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Predictive Value of Cardiac CTA, Cardiac MRI, and Transthoracic Echocardiography for Cardioembolic Stroke Recurrence

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BACKGROUND. Transthoracic echocardiography (TTE) is the standard of care for initial evaluation of patients with suspected cardioembolic stroke. Although TTE is useful for assessing certain sources of cardiac emboli, its diagnostic capability is limited in the detection of other sources, including left atrial thrombus and aortic plaques.

OBJECTIVE. The purpose of this article was to investigate sensitivity, specificity, and predictive value of cardiac CTA (CCTA), cardiac MRI (CMRI), and TTE for recurrence in patients with suspected cardioembolic stroke.

METHODS. We retrospectively included 151 patients with suspected cardioembolic stroke who underwent TTE and either CMRI ($n = 75$) or CCTA ($n = 76$) between January 2013 and May 2017. We evaluated for the presence of left atrial thrombus, left ventricular thrombus, vulnerable aortic plaque, cardiac tumors, and valvular vegetation as causes of cardioembolic stroke. The end point was stroke recurrence. Sensitivity, specificity, PPV, and NPV for recurrent stroke were calculated; the diagnostic accuracy of CMRI, CCTA, and TTE was compared between and within groups using AUC.

RESULTS. Twelve and 14 recurrent strokes occurred in the CCTA and CMRI groups, respectively. Sensitivity, specificity, PPV, and NPV were 33.3%, 93.7%, 50.0%, and 88.2% for CCTA; 14.3%, 80.3%, 14.3%, and 80.3% for CMRI; 14.3%, 83.6%, 16.7%, and 80.9% for TTE in the CMRI group; and 8.3%, 93.7%, 20.0%, and 84.5% for TTE in the CCTA group. Accuracy was not different ($p > .05$) between CCTA (AUC = 0.63; 95% CI, 0.49–0.77), CMRI (0.53; 95% CI, 0.42–0.63), TTE in the CMRI group (0.51; 95% CI, 0.40–0.61), and TTE in the CCTA group (0.51; 95% CI, 0.42–0.59). In the CCTA group, atrial and ventricular thrombus were detected by CCTA in three patients and TTE in one patient; in the CMRI group, thrombus was detected by CMRI in one patient and TTE in two patients.

CONCLUSION. CCTA, CMRI, and TTE showed comparably high specificity and NPV for cardioembolic stroke recurrence. CCTA and CMRI may be valid alternatives to TTE. CCTA may be preferred given potentially better detection of atrial and ventricular thrombus.

CLINICAL IMPACT. CCTA and CMRI have similar clinical performance as TTE for predicting cardioembolic stroke recurrence. This observation may be especially important when TTE provides equivocal findings.

Ischemic stroke is a leading cause of mortality and long-term disability worldwide. Its recurrence is considered to be the major cause of its associated mortality and morbidity [1, 2]. Cardiogenic strokes represent 20–30% of all ischemic cases and include various cardiac causes such as atrial fibrillation, acute myocardial infarction, or valvular heart diseases. Potential sources of cardiac emboli are divided into high-risk and medium-risk categories with respect to the relative risk of forming emboli [3–5]. Early identification of the origin of ischemic stroke, especially strokes of cardioembolic nature, is essential for proper risk assessment and patient management [3, 6].

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Transthoracic echocardiography (TTE) is the standard of care for initial evaluation of patients with suspected cardioembolic stroke [7]. Although TTE is useful for assessing certain sources of cardiac emboli (e.g., left ventricle), its diagnostic capability is limited in the detection of other sources, including left atrial thrombus, patent foramen ovale, and aortic plaques. This restriction is mostly because of limited acoustic windows [8]. Transesophageal echocardiography is often performed after an inconclusive TTE. Although transesophageal echocardiography is the reference standard for the detection of potential cardiothoracic sources of emboli and patent foramen ovale (especially with agitated saline contrast enhancement during the Valsalva maneuver), it is a semiinvasive procedure that creates physical discomfort and is associated, although rarely, with potential life-threatening complications [9]. Consequently, a reliable, noninvasive technique for the assessment of cardioembolic sources would be useful.

Studies have shown that cardiac CTA (CCTA) and cardiac MRI (CMRI) imaging can detect high-risk cardioembolic sources [10–13]. CCTA has proved to be accurate in the detection of vulnerable aortic plaques and intracardiac thrombi; likewise, CMRI has shown adequate visualization of left ventricular thrombi, cardiac masses, aortic plaques, and left atrial appendage thrombi [14–17]. In addition, high sensitivity and specificity have been reported for the detection of patent foramen ovale by CCTA and CMRI [18]. However, the confirmation or exclusion of small patent foramen ovale can be challenging with these techniques. In addition, the relative effectiveness of CCTA and CMRI in reliably ruling out stroke recurrence in the absence of intracardiac sources of embolism on imaging is insufficiently studied.

We speculate that CCTA and CMRI may be valid alternatives to echocardiography in the workup of stroke of cardioembolic origin. We thus conducted this investigation to quantify the sensitivity, specificity, and predictive values of CCTA, CMRI, and TTE for stroke recurrence in patients with suspected cardioembolic stroke.

HIGHLIGHTS

Key Finding

- *Specificity, NPV, and AUC (95% CI) of cardiac MRI (80.3%; 80.3%; 0.53 [0.42–0.63]) and cardiac CTA (93.7%; 88.2%; 0.63 [0.49–0.77]) were comparable to TTE (cardiac MRI group: 83.6%; 80.9%; 0.51 [0.40–0.61] and cardiac CTA group: 93.7%; 84.5%; 0.51 [0.42–0.59]) for predicting cardioembolic stroke recurrence.*

Importance

- *Given their high NPV, cardiac MRI and cardiac CTA are potential alternatives when echocardiography provides equivocal findings for cardioembolic stroke recurrence.*

Methods

Patient Selection

Our local institutional review board approved this single-center, retrospective, HIPAA-compliant study; the requirement for written informed consent was waived. At our institution (Medical University of South Carolina), patients with symptoms of acute stroke (onset < 7 days from admission) undergo on admission head CT and/or brain MRI in addition to CT and/or MRA of the intra- and extracranial vasculature according to a diagnostic protocol. Cerebral and/or carotid angiography is also performed if a blood clot is suspected in the intra- or extracranial vasculature. After the neuroimaging examinations, TTE is performed to rule out a cardiac thrombus. Patients undergo CCTA or CMRI only if previous findings are ambiguous or if there is high suspicion of cardiac embolus. Particularly, CCTA is performed in acutely ill patients and in those with a suspected aortic cause of embolism. CMRI is preferred in patients with previous myocardial infarction or with heart failure to assess cardiac function.

We initially identified 457 consecutive patients, 18 years old or older, admitted with symptoms of acute stroke between January 2013 and May 2017. Patients' charts were reviewed for the following imaging procedures: head CT; brain MRI; cerebral and carotid CT, MRI, and invasive angiography; CCTA; CMRI; and TTE. A total of 284 patients underwent a cardiac imaging assessment including TTE and CCTA or CMRI for a possible cardiac origin of cerebral embolism and were potentially eligible. For these patients, demographics, clinical information, and blood test examinations were retrieved from the medical record. Patient records were evaluated from the date of the stroke on admission until either the date of stroke recurrence or the last known date for which the absence of stroke recurrence was documented.

Further categorization of the 284 patients was performed according to the clinical and radiologic criteria in the acute stroke treatment classification system (Trial of Org 10172 in Acute Stroke Treatment, or TOAST) to exclusively select patients with suspected cardioembolic stroke [3]. Eight patients were excluded who did not present with an abrupt cerebral cortical impairment (aphasia, neglect, restricted motor involvement, for example) with or without dysfunctional symptoms related to the brainstem or cerebellum and who thus had an incongruous clinical presentation. A total of 55 patients were excluded who did not show a lesion compatible with ischemic stroke in more than one vascular territory on head CT or brain MRI. A total of 50 patients were excluded who showed severe atherosclerotic diseases of either or both of the intra- and extracranial vasculature on CT, MRI, or catheter angiography. An additional eight patients were excluded who had other underlying causes for stroke such as nonatherosclerotic vasculopathies, hypercoagulable states, or hematologic disorders. A total of 163 patients remained after these exclusions. Of these, 12 patients did not complete the TTE or the TTE was nondiagnostic because of a limited acoustic window or other reason and were excluded. This process left a final cohort of 151 patients with acute stroke of suspected cardioembolic origin who underwent CCTA or CMRI after TTE. The flowchart of patient selection is shown in Figure 1. Patients with recent myocardial infarction (< 4 weeks), atrial fibrillation or flutter, and sick sinus syndrome were not excluded.

Transthoracic Echocardiography Protocol

The Logiq E9 (GE Healthcare) or the iE33 (Philips Healthcare) ultrasound machines were used for M-mode and Doppler TTE in all patients. The echo protocol for stroke consisted of parasternal long- and short-axis imaging, including all valves and Doppler assessments.

Apical four-, two-, three-, and five-chamber views were obtained for the evaluation of any shunts. These focused on the interventricular and interatrial septum, as well as the right ventricle, including Doppler assessment of all valves. If there was poor visualization of the apex or if standard 2D imaging was suggestive of thrombus, commercial contrast enhancement was used. Additionally, subcostal and suprasternal notch images were obtained. Doppler assessment was performed across the interatrial septum in the subcostal views. A bubble-agitated saline study was performed in patients 55 years and younger to exclude the presence of atrial septum defects.

Cardiac CTA Protocol

CCTA was performed on a first- or second-generation dual-source CT scanner (Somatom Definition and Somatom Flash, Siemens Healthineers). To minimize radiation exposure, CT protocols were chosen according to individual patient characteristics (heart rate and rhythm, body mass index). These protocols

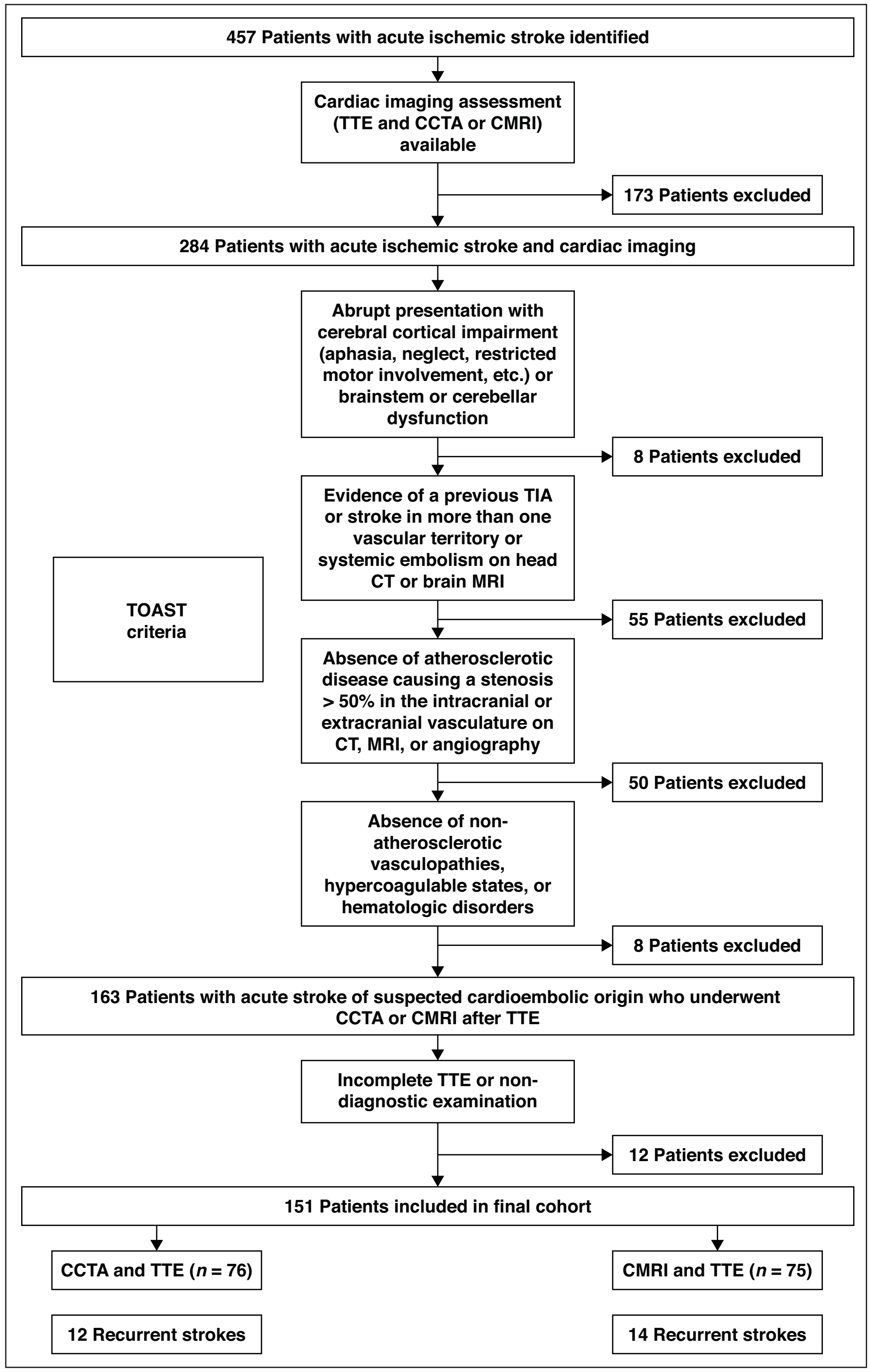

Fig. 1—Flowchart of patient selection. TTE = transthoracic echocardiography, CCTA = cardiac CTA, CMRI = cardiac MRI, TIA = transient ischemic attack, TOAST = Trial of Org 10172 in Acute Stroke Treatment classification system.

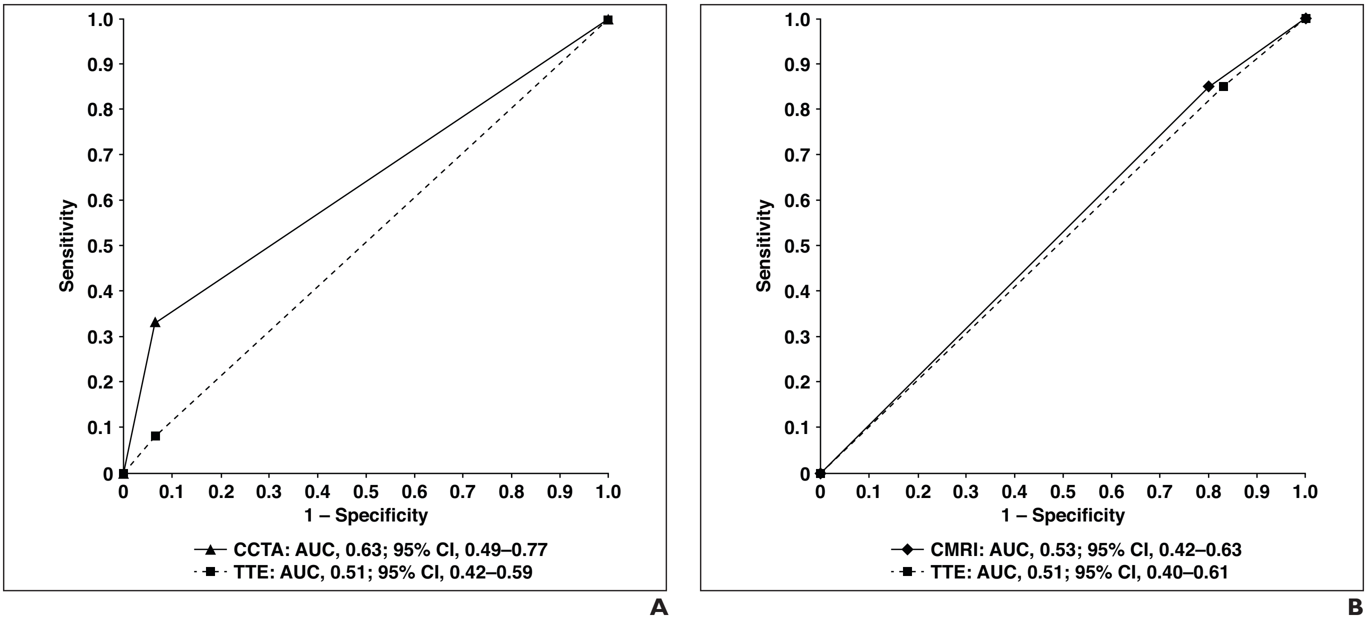

Fig. 2—ROC curves of diagnostic performance of three imaging modalities for excluding recurrent stroke in patients with suspected cardiac source of embolism.
A, ROC curves compare cardiac CTA (CCTA) and transthoracic echocardiography (TTE) in patients who underwent both examinations; their diagnostic performance was not significantly different (*p* = .06).
B, ROC curves compare cardiac MRI (CMRI) and TTE in patients who underwent both examinations; their diagnostic performance was not significantly different (*p* = .23).

TABLE 1: Patient Demographics

Characteristic	CCTA (*n* = 76)	CMRI (*n* = 75)	*p*
Sex			.51
Men	42 (55.3)	38 (50.7)	
Women	34 (44.7)	37 (49.3)	
Age (y)	63.3 ± 15.1	61.6 ± 17.3	.50
Body mass index[a]	27.7 ± 7.1	28 ± 6.9	.79
Comorbidity			
Diabetes	24 (31.6)	19 (25.3)	.36
Hypertension	58 (76.3)	53 (70.7)	.35
Congestive heart failure	17 (22.4)	14 (18.7)	.54
Vascular disease	9 (11.8)	8 (10.7)	.79
Atrial fibrillation or atrial flutter	25 (32.9)	14 (18.7)	.06
Current smoking	20 (26.3)	16 (21.3)	.44
Dyslipidemia	43 (56.6)	30 (40.0)	.06
Coronary artery disease	43 (56.6)	32 (42.7)	.06
Therapy			
Heparin	16 (21.1)	15 (20.0)	.84
Antiplatelet	48 (63.2)	29 (38.7)	< .01
Cholesterol (mg/dL)			
Total	147.2 ± 39.3	165.6 ± 46.5	.01
HDL	45.3 ± 12.7	47 ± 17.1	.06
LDL	83.6 ± 30.7	95 ± 35.1	.06
Triglyceride level (mg/dL)[b]	84 (63.5–109)	92 (71–148)	.08

Note—Unless otherwise indicated, values are represented as means ± SDs or frequency (percentages). Patients undergoing anticoagulant therapy were considered to be under chronic treatment. CCTA = cardiac CTA, CMRI = cardiac MRI, HDL = high-density lipoprotein, LDL = low-density lipoprotein.
[a]BMI is measured as weight in kilograms divided by the square of height in meters.
[b]Interquartile range is indicated in parentheses.

included traditional retrospective ECG gating with default use of ECG-dependent tube current modulation, prospective ECG triggering, and prospectively ECG-triggered high-pitch spiral acquisitions; 50–80 mL of iodinated contrast material (iopromide, Ultravist 370 mg I/mL, Bayer HealthCare) was injected at a rate of 4–6 mL/s, immediately followed by a 50-mL saline bolus. Beta-blocker was administered for heart rate control when necessary. The parameters of the CCTA protocol included the following: tube current–time product, 350–650 mAs; tube potential, 80–120 kVp; and gantry rotation time, 0.28–0.33 second. All examinations were obtained during breath-hold in the craniocaudal direction with *z*-axis coverage from the aortic arch to the diaphragm, specific in patients with stroke assessment. After 2 minutes, a delayed scan was acquired to discriminate between the presence of a thrombus or circulatory stasis in the left atrial appendage, according to our stroke protocol. The 2-minute delay also provided sufficient time for full opacification of the inferior vena cava and the right atrium. All images were reconstructed with a section thickness of 0.75 mm and 0.4-mm increments using a soft-tissue convolution kernel (B36f). Three-dimensional volume-rendering and multiplanar reformations were generated on a separate workstation (Syngo.via VB10B, Siemens Healthineers). Radiation exposure was estimated from the dose-length product. The calculated median dose-length product and the effective dose (conversion factor 0.014) were 699 mGy × cm (interquartile range [IQR], 401–1123) and 9.7 mSv (IQR, 5.6–17.2), respectively [19].

Cardiac MRI Protocol

CMRI studies were performed on a 1.5-T system (Magnetom Avanto, Siemens Healthineers). Images were acquired during breath-hold at end-expiration. Retrospective ECG-gated cine images were obtained in a double-oblique short-axis view. The whole heart was covered with 8-mm-thick slices and without interslice gaps using a balanced SSFP cine sequence. After IV administration of 0.2 mmol/kg of gadobenate dimeglumine (MultiHance, Bracco Diagnostics), either a time-resolved MRA of the aorta in a candy-cane view with interleaved stochastic trajectories VIBE, or rest first-pass myocardial

TABLE 2: Diagnostic Performance of Cardiac CTA (CCTA), Cardiac MRI (CMRI), and Transthoracic Echocardiography (TTE)

Characteristic	CCTA and TTE Group (*n* = 76)		CMRI and TTE Group (*n* = 75)	
	CCTA	TTE	CMRI	TTE
No. with recurrent strokes	12	12	14	14
True-positives	4	1	2	2
False-negatives	8	11	12	12
No. without recurrent stroke	64	64	61	61
True-negatives	60	60	49	51
False-positives	4	4	12	10
Median (IQR) time delay before cardiac examination after (d)				
First stroke	2 (1–4)	1 (0–1)	4 (2–6)	1 (0–2)
Recurrent stroke	10 (3–71)	19 (6–59)	15 (3–71)	21 (11-46)
Sensitivity				
Percentage	33.3	8.3	14.3	14.3
Raw numbers	4/4+8	1/1+11	2/2+12	2/2+12
Specificity				
Percentage	93.7	93.7	80.3	83.6
Raw numbers	60/60+4	60/60+4	49/49+12	51/51+10
PPV				
Percentage	50.0	20.0	14.3	16.7
Raw numbers	4/4+4	1/1+4	2/2+12	2/2+10
NPV				
Percentage	88.2	84.5	80.3	80.9
Raw numbers	60/60+8	60/60+11	49/49+12	51/51+12
AUC (95% CI)	0.63 (0.49–0.77)	0.51 (0.42–0.59)	0.53 (0.42–0.63)	0.51 (0.40–0.61)
p[a]				
CCTA	NA	.06	.23	NA
CMRI	.23	NA	NA	.15

Note—IQR = interquartile range, NA = not available.
[a]According to the DeLong method to compare AUCs between the techniques.

perfusion imaging in three short-axis slices of the left ventricle was performed. Early (2-minute) and late (10- to 15-minute) gadolinium enhancement imaging for the detection of thrombus and myocardial hyperenhancement was then performed. Left atrial and left ventricular thrombi were studied through short-axis and two-, three-, and four-chamber long-axis views on both the cardiac chambers. Early and late gadolinium enhancement images were obtained in long- and short-axis views using an inversion recovery balanced SSFP sequence. Inversion time was set at 500 milliseconds for early imaging to improve this technique's sensitivity for thrombus by decreasing its signal and was adjusted to null the signal from the normal myocardium for late gadolinium enhancement. MR images were reviewed on a PACS workstation.

Image Analysis

The clinical radiologic reports for each patient's neuroradiologic imaging were reviewed to identify patients with imaging suggestive of cardioembolic stroke. The examinations were interpreted clinically

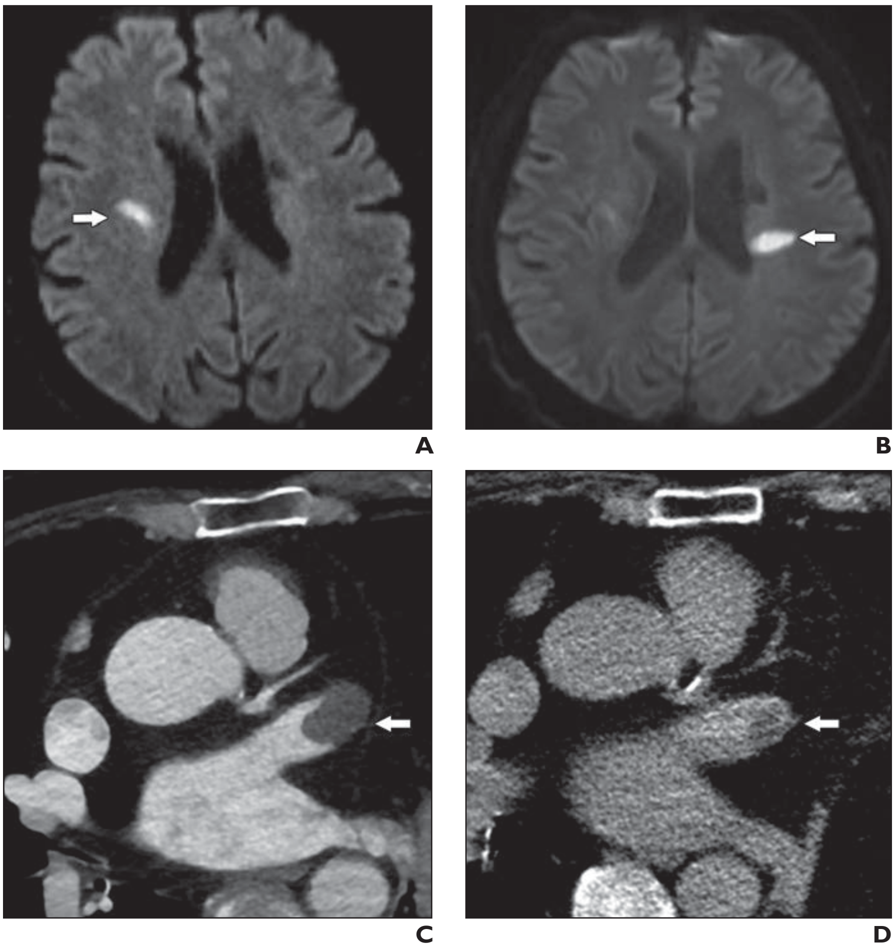

Fig. 3—53-year-old man with loss of consciousness.
A, DWI shows one area of restricted diffusion (*arrow*) in right corona radiata. Another acute lesion was found in white matter of left parietal lobe (not shown), suggestive of cardioembolic stroke. Patient was readmitted 45 days later.
B, DWI from repeat imaging 45 days later shows new acute ischemic area (*arrow*) in left corona radiata.
C and **D,** Early (**C**) and delayed (**D**) contrast-enhanced images from cardiac CTA performed 1 day after first stroke show round filling defect (*arrows*) in left atrial appendage persisting in both acquisition time points.

TABLE 3: Pathologic Findings Detected by Cardiac CTA (CCTA), Cardiac MRI (CMRI), and Transthoracic Echocardiography (TTE)

	CCTA and TTE ($n = 76$)				CMRI and TTE ($n = 75$)			
	CCTA		TTE		CMRI		TTE	
Pathologic Findings	TP	FP	TP	FP	TP	FP	TP	FP
Left atrial thrombus	1	2	0	0	1	3	1	0
Left ventricular thrombus	2	2	1	2	0	5	1	7
Vegetation	0	0	0	2	0	3	0	2
Vulnerable aortic plaque	1	0	0	0	1	1	0	0
Cardiac tumor	0	0	0	0	0	0	0	1
Total positives	4	4	1	4	2	12	2	10

Note—TP = true-positive (positive cardiac examination and recurrent stroke), FP = false-positive (negative cardiac examination but recurrent stroke).

TABLE 4: Prevalence of Atrial Fibrillation Between Patients With Recurrent Stroke Who Underwent Cardiac CTA (CCTA), Cardiac MRI (CMRI), and Transthoracic Echocardiography (TTE)

Patients	Total	With Atrial Fibrillation	Without Atrial Fibrillation	*p*
CCTA and TTE group (*n* = 76)				
CCTA				.38
True-positives	4	2	2	
False-negatives	8	6	2	
TTE				.14
True-positives	1	0	1	
False-negatives	11	8	3	
CMRI and TTE group (*n* = 75)				
CMRI				.82
True-positives	2	1	1	
False-negatives	12	5	7	
TTE				.82
True-positives	2	1	1	
False-negatives	12	5	7	

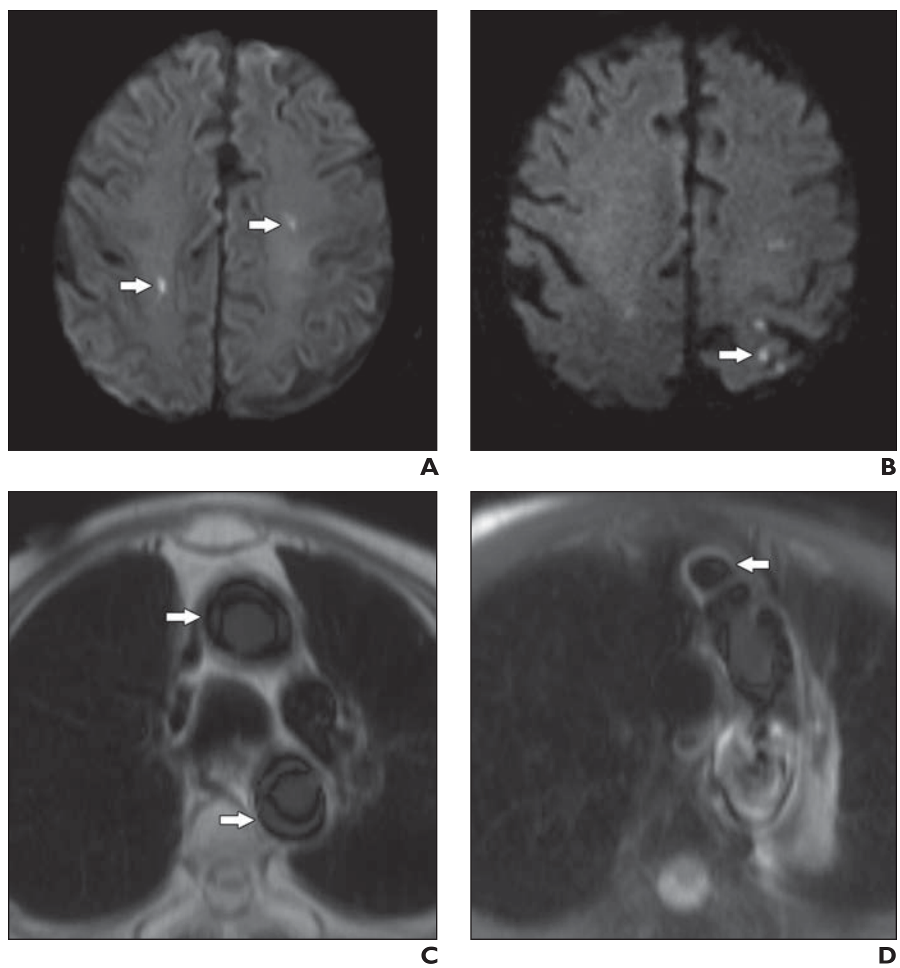

Fig. 4—76-year-old man with heart failure and sudden onset neurologic deficit.
A, DWI shows two small areas of restricted diffusion (*arrows*) in centrum semiovale bilaterally, suggestive of cardioembolic stroke.
B, DWI from repeat imaging performed after 3 days indicates that three acute ischemic areas (*arrow*) occurred in left parietal lobe.
C, Axial HASTE image shows concentric intramural hematoma (*arrows*) extending from proximal ascending aorta to descending aorta.
D, VIBE image shows extension into brachiocephalic artery (*arrow*).

by one of two nonauthor neuroradiologists as part of the patients' routine workup. This imaging included head CT; brain MRI; and CT, MRI, and invasive angiography of the intra- and extracranial vasculature. The radiologic reports were considered suggestive of cardioembolic stroke if describing either a corticosubcortical territorial lesion without large-vessel atherosclerotic disease causing a stenosis greater than 50% or multifocal ischemic lesions present at different vessel territories (e.g., cerebri posterior and cerebri media, or both left and right hemispheres) [20].

TTE, CCTA, and CMRI examinations were assessed for left atrial or left ventricular thrombus, vulnerable aortic plaque, cardiac tumors, or valvular vegetation. The TTE assessment was made according to the examinations' clinical reports; these were interpreted clinically by one of two cardiologists (S.E.L. with 21 years of experience and a nonauthor cardiologist with 6 years of experience) who performed the studies as part of routine patient care. Blinded to TTE results, clinical data, and CMRI and CCTA reports, a senior radiology resident (F.L., with 4 years of experience in cardiovascular imaging) reviewed CMRI and CCTA images. The original report and the resident's blinded reading agreed in 69 of 76 CCTA examinations and in 64 of 75 CMRI examinations. The discrepancies were resolved by a cardiovascular radiologist (J.W.N., with 5 years of experience). Cardiac imaging was considered positive for a cardioembolic source if thrombus, vulnerable aortic plaque, valvular vegetation, or intracardiac tumor was identified. The cardiac imaging study was considered negative in the absence of these findings. A thrombus was defined as a filling defect in the left chambers present in early and late phase images [21]. A vulnerable aortic plaque in the ascending aorta and aortic arch was identified as a plaque greater than 4 mm thick with complex morphologic features such as ulcerations or superimposed thrombi [22]. Valvular vegetation was defined as irregularly shaped, oscillating masses distinct from the endocardium of the mitral or aortic valve [23]. Cardiac tumors were defined as variably enhancing, heterogeneous intracardiac or myocardial masses [24].

The study end point of recurrent stroke was defined as the occurrence of a new ischemic lesion on head CT or brain MRI. Cases with positive cardiac examination and recurrent stroke were considered a true-positive; those with negative cardiac examination and without recurrent stroke were considered a true-negative. Cases with negative cardiac examination but recurrent stroke were considered a false-negative; those with positive cardiac examination but without recurrent stroke were considered a false-positive.

Statistical Analysis

All analyses were performed with SPSS software (version 24, IBM). Data were tested for normality using the Shapiro-Wilk test. Differences between categoric variables were analyzed using the chi-square test or the Fisher exact test. A chi-square test of independence with Cramér V was performed to test the relationship between recurrent stroke and chronic anticoagulant therapy. We also performed a one-sample nonparametric test between the false-negative and the true-positive cases to test the different prevalence of atrial fibrillation between patients with recurrent stroke. Differences between continuous variables were analyzed using the ANOVA test. Sensitivity, specificity, PPV, and NPV were calculated for CMRI, CCTA, and TTE in relation to recurrent stroke. The AUC was obtained to compare the diagnostic accuracy of CCTA, CMRI, and TTE in the two patient groups. Diagnostic accuracy between imaging modalities was compared using the DeLong method. A p value < .05 was considered significant.

Results

Patient Characteristics

A total of 151 patients (CCTA and TTE, n = 76; CMRI and TTE, n = 75) with suspected cardioembolic stroke were included (80 men [53.0%], 71 women [47.0%]; mean age, 62.4 ± 16.2 [SD] years). All CCTA and CMRI scans were complete and diagnostic. Table 1 shows patient characteristics. The clinical variables were not significantly different between the groups (p > .05), aside from a significantly higher (p < .01) rate of antiplatelet treatment in the CCTA group (63.2%) than the CMRI group (38.7%) and the significantly higher (p = .01) level of total cholesterol in the CMRI group (165.6 ± 46.5 mg/dL) than the CCTA group (147.2 ± 39.3 mg/dL).

Diagnostic Performance of Cardiac CTA, Cardiac MRI, and Transthoracic Echocardiography

A total of 26 recurrent strokes occurred, 12 in the CCTA group and 14 in the CMRI group. Among the 16 and 15 patients under heparin therapy in the CCTA and CMRI groups, three and two patients had a recurrent stroke, respectively. Heparin therapy and recurrent stroke were not associated in either group (CCTA group: p = .73, Cramér V = 0.04; and CMRI group: p = .55, Cramér V = 0.06). A total of 77 patients received antiplatelet therapy, 48 in the CCTA group and 29 in the CMRI group. The rate of stroke recurrence was 15.1% in the anticoagulant group and 14.5% in the antiplatelet group (p > .99).

The median (IQR) time delay between cardiac examination and recurrent stroke was 10 (3–71) and 19 (6–59) days for CCTA and TTE, respectively, in the CCTA group, versus 15 (3–71) and 21 (11–46) days for CMRI and TTE, respectively, in the CMRI group. The diagnostic accuracy of the imaging techniques is shown in Table 2. Sensitivity, specificity, PPV, and NPV were 33.3%, 93.7%, 50.0%, and 88.2% for CCTA; 14.3%, 80.3%, 14.3%, and 80.3% for CMRI; 14.3%, 83.6%, 16.7%, and 80.9% for TTE in the CMRI group; and 8.3%, 93.7%, 20.0%, and 84.5% for TTE in the CCTA group. Accuracy was not different (p > .05) between CCTA (0.63; 95% CI, 0.49–0.77), CMRI (0.53; 95% CI, 0.42–0.63), TTE in the CMRI group (0.51; 95% CI, 0.40–0.61), and TTE in the CCTA group (0.51; 95% CI, 0.42–0.59). Figure 2 shows the ROC curves of the different imaging techniques; the three AUCs were not significantly different (p > .05).

The pathologic findings detected by the three techniques are shown in Table 3, and the number of true-positive and false-negative cases are shown in Table 4. In the CCTA group, among 11 patients with a false-negative TTE for recurrent stroke, three had a positive CCTA. Among these three patients, one had a left ventricular thrombus, one had a left atrial thrombus, and one had a vulnerable aortic plaque (Fig. 3). In the CMRI group, one of the 12 false-negative TTE cases had a vulnerable aortic plaque with an intramural hematoma on CMRI (Fig. 4). No left atrial or left ventricular thrombus was detected on CMRI in patients with a false-negative TTE. Among three total cases of left atrial or left ventricular thrombus in the CCTA group, CCTA detected three and TTE detected one. Among 12 false-negative CMRI cases for recurrent stroke, one had a left ventricular thrombus on TTE. In the latter case, TTE was performed and medical therapy was started a day earlier than CMRI. None of the eight false-negative CCTA cases had a cardioembolic source on TTE. Valvular vegetation was suggested by CMRI in three patients but was ruled out by follow-up transesophageal ultrasound in all three cases. TTE suggested valvular vegetation as well in two of these three patients. Among three total cases of left atrial or left ventricular thrombus in the CMRI group, CMRI detected one, and TTE detected two.

Table 4 compares the prevalence of atrial fibrillation between patients with recurrent stroke that underwent CCTA, CMRI, and TTE, stratifying by true-positive versus false-negative results for each of the three techniques. The distribution of atrial fibrillation was not significantly different between true-positive and false-negative cases for any technique (CCTA, $p = .38$; CMRI, $p = .82$; TTE in the CCTA and CMRI groups, $p = .14$ and $p = .82$, respectively).

Discussion

This investigation quantified the diagnostic performance of CCTA, CMRI, and TTE for stroke recurrence in patients presenting with acute stroke of suspected cardioembolic origin. Although the performance of individual imaging techniques in this setting has been described, their comparative performance to reliably rule out stroke recurrence in the absence of intracardiac sources of embolism on imaging is insufficiently studied [7, 10–13]. CCTA, CMRI, and TTE all had high specificity and NPV for cardioembolic stroke recurrence (CCTA, 93.7% and 88.2%; CMRI, both 80.3%; TTE in the CCTA group, 93.7% and 84.5%; TTE in the CMRI group, 83.6% and 80.9%).

The low sensitivity and PPV (CCTA, 33.3% and 50.0%; CMRI, both 14.3%; TTE in the CCTA group, 8.3% and 20.0%; TTE in the CMRI group, 14.3% and 16.7%) may reflect the study design according to cardioembolic stroke recurrence. The specific therapy that was initiated according to initial diagnostic testing may have decreased the number of true-positives and resulted in false-positives on cardiac imaging, thereby lowering the PPV. A possible cause of stroke recurrence without any embolic source identified by cardiac imaging is the potential formation of a clot inside the cardiac chambers during the time delay between the cardiac examination and the stroke recurrence. Such occurrences could have contributed to the false-negatives that in turn resulted in low sensitivity. CCTA's higher sensitivity and PPV relative to CMRI and TTE may be from the technique's better performance in the detection of left atrial thrombi and vulnerable aortic plaque.

Left atrial thrombi and vulnerable aortic plaques are directly linked to the incidence of cardioembolic stroke and its recurrence [13, 25]. Although the three techniques showed comparable results overall, the higher diagnostic yield of CCTA in the identification of these two pathologic findings may impact the prediction of recurrent stroke. This implication is suggested by the lower proportion of false-negative CCTA cases and the higher number of true-positive CCTA cases compared with TTE. This higher diagnostic performance of CCTA compared with TTE may not have been statistically significant because of the small sample size.

Previous studies showed that TTE may not be reliable in the detection of left atrial thrombi and vulnerable aortic plaques [8]. Conversely, both CCTA and CMRI have good diagnostic accuracy in the identification of these two findings [15, 26]. Particularly, CCTA could detect more vulnerable plaques throughout the aortic arch and around the origins of the supraaortic arch vessels in comparison with transesophageal echocardiography [14, 27]. Although it is not the clinical protocol at our institution, the extension of CTA to the carotid arteries using a nongated scan has been shown to be beneficial for the evaluation of supraaortic arteries, especially in patients who have had a stroke [28].

In contrast with a previous study that showed that CMRI is a reliable technique in the detection of left ventricular thrombi [16], we observed a patient in whom TTE was able to detect a left ventricular thrombus not detected by CMRI. TTE was performed 1 day before CMRI in this patient, and we speculate that the medical therapy may have caused the dissolution of the thrombus inside the left ventricle with potential embolization to brain vessels. It is also possible that the inferior spatial resolution of CMRI compared with both TTE and CCTA contributed to missing small thrombi. On the other hand, CMRI detected an aortic valve vegetation that was not detected by TTE. This vegetation measured 5 × 9 mm. Although TTE has better spatial resolution than CMRI, its high operator dependency may have influenced the detection of this vegetation.

Although echocardiography is considered an integral part of the imaging strategy for the assessment of stroke, suitable criteria or established guidelines regarding the use of CCTA or CMRI for such assessment are currently lacking [29, 30]. Our study suggests that these two techniques may be valid alternatives to TTE in patients with high suspicion of cardioembolic stroke. In fact, in addition to having a similarly high specificity and NPV as TTE, CCTA and CMRI have the advantage of greater objectivity and reproducibility for a comprehensive assessment of patients who have had a stroke. Although all three techniques allow the study of extracardiac structures such as the carotid arteries in a single examination, each has its own benefits and limitations. TTE and carotid Doppler imaging can be performed in the same imaging session and provide relatively good spatial resolution and functional information. However, both are operator-dependent, and the examination's diagnostic certainty may be limited by inadequate acoustic windows and the inability to comprehensively study chest and vascular anatomy. Extending a CMRI session to a head and neck examination adds substantial imaging time and exposure to gadolinium-based contrast material. Although the ability of MRI to characterize plaque is limited, MRI provides excellent intracranial assessment. Finally, CCTA provides high spatial resolution and excellent ability to characterize plaques; however, the extension of a CCTA examination to a head and neck examination increases exposure to contrast material and radiation. Therefore, additional examinations must be individually and carefully chosen if a TTE examination is incomplete or provides inconclusive findings [8].

This study has a number of limitations. Because of the study's retrospective nature, information on the history of previous cerebrovascular accidents and ongoing statin and antiplatelet therapy were not available for all patients. Moreover, the study could not assess adherence to anticoagulant therapy, which may influence stroke recurrence. Transesophageal echocardiography, the reference standard for the detection of the cardiac source of embolism, was performed in a small fraction of patients and thus was not considered. Because a recurrent cerebrovascular event is the major cause of increased mortality and morbidity in patients with cardioembolic stroke, it is of paramount importance to define the risk of recurrence to select the most appropriate strategies for follow-up and therapy. For this reason, our results included stroke recurrence, for which avoidance is the main goal of diagnosis in this clinical scenario. Moreover, although transesophageal echocardiography excels in the detection of a medium-risk cardiac source, evidence is lacking regarding optimal management and therapy [31].

The time delay between the cardiac examinations and the recurrent stroke and medical therapy started as a result of the diagnostic tests may have influenced the occurrence of recurrence. However, our study was designed to precisely reflect the clinical and radiologic workup of patients with suspected cardioembolic stroke. Consequently, we considered the role of these factors important as part of the variables involved in this clinical scenario.

A high percentage of patients presented with atrial fibrillation and cardiac diseases, which may have increased the risk of recurrence in our cohort. We included these patients given that these diseases are considered high-risk sources of cardiac embolism. Nonetheless, atrial fibrillation was not more prevalent in patients with recurrent stroke, which likely reflects the chronic therapy in these patients.

We only evaluated the presence of high-risk cardiac sources (cardiac thrombi, valvular vegetation, cardiac tumors, and vulnerable aortic atheroma) that, when present, require immediate initiation of the appropriate clinical therapy [4]. However, this approach may have lowered the NPV of the three imaging techniques. The median time between the first and recurrent stroke episodes was relatively short. Thus, our investigation predominantly captured earlier recurrent strokes. Our single-center study included a limited number of highly selected patients because of the strict exclusion and inclusion criteria focusing solely on cardioembolic strokes. This investigation is hypothesis-generating, and future multicenter prospective studies are warranted to more granularly describe the comparative diagnostic performance of the imaging techniques under investigation.

In conclusion, CCTA, CMRI, and TTE all showed comparable high specificity and NPV for stroke recurrence. CCTA and CMRI may be useful alternatives to TTE. CCTA may be preferred given its better detection of left atrial and left ventricular thrombi.

References

1. Ko Y, Kim WJ, Jang MS, et al. Is aortic atherothrombotic disease detected using multidetector-row CT associated with an increased risk of early ischemic lesion recurrence after acute ischemic stroke? *Stroke* 2012; 43:764–769
2. Sacco RL, Adams R, Albers G, et al.; American Heart Association; American Stroke Association Council on Stroke; Council on Cardiovascular Radiology and Intervention; American Academy of Neurology. Guidelines for prevention of stroke in patients with ischemic stroke or transient ischemic attack: a statement for healthcare professionals from the American Heart Association/American Stroke Association Council on Stroke: co-sponsored by the Council on Cardiovascular Radiology and Intervention: the American Academy of Neurology affirms the value of this guideline. *Stroke* 2006; 37:577–617
3. Adams HP Jr, Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke: definitions for use in a multicenter clinical trial—TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke* 1993; 24:35–41
4. Doufekias E, Segal AZ, Kizer JR. Cardiogenic and aortogenic brain embolism. *J Am Coll Cardiol* 2008; 51:1049–1059
5. Hankey GJ, Jamrozik K, Broadhurst RJ, et al. Five-year survival after first-ever stroke and related prognostic factors in the Perth Community Stroke Study. *Stroke* 2000; 31:2080–2086
6. Lovett JK, Coull AJ, Rothwell PM. Early risk of recurrence by subtype of ischemic stroke in population-based incidence studies. *Neurology* 2004; 62:569–573
7. Cheitlin MD, Armstrong WF, Aurigemma GP, et al.; ACC; AHA; ASE. ACC/AHA/ASE 2003 Guideline update for the clinical application of echocardiography: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASE Committee to Update the 1997 Guidelines for the Clinical Application of Echocardiography). *J Am Soc Echocardiogr* 2003; 16:1091–1110
8. Rustemli A, Bhatti TK, Wolff SD. Evaluating cardiac sources of embolic stroke with MRI. *Echocardiography* 2007; 24:301–308; discussion, 308
9. Hilberath JN, Oakes DA, Shernan SK, Bulwer BE, D'Ambra MN, Eltzschig HK. Safety of transesophageal echocardiography. *J Am Soc Echocardiogr* 2010; 23:1115–1127; quiz, 1220–1221
10. Hur J, Kim YJ, Lee HJ, et al. Cardiac computed tomographic angiography for detection of cardiac sources of embolism in stroke patients. *Stroke* 2009; 40:2073–2078
11. Hur J, Kim YJ, Lee HJ, et al. Dual-enhanced cardiac CT for detection of left atrial appendage thrombus in patients with stroke: a prospective comparison study with transesophageal echocardiography. *Stroke* 2011; 42:2471–2477
12. Kronzon I, Tunick PA. Aortic atherosclerotic disease and stroke. *Circulation* 2006; 114:63–75
13. Lee K, Hur J, Hong SR, et al. Predictors of recurrent stroke in patients with ischemic stroke: comparison study between transesophageal echocardiography and cardiac CT. *Radiology* 2015; 276:381–389
14. Fayad ZA, Nahar T, Fallon JT, et al. In vivo magnetic resonance evaluation of atherosclerotic plaques in the human thoracic aorta: a comparison with transesophageal echocardiography. *Circulation* 2000; 101:2503–2509
15. Rathi VK, Reddy ST, Anreddy S, et al. Contrast-enhanced CMRI is equally effective as TEE in the evaluation of left atrial appendage thrombus in patients with atrial fibrillation undergoing pulmonary vein isolation procedure. *Heart Rhythm* 2013; 10:1021–1027
16. Srichai MB, Junor C, Rodriguez LL, et al. Clinical, imaging, and pathological characteristics of left ventricular thrombus: a comparison of contrast-enhanced magnetic resonance imaging, transthoracic echocardiography, and transesophageal echocardiography with surgical or pathological validation. *Am Heart J* 2006; 152:75–84
17. O'Donnell DH, Abbara S, Chaithiraphan V, et al. Cardiac tumors: optimal cardiac MR sequences and spectrum of imaging appearances. *AJR* 2009; 193:377–387
18. Buchholz S, Shakil A, Figtree GA, Hansen PS, Bhindi R. Diagnosis and management of patent foramen ovale. *Postgrad Med J* 2012; 88:217–225
19. Valentin J; International Commission on Radiation Protection. Managing patient dose in multi-detector computed tomography (MDCT): ICRP Publication 102. *Ann ICRP* 2007; 37:1–79, iii
20. Seo JY, Lee KB, Lee JG, et al. Implication of left ventricular diastolic dysfunction in cryptogenic ischemic stroke. *Stroke* 2014; 45:2757–2761
21. Pagán RJ, Parikh PP, Mergo PJ, et al. Emerging role of cardiovascular CT and MRI in the evaluation of stroke. *AJR* 2015; 204:269–280
22. Di Tullio MR, Sacco RL, Savoia MT, Sciacca RR, Homma S. Aortic atheroma morphology and the risk of ischemic stroke in a multiethnic population. *Am Heart J* 2000; 139:329–336
23. Hur J, Choi BW, Cardiac CT. Cardiac CT imaging for ischemic stroke: current and evolving clinical applications. *Radiology* 2017; 283:14–28
24. Araoz PA, Eklund HE, Welch TJ, Breen JF. CT and MR imaging of primary cardiac malignancies. *RadioGraphics* 1999; 19:1421–1434
25. Fuster V, Rydén LE, Cannom DS, et al.; American College of Cardiology/American Heart Association Task Force on Practice Guidelines; European Society of Cardiology Committee for Practice Guidelines; European Heart Rhythm Association; Heart Rhythm Society. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for

the Management of Patients With Atrial Fibrillation): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Circulation* 2006; 114:e257–e354

26. McDermott M, Hughes M, Rath T, et al. Negative predictive value of surveillance PET/CT in head and neck squamous cell cancer. *AJNR* 2013; 34:1632–1636
27. Chatzikonstantinou A, Krissak R, Flüchter S, et al. CT angiography of the aorta is superior to transesophageal echocardiography for determining stroke subtypes in patients with cryptogenic ischemic stroke. *Cerebrovasc Dis* 2012; 33:322–328
28. Zhao L, Bao J, Guo Y, et al. Ultra-low dose one-step CT angiography for coronary, carotid and cerebral arteries using 128-slice dual-source CT: a feasibility study. *Exp Ther Med* 2019; 17:4167–4175
29. Hendel RC, Patel MR, Kramer CM, et al.; American College of Cardiology Foundation Quality Strategic Directions Committee Appropriateness Criteria Working Group; American College of Radiology; Society of Cardiovascular Computed Tomography; Society for Cardiovascular Magnetic Resonance; American Society of Nuclear Cardiology; North American Society for Cardiac Imaging; Society for Cardiovascular Angiography and Interventions; Society of Interventional Radiology. ACCF/ACR/SCCT/SCMR/ASNC/NASCI/SCAI/SIR 2006 appropriateness criteria for cardiac computed tomography and cardiac magnetic resonance imaging: a report of the American College of Cardiology Foundation Quality Strategic Directions Committee Appropriateness Criteria Working Group, American College of Radiology, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, American Society of Nuclear Cardiology, North American Society for Cardiac Imaging, Society for Cardiovascular Angiography and Interventions, and Society of Interventional Radiology. *J Am Coll Cardiol* 2006; 48:1475–1497
30. Taylor AJ, Cerqueira M, Hodgson JM, et al.; American College of Cardiology Foundation Appropriate Use Criteria Task Force; Society of Cardiovascular Computed Tomography; American College of Radiology; American Heart Association; American Society of Echocardiography; American Society of Nuclear Cardiology; North American Society for Cardiovascular Imaging; Society for Cardiovascular Angiography and Interventions; Society for Cardiovascular Magnetic Resonance. ACCF/SCCT/ACR/AHA/ASE/ASNC/NASCI/SCAI/SCMR 2010 appropriate use criteria for cardiac computed tomography: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, the Society of Cardiovascular Computed Tomography, the American College of Radiology, the American Heart Association, the American Society of Echocardiography, the American Society of Nuclear Cardiology, the North American Society for Cardiovascular Imaging, the Society for Cardiovascular Angiography and Interventions, and the Society for Cardiovascular Magnetic Resonance. *J Am Coll Cardiol* 2010; 56:1864–1894
31. Yeo LLL, Holmin S, Andersson T, et al. Nongated cardiac computed tomographic angiograms for detection of embolic sources in acute ischemic stroke. *Stroke* 2017; 48:1256–1261

Editorial Comment on "Predictive Value of Cardiac CTA, Cardiac MRI, and Transthoracic Echocardiography for Cardioembolic Stroke Recurrence"

During my residency in radiology between 15 and 20 years ago, one specialty with which I had less contact was cardiology. Echocardiography was the domain of the cardiologist. We learned to evaluate the cardiomediastinal silhouette on radiographs, but in our hospital there was not yet a cardiac MRI (CMRI) program, and on the helical CT scanners at that time, the heart was just a blur. Nowadays, the discipline I coordinate in our institution is called thoracic and cardiovascular imaging, and our radiology fellows learn to report on cardiac CTA (CCTA) and CMRI. Radiology residents learn to look at the heart with different eyes, knowing that even on thoracic radiographs, as with chest CT, cardiac findings can be clinically significant [1].

In this study, the authors investigated the accuracy of CCTA, CMRI, and transthoracic echocardiography (TTE) for recurrence in patients with suspected cardioembolic stroke. A total of 151 patients were evaluated for the presence of left atrial thrombus, left ventricular thrombus, vulnerable aortic plaque, cardiac tumors, and valvular vegetation as causes of cardioembolic stroke. CCTA and CMRI showed similar clinical performance to TTE for predicting stroke recurrence, which may be especially important when TTE provides equivocal findings. CCTA was better for detection of atrial and ventricular thrombus.

A comprehensive evaluation of patients with ischemic stroke depends on the stroke's etiologic classification, which usually is multifactorial and dictates treatment during and after ictus, prognosis, and risk of recurrence [2]. Head and neck CTA is widely incorporated into acute stroke protocols and may be most useful in guiding therapeutic decisions when complemented by CCTA. The same complementary role may apply for brain MRI and CMRI. General radiologists should also be aware of the importance of stroke etiologic classification and actively search for cardiac findings that may be associated with cardioembolic disease (Zotin MCZ, et al., 2017 American Society of Neuroradiology meeting).

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References

1. Krueger M, Cronin P, Sayyouh M, Kelly AM. Significant incidental cardiac disease on thoracic CT: what the general radiologist needs to know. *Insights Imaging* 2019; 10:10
2. Adams HPJ Jr, Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke* 1993; 24:35–41