remote lesions visualized on DWI. In

Table 2 Multivariable model for variables associated with diffusion-weighted imaging (DWI) lesions (n = 491)

	OR	95% CI	p Value
Age (10 y)	0.721	0.583–0.891	0.002
First recorded SBP ^a (10 mm Hg)	1.121	1.041–1.206	0.002
δ MAP (10 mm Hg)	1.101	1.006–1.205	0.037
In-hospital antihypertensive treatment	0.748	0.366–1.528	0.425
Presence of microbleeds	1.994	1.196–3.324	0.008
WMH score (1 point)	1.157	1.057–1.266	0.002
Leukocyte count (per unit)	1.050	0.993–1.111	0.084
Race/ethnicity			0.388
Black vs white	1.329	0.729–2.422	
Hispanic vs white	0.933	0.492–1.770	

Abbreviations: CI = confidence interval; MAP = mean arterial pressure; OR = odds ratio; SBP = systolic blood pressure; WMH = white matter hyperintensity.

^aFirst recorded emergency department systolic blood pressure.

Table 3 Multivariable model for variables associated with poor 90-day outcome (n = 437)

	OR	95% CI	p Value
Age (10 y)	1.593	1.283-1.980	<0.0001
DWI lesion count	1.085	1.006-1.170	0.034
In-hospital antihypertensive treatment	1.343	0.705-2.558	0.370
Admission GCS	0.84	0.773-0.914	<0.0001
ICH volume, mL ^a	2.316	1.719-3.120	<0.0001
WMH score (1 point)	1.173	1.075-1.280	<0.0001
IVH presence	1.282	0.766-2.146	0.345
ICH location			<0.0001
Deep ^b vs lobar	3.526	1.896-6.558	
Cerebellum vs lobar	1.124	0.350-3.611	
Brainstem vs lobar	13.722	3.725-50.552	
Race			0.369
Black vs white	0.663	0.356-1.234	
Hispanic vs white	0.937	0.509-1.726	

Abbreviations: CI = confidence interval; DWI = diffusion-weighted imaging; GCS = Glasgow Coma Scale; ICH = intracerebral hemorrhage; IVH = intraventricular hemorrhage; OR = odds ratio; WMH = white matter hyperintensity.

^a ICH volume is modeled as natural log (volume + 1).

^b Includes pure IVH.

multivariable analyses, greater admission BP and greater changes in MAP prior to the MRI were associated with the presence of DWI lesions. Younger age and greater burden of biomarkers of small vessel angiopathy (leukoaraiosis and microbleeds) were also independent predictors of DWI lesions. Moreover, this study provides compelling evidence that DWI lesions remote from the index ICH are independently associated with poor functional outcomes at both 3 and 6 months.

Figure 2 Modified Rankin Scale (mRS) scores at 90 days for patients with and without ischemic diffusion-weighted imaging (DWI) lesions

Patients with DWI lesions had a higher frequency of poor outcomes (mRS 4-6).

These findings may have important implications for acute BP management in the setting of ICH. Recently, growing attention has focused on characterizing and understanding the pathophysiologic mechanisms leading to DWI lesions in the presence of acute, primary ICH.²⁵⁻²⁷ This interest reflects 2 observations: (1) a possible link between DWI lesions and acute BP reductions and (2) a potential association between DWI lesions and poor outcome. The possible association with BP reduction is of particular interest since recent randomized controlled trials have been designed to test the hypothesis that acute, intensive BP reduction decreases the likelihood of both hematoma expansion and poor long-term morbidity and mortality. The Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage 2 (INTERACT2) trial reported no reduction in the rate of death or severe disability, but did find improved functional outcomes in those with more intensive BP control.⁷ The Antihypertensive Treatment of Acute Cerebral Hemorrhage II (ATACH II) trial found no difference in the rate of death or disability with intensive BP lowering compared to standard reduction.^{8,28}

Our results confirm prior observations linking DWI lesions with acute BP dysregulation (large drops in mean arterial pressure) as well as markers of diffuse arteriopathy (leukoaraiosis, microbleed burden, prior stroke). However, the current study cannot inform a direction to the association between DWI lesions and BP dysregulation. It is possible that acute BP reduction produces DWI lesions, or alternatively, that patients with DWI lesions may be more likely to experience BP dysregulation. It remains possible that remote, ischemic lesions, in the setting of an acute ICH, represent an epiphenomenon or are caused by alternative mechanisms. Ischemic lesions have been reported in both the acute and subacute phases following ICH¹¹; this may reflect extended periods of disrupted autoregulation following ICH or may provide supportive evidence of an alternative mechanism.

Based on the results of this study, in conjunction with the body of literature to date, we hypothesize that patients with a greater burden of small vessel disease are at increased risk for loss of cerebral autoregulation during the acute hospitalization period. Intensive BP reductions during this period of aberrant cerebral autoregulation may precipitate small vessel ischemia. This increased risk might be greatest in patients with more severe microangiopathy and subsequent decreased vessel compliance in response to autoregulatory needs. It is also possible that the new hyperintense DWI lesions occur in the same areas of WMH that are more likely to be prone to ischemic injury in the setting of BP dysregulation. Future studies should explore this potential relationship. Loss of

autoregulation in the setting of severe hypertension (without fluctuations in BP) could also precipitate small vessel ischemia due to hypertension-induced vasospasm. While a recent analysis from the INTERACT2 study reported that intensive BP lowering was not associated with excess harm in patients with small vessel disease, white matter disease was graded on CT rather than MRI in that analysis.²⁹

If ischemia is precipitated by acute BP reductions in those ICH patients with a more severe underlying diseased vasculature, further studies are needed to determine whether (1) there is a level of acute BP reduction at which the risks outweigh the benefits and (2) a subgroup of patients at greater risk of ischemia (and potential harm) from acute antihypertensive treatment can be identified. The ongoing Intracerebral Hemorrhage Acutely Decreasing Arterial Pressure trial II (ICH ADAPT II) is specifically designed to determine if BP reduction is causally associated with DWI lesion formation.³⁰ As with ischemic stroke, it is likely that subgroups of patients can be identified who differentially benefit from acute treatments, including intense antihypertensive therapy. MRI may play an important role by quantifying imaging biomarkers of patients at greatest risk, including those with microbleeds and more severe leukoaraiosis. This information could be used in the future to guide individualized treatment.

Our results identified several previously unreported findings: the univariate association between DWI lesions with race/ethnicity and elevated leukocyte count, as well as the association with lower age on multivariable analyses. We hypothesize that the association between ischemic lesions and race may be due to the greater burden of vascular risk factors and small vessel disease in the black and Hispanic populations. This hypothesis is supported by prior studies, including one from the ERICH cohort, demonstrating a greater burden of microbleeds and white matter hyperintensities in black and Hispanic participants with ICH compared with non-Hispanic white participants.^{31,32} The association with younger age is counterintuitive and requires confirmation and further exploration in future studies. In our analysis, it is not explained by illicit drug use or performance of diagnostic angiography, both of which did not differ between groups. The possible association between DWI lesions and elevated leukocyte count is intriguing, and may indicate that inflammation plays a mechanistic role.^{33,34}

This study has several limitations. The subset of patients undergoing MRI studies was likely biased towards smaller, less severe hemorrhages. However, the median hematoma volume in our study (9.1 mL) is comparable to the majority of prior MRI-based reports.^{12–15} Of note, the median hematoma volume in

the INTERACT II study was 11 mL.⁷ MRIs were not all acquired at routine timepoints or with identical magnet strengths and sequence parameters. However, our analyses did not find a difference in frequency of DWI lesions based on magnet strength or microbleed presence based on magnet strength or sequences employed (GRE vs SWI). There were insufficient data on BP measurements at follow-up timepoints to examine the relationship between DWI lesions and BP curves over time. Finally, one recent report linked DWI lesions to enlarged perivascular spaces, a variable that we did not evaluate.¹⁹ However, compared to prior studies, strengths of this study include the large sample size, the multicenter, prospective study design, and inclusion of an equal number of participants from multiple races and ethnicities, particularly those at higher risk of ICH; these study design characteristics increase the generalizability of the study results compared to prior studies.

This large, prospective, multicenter study provides additional data supporting the hypothesis that acute BP dysregulation may precipitate ischemia in a subset of patients with greater burdens of microangiopathy, and that these lesions are, in turn, associated with poorer outcomes. Randomized controlled trials are needed to confirm these hypotheses, and should be designed to identify subsets of patients who are at increased risk with BP reductions and those who are more likely to benefit. The results of these studies may have important implications for acute BP management in patients presenting with primary ICH.

AUTHOR CONTRIBUTIONS

C.S.K., J.R., G.N., S.D., B.B.W., M.L.J., M.S.V.E., M.F., J.O., A.K., C.D.L., C.J.M., and D.W. contributed to data collection and provided critical review of the manuscript. D.W., J.R., C.L., C.S.K., and J.O. participated in study design and conduct. C.S.K., S.D., and G.N. participated in literature search and writing of the paper. C.J.M. participated in data management.

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DISCLOSURE

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