Published in final edited form as:

Neurocrit Care. 2009 ; 10(1): 28–34. doi:10.1007/s12028-008-9134-3.

Risk of Thromboembolism Following Acute Intracerebral Hemorrhage

Joshua N. Goldstein,

Department of Emergency Medicine, Massachusetts General Hospital, Zero Emerson Place,
Suite 3B, Boston, MA 02114, USA

Louis E. Fazen,

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

The Center for Human Genetic Research, Massachusetts General Hospital, Boston, MA, USA

Lauren Wendell,

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

Yuchiao Chang,

Department of Medicine, Massachusetts General Hospital, Boston, MA, USA

Natalia S. Rost,

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

The Center for Human Genetic Research, Massachusetts General Hospital, Boston, MA, USA

Ryan Snider,

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

The Center for Human Genetic Research, Massachusetts General Hospital, Boston, MA, USA

Kristin Schwab,

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

Rishi Chanderraj,

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

Christopher Kabrhel,

Department of Emergency Medicine, Massachusetts General Hospital, Zero Emerson Place,
Suite 3B, Boston, MA 02114, USA

Catherine Kinnecom,

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

Emilie FitzMaurice,

© Humana Press Inc. 2008

jgoldstein@partners.org.

Disclosures The sponsors had no role in the design or conduct of the study; data collection, management, analysis, or interpretation; or preparation, review, or approval of the manuscript. Dr. Goldstein had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Dr. Rosand has received research support from NovoNordisk A/S. Dr. Goldstein has received consulting fees from Novo Nordisk A/S, CSL Behring, and Genentech. The remaining authors report no conflict of interest.

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

Eric E. Smith,

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

Steven M. Greenberg, and

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

Jonathan Rosand

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

The Center for Human Genetic Research, Massachusetts General Hospital, Boston, MA, USA

Abstract

Introduction—Intracerebral hemorrhage (ICH) is the most feared complication of oral anticoagulant therapy (OAT). While anticoagulated patients have increased severity of bleeding following ICH, they may also be at increased risk for thromboembolic events (TEs) given that they had been prescribed OAT prior to their ICH. We hypothesized that TEs are relatively common following ICH, and that anticoagulated patients are at higher risk for these complications.

Methods—Consecutive patients with primary ICH presenting to a tertiary care hospital from 1994 to 2006 were prospectively characterized and followed. Hospital records were retrospectively reviewed for clinically relevant in-hospital TEs and patients were prospectively followed for 90-day mortality.

Results—For 988 patients of whom 218 (22%) were on OAT at presentation, median hospital length of stay was 7 (IQR 4–13) days and 90-day mortality was 36%. TEs were diagnosed in 71 patients (7.2%) including pulmonary embolism (1.8%), deep venous thrombosis (1.1%), myocardial ischemia (1.6%), and cerebrovascular ischemia (3.0%). Mean time to event was 8.4 ± 7.0 days. Rates of TE were 5% among those with OAT-related ICH and 8% among those with non-OAT ICH ($P = 0.2$). After multivariable Cox regression, the only independent risk factor for developing a TE was external ventricular drain placement (HR 2.1, 95% CI 1.1–4.1, $P = 0.03$). TEs had no effect on 90-day mortality (HR 0.7, 95% CI 0.5–1.1, $P = 0.1$).

Conclusions—The incidence of TEs in an unselected ICH population was 7.2%. Patients with OAT-related ICH were not at increased risk of TEs.

Keywords

Cerebral hemorrhage; Warfarin; Venous thrombosis; Pulmonary embolism; Brain ischemia; Myocardial ischemia

Introduction

Intracerebral hemorrhage (ICH) is the most fatal form of stroke, and survivors suffer high rates of functional disability [1]. A substantial proportion of this morbidity may be due to thromboembolic complications such as deep venous thrombosis (DVT), pulmonary embolism (PE), and myocardial ischemia (MI) [2–4]. While use of heparinoids following ischemic stroke appears to reduce the risk of DVT and is recommended by national

organizations [5], there is controversy over whether and when to initiate this intervention [6, 7]. In patients with ICH, DVT prophylaxis with anticoagulants may be delayed due to concerns of excess bleeding risk [8]. National guidelines reflect the tremendous uncertainty surrounding this issue, including whether or when to initiate heparinoids or even resume anticoagulation following ICH [9, 10].

Patients receiving oral anticoagulation (OAT) for prevention of thromboembolism account for up to 25% of ICH patients [11, 12]. While emergent reversal of anticoagulation is considered standard treatment for OAT-related ICH, the risks and benefits of this intervention are not known. These patients may be at particular risk of thromboembolic events (TEs) complicating cessation or reversal of anticoagulation [13]. Concerns regarding TE risks contribute to wide variation in practice and apparent underutilization of parenteral vitamin K [14–16]. It is difficult to evaluate whether such concerns are justified in the absence of data on the rate and frequency of TEs.

Accurate measurement of TE risk following ICH has clinical implications for patients whose ICH is unrelated to anticoagulation as well. Clinical trials of hemostatic therapy demonstrate that these agents may arrest ongoing bleeding and prevent hematoma expansion, but increase the risk of TEs [17]. Rates of TE were relatively low in these trials, but patients were selected to minimize underlying TE risk factors and were healthier than the average ICH population [18]. Furthermore, patients receiving OAT at the time of ICH, presumably because of a baseline increased risk of TE, were excluded. While case reports describing adverse events following use of factor VIIa have raised concerns that “real world” risks of TE may be higher [19–21], the expected rate of such events during the natural course of the disease is not known. We hypothesized that the rate of TEs in an unselected ICH cohort would be higher than the previously reported 2%, and that such events would be more frequent in patients taking warfarin at the time of presentation.

Methods

Patient Selection and Data Collection

This was a retrospective review of prospectively collected data on ICH outcome [11, 22]. We identified consecutive patients with ICH who presented to a tertiary care hospital from 1994 to 2006. Patients with secondary causes of ICH including head trauma, ischemic stroke with hemorrhagic transformation, tumor, vascular malformation, or vasculitis were excluded. In addition, patients who developed ICH while in hospital for another reason were excluded from this analysis. All aspects of the study were approved by the Institutional Review Board.

Subjects or their surrogates were prospectively interviewed when available for clinical data including history of diabetes (DM), coronary artery disease (CAD), and medications. Use of any antiplatelet agent was documented; in 97% of those taking such a medication, the agent was aspirin. For anticoagulated patients, the indication for anticoagulation was captured. No patients were receiving intravenous heparin at the time of presentation. Laboratory studies including serum glucose and international normalized ratio of the prothrombin time (INR) were recorded as the first levels available. The first documented systolic blood pressure

(SBP) was recorded as “admission SBP.” Admission Glasgow Coma Scale (GCS) score was recorded from the emergency department (ED) note or admission note when available. In order to capture long-term mortality, consenting patients were followed by telephone interview every 6 months, and the Social Security Death Index was reviewed every 6 months.

ICH volumes were determined from baseline CT scans as previously described [23]. Images were electronically transferred in DICOM format to a dedicated workstation for analysis using Alice™ software (Parexel Corporation, Waltham, MA, USA) and reviewed by study staff blinded to the patient's clinical status according to a method with high inter-rater reliability [23]. Acquisition of CT as digitized DICOM images began in 1998 and therefore hematoma volumes were not measured for 28% of the cohort. Hematoma location was categorized as lobar versus nonlobar on the basis of the CT scan by one of the study neurologists based on previously established criteria [11]. The presence of intraventricular hemorrhage (IVH) was scored as a dichotomous variable.

While the above data were collected prospectively, the development of any TE within 30 days following admission was determined retrospectively through structured review of patient discharge summaries, radiology reports, autopsy reports, paper charts, and cardiac enzyme levels for all patients with ICH presenting from July 1, 1994 to June 1, 2006. TEs were categorized as deep vein thrombosis (DVT), pulmonary embolism (PE), cerebral ischemia (CI), and myocardial ischemia (MI). We screened for cerebral venous sinus thrombosis or and arteriovenous graft thrombosis, but no patient suffered was diagnosed with either event. Events occurring following after presentation and during the initial hospitalization up to 30 days were scored. For DVT and PE, diagnoses were confirmed by radiology or autopsy report. DVTs were predominantly located in the lower limbs. As the diagnosis of acute coronary syndrome can be difficult to make in the setting of ICH [24], MI was operationally defined as any diagnosis of clinically relevant myocardial injury, ischemia, or infarction in the discharge summary. Similarly, CI can be difficult to diagnose given radiologic abnormalities that occur during the course of ICH; therefore, clinically relevant ischemic events were operationally defined as those considered significant by the treating team. A structured review was performed including computerized search terms such as “ischemia,” “ischemic,” “infarction,” “injury,” followed by research assistant and physician review. All TEs were adjudicated by at least one of three physician reviewers (JNG, EES, and JR). A structured chart review was performed to determine use of heparinoids and warfarin. All patients received pneumatic compression stockings during the study period.

Data Analysis

As most clinical trials report both arterial and venous TEs together as a single type of adverse event, our primary analysis used any TE as the outcome. In secondary analyses, TEs were separated into arterial versus venous events, as these likely represent different pathophysiologic processes. Time to TE event was analyzed with Cox proportional hazards models, and was scored as number of days to any TE, censored by death, hospital discharge, or 30 days from presentation, whichever occurred first. Multivariable analysis was

performed with a backward selection Cox regression model, including variables associated ($P < 0.2$) in univariate analysis, and removing variables in a stepwise fashion for $P > 0.1$. To compare time to arterial versus venous events, a competing risk analysis comparing the hazard functions from the two types of event was performed. An additional survival analysis was performed for time to death, censored at 90 days from presentation with TE event treated as a time-dependent covariate. Data on several variables were missing in more than 3% of cases including hypertension (3%), glucose (4%), SBP (7%), GCS (9%), CAD (10%), and ICH volume (28%). These variables were treated as categorical variables with an additional category for missing values in the analysis. ICH volume and GCS were categorized as previously published [25], and SBP was dichotomized at 180 mmHg. Lack of data was not associated with outcome. All analyses were performed with SAS software version 9.1 (SAS Institute, Cary, NC, USA).

Results

Out of a total of 1,046 patients presenting to our hospital with primary ICH during the study interval, complete records and radiology reports were available for 1004. Sixteen patients were enrolled in clinical trials of activated factor VII [26, 27]; as we could not determine whether they received placebo or drug, these patients were excluded, leaving 988 patients for analysis. Of these 988 patients, 71 (7.2%) developed a TE within 30 days of initial hospitalization (Table 1). The mean number of days to event among those who developed a TE was 8.4 ± 7.0 , and the incidence rate of TEs was 0.08 events/10 person-days. A total of 45 arterial events occurred (MI, CI), compared with 26 venous events (PE, DVT). In four patients, two events occurred (3 with both PE and DVT, 1 with both MI and CI); for these patients, the first event was scored for analysis. Arterial events were detected earlier than venous events (competing hazards model, $P = 0.001$). Hospital length of stay ranged from 1 to 185 days with a median of 7 (IQR 4–13) days. Out of 988 patients, 218 (22%) patients were taking warfarin at the time of ICH; common indications for anticoagulation were atrial fibrillation (47%), history of stroke or TIA (17%), prosthetic valve (8%), CAD (3%), history of DVT (3%), and PE (0.5%). Twelve patients in this cohort had prosthetic valves. Of the patients with OAT-ICH, 89% received warfarin reversal agents, including vitamin K (80%) and FFP (79%), and 6% were restarted on warfarin during their hospital stay. No patients received activated factor VII, which is not available at our hospital outside of a clinical trial.

Patients with OAT-related ICH were not at increased risk for developing in-hospital TEs (HR 0.6, 95% CI 0.3–1.2, $P = 0.2$) (Fig. 1). Among those who developed a TE (Table 2), 14% were taking warfarin at time of ICH compared to 23% in those who did not develop a TE. In order to assess whether the risk of TE in prior OAT users might be underestimated as a result of disproportionately early death, we restricted our analysis to those patients who were alive and still in-hospital after 10 days. Within this cohort of 347 patients, OAT users were not at increased risk of TEs (HR 0.6, 95% CI 0.3–1.3, $P = 0.2$). Table 3 shows that after multivariable analysis using Cox regression, including variables associated ($P < 0.2$) in univariate analysis, and removing variables in a stepwise fashion for $P > 0.1$, use of warfarin at the time of ICH did not mark an independent change in risk of TE (HR 0.7, 95% CI 0.3–1.3).

Finally, when arterial and venous events were analyzed separately (Table 4), we again found no increase in risk among patients with OAT-ICH. After multivariable Cox regression, there was no effect of OAT use, but we did note that patients with high blood pressure at triage were more likely to develop arterial TEs (HR 2.4, 1.2–4.8, $P = 0.02$). In addition, arterial TEs were less likely to be diagnosed following institution of a “Do Not Resuscitate” or “Comfort Measures Only” (DNR/CMO) order (HR 0.3, 95% CI 0.2–0.7, $P = 0.004$). None of the variables included were independent predictors of venous TEs.

We evaluated whether particular in-hospital interventions might be associated with risk of subsequent TE. There were 14/218 (6%) individuals with OAT-related ICH in whom warfarin anticoagulation was resumed after 10 days (IQR 3–20) following hospital admission. There was no apparent effect of reinstitution of warfarin on risk of any TE (HR 1.9, 95% CI 0.3–14, $P = 0.5$). Two hundred and nineteen patients received a heparinoid product at some point during their hospitalization. Use of any heparinoid (as a time-varying covariate) had no independent effect on risk of TE (HR 1.7, 95% CI 0.97–3.0) in multivariable Cox regression. Median time to initiation of a heparinoid was 4 (IQR 2–7) days. There did appear to be an increased frequency of arterial TEs in heparinoid-treated patients (Table 4).

Development of a TE had no independent effect on 90-day mortality (Table 3). In multivariable Cox regression, the most powerful predictors of mortality were institution of a DNR order (HR 5.3, 95% CI 4.1–6.9, $P < 0.0001$) and low GCS score (HR 8.6, 95% CI 6.2–12, $P < 0.0001$).

Conclusions

The rate of TEs in a large unselected ICH population is higher than that observed in recent clinical trials of ICH [26, 28]. It is possible that these trials, by excluding patients with low GCS scores and poor premorbid functional capacity, selected for patients at lower risk for such events. Indeed, most patients presenting with ICH do not meet these inclusion criteria [18, 29], and TEs may be more common in real-world populations than clinical trials [30]. The higher rate described in the present study may more accurately reflect outcomes in the typical ICH patient population.

Contrary to our primary hypothesis, patients taking warfarin at the time of ICH were not at increased risk of in-hospital TEs, whether arterial or venous. If anything, multivariable analysis suggested a trend toward fewer events in such patients. It may be that warfarin patients are more likely to receive early and aggressive in-hospital thromboprophylaxis, thus decreasing their risk for TEs. Inadequate warfarin reversal may also play a role, causing these patients to be persistently anticoagulated. However, in an overlapping cohort of 69 patients with warfarin-associated ICH, 83% achieved an INR < 1.4 within 24 h [14], suggesting that warfarin reversal was typically complete within the first day. In addition, in the present study, we found that controlling for institution of heparinoids and re-institution of warfarin did not affect our results. It is possible that early death among anticoagulated patients might have disproportionately reduce the duration of exposure to risk of in-hospital TEs. However, we controlled for this both with a Cox proportional hazards model, and by

analyzing only those patients who survived for 10 days. In conclusion, if anticoagulated patients are at higher risk of TEs, this increased risk must be extremely small.

Patients who received EVDs were more likely to develop TEs. This effect was independent of the presence of IVH. We were unable to examine whether EVD indication such as the presence of hydrocephalus may in fact account for this relationship, with the procedure itself simply serving as a marker for more severe underlying disease. While EVD placement may limit patients' mobility, placing them at increased risk for venous thromboembolism, it appears that arterial rather than venous TEs account for much of this excess risk.

Patients treated with heparinoids during hospitalization (32% of patients in this cohort) had more arterial TEs without a significant reduction in venous TEs. The reasons for this are not clear. The apparent effect on arterial TEs likely reflects that physician teams preferentially selected those patients for heparinoid treatment who they deemed to be at higher risk of TE. As far as prevention of venous TE, the use of heparinoids at all has been controversial, as any benefit of preventing venous TEs may be offset by an increased bleeding risk [31–33]. However, the use of heparinoids is currently recommended even in ICH patients [9, 10], and were likely underutilized in this cohort until recently. While pneumatic compression reduces the risk of DVT, approximately 5% of ICH patients treated with these still develop DVTs [3]. Determining the effect of heparinoids on risk of TEs, and defining the optimal dose and timing of DVT prophylaxis to maximize benefit while minimizing risk, will require further clinical trials.

There are a number of limitations to our analysis. First, this was a retrospective study; TEs were not prospectively ascertained, and were investigated at the discretion of care providers, a process which can underestimate their frequency [30]. Second, clinical care was not standardized, so it is difficult to measure the effect of potential confounders such as type of anticoagulation reversal, time of initiation of thromboembolism prophylaxis, or resumption of warfarin. In addition, some features of clinical management and neurocritical care may have changed during the study period. Third, while occurrence of DVT or PE can be clearly defined radiographically, this is not necessarily true of CI or MI. Abnormal radiographic findings concerning for cerebral ischemia were not uncommon, and often considered clinically irrelevant. Therefore, in order to maximize reliability, we operationally required a comment in the discharge summary regarding the relevance of any finding. As the quality and comprehensiveness of discharge summaries may be variable, true cerebral ischemic events are likely to be even more common than reported here. Similarly, myocardial ischemia can be difficult to diagnose in patients with ICH. Electrocardiographic abnormalities are relatively common [34], and there is debate as to whether cardiac enzyme elevations reflect coronary thromboocclusive disease in this setting (or whether the cutoff used to diagnose myocardial ischemia should be different) [35, 36]. Prospective studies including systematic examination of myocardial function [37] are necessary to determine how best to diagnose acute coronary syndrome in this setting. Finally, this cohort in a single academic center may not be fully representative of those seen in community hospitals or other academic settings.

In conclusion, the rate of TEs in an unselected ICH cohort was substantially higher than that reported in the placebo arms of recent clinical trials. Furthermore, patients taking warfarin at the time of ICH do not appear to be at increased risk of developing adverse TEs, despite possessing an indication for anticoagulation.

Acknowledgements

This work was supported by an unrestricted research grant from Novo Nordisk A/S, the Miles and Eleanor Shore 50th Anniversary Fellowship Award, the National Institute of Neurological Disorders and Stroke (NIH 1 K23 NS42695, R01 NS04217), and the Jerome Lyle Rappaport Charitable Foundation.

References

1. Towfighi A, Greenberg SM, Rosand J. Treatment and prevention of primary intracerebral hemorrhage. *Semin Neurol*. 2005; 25:445–52. doi:10.1055/s-2005-923538. [PubMed: 16342000]
2. Silver FL, Norris JW, Lewis AJ, Hachinski VC. Early mortality following stroke: a prospective review. *Stroke*. 1984; 15:492–6. [PubMed: 6729878]
3. Lacut K, Bressollette L, Le Gal G, Etienne E, De Tinteni A, Renault A, et al. Prevention of venous thrombosis in patients with acute intracerebral hemorrhage. *Neurology*. 2005; 65:865–9. doi:10.1212/01.wnl.0000176073.80532.a2. [PubMed: 16186525]
4. Kelly J, Rudd A, Lewis RR, Coshall C, Moody A, Hunt BJ. Venous thromboembolism after acute ischemic stroke: a prospective study using magnetic resonance direct thrombus imaging. *Stroke*. 2004; 35:2320–5. doi:10.1161/01.STR.0000140741.13279.4f. [PubMed: 15322298]
5. Adams HP Jr, del Zoppo G, Alberts MJ, Bhatt DL, Brass L, Furlan A, et al. Guidelines for the early management of adults with ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups: the American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists. *Stroke*. 2007; 38:1655–711. doi:10.1161/STROKEAHA.107.181486. [PubMed: 17431204]
6. Adams HP Jr. Effective prophylaxis for deep vein thrombosis after stroke: low-dose anticoagulation rather than stockings alone: for. *Stroke*. 2004; 35:2911–2. doi:10.1161/01.STR.0000147720.27350.09. [PubMed: 15499030]
7. Dennis MS. Effective prophylaxis for deep vein thrombosis after stroke: low-dose anticoagulation rather than stockings alone: against. *Stroke*. 2004; 35:2912–3. doi:10.1161/01.STR.0000147721.75537.ef. [PubMed: 15514184]
8. Bath PM, Iddenden R, Bath FJ. Low-molecular-weight heparins and heparinoids in acute ischemic stroke: a meta-analysis of randomized controlled trials. *Stroke*. 2000; 31:1770–8. [PubMed: 10884486]
9. Broderick J, Connolly S, Feldmann E, Hanley D, Kase C, Krieger D, et al. Guidelines for the management of spontaneous intra-cerebral hemorrhage in adults: 2007 update: a guideline from the American Heart Association/American Stroke Association Stroke Council, High Blood Pressure Research Council, and the Quality of Care and Outcomes in Research Interdisciplinary Working Group. *Stroke*. 2007; 38:2001–23. doi:10.1161/STROKEAHA.107.183689. [PubMed: 17478736]
10. Steiner T, Kaste M, Forsting M, Mendelow D, Kwiecinski H, Szikora I, et al. Recommendations for the management of intracranial haemorrhage—Part I: spontaneous intracerebral haemorrhage. The European Stroke Initiative Writing Committee and the Writing Committee for the EUSI Executive Committee. *Cerebrovasc Dis*. 2006; 22:294–316. [PubMed: 16926557]
11. Rosand J, Eckman MH, Knudsen KA, Singer DE, Greenberg SM. The effect of warfarin and intensity of anticoagulation on outcome of intracerebral hemorrhage. *Arch Intern Med*. 2004; 164:880–4. doi:10.1001/archinte.164.8.880. [PubMed: 15111374]
12. Flaherty ML, Kissela B, Woo D, Kleindorfer D, Alwell K, Sekar P, et al. The increasing incidence of anticoagulant-associated intracerebral hemorrhage. *Neurology*. 2007; 68:116–21. doi:10.1212/01.wnl.0000250340.05202.8b. [PubMed: 17210891]

13. Bertram M, Bonsanto M, Hacke W, Schwab S. Managing the therapeutic dilemma: patients with spontaneous intracerebral hemorrhage and urgent need for anticoagulation. *J Neurol*. 2000; 247:209–14. doi:10.1007/s004150050565. [PubMed: 10787117]
14. Goldstein JN, Thomas SH, Frontiero V, Joseph A, Engel C, Snider R, et al. Timing of fresh frozen plasma administration and rapid correction of coagulopathy in warfarin-related intracerebral hemorrhage. *Stroke*. 2006; 37:151–5. doi:10.1161/01.STR.0000195047.21562.23. [PubMed: 16306465]
15. Brody DL, Aiyagari V, Shackleford AM, Diringner MN. Use of recombinant factor VIIa in patients with warfarin-associated intracranial hemorrhage. *Neurocrit Care*. 2005; 2:263–7. doi: 10.1385/NCC:2:3:263. [PubMed: 16159073]
16. Sjoblom L, Hardemark HG, Lindgren A, Norrving B, Fahlen M, Samuelsson M, et al. Management and prognostic features of intracerebral hemorrhage during anticoagulant therapy: a Swedish multicenter study. *Stroke*. 2001; 32:2567–74. doi:10.1161/hs1101.098523. [PubMed: 11692018]
17. Diringner MN, Skolnick BE, Mayer SA, Steiner T, Davis SM, Brun NC, et al. Risk of thromboembolic events in controlled trials of rFVIIa in spontaneous intracerebral hemorrhage. *Stroke*. 2008; 39(3):850–6. [PubMed: 18239180]
18. Flaherty ML, Woo D, Haverbusch M, Moomaw CJ, Sekar P, Sauerbeck L, et al. Potential applicability of recombinant factor VIIa for intracerebral hemorrhage. *Stroke*. 2005; 36:2660–4. doi:10.1161/01.STR.0000189634.08400.82. [PubMed: 16269646]
19. Greenberg SM. Is “compassionate use” compassionate? rFVIIa for intracerebral hemorrhage. *Neurology*. 2006; 67:934. doi: 10.1212/01.wnl.0000239801.90927.80. [PubMed: 17000956]
20. Sugg RM, Gonzales NR, Matherne DE, Ribo M, Shaltoni HM, Baraniuk S, et al. Myocardial injury in patients with intracerebral hemorrhage treated with recombinant factor VIIa. *Neurology*. 2006; 67:1053. doi:10.1212/01.wnl.0000239154.51331.c4. [PubMed: 17000976]
21. O'Connell KA, Wood JJ, Wise RP, Lozier JN, Braun MM. Thromboembolic adverse events after use of recombinant human coagulation factor VIIa. *JAMA*. 2006; 295:293–8. doi:10.1001/jama.295.3.293. [PubMed: 16418464]
22. O'Donnell HC, Rosand J, Knudsen KA, Furie KL, Segal AZ, Chiu RI, et al. Apolipoprotein E genotype and the risk of recurrent lobar intracerebral hemorrhage. *N Engl J Med*. 2000; 342:240–5. doi:10.1056/NEJM200001273420403. [PubMed: 10648765]
23. Flibotte JJ, Hagan N, O'Donnell J, Greenberg SM, Rosand J. Warfarin, hematoma expansion, and outcome of intracerebral hemorrhage. *Neurology*. 2004; 63:1059–64. [PubMed: 15452298]
24. Kopelnik A, Zaroff JG. Neurocardiogenic injury in neurovascular disorders. *Crit Care Clin*. 2006; 22:733–52. abstract ix–x. doi:10.1016/j.ccc.2006.06.002. [PubMed: 17239752]
25. Hemphill JC III, Bonovich DC, Besmertis L, Manley GT, Johnston SC. The ICH score: a simple, reliable grading scale for intracerebral hemorrhage. *Stroke*. 2001; 32:891–7. [PubMed: 11283388]
26. Mayer SA, Brun NC, Begtrup K, Broderick J, Davis S, Diringner MN, et al. Recombinant activated factor VII for acute intracerebral hemorrhage. *N Engl J Med*. 2005; 352:777–85. doi:10.1056/NEJMoa042991. [PubMed: 15728810]
27. Mayer SA, Brun NC, Broderick J, Davis SM, Diringner MN, Skolnick BE, et al. Recombinant activated factor VII for acute intracerebral hemorrhage: US phase IIA trial. *Neurocrit Care*. 2006; 4:206–14. doi:10.1385/NCC:4:3:206. [PubMed: 16757825]
28. Lyden PD, Shuaib A, Lees KR, Davalos A, Davis SM, Diener HC, et al. Safety and tolerability of NXY-059 for acute intra-cerebral hemorrhage: the CHANT Trial. *Stroke*. 2007; 38:2262–9. doi: 10.1161/STROKEAHA.106.472746. [PubMed: 17569876]
29. Nadeau JO, Phillips S, Shi HS, Kapral MK, Gladstone DJ, Silver FL, et al. Intracerebral hemorrhage: outcomes and eligibility for factor VIIa treatment in a National Stroke Registry. *Cerebrovasc Dis*. 2006; 22:271–5. doi:10.1159/000094015. [PubMed: 16788301]
30. Reynolds MW, Shibata A, Zhao S, Jones N, Fahrbach K, Goodnough LT. Impact of clinical trial design and execution-related factors on incidence of thromboembolic events in cancer patients: a systematic review and meta-analysis. *Curr Med Res Opin*. 2008; 24(2):497–505. [PubMed: 18194590]

31. Kelly J, Rudd A, Lewis R, Hunt BJ. Venous thromboembolism after acute stroke. *Stroke*. 2001; 32:262–7. [PubMed: 11136946]
32. Boer A, Voth E, Henze T, Prange HW. Early heparin therapy in patients with spontaneous intracerebral haemorrhage. *J Neurol Neurosurg Psychiatry*. 1991; 54:466–7. [PubMed: 1865215]
33. Dickmann U, Voth E, Schicha H, Henze T, Prange H, Emrich D. Heparin therapy, deep-vein thrombosis and pulmonary embolism after intracerebral hemorrhage. *Klin Wochenschr*. 1988; 66:1182–3. doi:10.1007/BF01727666. [PubMed: 3062268]
34. Khechinashvili G, Asplund K. Electrocardiographic changes in patients with acute stroke: a systematic review. *Cerebrovasc Dis*. 2002; 14:67–76. doi:10.1159/000064733. [PubMed: 12187009]
35. Maramattom BV, Manno EM, Fulgham JR, Jaffe AS, Wijdicks EF. Clinical importance of cardiac troponin release and cardiac abnormalities in patients with supratentorial cerebral hemorrhages. *Mayo Clin Proc*. 2006; 81:192–6. [PubMed: 16471073]
36. Hays A, Diringer MN. Elevated troponin levels are associated with higher mortality following intracerebral hemorrhage. *Neurology*. 2006; 66:1330–4. doi:10.1212/01.wnl.0000210523.22944.9b. [PubMed: 16682662]
37. Jensen JK, Kristensen SR, Bak S, Atar D, Hoiland-Carlsen PF, Mickley H. Frequency and significance of troponin T elevation in acute ischemic stroke. *Am J Cardiol*. 2007; 99:108–12. doi: 10.1016/j.amjcard.2006.07.071. [PubMed: 17196472]

Fig. 1. Kaplan-Meier analysis of the rate of TE development. Data are stratified according to whether patients were taking warfarin at the time of ICH

Table 1

Frequency of thromboembolic events

Event	Total N = 988 (100%)	Days to event Mean $\pm$ SD	Incidence rate (per 10 person-days)
Any event	71 (7.2)	8.4 $\pm$ 7.0	0.08
Any arterial event ^a	45 (4.6)	6.1 $\pm$ 4.8	0.05
MI	16 (1.6)	6.9 $\pm$ 5.7	0.02
CI	30 (3.0)	5.9 $\pm$ 4.4	0.03
Any venous event ^a	26 (2.6)	12 $\pm$ 8.5	0.03
PE	18 (1.8)	11 $\pm$ 7.9	0.02
DVT	11 (1.1)	18 $\pm$ 9.0	0.01

^aTable reflects number of patients suffering an event rather than number of events; therefore, numbers do not add up to 100%

Table 2

Clinical characteristics of patients with TEs

	Thromboembolic event		Hazard ratio (95% CI)	P value
	No (N = 917)	Yes (N = 71)		
Age	74 (66–81)	72 (58–79)	0.9 (0.7–1.0)	0.1
Male sex	53%	62%	1.4 (0.9–2.3)	0.1
<i>Past medical history</i>				
HTN	74%	80%	1.2 (0.7–2.2)	0.5
DM	18%	21%	1.3 (0.8–2.4)	0.3
CAD	21%	17%	0.8 (0.4–1.5)	0.5
AF	11%	10%	1.0 (0.4–2.1)	0.9
Stroke	16%	23%	1.5 (0.8–2.6)	0.2
ICH	7%	4%	0.7 (0.2–2.2)	0.5
<i>Medications at the time of presentation</i>				
Antiplatelet agent	35%	41%	1.5 (0.9–2.3)	0.1
Warfarin	23%	14%	0.6 (0.3–1.2)	0.2
<i>Laboratory findings on admission</i>				
Serum Glucose (mg/dl)				
<140	49%	37%	Reference	
140–200	29%	32%	1.3 (0.7–2.2)	0.4
>200	18%	24%	1.8 (1.0–3.4)	0.05
For those on warfarin				
INR < 2	18%	30%	Reference	
INR 2–3	37%	20%	0.4 (0.1–2.4)	0.3
INR > 3	40%	50%	0.9 (0.2–3.6)	0.8
<i>Clinical presentation</i>				
GCS score				
3–4	15%	13%	1.5 (0.7–3.2)	0.3
5–12	28%	39%	1.2 (0.7–2.0)	0.5
13–15	48%	44%	Reference	
Systolic blood pressure (mmHg)				
<180	46%	35%		
180	47%	58%	1.6 (1.0–2.6)	0.07
ICH volume (cc)				
< 30	43%	48%		
30–59	13%	17%	1.0 (0.5–2.0)	0.9
60	15%	17%	1.4 (0.7–2.7)	0.3
IVH	44%	46%	1.0 (0.6–1.6)	1.0
Lobar location	42%	35%	0.8 (0.5–1.4)	0.5
<i>In hospital management</i>				
Hematoma evacuation	4%	11%	1.7 (0.8–3.5)	0.2
EVD	4%	15%	2.5 (1.3–1.8)	0.005

	Thromboembolic event			
	No (N = 917)	Yes (N = 71)	Hazard ratio (95% CI)	P value
LOS	7 (4–13)	17(12–32)	1.01 (1.0–1.02)	0.1

Continuous variables are summarized using median with interquartile range

Abbreviations: HTN, hypertension; CAD, coronary artery disease; DM, diabetes mellitus; AF, atrial fibrillation; ICH, intracerebral hemorrhage; GCS, Glasgow Coma Scale; EVD, external ventricular drain placement; LOS, hospital length of stay

Table 3

Multivariable analyses of clinical factors associated with thromboembolic events and 90 day mortality

Variable	HR (95% CI)	P value
<i>Hazard ratio for any TE</i>		
Warfarin use	0.7 (0.3–1.3)	0.2
EVD	2.1 (1.1–1.1)	0.03
Heparinoid	1.7 (0.97–3.0)	0.06
<i>Hazard ratio for mortality</i>		
TE	0.7 (0.5–1.1)	0.1
DNR order	5.3 (4.1–6.9)	< 0.0001
Age (per 10 years)	1.3 (1.2–1.5)	< 0.0001
Serum glucose > 200 mg/dl	1.8 (1.4–2.4)	< 0.0001
GCS 3–4	8.6 (6.2–12)	< 0.0001
GCS 5–12	2.6 (1.9–3.5)	< 0.0001
ICH volume 30–59 cc	1.5 (1.1–2.0)	0.02
ICH volume 60 cc	2.9 (2.2–3.9)	< 0.0001
SBP 180 mmHg	1.5 (1.2–1.9)	0.0006
Warfarin	1.5 (1.2–1.9)	0.006
IVH	1.3 (1.0–1.7)	0.02
Male sex	1.2 (1.0–1.5)	0.06

Table 4

Clinical factors associated with arterial and venous thromboembolic events

	<u>Arterial TE</u>		<u>Venous TE</u>	
	HR (95% CI)	P value	HR (95% CI)	P value
Age	0.8 (0.7–1.0)	0.1	0.9 (0.7–1.3)	0.7
Male	1.4 (0.8–2.6)	0.2	1.4 (0.6–3.0)	0.5
DM	1.6 (0.8–3.2)	0.2	0.9 (0.3–2.6)	0.9
CAD	0.7 (0.3–1.7)	0.5	1.0 (0.4–2.6)	1.0
HTN	1.5 (0.7–3.5)	0.3	0.8 (0.3–2.1)	0.7
AF	0.8 (0.3–2.3)	0.7	1.3 (0.4–4.2)	0.7
Prior stroke	1.6 (0.8–3.2)	0.2	1.2 (0.4–3.1)	0.7
Warfarin	0.6 (0.3–1.4)	0.2	0.7 (0.2–2.0)	0.5
SBP 180	2.6 (1.3–5.1)	0.008	0.8 (0.4–1.7)	0.6
Evacuation	2.3 (1.0–5.6)	0.05	0.9 (0.2–3.8)	0.9
EVD	3.3 (1.5–7.1)	0.002	1.4 (0.4–4.9)	0.6
Heparinoid	3.1 (1.5–6.2)	0.002	1.0 (0.4–2.3)	1.0
DNR order	0.3 (0.0–1.9)	0.2	0.9 (0.2–3.9)	0.9
OAT resumption	3.7 (0.5–27)	0.2	–	

Abbreviation: DNR order, “Do Not Resuscitate” or “Comfort Measures Only” order