Can a Subset of Intracerebral Hemorrhage Patients Benefit From Hemostatic Therapy With Recombinant Activated Factor VII?

Stephan A. Mayer, MD; Stephen M. Davis, MD; Brett E. Skolnick, PhD; Nikolai C. Brun, MD, PhD; Kamilla Begtrup, MSc; Joseph P. Broderick, MD; Michael N. Diringer, MD; Thorsten Steiner, MD

Background and Purpose—In the Factor Seven for Acute Hemorrhagic Stroke (FAST) trial, 80 μg/kg of recombinant activated factor VII (rFVIIa) significantly reduced intracerebral hemorrhage (ICH) expansion when given within 4 hours of onset. However, in contrast to an earlier Phase 2b study, rFVIIa did not improve survival or functional outcome. In this exploratory analysis, we hypothesized that earlier treatment and exclusion of patients with a poor prognosis at baseline might enhance the benefit of rFVIIa treatment.

Methods—Using the FAST data set, the impact of rFVIIa (80 μg/kg) on poor outcome at 3 months (modified Rankin Score of 5 or 6) was systematically evaluated within subgroups using clinically meaningful cut points in onset-to-treatment time, age, and baseline ICH and intraventricular hemorrhage volume. The effect of treatment on outcome was analyzed using logistic regression, and ICH volume was analyzed with linear mixed models.

Results—A subgroup (n=160, 19% of the FAST population) was identified comprising patients ≤70 years with baseline ICH volume <60 mL, intraventricular hemorrhage volume <5 mL, and time from onset-to-treatment ≤2.5 hours. The adjusted ORs for poor outcome with rFVIIa treatment was 0.28 (95% CI, 0.08 to 1.06), whereas the reduction in ICH growth was almost doubled (7.3±3.2 versus 3.8±1.5 mL, P=0.02). The improved effect was confirmed in an analysis of similar Phase 2 patients.

Conclusions—A prospective trial would be needed to determine whether younger patients with ICH without extensive bleeding at baseline can benefit from 80 μg/kg of rFVIIa given within 2.5 hours of symptom onset. (Stroke. 2009;40: 833-840.)

Key Words: hemostatic therapy ■ intracerebral hemorrhage ■ rFVIIa

Intracerebral hemorrhage (ICH) is the deadliest and least treatable form of stroke. Over one third of victims die within 1 month of symptom onset, and most survivors never regain functional independence. Because few advances have been made in ICH management over recent years, treatment during the acute phase has focused on blood pressure reduction, osmotherapy, seizure prevention, and treatment of hyperglycemia. Although the efficacy of such interventions has yet to be verified, treatment of patients with ICH in dedicated stroke or neurological intensive care units has been associated with improved outcomes. Surgical hematoma evacuation remains controversial with current evidence failing to show significant benefit over medical treatment for the majority of patients. The lack of proven treatments for ICH means that outcomes are generally poor, highlighting the need for alternative management strategies.

Hematoma volume is a critical determinant of 30-day mortality after ICH, and early hematoma growth has been found to be an independent determinant of poor outcome. Hematoma growth is common in ICH, occurring in 73% of patients, who undergo CT scanning within 3 hours of onset. Prevention of hematoma expansion therefore represents a logical treatment target. Recombinant activated factor VII (rFVIIa), originally developed for the treatment of bleeding in patients with hemophilia with inhibitors, exerts its hemostatic effect by binding to the surface of activated platelets to generate Factor Xa. In recent years, a growing body of clinical evidence also has indicated that rFVIIa promotes hemostasis in a variety of nonhemophilia bleeding situations.

The aim of the recent Factor Seven for Acute Hemorrhagic Stroke (FAST) trial was to confirm the findings of an earlier
Phase 2b study in which rFVIIa reduced hematoma growth and improved both survival and functional outcome in patients with ICH. Although FAST confirmed that treatment with rFVIIa at a dose of 80 μg/kg reduced ICH volume growth by 50% when given within 4 hours after ICH symptom onset (3.7 versus 7.5 mL in placebo, \( P=0.009 \)), there was no difference in the proportion of patients who were dead or severely disabled at Day 90 (29% with rFVIIa 80 μg/kg versus 24% with placebo). The safety profile of rFVIIa was similar to that found in the earlier Phase 2b trial with a 5% absolute increase in the frequency of arterial thromboembolic events.

Several baseline factors have been shown to be important determinants of poor outcome in patients with ICH. Advanced age, poor Glasgow Coma Scale (GCS) score, ICH size, infratentorial location, and presence of intraventricular hemorrhage (IVH) have all been shown to impact on recovery. Recent data also suggest that IVH, in particular, might significantly reduce the clinical benefits of rFVIIa. In patients known to be at high risk for poor outcome at baseline, it may be more difficult to demonstrate that the prevention of additional bleeding can substantially improve survival or functional recovery. Given that hematoma growth occurs most often immediately after the onset of ICH, earlier treatment might also improve the likelihood of demonstrating a clinical benefit with a hemostatic agent.

In this exploratory post hoc analysis, we hypothesized that earlier treatment and the exclusion of patients with a poor prognosis at baseline can enhance the ability of rFVIIa to positively impact on clinical outcome. Using the FAST trial data set, we systematically applied cut points to timing of treatment, age, and disease severity variables alone and in combination to determine their impact on the rFVIIa treatment effect. Our goal was to identify a subpopulation of patients with ICH who might benefit from rFVIIa in terms of clinical efficacy and therefore be suitable for inclusion in possible future studies.

Methods

Trial Design
The design of the FAST trial (ClinicalTrials.gov identifier NCT00127283) has been described in detail elsewhere. This was a randomized, multicenter, double-blind, placebo-controlled, Phase 3 trial in which patients with spontaneous ICH were randomly allocated to receive 20 μg/kg rFVIIa (N=276), 80 μg/kg rFVIIa (N=297), or placebo (N=268) within 4 hours of symptom onset. The primary end point was the proportion of patients who were severely disabled or dead at Day 90 as determined by modified Rankin Scale (mRS) scores of 5 or 6. The earlier Phase 2b Recombinant Activated Factor VII ICH Trial (ClinicalTrials.gov identifier NCT00426803) compared 40, 80, and 160 μg/kg rFVIIa to placebo using the same treatment window, similar inclusion and exclusion criteria, and radiographic and clinical end points as FAST.

Identification of Modulators of Treatment Effect
A superior hemostatic effect was observed with 80 μg/kg rFVIIa in FAST; thus, all exploratory analyses were performed comparing 80 μg/kg with placebo. The effect of excluding patients on the basis of onset-to-needle time and 5 established determinants of poor outcome (age, GCS score, ICH volume, presence of IVH, and infratentorial location) was first examined individually. To do this, we constructed logistic regression models calculating the odds of poor outcome with rFVIIa treatment while excluding patients that exceeded a graded continuous upper threshold for each risk factor.

Identification of the Target Subgroup
Based on graphic analysis of these models and histograms presenting the distribution of patients across each variable, one or more dichotomized cut points for each variable that showed a modulatory influence on the rFVIIa treatment effect were selected by consensus of the study team. The adjusted OR and 95% CI for poor outcome with rFVIIa treatment were calculated for all possible combinations of these cut points. An optimized target group was then selected based on maximizing both the magnitude of rFVIIa treatment effect on clinical outcome and the proportion of patients in the group.

Characterization of the Target Subgroup
Change in absolute ICH volume at 24 hours was characterized in patients given 80 μg/kg rFVIIa or placebo, both in the entire study population and in the target subgroup, using linear mixed models. Serious adverse events experienced by patients in the target group were compared with the FAST trial population as a whole. Finally, to evaluate the reproducibility of the rFVIIa treatment effect in the target subgroup, the odds of death or severe disability with rFVIIa treatment in the Phase 2b study was also compared between the target subgroup and the study population as a whole.

Statistical Methods
All analyses were performed according to the intention-to-treat principle. For surviving patients with missing mRS scores at Day 90, the last observation (Day 15 or discharge) was carried forward. The proportion of patients that were dead or severely disabled at Day 90 was analyzed using logistic regression, with age, gender, baseline ICH volume, prestroke mRS, and location (supra- versus infratentorial) as covariates. An ordinal approach, pooling mRS categories 5 and 6 at Day 90, was also applied to evaluate the distribution of mRS outcomes using a Cochran-Mantel-Haenszel test for independence. The mean percent change in ICH volume at 24 hours was calculated using mixed linear models with baseline ICH volume, symptom onset to CT, and CT-to-needle time as covariates. Probability values <0.025 (one-sided) in the logistic regression analyses were considered significant, whereas other analyses used a threshold of 0.05 (2-sided). Due to the exploratory nature of this analysis, multiplicity adjustments for statistical significance was not applied. The robustness of the target subgroup was assessed by replicating these analyses on 90-day mRS data from a comparable subgroup population in the earlier Phase 2b trial.

Results

Univariate Assessments
The odds of poor outcome with rFVIIa treatment began to fall when onset to needle was limited to ≤180 minutes and the rFVIIa treatment effect was optimized at 150 minutes or less (Figure 1A). Compared with the adjusted OR of poor outcome (mRS score 5 or 6) of 1.44 among all patients treated with 80 μg/kg rFVIIa versus placebo, the odds of poor outcome was 1.38 (95% CI, 0.80 to 2.37) in the subset among patients treated within 180 minutes and decreased to 0.85 (95% CI, 0.41 to 1.76) within 150 minutes. Based on these data, treatment interval cut points of 120, 150, and 180 minutes were selected for further analyses.

With respect to age, the rFVIIa treatment began to improve as patients >79 years were excluded with continued improvement as the upper age limit was further reduced (Figure 1B). Exclusion of patients aged >70 years resulted in an OR of poor outcome of 0.98 (95% CI, 0.52 to 1.85) with 80 μg/kg
rFVIIa relative to placebo. Based on these data, age cut points of 65, 70, 75, and 80 years were selected for further analyses.

Visual analysis showed minor improvement in the treatment signal when IVH volume was between 5 to 10 mL (Figure 1C). The odds of poor outcome were 1.15 (95% CI, 0.69 to 1.9) when patients with IVH volume >10 mL were excluded, 1.20 (95% CI, 0.72 to 2.01) when IVH baseline volumes of ≤5 mL were excluded, and 1.31 (95% CI, 0.70 to 2.46) when patients with any IVH were excluded. Based on these data, IVH volume limits of ≤5 mL and ≤10 mL were selected for further analyses.

Limiting ICH volume appeared to have little effect on the odds of poor outcome with 80 μg/kg rFVIIa relative to placebo (Figure 1D), although it is well recognized that ICH and IVH are highly correlated, limiting the interpretability of the univariate effect. Exclusion of patients with baseline ICH volumes >60 mL resulted in an OR for poor outcome of 1.33 (95% CI, 0.82 to 2.18). Exclusion of patients with baseline GCS scores that were ≤8 also had a minimal effect on the odds of poor outcome with rFVIIa treatment (OR, 1.34; 95% CI, 0.84 to 2.14). Finally, there appeared to be little influence of ICH location on treatment effect relative to placebo; the OR for having a poor outcome when excluding patients with infratentorial ICH was 1.50 (95% CI, 0.94 to 2.41). The decision was made to analyze the effects of limiting baseline ICH volume to 60 mL in further analyses based on the observation that a hemostatic agent would be unlikely to benefit patients with larger baseline hemorrhages because the mortality of patients with ICH volumes >60 mL has been reported to be >90% in population-based studies.1

Sensitivity Analysis of Target Subgroups
Figure 2A shows the adjusted OR for poor outcome with rFVIIa relative to placebo in 12 potential subgroups according to the 4 age and 3 onset-to-treatment cut points that were selected; the proportion of the original FAST study population retained within each subgroup is also displayed. Limiting treatment to ≤150 minutes resulted in a uniformly more favorable treatment effect than the ≤180 minute cut point, whereas limiting treatment to ≤120 minutes did not confer additional benefit. Limiting age from 65 to 80 years among patients treated within 150 minutes did not substantially influence the treatment effect. Based on this analysis, it was determined that a maximum time-to-treatment threshold of 150 minutes offered the best balance between rFVIIa treatment effect and sample size.

Figure 2B shows the effect of limiting age, ICH, and IVH volume alone or in combination in 8 potential subgroups of patients treated within 150 minutes of symptom onset and either <70 or 75 years of age. Exclusion of patients with >5 mL of IVH resulted in uniform improvement of the rFVIIa treatment effect; the additional exclusion of patients with ICH
Figure 2. A, Effect of time to treatment (<120, <150, and <180 minutes) and age (<65, <70, <75, <80 years) on adjusted OR comparing 80 μg/kg rFVIIa with placebo. B, Effect of baseline ICH volume (<60 mL), baseline IVH volume (<5 mL), and age (<70 and <75 years) on adjusted OR comparing 80 μg/kg rFVIIa with placebo.
Table 1. Baseline Characteristics and Timing of Treatment*

<table>
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<th>Full Sample</th>
<th>Target Subgroup†</th>
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<td>Age, years</td>
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<td>National Institutes of Health Stroke Scale score‖</td>
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<td>Onset-to-needle time, minutes</td>
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*Values are mean±SD, median (range), or percent. Values may not add up to 100% because of rounding.
†Subgroup includes patients aged ≤70 years with baseline intracerebral hemorrhage volume <60 mL, baseline intraventricular hemorrhage volume <5 mL, and dosed within 2.5 hours. The available subjects from the FAST study totals 160 subjects (59 placebo, 46 20 µg/kg and 55 80 µg/kg rFVIIa, of which only the placebo and 80 µg/kg groups are presented).
‡More than one region could be involved per patient.
§Range, 15=normal, 3=deep coma.
‖Range, 0=normal, 42=coma with quadriplegia.

>60 mL was not associated with further improvement. After excluding patients with >5 mL IVH, the rFVIIa treatment effect became incrementally more favorable as the upper age limit was reduced.

**Target Subgroup**

We identified a target subgroup (n=114, 20% of the 565 FAST patients randomized to 80 µg/kg or placebo) composed of patients ≤70 years with baseline ICH volume <60 mL, IVH volume <5 mL, and time from onset to treatment ≤150 minutes. No major differences in demographics and baseline characteristics were observed between the 80 µg/kg and placebo groups in this analysis set, and it is particularly noteworthy that the proportions of patients with IVH at baseline were comparable between treatment groups (Table 1). The adjusted OR for poor outcome with rFVIIa treatment in this subgroup was 0.28 (95% CI, 0.08 to 1.06; P=0.03), an observation that almost attained formal statistical significance (an alpha threshold of 0.025 was applied because a one-sided test was used). The improved treatment signal of 80 µg/kg rFVIIa in the target subgroup was consistent across the full range of mRS scores (Figure 3), although this did not reach statistical significance in the small sample (P=0.16 using the Cochran-Mantel-Haenzel test for independence). Importantly, more patients in the 80 µg/kg rFVIIa group than in the placebo group achieved a good outcome after 90 days as defined by an mRS score of 0 or 1 (29% versus 23%, respectively).

The improved clinical outcome in the target subgroup corresponded with a more pronounced hemostatic effect; the model-estimated absolute differences in ICH volume growth at 24 hours when comparing 80 µg/kg with placebo was 3.8 mL in the entire FAST population and 7.3 mL in the target subgroup (P=0.02).

**External Validation of the Target Subgroup in a Separate Population**

To assess the robustness of this target subgroup, we calculated the adjusted OR for poor outcome among patients enrolled in the rFVIIa ICH Phase 2b trial who met criteria for inclusion in the target subgroup. Because no patients treated with 80 µg/kg rFVIIa in this subgroup had a poor outcome, the dose groups of 80 and 160 µg/kg were combined to increase the sample size and obtain a more reliable estimate of treatment effect. In an analysis of the Phase 2b study, the

Figure 3. mRS outcomes at Day 90 in the target subgroups (patients aged <70 years with baseline ICH volume <60 mL, baseline IVH volume <5 mL, and dosed within 150 minutes with rFVIIa).
estimated mean percentage changes in 24-hour ICH volume for 80 and 160 µg/kg rFVIIa were 14% and 11%, respectively, suggesting a similar biological effect with these doses and the appropriateness of combining the 2 dose groups. Of 291 eligible patients in this study, 56 (19%) satisfied the subgroup criteria. The OR for poor outcome with rFVIIa treatment relative to placebo in this patient subgroup was 0.02 (95% CI, 0.00 to 0.64; \(P\) 0.016). For comparison, the corresponding OR in the intention-to-treat population was 0.47 (95% CI, 0.28 to 0.79; \(P\) 0.008).

**Safety**
The safety profile of rFVIIa within the target subgroup was similar to that of the entire FAST study population (Table 2). Thromboembolic adverse events in the target subgroup were slightly more frequent in the group receiving 80 µg/kg than in the placebo group, but these differences were not significant.

**Discussion**
In our earlier Phase 2b “proof-of-concept” study, rFVIIa given at doses of 40, 80, or 160 µg/kg within 4 hours of symptom onset significantly reduced ICH volume growth in a dose-related fashion. Although this study was not powered to detect effects on clinical outcome, rFVIIa treatment was also associated with a significant 38% relative reduction in mortality and with improved functional outcome. The Phase 3 FAST trial, the largest trial of a medical therapy for ICH to date, was designed to confirm these findings, but failed to do so. The hemostatic effect of the 80 µg/kg dose of rFVIIa was replicated in FAST as was the 5% absolute increase in arterial thromboembolic events (primarily cerebral infarcts and asymptomatic myocardial enzyme elevations). However, the proportion of patients left severely disabled or dead (mRS score of 5 or 6) at 90 days was similar in the placebo group and in the rFVIIa treatment arms of 20 and 80 µg/kg.

A number of explanations for the neutral results of the FAST trial have been proposed, including an imbalance in the proportion of patients with IVH at baseline (41% in the 80 µg/kg group versus 29% in placebo) and the inclusion of very elderly patients at high risk for neurological and nonneurological causes of death. It also remains possible that rFVIIa might benefit a subset of patients who were overrepresented in the active treatment groups of the Phase 2b trial and underrepresented in FAST. Earlier rFVIIa treatment is asso-
associated with larger reductions in ICH growth and might improve the likelihood of impacting on outcome. Very elderly patients and those with massive ICH or IVH at baseline face a very high risk of poor outcome and might limit the ability of a hemostatic drug to produce clinical improvement.

In this exploratory post hoc analysis of data from the FAST trial, the goal was to identify a subgroup of patients that appeared to benefit from treatment with rFVIIa. We compared 80 μg/kg rFVIIa with placebo because of the superior hemostatic effect of this dose. First we systematically examined how setting upper limits for onset-to-treatment interval, age, ICH, and IVH volume as well as excluding patients with low GCS scores and infratentorial ICH affected the rFVIIa clinical treatment response. We found that rFVIIa-treated patients tended to fare best when the maximal onset-to-treatment interval was limited to 150 minutes and that there was a progressive reduction in the likelihood of poor outcome with rFVIIa as the upper age limit was lowered from 80 years. In contrast, limiting maximal ICH or IVH volume in isolation did not appear to influence the rFVIIa treatment effect substantially, nor did exclusion of patients with infratentorial hematomas.

Next, we systematically analyzed the rFVIIa treatment effect and sample size that resulted from combining various onset-to-treatment, age, and baseline lesion volume cut points. We established that a maximal onset-to-treatment interval of 150 minutes provided the best balance between optimization of the rFVIIa treatment effect and sample size. Among those treated within 150 minutes, the rFVIIa treatment effect incrementally improved as the upper age limit was lowered, but the magnitude of this effect was relatively small. Finally, limiting IVH volume to 5 mL led to fairly substantial reductions in the odds of poor outcome with rFVIIa treatment, whereas limiting ICH volume to ≤60 mL did not.

In the final analysis, a target subgroup was identified that met the following criteria: treatment within 150 minutes of onset, maximal age of 70 years, a maximal IVH volume 5 mL, and a maximal ICH volume of 60 mL. We elected to limit ICH volume despite the lack of evidence that this would improve the rFVIIa treatment effect because hemorrhages >60 mL are almost uniformly associated with a poor outcome. Reduction of the time interval from 4 to 2.5 hours resulted in a doubling of the reduction in ICH volume growth relative to placebo from 3.8 to 7.3 mL. Among patients enrolled in FAST who met the target subgroup criteria (19% of eligible trial population), rFVIIa was associated with 0.28 OR (95% CI, 0.08 to 1.06) of poor outcome at 3 months, a finding that just missed formal statistical significance. For comparison, the odds of poor outcome among all patients treated with 80 μg/kg rFVIIa in the FAST study population was 1.44 (95% CI, 0.88 to 2.21). The enhancement of the rFVIIa treatment effect in the Phase 2b trial population was even more pronounced. Among this subgroup (which comprised 19% of potentially eligible patients treated with 80 or 160 μg/kg rFVIIa), the odds of poor outcome compared with placebo was 0.02 (P=0.02) compared with 0.47 (P=0.01) in the entire study population. In a pooled analysis (unpublished data) of data from FAST and the Phase 2b study, the 80 and 160 μg/kg doses of rFVIIa resulted in a nearly identical hemostatic effect (an estimated mean percent increase in ICH volume of 11.8% and 11.9%, respectively).

When applied alone, none of the individual predictive criteria was sufficient to identify a patient population that would benefit significantly from rFVIIa therapy. Instead, a combination of criteria was required to enable selection of patients in whom trial drug intervention was likely to be successful. We recognize that the exact cut points we selected for age and lesion volume to define the target subgroup described may have been subjective. We also recognize the well-documented pitfalls that are inherent in post hoc analyses of clinical trial data. In considering further options for testing rFVIIa as an emergency treatment for ICH, however, analysis of existing trial data would appear to be the only practical way to move forward. We elected to develop the initial target subgroup using the FAST trial data set alone rather than a larger combined Phase 2 and 3 trial data set, because this afforded us the opportunity to externally validate our findings in a separate data set. It is possible that the enhancement of the rFVIIa treatment effect that occurred when patients with >5 mL of IVH were excluded had more to do with eliminating the randomization imbalance than with the tendency of IVH to blunt the clinical benefits of rFVIIa. We also recognize that if patients with >5 mL of IVH were to be excluded from a future trial of rFVIIa for ICH, a simple, rapid, and reproducible scale that can identify these patients needs to be developed. Although a strict age criteria of 70 years could be considered when choosing a proposed candidate subgroup for further study, a broadening of the age criteria to 75 years of age could be considered if the study was sufficiently powered, because this would be more reflective of an appropriate age range for the ICH population. Finally, patients treated with 80 μg/kg rFVIIa in the target population had a small but nonsignificant increase in the frequency of thromboembolic complications than those in placebo. Any further testing should continue to carefully monitor safety.

Although the FAST results were disappointing, this trial has taught us 2 important lessons. First, we learned that the magnitude of the rFVIIa hemostatic effect when given within 4 hours does not simply translate into a consistent and reproducible clinical benefit. Further development of hemostatic therapy for ICH must focus on the identification of patients who are at high risk for hematoma growth and the exclusion of patients who are not at risk for further bleeding. In addition to earlier treatment, a promising way to identify patients with ICH at high risk for active bleeding is the demonstration of contrast extravasation into the hematoma on CT angiography. Second, the post hoc analysis that we performed suggests that the relationship between smaller stroke lesion volumes and improved clinical outcomes is easier to demonstrate when younger patients are studied. This may be because older patients are more likely to sustain hospital-acquired infections and other medical complications that are not always directly related to the severity of the initial neurological insult. Advanced age may be associated with worse neurological injury from ICH independent of size or location, and medical care decisions in elderly patients may...
be less aggressive. Without an upper age limit, it is quite possible that recent trials showing a beneficial effect with hemicraniectomy (age <60 years) for massive cerebral infarction"or hypothermia (age <75 years) for cardiac arrest," for instance, might have been negative.

Given the current lack of effective treatment and the dismal outcomes that most patients with ICH experience, there is a compelling rationale to continue to explore the potential benefits of hemosstatic therapy for ICH. A prospective trial would be needed to determine whether younger patients with ICH who have not already experienced extensive bleeding can benefit from 80 μg/kg rFVIIa given within 150 minutes of symptom onset. We appreciate that this may represent a significantly smaller study population of all ICH. If efficacy could be confirmed in this subgroup, however, this could serve as a spark for future studies directed at expanding the time window and age limit by identifying patients at high risk for active bleeding on the basis of novel imaging techniques. We have witnessed a similar story in the case of intravenous tissue plasminogen activator for acute ischemic stroke. Although tissue plasminogen activator is still used to treat only approximately 4% of ischemic stroke victims, it has stimulated the development of intravenous–intra-arterial bridging therapy, intra-arterial thrombolysis, and mechanical clot retractor devices, all designed to expand the time window for reperfusion. It seems intuitive that the simplest, quickest, and most broadly applicable way to treat patients with ICH who present rapidly is to give an intravenous dose of a hemostatic agent. However, the identification of this target subgroup should be viewed as hypothesis-generating only and will require prospective confirmation.

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