Results from trials with haemostatic drugs, such as intravenous recombinant factor VIIa (rFVIIa), have shown reductions in haematoma expansion, but have not consistently shown improved clinical outcomes. This apparent discrepancy might be due to the inclusion of a majority of patients unlikely to benefit from haemostatic therapy, since only one in three patients with ICH have substantial haematoma expansion within the first few hours. Furthermore, patients presenting to hospital with large haematomas will invariably have bad outcomes, with or without subsequent haematoma expansion. Perhaps the clinical efficacy of a haemostatic agent could be optimised by stratifying patients at highest risk of haematoma expansion, and excluding those destined for a poor outcome irrespective of therapy.4
A marker predictive of haematoma expansion could aid the selection of patients for haemostatic treatment, especially in patients presenting with small-to-moderate ICH volumes. One such important surrogate for identification of continued bleeding is contrast extravasation seen on CTA. The CTA spot sign refers to one or more foci of contrast enhancement within an acute primary parenchymal haematoma visible on the source images of CTA. Data from several single-centre studies9–14 show that the CTA spot sign is a marker of increased risk of haemorrhage growth. The CTA spot sign occurs in about a third of patients scanned within 3 h, and on the basis of data from the single-centre studies, the predictive value for substantial haematoma expansion within 3 h is high. Inter-reader reliability was good to very good (kappa ranging from 0·77 to 0·94) among physicians including neuroradiologists, fellows, and emergency doctors.9,10,12,15 Specificity and positive predictive value (PPV) decline with increasing time from onset, but negative predictive value (NPV) remains unchanged. Recently, a spot-sign score was developed on the basis of single-centre data, and it was predictive of extent of haematoma expansion11 and clinical outcome.16

The primary aim of the predicting haematoma growth and outcome in intracerebral haemorrhage using contrast bolus CT (PREDICT) study was to validate previous single-centre observations in a prospective multicentre study with blinded evaluation of haematoma volume and CTA spot-sign interpretation. We sought to establish the sensitivity, specificity, and predictive values of the CTA spot sign for predicting haematoma expansion and clinical outcome.

Methods

Patients

PREDICT was a multicentre, prospective, observational cohort study of patients aged 18 years or older who presented with an acute symptomatic and radiologically confirmed ICH. Patients were eligible for entry if they presented within 6 h of onset with a primary or anticoagulant-associated ICH of less than 100 mL (estimated using ABC/2 methods).7,10 Exclusion criteria included known renal impairment that precluded CTA, premorbid dependence defined as modified Rankin scale (mRS) score greater than 3, secondary cause of ICH (eg, tumour, arteriovenous malformation), deep coma, or major comorbid or terminal illness. Treatments such as off-label rFVIIa or surgical evacuation were allowed at the discretion of the treating physician. Patients were excluded from the primary analysis if surgery or other neurosurgical intervention was done before follow-up CT.

The PREDICT study protocol was approved by the research ethics board of the University of Calgary. CTA source image data were collected data and submitted it by fax to the coordinating centre at the University of Calgary. CTA spot-sign status did the volumetric analysis at the Department of Community Health Sciences, University of Calgary, Calgary, AB, Canada.

Procedures

We recorded baseline demographic characteristics, medical history, clinical presentation, baseline and follow-up imaging findings, type and timing of treatments, neurological deficits (National Institutes of Health stroke scale, NIHSS) at time of treatment, complications, presumed cause of ICH, cause of death, and outcome (mRS) at 3 months. Participating centres collected data and submitted it by fax to the coordinating centre at the University of Calgary. All patients enrolled in this study underwent CTA through the entire haematoma volume after the diagnostic non-contrast CT scan. The CTA was done using a bolus-tracking method by injecting 50–100 mL of non-ionic iodinated contrast at 4–6 mL/s; there were no CT specifications, and the protocol for the CTA varied slightly by institution, reflecting a pragmatic approach to acquisition of imaging data. CT haematoma volumes were analysed with the Quantomo computerised-planimetry software (Cybertral Inc, Calgary, Canada), which has been validated for use in ICH analysis.8 A stroke neurologist (AMD) masked to patient outcome, CTA scans, and spot-sign status did the volumetric analysis at the University of Calgary. CTA source image data were transferred to the University of Toronto for independent interpretation for the presence or absence of the spot sign by a neuroradiologist (RIA) who was masked to outcome and follow-up non-contrast CT. To ensure study integrity and masking of both readers, the project officer (DD) independently combined the two image interpretation datasets at a third institution, the University of Ottawa. The spot sign was defined according to four criteria: (1) serpiginous or spot-like appearance within the margin of a parenchymal haematoma without connection to an outside vessel; (2) contrast density greater than 1·5 mm in diameter in at least one dimension; (3) contrast density (Hounsfield units, HU) at least double that of the background haematoma; and (4) no hyperdensity at the corresponding location on non-contrast CT (figure 1).

The primary outcome was substantial haematoma expansion at follow-up CT defined as an absolute growth greater than 6 mL or relative growth of more than 33% from initial CT.14 Other definitions of haematoma expansion were also explored as a secondary analysis because no consensus existed on the preferred cutoff for clinically significant haematoma expansion; haematoma expansion greater than 12·5 mL correlated best to clinical outcome in a previous study of an ICH cohort.13 Secondary outcomes included early neurological worsening (defined as worsening of ≥4 points in the NIHSS score at 24 h compared with baseline), mRS score at 3 months, and mortality at 3 months.
### Statistical analysis

We analysed data using standard descriptive statistics stratified by presence of the CTA spot sign. A multivariable model was designed to allow for adjusted estimates of the role of the CTA spot sign in predicting the primary outcome. In this model we considered the CTA spot sign as a forced variable. We considered additional variables that showed univariable association with the primary outcome and included them in the final model if they showed evidence of a significant effect (p<0·05) or if the very evidence of confounding on the CTA spot-sign variable. We assessed two-way interactions among the variables in the final model only. We used a generalised linear mixed model, binomial family, with log link to directly generate risk ratios as an effect size measure. We calculated sensitivities, specificities, PPV, and NPV for a CTA spot sign to predict the primary outcome. Finally, we used Kaplan-Meier analysis to explore the relationship between spot-sign status and case-fatality. Several patients had missing clinical outcomes, and they were censored at day 1, since we knew their vital status at the time of their follow-up CT scan.

We did the statistical analyses using SPSS 18.0 and STATA 11.0. We estimated that a sample size of 162 patients, with about half in each of the 0–3 h and 0–6 h windows, would allow us to detect an absolute difference of 30% in the 0–3 h window and a 25% difference in the 3–6 h window in the proportion of patients with haematoma expansion, between those with a CTA spot-sign and those without it.

### Role of the funding source

The study sponsors had no role in study design, data collection, data analysis, data interpretation, or writing of the manuscript. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

### Results

268 patients were enrolled in 12 centres in six countries from June 24, 2006, to Sept 6, 2010. No adverse events were reported directly attributable to the CT angiogram. 40 patients were excluded from the primary analysis for the following reasons: 14 were treated with rFVIIa before follow-up CT; 15 were treated with surgical evacuation before follow-up CT; seven died before follow-up CT; and four did not have a follow-up CT for unknown reasons. The excluded population had a high spot-sign positive rate of 64% (14 of 22) with rFVIIa treatment, 57% (four of seven) with early death, and 47% (seven of 15) with early surgery.

The primary analysis included 228 patients. Their median baseline ICH volume was 19·9 mL (range 1·5–80·9) in the CTA spot-sign positive group and 10·0 mL (0·1–102·7) in the CTA spot-sign negative group (table I). For the primary study outcome, median ICH volume expansion was 8·6 mL (–9·3 to 121·7) in the CTA spot-sign positive group versus 0·4 mL (–11·7 to 98·3) in the CTA spot-sign negative group (p<0·001). The CTA spot positive sign was associated with a more severe clinical presentation.
Table 2: Primary and secondary study outcomes

<table>
<thead>
<tr>
<th></th>
<th>Spot-sign positive (n=61)</th>
<th>Spot-sign negative (n=167)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary imaging outcome</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Met either 6 mL or 33% growth criteria</td>
<td>37 (60.7%)</td>
<td>36 (21.6%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Component and secondary imaging outcomes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absolute ICH growth (mL) 8.6 (9.6 to 21.7)</td>
<td>4 (11.7 to 28.3)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Relative ICH growth (%) 37.7 (22.7 to 54.1)</td>
<td>5.0 (13.5 to 56.4)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Absolute NIHSS growth (mL) 9.6 (-12.3 to 36.3)</td>
<td>0.3 (-22.4 to 53.2)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Absolute total growth (mL) 12.7 (-15.1 to 200.0)</td>
<td>0.3 (-11.3 to 98.3)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Met 6 mL growth criteria 34 (55.7%)</td>
<td>23 (13.8%)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Met 12.5 mL growth criteria 28 (45.9%)</td>
<td>12 (7.2%)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Met 33% growth criteria 33 (54.1%)</td>
<td>31 (18.6%)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Met either 12.5 mL or 33% growth criteria 34 (55.7%)</td>
<td>32 (19.2%)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

**Secondary clinical outcomes**

- 4-point worsening in NIHSS score at 24 h
  - 175/32 (50.8%) vs 19/139 (14%) p=0.006
- mRS score at 90 days
  - 5 (0–6) vs 3 (0–6) p<0.001
- Mortality at 3 months
  - 23/53 (43.4%) vs 31/158 (19.6%) p=0.001

Data are n/N (%) or median (range). ICH=intracerebral haemorrhage. IVH=intraventricular haemorrhage.

Table 3: Predictors of the primary outcome

<table>
<thead>
<tr>
<th>Univariable (selected variables)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;80 years*</td>
<td>1.2 (0.8–1.9)</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.1 (0.7–1.7)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.0 (0.6–1.6)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.0 (0.6–1.6)</td>
</tr>
<tr>
<td>Antiplatelet use</td>
<td>1.2 (0.7–2.1)</td>
</tr>
<tr>
<td>Anticoagulant use</td>
<td>2.8 (2.0–3.9)</td>
</tr>
<tr>
<td>Systolic blood pressure &gt;200*</td>
<td>0.6 (0.3–1.2)</td>
</tr>
<tr>
<td>NIHSS score ≥18*</td>
<td>1.7 (1.1–2.5)</td>
</tr>
<tr>
<td>Onset-to-CTA time &lt;90 min</td>
<td>1.9 (1.2–2.7)</td>
</tr>
<tr>
<td>CTA spot-sign positive</td>
<td>2.8 (2.0–4.0)</td>
</tr>
</tbody>
</table>

Multivariable model†

| CTA spot-sign positive                            | 2.3 (1.6–3.1)                    |

RR-relative risk. NIHSS=National Institutes of Health stroke scale.
CTA=CT angiography. *Dichotomised at the population 75th percentile.
†Interaction term—anticoagulation use by onset-to-CTA time <90 min, p=0.006.

defined by lower Glasgow coma scale and higher NIHSS scores (table 1). Anticoagulant use seemed to be slightly more common in the CTA spot-sign positive group (13% vs 7%; p=0.17).

Time from onset to CTA was ≤180 min in 131 (57%) of all patients and 181–360 min in 97 (43%) patients. The CTA spot sign was not more common in the early imaging group ≤180 min from onset; p=0.29. For this reason, we present our results unstratified by onset-to-imaging time. Median time from baseline CT to follow-up CT was 23·8 h for spot-sign negative and 22·5 h for spot-sign positive patients. Median time from symptom onset to follow-up CT was 26·1 h for spot-sign negative and 24·2 h for spot-sign positive patients.

Site investigator interpretations for contrast extravasation were prospectively collected for 129 patients. A comparison of the interpretation of contrast extravasation by the site investigators and determination of the spot-sign by the core laboratory neuroradiologist revealed good agreement, with a kappa of 0.72, despite the fact that the definition of spot sign was not established at the start of the study and no formal site investigator training took place.

Haematoma expansion, according to all definitions used, was significantly more frequent in the CTA spot-sign positive group than in the spot-sign-negative group (table 2). Multivariable analysis did not alter the estimate of the effect size for the CTA spot sign (table 3). However, a multiplicative interaction between use of anticoagulants and time from onset to CTA was identified. The direction of effect of this interaction was such that if a patient was imaged within 90 min of onset, there was no effect of anticoagulation use in predicting haematoma expansion. If the patient was imaged later than 90 min after onset, anticoagulant use was an important predictor of haematoma expansion. Age, sex, clinical stroke severity, and blood pressure were not predictors of haematoma expansion.

Our biological premise was that the CTA spot sign is a marker of active haemorrhage that occurs before the ICH expands in volume, implying that the CTA spot sign and the resulting ICH volume are in a direct causal pathway. However, this premise might be incorrect in all or some cases. For example, peripheral CTA spot signs might be due to the mass effect of the ICH causing vascular tearing and contrast extravasation. Therefore, we also considered a model that included both the spot sign and baseline ICH volume as predictors of the primary outcome, adjusting for time from onset to CTA. In this model, the CTA spot sign continued to be a predictor of the primary outcome (relative risk, RR 2.6, 95% CI 1.8–3.7) whereas baseline ICH volume was not (RR 1.0, 0.9–1.0). There was no evidence of an interaction between ICH volume and the CTA spot sign in predicting the primary outcome, nor of significant confounding.

For a haematoma expansion >6 mL or >33%, the PPV for the CTA spot sign was 61% (95% CI 47–73), and the NPV was 78% (71–84), with 51% (39–63) sensitivity and 85% (78–90) specificity. For haematoma expansion, contrast extravasation assessed by site investigator had a PPV of 58%, NPV of 80%, 50% sensitivity, and 85% specificity.

Clinical neurological deterioration of four points or more on the NIHSS score occurred in 17 (32%) of 53 versus 19 (14%) of 139 patients with the CTA-spot sign (RR 2.3, 95% CI 1.3–4.2). mRS scores at 90 days were median 5 in the spot-sign positive group and 3 in the spot-sign negative group.

Mortality at 3 months was 43–4% (23 of 53) in the CTA spot-sign positive group versus 19–6% (31 of 158) in the CTA spot-sign negative group (age-adjusted hazard ratio,
Discussion

This prospective multicentre study confirms the association between the CTA spot sign and haematoma expansion. The CTA spot sign is highly predictive of haematoma expansion irrespective of haematoma expansion definition and for both intraparenchymal and intraventricular haemorrhage growth. The CTA spot sign is associated with a poor prognosis, high rates of early clinical deterioration, and mortality, often occurring within days after onset. The spot sign is also associated with larger haemorrhage, more severe clinical presentation, and decompression of the haemorrhage into the intraventricular space. Larger haemorrhages tend to cause more dramatic clinical symptoms and hence earlier presentation to hospital. Anticoagulation therapy might simply result in a greater phenotypic expression of the spot sign, such as multiple spot signs, and result in greater haematoma expansion by prevention of clotting. These correlations have implications for future trial design in patients with acute intracerebral haemorrhage. The relevance of the interaction between anticoagulant use and time from onset to CTA should be considered as hypothesis-generating and needs to be further explored. Although it might be biologically plausible, and consistent with previous studies, to consider time the most important variable in predicting haematoma expansion, the reasons why this interaction occurs are less than clear. Imaging studies using various techniques have identified a relationship between contrast extravasation and haematoma expansion (panel). In 1972, Kowada and colleagues showed contrast extravasation in five of 12 patients who underwent serial cerebral angiography within 5 h of ICH onset. Extravasated contrast in the arterial phase grew in size and density until the early venous phase and predicted haematoma expansion at surgical evacuation. Contrast extravasation on MRI has also been shown to be an indicator of continued haemorrhage in patients with acute ICH.

With the advent of multislice spiral CT, CTA is becoming a standard vascular imaging approach for the early assessment of patients with ischaemic stroke and for the identification of secondary causes of ICH, such as aneurysms and arteriovenous malformations. The link between CTA findings and ICH prognosis was first described in a large retrospective study by Becker and colleagues, in which they showed that extravasation of radiographic contrast on CTA was an independent predictor of in-hospital mortality. Contrast extravasation was seen in 52 (46%) of 113 patients at the time of CT. The presence of contrast extravasation was associated with increased mortality (63-5% vs 16-4% in those without it). Prediction of haematoma expansion by contrast extravasation on CTA has been described in reports of a number of single-centre studies. Wada and colleagues coined the term CTA spot sign to describe foci of contrast enhancement within an acute primary parenchymal haematoma seen on CTA source images. CTA spot sign occurred in about a third of patients scanned within 3 h of symptom onset. In three single-centre studies, specificity and PPV of the CTA spot sign declined with longer times from onset to CTA, although the NPV remained unaffected by time from onset to CTA.

The PREDICT study confirms the findings of these single-centre studies, but the PPV and NPV of the CTA

Figure 2: Risk of death by CTA spot-sign status

Log-rank test p=0·0006. Shaded areas represent 95% confidence intervals.

HR 2.4, 95% CI 1.4–4.0; p=0.002). The association between CTA spot-sign positive group and mortality remained significant in a sensitivity analysis whether patients lost to follow-up were assigned a mRS of 0 or 6 (data not shown). Kaplan-Meier analysis revealed an early difference in mortality between CTA spot-sign positive and CTA spot-sign negative groups, which was sustained during the follow-up period (p=0.0006; figure 2). In a post-hoc analysis, we assessed the role of coagulopathy in predicting outcome. Of 204 patients with international normalised ratio and activated partial thromboplastin time (aPTT) values at baseline, 169 (83%) had no evidence of coagulopathy (baseline international normalised ratio <1.2 or a PTT<40 s) and the spot-sign frequency was 25% (42 of 169), compared with 11 (31%) of 35 patients with a coagulopathy (p=0.406). For this subgroup analysis of patients without coagulopathy (169 patients) who had follow-up CT, the median baseline ICH volume was 18.8 mL (range 1.5–80.8) in the CTA spot-sign positive group and 10.0 mL (0.1–81.5) in the CTA spot-sign negative group (p<0.001). Median ICH volume expansion was 6.0 mL (–3.0 to 83.9) in the CTA spot-sign-positive patients versus 0.2 mL (–10.6 to 98.3) in the CTA spot-sign-negative patients (p<0.001). 24 patients had missing international normalised ratio vales, PTT values, or both, and among these eight had the spot sign of whom five met the primary outcome.

The PREDICT study confirms the findings of these single-centre studies, but the PPV and NPV of the CTA
Spot sign were not as robust. Positive predictive values from the single centre studies 9–11 varied considerably (24–77%, compared with 61% in the present study), whereas negative predictive values were higher (96–98%, compared with 78% in the present study). One explanation is that only first-pass CTA images were available for detection of the CTA spot sign in PREDICT. Recent studies have suggested that second-pass imaging done 1 min or more after initial administration of a contrast bolus can increase the yield and sensitivity of contrast extravasation.26,27 Furthermore, time-resolved dynamic CTA can detect late spot signs absent in first-pass CTA presumably because of poor cardiac output or high arterial resistance.27 These delayed imaging modalities might provide additional information on the pathophysiology of the CTA spot sign. Further prospective studies using second-pass CTA could refine the notion of contrast extravasation and risk of haematoma expansion. New CT technologies allow for dynamic contrast imaging over 1 min or longer producing dynamic CTA and CT-perfusion images. These techniques provide real-time information on contrast leakage and allow estimates of contrast leakage rate, which should correlate more closely with the magnitude of haematoma expansion than current “single snapshot in time” CTA imaging.28,29

There are other limitations of this study that should be considered when interpreting the results. Although the imaging data acquisition was pragmatic, using various CT systems, the radiological interpretation was not. To evaluate the primary outcome, we used a gold standard assessment of spot sign done by a core laboratory neuroradiologist. When an untrained site investigator interpreted the presence of contrast extravasation, the utility of CTA for predicting haematoma expansion was less robust. Several patients died very early (<24 h) after onset presumably owing to large ICH volumes or haematoma expansion that resulted in a change in do-not-resuscitate (DNR) status. This group had a high CTA spot-sign rate, and its exclusion might have produced an underestimation of haematoma expansion volume and CTA spot-sign prevalence. Another group of patients received treatments that make useful interpretation of their data for haematoma expansion impossible, such as early surgical evacuation and off-label use of rFVIIa. In future clinical trials of haemostatic drugs using spot-sign detection, early death or early surgery should be considered as secondary outcomes, given the frequency with which these events can occur.

One technical limitation might have been the variability in timing of contrast bolus administration among institutions, which might have altered the ability to detect a CTA spot sign, although we did not see significant differences in spot-sign positive frequency amongst our highest recruiting sites. A small number of patients with coagulopathic haemorrhages were grouped together with those with non-coagulopathic haemorrhages. Although the spot sign retains its importance in predicting future deterioration in both groups, it is clear that these types of haemorrhage are clinically different, and progress at different rates. Finally, we cannot exclude potential clinical care confounders such as DNR orders, blood pressure and glucose control, or intensive-care-unit care, that might have arisen based on the treating clinician’s knowledge of the spot-sign status of the patient. This limitation is inherent to the observational design of our study and will be addressed by ongoing clinical trials.

Given the robust value of CTA spot sign as a marker of haematoma expansion, these results confirm that a subpopulation of patients with ICH can be identified by CTA. The usefulness of the CTA spot sign should be tested in proof-of-concept trials of haemostatic drugs in patients with ICH. A phase 2 trial stratifying patients by presence of CTA spot sign should show a large reduction in haematoma expansion with early rFVIIa treatment and thereby translate into improved clinical outcomes. rFVIIa has already been shown to reduce haematoma expansion by 4 mL overall, even in a heterogeneous population of patients we can presume included many who were not actively bleeding.7 Enrolment of patients with the CTA spot sign is likely to magnify the reduction in haematoma expansion with rFVIIa because the population would be skewed toward those actively bleeding. Such an effect could compensate for any
downside risk associated with rFVIIa due to ischaemic complications, such as myocardial infarction and ischaemic stroke that were detected in the FAST trial.\textsuperscript{11} Two such trials stratifying patients according to the presence of a CTA spot sign have just begun recruitment in North America—SPOTLIGHT (NCT00810888) and STOP-IT (NCT01359202).

In conclusion, CTA can identify a subpopulation of patients with ICH with the spot sign who are at high risk of substantial intracerebral and intraventricular haematoma expansion, early neurological deterioration, and early mortality. Randomised trials of haemostatic treatment, such as rFVIIa, should be done in ICH patients with a positive spot sign on CTA.

Contributors
AMD and SS had the idea for the study, developed the case report forms and the clinical database, and encouraged international colleagues to contribute data to the study. AMD wrote the first draft of the manuscript and the final report. AMD supervised the design and execution of the study, and contributed to subsequent versions of the manuscript. DD and MDH did the statistical analyses. RA did all spot sign interpretations from CTA database and the volume segmentation done by AMD. AMD did all volume segmentations. RA did all spot sign interpretations from CTA source images. All remaining authors were site principal investigators who contributed by enrolling patients at their individual centres. All authors reviewed the study report, made comments or suggestions on the manuscript drafts, and approved the final version.

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Conflicts of interest
DJG is the principal investigator and AMD, RIA, and MDH are members of the executive committee of the SPOTLIGHT trial. All other authors declare that they have no conflicts of interest.

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References


