

# Detection of Left Ventricular Thrombus by Cardiac Magnetic Resonance in Embolic Stroke of Undetermined Source

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**Background and Purpose**—We aimed to use contrast-enhanced cardiac magnetic resonance (CE-CMR) imaging to elucidate the prevalence of left ventricular (LV) thrombus in patients suspected of embolic stroke of undetermined source (ESUS) with previous myocardial infarction or LV dysfunction (LV ejection fraction [LVEF] <50%).

**Methods**—We prospectively investigated 797 consecutive patients who presented to our hospital with acute ischemic stroke between 2014 and 2015. Patients with myocardial infarction or LVEF<50% underwent CE-CMR imaging. ESUS was diagnosed according to proposal criteria based on transthoracic echocardiography findings.

**Results**—The prevalence of ESUS was 22% (178 of 797) on initial diagnosis. Among 60 patients with myocardial infarction or LVEF<50%, the stroke subtypes were as follows: small artery disease, 17% (10 of 60); large artery atherosclerosis, 5% (3 of 60); cardioembolic stroke, 49% (29 of 60); ESUS, 23% (14 of 60); and undetermined causes other than ESUS, 6% (4 of 60). Of 60 patients examined via CE-CMR, LV thrombus was confirmed in 12 patients, whereas only 1 had been detected on transthoracic echocardiography ( $P=0.04$ ). Importantly, 29% (4 of 14) of patients with ESUS had LV thrombus. A prediction model based on CE-CMR findings showed higher performance in LV thrombus detection, permitting a net improvement of 0.46 (95% confidence interval, 0.08–0.82;  $P=0.016$ ) in cardioembolic stroke reclassification. Compared with patients without LV thrombus, those with LV thrombus had lower LVEF (median: 26% versus 40%;  $P=0.003$ ). Notably, 42% (5 of 12) of patients with LV thrombus had LVEF $\geq$ 30%.

**Conclusions**—When ESUS-suspected patients have myocardial infarction or LV dysfunction, CE-CMR may help improve detection of cardioembolic stroke and provide relevant information for anticoagulation therapy.

**Clinical Trial Registration**—URL: <http://www.clinicaltrials.gov>. Unique identifier: NCT02251665.

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**Key Words:** diagnosis ■ embolism ■ magnetic resonance imaging ■ stroke ■ thrombosis

The recently defined clinical construct of embolic stroke of undetermined source (ESUS)<sup>1,2</sup> has already achieved wide recognition. Patients with nonlacunar cryptogenic stroke are diagnosed with ESUS after excluding major-risk cardioembolic sources, such as atrial fibrillation (AF) or flutter, intracardiac thrombus, prosthetic cardiac valve, atrial myxoma, mitral stenosis, recent (<4 weeks) myocardial infarction (MI), severe left ventricular (LV) dysfunction defined as LV ejection fraction (LVEF) <30%, mitral stenosis, and valvular vegetations. To assess cardioembolic sources and diagnose ESUS, 12-lead ECG, cardiac monitoring ( $\geq$ 24 hours), and transthoracic echocardiography (TTE) are indispensable. Because the efficacy of anticoagulation therapy has not been established in patients with ESUS, detection of cardioembolic sources, such as intracardiac thrombus in patients suspected of ESUS, is

critical as it permits diagnosis of cardioembolic stroke (CES) and appropriate use of anticoagulant therapy.

Transesophageal echocardiography (TEE) is the gold standard technique for detecting thrombus of the left atrium or left atrial appendage although TTE is also widely used for excluding LV thrombus in patients with acute ischemic stroke.<sup>1,2</sup> However, recent studies have shown that contrast-enhanced cardiac magnetic resonance (CE-CMR) is superior to TTE and TEE in detecting LV thrombus in patients with history of MI<sup>3-6</sup> and LV dysfunction (LVEF<50%).<sup>7</sup> Srichai et al<sup>4</sup> found that among ischemic heart disease patients with surgical or pathological confirmation of LV thrombus, CE-CMR showed higher sensitivity and specificity (88% and 99%, respectively) than those of TTE (23% and 96%, respectively) and TEE (40% and 96%, respectively) for detecting LV thrombus. CE-CMR

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has another advantage in that it can detect other cardioaortic sources, such as left atrial appendage thrombus, intracardiac masses, patent foramen ovale, and aortic plaque.<sup>8</sup> Although several prospective studies have evaluated the incremental value of CMR imaging after TTE or TEE in ischemic stroke diagnosis,<sup>9,10</sup> to date, no studies have shown the incremental value of CMR imaging for detecting cardioaortic sources in cryptogenic stroke after TTE and TEE.<sup>10,11</sup> One possible reason for this lack of evidence is that these studies did not focus on detecting LV thrombus by CE-CMR because the prevalence of LV thrombus on CE-CMR has not been determined to date.

Although the LVEF cutoff value of 30% is defined as a major-risk cardioembolic source in the original ESUS construct<sup>1</sup> and in the Stop Stroke Study of the Trial of Org 10172 in Acute Stroke Treatment classification system,<sup>12,13</sup> there is insufficient evidence on the predictive capability of this cutoff value.<sup>14</sup>

The aim of the present study was to use CE-CMR imaging to evaluate the prevalence of LV thrombus in acute ischemic stroke patients with history of MI or LV dysfunction. In particular, we investigated the incremental value of CE-CMR imaging for detecting LV thrombus in patients with ESUS suspicion on TTE.

## Methods

### Study Design and Population

Between February 2014 and August 2015, 797 consecutive patients with acute ischemic stroke, admitted to our institute within 48 hours after stroke onset, were registered in the prospective database of the National Cerebral and Cardiovascular Center Stroke Registry and initially screened using TTE.

Among these 797 patients with stroke, 105 patients with history of MI or LVEF < 50% were considered at-risk for LV thrombus. History of MI was defined as previous MI (within  $\geq 4$  weeks before onset of acute MI) or recent MI (within < 4 weeks before onset of acute MI). Of these 105 patients, we excluded those with (1) estimated glomerular filtration rate < 45 mL/min per 1.73 m<sup>2</sup> (n=26), (2) severe general condition (n=9), (3) metal implant (n=7), (4) active phase of

bronchial asthma (n=1), or (5) refusal to provide informed consent for undergoing evaluation (n=2). Thus, 45 patients were excluded, and the remaining 60 patients (recent MI, 3 patients; previous MI, 27 patients; LV dysfunction without MI, 30 patients) were ultimately enrolled in the ADVENT (Assessment and Detection of left VENTricular Thrombus) study (Figure 1). TTE and CE-CMR imaging were performed at a mean of 3 $\pm$ 2 and 5 $\pm$ 2 days after admission, respectively.

The study was approved by the ethics committee of the National Cerebral and Cardiovascular Center in Osaka, Japan. Written informed consent for undergoing the investigative procedures was obtained from all patients or their relatives.

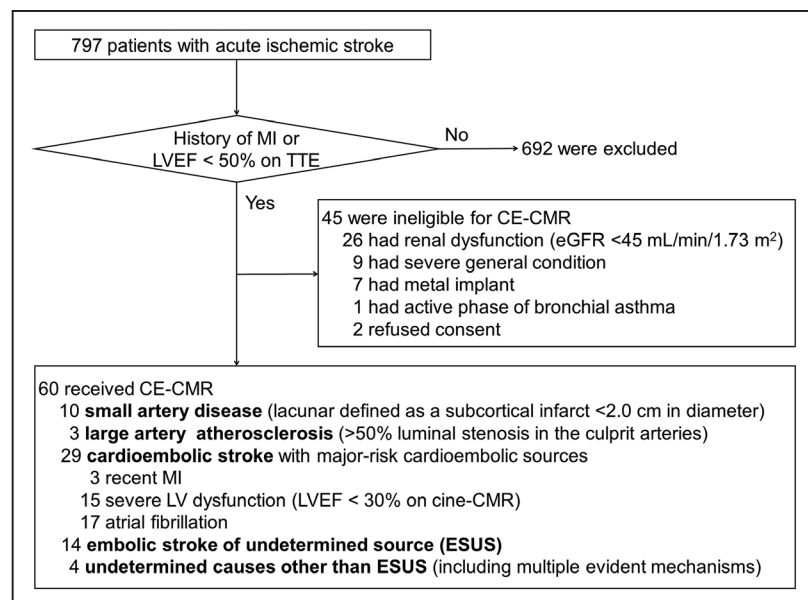
### Classification and Diagnostic Work-Up of Patients With Stroke

The following examinations were performed in all participants: laboratory tests, 12-lead ECG, cardiac monitoring  $\geq 24$  hours, carotid ultrasonography, brain computed tomography or MRI, and angiography. TTE was performed in 99.5% (992 of 997) of all patients evaluated for this study. TEE was performed for identifying potential embolic sources and intracardiac thrombus in patients with ESUS or major-risk cardioembolic sources. Based on the findings of these examinations, we classified the patients according to stroke subtype. We identified 6 subtypes of stroke according to the Stop Stroke Study of the Trial of Org 10172 in Acute Stroke Treatment classification<sup>12</sup> and ESUS criteria<sup>1</sup>: small artery disease (SAD) with a single subcortical infarction of < 2.0 cm at its maximum diameter within the territory of the basal or brain stem penetrating arteries; large artery atherosclerosis (LAA) with > 50% luminal stenosis in the extra/intracranial culprit arteries; CES with major-risk cardioembolic sources; other causes, such as arteritis, dissection, congenital coagulopathy, and vasospasm; ESUS; and undetermined causes (UND) other than ESUS, including multiple evident mechanisms. The participants were reclassified based on the combined findings of TTE and CE-CMR imaging.

### Imaging Protocol

Conventional TTE was performed by experienced cardiac sonographers using clinically available equipment. LV thrombus was defined as an echodense mass distinguishable from the LV wall and papillary muscles in at least 2 different views. Echocardiography findings were interpreted independently by 2 expert cardiologists.

CE-CMR was performed within 7 days after admission using a 1.5-T scanner (Magnetom Sonata; Siemens, Erlangen, Germany).



**Figure 1.** Flowchart of patient recruitment. CE-CMR indicates contrast-enhanced cardiac magnetic resonance; eGFR, estimated glomerular filtration rate; ESUS, embolic stroke of undetermined source; LV, left ventricular; LVEF, left ventricular ejection fraction; MI, myocardial infarction; and TTE, transthoracic echocardiogram.

Contrast-enhanced images for detection of LV thrombus were acquired in the short- and long-axis slices encompassing the entire LV at 1 to 5 minutes after gadolinium administration (0.15 mmol/kg). An ECG-gated inversion recovery prepared steady-state free precession pulse sequence (True-FISP, fast imaging with steady precession) was used with the following parameters: repetition time, 3.5 ms; echo time, 1.7 ms; flip angle, 60°; matrix size, 256×129; field of view, 340 mm; slice thickness, 3 to 5 mm; inversion time, 300 ms. On CE-CMR, LV thrombus appeared as a low-signal intensity mass distinguishable from surrounding high-intensity structures, such as cavity blood and myocardial scarring. Two experienced radiologists blinded to clinical data and outcomes independently determined the presence and location of LV thrombi. On disagreement of the 2 observers, consensus was reached through discussion. For quantification of LV volumes and LVEF, we manually traced the LV endocardial contours in end-systolic and end-diastolic frames on cine images processed using a dedicated software program (Argus system; Siemens, Erlangen, Germany). We used CMR-based LVEF rather than TTE-based LVEF for assessing LV systolic function because CMR has recently been recognized as the gold standard technique for LV function assessment.<sup>15</sup> In our study, 16 of 17 patients with severe LV dysfunction on CE-CMR also had LVEF<30% on TTE.

### Statistical Analysis

Categorical variables were expressed as frequencies and percentages. Continuous variables were expressed as mean±SD or median (interquartile range). Baseline characteristics and CE-CMR findings were compared between groups of patients defined in terms of the presence of LV thrombus on CE-CMR using  $\chi^2$  or Fisher exact test for categorical variables and Student *t* test or the Mann-Whitney *U* test for continuous variables, as appropriate. The net reclassification improvement<sup>16</sup> was calculated to evaluate the proportion of CES significantly reclassified by considering CE-CMR findings of LV thrombus in addition to TTE findings. Statistical analysis was performed using the R package version 3.3.1 (R Foundation for Statistical Computing, Vienna, Austria) with the rms package (<https://cran.r-project.org/web/packages/rms/rms.pdf>). A *P*<0.05 was considered to indicate statistical significance.

## Results

### Population Characteristics

Among 797 consecutive patients with acute ischemic stroke (age, 75±12 years; 488 men), the prevalence of AF, LV dysfunction (LVEF<50%), and history of MI was 35%, 9%, and 7%, respectively. Based on the Stop Stroke Study of the Trial of Org 10172 in Acute Stroke Treatment classification and ESUS criteria, the classification of stroke subtypes was as follows: SAD, 23% (182 of 797); LAA, 14% (113 of 797); CES, 35% (278 of 797); other causes, 3% (20 of 797); ESUS, 22% (178 of 797); and UND, 3% (26 of 797). Of 60 patients who underwent CE-CMR (Table 1), approximately half had pre-admission antiplatelet therapy whereas only 18% (11 of 60) had prior anticoagulant therapy. On admission, 19 patients (32%) received tissue-type plasminogen activator; these patients then underwent TTE and CE-CMR at a mean of 2±2 and 5±1 days after intravenous tissue-type plasminogen activator therapy, respectively. Furthermore, 92% (55 of 60) received anticoagulant therapy, including unfractionated heparin or oral anticoagulants, during hospitalization. The prevalence of patients receiving anticoagulant therapy at the time of the TTE and CE-CMR examinations was 68% (41 of 60) and 83% (50 of 60), respectively. Figure 1 shows the stratification of the 60 patients according to stroke subtype: SAD, 17% (10 of 60); LAA, 5% (3 of 60); CES, 49% (29 of 60); ESUS, 23% (14

of 60); and UND, 6% (4 of 60). There was no other determined cause of stroke in this cohort.

### Detection of LV Thrombus

Among the 60 patients who underwent CE-CMR investigations, 12 (20%) were determined to have LV thrombus, whereas only 1 was identified based on TTE findings (2%; *P*=0.04). The  $\kappa$  coefficients for intra- and interobserver agreement were 0.89 and 0.83, respectively. Representative findings indicating LV thrombus as assessed by CE-CMR and conventional TTE are shown in Figure 2. CE-CMR detected LV thrombi in the apex (n=9) and on the lateral or posterior wall (n=3), whereas TTE could not identify 8 small (<1 cm) apical thrombi and 3 lateral or posterior mural thrombi (Table 2).

The clinical and imaging characteristics of patients with and without LV thrombus on CE-CMR are summarized in Table 1. There was no significant difference in vascular risk factors, prior antithrombotic therapy, and emergent treatment between the 2 groups. Compared with patients without thrombus, those with thrombus had a higher prevalence of previous MI (*P*=0.02) and active cancer (*P*=0.04). Regarding CE-CMR findings, patients with thrombus had a lower LVEF (median [interquartile range]: 26% [17%–36%] versus 40% [33%–47%]; *P*=0.003; Figure 3), higher LV end-diastolic volume index (131 mL/m<sup>2</sup> [87–190 mL/m<sup>2</sup>] versus 97 mL/m<sup>2</sup> [80–124 mL/m<sup>2</sup>]; *P*=0.049), and higher LV end-systolic volume index (93 mL/m<sup>2</sup> [58–166 mL/m<sup>2</sup>] versus 56 mL/m<sup>2</sup> [41–88 mL/m<sup>2</sup>]; *P*=0.02). Notably, as shown in Figure 3, 42% (5 of 12) of patients with LV thrombus on CE-CMR imaging had LVEF≥30%. In terms of stroke subtypes, the prevalence of LV thrombus was 0% (0 of 10) in SAD, 0% (0 of 3) in LAA, 21% (6 of 29) in CES, and 50% (2 of 4) in UND. Importantly, of the 14 patients with ESUS on initial diagnosis, 4 patients (29%) had LV thrombus findings on CE-CMR.

### TEE Findings

Of the 60 patients who underwent CE-CMR, 32 patients (53%) also underwent TEE. Of the 14 patients with ESUS, 12 patients (86%) underwent TEE, which revealed patent foramen ovale in 6 cases, patent foramen ovale with atrial septal aneurysm in 1 case, and complex aortic plaque in another case. The remaining 2 patients with ESUS (14%) refused to undergo TEE examination. Of the 29 patients with CES, 18 patients (62%) underwent TEE, which revealed left atrial appendage thrombi in 3 cases. The remaining 11 patients with CES (38%) did not undergo TEE because of the following reasons: advanced age (≥85 years old; n=7), decompensated heart failure (n=2), high risk for aspiration (n=1), or advanced cancer (n=1). Of the 17 other patients including those with SAD (n=10), LAA (n=3), and UND (n=4), 2 patients (12%) underwent TEE, which revealed complex aortic plaque in one case.

### Reclassification of Stroke Subtypes

When considering the CE-CMR findings of LV thrombus in addition to the TTE findings, the reclassified prevalence of stroke subtypes was as follows: SAD, 17% (10 of 60); LAA,

**Table 1. Baseline Characteristics of Patients Stratified According to the Presence of LV Thrombus on CE-CMR**

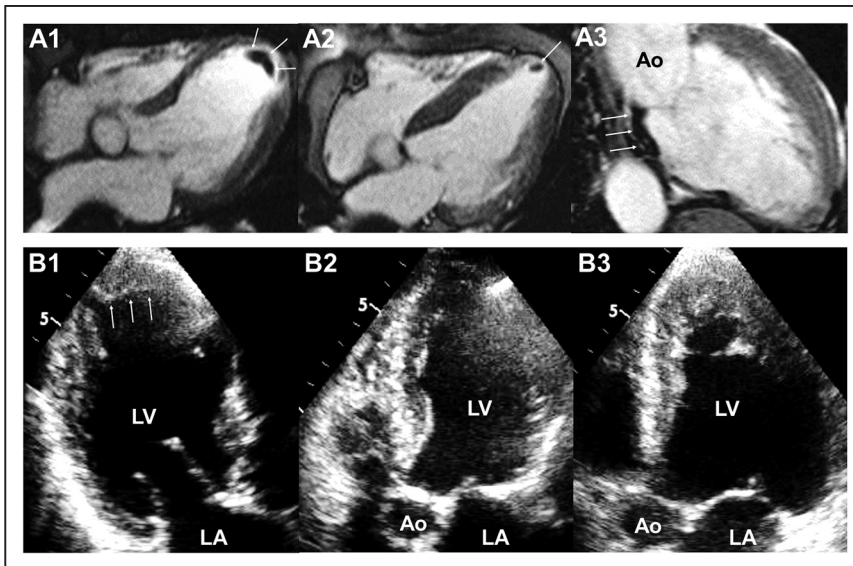
Characteristics	Overall (n=797)	Patients Stratified by CE-CMR Findings			
		Total (n=60)	LV Thrombus Present (n=12)	LV Thrombus Absent (n=48)	P Value
<b>Clinical</b>					
Age, y	75±12	74±12	71±12	75±12	0.26
Male sex	488 (61)	48 (80)	10 (83)	38 (79)	0.75
Initial NIHSS score	4 (2–13)	8 (2–16)	5 (2–18)	8 (2–16)	0.68
<b>Risk factors</b>					
Hypertension	626 (79)	48 (80)	9 (75)	39 (81)	0.63
Diabetes mellitus	205 (26)	21 (35)	5 (42)	16 (33)	0.59
Hyperlipidemia	481 (60)	41 (68)	10 (83)	31 (65)	0.21
Current smoker	148 (19)	15 (25)	3 (25)	12 (25)	1.0
<b>Comorbidities</b>					
Active cancer	25 (3)	3 (5)	2 (17)	1 (2)	0.04
Prior ischemic stroke	192 (24)	14 (23)	4 (33)	10 (21)	0.36
Recent MI	7 (1)	3 (5)	0	3 (6)	0.37
Previous MI	50 (6)	27 (45)	9 (75)	18 (38)	0.02
<b>Prior antithrombotics</b>					
Antiplatelets	250 (31)	32 (53)	8 (67)	24 (50)	0.30
Anticoagulants	150 (19)	11 (18)	2 (17)	9 (19)	0.87
<b>Stroke subtypes*</b>					
SAD	182 (23)	10 (17)	0	10 (21)	0.08
LAA	113 (14)	3 (5)	0	3 (6)	0.37
CES	278 (35)	29 (49)	6 (50)	23 (48)	0.90
Other causes	20 (3)	0	0	0	
ESUS	178 (22)	14 (23)	4 (33)	10 (21)	0.36
UND	26 (3)	4 (6)	2 (17)	2 (4)	0.12
<b>Emergent treatment</b>					
Intravenous t-PA	129 (16)	19 (32)	3 (25)	16 (33)	0.58
Endovascular therapy	55 (7)	13 (22)	3 (25)	10 (21)	0.75
Anticoagulants	616 (77)	55 (92)	11 (92)	44 (92)	1.0
<b>CMR findings</b>					
Onset to scan time, d		5±2	5±2	5±2	0.23
LVEF, %		37 (26–45)	26 (17–36)	40 (33–47)	0.003
LVEDVI, mL/m <sup>2</sup>		101 (80–134)	131 (87–190)	97 (80–124)	0.049
LVESVI, mL/m <sup>2</sup>		61 (42–94)	93 (58–166)	56 (41–88)	0.02

Values are mean±SD, n (%), or median (interquartile range). CE-CMR indicates contrast-enhanced cardiac magnetic resonance; CES, cardioembolic stroke; EDVI, end-diastolic volume index; ESUS, embolic stroke of undetermined source; ESVI, end-systolic volume index; LAA, large artery atherosclerosis; LV, left ventricular; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NIHSS, National Institute of Health Stroke Scale; SAD, small artery disease; t-PA, tissue-type plasminogen activator; and UND, undetermined causes other than ESUS.

\*Stroke subtypes were determined according to the Stop Stroke Study of the Trial of ORG 10172 in Acute Stroke Treatment classification system and ESUS criteria based on the outcomes of indicated examinations.

5% (3 of 60); CES, 55% (33 of 60); ESUS, 17% (10 of 60); and UND, 6% (4 of 60; Figure 4). Consideration of CE-CMR findings in addition to TTE findings resulted in a 29% relative

reduction in the prevalence of ESUS and a 14% relative increase in the prevalence of CES; compared with considering only the TTE findings, the net reclassification improvement



**Figure 2.** Representative left ventricular (LV) thrombi assessed on contrast-enhanced cardiac magnetic resonance (CE-CMR) images and conventional transthoracic echocardiogram (TTE). **A1, A2** (4-chamber view), and **A3** (sagittal view), CE-CMR. **B1–B3**, conventional TTE. A large apical thrombus (**arrows**) was visible on both CE-CMR (**A1**) and TTE (**B1**). The small apical thrombus (**A2; arrow**) was not visible on TTE (**B2**) because the apical view image was poor due to an artifact. The mural thrombus on the posterior wall (**A3**) could not be visualized (**B3**). Ao indicates ascending aorta; and LA indicates left atrium.

achieved by considering also CE-CMR findings was 0.46 (95% confidence interval, 0.08–0.82;  $P=0.016$ ).

### Discussion

The major findings of this study are as follows: (1) considering CE-CMR findings in addition to TTE findings improves the detection of LV thrombus and may help avoid missing CES in ESUS-suspected patients with history of MI or LV dysfunction (LVEF<50%); and (2) the current LVEF cutoff value of 30%, which is based on the diagnostic criteria for ESUS, may result in not identifying patients with high risk for recurrent CES. To our knowledge, this is the first prospective study indicating the use of CE-CMR for detecting LV thrombus in patients suspected of ESUS.

In their recent review, Yaghi et al<sup>8</sup> stated that CMR imaging is now recognized as a novel tool to evaluate the potential embolic sources, including functional and structural parameters of the left atrium and left atrial appendage in patients with cryptogenic stroke. Nevertheless, there have been no prospective studies describing the prevalence of LV thrombus on CE-CMR in acute ischemic stroke, with the exception of 1 single-center study involving 106 unselected patients with ischemic stroke,<sup>9</sup> which showed a 2% prevalence of LV thrombus on TTE alone and 4% on TTE plus CE-CMR imaging. In our study, CE-CMR findings confirmed LV thrombus in 12 (20%) selected stroke patients with history of MI or LV dysfunction, whereas TTE had failed to detect thrombus in 11 of 12 (92%) patients identified on CE-CMR. As previous studies have shown, TTE has difficulty in visualizing small apical thrombi (<1 cm), which is related to the limited near-field resolution, wherein adherent mural thrombi resemble the adjacent myocardium.<sup>3,4,17</sup> However, CE-CMR can identify such thrombi as dark masses with strong enhancement of the LV cavity, which makes them easily distinguishable from surrounding structures.<sup>4,5,7,18</sup> Furthermore, the use of unfractionated heparin in the acute phase might contribute to the low frequency of LV thrombus detection on TTE. In the Japanese guidelines for the management of ischemic stroke, the use of heparin can be considered for cerebral infarction

within 48 hours after stroke onset,<sup>19</sup> which could decrease thrombus size.

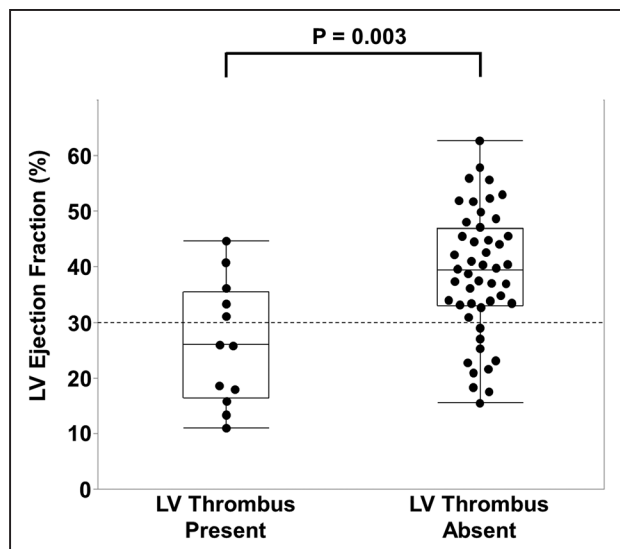
Our study shows the use of CE-CMR especially in ESUS patients with prior MI or LV dysfunction. In patients with ESUS, the potential causes of stroke are heterogeneous, involving covert AF, minor-risk cardioembolic sources, non-stenotic culprit lesions, aortic plaque, and occult cancer.<sup>1,2</sup> Among these potential causes, Ntaios et al<sup>20</sup> have shown that covert AF is the most prevalent source of emboli. In this context, detection of AF by ambulatory prolonged ECG monitoring<sup>21</sup> or insertable cardiac monitor<sup>22</sup> represents an area of active interest. Notably, our results indicate that the risk of LV thrombus formation should be considered in ESUS-suspected patients with prior MI or LV dysfunction.

As described above, severe LV dysfunction (LVEF<30%) is considered among major-risk cardioembolic sources, and there is insufficient evidence for this recommendation. Hays et al<sup>23</sup> demonstrated that even moderate LV dysfunction (LVEF≥30%) increased stroke risk, suggesting that not only severe but also moderate LV dysfunction could lead to thrombosis in the LV cavity. Our results strongly support this interpretation because ≈40% of stroke patients with LV thrombus on CE-CMR had LVEF≥30%. Thus, the current LVEF cutoff value of 30%, which is based on the diagnostic criteria for ESUS, may not be able to detect all patients at high risk for recurrent CES. In our cohort, the median LVEF in patients without LV thrombus was 40%. Therefore, we propose that

**Table 2. Detection of LV Thrombus by TTE and CE-CMR in 60 Patients With Acute Stroke**

Examination	Location of LV Thrombus	
	Apex	Lateral or Posterior Wall
TTE	1/60	0/60
CE-CMR	9/60	3/60

Of 12 LV thrombi (in 12 patients) detected on CE-CMR, TTE detected only 1 large apical thrombus. CE-CMR indicates contrast-enhancement cardiac magnetic resonance; LV, left ventricular; and TTE, transthoracic echocardiography.

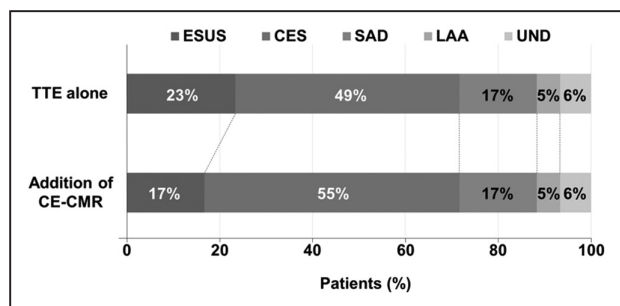


**Figure 3.** Left ventricular (LV) ejection fraction according to the presence or absence of LV thrombus. Boxes indicate the median with upper and lower quartile values, and whiskers indicate the minimum and maximum values. Dotted line indicates LV ejection fraction cutoff value of 30% based on current diagnostic criteria for embolic stroke of undetermined source. Notably, 5 of 12 patients (42%) with LV thrombus had LV ejection fraction  $\geq 30\%$ .

a cutoff LVEF of 40% is more suitable predicting major-risk cardioembolic sources requiring anticoagulants. Further studies are warranted to verify the significance of this increased LVEF cutoff as a major-risk cardioembolic source.

We found that active cancer was also a factor contributing to LV thrombus formation in patients with stroke. One possible explanation for this finding is that the hypercoagulable state may promote thrombophilia, which is considered a potential stroke pathogenesis in cryptogenic stroke.<sup>24,25</sup>

Our study has several limitations. First, the outcomes of this single-center study might reflect selection bias because related to the small sample size and exclusion of patients with renal dysfunction or unable to undergo CE-CMR imaging because of metal implants or intolerance. Consequently, 42%



**Figure 4.** Distribution of embolic stroke of undetermined source (ESUS) and cardioembolic stroke (CES) as diagnosed based on findings from transthoracic echocardiogram (TTE) alone or on findings from TTE and contrast-enhanced cardiac magnetic resonance (CE-CMR) imaging. Compared with using only TTE findings, including CE-CMR findings resulted in diagnosing ESUS 29% less often and CES 14% more often, permitting a net improvement of 0.46 (95% confidence interval, 0.08–0.82;  $P=0.016$ ) in CES reclassification. LAA indicates large artery atherosclerosis; SAD, small artery disease; and UND, undetermined causes other than ESUS.

(10 of 24) of ESUS patients with prior MI or LV dysfunction were ineligible for CE-CMR. Moreover, it should be noted that the prevalence of LV dysfunction and history of MI in our Japanese cohort are relatively low (9% and 7%, respectively) compared with those noted in a cohort from the United States (24% and 31%, respectively).<sup>23</sup> This finding might be related to the fact that the incidence of MI is generally lower in Japan than in Western countries as was reported in a previous study based on data obtained from several Japanese cohort studies and the Monitoring Trends and Determinants in Cardiovascular Disease (MONICA) Project.<sup>26</sup> Further studies are needed to verify our findings. Second, breath-hold instructions are sometimes difficult to follow for patients with stroke in acute phase because of aphasia or attention and consciousness disorders. In such cases, CE-CMR was performed under free-breathing conditions. However, the early phase of the CE-CMR assessment is less sensitive to motion artifacts of T1-shortening by gadolinium. For this reason, and also because the reliability of CE-CMR assessments was excellent, the quality of CE-CMR data obtained in this study is considered acceptable. Free-breathing imaging using a navigator echo technique may improve this shortcoming.<sup>27</sup>

## Conclusions

Our present findings suggest that when making a differential diagnosis with ESUS in patients with history of MI or LV dysfunction, complementing TTE with additional CE-CMR imaging may improve the detection of CES. CE-CMR may provide relevant information for appropriate indication of anticoagulation therapy in patients with acute ischemic stroke.

## Disclosures

None.

## References

- Hart RG, Diener HC, Coutris SB, Easton JD, Granger CB, O'Donnell MJ, et al; Cryptogenic Stroke/ESUS International Working Group. Embolic strokes of undetermined source: the case for a new clinical construct. *Lancet Neurol*. 2014;13:429–438. doi: 10.1016/S1474-4422(13)70310-7.
- Hart RG, Catanese L, Perera KS, Ntaios G, Connolly SJ. Embolic stroke of undetermined source: a systematic review and clinical update. *Stroke*. 2017;48:867–872. doi: 10.1161/STROKEAHA.116.016414.
- Mollet NR, Dymarkowski S, Volders W, Wathiong J, Herbots L, Rademakers FE, et al. Visualization of ventricular thrombi with contrast-enhanced magnetic resonance imaging in patients with ischemic heart disease. *Circulation*. 2002;106:2873–2876.
- Srichai MB, Junor C, Rodriguez LL, Stillman AE, Grimm RA, Lieber ML, 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. doi: 10.1016/j.ahj.2005.08.021.
- Weinsaft JW, Kim RJ, Ross M, Krauser D, Manoushagian S, LaBounty TM, et al. Contrast-enhanced anatomic imaging as compared to contrast-enhanced tissue characterization for detection of left ventricular thrombus. *JACC Cardiovasc Imaging*. 2009;2:969–979. doi: 10.1016/j.jcmg.2009.03.017.
- Delewi R, Nijveldt R, Hirsch A, Marcu CB, Robbers L, Hassell ME, et al. Left ventricular thrombus formation after acute myocardial infarction as assessed by cardiovascular magnetic resonance imaging. *Eur J Radiol*. 2012;81:3900–3904. doi: 10.1016/j.ejrad.2012.06.029.
- Weinsaft JW, Kim HW, Crowley AL, Klem I, Shenoy C, Van Assche L, et al. LV thrombus detection by routine echocardiography: insights into performance characteristics using delayed enhancement CMR. *JACC Cardiovasc Imaging*. 2011;4:702–712. doi: 10.1016/j.jcmg.2011.03.017.

8. Yaghi S, Liberman AL, Atalay M, Song C, Furie KL, Kamel H, et al. Cardiac magnetic resonance imaging: a new tool to identify cardio-aortic sources in ischaemic stroke. *J Neurol Neurosurg Psychiatry*. 2017;88:31–37. doi: 10.1136/jnnp-2016-314023.
9. Baher A, Mowla A, Kodali S, Polsani VR, Nabi F, Nagueh SF, et al. Cardiac MRI improves identification of etiology of acute ischemic stroke. *Cerebrovasc Dis*. 2014;37:277–284. doi: 10.1159/000360073.
10. Haeusler KG, Wollboldt C, Bentheim LZ, Herm J, Jäger S, Kunze C, et al. Feasibility and diagnostic value of cardiovascular magnetic resonance imaging after acute ischemic stroke of undetermined origin. *Stroke*. 2017;48:1241–1247. doi: 10.1161/STROKEAHA.116.016227.
11. Liberman AL, Kalani RE, Aw-Zoretic J, Sondag M, Daruwalla VJ, Mitter SS, et al. Cardiac magnetic resonance imaging has limited additional yield in cryptogenic stroke evaluation after transesophageal echocardiography [published online ahead of print April 24, 2017]. *Int J Stroke*. 2017. doi: 10.1177/1747493017706242. <http://journals.sagepub.com/doi/full/10.1177/1747493017706242>.
12. Ay H, Furie KL, Singhal A, Smith WS, Sorensen AG, Koroshetz WJ. An evidence-based causative classification system for acute ischemic stroke. *Ann Neurol*. 2005;58:688–697. doi: 10.1002/ana.20617.
13. Ay H, Benner T, Arsava EM, Furie KL, Singhal AB, Jensen MB, et al. A computerized algorithm for etiologic classification of ischemic stroke: the Causative Classification of Stroke System. *Stroke*. 2007;38:2979–2984. doi: 10.1161/STROKEAHA.107.490896.
14. Dunkman WB, Johnson GR, Carson PE, Bhat G, Farrell L, Cohn JN. Incidence of thromboembolic events in congestive heart failure. The V-HeFT VA Cooperative Studies Group. *Circulation*. 1993;87(6 suppl):VI94–V101.
15. Pontone G, Guaricci AI, Andreini D, Solbiati A, Guglielmo M, Mushtaq S, et al. Prognostic benefit of cardiac magnetic resonance over transthoracic echocardiography for the assessment of ischemic and non-ischemic dilated cardiomyopathy patients referred for the evaluation of primary prevention implantable cardioverter-defibrillator therapy. *Circ Cardiovasc Imaging*. 2016;9:e004956.
16. Pencina MJ, D'Agostino RB Sr, D'Agostino RB Jr, Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. *Stat Med*. 2008;27:157–172; discussion 207. doi: 10.1002/sim.2929.
17. Stratton JR, Lighty GW Jr, Pearlman AS, Ritchie JL. Detection of left ventricular thrombus by two-dimensional echocardiography: sensitivity, specificity, and causes of uncertainty. *Circulation*. 1982;66:156–166.
18. Weinsaft JW, Kim HW, Shah DJ, Klem I, Crowley AL, Brosnan R, et al. Detection of left ventricular thrombus by delayed-enhancement cardiovascular magnetic resonance prevalence and markers in patients with systolic dysfunction. *J Am Coll Cardiol*. 2008;52:148–157. doi: 10.1016/j.jacc.2008.03.041.
19. Kern R, Nagayama M, Toyoda K, Steiner T, Hennerici MG, Shinohara Y. Comparison of the European and Japanese guidelines for the management of ischemic stroke. *Cerebrovasc Dis*. 2013;35:402–418. doi: 10.1159/000351753.
20. Ntaios G, Papavasileiou V, Milionis H, Makaritsis K, Manios E, Spengos K, et al. Embolic strokes of undetermined source in the Athens stroke registry: a descriptive analysis. *Stroke*. 2015;46:176–181. doi: 10.1161/STROKEAHA.114.007240.
21. Gladstone DJ, Spring M, Dorian P, Panzov V, Thorpe KE, Hall J, et al; EMBRACE Investigators and Coordinators. Atrial fibrillation in patients with cryptogenic stroke. *N Engl J Med*. 2014;370:2467–2477. doi: 10.1056/NEJMoa1311376.
22. Sanna T, Diener HC, Passman RS, Di Lazzaro V, Bernstein RA, Morillo CA, et al; CRYSTAL AF Investigators. Cryptogenic stroke and underlying atrial fibrillation. *N Engl J Med*. 2014;370:2478–2486. doi: 10.1056/NEJMoa1313600.
23. Hays AG, Sacco RL, Rundek T, Sciacca RR, Jin Z, Liu R, et al. Left ventricular systolic dysfunction and the risk of ischemic stroke in a multiethnic population. *Stroke*. 2006;37:1715–1719. doi: 10.1161/01.STR.0000227121.34717.40.
24. Schwarzbach CJ, Schaefer A, Ebert A, Held V, Bolognese M, Klabau M, et al. Stroke and cancer: the importance of cancer-associated hypercoagulation as a possible stroke etiology. *Stroke*. 2012;43:3029–3034. doi: 10.1161/STROKEAHA.112.658625.
25. Gon Y, Sakaguchi M, Takasugi J, Kawano T, Kanki H, Watanabe A, et al. Plasma D-dimer levels and ischaemic lesions in multiple vascular regions can predict occult cancer in patients with cryptogenic stroke. *Eur J Neurol*. 2017;24:503–508. doi: 10.1111/ene.13234.
26. Ueshima H. Explanation for the Japanese paradox: prevention of increase in coronary heart disease and reduction in stroke. *J Atheroscler Thromb*. 2007;14:278–286.
27. Matsumoto H, Matsuda T, Miyamoto K, Nakatsuma K, Sugahara M, Shimada T. Feasibility of free-breathing late gadolinium-enhanced cardiovascular MRI for assessment of myocardial infarction: navigator-gated versus single-shot imaging. *Int J Cardiol*. 2013;168:94–99. doi: 10.1016/j.ijcard.2012.09.066.

## Detection of Left Ventricular Thrombus by Cardiac Magnetic Resonance in Embolic Stroke of Undetermined Source

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