In Europe, 1 in 7 women and 1 in 10 men who have (or experience) a stroke die each year from the disease or its complications. Treatment with intravenous thrombolysis (IVT) has been the standard pharmacological therapy for acute ischemic stroke after alteplase, a recombinant tissue-type plasminogen activator, was introduced in routine clinical practice in the early 2000s. Recently, endovascular thrombectomy was shown in several randomized trials to give additional strong clinical benefit to patients with stroke initially treated with IVT. The first European practice guidelines for the use of alteplase in stroke were formulated in 2003 by the European Stroke Initiative (EUSI). The European Stroke Organisation (ESO) was founded in December 2007 to replace EUSI and published new European guidelines for the management of acute ischemic stroke in May 2008, with revision in January 2009 (hereafter named ESO 2008/2009). 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WHAT IS KNOWN

• Acute stroke treatment with intravenous thrombolysis using alteplase is subject to label and guideline recommendations.
• The latest European guidelines for acute stroke treatment were published in 2008/2009 and incorporate scientific breakthroughs—namely intravenous thrombolysis in the elderly and ≤4.5 hours after symptom onset—that have not yet been updated in the European alteplase label from 2002.

WHAT THE STUDY ADDS

• This study demonstrates prompt adherence to the new 2008/2009 European guidelines in observational data of 18,400 intravenous thrombolysis-treated patients enrolled in the Safe Implementation of Treatments in Stroke registry, demonstrating that physicians follow the updates of guideline recommendations.
• After the introduction of the 2008/2009 European guidelines, rates of alteplase label violations doubled to reach half of the patient cohort, indicating that clinical practice grossly deviates from the unchanged label.
• Patient volume in a stroke center is a determining factor for nonadherence, with high-volume centers showing high rates of nonadherence to both label and guidelines.

Data Analysis
For calculation of significance of difference between proportions, we fitted a logistic mixed effects model to take into account the hierarchical structure of our data (patients are clustered in hospitals). To determine whether nonadherence was influenced by the source of recommendation (label versus EUSI 2003 versus ESO 2008/2009), nonadherence rates were additionally grouped according to source and time period for comparison. To determine whether nonadherence was associated with the number of IVT-treated patients per center and per 2-year period, patient volume was grouped into 4 strata: <50, 50 to 99, 100 to 199, and ≥200 patients and additionally grouped according to contraindication source and time period.

Ethical Approval
This project was reviewed and approved by the Central Ethical Review Board of the Stockholm County (EPN 2014/908-31/1) and by the SITS Scientific Committee.

Results
The number of patients with stroke treated with IVT nearly doubled in hospitals that participated in the SITS registry during both study periods, increasing from 6354 patients in 2006 to 12,046 in 2010 to 2011, when physicians were already familiar with the new guidelines, and 2006 to 2007, reflecting common practice before the new guidelines appeared. Practice in both periods was under the influence of the 2002 European Medicines Agency label for alteplase, commercialized in Europe by Boehringer Ingelheim as Actilyse, which remained unchanged. Available guideline recommendations for IVT in 2006 to 2007 were the 2003 EUSI guidelines (Figure 1, study timeline).8

Study Population
Anonymized data from patients treated with IVT for acute ischemic stroke in Europe were obtained from the SITS-International Stroke Thrombolysis Register (SITS-ISTR). SITS-ISTR has been a prospective, multinational, observational registry for medical centers documenting stroke treatments since 2002. The aims of the registry, collection of data, and structure of the database have been previously described.21 The need for ethical approval and patient consent for participation in the SITS-ISTR varied among enrolling countries. They were obtained in countries so requiring; other countries approved the registry for conduct as an anonymized audit. The SITS International Coordination Office monitored the registry data online and checked individual patient data monthly to identify errors or inconsistencies. Data on a total of 18,400 patients were collected from 232 hospitals in 19 European countries that were actively enrolling during both periods January 1, 2006, to December 31, 2007, and January 1, 2010, to December 31, 2011. The following variables were obtained from the database: time points of IVT treatment after stroke onset (onset-to-treatment time [OTT]), age, stroke severity per the National Institutes of Health Stroke Scale, SBP, diastolic blood pressure, and glucose levels on admission; medication with anticoagulants, diabetes mellitus with any previous stroke, and previous stroke within the last 3 months. Proportions were calculated excluding cases with missing or unknown values for each variable, as done in previous SITS publications.21,24

Concomitant treatment with oral anticoagulants. In some cases, similarities between the label and guidelines make it difficult to choose which should be adhered to, for example, upper systolic blood pressure (SBP) limits differing by only 1 mm Hg at >185 and >184 mm Hg, respectively, between the documents. A summary of label and guideline contraindications and their sources is shown in Table 1. It is often stated that many of the original label contraindications were based on expert opinion and may be too restrictive because they mostly derive from inclusion and exclusion criteria of randomized clinical trials.12,14-16 Many patients receive off-label IVT after physician assessment that the benefit outweighs the risk of serious adverse effects, such as intracranial or systemic bleeding. Reported off-label IVT treatment ranges from 34% to 51% of the total IVT-treated population in experienced centers17-20 and large registry cohorts including, SITS-Central and Eastern Europe (SITS-EAST)21 and Virtual International Stroke Trials Archive (VISTA).22

The aim of this study was to compare nonadherence to label and guideline contraindications for IVT in European hospitals registering patients in the SITS registry both before and after the release of ESO 2008/2009 guidelines.

Methods

Study Timeline
We chose to compare the proportions of patients treated despite guideline and label nonadherence between time periods after and before the 2008/2009 ESO guidelines’ publication: the years 2010 to 2011.
was notably lower than off-label treatment (not shown). From 2003 guidelines (with 7.0% and 4.6% missing values, respectively). The total numbers of patients per center volume stratum obtained for label in 2006 to 2007 versus 2010 to 2011 were as follows: 2885 versus 3015 in centers treating <50 patients; 1384 versus 2679 in centers treating 50 to 99 patients; 1329 versus 3789 in centers treating 100 to 199 patients; and 357 versus 1673 in centers treating ≥200 patients. The total numbers of patients per center volume stratum obtained for European guidelines in 2006 to 2007 versus 2010 to 2011 were as follows: 3003 versus 3085 in centers treating <50 patients; 1458 versus 2746 in centers treating 50 to 99 patients; 1354 versus 3784 in centers treating 100 to 199 patients; and 361 versus 1767 in centers treating ≥200 patients (Figure 2A).

Rates of Nonadherence per Center Volume and Source of Contraindications

Rates of nonadherence were the highest in centers with high patient volumes. In both time periods, there were significant increases in label nonadherence with increasing patient volumes, ranging from 19.9% to 34.7% in 2006 to 2007 and from 41.6% to 57.3% in 2010 to 2011. Significant increases in nonadherence with increasing center volume were also observed for EUSI guidelines in 2006 to 2007, ranging from 13.0% to 18.0%, and for ESO guidelines in 2010 to 2011, ranging from 9.4% to 13.9% (Figure 2B). Nonadherence to the label increased over time in both low- and high-volume centers. Inversely, nonadherence to European guideline recommendations decreased slightly over time in both low- and high-volume centers.

Number of Enrolling Hospitals per Center Volume

The number of hospitals active in both time periods and enrolling <50 patients decreased from 200 centers in 2006 to 2011.

<table>
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<tr>
<td>Age &gt;80 y</td>
<td>X</td>
<td>X</td>
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<tr>
<td>OTT &gt;3 h</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>OTT &gt;4.5 h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NIHSS score &gt;25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anticoagulation treatment</td>
<td>X</td>
<td></td>
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<td>SBP &gt;185 mmHg</td>
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<td>SBP &gt;184 mmHg</td>
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<td>X</td>
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<td>SBP &gt;180 mmHg</td>
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<td>X</td>
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<tr>
<td>DBP &gt;110 mmHg</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>DBP &gt;109 mmHg</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Previous stroke within the last 3 months</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus and previous stroke</td>
<td></td>
<td></td>
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<tr>
<td>Blood glucose &lt;2.8 or &gt;22.2 mmol/L</td>
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DBP indicates diastolic blood pressure; EUSI, European Stroke Initiative; European clinical practice guidelines published in 2003; ESO, European Stroke Organisation: clinical guidelines published in 2008/2009 to replace EUSI; label: license for alteplase in Europe since 2002; NIHSS, National Institutes of Health Stroke Scale; OTT, onset-to-treatment time; and SBP, systolic blood pressure.

Nonadherence increased significantly for nearly all label and guideline contraindications in 2010 to 2011; in particular for National Institutes of Health Stroke Scale score >25 (1.7%) and anticoagulation treatment (3.1%), both present in the label only; SBP >184 mmHg (6.3%) and diastolic blood pressure >109 mmHg (3.6%), present not only in the guideline but also in the label as SBP >185 and diastolic blood pressure >110 mmHg; and OTT >4.5 hours (1.8%), present in the guideline only. There was no significant increase in treatment despite contraindicated glucose levels or in patients with diabetes mellitus and any previous stroke (including previous stroke within the last 3 months). Notably, in the years 2006 to 2007, that is, before the more permissive guideline formulation, nonadherence to the label age contraindication was already 8.9%, and similarly, nonadherence to the label contraindication of treatment beyond 3 hours from symptom onset was 8.2%.

The overall proportion of patients treated in nonadherence to label more than doubled from 1407 of 5955 (23.6%) in 2006 to 2007 to 5701 of 11 156 (51.1%) in 2010 to 2011 (not shown). On the contrary, the proportion of patients treated outside the European guidelines remained relatively constant, with 886 of 6176 patients (14.3%) in 2006 to 2007 (per EUSI 2003 guidelines) decreasing slightly to 1328 of 11 382 patients (11.7%) in 2010 to 2011 (per ESO 2008/2009 guidelines) but was notably lower than off-label treatment (not shown).
2007 to 153 centers in 2010 to 2011, whereas the number of hospitals enrolling 50 to 99, 100 to 199, and ≥200 patients increased 2-, 3- and 8-fold, respectively (from 21–41, from 10–30, and from 1–8, respectively; Figure 2C). When examining adherence at each individual hospital, a clear decrease in label adherence in 2010 to 2011 is observed for most hospitals when ranking them from the least to the most adherent (Figure 3). Thus, even in the more adherent hospitals, there was a clear parting from label adherence after the ESO 2008/2009 update.

Comparison With Previous Off-Label IVT Treatment Studies
On the majority of contraindications in our study, that is, age, OTT, blood pressure, oral anticoagulation, previous stroke, and diabetes mellitus, our results were in line with previous studies. Table 3 shows a full comparison across time periods and with various publications.

Discussion
To our knowledge, this is the first study examining the effects of the ESO 2008/2009 guidelines in clinical practice and showing a difference between adherence to guideline recommendations and the product label for IVT treatment of acute ischemic stroke in European hospitals. The results can be summarized as follows: (1) after ESO guidelines for IVT in acute stroke were updated in 2008/2009 to include patients aged >80 years and an extended treatment time window from 3 to 4.5 hours, there was widespread and prompt adherence of stroke physicians to the new recommendations; (2) nonadherence to most guideline and label contraindications significantly increased in 2010 to 2011 compared with that in 2006 to 2007; (3) label nonadherence doubled in 2010 to 2011, from a quarter to half of all IVT-treated patients, whereas nonadherence to European guidelines remained at a similar level, with only a slight decrease; and (4) we demonstrate for the first time that nonadherence rises with increasing volume of treated patients, with the highest rates of nonadherence occurring in the highest volume centers.

The IVT-treated population registered in SITS-ISTR European centers doubled between 2006 to 2007 and 2010 to 2011, a change that has been described for individual European countries in the same time period (eg, Germany and Sweden). This reflects improved implementation of thrombolysis in local and national healthcare systems, guideline expansion of the time window to 4.5 hours, and removal of the upper age limit, allowing physicians to treat more patients.

Nonadherence in SITS-ISTR
Our results show a doubling of overall label nonadherence from 23.6% in 2006 to 2007 to 51.1% in 2010 to 2011. Factors explaining this overwhelming increase could be new guideline indications that had previously been (and still continue to be) label contraindications, treatment experience, and published reports of safety and efficacy of off-label IVT treatment in stroke. Reports on off-label treatment published in 2007 and 2010 showed benefit of IVT for a large number of contraindication violations with no overall increase in treatment risks. An important finding of our study is that label nonadherence increases with higher center patient volumes. This may reflect that high-volume centers built up more experience with off-label treatment, perceive also off-label treatment to have a favorable risk–benefit relationship, and thus confidently treat more patients. This is reflected by the fact that high-volume centers in our study also have high numbers of on-label and per-guideline treated patients. Also,
the number of individual hospitals achieving higher volumes of IVT-treated patients increased over time, which translates into more experience in more centers. Even in centers with the highest adherence rates, there was a clear parting from label adherence in the later time period (Figure 3).

Concerning European guidelines, nonadherence was shown to remain relatively stable with only a slight decrease from 14.3% in EUSI 2003 to 11.7% after the 2008/2009 update. Nonadherence to ESO 2008/2009 guidelines was slightly higher in the highest volume centers.

The most commonly violated guideline and label contraindications after the ESO 2008/2009 publication (ie, excluding age >80 years and OTT 3–4.5 hours, which were now guideline indications) were: (1) SBP >184 mm Hg (6.3%); (2) diastolic blood pressure >109 mm Hg (3.6%); (3) anti-coagulation (3.1%); and (4) diabetes mellitus and previous stroke (2.8%). Thus, rates of treatment above blood pressure limits or despite ongoing oral anticoagulation showed the highest statistically significant increases compared with those in 2006 to 2007. Furthermore, patients with severe stroke (National Institutes of Health Stroke Scale score >25) received IVT significantly more often in 2010 to 2011 (1.7%), which may reflect questioning of an upper National Institutes of Health Stroke Scale limit as a label contraindication or the absence of its mention in ESO 2008/2009. A statistically significant increase was also seen in treatment beyond 4.5 hours (1.8%). At the time, the ongoing randomized Third International Stroke Trial (IST-3), later published in 2012, was evaluating IVT ≤6 hours after onset, but a possible effect of this study on general clinical practice cannot be ascertained.30

### Appraisal of European Guideline Recommendations

As a measure of implementation, rates of adherence to new recommendations increased substantially in Europe, possibly indicating that physicians quickly became familiar with the new ESO 2008/2009 guidelines or similarly worded national or local guidelines updated at the time, after publication of new evidence.

In recent work by our research group using the electronic GuideLine Implementability Appraisal tool, we showed that the ESO 2008/2009 IVT guidelines have fewer barriers to executability and decidability, compared with the American Heart Association/American Stroke Association guidelines from 2013. Conversely, the ESO guidelines were also found...
Comparison With Previous Off-Label IVT Treatment Studies

Overall, the most common label violations reported in previous studies were OTT >3 hours, age >80 years, and blood pressure limits (Table 3). Similarly, age >80 years and OTT >3 hours were the 2 most common label violations in our study. Violations of the upper age limit of 80 years were at the same level of those in the Helsinki and VISTA cohorts, whereas our study shows the highest rate of nonadherence to OTT >3 hours.17,22 Thus, with regard to the studied time periods, the Helsinki cohort, SITS-EAST, and VISTA results can mainly be compared with the 2006 to 2007 period in our study, as data for those studies had been obtained largely before the ESO 2008/2009 guidelines. Recent reports from single centers in Verona, Bergen, and Madrid are more comparable with both time periods in our study and reflect prompt adoption of the new ESO 2008/2009 indications.18–20

Limitations of the Study

The SITS-ISTR data set used in this study represents clinical practice across a wide variety of demographics and hospital types in 19 European countries. However, giving a detailed picture of local and national practice traditions or treatment within experimental protocols in individual centers cannot be done using our study design. As with other registry-based reports, results are based on retrospective, explorative analysis of observational data, with the inherent limitations of observational study design.34,35 Data for relevant variables were missing in a maximum of ≈7% of patients, which is in line with, or below, previous publications from SITS and other large registries, such as the Get With The Guidelines program in the United States.34–36

Conclusions

European stroke centers adhered to a high extent to updated recommendations for IVT treatment in the 2008/2009 ESO guidelines. In general, nonadherence to single guideline or label contraindications increased between 2006 to 2007 and 2010 to 2011, with a doubling in overall label nonadherence. The fact that over half of all IVT-treated patients were in nonadherence to the label in 2010 to 2011 warrants label revision. Center volume played a significant role in label nonadherence. The SITS registry proved a useful tool for examining changes in nonadherence to clinical practice guidelines and medication label over time.

Acknowledgments

We thank all Safe Implementation of Treatments in Stroke-International Stroke Thrombolysis Register (SITS-ISTR) collaborators and centers for their contributions to the registry. We also thank all patients who participated in SITS-ISTR. We gratefully acknowledge Dr Frumento and Professor Matteo Bottai from the Biostatistics Core Facility and Institute for Environmental Medicine, Karolinska Institutet, Stockholm, Sweden, for excellent biostatistical consultations. The current SITS registry infrastructure is developed, maintained, and upgraded by Zitelab, Copenhagen, Denmark, in close collaboration with SITS International.

Sources of Funding

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Disclosures

M.V. Mazya is an employee of Safe Implementation of Treatments in Stroke (SITS) International, who received a grant from Boehringer Ingelheim for the SITS-Monitoring Study (SITS-MOST)/SITS-International Stroke Thrombolysis Register (SITS-ISTR). N. Ahmed is an employee of SITS International, who received a grant from Boehringer Ingelheim for the SITS-MOST/SITS-ISTR. N. Wahlgren

Table 3. Summary of Nonadherence Rates (%) in SITS-ISTR Compared With Recent Off-Label IVT Treatment Reports

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</thead>
<tbody>
<tr>
<td>Age &gt; 80 years</td>
<td>17.2</td>
<td>7.3</td>
<td>15.3</td>
<td>16.0</td>
<td>20.6</td>
<td>28.3</td>
<td>25.5</td>
</tr>
<tr>
<td>OTT &gt;3 h</td>
<td>27.9</td>
<td>13.1</td>
<td>N/A</td>
<td>10.0</td>
<td>12.2</td>
<td>7.5</td>
<td>22</td>
</tr>
<tr>
<td>NIHSS score &gt;25</td>
<td>1.7</td>
<td>1.2</td>
<td>N/A*</td>
<td>0.3</td>
<td>N/A</td>
<td>2.3</td>
<td>2.2</td>
</tr>
<tr>
<td>Any anticoagulation</td>
<td>3.1</td>
<td>4.2</td>
<td>2.5</td>
<td>4.0</td>
<td>6.4</td>
<td>1.5</td>
<td>8.1†</td>
</tr>
<tr>
<td>BP violations‡</td>
<td>5.4</td>
<td>8.3</td>
<td>16.9</td>
<td>11.0</td>
<td>6.2</td>
<td>17.7</td>
<td>N/A</td>
</tr>
<tr>
<td>Diabetes mellitus and</td>
<td>2.8</td>
<td>3.9</td>
<td>3.8</td>
<td>2.6</td>
<td>2.4</td>
<td>2.3</td>
<td>2.8</td>
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<tr>
<td>previous stroke</td>
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<td></td>
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</tr>
<tr>
<td>Glucose levels violations</td>
<td>0.3</td>
<td>0.3</td>
<td>0.4</td>
<td>0.1§</td>
<td>0.2§</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

BP indicates blood pressure; IVT, intravenous thrombolysis; N/A, not available; NIHSS, National Institutes of Health Stroke Scale; OTT, onset-to-treatment time; SITS-EAST, Safe Implementation of Treatments in Stroke in Central and Eastern Europe; SITS-ISTR, Safe Implementation of Treatments in Stroke-International Stroke Thrombolysis Register; and VISTA, Virtual International Stroke Trials Archive.

*In this study, a lower threshold of NIHSS score of >22 was used.
†In this study, only anticoagulation with an international normalized ratio of ≤1.7.
‡For all studies, the highest frequency reported for any systolic/diastolic blood pressure violations and intravenous antihypertensive usage.
§Only available for glucose >400 mg/dL.
is chairman of SITS International, who received unrestricted grants from Boehringer Ingelheim. T.P. Moreira received travel grants from Boehringer Ingelheim. The other authors report no conflicts.

References


References


Changes in European Label and Guideline Adherence After Updated Recommendations for Stroke Thrombolysis: Results From the Safe Implementation of Treatments in Stroke Registry

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