The Yield of Multimodal Computed Tomography among Emergency Department Patients with Suspected Large Vessel Occlusion Stroke

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Objectives: Endovascular therapy (EVT) improves outcomes for appropriately selected acute ischemic stroke patients. Guidelines suggest rapid acquisition of non-invasive vascular imaging to screen suspected ischemic stroke patients for large vessel occlusion (LVO) and candidacy for EVT. We sought to quantify the yield of an LVO stroke screening process in an undifferentiated emergency department (ED) suspected stroke population as well as identify predictors of successful EVT. *Methods*: We identified a cohort of consecutive ED patients who received CT angiography and brain perfusion (CTA/P) imaging to determine candidacy for EVT during 2016. In keeping with the guidelines at that time, hospital protocol directed physicians to obtain CTA/P studies if time from the onset of symptoms was less than or equal to 6 hours, and the National Institute of Health Stroke Scale (NIHSS) more than or equal to 6 or if recommended by the consulting stroke neurologist. Final discharge diagnoses, EVT attempts, and successful reperfusion (TICI 2b or better) were recorded. Yield of CTA/P was compared among patients based on NIHSS and duration of symptoms. *Results*: Over a 12-month period, 406 suspected stroke patients were screened with CTA/P; 273 (67%) received a final diagnosis of ischemic stroke. Among cases screened, 53 (13%) underwent attempted EVT; 35 (9%) achieved successful reperfusion. Only 1 of 113 (1%) patients with an NIHSS less than 6 was successfully treated with EVT compared to 34 of 285 (12%) with higher NIHSS ($p = 0.001$). The probability of successful EVT declined with increasing symptom duration ($p = 0.009$ for trend). In multivariable analysis, NIHSS more than or equal to 6 was associated with successful EVT (odds ratio [OR] 4.0 [1.6 to 9.9]) but presentation within 6 hours of onset was not (OR 2.3 [0.8 to 6.7]). *Conclusions*: EVT candidates were common among suspected stroke patients screened with CTA/P in the ED, however, patients with NIHSS less than 6 rarely received successful EVT.

Key Words: Computed tomography—diagnostic testing—large-vessel occlusion stroke—emergency department

Introduction

Acute ischemic stroke (AIS) causes a significant burden of death and disability worldwide.[1] AIS due to occlusion of large cerebral vessels such as the proximal middle cerebral or intracranial carotid arteries is especially devastating. While such large vessel occlusion (LVO) strokes account for only 40% of AIS cases, they are responsible for over 80% of permanent disability and over 95% of stroke-related deaths.[2] While intravenous tissue plasminogen activator (t-PA) has been the mainstay of acute stroke therapy since its approval for use in 1996, its use is limited by the brief window of time during which it may be safely given and it is frequently ineffective for LVO strokes.[3,4] Fortunately, recent trials have demonstrated dramatic clinical benefit when appropriately selected LVO stroke patients are treated with endovascular therapy (EVT) such as stent retriever devices.[5-9]

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Key to the success of these trials was appropriate patient selection. In all positive EVT trials, advanced imaging techniques were used to screen patients for the presence of LVO and the absence of a large amount of irreversible "core" infarct was achieved using advanced imaging. While randomized trials of EVT used varying approaches to image-based screening, the two trials with the most favorable outcomes (EXTEND-IA[8] and SWIFT PRIME[6]) predominantly used computed tomography (CT) angiogram and perfusion. This "multimodal" CT-based imaging technique employs iodinated contrast and serial CT images to reconstruct the cerebral circulation and measure changes in density as contrast diffuses through the brain.[10] Mathematical models estimate mean transit times for contrast diffusion, which are used to generate maps of cerebral blood flow. This technique provides not only an estimate of the size of irreversible infarct, but also an estimation of the size of hypo-perfused tissue that is at risk (i.e., the ischemic penumbra).

In response to the publication of the positive EVT trials, the American Heart Association/American Stroke Association (AHA/ASA) issued a scientific statement with guidance for treating LVO AIS patients with EVT in late 2015.[11] EVT was recommended (class I, level of evidence A) for stroke patients with a NIHSS ≥6 and onset time ≤6 hours following rapid noninvasive vascular imaging.[11] Patients outside of these criteria might also be considered for screening, depending on the clinical context (class IIb, level of evidence B-R). The impact of such a screening process in an undifferentiated emergency department (ED) suspected stroke population is unclear. While there is an opportunity for substantial benefit of screening to patients who receive successful EVT interventions, the costs of acquiring multimodal CT imaging are not insubstantial. These include contrast and radiation exposure, direct costs related to the performance and interpretation of scans, and the additional time required to obtain images, which may delay t-PA administration. We aimed to better understand the yield of multimodal imaging (NCCT and CTA with CTP) for identifying EVT candidates and identify factors predictive of successful EVT.

Methods

Study Design

This retrospective cohort study examined consecutive patients with suspected stroke who received advanced imagining (CTA/CTP) in the emergency department to screen for EVT eligibility over one calendar year. The goal of this analysis was to examine the yield of CTA/CTP and identify characteristics associated with attempted and successful delivery of EVT to patients with LVO stroke. The study protocol as approved by the study institution IRB with waiver of informed consent.

Study Population and Data Abstraction

Following publication of the positive EVT stroke trials in 2015, the study institutions initiated a screening protocol for identification of EVT candidates among ED patients presenting with stroke-like symptoms. Consistent with AHA guidelines released at that time, the protocol suggested CTA/P imaging for all patients who present within 6 hours of their last known well time (LKWT) and whose NIHSS was 6 or greater.[11] CTA/P imaging was also performed for the selected patients outside of those parameters based on clinical judgment following the discussion between the ED physician and a consulting stroke neurologist. This analysis utilized the hospital administrative database to identify consecutive adult patients who underwent screening CTA/P imaging in the ED. Patients were excluded if their stroke symptoms began after arrival in the ED. A standard data collection tool was used to abstract patient characteristic, arrival mode, medical history, initial NIHSS, imaging timing and results, treatments administered, and the final discharge diagnoses were abstracted from the electronic medical record. Decision for EVT was made by neurointerventional and stroke neurology physicians and based on the clinical and imaging characteristics of the patient.

Outcomes

The primary outcomes were the proportion of patients screened with CTA/P who received attempted and successful EVT. EVT was considered attempted any time cerebral angiogram was undertaken with a goal of treating an acute LVO stroke. EVT was considered successful if an intervention resulted in a post-treatment TICI flow 2b or 3 as recorded by the procedure note. Secondary outcomes included the conditional probability of attempted or successful EVT by severity of stroke (NIHSS) and LKWT.

Statistical Analysis

Descriptive statistics were used to characterize the patient population screened with CTA/P. We calculated the proportion of cases that received attempted or successful EVT in both the suspected stroke population (all screened cases) and the confirmed ischemic stroke population. We then subdivided patients according to time from onset to imaging (OTI) (≤120, 121-270, 271-360, 361-720, and ≥721 minutes) and stroke severity (NIHSS <6, 6-11, 12-20, >20) and examined for trends in the probability of attempted and successful EVT across severity and symptom duration strata using linear regression and chi-square tests for the trend. Patients were also categorized according to the imaging protocol criteria by stroke severity (NIHSS <6 versus ≥6) and time from LKW to the door (<6 hours versus ≥6) and the probabilities of attempted and successful EVT were quantified for each group. To

examine the independent relationships between EVT, time from LKW, and stroke severity, logistic regression were performed. Potential covariates included clinical and demographic characteristics and transfer status. Stroke severity and LKW were dichotomized according to the screening protocol guidance as described above. Covariates with a bivariate association with successful EVT ($P < .25$) were added to the multivariable model followed by backwards elimination of variables with nonsignificant associations ($P < .05$).

Results

Between January 2016 and January 2017, a total of 433 suspected stroke patients underwent screening for LVO with CTA/P in the ED; 406 met criteria for inclusion (Fig 1). Characteristics of the study population are summarized in Table 1. There was a slight predominance of females, a median age of 68, and a high prevalence of comorbidities such as HTN (73.2%) and atrial fibrillation (23.9%). There were 113 (27.8%) stroke mimics among patients screened with CTA/P. These patients received a variety of alternative diagnoses including conversion (n = 18), seizure (n = 14), drug or alcohol toxicity (n = 9), hypertensive urgency/emergency (n = 8), and complex migraine (n = 6, Fig 1).

In total, 53 patients screened with CTA/P in the ED underwent attempted EVT. This represented 13.1% of all 406 screened cases (95% confidence interval [CI] 10.1%-16.7%).

Table 1. *Characteristics of patients with suspected stroke who were screened with multimodal CT imaging in the ED*

	All screened (N = 406)
Age (IQR)	68 (55-80)
Female	209 (51.5)
Ischemic stroke	274 (67.5)
Time from onset	193 (87-330)
NIHSS (IQR)	9 (5-17.75)
Comorbidities	
HTN	297 (73.2)
DM	139 (34.2)
A fib	97 (23.9)
Prior stroke	168 (41.4)
EVT attempted	53 (13.1)
Among IS	53 (19.3)
EVT successful	35 (8.6)
Among IS	35 (12.8)

Abbreviations: CTA/P, CT angiography and brain perfusion; DM, diabetes mellitus; EVT, endovascular therapy; HTN, hypertension; NIHSS, the National Institute of Health Stroke Scale.

Thus, the number of suspected stroke cases that were screened with the multimodal CT protocol to identify one EVT candidate (number needed to scree [NNS]) was 8 (6-10). Intervention successfully achieved TICI IIb/III flow in 35 cases (8.6% [6.2-11.8%]), yielding NNS of 12 (9-17). Considering only the 274 confirmed AIS cases, the yield of multimodal CT imaging was higher since all 53 (19.3% [15.1-24.4%]) attempted EVT cases and 35 (12.8%

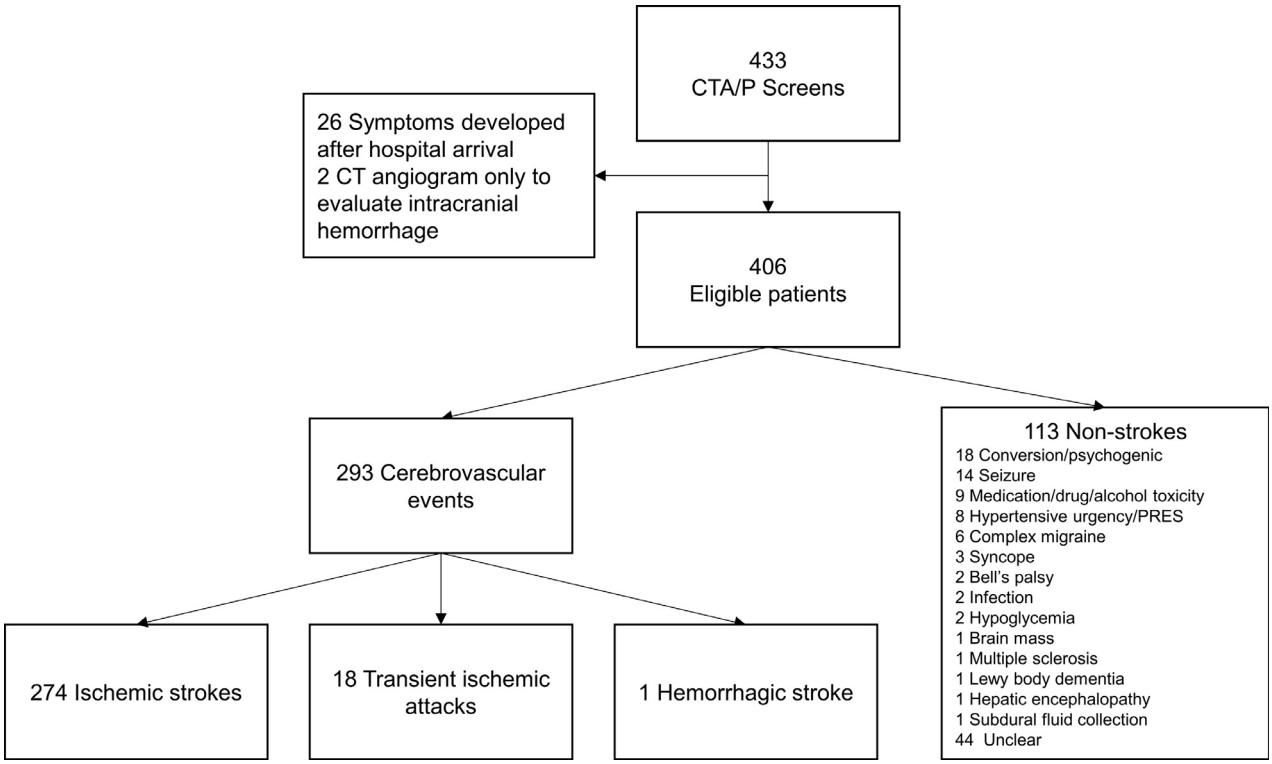

Figure 1. *Flow diagram of case ascertainment and final diagnoses.*

[9.3-17.3%]) successful EVT cases occurred among confirmed AIS patients.

The probability of both attempted and successful EVT trended higher with stroke severity (chi square test for trend $P < .001$ and .001, respectively). Conversely, the probability of attempted and successful EVT trended lower among patients with higher LKW to door times (chi square test for trend $P = .011$ and .009, Fig 2). When patients were categorized according to protocol-based criteria for CTA/P (NIHSS ≥6 and LKW ≤720 minutes), 218 patients met the default criteria for advanced imaging and 188 received discretionary screening. Of the 218 default imaging patients, 42 (19.3%) underwent attempted EVT versus 11 (5.6%) of 188 patients who underwent discretionary screening ($P < .001$). Likewise, 30 of 218 (13.8%) had successful EVT compared to 5 of 188 (2.7%, $P < .001$). Unadjusted comparisons between patients categorized by these two criteria revealed that patients who presented within 360 minutes of LKW time were more likely to undergo attempted EVT, but not more likely to receive successful EVT; patients with NIHSS ≥6 were more likely to receive both attempted and successful EVT (Table 2). Among the early presenters, those with NIHSS ≥6 were more likely to receive both attempted and successful EVT, but there were no significant differences by NIHSS among late presenters. Early presenters were not more likely to receive attempted or successful EVT than late presenters when subdivided by stroke severity.

Logistic regression results are summarized in Table 3. In univariable analysis, only NIHSS ≥6, LKW to door ≤360 minutes, and history of stroke in the past were associated with successful EVT. In multivariable logistic regression analysis adjusting for LKW time and prior stroke history, NIHSS ≥6 remained independently associated with successful EVT (adjusted OR 4.0) while prior

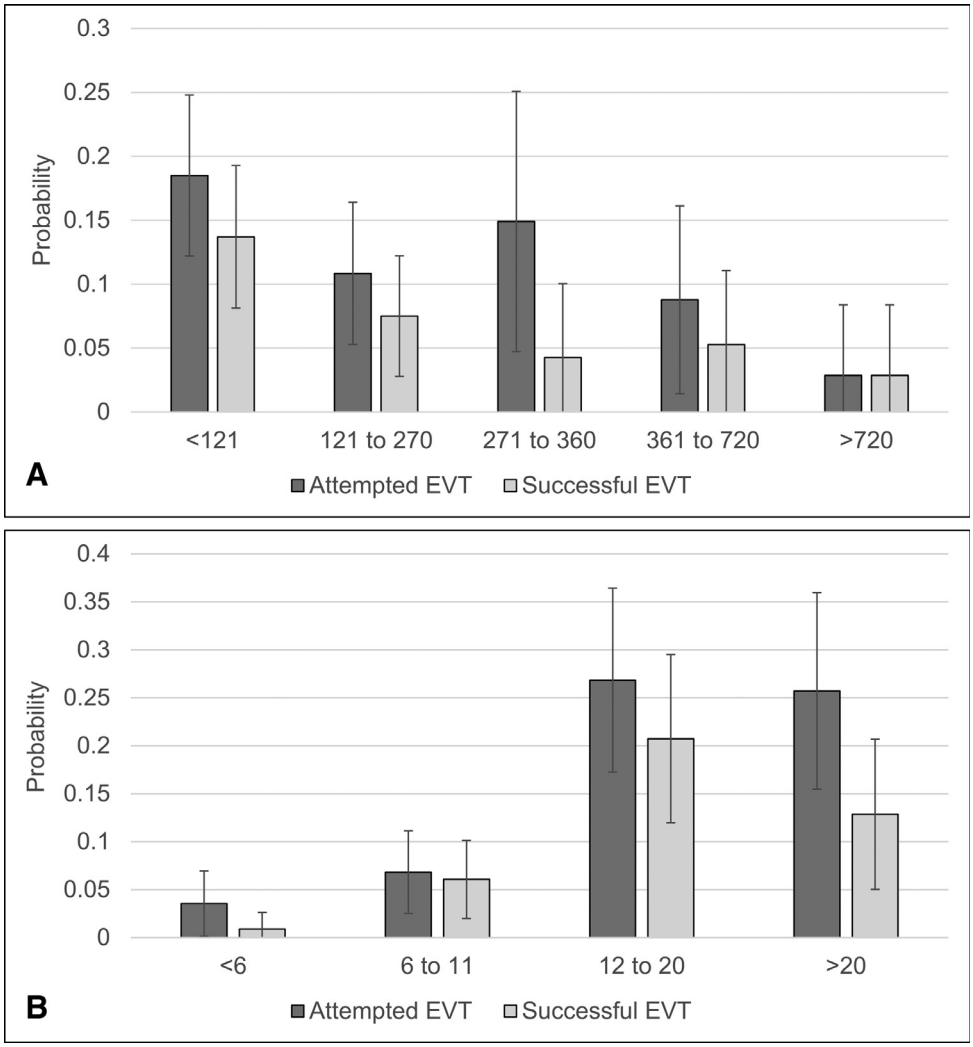

Figure 2. *Probability of attempted and successful endovascular therapy (EVT) by time from last known well (A) and NIHSS (B) among 406 patients screened with CTA/P. Error bars represent 95% confidence intervals.*

Table 2. *Proportions of patients who received attempted (A) or successful (B) EVT following multimodal CT imaging, categorized by stroke severity and time from LKW to ED arrival*

A: Attempted EVT	NIHSS ≥6	NIHSS <6	Not documented	Total
Early (≤360 Min from LKW)	44/230 (19.1)*	3/77 (3.9)*	0/7 (0)*	47/314 (17.6)†
Late (>360 Min from LKW)	5/55 (9.1)	1/36 (2.8)	0/1 (0)	6/92 (7)†
Total	49/285 (17.2)‡	4/113 (3.5)‡	0/8 (0) ‡	53/406 (15)
B: Successful EVT	NIHSS ≥6	NIHSS <6	Not documented	Total
Early (≤ 360 Min from LKW)	31/230 (13.5)§	0/77 (0)§	0/7 (0)§	31/314 (11)
Late (>360 Min from LKW)	3/55 (5.5)	1/36 (2.8)	0/1 (0)	4/92 (4.5)
Total	34/285 (11.9)‖	1/113 (0.9)‖	0/8 (0)‖	35/406 (9.4)

Abbreviations: LKW, last known well; NIHSS, National Institute of Health Stroke Scale; Min, minutes.

P values for chi square tests with significant results between rows, columns, and row/column totals are indicated in the footnotes.

*$P = .003$.

†$P = .029$.

‡$P = .001$.

§$P = .002$.

‖$P = .001$.

stroke remained a predictor of lower odds of successful EVT (adjusted OR 0.2).

Discussion

Patients with LVO stroke are at high risk for death and disability.[2] While EVT is highly effective in treating LVO strokes,[12] identifying appropriate candidates requires advanced imaging techniques.[13] Multimodal CT imaging with CTA/P is a common approach to screen patients with for EVT,[14] however, this test necessarily exposes patients to IV contrast, radiation, and monetary costs that may be of little benefit to those who prove not to be candidates for EVT. To better characterize the yield and utility of CTA/P screening, we describe a cohort of ED suspected-LVO patients who underwent a protocol-driven CTA/P-based screening process.

Among all patients who underwent CTA/P screening, about 13% proved to be candidates for EVT (NNS 8). This high yield is not unexpected since CTA/P imaging was pursued specifically in situations where there was a high clinical suspicion for LVO stroke. Given the magnitude of the potential benefit of EVT for those patients who are candidates, this yield suggests that the screening process outlined in the 2015 AHA scientific statement is relatively efficient.

Nevertheless, the probabilities of EVT candidacy and of successful EVT were not evenly distributed. The highest yield in both cases existed among the patients with an NIHSS ≥6. As per guideline recommendations,[11] our screening protocol allowed for pursuing CTA/P among patients with lower NIHSS if LVO was thought to be present. In our sample, more than one quarter of the studies were obtained among patients with an NIHSS <6; however, only one of these patients ultimately received a successful thrombectomy. Conversely, early presentation (within 6 hours of onset) did not emerge as an important predictor of EVT attempt or success following adjustment for severity. This finding is encouraging given new evidence that EVT is effective even among AIS patients who are as many as 24 hours out from the time last known well.[15,16] It should be noted, however, that in our protocol, CTA/P imaging was pursued on late-presenting patients based on clinical judgment and thus the 9% yield

Table 3. *Results of unadjusted and adjusted logistic regression analysis of predictors of successful EVT among 406 patients with suspected LVO screened with multimodal CT in the ED*

	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
NIHSS ≥6	3.7 (1.5-9.0)	4.0 (1.6-9.9)
LKW to door ≤360 min	2.5 (0.9-7.2)	2.3 (0.8-6.7)
Transfer arrival	1.1 (0.5-2.2)	
Age (continuous)	1.0 (1.0-1.0)	
Female	1.5 (0.7-3.0)	
History of stroke	0.3 (0.1-0.8)	0.2 (0.1-07)
HTN	0.7 (0.3-1.4)	
Atrial fibrillation	1.5 (0.7-3.2)	
Diabetes mellitus	1.1 (0.6-2.3)	

Abbreviations: EVT, endovascular therapy; HTN, hypertension; LVO, large vessel occlusion; LKW, last known well; NIHSS, the National Institute of Health Stroke Scale.

we observed in this population may be higher than if all patients presenting within 24 hours of the onset of neurological symptoms were screened.

While the primary goal of CTA/P in our ED screening protocol was to identify EVT candidates, this imaging may provide additional useful information. Focal neurologic deficits are a nonspecific clinical presentation. Clinical examination alone is insufficient to definitively diagnose AIS, as evidenced by the fact that between one-quarter and one-third of admissions to stroke units are stroke mimics.[17,18] More concerning, over 10% of patients who receive t-PA ultimately receive a non-stroke diagnosis,[19] which introduces unnecessary risk of adverse outcomes and substantial healthcare costs.[20] In our sample, 11% of patients who underwent CTA/P ultimately received a nonstroke diagnosis, with conversion, seizure, and drug/alcohol toxicity, the most common final diagnoses. None of these individuals received EVT or t-PA. It is not possible to tell from our data if t-PA decisions were influenced by CTA/P results; however, these are typically unavailable when t-PA decisions are made and thus, we suspect that they were not. Nevertheless, it may be that CTA/P could be used to assist clinicians in accurately diagnosing patients with neurologic symptoms, especially when imaging and clinical factors are combined.[21]

Limitations

Our study has several limitations. First, our outcome was based on EVT performance since an objective measure of CTA/P "positivity" was not available during the study period at our institution. It is possible that institutional variability in the selection of patients to take for EVT impairs the generalizability of our findings. Introduction of RAPID (iSchemiaView) software for quantitative interpretation of CTP imaging may provide a more consistent estimate of EVT candidacy. Second, given that this study was conducted during a time prior to the publication of trials demonstrated the benefit of EVT in patients presenting beyond 6 hours,[15,16] the screening protocol does not reflect current practice. We suspect that most institutions have expanded the use of CTA/P among those presenting beyond 6 hours. Finally, since we examined only those patients who underwent CTA/P, it is not known how many potential EVT candidates were not imaged due to their stroke severity or the timing of their presentation. This should not impact patients who met default criteria for imaging.

Conclusions

Advanced imaging modalities such as CTA/P have been integral to expanding opportunities for AIS treatment. Not only do they assist in identifying candidates for EVT, but a growing body of literature suggests that perfusion-based imaging techniques also may be used to select candidates for the IV thrombolytics among patients previously excluded from such treatment.[22,23] As such, the use of these techniques is likely to increase. Our results demonstrate that the guideline-based, protocol-driven imaging acquisition is reasonably efficient in identifying candidates for acute stroke therapies and those candidates are common even among those with delayed presentation to the ED. Yet, there appears to be an opportunity to further refine protocols to minimize unnecessary resource utilization, particularly among patients presenting with low NIHSS. Given the rapid changes in AIS care over the past few years, further study is needed to examine the current yield of CTA/P imaging.

Funding Sources/Disclosures

None.

Declaration of Competing Interest

The authors have no conflicts of interest to report.

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