No Increased Risk of Symptomatic Intracerebral Hemorrhage After Thrombolysis in Patients With European Cooperative Acute Stroke Study (ECASS) Exclusion Criteria

Carolyn A. Cronin, MD, PhD; Nikeith Shah; Tanya Morovati, MD, MPH; Lisa D. Hermann, MD; Kevin N. Sheth, MD

Background and Purpose—The European Cooperative Acute Stroke Study (ECASS) III trial used additional exclusion criteria not present in current guidelines for thrombolytic therapy in the United States (age >80 years; National Institutes of Health Stroke Scale >25, combination of previous stroke and diabetes, aggressive measures required to control blood pressure [intravenous infusion], and oral anticoagulant treatment). We tested the hypothesis that thrombolysis is not safe in patients with 1 of the additional exclusion criteria.

Methods—All patients treated with intravenous tissue-type plasminogen activator for acute stroke at our center between June 2006 and June 2010 were identified (n=191), and stratified based on presence of each of the exclusion criteria. Primary outcomes were rate of symptomatic intracerebral hemorrhage and in-hospital mortality. Additionally, patients with and without symptomatic intracerebral hemorrhage were analyzed for differences in baseline characteristics.

Results—No exclusion criterion was associated with increased risk of symptomatic intracerebral hemorrhage. Symptomatic intracerebral hemorrhage was associated with atrial fibrillation (5 of 9 [55%], versus 35 of 182 [19.2%]; P=0.021), larger final infarct volume (mean 173 mL³ versus 42 mL³; P=0.0002), and elevated glucose (mean 166 mg/dL versus 127 mg/dL; P=0.038). There was higher mortality in patients >80 years (5 of 31 [16%] versus 6 of 160 [4%]; P=0.0186) and those with National Institutes of Health Stroke Scale >25 (2 of 5 [40%] versus 7 of 159 [4.4%]; P=0.025).

Conclusions—In our cohort, none of the more stringent exclusion criteria from ECASS III were associated with increased risk of symptomatic intracerebral hemorrhage. Prospective randomized studies are needed clarify the safety and efficacy of tissue-type plasminogen activator in these patients through all treatment time windows. (Stroke. 2012;43:00-00.)

Key Words: acute stroke ■ exclusion criteria ■ thrombolysis

Only approximately 2% of patients with ischemic stroke are currently treated with intravenous tissue-type plasminogen activator (tPA) with the most common reason for exclusion from treatment being time to treatment. The positive results of the European Cooperative Acute Stroke Study (ECASS) III expanded the time window for treatment to 4.5 hours; however, it used more stringent exclusion criteria than are in use for the US Food and Drug Administration-approved 3-hour window in the United States. For patients who present 3 to 4.5 hours from symptom onset, the scientific advisory from the American Heart Association/American Stroke Association recommends use of the more narrow ECASS III criteria (this extended window has not yet received US Food and Drug Administration approval). We evaluated the outcomes of intravenous tPA-treated patients to test the hypothesis that thrombolysis is not safe in patients with 1 of the additional exclusion criteria (age >80 years, National Institutes of Health Stroke Scale [NIHSS] >25, combination of previous stroke and diabetes, or oral anticoagulant treatment). We also evaluated patients who required aggressive measures to control blood pressure (use of intravenous infusion), because this is also a difference between the ECASS criteria and current use in the United States, although it was not highlighted in the American Heart Association/American Stroke Association recommendations.

Methods

All patients with acute ischemic stroke treated with intravenous tPA at the University of Maryland Medical Center between June 2006 and June 2010 were identified through a search of our Get With The...
Results
A total of 191 consecutive patients treated with intravenous tPA for acute ischemic stroke were identified. There were 31 patients >80 years, 5 with NIHSS >25 at presentation, 14 with the combination of prior stroke and diabetes, 19 required continuous intravenous infusions to control blood pressure <185/110 mm Hg, and 11 were taking warfarin (all with international normalized ratio ≤1.7).

There were some differences in baseline characteristics between the groups (online-only Data Supplement Table I; http://stroke.ahajournals.org). Patients >80 years were more likely to have atrial fibrillation (38.7% versus 17.5%; *P* = 0.01) and hypertension (90.3% versus 70.0%; *P* = 0.02), presented with higher median NIHSS scores (15 versus 11.5; *P* = 0.05), and were less likely to be smokers (9.7% versus 32.5%; *P* = 0.01). Patients with the combination of stroke and diabetes were also more likely to have hypertension (100% versus 71%; *P* = 0.02). Interestingly, patients requiring an intravenous drip for blood pressure control were not more likely to carry the diagnosis of hypertension, but they did have a higher median NIHSS score on presentation (16 versus 12; *P* = 0.03).

No exclusion criterion was associated with increased risk of symptomatic intracerebral hemorrhage (Table). Symptomatic intracerebral hemorrhage was associated with atrial fibrillation (5 of 9 [55%] versus 35 of 182 [19.2%]; *P* = 0.021), larger final infarct volume (mean 173 mL^3^ [SEM 43.3] versus 42 mL^3^ [SEM 6.3]; *P* = 0.0002), and elevated glucose (mean 166 mg/dL [SEM 23.1] versus 127 mg/dL [SEM 4.1]; *P* = 0.038; online-only Data Supplement Table II). There was higher in-hospital mortality in patients >80 years (5 of 31 [16%] versus 6 of 160 [4%]; *P* = 0.0186) and those with NIHSS >25 (2 of 5 [40%] versus 7 of 159 [4.4%]; *P* = 0.025).

Discussion
In our cohort, none of the more stringent exclusion criteria from ECASS III were associated with increased risk of symptomatic intracerebral hemorrhage. In agreement with prior studies, we have found that older patients and those with more severe deficits at presentation have higher mortality, likely reflecting the underlying natural history in these patients regardless of treatment.

Many of the exclusion criteria used for the clinical trials of intravenous tPA were chosen by expert opinion with little to no prior data to guide the decisions. Some criteria were intended to protect patients who were presumed to be at increased risk for hemorrhagic complications. Others were likely chosen to exclude patients who are more likely to do poorly whether or not treatment is given, and their inclusion in a trial would therefore make it more difficult to demonstrate efficacy. The conservative approach to acute stroke care is to treat with intravenous tPA only those patients who exactly match inclusion criteria for the trials that demonstrated efficacy. However, it is important to acknowledge that for patients who were excluded from the trials, there is a lack of data, which is not the same thing as proof of no benefit or proof of harm. So strictly following the exclusion criteria from trials may result in withholding treatment from patients for whom it would be beneficial. Indeed, the randomized data that are available from the National Institute of Neurological Disorders and Stroke tPA trial indicated that there were no patient characteristics that affected the response to thrombolytic treatment, not even for those patients >75 years old and with NIHSS >20 at presentation.6

This study has some limitations. First, it represents the experience at a single academic medical center and therefore has a relatively small sample size. The retrospective design may also have introduced bias. We cannot rule out that with a larger data set, some of the criteria may yield significant differences in the primary outcomes. This analysis adds to the growing literature on patient outcomes with intravenous tPA in subgroups of patients who have been excluded from many of the randomized acute stroke treatment trials.7,8 See the online-only Data Supplement for additional related references.

Conclusion
Some patients currently excluded from thrombolysis based on trial entry criteria may benefit from treatment, and perhaps they should not be excluded from treatment a priori. Prospective randomized studies are needed to clarify the safety and efficacy of thrombolysis in these patients through all treatment time windows.

Disclosures
C.A.C. serves on the Regional Stroke Advisory Board for Genentech USA, Inc (modest).
References


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European Cooperative Acute Stroke Study (ECASS)의 제외 기준에 해당하는 환자에서 혈전증해술을 시행했을 때 증상성 뇌내출혈의 발생위험은 증가하지 않았다.

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Key Words: acute stroke ■ exclusion criteria ■ thrombolysis

배경과 목적
European Cooperative Acute Stroke Study (ECASS) III trial의 제외 기준에는 미국의 혈전증해술 진료지침에는 없는 사양들(나이 > 80세, NIH 뇌졸중도 > 25, 이전병력에 뇌졸중 및 당뇨가 함께 있었던 경우, 혈압을 조절하기 위해 공격적인 방법이 필요한 경우[정맥내 주입, 정구용 항응고제의 사용])을 추가로 적용하였다. 본 연구에서는 이러한 추가적인 제외 기준들을 한 가지를 가진 환자에서 혈전증해술이 안전하지 않는가에 대한 연구이다.

방법
2006년 6월에서 2010년 6월의 기간 동안 본 센터에서 급성 뇌졸중으로 인해 정맥내 조직플라스미노겐활성화제를 투여 받은 모든 환자를 확인한 후(n=191), 각 제외 조건이 존재여부에 따라 추출하였다. 일차결과표준은 증상성 뇌내출혈이 입원 중 사망이나, 추가적으로 증상성 뇌내출혈이 발생한 환자와 발생하지 않은 환자의 기본 임상적 특징을 비교하였다.

결과
어떤 제외 조건 중 증상성 뇌내출혈의 발생위험 증가와 연관이 없었다. 증상성 뇌내출혈은 심방세동(5 of 9 [55%], 대 35 of 182 [19.2%]; P=0.021), 최종 뇌경색 크기가 큰 경우(mean 173 mL 대 42 mL; P=0.0002), 혈당이 높은 경우(mean 166 mg/dL 대 127 mg/dL; P=0.038)와 연관이 있었다. 80세가 넘은 환자(5 of 31 [16%] versus 6 of 160 [4%]; P=0.01 86)와, NIH 뇌졸중도가 25점 초과하는 환자들에서(2 of 5 [40%] 대 7 of 159 [4.4%]; P=0.025) 사망률이 높았다.

결론
본 코호트에서 ECASS III 연구에서 적용한 더 엄격한 제외 기준들 중 증상성 뇌내출혈의 위험증가와 관련된 항목은 없었다. 모든 치료 시간 범위에 걸쳐 이 기준에 해당하는 환자들에서 조직플라스미노겐활성화제의 안전성과 효과를 확인하기 위한 전향적 무작위배정 임상연구가 필요하다.

| Table. Outcome by Exclusion Criteria |
|-------------------------------|---------|---------|----------------|
|                               | Any ICH | sICH    | In-Hospital |
|                               | No (%)  | No (%)  | Mortality   |
| All (n=191)                   | 41 (21.5)| 9 (4.7) | 11 (5.8)    |
| >80 y (n=31)                  | 7 (22.6)| 2 (6.5) | 5 (16.1)    |
| ≤80 y (n=160)                 | 25 (15.6)| 7 (4.4) | 6 (3.8)     |
| P value                       | 0.43    | 0.64    | 0.02        |
| NIHSS >25 (n=5)               | 3 (60)  | 1 (20)  | 2 (40)      |
| NIHSS ≤25 (n=159)             | 24 (15.1)| 5 (3.1)| 7 (4.4)     |
| P value                       | 0.03    | 0.17    | 0.02        |
| DM+stroke (n=14)              | 2 (14.3)| 1 (7.1) | 0           |
| No DM+stroke (n=177)          | 39 (22.0)| 8 (4.5)| 11 (6.2)    |
| P value                       | 0.74    | 0.50    | 1.00        |
| IV drip (n=19)                | 5 (26.3)| 2 (10.5)| 3 (15.8)    |
| No IV drip (n=172)            | 36 (20.9)| 7 (4.1)| 8 (4.7)     |
| P value                       | 0.56    | 0.22    | 0.08        |
| Warfarin (n=11)               | 4 (36.4)| 2 (18.2)| 1 (9.1)     |
| No warfarin (n=180)           | 37 (20.6)| 7 (3.9)| 10 (5.6)    |
| P value                       | 0.25    | 0.09    | 0.49        |

ICH indicates intracerebral hemorrhage; sICH, symptomatic intracerebral hemorrhage; NIHSS, National Institutes of Health Stroke Scale; DM, diabetes mellitus; IV, intravenous.