The effectiveness of thrombolytic therapy for ischemic stroke depends on the interval between symptom onset and treatment time. Meaningful reporting of temporal trends in the onset to treatment (OTT) time is important for understanding the wider impact of changes in service delivery and licensing criteria.

Changes in time interval data are typically reported using measures of central tendency, either mean or median and associated measures of variance, but these do not consider the entire distribution potentially masking important underlying effects. This report applies a novel method that compares OTT distributions from 2 cohorts of UK patients treated with intravenous thrombolysis.

The nonparametric relative distribution is a technique allowing direct comparisons between outcomes across their entire distributions providing insights that summary statistics may miss. In the context of thrombolysis, this could be important for understanding the full impact of new service initiatives, the accumulation of clinical experience, and change in time-related treatment criteria. This approach estimates where each case in a second (comparator) group would lie within the first (reference) group’s distribution. If the distributions are the same, the relative difference between positions will not be significantly different, but greater deviation from uniformity indicates that measures of central tendency are less representative of the impact of changes.

Background and Purpose—Analyses of trends in the delivery of time critical treatments typically report the median, but measures of central tendency may ignore important changes for specific patient groups. We considered whether this was an important effect during comparison of onset to treatment (OTT) time between 2 cohorts of patients with stroke receiving intravenous thrombolysis.

Methods—After controlling for stroke severity, a relative distributions technique compared OTT for UK patients treated with recombinant tissue-type plasminogen activator registered within the first and last quarters (each n=661) of the Safe Implementation of Thrombolysis in Stroke-Monitoring Study database between January 2003 and September 2010.

Results—Significant differences were found between OTT distributions. Overall, the second cohort’s OTT distribution demonstrated simultaneous increases in the proportion of patients with faster and slower OTT, which resulted in no net effect on the median after correction for stroke severity.

Conclusions—Medians did not adequately describe distributional changes. Faster OTT may be because of more efficient processes in acute stroke centers and improved symptom recognition by the public. Slower OTT is likely to reflect movement from a 3- to a 4.5-hour OTT target. Relative distributions offer new insights into historical trends and service evaluation where time critical treatments are involved. (Stroke. 2015;46:00-00. DOI: 10.1161/STROKEAHA.115.008724.)

Key Word: thrombolysis, therapeutic

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Methods

We applied relative distributions to OTT reported in the first (January 2003 to 2007) and last (October 2009 to September 2010) quarters of the population described by the Safe Implementation of Treatments in Stroke-UK registry4 between 2003 and 2010 (n=661 for each quartile), having first controlled for stroke severity by National Institutes for Health Stroke Scale.5 The Kullback and Leibler6 entropy measure was used to investigate the similarity between the 2 distributions, with larger values indicating larger differences. Population characteristics were compared by independent samples \( \chi^2 \) and \( t \) tests. All analyses were conducted using R statistical software7 and the reldist package8 (for description and example, see online-only Data Supplement).

Results

The Table shows baseline characteristics. The first cohort was accumulated over a time period of 4 years, the second over 13 months, reflecting more treatments per center and a greater number of active centers contributing data. Patients in the second cohort were older, but sex balance was unchanged.

Median National Institutes for Health Stroke Scale fell from 14 to 12, confirming the need to control for severity. Median OTT fell from 160 to 145 minutes possibly because of not only increased service efficiency and clinician experience but also suggestive of a shift toward treatment of less challenging milder cases.

Relative distributions of OTT and 95% confidence intervals are displayed in the Figure as (1) relative density (ie, overall difference between cohorts), (2) change in location (ie, distribution around the median), and (3) change in shape (ie, distribution of all cases), where unity represents no difference between the 2 cohorts. Either side of unity, the vertical axes assign a value to differences in the total, location, and shape of OTT distribution between the 2 cohorts, using the first cohort for reference. Despite the median OTT being lower in the second cohort, the Figure (A) shows that by the first cohort’s median treatment time \( \approx 160 \) minutes fewer patients in the second cohort had been treated \( \approx 40\% \). This indicates that the observed reduction in median OTT in the second cohort is because of faster treatment of only a proportion of cases, a gain that was partially but not totally offset by a larger number receiving treatment later.

After controlling for stroke severity, the uniform relative density and low Kullback–Leibler entropy value for the Figure (B) indicates that the 2 OTT distributions are similar and there is no median shift. This may reflect an important OTT-lowering effect in the second cohort from extending treatment to an increasing number of milder cases. The similar appearances and Kullback–Leibler entropy values for the Figure (A) and (C) confirm that differences in the distributions are at the tails, ie, toward the end of the OTT range, and that the median is concealing a more complex interaction between speed of treatment and case-mix (stroke severity and time after stroke onset).

OTT times are displayed on an upper horizontal axis. The Figure (A) shows that a larger proportion of second cohort patients had not only an OTT of <120 minutes relative to the first cohort (the relative density is >1) but also a higher proportion with OTT>180 minutes, indicating a polarization of differences in OTT with fewer cases treated around the median.

Table. Baseline Characteristics of Cohorts

<table>
<thead>
<tr>
<th>Test for Difference</th>
<th>First Cohort (n=661)</th>
<th>Second Cohort (n=661)</th>
<th>PValue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time frame</td>
<td>January 2003–2007</td>
<td>October 2009 to September 2010</td>
<td>…</td>
</tr>
<tr>
<td>Centers contributing</td>
<td>35</td>
<td>73</td>
<td>…</td>
</tr>
<tr>
<td>Age, y, mean (SD)</td>
<td>67.1 (12.7)</td>
<td>68.5 (11.6)</td>
<td>0.05*</td>
</tr>
<tr>
<td>Men, %</td>
<td>59.2</td>
<td>57.9</td>
<td>0.63†</td>
</tr>
<tr>
<td>Stroke severity, median NIHSS (IQR)</td>
<td>14 (9–19)</td>
<td>12 (7–17)</td>
<td>&lt;0.001‡</td>
</tr>
<tr>
<td>OTT, median minutes (IQR)</td>
<td>160 (130–176)</td>
<td>145 (116–180)</td>
<td>0.01‡</td>
</tr>
</tbody>
</table>

IQR indicates interquartile range; NIHSS, National Institutes for Health Stroke Scale; and OTT, onset to treatment.

* \( t \) test, †proportion test, and ‡Mann–Whitney U test.

Figure. Onset to treatment (OTT) time quartile 4 compared with quartile 1 patients. A, Relative density, (B) change in location, and (C) change in shape.
Discussion
After controlling for stroke severity, a retrospective comparison of 2 thrombolysis cohorts showed that there was little shift in median OTT but there were differences in the shape of the distribution. Decomposing overall relative density illustrated the loss of detail that can occur only when comparing medians. In the second cohort, more patients were treated sooner and more were treated later rather than a simple reduction in door-to-needle times across the whole distribution. The rapid exponential reduction of thrombolysis benefit over time makes it important to understand changes in OTT distribution rather than just median shift when considering the impact on patient outcomes.

This analysis offers no explanation for why the severity-corrected distribution of OTT has changed or whether this reflects changes between centers or within centers. Shorter OTT may stem from improvements in symptom recognition, emergency care efficiency, and increasing clinician experience. Longer postmedian OTT potentially reflects changes in clinical practice after the 2008 publication of the European Cooperative Acute Stroke Study (ECASS) III trial that demonstrated the continuing benefit of thrombolysis treatment between 3 and 4.5 hours after onset. Reports also suggest that door-to-needle times have lengthened for some patients because of a slowing of the emergency response after loss of a 3-hour target combined with attempts to treat complex patients who would not have been considered previously. When additional data are available, the relative distribution technique can be used to examine this effect in the context of overall trends in OTT since the change in the European license for Alteplase. More generally, relative distribution techniques could provide an important tool for those evaluating interventions with time critical elements and to compare center performance with time, whether in acute stroke care or elsewhere in emergency medicine.

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References
Relative Distributions: A Novel Method for Examining Trends Between Stroke Onset and Thrombolysis Time

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