Original Investigation

Association Between Blood Pressure Control and Risk of Recurrent Intracerebral Hemorrhage

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IMPORTANCE Intracerebral hemorrhage (ICH) is the most severe form of stroke. Survivors are at high risk of recurrence, death, and worsening functional disability.

OBJECTIVE To investigate the association between blood pressure (BP) after index ICH and risk of recurrent ICH.

DESIGN, SETTING, AND PARTICIPANTS Single-site, tertiary care referral center observational study of 1145 of 2197 consecutive patients with ICH presenting from July 1994 to December 2013. A total of 1145 patients with ICH survived at least 90 days and were followed up through December 2013 (median follow-up of 36.8 months [minimum, 9.8 months]).

EXPOSURES Blood pressure measurements at 3, 6, 9, and 12 months, and every 6 months thereafter, obtained from medical personnel (inpatient hospital or outpatient clinic medical or nursing staff) or via patient self-report. Exposure was characterized in 3 ways: (1) recorded systolic and diastolic measurements; (2) classification as adequate or inadequate BP control based on American Heart Association/American Stroke Association recommendations; and (3) stage of hypertension based on Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure 7 criteria.

MAIN OUTCOMES AND MEASURES Recurrent ICH and its location within the brain (lobar vs nonlobar).

RESULTS There were 102 recurrent ICH events among 505 survivors of lobar ICH and 44 recurrent ICH events among 640 survivors of nonlobar ICH. During follow-up adequate BP control was achieved on at least 1 measurement by 625 patients (54.6% of total [range, 49.2%-58.7%]) and consistently (ie, at all available time points) by 495 patients (43.2% of total [range, 34.5%-51.0%]). The event rate for lobar ICH was 84 per 1000 person-years among patients with inadequate BP control compared with 49 per 1000 person-years among patients with adequate BP control. For nonlobar ICH the event rate was 52 per 1000 person-years with inadequate BP control compared with 27 per 1000 person-years for patients with adequate BP control. In analyses modeling BP control as a time-varying variable, inadequate BP control was associated with higher risk of recurrence of both lobar ICH (hazard ratio [HR], 3.53 [95% CI, 1.65-7.54]) and nonlobar ICH (HR, 4.23 [95% CI, 1.02-17.52]). Systolic BP during follow-up was associated with increased risk of both lobar ICH recurrence (HR, 1.33 per 10-mm Hg increase [95% CI, 1.02-1.76]) and nonlobar ICH recurrence (HR, 1.54 [95% CI, 1.03-2.30]). Diastolic BP was associated with increased risk of nonlobar ICH recurrence (HR, 1.21 per 10-mm Hg increase [95% CI, 1.01-1.47]) but not with lobar ICH recurrence (HR, 1.36 [95% CI, 0.90-2.10]).

CONCLUSIONS AND RELEVANCE In this observational single-center cohort study of ICH survivors, reported BP measurements suggesting inadequate BP control during follow-up were associated with higher risk of both lobar and nonlobar ICH recurrence. These data suggest that randomized clinical trials are needed to address the benefits and risks of stricter BP control in ICH survivors.

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Intracerebral hemorrhage (ICH) represents the acute manifestation of progressive cerebral small-vessel disease. The 2 predominant pathological forms of cerebral small-vessel disease, arteriolosclerosis and cerebral amyloid angiopathy (CAA), can generally be identified on the basis of ICH location. Arteriolosclerosis-associated ICH occurs most commonly in the deep structures, whereas CAA-associated ICH occurs almost exclusively in the cortical-subcortical regions labeled lobar.[1] ICH is the most severe and least treatable form of stroke, responsible for almost 50% of stroke-related morbidity and mortality.[2] ICH survivors are at high risk for recurrent ICH,[3] and recurrent ICH is generally more severe than the preceding ICH. Improving secondary prevention of ICH is therefore vital.

Control of elevated blood pressure (BP) is the cornerstone of secondary prevention of recurrent nonlobar ICH, but there are few data to inform the optimal degree of BP reduction. The role of BP control in lobar ICH, on the other hand, remains poorly defined.[4] Preliminary evidence from secondary analyses of the Perindopril Protection Against Recurrent Stroke Study (PROGRESS) suggests that BP lowering reduces incidence of lobar as well as nonlobar ICH, but the limited sample size yielded large confidence intervals for observed effects.[5-7]

Blood pressure reduction in the elderly, the population most at risk for ICH, may not be without risk. Concerns remain that excessive reduction may be associated with increased risk of ischemic stroke and other complications. On the other hand, the hypothesis that benefit of BP reduction for recurrent ICH is dose-dependent has not been fully tested. Given the high rates of morbidity and mortality associated with ICH and its recurrence, testing this hypothesis was a high priority. We therefore sought to determine whether BP reduction and control are associated with risk of recurrence of lobar or nonlobar ICH in a single-center, longitudinal cohort of survivors of ICH.

Methods

Patient Recruitment and Baseline Data Collection

Participants were enrolled in an ongoing single-center longitudinal cohort study of ICH as previously described.[3] Participants were recruited among consecutive patients aged 18 years or older, admitted to Massachusetts General Hospital from July 1994 to December 2011 with acute ICH (onset of symptoms <24 hours prior to presentation) confirmed by computed tomography scan. Patients with hemorrhage resulting from trauma, conversion of an ischemic infarct, rupture of a vascular malformation or aneurysm, or brain tumor were excluded.

In light of known ethnic and racial variations in hypertension incidence and severity, participants were asked at enrollment to self-identify race and ethnicity, choosing from the options recommended by the Office for Management and Budget and the National Institutes of Health for use in research studies.[8] ICH location was assigned at the time of the incident ICH by study investigators blinded to clinical information. Lobar ICH was defined as selective involvement of cerebral cortex, underlying white matter, or both; nonlobar ICH was defined as selective involvement of thalami, basal ganglia, or brainstem. In accordance with previously published methods, individuals with cerebellar ICH were excluded from analysis given that both arteriolosclerosis and CAA are found at this location.[3,9] Pre-ICH baseline data were prospectively collected by trained study staff via in-person interview at time of enrollment and included demographic information, medical history, and pre-ICH drug exposure.

The study protocol was approved by the Massachusetts General Hospital institutional review board. Written informed consent was obtained from all study participants or their surrogates.

Longitudinal Follow-up

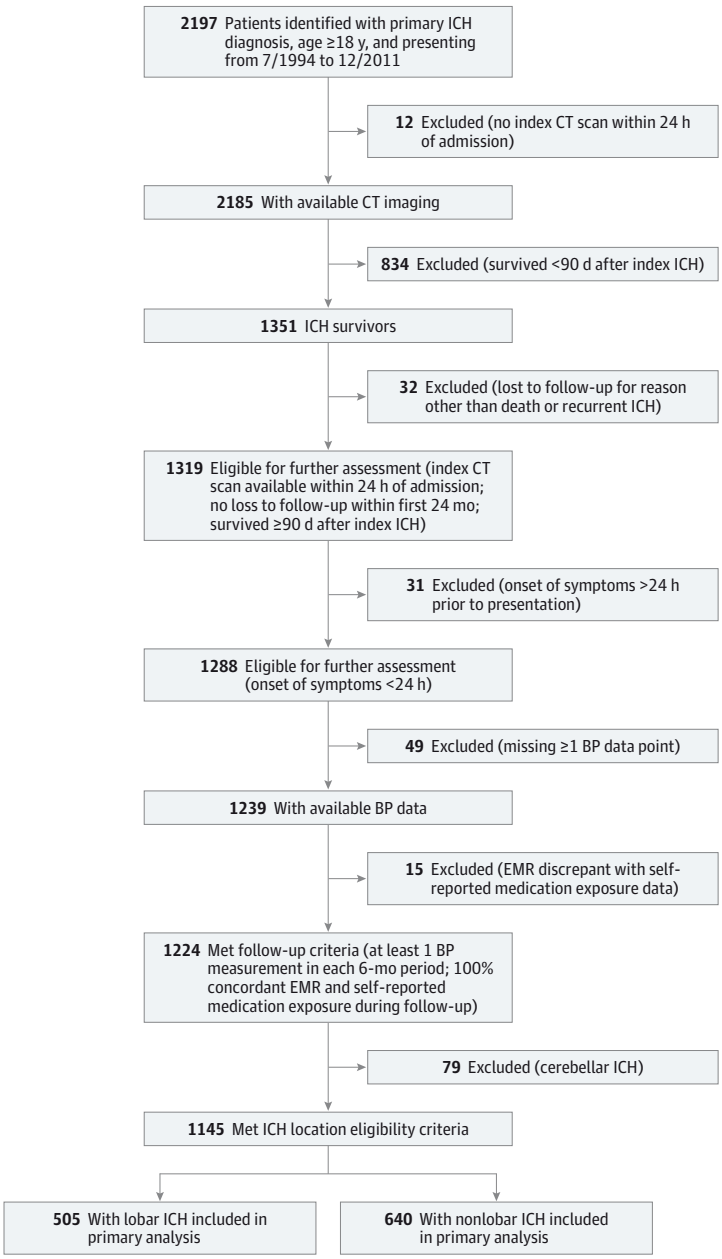
ICH survivors or their caregivers were contacted and interviewed by dedicated study staff at 3, 6, 9, and 12 months after index ICH and every 6 months thereafter, based on established protocols.[3] Investigators inquired about and collected imaging and medical records pertaining to ICH recurrence, death, and medication use and dosing. They also inquired about most recent ambulatory BP measurement obtained in a medical setting by medical personnel (no inquiry was made about home or self-obtained BP measurements). If patients were unable to provide exact BP measurements, medical records for reported encounters falling within the follow-up period were obtained via (1) manual review of longitudinal electronic medical records (EMRs) at Massachusetts General Hospital (including primary care, specialty outpatient, and inpatient records) and affiliated hospitals and (2) patient-provided external medical records. We prespecified data capture targets of 1 or more blood pressure measurements per 6-month period (including both telephone-based and EMR-based data).

EMR review was also used to obtain and confirm detailed information on medication use and interval clinical history. Discrepancies between telephone-collected and EMR-collected medication exposure data resulted in removal of 15 patients from the present study (**Figure 1**); their removal did not alter results substantially (eTable 3 in the Supplement). If the patient or caregiver reported death, new neurologic symptoms, ischemic stroke, or ICH or hospital admission, the relevant medical records and radiographic images were reviewed by study investigators blinded to other clinical data. We also queried the Social Security Death Index national database as an alternative way of identifying deaths among ICH survivors. Participants' data were censored in case of (1) recurrent ICH confirmed by neuroimaging; (2) death; or (3) loss to follow-up.

Statistical Methods

Age at index ICH was analyzed as a continuous variable. Race/ethnicity was analyzed as a categorical variable using white patients as reference (owing to their numerical preponderance). Educational level was dichotomized using a cutoff of 10 or more years of education. To ascertain the association between BP and risk of ICH recurrence we generated and analyzed 4 time-varying exposures: (1) a dichotomous variable based on whether participants achieved BP goals recommended by the American Heart Association/American Stroke Association (AHA/ASA) for post-ICH secondary prevention

Figure 1. Participant Enrollment and Sequential Application of Eligibility and Exclusion Criteria Leading to Definition of Final Study Population



BP indicates blood pressure; CT, computed tomography; EMR, electronic medical records; ICH, intracerebral hemorrhage.

(ie, systolic BP <140 mm Hg and diastolic BP <90 mm Hg if no evidence of diabetes; systolic BP <130 mm Hg and diastolic BP <80 mm Hg for individuals with diabetes)[4]; (2) hypertension stages as defined by the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure 7 (JNC 7) criteria[10]; (3) systolic BP as a continuous variable; and (4) diastolic BP as a continuous variable.

For all BP variables described, patients were assigned the single available value within each 3-month period during the first year of follow-up (months 3-6, 7-9, and 10-12 after index ICH) and for each 6-month period thereafter (months 13-18, 19-24, 25-30, etc, after index ICH) at all ICH recurrence times within that same time window. BP data capture and analysis are further illustrated in the eFigure in the Supplement.

We computed event rates for ICH recurrence per 1000 person-years using the following approach. Patients contributed time at risk to the adequate vs inadequate BP control groups within each 6-month follow-up period based on corresponding BP measurements. Events were assigned to the adequate vs inadequate BP control group based on last available systolic and diastolic BP values. Rates were calculated as ratio of number of events over time spent at risk in each BP control group.

Categorical variables were compared using Fisher exact test (2-tailed) and continuous variables using the Mann-Whitney

rank-sum or unpaired *t* test as appropriate. We determined bivariable factors associated with ICH recurrence using Kaplan-Meier plots with significance testing by the log-rank test. Cox regression analysis was performed to calculate bivariable hazard ratio (HR) as an estimate of the effect size. To determine the association of BP with ICH recurrence, we used Cox regression analysis with BP variables as time-varying covariates. Candidate covariates included all variables with $P < .20$ for association with recurrent ICH in bivariable analysis and factors potentially associated with recurrent ICH based on prior studies (previous symptomatic hemorrhage before index ICH, education level, race/ethnicity).[3,9] Backward elimination of nonsignificant variables ($P > .05$) was subsequently used to generate a minimal model. We prespecified forced reintroduction of antiplatelet and warfarin use if multivariable $P < .20$ (given established association with risk of ICH recurrence).[11] We also repeated analyses after forced adjustment for duration, number, or class of antihypertensive agents used and noted no difference in results (eTable 4 in the Supplement). Multicolinearity was assessed by computing variance inflation factors for all variables. Yearly estimated ICH recurrence risk was calculated for graphical plotting purposes by combining the Nelson-Aalen cumulative hazard function with Cox model–determined statistical risk effects using the *predictSurvProb* function in the *pec* R package. Additional information on statistical methodology is available in the eMethods in the Supplement. No formal statistical power calculations were performed.

All analyses were performed with R software v 3.2.0 (R Foundation for Statistical Computing). $P < .05$ (2-tailed) was considered statistically significant.

Results

Study Participants and ICH Recurrence Rates

A total of 2278 patients were screened for enrollment (Figure 1). Patients who declined consent for study participation (n = 81), survived fewer than 90 days after index ICH (n = 834), or were lost to follow-up within the first 24 months (n = 32) were excluded from all analyses. A total of 49 participants were missing BP measurements for 1 or more 6-month periods (Figure 1) and were removed from all analyses; their forced reintroduction did not alter results substantially (eTable 1 in the Supplement). A total of 893 of 1145 study participants (78%) had 100% of BP measurements captured via medical records. Multivariable analyses of BP with recurrent ICH restricted to these patients are presented in eTable 2 in the Supplement.

A total of 1145 patients (505 survivors of lobar ICH and 640 survivors of nonlobar ICH) (**Table 1**) were therefore included in our analyses having presented within the prespecified study enrollment period, survived at least 90 days, and met criteria for data availability during follow-up (Figure 1). For individuals who sustained multiple recurrent ICHs during follow-up (35 survivors of lobar ICH, 11 survivors of nonlobar ICH), data were censored at time of first recurrence. During a median follow-up of 36.8 months (interquartile range, 16.2-55.4) we observed 102 cases of recurrent lobar ICH (recurrence rate, 7.8%/y [95% CI, 5.1%-9.4%]) and 0 cases of recurrent nonlobar ICH among 505 survivors of lobar ICH. Among 640 survivors of nonlobar ICH we recorded 42 cases of recurrent nonlobar ICH (recurrence rate, 3.2%/y [95% CI, 1.4%-4.6%]) and 2 cases of recurrent lobar ICH (recurrence rate, 0.2%/y [95% CI, 0.1%-0.4%]). Recurrent lobar ICH in survivors of nonlobar ICH (n = 2) was considered qualifying for censoring (jointly with n = 42 recurrent nonlobar ICH events). Rate of recurrent ICH among survivors of lobar ICH (7.8%) exceeded the rate among survivors of nonlobar ICH (3.2%) ($P < .001$).[3]

Blood Pressure During Follow-up

Systolic and diastolic BP during follow-up and hypertension severity over time after index ICH are reported in **Table 2**. During the follow-up period, adequate BP control (defined by AHA/ASA guidelines) was achieved on at least 1 measurement by 54.6% (range, 49.2%-58.7%) of patients during follow-up, and consistently (ie, at all available time points) by 43.2% of patients (range, 34.5%-51.0%). Rates of ever and consistently adequate BP control did not differ when comparing survivors of lobar and nonlobar ICH ($P > .20$ for both). We found no association between duration of antihypertensive agent use, number of antihypertensive medications used, or both and ICH recurrence (either lobar or nonlobar, $P > .20$ for all). We also identified no association between specific antihypertensive drug classes (Table 1) and ICH recurrence (either lobar or nonlobar, $P > .20$ for all).

Recurrent Lobar ICH

Factors associated with recurrent lobar ICH in bivariable analysis included time-varying inadequate BP control as defined above ($P = .005$) (**Table 3**). For lobar ICH, calculated event rates were 84 per 1000 person-years among patients with inadequate BP control and 49 per 1000 person-years among those with adequate BP control. Multivariable Cox modeling (Table 3) confirmed associations between BP control and recurrent lobar ICH (HR, 3.53 [95% CI, 1.65-7.54]; $P < .001$). Similar multivariable Cox regression models (including as covariates preenrollment ICH, antiplatelet agents use, warfarin exposure, race/ethnicity, and education data) were constructed to explore whether a dose-dependent relationship exists between hypertension severity and recurrent ICH (**Table 4**). All hypertensive stages above normotension (defined as systolic BP 90-119 mm Hg and diastolic BP 60-79 mm Hg) were associated with increased risk of lobar ICH recurrence (Table 4) after accounting for proportion of time spent at each hypertension stage ($P < .05$ for all). There was an association between continuous systolic BP and ICH risk, accounting for dynamic changes in BP during follow-up (Table 4). Estimated yearly risk of lobar ICH recurrence based on mean systolic and diastolic BP are presented in **Figure 2**A.

Recurrent Nonlobar ICH

Time-varying inadequate BP control was associated with nonlobar ICH recurrence in bivariable analysis ($P = .03$) (Table 3). Nonlobar ICH event rates were 52 per 1000 person-years for inadequate BP control and 27 per 1000 person-years for adequate BP control. In multivariable Cox modeling inadequate BP control was associated with risk of recurrent ICH among sur-

Table 1. Cohort Characteristics

	Lobar ICH[a]				Nonlobar ICH[a]			
		Recurrence				Recurrence		
	All Patients	No	Yes	*P* Value[b]	All Patients	No	Yes	*P* Value[b]
No. of patients	505	403	102	NA	640	596	44	NA
Demographics								
Age, mean (SD), y	73.4 (11.4)	74.6 (8.2)	73.1 (11.8)	.11	68.7 (13.2)	68.7 (13.3)	68.2 (12.1)	.88
Men, %	51.6	49.2	52.3	.24	56	56	55	.74
Race/ethnicity, No. (%)								
White	435 (86.1)	355 (88.1)	80 (78.4)		542 (84.7)	508 (85.2)	34 (77.3)	
African American	41 (8.1)	30 (7.4)	11 (10.8)		50 (7.8)	44 (7.4)	6 (13.6)	
Asian	8 (1.6)	4 (1.0)	4 (3.9)	.01	5 (0.8)	4 (0.9)	1 (2.3)	<.001
Hispanic or Latino	16 (3.2)	11 (2.7)	5 (4.9)		37 (5.8)	35 (5.9)	2 (4.5)	
Other	5 (1.0)	3 (0.8)	2 (2.0)		6 (0.9)	5 (0.8)	1 (2.3)	
Education ≥10 y, No. (%)	335 (66.3)	285 (70.7)	50 (49.0)	<.001	422 (65.9)	401 (67.3)	21 (47.7)	<.001
Pre-ICH Medical History, No. (%)								
Hypertension	339 (67.1)	280 (69.5)	59 (57.8)	.03	535 (83.6)	498 (83.6)	38 (86.3)	.33
Ischemic heart disease	90 (17.2)	80 (19.8)	10 (9.8)	.02	128 (20.0)	115 (19.3)	13 (29.5)	.08
Atrial fibrillation	95 (18.1)	76 (18.8)	19 (18.6)	>.20	101 (15.8)	95 (15.9)	6 (13.6)	.40
Diabetes	71 (14.6)	62 (15.3)	9 (8.8)	.09	145 (22.7)	133 (22.3)	12 (27.3)	.40
Prior functional dependence	52 (12.2)	37 (10.9)	15 (17.4)	.09	57 (8.9)	53 (8.9)	4 (9.0)	.50
Prior cognitive impairment	75 (14.9)	54 (13.4)	21 (20.1)	.07	53 (8.3)	48 (8.1)	5 (11.4)	.23
Prior ICH								
Lobar	40 (7.79)	1 (0.25)	39 (38.2)	<.001	8 (1.3)	6 (1.0)	2 (4.5)	.10
Nonlobar	2 (0.39)	2 (0.50)	0	>.20	11 (1.7)	8 (1.3)	3 (6.8)	.03
Medication Use, No. (%)								
Before index ICH								
Antiplatelet agents	111 (22.0)	92 (22.8)	19 (18.6)	.25	116 (18.1)	108 (18.0)	8 (18.2)	.82
Warfarin	55 (10.9)	39 (9.7)	16 (15.7)	.13	62 (9.7)	55 (9.2)	7 (15.9)	.10
Statins	187 (37.0)	149 (33.8)	38 (37.3)	.39	279 (43.6)	260 (43.5)	19 (43.2)	.66
After index ICH[c]								
Antiplatelet agents	69 (13.7)	44 (10.9)	25 (24.5)	.002	89 (13.9)	82 (13.8)	7 (15.9)	.11
Warfarin	50 (9.9)	35 (8.7)	15 (14.7)	.09	49 (7.6)	44 (7.4)	5 (11.3)	.08
Statins	165 (32.7)	133 (33.0)	36 (35.3)	.45	269 (42.0)	252 (42.3)	17 (38.6)	.46
Antihypertensive Agent Use After Index ICH, No. (%)[c]								
Any agent used	298 (59.0)	246 (61.0)	52 (49.0)	.22	402 (62.8)	375 (62.9)	27 (61.4)	.67
No. of agents, No. (%)								
None	136 (26.9)	113 (28.0)	23 (22.5)		154 (24.1)	142 (23.8)	12 (27.3)	
1	192 (38.0)	145 (36.0)	47 (46.0)		269 (45.0)	248 (41.6)	21 (47.7)	
2	135 (26.7)	109 (27.1)	26 (25.5)		158 (24.7)	152 (25.5)	6 (13.6)	.52
≥3	42 (8.3)	36 (8.9)	6 (6.0)		59 (9.2)	54 (9.1)	5 (11.3)	
Drug class, No. (%)								
β-Blocker	139 (27.5)	89 (22.0)	50 (49.0)		288 (45.0)	262 (44.0)	26 (59.0)	
ACE inhibitor or ARB	155 (30.6)	103 (25.5)	52 (50.9)		243 (38.0)	226 (37.9)	17 (38.6)	
Calcium channel blocker	88 (17.4)	65 (16.1)	23 (22.5)	.73	128 (0.20)	114 (19.1)	14 (31.8)	.24
Diuretic	99 (19.6)	68 (16.9)	31 (30.4)		160 (0.25)	144 (24.1)	16 (36.6)	
Other	33 (6.5)	28 (6.9)	5 (4.8)		41 (6.4)	37 (6.2)	4 (9.0)	

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ICH, intracerebral hemorrhage; NA, not applicable.

[a] Values in parentheses represent percentage of overall survivors of lobar or nonlobar ICH (as appropriate) included in each cell, unless stated otherwise in variable description.

[b] Represent bivariable comparison of variable distribution between participants experiencing ICH recurrence and those without repeat bleeding events (separate comparison among survivors of lobar and nonlobar ICH, using the log-rank test).

[c] These variables represent intermittent exposures during follow-up.

vivors of nonlobar ICH (HR, 4.23 [95% CI, 1.02-17.52]; $P = .048$) (Table 3). Additional multivariable models were generated to explore whether hypertension severity (stages), continuous systolic and diastolic BP values, or both are associated with recurrent ICH (Table 4). Prehypertension and hypertension stage 1 were associated with ICH recurrence after accounting for time-varying exposure to each BP level (both $P < .05$, whereas hypertension stage 2 showed a nonsignificant association with

Table 2. Follow-up and Blood Pressure Data for Study Participants[a]

Follow-up Period (After ICH), mo	Follow-up Data, No.				Continuous BP Measures, Mean (95% CI)		JNC 7 Hypertension Stages, No. (%)			
	Patients Followed Up	Recurrent ICH Events	Deaths (Non-ICH-Related)	Patients Lost to Follow-up	Systolic	Diastolic	Normotension	Pre-hypertension	Hypertension Stage 1	Hypertension Stage 2
Lobar ICH (n = 505)										
0-3	505	0	0	0	141 (114-166)	78 (68-97)	25 (5)	237 (47)	203 (40)	40 (8)
4-6	505	1	0	0	138 (119-172)	79 (66-99)	35 (7)	263 (52)	172 (34)	35 (7)
7-9	504	14	12	0	140 (121-167)	80 (65-99)	25 (5)	270 (54)	190 (38)	19 (4)
10-12	478	21	18	0	139 (115-165)	76 (67-94)	29 (6)	225 (47)	191 (40)	33 (7)
13-18	439	23	14	0	138 (110-171)	77 (68-92)	31 (7)	220 (50)	167 (38)	22 (5)
19-24	402	12	18	0	140 (115-170)	79 (65-93)	20 (5)	197 (49)	157 (39)	28 (7)
25-30	372	7	11	0	142 (110-166)	77 (64-91)	26 (7)	168 (46)	145 (39)	30 (8)
31-36	354	4	17	4	141 (113-169)	80 (66-95)	28 (8)	156 (44)	144 (42)	21 (6)
37-42	329	5	15	9	138 (112-167)	78 (65-93)	16 (5)	165 (50)	132 (40)	16 (5)
43-48	300	3	14	10	136 (110-164)	79 (67-95)	21 (7)	153 (51)	114 (38)	12 (4)
49-54	273	4	16	12	140 (113-165)	75 (65-92)	22 (8)	129 (50)	98 (36)	16 (6)
55-60	241	3	19	11	139 (114-167)	81 (68-97)	17 (7)	113 (47)	85 (38)	19 (8)
Nonlobar ICH (n = 640)										
0-3	640	0	0	0	141 (115-170)	80 (66-101)	70 (11)	211 (33)	340 (53)	19 (3)
4-6	640	1	24	0	144 (118-166)	77 (63-100)	64 (10)	237 (37)	307 (48)	32 (5)
7-9	615	3	20	0	140 (119-170)	82 (64-103)	55 (9)	203 (33)	326 (53)	31 (5)
10-12	592	5	25	0	142 (115-163)	81 (65-98)	83 (14)	207 (35)	266 (45)	36 (6)
13-18	562	3	27	0	145 (114-165)	79 (66-100)	62 (11)	191 (34)	275 (49)	34 (6)
19-24	532	6	28	0	141 (119-169)	84 (61-99)	74 (14)	202 (38)	229 (43)	27 (5)
25-30	498	5	30	12	145 (114-167)	78 (62-96)	50 (10)	179 (36)	239 (48)	30 (6)
31-36	451	3	28	11	141 (116-166)	81 (64-99)	54 (12)	162 (36)	199 (44)	36 (8)
37-42	409	4	25	15	143 (114-164)	79 (63-101)	45 (11)	164 (40)	184 (45)	16 (4)
43-48	365	5	27	9	144 (116-171)	78 (65-97)	37 (10)	124 (34)	178 (49)	26 (7)
49-54	324	2	31	17	142 (112-167)	82 (64-102)	42 (13)	120 (37)	152 (47)	10 (3)
55-60	274	1	26	12	139 (117-174)	79 (65-99)	36 (13)	95 (35)	129 (47)	14 (5)

Abbreviations: ICH, intracerebral hemorrhage; JNC 7, Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure 7.

[a] For each period during first 5 years of follow-up (specified in months after index ICH), the number of participants remaining in the studies is specified, followed by the number of patients removed from subsequent analyses due to recurrent ICH, non-ICH caused death, and loss to follow-up for reason other than ICH or death. Absence of ICH recurrence events before 3 months and of loss to follow-up before 24 months are directly related to study inclusion criteria.

ICH recurrence [P = .06]). Continuous systolic BP and diastolic BP were also associated with ICH recurrence (Table 4). Figure 2B presents the estimated yearly risk of recurrence of nonlobar ICH based on systolic and diastolic BP mean values during follow-up.

Discussion

In this single-center observational cohort study, we demonstrated an association between BP and risk of recurrent ICH. This relationship was present for survivors of ICH in either the lobar or nonlobar brain regions. The association between elevated BP and ICH recurrence appeared to become stronger with worsening severity of hypertension (defined through JNC 7 severity stages[10]). Prehypertensive BP measurements were associated with increased risk of recurrent ICH in our study. These results confirm that ICH survivors are at high risk for recurrence and support the hypothesis that aggressive blood pressure control may reduce this risk substantially.

The role of hypertension in the arteriolosclerosis most commonly found in nonlobar ICH is well documented.[4,11] As a result, guidelines for secondary ICH prevention place particular emphasis on BP control for patients with radiographic characteristics most suggestive of hypertensive arteriolosclerosis (ie, nonlobar ICH).[4] However, our findings point to an association between BP control and ICH recurrence even in patients more likely to have sustained a CAA-related ICH, raising the hypothesis that the risks of poor BP control after ICH are high, regardless of the location of the original hemorrhage. Based on these findings, future studies exploring the role of BP control in ICH recurrence may benefit from combination of lobar and nonlobar ICH in a single outcome, to maximize statistical power for discovery of relevant associations.

We demonstrated an association between hypertension severity and risk of ICH recurrence. Of particular importance, we identified associations between ICH recurrence and prehypertensive BP measurements (ie, systolic BP 120-139 mm Hg and diastolic BP 80-89 mm Hg). Multiple recently published guidelines for outpatient BP control in the general population recommend

Table 3. Bivariable and Multivariable Analysis of Factors Associated With Recurrent ICH[a]

	Analysis			
	Bivariable		Multivariable	
Variable	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Lobar ICH (n = 505)				
Lobar ICH prior to index event	5.01 (2.24-11.21)	<.001	4.22 (1.40-15.71)	<.001
Antiplatelet agent use (after index ICH)[b]	2.77 (1.03-7.48)	.046	2.89 (1.32-6.30)	.008
Warfarin use (after index ICH)[b]	4.78 (1.02-22.49)	.049	5.64 (0.85-37.39)	.08
Education ≥10 y	0.66 (0.50-0.87)	.004	0.70 (0.52-0.95)	.02
Inadequate BP control[c]	3.19 (1.42-7.16)	.005	3.53 (1.65-7.54)	.001
Nonlobar ICH (n = 640)				
Nonlobar ICH prior to index event	3.01 (1.51-6.01)	.002	2.78 (1.52-5.09)	<.001
Antiplatelet agent use (after index ICH)[b]	1.71 (0.98-2.98)	.06	1.56 (0.98-2.48)	.06
Warfarin use (after index ICH)[b]	3.12 (0.62-13.43)	.18	2.88 (0.46-18.16)	>.20
Ischemic heart disease	2.33 (1.19-4.56)	.01	2.48 (1.26-4.90)	.009
Race				
White	1 [Reference]		1 [Reference]	
African American	2.67 (1.26-5.66)	.01	2.91 (1.37-6.17)	.006
Education (≥10 y)	0.60 (0.42-0.86)	.005	0.56 (0.36-0.88)	.01
Inadequate BP control[c]	3.99 (1.16-13.76)	.03	4.23 (1.02-17.52)	.048

Abbreviations: BP, blood pressure; HR, hazard ratio; ICH, intracerebral hemorrhage.

[a] Multivariable analyses of association between BP exposures and recurrent ICH. Covariates retained in final multivariable modeling are listed in the left column.

[b] Variables represent intermittent exposures during follow-up.

[c] Defined as a time-varying dichotomous yes/no variable based on whether study participants achieved BP goals recommended by the American Heart Association/American Stroke Association for post-ICH secondary prevention (ie, systolic BP <140 mm Hg and diastolic BP <90 mm Hg if no evidence of diabetes, systolic BP <130 mm Hg and diastolic BP <80 mm Hg for individuals with diabetes) within each follow-up period. See Methods for additional details.

Table 4. Multivariable Analyses: BP and Recurrence of ICH

	Recurrent ICH			
	Lobar (n = 505)[a]		Nonlobar (n = 640)[b]	
BP Exposure Variable	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Inadequate BP control[c]	3.53 (1.65-7.54)	.001	4.23 (1.02-17.52)	.048
Hypertension stage[d]				
Normotension	1 [Reference]		1 [Reference]	
Prehypertension	2.76 (1.32-5.82)	.007	3.06 (1.07-8.78)	.04
Hypertension stage 1	3.90 (1.36-11.17)	.01	3.88 (1.31-11.61)	.02
Hypertension stage 2	5.21 (2.74-9.91)	<.001	6.23 (0.90-42.97)	.06
Continuous BP values (for 10-mm Hg increase)[e]				
Systolic	1.33 (1.02-1.76)	.04	1.54 (1.03-2.30)	.04
Diastolic	1.36 (0.90-2.10)	.15	1.21 (1.01-1.47)	.05

Abbreviations: BP, blood pressure; HR, hazard ratio; ICH, intracerebral hemorrhage.

[a] All models adjusted for lobar ICH prior to index event, antiplatelet agent use, warfarin use, and education (<10 y vs ≥10 y).

[b] All models adjusted for nonlobar ICH prior to index event, antiplatelet agent use, warfarin use, ischemic heart disease, African American race, and education (<10 y vs ≥10 y).

[c] Defined as a time-varying dichotomous yes/no variable based on whether study participants achieved BP goals recommended by the American Heart Association/American Stroke Association for post-ICH secondary prevention (ie, systolic BP <140 mm Hg and diastolic BP <90 mm Hg if no evidence of diabetes, systolic BP <130 mm Hg and diastolic BP <80 mm Hg for individuals with diabetes) within each follow-up period. See Methods for additional details.

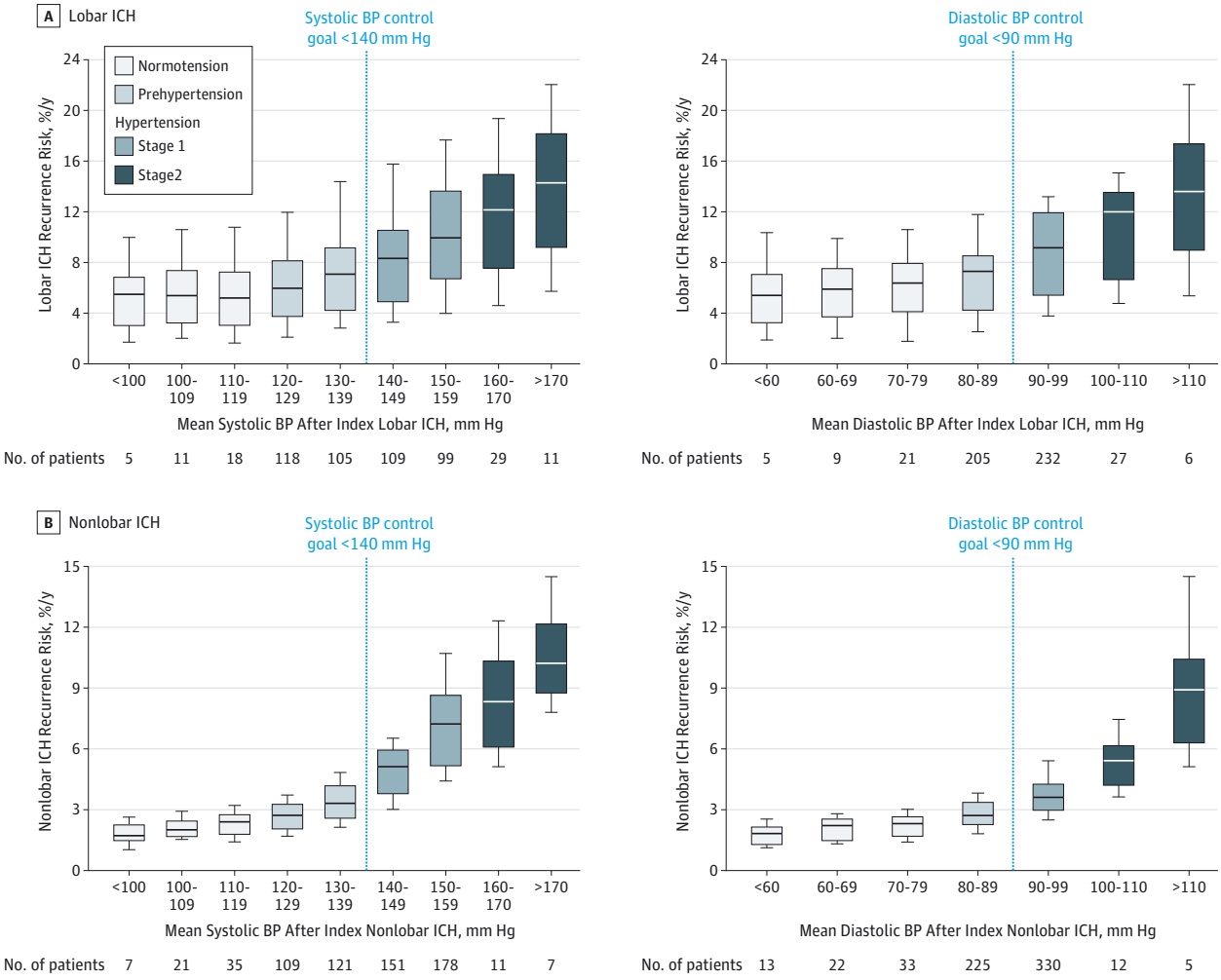
[d] Based on Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure 7 hypertension staging criteria.

[e] Time-varying systolic or diastolic BP values across entire observation time.

increasing the threshold BP for initiation of antihypertensive therapy in elderly patients. The Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure Guideline 8 (JNC 8) has recommended increasing the systolic BP threshold to higher than 150 mm Hg (compared with >140 mm Hg in the JNC 7 guidelines) for initiating BP-lowering treatment for patients 60 years or older.[12] This recommendation was based on lack of a clearly identified advantageous balance between risks (including incident stroke, cardiovascular disease, and renal failure) and benefits of more aggressive BP control in elderly patients. Our findings suggest that these recommendations may not be applicable to ICH survivors. Indeed, even the more stringent AHA/ASA guidelines may risk causing otherwise preventable hemorrhages.

The overall rate of inadequate BP control after ICH among our study participants was high. Fewer than 50% of ICH survivors achieved consistent BP control based on the definition proposed by AHA/ASA guidelines, and only 60% of patients ever achieved recommended systolic or diastolic BP goals. This is consistent with prior studies of effectiveness of BP control after ICH.[13] We identified an inverse association between educational level and risk of recurrence for both lobar and nonlo-

Figure 2. Estimated Yearly Risk of Recurrent ICH Based on Mean Blood Pressure Measurements During Follow-up



Box upper and lower margins indicate 25th and 75th percentiles of risk distributions, respectively; heavy horizontal lines in boxes indicate median risk values; error bars indicate maximum and minimum estimated risk values in each distribution. Vertical lines in blue indicate currently recommended blood pressure (BP) control goals among survivors of intracerebral hemorrhage (ICH) without diabetes, based on American Heart Association/American Stroke Association guidelines for post-ICH secondary prevention (lines are added for illustrative purposes only and have no direct impact on risk estimation results). A, Estimated yearly risk of recurrent lobar ICH based on systolic and diastolic BP measurements during follow-up. Estimated risk calculated adjusting for other factors associated with recurrence of lobar ICH (see main text and eMethods in the Supplement). B, Estimated yearly risk of recurrent nonlobar ICH based on systolic and diastolic BP measurements during follow-up. Risk is calculated assuming mean systolic and diastolic BP measurements as indicated on the horizontal axes and is expressed as % recurrent rate/y among survivors of nonlobar ICH. Estimated risk calculated adjusting for other factors associated with recurrence of nonlobar ICH (see main text and eTable 2 in the Supplement).

bar ICH. Given the limitations of our BP capture strategies, these findings are likely to reflect associations between educational achievements and unmeasured BP control via factors such as health literacy and lack of access to, or affordability of, health care because of socioeconomic status. Although clinical trials of aggressive vs conservative BP management in ICH survivors should be planned, more proactive management of BP for ICH survivors according to existing guidelines would substantially reduce the risk of ICH recurrence (and its associated toll in terms of mortality and disability).

Our study has several limitations. Because of its single-center observational nature, selection and severity bias may be reflected in the characteristics of our study population; our findings will therefore require replication in future studies, as well as extension to different health care settings. The nonstandardized data capture procedures in this study (ie, relying primarily on BP measurements obtained during routine delivery of care) also represent an important limitation. However, lack of standardization likely introduced additional imprecision in the BP exposure data, thus biasing findings toward the null hypothesis rather than risking generation of false-positive findings. Owing to the observational design of this study, BP management was determined by each patient's individual physician and did not follow prespecified or standardized protocols. We are therefore limited to describing associations between observed BP control and recurrent ICH,

rather than being able to establish a definitive causal link. Aggressive BP control has been associated in published studies with increased incidence of syncope and falls, ischemic stroke, incident coronary artery disease, and development or progression of chronic renal failure.[14-18] We did not capture these end points in our study and cannot therefore directly compare the detrimental effects of their increased incidence with the beneficial effects on reduction of ICH recurrence risk. However, the substantial increase in risk of ICH recurrence, as well as the increased mortality and disability associated with recurrent ICH, are likely to outweigh the decrease in survival rates and quality of life associated with the aforementioned detrimental outcomes of aggressive BP reduction. Indeed, a recently published cost-effectiveness analysis emphasized the greater benefit of BP control (according to JNC 8 guidelines) for individuals with known cardiovascular and cerebrovascular conditions.[19] We also did not evaluate whether BP variability is associated with risk of ICH recurrence. Based on prior evidence implicating BP variability in accumulation of neuroimaging markers of cerebral small-vessel disease, future studies focusing on this specific aspect of BP control may uncover such an association.[20]

Conclusions

In this observational single-center cohort study of ICH survivors, reported BP measurements suggesting inadequate BP control during follow-up were associated with higher risk of both lobar and nonlobar ICH recurrence. These data suggest that randomized clinical trials are needed to address the benefits and risks of stricter BP control in ICH survivors.

ARTICLE INFORMATION

Author Contributions: Drs Biffi and Rosand had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Biffi, Rosand.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Biffi.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Biffi.
Obtained funding: Rosand.
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Study supervision: Anderson, Viswanathan, Rosand.

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