Quality of Life and Healthcare Resource Use Associated With Angiographic Vasospasm After Aneurysmal Subarachnoid Hemorrhage

R. Loch Macdonald, MD, PhD; Elke Hunsche, PhD; René Schüler, MSc; John Wlodarczyk, PhD; Stephan A. Mayer, MD

Background and Purpose—In this analysis of data from a large clinical trial in aneurysmal subarachnoid hemorrhage, the impact of angiographic vasospasm (aVSP) on specific patient outcomes and inpatient healthcare resource use was assessed.

Methods—This was a post hoc analysis of exploratory end points collected for 409 patients with aneurysmal subarachnoid hemorrhage in the Clazosentan to Overcome Neurological Ischemia and Infarction Occurring After Subarachnoid Hemorrhage (CONSCIOUS-1) trial. Central reviewers graded severity of aVSP as none, mild, moderate, or severe based on comparison of catheter angiograms obtained at baseline and 7 to 11 days after aneurysmal subarachnoid hemorrhage. Assessments of cognitive status (Mini-Mental State Examination) and patient-relevant outcomes (EuroQol total score and visual analog scale and Functional Status Examination) were administered at Week 12. The relationship between severity of aVSP and these end points as well as inpatient healthcare resource use (intensive care, general ward, and total hospital lengths of stay) was assessed using univariate and multivariate analyses.

Results—Cognitive status and all patient-relevant outcome measures varied significantly (P<0.0001) with severity of aVSP (mean for severe aVSP versus no aVSP, respectively: Mini-Mental State Examination, 18.0 versus 27.6; EuroQol total, 0.38 versus 0.74; EuroQol visual analog scale, 50.9 versus 75.5; Functional Status Examination, 20.5 versus 11.7). A significant inverse relationship with severity of aVSP was observed for total hospital days (P=0.008) and days in the intensive care unit (P<0.0001). On average, patients with severe aVSP stayed in the hospital 5 days longer than those with no aVSP.

Conclusions—Severe aVSP is associated with poor cognition, worse patient-relevant outcomes, and greater inpatient healthcare resource use. Future studies assessing new aVSP treatments should include outcome measures that evaluate quality of recovery among survivors. (Stroke. 2012;43:00-00.)

Key Words: endothelin receptor antagonist ■ hospitalization ■ length of stay ■ patient-relevant outcomes ■ vasospasm

Aneurysmal subarachnoid hemorrhage (aSAH) is a rare disease that imposes a heavy burden on patients and the healthcare system. Case mortality has declined over the past 4 decades, reflecting improvements in treatment strategies and diagnostic methods. Nevertheless, morbidity associated with aSAH remains high. Even among patients recovering sufficiently from aSAH to return home, up to 95% have cognitive impairments and report emotional complaints that interfere with everyday functioning.

Vasospasm has long been implicated as a leading cause of morbidity in patients with aSAH, including delayed ischemic neurological deficits and cerebral infarction. Alternative mechanisms to vasospasm, however, such as cortical spreading depolarization and inflammation have been proposed to contribute to the pathogenesis of delayed ischemic neurological deficits and infarction. Assessing the impact of vasospasm on morbidity is complicated by inconsistent definitions for symptomatic (ie, clinical) and angiographic vasospasm. Clinical or symptomatic vasospasm has been shown to increase the likelihood of subsequent cognitive impairment, restricted activities of daily living, and poor health-related quality of life (HRQoL) as well as increased...
healthcare resource use (HCRU).15 By contrast, the influence of angiographic vasospasm (aVSP) on clinical outcomes is under question following trials in which interventions reduced the incidence of aVSP without improving outcomes.16,17 No study to date has examined the association between patient outcomes other than the extended Glasgow Outcome Scale (GOSE) and severity of aVSP as opposed to its presence or absence.

The nonpeptide endothelin receptor antagonist clazosentan targets endothelin, a potent, long-lasting endogenous vasoconstrictor implicated in the pathogenesis of aVSP.18 In 2 Phase II clinical trials, clazosentan significantly reduced the incidence of aVSP (the primary end point) but there was no treatment effect on clinical outcome as measured by the GOSE,19,20 although neither trial was powered to detect a treatment effect on global functional outcome. Exploratory cognitive status (Mini-Mental State Examination [MMSE]), patient-relevant outcomes (EuroQol [EQ-5D] total score and visual analog scale [VAS] and Functional Status Examination [FSE]) and inpatient HCRU data were collected in Clazosentan to Overcome Neurological Ischemia and Infarction Occurring After Subarachnoid Hemorrhage (CONSCIOUS-1).

The present post hoc analysis takes advantage of the opportunity presented by this large data set to assess the strength of association between severity of aVSP and patient cognition, HRQoL (EQ-5D total score and VAS), functional status, and inpatient HCRU.

**Methods**

**CONSCIOUS-1 Study Design**

The protocol of CONSCIOUS-1 has been reported elsewhere.19 This was an international, multicenter, randomized, double-blind, placebo-controlled, dose-finding study of clazosentan for the prevention of aVSP after aSAH treated by surgical clipping or endovascular coiling. Eligible patients were 18 to 70 years old with aSAH due to an aneurysm securing procedure and aneurysm location in the anterior communicating arteries, anterior communicating and/or supraclinoid internal carotid and/or vertebral arteries. The overall severity of aVSP was quantified in proximal cerebral arterial diameter on DSA between baseline and Day 7 to 11, classified as none/mild (0%–33%), moderate (34%–66%), or severe (67%–100%). Sites provided DSA that met image acquisition guidelines to ensure adequate image quality and standardization of angiographic images. DSA images were imported into image analysis software (Alicia; Parexel International Corp, Waltham, MA) and artery diameters measured and adjusted for magnification and technique variations by standardization to metal rings taped to the patient’s head and to the diameters of the extracranial internal carotid and vertebral arteries. The overall severity of aVSP was centrally assessed by 2 independent, blinded reviewers and categorized as none (1 or 2 segments with mild vasospasm), mild (2 or 3 segments with mild vasospasm and/or 1 segment with moderate vasospasm), moderate (2 segments with moderate vasospasm and/or 1 or 2 segments with severe vasospasm), or severe (≥3 segments with severe vasospasm). Disagreements between reviewers were adjudicated by a third reviewer.

Clinical outcome in CONSCIOUS-1 was measured by the GOSE assessed during a centrally administered telephone interview at Week 12 post-aSAH.

Cognitive, Patient-Relevant Outcome, and HCRU End Points

In addition to GOSE, further patient outcomes were recorded 12 weeks after aSAH. Cognitive status was assessed with the MMSE, which has been shown to be a sensitive measure of the effects of aSAH on cognitive functioning.23 The MMSE was completed at the study site by the investigator or a study nurse. Health status was measured by the EQ-5D, a generic instrument that assesses 5 domains of HRQoL.24 EQ-5D total scores were derived from these domains using valuations established for the United Kingdom with the worst-case utility set at −0.24.26 In addition, the EQ-5D records the respondent’s assessment of their overall health status on a 20-cm VAS anchored on 0 (worst imaginable health) and 100 (best imaginable health). The EQ-5D was completed by the patient at the study site at Week 12.

The FSE,27 which captures functional status domains important to aSAH survivors,28 was also recorded. The FSE was administered at the same centralized telephone interview as the GOSE at Week 12.

Inpatient HCRU end points included duration of hospitalization, categorized as days in the intensive care unit (ICU) or general ward, and total hospital days (ICU and general ward days combined). In addition, each patient’s disposition 12 weeks after aSAH was recorded, scored as fully independent, partially independent, in rehabilitation ward/facility, in nursing home, in long-term care facility/assisted living facility, or other (including patients who died or transferred to another hospital).

**Statistics**

Missing values of the MMSE, EQ-5D total, EQ-5D VAS, and FSE scores were imputed using GOSE scores. The validity of this approach was assessed by Kruskal-Wallis tests for differences in these measures across the 8 GOSE categories with no imputation of missing values. Results supported imputation of missing MMSE, EQ-5D total, EQ-5D VAS, or FSE data based on GOSE score, which was available for all patients. Accordingly, when a subject was living and not in a vegetative state, missing values of these end points were imputed by assigning the mean of their nonmissing results in that GOSE category. For dead or vegetative subjects, the worst-case score was assigned for the outcome: 0 for the MMSE and EQ-5D total score, and −0.24 for the EQ-5D total score.

If a patient had missing information on ICU or regular ward length of stay (LOS), these were replaced with the mean of the nonmissing LOS results in the GOSE category to which that subject belonged. Patients whose disposition was missing at Week 12 because they died were allocated a disposition of other; otherwise, missing disposition was not imputed.

The mean and 95% CI were used to summarize patient outcomes and hospital LOS within aVSP groups. A nonparametric test (Kruskal-Wallis) was used initially to test for differences in MMSE, EQ-5D total, EQ-5D VAS, and FSE scores across the 4 categories of severity of aVSP.

To evaluate whether or not severity of aVSP influenced HCRU, Kruskal-Wallis tests were performed on LOS in the ICU, general ward, and total hospital days across the 4 categories of severity of aVSP. Kruskal-Wallis tests were also used to assess the impact of GOSE score on the same measures of LOS.

Linear regression models were used to compare MMSE, EQ-5D total, EQ-5D VAS, and FSE scores across groups after adjusting for baseline age and WFNS grade. LOS data were log transformed before modeling. Univariate and multivariate methods produced similar results. In a sensitivity analysis, the model for MMSE also was adjusted for aneurysm securing procedure and aneurysm location. All statistical analyses were performed using SAS Version 9.1.2 (SAS Institute Inc). The distribution of subjects’ need for care and institutionalization pre-aSAH and at Week 12 was tabulated (no statistical tests were performed).

**Results**

Of 413 patients randomized in CONSCIOUS-1, 409 received at least 1 dose of study medication and were included in this
analysis. Baseline characteristics stratified by severity of aVSP are presented in Table 1. Forty-one percent of patients had no aVSP, whereas 12%, 29%, and 18% had mild, moderate, and severe aVSP, respectively. Patients with aVSP were similar in age, sex ratio, and ethnicity to those who did not have aVSP. However, patients with severe and moderate aVSP were more likely to be WFNS Grade IV than patients with no aVSP (38% and 28% versus 15%, respectively). Mean Glasgow Coma Scale scores also were lower among patients who developed severe aVSP than among those with no aVSP (12.2; 95% CI, 11.5–13.0 versus 13.7; 95% CI, 13.4–14.1, respectively).

MMSE, EQ-5D total, EQ-5D VAS, and FSE scores all differed significantly (P<0.0001) across GOSE categories (Table 2). Although the relationship was not always linear, in general these scores worsened with worsening GOSE, supporting the imputation of missing values based on GOSE score for analyses of impact of severity of aVSP on patient outcomes. Values were missing for 18%, 16%, 18%, and 4% of patients on the MMSE, EQ-5D total, EQ-5D VAS, and FSE, respectively. The majority of missing patient outcomes data occurred in patients who had severe disability and were unable to cooperate with testing.

Cognitive status (MMSE) and all 3 patient-relevant measures (EQ-5D total, EQ-5D VAS, and FSE) differed significantly (P<0.0001) across 4 categories of aVSP. Although mean MMSE was similar in patients with moderate, mild, or no aVSP (Figure 1A), the score was markedly lower in patients with severe aVSP (mean, 18.0; 95% CI, 15.0–21.0 versus 27.6; 95% CI, 26.7–28.4 in patients with no aVSP). This difference remained significant (P<0.0001) after adjusting for age and WFNS grade in the multivariate analysis. Additional adjustment for aneurysm securing procedure and aneurysm location made no material difference to the results (data not shown).

Health status measured by the EQ-5D total score did not differ in patients with mild and no aVSP, but moderate and severe aVSP were associated with decreasing health utility (Figure 1B). Patients with severe aVSP had a mean EQ-5D total score of 0.38 (95% CI, 0.28–0.49), approximately half the health utility of patients with no aVSP (0.74; 95% CI, 0.71–0.78). Health utility was also reduced in patients with moderate aVSP (0.65; 95% CI, 0.59–0.70). These results remained significant after adjustment for age and WFNS grade (P<0.0001 and P=0.034 for patients with severe and moderate aVSP, respectively, versus those with no aVSP). Similar trends were observed for health status scored on the EQ-5D VAS (Figure 1C); on average, patients with severe aVSP rated their health state an absolute 25% lower than those with no aVSP (50.9; 95% CI, 42.9–58.8 versus 75.5; 95% CI, 72.7–78.4, respectively). After adjusting for age and WFNS grade, EQ-5D VAS scores were lower in patients with severe aVSP than in those with no aVSP (P<0.0001) but did not differ significantly between patients with moderate, mild or no aVSP.

Functional status measured by FSE scores was similar in the mild- and no-aVSP groups but worsened with a moderate or severe aVSP (Figure 1D). Patients with severe aVSP had approximately twice the mean FSE score (indicating worse functioning) of those with no aVSP (50.9; 95% CI, 42.9–58.8 versus 27.6; 95% CI, 26.7–28.4). This difference remained significant (P<0.0001) after adjusting for age and WFNS grade in the multivariate analysis. Additional adjustment for aneurysm securing procedure and

### Table 1. Baseline Characteristics Stratified by Severity of aVSP

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Severe aVSP</th>
<th>Moderate aVSP</th>
<th>Mild aVSP</th>
<th>No aVSP</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>73</td>
<td>117</td>
<td>50</td>
<td>169</td>
<td>409</td>
</tr>
<tr>
<td>Age, y, mean (SD)</td>
<td>51.4 (11.0)</td>
<td>51.4 (9.9)</td>
<td>49.8 (10.1)</td>
<td>51.2 (11.4)</td>
<td>51.1 (10.7)</td>
</tr>
<tr>
<td>Male, no. (%)</td>
<td>18 (25)</td>
<td>26 (22)</td>
<td>15 (30)</td>
<td>61 (36)</td>
<td>120 (29)</td>
</tr>
<tr>
<td>Race, no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>68 (93)</td>
<td>101 (86)</td>
<td>44 (88)</td>
<td>152 (90)</td>
<td>365 (89)</td>
</tr>
<tr>
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<td>11 (9)</td>
<td>3 (6)</td>
<td>8 (5)</td>
<td>26 (6)</td>
</tr>
<tr>
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<td>1 (1)</td>
<td>3 (3)</td>
<td>...</td>
<td>2 (1)</td>
<td>6 (1)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>...</td>
<td>1 (1)</td>
<td>2 (4)</td>
<td>4 (2)</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Other</td>
<td>...</td>
<td>1 (1)</td>
<td>1 (2)</td>
<td>3 (2)</td>
<td>5 (1)</td>
</tr>
<tr>
<td>WFNS grade, no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>21 (29)</td>
<td>51 (44)</td>
<td>24 (48)</td>
<td>86 (51)</td>
<td>182 (45)</td>
</tr>
<tr>
<td>II</td>
<td>20 (27)</td>
<td>29 (25)</td>
<td>14 (28)</td>
<td>54 (32)</td>
<td>117 (29)</td>
</tr>
<tr>
<td>III</td>
<td>3 (4)</td>
<td>2 (2)</td>
<td>3 (6)</td>
<td>4 (2)</td>
<td>12 (3)</td>
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<tr>
<td>IV</td>
<td>28 (38)</td>
<td>33 (28)</td>
<td>9 (18)</td>
<td>25 (15)</td>
<td>95 (23)</td>
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<tr>
<td>V</td>
<td>1 (1)</td>
<td>2 (2)</td>
<td>...</td>
<td>...</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Glasgow Coma Scale</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No.</td>
<td>72</td>
<td>114</td>
<td>50</td>
<td>168</td>
<td>404</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>12.2 (3.1)</td>
<td>13.1 (2.7)</td>
<td>13.5 (2.4)</td>
<td>13.7 (2.1)</td>
<td>13.3 (2.5)</td>
</tr>
</tbody>
</table>

aVSP indicates angiographic vasospasm; WFNS, World Federation of Neurological Surgeons.
Patients who died had shorter hospital stays, whereas those in a vegetative state had long (and highly variable) stays. Although length of general ward stays did not track GOSE scores linearly for the remaining GOSE categories, length of ICU stays decreased in general with improving GOSE score. As a result, mean total hospital days decreased as GOSE score improved from lower severe disability to upper good recovery (29.8 days; 95% CI, 26.3–33.3 days versus 15.6 days; 95% CI, 13.4–17.8 days, respectively). These results supported the imputation of missing values based on GOSE score for analyses of impact of severity of aVSP on LOS.

A significant relationship with severity of aVSP was observed for LOS in the ICU (P<0.0001) but not in the general ward (P=0.062; Figure 2). After adjustment for age and WFNS grade, ICU LOS was longer in patients with severe or moderate aVSP (P=0.001 and P=0.0005, respectively) versus those with no aVSP but did not differ significantly between patients with mild or no aVSP. Because ICU stays were longer than general ward stays, the trend for ICU stays outweighed the lack of trend for ward stays when both were combined, resulting in a significant relationship between severity of aVSP and total hospital days (P=0.008).

On average, patients with severe aVSP stayed in the hospital 5 days longer than those with no aVSP (24.5; 95% CI, 20.7–28.4 versus 19.8; 95% CI, 18.1–21.6, respectively). Duration of hospitalization was comparable between patients with mild and no aVSP.

Requirement for care and institutionalization at 12 weeks was associated with severity of aVSP (Supplemental Table I; http://stroke.ahajournals.org). Among patients with no aVSP, 49% of patients were fully independent at Week 12. In contrast, only 10% of subjects in the severe aVSP group were fully independent at Week 12.

### Discussion

In this post hoc analysis of exploratory end points from the CONSCIOUS-1 trial, the severity of aVSP was significantly associated with cognitive status (MMSE), health utility, and overall health status (EQ-5D total and VAS) and functional status (FSE) 12 weeks after aSAH. Worse patient outcomes as measured by these 4 end points was most evident among patients with severe aVSP, and to a lesser extent moderate aVSP, with no apparent differences between patients with mild and no aVSP. These results were not affected by adjustment for age and WFNS grade. Increasing severity of aVSP was also associated with increased ICU and total hospital stays.
hospital LOS. These findings suggest that as mortality continues to fall after aSAH,2 outcome measures that reflect quality of recovery among survivors may be needed to fully evaluate new treatments for aVSP.

The relationship between GOSE and these outcomes was generally consistent with their relationship with severity of aVSP. These results are consistent with a previous study, which reported that the original (nonextended) GOSE at hospital discharge was significantly associated with HRQoL measured at 4 months after aSAH using the 36-Item Short Form Health Survey (SF-36).29

A major contribution of this study is the assessment of patient outcomes (MMSE, EQ-5D total, EQ-5D VAS, and FSE) and inpatient HCRU using data prospectively gathered in a large, international, multicenter study in relation to severity of aVSP categorized according to strictly defined quantitative criteria based on angiograms performed on all patients. Previous studies have examined such end points only in relation to the presence or absence of aVSP or have included study populations in which only selected patients received angiograms. In the Columbia University SAH Outcomes Project, 580 patients with SAH were studied, including 88% who had aSAH.6 Symptomatic vasospasm and delayed cerebral ischemia were assessed but not all patients had DSA and some cases of vasospasm were detected by transcranial Doppler ultrasound, which may not correlate well with DSA.30 The authors found that delayed cerebral ischemia but not symptomatic vasospasm was significantly associated with worse activities of daily living, cognitive impairment, and poor quality of life.6 Patients in CONSCIOUS-1 with severe aVSP were more likely to develop cerebral infarction than those with milder aVSP.31

Both severity of aVSP and GOSE were associated with duration of hospitalization. Severity of aVSP was not significantly associated with days in the general ward, which may reflect the minimum hospital stay specified in the study protocol (7–11 days) and patients having to wait in the hospital before being able to enter a rehabilitation facility. However, there was an increase in days in the ICU (and total hospital days) with increasing severity of aVSP. These results are consistent with results from the Columbia University SAH Outcomes Project, which found that both hospital and ICU LOS were significantly longer in patients with aVSP, transcranial Doppler ultrasound VSP, delayed cerebral ischemia, and symptomatic VSP.6 Similarly, in a retrospective chart review of 189 patients with aSAH, mean hospital LOS (adjusted for baseline characteristics and clinical confounders) was 1.2 times longer for patients with VSP than for those without (P<0.01), both for transcranial Doppler ultrasound-defined and symptomatic VSP.15 Considering the costs of ICU stays, preventing aVSP could reduce the healthcare burden and therefore treatment costs of aSAH.

Furthermore, patients with severe aVSP were unlikely to be independent 12 weeks after aSAH. Thus, severe aVSP imposes a burden not only on the healthcare system, but also on other care systems and caregivers. The financial impact of this burden may be considerable; in an analysis of the cost burden of aSAH in the United Kingdom, the opportunity costs of unpaid support from caregivers were estimated to be £ 42 million in 2005 ($79 million US in 2005).1

In CONSCIOUS-1, clazosentan significantly reduced aVSP but had no significant effect on the GOSE. Of note, the study was not powered to detect an effect on the GOSE. The association of moderate-to-severe aVSP with outcomes relevant to patients and clinicians reported here seems inconsis-
Figure 2. Mean length of stay in the intensive care unit (A), general ward (B), and both combined (C) stratified by severity of angiographic vasospasm (aVSP). Error bars are 95% CIs. \(P<0.0001\), \(P=0.062\), and \(P=0.008\) for Kruskal-Wallis 1-way comparison across aVSP categories for days in the intensive care unit, general ward, and total hospital days, respectively.

Conclusion

Severe aVSP is associated with poor patient cognition, HRQoL and functional status, and greater hospital HCRU. However, moderate vasospasm had a variable effect and no effect of mild or no aVSP on these end points was seen. These findings imply that severity of aVSP is a valid but only partial surrogate for the pathophysiological mechanisms that determine clinical outcomes in patients with aSAH.

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Disclosures

R.L.M. received research support from the Heart and Stroke Foundation of Canada. He is a consultant for Actelion Pharmaceuticals Ltd; J.W. is a consultant for Actelion Pharmaceuticals Ltd; R.S. and E.H. are employees of Actelion Pharmaceuticals Ltd; S.M. is a consultant for Actelion Pharmaceuticals Ltd and Edge Therapeutics.

References


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SUPPLEMENTAL MATERIAL

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Supplemental Table S1. Patient disposition at week 12, stratified by severity of aVSP.

<table>
<thead>
<tr>
<th>Functional status, n (%)</th>
<th>Severe aVSP</th>
<th>Moderate aVSP</th>
<th>Mild aVSP</th>
<th>No aVSP</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fully independent</td>
<td>7 (10)</td>
<td>37 (32)</td>
<td>28 (56)</td>
<td>83 (49)</td>
<td>155 (38)</td>
</tr>
<tr>
<td>Partially independent</td>
<td>4 (5)</td>
<td>21 (18)</td>
<td>4 (8)</td>
<td>12 (7)</td>
<td>41 (10)</td>
</tr>
<tr>
<td>Rehabilitation ward</td>
<td>38 (52)</td>
<td>41 (35)</td>
<td>16 (32)</td>
<td>59 (35)</td>
<td>154 (38)</td>
</tr>
<tr>
<td>Nursing home</td>
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<td>1 (1)</td>
<td>.</td>
<td>1 (1)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Long term care facility</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>1 (1)</td>
<td>1 (0)</td>
</tr>
<tr>
<td>Other</td>
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<td>14 (12)</td>
<td>2 (4)</td>
<td>13 (8)</td>
<td>50 (12)</td>
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<td>3 (3)</td>
<td>.</td>
<td>.</td>
<td>5 (1)</td>
</tr>
</tbody>
</table>

aVSP: angiographic vasospasm; Other: includes patients who died or were transferred to another hospital.