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IV tissue plasminogen activator use in acute stroke

Experience from a statewide registry

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Abstract—Objective: To assess the use of IV recombinant tissue plasminogen activator (rt-PA) in a statewide hospital-based stroke registry and to identify factors associated with its use among eligible patients. Methods: A modified stratified sampling scheme was used to obtain a representative sample of 16 hospitals. Prospective case ascertainment and data collection were used to identify all acute stroke admissions over a 6-month period. Subjects eligible for IV rt-PA were defined as those who arrived within 3 hours of onset, who had no evidence of hemorrhage on initial brain image, and who had no physician-documented reasons for non-treatment with IV rt-PA. Multivariate logistic regression was used to identify factors associated with IV rt-PA use. Results: Of 2,566 stroke admissions, 330 (12.9%) met the eligibility criteria for rt-PA treatment, and of these 43 (13%) received IV rt-PA treatment. Among 2,236 admissions excluded from consideration, 21% had evidence of hemorrhage on initial imaging, 35% had unknown stroke onset times, 38% had an onset to arrival time >3 hours, and 6% had physician documented contraindications. Among eligible patients, being male, use of emergency medical services, and rapid presentation were associated with increased IV rt-PA use. Conclusions: Treatment with IV rt-PA was underutilized in this hospital-based stroke registry. The primary reason for nontreatment was delayed presentation. Reducing prehospital and in-hospital response times would help increase IV rt-PA use, as would greater emergency medical services use. Improving the documentation of onset times would help clarify the underlying causes of delayed presentation.
The objectives of this study were to use data from a statewide hospital-based stroke registry that prospectively identified acute stroke admissions to describe the use of IV rt-PA treatment, and to identify factors associated with its use among eligible patients.

Methods. Study design and hospital selection. The Michigan Acute Stroke Care Overview & Treatment Surveillance System (MASCOTS) was a statewide, hospital-based, stroke registry prototype that was part of the initial development phase of the PC-NASH. A single-stage cluster design was used, whereby a sample of hospitals was obtained from a modified stratified sampling regime. First, in the initial pilot phase of the project, we selected eight hospitals with certainty from four urban communities that were participating in a community-based stroke awareness project. These hospitals represented larger urban and academic institutions. Second, the remaining 114 statewide acute care hospitals that had at least 30 stroke discharges in 2000 were ranked according to their total number of stroke discharges, and four equal sized strata were created. Two hospitals were then randomly selected, with probability proportional to size, from each of the four strata, which in conjunction with the eight pilot phase hospitals resulted in a final sample of 16 hospitals. These 16 hospitals treated 26% of the 36,000 annual stroke discharges statewide. A standardized data collection instrument was developed to obtain information on demographics; use of emergency medical services (EMS); ED arrival and evaluation; initial brain imaging; stroke onset time; NIH Stroke Scale (NIHSS); rt-PA treatment; in-hospital diagnosis, procedures, and treatment; prior medical history; discharge status; and secondary prevention interventions. Information on the initial ED evaluation, treatment, and the decision to treat with IV rt-PA was collected at the time the patient arrived at the hospital. Other data, such as in-hospital procedures, treatments, discharge instructions, modified Rankin Scale (mRS) at discharge, and in-hospital mortality, were abstracted from the charts after discharge. In order to ensure the accuracy and uniformity of data collection across the sites, the data coordinators attended a training session prior to the onset of data collection and had access to ongoing training and technical support throughout the study. All data submitted to the main study center underwent an extensive series of quality and logic checks that allowed the hospital staff to update the information through an iterative process of data editing.

Prior to the start of the study, a survey of the 16 participating hospitals was conducted to obtain hospital-level information relevant to acute stroke care. This included basic hospital characteristics (i.e., the number of admissions, bed size of the hospital, rural or urban location), the presence of an acute stroke team, the availability of stroke specialists, the use of written clinical guidelines and care pathways, access to imaging technology, use of in-hospital rehabilitation therapy services, the presence of stroke quality improvement programs, and participation in databank or other registry-like activities.

Human subjects’ approval was obtained from each hospital’s Institutional Review Board (IRB) before the start of the study. All IRBs approved the project’s exempt status because the registry’s primary purpose was quality improvement, and no direct patient contact was involved. It was therefore not possible to collect outcomes data post-discharge.

Definition of eligible subjects for IV rt-PA therapy. Subjects eligible for IV rt-PA treatment were defined as all acute stroke admissions seen in the ED within 3 hours of stroke onset, who had no evidence of hemorrhage on the initial brain image, and who had no physician-documented reasons for non-treatment with IV rt-PA.

Outcome measures and statistical analysis. The primary outcomes of interest were the proportion of eligible patients who received IV rt-PA, and the occurrence of symptomatic ICH within 36 hours of IV rt-PA treatment in stroke patients treated with IV rt-PA. The occurrence of hemorrhage requiring blood transfusions within 7 days of treatment was considered a secondary outcome measure.

Results. One of the original 16 hospitals closed down during the early phase of the study. A total of 2,566 acute stroke patients were admitted to the 15 remaining hospitals during the 6-month period. Of these 2,566 stroke admissions, 469 (18.3%) had hemorrhagic signs on their initial brain image and were excluded from further consideration (figure). Among the remaining 2,097 nonhemorrhagic acute stroke admissions, 793 (37.8%) were excluded because their stroke onset times were unknown, 851 (40.6%) were excluded because they arrived 3 or more hours after onset, and 123 (5.9%) had physician-documented contraindications to IV rt-PA treatment. The remaining 330 patients, representing 12.9% of the 2,566 admissions, were therefore considered eligible for IV rt-PA therapy. Among these, a total of 47 patients (14.2%) received IV rt-PA therapy, of which 43 (13%) received IV rt-PA (see figure). These 43 patients represented 2.1% of the 2,097 acute non-hemorrhagic stroke admissions, or 1.7% of the 2,566 admissions.

The two major reasons documented by the treating phy-
sion for not giving IV rt-PA to the 123 subjects were that the patient had undergone a significant improvement (n = 44, 35.8%), and that the stroke severity was considered too mild (n = 22, 17.9%). Other physician-documented reasons for exclusion included abnormal activated partial thromboplastin time (n = 6), life expectancy < 1 year or severe comorbidity (n = 4), stroke too severe (n = 4), history of ICH, or brain aneurysm, or tumor (n = 4), CT suggested an alternative diagnosis (n = 3), advanced age (n = 2), seizure at onset (n = 2), recent surgery/trauma (n = 2), recent intracranial (IC) surgery (3 months) or head trauma (n = 2), uncontrolled hypertension (n = 1), or other miscellaneous reasons (n = 17). Finally, consent was not available or the family refused treatment in 10 patients.

Univariate logistic analyses that compared the 43 IV tPA-treated patients to the 283 non-treated patients found differences (p < 0.05) by sex, arrival mode, and onset to ED arrival time (table 1). The past medical histories did not differ significantly between treated and non-treated groups (data not shown). The results of the final multivariable logistic regression analysis are shown in table 2. Sex, ED arrival mode, and stroke onset to ED arrival time remained significant in the final model. Female patients were significantly less likely to get IV rt-PA treatment than male patients (OR = 0.4, 95% CI = 0.2 to 0.8), and patients who arrived via EMS were seven times (OR = 7.3, 95% CI = 2.9 to 18.2) more likely to receive IV rt-PA treatment, compared to patients who arrived by non-EMS. Stroke onset to ED arrival time was strongly associated with likelihood of IV rt-PA treatment. Patients who arrived during the second hour after stroke onset were less than half as likely to receive IV rt-PA compared to those who arrived within an hour of onset (OR = 0.4, 95% CI = 0.2 to 0.9), while those who arrived between 2 and 3 hours after onset were 33 times less likely to receive treatment (OR = 0.03, 95% CI = 0.003 to 0.2). After adjustment, neither age (p = 0.5) nor race (p = 0.8) had an effect on the likelihood of IV rt-PA use. Finally, two-way interaction terms between arrival mode and age, sex and race, 

**Table 1** Demographic and clinical characteristics of IV rt-PA-treated vs non-treated subjects among eligible patients (n = 326)*

<table>
<thead>
<tr>
<th>IV rt-PA treated</th>
<th>Non-treated</th>
<th>p Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 43</td>
<td>n = 283</td>
<td></td>
</tr>
<tr>
<td>Age, y, mean ± SD</td>
<td>66.4 ± 14.8</td>
<td>70.0 ± 14.0</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>28 (65.1)</td>
<td>128 (45.2)</td>
</tr>
<tr>
<td>Female</td>
<td>15 (34.9)</td>
<td>155 (54.8)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>33 (76.7)</td>
<td>221 (78.1)</td>
</tr>
<tr>
<td>Black</td>
<td>5 (11.6)</td>
<td>41 (14.5)</td>
</tr>
<tr>
<td>Other</td>
<td>5 (11.6)</td>
<td>21 (7.4)</td>
</tr>
<tr>
<td>ED arrival mode</td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>ED arrival mode</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>7 (16.3)</td>
<td>147 (51.9)</td>
</tr>
<tr>
<td>ED arrival time</td>
<td></td>
<td>0.01</td>
</tr>
<tr>
<td>0.00–06:00</td>
<td>26 (60.5)</td>
<td>78 (27.6)</td>
</tr>
<tr>
<td>06:00–17:59</td>
<td>16 (37.2)</td>
<td>119 (42.1)</td>
</tr>
<tr>
<td>18:00–23:59</td>
<td>2 (4.8)</td>
<td>107 (38.1)</td>
</tr>
<tr>
<td>ED arrival day</td>
<td></td>
<td>0.33</td>
</tr>
<tr>
<td>Weekday</td>
<td>34 (79.1)</td>
<td>204 (72.1)</td>
</tr>
<tr>
<td>Weekend/holiday</td>
<td>9 (20.9)</td>
<td>79 (27.9)</td>
</tr>
<tr>
<td>Image results</td>
<td></td>
<td>0.61</td>
</tr>
<tr>
<td>Normal</td>
<td>19 (44.2)</td>
<td>99 (35.0)</td>
</tr>
<tr>
<td>Old infarct</td>
<td>11 (25.6)</td>
<td>76 (26.9)</td>
</tr>
<tr>
<td>Pre-stroke status</td>
<td></td>
<td>0.74</td>
</tr>
<tr>
<td>Ambulates independently</td>
<td>40 (95.2)</td>
<td>255 (93.4)</td>
</tr>
<tr>
<td>Ambulates with assistance</td>
<td>1 (2.4)</td>
<td>13 (4.8)</td>
</tr>
<tr>
<td>Nonambulatory</td>
<td>1 (2.4)</td>
<td>5 (1.8)</td>
</tr>
</tbody>
</table>

* Four cases treated with IA rt-PA are excluded from the original 330 eligible subjects.
† p Value generated from univariate logistic regression analyses.
‡ Includes non-stroke related findings such as atrophy (37 cases), age-related change/degenerative (10 cases), calcification (6 cases), low density lesions (6 cases), small vessels disease (3 cases), and other miscellaneous findings (21 cases).

ED = emergency department; EMS = emergency medical services.
and onset to ED arrival time and age, sex, and race were tested but none was significant. We conducted a sensitivity analysis to evaluate the effect of removing subjects who arrived between 2 and 3 hours of onset (n = 87) from the eligible pool. The IV rt-PA treatment rate increased to 17.6% (i.e., 42/239); however, no meaningful changes to the final model were observed (data not shown).

Five of the 43 (11.6%) IV rt-PA treated patients had bleeding complications after treatment. Intracranial hemorrhage occurred in two patients (4.6%), one of whom died as a consequence. This patient was treated at exactly 3 hours after stroke onset, and had a pre-treatment NIHSS of 28. The other three patients received rt-PA between 2 to 3 hours after stroke onset, and their bleeding complications were limited to the gastrointestinal tract.

All 43 of the IV rt-PA treated patients had a final diagnosis of ischemic stroke at discharge, compared to 58% (n = 165) of the 283 non-treated patients. Forty percent of the untreated patients had a final diagnosis of TIA (n = 114), while 1.4% (n = 4) had a final diagnosis of hemorrhagic stroke. We evaluated the effect of removing the untreated TIA cases from the eligible pool—the IV rt-PA treatment rate increased to 20% (43/212), however there were no meaningful changes to the final model results (data not shown).

Information on stroke severity prior to treatment (as measured by the NIHSS) was available for only 51 (15.6%) of all eligible patients; 26 (9.2%) of the 283 non-treated patients had NIHSS documented with a median score of 8.0 (range: 1.0 to 21.0), compared with 25 (58%) of the 43 IV rt-PA-treated cases with a median score of 12.0 (range: 2.0 to 28.0) (p = 0.02). Among all eligible subjects with a final diagnosis of ischemic stroke, the in-hospital mortality rate was 9.3% among the IV rt-PA treated cases and 2.6% in non-treated group (p = 0.01). A higher proportion of patients who received IV rt-PA therapy had moderate to severe disability (i.e., mRS 4 or 5) at discharge, compared to those not treated (51.3% vs 33.6%, p = 0.06). Because the majority of eligible subjects lacked adequate information on NIHSS, we were unable to adjust these outcomes for the underlying stroke severity.

**Discussion.** In this study, only 13% (n = 330) of all acute stroke admissions were eligible for IV rt-PA treatment.
treatment, and of this group, only 13% (n = 43) received IV rt-PA treatment. These 43 patients represent only 2.1% of the non-hemorrhagic stroke admissions to the MASCOTS hospitals. This figure is similar to other US-based studies of IV rt-PA, where treatment rates have varied from a low of 1.2% in a statewide administrative database to 9% in one experienced medical center. Similarly, the IV rt-PA treatment rate of 13% among the eligible population is comparable to the 14% figure reported by the Canadian stroke registry.

Of the 283 eligible patients who did not receive IV rt-PA, no specific reasons for withholding treatment were recorded. We therefore hypothesize that a combination of in-hospital delays, lack of appropriate health care resources, and individual hospital or physician preferences against the use of rt-PA attributed to this non-use. However, it is possible that incomplete medical record documentation resulted in some subjects being classified as eligible for treatment, whereas in fact it was determined during their initial evaluation that the subject was not a candidate for rt-PA therapy. It is important to note that our eligible population for rt-PA treatment included subjects who were eventually diagnosed as having TIA or even hemorrhagic stroke. These non-ischemic stroke subtypes are typically excluded from other studies, however, we chose to include them because they were considered for rt-PA treatment during their initial presentation, and the final determination of their stroke subtype was not made until after discharge. This approach results in a conservative (or worst-case) estimate of the IV rt-PA treatment rate. We therefore calculated a best-case scenario by excluding the 114 TIA cases in the untreated group. The IV rt-PA treatment rate increased from 13% to 20%; however, the multivariable model results did not materially change.

Reasons for patient ineligibility for IV rt-PA treatment can be viewed as either occurring during the preadmission period or the in-hospital period. Before admission, the most common reasons for subjects being ineligible for IV rt-PA use were delayed presentation (>3 hours since onset) and the lack of information on stroke onset time. Sixty-five percent of the subjects with a known onset time arrived after 3 hours of their stroke onset. Despite the fact that the PCNASR data collection instrument allowed for the detailed recording of information surrounding the onset of stroke—including the designation of an estimated time (within a 6-hour window) when the onset was not witnessed or the patient awoke with symptoms, and the use of date last seen normal for subjects with no known onset time—almost 40% of the admissions did not have any information on stroke onset time documented. Compared to those with documented onset times, subjects without documented onset times were more likely to be older, female, and residing in a nursing home (data not shown)—findings that indicate that onset time information is not missing at random.

We can only speculate on the underlying reasons for the poor documentation of stroke onset times in this study. It is likely that the majority of cases missing this information did arrive after 3 hours of onset, and that perhaps the attending medical staff therefore saw no reason to document the onset time. Alternatively, other reasons for non-treatment of rt-PA (such as contraindications or mild stroke) that were not documented in the chart may have been observed, which again led the staff to not record the onset time. Beyond these medical documentation issues, patient factors may also have contributed to the lack of information on onset times. There is poor knowledge regarding stroke signs and symptoms in the general population, which is thought to contribute to the prehospital delay of patients. However, this lack of knowledge could also contribute to the poor documentation of stroke onset times if patients are unable to recognize the onset of stroke symptoms, or fail to understand the importance of reporting them accurately to medical staff. The poor documentation of onset times clearly limits our ability to fully understand the underlying causes for why cases are ineligible for rt-PA treatment. The development of data systems to improve the documentation of onset times is needed. As an example, the use of pre-hospital stroke screening tools by EMS personnel could help improve the documentation of onset times, in addition to improving the identification of patients with stroke and expediting the delivery of acute treatment.

EMS played an important role in facilitating IV rt-PA treatment in our study. We found that patients who knew their stroke onset time were more likely to call an ambulance (47.5% vs 36.1%, p < 0.01), and that patients using EMS were more likely to arrive within 3 hours of stroke onset (56.3% vs 41.1%). Even among our eligible population who all arrived within 3 hours of stroke onset, those who used EMS were seven times more likely to receive IV rt-PA therapy, compared to those who arrived by car, walk-in, bus, or other means. Previous studies have shown an association among stroke severity, EMS use, and presentation time; patients who arrive earlier have more severe strokes and are more likely to call EMS. Given that studies have shown that travel time to the hospital is just a small proportion of the total prehospital delay, it is likely that the positive effects of EMS use are derived, in part, from its impact on reducing in-hospital delays—as described in several previous studies.

We found that the odds of getting IV rt-PA treatment for women was 40% that of men. A study conducted in 137 community hospitals in the United States found a similar trend toward women being less likely to receive IV rt-PA for stroke. The underlying reasons for this sex difference are unknown; however, a previous study of acute stroke care in Houston found that women got to the hospital significantly later than men, and that ED physicians saw men significantly faster than women, even after con-
trolling for other factors including stroke type and severity.29

Information on the pretreatment stroke severity (i.e., NIHSS) was missing in the majority (84%) of eligible subjects in this study. Because there is clearly selection bias in the subjects who are treated with IV r-tPA (i.e., cases with greater severity are more likely to receive treatment), no meaningful conclusion can be made based on the findings, which demonstrated higher in-hospital mortality, and poorer mRS scores at discharge among the treated cases. It should be noted that both of these findings are consistent with prior studies4,5,28; however, we present these data primarily to illustrate the importance of collecting stroke severity data for every subject included in a stroke registry. These findings also help illustrate the limitation of not having postdischarge follow-up data to determine longer-term outcomes, especially since the benefits to rt-PA treatment across Michigan. This study has several limitations, however. The design of this registry means that the data should reflect real life practice of acute stroke care and treatment across Michigan. This study has several limitations, however. First, our definition of eligibility is dependent on the adequacy of prospective data collection and chart documentation. As discussed previously, the fact that the untreated group included TIA cases suggests that some of these subjects were probably not eligible for rt-PA at the time of initial evaluation, but these facts were not adequately documented. Second, poor documentation of NIHSS score, the absence of other measures of stroke severity, and the lack of outcomes data from the postdischarge period preclude the valid evaluation of patient outcomes.

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