The VASOGRADE
A Simple Grading Scale for Prediction of Delayed Cerebral Ischemia After Subarachnoid Hemorrhage

Airton Leonardo de Oliveira Manoel, MD; Blessing N. Jaja, MD, PhD; Menno R. Germans, MD, PhD; Han Yan, BSc; Winnie Qian, BA; Ekaterina Kouzmina, BSc; Tom R. Marotta, MD; David Turkel-Parrella, MD; Tom A. Schweizer, PhD; R. Loch Macdonald, MD, PhD; and the SAHIT collaborators

Background and Purpose—Patients are classically at risk of delayed cerebral ischemia (DCI) after aneurysmal subarachnoid hemorrhage. We validated a grading scale—the VASOGRADE—for prediction of DCI.

Methods—We used data of 3 phase II randomized clinical trials and a single hospital series to assess the relationship between the VASOGRADE and DCI. The VASOGRADE derived from previously published risk charts and consists of 3 categories: VASOGRADE-Green (modified Fisher scale 1 or 2 and World Federation of Neurosurgical Societies scale [WFNS] 1 or 2); VASOGRADE-Yellow (modified Fisher 3 or 4 and WFNS 1–3); and VASOGRADE-Red (WFNS 4 or 5, irrespective of modified Fisher grade). The relation between the VASOGRADE and DCI was assessed by logistic regression models. The predictive accuracy of the VASOGRADE was assessed by receiver operating characteristics curve and calibration plots.

Results—In a cohort of 746 patients, the VASOGRADE significantly predicted DCI (P<0.001). The VASOGRADE-Yellow had a tendency for increased risk for DCI (odds ratio [OR], 1.31; 95% CI, 0.77–2.23) when compared with VASOGRADE-Green; those with VASOGRADE-Red had a 3-fold higher risk of DCI (OR, 3.19; 95% CI, 2.07–4.50). Studies were not a significant confounding factor between the VASOGRADE and DCI. The VASOGRADE had an adequate discrimination for prediction of DCI (area under the receiver operating characteristics curve=0.63) and good calibration.

Conclusions—The VASOGRADE results validated previously published risk charts in a large and diverse sample of subarachnoid hemorrhage patients, which allows DCI risk stratification on presentation after subarachnoid hemorrhage. It could help to select patients at high risk of DCI, as well as standardize treatment protocols and research studies. (Stroke. 2015;46:1826-1831. DOI: 10.1161/STROKEAHA.115.008728.)

Key Words: cerebral ischemia ■ subarachnoid hemorrhage

Aneurysmal subarachnoid hemorrhage (SAH) is a disease with significant mortality and a high number of patients remaining in a dependent state.1,2 Clinical outcomes are influenced by patient characteristics (ie, initial neurological examination, age, comorbidities),3 hemorrhage severity (ie, amount and thickness of blood on initial computed tomography [CT]),4 and aneurysm treatment modality.5,6 Many studies have focused on the development of clinical and radiological scales, with the aim to predict the outcome, to guide treatment decisions, and to standardize patient assessment for medical research.7

The most commonly used SAH clinical grading scales are the Hunt and Hess8 and the World Federation of Neurosurgical Societies (WFNS) scales.9 Subarachnoid clot thickness has been assessed by the Fisher Scale8 or its modified version.10,11 Many other grading scales have been described, some of them adding supplementary factors to increase the prognostic accuracy for outcome or delayed cerebral ischemia (DCI) risk stratification.12,13 However, their complexity and only marginally enhanced prognostic ability makes them less likely to be adopted for routine use.13,14 Efforts exist to predict patients who would15 or would not16 develop DCI, triaging them in and...
out of monitoring units. A method to better predict DCI would be useful to standardize treatment protocols and research studies, and it would also help clinicians to early recognize and safely discharge patients with low risk of DCI, decreasing costs associated with DCI monitoring and complications associated with prolonged hospital length of stay.17

This analysis presents the external validation of a simple grading scale, the VASOGRADE (Figure 1), which was developed to predict DCI. The ingredients for the VASOGRADE were largely derived from de Rooij et al15 (ie, WFNS grade and modified Fisher scale9–11) and Crobeddu et al16 and validated in a large group of SAH patients.

### Material and Methods

Subjects for this study were selected from the Subarachnoid Hemorrhage International Trialists (SAHIT) data repository18,19 combined with a single center cohort of patients treated in a high-volume SAH center (Table I in the online-only Data Supplement). Specifically for this study, data from the SAHIT repository was derived from the phase II randomized placebo-controlled trial Effects of Acute Treatment With Pravastatin on Cerebral Vasospasm, Autoregulation, and Delayed Ischemic Deficits After Aneurysmal Subarachnoid Hemorrhage (STATIN trial)20; the phase 2b study, Clazosentan in Preventing the Occurrence of Cerebral Vasospasm Following an Aneurysmal Subarachnoid Hemorrhage (CONSCIOUS-1)21; and the phase II randomized, double-blind, placebo-controlled trial Acute Systemic Erythropoietin Therapy to Reduce Delayed Ischemic Deficits Following Aneurysmal Subarachnoid Hemorrhage (EPO trial).22

The STATIN trial cohort was enrolled in a single center in the United Kingdom in 2004 and compared the effect of daily oral pravastatin (40 mg/d for ≤14 days) versus placebo in the incidence, duration, and severity of angiographic cerebral vasospasm and duration of impaired autoregulation detected by transcranial Doppler.20

The EPO trial cohort was enrolled in a single center in United Kingdom and compared the effect of intravenous erythropoietin (30000 U every 48 hours for a total of 90000 U versus placebo) on the development of angiographic vasospasm detected by transcranial Doppler ultrasonography.22

Baseline individual data, such as age, sex, medical history, initial SAH clinical grade according to the WFNS, were collected in the trials and were also available in the SAHIT repository, which allowed us performing secondary data analysis to validate our grading system.19 Additionally, radiological features, including the Fisher grade on CT, the presence or absence of hydrocephalus, the presence or absence of intraventricular hemorrhage (IVH), and aneurysm location, were also available. The presence or absence of IVH was used to covert retrospectively the Fisher scale4 into the modified Fisher version,10 which was used in our grading system.

Finally, consecutive SAH patients managed between January 2012 and June 2013 at St Michael’s Hospital, Toronto, Canada, were gathered with the above-mentioned cohorts. The St Michael’s Hospital baseline and radiological data on adult patients (older than age 18 years) were retrospectively collected for quality assurance purposes. The clinical severity was classified according to the WFNS score graded after the initial resuscitation. The initial CT was graded

### Table 1. Distribution of Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Green (N=373; 53.8%)</th>
<th>Yellow (N=115; 16.6%)</th>
<th>Red (N=205; 29.6)</th>
<th>Total (N=693)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>51.92±11.33</td>
<td>54.63±13.52</td>
<td>54.01±11.60</td>
<td>54.01±11.60</td>
</tr>
<tr>
<td>Female</td>
<td>257 (68.9)</td>
<td>84 (73.0)</td>
<td>136 (66.3)</td>
<td>477 (68.8)</td>
</tr>
<tr>
<td>WFNS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>221 (59.2)</td>
<td>75 (65.2)</td>
<td>…</td>
<td>296 (42.7)</td>
</tr>
<tr>
<td>2</td>
<td>152 (40.8)</td>
<td>29 (25.2)</td>
<td>…</td>
<td>181 (26.1)</td>
</tr>
<tr>
<td>3</td>
<td>…</td>
<td>11 (9.6)</td>
<td>…</td>
<td>11 (1.6)</td>
</tr>
<tr>
<td>4</td>
<td>…</td>
<td>…</td>
<td>139 (67.8)</td>
<td>139 (20.1)</td>
</tr>
<tr>
<td>5</td>
<td>…</td>
<td>…</td>
<td>66 (32.2)</td>
<td>66 (9.5)</td>
</tr>
<tr>
<td>Modified Fisher</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>90 (24.1)</td>
<td>…</td>
<td>16 (7.8)</td>
<td>106 (15.3)</td>
</tr>
<tr>
<td>2</td>
<td>283 (75.9)</td>
<td>…</td>
<td>124 (60.5)</td>
<td>407 (58.7)</td>
</tr>
<tr>
<td>3</td>
<td>…</td>
<td>85 (73.9)</td>
<td>23 (11.2)</td>
<td>108 (15.6)</td>
</tr>
<tr>
<td>4</td>
<td>…</td>
<td>30 (26.1)</td>
<td>42 (20.5)</td>
<td>72 (10.4)</td>
</tr>
<tr>
<td>Aneurysm location</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior</td>
<td>255 (68.4)</td>
<td>81 (70.4)</td>
<td>139 (67.8)</td>
<td>475 (69.3)</td>
</tr>
<tr>
<td>Posterior</td>
<td>103 (27.6)</td>
<td>53 (46.1)</td>
<td>54 (26.3)</td>
<td>210 (30.7)</td>
</tr>
<tr>
<td>Repair modality</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coiling</td>
<td>187 (50.1)</td>
<td>76 (66.1)</td>
<td>98 (47.8)</td>
<td>361 (54.9)</td>
</tr>
<tr>
<td>Clipping</td>
<td>182 (48.8)</td>
<td>33 (28.7)</td>
<td>83 (40.5)</td>
<td>298 (45.1)</td>
</tr>
<tr>
<td>DCI: present</td>
<td>57 (15.3)</td>
<td>22 (19.1)</td>
<td>72 (36.6)</td>
<td>151 (22.0)</td>
</tr>
</tbody>
</table>

*Table excludes missing data, and figures in parenthesis are percentages. DCI indicates delayed cerebral ischemia; and WFNS, World Federation of Neurosurgical Societies scale.*
according to the modified Fisher Scale\textsuperscript{10,11} by one of the authors blinded to the clinical evolution. Our group established the VASOGRADE during the development of our institutional SAH protocol. The main idea was to create an ease-to-remember, ease-to-use, and practical grading system that would allow clinicians to tailor monitoring strategies and treatment aggressiveness according to the different grades. The VASOGRADE derived from previously published studies by de Rooij et al\textsuperscript{15} and Crobeddu et al\textsuperscript{16} which showed clinical condition on admission and the amount of blood on CT (associated with age), as the major risk factors for DCI and DCI-related cerebral infarction. This analysis represents, therefore, the external validation of de Rooij et al\textsuperscript{15} in a large and diverse sample of SAH patients. Thereafter, patients were retrospectively divided into 3 VASOGRADE categories according to their admission WFNS and modified Fisher scales (Figure 1). DCI was the primary outcome, and it was similarly defined across all studies (for additional details, please refer to online-only Data Supplement), which is consistent with the definition proposed by an international panel of experts.\textsuperscript{23}

**Statistical Analysis**

The distribution of baseline variables according to VASOGRADE by cross tabulation and the relationship between VASOGRADE and DCI by fitting a logistic regression model was evaluated. Because the patients originated from multiple studies, a potential presence of a study effect was assessed by performing a likelihood ratio test comparing the regression model fitted with and without a dummy variable for study. We assessed the performance of VASOGRADE by calculating the area under the receiver operator characteristics curve for discrimination and by plots of observed versus predicted probabilities of DCI for calibration. The value of the VASOGRADE as a screening tool was identified for patients at low risk of DCI by computing the sensitivity, specificity, and likelihood ratios for cut-point value of VASOGRADE-Green versus VASOGRADE-Yellow and Red. In case of missing data, we imputed data using multiple imputations by chained equations to generate 10 data sets with the imputation model based on all variables in the data set. The first imputed data set was used for the analysis. Statistical significance was set at 5% significance level. The analysis was performed on Stata version 12 platform (Stata Corporation, College Station, TX).

**Results**

A total of 746 patients with acute SAH were included in the final analysis, which included 413 patients from CONSCIOUS-1 trial\textsuperscript{24}; 160 patients from EPO-Statin trials\textsuperscript{20,22}; and 173 patients from our St Michael’s Hospital cohort (Table I in the online-only Data Supplement).

Baseline characteristics of the 746 patients are reported in Table I. The average age was 53±12 years, with most of them being women (69%). Most patients were classified as VASOGRADE-Green (54%), followed by VASOGRADE-Red (30%) and VASOGRADE-Yellow (16%). The majority of patients had anterior circulation aneurysms (69%), and endovascular coiling was the modality of aneurysm repair in 55% of cases.

DCI was present in 151 patients (22% of the entire cohort). The proportion of patients in the VASOGRADE-Green, -Yellow, and -Red groups who developed DCI was 15%, 19%, and 37%, respectively. Compared with VASOGRADE-Green, patients who were classified as VASOGRADE-Yellow had a tendency for a higher risk for DCI (odds ratio \([OR]\), 1.31; 95% CI, 0.77–2.23), whereas patients who were classified as VASOGRADE-Red had a significant increased risk for development of DCI (OR, 3.05; 95% CI, 2.07–4.50). We found no significant study effect on the relationship between the VASOGRADE and DCI (likelihood ratio test \(P\) value=0.19).

The area under the receiver operator characteristics curve of VASOGRADE for predicting the presence of DCI was 0.63 (95% CI, 0.58–0.68; Figure 2). The agreement between observed and predicted probabilities of DCI was presented in Figure 3. The VASOGRADE systematically underestimated risk of DCI, especially for patients at the higher end of predicted probability. Table 2 shows sensitivity, specificity, and likelihood ratios for the different cut points of the VASOGRADE categories. VASOGRADE-Red has a sensitivity of 49% and a specificity of 75% for identifying patients with DCI. Overall, DCI status was correctly identified in 69% of patients.

The proportion of missing data was 8.2%. The results with solely the complete data were comparable to the analysis with imputed missing data.

**Discussion**

In this study, we externally validated a grading system, the VASOGRADE, a simple, semiquantitative, 3-category scale, which was developed as an ease-to-remember, ease-to-use, and practical grading system to predict the development of DCI.\textsuperscript{24} The VASOGRADE derived from the studies published by de Rooij et al\textsuperscript{15} and Crobeddu et al,\textsuperscript{16} who developed risk charts to predict who would or would not develop DCI, respectively, combining the WFNS\textsuperscript{8} and the modified Fisher scales.\textsuperscript{10,11}

Grading scales play a major role in the initial assessment and management of patients having acute brain injury. Specifically to SAH, there are more than a dozen described scales, which are used for different purposes, such as prognostication, prediction of angiographic vasospasm, or development of DCI.\textsuperscript{14} Widely used prognostic scales in the setting of SAH include the Glasgow coma scale (which was originally described for traumatic brain injury),\textsuperscript{25} the Hunt-Hess,\textsuperscript{5} and WFNS.\textsuperscript{9} Other less commonly used scales derived from the Glasgow coma scale or the WFNS, such as the Prognosis on Admission of Aneurysmal Subarachnoid Hemorrhage scale\textsuperscript{26} and the modified WFNS\textsuperscript{27} respectively, have been described to predict patients’ outcome. The Prognosis on Admission of Aneurysmal Subarachnoid Hemorrhage and WFNS scales have similar performance for outcome prediction.\textsuperscript{26} The modified WFNS\textsuperscript{27} adds 7 variables

![Figure 2. The VASOGRADE area under receiver operator characteristics (ROC) curve (AUC) for delayed cerebral ischemia (DCI) discrimination.](http://stroke.ahajournals.org/).
to the WFNS (ie, age, history of hypertension, systolic blood pressure at admission, ruptured aneurysm location and size, blood clot thickness on computed tomographic scans, and angiographic vasospasm at admission), leading to better outcome prediction. However, these additional factors may not be readily available, which adds more complexity to the scale calculation, making it less likely to be adopted for routine use.

Other studies have described the association between CT features and the risk of angiographic vasospasm or DCI. Fisher et al described the relationship between the thickness of blood layer in the basal cisterns and the development of angiographic vasospasm. Four groups arose from the original cohort of Fisher’s patients: no subarachnoid blood (Group 1), diffuse subarachnoid blood (Group 2), clot or thick layer (Group 3), and diffuse or none subarachnoid blood associated with intraparenchymal or IVH (Group 4). Only patients in the Group 3 (23 out of 24 patients) developed severe angiographic vasospasm by conventional angiography associated with neurological symptoms. The patient in Group 3 who presented the smallest clot associated with severe vasospasm had a 5×3 mm clots in the Sylvian fissure(s). Therefore, the authors concluded that patients with no blood in the initial CT or with a thin layer (<1 mm) present a low risk of severe angiographic vasospasm, whereas patients with large clots (>5×3 mm) or layers of blood ≥1 mm in fissures or vertical cisterns have high risk of angiographic vasospasm because they developed severe spasm in 96% of the cases (23/24 patients). It is important to note that the mm measurements are not actual clot thicknesses in vivo. The Fisher scale was modified by Claassen et al, who described the role of IVH in the development of DCI, adding the concept that IVH in both lateral ventricles is an independent risk factor for the development of DCI (OR, 4.1; 95% CI, 1.7–9.8). The risk is greatest when there are subarachnoid blood filling completely any cistern or fissure and IVH in both lateral ventricles.

Age, the third main independent factor for the development of DCI, was left out of our grading system. Although age is well described as an independent predictor of outcome and advanced age has been consistently associated with lower incidence of angiographic vasospasm and DCI aging is inversely related to favorable outcomes. Older age is associated with larger subarachnoid clot volume, and elderly patients (>60 years) have significant increased risk of poor outcome because of higher rates of medical complications. The main reason age was not included in our grading scale.

Other groups have developed risk charts for early DCI prediction, with similar results. Crobeddu et al developed a predictive model where age ≥68 years and WFNS I-III and Modified Fisher 1 to 2 was 100% specific for the absence of DCI. Although highly specific for the absence of DCI, the model was applicable in only 4% (12/307) of their sample. Another recent study published by de Rooij et al found the same predictors (clinical condition on admission, amount of cisternal and amount of intraventricular blood on CT, and age) as the main factors associated with the risk of DCI. In their model, the risk of developing DCI-related infarction was lowest (12%) in older patients with good clinical condition on admission (WFNS I) and no or thin layer of subarachnoid blood. The highest risk of DCI-related infarction (61%) was found in the group of young patients (<55 years) with poor grade on admission (WFNS V) and thick layer of subarachnoid or intraventricular blood. Interestingly, this model described by de Rooij et al had a similar area under the receiver operating characteristic curve (0.63). Therefore, the VASOGRADE results validated the risk chart developed by de Rooij et al, in a large and diverse sample of SAH patients, in a different setting, which combines multiple healthcare systems. In total, 746 patients with acute SAH enrolled from >50 sites worldwide in 4 different data sets were included in our analysis (Table I in the online-only Data Supplement).

We foresee multiple practical clinical applications for the de Rooij et al risk chart and the VASOGRADE, such as the following:

a. Predict DCI risk for tailoring monitoring strategies: Imaging is one of the most costly interventions related to the total medical costs in the management of SAH patients. A possible way to decrease the costs associated to imaging usage would be to reduce or avoid unnecessary imaging surveillance. Low risk patients (VASOGRADE-Green) may be monitored less aggressively, probably only with frequent neurological examination. Patients predicted to have higher risk of DCI

Table 2. Sensitivity, Specificity, and Likelihood Ratios of VASOGRADE

<table>
<thead>
<tr>
<th>VASOGRADE</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>Correctly Classified</th>
<th>LR+</th>
<th>LR−</th>
</tr>
</thead>
<tbody>
<tr>
<td>Green</td>
<td>100</td>
<td>0.00</td>
<td>21.6</td>
<td>1</td>
<td>…</td>
</tr>
<tr>
<td>Yellow</td>
<td>63.5</td>
<td>57.6</td>
<td>58.9</td>
<td>1.49</td>
<td>0.63</td>
</tr>
<tr>
<td>Red</td>
<td>49.1</td>
<td>74.7</td>
<td>69.2</td>
<td>1.94</td>
<td>0.68</td>
</tr>
</tbody>
</table>

LR indicates likelihood ratio.
(VASOGRADE-Yellow and -Red) should probably undergo frequent neurological examination (every hour) by bedside nurses combined with other types of neurological surveillance (eg, transcranial Doppler, CT perfusion, continuous electroencephalography).\textsuperscript{36} 

b. Decision on disposition and length of stay: Two thirds of the total direct medical costs generated during a 1-year follow-up in patients with aneurysmal SAH is because of hospital inpatient days.\textsuperscript{17} Only decreasing the average length of stay, especially in the ICU, can reduce these costs. Because of high risk of DCI, VASOGRADE-Yellow and -Red patients should probably be admitted to a step-down or intensive care unit, respectively, for \(\approx14\) days,\textsuperscript{24,36} whereas VASOGRADE-Green patients, especially if older and without SAH-related medical complications,\textsuperscript{16} may be discharged to a regular ward earlier, by the end of the first week.\textsuperscript{25,36} 
c. Treatment aggressiveness: VASOGRADE-Red patients are at high risk of developing cardiac and pulmonary complications; therefore, they may benefit from invasive hemodynamic monitoring (eg, transpulmonary thermodilution).\textsuperscript{37} Additionally, aggressive strategies to avoid hypovolemia should be implemented (eg, goal-directed therapy, daily sodium balance, daily weight, prophylactic use of fluidcortisone) in this patient population because hypovolemia increases even further the risk of DCI.\textsuperscript{37} Other strategies, such as early mobilization, the prophylactic use of antifibrinolytics (to prevent ultraearly rebleeding), and fluidcortisone (to avoid hypovolemia and hyponatremia), could take de Rooij et al\textsuperscript{35} or the VASOGRADE into account.

Although the VASOGRADE was developed and validated for DCI prediction and risk stratification, it could be validated for different purposes, such as prognostication, or use to improve communication and consistency among healthcare providers looking after SAH patients. Additional to this practical application of stratifying risk of DCI after SAH, which could allow for earlier intensive care discharge and less aggressive DCI monitoring, the VASOGRADE could potentially be used to standardize treatment protocols and enrollment criteria for clinical research.\textsuperscript{24,36}

Study Limitations

The first limitation is the use of a data set for secondary data analysis. The main limitation of secondary data analysis is that the data set was not designed to answer the specific question the study is trying to answer. Therefore, we did not have control over how the variables were collected and recorded (eg, how the CT scans were analyzed and classified according to modified Fisher score), the patients included (inclusion and exclusion criteria defined by each specific trial), and the integrity of the data (Table II in the online-only Data Supplement).\textsuperscript{38} 

Second, the secondary use of data from randomized clinical trials cares the limitation of results generalizability because randomized clinical trials usually enroll only a small fraction of screened patients. Additionally, the inclusion of a placebo group could add a confounding factor into the model, especially whether the intervention was positive. For example, the use of a placebo group of a nimodipine treatment trial after SAH would be problematic because this therapy is well known to improve long-term outcome. This approach could increase the number of events depending on how the exposure and outcome measures were defined.

Finally, the use of qualitative, categorical classification criteria, such as the Fisher and modified Fisher scores, carries the considerable risk of interobserver variability in the interpretation of CT scans. Ibrahim et al using the data of 413 patients enrolled in the CONSCIOUS-1 trial showed only fair to moderate interobserver agreement between reviewers when determining the extent of SAH (by classifying SAH as thick or thin and diffuse or localized—kappa 0.41; 95% CI 0.33–0.49).\textsuperscript{39}

Conclusions

The VASOGRADE is a simple grading scale that combines the WFNS and the modified Fisher score, allowing DCI risk stratification on presentation after SAH. The VASOGRADE results validated previously published risk charts in a large and diverse sample of SAH patients, and it could help to select patients who are at high risk for the development of DCI, as well as standardize treatment protocols and research studies.

Appendix

The SAHIT Collaborators

Nima Emtnan, MD (Department of Neurosurgery, Medical Faculty Heinrich Heine University, Düsseldorf). Daniel Hanggi, MD (Department of Neurosurgery, Medical Faculty Heinrich Heine University, Düsseldorf). David Hasan, MD (University of Iowa). S. Claiborne Johnston, MD, PhD (University of Texas, Austin). Peter Le Roux, MD (MLHC Brain & Spine Center at Lankenau Medical Center). Stephan Mayer, MD (Mount Sinai University). Andrew Molyneux, MD (Oxford University). Adam Noble, PhD (Kings College London). Audrey Quinn, MD (The General Infirmary, Leeds). Thomas Schenk, PhD (Friedrich-Alexander University, Erlangen). Julian Spears, MD (St. Michael’s Hospital, University of Toronto). Michael Todd, MD (University of Iowa). JamesTorner, PhD (University of Iowa). Ming Tseng, MD (Medicines and Healthcare products Regulatory Agency). William van den Bergh, MD (University Medical Center Groningen). Mervyn D.I. Vergouwen, MD, PhD (University Medical Center Utrecht). George K.C. Wong, MD (Chinese University of Hong Kong). Dr Ming-Yuan Tseng (Department of Neurosurgery, Addenbrooke’s Hospital, University of Cambridge).

Sources of Funding

Actelion Pharmaceuticals, Ltd, was the sponsor of the CONSCIOUS-1 trial; the company provided the authors with the trial data set, but had no role in this analysis nor the development of the article. The data analysis and writing are the work of the authors. Also, we acknowledge the support through research funding provided by the Bitove Foundation.

Disclosures

Dr Macdonald receives grant support from the Physicians Services Incorporated Foundation, Brain Aneurysm Foundation, Canadian Institutes for Health Research, and the Heart and Stroke Foundation of Canada and is Chief Scientific Officer of Edge Therapeutics, Inc. The other authors report no conflicts.

References


The VASOGRADE: A Simple Grading Scale for Prediction of Delayed Cerebral Ischemia After Subarachnoid Hemorrhage
Airton Leonardo de Oliveira Manoel, Blessing N. Jaja, Menno R. Germans, Han Yan, Winnie Qian, Ekaterina Kouzmina, Tom R. Marotta, David Turkel-Parrella, Tom A. Schweizer and R. Loch Macdonald

Stroke. 2015;46:1826-1831; originally published online May 14, 2015;
doi: 10.1161/STROKEAHA.115.008728
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2015 American Heart Association, Inc. All rights reserved.
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/46/7/1826

Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2015/05/14/STROKEAHA.115.008728.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/
## Supplemental Table I - Summary of Studies Characteristics

<table>
<thead>
<tr>
<th>Study</th>
<th>Study designed and intervention</th>
<th>Period of Enrollment</th>
<th>Number of patients</th>
<th>Number of centers</th>
<th>Number of countries</th>
<th>Radiological information</th>
<th>Baseline data</th>
</tr>
</thead>
</table>
| CONSCIOUS 1            | Phase 2b randomized double-blind, placebo-controlled, dose-finding study of clazosentan (1, 5, or 15 mg/h [1:1:1:1]) | January 2005 and March 2006 | 413                | 52                | 11                                     | • Clot thickness:  
  a) Thick diffuse  
  b) Thick local  
  c) Thin diffuse  
  d) Thin local  
  • Intraventricular hemorrhage  
  • Hydrocephalus  
  • Intraparenchymal hemorrhage | • Age, gender, medical history  
 • WFNS  
 • Treatment modality |
| EPO trial              | Phase II randomized, double-blind, placebo-controlled trial of intravenous erythropoietin (30,000 U) or placebo every 48 hours for a total of 90,000 U | April 2005 and April 2006 | 80                 | 1                 | 1                                      | • Fisher grade on CT  
• Presence of hydrocephalus or intraventricular hemorrhage  
 • Aneurysm location on cerebral angiography | • Age, gender, medical history  
 • WFNS  
 • Treatment modality |
| Statin trial           | Phase II randomized, double-blind, placebo-controlled trial of oral pravastatin (40 mg) or placebo daily for up to 14 days | 2004                       | 80                 | 1                 | 1                                      | • Fisher grade on CT  
• Presence of hydrocephalus or intraventricular hemorrhage  
 • Aneurysm location on cerebral angiography | • Age, gender, medical history  
 • WFNS |
| St. Michael’s Hospital cohort | Retrospective single center cohort                                                               | January 2012 and June 2013 | 173                | 1                 | 1                                      | • Fisher grade on CT  
• Presence of hydrocephalus or intraventricular hemorrhage  
 • Aneurysm location on cerebral angiography or CTA  
 • Intraparenchymal hemorrhage | • Age, gender, medical history  
 • WFNS  
 • Treatment modality |
Studies Definitions

A) CONSCIOUS 1

- **Exclusion criteria:** (1) SAH from a lesion other than a ruptured saccular aneurysm; (2) intraventricular or intracerebral blood in the absence of localized thick or diffuse SAH; (3) no or localized thin SAH on CT; (4) cerebral vasospasm on admission DSA; (5) hypotension (systolic blood pressure < 90 mm Hg) refractory to fluid therapy; (6) neurogenic pulmonary edema or cardiac failure requiring inotropic support; (7) severe or unstable concomitant condition or disease or chronic condition, which, in the opinion of the investigator, could affect assessment of the safety or efficacy of the study drug; (8) kidney (plasma creatinine ≥177 mol/L) and/or liver disease (total bilirubin > 51.3 µmol/L); and (9) prior cerebral damage on CT scan such as stroke (> 2 cm maximum diameter), traumatic brain injury, previously treated cerebral aneurysm, arterial venous malformation, or pre-existing cerebrovascular disorder that would affect diagnosis and evaluation of SAH. Women of childbearing potential had negative pretreatment serum pregnancy tests.

- **Delayed ischemic neurological deficit (DIND)** due to vasospasm within 14 days of SAH was defined as locally defined vasospasm on digital subtraction angiography (DSA) or transcranial Doppler associated with neurological worsening lasting for at least 2 hours. Neurological worsening was defined as a decline of at least 2 points in the modified Glasgow Coma Scale or an increase of at least 2 points in the abbreviated National Institutes of Health Stroke Scale. When patients were not evaluable neurologically, DIND was
defined as clinical signs of vasospasm (eg, unexplained fever, new neurological deficit) with vasospasm on DSA or transcranial Doppler or when a new hypodensity was observed on a postprocedure CT scan. Transcranial Doppler criteria for vasospasm were a Lindegaard ratio ≥ 3, a mean middle or anterior cerebral artery flow velocity ≥ 200 cm/s, or an increase > 50 cm/s/24 hours. Other causes of neurological worsening had to be excluded.

- **Computed Tomography:** CT scan was performed on admission within 48 hours of SAH, 24 to 48 hours after the aneurysm-securing procedure, 6 weeks after SAH, and whenever there was neurological worsening. The images were submitted to Perceptive and reviewed centrally by 2 independent, blinded reviewers.

- **Primary point:** moderate or severe vasospasm within 14 days of SAH.

- **Secondary end point:** morbidity and mortality within 6 weeks of SAH defined as at least one of the following: death within 6 weeks of SAH from any cause; new cerebral infarct within 6 weeks of SAH compared with postprocedure CT scan; delayed ischemic neurological deficit due to vasospasm within 14 days of SAH; and rescue therapy for DSA or transcranial Doppler vasospasm within 14 days of SAH.
B) Effects of Acute Treatment With Pravastatin on Cerebral Vasospasm, Autoregulation, and Delayed Ischemic Deficits After Aneurysmal Subarachnoid Hemorrhage

- **Exclusion criteria:** nonaneurysmal SAH, pregnancy, preictal statin therapy, and contraindications to statin use (e.g. history of liver or renal dysfunction or alanine aminotransferase [ALT] > 50 U/L).

- **Delayed ischemic deficit (DID)** was defined as development of focal neurological deficits or a drop in the Glasgow Coma Scale by ≥ 2 points. DID was also defined as vasospasm-related if it was associated with severe vasospasm on TCD. Other possible conditions causing neurological deterioration (e.g. hydrocephalus, intracerebral hemorrhage, surgical complications, metabolic abnormalities, or infection) were excluded by repeated imaging (CT, xenon CT, or cerebral angiography) and metabolic screening.

- **Computed Tomography:** Radiological information included the Fisher grade on CT, presence of hydrocephalus or intraventricular hemorrhage, and aneurysm location on cerebral angiography. There is no description or data on how the images were read.

- **Primary end points:** (1) incidence, severity, and duration of vasospasm on transcranial Doppler (TCD) indices; and (2) duration of impaired cerebral autoregulation.

- **Secondary end points:** (1) incidence of vasospasm-related DIDs; and (2) disability at discharge.
C) Acute systemic erythropoietin therapy to reduce delayed ischemic deficits following aneurysmal subarachnoid hemorrhage

- **Exclusion criteria:** nonaneurysmal SAH, uncontrolled hypertension (systolic blood pressure > 220 mm Hg) and history of malignancy or thromboembolism.

- **Delayed ischemic deficit (DID)** was defined as new focal neurological deficit or reduction in the Glasgow Coma Scale ≥ 2 points and were further categorized as vasospasm related if the criteria for vasospasm on TCD ultrasound were met. Other causes of neurological deterioration were excluded by repeated CT scanning, metabolic screening, and electroencephalographic monitoring.

- **Angiographic vasospasm** was defined according to TCD: 1) mean flow velocity > 120 cm/second (> 200 cm/second for severe vasospasm); 2) Lindegaard ratio > 3; and 3) an increase in mean flow velocity > 50cm/second within 24 hours.

- **Computed Tomography:** There is no description or data on how the images were read.

- **Primary end points:** 1) incidence, duration, and severity of vasospasm on TCD ultrasound; and 2) duration of impaired autoregulation on transient hyperemic response test (THRT).

- **Secondary end points:** 1) the incidence of DIDs; and 2) outcome at discharge and at 6 months.
D) St. Michael’ Hospital Series

- **Exclusion criteria:** traumatic SAH, benign perimesencephalic hemorrhage or SAH from a lesion other than a ruptured cerebral aneurysm (e.g. arterio-venous malformation).

- **Delayed cerebral ischemia (DCI) was defined according to the multidisciplinary research group:** “The occurrence of focal neurological impairment (such as hemiparesis, aphasia, apraxia, hemianopia, or neglect), or a decrease of at least 2 points on the Glasgow coma scale (either on the total score or on one of its individual components [eye, motor on either side, verbal]). This should last for at least 1 hour, is not apparent immediately after aneurysm occlusion, and cannot be attributed to other causes by means of clinical assessment, CT or MRI scanning of the brain, and appropriate laboratory studies”.

- **Computed Tomography:** The initial computed tomography was graded by a senior neuroradiologists according to the Modified Fisher Scale. They were unaware of the study and the grading took place for clinical purposes at the moment of patients’ hospital admission.

- **Primary point:** Not applicable.

- **Secondary end point:** Not applicable.
E) International panel of experts definition of delayed cerebral ischemia

- “The occurrence of focal neurological impairment (such as hemiparesis, aphasia, apraxia, hemianopia, or neglect), or a decrease of at least 2 points on the Glasgow coma scale (either on the total score or on one of its individual components [eye, motor on either side, verbal]). This should last for at least 1 hour, is not apparent immediately after aneurysm occlusion, and cannot be attributed to other causes by means of clinical assessment, CT or MRI scanning of the brain, and appropriate laboratory studies.”
### Supplemental Table II - Criteria for assessing the coverage and accuracy of a clinical database

<table>
<thead>
<tr>
<th>Quality Domain</th>
<th>Explanation</th>
<th>SAHIT Repository</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Coverage</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Representativeness</td>
<td>How well does the data source represent the population that it intends to?</td>
<td>Level 3 - Good evidence eligible population is representative</td>
</tr>
<tr>
<td>Completeness of recruitment</td>
<td>This feature measures the extent to which all eligible individuals have been included in the data collection scheme</td>
<td>Level 3 – Most (90-97%)</td>
</tr>
<tr>
<td>Variables included</td>
<td>What is the extent of the data collected on each individual? Are demographic, exposure, outcome, and confounding variables present?</td>
<td>Level 4 – condition, intervention, short and long-term outcome, major known confounders</td>
</tr>
<tr>
<td>Completeness of variables</td>
<td>What is the extent of the missing data?</td>
<td>Level 3 – Most (80 – 97%)</td>
</tr>
<tr>
<td><strong>Accuracy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Collection of raw data</td>
<td>Is the raw data collected or are aggregate averages collected?</td>
<td>Unknown</td>
</tr>
<tr>
<td>Explicit definitions</td>
<td>Are the variables explicitly defined?</td>
<td>Level 3 - Most (50-97%)</td>
</tr>
<tr>
<td>Explicit rules</td>
<td>Are there explicit rules for deciding how variables are recorded? For example, the timing of physiologic variables.</td>
<td>Level 3 - Most (50-97%)</td>
</tr>
<tr>
<td>Reliability of coding</td>
<td>Was the reliability of coded conditions and interventions tested?</td>
<td>Level 3 - Fair</td>
</tr>
<tr>
<td>Independence of observations</td>
<td>Was the data recorder blinded to patient outcome at the time the data were collected?</td>
<td>Level 4 - Independent observer blinded to intervention or not necessary as objective outcome (e.g. death or lab test)</td>
</tr>
<tr>
<td>Data validation</td>
<td>Were data validated using outside sources? Were there consistency checks?</td>
<td>Level 4 - Range and consistency checks plus external validation using alternative source</td>
</tr>
</tbody>
</table>

The coverage and accuracy improves from level 1 to level 4, level 1 meaning low coverage and low accuracy, while level 4 represents the highest possible coverage and accuracy. Level 2 and 3 are intermediate levels.