Published in final edited form as:

Ann Neurol. 2017 November ; 82(5): 755–765. doi:10.1002/ana.25079.

Oral Anticoagulation and Functional Outcome after Intracerebral Hemorrhage

Alessandro Biffi, MD^{1,2,3,*}, Joji B. Kuramatsu, MD^{4,*}, Audrey Leasure, BS⁵, Hooman Kamel, MD⁶, Christina Kourkoulis, BS^{1,2,3}, Kristin Schwab, BA^{1,3}, Alison M. Ayres, BA^{1,3}, Jordan Elm, PhD⁷, M. Edip Gurol, MD, MSc^{1,3}, Steven M. Greenberg, MD, PhD^{1,3}, Anand Viswanathan, MD, PhD^{1,3}, Christopher D. Anderson, MD, MMSc^{1,2,3}, Stefan Schwab, MD⁴, Jonathan Rosand, MD, MSc^{1,2,3}, Fernando D. Testai, MD, PhD⁸, Daniel Woo, MD, MS⁹, Hagen B. Huttner, MD^{4,*}, and Kevin N Sheth, MD^{5,*}

¹Department of Neurology, Massachusetts General Hospital, Boston, MA

²Center for Human Genetic Research, Massachusetts General Hospital (MGH), Boston, MA

³Hemorrhagic Stroke Research Program, J. Philip Kistler Stroke Research Center, MGH, Boston, MA

⁴Department of Neurology, University of Erlangen-Nuremberg, Erlangen, Germany

⁵Department of Neurology, Yale University School of Medicine, New Haven, CT

⁶Department of Neurology, Weill Cornell College of Medicine, New York, NY

⁷Department of Public Health Sciences, Medical University of South Carolina, Charleston, SC

⁸Department of Neurology and Rehabilitation, University of Illinois College of Medicine, Chicago, IL

⁹Department of Neurology and Rehabilitation Medicine, University of Cincinnati, Cincinnati, OH

Abstract

Objective—Oral anticoagulation treatment (OAT) resumption is a therapeutic dilemma in intracerebral hemorrhage (ICH) care, particularly for lobar hemorrhages related to amyloid angiopathy. We sought to determine whether OAT resumption after ICH is associated with long-term outcome, accounting for ICH location (ie, lobar vs nonlobar).

Methods—We meta-analyzed individual patient data from: (1) the multicenter RETRACE study (n = 542), (2) a U.S.-based single-center ICH study (n = 261), and (3) the Ethnic/Racial Variations of Intracerebral Hemorrhage study (n = 209). We determined whether, within 1 year from ICH,

Address correspondence to Dr Sheth, Division of Neurocritical Care and Emergency Neurology, Department of Neurology, Yale School of Medicine and Yale New Haven Hospital, 15 York Street, LLCI 10th floor, Room 1003C, PO Box 208018, New Haven, CT 06520. kevin.sheth@yale.edu.

*These authors contributed equally to the present study.

Author Contributions

Study concept and design: A.B., J.B.K., H.K., H.B.H., K.N.S. Data acquisition and analysis: all authors. Manuscript preparation: A.B., J.B.K., H.K., J.E., H.B.H., K.N.S.

Potential Conflicts of Interest

Nothing to report.

OAT resumption was associated with: (1) mortality, (2) favorable functional outcome (modified Rankin Scale = 0–3), and (3) stroke incidence. We separately analyzed nonlobar and lobar ICH cases using propensity score matching and Cox regression models.

Results—We included 1,012 OAT-related ICH survivors (633 nonlobar and 379 lobar). Among nonlobar ICH survivors, 178/633 (28%) resumed OAT, whereas 86/379 (23%) lobar ICH survivors did. In multivariate analyses, OAT resumption after nonlobar ICH was associated with decreased mortality (hazard ratio [HR] = 0.25, 95% confidence interval [CI] = 0.14–0.44, $p < 0.0001$) and improved functional outcome (HR = 4.22, 95% CI = 2.57–6.94, $p < 0.0001$). OAT resumption after lobar ICH was also associated with decreased mortality (HR = 0.29, 95% CI = 0.17–0.45, $p < 0.0001$) and favorable functional outcome (HR = 4.08, 95% CI = 2.48–6.72, $p < 0.0001$). Furthermore, OAT resumption was associated with decreased all-cause stroke incidence in both lobar and nonlobar ICH (both $p < 0.01$).

Interpretation—These results suggest novel evidence of an association between OAT resumption and outcome following ICH, regardless of hematoma location. These findings support conducting randomized trials to explore risks and benefits of OAT resumption after ICH.

Intracerebral hemorrhage (ICH) accounts for 10 to 20% of all acute cerebrovascular events, and it is responsible for the majority of stroke-related disability and mortality.¹ Oral anticoagulation treatment (OAT) is associated with increased ICH risk, with 10 to 15% of all ICH cases occurring in the setting of therapeutic anti-coagulation for prevention of cardioembolic stroke due to atrial fibrillation.^{2–5} Patients and clinicians are faced with a critical therapeutic dilemma in regard to OAT resumption after ICH, with increased risk of recurrent bleeding being balanced against protection from thromboembolic events.

Definitive evidence is currently lacking on this topic, with current (2014) European Stroke Organization guidelines providing no specific recommendations for OAT resumption.⁶ Nonetheless, ICH location is often factored in decision making, because lobar ICH (etiologically related to cerebral amyloid angiopathy [CAA]) demonstrates significantly higher recurrence rates than nonlobar ICH (caused by hypertensive small vessel disease).^{7–9} Current (2015) American Stroke Association guidelines recommend avoiding OAT following lobar ICH, whereas resumption can be considered after nonlobar ICH on a case-by-case basis.¹⁰ However, no study to date has evaluated the impact of ICH location on potential risks/benefits of OAT resumption.^{11–15} Furthermore, published studies to date focused on the effect on OAT resumption on stroke recurrence, but failed to explore its impact on functional status outcomes of immediate relevance to patients, families, and health care providers.¹⁴

We therefore sought to investigate whether, following lobar and nonlobar ICH, resumption of OAT for prevention of cardioembolic infarcts in the setting of atrial fibrillation is associated with functional outcome, long-term mortality, and all-cause stroke risk. We present joint analyses of individual-level data from 3 large studies of ICH: (1) the multicenter RETRACE (German-wide Multicenter Analysis of Oral Anticoagulation associated Intracerebral Hemorrhage) study of OAT-ICH conducted in Germany,¹¹ (2) a single-center longitudinal study of ICH conducted in Boston, Massachusetts,⁷ and (3) the U.S.-based multicenter Ethnic/Racial Variations of Intracerebral Hemorrhage (ERICH)

study.¹⁶ This large collaborative effort allowed us to apply state-of-the-art statistical tools to highly curated individual-level data for a large number of consecutive OAT-ICH cases.

Materials and Methods

Participating Studies

The analyses presented include data from the 3 participating studies: (1) the multicenter RETRACE study, conducted in 19 tertiary care centers across Germany (7 university hospitals and 12 university-affiliated community hospitals) from 2006 to 2010, with the University of Erlangen-Nuremberg (Erlangen, Germany) serving as coordinating center¹¹; (2) the single-center longitudinal study of ICH conducted at Massachusetts General Hospital (MGH) in Boston, Massachusetts from 1994 onward and currently ongoing⁷; (3) the multicenter ERICH study, including 19 clinical recruitment centers across the United States coordinated by the University of Cincinnati (Cincinnati, OH) and enrolling ICH cases and controls from 2011 to 2015.¹⁶ Of note, because MGH enrolled a number of participants in the ERICH study, all ERICH participants enrolled at MGH were included only in the ERICH analyses, to avoid data duplication.

Participant Enrollment

Eligible participants from each study included patients fulfilling the following criteria: (1) diagnosed with acute ICH (confirmed on computed tomography [CT] scan) at a participating center, (2) age 18 years or older at time of ICH, (3) without history of prior ICH (before the index event at enrollment), (4) on active OAT for prevention of cardioembolic stroke due to previously diagnosed atrial fibrillation at time of ICH, and (5) alive and eligible for potential OAT resumption (ie, with care not focused on comfort measures only) at time of discharge from inpatient hospital stay for index ICH. OAT was specifically defined as use of oral vitamin K antagonists documented in medical records and international normalized ratio (INR) > 1.5 at time of symptom onset. Only individuals receiving OAT for secondary stroke prevention in the setting of documented diagnosis of nonvalvular atrial fibrillation were considered eligible. ICH events associated with trauma, vascular malformation, tumor or other mass, and transformation of ischemic infarct were not considered eligible for analysis. Informed consent for participation in each individual study (including data sharing) was obtained from all participants or their legally designated surrogates. Institutional review boards or ethical committees reviewed and approved all study protocols.

Baseline Data Acquisition

Data on demographics, medical history, pre-ICH medication exposures, and laboratory results were obtained via structured interview of patients and/or informants at time of enrollment, supplemented by review of available medical records at each individual institution.^{7,11,16} Medical records were also reviewed to determine initial ICH severity (defined as Glasgow Coma Scale [GCS]) score and functional status at discharge (defined as modified Rankin Scale [mRS]). Available information was used to compute values for the CHA₂DS₂-VASc and HAS-BLED scores.^{17,18} ICH location was assigned at the time of incident ICH by study investigators blinded to clinical information.^{7,11,16} Lobar ICH was defined as selective involvement of cerebral cortex, underlying white matter, or both.

Nonlobar ICH was defined as selective involvement of thalami, basal ganglia, cerebellum, or brainstem. ICH volumes were determined on first-available CT scan after onset of ICH symptoms, using either the ABC/2 method¹⁹ (RETRACE study) or a previously validated semiautomated method^{7,16} (MGH and ERICH studies). For lobar ICH survivors with available magnetic resonance imaging (MRI) data, diagnosis of probable versus possible CAA was formulated according to the 2010 modified Boston criteria.²⁰ All imaging analyses were conducted at a centrally designated neuroimaging analysis core (RETRACE, University of Erlangen; MGH study and ERICH, MGH) by study staff blinded to clinical data.

Longitudinal Follow-up

Follow-up information was obtained via semistructured telephone interviews, including determination of OAT resumption, mortality, mRS, and new stroke events (including both recurrent ICH and incident ischemic stroke).^{7,11,16} All follow-up phone interviews and outcome adjudications were conducted centrally by the coordinating center for each of the 3 participating studies. Interviews were conducted at 3 months, 6 months, and 1 year from index ICH. In addition, individuals enrolled in the MGH ICH study were then followed at 6-month intervals after the first year. Patient-derived follow-up information was corroborated by review of pertinent medical records. In particular, INR values were extracted from medical records for all participating individuals, with at least a single value available at each follow-up. We then utilized INR values to calculate time in treatment range for each individual, assuming an INR goal of 2.0 to 3.0, using the tests ratio method. Individual-level data were compiled by coordinating centers for each study and shared for centralized statistical analyses performed by the Hemorrhagic Stroke Research Group at MGH.

Statistical Methods

OVERALL ANALYSIS PLAN—All analyses were conducted separately for all ICH (regardless of location), nonlobar and lobar ICH; in the latter group, we conducted separate analyses for participants meeting criteria for diagnoses of possible or probable CAA. We initially conducted univariate and multivariate analyses as detailed below within each individual study dataset. Results from multivariate regression analyses in individual studies were then meta-analyzed using a conservative inverse variance-based random effects pooling method (DerSimonian–Laird).²¹ Cochran Q test was used to estimate heterogeneity, followed by calculation of I^2 (percentage of effect size attributable to heterogeneity).²² Effect size heterogeneity was considered significant for heterogeneity p values < 0.10 or $I^2 > 0.20$. All effect size estimates and corresponding confidence intervals (tables and text) are derived from the aforementioned metaanalyses. $p < 0.05$ (2-tailed) was considered statistically significant, after adjustment for multiple testing using the false discovery rate (FDR) method as proposed by Benjamini and Hochberg.²³ All reported p values (tables and text) were adjusted for multiple testing using the FDR method. All analyses were performed with R software v3.3.1 (R Foundation for Statistical Computing).

UNIVARIATE ANALYSES—Categorical variables were compared using Fisher exact test (2-tailed) and continuous variables using the Mann–Whitney rank-sum or unpaired t test, as appropriate. We performed univariate time-to-event analyses for primary outcomes

(favorable outcome, mortality, stroke recurrence) using the log-rank test. We defined favorable outcome as achieving and retaining during entire follow-up an mRS ≤ 3 . We also conducted additional analyses using mRS at 1 year as an ordinal variable.

OAT RESUMPTION ANALYSES—We used multivariate logistic regression to identify variables associated with decision to resume OAT. Results from individual study-specific logistic regression models were meta-analyzed using methods described above. We sought to minimize confounding by indication in our primary analyses of long-term outcomes after OAT resumption (details below) by performing propensity score matching. We used the balanced, parallel, variable ratio (1:n) nearest-neighbor approach to create clusters of matched patients for analyses.²⁴ Clusters were defined by pairing OAT resumption individuals with nearest-neighbor non-OAT individuals based on prespecified predictors of interest, including: (1) CHA₂DS₂-VASc score (subdivided by tertiles), (2) HAS-BLED score (≤ 3 or > 3), (3) admission GCS (< 13 , $13-15$), (4) discharge mRS (0–2, 3, or 4–5), (5) intraventricular hemorrhage presence (yes/ no), and (6) ICH volume (dichotomized based on median values for nonlobar/lobar ICH). We also prespecified inclusion in the propensity score of all variables associated (at $p < 0.10$) with OAT resumption in our previously described logistic regression models. All clusters with identical propensity parameters were then collapsed to form strata for subsequent multivariate analyses of primary outcomes. Because OAT resumption was incorporated in our analyses as a time-varying covariate (see below), propensity score matching was also computed separately for each analysis interval, in a time-varying fashion.²⁵

PRIMARY OUTCOME ANALYSES—After propensity matching, we inspected survival and functional outcome curves using the Kaplan–Meier method. OAT resumption was defined as a time-varying covariate, indicating whether participants were exposed to therapeutic anticoagulation at each analysis time point. Multivariate modeling for mortality, favorable outcome, and stroke incidence employed propensity-adjusted Cox models. For all multivariate models, candidate covariates included all variables with $p < 0.20$ for association with any outcome of interest. We prespecified exposure to antiplatelet agents as a covariate of interest for initial modeling, regardless of association p values. Backward elimination of nonsignificant variables ($p > 0.05$) was subsequently used to generate a minimal model. The proportional hazard assumption was tested separately within each study by means of graphical checks and Schoenfeld residual-based tests. Multicollinearity was assessed by computing variance inflation factors for all variables.

SECONDARY ANALYSES—We prespecified completion of several secondary exploratory analyses as part of our study design. First, we sought to clarify whether OAT resumption was associated with early mortality (within 90 days) following index ICH. We used propensity-adjusted Cox models (as described above) investigating the association of OAT resumption before 90 days (defined as a time-varying covariate) and mortality. Second, although our primary analyses in all 3 studies extended out to 1 year after index ICH, we also conducted additional analyses with extended follow-up (beyond 1 year) in the MGH study, utilizing identical methods. These analyses included follow-up information from the first year of follow-up. Third, for lobar ICH patients with MRI-based definition of probable

CAA, we tested whether presence of multiple (≥ 2) cerebral microbleeds or cortical superficial siderosis modified the association between OAT resumption and mortality/functional outcome after ICH. To do so, we repeated all multivariate analyses for probable CAA ICH survivors after inclusion of interaction terms between OAT resumption and: (1) presence of multiple (≥ 2) cerebral microbleeds and (2) presence of cortical superficial siderosis. Finally, we also conducted additional analyses using ordinal logistic regression models to explore the association between OAT resumption and mRS at 1 year as an ordinal variable. All aforementioned analyses utilized previously described methods for covariate selection and multivariate modeling described for primary outcome analyses.

Results

Study Participants

After application of prespecified inclusion and exclusion criteria, we analyzed data for 1,012 OAT-ICH survivors, including 633 nonlobar ICH events and 379 lobar ICH events. Participating individuals' characteristics (subdivided by study and ICH location) are presented in Table 1. Among participating nonlobar ICH survivors, 178/633 (28%) resumed OAT, whereas 87/379 (23%) of participating lobar ICH survivors did. We present characteristics of participating individuals based on OAT resumption status in Table 2. OAT resumption rate was higher in the MGH ICH study (43%) compared to the RETRACE (20%) and ERICH (22%) studies ($p < 0.05$ for both comparisons). Individuals participating in the MGH ICH study, however, resumed OAT later than participants enrolled in RETRACE and ERICH. Among patients who resumed OAT in the MGH study, median resumption time was 44 days after ICH (interquartile range [IQR] = 31–89) versus median resumption time of 35 days after ICH in the RETRACE and ERICH studies (IQR = 22–63, $p = 0.013$ for comparison with the MGH study). These statistical differences in resumption time among individuals who were restarted on OAT were also significant when analyses were repeated separately for both lobar and nonlobar ICH (all $p < 0.05$). All other medical history characteristics (including CHA₂DS₂-VASc and HAS-BLED scores) did not differ among studies (all $p > 0.20$). We also compared mRS values at discharge, 3 months, 6 months, and 1 year and found no statistically significant differences across studies (all $p > 0.20$). Mortality rates, ICH recurrence rates, and ischemic stroke recurrence rates also did not differ across studies (all $p > 0.20$).

Anticoagulation Resumption

We sought to determine factors associated with OAT resumption to perform propensity score matching in our primary analyses. We prespecified for inclusion in this analysis several parameters associated with either: (1) ICH outcome, (2) risk of hemorrhagic OAT complications, and (3) risk of stroke in atrial fibrillation. We identified discharge mRS as the only factor significantly associated with OAT resumption, and in lobar ICH only in both univariate (see Table 2) and multivariate analyses (odds ratio [OR] = 0.77 for each mRS point, 95% confidence interval [CI] = 0.62–0.96, $p = 0.02$). Of all other available patient characteristics, none was significantly associated with OAT resumption (all univariate and multivariate $p > 0.20$).

Anticoagulation Resumption after ICH and Mortality/Functional Outcome

We subsequently examined the association between anticoagulation resumption and outcome from index OAT-ICH (Table 3). Among nonlobar ICH survivors, 190/633 (30%) had died at 1 year from index ICH, whereas among lobar ICH survivors 123/379 (33%) were dead at 1 year. For both nonlobar and lobar ICH survivors, we found associations between OAT resumption and decreased mortality in univariate analyses; propensity-score matching confirmed these findings (see Table 3). OAT resumption was also associated with increased likelihood of favorable outcome, defined as mRS values of 0 to 3. Furthermore, in ordinal logistic regression analyses, we found that OAT resumption was associated with lower mRS for survivors of both nonlobar ICH (OR = 2.36 for 1-point decrease in mRS, 95% CI = 1.48–3.37, $p < 0.001$) and lobar ICH (OR = 2.59 for 1-point decrease in mRS, 95% CI = 1.54–3.46, $p < 0.001$).

A total of 17/633 (3%) nonlobar ICH survivors and 9/379 (2%) lobar ICH survivors fulfilling study eligibility criteria experienced early mortality after ICH (ie, within 90 days). We found no association between OAT resumption and early mortality for either nonlobar ICH (hazard ratio [HR] = 1.22, 95% CI = 0.61–2.45, $p = 0.58$) or lobar ICH (OR = 0.93, 95% CI = 0.70–1.23, $p = 0.62$). Of note, none of the early mortality events we identified was associated with hemorrhagic or thromboembolic events (including recurrent ICH, ischemic stroke, systemic bleeding, and/or systemic thromboembolism).

All meta-analyses showed no evidence of between-studies heterogeneity ($I^2 = 0\%$ for all analyses, and all heterogeneity p value > 0.20). We present detailed information on 1-year mRS values by OAT resumption status in Figure 1.

Anticoagulation Resumption after ICH and Stroke Incidence

We observed a total of 18 recurrent ICH and 58 ischemic stroke events among nonlobar ICH survivors. As presented in detail in Table 3, OAT resumption among nonlobar ICH survivors resulted in decreased all-stroke and ischemic stroke incidence, without evidence of increased ICH recurrence. We identified 21 recurrent ICH and 27 ischemic stroke events among lobar ICH survivors. OAT resumption was associated with decreased all-cause stroke and ischemic stroke incidence in propensity-score adjusted analyses (see Table 3). Anti-platelet agent exposure was associated with decreased ischemic stroke risk in both lobar (HR = 0.78, 95% CI = 0.62–0.98, $p = 0.036$) and nonlobar (HR = 0.80, 95% CI = 0.65–0.98, $p = 0.032$) ICH survivors. We did not identify associations between exposure to antiplatelet agents and ICH recurrence after either nonlobar ICH (HR = 1.28, 95% CI = 0.57–2.86, $p = 0.55$) or lobar ICH (HR = 1.10, 95% CI = 0.89–1.36, $p = 0.37$). When compared exclusively with antiplatelet therapy, OAT resumption continued to be associated with decreased all-cause stroke and ischemic stroke incidence in both lobar and nonlobar ICH (all $p < 0.01$). We found no evidence of between-studies heterogeneity in all aforementioned stroke risk analyses ($I^2 = 0\%$ for all analyses, and all heterogeneity p value > 0.20).

Long-term Outcomes and Resumption of Oral Anticoagulation

We sought to investigate whether OAT resumption was associated with outcomes of interest beyond 1 year from index ICH. To this end, we analyzed long-term follow-up data for 102

lobar ICH survivors and 159 nonlobar ICH survivors followed long-term as part of the MGH study. We followed lobar ICH survivors for a median of 48.6 months (IQR = 33.9–65.4) after index ICH, during which we observed 20 recurrent ICH and 22 ischemic stroke events. Among lobar ICH survivors, OAT resumption was significantly associated with long-term functional outcome, mortality, and stroke recurrence (Table 4). We followed nonlobar ICH survivors for a median of 46.7 months (IQR = 32.6–63.4), during which we observed 14 recurrent ICH and 29 ischemic stroke events. OAT resumption was significantly associated with long-term functional outcome, mortality, and stroke recurrence among nonlobar ICH survivors (see Table 4). When compared with 1-year outcome analyses in the RETRACE and ERICH studies, none of the long-term outcome analyses showed evidence of between-studies heterogeneity ($I^2 = 0\%$ for all analyses, and all heterogeneity p value > 0.20).

Anticoagulation Resumption after Lobar ICH Related to Possible/Probable CAA

A total of 190/379 lobar ICH survivors (50%) had available MRI data to formulate a diagnosis of possible ($n = 136$) or probable ($n = 54$) CAA. None of the patients' characteristics listed in Table 1 was associated with MRI data availability (all $p > 0.20$). OAT resumption was associated with decreased mortality and favorable outcome in both possible and probable CAA (Table 5). Presence of multiple (≥ 2) cerebral microbleeds or of cortical superficial siderosis did not modify the associations between OAT resumption and mortality/favorable outcome after lobar ICH (all interaction p values > 0.20). Due to the limited number of strokes occurring in this subset of lobar ICH patients (11 recurrent ICH cases and 12 ischemic strokes), we opted not to perform analyses investigating the association of OAT resumption with stroke incidence.

Discussion

We presented evidence from joint analyses of 3 large observational studies, identifying for the first time associations between oral anticoagulation resumption after ICH and favorable functional outcome at 1 year. We also demonstrated evidence of association between OAT resumption and decreased all-cause stroke incidence at 1 year. Specifically, we found that OAT resumption was associated with decreased ischemic stroke risk after lobar and nonlobar ICH, but not with increased ICH recurrence risk. These findings are in contrast with currently available practice guidelines, but should not be used to directly inform treatment decisions. Instead, they provide a basis for the design of a prospective, randomized, blinded trial to definitively address this critical therapeutic dilemma.

ICH location (ie, lobar vs nonlobar) represents a helpful indicator as to the underlying small vessel disease pathophysiology.²⁶ Nonlobar ICH has been consistently associated with hypertensive microvascular disease, whereas lobar ICH is considered a manifestation of underlying CAA. Recent randomized trial and observational data findings, however, seem to suggest that hypertension may play a role in recurrence of both lobar and nonlobar ICH.^{7,27} Nonetheless, hematoma location has consistently been associated with widely diverging risks of ICH recurrence, thus motivating the inclusion of location as a consideration for OAT resumption in current guidelines.¹⁰ Results from our analyses, however, suggest that both lobar and nonlobar ICH survivors may benefit from OAT resumption. Even when using

more sophisticated tools to separate amyloid-related from hypertension-related ICH (ie, the CAA Boston criteria), OAT resumption was still associated with decreased mortality and favorable functional outcome. These findings could be accounted for by a number of different factors. Most OAT-ICH survivors with atrial fibrillation are at higher risk for ischemic stroke than ICH recurrence, even in the lobar ICH patient subgroup (as is the case in our analyses). Interventions equally decreasing ischemic stroke risk and causing increased ICH recurrence may therefore result in a net beneficial long-term effect. It is also possible that subclinical ischemic stroke events (resulting in central nervous system additional damage and hindering recovery) are not being fully captured among ICH survivors. In turn, this could partly explain the association between prevention of thromboembolism and functional outcome. Should our findings be replicated in randomized clinical trials, additional exploration of the effects of anticoagulation on post-ICH recovery would be critical to address these issues.

Our study has a number of limitations. First and foremost, the observational nature of participating studies implies the potential for bias due to confounding, and particularly for severity/indication bias. Lack of randomization in OAT resumption may have led to preferential assignment to anticoagulation of patients at higher likelihood to experience favorable outcome to begin with. Our observation of lower mRS scores at discharge for lobar ICH survivors restarted on OAT may well represent evidence of such a mechanism at play. The availability of individual-level data, however, allowed us to perform detailed analyses using specific statistical techniques to address this limitation. In particular, our propensity-score matching analyses stratified individuals based on potential predictors of favorable outcome (including discharge mRS). These analyses confirmed all unadjusted findings, thus lending support to the robustness of our conclusions. Ultimately, only a randomized clinical trial of OAT resumption after ICH would provide more definitive validation of our findings. We also utilized only a single, global measure of functional outcome after ICH, that is, the modified Rankin scale. Future studies of OAT resumption after ICH would benefit from including multiple, ideally more detailed assessments of functional outcome.²⁸ We also have follow-up information consistently available in all participating studies only for the first year following index ICH, thus limiting our ability to investigate the impact of OAT resumption on longer-term outcomes. However, previous studies suggest that ICH recurrence and ischemic stroke incidence rates do not increase substantially after the initial 12 months from cerebral hemorrhage, thus allowing some generalizability of our findings to lifetime risk–benefit analysis for OAT resumption.^{7–9} Our long-term analyses in the MGH study were consistent with our primary analyses, as we identified persistent benefit from OAT resumption in terms of functional outcome, mortality, and stroke incidence.

Our study also displays a number of notable strengths. Our collaborative effort allowed us to analyze a large number of OAT-ICH events with in-depth clinical and neuroimaging data. Several recent studies suggested potential benefits from OAT resumption after ICH,^{11,14,15} but were unable to address the highly relevant issue of whether ICH location (and, by extension, etiology) alters the risk/benefit balance for individual patients. Also because of collaborative efforts, statistical analyses could be performed directly on individual-level data. As mentioned above, this allowed for application of sophisticated statistical tools

aimed at controlling confounding. We also gathered OAT-ICH cases from a variety of clinical settings (tertiary care academic centers, community-based academic hospitals, and community institutions) in 2 different countries with widely diverging health care delivery models, thus greatly enhancing the generalizability of our findings. Finally, we were able to investigate the association between OAT and a harmonized functional outcome metric of immediate relevance for patients and health care providers alike. All prior studies focused on binary outcomes (ie, did stroke/mortality occur or not) following OAT resumption. This approach does not take into account the severity and resulting functional impact of recurrent strokes, which can vary dramatically and are ultimately of greatest practical relevance for patients. There is increasing recognition that outcome measures in stroke research must be more patient-centered, and account for functional impact.²⁹ Our study represents the first exploration of these highly relevant questions among ICH survivors.

In conclusion, we present evidence from a large collaborative effort identifying novel associations between resumption of oral anticoagulation after ICH in the setting of atrial fibrillation and long-term outcomes in terms of mortality and functional status. We also found evidence of association between resumption of oral anti-coagulation and all-cause stroke incidence. Because of the stated limitations, including the possibility of bias, our data do not reach the threshold of triggering a change in clinical practice. However, these results do contrast with currently available guidelines. We therefore consider additional investigations into the potential risks and benefits of OAT resumption after ICH to be high priority. Randomized clinical trials in particular are urgently needed to more accurately guide optimal decision making for these patients and their health care providers.

Acknowledgments

The authors' work on this study was supported by funding from the NIH (R25NINDS065743, U01NINDS069763, R01NINDS093870, P50NINDS051343, and R01NI A26484) and the Johannes and Frieda Marohn Foundation. The funding entities had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

References

1. Poon MT, Fonville AF, Al-Shahi Salman R. Long-term prognosis after intracerebral haemorrhage: systematic review and meta-analysis. *J Neurol Neurosurg Psychiatry*. 2014; 85:660–667. [PubMed: 24262916]
2. Eckman MH, Rosand J, Knudsen KA, et al. Can patients be anticoagulated after intracerebral hemorrhage? A decision analysis. *Stroke*. 2003; 34:1710–1716. [PubMed: 12805495]
3. Eckman MH, Singer DE, Rosand J, Greenberg SM. Moving the tipping point: the decision to anticoagulate patients with atrial fibrillation. *Circ Cardiovasc Qual Outcomes*. 2011; 4:14–21. [PubMed: 21139092]
4. Flaherty ML, Haverbusch M, Sekar P, et al. The increasing burden of anticoagulant-associated intracerebral hemorrhage. *Stroke*. 2006; 37:623.
5. Witt DM, Delate T, Hylek EM, et al. Effect of warfarin on intracranial hemorrhage incidence and fatal outcomes. *Thromb Res*. 2013; 132:770–775. [PubMed: 24521790]
6. Steiner T, Al-Shahi Salman R, Beer R, et al. European Stroke Organisation (ESO) guidelines for the management of spontaneous intracerebral hemorrhage. *Int J Stroke*. 2014; 9:840–855. [PubMed: 25156220]

7. Biffi A, Anderson C, Battey TW, et al. Association between blood pressure control and risk of recurrent intracerebral hemorrhage. *JAMA*. 2015; 9:904–912.
8. Hanger HC, Wilkinson TJ, Fayed-Iskander N, Sainsbury R. The risk of recurrent stroke after intracerebral haemorrhage. *J Neurol Neurosurg Psychiatry*. 2007; 78:836–840. [PubMed: 17220294]
9. Hill MD, Silver FL, Austin PC, Tu JV. Rate of stroke recurrence in patients with primary intracerebral hemorrhage. *Stroke*. 2000; 31:123–127. [PubMed: 10625726]
10. Hemphill JC III, Greenberg SM, Anderson CS, et al. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2015; 46:2032–2060. [PubMed: 26022637]
11. Kuramatsu JB, Gerner ST, Schellinger PD, et al. Anticoagulant reversal, blood pressure levels, and anticoagulant resumption in patients with anticoagulation-related intracerebral hemorrhage. *JAMA*. 2015; 313:824–836. [PubMed: 25710659]
12. Poli D, Antonucci E, Dentali F, et al. Recurrence of ICH after resumption of anticoagulation with VK antagonists: CHIRONE study. *Neurology*. 2014; 82:1020–1026. [PubMed: 24562060]
13. Claassen DO, Kazemi N, Zubkov AY, et al. Restarting anticoagulation therapy after warfarin-associated intracerebral hemorrhage. *Arch Neurol*. 2008; 65:1313–1318. [PubMed: 18852344]
14. Nielsen PB, Larsen TB, Skjoth F, et al. Restarting anticoagulant treatment after intracranial hemorrhage in patients with atrial fibrillation and the impact on recurrent stroke, mortality, and bleeding: a nationwide cohort study. *Circulation*. 2015; 132:517–525. [PubMed: 26059010]
15. Chao TF, Liu CJ, Liao JN, et al. Use of oral anticoagulants for stroke prevention in patients with atrial fibrillation who have a history of intracranial hemorrhage. *Circulation*. 2016; 133:1540–1547. [PubMed: 26969761]
16. Woo D, Rosand J, Kidwell C, et al. The Ethnic/Racial Variations of Intracerebral Hemorrhage (ERICH) study protocol. *Stroke*. 2013; 44:e120–e125. [PubMed: 24021679]
17. Fang MC, Go AS, Chang Y, et al. Comparison of risk stratification schemes to predict thromboembolism in people with nonvalvular atrial fibrillation. *J Am Coll Cardiol*. 2008; 51:810–815. [PubMed: 18294564]
18. Pisters R, Lane DA, Nieuwlaar R, et al. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest*. 2010; 138:1093–1100. [PubMed: 20299623]
19. Kothari RU, Brott T, Broderick JP, et al. The ABCs of measuring intracerebral hemorrhage volumes. *Stroke*. 1996; 27:1304–1305. [PubMed: 8711791]
20. Linn J, Halpin A, Demaerel P, et al. Prevalence of superficial siderosis in patients with cerebral amyloid angiopathy. *Neurology*. 2010; 74:1346–1350. [PubMed: 20421578]
21. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986; 7:177–188. [PubMed: 3802833]
22. Ioannidis JP. Interpretation of tests of heterogeneity and bias in meta-analysis. *J Eval Clin Pract*. 2008; 14:951–957. [PubMed: 19018930]
23. Hsueh HM, Chen JJ, Kodell RL. Comparison of methods for estimating the number of true null hypotheses in multiplicity testing. *J Biopharm Stat*. 2003; 13:675–689. [PubMed: 14584715]
24. Rassen JA, Shelat AA, Myers J, et al. One-to-many propensity score matching in cohort studies. *Pharmacoepidemiol Drug Saf*. 2012; 21(suppl 2):69–80. [PubMed: 22552982]
25. Ray WA, Liu Q, Shepherd BE. Performance of time-dependent propensity scores: a pharmacoepidemiology case study. *Pharmacoepidemiol Drug Saf*. 2015; 24:98–106. [PubMed: 25408360]
26. Pantoni L. Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. *Lancet Neurol*. 2010; 9:689–701. [PubMed: 20610345]
27. Arima H, Tzourio C, Anderson C, et al. Effects of perindopril-based lowering of blood pressure on intracerebral hemorrhage related to amyloid angiopathy: the PROGRESS trial. *Stroke*. 2010; 41:394–396. [PubMed: 20044530]
28. Harrison JK, McArthur KS, Quinn TJ. Assessment scales in stroke: clinimetric and clinical considerations. *Clin Interv Aging*. 2013; 8:201–211. [PubMed: 23440256]

29. Katzan IL, Spertus J, Bettger JP, et al. Risk adjustment of ischemic stroke outcomes for comparing hospital performance: a statement for healthcare professionals from the American Heart Association/ American Stroke Association. *Stroke*. 2014; 45:918–944. [PubMed: 24457296]

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

FIGURE 1.

Functional outcome at 1 year, stratified by anticoagulation resumption and intracerebral hemorrhage (ICH) location. Functional outcome (defined as modified Rankin Scale) at 1 year is shown for lobar (A) and nonlobar (B) ICH. Scale scores increase from 0 (leftmost box) to 6 (rightmost box). Values ranging from 0 to 3 (*solid background boxes*) are considered favorable functional outcome. Numbers in each box represents counts of participating individuals in each category. OAT = oral anti-coagulation treatment.

Characteristics of Participating Subjects

TABLE 1

Variable	RETRACE		MGH		ERICH	
	Nonlobar ICH	Lobar ICH	Nonlobar ICH	Lobar ICH	Nonlobar ICH	Lobar ICH
No. of subjects	340	202	159	102	134	75
Demographics						
Age, yr ^a	74.6 (7.8)	74.7 (7.9)	70.5 (9.8)	73.4 (10.5)	71.7 (11.8)	73.8 (11.1)
Sex, male	211 (62)	119 (59)	98 (62)	51 (50)	75 (56)	45 (60)
Medical history						
Hypertension	289 (85)	173 (86)	133 (84)	77 (76)	121 (90)	72 (96)
Diabetes	113 (33)	60 (30)	32 (20)	16 (17)	57 (43)	26 (35)
Dyslipidemia	103 (30)	71 (35)	40 (25)	24 (24)	66 (49)	24 (32)
Prior stroke	107 (31)	55 (27)	24 (15)	13 (13)	37 (28)	24 (31)
CAD	156 (46)	90 (46)	59 (37)	20 (20)	46 (34)	27 (36)
CHA ₂ DS ₂ -VASc ^b	5 (4-6)	5 (3-6)	5 (4-6)	5 (4-6)	5 (4-6)	5 (4-6)
HAS-BLED ^b	3 (3-4)	3 (3-4)	3 (3-4)	3 (3-4)	3 (3-4)	3 (3-4)
Index ICH characteristics						
ICH volume ^b	10.2 (4.8–22.0)	26.9 (10.5–56.0)	11.8 (4.6–22.5)	27.3 (11.0–57.4)	6.2 (1.6–15.8)	18.4 (6.2–41.2)
IVH presence	147 (43)	62 (31)	50 (31)	30 (28)	49 (35)	21 (28)
mRS at discharge ^b	4 (3–5)	4 (3–5)	4 (3–5)	4 (3–5)	4 (3–4)	4 (3–4)
Follow-up data						

Variable	RETRACE		MGH		ERICH	
	Nonlobar ICH	Lobar ICH	Nonlobar ICH	Lobar ICH	Nonlobar ICH	Lobar ICH
OAT resumption	72 (21)	38 (19)	73 (46)	38 (36)	33 (24)	11 (15)
Antiplatelet use	182 (54)	113 (56)	43 (27)	20 (20)	41 (29)	20 (26)
Outcome data at 1 year						
mRS ^b	4 (3–6)	3 (2–6)	4 (3–6)	4 (3–6)	3 (2–5)	4 (2–6)
Favorable outcome, mRS 0–3	134 (39)	106 (52)	72 (45)	39 (38)	63 (45)	38 (51)
Mortality	105 (31)	60 (30)	55 (34)	38 (37)	30 (22)	25 (32)
Recurrent ICH	4 (1)	6 (3)	3 (2)	4 (4)	2 (1)	2 (3)
Ischemic stroke	6 (2)	4 (2)	2 (1)	1 (1)	2 (1)	1 (1)
Systemic bleeding	0 (0)	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)
Systemic thrombosis	2 (1)	3 (1)	2 (1)	2 (2)	2 (1)	1 (1)
Other cause	93 (27)	46 (23)	47 (30)	31 (30)	24 (18)	21 (28)
Recurrent ICH	9 (3)	10 (5)	5 (3)	7 (7)	4 (3)	4 (4)
Ischemic stroke	36 (11)	17 (8)	9 (6)	5 (5)	13 (9)	5 (6)

All values displayed as count (%) unless otherwise specified.

^aValues displayed as mean (standard deviation).

^bValues displayed as median (interquartile range).

CAD = coronary artery disease; ERICH = Ethnic/Racial Variations of Intracerebral Hemorrhage; ICH = intracerebral hemorrhage; IVH = intraventricular hemorrhage; MGH = Massachusetts General Hospital; mRS = modified Rankin Scale; OAT = oral anticoagulation treatment.

TABLE 2

Patient Characteristics Based on Oral Anticoagulation Resumption Status

Variable	Nonlobar ICH			Lobar ICH		
	OAT Resumption ^a	No OAT Resumption ^a	<i>p</i>	OAT Resumption ^a	No OAT Resumption ^a	<i>p</i>
No. of subjects	178	455	—	87	292	—
Enrollment study	<0.001 ^b			<0.001 ^b		
RETRACE	72 (21)	268 (79)		38 (19)	164 (81)	
MGH	73 (46)	86 (54)		38 (36)	64 (64)	
ERICH	33 (24)	101 (76)		12 (15)	63 (85)	
Age, yr ^c	72.3 (9.3)	72.7 (10.2)	0.56	73.5 (10.2)	73.2 (9.9)	0.22
Sex, male	105 (59)	279 (61)	0.66	46 (53)	171 (59)	0.43
Hypertension	148 (83)	395 (87)	0.30	72 (83)	250 (86)	0.63
Diabetes	53 (30)	149 (33)	0.53	25 (29)	77 (26)	0.77
Dyslipidemia	57 (36)	152 (33)	0.81	29 (33)	90 (31)	0.75
Prior stroke	48 (27)	120 (26)	0.99	21 (24)	71 (24)	0.70
CAD	69 (39)	192 (42)	0.48	29 (33)	108 (37)	0.62
CHA ₂ DS ₂ -VASC ^d	5 (4–6)	5 (4–6)	0.44	5 (4–6)	5 (4–6)	0.60
HAS-BLED ^d	3 (3–4)	3 (3–4)	0.74	3 (3–4)	3 (3–4)	0.38
Time to OAT resumption, days ^d	35 (22–64)	—	—	38 (29–72)	—	—
TTR > 60%	128 (72)	—	—	68 (78)	—	—
ICH volume, ml ^d	9.9 (4.7–23.1)	10.3 (4.9–23.5)	0.65	24.7 (10.6–52.1)	25.1 (11.0–53.2)	0.076

Variable	Nonlobar ICH			Lobar ICH		
	OAT Resumption ^a	No OAT Resumption ^a	<i>p</i>	OAT Resumption ^a	No OAT Resumption ^a	<i>p</i>
IVH presence	66 (37)	177 (38)	0.26	27 (30)	87 (29)	0.14
GCS at presentation ^d	14 (12–15)	14 (12–15)	0.37	14 (12–15)	14 (12–15)	0.27
mRS at discharge ^d	4 (3–5)	4 (3–5)	0.39	3 (3–4)	4 (3–5)	0.033 ^b
Early mortality, within 90 days	5 (3)	12 (3)	0.44	2 (2)	7 (2)	0.28
Antiplatelet use, during follow-up	15 (8)	251 (55)	<0.001 ^b	7 (8)	146 (50)	<0.001 ^b

All values are displayed as count (%) unless otherwise specified. Probability values are derived from univariate comparisons.

^aOAT resumption status based on whether oral anticoagulation was restarted within 90 days of index ICH.

^bStatistically significant.

^cValues reported as mean (standard deviation).

^dValues reported as median (interquartile range).

CAD = coronary artery disease; ERICH = Ethnic/Racial Variations of Intracerebral Hemorrhage; GCS = Glasgow Coma Scale; ICH = intracerebral hemorrhage; IVH = intraventricular hemorrhage; MGH = Massachusetts General Hospital; mRS = modified Rankin Scale; OAT = oral anticoagulation treatment; TTR = time in treatment range.

TABLE 3

Oral Anticoagulation Resumption and Outcomes following Intracerebral Hemorrhage

Outcome ^a	All ICH			Nonlobar ICH			Lobar ICH		
	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p
Mortality	0.27	0.19–0.40	<0.0001 ^b	0.25	0.14–0.44	<0.0001 ^b	0.29	0.17–0.45	<0.0001 ^b
Favorable outcome, mRS = 0–3	4.15	2.92–5.90	<0.0001 ^b	4.22	2.57–6.94	<0.0001 ^b	4.08	2.48–6.72	<0.0001 ^b
All-cause stroke	0.47	0.36–0.64	<0.0001 ^b	0.41	0.25–0.67	0.0004 ^b	0.51	0.37–0.76	0.0006 ^b
Recurrent ICH	1.20	0.95–1.58	0.21	1.17	0.89–1.54	0.27	1.26	0.88–1.71	0.22
Ischemic stroke	0.44	0.29–0.66	<0.0001 ^b	0.39	0.21–0.74	0.004 ^b	0.48	0.25–0.75	0.003 ^b

^a All analyses were adjusted by means of propensity score matching using the following parameters: Glasgow Coma Scale at presentation, ICH volume, presence of intraventricular hemorrhage, discharge mRS, CHA₂DS₂-VAsc score, and HAS-BLED score.

^b Statistically significant.

CI = confidence interval; HR = hazard ratio; ICH = intracerebral hemorrhage; mRS = modified Rankin Scale.

TABLE 4

Oral Anticoagulation Resumption and Long-Term Outcomes following Intracerebral Hemorrhage

Outcome ^a	All ICH			Nonlobar ICH			Lobar ICH		
	HR	95% CI	<i>p</i>	HR	95% CI	<i>p</i>	HR	95% CI	<i>p</i>
Mortality	0.32	0.15–0.66	0.002 ^b	0.30	0.10–0.91	0.035 ^b	0.33	0.12–0.87	0.026 ^b
Favorable outcome, mRS = 0–3	3.99	1.76–9.05	0.001 ^b	4.10	1.24–13.57	0.022 ^b	3.89	1.26–11.98	0.019 ^b
All-cause stroke	0.50	0.32–0.79	0.003 ^b	0.49	0.26–0.93	0.031 ^b	0.51	0.26–0.99	0.047 ^b
Recurrent ICH	1.10	0.96–1.26	0.20	1.10	0.94–1.28	0.23	1.21	0.86–1.70	0.27
Ischemic stroke	0.46	0.28–0.75	0.002 ^b	0.44	0.22–0.90	0.025 ^b	0.48	0.25–0.94	0.032 ^b

^a All analyses were adjusted by means of propensity score matching using the following parameters: Glasgow Coma Scale at presentation, ICH volume, presence of intraventricular hemorrhage, discharge mRS, CHA₂DS₂-VAsC score, and HAS-BLED score.

^b Statistically significant.

CI = confidence interval; HR = hazard ratio; ICH = intracerebral hemorrhage; mRS = modified Rankin Scale.

Oral Anticoagulation Resumption and Outcomes following Lobar Intracerebral Hemorrhage related to Possible versus Probable CAA

TABLE 5

Outcome ^a	Possible CAA			Probable CAA		
	HR	95% CI	p	HR	95% CI	p
Mortality	0.27	0.08–0.86	0.028 ^b	0.30	0.10–0.92	0.037 ^b
Favorable outcome, mRS 0–3	3.40	1.22–9.46	0.020 ^b	3.11	1.08–8.97	0.038 ^b

^a All analyses were adjusted by means of propensity score matching using the following parameters: Glasgow Coma Scale at presentation, intracerebral hemorrhage volume, presence of intraventricular hemorrhage, discharge mRS, CHA₂DS₂-VAsc score, and HAS-BLED score.

^b Statistically significant.

CAA = cerebral amyloid angiopathy; CI = confidence interval; HR = hazard ratio; mRS = modified Rankin Scale.