

# Multiphase CT Angiography: A New Tool for the Imaging Triage of Patients with Acute Ischemic Stroke<sup>1</sup>

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## Purpose:

To describe the use of an imaging selection tool, multiphase computed tomographic (CT) angiography, in patients with acute ischemic stroke (AIS) and to demonstrate its interrater reliability and ability to help determine clinical outcome.

## Materials and Methods:

The local ethics board approved this study. Data are from the pilot phase of PROveIT, a prospective observational study analyzing utility of multimodal imaging in the triage of patients with AIS. Patients underwent baseline unenhanced CT, single-phase CT angiography of the head and neck, multiphase CT angiography, and perfusion CT. Multiphase CT angiography generates time-resolved images of pial arteries. Pial arterial filling was scored on a six-point ordinal scale, and interrater reliability was tested. Clinical outcomes included a 50% or greater decrease in National Institutes of Health Stroke Scale (NIHSS) over 24 hours and 90-day modified Rankin Scale (mRS) score of 0–2. The ability to predict clinical outcomes was compared between single-phase CT angiography, multiphase CT angiography, and perfusion CT by using receiver operating curve analysis, Akaike information criterion (AIC), and Bayesian information criterion (BIC).

## Results:

A total of 147 patients were included. Interrater reliability for multiphase CT angiography is excellent ( $n = 30$ ,  $\kappa = 0.81$ ,  $P < .001$ ). At receiver operating characteristic curve analysis, the ability to predict clinical outcome is modest ( $C$  statistic = 0.56, 95% confidence interval [CI]: 0.52, 0.63 for  $\geq 50\%$  decrease in NIHSS over 24 hours;  $C$  statistic = 0.6, 95% CI: 0.53, 0.68 for 90-day mRS score of 0–2) but better than that of models using single-phase CT angiography and perfusion CT ( $P < .05$  overall). With AIC and BIC, models that use multiphase CT angiography are better than models that use single-phase CT angiography and perfusion CT for a decrease of 50% or more in NIHSS over 24 hours (AIC = 166, BIC = 171.7; values were lowest for multiphase CT angiography) and a 90-day mRS score of 0–2 (AIC = 132.1, BIC = 137.4; values were lowest for multiphase CT angiography).

## Conclusion:

Multiphase CT angiography is a reliable tool for imaging selection in patients with AIS.

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In the past few years, the treatment of acute ischemic stroke (AIS) has changed dramatically (1). Newer mechanical devices offer rapid and successful recanalization in the majority of patients who undergo treatment (2–4). Even with this progress, many patients who have undergone treatment do not do well clinically (5,6). Nonetheless, data from previous trials show that clinical outcome improves if patients (a) have a salvageable brain at presentation and (b) undergo early recanalization (6–8). Every 30-minute delay in treatment could increase the risk of poor clinical outcome by around 14% (9). Thus, an ideal imaging selection tool should enable one to detect a salvageable brain quickly and reliably and should be widely available.

Current imaging techniques include unenhanced computed tomography

(CT), single-phase CT angiography, perfusion CT, and magnetic resonance (MR) imaging. Unenhanced CT has moderate interrater reliability, even among experts (10–13). Reliability in interpreting early ischemic changes is less in patients who present within 90 minutes after stroke symptom onset and in those who are aged, and it is affected by patient motion (14). Single-phase CT angiography does not have temporal resolution; therefore, collateral status is mislabeled in many patients (15). Both perfusion CT and MR imaging are susceptible to patient motion and require trained personnel to process the data (16,17). Dynamic CT angiography is a technique that derives time-resolved images of pial arterial filling from perfusion CT images; however, it needs postprocessing and whole-brain perfusion CT (18,19). Conventional angiography is invasive, resource intensive, and not feasible as a fast diagnostic tool (20).

Thus, we developed an imaging tool, multiphase CT angiography, that gives clinicians information on degree and extent of pial arterial filling in the whole brain in a time-resolved manner. Furthermore, this technique is quick to perform and yields images that are easy to acquire and interpret. In this study, we used pilot data from the PROveIT (Precise and Rapid assessment of collaterals using multi-phase CTA in the triage of patients with acute ischemic stroke for IA Therapy) study, an ongoing prospective observational study that seeks to understand the utility of multimodal imaging in the imaging triage

of patients with AIS. Herein, we will describe the tool, its interrater reliability, and its utility for making clinical decisions in patients with AIS.

## Materials and Methods

Inclusion criteria for the study are as follows: (a) patient presented to the emergency department with symptoms consistent with ischemic stroke, (b) patients older than 18 years, and (c) baseline imaging included multiphase CT angiography performed within 12 hours of stroke symptom onset and initiated before recanalization therapy. Exclusion criteria were as follows: (a) intracranial hemorrhage identified at baseline CT; (b) previous moderate to large stroke in the ipsilesional hemisphere; (c) modified Rankin scale (mRS) score greater than 2 at baseline; (d) patient unable to undergo CT angiography because of recent estimated creatinine clearance of less than 60 mL/min, contrast material allergy, or other reasons; (e) participation in another study that results in the patient receiving an investigational drug

## Advances in Knowledge

- Multiphase CT angiography is an imaging tool that provides three time-resolved images of pial arterial filling in the whole brain, unlike conventional single-phase CT angiography.
- Interrater reliability for multiphase CT angiography is excellent ( $n = 30$ ,  $\kappa = 0.81$ ,  $P < .001$ ).
- At receiver operating curve analysis, the ability to predict clinical outcome ( $\geq 50\%$  decrease in National Institutes of Health Stroke Scale from baseline to 24 hours) based on assessment of pial arterial filling in the ischemic region is modest ( $C$  statistic = 0.56; 95% confidence interval [CI]: 0.52, 0.63) but higher than that for single-phase CT angiography ( $C$  statistic = 0.55; 95% CI: 0.49, 0.6), perfusion CT mismatch ratio greater than 1.8 ( $C$  statistic = 0.49; 95% CI: 0.45, 0.52), mismatch ratio greater than 3 ( $C$  statistic = 0.47; 95% CI: 0.41, 0.53), and perfusion CT infarct volume greater than 80 mL ( $C$  statistic = 0.46; 95% CI: 0.4, 0.5) ( $P = .01$  for comparison of  $C$  statistic).

## Implications for Patient Care

- Multiphase CT angiography is an imaging tool with excellent interrater reliability that can be used to predict clinical outcomes in patients with acute ischemic stroke.
- Unlike perfusion CT, multiphase CT angiography does not need any mathematical algorithm or complex postprocessing at an independent workstation; it also requires a lower radiation dose and no additional contrast material.

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## Abbreviations:

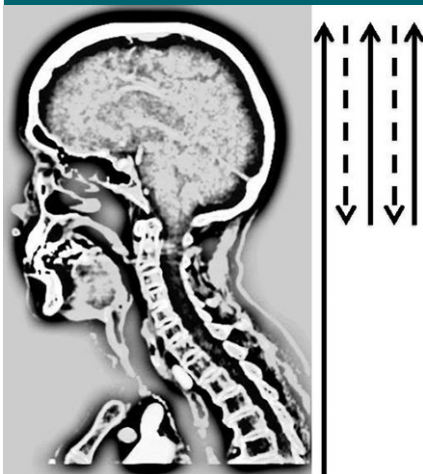
AIC = Akaike information criterion  
 AIS = acute ischemic stroke  
 BIC = Bayesian information criterion  
 CBF = cerebral blood flow  
 CI = confidence interval  
 MCA = middle cerebral artery  
 mRS = modified Rankin Scale  
 NIHSS = National Institutes of Health Stroke Scale  
 TICl = Thrombolysis in Cerebral Infarction

## Author contributions:

Guarantors of integrity of entire study, B.K.M., M.G.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; agrees to ensure any questions related to the work are appropriately resolved, all authors; literature research, B.K.M., C.D.d.E., E.M.Q., A.M.D.; clinical studies, B.K.M., E.M.Q., M.A., A.M.D., M.G.; experimental studies, B.K.M., E.M.Q., A.M.D., M.G.; statistical analysis, B.K.M., C.D.d.E., E.M.Q.; and manuscript editing, B.K.M., C.D.d.E., E.M.Q., A.M.D., M.G.

Conflicts of interest are listed at the end of this article.

Figure 1



**Figure 1:** Multiphase CT angiography image, with each phase represented by an arrow. The first phase (long solid arrow) is conventional arch-to-vertex CT angiography. The next two phases (short solid arrows) are sequential skull base-to-vertex acquisitions performed in the midvenous and late venous phases. Dashed arrows indicate movement of the scanner in between image acquisitions.

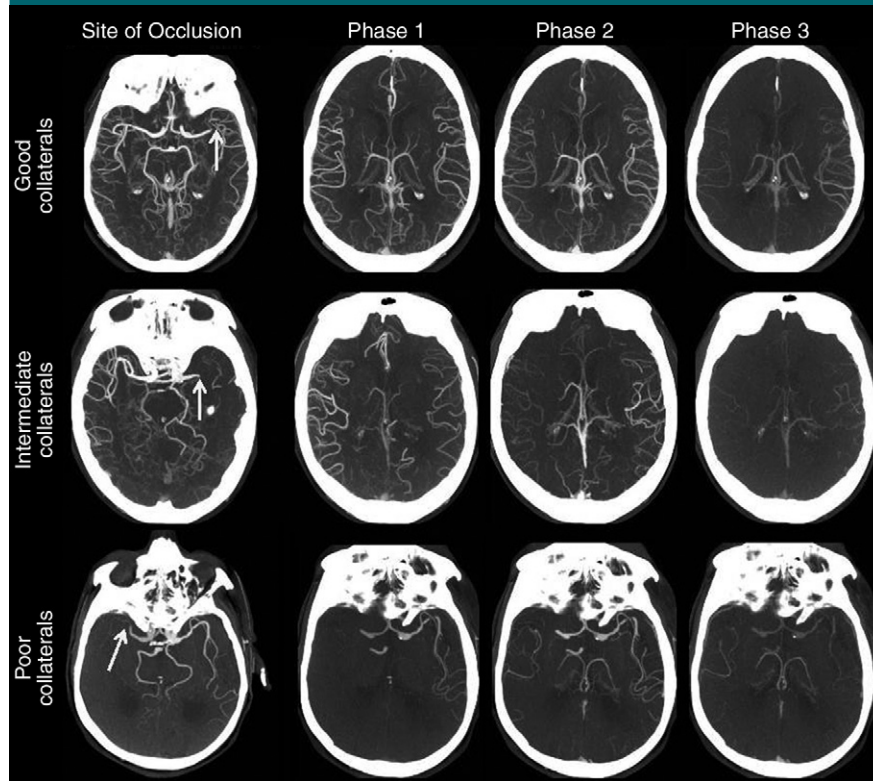
or therapy; and (f) any terminal illness (patient not expected to survive longer than 1 year). We analyzed two clinical outcomes in this study, namely (a) major neurologic improvement at 24-hour follow-up, defined as a 50% decrease in National Institutes of Health Stroke Scale (NIHSS) over 24 hours and (b) mRS score of 0–2 at 90 days. The local institutional review board approved the study.

### Imaging Protocol and Analysis

All patients underwent standard unenhanced CT with 5-mm section thickness followed by head and neck CT angiography, including multiphase CT angiography and perfusion CT.

**Multiphase CT angiography.**—This technique generates time-resolved cerebral angiograms of brain vasculature from the skull base to the vertex in three phases after contrast material injection (Figs 1, 2). Aortic arch vertex CT angiography performed with a multidetector CT scanner made up the first phase. Image acquisition was timed to occur during the peak arterial phase in the healthy brain and was triggered by bolus monitoring. The remaining two phases

Figure 2



**Figure 2:** Multiphase CT angiography images. Top row: Images in a patient with a left M1 MCA occlusion (arrow) and good collaterals (backfilling arteries). Middle row: Images in a patient with a left M1 MCA occlusion (arrow) and intermediate collaterals. Bottom row: Images in a patient with a right M1 MCA occlusion (arrow) and poor collaterals (minimal backfilling arteries).

are from the skull base to the vertex in the equilibrium/peak venous and late venous phases in the healthy brain. Images were acquired with a 0.625-mm section thickness. The first phase of CT angiography from the arch to the vertex was acquired in less than 7 seconds, with an average dose length product of 700–800 mGy·cm. The second phase was acquired after a delay of 4 seconds that allows for table repositioning to the skull base. Scanning duration for each additional phase was 3.4 seconds. Thus, the three phases were each 8 seconds apart. A total of 80 mL of contrast material (68% ioversol, Optiray 320; Mallinckrodt, St Louis, Mo) was injected at a rate of 5 mL/sec and followed by a 50-mL normal saline chase at a rate of 6 mL/sec. The axial images were reconstructed at 1-mm overlapping sections, and multiplanar reconstructions

for axial, coronal, and sagittal images of the circle of Willis were performed with 3-mm thickness at 1-mm intervals. Thick-section axial maximum intensity projections at 24-mm thickness and 4-mm intervals were also reconstructed. An important feature of our imaging protocol was that the two additional phases of multiphase CT angiography use no additional contrast material; the total radiation dose as per our imaging protocol was less than that in many established stroke centers (21) (Table 1). In addition, we used an AccuProbe meter (RadCal, Monrovia, Calif) equipped with a 20X5-3 ion chamber and a human head phantom to measure the total absorbed radiation dose (in milligrays) for the eye with single-phase CT angiography, multiphase CT angiography, and perfusion CT (Table 1). This analysis revealed that the total radiation dose for

**Table 1**

**Mean Effective Radiation Dose with Our Protocol for Multimodal Imaging Including Multiphase CT Angiography When Compared with a Conventional Protocol for Multimodal Imaging**

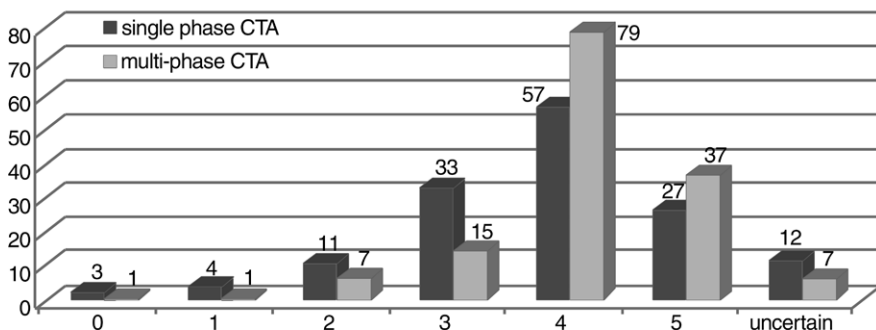
Type of Examination	Mean Estimated Effective Dose in an Established Center (mSv)*	Mean Estimated Effective Dose at Our Center (mSv)	Radiation Dose to the Eye (mGy)†
Unenhanced head CT	2.7 ± 0.3	2.0 ± 0.5	NA
Routine head and neck CT angiography	5.4 ± 2.2	5.0 ± 0.5	15
Two additional phases of multiphase CT angiography	NA	1.0 ± 0.5	45
CT perfusion	4.9 ± 0.0	3.5 ± 0.5	200
Contrast-enhanced head CT	2.6 ± 0.2	NA	NA
Smart prep	0.1 ± 0.1	0.1 ± 0.1	NA
Total dose	16	12	...

Note.—NA = not applicable.

\* Center data is from Mnyusiwalla et al (21).

† Measured by using the aforementioned meter equipped with a 20X5-3 ion-chamber and a human head phantom. These radiation doses conform to the 2012 International Commission on Radiological Protection guidelines (22).

**Figure 3**



**Figure 3:** Pial arterial filling at single-phase CT angiography (CTA) and multiphase CT angiography shows incongruence between the scores and mislabeling of many patients with better pial arterial filling at multiphase CT angiography as having a poor score at single-phase CT angiography.

the eye with multiphase CT angiography was well within the acceptable limits (as per the International Commission on Radiological Protection Guidelines 2012) and significantly less than that with perfusion CT (22).

All postprocessing with multiphase CT angiography is automated and available for review within 2–3 minutes of CT angiography. Pial arterial filling in the ischemic territory was measured in the first phase of CT angiography (single-phase CT angiography) and during multiphase CT angiography by comparing it to similar arteries in the unaffected hemisphere

by using a six-point scale (Fig 3). If no occlusion was evident, pial filling of the symptomatic hemisphere was compared with that of the contralateral side. The six-point scale was then trichotomized into three categories of pial arterial filling. The method for scoring pial arterial filling at single-phase and multiphase CT angiography is described in Table 2. Two raters (B.K.M., M.A.) who were blinded to treatment decisions, perfusion CT, and follow-up data scored unenhanced CT, single-phase CT angiography, and multiphase CT angiography images by consensus.

**CT perfusion.**—A total of 45 mL of the same contrast agent was injected at a rate of 4.5 mL/sec followed by a saline chase of 40 mL at a rate of 6 mL/sec. Axial shuttle (step-and-shoot) mode was used to cover an 8-cm section of the brain, including the intracranial artery at a 5-mm section thickness. Scanning began after a 5-second delay after contrast material injection, with 24 passes performed over 66 seconds. Total exposure time was 19.20 seconds. See Appendix E1 (online) for CT perfusion postprocessing details.

**Recanalization and reperfusion.**—Recanalization and reperfusion were assessed either on conventional cerebral angiograms obtained at the end of the intraarterial procedure (by using the Thrombolysis in Cerebral Infarction [TICI] score) or on CT angiograms of the circle of Willis obtained within 2–4 hours after baseline imaging in patients who underwent only intravenous tissue plasminogen activator by using the TICI CT angiography score. Successful recanalization was defined as a modified TICI score of 2b/3 or a TICI CT angiography score of 2b/3 (23).

**Testing Multiphase CT Angiography**

The various steps in testing multiphase CT angiography are described in Figure E1 (online).

**Interrater reliability.**—Two raters (B.K.M., M.A.) independently assessed multiphase CT angiography in 30 randomly chosen subjects by using the six-point ordinal scale that was then reclassified into three clinically relevant categories (ie, good, intermediate, and poor pial arterial filling) (Table 2). Interrater reliability was measured by using unweighted k values. (Details on the statistical method are given in Appendix E1 [online]).

**Agreement on clinical decision making.**—Since we did not have a reference standard with which to assess concurrent validity (agreement) of multiphase CT angiography vis-à-vis other imaging tools, we compared its ability to assist in making a clinical decision with that of other available imaging tools. We did this by designing an imaging experiment in which two authors (B.K.M., M.A.)

Table 2

## Pial Arterial Filling Score within the Symptomatic Ischemic Territory Using Single- and Multiphase CT Angiography

Score	Single-Phase CT Angiography	Multiphase CT Angiography
5	When compared with asymptomatic contralateral hemisphere, there is increased or normal prominence and extent of pial vessels within the ischemic territory in the symptomatic hemisphere	When compared with the asymptomatic contralateral hemisphere, there is no delay and normal or increased prominence of pial vessels/normal extent within the ischemic territory in the symptomatic hemisphere
4	When compared with the asymptomatic contralateral hemisphere, there is slightly reduced prominence and extent of pial vessels within the ischemic territory in the symptomatic hemisphere	When compared with the asymptomatic contralateral hemisphere, there is a delay of one phase in filling in of peripheral vessels, but prominence and extent is the same
3	When compared with the asymptomatic contralateral hemisphere, there is moderately reduced prominence and extent of pial vessels within the ischemic territory in the symptomatic hemisphere	When compared with the asymptomatic contralateral hemisphere, there is a delay of two phases in filling in of peripheral vessels or there is a one-phase delay and significantly reduced number of vessels in the ischemic territory
2	When compared with the asymptomatic contralateral hemisphere, there is decreased prominence and extent and regions with no vessels within the ischemic territory in the symptomatic hemisphere	When compared with the asymptomatic contralateral hemisphere, there is a delay of two phases in filling in of peripheral vessels and decreased prominence and extent or a one-phase delay and some ischemic regions with no vessels
1	When compared with the asymptomatic contralateral hemisphere, there are just a few vessels visible in the occluded vascular territory	When compared with the asymptomatic contralateral hemisphere, there are just a few vessels visible in any phase within the occluded vascular territory
0	When compared with the asymptomatic contralateral hemisphere, there are no vessels visible within the ischemic territory	When compared with the asymptomatic contralateral hemisphere, there are no vessels visible in any phase within the ischemic vascular territory

assessed unenhanced CT followed by single-phase CT angiography, multiphase CT angiography, and perfusion CT to answer the following two questions: Is the patient a candidate for intravenous tissue plasminogen activator? Is the patient a candidate for intraarterial therapy? All patients were assumed to have fulfilled clinical characteristics for treatment eligibility when images were being read. The readers were not provided information on the time from when normal images were last obtained. Responses recorded for each imaging modality were “yes,” “no,” or “uncertain.” Uninterpretable images were classified as uncertain. The raters used clinically relevant commonly used prespecified rules for image interpretation. These rules are described in detail in Appendix E1 (online). Salvageable brain was measured by using predefined perfusion thresholds and two predefined mismatch ratios (ie,  $>1.8$  and  $>3.0$ ) (24,25). Baseline infarct volume of 80 mL or more at perfusion CT was considered large; therefore, in such cases the response was “no” for both intravenous tissue plasminogen activator and intraarterial therapy (26,27). Severe noncorrectable patient motion (Fig E2 [online]) and lack of appropriate arterial input function

were recorded as an uncertain response. All responses (“yes,” “no,” and “uncertain”) for each imaging modality were reported as proportions.

**Predictive ability.**—We compared the ability of multiphase CT angiography to enable prediction of both clinical outcomes vis-à-vis single-phase CT angiography and perfusion CT. For single-phase CT angiography, a pial arterial filling score of 0–2 was considered poor; therefore, the patient was not likely to benefit from recanalization. For multiphase CT angiography, a score of 0–3 was considered poor and therefore unlikely to benefit from recanalization (Table 2). Separate logistic regression models were developed for each diagnostic tool (ie, single-phase CT angiography, multiphase CT angiography, and perfusion CT [with mismatch ratios  $>1.8$  vs  $\leq 1.8$  and  $>3.0$  vs  $\leq 3.0$  and infarct volume  $<80$  mL vs  $\geq 80$  mL]) as predictor variable. For each model, the ability of the individual diagnostic tool to aid in determining clinical outcome was assessed by using the area under the receiver operating characteristic curve (or *C* statistic) derived from the receiver operating characteristic curves of the logistic regression model. The *C* statistics of

models were compared by using the  $\chi^2$  test of Gönen (28). Since comparison of models by using receiver operating characteristic curves may result in misclassification errors, we also used Akaike information criterion (AIC) and Bayesian information criterion (BIC) to compare models (29). These latter methods have the ability to express the probability that each model is correct when compared with the best model (ie, the one with the highest probability to minimize information loss). A model with the lowest AIC or BIC score is the best model (29). Each of the previously mentioned analyses was restricted to patients in whom all information on the dependent variable and classifier was available. We also performed additional sensitivity analyses with the previously described models restricted to patients (a) with proximal anterior circulation occlusions, (b) who underwent revascularization therapy, and (c) who had early recanalization data.

## Results

A total of 147 patients were included in the present study. Mean age was 72 years  $\pm$  13.1 (standard deviation),

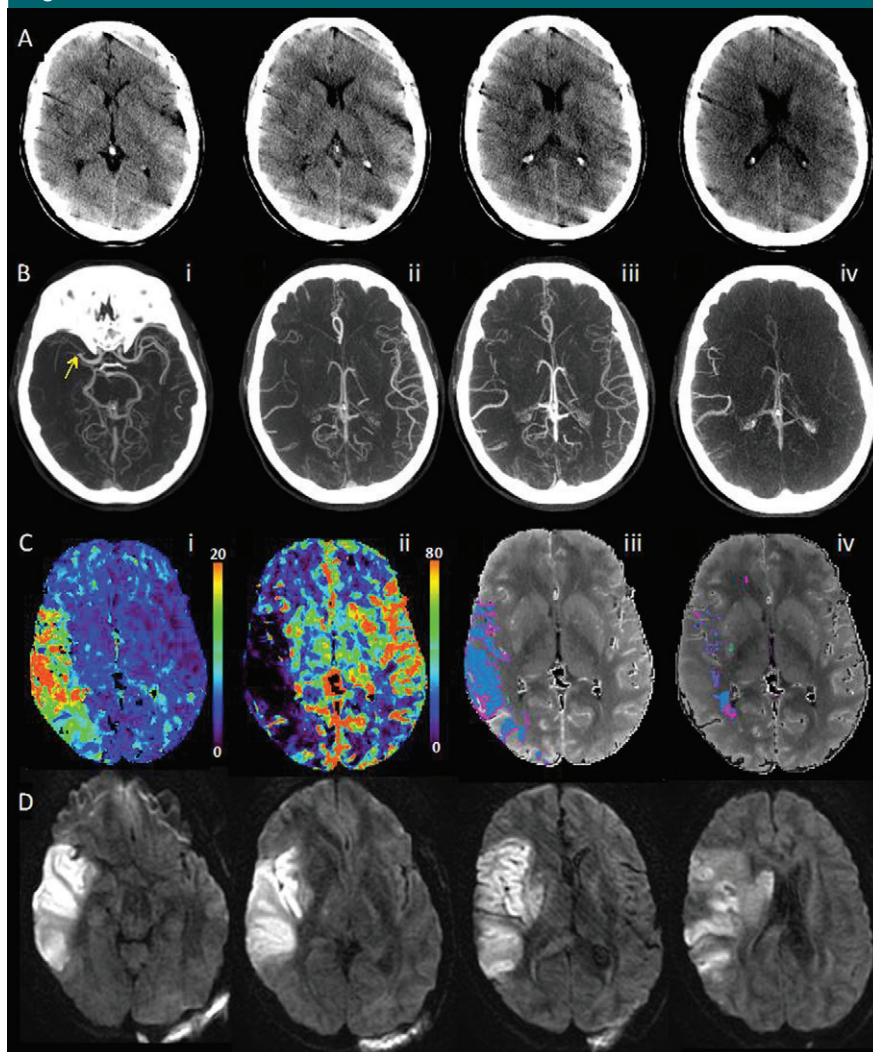
**Table 3**

**Certainty in Clinical Decision Making for Intravenous Tissue Plasminogen Activator Administration and Intraarterial Therapy with Each Baseline Imaging Modality and Paradigm**

Imaging Modality and Criteria	Intravenous Tissue Plasminogen Activator				Intraarterial Therapy			
	No. of Patients	Yes (%)	No (%)	Uncertain (%)	No. of Patients	Yes (%)	No (%)	Uncertain (%)
Unenhanced CT	147	89.8	7.5	2.7	147	32.6	8.8	58.5
Multiphase CT angiography and unenhanced CT	147	90.5	8.8	0.7	147	51.0	47.6	1.4
Single-phase CT angiography and unenhanced CT	147	83.0	14.3	2.7	147	44.2	51.0	4.8
Baseline infarct volume <80 mL	145	88.9	6.9	4.1	85	37.2	58.6	4.1
Mismatch ratio ≤1.8	145	92.4	3.4	4.1	85	40.7	55.2	4.1
Mismatch ratio ≤3.0	145	82.7	13.1	4.1	85	34.5	61.4	4.1

Note.—Agreement between imaging modalities for clinical decision making is described in the text.

**Figure 4**



**Figure 4:** Multimodal CT imaging at 2 hours 51 minutes after symptom onset in a 47-year-old woman with NIHSS of 20 and right hemisphere symptoms. *A*, Unenhanced CT shows movement artifact; however, ASPECTS score was 7. *B*, A proximal right M1 MCA occlusion is seen (*i*). Multiphase CT angiography (three phases) maximum intensity projection images are shown (*ii, iii, iv*). Pial arterial filling is modest, with delay of two phases and some regions indicating minimal filling when compared with the contralateral side, thus indicating that no treatment be performed. *C*, Perfusion CT Tmax and cerebral blood flow (CBF) maps (*i, ii*). Tissue with Tmax greater than 6 seconds (pink) is superimposed onto the CT perfusion average maps for both gray and white matter (*iii* and *iv*, respectively). CBF less than 10 mL·min<sup>-1</sup>·100 g<sup>-1</sup> and less than 7 mL·min<sup>-1</sup>·100 g<sup>-1</sup> for gray and white, respectively, is flooded in blue on the CT perfusion average maps (*iii, iv*). CBF-defined infarct core is 100 mL. A mismatch ratio (total Tmax hypoperfusion volume/total CBF infarct volume) of 1.7 and a large infarct core indicates that no treatment should be performed. Multiphase CT angiography and perfusion CT imaging are congruent for treatment decision. *D*, Diffusion MR images at 24 hours after admission show the final infarct as hyperintense.

49.7% were male, median baseline NIHSS was 9 (interquartile range, 13), median Alberta Stroke Program Early CT Score at unenhanced CT was 9 (interquartile range, 4), and median time from stroke symptom onset to baseline CT was 133 minutes (interquartile range, 188 minutes). Distribution of occlusions was as follows: internal carotid

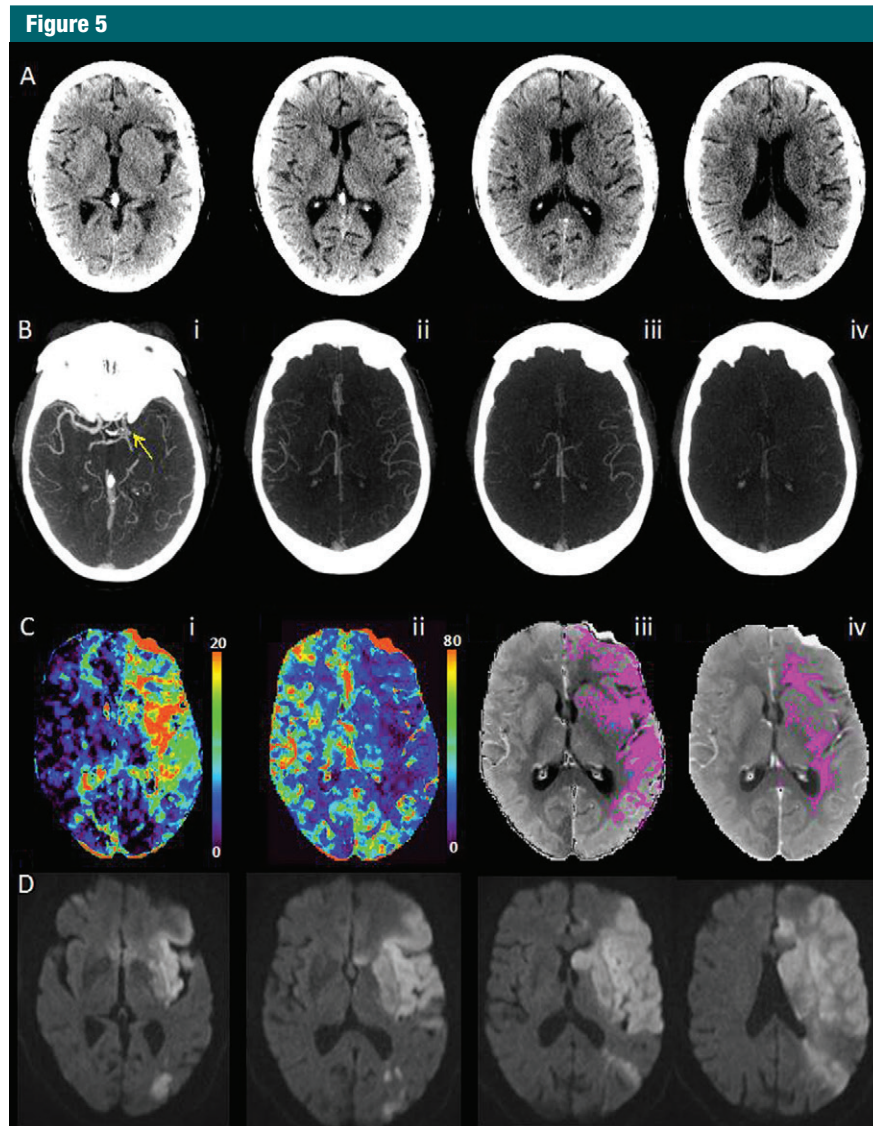
artery (six of 147 patients), M1 middle cerebral artery (MCA) (60 of 147 patients), M2 MCA (21 of 147 patients), posterior cerebral artery (three of 147 patients), distal occlusions (24 of 147 patients), and no occlusions (33 of 147 patients). Distribution of pial arterial filling with single- and multiphase CT angiography is shown in Figure 3. Single-phase CT angiography consistently resulted in underestimation of pial arterial filling when compared with multiphase CT angiography; thus, many patients with moderate pial arterial filling at multiphase CT angiography were labeled as having a poor score. When we used a priori thresholds for infarct and penumbra for both gray and white matter at perfusion CT, median mismatch ratio was 6.6 (range, 1.2–319.6), while mean baseline infarct volume was  $18.9 \text{ mL} \pm 31.1$ . Fifty-one patients underwent intravenous thrombolysis, 24 underwent intravenous and intraarterial therapy, seven underwent intraarterial therapy alone, and 44 underwent conservative treatment. Early reperfusion data were available in 71 patients; 42 (59%) achieved reperfusion. Fifty-six (38.1%) patients achieved the primary clinical outcome (50% decrease in NIHSS over 24 hours), while 72 of 119 (60.5%) had an mRS score of 0–2 at 90 days.

#### Interrater Reliability

Interrater reliability for pial arterial filling with multiphase CT angiography was excellent ( $n = 30$ ,  $\kappa = 0.81$ ,  $P < .001$ ).

#### Agreement on Clinical Decision Making

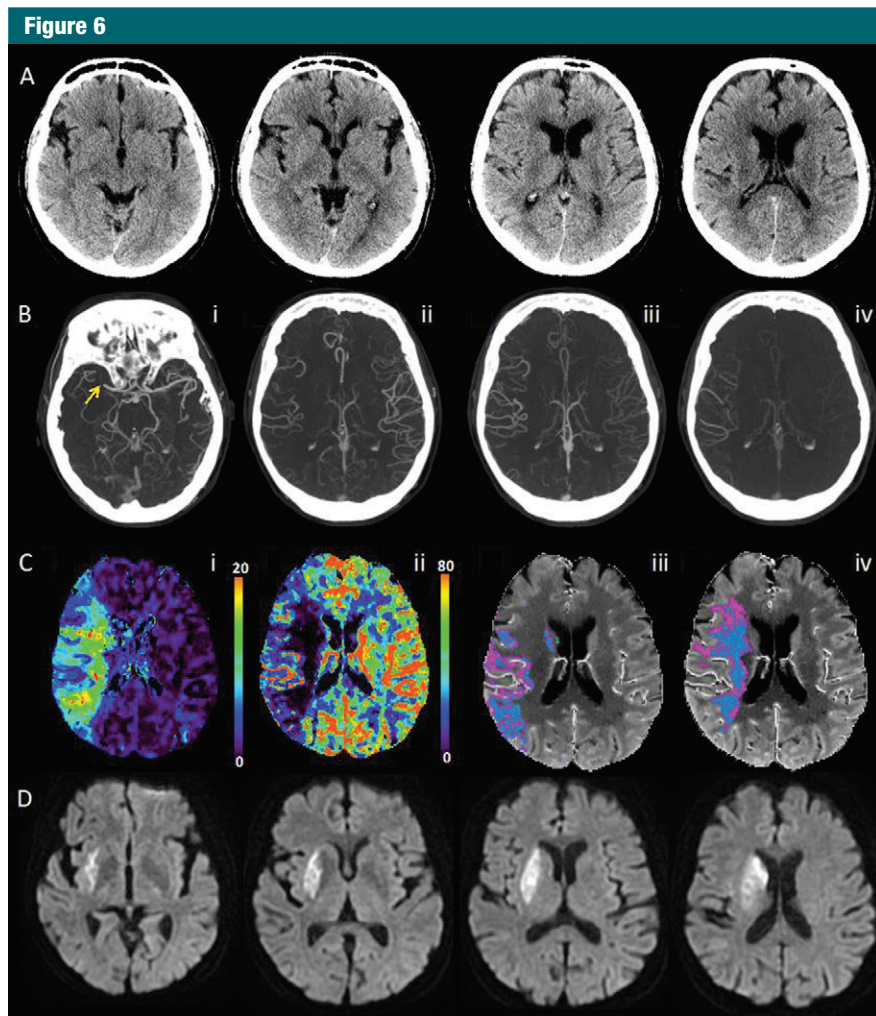
Table 3 describes “yes,” “no,” and “uncertain” for intravenous tissue plasminogen activator and intraarterial treatment with each imaging modality. Detailed results are described in Appendix E1 (online). For intravenous tissue plasminogen activator decision making, maximal agreement (92.5%,  $\kappa = 0.68$ ) was seen between single- and multiphase CT angiography. The next best agreement was between unenhanced CT and multiphase CT angiography (89.1%,  $\kappa = 0.4$ ) and then between unenhanced CT and single-phase CT angiography (85.7%,  $\kappa = 0.41$ ). Agreement for all other pairs was 70.1% or less. For intraarterial



**Figure 5:** Multimodal CT images obtained 2 hours 18 minutes after symptom onset in an 87-year-old woman with an NIHSS of 15 and left hemisphere symptoms. *A*, Unenhanced CT ASPECTS score was 6. *B*, A proximal left M1 MCA occlusion (*i*). Multiphase CT angiography (three phases) maximum intensity projection images (*ii*, *iii*, *iv*) are indicative of one phase delay at worst, with similar extent and prominence when compared with the contralateral side. These indicate of a score of 4 and suggest the patient should undergo treatment. *C*, CT perfusion Tmax and CBF maps (*i*, *ii*). A CBF-defined infarct core is 1 mL (*iii*, no blue regions). A mismatch ratio of 106 and a small infarct core suggests the patient should undergo treatment. Multiphase CT angiography and perfusion CT imaging are congruent for treatment decision. *D*, MR diffusion images at 26 hours after admission show the final infarct as hyperintense. This patient did not attain recanalization with endovascular therapy.

treatment decision, maximal agreement (89.8%,  $\kappa = 0.8$ ) was seen between single- and multiphase CT angiography. The next best agreement was between multiphase CT angiography and perfusion CT mismatch ratio greater than 3 (72.5%,

$\kappa = 0.46$ ) and between multiphase CT angiography and perfusion CT mismatch ratio greater than 1.8 (72.1%,  $\kappa = 0.45$ ). Agreement for all other pairs was 45% or less. Figures 4–7 show various combinations of congruence or incongruence



**Figure 6:** Multimodal CT images obtained 1 hour 28 minutes after symptom onset in a 78-year-old woman with NIHSS of 18 and right hemisphere symptoms. *A*, Unenhanced CT ASPECTS score is 8. *B*, Proximal right M1 MCA occlusion (*i*). Multiphase CT angiography (three phases) maximum intensity projection images (*ii*, *iii*, *iv*) are indicative of one phase delay, with similar extent and prominence when compared with the contralateral side. These suggest a score of 4 and that the patient should undergo treatment. *C*, CT perfusion Tmax and CBF maps (*i*, *ii*). A CBF-defined predicted infarct core is 113 mL (blue) and mismatch ratio (blue/pink areas) (*iii*, *iv*) is 1.7; this indicates the patient should not undergo treatment. Multiphase CT angiography and perfusion CT imaging are incongruent for treatment decision. *D*, MR diffusion images at 26 hours after admission show the final infarct as hyperintense. This M1 MCA clot recanalized with intraarterial therapy.

in clinical decision making between unenhanced CT, multiphase CT angiography, and perfusion CT in our data.

#### Predictive Ability

The *C* statistic for models using single-phase CT angiography, multiphase CT angiography, and perfusion CT (with mismatch ratios >1.2, >1.8, and >3.0 and infarct volume <80 mL vs ≥80 mL) in determining a 50% decrease in NIHSS

at 24 hours is described in Table 4. The *C* statistic was highest for multiphase CT angiography ( $\chi^2$  test for model comparison,  $P = .007$ ); nonetheless, multiphase CT angiography has only modest discrimination, while the other imaging modalities fared worse. Model comparisons on the same data set with AIC and BIC are also described in Table 4. AIC suggests that multiphase CT angiography is the best imaging modality

in determination of primary clinical outcome. The model with baseline infarct volume greater than or equal to 80 mL versus that with baseline infarct volume of less than 80 mL at perfusion CT is next best; it is 0.41 times as probable to minimize information loss as the model with multiphase CT angiography. Other models with diminishing probability of minimizing information loss when compared with the best model (multiphase CT angiography) are as follows: single-phase CT angiography (0.16 times); mismatch ratio greater than 1.8 (0.06 times), and mismatch ratio greater than 3 (0.061 times). Results with BIC are similar to those with AIC (Table 4). Similar results were seen when we compared models with receiver operating characteristic analysis, AIC, and BIC, with an mRS score of 0–2 at 90 days as the clinical outcome ( $n = 102$ ) (Table 5).

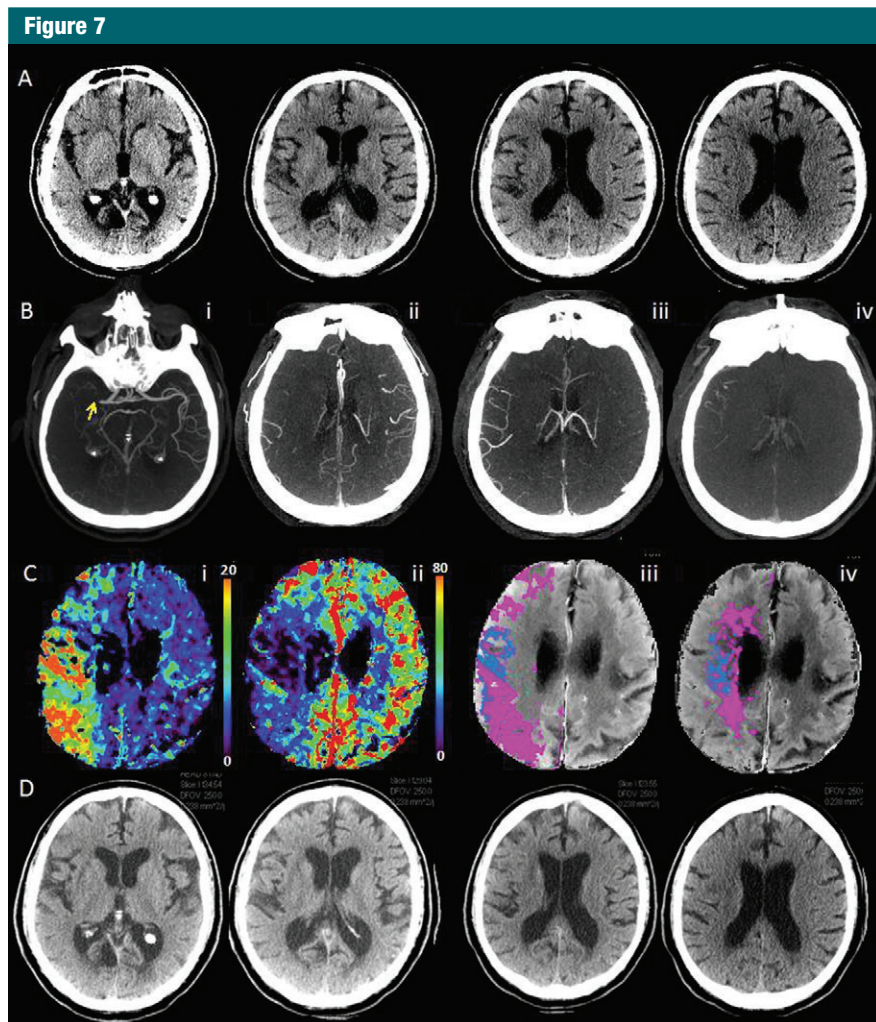
#### Sensitivity Analyses

In sensitivity analyses restricted to patients with only intracranial artery, M1 MCA, or proximal M2 MCA occlusions, the *C* statistic was highest with multiphase CT angiography (*C* statistic = 0.6; 95% CI: 0.54, 0.67). In sensitivity analyses restricted to the patients who underwent revascularization therapy (intravenous tissue plasminogen activator ± intraarterial therapy), the *C* statistic was again highest for multiphase CT angiography (*C* statistic = 0.57; 95% CI: 0.5, 0.65). Similarly, in sensitivity analyses restricted to patients with early recanalization/reperfusion data, the *C* statistic was highest for multiphase CT angiography (*C* statistic = 0.57; 95% CI: 0.46, 0.67); other imaging modalities had a lower *C* statistic. Recanalization or reperfusion (TICI = 2b/3), however, was the best predictor of primary clinical outcome (*C* statistic = 0.66; 95% CI: 0.54, 0.77) whenever those data were available.

#### Discussion

Multiphase CT angiography is a quick and easy-to-use imaging tool in patients with AIS. Our study shows that multiphase CT angiography has good





**Figure 7:** Multimodal CT images obtained 1 hour 32 minutes after symptom onset in a 67-year-old man with NIHSS of 17 and right hemisphere symptoms. *A*, Unenhanced CT ASPECTS score is 7. *B*, A proximal right M1 MCA occlusion extending to M2 MCA is seen (*i*). Multiphase CT angiography (three phases) maximum intensity projection images (*ii*, *iii*, and *iv*) are indicative of, at worst, one phase delay but with large regions having minimal pial arterial filling when compared with the contralateral side. The multiphase CT angiography score is 3, which indicates no treatment should be performed. *C*, Perfusion CT Tmax and CBF maps (*i*, *ii*). A CBF-defined predicted infarct core is 19 mL (*iii*, *iv*). A mismatch ratio of 7.1 indicates treatment should be performed. Multiphase CT angiography and CT perfusion images are incongruent for treatment decision. Fast (<60 minutes) recanalization was achieved by using endovascular thrombectomy. *D*, Unenhanced CT 3 days after admission shows the final infarct as hypointense.

interrater reliability. It reduces uncertainty in clinical decision making and may be slightly better in the prediction of clinical outcome than currently used techniques, such as unenhanced CT, single-phase CT angiography, and perfusion CT. Other advantages include minimal additional radiation, no additional contrast material, whole-brain coverage, and no postprocessing.

There is currently no reference standard for imaging selection in patients with AIS. Perfusion CT, however, is used in many centers for patient selection. Clinical trials Echoplanar Imaging Thrombolytic Evaluation Trial (or EPITHET) and Diffusion Weighted Imaging Evaluation for Understanding Stroke Evolution Study-2 (or DEFUSE-2) have shown that a strategy of delineating

infarct core and penumbra can be used to select patients for intravenous tissue plasminogen activator or endovascular therapy 3 hours after onset of stroke symptoms (27,30). Perfusion CT, however, requires 10–20 minutes from image acquisition to interpretation and needs algorithms for postprocessing images that are vendor specific, not standardized, and therefore variable across centers. Perfusion CT also needs trained personnel to process these images (16,31,32). In addition, image quality is affected to some extent by patient motion (17). Additional radiation dose is also a concern (21). By acquiring temporal information at three data points, multiphase CT angiography is conceptually similar to perfusion CT (and dynamic CT angiography that is derived from perfusion CT images) (18,19). Differences from perfusion CT are therefore in using less information and avoiding the need for postprocessing. Of note, our study shows that currently available perfusion CT thresholds for infarct or penumbra are not better than multiphase CT angiography in clinical decision making or outcome prediction. A possible explanation could be that these externally validated thresholds are not internally valid within our own data set and that we need to derive our own thresholds for infarct core and penumbra (17). We plan to derive such thresholds. Nonetheless, the fact that neither we nor our vendors currently have validated thresholds from literature that we can apply prospectively to our data set is an inherent limitation to the widespread use of perfusion CT in the real world. However, automated perfusion-based algorithms now available are capable of providing information to clinicians in a rapid manner like multiphase CT angiography (33).

Unenhanced CT is widely used for patient selection. Unenhanced CT, however, has moderate interrater reliability even among experts (10–13). Single-phase CT angiography lacks temporal resolution; therefore, this modality leads to risk of mislabeling pial arterial filling when compared with multiphase CT angiography (18,19) (Fig 3). Unlike contrast-enhanced CT, multiphase CT angiography provides clinicians with three time-resolved

Table 4

**Ability of Each Imaging Modality to Discriminate Clinical Outcome (50% or More Decrease in NIHSS from Baseline to 24 Hours) Using Logistic Regression Analysis Receiver Operating Curve Analysis, AIC, and BIC**

Imaging Modality and Criteria	No. of Patients	Odds Ratio	P Value	C Statistic	AIC	BIC
Multiphase CT angiography (>3 vs ≤3)	126	4.3 (1.2, 15.7)	.02	0.58	166.0	171.7
Single-phase CT angiography (>2 vs ≤2)	126	2.8 (0.75, 10.6)	.12	0.55	169.6	175.4
Baseline infarct volume (<80 mL vs ≥80 mL)	126	5.2 (1.1, 27.1)	.05	0.45	167.8	173.5
Mismatch ratio (≤1.8 vs >1.8)	126	3.2 (0.3, 36.6)	.34	0.49	171.4	177.1
Mismatch ratio (≤3 vs >3)	126	1.6 (0.6, 4.8)	.33	0.47	171.5	177.1

Note.—Data in parentheses are 95% CIs. Higher C statistics imply better models, whereas lower AIC and BIC values imply better models.

Table 5

**Ability of Each Imaging Modality to Discriminate Clinical Outcome (mRS 0–2 at 90 Days) Using Logistic Regression Analysis Receiver Operating Curve Analysis, AIC, and BIC**

Imaging Modality and Criteria	No. of Patients	Odds Ratio	P Value	C Statistic	AIC	BIC
Multiphase CT angiography (>3 versus ≤3)	102	5.5 (1.6, 18.8)	.01	0.60	132.1	137.4
single-phase CT angiography (>2 versus ≤2)	102	3.3 (1.0, 10.7)	.05	0.57	136.4	141.7
Baseline Infarct volume <80 mL versus ≥80 mL	102	1.2 (0.25, 5.5)	.84	0.50	140.6	145.8
Mismatch ratio ≤1.8 versus >1.8	102	0.8 (0.1, 8.8)	.80	0.50	140.6	145.8
Mismatch ratio ≤3 versus >3	102	1.4 (0.4, 4.5)	.58	0.52	140.3	145.6

Note.—Data in parentheses are 95% CIs. Higher C statistics imply better models, whereas lower AIC and BIC values imply better models.

images and therefore a more nuanced assessment of pial arterial filling in both the normal brain and the ischemic brain. An example is the ability of multiphase CT angiography to enable discrimination between a one- and two-phase delay whereas contrast-enhanced CT labels both the same. Finally, when compared with multiphase CT angiography, MR imaging has practical drawbacks. MR imaging takes up to 30 minutes to screen patients, perform the examination, and interpret the results (16). Many patients do not tolerate it well, and image quality is affected by patient motion. MR imaging also has limited availability after working hours (34).

Our tool, multiphase CT angiography, has limitations. The presence of flow-limiting proximal stenosis and circuitous base-of-skull collaterals can result in delay in contrast material filling of the pial arteries, even in the healthy hemisphere, thus potentially leading to mislabeling of pial arterial filling status.

Even though we did not find any such case in the current study, this possibility cannot be discounted. Thus, we recommend that multiphase CT angiography images always be interpreted in conjunction with head and neck CT angiography images. Poor cardiac function can also interfere with pial arterial filling, even though our data did not show this. A protocol that includes an additional delayed fourth phase may help in such scenarios. Finally, multiphase CT angiography cannot as yet be used in patients with posterior circulation stroke, except when involving the PCA, because of poorly understood collateral hemodynamics of the posterior circulation.

In summary, we describe multiphase CT angiography, an imaging tool for clinical decision making in patients with AIS. In this article, we have shown its reliability and ability to help predict clinical outcome. Larger studies are needed to conclusively demonstrate its utility in triage and clinical decision making.

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