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## **High-resolution Late Gadolinium-enhanced Magnetic Resonance for the Diagnosis of Myocardial Infarction with Non-obstructed Coronary Arteries**

**Brief Title:** High-resolution LGE CMR for the diagnosis of MINOCA

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## ABSTRACT

**Objectives:** To assess the diagnostic yield of cardiac magnetic resonance (CMR) including high-resolution late gadolinium-enhanced imaging (HR-LGE) using a 3-dimensional respiratory-navigated method in patients with myocardial infarction and non-obstructed coronary arteries (MINOCA).

**Background:** CMR plays a pivotal role for the diagnosis of patients with MINOCA. However, the diagnosis remains inconclusive in a significant number of patients, CMR being either negative or uncertain (i.e. compatible with multiple diagnoses).

**Methods:** Consecutive patients categorized as MINOCA after blood testing, ECG, coronary angiography, and echocardiography, underwent conventional CMR including cine, T2-weighted, first-pass perfusion and conventional breath-held LGE imaging. HR-LGE using a free-breathing method allowing for improved spatial resolution (voxel 1.25x1.25x2.5mm) was added to the protocol when conventional CMR was inconclusive, and was optional otherwise. Diagnoses retained after reviewing conventional CMR were compared to those retained after the adjunction of HR-LGE.

**Results:** From 2013 to 2016, 229 patients were included (age 56±17 years, 45% women). HR-LGE was performed in 172(75%) patients. In this subpopulation, a definite diagnosis was retained after conventional CMR in 86(50%) patients: infarction in 39(23%), myocarditis in 32(19%), tako-tsubo cardiomyopathy in 13(8%), and other in 2(1%). In the remaining 86(50%) patients, CMR was inconclusive: negative CMR in 54(31%), consistent with multiple diagnoses in 32(19%). HR-LGE led to a change in final diagnosis in 45(26%) and to a lower rate of inconclusive final diagnosis (29%, P<0.001). Particularly, HR-LGE could reveal/ascertain the diagnosis of infarction in 14%, and rule out the diagnosis of infarction in 12%. HR-LGE was particularly useful when TTE, ventriculography, and conventional CMR were negative, with a 48% rate of modified diagnosis in this subpopulation.

**Conclusions:** HR-LGE imaging has high diagnostic value in patients with MINOCA and inconclusive findings on conventional CMR. This has major diagnostic, prognostic and therapeutic implications.

**Keywords:** Cardiac magnetic resonance; Late gadolinium enhancement; Myocardial infarction with non-obstructed coronary arteries

### Abbreviations:

AHA: American Heart Association

CAD: Coronary Artery Disease

CMR: Cardiac Magnetic Resonance

CRP: C-Reactive Protein

ECG: Electrocardiogram

EF: Ejection Fraction

ESC: European Society of Cardiology

HR: High-Resolution

LGE: Late Gadolinium Enhancement

LV: Left Ventricle

MINOCA: Myocardial Infarction with Non-Obstructed Coronary Arteries

RV: Right Ventricle

## **INTRODUCTION**

Patients with myocardial infarction and non-obstructed coronary arteries (MINOCA) represent a major diagnostic, prognostic, and therapeutic challenge in cardiology (1). Up to 5-10% of patients referred for coronary angiography for suspected myocardial infarction show no evidence of obstructive coronary artery disease (CAD) (2). In these, the term MINOCA has been introduced as a “working diagnosis”, given the multiple underlying mechanisms that can lead to such presentation. These include ischemic injuries secondary to type-1 or type-2 acute myocardial infarction (3), as well as tako-tsubo cardiomyopathy and acute myocarditis. The clinical management and prognosis being highly different according to the underlying etiology, a dedicated diagnostic work-up is recommended (1). In this context, cardiac magnetic resonance (CMR) plays a pivotal role (4). Among other methods, late gadolinium-enhanced imaging (LGE) is critical, the final diagnosis being largely based on the detection and assessment of the transmural distribution of myocardial injuries (5). However, in a substantial number of patients the underlying etiology remains uncertain after CMR, the latter being either negative or compatible with multiple diagnoses (2,6,7). Because patients with negative CMR have lower troponin values (8,9), we hypothesized that one major limitation of CMR is its spatial resolution, insufficient to detect small areas of myonecrosis. Free-breathing LGE imaging was recently introduced for high resolution imaging of the left atrial wall (10). It has also been shown valuable in providing a detailed 3-dimensional architecture of ventricular scars to guide catheter ablation for ventricular arrhythmia (11). Using this method, the spatial resolution is improved, with a voxel size decreased by 4-fold as compared to conventional breath-held methods. The aim of the present study was to assess the diagnostic yield of CMR including high-resolution late gadolinium-enhanced imaging (HR-LGE) in patients presenting with MINOCA.

## **METHODS**

### **Population and Study Design**

From January 2013 to March 2016, consecutive patients referred to the University Hospital of Bordeaux for the management of MINOCA were prospectively recruited. The pre-inclusion diagnostic work-up comprised blood testing including cardiac troponin, CRP and leukocyte count, ECG, coronary angiography and trans-thoracic echocardiography (TTE). Inclusion criteria were in line with the recent ESC position paper defining MINOCA (1) : 1/ criteria for acute myocardial infarction including troponin rise above the 99<sup>th</sup> percentile upper reference limit and corroborative clinical evidence of infarction according to the 4<sup>th</sup> universal definition of myocardial infarction (4), 2/ absence of obstructive CAD  $\geq 50\%$  stenosis on coronary angiography, 3/ no clinically overt specific cause for the acute presentation. Patients diagnosed as clinically suspected myocarditis according to the ESC 2013 myocarditis Task Force (12) were not considered for inclusion. Exclusion criteria were contra-indications to CMR, including patients with implantable cardioverter defibrillators, and prior history of acute coronary syndrome associated with troponin rise. All patients underwent conventional CMR including LGE imaging using usual breath-held methods. Free-breathing HR-LGE was systematically added to the protocol in patients with inconclusive findings after conventional CMR, and was optional otherwise, depending on the clinical workflow.

### **CMR Acquisition**

Studies were performed on a 1.5 Tesla system (Magnetom Avanto, Siemens Medical Systems, Erlangen, Germany) equipped with a 32-channel cardiac coil. The protocol comprised cine, T2-weighted, and first pass perfusion imaging, as well as conventional LGE imaging performed 10

min post-contrast using 2 breath-held methods in 3 stacks of contiguous slices encompassing the whole ventricles in short-axis, 2-chamber, and 4-chamber orientations. The first method was a 3-dimensional inversion recovery-prepared turbo Fast Low Angle Shot sequence (voxel size 1.8×1.4×6mm), and the second a 2-dimensional phase sensitive inversion recovery sequence (pixel size 1.8×1.3mm, thickness 6mm). Conventional CMR findings were reviewed in real time during the CMR study by one reader (15 years' experience in CMR). Free-breathing HR-LGE was systematically added to the protocol in patients with inconclusive findings after conventional CMR, and was optional otherwise, depending on the clinical workflow. In patients eligible for HR-LGE, an additional TI-scout scan was performed after conventional LGE imaging, hence 15-20 min after contrast injection. HR-LGE imaging was then performed using a 3-dimensional, inversion-recovery-prepared, ECG-gated, respiration-navigated gradient-echo pulse sequence with fat-saturation (voxel size 1.25×1.25×2.5mm; acquisition time 8–12 minutes depending on patient's heart and breath rate). (9) Detailed protocols and sequence parameters are provided in **Appendix**.

### **CMR Analysis and Interpretation**

CMR interpretation was performed retrospectively, after the completion of patients' inclusion. Two readers (with 5 and 15 years' experience in CMR) analyzed all conventional CMR studies in a random order. This interpretation was performed months or years after the CMR study, and the readers were blinded to the initial CMR report. Thus, the interpretation of conventional CMR images was truly blinded to the 3D HR-LGE dataset, and the readers did not know whether HR-LGE had been subsequently performed. Then, the same readers analyzed again the entire population, this time adding HR-LGE to the conventional CMR analysis. In addition, one reader

(5 years' experience) read all studies twice in a random order to document intra-observer agreement. Left ventricular (LV) volumes and ejection fraction (EF) were quantified using Argus software (Siemens Medical Systems, Erlangen, Germany). Ventricular dilatation and systolic dysfunction were defined based on previously reported normal values (13). Cine images were visually assessed to look for LV or RV wall motion abnormalities and pericardial effusion. T2-weighted images were analyzed to look for myocardial oedema. Perfusion imaging was reviewed to look for perfusion defects at rest. LGE imaging was analyzed to look for myocardial or pericardial LGE. Conventional LGE images were reviewed in the 3 acquired orientations. The HR-LGE imaging volume could be reviewed in multiplanar reformations of any orientation, depending on LGE location. For each sequence, magnification and windowing could be optimized by readers. To document a potential uncertainty in the interpretation of LGE images, positive LGE findings were categorized as definite when the reader had no doubt in his interpretation, and possible when the positivity of LGE was considered unclear. In each patient, the distribution of LGE was described as subendocardial, subepicardial, and/or midwall. LGE was considered transmural if involving the entire myocardial thickness on at least one location. In case of unclear transmural location, the LGE pattern was categorized as uncertain. The extent of LGE was quantified in numbers of segments involved, using the 17-segment AHA model. The criteria to diagnose myocardial infarction on CMR were the presence of a definite subendocardial or transmural LGE (14). The criteria to diagnose myocarditis were the presence of definite midwall and/or subepicardial LGE in the absence of subendocardial LGE (15). The criteria to diagnose tako-tsubo cardiomyopathy was either 1/ a wall motion abnormality involving the entire apical or basal levels in the absence of myocardial LGE (14), or 2/ a similar wall motion abnormality documented on pre-inclusion ventriculography or TTE in a patient with

normal wall motion and negative LGE on CMR. CMR was categorized as conclusive when patients fulfilled the criteria for a definite diagnosis, and as non-conclusive otherwise: negative CMR or uncertain CMR findings (possible LGE or definite LGE with an uncertain pattern, i.e. compatible with multiple diagnoses). Each reader established a first diagnosis based on non-CMR diagnostic tests and conventional CMR only, blinded to the 3D HR-LGE. Patients with HR-LGE were analyzed a second time and a final diagnosis was established based on non-CMR diagnostic tests and CMR including HR-LGE.

### **Follow-up**

Patients with a final diagnosis of tako tsubo cardiomyopathy underwent follow-up imaging using CMR or TTE at 3 months. Subsequent outcome was analysed in the subset of the population that could be practically followed in our institution (follow-up at 3 months and then every year). In case of recurrent acute coronary syndrome, the diagnosis of the episode was compared to the diagnosis retained after the initial MINOCA episode.

### **Statistical Analysis**

The Shapiro-Wilk test of normality was used to assess whether quantitative data conformed to the normal distribution. Continuous data are expressed as mean  $\pm$  standard deviation when following a normal distribution, and as median [interquartile range Q1-Q3] otherwise. Categorical data are expressed as fraction (%). Non-weighted Cohen's kappa coefficients were used to analyse intra- and inter-observer agreements on the final diagnosis. Independent continuous variables were compared using independent-sample parametric (unpaired Student's t-test, ANOVA) or non-parametric tests (Mann-Whitney U test, Kruskal-Wallis test) depending on



data normality. When differences were found among groups by using ANOVA (or Kruskal-Wallis test), the multiple comparisons Tukey–Kramer’s method (or the Conover-Iman test) was used to compare all pairs of groups. Dependent continuous variables were compared using paired-sample parametric or non-parametric tests (paired Student’s t-test, Wilcoxon signed-rank test) depending on data normality. Independent categorical variables were compared using Chi-square test when expected frequencies were  $\geq 5$ , and Fisher’s exact test when they were  $< 5$ . When difference was found by testing multiple ( $>2$ ) categorical samples, the Marascuillo procedure was used to compare all pairs of groups. Dependent categorical variables were compared using the paired-sample McNemar's test. All statistical tests were two-tailed. A P value  $<0.05$  was considered to indicate statistical significance. Analyses were performed using NCSS 8 (NCSS Statistical Software, Kaysville, UT, USA).

## RESULTS

### Population

A total of 229 patients presenting with MINOCA were recruited (age  $56\pm 17$  years, 45% women). The characteristics of the studied population are shown in **Table 1**. Median troponin rise was of 35[10-120] times the upper limit of normal. ECG showed STEMI in 85(37%). TTE was negative in 124(54%), and showed diffuse and regional wall motion abnormalities in 41(18%) and 90(39%), respectively. Coronary angiography showed normal arteries in 125(55%) and non-obstructive CAD in 104(45%). All patients underwent CMR including cine imaging, T2-weighted imaging, and LGE imaging using breath held methods. First pass perfusion imaging at rest was not available in 76(33%). The delay between the onset of chest pain and the CMR study was 4[2-8] days. Conventional CMR findings in the total population are listed in **Table 2**.

Examples of definite diagnoses of acute myocardial infarction, acute myocarditis, and tako-tsubo cardiomyopathy are shown in **Supplemental Figure 1, 2 and 3**, respectively.

### **Population studied with HR-LGE imaging**

HR-LGE imaging was added to the protocol when the diagnosis remained inconclusive after conventional LGE imaging, and was optional otherwise. A total of 5 patients with negative findings after conventional CMR did not complete HR-LGE imaging due to poor tolerance during CMR. In total, HR-LGE was performed in 172 (75%) of the population. The characteristics of patients with (N=172) and without (N=57) HR-LGE are compared in **Supplemental Table 1**. The population with additional HR-LGE imaging was, as expected, more likely to show uncertain diagnosis after conventional CMR (50% vs. 9%,  $P<0.001$ ). In addition, the troponin peak and the rate of elevated CRP were lower ( $P<0.001$  and  $P=0.02$ , respectively), and TTE and ventriculography more frequently negative ( $P=0.03$  and  $P=0.02$ , respectively).

### **Conventional vs. HR-LGE findings**

After reviewing conventional CMR findings in this subpopulation (N=172), a definite diagnosis could be retained in 86(50%) patients, including myocardial infarction in 39(23%), acute myocarditis in 32(19%), tako-tsubo cardiomyopathy in 13(8%), and other in 2(1%, hypertrophic cardiomyopathy and endomyocardial fibrosis). In the remaining 86(50%) patients conventional CMR was non-conclusive: either negative in 54(31%), or consistent with multiple diagnoses (infarction or myocarditis in 14(8%), myocarditis or negative CMR in 12(7%), infarction or negative CMR in 4(2%), and infarction or tako tsubo cardiomyopathy in 2(1%). CMR results

before and after reviewing HR-LGE are compared in Table 3. The rate of definite myocardial LGE was higher on HR-LGE than on conventional LGE (64% vs. 51%,  $P < 0.001$ ). Likewise, the rate of uncertain LGE transmural location was lower on HR-LGE (1% vs. 15%,  $P < 0.001$ ).

Comparisons between conventional and HR-LGE images are shown in **Figure 1**. The interpretation of myocardial injuries derived from HR-LGE led to a modification of the diagnosis in 45/172(26%). Diagnostic changes before and after the addition of HR-LGE are shown in the **Central Illustration**. Most diagnostic changes, i.e. 41/45(91%), occurred in patients with non-conclusive diagnoses after conventional CMR. After the addition of HR-LGE the rate of non-conclusive CMR decreased from 86 to 50/172(50% vs. 29%,  $P < 0.001$ ). Likewise, the number of patients with definite diagnoses of myocardial infarction and myocarditis increased ( $P < 0.001$  and  $P = 0.002$ ). Particularly, the addition of HR-LGE could reveal or ascertain myocardial infarction in 24(14%) of the patients. In these, conventional CMR had been interpreted as negative in 4, compatible with multiple diagnoses in 17, and suggestive of a different diagnosis in 3 (2 as definite myocarditis, and 1 as hypertrophic cardiomyopathy in whom HR-LGE showed definite infarction). In addition, HR-LGE could rule out the diagnosis of myocardial infarction in 21(12%) of the patients. In these, conventional CMR had been interpreted as negative in 7, compatible with multiple diagnoses including infarction in 13, and as definitely suggestive of infarction in 1 (interpreted as definite myocarditis after HR-LGE).

### **Characteristics of patients benefiting from HR-LGE**

In a total of 40 patients, a definite diagnosis was introduced after reviewing HR-LGE images while conventional CMR was inconclusive or suggestive of another diagnosis. The characteristics of these patients benefiting from HR-LGE are analyzed in **Table 4**. They showed

more frequently negative findings on TTE, ventriculography, and cine MR (P=0.01, P=0.02, and P=0.04 respectively), and the pattern of hyper enhancement on conventional LGE was more frequently uncertain (P<0.001). The diagnosis after conventional CMR was more often negative or uncertain (P<0.001) and less often consistent with myocarditis, infarction or tako-tsubo cardiomyopathy (P=0.01, P<0.001, and P=0.04, respectively). Examples of definite diagnoses introduced thanks to the addition of HR-LGE are shown in **Figures 2, 3 and 4**.

### **Intra- and inter-observer agreement on final diagnosis**

Agreements on final diagnosis after conventional CMR and after HR-LGE are listed in **Table 6**. The intra- and inter-observer agreements on final diagnosis were excellent for both conventional and HR-LGE. Intra-observer agreements were significantly higher than inter-observer agreements (P<0.05 for both conventional CMR and HR-LGE). Intra- and inter-observer agreements were higher after HR-LGE than after conventional CMR methods only although the difference was not found statistically significant (P=NS).

### **Patient characteristics according to final diagnosis**

Including all available information and in the total population, the final diagnoses were myocarditis in 71/229(31%), myocardial infarction in 79/229(34%), tako-tsubo cardiomyopathy in 22/229(10%), negative CMR in 53/229(23%), and uncertain CMR in 4/229(2%). Patient characteristics according to the final diagnosis are compared in **Table 6**.

### **Patient outcomes**

All 22 patients with definite diagnosis of tako tsubo cardiomyopathy underwent follow-up

imaging (CMR in 8, TTE in 14), revealing a normalization of LV wall motion in all cases. Clinical follow-up information could only be retrieved in 116/229(51%), because other patients were not followed in our institution. The median follow-up duration was 2.9[1.0-3.7] years. Adverse outcomes included re-hospitalization in a cardiology department in 20/116(17%), including 8/116(7%) patients due to recurrence of acute coronary syndrome. In these 8 patients, initial diagnoses were infarction in 4, myocarditis in 3, and negative CMR in 1. These were also retained after recurrence, except for the patient with initial negative CMR whose recurrence was attributed to myocardial infarction secondary to coronary vasospasm. Death occurred in 5/116(4%), including 1(1%) attributed to a cardiac cause (sudden cardiac arrest in a patient with initial diagnosis of myocardial infarction). The comparison of outcomes according to the final diagnosis retained after the initial MINOCA episode is shown in **Table 7**.

## **DISCUSSION**

The present study is the first to introduce the use of free-breathing high-resolution LGE imaging for the diagnostic work-up of MINOCA. Studying a series of 229 consecutive patients with MINOCA, including 172 with both conventional and free-breathing LGE methods, it shows that the addition of HR-LGE leads to a higher rate of definite myocardial LGE and a lower rate of LGE of uncertain transmural location. This translates into a change in final diagnosis in 26% of the patients undergoing both methods, and a lower rate of non-conclusive CMR. Most diagnostic changes occur in patients with negative or uncertain diagnostic work-up after TTE, ventriculography and conventional CMR methods.

### **Population characteristics and conventional CMR findings**

The inclusion criteria conformed to the definition of MINOCA (1). The demographics and risk factors of the population are consistent with prior large series of MINOCA (2,16). ECG findings are also consistent with prior reports on MINOCA, with less than 40% exhibiting ST elevation (2,17). Likewise, the rates of negative TTE and non-obstructive CAD on angiography are in agreement with past studies (2,18,19). The conventional CMR protocol conformed to the guidelines of the Society for Cardiovascular Magnetic Resonance (20). The rate of negative findings on CMR and the distribution of etiologies in patients with positive CMR are consistent with past CMR series in MINOCA (2,5,6,8,21,22). Regarding CMR methods, our results confirm that LGE is the cornerstone of the etiological diagnosis in patients with MINOCA while cine, T2-weighted and first pass perfusion imaging are often negative. The limited sensitivity of T2 imaging in the present study may be explained by incomplete cardiac coverage or by the intrinsic limitations of T2-weighted imaging for the assessment of myocardial oedema. The negativity of T2 and cine imaging may also be explained by the delay between the onset of chest pain and the CMR study. Most patients were studied within the first week but myocardial oedema is known to show dynamic changes over that period (23-24). Likewise, transient wall motion abnormalities secondary to ischemic myocardial stunning or stress-induced cardiomyopathy may only last a few days, and cine imaging performed several days after the episode may be less sensitive than TTE performed on day one. This appeared to be quite common in our series, as 34% of the patients with negative CMR findings showed wall motion abnormalities on TTE at admission.

### **HR-LGE findings**

In line with prior studies, we found high rates of negative or uncertain findings after

conventional CMR methods (2). As compared to conventional breath-held LGE methods, the amount of myocardium contained in each single voxel is decreased by 4-fold using HR-LGE (from 15.1 to 3.9 mm<sup>3</sup>). The addition of HR-LGE led to a higher rate of definite myocardial LGE and a lower rate of LGE of uncertain transmural location. The detection of LGE and the accurate description of its transmural distribution are major determinants of CMR diagnosis (6,14), and are often a complex interpretation. When LGE is focally transmural, it may be uneasy to distinguish between a subendocardial and a subepicardial primary location of the injury. Likewise, small subendocardial injuries may be missed due to poor contrast with the blood pool, while those adjacent to trabeculations or papillary muscles may be misinterpreted as of intramural location (25). Last, subepicardial LGE may be mistaken for epicardial fat or coronary vessels. The addition of HR-LGE translated into a change in final diagnosis in 26% of the patients undergoing both methods, and a lower rate of non-conclusive CMR. Of note, most diagnostic changes introduced by HR-LGE were due to improved diagnostic confidence rather than to the detection of new myocardial lesions undetected by conventional LGE (2/3 vs. 1/3, see Central Illustration). This highlights the practical challenge of LGE interpretation in the context of MINOCA, where myocardial injuries are smaller. Our results show that resolving these uncertainties has a significant impact on patient management. Particularly, HR-LGE could reveal or ascertain myocardial infarction in 14%, and rule out myocardial infarction in 12%. Most diagnostic changes occurred in patients with non-conclusive diagnosis after TTE, ventriculography and conventional CMR. The rate of modified diagnosis was 41/86 (48%) in this subpopulation vs. 4/86 (5%) in those with a definite diagnosis retained after conventional CMR methods. Thus the implementation of HR-LGE in clinical practice should primarily focus on these patients.

### **Clinical implications**

The management of patients with MINOCA and uncertain diagnosis is a major dilemma in clinical cardiology. In these, myocardial infarction has not been ruled out or ascertained, and the therapeutic management remains empirical or based on observational non-randomized studies (26,27). A variety of methods has been proposed to detect occult causes of infarction, including imaging the coronary wall with intra-vascular ultrasound (28) or optical coherence tomography (29), or identifying a biological substrate for thrombophilia (30). The present study suggests that increasing the spatial resolution of CMR may also be instrumental in retaining or excluding the diagnosis of myocardial infarction, with major implications for patient management. Given that most MRI vendors have a free-breathing LGE solution available, our study supports the systematic integration of the method in patients undergoing CMR in the context of MINOCA, particularly when conventional CMR results are non-conclusive. Applying such strategy would lead to a prolongation of the CMR study of about 10 min in about 40% of the patients, which in our opinion is acceptable.

### **Study limitations**

One main limitation is the absence of follow-up data in part of our population. Unfortunately, a standardized follow-up was not practically doable in patients managed outside our institution. Another limitation is the absence of HR-LGE in 25% of the patients. For practical reasons, a prolongation of the CMR study in every patient was not compatible with our clinical work-flow. However, HR-LGE was systematically performed when conventional CMR methods were inconclusive, which is the population benefiting the most from HR-LGE. HR-LGE was also



performed in a sufficient number of patients with conclusive conventional CMR to conclude that the method is less valuable in this population. Last, since T1 and T2 mapping methods (31) were not locally available when the study was initiated, the incremental diagnostic value of HR-LGE in comparison with a CMR protocol including these sequences has not been evaluated.

## **CONCLUSION**

In patients with MINOCA, the addition of HR-LGE using a free breathing method improves the detection and the assessment of the transmural distribution of myocardial injuries. This translates into a change in final diagnosis in about half of the patients with inconclusive findings after conventional CMR methods. Particularly, HR-LGE can ascertain or rule out the diagnosis of myocardial infarction in a significant number of patients. These results have major implications for the management of patients with MINOCA.

## **PERSPECTIVES**

### **Clinical Competencies**

Improving spatial resolution of LGE imaging leads to a lower rate of non-contributive CMR in patients with MINOCA.

### **Translational Outlook**

Future research should aim at developing LGE CMR methods with higher spatial resolution and acceptable acquisition times to be implemented as part of standard care for the diagnostic management of MINOCA.

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## FIGURES

**Figure 1: Comparison between conventional and HR-LGE images in patients with MINOCA.** LGE images from conventional breath-held (left columns) and free-breathing LGE at higher spatial resolution (HR-LGE, right columns) are provided in 12 patients. In all, the addition of HR-LGE led to a modification of the final diagnosis, either because of improved detection of myocardial injuries, or because of improved assessment of LGE transmural location

**Figure 2: Thirty-three-year-old woman benefiting from HR-LGE imaging.** The patient presented with typical angina and mild troponin rise. ECG, TTE and coronary angiography were normal. On CMR on day 2, cine (A: end-diastole and B: end-systole), T2-weighted (C), first-pass rest perfusion (D), and conventional LGE imaging (E,F) were considered negative. HR-LGE showed focal subendocardial enhancement on infero-latero-mid segment, consistent with microinfarction (arrows in G and H). An additional diagnostic work-up revealed no overt embolic cause on 24-Holter, no biological substrate for thrombophilia, and no evidence of systemic vasculitis

**Figure 3: Fifty-five-year-old woman benefiting from HR-LGE imaging.** The patient presented with atypical chest pain, troponin rise, elevated C-reactive protein and high leukocyte count. ECG and TTE were normal. Coronary angiography revealed non-obstructive CAD. On CMR performed on day 5, cine (A: end-diastole and B: end-systole), T2-weighted (C) and conventional LGE imaging (D,E) were considered negative. HR-LGE showed myocardial infarction in the right ventricular outflow tract area, with microvascular obstruction (arrows in F and G). Given the presence of non-obstructive CAD, a mechanism of plaque disruption with spontaneous thrombus resorption was suspected

**Figure 4: Sixty-year-old man benefiting from HR-LGE imaging.** The patient presented with atypical chest pain and mild troponin rise. ECG, TTE, coronary angiography and ventriculography were normal. On CMR performed on day 5, cine, T2-weighted (A), and rest perfusion imaging (B) were negative. On conventional LGE, a focal enhancement was suspected on infero-mid segment, although categorized as uncertain (C,D). HR-LGE showed definite subendocardial enhancement consistent with infarction (E,F). An additional diagnostic work-up revealed no overt cause of myocardial infarction

**Central Illustration: Diagnostic changes introduced by HR-LGE imaging (N=172 patients with both conventional and HR-LGE).** The diagnoses retained after conventional CMR methods and after the addition of HR-LGE are shown in left and right columns, respectively. Connecting lines indicate diagnostic changes, the number of patients concerned being overlaid on each line. AM: acute myocarditis; CMR: cardiac magnetic resonance; HR-LGE: high-resolution late gadolinium enhancement; MI: acute myocardial infarction; TT: tako tsubo cardiomyopathy

Conventional LGE

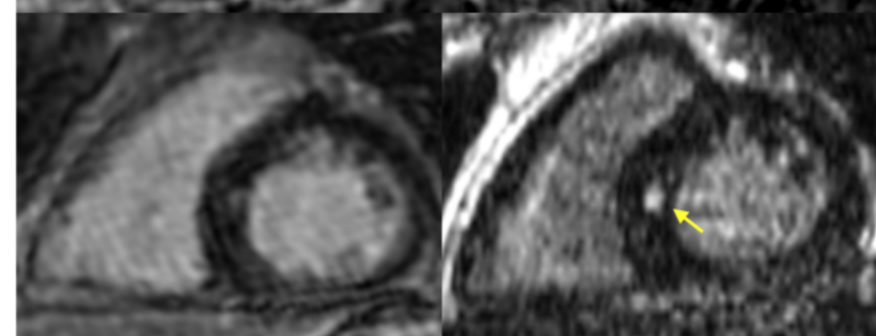
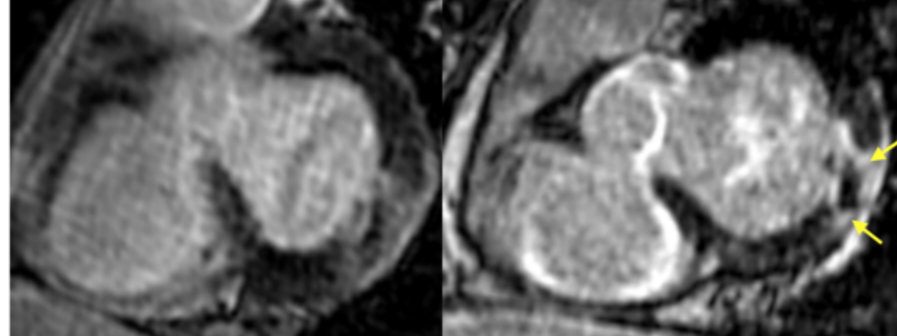
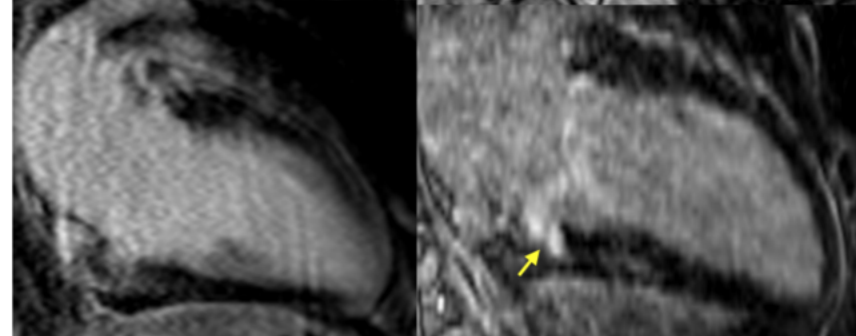
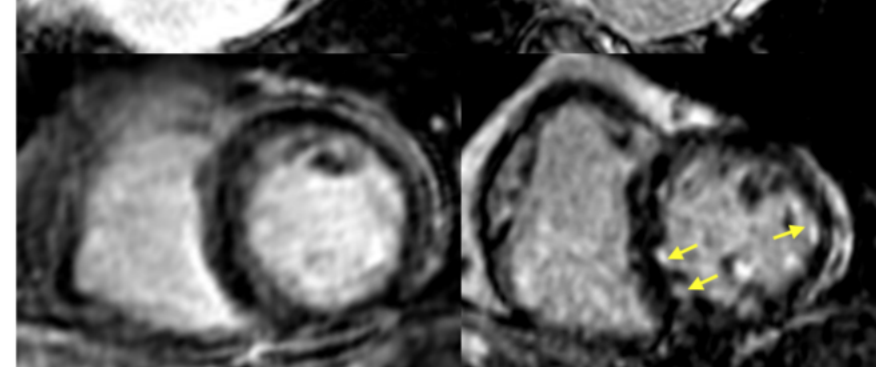
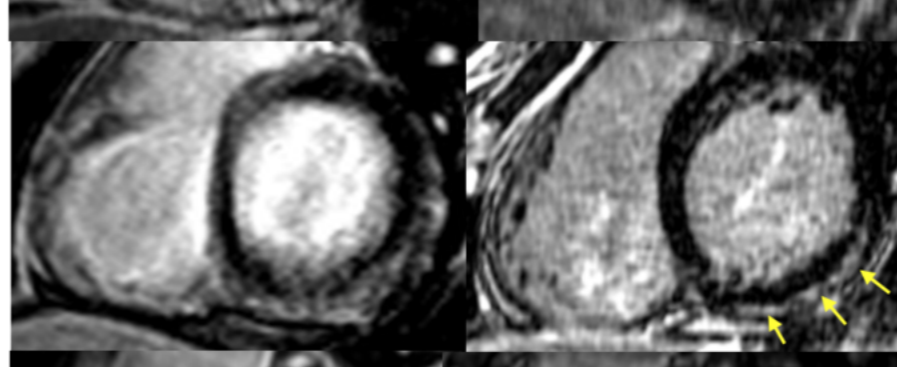
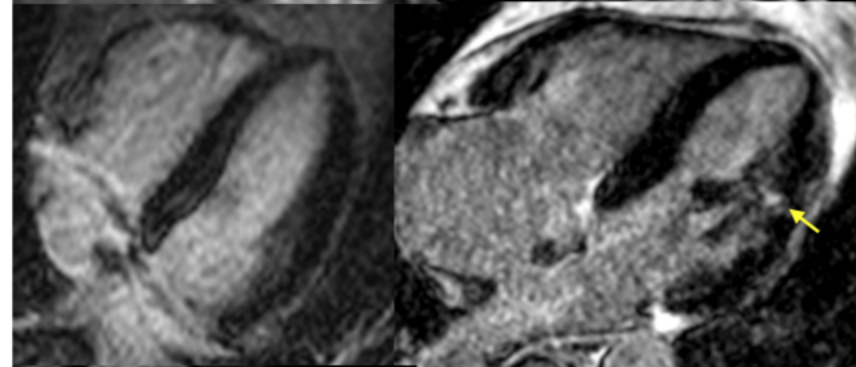
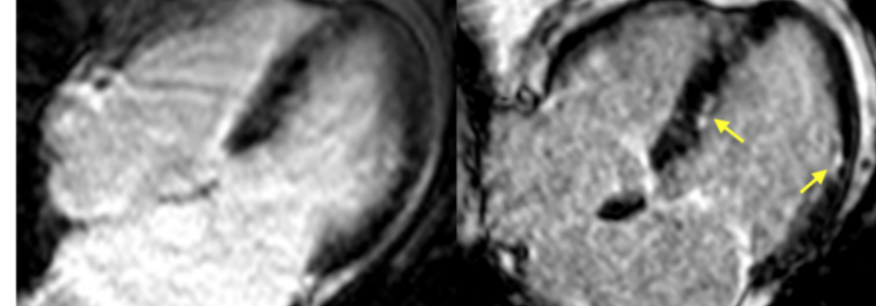
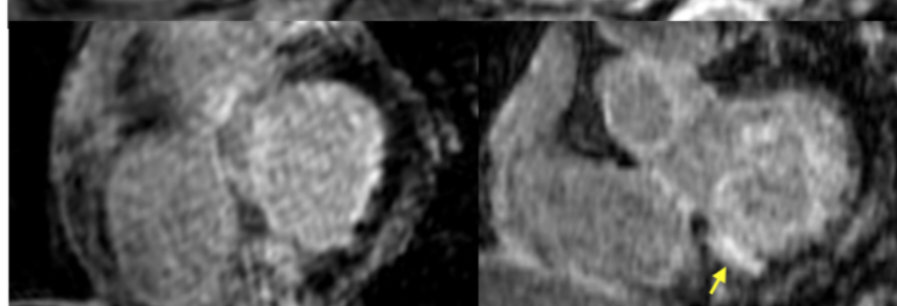
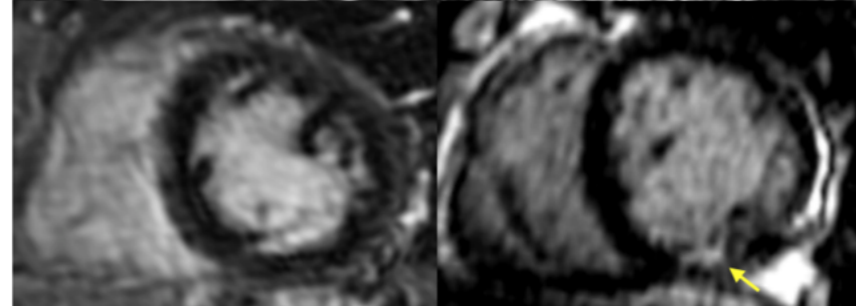
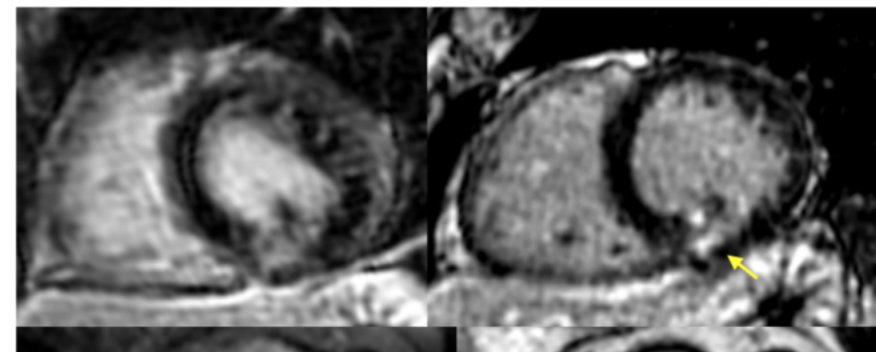
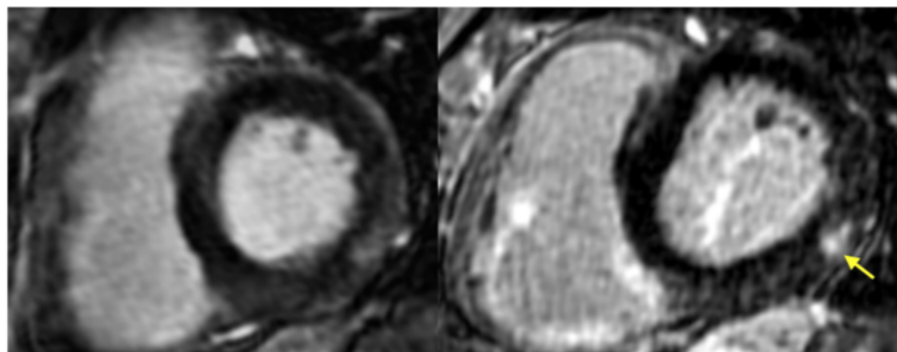
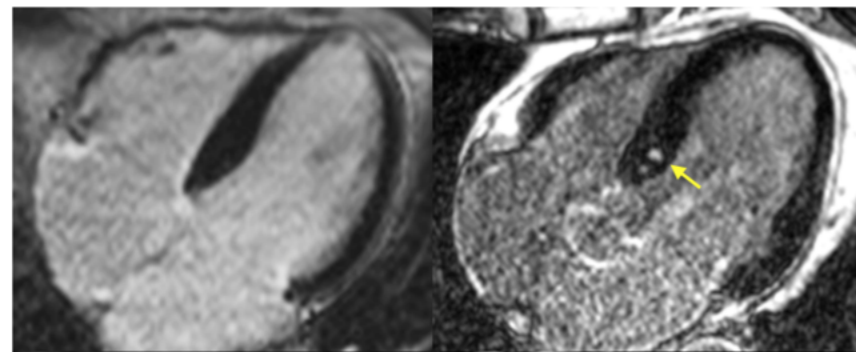
HR-LGE

Conventional LGE

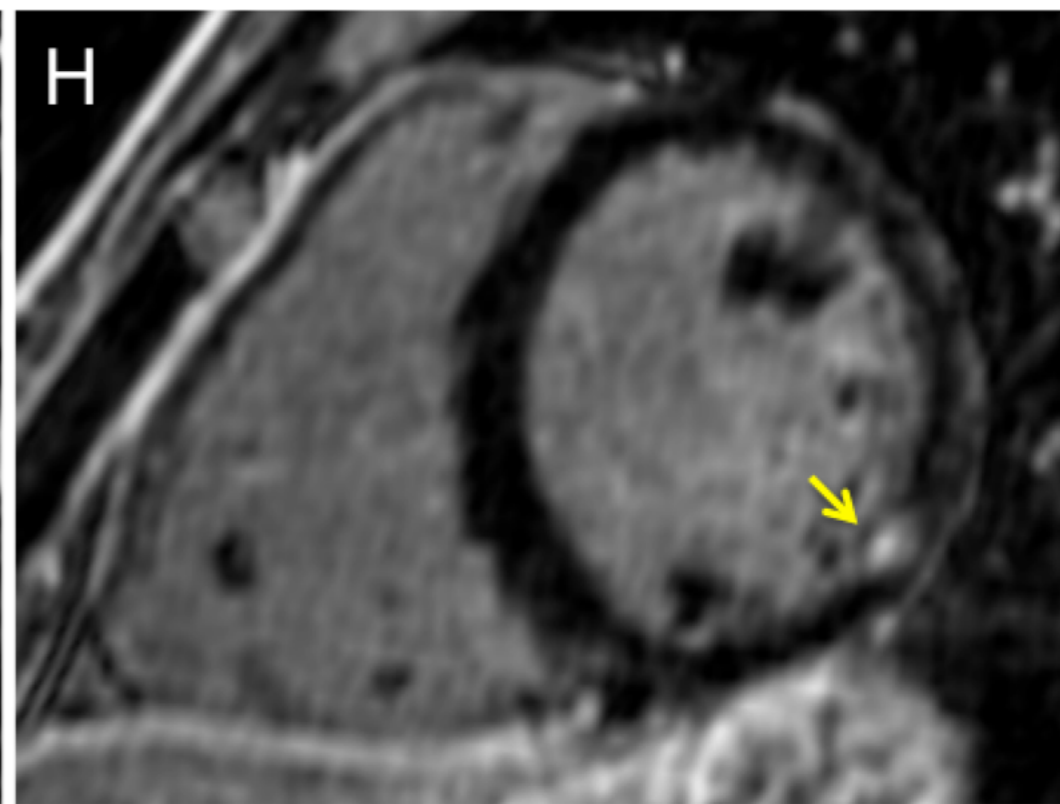
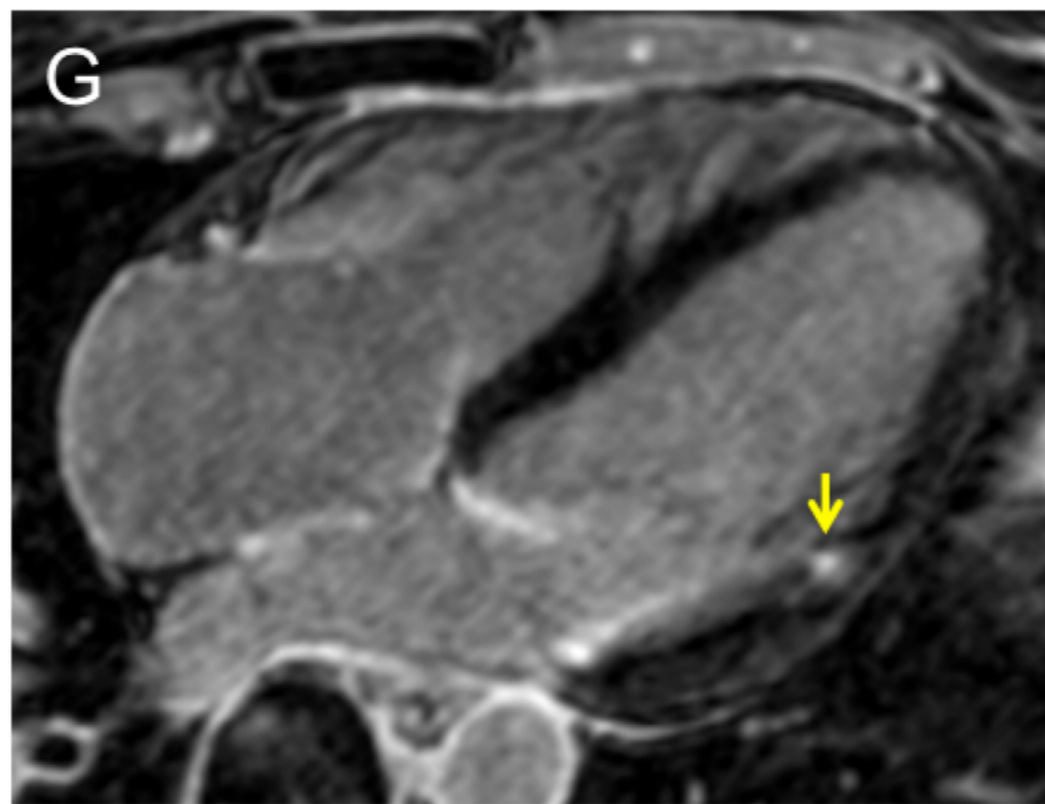
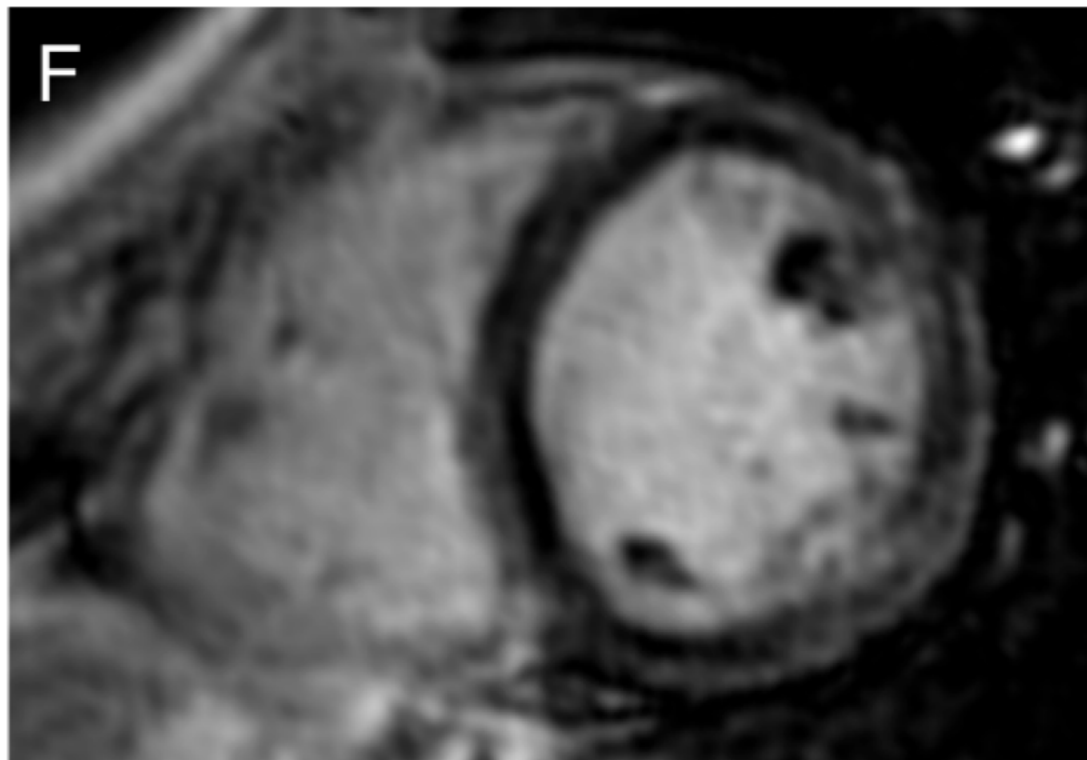
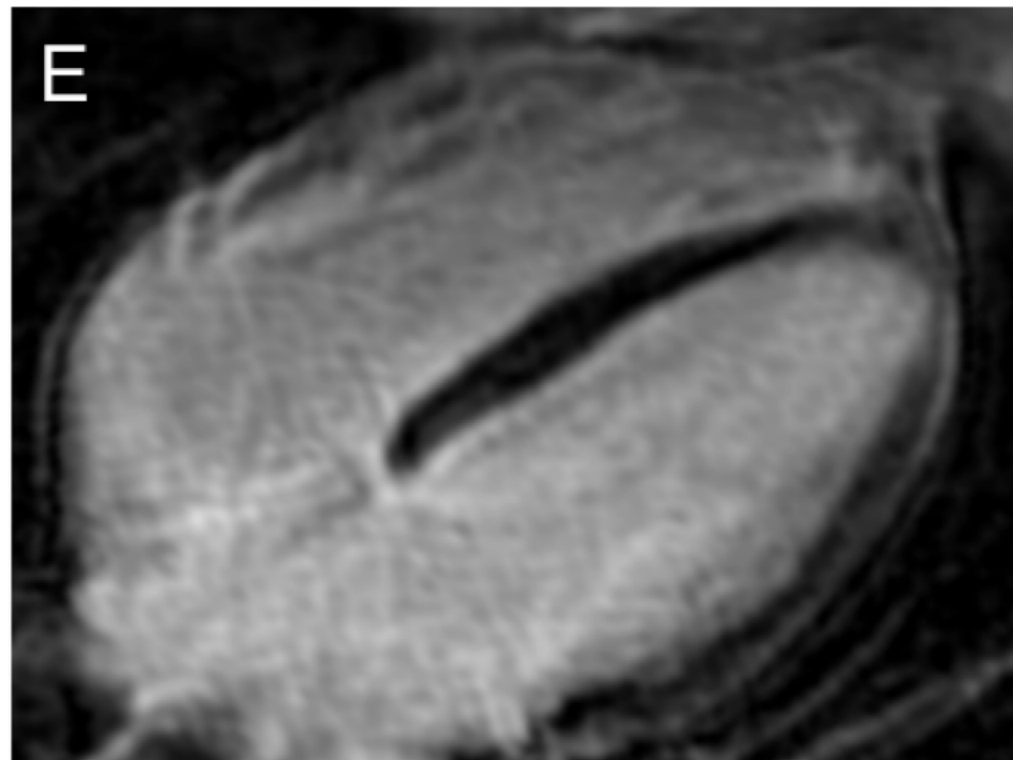
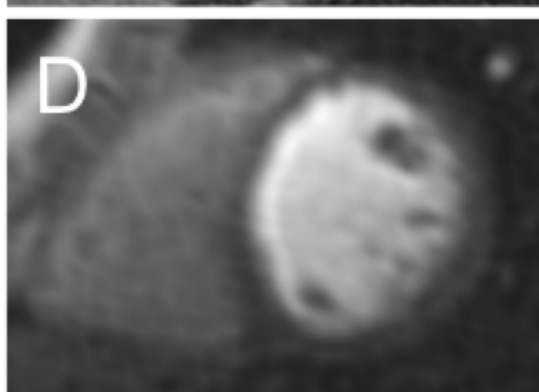
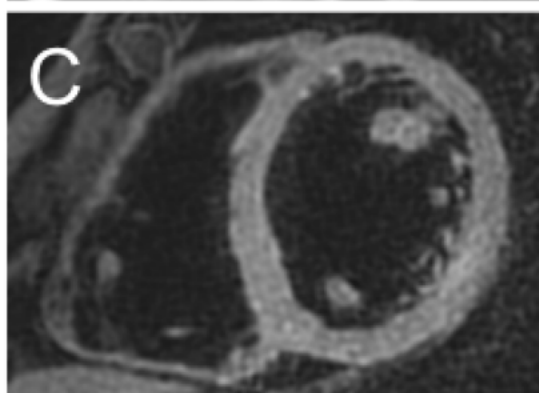
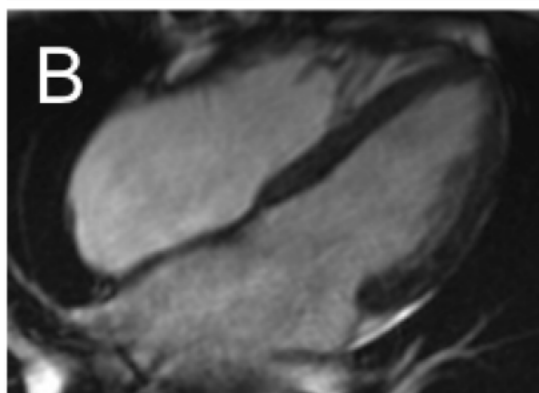
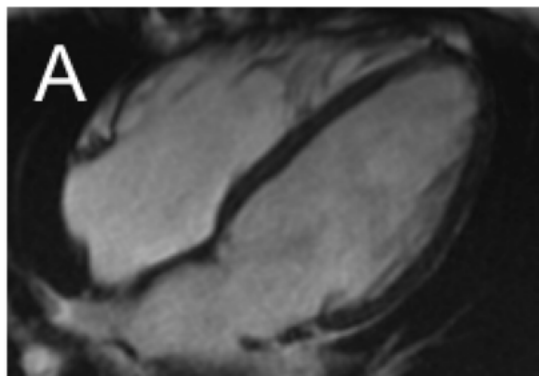
HR-LGE

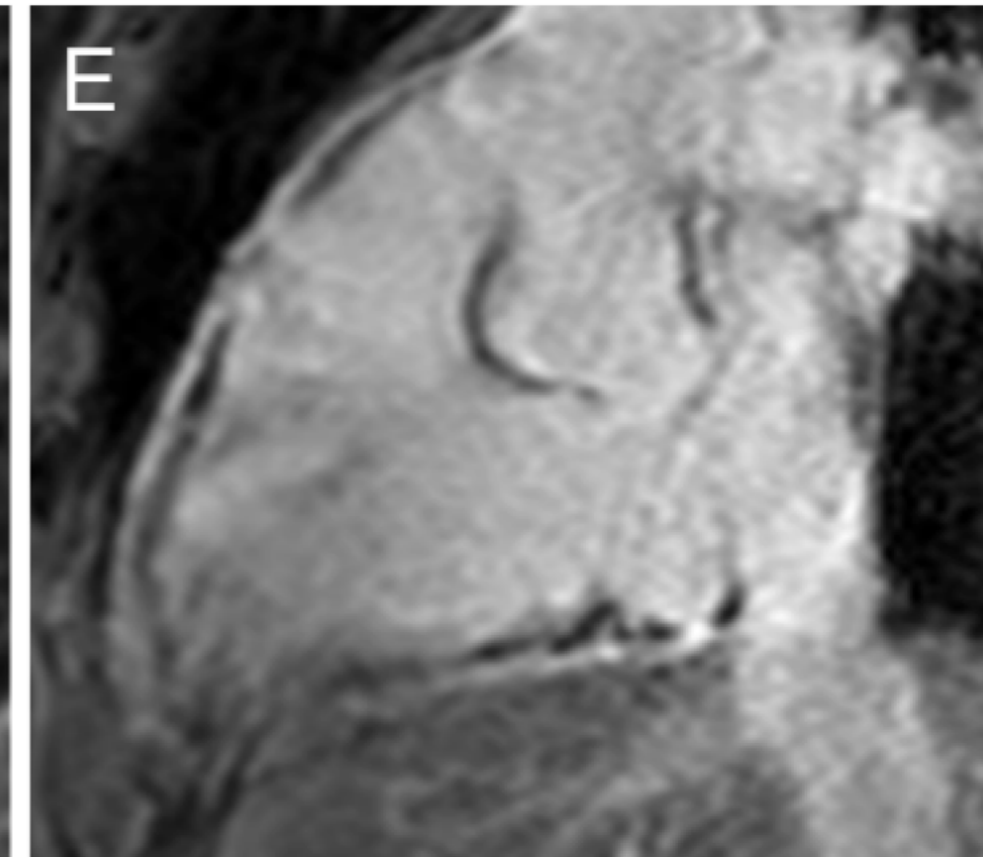
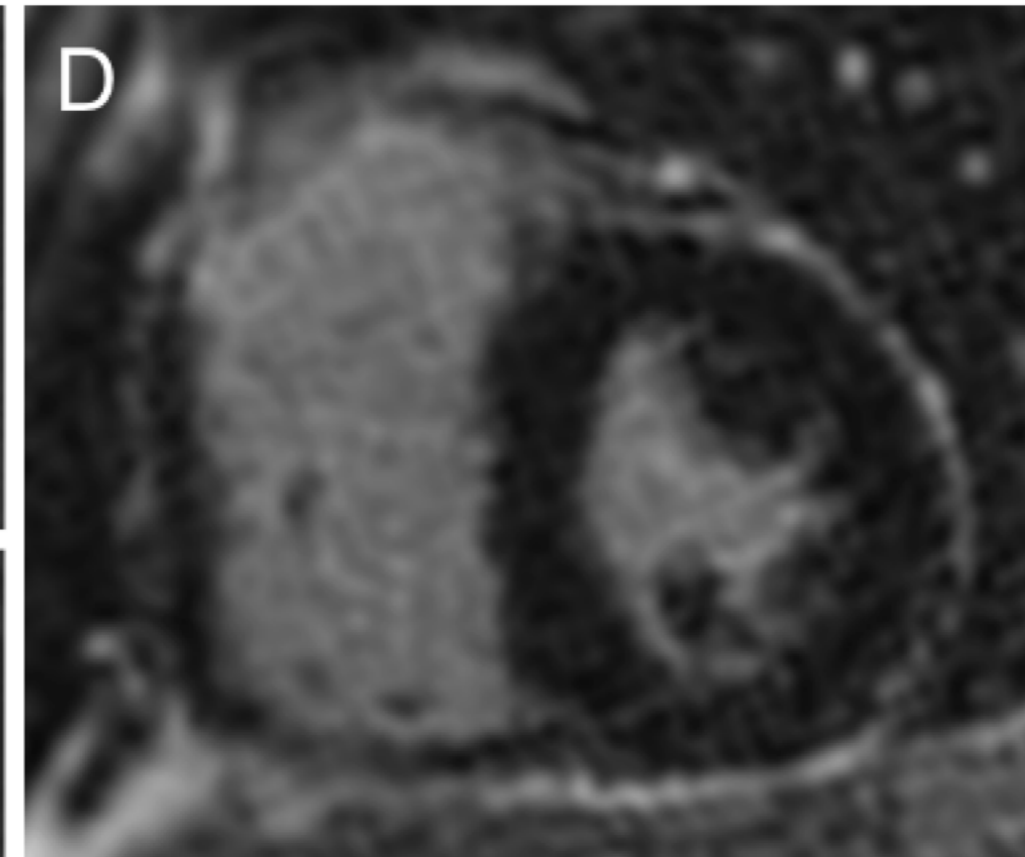
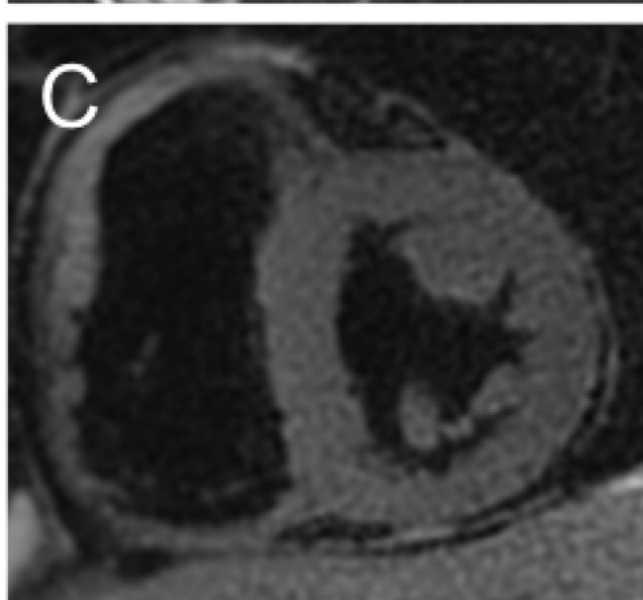
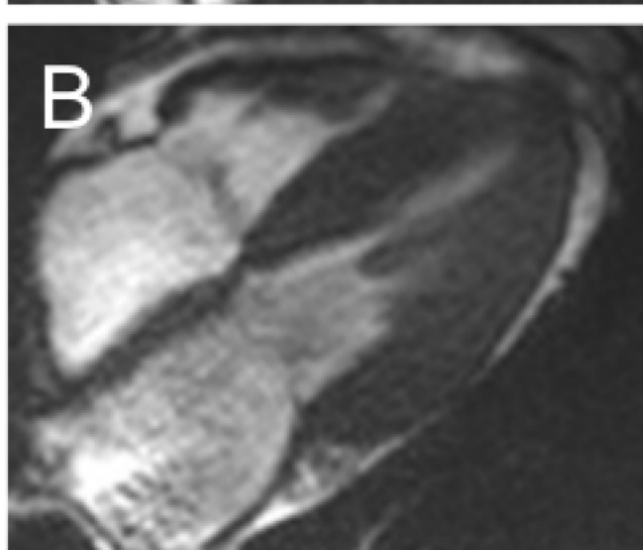
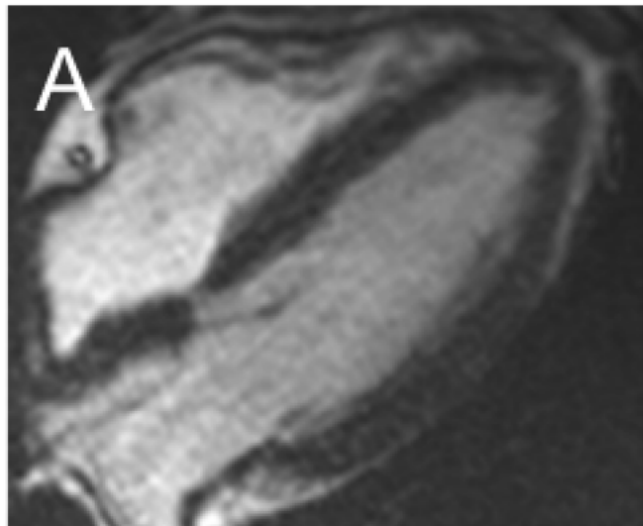
Conventional LGE

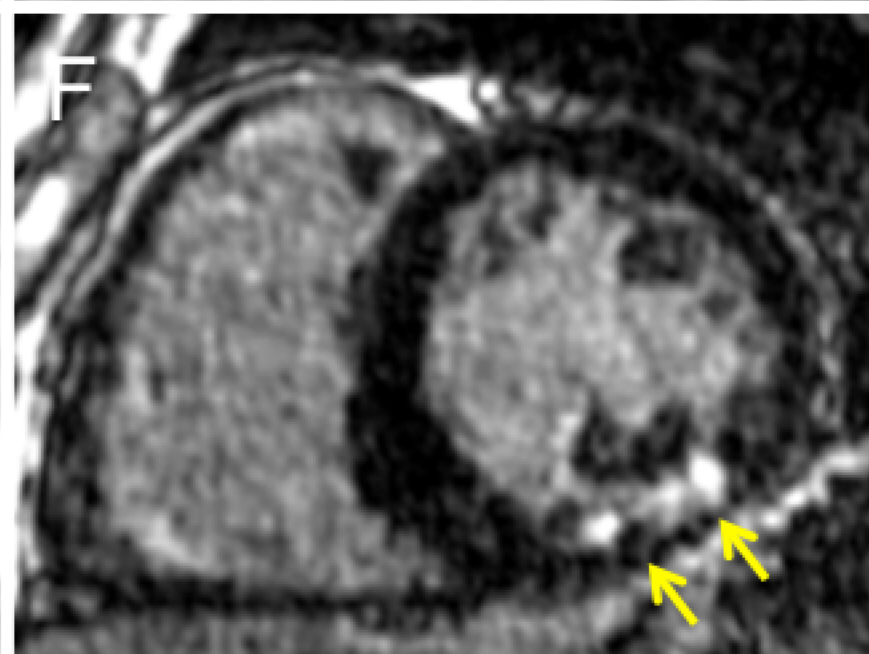
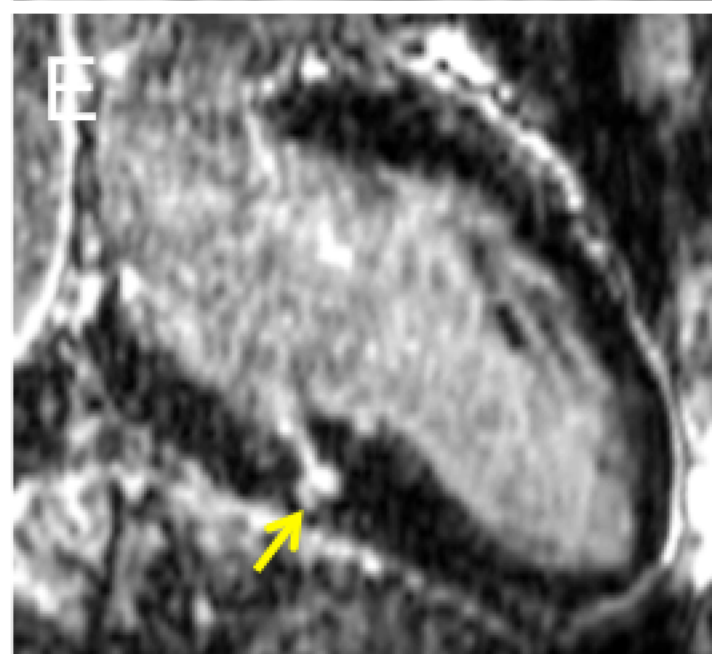
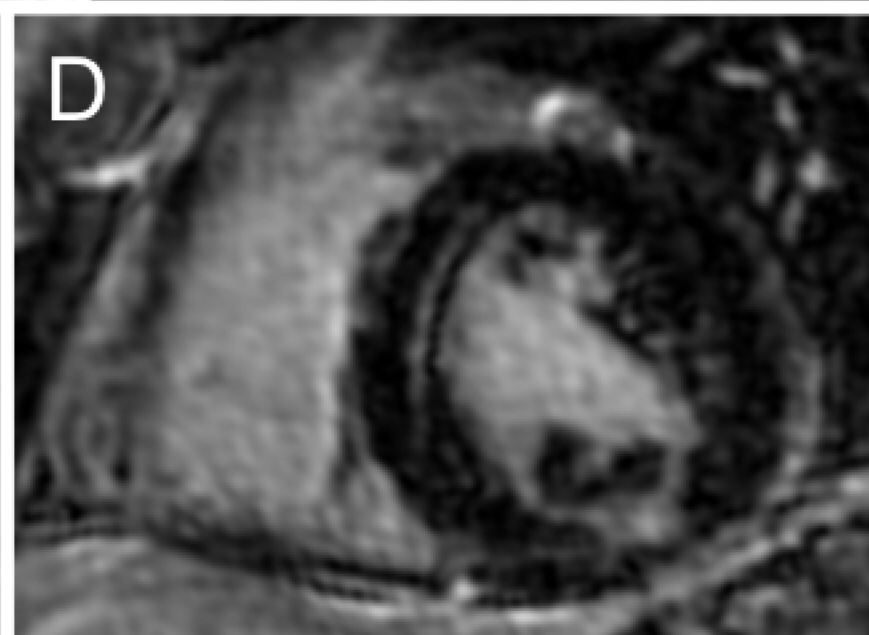
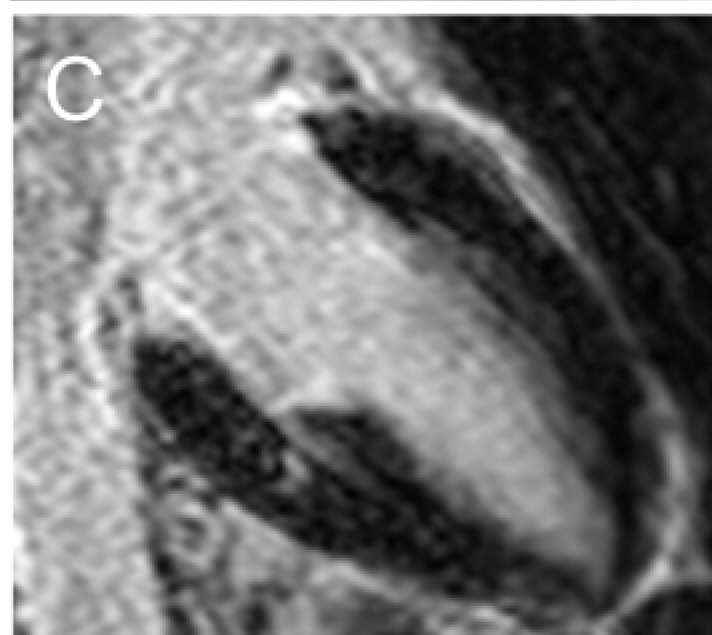
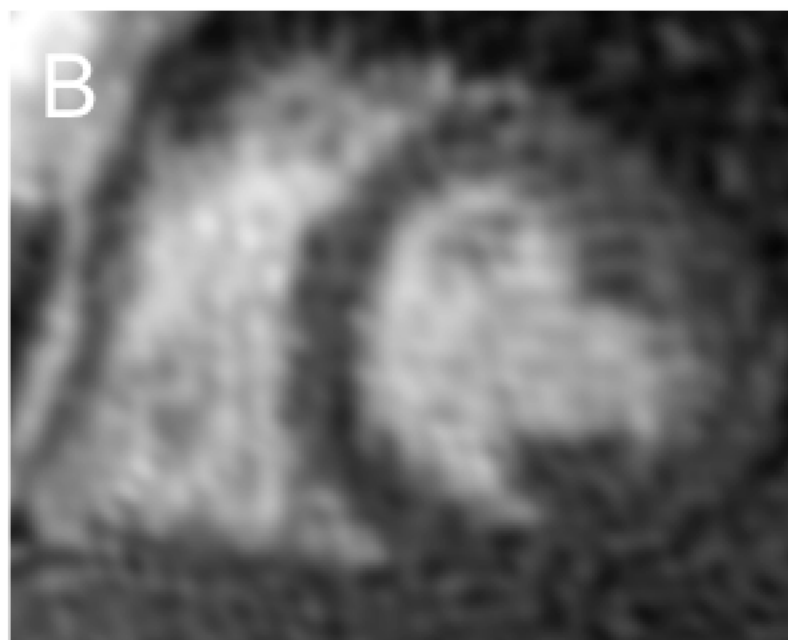
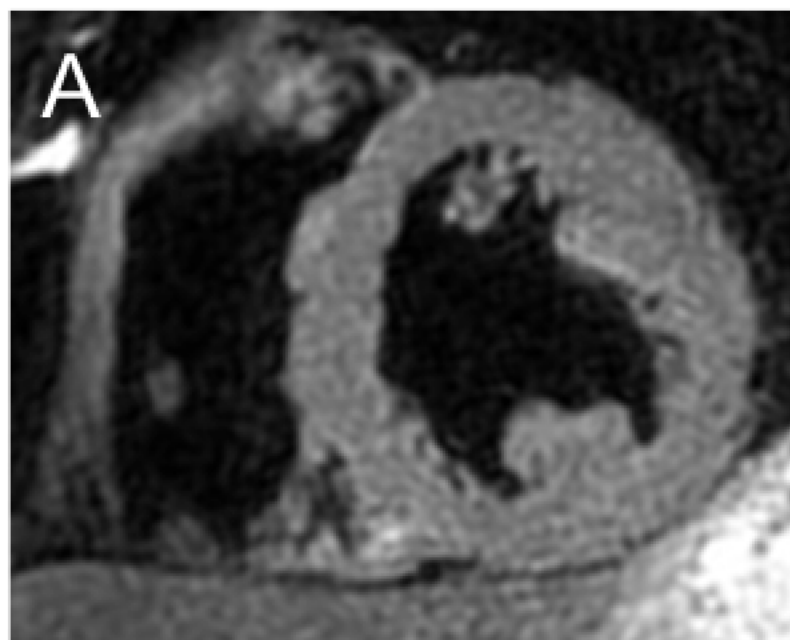
HR-LGE











# CONVENTIONAL CMR

# CMR WITH HR-LGE

Definite diagnoses

Definite AM  
N=32 (19%)

Definite TT  
N=13 (8%)

Others  
N=2 (1%)

Definite MI  
N=39 (23%)

Definite AM  
N=46 (27%)

Definite TT  
N=13 (8%)

Others  
N=1 (1%)

Definite MI  
N=62 (36%)

Non-conclusive diagnoses

Negative CMR  
N=54 (31%)

AM or MI  
N=14 (8%)

MI or Negative  
N=4 (2%)

MI or TT  
N=2 (1%)

AM or Negative  
N=12 (7%)

Negative CMR  
N=48 (28%)

AM or MI  
N=1 (1%)

MI or Negative  
N=0 (0%)

MI or TT  
N=0 (0%)

AM or Negative  
N=1 (1%)

