Characteristic Adverse Events and Their Incidence Among Patients Participating in Acute Ischemic Stroke Trials

Kerrick Hesse, BMedSc; Rachael L. Fulton, PhD; Azmil H. Abdul-Rahim, MRCP(UK), MBChB; Kennedy R. Lees, MD, FRCP; and for the VISTA Collaborators*

Background and Purpose—Adverse events (AE) in trial populations present a major burden to researchers and patients, yet most events are unrelated to investigational treatment. We aimed to develop a coherent list of expected AEs, whose incidence can be predicted by patient characteristics that will inform future trials and perhaps general poststroke care.

Methods—We analyzed raw AE data from patients participating in acute ischemic stroke trials. We identified events that occurred with a lower 99% confidence bound greater than nil. Among these, we applied receiver operating characteristic principles to select the fewest types of events that together represented the greatest number of reports. Using ordinal logistic regression, we modeled the incidence of these events as a function of patient age, sex, baseline National Institutes of Health Stroke Scale, and multimorbidity status, defining P<0.05 as statistically significant.

Results—We analyzed 5775 placebo-treated patients, reporting 21217 AEs. Among 756 types of AEs, 132 accounted for 82.7%, of which 80% began within 10 days after stroke. Right hemisphere (odds ratio [OR], 1.67), increasing baseline National Institutes of Health Stroke Scale (OR, 0.99), multimorbidity status (OR, 1.09), smoking (OR, 0.99), and baseline National Institutes of Health Stroke Scale, and multimorbidity status, defining P<0.05 as statistically significant.

Conclusions—A list of 132 expected AEs after acute ischemic stroke may be used to simplify interpretation and reporting of complications. AEs can be modestly predicted by patient characteristics, facilitating stratification of patients by risk for poststroke complications. (Stroke. 2014;45:00-00.)

Key Words: complications ■ prognosis ■ stroke

Among the many sources of effort and expense associated with conducting clinical trials in patients with acute stroke, the reporting and interpretation of adverse events (AE) may be amenable to limitation. More than half of patients experience poststroke AE, and a substantial proportion of the events that are reported are probably incidental rather than related to the investigational treatment.1–4 This may lead to unnecessary inflation of trial costs and more important, a lower sensitivity for genuine complications of novel treatments. Regulatory guidance permits trial protocols to specify events that can be excluded from expedited reporting.4–6

A second consideration is that AEs can themselves have an effect on patient outcome, and some of these complications can be predicted by certain patient prognostic factors.2,3,7–9 For example, pneumonia and urinary tract infections are predicted by sex and stroke severity, and either infection is associated with poorer outcome after 3 months.3 A more comprehensive understanding of typical complications could offer direct clinical benefit if preventive procedures could be appropriately targeted.2,3,9

An initial systematic review of randomized controlled trials in acute ischemic stroke reinforced the desirability of a formal analysis of raw AE data (K. Hesse, BMedSc, unpublished observation, 2013). Of 33 reviewed trials, some reported that ≤100% of their participants experienced a complication. However, only 7 reported cumulative AE incidences, the majority instead publishing either only bleeding complications or the most common AEs.10–44 This undermines appraisal of typical poststroke complications. There is a clear need for extensive characterization of poststroke AEs.

We aimed to develop a reference list of expected AEs for future international acute ischemic stroke trial protocols. We
hypothesized that the rates of various AEs after stroke are stable and predictable after adjustment for certain patient prognostic factors. We sought to model the incidence of these complications because this may inform strategies to limit their effect.

Methods

Data Source

We sought data from patients with acute ischemic stroke, who had participated in randomized clinical trials from which raw data are held in the Virtual International Stroke Trials Archive (VISTA). We restricted our primary analyses to placebo-treated patients for whom complete data were available. However, we also performed validity checks at various stages, using data from the combined active and control populations.

Study Design

We performed a retrospective analysis of raw AE data, according to a protocol approved in advance by the VISTA-Acute Steering Committee. Ethical approval was not required because anonymized historical patient data were used.

Variables

Variables of interest included patient age (years), sex, weight (kg), height (cm), baseline glucose (mmol/L), baseline blood pressure (BP; mm Hg), baseline creatinine (μmol/L), smoking status, baseline National Institutes of Health Stroke Scale (NIHSS), hemispheric lateralization, thrombolysis treatment, and comorbidities. In addition, the following variables were calculated: estimated glomerular filtration rate (mL/min per 1.73 m²) and multimorbidity status (number of diseases per patient). AEs with their start day were collected and coded using the Medical Dictionary for Regulatory Activities system. They were classified at checks at various stages, using data from the combined active and control populations. AE (SAE) occurrences, included in the complete and control-arm data set from trials, published between 1998 and 2008 inclusive. Primary recordings of AEs refer to the first report of an AE noted multiple times in a single patient.

Statistical Analysis

Frequency of AEs

We described the incidence of specific AEs in our sample. To discriminate commonly experienced complications from complications that occurred by chance, we calculated 99% confidence intervals (CI) for the incidence of each type of AE per 1000 patients. Complications with a 99% CI that included nil were considered to be potential because of chance.

Table 1. Baseline Demographics of Placebo-Treated Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>n=5775</th>
</tr>
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<tbody>
<tr>
<td>Demographics (mean±SD)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>69.3±12.3</td>
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<tr>
<td>Sex, n (%)</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>3107 (53.8)</td>
</tr>
<tr>
<td>Women</td>
<td>2656 (46.0)</td>
</tr>
<tr>
<td>Unknown</td>
<td>12 (0.2)</td>
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<tr>
<td>Weight, kg</td>
<td>75.5±15.6</td>
</tr>
<tr>
<td>Height, cm</td>
<td>168±9.75</td>
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<tr>
<td>Baseline glucose, mmol/L</td>
<td>7.61±3.16</td>
</tr>
<tr>
<td>Baseline systolic BP, mm Hg</td>
<td>155±26.3</td>
</tr>
<tr>
<td>Baseline diastolic BP, mm Hg</td>
<td>82.9±16.3</td>
</tr>
<tr>
<td>Baseline creatinine, μmol/L, median (IQR)</td>
<td>80.0 (27.0)</td>
</tr>
<tr>
<td>Baseline eGFR, mL/min per 1.73 m², median (IQR)</td>
<td>74.7 (44.8)</td>
</tr>
<tr>
<td>Current/past smoker, n (%)</td>
<td>2277 (39.4)</td>
</tr>
<tr>
<td>Baseline NIHSS, median (IQR)</td>
<td>13.0 (9.0)</td>
</tr>
<tr>
<td>Hemisphere of stroke, n (%)</td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>2711 (46.9)</td>
</tr>
<tr>
<td>Right</td>
<td>2795 (48.4)</td>
</tr>
<tr>
<td>Unknown</td>
<td>269 (4.7)</td>
</tr>
<tr>
<td>Thrombolysis treatment, n (%)</td>
<td>1356 (23.5)</td>
</tr>
<tr>
<td>Multimorbidity status, median (IQR)</td>
<td>2.0 (2.0)</td>
</tr>
<tr>
<td>Medical history, n (%)</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1199 (20.8)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3744 (64.8)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1454 (25.2)</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>1354 (23.4)</td>
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<tr>
<td>Previous transient ischemic attack</td>
<td>362 (6.3)</td>
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<tr>
<td>Ischemic heart disease</td>
<td>1094 (18.9)</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>763 (13.2)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>4.10 (238)</td>
</tr>
</tbody>
</table>

Table 1. Baseline Demographics of Placebo-Treated Patients

All continuous variables in mean±SD unless stated otherwise. BP indicates blood pressure; eGFR, estimated glomerular filtration rate; IQR, interquartile range; and NIHSS, National Institutes of Health Stroke Scale.
Variables included were patient age, sex, weight, height, baseline glucose levels, systolic BP, diastolic BP, estimated glomerular filtration rate, smoking status, baseline NIHSS, hemispheric lateralization, thrombolysis treatment, and multimorbidity status. Statistical significance in the model was assessed at conventional $P<0.05$.

Furthermore, bootstrap analysis was used to validate our final model in the control-arm data set. Sampling methods included a random 60% of all patients and of types of AEs with 1000 reiteration, respectively. Ninety-five percent CIs for the mean odds ratios of the important variables were generated. Statistical analysis was performed using SPSS version 21.0 (SPSS, Inc, Chicago, IL) and R version 2.15.2.

Results
Data from 10,311 patients were available, from whom we identified 5775 placebo-treated patients for our primary analysis (Figure 1). Table 1 shows the baseline demographics of the patients in the control-arm data set. Their mean age was 69.3±12.3 years, 53.8% were men and the median baseline NIHSS was 13 (interquartile range, 9–18).

Frequency of AEs
There were 21,217 AE occurrences, comprising 756 types of AEs. The AEs that occurred ≥7x had an incidence of ≥1.21 per 1000 patients (with 99% CI, 0.03–2.39), whereas the 99% CI for 6 or fewer events encompassed zero. Adjustment for individual trials did not alter these confidence limits.

Receiver operating characteristic analysis indicated that to minimize the number of types of events yet maximize the total number of AE reports, the 133 types of AEs shown in Table I in the online-only Data Supplement should be chosen. These 133 events with the highest incidence accounted for 82.7% of all occurrences (Figure 2). A sensitivity analysis, using our expanded data set, overlapped for 130 of these AEs. The threshold for inclusion differed for only sputum increased, bacterial infection, and hyperkalemia. The last 2 of these met the occurrence criteria for retention in our list. Our list included 53 of 68 types of SAEs, identified through receiver operating characteristic analysis and found in Table II in the online-only Data Supplement.

Time of AE Presentation
Cluster analysis showed that >80% of AEs occurred within the first 10 days. Approximately 8% of AEs occurred ≥3 weeks after stroke (Figure 3).

Effect of Patient Factors on AEs
We were able to consider 2817 placebo-treated patients who had complete prognostic factor data to model AE incidence. The median number of events per patient was 2 (interquartile range, 1–4); 536 patients reported no event.

The results of the ordinal logistic regression are presented in Table 2. The likelihood of developing increasing numbers of AEs was independently predicted by hemispheric lateralization, baseline NIHSS, multimorbidity status, age, height, baseline diastolic BP, and smoking status ($P<0.05$). After adjustment for individual trials, thrombolysis treatment, sex, and baseline glucose were also found to be important variables ($P<0.05$), but baseline diastolic BP became insignificant (Table III in the online-only Data Supplement). Sensitivity analysis with the complete data set confirmed this finding.

Bootstrap analysis produced comparable estimates with narrow CIs for the odds ratios of all 7 variables included in the final model of the control-arm data set. Table 3 presents the results of repeated sampling of 60% of patients (n=1691) and of 60% of types of AEs (n=80). The variability in number of AEs experienced by patients, explained by the final regression model, was also maintained in the bootstrap estimates ($100r^2=13.1\%, 13.3\%, and 10.7\%$, respectively).

Discussion
Complications after an acute ischemic stroke are a major burden for patients and researchers. In a prospective study of patients admitted for inpatient stroke rehabilitation, Roth et al9
reported that ≤75% of their sample experienced ≥1 medical complications. We sought to define these poststroke complications more clearly to inform trial safety and perhaps also poststroke patient care.

Both the European Medicines Agency and the Food and Drug Administration require expedited reporting of suspected unexpected serious adverse reactions to improve patient safety. However, the increasing size and decentralization of trials have led to more AE reporting, frequently without context or detail. This inhibits rather than enhances patient protection.

We have now empirically defined a list of 132 expected AEs that together account for ≥82% of AE occurrences, seen

Table 2. Results of the Ordinal Logistic Regression, Describing the Factors Independently Associated With the Development of More Adverse Events in the Control-Arm and Complete Data Set

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control-Arm Data Set</th>
<th>Complete Data Set</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right hemisphere</td>
<td>1.67</td>
<td>1.46–1.91</td>
</tr>
<tr>
<td>Baseline NIHSS</td>
<td>1.11</td>
<td>1.10–1.13</td>
</tr>
<tr>
<td>Multimorbidity status</td>
<td>1.09</td>
<td>1.04–1.15</td>
</tr>
<tr>
<td>Age</td>
<td>1.01</td>
<td>1.01–1.02</td>
</tr>
<tr>
<td>Height</td>
<td>1.01</td>
<td>1.00–1.01</td>
</tr>
<tr>
<td>Baseline diastolic BP</td>
<td>0.99</td>
<td>0.98–0.99</td>
</tr>
<tr>
<td>Current/past smoker</td>
<td>0.82</td>
<td>0.72–0.94</td>
</tr>
<tr>
<td>Thrombolysis treatment</td>
<td>N/A</td>
<td>1.26</td>
</tr>
<tr>
<td>Sex (women)</td>
<td>N/A</td>
<td>1.26</td>
</tr>
<tr>
<td>Baseline glucose</td>
<td>N/A</td>
<td>1.02</td>
</tr>
<tr>
<td>Weight</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Baseline systolic BP</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Baseline eGFR</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

BP indicates blood pressure; Cl, confidence interval; eGFR, estimated glomerular filtration rate; N/A, not applicable; NIHSS, National Institutes of Health Stroke Scale; and OR, odds ratio.

in placebo-treated patients of acute ischemic stroke trials. Because we restricted analysis to placebo-treated patients, it is clear that these complications are not investigational treatment-related complications and should not be reported immediately. Our sensitivity analysis, using both placebo and drug-treated patients, confirmed that 99% of these AEs were also frequently encountered among patients receiving the active comparator in trials. Attribution of such events to a novel treatment both harms perception of treatment safety and creates noise that will limit recognition of true adverse reactions. Using our list, future trial investigators may be able to reduce their AE reporting and, paradoxically, improve trial safety. It can be used to identify objectively, which AEs require special attention and expedited reporting (ie, the suspected unexpected serious adverse reactions) and which AEs could be reported by a tick box list at the end of a reporting year. In addition, the incidence of individual AEs may be used as a benchmark to identify treatment-related increases in the rates of these events. This could be especially important in smaller or uncontrolled trial cohorts. More generally, these incidences can adequately inform prospective insurers of the typical AE burden seen in trials and perhaps also reflect the standard of care available to patients with stroke in the future.

The reporting of SAEs, a subgroup of AEs with their own definition, can also be reduced. Our original list of AEs covered 78% of important SAEs. The types and numbers of these SAEs have to be interpreted with caution. They are likely to be under-represented in the acute phase after stroke and their definition is investigator dependent.

Most AEs occurred during the first week after the stroke, followed by a smaller peak in incidence 3 weeks later. This agrees with the findings from other studies. However, these peaks may reflect scheduled review visits, mandated by the research protocols, as well as true variation in the frequency of comorbidity with acute stroke disease. For example, Davis et al and Lyden et al monitored patients closely for AEs during the first week, but thereafter noted only SAEs through 90 days after the treatment. Conversely, Johnston et al reported high numbers of deaths during the first week and at week 3 after the stroke. This matches our bimodal distribution of AE
incidences and could warrant further investigation into the influence of complications on outcome.

We explored whether certain patient characteristics predict the likelihood of complications after stroke. Of the 13 variables tested, hemispheric lateralization, baseline NIHSS, multimorbidity status, age, height, baseline diastolic BP, and smoking status were predictive. Sensitivity analysis in a larger data set, with resulting greater statistical power, found an additional 3 significant variables: thrombolysis treatment, sex, and baseline glucose. Five of these variables (hemispheric lateralization, baseline NIHSS, multimorbidity status, age, and sex) have previously been reported as strongly associated with complications after stroke.\(^9\)

This model can stratify patients by risk for the development of AEs, offering new avenues to implement more cost-effective and preventative poststroke management. High-risk patients may benefit from closer monitoring until they are stabilized. Prophylactic antibiotics, appropriate intubation, sparing use of catheters, and anticoagulants may be considered to reduce the likelihood of complications, such as pneumonias, urinary tract infections, and deep vein thrombosis.\(^7\)\(^9\)

The good agreement between the odds ratio estimates in the placebo data set and the bootstrap samples suggests robustness in the face of changing patient populations or AEs. Our sample of 2817 patients used to generate the model is similar in size to the largest of international multicenter stroke trials (eg, the Stroke-Acute Ischemic NXY Treatment [SAINT] II trial with 3306 patients).\(^1\) We did not test all variables previously found to predict AEs, such as hypoalbuminemia, low hemoglobin levels, and elevated white blood cell counts, nor did we consider the length of hospital stay and the interaction between AEs.\(^9\) The variable multimorbidity status was also a simplified measure of health that did not consider the effect of individual diseases. In view of this and more important, the poor fit and complexity of our model, further development is necessary before clinical application may be considered.

The strength of our analyses derives from the strict criteria that trials have to fulfill to be included in VISTA.\(^7\) Some between-trial heterogeneity in the reporting of AEs may still have existed, but variability among researchers is probably greater; the large number of investigators who will have contributed should mitigate the effect of such variability. A few AEs had to be translated into Medical Dictionary for Regulatory Activities terms, introducing possible recording errors; however, rare complications would be at greatest risk of this and were anyway excluded from our analyses. Furthermore, we described AEs from trial populations in which the standard of care is potentially higher than in daily clinical practice. Before application to an unselected stroke population, our model should be validated in a comprehensive disease-based registry.\(^7\)

**Conclusions**

Our interrogation of a large database of raw AE data from acute ischemic stroke trials helped define a list of expected AEs. The use of this list may streamline their reporting and thereby improve our ability to detect the more relevant complications of new treatments. We also developed a robust model that predicts, albeit modestly, the likelihood of AEs. This may be a step toward the stratification of patients by risk for AEs in future acute ischemic stroke trials.

**Appendix**


**Acknowledgments**

We thank all Virtual International Stroke Trials Archive (VISTA) collaborators, who contributed previous clinical trial data Dr Lees conceived and supervised the project. K. Hesse conducted the analyses and drafted the initial manuscript. Dr Fulton provided statistical guidance and ran the bootstrap analyses. K. Hesse, A.H. Abdul-Rahim, and Dr Lees were involved in reviewing and reporting of the work. All authors approved the final version. Members of the Virtual International Stroke Trials Archive (VISTA)–Acute Steering Committee approved the study plan in advance and approved the final article.

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**Disclosures**

None.

**References**


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*Authors:*

*Kerrick Hesse, Rachael L. Fulton, Azmil H. Abdul-Rahim, Kennedy R. Lees,*

*for the VISTA collaborators*

*Supplemental Table: I*

*Supplemental Table: II*

*Supplemental Table: III*
**Supplemental Table I**: List of adverse events for future acute ischemic stroke trials.

<table>
<thead>
<tr>
<th>Adverse Event (AE)</th>
<th>Number of Occurrences</th>
<th>% of Total AE Occurrences</th>
<th>Cumulative % of AE Occurrences</th>
<th>Incidence (AEs/1,000 patients)</th>
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<tr>
<td>Pyrexia</td>
<td>1091</td>
<td>5.142</td>
<td>5.14</td>
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<td>4.261</td>
<td>9.40</td>
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<td>Urinary Tract Infection</td>
<td>638</td>
<td>3.007</td>
<td>12.41</td>
<td>87.45</td>
</tr>
<tr>
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<td>612</td>
<td>2.884</td>
<td>15.29</td>
<td>90.04</td>
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<td>Constipation</td>
<td>584</td>
<td>2.753</td>
<td>18.05</td>
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<td>28.53</td>
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<tr>
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<td>1.673</td>
<td>31.91</td>
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<td>33.42</td>
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<tr>
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<td>1.254</td>
<td>36.02</td>
<td>39.31</td>
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<td>1.178</td>
<td>37.20</td>
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<td>0.886</td>
<td>47.15</td>
<td>28.57</td>
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<td>Condition</td>
<td>Count</td>
<td>Probability</td>
<td>Mortality</td>
<td>Morbidity</td>
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<tr>
<td>-----------------------------------------</td>
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<tr>
<td>Cerebral Hemorrhage</td>
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<td>48.01</td>
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<td>Angina Pectoris</td>
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<td>0.830</td>
<td>48.84</td>
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<td>0.825</td>
<td>49.66</td>
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<tr>
<td>Cough</td>
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†Sputum increased: Adverse event was excluded from the list and further analyses as it missed the minimum occurrence threshold in the complete dataset analysis (31 vs. 40 occurrences). ICP indicates intracranial pressure; COPD: chronic obstructive pulmonary disease; ALT: alanine transaminase.
Supplemental Table II: List of serious adverse events for future acute ischemic stroke trials.

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Underlined SAEs are events not found on the original adverse event list. ICP indicates intracranial pressure; COPD: chronic obstructive pulmonary disease.
**Supplemental Table III:** Results of the ordinal logistic regression, describing the factors independently associated with the development of more adverse events in the control-arm after adjusted for individual trials.

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