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

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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].

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Table 1.
The Spot Sign Score.

Spot Sign Characteristic	Points
Number of Spot Signs	
1–2	1
≥3	2
Maximum axial dimension	
1–4 mm	0
≥5 mm	1
Maximum attenuation	
120–179 HU	0
≥180 HU	1

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

Spot Sign score	Risk of expansion (%)	Increased volume (ml)	% Change in volume	Likelihood of good outcome (%)
0 (*n* = 296)	2	11 (2–19)	39 (10–140)	54
1 (*n* = 18)	33	9 (3–22)	21 (5–38)	34
2 (*n* = 18)	50	9 (3–18)	39 (16–128)	22
3 (*n* = 18)	94	21 (5–80)	68 (10–448)	18
4 (*n* = 17)	100	36 (6–136)	72 (13–293)	9

Continuous variables presented as mean (range). Good outcome defined as mRS 0–3.

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.

A number of groups have examined which patients are at highest risk of expansion. One clinical feature is early time from symptom onset; the sooner patients undergo baseline CT scan, the more likely it is that a follow-up CT scan will demonstrate hematoma growth [2,10,22]. Other features include larger hematoma volumes and ApoE genotype [11,23]. Unfortunately, larger hematoma volumes are also associated with such poor neurologic status that such patients cannot be enrolled in clinical trials, and genotyping is not currently available in the acute setting. Therefore, there is a need for an improved ability to mark, in the acute setting, those patients with a reasonable neurologic status on arrival that are at risk of ongoing bleeding and deterioration.

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.

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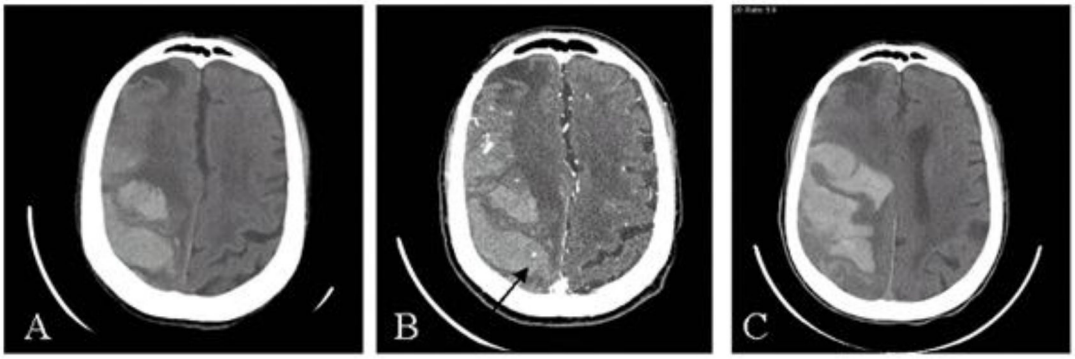

Figure 1. CT scans of an 83-year-old woman with acute onset of left-sided weakness. **a** Unenhanced CT with a right fronto-parietal hemorrhage. **b** CT angiogram showing normal cerebral vascular enhancement and punctate foci of intrahematomal contrast (one shown by *arrow*) with no clear vascular source. **c** Unenhanced CT performed 1 h later showing evidence of hematoma expansion. (Reprinted from Delgado Almandoz *et al* with permission.)

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

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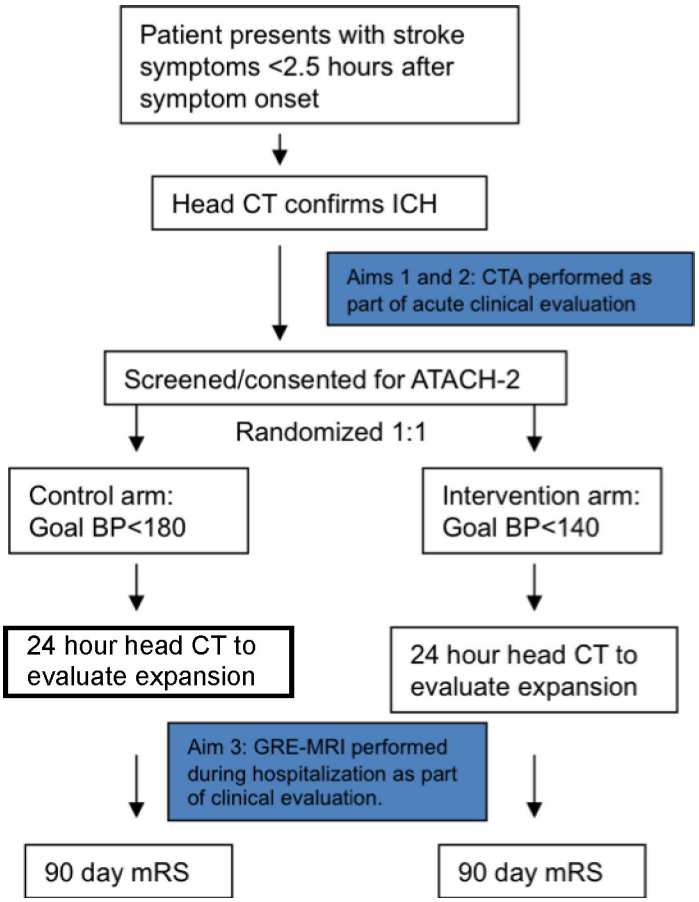

Figure 2. Schema for ATACH-2 with *boxes in blue* indicating where imaging required for SCORE-IT will be performed.

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.

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References

1. Brott T, Broderick J, Kothari R, Barsan W, Tomsick T, Sauerbeck L, Spilker J, Duldner J, Khoury J. Early hemorrhage growth in patients with intracerebral hemorrhage. *Stroke* 1997;28:1–5.
2. Kazui S, Naritomi H, Yamamoto H, Sawada T, Yamaguchi T. Enlargement of spontaneous intracerebral hemorrhage. Incidence and time course. *Stroke* 1996;27:1783–7.

3. Fisher CM. Pathological observations in hypertensive cerebral hemorrhage. *J Neuropathol Exp Neurol* 1971;30:536–50.
4. Greenberg SM, Nandigam RN, Delgado P, Betensky RA, Rosand J, Viswanathan A, Frosch MP, Smith EE. Microbleeds versus macrobleeds: evidence for distinct entities. *Stroke* 2009;40:2382–6.
5. Xi G, Wagner KR, Keep RF, Hua Y, de Courten-Myers GM, Broderick JP, Brott TG, Hoff JT, Muizelaar JP. Role of blood clot formation on early edema development after experimental intracerebral hemorrhage. *Stroke* 1998;29:2580–6.
6. Rosenberg GA, Navratil M. Metalloproteinase inhibition blocks edema in intracerebral hemorrhage in the rat. *Neurology* 1997;48:921–6.
7. Mayer SA. Ultra-early hemostatic therapy for intracerebral hemorrhage. *Stroke* 2003;34:224–9.
8. Flibotte JJ, Hagan N, O'Donnell J, Greenberg SM, Rosand J. Warfarin, hematoma expansion, and outcome of intracerebral hemorrhage. *Neurology* 2004;63:1059–64.
9. Davis SM, Broderick J, Hennerici M, Brun NC, Diringer MN, Mayer SA, Begtrup K, Steiner T. Hematoma growth is a determinant of mortality and poor outcome after intracerebral hemorrhage. *Neurology* 2006;66:1175–81.
10. Fujii Y, Takeuchi S, Sasaki O, Minakawa T, Tanaka R. Multivariate analysis of predictors of hematoma enlargement in spontaneous intracerebral hemorrhage. *Stroke* 1998;29:1160–6.
11. Goldstein JN, Fazen LE, Snider R, Schwab K, Greenberg SM, Smith EE, Lev MH, Rosand J. Contrast extravasation on CT angiography predicts hematoma expansion in intracerebral hemorrhage. *Neurology* 2007;68:889–94.
12. Broderick JP, Brott TG, Duldner JE, Tomsick T, Huster G. Volume of intracerebral hemorrhage. a powerful and easy-to-use predictor of 30-day mortality. *Stroke* 1993;24:987–93.
13. Hemphill JC 3rd, Bonovich DC, Besmertis L, Manley GT, Johnston SC. The ICH score: a simple, reliable grading scale for intracerebral hemorrhage. *Stroke* 2001;32:891–7.
14. Davis SM, Broderick J, Hennerici M, Brun NC, Diringer MN, Mayer SA, Begtrup K, Steiner T. Hematoma growth is a determinant of mortality and poor outcome after intracerebral hemorrhage. *Neurology* 2006;66:1175–81.
15. Hedner U. Recombinant activated factor VII as a universal haemostatic agent. *Blood Coagul Fibrin* 1998;9(Suppl 1):S147–52.
16. Hedner U, Ingerslev J. Clinical use of recombinant FVIIa (rFVIIa). *Transfus Sci* 1998;19:163–76.
17. Monroe DM, Hoffman M, Oliver JA, Roberts HR. A possible mechanism of action of activated factor VII independent of tissue factor. *Blood Coagul Fibrin* 1998;9(Suppl 1):S15–20.
18. Mayer SA. Ultra-early hemostatic therapy for primary intracerebral hemorrhage: a review. *Canadian J Neurol Sci* 2005;32(Suppl 2):S31–7.
19. Mayer SA, Brun NC, Begtrup K, Broderick J, Davis S, Diringer MN, Skolnick BE, Steiner T. Recombinant activated factor Viiihti. Recombinant activated factor Vii for acute intracerebral hemorrhage [see comment]. *N Engl J Med* 2005;352:777–85.
20. Mayer SA, Brun NC, Begtrup K, Broderick J, Davis S, Diringer MN, Skolnick BE, Steiner T, The FTI. Efficacy and safety of recombinant activated factor VII for acute intracerebral hemorrhage. *N Engl J Med* 2008;358:2127–37.
21. Qureshi AI. Antihypertensive treatment of acute cerebral hemorrhage. *Crit Care Med* 2010;38:637–48.
22. Brott T, Broderick J, Kothari R, Barsan W, Tomsick T, Sauerbeck L, Spilker J, Duldner J, Khoury J. Early hemorrhage growth in patients with intracerebral hemorrhage. *Stroke* 1997;28:1–5.
23. Brouwers HB, Biffi A, Ayres AM, Schwab K, Cortellini L, Romero JM, Rost NS, Viswanathan A, Greenberg SM, Rosand J, Goldstein JN. Apolipoprotein E genotype predicts hematoma expansion in lobar intracerebral hemorrhage. *Stroke* 2012
24. Oleinik A, Romero JM, Schwab K, Lev MH, Jhawar N, Delgado Almandoz JE, Smith EE, Greenberg SM, Rosand J, Goldstein JN. CT angiography for intracerebral hemorrhage does not increase risk of acute nephropathy. *Stroke* 2009;40:2393–7.
25. Delgado Almandoz JE, Schaefer PW, Forero NP, Falla JR, Gonzalez RG, Romero JM. Diagnostic accuracy and yield of multidetector CT angiography in the evaluation of spontaneous intraparenchymal cerebral hemorrhage. *AJNR Am J Neuroradiol* 2009
26. Thompson AL, Kosior JC, Gladstone DJ, Hopyan JJ, Symons SP, Romero F, Dzialowski I, Roy J, Demchuk AM, Aviv RI, PREDICTS/Sunnybrook ICH CTA Study Group. Defining the CT angiography 'Spot Sign' in primary intracerebral hemorrhage. *Can J Neurol Sci.* Jul;2009 36(4):456–61.
27. Wada R, Aviv RI, Fox AJ, Sahlas DJ, Gladstone DJ, Tomlinson G, Symons SP. CT angiography 'Spot Sign' predicts hematoma expansion in acute intracerebral hemorrhage. *Stroke* 2007;38:1257–1262.
28. Li N, Wang Y, Wang W, Ma L, Xue J, Weissenborn K, Dengler R, Worthmann H, Wang DZ, Gao P, Liu L, Zhao X. Contrast extravasation on computed tomography angiography predicts clinical outcome in primary intracerebral hemorrhage: a prospective study of 139 cases. *Stroke* 2011;42:3441–6.
29. Hallevi H, Abraham AT, Barreto AD, Grotta JC, Savitz SI. The Spot Sign in intracerebral hemorrhage: the importance of looking for contrast extravasation. *Cerebrovasc Dis* 2010;29:217–20.
30. Demchuk AM, Dowlatshahi D, Rodriguez-Luna D, Molina CA, Blas YS, Dzialowski I, Kobayashi A, Boulanger JM, Lum C, Gubitz G, Padma V, Roy J, Kase CS, Kosior J, Bhatia R, Tymchuk S, Subramaniam S, Gladstone DJ, Hill MD, Aviv RI. Prediction of haematoma growth and outcome in patients with intracerebral haemorrhage using the Ct-angiography Spot Sign (Predict): a prospective observational study. *Lancet Neurol* 2012;11:307–14.
31. Delgado Almandoz JE, Yoo AJ, Stone MJ, Schaefer PW, Goldstein JN, Rosand J, Oleinik A, Lev MH, Gonzalez RG, Romero JM. Systematic characterization of the computed tomography angiography Spot Sign in primary intracerebral hemorrhage identifies patients at highest risk for hematoma expansion: the Spot Sign score. *Stroke* 2009;40:2994–3000.
32. Kim J, Smith A, Hemphill JC 3rd, Smith WS, Lu Y, Dillon WP, Wintermark M. Contrast extravasation on CT predicts mortality in primary intracerebral hemorrhage. *AJNR Am J Neuroradiol* 2008;29:520–5.
33. Almandoz JE, Yoo AJ, Stone MJ, Schaefer PW, Oleinik A, Brouwers HB, Goldstein JN, Rosand J, Lev MH, Gonzalez RG, Romero JM. The Spot Sign score in primary intracerebral hemorrhage identifies patients at highest risk of in-hospital mortality and poor outcome among survivors. *Stroke* 2010;41:54–60.
34. Delgado Almandoz JE, Yoo AJ, Stone MJ, Schaefer PW, Oleinik A, Brouwers HB, Goldstein JN, Rosand J, Lev MH, Gonzalez RG, Romero JM. The Spot Sign score in primary intracerebral hemorrhage identifies patients at highest risk of in-hospital mortality and poor outcome among survivors. *Stroke* 2010;41:54–60.
35. Evans A, Demchuk A, Symons SP, Dowlatshahi D, Gladstone DJ, Zhang L, Fox AJ, Aviv RI. The Spot Sign is more common in the absence of multiple prior microbleeds. *Stroke* 2010;41:2210–7.

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36. Greenberg SM, Vernooij MW, Cordonnier C, Viswanathan A, Al-Shahi Salman R, Warach S, Launer LJ, Van Buchem MA, Breteler MM. Cerebral microbleeds: a guide to detection and interpretation. *Lancet Neurol* 2009;8:165–74.

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