

Infarct Volume-Based Subgroup Selection in Acute Ischemic Stroke Trials

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Background and Purpose—We investigated whether hyperintensities with a diameter of at least 3, 3.5, and 4 cm and visible on at least 3 slices on diffusion-weighted imaging enables patient selection with an infarct volume of ≥ 15 mL.

Methods—Consecutive acute stroke patients were screened for the AXIS2 trial and examined according to a standardized magnetic resonance imaging protocol in 65 sites. Diffusion-weighted lesion diameters were measured and compared with volumetric assessments.

Results—Out of 238 patients, 86.2% (N=206) had infarct diameter of at least 3 cm. Volumetric assessments showed infarct volume of ≥ 15 mL in 157 patients. A cut-off value of 3 cm led to 96.8% sensitivity and 33.3% specificity for predicting lesion volume of ≥ 15 mL. Analogously, a 3.5 cm cut-off led to 96.8% sensitivity and 50.6% specificity and a 4 cm cut-off led to 91.7% sensitivity and 61.7% specificity.

Conclusions—Lesion diameter measures may enable multicentric patient recruitment with a prespecified minimal infarct volume.

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Key Words: clinical trial ■ infarction ■ stroke

Magnetic resonance imaging is increasingly being used in stroke trials for early assessment and diagnosis of acute ischemic stroke. In many stroke trials, a cut-off infarct volume is used as an inclusion criterion for enrollment because previous studies have shown differences in response to thrombolytic treatment based on infarct size.¹ However, current methods for measurement of lesion size remain laborious and time-consuming. For example, the gold standard planimetric method entails manual delineation of infarct borders on all slices. Therefore, in the time-sensitive setting of acute stroke treatment, there is a need for an efficient and reliable method to aid in the estimation of infarct volume.

The recently completed AXIS2 trial was a multicenter, randomized, placebo-controlled trial with the primary aim to investigate the clinical efficacy of granulocyte colony-stimulating factor in acute ischemic stroke patients.² One of the main inclusion criterion for enrollment was a baseline infarct volume of ≥ 15 mL based on the following rule: patients whose largest extension of the infarct measures to be ≥ 3 cm and whose infarct is present on ≥ 3 consecutive diffusion-weighted imaging (DWI) slices.

We aimed to determine the sensitivity and specificity of this rule in the estimation of infarct volume. We also investigated whether hyperintensities on DWI with a diameter of at least 3.5 and 4 cm and visible on at least 3 consecutive slices on diffusion-weighted imaging enables patient selection with a minimal infarct volume of 15 mL.

Methods

This is a secondary study of consecutive acute stroke patients screened within 9 hours of symptom onset with standardized stroke Magnetic resonance imaging protocol (AXIS2 trial; NCT00927836; www.clinicaltrials.gov). Major inclusion criteria included a ≤ 9 -hour time window after onset, infarct localization in the middle cerebral artery territory, baseline NIHSS range from 6 to 22, and a baseline lesion volume on DWI of ≥ 15 mL. DWI lesion volumes were estimated using the aforementioned rule (largest infarct diameter ≥ 3 cm and visible infarct on 3 consecutive slices). Subsequently, lesion volumes were determined by manual planimetric delineation. Diffusion restriction in cortical and subcortical regions was

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Table. Basic Demographics and Baseline Clinical Parameters of Study Group

| Basic Demographics | |
|--|------------------|
| N | 238 |
| Age, median (IQR) | 71 (63–77) |
| Female, % (n) | 47.5% (113) |
| BMI, median (IQR) | 26.8 (24.5–30.1) |
| NIHSS on admission, median (IQR) | 11 (9–17) |
| Time to infusion of study treatment in hours, median (IQR) | 7.0 (5.8–8.4) |
| Baseline DWI lesion volume in mL, median (IQR) | 26 (10.7–62.2) |
| Number of slices with DWI restriction, median (IQR) | 8 (6–11) |

BMI indicates body mass index; DWI, diffusion-weighted imaging; and IQR, interquartile range.

differentiated; total lesion volume was calculated as a sum of both volumes.

In this study, all acute DWI images were assessed; the total number of consecutive slices in which an infarct was visible was counted and the most extensive diameter was measured. Lesion diameter was compared with volumetric assessments; cut-off diameters of 3, 3.5, and 4 cm were assessed for their sensitivity and specificity in predicting a lesion volume of ≥ 15 mL. All statistical analyses were performed using SPSS version 19 (Chicago, IL).

Results

In the AXIS2 trial, 328 patients were enrolled; 87 patients had DWIs that were not compatible with our Image Viewing Software (MRICroN and Efilm), and 3 patients' DWI had extensive movement artifacts, which did not allow for volumetric

analysis. Therefore, 238 patients were included for final analysis. Basic demographics and baseline clinical parameters are summarized in Table. Volumetric assessments showed infarct volume of < 15 mL in 81 patients and ≥ 15 mL in 157 patients.

A cut-off value of 3 cm led to a 96.8% sensitivity and 33.3% specificity. Fifty-four cases were false positives, in which infarct diameter was ≥ 3 cm, yet lesion volume was < 15 mL (Figure). Twenty-seven cases were true negatives, in which infarct diameter was ≤ 3 cm, correctly predicting an infarct volume of at least 15 mL. The false positives and true negatives differed significantly in terms of infarct volume (median of 8.8 mL IQR [5.6–11.8] versus Median of 2.8 mL IQR [1.6–6.1]; $P < 0.001$) and in terms of consecutive slices with visible diffusion restriction (median number of slices 6 IQR [5–7.25] versus 4 IQR [3–5]; $P < 0.001$). The ratio of cortical restriction volume to subcortical restriction volume did not differ among groups (0.14 IQR [0.11–0.67] versus 0.01 IQR [0.0–0.65]; $P = 0.15$).

A cut-off value of 3.5 cm predicted infarct volume ≥ 15 mL with 96.8% sensitivity and 50.6% specificity; a cut-off value of 4 cm led to a 91.7% sensitivity and 61.7% specificity.

Discussion

Although a cut-off infarct diameter of 3 cm identifies patients with an infarct volume of ≥ 15 mL with high sensitivity (96.8%), specificity (33.3%) remains low because of overestimation of infarct volume in $\approx 23\%$ of cases. The patients who were falsely estimated to have infarct volumes of ≥ 15 mL tend to have larger DWI lesion volumes spanning across more slices than the true negatives. Therefore, a mere transversal diameter measurement may overestimate lesion size in borderline cases. A cut-off diameter of 3.5 cm did not

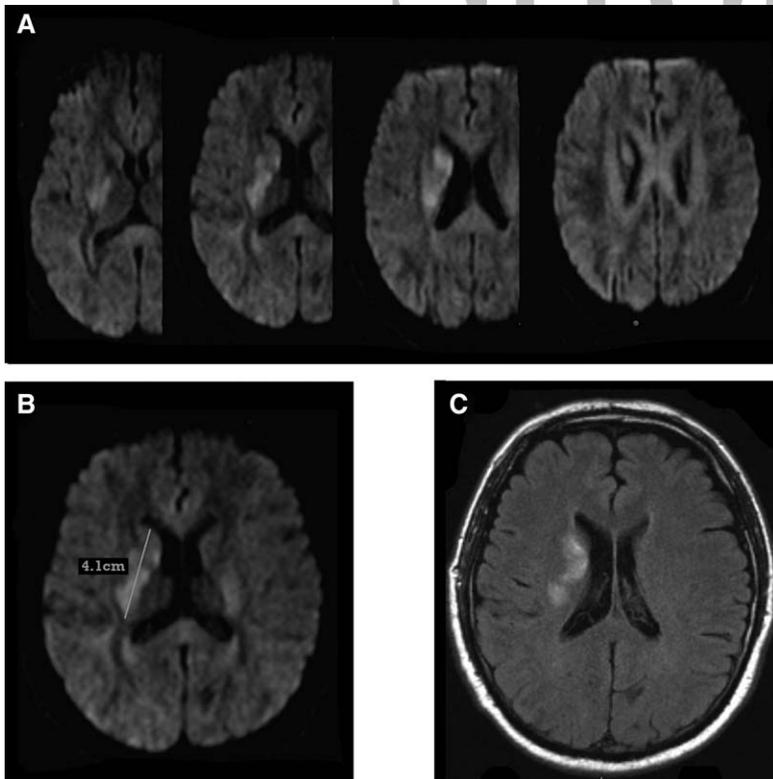


Figure. An example of a patient enrolled in AXIS2 trial based on volumetric assessment. The diffusion restriction spanned only over 3 consecutive slices (A), and maximum infarct diameter measured 4.1 cm (B). However, infarct volume was only 3.6 mL. Final lesion is depicted on follow-up FLAIR (C).

change the sensitivity (96.8%), yet increased the specificity (50.6%) of this technique, leading to an overestimation of lesion size in only 17% of patients. In other words, a cut-off diameter of 3.5 cm allocated more borderline cases correctly to either $<$ or ≥ 15 mL infarct volume compared with the 3 cm cut-off value. The use of a 4 cm cut-off increased specificity at the expense of sensitivity. Lesion localization in terms of cortical and subcortical restriction patterns did not seem to influence the estimation of lesion size using this rule.

Of note, in the AXIS2 trial, patients who did not meet the 3 cm diameter rule because of irregular infarct shape or partially separate volumes on the slices, could be included if the investigator provided written justification that the patient fulfilled this inclusion criteria. This may explain the low specificity in this analysis. The significantly higher DWI lesion volumes in the false-positive group compared with the true negative group supports this postulation.

An alternative method—the ABC/2 technique—was recently proposed as an efficient way to estimate lesion volume but was also shown to consistently overestimate lesion size.^{3,4} Although the ABC/2 method and simple diameter methods—such as this 3 cm cut-off rule—may be fast volumetric methods in estimating lesion size, the accuracy of these techniques may vary with other baseline characteristics like time from symptom onset.

Approximately 25% of patients from the original AXIS database (N=328) were excluded from this analysis because of the incompatibility of the raw imaging data with our local reading software. This is a limitation of this study; however, we found no significant differences between excluded and included patients in terms of age, stroke severity, or infarct volume. Furthermore, it should be noted that patients enrolled in the AXIS trial were imaged within 9 hours of symptom onset, which is not the case in all trials. Therefore, the applicability of these results should be viewed with some caution when implemented in patient groups imaged in differing time windows.

Summary and Conclusions

In conclusion, although the volumetric method used in the AXIS2 trial confirmed correctly estimated lesion volume in 75% of cases, a cut-off diameter of 3 cm lead to an overestimation in 23% of cases. A cut-off value of 3.5 cm may lead to a more specific estimation of lesion size without loss of sensitivity. Diameter-based estimation of infarct volume is a robust tool for harmonization of a study cohort in multicentric clinical trials; however, overestimation should be considered. A cut-off value should be chosen based on existing multicenter data sets.

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