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ORIGINAL RESEARCH

Antithrombotic Treatment, Prehospital Blood Pressure, and Outcomes in Spontaneous Intracerebral Hemorrhage

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BACKGROUND: In acute intracerebral hemorrhage, both elevated blood pressure (BP) and antithrombotic treatment are associated with poor outcome. Our aim was to explore interactions between antithrombotic treatment and prehospital BP.

METHODS AND RESULTS: This observational, retrospective study included adult patients with spontaneous intracerebral hemorrhage diagnosed by computed tomography within 24 hours, admitted to a primary stroke center during 2012 to 2019. The first recorded prehospital/ambulance systolic and diastolic BP were analyzed per 5 mm Hg increment. Clinical outcomes were in-hospital mortality, shift on the modified Rankin Scale at discharge, and mortality at 90 days. Radiological outcomes were initial hematoma volume and hematoma expansion. Antithrombotic (antiplatelet and/or anticoagulant) treatment was analyzed both together and separately. Modification of associations between prehospital BP and outcomes by antithrombotic treatment was explored by multivariable regression with interaction terms. The study included 200 women and 220 men, median age 76 (interquartile range, 68–85) years. Antithrombotic drugs were used by 252 of 420 (60%) patients. Compared with patients without, patients with antithrombotic treatment had significantly stronger associations between high prehospital systolic BP and in-hospital mortality (odds ratio [OR], 1.14 versus 0.99, *P* for interaction 0.021), shift on the modified Rankin Scale (common OR, 1.08 versus 0.96, *P* for interaction 0.001), and hematoma volume (coef. 0.03 versus −0.03, *P* for interaction 0.011).

CONCLUSIONS: In patients with acute, spontaneous intracerebral hemorrhage, antithrombotic treatment modifies effects of prehospital BP. Compared with patients without, patients with antithrombotic treatment have poorer outcomes with higher prehospital BP. These findings may have implications for future studies on early BP lowering in intracerebral hemorrhage.

Key Words: antithrombotic treatment ■ intracerebral hemorrhage ■ prehospital blood pressure

In acute, spontaneous intracerebral hemorrhage (ICH), elevated blood pressure (BP) is associated with poor outcome.[1–3] To mitigate hematoma expansion, guidelines recommend acute BP lowering.[4,5] Early BP lowering reduces hematoma expansion, but this reduction has not been shown to translate into a clear clinical benefit.[6] Part of the explanation might be time delay from symptom onset to treatment. Most hematoma expansion occurs within the first 3 hours,[7] but in studies of early BP lowering the mean time to in-hospital treatment was 5.7 hours.[8,9] Also in the prehospital phase of ICH, high BP is associated with worse outcome.[10–13] Hyperacute, prehospital BP lowering in suspected stroke has been investigated, but not yet proven effective in patients with ICH.[14,15]

About half of patients with ICH are using antithrombotic (antiplatelet and/or anticoagulant) drugs at the time of the event.[16–18] In aging populations, the number of patients with ICH on antithrombotic treatment

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CLINICAL PERSPECTIVE

What Is New?

- High blood pressure (BP) in the acute phase of intracerebral hemorrhage is unfavorable, but whether there is heterogeneity by preceding antithrombotic treatment is uncertain.
- We found stronger associations between higher prehospital BP and poor outcome in patients on antithrombotic treatment, particularly in patients on anticoagulant treatment, compared with patients on no such treatment.

What Are the Clinical Implications?

- Future clinical studies assessing effects of early BP lowering in intracerebral hemorrhage may consider stratifying patients by antithrombotic treatment to investigate heterogeneity of effects of BP-lowering treatment.
- Patients with acute intracerebral hemorrhage and a combination of high prehospital BP and preceding anticoagulant treatment have particularly poor prognosis, and a "bundle of care" including both rapid BP lowering, and anticoagulant reversal is a promising approach for further investigation.

Nonstandard Abbreviations and Acronyms

ICH	intracerebral hemorrhage
mRS	modified Rankin Scale
OAC	oral anticoagulant
SBP	systolic blood pressure
VKA	vitamin K antagonist

is increasing, since age increases the risk of both ICH and vascular occlusive disease. Antithrombotic treatment at ICH onset is associated with poor prognosis.[19,20] Interactions between antithrombotic treatment and early, in-hospital BP lowering were investigated in a post hoc analysis from the INTERACT1 and 2 (Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trials).[21] They found no significant interactions between antithrombotic treatment and BP lowering on mortality or dependency, or hematoma expansion. However, the included participants may not have been entirely representative for the general ICH population because of stringent eligibility criteria. Also, it may be speculated that much of the hematoma expansion had occurred before hospital admission and trial enrollment. Whether antithrombotic treatment modifies associations between BP in the hyperacute phase of ICH and outcome is unknown.

The aim of the present study was to explore the impact of antithrombotic treatment on associations between prehospital BP and clinical and radiological outcomes in a historical cohort of patients with acute, spontaneous ICH.

METHODS

Data Availability

The corresponding author has full access to all the data in the study and takes responsibility for its integrity and the data analyses. Anonymized data supporting the results are available from the corresponding author on reasonable request.

Study Design and Setting

The ASIST-1 (Akershus Study of Ischemic Stroke and Thrombolysis 1) is an observational, retrospective registry comprising all consecutive patients with ICH admitted to Akershus University Hospital between 2012 and 2019. Akershus University Hospital is a primary stroke center covering an area of 550 000 inhabitants, making it the largest emergency hospital in Norway and, according to Statistics Norway, reasonably representative for the total Norwegian population. According to the standards of the European Stroke Organization, the stroke unit is classified as a comprehensive stroke center.

Ethics Approval and Reporting Guidelines

The Regional Committee for Medical Research Ethics (REK 2018/498) and the local Data Protection Official approved the study and waived the informed consent requirement in accordance with the Norwegian law on medical research. The STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) guidelines were followed in preparation of this manuscript.

Study Population and Data Collection

All consecutively admitted patients who received an ICH diagnosis code according to the *International Classification of Diseases*, *Tenth Revision* (*ICD-10*) were identified retrospectively by searching the electronical patient database, and included if they were aged ≥18 years, had a spontaneous ICH, were primarily admitted to Akershus University Hospital, and diagnosed by computed tomography (CT) within 24 hours of symptom onset, and had at least 1 prehospital systolic BP (SBP) recorded. ICH caused by trauma, underlying structural vessel abnormalities, thrombolysis, cerebral venous thrombosis, or cerebral tumor were excluded. Pure intraventricular hemorrhage and recurrent ICH during the inclusion period were also excluded, as were patients with missing information about antithrombotic treatment.

By retrospective review of hospital records, information was recorded about demographics, medical history including use of antithrombotic drugs, clinical characteristics, prehospital and in-hospital course, and outcomes. The time when the patient was last seen well was regarded as symptom onset. Scores on the National Institute of Health Stroke Scale and modified Rankin Scale (mRS) were collected from relevant time points or scored retrospectively based on clinical information in the hospital records.[22]

BP Variables

The first prehospital BP measured in the ambulance and recorded in the Emergency Medical Services report was collected. SBP and diastolic BP were included in the analyses.

Antithrombotic Treatment

Antithrombotic treatment was defined as ongoing treatment with antiplatelet or anticoagulant drugs, or a combination of these, at the time of ICH. Antiplatelet treatment was defined as antiplatelet drugs only (not in combination with anticoagulant drugs), and were either acetylsalicylic acid (ASA), clopidogrel, dipyridamole, or a combination of these. Anticoagulant treatment was defined as anticoagulant drugs only (not in combination with antiplatelet drugs) and were either a vitamin K antagonist (VKA), direct oral anticoagulant, or low-molecular-weight heparin in therapeutic doses (>5000 IU dalteparin or >40 mg enoxaparin per day).

Outcome Variables

Clinical outcomes were in-hospital mortality, shift on the mRS at discharge, and mortality at 90 days. Radiological outcomes were initial hematoma volume, and hematoma expansion, defined as >6 mL and/or >33% increase in volume between the initial and the follow-up CT.[7,23]

Mortality

Because information about all deaths in Norway is constantly updated in the electronic patient records from the National Population Register, and because data were collected >1 year after the last ICH event, date of death up to 1 year was obtainable for all deceased patients.

Imaging

Two experienced radiologists assessed hematomas on the initial noncontrast cerebral CT and on the follow-up CT performed at a maximum of 25 hours after admission. The time limit of 25 hours aimed to include all follow-up scans within 24 hours after the initial scan. Only the largest hematoma was assessed if there were >1 present. The radiologists evaluated hematoma location and presence of intraventricular blood on the initial and the follow-up CT. The evaluation by radiologists for the present study also served as a validation of the diagnosis of a nontraumatic ICH. A third author estimated hematoma volumes by using the MIStar software version 3.2 (Apollo Medical Imaging Technology Pty Ltd, Melbourne, VIC, Australia), which provides a semiautomated, planimetric method of volume measurement.[24] A region of interest was manually drawn inside the hematoma borders on each axial slice. The software automatically increased the region to enclose the whole area of blood on the slice. The volume was estimated by adding up the areas of blood and multiplying by the slice thickness. Intraventricular blood was excluded from the volume estimation.

Statistical Analysis

Stata statistical software (StataCorp. 2021. *Stata Statistical Software: Release 17*. College Station, TX: StataCorp LLC.) was used for the statistical analyses. The significance level was set to $P<0.05$, with no adjustment for multiple comparisons attributable to the exploratory nature of the study. An analysis plan was made before any analyses for the present study were performed.

Continuous variables are reported as medians with interquartile ranges (IQR) and categorical variables as proportions (n/N) with percentages. Baseline characteristics and outcomes were stratified according to antithrombotic treatment at the time of ICH occurrence. The groups were compared by Pearson Chi-squared test or Mann Whitney *U* test, as appropriate.

Because of non-normal distribution of initial hematoma volume, this variable was transformed by the natural logarithm and analyzed as a continuous outcome variable with linear regression. Hematoma expansion, in-hospital mortality, and mortality at 90 days were analyzed as dichotomous outcomes by logistic regression. Shift on the mRS at discharge was analyzed by ordinal logistic regression.

Univariate and multivariable regression models were used to explore associations between the different types of antithrombotic treatment and outcomes, with “no antithrombotic” as reference group. Multivariable regression models were used to explore associations between the continuous prehospital BP variables (per 5 mm Hg increment) and outcomes, according to subgroups of antithrombotic treatment. Modification by antithrombotic treatment was explored by adding an interaction term to the multivariable regression models. “No antithrombotic treatment” was reference group for the antithrombotic subgroups (any antithrombotic treatment, antiplatelet, and anticoagulant).

All multivariable regression analyses were adjusted for age, sex, diabetes, antihypertensive treatment, Glasgow Coma Scale score on admission, mRS score pre-ICH, time from symptom onset to admission, and presence of intraventricular blood on the initial CT. Except for initial hematoma volume, all analyses were also adjusted for acute BP-lowering treatment, defined as acute, rapid, intravenous and/or transdermal BP-lowering drugs given during the initial phase of hospitalization and aiming at reducing hematoma expansion. Analyses of hematoma expansion were also adjusted for initial hematoma volume. The multivariable models excluded patients with missing data (ie, complete case analyses).

Comparison of patients with and without follow-up CT, relevant for the analyses of hematoma expansion, was done by Pearson Chi-squared test or Mann Whitney *U* test, as appropriate.

Sensitivity Analyses

Several sensitivity analyses were performed. Patients on anticoagulant treatment were also analyzed by additionally adjusting for anticoagulant reversal treatment (≥1 of the following: prothrombin complex concentrate, vitamin K, fresh frozen plasma, or a specific anticoagulant antidote). The mortality outcomes were also analyzed by excluding patients who died within the first day and additionally adjusting for surgical intervention (extraventricular drainage and/or hematoma evacuation) and do-not-resuscitate order during the hospital stay (including patients who received palliative care and patients kept on respiratory support in case organ donation would be the outcome). Hematoma expansion was also analyzed in patients admitted <6 hours after symptom onset, and by including new presence of intraventricular blood on follow-up CT and in-hospital mortality to the definition of hematoma expansion. Hematoma expansion was also analyzed after excluding patients with the lowest quartile of initial hematoma volumes. Because of small sample size in the subgroups of the latter 2 sensitivity analyses, these were only adjusted for age and sex.

RESULTS

A total of 672 patients with spontaneous ICH were identified, of whom 420 (63%) were eligible for the present study (flowchart, Figure S1–S8). Baseline characteristics stratified by antithrombotic treatment are presented in Table 1. The median age was 76 (interquartile range [IQR], 68–85) years and 200 (48%) were women. Antithrombotic drugs were used by 252 of 420 (60%) at the time of ICH occurrence. Patients who used antithrombotic drugs were older, more often men, had higher pre-ICH mRS scores, more often a history of ischemic stroke, coronary artery disease, diabetes, atrial fibrillation, and treated hypertension. Of the total population, 55% arrived in hospital and 50% had CT scanning within 3 hours from symptom onset. Median prehospital SBP was 180 (IQR, 160–197) mm Hg and median prehospital diastolic BP was 100 (IQR, 86–112) mm Hg, with no significant differences between patients with and without antithrombotic treatment.

Antithrombotic Treatment

Distribution of antiplatelet and anticoagulant drugs used at ICH occurrence are shown in Figure S2. Antiplatelet only was used by 137 of 420 patients (33%), anticoagulant only by 92 of 420 (22%), a combination of antiplatelet and anticoagulant by 23 of 420 (5%). Because of the small number of patients in the latter group, this was not analyzed separately. Overall, 120 patients were using ASA, 29 a combination of ASA and dipyridamole, 4 clopidogrel, 1 dipyridamole only, and 6 a combination of ASA and clopidogrel. Direct oral anticoagulant was used by 55 patients, 54 used VKA, and 6 used low-molecular-weight heparin in therapeutic doses.

Antithrombotic Treatment and Outcomes

Table S1 shows outcomes for the total study population stratified by antithrombotic treatment at ICH occurrence. In the total population, 116 of 420 (28%) died during the hospital stay, 366 of 416 (88%) had mRS 3 to 6 at discharge and 159 of 420 (38%) died within 90 days. The median initial hematoma volume was 8.4 (IQR, 3.2–24.5) mL, and 49 of the 183 patients with a follow-up CT (27%) had hematoma expansion. Patients on antithrombotic treatment had more in-hospital mortality (34% versus 18%, $P<0.001$), larger proportion of mRS score 3 to 6 at discharge (93% versus 81%, $P<0.001$), higher mortality at 90 days (44% versus 28%, $P<0.001$), nonsignificantly larger initial hematoma volumes (9.2 mL versus 7.6 mL, $P=0.07$), and more hematoma expansion (33% versus 18%, $P=0.026$). Figure S3 shows mRS scores at discharge stratified by antithrombotic treatment. mRS scores at discharge were available in the hospital records for 40 patients and scored retrospectively for 376 patients.

Table 2 shows associations between subtypes of antithrombotic treatment (any antithrombotic treatment, antiplatelet, and anticoagulant) and outcomes in crude and adjusted regression analyses. "Any antithrombotic treatment" was associated with 4 out of 5 outcomes in crude analyses, but with only hematoma expansion in adjusted analyses. Antiplatelet was associated with in-hospital mortality, mRS at discharge, and mortality at 90 days in crude analyses, and with initial hematoma volume in adjusted analyses. Anticoagulant was associated with in-hospital mortality, mRS at discharge, and

Table 1. Baseline Characteristics for the 420 Included Patients, Stratified by Antithrombotic Treatment at ICH Occurrence

	Total N=420	Antithrombotic treatment N=252	No antithrombotic treatment N=168	*P* value
Age, y, median (IQR)	76 (68–85)	79 (72–85)	73 (56–82)	<0.001*
Women, n/N (%)	200/420 (48)	108/252 (43)	92/168 (55)	0.017*
Pre-ICH mRS score, n/N (%)				<0.001*
0	116/419 (28)	49/252 (19)	67/167 (40)	
1	112/419 (27)	75/252 (30)	37/167 (22)	
2	74/419 (18)	44/252 (17)	30/167 (18)	
3	71/419 (17)	50/252 (20)	21/167 (13)	
4	43/419 (10)	31/252 (12)	12/167 (7)	
5	3/419 (1)	3/252 (1)	0/167 (0)	
History of ischemic stroke, n/N (%)	92/416 (22)	83/249 (33)	9/167 (5)	<0.001*
Coronary artery disease, n/N (%)	82/419 (20)	78/252 (31)	4/167 (2)	<0.001*
Diabetes, n/N (%)	60/420 (14)	44/252 (17)	16/168 (10)	0.023*
Atrial fibrillation, n/N (%)	101/419 (24)	99/251 (39)	2/168 (1)	<0.001*
Using antihypertensive drugs, n/N (%)	236/413 (57)	181/246 (74)	55/167 (33)	<0.001*
Time from onset to admission, n/N (%)				0.32
<3 h	233/420 (55)	133/252 (53)	100/168 (60)	
3–6 h	68/420 (16)	47/252 (19)	21/168 (13)	
6–12 h	62/420 (15)	39/252 (15)	23/168 (14)	
12–24 h	57/420 (14)	33/252 (13)	24/168 (14)	
Prehospital SBP, median (IQR)	180 (160–197)	175 (156–195)	180 (160–200)	0.36
Prehospital DBP, median (IQR)	100 (86–112)	100 (86–110)	100 (86–117)	0.25
GCS on admission, median (IQR)	14 (10–15)	14 (10–15)	14 (11–15)	0.096
NIHSS on admission, median (IQR)	9 (3–15)	9 (4–15)	8 (2–16)	0.41
Hematoma location, n/N (%)				0.024*
Lobar	137/420 (33)	88/252 (35)	49/168 (29)	
Deep	204/420 (49)	108/252 (43)	96/168 (57)	
Infratentorial	55/420 (13)	38/252 (15)	17/168 (10)	
Uncertain	24/420 (6)	18/252 (7)	6/168 (4)	
Intraventricular blood on initial CT, n/N (%)	155/409 (38)	103/247 (42)	52/162 (32)	0.050
Acute BP-lowering treatment, n/N (%)	222/420 (53)	126/252 (50)	96/168 (57)	0.15
Surgical intervention, n/N (%)	28/417 (7)	11/249 (4)	17/168 (10)	0.023*
DNR order during admission, n/N (%)	186/419 (44)	132/252 (52)	54/167 (32)	<0.001*

Data are median (interquartile range) for continuous variables and n/N (%) for categorical variables. Medians were compared by the Mann Whitney *U* test, proportions by Pearson Chi-squared test. BP indicates blood pressure; CT, computed tomography; DBP, diastolic blood pressure; DNR, do not resuscitate; GCS, Glasgow Coma Scale; ICH, intracerebral hemorrhage; IQR, interquartile range; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; and SBP, systolic blood pressure.

**P* values indicate significant differences.

mortality at 90 days in crude analyses, and with hematoma expansion in both crude and adjusted analyses. All significant associations were consistently directed at worse outcome with antithrombotic treatment.

Prehospital BP and Outcomes According to Subgroups of Antithrombotic Treatment

Table 3 shows associations between prehospital BP (per 5 mm Hg increment) and outcomes according to antithrombotic subgroups, and *P* value for the interaction between antithrombotic subgroups and prehospital BP. In the "no antithrombotic" subgroup, no associations were found between prehospital BP and outcomes. In the "any antithrombotic" subgroup, prehospital SBP was associated with in-hospital mortality (OR, 1.14 [95% CI, 1.06–1.23]), mRS at discharge (common OR, 1.08 [95% CI, 1.03–1.13]), and initial hematoma volume (coef. 0.03 [95% CI, 0.00–0.06]). There were significant interactions between "any antithrombotic" and prehospital SBP for in-hospital mortality (*P*=0.021), mRS at discharge (*P*=0.001), and initial hematoma volume (*P*=0.011). In the antiplatelet subgroup, no associations were found between prehospital BP

Table 2. Regression Analyses of Antithrombotic Treatment and Outcomes

		Any antithrombotic treatment†	AP	AC
In-hospital mortality, OR (95% CI)	Crude	2.25 (1.41 to 3.60)‡ n=420	1.76 (1.03 to 3.01)‡ n=305	3.25 (1.84 to 5.74)‡ n=260
	Adjusted*	1.61 (0.79 to 3.26) n=374	1.45 (0.65 to 3.23) n=274	1.98 (0.81 to 4.88) n=231
mRS at discharge, common OR (95% CI)	Crude	2.19 (1.53 to 3.12)‡ n=416	1.77 (1.18 to 2.66)‡ n=301	3.06 (1.90 to 4.91)‡ n=258
	Adjusted*	1.21 (0.76 to 1.91) n=372	1.12 (0.68 to 1.84) n=272	1.58 (0.83 to 3.00) n=230
Mortality at 90 d, OR (95% CI)	Crude	2.06 (1.36 to 3.13)‡ n=420	1.62 (1.00 to 2.63)‡ n=305	2.81 (1.65 to 4.77)‡ n=260
	Adjusted*	1.00 (0.53 to 1.89) n=374	0.80 (0.39 to 1.61) n=274	1.14 (0.49 to 2.62) n=231
Initial hematoma volume, transformed, Coef (95% CI)	Crude	0.30 (−0.03 to 0.62) n=418	0.35 (−0.02 to 0.72) n=304	0.23 (−0.19 to 0.64) n=259
	Adjusted*	0.25 (−0.07 to 0.58) n=374	0.39 (0.04 to 0.73)‡ n=274	0.05 (−0.41 to 0.51) n=231
Hematoma expansion, OR (95% CI)	Crude	2.25 (1.09 to 4.61)‡ n=183	1.47 (0.64 to 3.40) n=135	3.15 (1.29 to 7.65)‡ n=110
	Adjusted*	3.10 (1.21 to 7.92)‡ n=167	2.78 (0.92 to 8.40) n=126	6.22 (1.66 to 23.29)‡ n=98

AC indicates anticoagulant treatment; AP, antiplatelet treatment; mRS, modified Rankin Scale; and OR, odds ratio. Reference group: No antithrombotic treatment.

*Adjusted for age, sex, diabetes, antihypertensive treatment, Glasgow Coma Scale score on admission, modified Rankin Scale score pre-intracerebral hemorrhage, time from symptom onset to admission, and presence of intraventricular blood on the initial computed tomography (all outcomes except initial hematoma volume were also adjusted for acute blood pressure-lowering treatment, and hematoma expansion was also adjusted for initial hematoma volume).

†Any antithrombotic treatment=antiplatelet and/or anticoagulant.

‡Values indicate significant associations (P<0.05).

and outcomes, but there was a significant interaction between antiplatelet and prehospital SBP for mRS at discharge (P=0.024). In the anticoagulant subgroup, prehospital SBP was associated with in-hospital mortality (OR, 1.30 [95% CI, 1.11–1.54]), mRS at discharge (common OR, 1.14 [95% CI, 1.03–1.25]), and initial hematoma volume (coef. 0.07 [95% CI, 0.02–0.13]). There were significant interactions between anticoagulant and prehospital SBP for these 3 outcomes (P=0.012, P=0.002, and P=0.004, respectively). For the outcome hematoma expansion, no significant associations or interactions were found in any of the antithrombotic subgroups.

Figure 1 visualizes interactions between any antithrombotic treatment and prehospital SBP. The corresponding interactions for antiplatelet and anticoagulant treatment are shown in Figures 2 and 3.

Patient Characteristics Stratified by Presence of Follow-Up CT

Follow-up CT was performed on 183 of 420 patients (44%), who were included in analyses of hematoma expansion. Patients without follow-up CT were older, more often women, had higher pre-ICH mRS scores, lower prehospital SBP and diastolic BP, lower Glasgow Coma Scale, and higher National Institute of Health Stroke Scale scores on admission, larger initial hematoma volumes, and higher mortality rates during the hospital stay and within 90 days (Table S2).

Sensitivity Analyses

Sensitivity analyses of patients on anticoagulant treatment by additionally adjusting for anticoagulant reversal treatment did not change the associations between prehospital BP and outcomes (Table S3). Sensitivity analyses by excluding patients who died within the first day and additionally adjusting for surgical intervention and do-not-resuscitate order did not change the associations between antithrombotic treatment and mortality outcomes (Table S4) or the associations between prehospital BP and mortality outcomes in subgroups by antithrombotic treatment, except for the interaction between antiplatelet and prehospital SBP on in-hospital mortality, which turned significant (Table S5). Sensitivity analyses of hematoma expansion by excluding patients who arrived in hospital >6 hours after symptom onset and including new presence of intraventricular blood on follow-up CT and in-hospital mortality to the definition of hematoma expansion changed the adjusted association between any antithrombotic treatment and hematoma expansion to nonsignificant, but the adjusted association between anticoagulant and hematoma expansion remained significant (Table S6). The same sensitivity analyses did

Table 3. Multivariable Regression Analyses of Prehospital Systolic and Diastolic Blood Pressure (per 5 mm Hg Increment) and Outcomes According to Subgroups of Antithrombotic Treatment, and *P* for Interaction

		No anti-thrombotic treatment (ref.)	Any anti-thrombotic treatment*	*P* for interaction: any anti-thrombotic treatment and BP	AP	*P* for interaction: AP and BP	AC	*P* for interaction: AC and BP
In-hospital mortality, OR (95% CI)	Prehosp SBP	0.99 (0.89 to 1.09) n=152	1.14 (1.06 to 1.23)‡ n=222	0.021‡ n=374	1.08 (0.98 to 1.18) n=122	0.15 n=274	1.30 (1.11 to 1.54)‡ n=79	0.012‡ n=231
	Prehosp DBP	0.96 (0.83 to 1.11) n=152	1.15 (1.04 to 1.28)‡ n=220	0.055 n=372	1.13 (0.98 to 1.30) n=120	0.09 n=272	1.29 (1.03 to 1.61)‡ n=79	0.085 n=231
mRS discharge, common OR (95% CI)	Prehosp SBP	0.96 (0.91 to 1.01) n=151	1.08 (1.03 to 1.13)‡ n=221	0.001‡ n=372	1.05 (0.98 to 1.12) n=121	0.024‡ n=272	1.14 (1.03 to 1.25)‡ n=79	0.002‡ n=230
	Prehosp DBP	0.98 (0.91 to 1.05) n=151	1.08 (1.00 to 1.17) n=219	0.12 n=370	1.02 (0.92 to 1.14) n=119	0.38 n=270	1.21 (1.03 to 1.42)‡ n=79	0.047‡ n=230
Mortality at 90 d, OR (95% CI)	Prehosp SBP	1.00 (0.92 to 1.10) n=152	1.06 (1.00 to 1.14) n=222	0.24 n=374	1.06 (0.97 to 1.16) n=122	0.34 n=274	1.10 (0.98 to 1.25) n=79	0.21 n=231
	Prehosp DBP	0.99 (0.88 to 1.11) n=152	1.05 (0.94 to 1.16) n=220	0.32 n=372	1.04 (0.91 to 1.20) n=120	0.31 n=272	1.06 (0.87 to 1.29) n=79	0.45 n=231
Initial hematoma volume, transformed, Coef (95% CI)	Prehosp SBP	−0.03 (−0.06 to 0.01) n=152	0.03 (0.00 to 0.06)‡ n=222	0.011‡ n=374	0.02 (−0.02 to 0.06) n=122	0.08 n=274	0.07 (0.02 to 0.13)‡ n=79	0.004‡ n=231
	Prehosp DBP	−0.03 (−0.08 to 0.02) n=152	0.04 (−0.01 to 0.09) n=220	0.053 n=372	0.02 (−0.04 to 0.09) n=120	0.20 n=272	0.11 (0.03 to 0.20)‡ n=79	0.005‡ n=231
Hematoma expansion, OR (95% CI)	Prehosp SBP	1.13 (0.99 to 1.28)† n=69	1.04 (0.96 to 1.13)† n=100	0.97 n=167	0.95 (0.82 to 1.10)† n=59	0.40 n=126	1.09 (0.92 to 1.30)† n=31	0.40 n=98
	Prehosp DBP	1.20 (0.99 to 1.44)† n=69	1.10 (0.97 to 1.24)† n=99	0.87 n=166	1.15 (0.95 to 1.40)† n=58	0.88 n=125	1.06 (0.83 to 1.35)† n=31	0.68 n=98

AC indicates anticoagulant treatment; AP, antiplatelet treatment; BP, blood pressure; DBP, diastolic blood pressure; mRS, modified Rankin Scale; OR, odds ratio; prehosp, prehospital; SBP, systolic blood pressure. Reference group: no antithrombotic treatment. All analyses were adjusted for age, sex, diabetes, antihypertensive treatment, Glasgow Coma Scale score on admission, modified Rankin Scale score pre-intracerebral hemorrhage, time from symptom onset to admission, and presence of intraventricular blood on the initial computed tomography (all outcomes except initial hematoma volume were also adjusted for acute blood pressure-lowering treatment, and hematoma expansion was also adjusted for initial hematoma volume).

*Any antithrombotic treatment=antiplatelet and/or anticoagulant.

†Diabetes and presence of intraventricular blood on the initial computed tomography were removed from the model because these 2 variables predicted the outcome perfectly.

‡Values indicate significant associations ($P<0.05$).

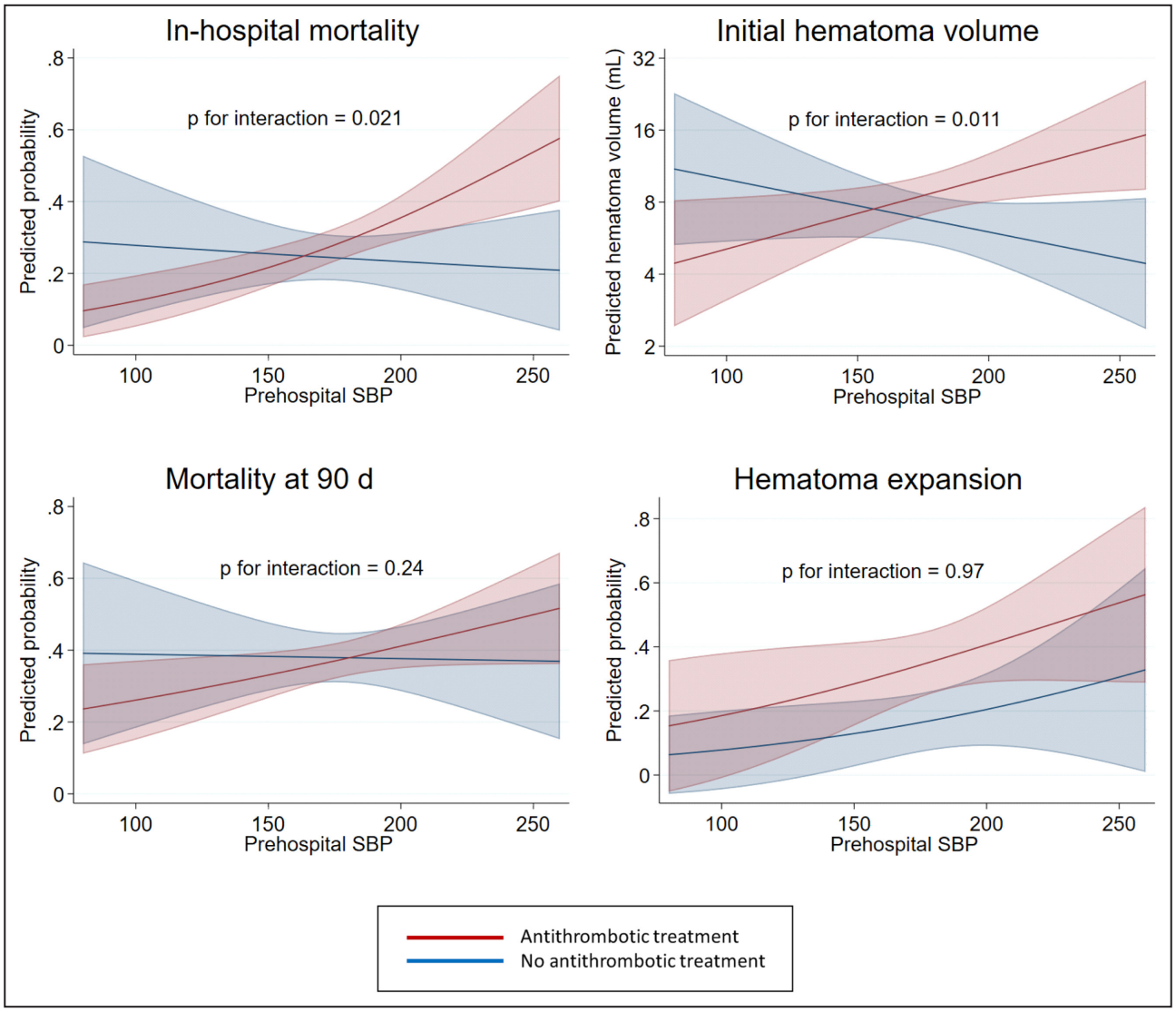

Figure 1. Interactions between antithrombotic treatment and prehospital systolic blood pressure on outcomes.
All analyses were adjusted for age, sex, diabetes, antihypertensive treatment, Glasgow Coma Scale score on admission, modified Rankin Scale score pre-intracerebral hemorrhage, time from symptom onset to admission, and presence of intraventricular blood on the initial computed tomography (all outcomes except initial hematoma volume were also adjusted for acute blood pressure-lowering treatment, and hematoma expansion was also adjusted for initial hematoma volume). SBP indicates systolic blood pressure. Any antithrombotic treatment=antiplatelet and/or anticoagulant treatment. Red line=antithrombotic treatment, blue line=no antithrombotic treatment. Red and blue zones indicate upper and lower 95% confidence bounds.

not change the associations between prehospital BP and hematoma expansion in subgroups by antithrombotic treatment (Table S7). Sensitivity analyses by excluding patients with the lowest quartile of hematoma volumes did not change the associations between prehospital BP and hematoma expansion in subgroups by antithrombotic treatment (Table S8).

DISCUSSION

In this study of 420 consecutive patients with acute, spontaneous ICH, antithrombotic treatment modified associations between prehospital BP and in-hospital mortality, mRS at discharge, and initial hematoma volume. In both the "any antithrombotic" and the anticoagulant subgroups, higher prehospital BP was associated with these 3 outcomes. In the "no antithrombotic" subgroup, no significant associations were found between prehospital BP and outcomes. Overall, there was consistency in directions of effects of prehospital BP and heterogeneity by antithrombotic subgroups. The figures imply that some of the outcomes improved with higher prehospital SBP in patients on no antithrombotic treatment. However, the corresponding effect estimates with CIs reported in the tables show that these associations were not

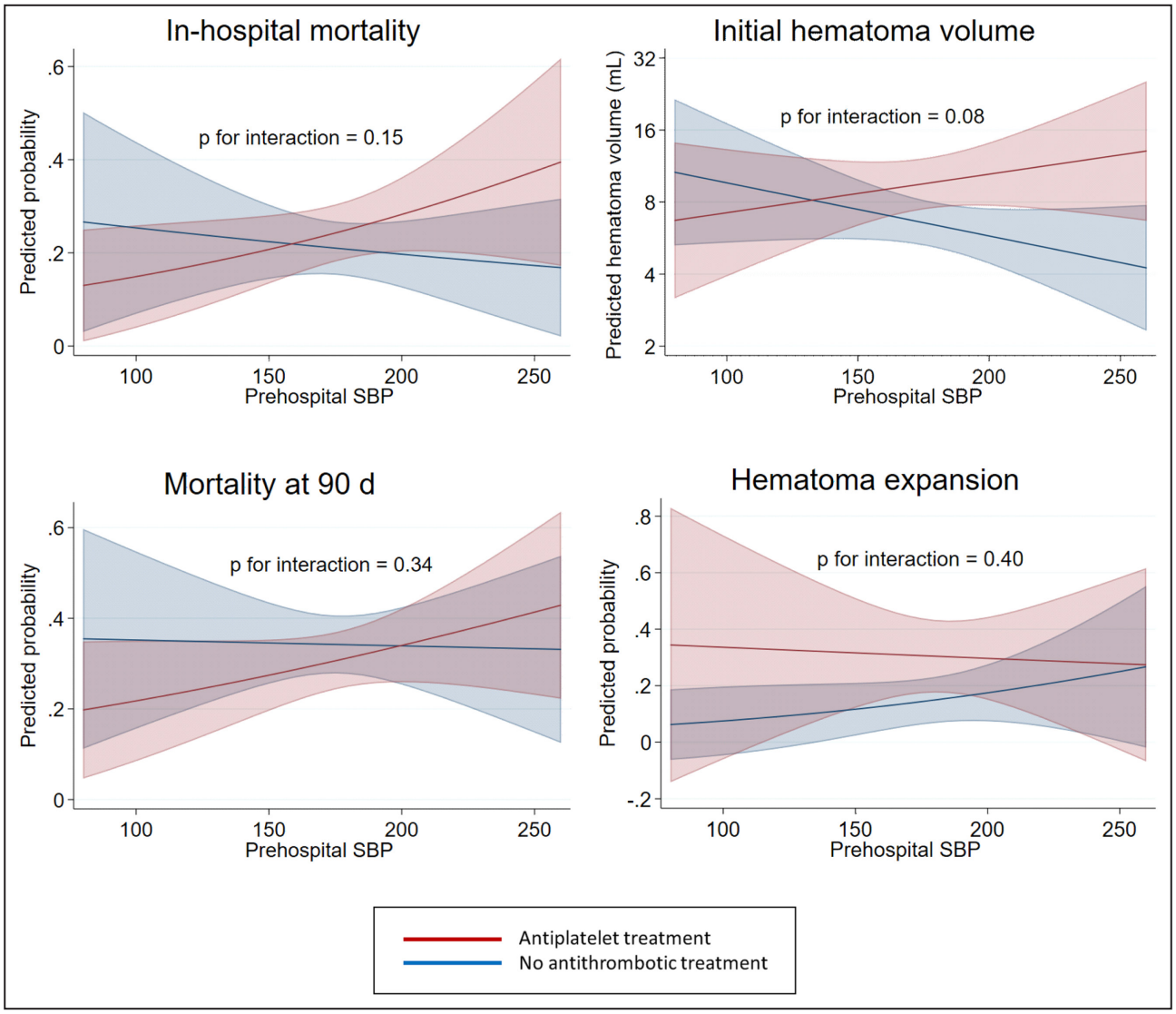

Figure 2. Interactions between antiplatelet treatment and prehospital systolic blood pressure on outcomes.
All analyses were adjusted for age, sex, diabetes, antihypertensive treatment, Glasgow Coma Scale score on admission, modified Rankin Scale score pre-intracerebral hemorrhage, time from symptom onset to admission, and presence of intraventricular blood on the initial computed tomography (all outcomes except initial hematoma volume were also adjusted for acute blood pressure-lowering treatment, and hematoma expansion was also adjusted for initial hematoma volume). SBP indicates systolic blood pressure. Red line=antiplatelet treatment, blue line=no antithrombotic treatment. Red and blue zones indicate upper and lower 95% confidence bounds.

significant, in contrast to the associations for patients on antithrombotic treatment.

The present findings indicate that higher prehospital BP is more unfavorable in patients with antithrombotic treatment than in those without, particularly in patients on anticoagulant treatment. Based on the observational nature of the study, we cannot draw conclusions about the underlying mechanisms for these findings. Patients with antithrombotic treatment were older and had more morbidity and despite adjustment for potential confounding factors, there is a chance of residual confounding. However, the consistent findings suggest that early BP interventions may potentially have greater effects on certain outcomes in patients with antithrombotic treatment than in those without. Despite well-known associations between elevated BP in the acute phase of ICH and poor outcome, large clinical trials have failed to show clear and consistent benefits of acute BP lowering on functional outcome. Delay from symptom onset to treatment may be 1 factor, and patient heterogeneity may be another. The findings from the present study may also suggest that future therapeutic trials of acute BP lowering in ICH could consider stratifying participants by antithrombotic treatment to investigate heterogeneity of effects of BP-lowering treatment and perhaps increase their ability to show

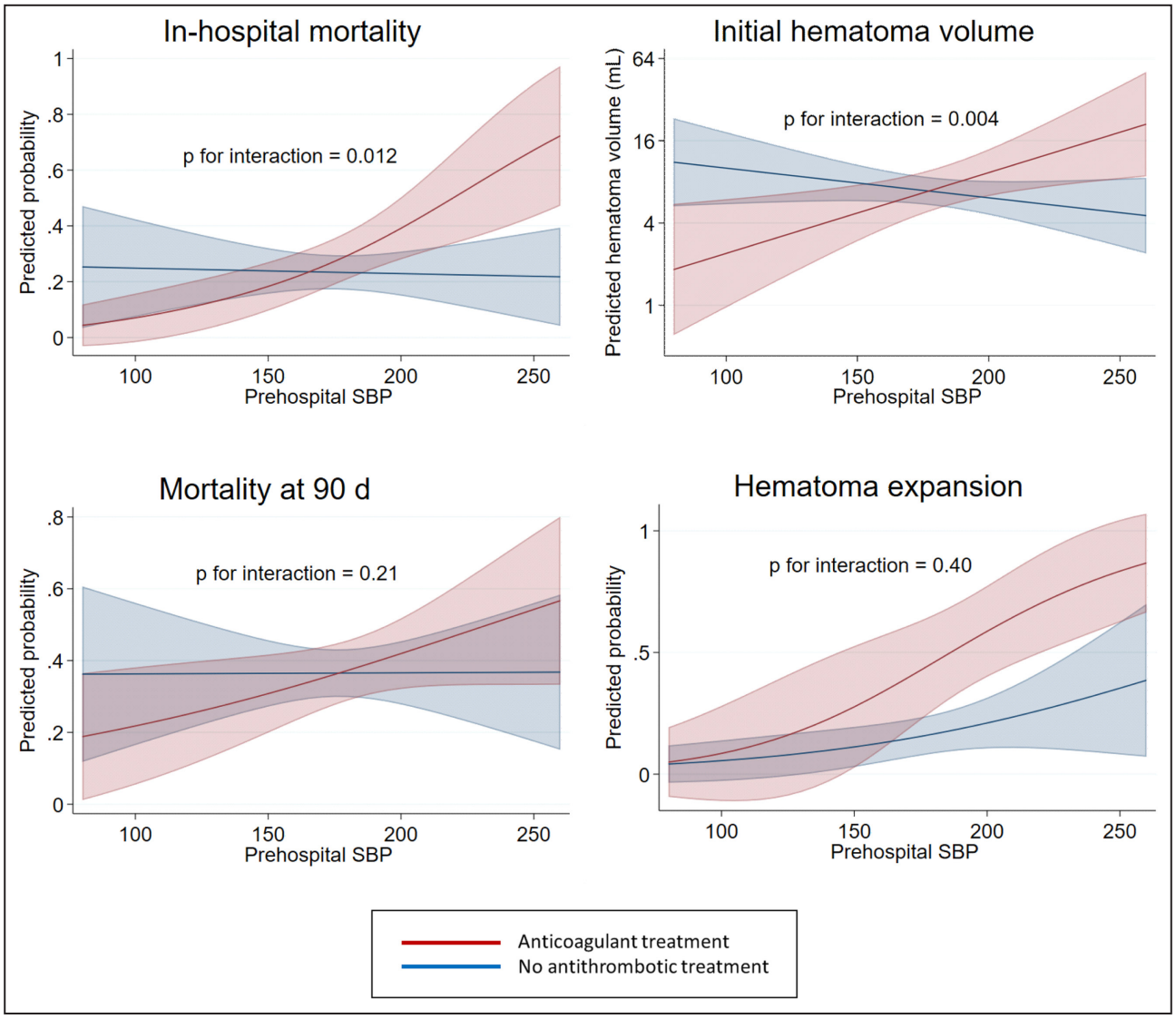

Figure 3. Interactions between anticoagulant treatment and prehospital systolic blood pressure on outcomes.
All analyses were adjusted for age, sex, diabetes, antihypertensive treatment, Glasgow Coma Scale score on admission, modified Rankin Scale score pre-intracerebral hemorrhage, time from symptom onset to admission, and presence of intraventricular blood on the initial computed tomography (all outcomes except initial hematoma volume were also adjusted for acute blood pressure-lowering treatment, and hematoma expansion was also adjusted for initial hematoma volume). SBP indicates systolic blood pressure. Red line=anticoagulant treatment, blue line=no antithrombotic treatment. Red and blue zones indicate upper and lower 95% confidence bounds.

effects. The results seem to be driven mainly by anticoagulant rather than antiplatelet treatment, which suggests that the more potent anticoagulant effect itself modifies the association between prehospital BP and outcomes. This also highlights the relevance of the "care bundle" approach for acute ICH that includes several simultaneous treatment strategies, including both acute BP-lowering treatment and anticoagulant reversal in patients with anticoagulant.[25]

The post hoc analysis from the INTERACT1 and 2 trials assessed effects of early, in-hospital BP lowering in patients with and without antithrombotic treatment (antiplatelet and/or oral anticoagulant drugs).[21] There was no heterogeneity of effects on death or dependency (mRS scores 3–6), or hematoma expansion. However, a low proportion of participants in these studies were on antithrombotic treatment (11%), and patients were younger (62–72 versus 76 years) and more often men (63% versus 52%) compared with the present study. Because of relatively stringent eligibility criteria with exclusion of patients with large hematomas and poor prognosis, the INTERACT studies may not have been completely representative for the general ICH population.

The proportion of patients on antithrombotic treatment in the present study (60%) was larger than in previously described ICH populations,[16] and may reflect the increasing use of antithrombotic drugs in the

general population over recent years.[26] In line with previous knowledge, the present study showed consistent associations between any antithrombotic treatment and poor outcome in crude analyses.[27,28]

Strengths of this study include a relatively large sample size compared with previous studies of prehospital BP in ICH. The observational design with collection of data from 8 years of consecutive admissions in a large primary hospital minimized selection bias. Despite the single-center design, the study population is probably reasonably representative for the general, Norwegian ICH population because of few exclusion criteria. The mortality rates and the distribution of subtypes of antithrombotic treatment indicate an unselected cohort. Although the median hematoma volume in the present study (8.4 mL) was relatively small compared with previous findings,[29] semiautomatic volume estimation methods used are considered more accurate than other methods like the A×B×C/2 formula,[24] and sensitivity analyses of hematoma expansion with exclusion of the smallest hematomas did not alter the results significantly. The other sensitivity analyses also demonstrated robustness of the main findings.

The study also has limitations. The retrospective, observational design increases the risk of confounding, and we can only draw conclusions about associations and not causal relationships. There is also a risk that certain information was not captured despite thorough review of the hospital records. Retrospective scoring of National Institute of Health Stroke Scale and mRS may have introduced bias but was only performed when the available information was considered sufficient for scoring. The single-center design may be a limitation for the generalizability to various ICH populations, particularly in other parts of the world. mRS at 3 months is a widely used outcome measure in stroke, but information about functional outcome at 3 months was too scarce in the hospital records. mRS at discharge was therefore used, although this may not be completely representative for the long-term functional outcome. However, outcome at 3 months was also covered by mortality at 90 days. Information about palliative care early after hospital admission was not collected as a separate variable and these patients could not be excluded from the mortality analyses. Length-of-stay was not recorded. Systematic follow-up BP measurements from the prehospital phase were not available and prehospital BP variability could not be calculated. Associations between prehospital BP and outcomes in ICH may not be linear, but to avoid too complex combinations of exposures, outcomes and effect modifiers, only linear associations were investigated. The power of the present study was too low to investigate heterogeneity by different subtypes of antiplatelet and anticoagulant treatment (eg, ASA versus clopidogrel; direct oral anticoagulant versus VKA). The exploratory nature of the study, which contained multiple tests, increases the risk of chance findings, but the consistent and 1-directional results increase the credibility of the findings.

Limiting hematoma expansion is a promising treatment target. There were no significant associations between prehospital BP and hematoma expansion in the different antithrombotic subgroups in the present study. Follow-up CT was lacking for a considerable number of patients (56%), probably because of poor prognosis in these patients, who were older, more morbid, and had larger initial hematoma volumes. This may have both underpowered and biased the analyses of BP and hematoma expansion, and these results should be interpreted with caution. Associations between hyperacute BP and hematoma expansion stratified by antithrombotic treatment should therefore be investigated further in well-designed prospective studies.

CONCLUSIONS

In patients with acute ICH, antithrombotic treatment modifies associations between prehospital BP and outcomes. Higher prehospital BP is more strongly associated with poor outcome in patients with antithrombotic treatment than in patients without, particularly in patients with anticoagulant treatment. Future studies may consider stratifying patients by antithrombotic treatment when assessing effects of early BP lowering in ICH. For acute ICH patients with a combination of high BP and preceding anticoagulant treatment, further investigation of a “care bundle” targeting both BP lowering and anticoagulant reversal is warranted.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Tables S1–S8.
Figures S1–S3.

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SUPPLEMENTAL MATERIAL

Table S1. Outcomes for the 420 included patients, stratified by antithrombotic treatment at intracerebral hemorrhage occurrence

	Total N=420	Antithrombotic treamtent N=252	No antithrombotic treatment N=168	P
In-hospital mortality, n/N (%)	116/420 (28)	85/252 (34)	31/168 (18)	**<0.001**
mRS 3-6 at discharge, n/N (%)	366/416 (88)	232/250 (93)	134/166 (81)	**<0.001**
Mortality at 90 days, n/N (%)	159/420 (38)	112/252 (44)	47/168 (28)	**<0.001**
Initial hematoma volume (mL), median (IQR)	8.4 (3.2-24.5)	9.2 (3.1-28.6)	7.6 (3.2-20.0)	0.068
Hematoma expansion, n/N (%)	49/183 (27)	36/110 (33)	13/73 (18)	**0.026**

mRS = modified Rankin Scale; IQR = interquartile range. Data are median (IQR) for continuous variables and n/N (%) for categorical variables. Medians were compared by the Mann Whitney U test, proportions by Pearson's chi-squared test. Bold p-values indicate significant differences.

Table S2. Characteristics and outcomes for the 420 patients, stratified by presence of follow-up CT

		Follow-up CT N=183	No follow-up CT N=237	P
Age (years), median (IQR)		74 (64-82)	78 (69-86)	**0.002**
Female, n/N (%)		73/183 (40)	127/237 (54)	**0.005**
Pre-ICH mRS score, n/N (%)				**<0.001**
	0	68/183 (37)	48/236 (20)	
	1	53/183 (29)	59/236 (25)	
	2	31/183 (17)	43/236 (18)	
	3	24/183 (13)	47/236 (20)	
	4	7/183 (4)	36/236 (15)	
	5	0/183 (0)	3/236 (1)	
History of ischemic stroke, n/N (%)		40/182 (22)	52/234 (22)	0.95
Coronary artery disease, n/N (%)		41/183 (22)	41/236 (17)	0.20
Diabetes mellitus, n/N (%)		21/183 (11)	39/237 (16)	0.15
Atrial fibrillation, n/N (%)		39/182 (21)	62/237 (26)	0.26
Using antihypertensive agents, n/N (%)		104/183 (57)	132/230 (57)	0.91
Using antiplatelet drugs, n/N (%)		73/183 (40)	87/234 (37)	0.57
Using anticoagulant drugs, n/N (%)		48/183 (26)	67/235 (29)	0.60
Time from symptom onset to admission, n/N (%)				0.17
	<3 hours	111/183 (61)	122/237 (51)	
	3-6 hours	30/183 (16)	38/237 (16)	
	6-12 hours	21/183 (11)	41/237 (17)	
	12-24 hours	21/183 (11)	36/237 (15)	
Time from symptom onset to CT, n/N (%)				0.086
	<3 hours	101/183 (55)	107/237 (45)	
	3-6 hours	33/183 (18)	39/237 (16)	
	6-12 hours	26/183 (14)	45/237 (19)	
	12-24 hours	23/183 (13)	46/237 (19)	
Prehospital SBP, median (IQR)		180 (160-200)	175 (155-194)	**0.044**
Prehospital DBP, median (IQR)		100 (90-115)	100 (83-110)	**0.033**

GCS on admission, median (IQR)	14 (13-15)	13 (8-15)	**<0.001**
NIHSS on admission, median (IQR)	8 (3-13)	10 (3-18)	**0.007**
Initial hematoma volume (mL), median (IQR)	6.4 (2.2-16.6)	12.7 (4.0-37.2)	**<0.001**
In-hospital mortality, n/N (%)	30/183 (16.4)	86/237 (36.3)	**<0.001**
90 days mortality, n/N (%)	43/183 (23.5)	116/237 (48.9)	**<0.001**
Hematoma location, n/N (%)			**0.004**
Lobar	58/183 (32)	79/237 (33)	
Deep	101/183 (55)	103/237 (43)	
Infratentorial	21/183 (11)	34/237 (14)	
Uncertain	3/183 (2)	21/237 (9)	
Intraventricular blood on initial CT, n/N (%)	29/181 (16)	126/228 (55)	**<0.001**
Acute BP lowering treatment, n/N (%)	130/183 (71)	92/237 (39)	**<0.001**

CT = computed tomography; SBP = systolic blood pressure; DBP = diastolic blood pressure; IQR = interquartile range; mRS = modified Rankin Scale; GCS = Glasgow Coma Scale; NIHSS = National Institute of Health Stroke Scale; BP = blood pressure. Data are median (IQR) for continuous variables and n/N (%) for categorical variables. Medians were compared by the Mann Whitney U test, proportions by Pearson's chi-squared test. Bold p-values indicate significant differences.

Table S3. Sensitivity analyses: Multivariable regression analyses of prehospital systolic and diastolic blood pressure (per 5 mmHg increment) and outcomes **in patients on anticoagulant treatment – additionally adjusted for anticoagulant reversal treatment**

		AC
In-hospital mortality OR (95% CI)	Prehosp SBP	**1.36 (1.11-1.66) N=78**
	Prehosp DBP	**1.29 (1.01-1.65) N=78**
mRS discharge Common OR (95% CI)	Prehosp SBP	**1.14 (1.03-1.27) N=78**
	Prehosp DBP	**1.21 (1.03-1.43) N=78**
Mortality 90 days OR (95% CI)	Prehosp SBP	1.11 (0.98-1.26) N=78
	Prehosp DBP	1.05 (0.86-1.28) N=78
Initial hematoma volume (transf.) Coef (95% CI)	Prehosp SBP Prehosp DBP	N.a.*
Hematoma expansion OR (95% CI)	Prehosp SBP	1.12 (0.90-1.38) N=31
	Prehosp DBP	0.99 (0.74-1.31) N=31

AC = anticoagulant treatment; OR = odds ratio; CI = confidence interval; SBP = systolic blood pressure; DBP = diastolic blood pressure; mRS = modified Rankin Scale. All analyses were adjusted for age, sex, diabetes mellitus, antihypertensive treatment, Glasgow Coma Scale score on admission, mRS pre-ICH, time from symptom onset to admission, presence of intraventricular blood on the initial computed tomography, acute blood pressure lowering treatment, and AC reversal treatment. The outcome hematoma expansion was also adjusted for initial hematoma volume. Bold values indicate significant associations ($p < 0.05$). *Initial hematoma volume was not analysed because AC reversal treatment was given after the initial computed tomography.

Table S4. Sensitivity analyses: Regression analyses of antithrombotic treatment and mortality outcomes – **exclusion of patients who died within the first day, and additional adjustment for surgical intervention (extra-ventricular drainage and/or hematoma evacuation) and do-not-resuscitate order during the hospital stay (including patients receiving palliative care or kept on respiratory support in case organ donation would be the outcome)**

		Any antithrombotic treatment†	AP	AC
In-hospital mortality OR (95% CI)	Crude	**2.12 (1.19-3.76) N=372**	**2.06 (1.09-3.90) N=282**	**2.58 (1.27-5.26) N=228**
	Adjusted*	1.37 (0.59-3.18) N=333	1.38 (0.51-3.76) N=254	1.56 (0.51-4.74) N=205
Mortality at 90 days OR (95% CI)	Crude	**1.88 (1.17-3.00) N=372**	**1.73 (1.02-2.93) N=282**	**2.2 (1.20-4.03) N=228**
	Adjusted*	0.75 (0.34-1.65) N=333	0.60 (0.23-1.55) N=254	0.73 (0.25-2.17) N=205

AP = antiplatelet treatment; AC = anticoagulant treatment; OR = odds ratio. Reference group: No antithrombotic treatment. *Adjusted for age, sex, diabetes mellitus, antihypertensive treatment, Glasgow Coma Scale score on admission, modified Rankin Scale score pre-ICH, time from symptom onset to admission, presence of intraventricular blood on the initial computed tomography, acute blood pressure lowering treatment, surgical intervention, and do-not-rescusitate order. †Any antithrombotic treatment = AP and/or AC. Bold values indicate significant associations ($p < 0.05$).

Table S5. Sensitivity analyses: Multivariable regression analyses of prehospital systolic and diastolic blood pressure (per 5 mmHg increment) and mortality outcomes according to subgroups of antithrombotic treatment, and p for interaction – **exclusion of patients who died within the first day, and additional adjustment for surgical intervention (extraventricular drainage and/or hematoma evacuation) and do-not-resuscitate order during the hospital stay (including patients receiving palliative care or kept on respiratory support in case organ donation would be the outcome)**

		No anti-thrombotic treatment (ref.)	Any anti-thrombotic treatment*	P for interaction: Any anti-thrombotic treatment and BP	AP	P for interaction: AP and BP	AC	P for interaction: AC and BP
In-hospital mortality OR (95% CI)	Prehosp SBP	0.85 (0.72-1.01) N=142	**1.10 (1.01-1.19) N=191**	**0.011 N=333**	1.03 (0.91-1.16) N=112	**0.021 N=254**	**1.21 (1.01-1.45) N=63**	**0.019 N=205**
	Prehosp DBP	0.90 (0.73-1.10) N=142	**1.14 (1.01-1.29) N=190**	0.055 N=332	1.12 (0.93-1.33) N=111	0.068 N=253	**1.48 (1.04-2.11) N=63**	0.076 N=205
Mortality 90 days OR (95% CI)	Prehosp SBP	0.92 (0.80-1.05) N=142	1.00 (0.93-1.08) N=191	0.38 N=333	1.01 (0.91-1.13) N=112	0.23 N=254	0.99 (0.85-1.14) N=63	0.65 N=205
	Prehosp DBP	0.94 (0.81-1.09) N=142	1.02 (0.91-1.14) N=190	0.41 N=332	1.01 (0.86-1.19) N=111	0.28 N=253	0.98 (0.78-1.24) N=63	0.62 N=205

AP = antiplatelet treatment; AC = anticoagulant treatment; OR = odds ratio; CI = confidence interval; SBP = systolic blood pressure; DBP = diastolic blood pressure. Reference group: No antithrombotic treatment. All analyses were adjusted for age, sex, antihypertensive treatment, Glasgow Coma Scale score on admission, modified Rankin Scale score pre-ICH, time from symptom onset to admission, presence of intraventricular blood on the initial computed tomography, acute blood pressure lowering treatment, surgical intervention, and do-not-resuscitate order. Diabetes mellitus was removed from the model because this variable predicted outcomes perfectly. *Any antithrombotic treatment = AP and/or AC. Bold values indicate significant associations ($p < 0.05$).

Table S6. Sensitivity analyses: Regression analyses of antithrombotic treatment and hematoma expansion – **exclusion of patients who arrived in hospital more than six hours after symptom onset, and inclusion of new intraventricular blood on follow-up CT and in-hospital mortality to the definition of hematoma expansion**

		Any antithrombotic treatment†	AP	AC
Hematoma expansion, new definition OR (95% CI)	Crude	**1.95 (1.08-3.52) N=194**	1.45 (0.75-2.81) N=141	**3.17 (1.36-7.36) N=109**
	Adjusted*	1.91 (0.77-4.72) N=173	1.86 (0.67-5.13) N=126	**4.10 (1.02-16.46) N=96**

AP = antiplatelet treatment; AC = anticoagulant treatment; OR = odds ratio; CT = computed tomography. Reference group: No antithrombotic treatment. *Adjusted for age, sex, diabetes mellitus, antihypertensive treatment, Glasgow Coma Scale score on admission, modified Rankin Scale score pre-ICH, time from symptom onset to admission, presence of intraventricular blood on the initial CT, acute blood pressure lowering treatment, and initial hematoma volume. †Any antithrombotic treatment = AP and/or AC. Bold values indicate significant associations ($p < 0.05$).

Table S7. Sensitivity analyses: Multivariable regression analyses of prehospital systolic and diastolic blood pressure (per 5 mmHg increment) and hematoma expansion according to subgroups of antithrombotic treatment, and p for interaction – **exclusion of patients who arrived in hospital more than six hours after symptom onset, and inclusion of new intraventricular blood on follow-up CT and in-hospital mortality to the definition of hematoma expansion**

		No anti-thrombotic treatment (ref.)	Any anti-thrombotic treatment*	P for interaction: Any anti-thrombotic treatment and BP	AP	P for interaction: AP and BP	AC	P for interaction: AC and BP
Hematoma expansion, new definition OR (95% CI)	Prehosp SBP	1.00 (0.93-1.08) N=71	1.02 (0.96-1.08) N=123	0.75 N=194	0.99 (0.92-1.06) N=70	0.77 N=141	1.08 (0.96-1.22) N=38	0.29 N=109
	Prehosp DBP	0.99 (0.88-1.11) N=71	1.05 (0.96-1.14) N=121	0.55 N=192	1.04 (0.94-1.16) N=68	0.54 N=139	1.19 (0.95-1.49) N=38	0.20 N=109

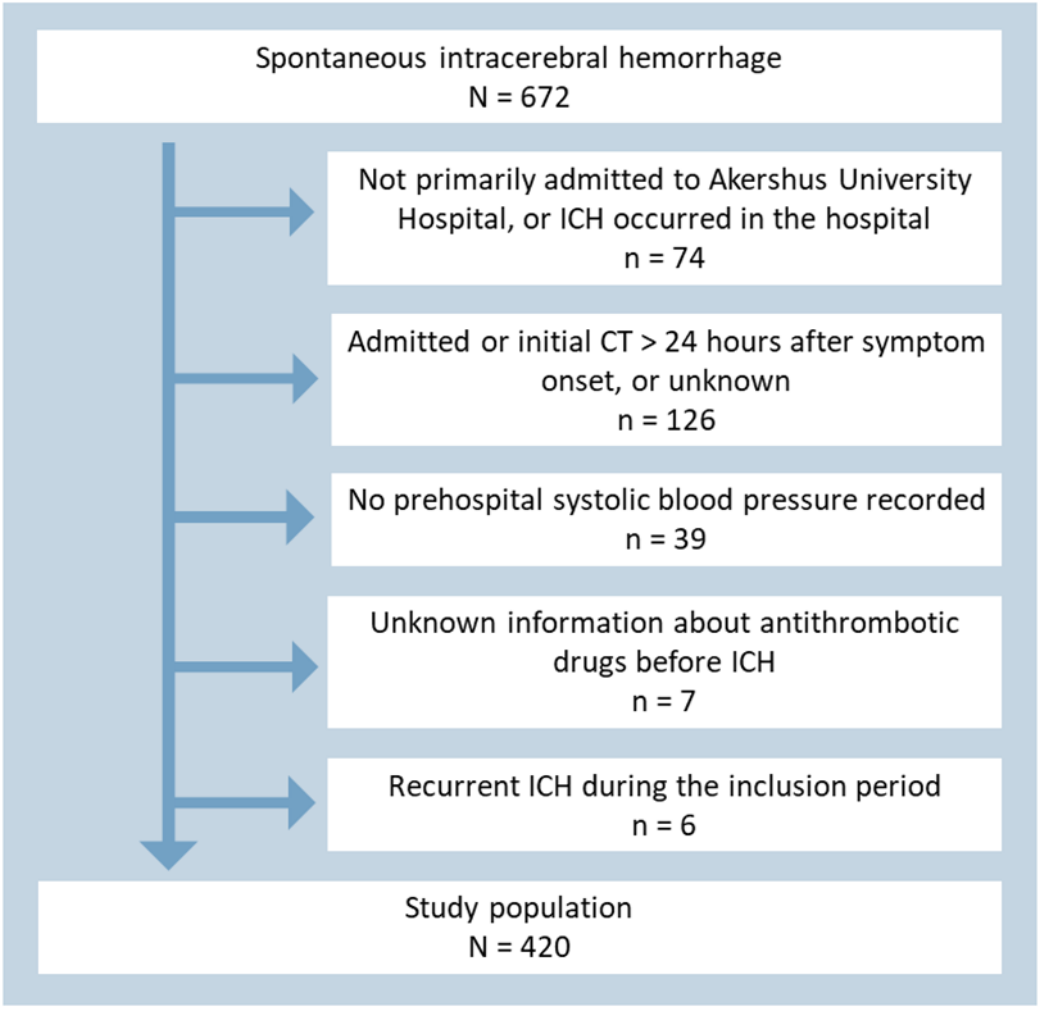
CT = computed tomography; AP = antiplatelet treatment; AC = anticoagulant treatment; OR = odds ratio; CI = confidence interval; SBP = systolic blood pressure; DBP = diastolic blood pressure. Reference group: No antithrombotic treatment. Due to small sample size, the analyses were only adjusted for age and sex. *Any antithrombotic treatment = AP and/or AC.

Table S8. Sensitivity analyses: Multivariable regression analyses of prehospital systolic and diastolic blood pressure (per 5 mmHg increment) and hematoma expansion according to subgroups of antithrombotic treatment, and p for interaction – **exclusion of patients with the lowest quartile of hematoma volumes**

		No anti-thrombotic treatment (ref.)	Any anti-thrombotic treatment*	P for interaction: Any anti-thrombotic treatment and BP	AP	P for interaction: AP and BP	AC	P for interaction: AC and BP
Hematoma expansion OR (95% CI)	Prehosp SBP	1.02 (0.92-1.14) N=52	1.08 (1.00-1.16) N=74	0.60 N=126	1.02 (0.92-1.14) N=47	0.91 N=99	1.10 (0.92-1.31) N=21	0.22 N=73
	Prehosp DBP	1.08 (0.92-1.28) N=52	1.11 (0.99-1.25) N=73	0.68 N=125)	1.12 (0.95-1.33) N=46	0.96 N=98	1.07 (0.86-1.34) N=21	0.67 N=73

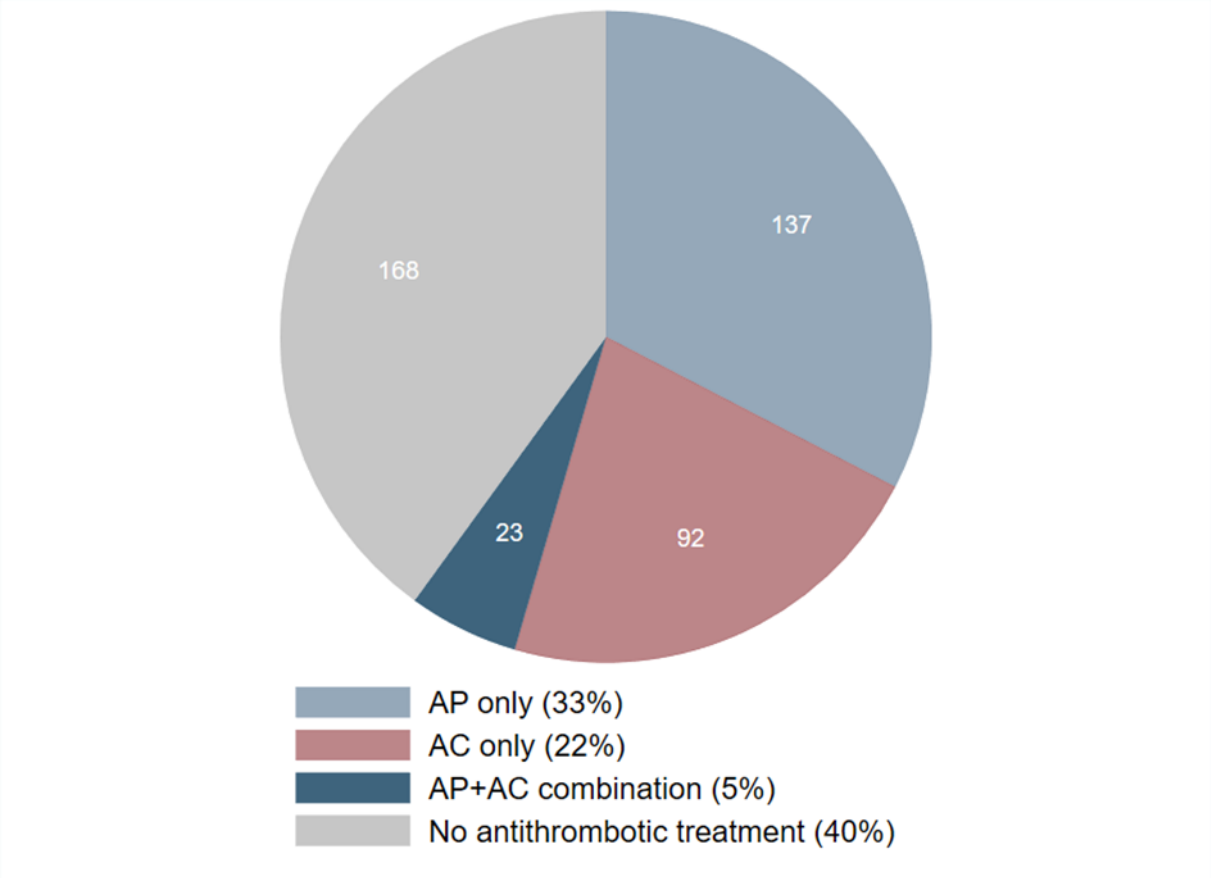
AP = antiplatelet treatment; AC = anticoagulant treatment; OR = odds ratio; CI = confidence interval; SBP = systolic blood pressure; DBP = diastolic blood pressure. Reference group: No antithrombotic treatment. Due to small sample size, the analyses were only adjusted for age and sex. *Any antithrombotic treatment = AP and/or AC.

Figure S1. Flow chart of patient inclusion



ICH = intracerebral hemorrhage; CT = computed tomography.

Figure S2. Types of antithrombotic drugs used at the time of intracerebral hemorrhage occurrence (n/420)



AP = antiplatelet drugs; AC = anticoagulant drugs.

Figure S3. Distribution of modified Rankin Scale scores at discharge for patients without (N=166) and with (N=250) antithrombotic treatment at intracerebral hemorrhage occurrence