Dissociation of Early and Delayed Cerebral Infarction After Aneurysmal Subarachnoid Hemorrhage

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**Background and Purpose**—Cerebral infarction after aneurysmal subarachnoid hemorrhage is a significant cause of substantial morbidity and mortality. Because early and delayed cerebral infarction after aneurysmal subarachnoid hemorrhage may be mediated by different processes, we evaluated whether aneurysm-securing methods contributed to infarcts and whether long-term outcomes differ between early and delayed infarcts.

**Methods**—A post hoc analysis of the CONSCIOUS-1 study (Clazosentan to Overcome Neurological Ischemia and Infarction Occurring After Subarachnoid Hemorrhage) was performed. Using multivariate logistic regression analysis and propensity matching, independent clinical risk factors associated with infarctions were identified, and the contribution of cerebral infarcts to long-term outcomes was evaluated.

**Results**—Within the cohort of 413 subjects, early infarcts were present in 76 subjects (18%), whereas delayed infarcts occurred in 79 subjects (19%), and 36 subjects (9%) had new infarctions that were present on both early and delayed imaging. Propensity score matching revealed a significantly higher proportion of early infarcts after clipping (odds ratio, 4.62; 95% confidence interval, 1.99–11.57; P=0.00012). Multivariate logistic regressions identified clipping as an independent risk factor for early cerebral infarction (odds ratio, 0.26; 95% confidence interval, 0.15–0.48; P<0.001), and angiographic vasospasm was an independent risk factor for delayed cerebral infarction (odds ratio, 1.79; 95% confidence interval, 1.03–3.13; P=0.039). Early infarcts were a significant independent risk factor for poor long-term outcomes at 3 months (odds ratio, 2.34; 95% confidence interval, 1.18–4.67; P=0.015).

**Conclusions**—Clipping is an independent risk factor for the development of early cerebral infarcts, whereas delayed cerebral infarcts are associated with angiographic vasospasm. Early cerebral infarcts are stronger predictors of worse outcome than delayed infarction.

**Clinical Trial Registration**—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00111085. (Stroke. 2016;47:2945-2951. DOI: 10.1161/STROKEAHA.116.014794.)

**Key Words:** algorithms ▪ angiography ▪ cerebral infarction ▪ risk factors ▪ subarachnoid hemorrhage

Despite advances in the understanding of aneurysmal subarachnoid hemorrhage (aSAH) pathophysiology, sequelae such as cerebral infarction continue to make substantial contributions to poor outcomes. Cerebral infarction after aSAH is common and can be classified as early or delayed. Infarction may occur as early brain injury because of initial aneurysm rupture, or as delayed cerebral ischemia, often attributed to arterial vasospasm. Increasingly, evidence also points to infarction as a result of iatrogenic injury caused by either neurosurgical clipping or endovascular coiling.

Recent studies have revealed a dissociation between early and delayed cerebral infarction with respect to their contributions to neurological outcomes. Given that these events may be associated with differing causes, risk factors, and treatment strategies, an understanding of the differences between early and delayed infarction may be critical in devising appropriate algorithms to mitigate secondary injury after aneurysm rupture. The interpretation of previous studies and therefore the ability to derive meaningful conclusions on infarction subtypes after aSAH is, however, significantly limited. Past studies have not directly compared the incidence of early and delayed infarctions between different aneurysm-securing procedures. Additionally, their retrospective design precluded the inference of strong conclusions.

In the current study, we analyzed clinical features that were associated with early (24–48 hours after aneurysm repair) and delayed (6 weeks after aSAH) cerebral infarcts identified on computed tomography (CT) scans of patients enrolled in the CONSCIOUS-1 study (Clazosentan to Overcome Neurological Ischemia and Infarction Occurring After Subarachnoid Hemorrhage). These data included patients who underwent neurosurgical clipping and endovascular...
coiling and were randomized to receive clazosentan for the prevention of angiographic vasospasm. Each patient in the study underwent CT imaging at defined time points and catheter angiography in a prospective and protocol-driven design. The contributions of clinical factors to early and delayed cerebral infarcts were analyzed, and the contribution of early and delayed infarcts to long-term neurological outcome was determined.

Methods

Study Population

Data were obtained from 413 subjects recruited into the CONSCIOUS-1 study.14 Each subject enrolled in the initial study was recruited within 48 hours after aSAH.

Clinical Assessment

Patients were admitted to the respective neurosurgical services if they had a CT-confirmed aSAH. Information on clinical and demographic factors was collected for all subjects. The World Federation of Neurosurgical Societies (WFNS) scale15 was used to classify the subjects’ presenting symptoms. The extended Glasgow outcome scale (eGOS) score at 12 weeks after aSAH was used to index clinical outcome.16 A long-term outcome score indicating a disability worse than moderate disability (eGOS <5) was considered a poor neurological outcome.

Radiology

All patients underwent CT scans at 3 predetermined time points: (1) on presentation and before any aneurysm-securing procedure; (2) within 24 to 48 hours after the aneurysm-securing procedure; and (3) at 6 weeks after the aneurysm rupture. Each scan was independently, centrally reviewed, with documentation of the presence and volume of infarction and comparison to the previous CT scan for each patient. The presence of a hypodensity on the first post–aneurysm-securing scan that was not present on the CT at initial presentation was defined as an early infarction. Hypodensities identified on CT at 6 weeks after aSAH that were not present on the postprocedure scan were defined as delayed infarctions. Scans for each patient were reviewed in total, and the final follow-up scan was used to confirm whether early hypodensities on CT were infarcts or not. The Hijdra scale17 was used to quantify the subarachnoid clot burden and evaluate the amount of clot in 10 fissures and cisterns for a range of scores from 0 to 30. The extent of intraventricular hemorrhage was quantified using a modification of the Graeb score18,19 for a maximum possible score of 12. Digital subtraction angiography was performed for each patient within 48 hours of intracranial aneurysm rupture and between 7 and 11 days post aSAH. The percent change in the diameter of large proximal arteries between baseline and follow-up angiography was used to quantify angiographic vasospasm (classified as none/mild: 0% to 33%; moderate: 34% to 66%; severe: 67% to 100%). The interobserver variability in the documentation of imaging findings has been previously reported.9

Statistical Analysis

Data are presented as mean±SD or median with interquartile range (IQR), where stated. The primary outcomes of interest were the incidence and volumes of early and delayed cerebral infarctions and their associations with neurological outcomes. We undertook several analyses to examine the primary outcomes. First, we analyzed the incidence of early and delayed infarcts, as well as clinical factors associated with each type of infarct. Differences in demographic and clinical factors were initially compared using the Mann–Whitney U test for continuous variables and Fisher exact test for categorical variables. Any test result reaching a liberal statistical threshold of P<0.2 for each comparison between an infarct group and the group without any infarct was then entered into a multivariate logistic regression to identify factors independently predictive of infarction.

We also evaluated the contribution of cerebral infarction to long-term outcomes based on the dichotomized eGOS (eGOS <5 as poor outcome at 12 weeks after aSAH) using a multivariate logistic regression. Independent covariates included in this analysis were previously identified predictors of outcome from previous analyses based on the CONSCIOUS-1 study20,21 and those previously identified as independent prognostic factors for poor outcome after aSAH.22 These included age, preexisting hypertension, poor WFNS scores on admission (dichotomized as WFNS IV–V versus I–III), subarachnoid clot burden, aneurysm location (posterior versus anterior), aneurysm size (<5 mm versus >5 mm), and angiographic vasospasm (none/mild versus moderate/severe).

Propensity score matching was performed, with angiography-securing procedure as the dependent variable, to decrease variability between the clipping and coiling cohorts as patients in this study were not randomized to clipping or coiling. Subjects were matched for age, sex, nicotine use, history of hypertension, preexisting heart conditions, WFNS scores at admission, aneurysm location, aneurysm size, Hijdra score, presence of intracerebral hemorrhage, and intraventricular hemorrhage. Propensity score matching was performed using calipers with a width of 0.25, as previously reported.23 The distribution of propensity scores is presented in the online-only Data Supplement.

Finally, we performed receiver–operator characteristic curve analysis to determine the ability of infarction volume to predict poor clinical outcome on the eGOS and optimal predictive thresholds.24 For all final models, statistical significance was set at P<0.05. Analysis was performed using R statistical software using custom scripts written in-house.

Results

Patient Demographic Data

Four-hundred and thirteen patients were enrolled in the CONSCIOUS-1 trial. The mean age of subjects in the study was 51±11 years, and 124 subjects (30%) were men. Demographic and clinical data are summarized in Table 1. Each patient in the study received baseline CT imaging before the aneurysm-securing procedure, postprocedure CT imaging within 24 to 48 hours after neurosurgical clipping or endovascular coiling, and again 6 weeks after aSAH. In this study, 45% (191 of 413) of patients had CT-confirmed cerebral infarcts after repair of a ruptured intracranial aneurysm. Early infarcts were present in 18% of patients (76 of 413). Delayed infarcts occurred in 19% of patients (79 of 413). A subset of patients (8.8%, 36 of 413) had new infarcts that were present on both the early and delayed CT scans. Fifty-four percent of patients (222 of 413) did not have any infarct detectable by CT imaging (Table 1).

Clinical Factors Associated With Early and Delayed Infarcts

Patients with early or delayed infarction, or both, were first compared with the group of patients that did not have any  

infarct on CT (Table 1). On univariate analysis, patients with  

any infarct identified by CT were less likely to present with a 

good neurological grade (grade I–III; P=0.049; 95% confidence interval [CI], 0.28–1.04; delayed: 67% grade I–III; P=0.011; 95 CI, 0.24–0.84; both: 67% grade I–III; P=0.043; 95% CI, 0.19–1.05; versus no infarct group, 82% grade I–III). Patients with delayed infarcts were more likely to have a history of hypertension (delayed: 51% versus
none: 37%; \( P=0.045 \); 95% CI, 1.01–3.04), a higher subarachnoid clot burden (delayed: 19.31±6.13 versus none: 17.69±5.74; \( P=0.019 \)), and an intracerebral hemorrhage (delayed: 20% versus none: 9.5%; \( P=0.017 \); 95% CI, 1.11–5.21). Additionally, patients with delayed infarcts tended to have larger aneurysms (\( P=0.032 \)). Development of moderate or severe vasospasm occurred significantly more often in patients with early or delayed infarcts than in those without infarcts (early: 39%; \( P=0.018 \); 95% CI, 1.09–3.55; delayed: 46%; \( P<0.0001 \); 95% CI, 1.81–6.03; versus none: 24.77%). Early cerebral infarcts occurred with significantly higher frequencies in patients who underwent neurosurgical clipping of ruptured aneurysms, as compared with patients with no infarcts (early: 72%; \( P<0.0001 \); 95% CI, 2.44–8.52; both early and delayed: 61%; \( P=0.0045 \); 95% CI, 1.34–7.03 versus none: 37%). Patients with any infarct had significantly longer admissions in an intensive care unit compared with patients without infarcts (early: 13.26±9.15 days; \( P=0.011 \); delayed: 14.67±12.09 days; \( P=0.0069 \); both: 20.17±15.25; \( P<0.0001 \) versus none: 10.45±8.78 days).

When the cohort of patients with early infarction were compared with that with delayed infarction (Table 1), patients with early infarcts were less likely to have an intracerebral hemorrhage (\( \text{early: } 0.037 \); 95% CI, 0.10–0.98) and more often underwent neurosurgical clipping compared with endovascular coiling (\( \text{early: } 0.0001 \); 95% CI, 2.53–11.59) on univariate analysis.

### Table 1. Demographic and Clinical Factors of 413 Patients After aSAH

<table>
<thead>
<tr>
<th></th>
<th>Early Infarct (n=76)</th>
<th>Early vs None, ( P ) Value</th>
<th>Delayed Infarct (n=79)</th>
<th>Delayed vs None, ( P ) Value</th>
<th>Both Early and Delayed Infarcts (n=36)</th>
<th>Both vs None, ( P ) Value</th>
<th>No Infarct (n=222)</th>
<th>Early vs Delayed, ( P ) Value</th>
<th>Clipped (n=183)</th>
<th>Clipped vs Coiled, ( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, y</strong></td>
<td>51.14±10.68</td>
<td>0.88</td>
<td>51.66±11.22</td>
<td>0.44</td>
<td>52.22±10.82</td>
<td>0.32</td>
<td>50.5±10.68</td>
<td>0.59</td>
<td>50.66±10.59</td>
<td>0.38</td>
</tr>
<tr>
<td><strong>Male sex</strong></td>
<td>18(23.68)</td>
<td>0.12</td>
<td>16(20.25)</td>
<td>0.032</td>
<td>15(41.67)</td>
<td>0.029</td>
<td>75(33.78)</td>
<td>0.69</td>
<td>51(27.87)</td>
<td>63(29.4)</td>
</tr>
<tr>
<td><strong>Nicotine use</strong></td>
<td>38(50.00)</td>
<td>0.35</td>
<td>39(49.37)</td>
<td>0.29</td>
<td>15(41.67)</td>
<td>0.9</td>
<td>125(56.31)</td>
<td>0.99</td>
<td>83(45.36)</td>
<td>99(46.26)</td>
</tr>
<tr>
<td><strong>Preexisting</strong></td>
<td>36(47.37)</td>
<td>0.13</td>
<td>40(50.63)</td>
<td>0.045</td>
<td>17(47.22)</td>
<td>0.27</td>
<td>82(36.94)</td>
<td>0.75</td>
<td>78(42.62)</td>
<td>89(41.59)</td>
</tr>
<tr>
<td><strong>WFNS score I–III</strong></td>
<td>54(71.05)</td>
<td>0.049</td>
<td>53(67.10)</td>
<td>0.111</td>
<td>24(66.67)</td>
<td>0.043</td>
<td>182(81.96)</td>
<td>0.61</td>
<td>141(77.05)</td>
<td>160(74.77)</td>
</tr>
<tr>
<td><strong>Intraventricular</strong></td>
<td>60(78.95)</td>
<td>0.87</td>
<td>61(77.22)</td>
<td>0.9</td>
<td>30(83.33)</td>
<td>0.52</td>
<td>171(77.02)</td>
<td>0.85</td>
<td>146(79.78)</td>
<td>165(77.10)</td>
</tr>
<tr>
<td><strong>Aneurysm size</strong></td>
<td>43(56.58)</td>
<td>0.89</td>
<td>53(67.09)</td>
<td>0.017</td>
<td>16(40.25)</td>
<td>0.24</td>
<td>21(9.64)</td>
<td>0.037</td>
<td>25(13.67)</td>
<td>23(10.75)</td>
</tr>
<tr>
<td><strong>Anterior</strong></td>
<td>73(96.05)</td>
<td>0.032</td>
<td>70(88.61)</td>
<td>0.9</td>
<td>29(80.56)</td>
<td>0.52</td>
<td>198(89.19)</td>
<td>0.063</td>
<td>177(96.72)</td>
<td>178(83.18)</td>
</tr>
<tr>
<td><strong>Posterior</strong></td>
<td>1(1.32)</td>
<td>0.032</td>
<td>7(8.86)</td>
<td>4(11.11)</td>
<td>19(58.56)</td>
<td>2(1.09)</td>
<td>28(13.08)</td>
<td>0.0089(74)</td>
<td>0.0001</td>
<td></td>
</tr>
</tbody>
</table>

### Aneurysm location

- **Anterior circulation**: 73(96.05) 0.032 70(88.61) 0.99 29(80.56) 0.52 198(89.19) 0.063 177(96.72) 178(83.18) 0.0001
- **Posterior circulation**: 1(1.32) 7(8.86) 4(11.11) 19(58.56) 2(1.09) 28(13.08)

### Vasospasm

- **Moderate/severe**: 30(39.47) 0.018 36(45.57) 0.0001 8(22.22) 0.84 55(24.77) 0.14 65(35.52) 57(26.63) 0.064
- **None/mild**: 46(60.53) 33(41.77) 28(77.78) 167(75.23) 118(64.48) 157(73.36)
- **Clip**: 55(72.37) <0.0001 25(31.65) 0.58 22(61.11) 0.0045 81(36.49) <0.0001 183
- **Coil**: 20(26.32) 49(62.03) 12(33.33) 133(59.91) 214
- **Days in intensive care unit**: 13.26±9.15 0.011 14.67±12.09 0.007 20.17±20.25 <0.0001 10.45±8.78 0.80 12.56±9.98 0.59
- **eGOS <5**: 35(46.05) <0.0001 30(37.97) 0.0024 15(41.67) 0.0094 45(20.27) 0.33 63(34.43) 0.31

Units in parenthesis represent percentages; error expressed as ±SD. aSAH indicates aneurysmal subarachnoid hemorrhage; eGOS, extended Glasgow outcome scale; and WFNS, World Federation of Neurosurgical Societies.
Table 2. Multivariable Logistic Regression of Predictors of Early Cerebral Infarcts

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>1.42</td>
<td>0.76–2.65</td>
<td>0.27</td>
</tr>
<tr>
<td>Preexisting hypertension</td>
<td>1.39</td>
<td>0.81–2.40</td>
<td>0.24</td>
</tr>
<tr>
<td>WFNS scale (IV–V vs I–III)</td>
<td>1.34</td>
<td>0.72–2.50</td>
<td>0.36</td>
</tr>
<tr>
<td>SAH clot burden (Hijdra score)</td>
<td>1.01</td>
<td>0.96–1.06</td>
<td>0.69</td>
</tr>
<tr>
<td>Aneurysm location (posterior vs anterior)</td>
<td>0.24</td>
<td>0.03–1.83</td>
<td>0.17</td>
</tr>
<tr>
<td>Coiling (vs clipping)</td>
<td>0.26</td>
<td>0.15–0.48</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Vasospasm (moderate/severe vs none/mild)</td>
<td>1.25</td>
<td>0.69–2.22</td>
<td>0.46</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; OR, odds ratio; SAH, subarachnoid hemorrhage; and WFNS, World Federation of Neurosurgical Societies.

Patients undergoing coiling were significantly more likely to have aneurysms larger than 5 mm (clipped: 51.37%; versus coiled: 45.42%; P=0.0089; odds ratio [OR], 1.74; 95% CI, 1.13–2.69). Patients with posterior circulation aneurysms were clipped in a significantly higher proportion than those clipped (clipped: 1.1% versus coiled: 13.1%; P<0.001; OR, 3.41; 95% CI, 3.41–121.95).

On multivariate logistic regression analysis of covariates associated with early infarction, only neurosurgical clipping, as opposed to endovascular coiling, was independently associated with infarcts occurring in the first 24 to 48 hours after the procedure (OR, 0.26; 95% CI, 0.15–0.48; P<0.0001; Table 2). On multivariate logistic regression analysis of covariates associated with delayed infarction, moderate or severe angiographic vasospasm was independently associated with delayed infarcts at 6 weeks after the aneurysm-securing procedure (OR, 1.79; 95% CI, 1.03–3.13; P=0.039; Table 3). Aneurysm clipping was also an independent risk factor for patients who had both early and delayed infarcts identified on CT (OR, 0.45; 95% CI, 0.21–0.94; P=0.036; Table 4).

Cerebral Infarction and Long-Term Outcome

We subsequently examined whether early, delayed, or a combination of early and delayed infarctions were independently associated with long-term outcomes (Table 5). On multivariate logistic regression, the presence of an early cerebral infarct on CT imaging was independently associated with poor neurological outcome on the eGOS (OR, 2.34; 95% CI, 1.18–4.67; P=0.015). Other clinical covariates associated with poor neurological outcomes included WFNS grade IV–V (OR, 4.27; 95% CI, 2.42–7.53; P<0.0001), greater subarachnoid clot burden (OR, 1.06; 95% CI, 1.01–1.11; P=0.018), and moderate or severe angiographic vasospasm (OR, 3.56; 95% CI, 2.06–6.16; P<0.0001).

Infarct Volume

The mean volumes of infarcts in the early and delayed groups were 18.69±34.97 cm³ and 27.32±67.88 cm³, respectively. There were no differences between the median volumes of early (5.49 cm³; IQR, 2.68–14.84) and delayed infarcts (4.67 cm³; IQR, 1.24–20.27; P=0.41). To ensure that differences in early and delayed infarct volumes did not account for the differing contributions to patient outcome, we performed a subgroup analysis on patients with large infarctions (generally defined in the literature as >30 cm³). Within this select cohort, there remained no differences in infarct volumes among those with early or delayed infarctions (median volume: early >30 cm³: n=14; 59.56 cm³; IQR, 37.11–106.22 versus delayed >30 cm³: n=20; 50.47 cm³; IQR, 28.75–112.62; P=0.64). There were also no differences within this cohort with respect to the proportion of patients who were clipped (early >30 cm³: 7 of 14 versus delayed >30 cm³: 13 of 18; P=0.26) or with poor neurological outcomes (early >30 cm³: 7 of 14 versus delayed >30 cm³: 13 of 20; P=0.49).

To identify accurate thresholds for infarct volumes that predicted poor neurological outcomes, we constructed receiver–operator characteristic curves. Increasing infarction volume, regardless of the time of occurrence, was associated with poor long-term neurological outcomes (area under the curve, 0.62; 95% CI, 0.54–0.70; P=0.009). The optimal predictive threshold of infarct volume for poor outcome was 10.1 cm³ (sensitivity: 50.0; specificity: 70.3; Figure). When we dichotomized the data based on the optimal predictive threshold, there was no difference in the proportion of patients who underwent...
clipping versus coiling (large >10 cm³: 35 of 73 clipped versus small <10 cm³: 67 of 118; P = 0.44). Patients with infarcts >10 cm³ were significantly more likely to have a poor long-term outcome (large >10 cm³: 54.79% [40 of 73] versus small <10 cm³: 32.20% [38 of 118]; OR, 2.54; 95% CI, 1.34–4.87; P = 0.0025).

Discussion

Previous studies examining procedure-related cerebral infarction after neurosurgical clipping have not compared clipping directly to endovascular coiling.2,12,25 It is possible that both procedures can contribute to infarction, for instance, through vessel manipulation during clipping or via thromboembolic events during endovascular treatment. Studies have often focused on cerebral infarction identified at long-term follow-up with imaging3,12,25–27 or have only identified infarcts on imaging in patients who became symptomatic and were subsequently imaged in hospital.8,13 These strategies may significantly underestimate the incidence of both early and delayed infarction. The current study is the first to examine the frequency of early procedure-related and delayed cerebral infarction in a prospectively collected and protocol-driven data set and to directly compare differences between patients treated by clipping or coiling.

A surprising finding of our study was that early infarction was more strongly associated with poor neurological outcomes than delayed infarction. A recent study by Kumar et al8 found that early infarctions occur after neurosurgical clipping, however, they did not correlate their findings with overall patient outcomes. The literature is also replete with studies demonstrating that when equipoise between the 2 treatment strategies is achieved, those undergoing endovascular coiling have better outcomes compared with those undergoing neurosurgical clipping.30–32 We have, also, previously demonstrated that perioperative complications can contribute to outcome differences between patients undergoing clipping or coiling after aSAH.21,33 The current data provide additional support

Table 4. Multivariable Logistic Regression of Predictors of Patients With Both Early and Delayed Cerebral Infarcts

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>0.66</td>
<td>0.06–0.89</td>
<td>0.28</td>
</tr>
<tr>
<td>WFNS scale (IV–V vs I–III)</td>
<td>1.32</td>
<td>0.58–3.03</td>
<td>0.51</td>
</tr>
<tr>
<td>Intracerebral hemorrhage</td>
<td>1.79</td>
<td>0.69–4.62</td>
<td>0.23</td>
</tr>
<tr>
<td>Coiling (vs clipping)</td>
<td>0.45</td>
<td>0.21–0.94</td>
<td>0.036</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; OR, odds ratio; and WFNS, World Federation of Neurosurgical Societies.

Table 5. Multivariable Logistic Regression of Predictors of Long-Term Neurological Outcomes After aSAH

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.02</td>
<td>0.99–1.05</td>
<td>0.19</td>
</tr>
<tr>
<td>Preexisting hypertension</td>
<td>1.54</td>
<td>0.89–2.67</td>
<td>0.12</td>
</tr>
<tr>
<td>WFNS score (IV–V vs I–III)</td>
<td>4.27</td>
<td>2.42–7.53</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Subarachnoid clot burden (Hijdra score)</td>
<td>1.06</td>
<td>1.01–1.11</td>
<td>0.018</td>
</tr>
<tr>
<td>Aneurysm size (&lt;5 mm vs &gt;5 mm)</td>
<td>1.00</td>
<td>0.58–1.75</td>
<td>0.98</td>
</tr>
<tr>
<td>Aneurysm location (posterior vs anterior circulation)</td>
<td>1.24</td>
<td>0.46–3.35</td>
<td>0.66</td>
</tr>
<tr>
<td>Vasospasm (moderate/severe vs none/mild)</td>
<td>3.56</td>
<td>2.06–6.16</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Coiling (vs clipping)</td>
<td>0.67</td>
<td>0.38–1.19</td>
<td>0.17</td>
</tr>
<tr>
<td>Early infarcts</td>
<td>2.34</td>
<td>1.18–4.67</td>
<td>0.015</td>
</tr>
<tr>
<td>Delayed infarcts</td>
<td>1.49</td>
<td>0.75–2.98</td>
<td>0.25</td>
</tr>
<tr>
<td>Both early and delayed infarcts</td>
<td>2.42</td>
<td>0.94–6.22</td>
<td>0.06</td>
</tr>
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aSAH indicates aneurysmal subarachnoid hemorrhage; CI, confidence interval; OR, odds ratio; and WFNS, World Federation of Neurosurgical Societies.
for the importance of periprocedural period and encourage efforts to mitigate the morbidity of microsurgical strategies.

Importantly, several previous studies have revealed higher rates of delayed cerebral ischemia in patients undergoing clipping compared with coiling,\textsuperscript{5,6} which may contribute to outcome differences between the 2 cohorts. We have previously shown that even with expert consensus, it may be difficult to retrospectively attribute hypodensities on CT to angiographic vasospasm.\textsuperscript{6} It is possible that studies measuring delayed cerebral ischemia and attributing worse outcomes in patients undergoing clipping were indeed mistaken for early infarction.

There are several limitations associated with the current study. The purpose of the CONSCIOUS-1 study was to examine the effect of clazosentan on angiographic vasospasm and outcome after aSAH, rather than cerebral infarction. Although patients were not randomized to neurosurgical clipping or endovascular coiling, each patient in this unique data set underwent CT imaging and catheter angiography at the same time points, minimizing any clinical bias. With a predetermined imaging protocol, every patient in this study was imaged at the same time points after aSAH, which is in contrast to most previous studies that scan patients when their clinical status changes. In this data set, patients with a posterior circulation aneurysm were significantly more likely to be coiled, rather than clipped, and there were more patients with aneurysms greater than 5 mm who were coiled. It is possible that both of these factors could contribute to differences between early and late infarcts. The fact that only 2 patients with posterior circulation aneurysms were clipped, compared with 28 patients who were coiled, reflects the contemporary standard of care. And importantly, the small fraction of patients with posterior circulation aneurysms that were clipped did not disproportionately affect the event rate of early infarcts in our study because there were only 2 patients in this group. Furthermore, there were significantly more patients with aneurysms larger than 5 mm who were coiled, rather than clipped. Previous work has demonstrated that larger aneurysm size is an independent risk factor for cerebral infarct and worse outcome after aneurysm securing.\textsuperscript{7,8} But more patients in our study with larger aneurysms underwent coiling rather than clipping. To account for the nonrandomization of patients to clipping or coiling, we performed propensity score matching analysis, a method to balance covariates between 2 groups that were not initially randomized.\textsuperscript{23} Although there are limitations when drawing conclusions from data that are nonrandomized, are in the case of clipping and coiling in this study, the propensity score matching analysis supports the original data by demonstrating that a significantly larger proportion of patients that underwent neurosurgical clipping had early cerebral infarcts. Confounding factors that could explain the higher incidence of early infarction after clipping include challenging aneurysm morphology, which was not measured in the trial. Importantly, one reason that delayed infarction was not significantly associated with outcome on multivariate analysis is a strong collinearity with angiographic vasospasm. Locations of cerebral infarcts were not available in this data set but may be associated with outcomes.\textsuperscript{8} Additionally, early vasospasm occurring in the first 72 hours after aSAH, which may account for some early infarcts, cannot be excluded.\textsuperscript{3,9} The impact of early brain injury\textsuperscript{9} caused by the initial hemorrhage was not determined in our study. Finally, CT scans provide limited information on the cause of infarction.\textsuperscript{9} Future studies should aim to better understand the occurrence of early infarction by examining the timing, location, volumes, clinical symptoms, and their association with outcome to develop strategies to mitigate early infarction.

**Conclusions**

Neurosurgical clipping is an independent risk factor for the development of early cerebral infarcts, whereas angiographic vasospasm is an independent risk factor for delayed cerebral infarcts after aSAH. Early cerebral infarcts are strongly associated with poor long-term neurological outcomes. Early and delayed cerebral infarcts after aneurysm-securing procedures can be seen as distinct occurrences, and strategies should be used to mitigate early cerebral infarction and minimize poor outcomes.

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**Disclosures**

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**References**

Intraventricular hemorrhage in blunt head trauma: an analysis of 43 cases. 


Dissociation of Early and Delayed Cerebral Infarction After Aneurysmal Subarachnoid Hemorrhage

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Supplemental Figure 1

Supplemental Figure 1. Histograms of before propensity matching of clipped (raw treated) and coiled (raw control) patients. The histograms prior to propensity matching of selected
covariates were not matched as seen by their differing distributions. Histograms after propensity score matching of clipped (matched treated) and coiled (matched control) demonstrates similar distributions and suitability of the propensity matching algorithm.