Original Investigation

Anticoagulant Reversal, Blood Pressure Levels, and Anticoagulant Resumption in Patients With Anticoagulation-Related Intracerebral Hemorrhage

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IMPORTANCE Although use of oral anticoagulants (OACs) is increasing, there is a substantial lack of data on how to treat OAC-associated intracerebral hemorrhage (ICH).

OBJECTIVE To assess the association of anticoagulation reversal and blood pressure (BP) with hematoma enlargement and the effects of OAC resumption.

DESIGN, SETTING, AND PARTICIPANTS Retrospective cohort study at 19 German tertiary care centers (2006-2012) including 1176 individuals for analysis of long-term functional outcome, 853 for analysis of hematoma enlargement, and 719 for analysis of OAC resumption.

EXPOSURES Reversal of anticoagulation during acute phase, systolic BP at 4 hours, and reinitiation of OAC for long-term treatment.

MAIN OUTCOMES AND MEASURES Frequency of hematoma enlargement in relation to international normalized ratio (INR) and BP. Incidence analysis of ischemic and hemorrhagic events with or without OAC resumption. Factors associated with favorable (modified Rankin Scale score, 0-3) vs unfavorable functional outcome.

RESULTS Hemorrhage enlargement occurred in 307 of 853 patients (36.0%). Reduced rates of hematoma enlargement were associated with reversal of INR levels <1.3 within 4 hours after admission (43/217 [19.8%]) vs INR of ≥1.3 (264/636 [41.5%]; $P < .001$) and systolic BP <160 mm Hg at 4 hours (167/504 [33.1%]) vs ≥160 mm Hg (98/187 [52.4%]; $P < .001$). The combination of INR reversal <1.3 within 4 hours and systolic BP of <160 mm Hg at 4 hours was associated with lower rates of hematoma enlargement (35/193 [18.1%] vs 220/498 [44.2%] not achieving these values; OR, 0.28; 95% CI, 0.19-0.42; $P < .001$) and lower rates of in-hospital mortality (26/193 [13.5%] vs 103/498 [20.7%]; OR, 0.60; 95% CI, 0.37-0.95; $P = .03$). OAC was resumed in 172 of 719 survivors (23.9%). OAC resumption showed fewer ischemic complications (OAC: 9/172 [5.2%] vs no OAC: 82/547 [15.0%]; $P < .001$) and not significantly different hemorrhagic complications (OAC: 14/172 [8.1%] vs no OAC: 36/547 [6.6%]; $P = .48$). Propensity-matched survival analysis in patients with atrial fibrillation who restarted OAC showed a decreased HR of 0.258 (95% CI, 0.125-0.534; $P < .001$) for long-term mortality. Functional long-term outcome was unfavorable in 786 of 1083 patients (72.6%).

CONCLUSIONS AND RELEVANCE Among patients with OAC-associated ICH, reversal of INR <1.3 within 4 hours and systolic BP <160 mm Hg at 4 hours were associated with lower rates of hematoma enlargement, and resumption of OAC therapy was associated with lower risk of ischemic events. These findings require replication and assessment in prospective studies.

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The prevalence of cardiovascular diseases requiring long-term oral anticoagulation (OAC) is increasing, notably the incidence and prevalence of atrial fibrillation.[1,2] The most significant complication of OAC is intracerebral hemorrhage (ICH).[3] Based on OAC-induced coagulopathy, large hematoma volumes and increased rates of hematoma enlargement are characteristics of OAC-associated ICH (OAC-ICH) and contribute to an even higher mortality when compared with ischemic stroke or primary ICH.[4-7]

Among all stroke subtypes is a substantial lack of data about how to manage OAC-ICH.[8] Current European Stroke Organisation guidelines, World Stroke Organization reviews, and American Heart Association Stroke Council recommendations only provide Level C evidence and Class II recommendations regarding treatment of OAC-ICH.[3,9,10] Two of the most pressing unsettled questions are how to prevent hematoma enlargement and how to manage anticoagulation in the long-term.[8,11] Consensus exists that elevated international normalized ratio (INR) levels should be reversed to minimize hematoma enlargement, yet mode, timing, and extent of INR reversal are unclear.[3,9,10] Valid data on safety and clinical benefit of OAC resumption are missing and remain to be established.[11]

This study investigated (1) the relationship between anticoagulation reversal and blood pressure with hematoma enlargement and (2) the association of restarting anticoagulation with incidence of hemorrhagic and ischemic complications with outcomes among patients with OAC-ICH.

Methods

We chose a retrospective observational study design, and 19 tertiary care centers across Germany participated (7 university hospitals and 12 university-affiliated community hospitals; eFigure 1 in the Supplement). We collected data from all consecutive adult patients with spontaneous ICH (*International Statistical Classification of Diseases, Tenth Revision* coding: I61.xx) related to anticoagulation admitted to neurological departments between the years 2006 and 2010 with a 1-year follow-up period ending in January 2012. Specifically, the definition of OAC-ICH required effective use of vitamin K antagonists with an INR value of greater than 1.5 on hospital admission.[12] We excluded ICH patients with secondary etiologies, ie, ICH related to trauma, tumor, arteriovenous malformation, aneurysmal subarachnoid hemorrhage, acute thrombolysis, or other coagulopathies. Informed consent was obtained from all patients, legal representatives, or closest relatives. Institutional review boards of all participating centers approved the study based on the central vote from the ethics committee at the University of Erlangen-Nuremberg. The study was titled RETRACE (German-wide Multicenter Analysis of Oral Anticoagulation-associated Intracerebral Hemorrhage) and was conducted on behalf of IGNITE (Initiative of German Neurointensive Trial Engagement). **Figure 1** provides an overview of our 3-tiered analyses.

Data Acquisition

We extracted data on demographics, prior comorbidities, in-hospital parameters, and laboratory data through review of patients' medical records and institutional prospective databases (see the eMethods in the Supplement for a detailed list of parameters and definitions). Review of medical records and emergency protocols determined neurological status consisting of Glasgow Coma Scale (GCS), National Institutes of Health Stroke Scale (NIHSS), and ICH score. The $CHADS_2$ and HAS-BLED were scored as appropriate.[13,14] After the end of the study follow-up, we conducted retrospective data evaluation, which was controlled by repeated visits (≥2) of all participating centers.

We obtained follow-up data on mortality, functional outcome, long-term treatment, and complications by mailed questionnaires and—if not returned or incomplete—by semiquantitative telephone interviews. Two scale-trained physicians, certified for data collection on disability and quality of life, performed the interviews. In situations of missing contact information, a local registry office inquiry was carried out to complete outcome assessment. Cross-checking of centralized data with existing local prospective stroke registries and rehabilitation facility reports ensured data integrity.

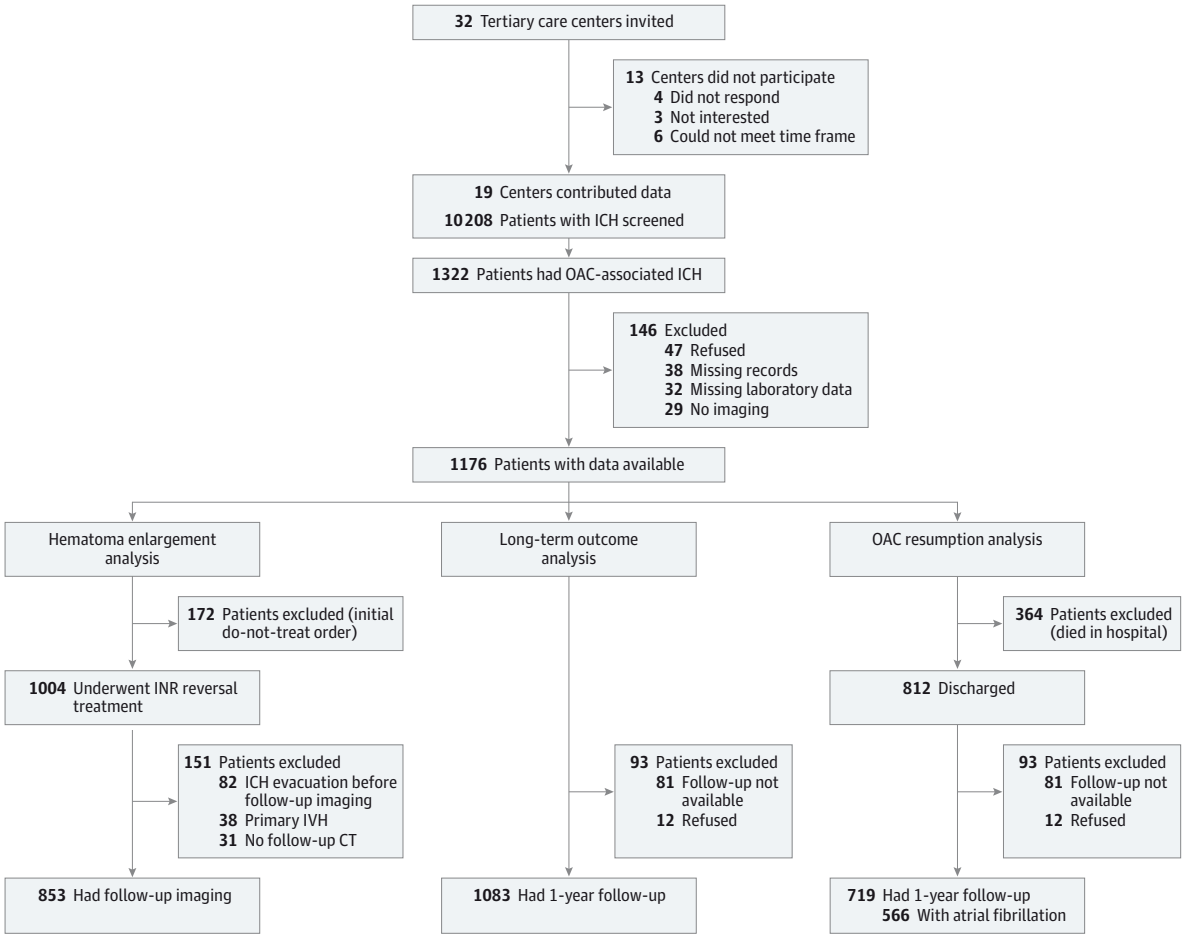
Data Synthesis and Analysis

Hematoma Enlargement

We analyzed hematoma enlargement in relation to INR reversal and blood pressure. Hematoma enlargement was defined as a relative parenchymal volume increase of more than 33% from initial to follow-up imaging.[15] We used this conservative threshold, as used in various trials,[16,17] to exclude false-positive scoring due to technical variability in computed tomography imaging.[15] We evaluated all available computed tomography and magnetic resonance imaging scans of each patient and calculated parenchymal ICH volume according to hematoma shape, as previously described (ABC/2 and ABC/3).[18,19] When comparing different imaging modalities, we used validated conversion models for precise volume calculation.[20] Intraventricular hemorrhage was recorded and its extent scored by the Graeb score summation.[21]

We recorded all different agents and dosages used for INR reversal as well as timing and extent of achieved INR levels. Reversal treatment consisted of prothrombin complex concentrates ([PCCs] 4-factor concentrate, containing coagulation factors II, VII, IX, and X as well as protein C and S),[22] fresh-frozen plasma (FFP), antithrombin, and intravenous vitamin K—eventually in combinations. The first INR value obtained after initiation of reversal treatment is referred to as first INR monitoring after reversal throughout the article. Specifically, we evaluated all available laboratory results of coagulation parameters for 72 hours after admission and chose laboratory accessioning times as data points for monitoring of serial INR values. For accuracy of data on INR reversal, the initial laboratory parameters for transferred patients were retrieved from referring hospitals. For the association of hematoma enlargement with blood pressure, we recorded mean arterial blood pressure and systolic and diastolic blood pressures in 4-hour intervals from admission for 24 hours.

Figure 1. Flow Diagram of Participating Centers, Study Participants, and 3-Tiered Analyses



Hematoma enlargement (analysis n = 853) was defined as a relative volume increase >33% on follow-up imaging. Overall, 160 patients received surgical hematoma evacuation; of these, we included 78 patients with follow-up imaging before surgery and excluded 82 patients without follow-up imaging before surgery. Analysis of functional long-term outcome included all the patients in the study (n = 1176). Long-term outcome was assessed at 1 year. Analysis of oral anticoagulation (OAC) resumption (n = 719) compared surviving patients who restarted OAC vs patients who did not restart OAC. CT indicates computer tomography; ICH, intracerebral hemorrhage; INR, international normalized ratio; IVH, intraventricular hemorrhage. (For details on center selection, see eFigure 1 in the Supplement.)

OAC Resumption

Among all patients surviving acute hospitalization, we compared patients who restarted anticoagulation (referred to as OAC resumption) with patients not receiving anticoagulation (referred to as no OAC resumption). Specifically, antithrombotic therapy used exclusively vitamin K antagonists (there was no approval of thrombin and factor Xa inhibitors for stroke prevention in Germany before the end of 2011) or no oral anticoagulants (antiplatelet agents, low-dose heparins, or no pharmacological treatment). For all patients, starting time point (in days) and mode of antithrombotic treatment were recorded. Patients were counted as having resumed OAC at the time of restarted OAC or if they received active heparinization before OAC resumption.

Resumption analysis included noting during the 1-year follow-up any new ischemic events, classified as either cerebral (ischemic stroke including transient ischemic attacks) or noncerebral. The latter included peripheral arterial emboli in lungs, gastrointestinal organs, or extremities and myocardial infarction.[23] Recurrent hemorrhagic events were recorded as either cerebral-parenchymal or extracranial bleedings. Extracerebral hemorrhages included gastrointestinal, intraocular, and intramuscular hemorrhage and hematuria.[23] Complications, either ischemic or hemorrhagic, were noted when requiring hospitalization.

Long-term Functional Outcome

Functional outcome was evaluated using the modified Rankin Scale (mRS) at discharge, 3 months (short-term), and 1 year (long-term). We distinguished favorable functional outcome (mRS = 0-3) from unfavorable functional outcome (mRS = 4-6).[24] For analysis of overall mortality, we censored patients who were alive at the end of the study period or recorded cause and time of death.

Statistical Analysis

Analyses of hematoma enlargement used multivariable regression analysis to identify associated parameters, which were prioritized for consecutive analysis according to relative risk ratio (RR). First, receiver operating characteristics determined the highest Youden index of the best INR cut point to prevent hematoma enlargement.[25] Second, we assessed optimal timing of INR reversal by analyzing categorized frequency distributions over selected INR and time intervals. We calculated an univariate logistic regression model using generalized estimating equations[26] to examine the association of INR reversal with hematoma enlargement over time. Generated odds ratio (OR) estimates for various time points after initiation of reversal treatment were weighted according to available patient data and smoothed by the method of moving averages to correct for overestimation.[27] Third, we investigated associations of systolic blood pressure with hematoma enlargement. We categorized blood pressure in 20-mm Hg intervals (range, <120-≥180 mm Hg) assessed (at 4-hour intervals) from time of hospital admission for 24 hours. To display the combined associations of timing and extent of INR reversal and systolic blood pressure with hematoma enlargement, we used multivariable regression analysis adjusting for associated covariates (forest plot adjusted for covariates).

Analyses of OAC resumption consisted of graphical displays comparing patients who restarted OAC vs no OAC for ischemic and hemorrhagic events of the entire cohort. Further analyses of OAC resumption were solely based on patients with atrial fibrillation. To minimize confounding by indication, we performed propensity score matching using the balanced, parallel, variable ratio (1:n) nearest-neighbor approach.[28] The propensity score was calculated from parameters showing statistical associations ($P < .10$) with OAC resumption. Propensity-matched survival, displayed using the Kaplan-Meier method, was compared using log-rank, Breslow, and Tarone-Ware tests. Crude event and incidence rates (per 100 patient-years) for new ischemic and recurrent hemorrhagic strokes were calculated for all individuals and their total number of days receiving target therapy (OAC vs no OAC) until 1-year follow-up. To assess hazard ratios (HRs) for patients who restarted OAC for long-term mortality, we performed unadjusted and adjusted Cox regression analyses for the propensity-matched cohort of patients with atrial fibrillation; variables met assumption of proportionality.[28]

To identify parameters independently associated with functional long-term outcome, we calculated 3 log-binomial regression models: to describe improvement to favorable outcome for patients discharged with mRS of 4 and 5 and to display associations with unfavorable functional outcome for both the unmatched entire cohort as well as for the propensity-matched atrial fibrillation cohort.

For outcome analyses, we considered multiple imputation analyses calculated with all parameters available, ie, baseline characteristics, neurological status, imaging, in-hospital measures, and follow-up measures. Nevertheless, after careful evaluation of missing and auxiliary data for multiple imputation analyses, we decided to conduct complete case analyses for OAC resumption and long-term outcome.[29]

For statistical analyses, we used SPSS version 20.0 and R version 2.12.0. Statistical tests were 2-sided, and the significance level was set at $\alpha = .05$ and consequently corrected for multiple comparisons by the Bonferroni method (eMethods in the Supplement).

Results

Our study cohort consisted of 1176 patients with a complete primary data set. The study cohort was selected from screening of 10 208 consecutive patients with ICH, of whom 1322 patients had OAC-ICH (period prevalence rate of 13.0%). Details about the excluded patients (n = 146) are provided in Figure 1. Patients with OAC-ICH had a mean (SD) age of 74.1 (9.2) years, a median initial ICH volume of 19.3 cm^3 (interquartile range [IQR],6.9-52.8), and a median INR level at time of hospital admission of 2.77 (IQR, 2.28-3.50). Based on the number of patients and their epidemiological, neurological, and radiological profile (eTable 1 in the Supplement), our cohort was representative of patients with OAC-ICH.[11,12,30]

Hematoma Enlargement

A total of 853 patients were eligible for analysis of hematoma enlargement (Figure 1). Hematoma enlargement occurred in 307 of 853 patients (36.0%), with a median volume increase of 14.0 cm^3 (IQR, 4.7-36.8), and secondary intraventricular hemorrhage in 76 of 307 patients (24.8%) (**Table 1**). Hematoma enlargement rates were time-dependent and occurred more often in patients admitted earlier (median split onset to initial imaging; hematoma enlargement in 137/271 [50.6%] with early imaging [<130 minutes] vs 95/278 [34.2%] with late imaging [≥130 min]; $P < .001$). When comparing patients with and without hematoma enlargement, there was no difference with respect to initial INR or agents used for its reversal. We noted that PCCs reversed elevated INR levels to a greater extent (absolute median INR reversal using PCCs, 1.45 [IQR, 0.97-2.10] vs FFP, 0.36 [IQR, 0.04-0.86]; $P < .001$); however, sample size (of patients with FFP only) was too small to draw firm conclusions regarding efficacy (**Table 2**). Multivariable adjustments showed that shorter duration from symptom onset to imaging (RR, 2.284; 95% CI, 1.445-2.949; $P < .001$), longer duration from diagnosis until treatment (RR, 1.559; 95% CI, 1.142-2.130; $P = .005$), deep ICH location (RR, 1.389; 95% CI, 1.012-1.905; $P = .04$), INR levels at first INR monitoring after reversal (RR, 2.294; 95% CI, 1.282-4.098; $P = .005$), systolic blood pressure at 4 hours (RR, 1.007; 95% CI, 1.002-1.014; $P = .02$), and history of coronary artery disease (RR, 1.531; 95% CI, 1.018-2.092; $P = .007$) were associated with hematoma enlargement (eTable 2 in the Supplement). Hence, there were 3 parameters susceptible to modification: time until initiation of INR reversal, extent of INR reversal, and systolic blood pressure.

We used 2 approaches to identify the "optimal" timing and extent of INR reversal. First, receiver operating characteristics analysis provided an INR value less than 1.3 with the strongest positive association to prevent hematoma enlargement (area under the curve, 0.636; 95% CI, 0.596-0.676; $P < .001$;

Table 1. Clinical Characteristics of Patients With and Without Hematoma Enlargement[a]

Patients With Follow-up Imaging (n = 853)	With Hematoma Enlargement (n = 307)	Without Hematoma Enlargement (n = 546)	*P* Value
Age, mean (SD), y	72.8 (9.9)	74.1 (8.6)	.07
Female sex, No. (%)	107 (34.9)	216 (39.6)	.17
Prior comorbidities, No. (%)			
Hypertension	273 (88.9)	462 (84.6)	.08
Diabetes mellitus	91 (29.6)	167 (30.6)	.78
Dyslipidemia	81 (26.4)	168 (30.8)	.18
Prior stroke	89 (29.0)	162 (29.7)	.84
Coronary artery disease	154 (50.2)	225 (41.2)	.01[b]
Congestive heart failure	34 (11.1)	74 (13.6)	.30
Abnormal kidney function	80 (26.1)	153 (28.0)	.54
Abnormal liver function	6 (2.0)	11 (2.0)	.84
Antiplatelet medication	31 (10.1)	52 (9.5)	.79
OAC indications, No. (%)			
Atrial fibrillation	235 (76.5)	429 (78.6)	.49
Mechanical heart valve	32 (10.4)	35 (6.4)	.04[b]
Pulmonary embolism	11 (3.6)	26 (4.8)	.42
Deep vein thrombosis	12 (3.9)	22 (4.0)	.92
Other indications	17 (5.5)	34 (6.2)	.68
$CHADS_2$ score[c]			
Mean (SD)	2.5 (1.2)	2.6 (1.2)	
Median (IQR)	2 (2-3)	2 (2-3)	.55
High risk (≥2), No. (%)	183 (77.8)	353 (82.3)	.17
HAS-BLED score[d]			
Mean (SD)	3.2 (1.1)	3.0 (1.1)	
Median (IQR)	3 (2-4)	3 (2-4)	.28
High risk (≥3), No. (%)	166 (70.6)	297 (69.2)	.71
Admission status, median (IQR)			
Glasgow Coma Scale[e]	14 (12-15)	14 (12-15)	.16
NIHSS[f]	14 (6-18)	9 (4-16)	<.001
ICH score[g]	1 (0-2)	1 (0-2)	.75
Initial imaging			
Deep ICH, No. (%)	173 (56.4)	233 (42.7)	<.001
Lobar ICH, No. (%)	95 (30.9)	229 (41.9)	.001[b]
Cerebellar ICH, No. (%)	25 (8.1)	71 (13.0)	.03[b]
Brainstem ICH, No. (%)	14 (4.6)	13 (2.4)	.08
Left hemisphere, No. (%)	146 (47.6)	275 (50.4)	.43
ICH volume, median (IQR), cm^3	13.5 (5.0-27.6)	12.1 (5.3-26.9)	.45
Intraventricular hemorrhage, No. (%)	94 (30.6)	190 (34.8)	.21
Graeb score, median (IQR)[h]	4 (2-6)	4 (2-7)	.95
Follow-up imaging			
Time to control CT, median (IQR), h	13 (5-25)	20 (9-31)	<.001
ICH volume, median (IQR), cm^3	29.7 (12.0-72.5)	12.5 (5.2-27.2)	<.001
ICH volume increase, median (IQR), cm^3	14.0 (4.7-36.8)	0.5 (0.1-1.8)	<.001
New IVH, No. (%)	76 (24.8)	27 (4.9)	<.001
Graeb score, median (IQR)	5 (3-8)	4 (2-6)	<.001
Time windows, median (IQR), min			
Symptom onset to imaging	104 (70-179)	143 (87-266)	<.001
Symptom onset to treatment	218 (150-349)	230 (144-420)	.35
Admission to treatment	117 (64-234)	103 (62-186)	.08
Diagnosis to treatment	95 (44-180)	70 (36-133)	.001

(continued)

Table 1. Clinical Characteristics of Patients With and Without Hematoma Enlargement[a] (continued)

Patients With Follow-up Imaging (n = 853)	With Hematoma Enlargement (n = 307)	Without Hematoma Enlargement (n = 546)	*P* Value
Mode of reversal treatment			
PCC, median (IQR), IU	2000 (1200-2400)	2000 (1200-2400)	.53
PCC + vitamin K, No. (%)	192 (62.5)	359 (65.8)	.35
PCC only, No. (%)	42 (13.7)	57 (10.4)	.16
PCC + FFP + vitamin K, No. (%)	19 (6.2)	40 (7.3)	.53
PCC + combinations, No. (%)	15 (4.9)	35 (6.4)	.36
FFP only, No. (%)	5 (1.6)	6 (1.1)	.54
Vitamin K only, No. (%)	34 (11.1)	49 (9.0)	.31
Initial coagulation parameters, median (IQR)			
INR	2.80 (2.30-3.41)	2.68 (2.23-3.38)	.13
PTT, s	43 (37-50)	41 (36-49)	.13
Serial monitoring of coagulation parameters, median (IQR)			
INR after reversal[i]	1.38 (1.20-1.71)	1.27 (1.16-1.44)	<.001
PTT after reversal, s[i]	34 (31-39)	33 (30-38)	.32
INR at 24 h	1.30 (1.20-1.44)	1.23 (1.13-1.48)	<.001
INR at 48 h	1.23 (1.14-1.38)	1.20 (1.10-1.31)	.002[b]
INR at 72 h	1.23 (1.13-1.40)	1.19 (1.10-1.30)	.001[b]
Laboratory values, median (IQR)			
Hemoglobin, g/L	137 (120-149)	140 (125-153)	.02[b]
Hematocrit	0.41 (0.37-0.44)	0.42 (0.38-0.45)	.11
Thrombocytes, 10^9/L	199 (166-241)	202 (170-248)	.25
Leukocytes, 10^9/L	8.1 (6.2-9.7)	8.5 (6.8-10.2)	.01[b]
Blood pressure, mean (SD), mm Hg			
Admission systolic	172 (31)	168 (30)	.12
Admission mean arterial	119 (21)	116 (21)	.09
Admission diastolic	92 (18)	91 (18)	.30
4-h Systolic	153 (28)	139 (23)	<.001
4-h Mean arterial	103 (22)	93 (17)	.01[b]
4-h Diastolic	79 (19)	71 (15)	.002[b]
8-h Systolic	142 (25)	138 (22)	.17
8-h Mean arterial	94 (18)	91 (16)	.27
8-h Diastolic	71 (16)	68 (15)	.06
12-h Systolic	141 (24)	138 (23)	.37
12-h Mean arterial	93 (18)	92 (16)	.93
12-h Diastolic	70 (16)	69 (15)	.32
16-h Systolic	142 (23)	140 (22)	.50
16-h Mean arterial	94 (15)	93 (16)	.61
16-h Diastolic	71 (17)	70 (15)	.57

Abbreviations: CT, computed tomography; FFP, fresh-frozen plasma; ICH, intracerebral hemorrhage; INR, international normalized ratio; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; OAC, oral anticoagulation; PCC, prothrombin complex concentrates; PTT, partial thromboplastin time.

[a] Hematoma enlargement was defined as volume increase >33% on follow-up imaging.

[b] Not significant after Bonferroni correction (corrected significance level $P < .00104$).

[c] $CHADS_2$ score range, 0-6, from low to high risk of thromboembolism.

[d] HAS-BLED score range, 0-9, from low to high risk of bleeding complication under OAC.

[e] Glasgow Coma Scale range, 3-15, from deep coma to alert.

[f] NIHSS range, 0-40, from no deficit to severe neurological deficit (42 = maximum sum, but for comatose patient, ataxia is not scored).

[g] ICH score range, 0-6, from low to high risk of mortality.

[h] Graeb score of ventricular involvement range, 0-12, from no intraventricular blood to tamponade of all ventricles.

[i] Indicates first value of serial monitoring of coagulation parameters after initiation of reversal treatment.

Youden index: 0.228). Second, investigating different INR levels confirmed that patients reaching INR below 1.3 showed significantly fewer rates of hematoma enlargement (INR <1.3: 116/432 [26.9%] vs INR ≥1.3: 191/421 [45.4%]; $P < .001$). Specifically, we noted a significant relationship between timing and extent of INR reversal with frequency and relative risk of hematoma enlargement (INR levels <1.3 within 4 hours after admission: 43/217 [19.8%] vs INR ≥1.3 not within 4 hours: 264/636 [41.5%]; $P < .001$) (eTable 3 in the Supplement). To investigate associations of optimal timing for INR reversal (<1.3) with hematoma enlargement, we calculated an estimated OR model (**Figure 2**).[26] Reduced hematoma enlargement was observed until 4 hours and 13 minutes (95% CI intercepts 1) with an unadjusted pooled OR of 0.37 (95% CI, 0.24-0.67; $P < .001$) (Figure 2). We did not observe an additional benefit of reaching INR less than 1.2. Thus, our data indicate that INR reversal to values below 1.3 achieved within 4 hours was associated with fewest rates of hematoma enlargement.

The association of blood pressure with hematoma enlargement is shown in eTable 4 in the Supplement. Systolic blood pressure values of 160 mm Hg or greater assessed 4 hours after admission showed increased rates of hematoma enlargement (<160 mm Hg: 167/504 [33.1%] vs ≥160 mm Hg: 98/187 [52.4%]; $P < .001$). To investigate the additional importance of systolic

blood pressure, we performed 3 adjusted multivariable analyses taking into account all 5 nonmodifiable parameters associated with hematoma enlargement (eTable 2 in the Supplement). When investigating the association of the combination of the 3 modifiable parameters (extent, timing of INR reversal, blood pressure) with hematoma enlargement and imputing the variables into consecutive multivariable models, we found the following hematoma enlargement rates: for INR values less than 1.3: 116/432, or 26.9% (OR, 0.37; 95% CI, 0.26-0.59; $P < .001$); for INR values below 1.3 achieved within 4 hours: 43/217, or 19.8% (OR, 0.27, 95% CI, 0.15-0.43; $P < .001$); and for INR values below 1.3 achieved within 4 hours and systolic blood pressure less than 160 mm Hg at 4 hours: 35/193, or 18.1% (OR, 0.17; 95% CI, 0.11-0.33; $P < .001$) (**Figure 3**).

Comparing the frequency of hematoma enlargement among patients fulfilling all 3 criteria (hematoma enlargement rate: 35/193 [18.1%]) with the remainder of the cohort (hematoma enlargement rate: 220/498 [44.2%]; OR, 0.28; 95% CI, 0.19-0.42; $P < .001$) revealed an absolute risk difference of 26.1%, which translated into a significant absolute risk difference of 7.2% for in-hospital mortality (all 3 criteria: 26/193 [13.5%] vs not all 3 criteria: 103/498 [20.7%]; OR, 0.60; 95% CI, 0.37-0.95; $P = .03$). Therefore, adding systolic blood pressure of less than 160 mm Hg at 4 hours to INR reversal below 1.3 achieved within 4 hours was associated with further reduction in the frequency of hematoma enlargement and rate of in-hospital mortality.

Table 2. Subgroup Analysis for Mode of Reversal Treatment, Comparing Fresh-Frozen Plasma vs Prothrombin Complex Concentrates

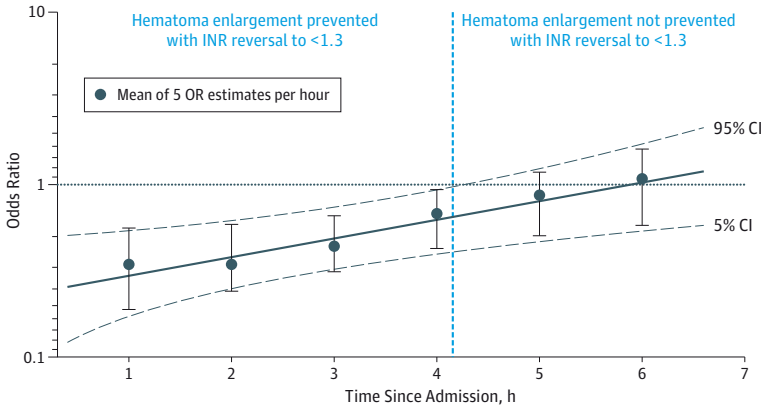
	Fresh-Frozen Plasma (n = 11)	Prothrombin Complex Concentrates (n = 650)	*P* Value
Initial coagulation parameters			
INR, median (IQR)	2.20 (1.84-3.45)	2.79 (2.30-3.45)	.11
PTT, median (IQR), s	40 (34-49)	42 (36-49)	.66
First monitoring after reversal[a]			
INR, median (IQR)	1.66 (1.20-2.42)	1.27 (1.15-1.44)	.01[b]
PTT, median (IQR), s	34 (32-38)	33 (30-37)	.35
Absolute INR reversal, median (IQR)	0.36 (0.04-0.86)	1.45 (0.97-2.10)	<.001
Hematoma enlargement, No. (%)	5 (45.4)	236 (36.3)	.75

Abbreviations: INR, international normalized ratio, IQR, interquartile range; PTT, partial thromboplastin time.

[a] Indicates first value of serial monitoring of coagulation parameters after initiation of reversal treatment.

[b] Not significant after Bonferroni correction (corrected significance level $P < .00104$).

Figure 2. Association of Timing and Extent of INR Reversal With Hematoma Enlargement



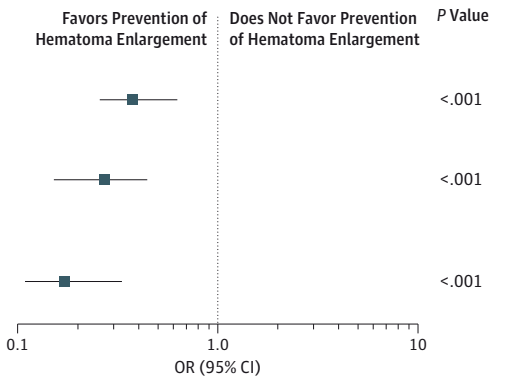
Patients with hematoma enlargement, shown as No./No. achieving INR (%)

INR <1.3	5/26 (19.2)	9/51 (17.6)	14/73 (19.2)	15/67 (22.4)	7/22 (31.8)	9/25 (36.0)
INR ≥1.3	6/17 (35.3)	11/30 (36.7)	25/64 (39.1)	27/64 (42.2)	11/28 (39.3)	13/29 (44.8)

Logistic regression model using generalized estimating equations to visualize the association of "optimal" international normalized ratio (INR) reversal (INR <1.3 vs INR ≥1.3 on first monitoring after reversal treatment) with hematoma enlargement over time. Hematoma enlargement was defined as relative volume increase of >33% on follow-up imaging. The thick blue line represents a regression of odds ratio (OR) estimates generated every 12 min. Each OR estimate included available data covering ±12 minutes (actual data started at 00:24 hours); ie, the first OR estimate was calculated at 00:36 hours and included all available data from 00:24-00:48 hours. Data markers represent the mean of those 5 OR estimates that encompassed full hours; eg, the OR estimate at hour 1 represents a mean of the 5 included OR estimates at 00:36 hours (ie, all data 00:24-00:48), at 00:48 hours (ie, all data 00:36-01:00), at 01:00 hours (ie, all data 00:48-01:12), at 01:12 hours (ie, all data 01:00-01:24), and at 01.24 hours (ie, all data 01:12-01:36). Each OR was weighted according to available data points within each time interval, and generation included the method of moving averages (binning of 5 subsequent ORs).[27] The vertical dashed line indicates the last significant OR estimate at 04:12 hours. We only included those patients for analysis (n = 496) for whom the first INR value obtained after initiation of reversal treatment was available within the assessed time frame (00:24-06:36 hours). Error bars indicate 95% CIs.

Figure 3. Adjusted Graphical Regression Analysis of Combined Associations of INR Reversal, Systolic Blood Pressure, and Timing With Hematoma Enlargement

	No. of Patients	Patients With Hematoma Enlargement, No. (%)	OR (95% CI)	P Value
INR <1.3				
Achieved	432	116 (26.9)	0.37 (0.26-0.59)	<.001
Did not achieve	421	191 (45.4)		
INR <1.3 within 4 hours				
Achieved	217	43 (19.8)	0.27 (0.15-0.43)	<.001
Did not achieve	636	264 (41.5)		
INR <1.3 within 4 hours and systolic BP <160 mm Hg within 4 hours				
Achieved	193	35 (18.1)	0.17 (0.11-0.33)	<.001
Did not achieve	498	220 (44.2)		



Multivariable model for the combined associations, ie, extent and timing of international normalized ratio (INR) reversal and systolic blood pressure (BP), with hematoma enlargement. Hematoma enlargement was defined as relative volume increase of >33% on follow-up imaging. Adjustments consisted of all nonmodifiable parameters associated with hematoma enlargement, ie, time from symptom onset to imaging, deep intracerebral hemorrhage location, National Institutes of Health Stroke Scale score, and comorbidity (eTable 2 in the Supplement). OR indicates odds ratio.

OAC Resumption

Complete 1-year follow-up data were available for 719 patients discharged alive. We excluded a total of 93 patients (81 patients had missing follow-up data and 12 withdrew consent) and restricted all outcome analyses to patients with complete data at 1-year follow-up (Figure 1). Oral anticoagulation was restarted in 172 of 719 patients (23.9%), with the highest rates noted among patients with mechanical heart valves (34/50 [68.0%]); the rate among patients with atrial fibrillation was 19.4% (110/566) (eTable 5 in the Supplement). Median time until OAC resumption was 31 days (IQR, 18-65). Within analysis of all surviving patients, we observed ischemic complications significantly more often without OAC resumption as compared with patients who did restart (OAC: 9/172 [5.2%] vs no OAC: 82/547 [15.0%]; $P < .001$). In contrast, the rate of hemorrhagic complications was not significantly different (OAC: 14/172 [8.1%] vs no OAC: 36/547 [6.6%]; $P = .48$) (**Figure 4**).

Atrial fibrillation is the major indication for anticoagulation, clinically of increasing relevance, and patients with atrial fibrillation represented the largest subgroup (n = 566) within our study population. Thus, we based all further analyses of OAC resumption on patients with atrial fibrillation. Within this subgroup, patients who restarted OAC showed a significantly decreased mortality (OAC: 9/110 [8.2%] vs no OAC: 171/456 [37.5%]; $P < .001$) and a reduced rate of ischemic complications (OAC: 6/110 [5.5%] vs no OAC: 68/456 [14.9%]; $P = .008$), and rates of hemorrhagic complications were not different (OAC: 8/110 [7.3%] vs no OAC: 26/456 [5.7%]; $P = .53$) (eFigure 2 in the Supplement). Furthermore, we noticed significant differences in baseline characteristics. Specifically, patients who resumed OAC were significantly younger and less severely affected at time of admission and showed superior functional status at time of discharge (eTable 6 in the Supplement).

To minimize confounding, we carried out propensity score matching for factors showing a statistical association with resumption status. The matching resulted in 2 evenly balanced cohorts of patients with atrial fibrillation (range of standardized mean differences, 0.01-0.07) (eTable 7 in the Supplement). When comparing stroke incidence of the matched cohort, we noted a significantly decreased rate of cerebral infarctions (incidence rate per 100 patient-years) for patients who restarted OAC within this matched analysis (OAC: 3.9/100 patient-years [95% CI, 1.9-5.8] vs no OAC: 12.7/100 patient-years [95% CI, 6.5-19.1]; $P = .02$) (eTable 8 in the Supplement). Recurrent ICH occurred without a statistical difference between patients who restarted or did not restart OAC (OAC: 3.9/100 patient-years [95% CI, 1.9-5.8] vs no OAC: 3.9/100 patient-years [95% CI, 2.2-5.7]; $P = .92$). Mortality analyses of the matched cohort at 1 year showed that 9 of 108 restarted patients (8.3%) vs 47 of 153 patients without OAC (30.7%) had died ($P < .001$) (**Figure 5**). This large difference of more than 22% triggered a multivariable-adjusted Cox regression analysis for long-term mortality of the matched atrial fibrillation cohort. Among patients who restarted OAC treatment, there was a significantly decreased HR for long-term mortality of 0.258 (95% CI, 0.125-0.534; $P < .001$) (eTable 9 in the Supplement).

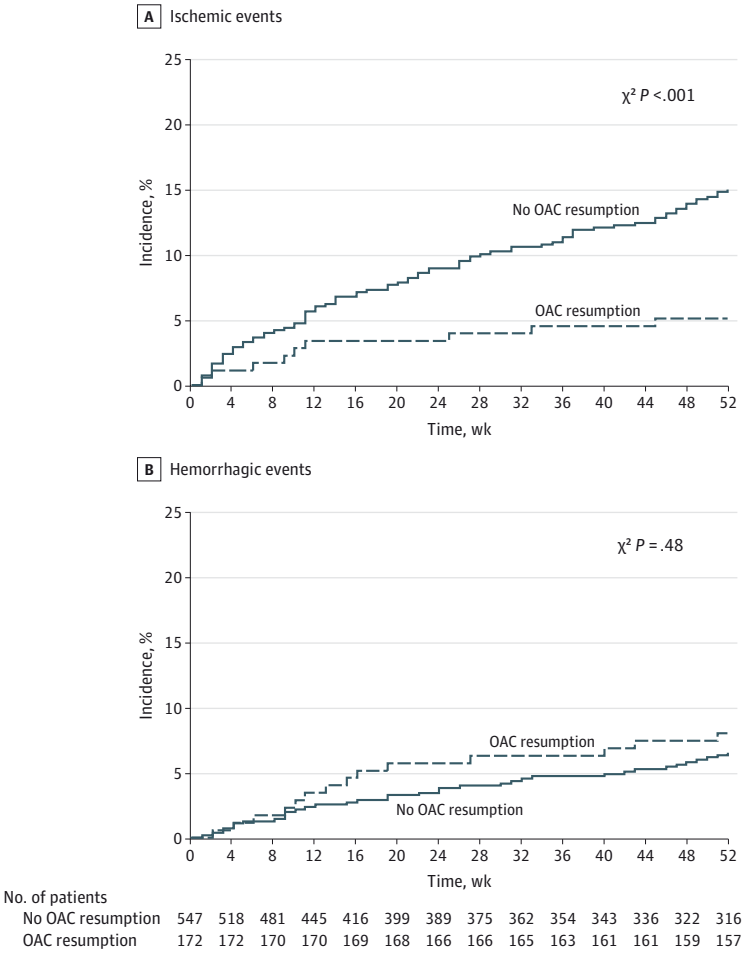
Long-term Functional Outcome

Investigation of long-term functional outcomes used the entire cohort (n = 1176), and mortality was 364 of 1176 (31.0%) at hospital discharge, 475 of 1102 (43.1%) at 3 months, and 608 of 1083 (56.1%) after 1 year (**Figure 6**). Of all deceased patients during follow-up, 224 of 244 patients (91.8%) were discharged with a functional status of 4 or 5 on the mRS, and of these poor-grade discharged patients, 224 of 511 died (43.8%). Unfavorable functional outcome (mRS = 4-6) was observed in 928 of 1176 patients (78.9%) at time of discharge and decreased to 786 of 1083 patients (72.6%) at 1 year. Hence, the proportion of patients reaching favorable functional outcome increased only by 6.3% during follow-up.

To identify factors in poor-grade survivors (mRS = 4-5) associated with long-term improvement (change to mRS = 0-3), we performed a multivariable analysis and identified the following independent parameters associated with lack of im-

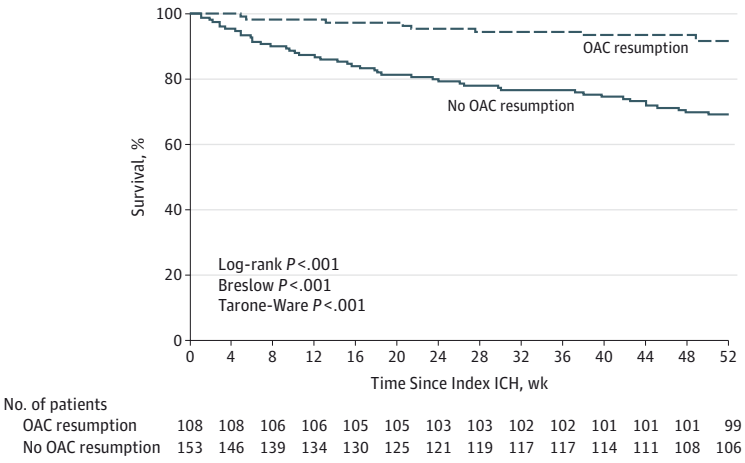
provement during follow-up: age (RR, 0.968; 95% CI, 0.945-0.993; P = .01), neurological status (NIHSS, RR: 0.956; 95% CI, 0.922-0.992; P = .02), ICH volume (RR: 0.576; 95% CI, 0.334-0.994; P = .04), and new ischemic stroke (RR: 0.113; 95% CI, 0.016-0.792; P = .03). Only higher hemoglobin levels at time of admission was significantly associated with functional im-

Figure 4. Crude Incidence Rates of Ischemic and Hemorrhagic Complications During 1-Year Follow-up in Patients With and Without OAC Resumption



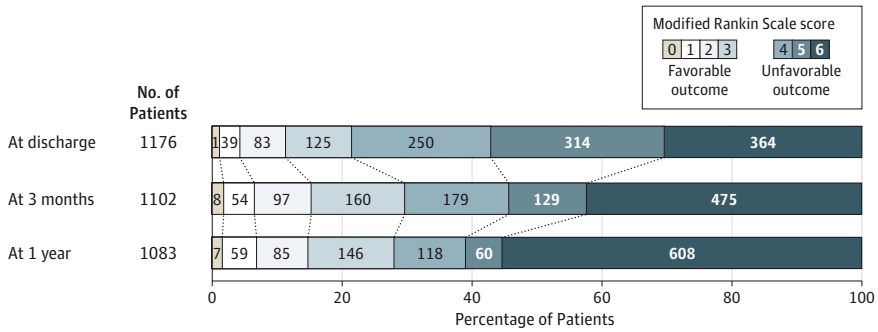
Incidence rates of (A) new ischemic and (B) hemorrhagic events comparing all surviving patients who restarted oral anticoagulation (OAC) vs those who did not restart OAC. Analyses were based on all patients with complete 1-year follow-up data.

Figure 5. Kaplan-Meier Survival Rates of Patients With Atrial Fibrillation With and Without OAC Resumption



Kaplan-Meier survival curves of the propensity-matched cohort (which included only patients who were discharged alive) comparing patients with atrial fibrillation who restarted oral anticoagulation (OAC) vs those who did not restart OAC. Survival is presented from index intracerebral hemorrhage (ICH) until 1-year follow-up and analyzed by log-rank, Breslow, and Tarone-Ware testing.

Figure 6. Long-term Functional Outcome of the Entire Cohort



Distribution of functional outcome at discharge, 3 months, and 1 year using the modified Rankin Scale (mRS). An mRS of 0 indicates no symptoms; mRS 1, no significant disability, able to carry out all activities prior to stroke, some symptoms; mRS 2, slight disability, unable to carry out all activities prior to stroke, able to look after own affairs; mRS 3, moderate disability, requiring help, walking with cane or walker but without assistance; mRS 4, moderately severe disability, unable to attend bodily needs and to walk without assistance; mRS 5, severe disability, bedridden, requiring constant nursing care and attention; and mRS 6, death.

provement (RR: 1.197; 95% CI, 1.070-1.338; P = .002) (eTable 10 in the Supplement).

Analysis of unfavorable long-term outcome showed associations for parameters similar to those established for spontaneous ICH (eTable 11 and eTable 12 in the Supplement).[31] When investigating independent associations of unfavorable functional long-term outcome in the unmatched cohort, we noted an increased risk for both new ischemic stroke and recurrent ICH (ischemic stroke: 45/63 [71.4%] vs no ischemic stroke: 384/656 [58.5%]; RR, 1.554; 95% CI, 1.101-2.419; P = .02; recurrent ICH: 27/30 [90.0%] vs no ICH: 394/689 [57.2%]; RR, 2.884; 95% CI, 1.203-8.636; P = .03). The only parameter significantly associated with a decreased RR for unfavorable functional long-term outcome was OAC resumption (OAC: 54/172 [31.4%] vs no OAC: 367/547 [67.1%]; RR, 0.330; 95% CI, 0.205-0.531; P < .001).

To reduce possible confounding of these results, we calculated a multivariable model of the matched cohort in patients with atrial fibrillation to analyze functional outcome (eTable 13 in the Supplement). Analogous to findings of the unmatched entire cohort, we noticed independent associations for ischemic and hemorrhagic stroke with unfavorable outcome (ischemic stroke 13/20 [65.0%] vs no ischemic stroke: 98/241 [40.7%]; RR, 1.432; 95% CI, 1.055-1.943; P = .02 and hemorrhagic stroke: ICH: 8/9 [88.9%] vs no ICH: 103/252 [40.9%]; RR, 2.581; 95% CI, 1.708-3.900; P < .001), whereas age, ICH volume, and intraventricular hemorrhage were no longer significantly associated. In contrast, OAC resumption was independently related to a decreased risk of unfavorable outcome at 1 year (OAC: 30/108 [27.8%] vs no OAC: 91/153 [52.9%]; RR, 0.552; 95% CI, 0.394-0.775; P = .001). The propensity-matched and adjusted analyses provided results with reduced bias and confounding. Hence, there was a decreased ischemic stroke incidence and decreased risk of experiencing unfavorable functional long-term outcomes among patients who restarted OAC therapy after OAC-ICH.

Comparing baseline characteristics of patients lost to follow-up with those of patients included for complete case analyses did not show a statistically significant difference regarding all evaluated parameters (eTable 14 in the Supplement). A multiple imputation analysis (eTable 15) resulted in increasing incidences of both ischemic and hemorrhagic complications (introduction of 83 new events: 34 ischemic and 49 hemorrhagic) while mortality and functional outcome would paradoxically decrease at 1-year follow-up. Thus, we conducted complete case analyses to evaluate associations of OAC resumption and long-term outcome.

Discussion

The study represents the largest cohort of patients with OAC-ICH to date and reports 2 clinically valuable associations. First, rates of hematoma enlargement were decreased in patients with INR values reversed below 1.3 within 4 hours of admission and systolic blood pressures of less than 160 mm Hg at 4 hours. Second, rates of ischemic events were decreased among patients who restarted OAC without increased rates of bleeding complications.

The occurrence of hematoma enlargement is an established risk factor for poor outcome in both primary and OAC-associated ICH.[6,17,24] Pharmacological interventions targeting hemostasis or blood pressure lowering have been shown to prevent hematoma enlargement in primary ICH; however, the effects on clinical end points are uncertain.[16,32,33] In OAC-ICH, the pathophysiological mechanism of hematoma enlargement is complex,[8] its occurrence protracted and mainly driven by altered coagulation.[6,7] This difference from primary ICH constitutes a target for aggressive medical treatment to minimize hematoma enlargement and possibly affect outcome.[6,7] Although it seems warranted to prospectively investigate the optimal INR reversal and its influence on clinical end points after OAC-ICH, it appears unlikely that sufficiently powered randomized trials will be realized (including a trial of whether PCCs sustain their benefit as an easily available and timely treatment compared with FFP[34,35]).

The clinical risks and benefits of restarting anticoagulation after OAC-ICH remain intensely debated and were re-

cently revived by data from the CHIRONE study.[11] Patients with ICH have an elevated risk for recurrent ICH,[36] which may be increased by restarting OAC.[11] However, our data strengthen previous findings that patients restarting OAC do not show greater risk for recurrent ICH.[30] Based on a considerably high thromboembolic risk without OAC[12,37] ($CHADS_2$ score ≥2 in 79% of our patients), the increased incidence rate of ischemic stroke observed with our propensity-matched analyses argue in favor of OAC resumption. Only a randomized trial, at least using cluster randomization, will settle the question about which stroke type is clinically more significant: increased rates of ischemic stroke vs lower rates of recurrent, possibly more severe ICH.[11,12,30] In this regard, the use of new anticoagulants may further decline risk of recurrent ICH and—given acceptable adherence rates—also the hesitation about resuming anticoagulation[38] counterbalancing self-fulfilling outcome evolutions.[39]

The present study has several strengths, including a large sample size with 1-year follow-up data from 19 tertiary care centers. Analyses exploited rigorous statistical means to correct for bias and confounding. Nevertheless, some drawbacks limit the interpretation of our findings, the first its retrospective nature, which attenuated data quality. With regards to the determination of hematoma volume and presence of hematoma enlargement, some imprecisions in exact volume assessment remain because the measurements were not computer-assisted. The association of systolic blood pressure with hematoma enlargement may have been influenced by compensatory mechanisms to maintain cerebral perfusion pressure in a subset of patients.[40] Moreover, blood pressure values were not assessed continuously, which left room for uncertainty between the obtained 4-hour intervals.

Comparable with recursive partitioning, our analyses of hematoma enlargement used sequential analyses, leaving room for arbitrariness of used subdivision-related cut points. Hence, this statistical approach may only reflect the characteristics of this study population, which highlights the need for external validation of the reported results by independent populations. With regards to our findings on long-term outcome as well as safety and efficacy of OAC resumption, missing data for patients lost to follow-up potentially biased results. We favored complete-case analyses instead of multiple imputations as comprehensive and meaningful auxiliary may not have been fully assessed (eTable 14 and eTable 15 in the Supplement). Large confidence intervals may reflect certain data instability. We only included ischemic and hemorrhagic events leading to hospitalization and did not longitudinally balance the clinical importance of these events. Although propensity matching minimized confounding by indication, residual bias of parameters not investigated as well as healthy cohort and center effects may not be fully excluded.[28] Finally, long-term follow-up information may have been influenced by erroneously answered questionnaires affecting the validity of mRS estimation.

Conclusions

Among patients with OAC-associated ICH, reversal of INR below 1.3 within 4 hours and systolic blood pressure less than 160 mm Hg at 4 hours were associated with lower rates of hematoma enlargement, and resumption of anticoagulant therapy was associated with lower risk of ischemic events without increased bleeding complications. These retrospective findings require replication and assessment in prospective studies.

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Study concept and design: Kuramatsu, Schellinger, Erbguth, Schwab, Huttner.
Acquisition, analysis, or interpretation of data: Kuramatsu, Gerner, Schellinger, Glahn, Endres, Sobesky, Flechsenhar, Neugebauer, Jüttler, Grau, Palm, Röther, Michels, Hamann, Hüwel, Hagemann, Barber, Terborg, Trostdorf, Bäzner, Roth, Wöhrle, Keller, Schwarz, Reimann, Volkmann, Müllges, Kraft, Classen, Hobohm, Horn, Milewski, Reichmann, Schneider, Schimmel, Fink, Dohmen, Stetefeld, Witte, Günther, Neumann-Haefelin, Racs, Nueckel, Erbguth, Kloska, Doerfler, Köhrmann, Huttner.
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Milewski, Reichmann, Schneider, Schimmel, Fink, Dohmen, Stetefeld, Witte, Günther, Neumann-Haefelin, Racs, Nueckel, Erbguth, Kloska, Doerfler, Köhrmann, Schwab, Huttner.
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Study supervision: Kuramatsu, Schellinger, Jüttler, Wöhrle, Classen, Horn, Erbguth, Schwab, Huttner.

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