Hematoma Growth in Oral Anticoagulant Related Intracerebral Hemorrhage

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Background and Purpose—Limited data suggest that intracerebral hemorrhage related to oral anticoagulant therapy (OAT ICH) is associated with more hemorrhage expansion and a worse prognosis than spontaneous ICH (SICH).

Methods—We examined patients enrolled in the placebo arm of the CHANT study, a prospective randomized trial of a putative neuroprotectant in patients with ICH. All patients had neuroimaging within 6 hours of symptom onset and at 72 hours. Initial ICH volume and hemorrhage expansion were determined by a central reader. Multivariable logistic regression was used to determine factors associated with ICH expansion and mortality at 90 days.

Results—Of 303 patients included, 21 (6.9%) had OAT ICH. Baseline median ICH volume was greater in patients with OAT ICH compared to SICH (30.6 versus 14.4 mL, \( P=0.03 \)). Hemorrhage expansion (defined as \( >33\% \) increase in ICH volume) occurred in 56% of patients with OAT ICH compared to 26% of SICH (\( P=0.006 \)). Mortality was substantially higher in OAT ICH (62% versus 17%, \( P<0.001 \)). In multivariable analysis, time to neuroimaging and oral anticoagulant use were independently associated with hemorrhage expansion, and age, gender, and oral anticoagulant use were independently associated with mortality.

Conclusions—These findings confirm that OAT ICH is associated with more hemorrhage expansion and greater mortality than SICH. (Stroke. 2008;39:2993-2996.)

Key Words: warfarin ■ intracerebral hemorrhage ■ anticoagulation

Intracerebral hemorrhage (ICH) related to oral anticoagulant therapy (OAT) has been associated with substantially worse outcome than spontaneous ICH (SICH).\(^1\) Hemorrhage expansion is a clear determinant of outcome in SICH, and a greater risk of hemorrhage expansion in OAT ICH may, at least partially, explain the worse prognosis with this condition.\(^2,3\) However, at present there is relatively little information on the rate of hemorrhage expansion in OAT ICH compared to SICH. As the effectiveness of treatments directed at reversing coagulopathy in OAT ICH are likely mediated by their impact on hemorrhage expansion, accurate characterization of this aspect of OAT ICH may have important implications for selection of therapy and design of future therapeutic trials. In this study, we use data from a large prospective trial to compare hemorrhage expansion and clinical outcome in patients with OAT ICH and SICH.

Methods

A detailed description of the Cerebral Hematoma And NXY Treatment (CHANT) trial has been published previously.\(^4\) Briefly, this was a randomized placebo-controlled trial of the putative neuroprotectant NXY-059 in patients with acute ICH. The study was conducted at 131 sites in 20 countries. Subjects had to be enrolled within 6 hours of symptom onset, and limb weakness as part of the neurological deficit was required. Patients with hemorrhagic conversion of ischemic stroke, ICH attributable to trauma, or in coma at time of evaluation were excluded. All patients had brain imaging (CT or MRI) at baseline and at 72 hours. Detailed clinical information, including concomitant medications and baseline laboratory studies, was recorded in the study documents. Clinical assessments were performed at multiple time points over the first 90 days, and included baseline NIHSS and modified Rankin scale at 90 days. Procedures for ICH management, including reversal of coagulopathy, were not specified as part of the CHANT protocol and were left to the discretion of the local treating physician. For the purposes of this analysis, we used data only from the placebo arm of CHANT.

Brain imaging studies were reviewed by a central neuroradiologist blinded to patient clinical information. Imaging studies were digitized and hemorrhage volume at baseline and at 72 hours was computed using semiautomated planimetry and reconstruction using proprietary software (ALICE, Perceptive Informatics). The presence of intraventricular hemorrhage (IVH) was recorded. Hemorrhage location was scored using a detailed mapping grid dividing the brain into 11 regions on each side (frontal, temporal, parietal, occipital, subcortical white matter, putamen, internal capsule, caudate, thalamus, brain stem, cerebellum), and defined as lobar if involvement of a cortical region was present.

Hemorrhages were categorized as oral-anticoagulant associated ICH if the enrolling investigator indicated that the patient had a history of prior anticoagulant use and an oral anticoagulant use was identified in the patient’s current medications at the time of enrollment as recorded in study documentation. For the primary analysis,
hemorrhage expansion was defined as $>33\%$ increase in baseline ICH volume, as has been done in prior studies.\(^6\) Patients who underwent surgical evacuation before 72-hour neuroimaging were excluded from the analysis of hemorrhage expansion. Mortality and poor clinical outcome, defined as a modified Rankin Scale of 4 to 6, were determined at day 90.

### Statistical Analysis

Continuous variables were compared using the unpaired \(t\) test, and categorical variables using Fisher exact test or \(\chi^2\) test as appropriate. Variables with a non-normal distribution were analyzed using the Wilcoxon rank-sum test. Univariate analysis was performed to identify associations between hemorrhage expansion and medical history, demographic features, and factors previously associated with, or that might plausibly be associated with, hemorrhage expansion.\(^6\) Multivariable analysis of the effect of OAT on hemorrhage expansion used stepwise logistic regression including variables associated at the \(P<0.20\) level with expansion in univariate analysis. Similar analysis was undertaken to examine the effect of OAT on mortality. Factors related to the index ICH, for instance baseline ICH volume, were not included in the initial multivariable analysis of mortality as such factors were plausibly influenced by OAT and could mechanistically account for the effect of OAT on outcome. Subsequently, baseline ICH volume and hemorrhage expansion were added to the multivariable analysis to assess the association of these factors with mortality.

### Results

There were 303 patients in the CHANT placebo arm, and 21 (6.9\%) were receiving OAT at enrollment. Patients with OAT ICH were older, had a greater prevalence of diabetes, atrial fibrillation, prior stroke and ischemic heart disease, had greater clinical stroke severity as determined by baseline NIHSS and GCS, and had higher baseline glucose and INR levels (Table 1). Baseline median ICH volume was significantly greater in patients with OAT ICH (30.6 versus 14.4 mL, \(P=0.03\)), and lobar location was more common (43\% versus 14\%, \(P<0.001\)).

### Hemorrhage Expansion and Clinical Outcome

Follow-up neuroimaging data at 72 hours was available for 285 patients (267/282 in SICH group, 18/21 in OAT group). Of patients not included in the follow-up neuroimaging analysis, 5 patients were excluded because of surgical evacuation, all in the SICH group, 6 patients died (3 in OAT group, 3 in SICH group), and 7 patients had missing imaging data. Hemorrhage expansion was greater in patients with oral anticoagulant use, and clinical outcome was worse (Table 2). Of the patients in the OAT ICH group who died, the median day of death was day 3 and all deaths occurred within the first 21 days after symptom onset.

In univariate analysis, significant predictors of hemorrhage expansion (defined as $>33\%$ increase in ICH volume) were time to neuroimaging and OAT; a trend toward significance was also seen with prior stroke (Table 3). In multivariable analysis, factors independently associated with hemorrhage expansion were time to neuroimaging (OR per 30 minutes 0.79, 95\% CI 0.69 to 0.91, \(P=0.001\)) and OAT (OR 3.49, 95\% CI 1.27 to 9.55, \(P=0.015\)), with a trend toward significance for prior stroke (OR 2.03, 95\% CI 0.91 to 4.55, \(P=0.08\)). Addition of baseline ICH volume to this model did not alter these results.
Predictors of mortality in univariate analysis included age, prior ischemic heart disease, prior stroke, OAT, atrial fibrillation, baseline ICH volume, presence of IVH, and lobar location (Table 4). Multivariable analysis for mortality including only factors present before the index ICH demonstrated that age, gender, and OAT were associated with mortality (Table 5a). Addition of baseline ICH volume to the model attenuated the effect of OAT on mortality (Table 5b), and addition of hemorrhage expansion further diminished the effect of OAT such that it was no longer significantly associated with mortality (Table 5c).

An exploratory linear regression analysis was performed using the absolute change in hemorrhage volume instead of categorical change (ie, >33% expansion) as the outcome measure and testing baseline ICH volume and OAT as the covariates. In this analysis, both baseline hemorrhage volume (0.2 mL expansion per 1 mL of baseline volume, 95% CI 0.1 to 0.3, P=0.003) and OAT (22 mL compared to SICH, 95% CI 12 to 33, P=0.001) were independently associated with absolute ICH volume change.

### Discussion

To our knowledge, this is the first prospective study using systematic serial brain imaging to evaluate the frequency of hemorrhage expansion in OAT ICH compared to SICH. We found a significantly increased rate of hemorrhage expansion associated with OAT ICH compared to SICH. We also found very poor outcomes in patients with OAT ICH, consistent with prior reports. Our multivariable analyses demonstrate that the association of OAT with increased mortality is mediated by both higher baseline ICH volumes as well as a greater rate of hemorrhage expansion.

Prior studies of hemorrhage expansion in OAT ICH have reported variable results and had significant limitations in study design. In one retrospective study of 55 patients with OAT ICH <12 hours from symptom onset, hemorrhage expansion (defined as >33% increase in volume) was found in 27% of patients on follow-up CT at 24 hours after presentation. Two other retrospective studies have reported similar rates of hemorrhage expansion using similar definitions. In the latter two studies, the time from symptom onset to initial CT was not reported, follow-up CT scans were performed at variable time points after onset, and hemorrhage volume was calculated using the ABC/2 method. Previous data have suggested that more than half of OAT ICHs are irregularly shaped, and use of the traditional ABC/2 rule in such cases will result in an overestimate of hematoma volume. Most importantly, none of these studies have included a comparator group of patients with SICH. A pooled analysis of patients with SICH presenting within 3 hours of...
symptom onset and having follow-up CT scanning at 24 hours demonstrated a hemorrhage expansion rate of 32%, comparable to the rate reported in the above studies of OAT ICH.2

Only one study that we are aware of has included a comparator group. In this single-center retrospective study, hemorrhage expansion (also defined as >33% increase in volume) was seen in 16% (9/57) of patients with SICH versus 54% (7/13) with OAT ICH.9 However, follow-up CT scanning in this study was performed based on clinical practice and not protocol driven, such that scans were performed at different times after symptom onset and possibly in response to changes in the clinical examination. Patients were only included in the hemorrhage expansion analysis if more than one CT scan was performed, and the 13 patients with OAT ICH included represented fewer than half of the total identified patients with OAT ICH in the study population. Finally, patients with SICH had a median time from symptom onset to baseline CT of 2.4 hours, compared to 14.1 hours for the OAT group, potentially underestimating the rate of hemorrhage expansion with OAT if significant hemorrhage expansion occurred early. Despite the design limitations of this study, our findings were remarkably similar, with hemorrhage expansion occurring in 56% of OAT ICH versus 26% of SICH.

Several limitations of our study should be noted. First, repeat neuroimaging took place at 72 hours after enrollment. We therefore cannot comment with precision on when during this initial period hemorrhage enlargement is most likely to occur. In the case of SICH, current data suggest that most hemorrhage enlargement occurs within the first few hours after presentation. While there is considerable speculation that the time period during which hemorrhage expansion occurs may be longer in OAT ICH, this remains an area of considerable uncertainty. Second, patients in coma or who were poor candidates for a clinical trial were excluded from enrollment in CHANT, and this may limit the generalizability of our findings. Finally, a common difficulty shared by all the studies cited above, including our own, is the confounding effect of variable treatment interventions to reverse the coagulopathy in OAT ICH. At least one study found a significant reduction in the rate of hemorrhage expansion in patients treated with prothrombin complex concentrates compared to those who received vitamin K or fresh frozen plasma, although this observation was limited by the small number of patients included and the nonrandomized design of the study.9 Other studies have suggested that INR correction reduces the likelihood of hemorrhage expansion.10 We do not have detailed information on the selection and timing of treatment strategies initiated to reverse the coagulopathy associated with OAT ICH in our study. However, establishing that hemorrhage expansion is a major contributor to clinical outcome in OAT ICH provides justification for trials of strategies to reverse coagulopathy. As the data we present reflect OAT reversal in current clinical practice, it may be useful in the organization of trials of future therapeutic approaches compared to standard clinical practice. Indeed, the need for well-designed clinical trials in this area has been emphasized.3

Disclosures
None.

References
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Stroke. 2008;39:2993-2996; originally published online August 14, 2008; doi: 10.1161/STROKEAHA.108.520668

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