SCORE-IT: the Spot Sign score in restricting ICH growth—an Atach-II ancillary study

JN Goldstein 1,2,3,*, HB Brouwers 1,2,4, JM Romero 2, K McNamara 1, K Schwab 1, SM Greenberg 1,2, and J Rosand 1,2,4,5

1Hemorrhagic Stroke Research Group, Massachusetts General Hospital, Boston, MA, USA
2Division of Neurocritical Care and Emergency Neurology, Department of Neurology, Massachusetts General Hospital, Boston, MA, USA
3Department of Emergency Medicine, Massachusetts General Hospital, Zero Emerson Place, Suite 3B, Boston, MA 02114, USA
4Center for Human Genetic Research, Massachusetts General Hospital, Boston, MA, USA
5Neuroradiology Service, Department of Radiology, Massachusetts General Hospital, Boston, MA, USA

Abstract

Introduction: The ATACH-II trial is designed to evaluate whether intensive blood pressure reduction can reduce hematoma growth and improve outcome. However, it is difficult to determine, at presentation, which patients are at highest risk of ongoing bleeding, and will receive the most clinical benefit from blood pressure therapy. It may be that improved predictive markers will lead to efficient, personalized selection of optimal therapy. We hypothesize that specific imaging findings on CT angiography (CTA) and MRI will mark those patients who receive the most benefit from intensive blood pressure reduction.

Methods: Many patients enrolled in ATACH-II will undergo CTA and/or MRI as part of routine clinical care. We will perform a blinded analysis of these images. For CTA, we will determine the presence of contrast pooling (also termed contrast extravasation or the “Spot Sign”). In addition, we will calculate a Spot Sign Score, a score that includes number of Spot Signs, diameter, and contrast density. For MRI, we will focus on the presence, number, and location of cerebral microbleeds (CMBs) on sensitive T2*-weighted MRI sequences.

Results: We will test the hypothesis that patients with a Spot Sign will receive clinical benefit from intensive blood pressure reduction. In addition, we will determine whether patients with the highest Spot Sign Scores receive the most benefit from intensive blood pressure reduction. Finally, we will determine whether the absence of CMBs marks those at higher risk for hematoma expansion, and therefore more likely to benefit from treatment.

Conclusion: This ancillary study offers the tremendous opportunity to determine whether imaging findings can risk stratify ICH patients for acute therapies aimed at limiting hematoma growth.

Keywords
intracerebral hemorrhage; CT angiography; blood pressure

Introduction

As many as 30–40% of patients with ICH experience ongoing bleeding and clinically significant expansion of their ICH volume after presentation [1,2]. Proposed theories for hematoma expansion include (1) secondary bleeding at the periphery of the hemorrhage [3,4], (2) potentiation of hemorrhage by fibrin degradation products and plasmin exuded from the clot [5,6], and (3) continued bleeding from the primary ruptured vessel [7]. It appears that the earlier patients present, the more likely they are to experience ongoing bleeding and hematoma expansion [8–11].
Because the final size of the hematoma plays such a large role in prognosis [8,12–14] and hematoma expansion independently worsens outcome [14], prevention of this expansion has become a key target for novel acute treatments for ICH. Placebo-controlled trials of activated recombinant factor VII (fVIIa) [15–19] demonstrated reductions in hematoma expansion, but without consistent benefit on patient outcome [19,20]. Phase II studies of early intensive antihypertensive treatment have also demonstrated an effect on hematoma expansion, but once again, without clear gains for patients [21,22]. One major challenge has been determining which patients will continue to bleed and are at risk for worsened disability or death. Accurate prediction of an individual’s risk would allow anti-expansion treatments to be applied specifically to those with the potential to benefit. This development would result in two major improvements: (a) increased efficiency of subject selection for future clinical trials and (b) avoiding the risks of potentially toxic agents (both in clinical trials and in future clinical practice) for those with no chance of benefit.

Neuroimaging may provide a tool for such risk stratification. CT angiography (CTA) is commonly performed in patients with ICH to evaluate for underlying secondary causes, with a relatively high yield and good safety profile [24,25]. The presence of intrahematomal contrast on these studies appears to represent contrast extravasation and ongoing bleeding [11,26,27]. This finding has been termed the “Spot Sign,” and its value has been replicated in several cohorts for prediction of both hematoma expansion and worse outcome [28–32]. In addition, it appears that patients with more Spot Signs, larger diameter, and higher signal intensity show even higher rates of expansion and worse outcome [31,33]. This finding led to the development of the Spot Sign Score [34] (Tables 1 and 2). It may be that higher score marks those at highest risk who will benefit the most from therapies aimed at limiting ongoing bleeding.

### Table 1.
The Spot Sign Score.

<table>
<thead>
<tr>
<th>Spot Sign Characteristic</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Spot Signs</td>
<td></td>
</tr>
<tr>
<td>1–2</td>
<td>1</td>
</tr>
<tr>
<td>≥3</td>
<td>2</td>
</tr>
<tr>
<td>Maximum axial dimension</td>
<td></td>
</tr>
<tr>
<td>1–4 mm</td>
<td>0</td>
</tr>
<tr>
<td>≥5 mm</td>
<td>1</td>
</tr>
<tr>
<td>Maximum attenuation</td>
<td></td>
</tr>
<tr>
<td>120–179 HU</td>
<td>0</td>
</tr>
<tr>
<td>≥180 HU</td>
<td>1</td>
</tr>
</tbody>
</table>

### Table 2.
Spot Sign score predicts hematoma expansion and outcome.

<table>
<thead>
<tr>
<th>Spot Sign score</th>
<th>Risk of expansion (%)</th>
<th>Increased volume (ml)</th>
<th>% Change in volume</th>
<th>Likelihood of good outcome (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (n = 296)</td>
<td>2</td>
<td>11 (2–19)</td>
<td>39 (10–140)</td>
<td>54</td>
</tr>
<tr>
<td>1 (n = 18)</td>
<td>33</td>
<td>9 (3–22)</td>
<td>21 (5–38)</td>
<td>34</td>
</tr>
<tr>
<td>2 (n = 18)</td>
<td>50</td>
<td>9 (3–18)</td>
<td>39 (16–126)</td>
<td>22</td>
</tr>
<tr>
<td>3 (n = 18)</td>
<td>94</td>
<td>21 (5–80)</td>
<td>68 (10–448)</td>
<td>18</td>
</tr>
<tr>
<td>4 (n = 17)</td>
<td>100</td>
<td>36 (6–136)</td>
<td>72 (13–293)</td>
<td>9</td>
</tr>
</tbody>
</table>

Continuous variables presented as mean (range). Good outcome defined as mRS 0–3.
In addition, it is possible that the patient’s underlying pathophysiology influences risk of expansion. Not only does ApoE genotype influence risk, but one group has found that the pattern of cerebral microbleeds (CMBs) on MRI may mark small vessel disease and risk of expansion [35]. The number and spatial distribution of CMB can indicate both the type of underlying small vessel disease (hypertensive vasculopathy vs. cerebral amyloid angiopathy) and key aspects of small vessel structure (thin vs. thick vessel walls) [4]. It may be that the vessel characteristics (such as wall thinning) that promote “macrobleeds” rather than CMBs also predispose to ongoing bleeding leading to hematoma expansion. While the application of CMB detection to assessing risk of ICH expansion remains to be established and validated (among the goals of SCORE-IT), it offers the exciting possibility of using another readily available clinical neuroimaging procedure to provide independent and complementary prediction of ICH expansion, response to treatment, and ICH pathophysiology.

The SCORE-IT ancillary study offers the tremendous opportunity to leverage the work being done by the ATACH-2 team to address these important questions. We will capture imaging data performed as part of routine care to determine whether this data can identify those ICH patients most likely to expand and most likely to benefit from blood pressure reduction. Specific aims are as follows:

**Specific Aim 1**: To validate the Spot Sign Score as a predictor of hematoma expansion across the wide range of centers enrolling in ATACH-2.

**Specific Aim 2**: To determine whether Spot Sign Score predicts clinical benefit received from aggressive blood pressure reduction in ATACH-2.

**Specific Aim 3**: To determine whether the absence of MRI-detectable microbleeds is associated with hematoma expansion and clinical benefit received from aggressive blood pressure reduction in ATACH-2.

**Methods**

SCORE-IT is a prospective observational study nested within the ATACH-2 randomized controlled clinical trial. As part of this design, no additional workload was imposed upon sites; neither CTA nor MRI could be mandated, as this would risk interfering with enrollment. This design therefore leverages the existing workload for ATACH-2, promising insight into neuroimaging biomarkers of ICH expansion and response to blood pressure lowering, without affecting the execution of the parent study (Figure 1).

Inclusion criteria for the overall SCORE-IT study are (1) Enrollment in ATACH-2, (2) CTA performed as part of standard care during hospitalization, and (3) MRI with T2*-weighted GRE sequences performed at any point during hospitalization. Figure 2 shows the study design.

Data to be collected as part of SCORE-IT include: CTA imaging data, imaging parameters used for CTA acquisition, brain MRI(s) performed during initial hospitalization, and imaging parameters used for MRI acquisition.

The primary analysis for Aims 1 and 2 will include only those CTAs performed prior to or concurrently with enrollment, from centers that perform CTA routinely for the emergency evaluation of ICH. However, secondary analyses will include CTAs performed at centers that do not do them routinely, as well as CTAs performed after...
enrollment. These analyses will explore whether Spot Signs are detected later in hospital course and their predictive ability. Imaging will be reviewed centrally.

The primary analysis for Aim 3 will include the first T2*-weighted MRI performed during hospitalization (if any) for ATACH-2 patients. Microbleeds (CMBs) will be identified according to criteria proposed by the Microbleed Study Group [4,36].

Data management and analysis will be performed in coordination with the Data Coordination Unit (DCU) in the Division of Biostatistics and Epidemiology at Medical University of South Carolina. Based on our preliminary studies, if 300 patients in ATACH-II undergo CTA, we expect to have 80% power to detect a 30% increase in the proportion of spot + patients who have a good neurologic outcome due to antihypertensive therapy. If 600 patients, we will have 80% power to detect a 20% increase.

Conclusions
Overall, the SCORE-IT ancillary study will leverage the tremendous strength and breadth of the ATACH-2 trial to answer important questions regarding the value of neuroimaging in predicting hematoma expansion. In addition, we hope to demonstrate that imaging findings such as Spot Signs can be used in clinical practice to stratify patients for acute therapies such as intensive blood pressure reduction.

Acknowledgements
This study was supported by NINDS R01-NS073344.

References