Impact of Guidelines on Clinical Practice

Intravenous Heparin Use for Acute Ischemic Stroke

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**Background and Purpose**—Since its introduction, controversy has existed about the administration of intravenous heparin for the treatment of acute ischemic stroke. We studied trends in the intravenous heparin use during a 6-year time period and the potential influence of clinical guidelines in national language on intravenous heparin administration in Korea.

**Methods**—On the basis of a prospective nationwide multicenter stroke registry, we collected data on patients with acute ischemic stroke who arrived within 7 days of symptom onset during the time period 2008 to 2013. We studied patient demographics, prestroke medical history, stroke characteristics, and stroke treatment. Data from a total of 23,425 patients from 12 university hospitals or regional stroke centers were analyzed.

**Results**—The administration of intravenous heparin steadily decreased throughout the study period: 9.7% in 2008, 10.9% in 2009, 9.4% in 2010, 6.0% in 2011, 4.7% in 2012, and 4.3% in 2013 (P for trend <0.001). The reduced intravenous heparin use was associated with moderate stroke severity, atrial fibrillation, and stroke of cardioembolic, other-, and undetermined etiology. In a multivariable logistic model, increase of 1 calendar year (odds ratio, 0.89; 95% confidence interval, 0.84–0.95; P<0.001) and release of clinical practice guidelines in Korean (odd ratio, 0.74; 95% confidence interval, 0.59–0.91; P<0.01) were independent factors associated with reduction in the frequency of intravenous heparin use.

**Conclusions**—Use of intravenous heparin for acute ischemic stroke treatment has decreased in Korea, and this change may be attributable to the spread and successful implementation of regional clinical practice guidelines. (Stroke. 2016;47:1577-1583. DOI: 10.1161/STROKEAHA.116.012639.)

**Key Words:** cerebral infarction ▪ guideline adherence ▪ heparin ▪ stroke ▪ trends

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Since the introduction of intravenous heparin for the treatment of acute ischemic stroke in 1941,1 there has been controversy about its use.2,3 The main rationale for emergent administration of intravenous heparin in patients with acute stroke have included prevention of neurological worsening or recurrent embolization. Intracranial hemorrhage and systemic bleeding are significant adverse events associated with such therapy.4 Series of studies including clinical trials have failed to show benefit of heparin treatment in acute ischemic stroke.5–9 A single-center trial, however, reported benefit of intravenous heparin given within 3 hours of stroke onset in relation to 3-month functional outcome.10 A systematic review of anticoagulants in treatment of acute ischemic stroke concluded that immediate anticoagulant therapy was not associated with any net short- or long-term benefit.11

American Heart Association/American Stroke Association guidelines do not recommend urgent anticoagulation for acute ischemic stroke for the prevention of early recurrent stroke, halting neurological worsening, or improving outcomes.12 In 2009, the first Korean clinical practice guidelines (CPG, by Clinical Research Center for Stroke, Figure I in the online-only Data Supplement) indicated that there was no scientific evidence to support the administration of heparin within 48 hours of ischemic cerebral infarction.13,14 However, there is a paucity of information on contemporary use of intravenous heparin for the treatment of ischemic stroke, the secular trend for its administration, and characteristics of patients treated with intravenous heparin.

In this study, we evaluated recent trends of antithrombotic therapies and placed special emphasis on intravenous heparin administration for acute ischemic stroke. The study was carried out in 12 hospitals in Korea to capture current practice patterns.

Materials and Methods

Study Design and Population

We collected data on a consecutive series of patients who were hospitalized for the treatment of acute ischemic stroke within 7 days of symptom onset between April 1, 2008 and November 30, 2013. The data source was a prospective, nationwide, multicenter, web-based acute stroke registry (Clinical Research Center for Stroke–fifth Division, CRCS-5) in Korea. The registry included consecutive acute stroke within 7 days of symptom onset were registered and during the study period, 23,425 patients were admitted to the participating centers. Approval was obtained from the institutional review board for collection of anonymized clinical data without patient consent as the goal of the study was to monitor and improve the quality of stroke care.

Ascertainment of Information on Patient Characteristics and Management

Evaluation and management of acute ischemic stroke at the participating centers were performed according to contemporary CPG, institutional protocols, and at the discretion of the individual physicians in charge of patient care.15,16 A predefined case report form was used to collect information. The form included information on recanalization treatment (intravenous thrombolysis, endovascular treatment, or combined treatment) and antithrombotic treatment during hospitalization (antiplatelet agents, warfarin, low-molecular-weight heparin, or intravenous heparin) and after discharge (antiplatelet agents, warfarin, or novel oral anticoagulant). Demographics, vascular risk factors, prestroke medications, and stroke characteristics including stroke subtypes according to the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria with minor modifications18 were obtained from the registry database.

Statistical Analyses

Summary statistics were presented as means±SD or frequencies (percentage), as appropriate. The baseline characteristics of patients with ischemic stroke by the year of admission were compared using Pearson χ² tests for categorical variables and 1-way ANOVA for continuous variables. Statistical significance of secular trends for patients’ characteristic and use of antithrombotics including intravenous heparin was examined by a likelihood ratio test for trend. Multivariable binary logistic regression analysis was performed to determine factors associated with intravenous heparin use. A generalized linear mixed model (using a random intercept model) was applied to account for the differences between institutional preferences toward intravenous heparin in the analysis. In addition, post hoc analyses with 3 different models were performed to investigate the effects of calendar year and release of CPG on intravenous heparin use (model 1, year of admission as an interval variable; model 2, year of admission as an ordinal variable; and model 3, year of admission as an interval variable and release of CPG as a categorical variable). Release of CPG was dichotomized into pre- and post-CPG release based on each patient’s date of admission and the date of the first Stroke CPG release in Korea (October 30, 2009).

To explore the factors accounting for changes in intravenous heparin use, preplanned subgroup analyses were performed for age groups (<65 years, 65–84 years, and ≥85 years),19,20 atrial fibrillation, initial stroke severity using National Institutes of Health stroke scale (NIHSS score of <8, 8–16, and ≥17),17 and ischemic stroke subtype (TOAST).18 Significance levels were set at a 2-tailed P<0.05. Statistical analyses were performed using SAS 9.3 (SAS Institute, Cary, NC).

Results

During the study period, 23,425 patients with acute ischemic stroke within 7 days of symptom onset were registered and included in the study. During the study period, patient age at admission and sex distribution did not change. However, clinical characteristics varied significantly (Table I; Table I in the online-only Data Supplement). Initial systolic blood pressure, serum glucose, and total cholesterol decreased over time (P for trend <0.001). Among other factors, hypercholesterolemia and atrial fibrillation increased in frequency, and history of previous coronary heart disease decreased (P for trend <0.001). Before the index stroke, patients taking antiplatelet agents, antihypertensive medication, anti-diabetic medication, and statins increased in frequency (P for trend all <0.05). Regarding stroke subtypes, the most significant change was the decrease of small vessel occlusion over time and cardioembolic stroke increased only slightly. Across the study period, the time interval from symptom onset to hospital arrival decreased (P for trend <0.01) and the proportion receiving recanализation treatments (intravenous thrombolysis, endovascular treatment, and combined treatment) increased (P for trend all <0.001). The frequency of intravenous thrombolysis administration among patients arriving within 4.5 hours of onset was 17.9% in 2008, 20.3% in 2009, 20.2% in 2010, 23.5% in 2011, 26.0% in 2012, and 25.0% in 2013 (P for trend <0.001).

Use of antithrombotics according to year of admission showed significant change of clinician’s preference for specific
antithrombotic agents (Table 2; Table II in the online-only Data Supplement). Among antiplatelet agents, aspirin was consistently the most favored treatment choice, prescribed to >80% of patients during hospitalization and >65% after hospital discharge. Use of clopidogrel during hospitalization increased abruptly from 2008 (29.0%) to 2010 (36.2%), and decreased thereafter (29.1% in 2013). Clopidogrel was more likely to be prescribed after hospital discharge than during hospitalization, 34.9% after discharge versus 31.4% during hospitalization. Use of cilostazol increased and triflusal decreased during the study period for both acute period and after discharge. Use of ticlopidine minimally increased only after discharge.

With respect to anticoagulants, the most significant change was the use of intravenous heparin during hospitalization. During the study period, the use of intravenous heparin decreased according to the following pattern: 9.7% in 2008, 10.9% in 2009, 9.4% in 2010, 6.0% in 2011, 4.7% in 2012, and 4.3% in 2013 \((P\text{ for trend} <0.001)\). In contrast, administration of warfarin and low-molecular-weight heparin during hospitalization increased. However,
the percentage of patients taking warfarin after discharge did not change. Novel oral anticoagulant prescription became available in Korea in January 2013, and 159 (3.3%) patients were treated with apixaban, dabigatran, or rivaroxaban on discharge in 2013.

Multivariable binary logistic regression analyses were performed to investigate factors associated with intravenous heparin use (Table 3). Older age, longer time interval from symptom onset to arrival, and higher initial NIHSS score were associated with less frequent use of intravenous heparin, whereas atrial fibrillation was associated with more frequent use of intravenous heparin. Among stroke subtypes, cardioembolic stroke and stroke with other- and undetermined etiology were associated with more frequent use of intravenous heparin compared with large artery atherosclerosis. In contrast, small vessel occlusion was associated with less frequent use of intravenous heparin. From analyses based on 3 post hoc regression models, we found that year of admission was independently associated with less frequent use of intravenous heparin (1) model 1: odds ratio, 0.82; 95% confidence interval, 0.80–0.85; (2) model 2: the odds ratio of year 2013 compared with year 2008: 0.89 (0.84–0.95) <0.001; and (3) model 3: odds ratio, 0.89; 95% confidence interval, 0.84–0.95 (Table 4).

Furthermore, in model 3, release of CPG in Korea significantly reduced intravenous heparin use independent of year of admission (odds ratio, 0.74; 0.59–0.91). The degree of multicollinearity between year of admission (odds ratio, 0.74; 95% confidence interval, 0.59–0.91). The degree of multicollinearity between year of admission and release of CPG was accessed using a variance inflation factor (VIF=4.09).

Figure illustrates the results of the subgroup analyses that were performed to explore factors responsible for the decrease of intravenous heparin use. Secular trends of intravenous heparin use were not different according to patient age at stroke onset (P for interaction, 0.51). However, initial stroke severity, atrial fibrillation, and stroke subtype showed significant interactions with secular trends of intravenous heparin use (P for interaction all <0.01). Details of age and NIHSS score as categorical variable used to generate Figure is presented in Table III in the online-only Data Supplement.
**Discussion**

The major findings of this study are as follows. First, use of intravenous heparin for the treatment of acute ischemic stroke significantly decreased during the 6-year study period. Second, older age, delayed arrival at the hospital, and more severe initial neurological deficits were associated with less frequent use of intravenous heparin. Third, the decrease of intravenous heparin use was primarily driven by and associated with moderate stroke severity, atrial fibrillation, and stroke of cardioembolic, other- and undetermined etiology. Finally, release of CPG was independently associated with a decreased frequency of intravenous heparin use.

In the past, intravenous heparin treatment has been administered by American, Canadian, and Korean neurologists in clinical scenarios, such as acute ischemic stroke with atrial fibrillation or progression of ischemic stroke. In direct comparisons of factors associated with intravenous heparin use between 2008 and 2013, younger age, previous history of ischemic stroke, atrial fibrillation, current smoking, and stroke subtype were associated with intravenous heparin use in 2008, whereas in 2013 atrial fibrillation, stroke subtypes, and intravenous thrombolysis were associated factors (Table IV in the online-only Data Supplement). Atrial fibrillation and cardioembolic stroke were associated with intravenous heparin use in both of 2008 and 2013; however, a significant decrease in the use of intravenous heparin was observed among patients with atrial fibrillation during this time period (Figure).

We think that in Korea the decrease in frequency of intravenous heparin use for acute ischemic stroke and changes in factors associated with intravenous heparin use could be attributed to the spread and implementation of contemporary stroke guidelines because CPG was independently associated with the reduced frequency. The first Korean stroke CPG released on October 2009 strongly discouraged the use of intravenous heparin for acute ischemic stroke. Concordant with the recommendations, we observed a significant decrease of frequency of intravenous heparin use during the study period. Our results are in agreement with the results of the Riks-Stroke registry in Sweden, which also demonstrated declining trends in the use of intravenous heparin. Furthermore, intravenous heparin administration within 24 hours of intravenous thrombolysis was not recommended in the US guideline (level of evidence: B). In our study, intravenous thrombolysis was independently associated with less frequent use of intravenous heparin not in 2008 but in 2013. This finding may be explained by better adherence to practice guidelines over time.

With respect to intravenous heparin use among stroke patients with atrial fibrillation, the US guideline did not provide specific recommendations, but mentions the results of subgroup analysis of the International Stroke Trial, which

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**Figure.** Secular trends of intravenous heparin use for acute ischemic stroke by subgroups. P for interaction: (A) year of admission×age groups, 0.51; (B) year of admission×admission National Institutes of Health Stroke Scale (NIHSS) score categories, <0.01; (C) year of admission×atrial fibrillation, <0.001; and (D) year of admission×stroke subtype, <0.001. CE indicates cardioembolism; LAA, large artery atherosclerosis; OD, other determined etiology; SVO, small vessel occlusion; and UD, undetermined etiology.
reported no benefit of heparin administration. The frequency of intravenous heparin use dropped dramatically from 33% to 13% among stroke patients with atrial fibrillation between 2009 and 2013 in our study.

The impact of CPG on clinical practice has been investigated previously in the medical literature. CPG is recognized to influence physician’s behavior and improve quality of care. However, practice patterns in relation to implementation of CPG may vary according to physician incentives, hospital and geographical factors, and specific strategies tailored to individual recommendations. The importance of language concordance has been reported in terms of patient’s medication adherence and medical outcomes. However, a paucity of data exists on the influence of CPG language in non-English literature on physician’s adherence and attitude toward CPG. Our study indicated that release of the national stroke CPG in Korean has changed physician practice with respect to intravenous heparin use for acute ischemic stroke. Another marker of physician practice change in relation to guideline dissemination and implementation was the increase of frequency of intravenous thrombolysis. The frequency of intravenous thrombolysis among all patients with ischemic stroke increased from 6.5% in 2008 to 10.6% in 2013 and that among patients arriving within 4.5 hours of onset increased from 17.9% in 2008 to 25.0% in 2013. In a survey conducted in 2011, Korean neurologists were reported to support (ie, had positive attitudes at a frequency of 85%) toward the use of the national guidelines, and >60% of the physicians reported adherence to the Korean stroke guideline in dyslipidemia management for the secondary prevention of stroke. We speculate that the spread and implementation of the stroke CPG in our national language may have improved physician adherence to the guidelines.

Limitations of this study are acknowledged. First, this is a multicenter study of 12 university hospitals or regional stroke centers in Korea, and thus, generalizability of the study results may be limited. However, the study subjects may be representative of the population with stroke in Korea because universal public health insurance provided by the national healthcare system in Korea allows for easy access to participating stroke centers. Furthermore, the distribution of age and sex of the patients with stroke in the CRCS-5 registry has been reported to be almost identical to that of the broader Korean population. Second, although we controlled for confounding in our main analyses, a retrospective study of this type could be subject to residual and unmeasured confounding. Finally, the nature of the study design limits one from concluding that there is causality between spread of CPG in a native language and physician adherence.

Conclusions
This study shows that the frequency of intravenous heparin use for the treatment of acute ischemic stroke is decreasing in Korea in accordance with the current national guideline recommendations. Furthermore, quality of care as represented by frequency of the use of reperfusion treatment for patients with hyperacute stroke has improved during the study period. Such trends during a relatively a short time period could be the result of regional stroke physician adherence to national CPG for stroke. Future studies addressing the impact of improvement in quality of care on relevant patient outcomes may be warranted.

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Disclosures
Dr Gorelick reports serving as an advisory for course development and speaker on acute stroke care, tissue-type plasminogen activator administration, and mechanical thrombectomy for Vindico Medical Education. The other authors report no conflicts.

References
Recent Trends of Intravenous Heparin for Ischemic Stroke

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on the behalf of CRCS-5 Investigators

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SUPPLEMENTAL MATERIAL

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Figure I. Clinical Practice Guidelines for Stroke by CRCS in Korea

Table I. Laboratory findings, pre-stroke medication history, and recanalization treatment, stratified by year of admission

Table II. Secular trend of antithrombotic use for the treatment of acute ischemic stroke after discharge

Table III. Age and NIHSS score at admission as categorical variable used in Figure 1

Table IV. Factors associated with intravenous heparin use in 2008 versus 2013
Figure I. Clinical Practice Guidelines for Stroke by CRCS in Korea

(A) Covers of first and second version of clinical practice guidelines for stroke in Korean. (B) Covers of first and second version of clinical practice guidelines for stroke in English.

PDF versions of current Korean clinical practice guidelines for stroke are available on-line.
- Korean version
  : http://www.stroke.or.kr/image/CRCS%20CPG%20%EA%B0%9C%EC%A0%95%20(ICH)20140625.pdf
- English version
  : http://www.stroke.or.kr/image/CPGStrok(English)20130730.pdf

Abbreviation: CRCS, clinical research center for stroke.
Table I. Laboratory findings, pre-stroke medication history, and recanalization treatment, stratified by year of admission

<table>
<thead>
<tr>
<th></th>
<th>2008 (n=2,272)</th>
<th>2009 (n=3,232)</th>
<th>2010 (n=3,277)</th>
<th>2011 (n=4,667)</th>
<th>2012 (n=5,175)</th>
<th>2013 (n=4,802)</th>
<th>( P ) for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body mass index (kg/m(^2)) - mean ± SD</td>
<td>23.4±3.2</td>
<td>23.5±3.4</td>
<td>23.4±3.3</td>
<td>23.6±3.3</td>
<td>23.5±3.3</td>
<td>23.5±3.2</td>
<td>0.21</td>
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<tr>
<td>Systolic blood pressure (mmHg) - mean ± SD</td>
<td>148.2±27.2</td>
<td>148.7±27.3</td>
<td>147.7±27.6</td>
<td>147.1±27.2</td>
<td>146.1±26.7</td>
<td>145.4±27.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Glucose (mg/dL) - mean ± SD</td>
<td>137.1±63.1</td>
<td>127.6±55.1</td>
<td>122.2±49.7</td>
<td>117.5±47.4</td>
<td>124.4±52.8</td>
<td>123.9±49.2</td>
<td>&lt;0.001</td>
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<tr>
<td>Total Cholesterol (mg/dL) - mean ± SD</td>
<td>186.0±41.8</td>
<td>183.6±43.1</td>
<td>179.3±41.5</td>
<td>178.1±42.0</td>
<td>177.2±43.5</td>
<td>175±43.0</td>
<td>&lt;0.001</td>
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<tr>
<td>LDL Cholesterol (mg/dL) - mean ± SD</td>
<td>109.6±34.5</td>
<td>110.4±36.5</td>
<td>109.1±35.7</td>
<td>111.3±36.4</td>
<td>110.8±36.9</td>
<td>110.2±37.4</td>
<td>0.22</td>
</tr>
<tr>
<td>Pre-stroke medication</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiplatelet</td>
<td>625 (27.5)</td>
<td>856 (26.5)</td>
<td>953 (29.1)</td>
<td>1388 (29.7)</td>
<td>1497 (28.9)</td>
<td>1384 (28.8)</td>
<td>0.04</td>
</tr>
<tr>
<td>Warfarin</td>
<td>119 (5.2)</td>
<td>132 (4.1)</td>
<td>132 (4.0)</td>
<td>192 (4.1)</td>
<td>228 (4.4)</td>
<td>216 (4.5)</td>
<td>0.76</td>
</tr>
<tr>
<td>Antihypertensive medication</td>
<td>1086 (47.8)</td>
<td>1722 (53.3)</td>
<td>1744 (53.2)</td>
<td>2541 (54.4)</td>
<td>2772 (53.6)</td>
<td>2567 (53.5)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Diabetes medication</td>
<td>487 (21.4)</td>
<td>801 (24.8)</td>
<td>782 (23.9)</td>
<td>1172 (25.1)</td>
<td>1353 (26.1)</td>
<td>1150 (23.9)</td>
<td>0.02</td>
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<tr>
<td>Statin</td>
<td>242 (10.7)</td>
<td>371 (11.5)</td>
<td>450 (13.7)</td>
<td>657 (14.1)</td>
<td>881 (17.0)</td>
<td>803 (16.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Recanalization treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intravenous thrombolysis</td>
<td>142 (6.3)</td>
<td>239 (7.4)</td>
<td>256 (7.8)</td>
<td>454 (9.7)</td>
<td>535 (10.3)</td>
<td>509 (10.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Endovascular treatment</td>
<td>40 (1.8)</td>
<td>59 (1.8)</td>
<td>68 (2.1)</td>
<td>92 (2.0)</td>
<td>136 (2.6)</td>
<td>129 (2.7)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Combined thrombolysis</td>
<td>46 (2.0)</td>
<td>45 (1.4)</td>
<td>72 (2.2)</td>
<td>175 (3.7)</td>
<td>185 (3.6)</td>
<td>180 (3.7)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Abbreviations: SD, standard deviation; LDL, low density lipoprotein.
Table II. Secular trend of antithrombotic use for the treatment of acute ischemic stroke after discharge

<table>
<thead>
<tr>
<th></th>
<th>2008 (n=2,272)</th>
<th>2009 (n=3,232)</th>
<th>2010 (n=3,277)</th>
<th>2011 (n=4,667)</th>
<th>2012 (n=5,175)</th>
<th>2013 (n=4,802)</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiplatelet</td>
<td>1754 (77.2)</td>
<td>2503 (77.4)</td>
<td>2532 (77.3)</td>
<td>3721 (79.7)</td>
<td>3846 (74.3)</td>
<td>3773 (78.6)</td>
<td>0.76</td>
</tr>
<tr>
<td>Aspirin</td>
<td>1,564 (68.8)</td>
<td>2,221 (68.7)</td>
<td>2,260 (69.0)</td>
<td>3,249 (69.6)</td>
<td>3,437 (66.4)</td>
<td>3,471 (72.3)</td>
<td>0.06</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>861 (37.9)</td>
<td>1,223 (37.8)</td>
<td>1,283 (39.2)</td>
<td>1,694 (36.3)</td>
<td>1,624 (31.4)</td>
<td>1,499 (31.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cilostazol</td>
<td>146 (6.4)</td>
<td>203 (6.3)</td>
<td>193 (5.9)</td>
<td>374 (8.0)</td>
<td>400 (7.7)</td>
<td>407 (8.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triflusal</td>
<td>42 (1.8)</td>
<td>76 (2.4)</td>
<td>43 (1.3)</td>
<td>66 (1.4)</td>
<td>57 (1.1)</td>
<td>30 (0.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ticlopidine</td>
<td>5 (0.2)</td>
<td>20 (0.6)</td>
<td>35 (1.1)</td>
<td>66 (1.4)</td>
<td>64 (1.2)</td>
<td>34 (0.7)</td>
<td>0.01</td>
</tr>
<tr>
<td>Warfarin</td>
<td>419 (18.4)</td>
<td>592 (18.3)</td>
<td>625 (19.1)</td>
<td>826 (17.7)</td>
<td>927 (17.9)</td>
<td>832 (17.3)</td>
<td>0.10</td>
</tr>
<tr>
<td>NOAC</td>
<td>159 (3.3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are number (percent).

Abbreviation: NOAC, novel oral anticoagulant.
Table III. Age and NIHSS score at admission as categorical variable used in Figure 1

<table>
<thead>
<tr>
<th></th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, categorized groups</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.64</td>
</tr>
<tr>
<td>Age, &lt;65</td>
<td>776 (34.2)</td>
<td>1133 (35.1)</td>
<td>1180 (36.0)</td>
<td>1665 (35.7)</td>
<td>1767 (34.1)</td>
<td>1685 (35.1)</td>
<td></td>
</tr>
<tr>
<td>Age, 65–84</td>
<td>1342 (59.1)</td>
<td>1893 (58.6)</td>
<td>1865 (56.9)</td>
<td>2696 (57.8)</td>
<td>3044 (58.8)</td>
<td>2773 (57.7)</td>
<td></td>
</tr>
<tr>
<td>Age, ≥85</td>
<td>154 (6.8)</td>
<td>206 (6.4)</td>
<td>232 (7.1)</td>
<td>306 (6.6)</td>
<td>364 (7.0)</td>
<td>344 (7.2)</td>
<td></td>
</tr>
<tr>
<td><strong>NIHSS at admission, categorized groups</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.10</td>
</tr>
<tr>
<td>NIHSS, &lt;8</td>
<td>1602 (70.5)</td>
<td>2313 (71.6)</td>
<td>2296 (70.1)</td>
<td>3344 (71.7)</td>
<td>3676 (71.0)</td>
<td>3415 (71.1)</td>
<td></td>
</tr>
<tr>
<td>NIHSS, 8–16</td>
<td>457 (20.1)</td>
<td>596 (18.4)</td>
<td>613 (18.7)</td>
<td>892 (19.1)</td>
<td>1025 (19.8)</td>
<td>903 (18.8)</td>
<td></td>
</tr>
<tr>
<td>NIHSS, ≥17</td>
<td>213 (9.4)</td>
<td>323 (10.0)</td>
<td>368 (11.2)</td>
<td>431 (9.2)</td>
<td>474 (9.2)</td>
<td>484 (10.1)</td>
<td></td>
</tr>
</tbody>
</table>

Values are number (percent) unless noted otherwise.

Abbreviation: NIHSS, National Institutes of Health stroke scale.
Table IV. Factors associated with intravenous heparin use in 2008 versus 2013

<table>
<thead>
<tr>
<th></th>
<th>In 2008</th>
<th></th>
<th>In 2013</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Multivariable OR (CI)</td>
<td>P Value</td>
<td>Multivariable OR (CI)</td>
<td>P Value</td>
</tr>
<tr>
<td>Age (year) - by 5 increase</td>
<td>0.93 (0.87-0.99)</td>
<td>0.02</td>
<td>0.997 (0.929-1.069)</td>
<td>0.92</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg) - by 10 increase</td>
<td>0.95 (0.90-1.01)</td>
<td>0.12</td>
<td>0.98 (0.93-1.04)</td>
<td>0.98</td>
</tr>
<tr>
<td>Total Cholesterol (mg/dL) - by 10 increase</td>
<td>1.06 (0.98-1.15)</td>
<td>0.15</td>
<td>0.94 (0.86-1.03)</td>
<td>0.18</td>
</tr>
<tr>
<td>LDL Cholesterol (mg/dL) - by 10 increase</td>
<td>0.94 (0.85-1.03)</td>
<td>0.16</td>
<td>1.05 (0.95-1.16)</td>
<td>0.32</td>
</tr>
<tr>
<td>Previous ischemic stroke</td>
<td>1.50 (1.05-2.12)</td>
<td>0.02</td>
<td>1.09 (0.76-1.56)</td>
<td>0.66</td>
</tr>
<tr>
<td>Previous coronary heart disease</td>
<td>1.34 (0.86-2.09)</td>
<td>0.19</td>
<td>0.86 (0.53-1.40)</td>
<td>0.55</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.26 (0.88-1.79)</td>
<td>0.21</td>
<td>0.95 (0.68-1.35)</td>
<td>0.78</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.995 (0.708-1.398)</td>
<td>0.98</td>
<td>0.99 (0.71-1.39)</td>
<td>0.97</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>1.18 (0.80-1.75)</td>
<td>0.40</td>
<td>0.98 (0.69-1.39)</td>
<td>0.89</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>3.49 (2.06-5.93)</td>
<td>&lt;0.001</td>
<td>2.34 (1.50-3.63)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current smoking</td>
<td>1.48 (1.03-2.11)</td>
<td>0.03</td>
<td>0.87 (0.57-1.32)</td>
<td>0.52</td>
</tr>
<tr>
<td>Onset to arrival (hour)</td>
<td>0.998 (0.993-1.003)</td>
<td>0.43</td>
<td>0.996 (0.990-1.002)</td>
<td>0.15</td>
</tr>
<tr>
<td>NIHSS at admission</td>
<td>0.976 (0.951-1.002)</td>
<td>0.07</td>
<td>1.005 (0.982-1.028)</td>
<td>0.68</td>
</tr>
<tr>
<td>TOAST classification</td>
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<td></td>
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<tr>
<td>Large artery atherosclerosis</td>
<td>1</td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Small vessel occlusion</td>
<td>0.31 (0.17-0.56)</td>
<td>&lt;0.001</td>
<td>0.13 (0.03-0.56)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Cardioembolism</td>
<td>2.05 (1.16-3.62)</td>
<td>0.01</td>
<td>3.56 (2.04-6.19)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Other determined</td>
<td>4.28 (1.78-10.31)</td>
<td>0.001</td>
<td>4.62 (1.62-13.19)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Undetermined</td>
<td>1.04 (0.64-1.69)</td>
<td>0.88</td>
<td>1.98 (1.23-3.20)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Recanalization treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intravenous thrombolysis</td>
<td>0.78 (0.42-1.42)</td>
<td>0.41</td>
<td>0.54 (0.33-0.88)</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>Odds Ratio (CI)</td>
<td>p-value</td>
<td>Odds Ratio (CI)</td>
<td>p-value</td>
</tr>
<tr>
<td>--------------------------</td>
<td>----------------</td>
<td>---------</td>
<td>----------------</td>
<td>---------</td>
</tr>
<tr>
<td>Endovascular treatment</td>
<td>0.76 (0.25-2.34)</td>
<td>0.63</td>
<td>1.02 (0.42-2.47)</td>
<td>0.97</td>
</tr>
<tr>
<td>Combined thrombolysis</td>
<td>0.15 (0.02-1.12)</td>
<td>0.06</td>
<td>1.19 (0.62-2.28)</td>
<td>0.60</td>
</tr>
</tbody>
</table>

Abbreviations: OR, odds ratio; CI, confidence interval; LDL, low density lipoprotein; NIHSS, National Institutes of Health stroke scale; TOAST, trial of ORG 10172 in acute stroke treatment.