Impact of Both Ends of the Hemoglobin Range on Clinical Outcomes in Acute Ischemic Stroke

Young Ho Park, MD; Beom Joon Kim, MD; Jun-Soon Kim, MD; Mi Hwa Yang, RN; Myung Suk Jang, AD; Nayoung Kim, MD; Moon-Ku Han, MD, PhD; Ji Sung Lee, PhD; Juneyoung Lee, PhD; SangYun Kim, MD, PhD; Hee-Joon Bae, MD, PhD

Background and Purpose—Although both ends of the hemoglobin range may negatively influence clinical outcomes in acute ischemic stroke, most studies have examined the linear relationship or focused on the lower end of the range. Furthermore, it is unclear whether hemoglobin concentrations at different time points during hospitalization correlate with clinical outcomes in the same manner.

Methods—We identified 2681 consecutive patients with acute ischemic stroke from a prospective stroke registry database and grouped them into hemoglobin concentration quintiles using the following 5 indices: initial, nadir, time-averaged, discharge hemoglobin, and hemoglobin drop. To examine the effect of both ends of hemoglobin range, the third quintile was selected as a reference category except for hemoglobin drop, for which the first quintile was used. As outcome variables, 3-month modified Rankin Scale as an ordinal scale and 3-month mortality were used.

Results—With respect to higher modified Rankin Scale scores, the adjusted odds ratios and 95% confidence intervals of the first quintiles of initial, nadir, time-averaged, and discharge hemoglobin were 1.74 (1.31–2.31), 2.64 (2.09–3.33), 1.81 (1.42–2.30), and 1.65 (1.29–2.13), respectively. The opposite ends of these hemoglobin indices were not significantly associated. The adjusted odds ratio of the fifth quintile of hemoglobin drop (greatest hemoglobin drop) was 2.09 (1.51–2.89). The mortality analysis showed similar results except for initial hemoglobin.

Conclusions—In acute ischemic stroke, poor outcome was related to the lower but not the higher end of the hemoglobin range, regardless of when and how hemoglobin concentrations were measured. (Stroke. 2013;44:00-00.)

Key Words: cerebral infarction ▪ functional outcome ▪ hemoglobins

A sudden interruption of oxygen to the brain is a crucial step in acute ischemic stroke (AIS). As red blood cells (RBCs) transport oxygen to the tissues and influence blood flow, RBC indices such as hemoglobin concentration or hematocrit could affect outcome of AIS.

However, the results of previous studies have been inconsistent, which may be explained, at least partly, by the hasty assumption regarding the shape of the relationship between RBC indices and clinical outcomes in AIS. Although both ends of the range of the RBC indices could negatively influence clinical outcome in AIS, most studies have examined the linear relationship or focused on the lower end of the range. Furthermore, RBC indices measured at different time points of hospitalization may behave differently with respect to clinical outcomes, but most studies only dealt with the RBC indices obtained at the time of admission. Here we report the impact of both ends of the hemoglobin range on clinical outcomes in AIS using hemoglobin indices measured at different time points of hospitalization.

Methods

A consecutive series of patients who were admitted to Seoul National University Bundang Hospital for AIS within 7 days of onset between January 2004 and November 2009 were identified using a prospective stroke registry. Modified Rankin Scale (mRS) score and mortality at 3 months were used as outcome variables.

We used the following 5 indices of hemoglobin concentration: initial, nadir, time-averaged, discharge hemoglobin, and hemoglobin drop (see online-only Data Supplement for definitions). Patients were categorized into quintiles according to each hemoglobin concentration. The third quintile was selected as a reference category except for hemoglobin drop, for which the first quintile was used. To examine the association between each quintile group and clinical outcomes, ordinal logistic regression analysis for a mRS score or binary logistic regression analysis for mortality was performed.

Received June 30, 2013; final revision received July 26, 2013; accepted July 30, 2013.

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The online-only Data Supplement is available with this article at http://stroke.ahajournals.orglookup/suppl/doi:10.1161/STROKEAHA.113.002672/-/DC1.

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Stroke is available at http://stroke.ahajournals.org DOI: 10.1161/STROKEAHA.113.002672
Covariates whose associations with the initial hemoglobin were clinically relevant and whose $P$ values for those associations were <0.2 were selected for adjustment. The hemoglobin indices other than initial hemoglobin required ≥2 measurements of hemoglobin concentration during hospitalization. We used the sequential regression multiple imputation method to impute missing values of hemoglobin indices if hemoglobin concentration was measured only once. A complete case analysis was also performed as sensitivity analysis, and its results were also presented. Further details on the study methods are provided in the online-only Data Supplement.

**Results**

The study population consisted of 2681 patients whose hemoglobin concentration was measured once (n=891) or more (n=1790) during hospitalization (Figure I in the online-only Data Supplement). Baseline characteristics were summarized (Table I in the online-only Data Supplement) and compared according to the initial hemoglobin quintiles (Table II in the online-only Data Supplement).

With respect to the initial hemoglobin, the odds of higher mRS scores at 3 months significantly increased only in the first quintile (Table III in the online-only Data Supplement). The adjusted odds ratio (OR) of the first quintile was 1.74 with a 95% confidence interval of 1.31 to 2.31 (Figure 1). With respect to the nadir, time-averaged, and discharge hemoglobin values, the adjusted ORs for increments of mRS scores also significantly increased in the first quintiles but not in the remaining quintiles (Figure 2). For the hemoglobin drop, the adjusted OR for increments of mRS scores elevated only in the fifth quintile.

As for mortality, significant increases in the adjusted ORs were observed in the first quintiles of the initial (Figure 1), nadir, time-averaged, and discharge hemoglobin (Figure 3); no significant changes were observed in the remaining quintiles except for the initial hemoglobin (Table III in the online-only Data Supplement). Notably, the adjusted ORs of initial hemoglobin for mortality significantly increased in the fourth and fifth quintiles. With respect to the hemoglobin drop, the OR for mortality significantly increased in the fifth quintile only.

The results of complete case analysis using the proportional odds models (Table IV in the online-only Data Supplement)
Discussion

This study demonstrates that worse functional outcome measured by mRS and mortality 3 months after stroke were related to the lower but not the higher end of the hemoglobin range. These nonlinear relationships were consistent regardless of when and how hemoglobin concentrations were measured, which may contradict a recent report that highlighted the importance of the nadir hemoglobin.6

The multiple imputation technique in this study included many replacements of missing values using models based on the data. Therefore, the uncertainty of such replacements remains. However, because excluding cases or variables with missing values from analysis may lead to bias, the multiple imputation analysis is considered a better alternative to simply abandoning observed data due to missing values.8

The putative association between hemoglobin concentration and clinical outcome might indicate that hemoglobin concentration is a useful treatment target. Indeed, transfusion of hemoglobin polymers actually reduced infarct volume in an animal model.9 Furthermore, blood transfusion to patients with acute myocardial infarction and anemia decreased mortality.10 However, the effect of transfusion in anemic patients with AIS has not been evaluated to date and should be examined in future studies.

Sources of Funding

This study was supported by grants from the Korea Healthcare Technology Research & Development Project, Ministry of Health and Welfare, Republic of Korea (A102065).

Disclosures

None.

References

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Stroke. published online September 3, 2013;
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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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/2013/09/03/STROKEAHA.113.002672

Data Supplement (unedited) at:
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SUPPLEMENTAL MATERIAL

Impact of Both Ends of the Hemoglobin Range on Outcome in Acute Ischemic Stroke

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Supplemental methods
We performed a retrospective analysis of hospitalized stroke patients based on a prospective stroke registry database. A consecutive series of patients who were admitted to Seoul National University Bundang Hospital between January 2004 and November 2009 for acute ischemic stroke (AIS) were identified using the registry. Patients who were hospitalized within 7 days of symptom onset and showed relevant ischemic lesions on diffusion-weighted magnetic resonance imaging were included, and those whose clinical outcomes at 3 months or hemoglobin (Hb) concentrations during hospitalization were unavailable were excluded.

 Patients’ demographics, clinical profiles, acute management, and laboratory findings were obtained directly from the registry database or by review of electronic medical records. Stroke subtype was determined according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification. Three-month modified Rankin scale (mRS) score and mortality were used as outcome variables and were prospectively collected by an experienced stroke nurse (Yang MH) by chart review and telephone interview as a part of the institution’s quality-of-care monitoring program for hospitalized stroke patients.

In hospitalized stroke patients, Hb concentration was usually measured first within one hour of arrival, and further measurements are performed at various time points at the discretion of treating physicians during hospitalization. We considered the following 5 indices for Hb concentration: (i) initial Hb (concentration at the time of admission); (ii) nadir Hb (lowest concentration during hospitalization); (iii) time-averaged Hb (defined by the area under the curve of all Hb concentrations during hospitalization divided by the length of hospitalization), which was modified from the glucometric analysis; (iv) discharge Hb (last Hb concentration obtained during hospitalization); and (v) Hb drop (the gap between initial and nadir Hb).

Study subject selection and dataset construction were described in Supplemental Figure I.

Statistical analysis
The 5 Hb indices were categorized into quintiles as follows; male and female subjects were grouped respectively into sex-specific quintiles according to their Hb concentrations, and the same quintile groups of male and female were, then, combined into a single quintile group. The third quintile was selected as a reference category, except for Hb drop, for which the first quintile was used. Comparisons of baseline characteristics among quintiles were made using an analysis of variance for continuous variables or Pearson’s chi-squared test for categorical variables. To examine the association between Hb indices and outcomes, an ordinal logistic regression analysis for the mRS score or binary logistic regression analysis for mortality was performed. Variables whose associations with initial Hb were clinically relevant and whose p values for those associations were <0.2 were selected for adjustments. The National Institutes of Health Stroke Scale (NIHSS) scores were categorized into quartiles for multivariable analysis.

Hb concentration was measured only once during hospitalization for some patients. However, Hb indices used for our analysis, except initial Hb, required 2 or more measurements. To minimize potential bias arising from excluding patients whose Hb concentration was measured once, we performed the multiple imputation analysis using the sequential regression multiple imputation (SRMI) method. Details of the study data structure and a process of multiple imputation we employed are as follows: With a total of 2,681 study subjects having 39 variables in our database, we used the 3-month mRS as an outcome variable and variables of age, sex, systolic blood pressure (BP), diastolic BP, prestroke mRS, the TOAST classification, NIHSS score, prior stroke history, hypertension, diabetes, atrial fibrillation, smoking status and an initial Hb concentration as independent variables. The
main analysis was an ordinal logistic regression analysis. The missing rate of Hb indices in patients who met the eligibility criteria was about 33%. Assuming missing at random as a missing mechanism, imputation of missing values in nadir Hb, time-averaged Hb, discharge Hb, and Hb drop was performed. As variables affecting an occurrence of missingness, we chose age, sex, NIHSS score, duration of hospitalization, time interval from onset to admission, and initial Hb concentration. All the variables required for the planned main analysis including outcome variables were put into the imputation models. The strategy of SRMI was employed using the IVEware software (University of Michigan Survey Research Center, Ann Arbor, MI, USA. http://www.isr.umich.edu/src/smp/ive/).

Followings are a summary of programs used for the missing imputation procedures:

First, a total of five complete datasets were created.

```plaintext
/*Impute module*/
%IMPUTE(name=mysetup, dir='D:\', setup=new);
data 'SAS dataset';
dataout 'Imputed SAS dataset';
default 'included continuous variables';
categorical 'included categorical variables';
minrsqd .01;
iterations 5;
multiples 5;
seed 'seed value';
RUN;
```

Second, a standard statistical analysis was performed for each of the five complete datasets.

```plaintext
DATA 'Imputed SAS dataset';
SET 'Imputed SAS dataset';
RENAME _mult_= _Imputation_;
RUN;

PROC SORT DATA = 'Imputed SAS dataset';
   BY _Imputation_;
RUN;

PROC LOGISTIC DATA = 'Imputed SAS dataset' desc;
   CLASS 'included categorical variables' / param=ref ref=first;
   MODEL mrs_3mo= 'included independent variables' / covb;
   BY _Imputation_;
   ODS OUTPUT ParameterEstimates=lgsparms CovB=lgscovb;
RUN;
```

Finally, the results from five complete datasets were combined in order to produce our inferential results.

```plaintext
ODS output ParameterEstimates = PE;
PROC MIANALYZE PARMS(classvar=CLASSVAL)=lgsparms
   covb(effectvar=stacking)=lgscovb;
   class Intercept 'included categorical variables';
   modeleffects Intercept 'included independent variables';
RUN;
```

The results presented in this paper were obtained from imputed data with 5 iterations to achieve convergence (Supplemental Table III). We also performed a complete-case
analysis (CCA) as an ad hoc approach (Supplemental Table IV), and its results were compared with those of SRMI. In addition, the CCA restricting the study population to patients who were hospitalized within 48 hours of onset was performed as a sensitivity analysis (Supplemental Table VI).

An ordinal logistic regression analysis using the proportional odds model was conducted to evaluate the effect of Hb concentration across the entire range of the mRS. In the CCA, due to a violation of the so-called proportional odds assumption in Hb concentration across levels of mRS outcome, a partial proportional odds model was applied. Separate OR’s for the Hb concentration, then, reported for each level of the mRS outcome (Supplemental Table V). Up to authors’ understanding, since there is no method of adjustment when the proportional odds assumption is violated in applying SRMI, and the rejection of the proportional odds assumption does not necessarily imply a practical insignificance, the standard ordinal logistic regression model was used.

As low Hb concentration may be due to acute bleeding which is associated with a drop in BP, we also included BP drop in the logistic regression as an ad hoc approach. We calculated the baseline mean arterial BP [MAP=(2×diastolic BP+systolic BP)/3], defined BP drop as decrease of >30% from baseline MAP at any time point during hospitalization, and added it as a covariate to the existing models.

Statistical analyses were performed using SPSS statistical software version 15.0 (SPSS Inc., Chicago, IL, USA) for most of casual analyses, SAS version 9.2 (SAS Institute Inc., Cary, NC, USA) and STATA version 9.0 (Stata Corporation, College Station, TX, USA) for ordinal logistic regression analysis and IVWare software (University of Michigan Survey Research Center, Ann Arbor, MI, USA) for SRMI. The study protocol was approved by the local institutional review board with a waiver of informed consent due to its retrospective nature and minimal risk to participants.
References

### Supplemental Table I. Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>N = 2,681</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, mean (SD)</strong></td>
<td>67.18 (12.49)</td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td>1,594 (59.5%)</td>
</tr>
<tr>
<td><em><em>Initial SBP</em>, mean (SD)</em>*</td>
<td>158.0 (27.54)</td>
</tr>
<tr>
<td><em><em>Initial DBP</em>, mean (SD)</em>*</td>
<td>85.33 (16.35)</td>
</tr>
<tr>
<td><strong>Prestroke mRS</strong></td>
<td></td>
</tr>
<tr>
<td>0-1</td>
<td>2,548 (95.0%)</td>
</tr>
<tr>
<td>2-5</td>
<td>133 (5.0%)</td>
</tr>
<tr>
<td><strong>TOAST classification</strong></td>
<td></td>
</tr>
<tr>
<td>LAD</td>
<td>1,029 (38.4%)</td>
</tr>
<tr>
<td>SVO</td>
<td>536 (20.0%)</td>
</tr>
<tr>
<td>CE</td>
<td>545 (20.3%)</td>
</tr>
<tr>
<td>Other determined</td>
<td>76 (2.8%)</td>
</tr>
<tr>
<td>Undetermined</td>
<td>495 (18.5%)</td>
</tr>
<tr>
<td><strong>NIHSS, median (IQR)</strong></td>
<td>4 (2–7)</td>
</tr>
<tr>
<td><strong>Prior stroke</strong></td>
<td>591 (22.0%)</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>1,682 (62.7%)</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>800 (29.8%)</td>
</tr>
<tr>
<td><strong>Dyslipidemia</strong></td>
<td>468 (17.5%)</td>
</tr>
<tr>
<td><strong>Atrial fibrillation</strong></td>
<td>193 (7.2%)</td>
</tr>
<tr>
<td><strong>Smoking</strong></td>
<td>1,023 (38.2%)</td>
</tr>
<tr>
<td><strong>Initial FBG†, mean (SD)</strong></td>
<td>1.472 (0.9001)</td>
</tr>
<tr>
<td><strong>IV &amp; IA Thrombolysis</strong></td>
<td>306 (11.4%)</td>
</tr>
</tbody>
</table>

Values are number (%) if not indicated.

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; mRS, modified Rankin Scale; TOAST, Trial of Org 10172 in Acute Stroke Treatment; LAD, large artery disease; SVO, small vessel occlusion; CE, cardiac embolism; NIHSS, National Institutes of Health stroke scale; IQR, interquartile range; FBG, fasting blood glucose; IV, intravenous; IA, intra-arterial.

*We used mmHg as the unit of measure of SBP and DBP.
†We used g/L as the unit of measure of initial FBG.
Supplemental Table II. Baseline characteristics according to initial Hb quintiles

<table>
<thead>
<tr>
<th></th>
<th>First quintile (n = 532)</th>
<th>Second quintile (n = 545)</th>
<th>Third quintile (n = 556)</th>
<th>Fourth quintile (n = 530)</th>
<th>Fifth quintile (n = 518)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>71.7 (11.2)</td>
<td>69.1 (11.4)</td>
<td>67.2 (11.9)</td>
<td>64.5 (12.6)</td>
<td>63.2 (13.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Men</td>
<td>312 (58.6%)</td>
<td>335 (61.5%)</td>
<td>321 (57.7%)</td>
<td>316 (59.6%)</td>
<td>310 (59.8%)</td>
<td>0.78</td>
</tr>
<tr>
<td>Initial SBP in mmHg, mean (SD)</td>
<td>152 (28.2)</td>
<td>155 (25.1)</td>
<td>158 (26.0)</td>
<td>160 (28.7)</td>
<td>165 (27.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prestroke mRS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>0–1</td>
<td>474 (89.1%)</td>
<td>521 (95.6%)</td>
<td>535 (96.2%)</td>
<td>513 (96.8%)</td>
<td>505 (97.5%)</td>
<td></td>
</tr>
<tr>
<td>2–5</td>
<td>58 (10.9%)</td>
<td>24 (4.4%)</td>
<td>21 (3.8%)</td>
<td>17 (3.2%)</td>
<td>13 (2.5%)</td>
<td></td>
</tr>
<tr>
<td>TOAST classification</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.03</td>
</tr>
<tr>
<td>LAD</td>
<td>200 (37.6%)</td>
<td>206 (37.8%)</td>
<td>227 (40.8%)</td>
<td>191 (36.0%)</td>
<td>205 (39.6%)</td>
<td></td>
</tr>
<tr>
<td>SVO</td>
<td>81 (15.2%)</td>
<td>110 (20.2%)</td>
<td>125 (22.5%)</td>
<td>115 (21.7%)</td>
<td>105 (20.3%)</td>
<td></td>
</tr>
<tr>
<td>CE</td>
<td>114 (21.4%)</td>
<td>110 (20.2%)</td>
<td>103 (18.5%)</td>
<td>110 (20.8%)</td>
<td>108 (20.8%)</td>
<td></td>
</tr>
<tr>
<td>Other determined</td>
<td>27 (5.1%)</td>
<td>14 (2.6%)</td>
<td>8 (1.4%)</td>
<td>14 (2.6%)</td>
<td>13 (2.5%)</td>
<td></td>
</tr>
<tr>
<td>Undetermined</td>
<td>110 (20.7%)</td>
<td>105 (19.3%)</td>
<td>93 (16.7%)</td>
<td>100 (18.9%)</td>
<td>87 (16.8%)</td>
<td></td>
</tr>
<tr>
<td>NIHSS, median (IQR)</td>
<td>4 (2–9)</td>
<td>4 (2–7)</td>
<td>4 (2–7)</td>
<td>3 (1–6)</td>
<td>3 (2–7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prior stroke</td>
<td>162 (30.5%)</td>
<td>127 (23.5%)</td>
<td>105 (18.9%)</td>
<td>103 (19.4%)</td>
<td>94 (18.1%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>369 (69.4%)</td>
<td>339 (62.2%)</td>
<td>339 (61.0%)</td>
<td>314 (59.2%)</td>
<td>321 (62.0%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Diabetes</td>
<td>217 (40.8%)</td>
<td>166 (30.5%)</td>
<td>152 (27.3%)</td>
<td>138 (26.0%)</td>
<td>127 (24.5%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>83 (15.6%)</td>
<td>95 (17.4%)</td>
<td>98 (17.6%)</td>
<td>92 (17.4%)</td>
<td>100 (19.3%)</td>
<td>0.64</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>44 (8.3%)</td>
<td>38 (7.0%)</td>
<td>43 (7.7%)</td>
<td>38 (7.2%)</td>
<td>30 (5.8%)</td>
<td>0.60</td>
</tr>
<tr>
<td>Smoking</td>
<td>172 (32.3%)</td>
<td>208 (38.2%)</td>
<td>208 (37.4%)</td>
<td>214 (40.4%)</td>
<td>221 (42.7%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Initial FBG in mg/dL, mean (SD)</td>
<td>143 (77.6)</td>
<td>146 (93.0)</td>
<td>149 (101)</td>
<td>148 (91.4)</td>
<td>150 (85.1)</td>
<td>0.76</td>
</tr>
<tr>
<td>IV or IA Thrombolysis</td>
<td>51 (9.6%)</td>
<td>69 (12.7%)</td>
<td>70 (12.6%)</td>
<td>55 (10.4%)</td>
<td>61 (11.8%)</td>
<td>0.41</td>
</tr>
</tbody>
</table>

Values are n (%) if not indicated.
*P values were obtained with analysis of variance or chi-squared test as appropriate. Abbreviations: CE, cardiac embolism; FBG, fasting blood glucose; Hb, hemoglobin; IA, intra-arterial; IQR, interquartile range; IV, intravenous; LAD, large artery disease; mRS, modified Rankin Scale; NIHSS, National Institutes of Health stroke scale; SBP, systolic blood pressure; SVO, small vessel occlusion; TOAST, Trial of Org 10172 in Acute Stroke Treatment.
Supplemental Table III. Crude and adjusted ORs and their 95% CIs for higher mRS and mortality according to various Hb indices using SRMI (N=2,681)

<table>
<thead>
<tr>
<th></th>
<th>Functional Outcome</th>
<th></th>
<th>Mortality</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Crude OR (95% CI)</td>
<td>Adjusted OR* (95% CI)</td>
<td>Crude OR (95% CI)</td>
<td>Adjusted OR* (95% CI)</td>
</tr>
<tr>
<td><strong>Initial Hb†</strong></td>
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</tr>
<tr>
<td>Q1</td>
<td>2.28 (1.76–2.96)</td>
<td>1.74 (1.31–2.31)</td>
<td>4.17 (2.39–7.31)</td>
<td>3.74 (2.03–6.89)</td>
</tr>
<tr>
<td>Q2</td>
<td>1.13 (0.87–1.45)</td>
<td>1.01 (0.77–1.33)</td>
<td>1.58 (0.85–2.95)</td>
<td>1.64 (0.84–3.18)</td>
</tr>
<tr>
<td>Q3</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Q4</td>
<td>0.87 (0.67–1.13)</td>
<td>1.08 (0.82–1.43)</td>
<td>1.71 (0.91–3.19)</td>
<td>2.16 (1.11–4.22)</td>
</tr>
<tr>
<td>Q5</td>
<td>0.88 (0.68–1.14)</td>
<td>1.09 (0.83–1.43)</td>
<td>1.63 (0.87–3.05)</td>
<td>1.99 (1.02–3.91)</td>
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<tr>
<td><strong>Nadir Hb</strong></td>
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<tr>
<td>Q1</td>
<td>4.58 (3.64–5.77)</td>
<td>2.64 (2.09–3.33)</td>
<td>7.14 (3.97–12.87)</td>
<td>4.44 (2.35–8.37)</td>
</tr>
<tr>
<td>Q2</td>
<td>1.43 (1.13–1.80)</td>
<td>1.11 (0.88–1.40)</td>
<td>2.11 (1.11–4.01)</td>
<td>1.65 (0.84–3.23)</td>
</tr>
<tr>
<td>Q3</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
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</tr>
<tr>
<td>Q4</td>
<td>0.85 (0.66–1.09)</td>
<td>0.93 (0.70–1.23)</td>
<td>1.14 (0.55–2.35)</td>
<td>1.25 (0.59–2.68)</td>
</tr>
<tr>
<td>Q5</td>
<td>0.74 (0.58–0.95)</td>
<td>0.89 (0.68–1.18)</td>
<td>0.86 (0.40–1.86)</td>
<td>1.01 (0.45–2.25)</td>
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<tr>
<td><strong>Time-averaged Hb</strong></td>
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<tr>
<td>Q1</td>
<td>3.07 (2.43–3.88)</td>
<td>1.81 (1.42–2.30)</td>
<td>4.30 (2.61–7.08)</td>
<td>2.62 (1.52–4.51)</td>
</tr>
<tr>
<td>Q2</td>
<td>1.26 (1.00–1.59)</td>
<td>1.00 (0.80–1.25)</td>
<td>1.55 (0.88–2.74)</td>
<td>1.25 (0.68–2.29)</td>
</tr>
<tr>
<td>Q3</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Q4</td>
<td>0.79 (0.60–1.05)</td>
<td>0.86 (0.64–1.17)</td>
<td>0.77 (0.40–1.49)</td>
<td>0.78 (0.39–1.55)</td>
</tr>
<tr>
<td>Q5</td>
<td>0.69 (0.53–0.91)</td>
<td>0.84 (0.64–1.10)</td>
<td>0.84 (0.44–1.59)</td>
<td>0.95 (0.48–1.88)</td>
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<tr>
<td><strong>Discharge Hb</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Q1</td>
<td>2.45 (1.93–3.12)</td>
<td>1.65 (1.29–2.13)</td>
<td>6.11 (3.22–11.57)</td>
<td>4.86 (2.46–9.58)</td>
</tr>
<tr>
<td>Q2</td>
<td>1.07 (0.86–1.34)</td>
<td>0.92 (0.70–1.22)</td>
<td>2.07 (1.08–4.00)</td>
<td>1.87 (0.89–3.92)</td>
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<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Q4</td>
<td>0.80 (0.63–1.01)</td>
<td>0.89 (0.70–1.12)</td>
<td>1.04 (0.46–2.32)</td>
<td>1.16 (0.48–2.79)</td>
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<tr>
<td>Q5</td>
<td>0.78 (0.59–1.03)</td>
<td>0.91 (0.68–1.21)</td>
<td>1.54 (0.76–3.11)</td>
<td>1.75 (0.84–3.67)</td>
</tr>
<tr>
<td><strong>Hb drop</strong></td>
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<td></td>
</tr>
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<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Q2</td>
<td>0.99 (0.77–1.27)</td>
<td>0.98 (0.76–1.26)</td>
<td>0.78 (0.40–1.51)</td>
<td>0.74 (0.36–1.53)</td>
</tr>
<tr>
<td>Q3</td>
<td>1.07 (0.81–1.41)</td>
<td>1.02 (0.79–1.30)</td>
<td>0.99 (0.53–1.85)</td>
<td>0.85 (0.45–1.61)</td>
</tr>
<tr>
<td>Q4</td>
<td>1.26 (0.97–1.63)</td>
<td>1.06 (0.81–1.39)</td>
<td>1.23 (0.66–2.31)</td>
<td>0.92 (0.47–1.78)</td>
</tr>
<tr>
<td>Q5</td>
<td>3.14 (2.32–4.25)</td>
<td>2.09 (1.51–2.89)</td>
<td>4.03 (2.45–6.63)</td>
<td>2.45 (1.40–4.30)</td>
</tr>
</tbody>
</table>

Abbreviations: mRS, modified Rankin Scale; OR, odds ratio; CI, confidence interval; Hb, hemoglobin; SRMI, sequential regression multiple imputation; Q1, first quintile; Q2, second quintile; Q3, third quintile; Q4, fourth quintile; Q5, fifth quintile.

*Adjusted variables included age, gender, initial systolic blood pressure, prestroke mRS, Trial of Org 10172 in Acute Stroke Treatment classification, National Institutes of Health Stroke Scale at admission, previous stroke, hypertension, diabetes, dyslipidemia, atrial fibrillation, initial fasting blood glucose, and thrombolysis. The ORs were obtained by ordinal logistic regression analysis using a proportional odds model for functional outcome and binary
logistic regression analysis for mortality.
†As SRMI was not required in the initial Hb, complete-case analysis was used.
Supplemental Table IV. Crude and adjusted ORs and their 95% CIs for higher mRS and mortality according to various Hb indices using CCA (N=1,790)

<table>
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<th>Functional Outcome</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Crude OR (95% CI)</td>
<td>Adjusted OR* (95% CI)</td>
</tr>
<tr>
<td><strong>Nadir Hb</strong></td>
<td></td>
<td></td>
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<tr>
<td>Q1</td>
<td>5.32 (4.05–6.97)</td>
<td>3.16 (2.38–4.21)</td>
</tr>
<tr>
<td>Q2</td>
<td>1.73 (1.33–2.24)</td>
<td>1.14 (0.87–1.50)</td>
</tr>
<tr>
<td>Q3</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Q4</td>
<td>0.73 (0.57–0.95)</td>
<td>0.88 (0.67–1.15)</td>
</tr>
<tr>
<td>Q5</td>
<td>0.68 (0.52–0.88)</td>
<td>0.89 (0.68–1.18)</td>
</tr>
<tr>
<td><strong>Time-averaged Hb</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q1</td>
<td>3.19 (2.45–4.16)</td>
<td>2.08 (1.57–2.76)</td>
</tr>
<tr>
<td>Q2</td>
<td>1.46 (1.13–1.89)</td>
<td>1.11 (0.84–1.45)</td>
</tr>
<tr>
<td>Q3</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Q4</td>
<td>0.76 (0.58–0.98)</td>
<td>0.96 (0.73–1.26)</td>
</tr>
<tr>
<td>Q5</td>
<td>0.64 (0.50–0.84)</td>
<td>0.90 (0.68–1.19)</td>
</tr>
<tr>
<td><strong>Discharge Hb</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q1</td>
<td>3.00 (2.31–3.89)</td>
<td>2.20 (1.67–2.89)</td>
</tr>
<tr>
<td>Q2</td>
<td>1.29 (1.00–1.68)</td>
<td>0.97 (0.74–1.28)</td>
</tr>
<tr>
<td>Q3</td>
<td>Reference</td>
<td>Reference</td>
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<tr>
<td>Q4</td>
<td>0.84 (0.65–1.08)</td>
<td>1.01 (0.77–1.32)</td>
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<tr>
<td>Q5</td>
<td>0.83 (0.65–1.07)</td>
<td>1.03 (0.79–1.36)</td>
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<tr>
<td><strong>Hb drop</strong></td>
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<tr>
<td>Q1</td>
<td>Reference</td>
<td>Reference</td>
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<tr>
<td>Q2</td>
<td>0.90 (0.69–1.16)</td>
<td>1.05 (0.80–1.37)</td>
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<td>Q3</td>
<td>0.98 (0.76–1.28)</td>
<td>1.05 (0.80–1.39)</td>
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<td>Q4</td>
<td>1.35 (1.04–1.75)</td>
<td>1.19 (0.91–1.56)</td>
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<td>Q5</td>
<td>4.73 (3.61–6.19)</td>
<td>2.73 (2.05–3.65)</td>
</tr>
</tbody>
</table>

Abbreviations: mRS, modified Rankin Scale; OR, odds ratio; CI, confidence interval; Hb, hemoglobin; SRMI, sequential regression multiple imputation; Q1, first quintile; Q2, second quintile; Q3, third quintile; Q4, fourth quintile; Q5, fifth quintile.

*Adjusted variables included age, gender, initial systolic blood pressure, prestroke mRS, Trial of Org 10172 in Acute Stroke Treatment classification, National Institutes of Health Stroke Scale at admission, previous stroke, hypertension, diabetes, dyslipidemia, atrial fibrillation, initial fasting blood glucose, and thrombolysis. The ORs were obtained by ordinal logistic regression analysis using a proportional odds model for functional outcome and binary logistic regression analysis for mortality.
Supplemental Table V. Impact of various Hb indices on 3-month mRS at each cutoff point of the mRS scores in CCA

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<th>Adjusted ORs (95% CI) for mRS score*</th>
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<td><strong>Initial Hb</strong></td>
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<tr>
<td>Q1</td>
<td>1.78 (1.36-2.32)</td>
</tr>
<tr>
<td>Q2</td>
<td>0.91 (0.69-1.20)</td>
</tr>
<tr>
<td>Q3</td>
<td>Reference</td>
</tr>
<tr>
<td>Q4</td>
<td>1.11 (0.83-1.48)</td>
</tr>
<tr>
<td>Q5</td>
<td>1.25 (0.92-1.68)</td>
</tr>
<tr>
<td><strong>Nadir Hb</strong></td>
<td></td>
</tr>
<tr>
<td>Q1</td>
<td>1.04 (0.68-1.59)</td>
</tr>
<tr>
<td>Q2</td>
<td>0.91 (0.63-1.32)</td>
</tr>
<tr>
<td>Q3</td>
<td>Reference</td>
</tr>
<tr>
<td>Q4</td>
<td>0.84 (0.64-1.10)</td>
</tr>
<tr>
<td>Q5</td>
<td>0.84 (0.64-1.11)</td>
</tr>
<tr>
<td><strong>Time-averaged Hb</strong></td>
<td></td>
</tr>
<tr>
<td>Q1</td>
<td>1.09 (0.72-1.64)</td>
</tr>
<tr>
<td>Q2</td>
<td>0.72 (0.50-1.03)</td>
</tr>
<tr>
<td>Q3</td>
<td>Reference</td>
</tr>
<tr>
<td>Q4</td>
<td>0.93 (0.71-1.23)</td>
</tr>
<tr>
<td>Q5</td>
<td>0.85 (0.65-1.13)</td>
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<td><strong>Discharge Hb</strong></td>
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</tr>
<tr>
<td>Q1</td>
<td>1.00 (0.67-1.47)</td>
</tr>
<tr>
<td>Q2</td>
<td>0.68 (0.47-0.97)</td>
</tr>
<tr>
<td>Q3</td>
<td>Reference</td>
</tr>
<tr>
<td>Q4</td>
<td>0.97 (0.74-1.27)</td>
</tr>
<tr>
<td>Q5</td>
<td>0.99 (0.75-1.29)</td>
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<td><strong>Hb drop</strong></td>
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Hemoglobin
<table>
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<td>1.03</td>
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<tr>
<td></td>
<td>(0.79-1.35)</td>
<td>(0.79-1.35)</td>
<td>(0.79-1.35)</td>
<td>(0.79-1.35)</td>
<td>(0.79-1.35)</td>
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<tr>
<td>Q3</td>
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<td>1.04</td>
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<tr>
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<td>(0.79-1.37)</td>
<td>(0.79-1.37)</td>
<td>(0.79-1.37)</td>
<td>(0.79-1.37)</td>
<td>(0.79-1.37)</td>
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<td>Q4</td>
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<td>1.19</td>
<td>1.19</td>
<td>1.19</td>
<td>1.19</td>
</tr>
<tr>
<td></td>
<td>(0.90-1.56)</td>
<td>(0.90-1.56)</td>
<td>(0.90-1.56)</td>
<td>(0.90-1.56)</td>
<td>(0.90-1.56)</td>
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<tr>
<td>Q5</td>
<td>1.17</td>
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<td>3.89</td>
<td>3.45</td>
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<tr>
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<td>(0.78-1.77)</td>
<td>(1.37-2.90)</td>
<td>(1.75-3.51)</td>
<td>(2.76-5.48)</td>
<td>(2.42-4.93)</td>
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</tr>
</tbody>
</table>

Abbreviations: CCA, complete-case analysis; Hb, hemoglobin; mRS, modified Rankin Scale; OR, odds ratio; CI, confidence interval; Q1, first quintile; Q2, second quintile; Q3, third quintile; Q4, fourth quintile; Q5, fifth quintile

*Adjusted ORs and 95% CIs were obtained by an ordinal logistic regression analysis with the partial proportional odds model. ORs were adjusted for age, gender, initial systolic blood pressure, prestroke mRS, Trial of Org 10172 in Acute Stroke Treatment classification, National Institutes of Health Stroke Scale at admission, previous stroke, hypertension, diabetes, dyslipidemia, atrial fibrillation, initial fasting blood glucose, and thrombolysis.
Supplemental Table VI. Crude and adjusted ORs and their 95% CIs for higher mRS and mortality according to various Hb indices restricting the study population to patients hospitalized within 48 hours of onset (N=1,417)

<table>
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<th>Functional Outcome</th>
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<th>Mortality</th>
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</thead>
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<td></td>
<td>Crude OR (95% CI)</td>
<td>Adjusted OR* (95% CI)</td>
<td>Crude OR (95% CI)</td>
<td>Adjusted OR* (95% CI)</td>
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<td></td>
</tr>
<tr>
<td>Q1</td>
<td>2.57 (2.02–3.27)</td>
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<td>4.57 (2.58–8.08)</td>
<td>3.97 (2.13–7.41)</td>
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<tr>
<td>Q2</td>
<td>1.12 (0.89–1.43)</td>
<td>1.00 (0.78–1.28)</td>
<td>1.58 (0.82–3.03)</td>
<td>1.47 (0.74–2.94)</td>
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<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Q4</td>
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<td>2.20 (1.11–4.36)</td>
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<td>1.06 (0.82–1.37)</td>
<td>1.39 (0.71–2.72)</td>
<td>1.76 (0.86–3.62)</td>
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<tr>
<td><strong>Nadir Hb</strong></td>
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</tr>
<tr>
<td>Q1</td>
<td>5.58 (4.11–7.59)</td>
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<td>7.41 (4.00–13.73)</td>
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<td>1.74 (1.30–2.33)</td>
<td>1.22 (0.90–1.66)</td>
<td>2.39 (1.22–4.70)</td>
<td>1.94 (0.95–3.94)</td>
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<td>Reference</td>
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<td>0.72 (0.54–0.96)</td>
<td>0.87 (0.64–1.19)</td>
<td>0.71 (0.30–1.68)</td>
<td>0.94 (0.39–2.31)</td>
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<tr>
<td>Q5</td>
<td>0.66 (0.50–0.89)</td>
<td>0.88 (0.65–1.20)</td>
<td>0.75 (0.32–1.73)</td>
<td>1.07 (0.45–2.56)</td>
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<tr>
<td><strong>Time-averaged Hb</strong></td>
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</tr>
<tr>
<td>Q1</td>
<td>3.39 (2.52–4.57)</td>
<td>2.32 (1.69–3.20)</td>
<td>3.95 (2.32–6.73)</td>
<td>2.90 (1.62–5.20)</td>
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<tr>
<td>Q2</td>
<td>1.35 (1.01–1.80)</td>
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<td>1.27 (0.69–2.35)</td>
<td>1.15 (0.60–2.19)</td>
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<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
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</tr>
<tr>
<td>Q4</td>
<td>0.78 (0.58–1.04)</td>
<td>0.96 (0.71–1.31)</td>
<td>0.58 (0.28–1.21)</td>
<td>0.70 (0.32–1.51)</td>
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<tr>
<td>Q5</td>
<td>0.61 (0.46–0.82)</td>
<td>0.83 (0.60–1.13)</td>
<td>0.59 (0.28–1.23)</td>
<td>0.81 (0.37–1.75)</td>
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<tr>
<td><strong>Discharge Hb</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q1</td>
<td>3.23 (2.40–4.34)</td>
<td>2.73 (1.99–3.74)</td>
<td>9.38 (4.73–18.60)</td>
<td>8.08 (3.96–16.48)</td>
</tr>
<tr>
<td>Q2</td>
<td>1.22 (0.91–1.63)</td>
<td>1.05 (0.77–1.42)</td>
<td>2.48 (1.16–5.31)</td>
<td>2.08 (0.94–4.60)</td>
</tr>
<tr>
<td>Q3</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Q4</td>
<td>0.81 (0.61–1.09)</td>
<td>1.04 (0.76–1.41)</td>
<td>1.19 (0.51–2.80)</td>
<td>1.35 (0.55–3.32)</td>
</tr>
<tr>
<td>Q5</td>
<td>0.81 (0.61–1.08)</td>
<td>1.03 (0.75–1.40)</td>
<td>1.68 (0.75–3.77)</td>
<td>2.03 (0.88–4.70)</td>
</tr>
<tr>
<td><strong>Hb drop</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q1</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Q2</td>
<td>0.77 (0.57–1.03)</td>
<td>0.89 (0.66–1.21)</td>
<td>0.40 (0.18–0.90)</td>
<td>0.41 (0.18–0.95)</td>
</tr>
<tr>
<td>Q3</td>
<td>0.93 (0.69–1.25)</td>
<td>0.90 (0.66–1.23)</td>
<td>0.97 (0.51–1.86)</td>
<td>0.98 (0.49–1.96)</td>
</tr>
<tr>
<td>Q4</td>
<td>1.25 (0.93–1.67)</td>
<td>1.07 (0.78–1.45)</td>
<td>1.01 (0.54–1.92)</td>
<td>0.76 (0.38–1.52)</td>
</tr>
<tr>
<td>Q5</td>
<td>4.60 (3.40–6.24)</td>
<td>2.47 (1.77–3.43)</td>
<td>3.80 (2.23–6.47)</td>
<td>2.33 (1.28–4.23)</td>
</tr>
</tbody>
</table>

Abbreviations: mRS, modified Rankin Scale; OR, odds ratio; CI, confidence interval; Hb, hemoglobin; SRMI, sequential regression multiple imputation; Q1, first quintile; Q2, second quintile; Q3, third quintile; Q4, fourth quintile; Q5, fifth quintile.

*Adjusted variables included age, gender, initial systolic blood pressure, prestroke mRS, Trial of Org 10172 in Acute Stroke Treatment classification, National Institutes of Health Stroke Scale at admission, previous stroke, hypertension, diabetes, dyslipidemia, atrial fibrillation, initial fasting blood glucose, and thrombolysis. The ORs were obtained by ordinal logistic regression analysis using a proportional odds model for functional outcome and binary.
logistic regression analysis for mortality.
Supplemental Figure I. Study subject selection and dataset construction.
Abbreviations: Hb, hemoglobin
Supplemental Figure II. Adjusted ORs for higher 3-month mRS in complete-case analysis

The horizontal line and the number in the center of each vertical line denote the OR, and the whiskers indicate the 95% confidence interval for nadir Hb (A), time-averaged Hb (B), discharge Hb (C), and Hb drop (D). The numbers below the x-axis are the cutoff Hb concentrations in g/dL between quintile groups in males and females, respectively.

Abbreviations: Hb, hemoglobin; OR, odds ratio; Q1, first quintile; Q2, second quintile; Q3, third quintile; Q4, fourth quintile; Q5, fifth quintile
Supplemental Figure III. Adjusted OR for 3-month mortality in complete-case analysis
The horizontal line and the number in the center of each vertical line denote the OR, and the whiskers indicate the 95% confidence interval for nadir Hb (A), time-averaged Hb (B), discharge Hb (C), and Hb drop (D). The numbers below the x-axis are the cutoff Hb concentrations in g/dL between quintile groups in males and females, respectively.
Abbreviations: Hb, hemoglobin; OR, odds ratio; Q1, first quintile; Q2, second quintile; Q3, third quintile; Q4, fourth quintile; Q5, fifth quintile
Remark

This work was presented at the 63rd American Academy of Neurology Annual Meeting, Honolulu, Hawaii, April 9–16, 2011.