

Potential Applicability of Recombinant Factor VIIa for Intracerebral Hemorrhage

Matthew L. Flaherty, MD; Daniel Woo, MD, MS; Mary Haverbusch, BSN;
Charles J. Moomaw, PhD; Padmini Sekar, MS; Laura Sauerbeck, RN, MS; Brett Kissela, MD;
Dawn Kleindorfer, MD; Joseph P. Broderick, MD

Background and Purpose—To date, there are no proven, effective treatments for intracerebral hemorrhage (ICH) beyond supportive medical care. A recent randomized, blinded, placebo-controlled trial of recombinant factor VIIa (rFVIIa) administered intravenously within 4 hours of ICH onset reported a reduction in morbidity and mortality compared with placebo. We sought to determine the potential applicability of rFVIIa in a large, population-based cohort of ICH patients.

Methods—All of the patients age ≥ 18 years hospitalized with nontraumatic ICH in the Greater Cincinnati region were identified from May 1998 to July 2001 and August 2002 to April 2003. Patient demographics were compared with the inclusion and exclusion criteria from the rFVIIa trial to determine eligibility for treatment and reasons for exclusion. Mortality in the eligible patient group was compared with the placebo group in the rFVIIa trial.

Results—Over 4 calendar years, 1018 ICH patients were identified; of these, 133 (13.1%) had no exclusions and presented within the prescribed time window. An additional 45 patients (4.4%) may have been eligible but had uncertain onset or computed tomography scan times. The most common reasons for exclusion (not mutually exclusive) were late presentation (n=398), vaso-occlusive disease (n=369), deep coma (n=219), and prolonged international normalized ratio or partial thromboplastin time (n=200). Mortality at 90 days among potentially eligible patients was the same as for the placebo group in the rFVIIa trial (29% versus 29%; $P=0.99$).

Conclusions—In this large, population-based ICH cohort, 13.1% to 17.5% of patients would have qualified for treatment with rFVIIa by trial criteria. (*Stroke*. 2005;36:2660-2664.)

Key Words: intracerebral hemorrhage ■ epidemiology ■ outcome

Intracerebral hemorrhage (ICH) is conservatively estimated to occur in 67 000 Americans annually and disproportionately affects blacks and Hispanics.¹⁻³ It is frequently a devastating illness, with case fatality rates of 40% to 50%.^{4,5} There have been no proven, effective treatments for ICH. However, a recent randomized, placebo-controlled, phase IIb trial of recombinant activated factor VII (rFVIIa) in acute ICH showed a reduction in morbidity and mortality among patients given study drug.⁶ If the safety and efficacy of rFVIIa are confirmed in a phase III trial, it will represent a major advance in the treatment of hemorrhagic stroke.

The successful translation of new treatments, such as rFVIIa, from controlled trials to clinical practice is of vital importance. As an analogous example, recombinant tissue plasminogen activator (rtPA), shown to reduce morbidity in appropriately selected patients with acute ischemic stroke in 1995, is the only US Food and Drug Administration (FDA)-approved treatment for this condition.⁷ Despite initial enthusiasm, subsequent experience has shown that very few

ischemic stroke patients actually receive thrombolysis. Estimates indicate that 6% to 8% of ischemic stroke patients are potentially eligible for rtPA based on published criteria and that 3% to 4% receive the medication.⁸⁻¹⁰

Just as use of rtPA for ischemic stroke requires diligent patient selection, the trial of rFVIIa for ICH specified strict inclusion and exclusion criteria intended to maximize the potential benefit and minimize adverse effects.^{6,7} Patients were required to have a computed tomography (CT) scan within 3 hours of symptom onset, and patients with a history of vaso-occlusive disease were excluded, given the potential of rFVIIa to accentuate thrombosis and induce ischemic stroke or myocardial infarction.⁶ We sought to determine the potential applicability of rFVIIa in practice by applying trial inclusion and exclusion criteria to a large, population-based cohort of ICH patients.

Methods

We have previously described a population-based ICH cohort assembled as part of the Genetic and Environmental Risk Factors for

Received June 17, 2005; final revision received July 20, 2005; accepted August 9, 2005.

From the Departments of Neurology (M.L.F., D.W., M.H., C.J.M., L.S., B.K., D.K., J.P.B.) and Environment Health (P.S.), University of Cincinnati Medical Center, Cincinnati, OH.

Correspondence to Matthew L. Flaherty, MD, 231 Albert Sabin Way, MSB Room 5060, University of Cincinnati Medical Center, Cincinnati, OH, 45267-0525. E-mail matthew.flaherty@uc.edu

© 2005 American Heart Association, Inc.

Stroke is available at <http://www.strokeaha.org>

DOI: 10.1161/01.STR.0000189634.08400.82

Hemorrhagic Stroke (GERFHS) Study.² All of the patients ≥ 18 years of age who were hospitalized with nontraumatic ICH in the 5-county Greater Cincinnati/Northern Kentucky (GCNK) metropolitan area were identified from May 1998 to July 2001 and August 2002 to April 2003 by active surveillance (“hot pursuit”) at several hospitals that treat most ICH in the area and by retrospective screening of primary and secondary ICD-9 codes (430 to 432 through October 1999 and 430 to 438.9 thereafter) at all of the regional hospitals. The period August 2001 to July 2002 was not included because of an interruption of study funding during that time. Study physicians personally reviewed each abstracted file to determine whether it qualified as a case.

The GCNK region has a population of 1.3 million persons with socioeconomic demographics and a balance of blacks and whites similar to the US population.¹¹ Residents of the 5-county GCNK region seek care almost exclusively at 1 of the 16 participating metropolitan hospitals, ensuring nonbiased case ascertainment.¹² The definition of ICH used has been described elsewhere.¹³ The present cohort excluded patients with previous ICH (but not previous ischemic stroke), traumatic ICH, pure intraventricular hemorrhage, hemorrhagic cerebral infarction, and hemorrhage associated with brain tumor, encephalitis, endarterectomy, and thrombolytic treatment of ischemic stroke. ICHs associated with vascular malformations or anticoagulation were included. The GERFHS Study was approved by the Institutional Review Boards at all of the participating hospitals.

The inclusion criteria of the rFVIIa trial were age ≥ 18 years, spontaneous ICH documented by CT scan within 3 hours of onset, and drug administration within 1 hour of CT scan.⁶ Exclusion criteria are listed in Table 1. These criteria were applied to the clinical characteristics of patients in our ICH cohort to determine eligibility for treatment with rFVIIa. For criteria other than time from onset to CT scan, elements of missing data were not considered exclusionary

(eg, aphasic patients without an available, documented history of vaso-occlusive disease were considered free of this condition). The criteria for anticoagulant use and coagulopathy were estimated by excluding patients with international normalized ratio (INR) values of ≥ 1.4 or partial thromboplastin time (PTT) values of ≥ 35 . Patients who met all of the eligibility criteria and had documented ICH onset to CT scan times of < 3 hours were considered eligible for treatment, whereas patients with documented onset to CT scan times of > 3 hours were considered ineligible. Patients who met all of the eligibility criteria but had unknown onset to CT scan times were considered “possibly eligible.” Although patients with unknown onset times would not have been enrolled in the rFVIIa trial, in some of our cases these data may have been available and not recorded or available and not vigorously pursued by treating physicians, because it would not have changed management. For these reasons, we wished to provide a range of potentially eligible patients.

Patient survival was assessed by querying GERFHS Study records, the Social Security Death Index, and Ohio and Kentucky death registers. Separate survival curves for “eligible+possibly eligible” and “ineligible” patients from our population were created using actuarial methods and were compared by log-rank test. Survival in our “eligible+possibly eligible” population was also compared with survival among placebo patients in the rFVIIa trial.

Results

Over 4 calendar years, 1018 ICH patients were identified. Of these patients, 133 (13.1%) had no exclusions and presented within the prescribed time window. An additional 45 patients (4.4%) may have qualified but had uncertain onset or CT scan times that potentially overlapped the acceptable time frame. In total, 133 to 178 patients (13.1% to 17.5%) with ICH would have been eligible for rFVIIa. The reasons for exclusion are presented in Table 1. The most common (not mutually exclusive) reasons for exclusion were late presentation (n=398; 39%), history of vaso-occlusive disease (n=369; 36%), deep coma (n=219; 22%), and prolonged INR or PTT (n=200; 20%). If time were not a factor, an additional 183 patients (18%) would have qualified for treatment. If a history of vaso-occlusive disease was not an exclusion, an additional 58 to 91 patients would have qualified, increasing the overall eligibility to 19% to 26%. Of the 130 patients with a prolonged INR or PTT who were possibly scanned within 3 hours, only 26 patients had no other contraindications to rFVIIa.

The 5-county Greater Cincinnati/Northern Kentucky region currently has 16 general hospitals and 1 children’s hospital. Cases of ICH in the area are usually transferred to 1 of 3 tertiary centers, unless care is anticipated to be nonoperative or limited to end-of-life measures. Only 287 of 1018 ICH patients (28%) originally presented to 1 of these tertiary centers, including 59 patients potentially eligible for rFVIIa (33% of eligible patients).

A comparison of baseline characteristics among placebo patients from the rFVIIa trial and patients from our ICH cohort is presented in Table 2. Survival curves for patients from the rFVIIa trial and patients from our population who would have been potentially eligible and ineligible for rFVIIa are presented in the Figure. Among our population, mortality at 90 days was 29% for potentially eligible patients versus 52% for ineligible patients ($P < 0.001$). In the rFVIIa trial, 90-day mortality among placebo patients was 29%, the same as our potentially eligible group ($P = 0.99$ by χ^2 test; $P = 0.80$ by log rank test).⁶ The absolute mortality benefit for rFVIIa

TABLE 1. Application of rFVIIa Trial Criteria to the GCNK ICH Cohort

Exclusion Criteria*	ICH Onset to CT Scan within 3 hours?			
	Definitely (%)	Possibly† (%)	No (%)	Total (%)
All patients	340 (33)	280 (28)	398 (39)	1018 (100)
History of thrombotic or vaso-occlusive disease‡	112 (11)	118 (12)	139 (14)	369 (36)
Deep coma (GCS 3–5)	83 (8)	99 (10)	37 (4)	219 (22)
INR ≥ 1.4 or PTT > 35	53 (5)	77 (8)	70 (7)	200 (20)
Baseline mRS score > 2	27 (3)	61 (6)	56 (6)	144 (14)
Surgical drainage within 24 hours	26 (3)	21 (2)	18 (2)	65 (7)
ICH from aneurysm or vascular malformation	10 (1)	3 (0)	10 (1)	23 (2)
Platelet count $\leq 50\,000$	2 (0)	7 (1)	1 (0)	10 (1)
Coagulopathy, DIC, or hypercoagulable state	1 (0)	1 (0)	1 (0)	3 (0)
Pregnancy	2 (0)	0 (0)	0 (0)	2 (0)
Crush injury	0 (0)	0 (0)	0 (0)	0 (0)
Acute sepsis	0 (0)	0 (0)	0 (0)	0 (0)
No exclusions	133 (13)	45 (4)	183 (18)	361 (35)

GCS indicates Glasgow Coma Scale; mRS, modified Rankin Scale; DIC, disseminated intravascular coagulation. *Because some patients have > 1 reason for exclusion, the sum of the individual categories exceeds the number in the “all patients” category; †includes patients with uncertain ICH onset times or CT scan times that potentially overlapped the acceptable time frame; ‡including history of angina, claudication, deep vein thrombosis, cerebral infarction, or myocardial infarction.

TABLE 2. Comparison of rFVIIa Study Patients and the GCNK ICH Cohort

Variable	rFVIIa Study, Placebo Group ⁶	GCNK Cohort, Eligible Patients	GCNK Cohort, Eligible and Possibly Eligible Patients*	GCNK Cohort, Not Eligible
No.	96	133	178	840
Age, mean (SD)	68 (12)	66 (16)	67 (16)	71 (15)
Male, %	53	47	46	44
Race or ethnic group				
White, %	81	72	74	79
Black, %	NR	28	26	19
Asian or Pacific Islander, %	15	0	0	1
Other, %	4	0	0	0
Location of ICH, %†				
Deep cerebral ICH	‡	68	65	45
Lobar ICH	21	23	27	37
Cerebellar ICH	2	2	3	12
Brainstem ICH	6	5	5	7
GCS, median	14	15	15	13
GCS, range	3–15	6–15	6–15	3–15

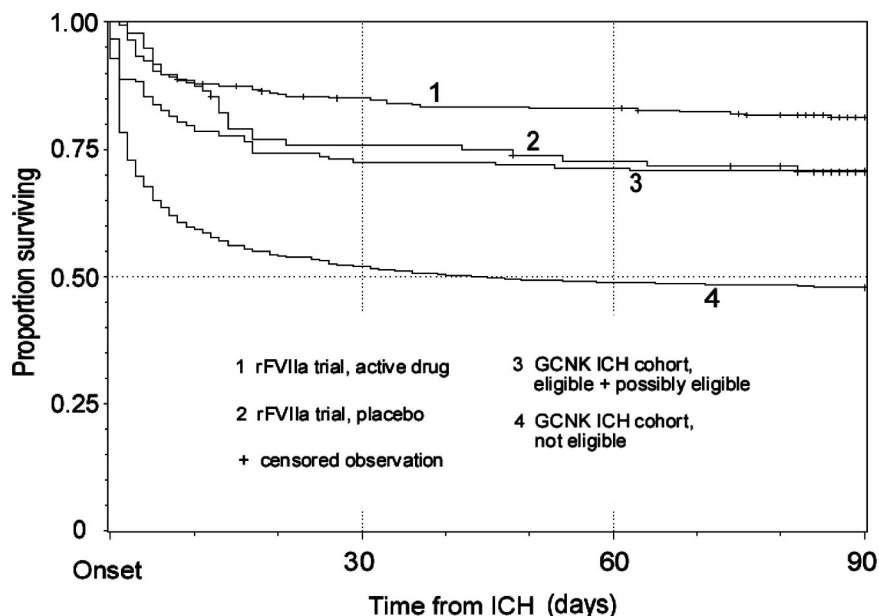
NR indicates not reported. *Includes patients with uncertain ICH onset times or CT scan times that potentially overlapped the acceptable time frame; †>1 region could be involved in a given patient in the rFVIIa study; therefore, percentages by location do not total 100%. Percentages by location in the GCNK cohort do not total 100% because of rounding; ‡Putamen or globus pallidus is 58% and thalamus is 30%.

patients compared with placebo patients in the trial was 11% ($P=0.02$).⁶ If this benefit is applied to the eligible group in our ICH cohort, 90-day mortality for our entire cohort (both eligible and ineligible patients) would have dropped from 48% to 46%. Death or severe disability at 3 months (as defined by modified Rankin Scale scores of 4 to 6 and extended Glasgow Outcome Scale scores of 1 to 4) occurred in 69% of placebo patients and 53% of rFVIIa-treated patients ($P=0.004$).⁶ If 17.5% of the estimated 67 000 annual ICHs in the United States were treated with rFVIIa, and their natural history paralleled the rFVIIa trial group, this would

translate into 1290 lives saved and 1876 patients prevented from experiencing death or severe disability.^{1,6} In the rFVIIa trial, 2% of placebo patients and 7% of rFVIIa patients experienced thromboembolic serious adverse events ($P=0.12$).⁶ Extrapolated nationally, this would result in an excess of 586 serious adverse events among treated patients.

Discussion

The majority of ICH mortality occurs early in the clinical course.⁵ More than one third of ICH patients experience substantial hematoma growth within a day of ictus, and this



growth is associated with increased morbidity and mortality.^{14–16} Thus, prompt intervention to prevent hematoma expansion, as with intravenous administration of rFVIIa, may improve patient outcomes. A phase III trial of rFVIIa in ICH is currently underway. If rFVIIa proves safe and effective and is given FDA approval for use in ICH, its applicability will be of importance.

It is useful to compare the potential applicability of rFVIIa for treatment of ICH with the use of rt-PA for ischemic stroke in community patients. Despite enthusiasm among many physicians following FDA approval of rtPA in 1996, thrombolytic treatment of ischemic stroke remains rare, with 6% to 8% of patients potentially qualifying for rt-PA and 3% to 4% of patients receiving treatment in community-based surveillance.^{9,10,17} Approximately 15% to 27% of ischemic stroke patients arrive in the emergency department within 3 hours of onset.^{8,10,17} The number eligible for rt-PA is additionally reduced by factors including strokes judged too mild for thrombolytic treatment, comorbid medical conditions, and inefficient medical systems.

Approximately 13% to 18% of our ICH cohort would have qualified for rFVIIa treatment, 2 to 3 times the rtPA eligibility rate of ischemic stroke patients. It should be noted, however, that the absolute number of ICH patients treated would likely be less than ischemic stroke patients receiving rtPA, because the incidence of ICH is considerably lower than that of ischemic stroke.¹

Our study confirms that patients with ICH present to the emergency department more quickly than patients with ischemic stroke, presumably because greater severity of deficits prompts a more rapid recognition of the need for medical care.^{18,19} CT scanning was performed in 340 of 1018 patients within 3 hours of symptom onset, and another 280 may have received a scan within this time (33% to 60% of patients). Attempts to educate the public about the importance of early medical evaluation for the signs and symptoms of stroke have been marginally successful thus far.²⁰

Aside from late presentation, other common reasons that hemorrhage patients would be excluded from potential treatment are deep coma, a history of vaso-occlusive disease, and anticoagulant use. Patients in deep coma from ICH have very poor prognoses and are unlikely to benefit from rFVIIa.²¹ Patients with vaso-occlusive disease may benefit from rFVIIa but may also be at increased risk of adverse events, such as myocardial infarction, cerebral infarction, and pulmonary embolism. The ongoing phase III trial of rFVIIa includes patients with a history of vaso-occlusive disease (but not acute thromboembolic events). By our estimates, this may increase rFVIIa applicability to 19% to 26% of ICH patients, but its affect on adverse event rates is unknown and of great importance.

The most logical potential extension of rFVIIa treatment is for cases of warfarin-associated ICH, because these patients have greater hematoma expansion and worse outcomes than other ICH patients.²² rFVIIa use has been reported in several small series of warfarin-related bleeding with encouraging results.^{23–25} Although rFVIIa rapidly reverses INR prolongation, it does not replace all of the deficient coagulation factors, and “correction” of INR values in this setting may not

reflect the therapeutic mechanism of rFVIIa or the status of the underlying coagulopathy.^{26,27} In our population, 200 patients (20%) with ICH had a prolonged INR or PTT, including 130 patients possibly receiving a CT scan within 3 hours of onset. However, 104 of these 130 patients had other reasons for exclusion (most commonly a history vaso-occlusive disease or deep coma). Thus, if prolonged PTT or INR values were not exclusions, only an additional 26 patients (3%) would have qualified.

Although the rFVIIa study showed an impressive reduction in mortality among treated ICH patients, application of these findings to our entire population of ICH patients produced a modest 2% reduction in overall 90-day mortality. Nonetheless, this mortality reduction could save >1200 lives annually in the United States and prevent death or severe disability in >1800 patients. The impact may be even greater in Asian countries, which have higher rates of ICH than the United States or Europe.^{28–30} The fact that mortality rates in the rFVIIa placebo group and our potentially eligible patient group were identical suggests that the rFVIIa trial included a representative sample of ICH patients who met inclusion criteria and increases the likelihood that study findings will translate into benefit in clinical practice.

Finally, most of our ICH patients presented to hospitals that do not offer tertiary care for this condition. In communities like ours, without preferential triage of stroke patients to select medical centers by emergency services, community hospitals will need to be capable of administering rFVIIa to appropriate patients.

Our study has several limitations. Our cohort did not include patients with ICH related to trauma, tumor, infection, or cerebral infarction, and so we cannot comment on their prevalence. Each of these conditions was an exclusion criterion in the rFVIIa study. Our cohort also excluded patients with previous ICH, who may benefit from rFVIIa treatment. Because data collection was often retrospective, values were sometimes missing or not aggressively pursued by attending physicians when deemed irrelevant to patient care. If rFVIIa is proven effective, emergency care of ICH patients may change and with it drug applicability.

Acknowledgments

Supported in part by National Institute of Neurological Disorders and Stroke (R-01-NS 36695). Special thanks to Dr Nikolai C. Brun, Dr Kamilla Begtrup, and Novo Nordisk for providing mortality data from the rFVIIa Intracerebral Hemorrhage Trial.

References

1. Kissela B, Schneider A, Kleindorfer D, Khoury J, Miller R, Alwell K, Woo D, Szaflarski J, Gebel J, Moomaw CJ, Pancioli A, Jauch E, Shukla R, Broderick J. Stroke in a biracial population: the excess burden of stroke among blacks. *Stroke*. 2004;35:426–431.
2. Flaherty ML, Woo D, Haverbusch M, Sekar P, Khoury J, Sauerbeck L, Moomaw CJ, Schneider A, Kissela B, Kleindorfer D, Broderick JP. Racial variations in location and risk of intracerebral hemorrhage. *Stroke*. 2005;36:934–937.
3. Morgenstern LB, Smith MA, Lisabeth LD, Risser JM, Uchino K, Garcia N, Longwell PJ, McFarling DA, Akuwumi O, Al-Wabil A, Al-Senani F, Brown DL, Moya LA. Excess stroke in Mexican Americans compared with non-Hispanic whites: the Brain Attack Surveillance in Corpus Christi Project. *Am J Epidemiol*. 2004;160:376–383.
4. Dennis MS. Outcome after brain haemorrhage. *Cerebrovasc Dis*. 2003; 16(Suppl 1):9–13.

5. Broderick J, Brott T, Tomsick T, Tew J, Duldner J, Huster G. Management of intracerebral hemorrhage in a large metropolitan population. *Neurosurgery*. 1994;34:882–887.
6. Mayer SA, Brun NC, Begtrup K, Broderick J, Davis S, Diringer MN, Skolnick BE, Steiner T, for the Recombinant Activated Factor VII Intracerebral Hemorrhage Trial Investigators. Recombinant activated factor VII for acute intracerebral hemorrhage. *N Engl J Med*. 2005;352:777–785.
7. NINDS rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med*. 1995;333:1581–1587.
8. Kleindorfer D, Kissela B, Schneider A, Woo D, Khoury J, Miller R, Alwell K, Gebel J, Szaflarski J, Pancioli A, Jauch E, Moomaw C, Shukla R, Broderick JP. Eligibility for recombinant tissue plasminogen activator in acute ischemic stroke: a population-based study. *Stroke*. 2004;35:e27–e29.
9. Kleindorfer D, Khoury J, Alwell K, Miller R, Shukla R, Kissela BM, Panagos P, Schneider A, Woo D, Moomaw CJ, Broderick J. rt-PA use in a population-based study: the post-FDA approval era. *Stroke*. 2003;34(Suppl):283. (Abstract).
10. Katzan IL, Hammer MD, Hixson ED, Furlan AJ, Abou-Chebl A, Nadzam DM, for the Cleveland Clinic Health System Stroke Quality Improvement Team. Utilization of intravenous tissue plasminogen activator for acute ischemic stroke. *Arch Neurol*. 2004;61:346–350.
11. Broderick J, Brott T, Kothari R, Miller R, Khoury J, Pancioli A, Gebel J, Mills D, Minneci L, Shukla R. The Greater Cincinnati/Northern Kentucky Stroke Study: preliminary first-ever total incidence rates of stroke among blacks. *Stroke*. 1998;29:415–421.
12. Broderick J, Brott T, Tomsick T, Huster G, Miller R. The risk of subarachnoid and intracerebral hemorrhages in blacks as compared with whites. *N Engl J Med*. 1992;326:733–736.
13. Woo D, Sauerbeck LR, Kissela BM, Khoury JC, Szaflarski JP, Gebel J, Shukla R, Pancioli AM, Jauch EC, Menon AG, Deka R, Carrozzella JA, Moomaw CJ, Fontaine RN, Broderick JP. Genetic and environmental risk factors for intracerebral hemorrhage: preliminary results of a population-based study. *Stroke*. 2002;33:1190–1196.
14. Brott T, Broderick J, Kothari R, Barsan W, Tomsick T, Sauerbeck L, Spilker J, Duldner J, Khoury J. Early hemorrhage growth in patients with intracerebral hemorrhage. *Stroke*. 1997;28:1–5.
15. Fujii Y, Takeuchi S, Sasaki O, Minakawa T, Tanaka R. Multivariate analysis of predictors of hematoma enlargement in spontaneous intracerebral hemorrhage. *Stroke*. 1998;29:1160–1166.
16. Leira R, Davalos A, Silva Y, Gil-Peralta A, Tejada J, Garcia M, Castillo J, for the Stroke Project Cerebrovascular Diseases Group of the Spanish Neurological Society. Early neurologic deterioration in intracerebral hemorrhage: predictors and associated factors. *Neurology*. 2004;63:461–467.
17. Barber PA, Zhang J, Demchuk AM, Hill MD, Buchan AM. Why are stroke patients excluded from tPA therapy? An analysis of patient eligibility. *Neurology*. 2001;56:1015–1020.
18. Yu RF, San Jose MC, Manzanilla BM, Oris MY, Gan R. Sources and reasons for delays in the care of acute stroke patients. *J Neurol Sci*. 2002;199:49–54.
19. Fogelholm R, Murros K, Rissanen A, Ilmavirta M. Factors delaying hospital admission after acute stroke. *Stroke*. 1996;27:398–400.
20. Kleindorfer D, Alwell K, Khoury J, Ewing I, Schneider A, Flaherty ML, Moomaw CJ, Miller R, Khatri P, Stettler BA, Broderick JP. Temporal trends in emergency department arrival times for acute ischemic stroke: a population-based study. *Stroke*. 2005;36:494.
21. Hemphill JC 3rd, Bonovich DC, Besmertis L, Manley GT, Johnston SC. The ICH score: a simple, reliable grading scale for intracerebral hemorrhage. *Stroke*. 2001;32:891–897.
22. Flibotte JJ, Hagan N, O'Donnell J, Greenberg SM, Rosand J. Warfarin, hematoma expansion, and outcome of intracerebral hemorrhage. *Neurology*. 2004;63:1059–1064.
23. Deveras RA, Kessler CM. Reversal of warfarin-induced excessive anticoagulation with recombinant human factor VIIa concentrate. *Ann Intern Med*. 2002;137:884–888.
24. Sorensen B, Johansen P, Nielsen GL, Sorensen JC, Ingerslev J. Reversal of the international normalized ratio with recombinant activated factor VII in central nervous system bleeding during warfarin thromboprophylaxis: clinical and biochemical aspects. *Blood Coagul Fibrinolysis*. 2003;14:469–477.
25. Lin J, Hanigan WC, Tarantino M, Wang J. The use of recombinant activated factor VII to reverse warfarin-induced anticoagulation in patients with hemorrhages in the central nervous system: preliminary findings. *J Neurosurg*. 2003;98:737–740.
26. Goodnough LT, Lublin DM, Zhang L, Despotis G, Eby C. Transfusion medicine service policies for recombinant factor VIIa administration. *Transfusion*. 2004;44:1325–1331.
27. Hoffman M. Laboratory monitoring of high-dose factor VIIa therapy. *Ann Intern Med*. 2003;139:791.
28. Inagawa T, Ohbayashi N, Takechi A, Shibukawa M, Yahara K. Primary intracerebral hemorrhage in Izumo City, Japan: incidence rates and outcome in relation to the site of hemorrhage. *Neurosurgery*. 2003;53:1283–1298.
29. Tanaka H, Ueda Y, Date C, Baba T, Yamashita H, Hayashi M, Shoji H, Owada K, Baba K, Shibuya M, Kon T, Detels R. Incidence of stroke in Shibata, Japan: 1976–1978. *Stroke*. 1981;12:460–466.
30. Yang QD, Niu Q, Zhou YH, Liu YH, Xu HW, Gu WP, Tian FF, Xie YQ, Zhang L, Xia J. Incidence of cerebral hemorrhage in the Changsha community: a prospective study from 1986 to 2000. *Cerebrovasc Dis*. 2004;17:303–313.