Background and Purpose—We assessed the diagnostic performance of 2-phase 64-slice cardiac computed tomographic angiography (CCTA) for the detection of a cardiac source of embolism in stroke patients using transesophageal echocardiography (TEE) as the reference standard.

Methods—We selected 137 patients who had experienced a recent episode of stroke and had undergone both 2-phase 64-slice CCTA and TEE within a period of 5 days. A potential cardiac source of embolism detected at both CCTA and TEE was recorded, and echocardiographic findings were categorized into high- and medium-risk sources based on the TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification.

Results—Of 137 patients, 100 abnormal findings in 91 patients were found on TEE, and 46 patients had no abnormal finding on TEE. The overall sensitivity, specificity, positive predictive value, and negative predictive value of the 64-slice CCTA for detecting cardiac sources of embolism were 89% (95% CI, 82%, 95%), 100% (95% CI, 90%, 100%), 100% (95% CI, 95%, 100%), and 81% (95% CI, 70%, 92%), respectively. TEE detected a total of 47 high-risk sources of cerebral embolism, whereas CT detected 44 lesions. For medium-risk sources of cardiac embolic stroke, TEE detected a total of 53 abnormal findings, whereas CT detected 44 abnormal findings. Of 53 lesions, there were 8 false-negative results on CT (5 patent foramen ovale and 3 atrial septal aneurysm).

Conclusions—Two-phase 64-slice CCTA is a noninvasive and useful modality for detecting high-risk cardiac sources of embolism in stroke patients. (Stroke. 2009;40:2073-2078.)

Key Words: cardiac computed tomographic angiography • embolism • stroke • transesophageal echocardiography

Cardiac Computed Tomographic Angiography for Detection of Cardiac Sources of Embolism in Stroke Patients

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Cardiogenic emboli have been estimated to be the causative factor in 20% to 40% of all stroke cases. Therefore, identification of a cardiac source of embolism in stroke patients is important for proper therapeutic management.

Currently, transesophageal echocardiography (TEE) is considered the reference standard method for the detection of potential sources of cerebral embolism. TEE offers high-resolution images of the left atrium (LA) and its appendage as well as the thoracic aorta for the evaluation of left atrial blood stasis and aortic atherosclerosis. Although TEE is widely available, it is a semi-invasive test, usually performed under conscious sedation.

Recently introduced 64-slice cardiac computed tomographic angiography (CCTA) with subsecond rotation times and a dedicated cardiac reconstruction algorithm can acquire 3-dimensional data of the heart, enabling detailed visualization of not only the coronary arteries but also other cardiac structures such as the left atrial appendage (LAA), myocardium, valves, and septa. By previous reports, CT has shown its diagnostic capability in the detection of intracardiac thrombi and patent foramen ovale (PFO).

The aim of this study was to assess the diagnostic performance of 2-phase 64-slice CCTA for the detection of a cardiac source of an embolism in stroke patients using TEE as the reference standard.

Materials and Methods

Patient Selection

Our Institutional Review Board approved this study, and patients were provided with informed consent. From January 2008 to July 2008, 331 consecutive patients were admitted to our hospital for a recent stroke (onset within the previous 7 days) and prospectively enrolled in the current study. Of these patients, 248 patients underwent TEE for suspected cardioembolic stroke within 1 week of the initial stroke, except in patients (n=83) with decreased consciousness, impending brain herniation, poor systemic conditions, tracheal intubations, or failure in receiving an esophageal transducer. Of these, 142 patients, who had >2 risk factors for coronary artery disease were prospectively enrolled to perform 2-phase CCTA for
evaluation of coronary artery disease and potential cardiac embolic sources. Five patients who had contrast agent allergy (n=2), renal dysfunction (n=1), or failed to provide an informed consent (n=2) were excluded. Finally, the remaining 137 patients with >2 risk factors for coronary artery disease were included. All examinations were performed within a 5-day interval (mean, 2.8 days). All patients underwent brain CT or brain MRI to characterize the stroke and to exclude hemorrhages and other causes. The patients consisted of 91 men and 46 women, aged from 37 to 85 years (mean age, 61 years).

Baseline clinical characteristics, including systemic hypertension, hyperlipidemia, diabetes mellitus, and smoking habits, were determined from medical records and routine laboratory data.

**CTTA Examination**

We performed 2-phase CTTA using a 64-slice helical CT (Sensation 64; Siemens Medical Solutions). The scan protocol included both an early-phase scan to evaluate the coronary arteries, and cardioembolic sources (eg, intracardiac thrombus, intracardiac shunt), and a late-phase scan to differentiate between a thrombus and circulatory stasis and to evaluate aortic atheromas. The mean laboratory testing of BUN and creatinine of the 137 stroke patients was 11.5 mg/dL (range, 7.4–19.8) and 0.94 mg/dL (range, 0.67–1.21), respectively. There were no renal complications in all patients after 2-phase CTTA examinations.

A β-blocker (40 mg propranolol hydrochloride; Pranol; Daewoong) was administered orally to reduce the heart rate 1 to 2 hours before examination in patients with a heart rate >65 beats per minute. The mean heart rate was 61±12 beats per minute (range, 51–87 bpm) during the CT examination. Contrast solution, composed of 75 mL of nonionic contrast agent (370 iodine mg/mL; Iopamiro; Bracco) chased by a 50-mL saline solution was administered intravenously at a rate of 5 mL/sec using a power injector (Envision CT; Medrad).

Early-phase scanning was started with a time delay determined by the bolus-tracking technique using a region of interest in the ascending aorta to monitor a threshold of +100 Hounsfield units above the baseline attenuation. The following scan parameters were used: 330-ms gantry rotation time, 120 kV, 800 mAs, 0.6-mm slice collimation, 1-mm slice width, and 3.3-mm table feed/rotation to cover the entire heart. The scan was acquired in a single breath-hold using retrospective ECG gating.

Late-phase images were started 30 seconds later, after the end of the early-phase scan. To reduce the radiation dose, we used the following parameters: 30×0.6 mm, 120 kV, and 200 mAs to cover the aortic arch to the middle of the left ventricle. The scan was acquired using prospective ECG gating. The calculated radiation dose was ~6 to 8 mSv for early-phase imaging and 0.5 to 1 mSv for late-phase imaging.

The reconstruction parameters were as follows: 0.8-mm slice thickness, 0.5-mm increment, 512×512 pixel image matrix, a medium smooth kernel, and 18- to 20-cm field of view. The early- and late-phase image sets were sent to the workstation (Wizard; Siemens Medical Solutions) and reviewed by 2 cardiac radiologists. In addition, axial and oblique sagittal multi-planar images perpendicular to the arial septum were reconstructed and evaluated at an off-line workstation (AquarisNet Viewer V1.8.0.3; TeraRecon, Inc).

**TEE**

Transesophageal 2-dimensional and Doppler echocardiography was performed by an experienced cardiologist with a 5-MHz, phased-array transducer attached to the tip of a commercially available gastroscope (Acuson/Siemens). For each patient, all images were recorded as movie images on digital videotape in real-time for display and evaluation. The images of the LA and the LAA were evaluated in both the horizontal (0°) plane and the plane obtained by rotation of the imaging sector from 0° to 180° during continuous visualization of the LAA. All patients underwent intravenous agitated saline injection with a Valsalva maneuver to exclude an intracardiac shunt. At least 2 saline injections without a Valsalva maneuver and 2 injections during the Valsalva maneuver were performed, and images of the interatrial septum and right and left atrium were recorded in each patient. All segments of the thoracic aorta, including both the ascending/descending aorta and the aortic arch, were evaluated for the presence of plaques between angles of 0° and 90°. Plaque thickness was defined as the thickness of the intima and media layers of the walls measured perpendicularly during systole on a frozen frame. The maximum thickness of the plaques in each region was recorded.

**Image Analysis**

Two experienced cardiologists prospectively and independently reviewed the TEE images of the 137 patients. In cases of disagreement, a consensus was achieved by a joint reading.

The following echocardiographic abnormalities were considered a possible cardiac source of embolism: LA or LAA thrombus, left ventricle thrombus, cardiac tumors, valvular vegetations, infective en-
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Medium risk sources were seen in the left-side cardiac chambers within 3 cardiac cycles of main cavity. PFO was considered to be present if any microbubbles swirling patterns in the LAA, usually with a similar density in the entire cardiac cycle; and severe, intense echodensity and very slow during the cardiac cycle; moderate, dense swirling pattern during the cardiac cycle; none, the absence of this phenomenon; mild, minimal echogenicity of echoes curling slowly in a circular or spiral shape within the LAA as compared to the valve. SEC was characterized by dynamic clouds densities on the mitral or aortic valves that had independent motion formly consistent, echo-reflective mass of a different texture from classification system.13,14

Two experienced radiologists prospectively and independently reviewed the CCTA images of the 137 patients. Differences in assessment were resolved by consensus. Each reader was blinded to the results of other examinations and clinical data.

On CT, we defined a thrombus as a filling defect that appeared on both early- and late-phase images with an oval or round shape on late-phase images. Valvular vegetations were diagnosed as a filling defect that appeared as an oval or round shape on both early- and late-phase images on the mitral or aortic valve. Circulatory stasis was defined as a filling defect that appeared as a triangular shape in the LAA only on early-phase images but was absent on late-phase images. PFO was defined as the presence of a contrast jet from the contrast-filled LA to the saline-filled right atrium (RA) toward the inferior vena cava (IVC) with a channel-like appearance of the interarterial septum.11,12 Atrial septal defect was defined as the presence of a contrast jet from contrast-filled LA to the saline-filled right atrium perpendicular to the septum without the channel-like appearance of an interarterial septum. ASA was defined as an abnormally bulging of the interatrial septum with an excursion of ≥10 mm and a base span ≥15 mm. Sessile atheroma was considered to be a discrete, nonmobile lesion ≥4 mm in the ascending aorta, or the aortic arch.16

Table 2. Potential Cardiac Sources of Embolism in 137 Stroke Patients Assessed by CT and TEE

<table>
<thead>
<tr>
<th>Findings</th>
<th>CT</th>
<th>TEE</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-risk sources</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombus*</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>LAA</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>LA</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cardiac tumor</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Valvular vegetation</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Infective endocarditis</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Aortic atheroma (AA or arch)</td>
<td>31</td>
<td>33</td>
</tr>
<tr>
<td>Medium risk sources</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Circulatory stasis/SEC†‡</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>PFO‡/ASD</td>
<td>17 (14/3)</td>
<td>22 (19/3)</td>
</tr>
<tr>
<td>ASA</td>
<td>8</td>
<td>11</td>
</tr>
<tr>
<td>Mitral annular calcification</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>No abnormality</td>
<td>57</td>
<td>46</td>
</tr>
</tbody>
</table>

AA indicates ascending aorta.

In TEE, a thrombus was defined as a well-circumscribed, uniformly consistent, echo-reflective mass of a different texture from the LA or LAA wall. Valvular vegetations were diagnosed as echo densities on the mitral or aortic valves that had independent motion as compared to the valve. SEC was characterized by dynamic clouds of echoes curling slowly in a circular or spiral shape within the LAA cavity. The severity of SEC was divided into 4 grades as follows: none, the absence of this phenomenon; mild, minimal echogenicity only transiently detectable with optimal gain settings transiently during the cardiac cycle; moderate, dense swirling pattern during the entire cardiac cycle; and severe, intense echodensity and very slow swirling patterns in the LA, usually with a similar density in the main cavity. PFO was considered to be present if any microbubbles were seen in the left-side cardiac chambers within 3 cardiac cycles of the maximum right atrium opacification or if a turbulent color jet was seen within the atrial septum on color Doppler. ASA was defined as an abnormally redundant interatrial septum with an excursion of ≥10 mm and a base span ≥15 mm.13 Sessile atheroma was considered to be a discrete, nonmobile lesion ≥4 mm in the ascending aorta, or the aortic arch.16

Statistical Analysis

Categorical baseline characteristics were expressed as numbers and percentages, and were compared between 2 groups with the χ² test. Continuous variables were expressed as mean (SD) and were compared with the Student t test for independent samples.

For all imaging modalities, we recorded the number of the detected cardiac sources of embolism. Using TEE as the reference standard, the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of CCTA for detecting cardiac sources of embolism were calculated; 95% CI were calculated by using the method of exact binomial tail areas.17 The analysis was performed on a per-lesion and per-patient basis. On a per-patients analysis, patients with both high- and medium-risk sources were categorized as high-risk sources.

All statistical analyses were performed with SPSS software (Version 10.0; Statistical Package for the Social Sciences). The image quality of all CCTA examinations was considered acceptable for the evaluation of intracardiac abnormalities. However, there were some nonassessable segments for eval-

Table 3. CT Results in the Detection of Potential Cardiac Sources of Embolism in 137 Stroke Patients (per Lesion and per Patient Analyses)

<table>
<thead>
<tr>
<th>Cardiac Sources</th>
<th>All</th>
<th>High-Risk</th>
<th>Medium-Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lesions</td>
<td>Patients</td>
<td>Lesions</td>
</tr>
<tr>
<td>True-positive</td>
<td>89</td>
<td>85</td>
<td>44</td>
</tr>
<tr>
<td>True-negative</td>
<td>46</td>
<td>46</td>
<td>46</td>
</tr>
<tr>
<td>False-positive</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>False-negative</td>
<td>11</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Sensitivity (%)</td>
<td>89</td>
<td>93</td>
<td>94</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>PPV (%)</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>NPV (%)</td>
<td>81</td>
<td>88</td>
<td>94</td>
</tr>
</tbody>
</table>

*In a per-patient analysis, patients with both high- and medium-risk sources were categorized as high-risk sources.
in 91 patients were found on TEE. Furthermore, 10 patients had atrial fibrillation (AF).

The clinical characteristics of the 137 patients are summarized in Table 1. Of these 137 patients, 100 abnormal findings were detected in 91 patients, whereas 89 abnormal findings were detected in 91 patients by CT, including 11 false-negative results (Table 2). Using TEE as the reference standard, the overall sensitivity, specificity, PPV, and NPV of the 64-slice CCTA for detecting cardiac sources of embolism were 91% (95% CI, 81%, 100%), 100% (95% CI, 90%, 100%), 100% (95% CI, 90%, 100%), and 94% (95% CI, 91%, 100%), respectively (Table 3).

In a per-patient analysis, 47 patients had at least 1 high-risk source on TEE. Of these 47 patients, 2 patients had missed cardiac embolic sources with CT. Using TEE as the reference standard, the overall sensitivity, specificity, PPV, and NPV of the 64-slice CCTA for detecting cardiac sources of embolism were 96% (95% CI, 89%, 100%), 100% (95% CI, 90%, 100%), 100% (95% CI, 90%, 100%), and 96% (95% CI, 89%, 100%), respectively (Table 3).

TEE detected a total of 12 thrombi (11 located in the LAA and 1 located in the LA). On CCTA, a total of 12 filling defects (11 filling defects in the LAA and 1 filling defect in the LA) showed persistent filling defects on both early- and delayed-phase images, which is a typical finding of thrombus (Figure 1). Of the 47 lesions, there were 3 false-negative results on CT. One of the mitral valve vegetations was misdiagnosed as mitral valve thickening on CT. Two aortic atheromas in the aortic arch were not considered high-risk sources by CT because the size of atheromas measured by CT was <4 mm.

For the detection of medium-risk sources of cardiac embolic stroke, TEE detected a total of 53 abnormal findings, whereas CT detected 45 abnormal findings (Table 2). Using TEE as the reference standard, the overall sensitivity, specificity, PPV, and NPV of the 64-slice CCTA for detecting medium-risk cardiac sources of embolism were 83% (95% CI, 71%, 94%), 100% (95% CI, 90%, 100%), 100% (95% CI, 90%, 100%), and 84% (95% CI, 73%, 95%), respectively (Table 3).

In a per-patient analysis, 44 patients had medium-risk sources on TEE. Of these 44 patients, 4 patients had missed cardiac embolic sources with CT. Using TEE as the reference standard, the overall sensitivity, specificity, PPV, and NPV of the 64-slice CCTA for detecting medium-risk cardiac sources of embolism were 89% (95% CI, 82%, 95%), 100% (95% CI, 90%, 100%), 100% (95% CI, 90%, 100%), and 81% (95% CI, 70%, 92%), respectively (Table 3).

For the detection of high-risk sources for cardiac embolic stroke, TEE detected a total of 47 abnormal findings, whereas CT detected 44 abnormal findings (Table 2). Using TEE as the reference standard, the overall sensitivity, specificity, PPV, and NPV of the 64-slice CCTA for detecting high-risk cardiac sources of embolism were 93% (95% CI, 87%, 99%), 100% (95% CI, 90%, 100%), 100% (95% CI, 90%, 100%), and 98% (95% CI, 78%, 98%), respectively (Table 3).

In a per-patient analysis, 47 patients had at least 1 high-risk source on TEE. Of these 47 patients, 2 patients had missed cardiac embolic sources with CT. Using TEE as the reference standard, the overall sensitivity, specificity, PPV, and NPV of the 64-slice CCTA for detecting high-risk cardiac sources of embolism were 96% (95% CI, 89%, 100%), 100% (95% CI, 90%, 100%), 100% (95% CI, 90%, 100%), and 96% (95% CI, 89%, 100%), respectively (Table 3).

On TEE, there was a total of 15 SEC, and all were correctly detected by 2-phase 64-slice CCTA. By CT, all SEC detected on TEE showed typical finding of a filling defect that appeared as a triangular shape in the LAA only on early-phase imaging.
images but was absent on late-phase images (Figure 2). Of the 15 filling defects diagnosed correctly as circulatory stasis without thrombus by CT, SEC was categorized as severe in 6 cases, moderate in 7 cases, and mild in 2 cases. TEE detected a total of 19 PFO and 3 atrial septal defects. Fifteen of 19 patients had PFO diagnosed by the showing of microbubbles on the left-side cardiac chambers within 3 cardiac cycles of the maximum right atrium opacification after agitated saline injection, whereas 4 of 19 cases were diagnosed by a showing of a turbulent color jet within the interarterial septum on Doppler TEE, even though no microbubbles were seen. On CT, LA to right atrium contrast jet toward the inferior vena cava was found in 14 patients, and contrast jet perpendicular to the septum was found in 3 patients (Figure 3). All 3 atrial septal defects were correctly diagnosed by CT. However, of the 19 PFO, 14 lesions were correctly diagnosed by CT (73%, 14 of 19). Four PFO were combined with ASA, and 3 of 4 lesions were correctly diagnosed by CT. Of the 11 ASA, 8 lesions were correctly diagnosed by CT (73%, 8 of 11; Figure 4).

Discussion

This study demonstrates that 2-phase 64-slice CCTA is a useful modality for the detection of cardiac sources of embolism in stroke patients. The diagnostic performance for the detection of high-risk cardiac sources of embolism by 2-phase 64-slice CCTA was excellent and comparable to TEE.

In our study, we categorized cardiac sources of embolism detected on TEE into high- and medium-risk sources according to the TOAST classification systems. The TOAST classification system defines high- and medium-risk cardiac sources based on their relative propensities for causing an embolism. For high-risk embolic sources, anticoagulation is an indication for therapeutic management; however, medium-risk sources have more modest or undefined risks and little randomized comparative evidence to guide management. Therefore, in determining the effectiveness of therapeutic management, the detection of high-risk cardiac sources is more important.

In our study, 2-phase CCTA showed high sensitivity (94%) and high specificity (100%) in the detection of high-risk cardiac sources as compared with TEE. The highly accurate diagnostic performance strongly suggests that 2-phase CCTA could be useful in the detection of high-risk cardiac sources of embolism in stroke patients. Although there were 3 false-negative results, the 12 thrombi diagnosed by TEE were all correctly diagnosed by CCTA.

For the detection of medium-risk sources, the diagnostic yield of CT was lower compared to TEE, especially for diagnosing PFO. Recently, there have been a few reports on the multi-detector row CT findings of a PFO that were channel-like appearances of the interarterial septum and left-to-right interatrial shunt. In our study, LA to right atrium contrast jet toward the inferior vena cava was found in 14 patients on CT, and all these patients had PFO diagnosed with TEE. We believe that the lower sensitivity for diagnosing PFO by CT is caused by the fundamentally different principles for diagnosing PFO between TEE and CT. TEE diagnoses of PFO were made by detecting momentary right-to-left shunts with a provocative maneuver, whereas CT diagnoses were made by detecting a left-to-right shunt in the resting state. Therefore, in diagnosing PFO, CT has its limitation in that although routine cardiac CT during the resting state can anatomically detect PFO, it fails to analyze the functional aspects of PFO by pointing out the clinically significant cases. For example, PFO with high membrane mobility and right-to-left shunting at rest are more associated with cryptogenic stroke.
In our study, the diagnostic yield of CT for detection of thrombus, aortic atheroma, and SEC were high, which can be anatomically detected by CT. However, the diagnostic yield for detection of PFO or ASA was lower by CT as compared to TEE, which need provocative maneuver for their diagnosis. This result suggests that CT can have limitation in the detection of cardioembolic sources, especially in younger stroke patients, because it is known that the incidence of PFO, ASA, or a combination of both are higher in younger stroke patients or with cryptogenic stroke.\textsuperscript{19,20}

For many cardiac risk sources of embolism, referred to as medium-risk sources, the optimal choice of therapy is not clear. At present, there is not enough evidence in the literature to recommend anticoagulation therapy over aspirin in patients with medium-risk factors; therefore, TEE does not provide therapeutic gains in terms of medical treatment.\textsuperscript{21–24} Furthermore, the diagnostic performance of the CCTA for detecting medium-risk sources was improved in a per-patient analysis. In that respect, we believe that 2-phase CCTA can be used as a screening test for detecting potential cardiac sources of embolism in selected stroke patients before TEE, because it has high diagnostic accuracy in the detection of high-risk cardiac sources of embolism and is a noninvasive modality. Our study had several limitations. First, we did not perform CCTA studies in all stroke patients who underwent TEE. For CCTA indication, we selected patients who had CCTA studies in all stroke patients who underwent TEE. For cardiac sources of embolism and is a noninvasive modality. In that respect, we believe that 2-phase CCTA can be used as a screening test for detecting potential cardiac sources of embolism in selected stroke patients before TEE, because it has high diagnostic accuracy in the detection of high-risk cardiac sources of embolism and is a noninvasive modality. Our study had several limitations. First, we did not perform CCTA studies in all stroke patients who underwent TEE. For CCTA indication, we selected patients who had 2-phase factors for coronary artery disease. This would potentially yield an older stroke population with increased likelihood that CCTA would identify high-risk sources of embolism, such as aortic plaques. It is known that the prevalence of medium-risk sources would be expected to be higher in a younger population.\textsuperscript{19,20} Therefore, the frequencies of some cardiac sources of embolism, particularly those that are dependent on echocardiographic studies, could be underestimated and the overall results could be affected. Second, we did not perform the 2 examinations on the same day. All examinations were performed within a 5-day interval to evaluate for intracardiac sources of embolism. A further limitation was radiation exposure. Although we performed 2-phase imaging, we used prospective ECG gating and lowered the mAs to 200 for the late-phase imaging to reduce the radiation dose. Therefore, the additional radiation dose for late-phase imaging was small.

**Conclusion**

Two-phase 64-slice CCTA is a useful modality for detecting potential cardiac sources of embolism in stroke patients. In addition, 2-phase CCTA exhibits excellent diagnostic performance in the detection of high-risk cardiac sources of embolism, which have absolute indications for oral anticoagulation therapy.

**Disclosures**

None.

**References**

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