Stroke Thrombolysis: Having More Time Translates Into Delayed Therapy

Data From the Austrian Stroke Unit Registry

Julia Ferrari, MD; Michael Knoflach, MD; Stefan Kiechl, MD; Johann Willeit, MD; Benjamin Matošević, MD; Leonhard Seyfang, MoS; Wilfried Lang, MD; for the Austrian Stroke Unit Registry Collaborators

Background and Purpose—Efficacy of intravenous thrombolysis in acute ischemic stroke declines with increasing time to treatment initiation. Previous small-scale studies suggested that the earlier patients arrive, the longer it takes to administer recombinant tissue plasminogen activator.

Methods—Of 32,529 patients with stroke prospectively enrolled in the Austrian Stroke Unit Registry (2004 to 2009), 3287 received intravenous thrombolysis and 2663 of them were eligible for the current analysis.

Results—Median (interquartile range) onset-to-door and door-to-needle times were 70 (50 to 100) and 50 (35 to 70) minutes. Of note, both time intervals were inversely correlated with each other. After adjustment for multiple stroke characteristics, the door-to-needle time of patients arriving in the hospital within the first hour after stroke onset was 6.9 minutes ($P<0.001$) and 13.9 minutes ($P<0.001$) longer than those for patients arriving between 61 to 120 and 121 to 180 minutes. Findings were consistent in subgroups.

Conclusions—Early hospital arrival translates into a significant delay in the application of intravenous thrombolysis among patients with acute stroke. This finding calls for concerted measures to ensure that all patients with stroke are treated with the same urgency irrespective of the time available. (Stroke. 2010;41:00-00.)

Key Words: acute stroke thrombolysis time delay

Intravenous recombinant tissue plasminogen activator (rtPA) is the first-choice therapy for acute ischemic stroke with a high level of scientific evidence regarding efficacy and safety.1–3 Because treatment effects decline rapidly with the time passed after symptom onset,4 early administration of rtPA is a major challenge. Numerous critical reviews about delays in time intervals from symptom onset until hospital arrival (onset-to-door time [ODT]) and from hospital arrival until administration of thrombolysis (door-to-needle time [DNT]) have been performed.5–7 Interestingly, some small-scale studies suggested an inverse correlation between ODT and DNT indicating that the earlier the patient arrives, the longer it takes to administer intravenous thrombolysis.8–14 Results of the European-Australian Acute Stroke Study (ECASS) 3 trial15 establishing efficiency and safety of rtPA between 3 and 4.5 hours after stroke onset could be misinterpreted as “having more time” and potentially lead to “taking more time.”

We have specifically analyzed the relationship between ODT and DNT in the large nationwide prospective registry of Austrian stroke units and monitored trends over the past 6 years. The study has a power of 80% ($\alpha=0.05$) to detect a delay in the DNT as low as 1.77 minutes between subjects arriving within the first hour versus those coming later.

Methods

Since 2003, a growing network of Austrian stroke units (Austrian SU Network) prospectively collected data on standard characteristics and acute management of all patients with stroke admitted to 32 of 34 Austrian stroke units. Data collection and ratings were performed by experienced stroke neurologists using standardized variable definitions and scores. To ensure high data quality, immediate data entry was obligatory, and the web-based database featured online plausibility checks and help. Most centers performed a local quality assessment in terms of a daily or weekly check of registry entries and admission/discharge lists to ensure complete entry of patients into the database. In biannual meetings of stroke neurologists from the participating centers, details about scoring procedures and variable assessment are thoroughly discussed. The registry is part of a governmental quality assessment program for stroke care in Austria financed by the Federal Ministry of Health. Anonymized data are centrally administered by the Gesundheit Österreich GmbH and scientific analyses are approved and supervised by an academic review board. Details on the registry have been reported previously.16 In April 2004, the registry was enriched by documentation of

Received May 12, 2010; accepted June 10, 2010.

From the Department of Neurology (J.F., W.L.), Hospital Barmherzige Brüderschaft, Vienna, Austria; the Department of Neurology (M.K., S.K., J.W., B.M.), Innsbruck Medical University, Innsbruck, Austria; and Danube University Krems (L.S.), Gesundheit Österreich GmbH/BIQG, Austria. Correspondence to Wilfried Lang, MD, Department of Neurology, KH der Barmherzigen Brüderschaft, A-1020 Vienna, Grosse Hockengasse 9, Austria. E-mail wilfried.lang@bbwien.at

© 2010 American Heart Association, Inc.

Stroke is available at http://stroke.ahajournals.org DOI: 10.1161/STROKEAHA.110.590372
the ODT and DTN involving details and timing of intrahospital management. Between April 1, 2004, and December 31, 2009, a total of 32,529 patients with an acute ischemic stroke were treated on Austrian stroke units and enrolled in the registry forming our study population. Data sets were complete in 29,899 patients, 3,287 of whom received intravenous thrombolysis.

As a statistical environment, R (Version 2.7.1)\(^{17}\) was used. We performed linear regression analysis with the DNT (measured in minutes) applied as the dependent variable. Collinearity was tested by calculation of the generalized variance inflation factor. The following variables were included in the multivariate regression model built by a stepwise selection procedure (optimizing the Akaike Information Criteria): age category (0 to 59, 60 to 79, and 80 to 103 years), gender, year of admission (2004 to 2009), stroke center, ODT categorized in 60-minute steps (0 to 60, 61 to 120, 121 to 180, and 181 to 240 minutes), stroke severity measured by the National Institutes of Health Stroke Scale (categorized 0 to 3, 4 to 16, 17 to 25, and 26 to 42), means of transport (ambulance with or without emergency physician, helicopter, or private transport), MR tomography as the primary imaging modality (yes/no), weekend admission (yes/no), secondary transportation through other hospitals (yes/no), and direct transportation to stroke unit within given hospitals (yes/no). The first-order interactions were in the scope of the model but not selected by the stepwise selection procedure. In a sensitivity analysis, DNT values were transformed by the Box-Cox power transformation to better approximate a normal distribution (Shapiro-Wilk normality test) and multivariate regression models constructed in the way described previously. All findings were very similar; thus, for ease of interpretation, we present data from the primary analysis only. Finally, analysis was performed in different subgroups according to gender, National Institutes of Health Stroke Scale, age, primary imaging modality, and center’s experience for thrombolytic therapy (centers having <20 patients with stroke with intravenous rtPA per year versus centers performing ≥20 stroke thrombolysis).

### Results

In the study period between April 1, 2004, and December 31, 2009, 3,287 (12.8%) of the patients with acute ischemic stroke treated in Austrian stroke units received intravenous thrombolysis. After excluding individuals with unknown ODT (especially awakening strokes), thrombolysis before stroke unit admission (administered in local hospitals with subsequent transport to the next stroke center) and a DNT >240 minutes (especially strokes happening to in-hospital patients), 2,663 subjects remained and formed the current study population. Population characteristics are summarized in the Table. Median (interquartile range) ODT in this nationwide survey was 70 (50 to 100) minutes and median (interquartile range) DNT 50 (35 to 70) minutes. Within the study period, median DNTs tended to decline by an annual average of approximately 2 minutes, whereas OTDs remained unchanged. Figure A visualizes absolute levels of and changes in the median DNT between 2004 and 2009 conditional on given OTDs. The graph clearly indicates that the DNT is highest (black line) in patients arriving early after stroke; however, there is a tendency of DNTs in the various categories of arrival (ODT) to converge over time. In multivariate logistic regression analysis; findings remained significant after controlling for age, gender, stroke severity, center, transportation to and within the hospital, weekend admission, imaging modality; and year (P<0.001). After multivariate adjustment, the DNTs of patients arriving in the hospital between 61 to 120 and 121 to 180 minutes after stroke onset were 6.9 minutes and 13.9 minutes shorter, respectively, than that of patients with an ODT of 0 to 60 minutes (each

### Table. Characteristics of the Study Population (N=2663)

<table>
<thead>
<tr>
<th>Demographics</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years(^a)</td>
<td>73 (64–80)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male sex, no. (%)</td>
<td>1445 (54.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke severity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NIHSS on admission(^a)</td>
<td>10 (6–16)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time intervals</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ODT, minutes(^a)</td>
<td>70 (50–100)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DNT, minutes(^a)</td>
<td>50 (35–70)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imaging modality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MR, no. (%)</td>
<td>448 (17)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Details of patients admission</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weekend admission, no. (%)</td>
<td>713 (26.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prehospital transport</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emergency ambulance, no. (%)</td>
<td>1139 (42.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ambulance, no. (%)</td>
<td>1221 (45.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Helicopter, no. (%)</td>
<td>215 (8.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary transport, no. (%)(^a)</td>
<td>259 (9.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In-house management</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary care in the emergency room, no. (%)</td>
<td>1764 (66.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Direct transport to stroke unit, no. (%)</td>
<td>899 (33.8)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)Values presented are medians (interquartile range). \(†\)Patients primarily admitted to a local hospital and immediately transferred to the stroke unit for intervention. NIHSS indicates National Institutes of Health Stroke Scale.

P<0.001). The delay was consistent in various subgroups (Figure B).

### Discussion

Our analysis in the nationwide registry of Austrian stroke units clearly demonstrates that the earlier a patient with acute stroke arrives in the hospital, the longer it takes to administer intravenous rtPA. The delay in the DNT for those arriving in the first hour, previously termed the “golden hour,” persisted after adjustment for multiple stroke and stroke care characteristics; emerged as highly consistent in various subgroups including patients with distinct stroke severity, men and women, center size, and age groups (Figure B); and was clinically relevant (plus 13.9 minutes when compared with those arriving in the third hour). Although patients with acute stroke are treated with highest priority in our specialist stroke units, the feeling of “having more time” might induce small delays on various levels of patient management. Three small-scale studies including a total of 502 patients reported a similar inverse association between ODT and DNT, yet the magnitude of time delay in these evaluations, conducted between 1997 and 2002, was more pronounced.\(^{12–14}\) Moreover, recent analysis of data from “Get With The Guidelines—Stoke” hospitals (presented at the 2009 International Stroke Conference but not yet published in full)\(^{11}\) yielded a treatment delay highly consistent with that observed in our survey.

Of note, we observed a continuous decline in the delay of rtPA application among patients arriving early after stroke over the past years (Figure A) along with a decline in median DTNs. There are 2 potential reasons for this trend. First, the
percentage of patients with ischemic stroke who received thrombolytic therapy gradually increased from 2004 to 2009: 6.8% (2004), 7.4% (2005), 9.5% (2006), 10.5% (2007), 13.0% (2008), and 15.1% (2009). Increasing frequency of thrombolysis therapy reflects advances in stroke care organization with a broad implementation of thrombolysis protocols and stroke care maps (promoted by continuous educational activities in biannual meetings of stroke unit operators) and is inherently linked with more experience and accelerated management of patients with acute stroke. Second, in 2007, we have implemented a tool that gave stroke units online access to their registry data. Each stroke unit received detailed information about its performance (eg, thrombolysis frequency, ODT, and DNT) in comparison with all other stroke units. We believe that this measure enabled identification of local problems and helped to improve and standardize stroke care.

Of note, publication of the results of ECASS 3 in 2008 had no measurable effect on the DNT and in particular did not lead to a reversal of the aforementioned trend.

Our study is unique for its size and the fact that it includes the vast majority of patients with intravenous stroke thrombolysis in the whole of Austria providing a safeguard against selection bias.

**Conclusions**

Early hospital arrival is linked to a significant and clinically meaningful delay in the application of intravenous rtPA among patients with stroke. Every effort has to be undertaken to improve this situation and make sure that candidates for thrombolysis all are managed and treated with the same urgency irrespective of the residual time available. Potential means of avoiding treatment delays and further lowering DNTs include feedback of the presented data to the Austrian stroke unit network in “benchmarking” sessions, the general introduction of point-of-care laboratory testings, and best practice models.

**Disclosures**

None.

**References**


Stroke Thrombolysis: Having More Time Translates Into Delayed Therapy. Data From the Austrian Stroke Unit Registry
Julia Ferrari, Michael Knoflach, Stefan Kiechl, Johann Willeit, Benjamin MatoSevic, Leonhard Seyfang and Wilfried Lang
for the Austrian Stroke Unit Registry Collaborators

Stroke. published online August 5, 2010;
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2010 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/early/2010/08/05/STROKEAHA.110.590372.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/