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## Cardiovascular Magnetic Resonance May Avoid Unnecessary Coronary Angiography in Patients With Unexplained Left Ventricular Systolic Dysfunction: A Retrospective Diagnostic Pilot Study

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► **To cite this version:**

Louis-Marie Desroche, Olivier Milleron, Benjamin Safar, Phalla Ou, Eric Garbarz, et al.. Cardiovascular Magnetic Resonance May Avoid Unnecessary Coronary Angiography in Patients With Unexplained Left Ventricular Systolic Dysfunction: A Retrospective Diagnostic Pilot Study. *Journal of Cardiac Failure*, 2020, 26, pp.1067 - 1074. 10.1016/j.cardfail.2020.09.005 . hal-03492728

**HAL Id: hal-03492728**

**<https://hal.science/hal-03492728>**

Submitted on 15 Dec 2022

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1 **Cardiovascular Magnetic Resonance may avoid unnecessary coronary angiography in**  
2 **patients with unexplained left ventricular systolic dysfunction: a retrospective diagnostic**  
3 **pilot study**

4  
5 **Short title: First-line Cardiovascular Magnetic Resonance in dilated cardiomyopathy**

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26 **ABSTRACT**

27

28 **Backgrounds:**

29 Coronary angiography(CA) is usually performed in patients with reduced left ventricular  
30 ejection fraction(LVEF) to search ischemic cardiomyopathy. Our aim was to examine the  
31 agreement between CA and cardiovascular magnetic resonance(CMR) among a cohort of  
32 patients with unexplained reduced LVEF, and estimate what would have been the  
33 consequences of using CMR as the first-line exam.

34 **Methods:**

35 Three hundred and five patients with unexplained reduced  $LVEF \leq 45\%$  who underwent both  
36 CA and CMR were retrospectively registered. Patients were classified as  $CMR^+$  or  $CMR^-$   
37 according to presence or absence of myocardial ischemic scar, and classified  $CA^+$  or  $CA^-$   
38 according to presence or absence of significant coronary artery disease(CAD).

39 **Results:**

40  $CMR^+(n=89)$  included all 54 $CA^+$  patients, except 2 with distal CAD in whom no  
41 revascularization was proposed. Among the 247 $CA^-$  patients, 15% were  $CMR^+$ . CMR had  
42 96% sensitivity, 85% specificity, 99% negative predictive value, and 58% positive predictive  
43 value for detecting  $CA^+$  patients. Revascularization was performed in 6.5% of the patients  
44 (all  $CMR^+$ ). Performing CA only for  $CMR^+$  patients would have decreased the number of  
45 CAs by 71%.

46 **Conclusions:**

47 In reduced LVEF, performing CA only in  $CMR^+$  patients may significantly reduce the  
48 number of unnecessary CAs performed, without missing any patients requiring  
49 revascularization.

50

51 **Key words:** coronary artery disease; cardiovascular magnetic resonance imaging; left  
52 ventricular systolic dysfunction.

53

54

## 55 **Introduction**

56 Reduced left ventricular ejection fraction (LVEF) is present in 3-7% of the general  
57 population, which is expected to increase with the aging of the population[1,2]. Its most  
58 common cause is ischemic cardiomyopathy[3], but the most favorable process of identifying  
59 patients benefiting from invasive coronary angiography (CA) remains unclear[3,4]. CA is  
60 almost systematically performed[4,5] to identify coronary artery disease (CAD): indeed, in  
61 the STICHES study[6], the patients with ischemic cardiomyopathy had their survival  
62 improved by revascularization. However in the absence of chest pain, three-fourths of patients  
63 with reduced LVEF do not have CAD[7,8] but nevertheless undergo CA with its cost and  
64 complications[9]. A method for identifying individuals with reasonable probability of having  
65 CAD prior to CA would be beneficial. Furthermore CA may not correctly identify all  
66 ischemic cardiomyopathies: post-mortem[10] and cardiovascular magnetic resonance imaging  
67 (CMR)[7,8] studies have shown that 12-17% of “idiopathic dilated cardiomyopathies” may  
68 actually be ischemic following myocardial infarction with non-obstructive coronary arteries  
69 (MINOCA)[11].

70 The diagnostic performance of subendocardial late gadolinium enhancement (LGE) on CMR  
71 for the diagnosis of myocardial infarction is very high [12,13]. Some series[7,8,14,15] which  
72 evaluate CMR for the detection of ischemic cardiomyopathy in patients with LVEF reduction  
73 have been encouraging (sensitivity of 85-100%), but based on a limited number of patients

74 (60-120 patients), and they did not formally assess the benefits and risks of a strategy based  
75 on CMR in first-line.  
76 This study was based on the hypothesis that at least one myocardial segment is expected to  
77 have an infarction pattern on CMR in patients with significant reduction in LVEF due to  
78 CAD. We aimed to evaluate the potential medical benefits of using CMR as a first-line  
79 investigation to identify ischemic cardiomyopathy in patients with unexplained reduced  
80 LVEF. Our main hypothesis was that the NPV of CMR for predicting ischemic  
81 cardiomyopathy approaches 100% which would allow to avoid CA when no ischemic pattern  
82 is found on CMR. The main objective of this study was to examine the agreement between  
83 CA and cardiovascular magnetic resonance(CMR) among a cohort of patients with  
84 unexplained reduced LVEF, and estimate what would have been the consequences of using  
85 CMR as the first-line exam. Our secondary objectives were to compare the diagnostic value of  
86 CMR with those of ECG and transthoracic echocardiography(TTE) in predicting the presence  
87 of significant CAD, and to evaluate the economic benefits of the "alternative strategy"  
88 consisting in a systematic first-line CMR, with CA performed only when an ischemic scar is  
89 found on CMR.

90

## 91 **Material and Methods**

92 Patients with unexplained reduced LVEF from 2 institutions, hospitalized between  
93 March 2009 and October 2015 were eligible to be included in this retrospective study, if CMR  
94 and CA were performed less than 3 months apart. LVEF  $\leq$  45% on 2D TTE was chosen as  
95 indicative of incipient systolic dysfunction; this threshold was selected taking into  
96 consideration the European Society of Cardiology definition (LVEF  $\leq$  50%)[3] and the 5%  
97 inter- and intra-observer variability of the LVEF on TTE[16], and has also been used in large  
98 clinical studies on heart failure[17,18]. Patients with an obvious ischemic (myocardial

99 infarction or typical angina), valvular ("moderate-to-severe" or "severe" left valvular  
100 regurgitation, or "severe" aortic stenosis, according to the European Association of  
101 Cardiovascular Imaging[19]), or rhythmic (arrhythmia greater than 120 bpm on initial  
102 assessment) cause of the LVEF impairment were excluded.

103 This observational retrospective study did not interfere with the usual care of patients.  
104 CMR and CA were performed in the context of care. Since the study met the criteria of the  
105 reference methodology MR-005 of French regulations, no approval from a local commission  
106 or consent was required.

107 ECG and TTE data were collected; left ventricular dilatation was defined by a left  
108 ventricular end diastolic volume index  $\geq 87\text{ml/m}^2$  for men and  $74\text{ml/m}^2$  for women[20].

109 CMR was performed using 1.5-T scanners: MAGNETOM Avanto (Siemens) in the first  
110 institution and Signa TwinSpeed (General Electric) in the second. Contiguous short-axis  
111 locations encompassing the left ventricle were acquired in the cine steady-state free  
112 precession sequence. Each slice was acquired during one short breath-hold. Delayed enhanced  
113 images were obtained 10 minutes after a gadolinium-based contrast agent injection  
114 (DOTAREM<sup>®</sup>, Guerbet; 0.4 mL/kg) using a 3D segmented inversion-recovery gradient-echo  
115 pulse sequence, with the slice position identical to that of the cine images (field of view 300-  
116 360 mm, slice thickness 6.0 mm, inversion time 200-280 ms). LGE assessment was  
117 qualitative, describing the number of segments with LGE according to the 17-segment model  
118 of the American Heart Association and the myocardial layer involved. Subendocardial LGE  
119 was defined with areas of bright signal, and an increasing degree of transmural extension,  
120 depending on the extent of the infarct. The four CMR readers had the national diploma  
121 required for CMR reading, and each experienced over 1000 CMR analyses in 2009; two of  
122 whom had a Ph.D.

123 *Classification of patients*

124 Patients were classified as CMR<sup>+</sup> if subendocardial (or transmural depending on the  
125 extension) LGE was present in at least one segment; they were otherwise categorised as being  
126 “CMR<sup>-</sup>”.

127 The gold standard exam was CA. They were classified as CA<sup>+</sup> if significant CAD was present  
128 according to Felker’s criteria concerning prognostically significant CAD[21]: i.e.,  $\geq 75\%$   
129 stenosis of left main or proximal left anterior descending artery (LAD), or  $\geq 75\%$  stenosis of  
130 two or more epicardial vessels. Otherwise they were classified as CA<sup>-</sup>. Eight patients had  
131 only one coronary stenosis  $> 75\%$  not including left main or proximal LAD and they have  
132 thus been classified as CA<sup>-</sup>. Their CMR result and medical care are described in a specific  
133 paragraph of the results section.

134 Felker's criteria was used because the benefit of revascularization of a stenosis not meeting  
135 these criteria is doubtful. The benefit of revascularization in patients with LVEF reduction  
136 was even difficult to demonstrate in patients with stenosis meeting Felker's criteria: STICH  
137 trial[22] did not show any significant benefit after 5 years. After an extended-follow up,  
138 STICHES[7] finally showed a benefit after 10 years.

### 139 *Statistical analysis*

140 This was a proof of concept study(pilot study); no calculation of the number of  
141 subjects required has been performed in this retrospective study. Indeed, this pilot study was  
142 designed for the CAMAREC prospective and multicenter study (Clinical Trials Registration  
143 No.NCT03231189). A large number of patients was therefore required to have an accurate  
144 estimate of the diagnostic performance of CMR in this situation.

145 Statistical analyses were performed using XLSTAT. In this diagnostic study, the  
146 patients were separated into four groups depending on CA and CMR results: CA<sup>-</sup>CMR<sup>-</sup>,  
147 CA<sup>-</sup>CMR<sup>+</sup>, CA<sup>+</sup>CMR<sup>+</sup>, and CA<sup>+</sup>CMR<sup>-</sup>. Sensitivity, specificity, positive and negative  
148 predictive value, positive and negative likelihood ratio, and diagnostic accuracy, with

149 confidence intervals of 95%, were calculated to evaluate the diagnostic value of CMR for  
150 detecting CA<sup>+</sup> patients.  
151 This calculation was also performed for the electrocardiogram, regional wall motion  
152 abnormalities on TTE, and the combination of both. The net reclassification improvement[23]  
153 was calculated to evaluate the additional benefit of using CMR for the detection of CA+  
154 patients compared to the combination of electrocardiogram and regional wall motion  
155 abnormalities on TTE.

156 To test the reproducibility of the first real-life interpretation of the CA and CMR, all  
157 exams were reinterpreted by both an interventional cardiologist and a cardio-radiologist who  
158 had not participated in the original interpretations; they were blinded to clinical,  
159 echocardiographic, CMR and CA data. Agreement with the original interpretation was  
160 calculated for both CA and CMR using kappa statistics, with  $\kappa > 0.6$  indicating substantial  
161 agreement[24].

### 162 ***Cost and complication analysis between the current and the alternative strategy***

163 The cost per patient of the "alternative strategy" consisting of performing CA only in CMR<sup>+</sup>  
164 patients was compared to the cost per patient of the "current practice". The "current practice"  
165 was evaluated according to number of CMR and CA performed in the initial real-life samples  
166 of patients with newly diagnosed and unexplained reduced LVEF.

167 We first took the standpoint of the French healthcare system with €4,854 for CA (including  
168 the procedure and physicians' fees), and the cost of CMR based on physician fees and  
169 materials costs, for an out-patient (€303: €69 for physician fees, €173 for equipment cost, and  
170 €61 per dose of gadolinium). Then we used the Centers for Medicare Medicaid Services cost  
171 schedule for 2018, and used \$512 for CMR and \$12,276 for CA.



172 The incidence of complications was also compared between the current and the alternative  
173 strategy, using a major complication rate of 1.5% for CA [25] comprising vascular  
174 complication, stroke, renal injury, cholesterol emboli syndrome and death.

175

## 176 **Results**

### 177 *Population*

178 On 604 patients admitted to investigate a newly diagnosed reduced LVEF  $\leq 45\%$ , by  
179 TTE (figure 1), 202 were excluded because they did not undergo CMR, because CMR was not  
180 easily accessible mainly in the early years of the study; thereafter, CMR became part of the  
181 systematic investigation of any unexplained alteration of LVEF, regardless of CA results. CA  
182 was not proposed to 2/604 patients due to a low cardiovascular risk and the absence of LGE  
183 on CMR. 22 patients were excluded because CA and CMR were not performed within 3  
184 months apart, 63 because etiology of the LVEF reduction was known, and 10 because CMR  
185 interpretation was not possible (7 because of a technical problem and 3 because of  
186 claustrophobia) (figure 1).

187 Ultimately, 305 patients were included in the study. The mean delay between CA and  
188 CMR was 15.4 days, the CMR having been done first in 41% of the cases. Twenty patients  
189 (6.5%) underwent revascularization: 16 (5%) received percutaneous coronary intervention  
190 and 4 (1.5%) coronary artery bypass grafting. No patients were revascularized prior to CMR.  
191 Two patients had a pacemaker, and none had an Implantable-Cardioverter-Defibrillator. Table  
192 1 summarizes the characteristics of these patients. Supplemental Table S1 compares our  
193 population to the patients excluded because no CA or CMR was performed.

194 **TABLE 1.** Population characteristics

Clinical features	n
Male gender	214 (70%)

Age (years $\pm$ SD)	60.2 $\pm$ 13.0
Diabetes mellitus	70 (23%)
Smoker	157 (51%)
Hypertension	146 (48%)
Dyslipidaemia	97 (32%)
Family history of coronary artery disease	12 (4%)
Heavy alcohol consumption	39 (13%)
HIV	7 (2%)
Anthracycline	17 (6%)
Family history of DCM	7 (2%)
Initial presentation:	
1) Class II, III or IV NYHA	230 (75%)
2) Fortuitous discovery	31 (10%)
3) Atypical chest pain	19 (6%)
4) Palpitations	11 (4%)
5) Syncope	7 (2%)
6) Peripheral embolism	7 (2%)
ECG	
-Bundle branch block (left/right)	98 (32%)
-T wave abnormality	100 (33%)
-Q wave	27 (9%)
TTE	
-Left ventricular dilatation	234 (77%)
-LVEF mean (% $\pm$ SD)	31,2 $\pm$ 10,0
-Regional WMA $\geq$ 1 segment	126 (43%)
CA <sup>+</sup> :	54 (18%)
-Single vessel disease (proximal LAD)	9 (3%)
-Double vessel disease	18 (6%)
-Triple vessel disease	27 (9%)
CMR:	
-Indexed volume (mL/m <sup>2</sup> $\pm$ SD)	125 $\pm$ 38,7
-LVEF mean (% $\pm$ SD)	29.8 $\pm$ 10.1
-CMR <sup>+</sup> :	89 (29%)

-CMR <sup>-</sup> :	216 (71%)
Midwall LGE	55 (18%)
Subepicardial LGE	23 (8%)
No LGE	138 (45%)

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195

196 CA<sup>+</sup>: significant coronary stenosis; CMR: cardiovascular magnetic resonance imaging;  
 197 CMR<sup>+</sup>: subendocardial LGE on at least 1 segment; CMR<sup>-</sup>: no subendocardial LGE; DCM:  
 198 dilated cardiomyopathy; LAD: left anterior descending coronary; LGE: late gadolinium  
 199 enhancement; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association;  
 200 SD: Standard deviation; TTE: transthoracic echocardiography.

201 ***Classification of patients***

202       In the reproducibility testing of the interpretations of CA and CMR, the agreement rate  
 203 between the reinterpretation and the original interpretation was high ( $\kappa = 0.85$  and  $\kappa = 0.76$ ,  
 204 respectively). One patient initially classified as CA<sup>-</sup>CMR<sup>-</sup> was reclassified as CA<sup>-</sup>CMR<sup>+</sup> and  
 205 another initially classified as CA<sup>+</sup>CMR<sup>+</sup> was reclassified as CA<sup>-</sup>CMR<sup>+</sup>.

206       Figure 2 shows the distribution of patients according to the results of CA and CMR.  
 207 Figure 3 represents the alternative strategy using first-line CMR. All CMR<sup>-</sup> patients were also  
 208 CA<sup>-</sup>, except 2 patients (0.7% of 216 CMR<sup>-</sup> patients) who had a CAD too distal to explain  
 209 such LV dysfunction (15% and 25% LVEF) and to have revascularization. Therefore, no  
 210 revascularization was proposed in any CMR<sup>-</sup> patient, and LV systolic dysfunction was not  
 211 explained by ischemic cardiomyopathy in any of them.

212       Among the 89 CMR<sup>+</sup> patients, CA identified significant CAD according to Felker's  
 213 criteria in 52 CA<sup>+</sup> patients; and revascularization was performed in 20 patients. 37 CMR<sup>+</sup>  
 214 were CA<sup>-</sup>. They were younger (59 years vs. 62 years), and more likely to be female (21% vs.  
 215 16%), with less dyslipidaemia (27% vs. 50%).

216 CMR sensitivity for detecting significant CAD(CA+) was 96%, specificity 85%,  
 217 negative predictive value 99%, and positive predictive value 58% (Table 2). Negative  
 218 predictive value was 100% for identification of coronary artery stenosis requiring  
 219 revascularization and explaining the reduced LVEF. Positive and negative likelihood ratio of  
 220 CMR for predicting CA+ patients were respectively 6.53 (95% confidence interval 4.83-8.84)  
 221 and 0.04 (95% confidence interval 0.01-0.17). Conversely, if CMR was considered the gold  
 222 standard, the sensitivity of CA for detecting CMR+ patients would only be 64% (95% CI:  
 223 53%-74%).

224

225 **TABLE 2.** Diagnostic value of basic tests and CMR for predicting ischemic cardiomyopathy

	<b>Se</b>	<b>Sp</b>	<b>NPV</b>	<b>PPV</b>	<b>D.A.</b>
T abnormality	17 (8-29)	64 (57-70)	78 (75-80)	9 (5-15)	55 (50-61)
Q-wave	33 (21-47)	96 (93-98)	87 (85-89)	67 (49-81)	85 (81-89)
WMA	62 (51-72)	18 (13-24)	54 (44-64)	23 (20-26)	30 (25-36)
Q-wave or WMA	74 (60-85)	65 (58-70)	92 (88-95)	31 (26-36)	66 (61-72)
CMR	96 (87-100)	85 (80-89)	99 (96-100)	58 (51-66)	87 (83-91)

226 All values are expressed as the number and percentage, n (%), (95% confidence interval).

227 CA: coronary angiography; CMR: cardiovascular magnetic resonance imaging; D.A.:  
 228 diagnostic accuracy; ECG: electrocardiogram; ECG+WMA: combination of ECG and WMA;  
 229 NPV: negative predictive value; PPV: positive predictive value; Se: sensitivity; Sp:  
 230 specificity; WMA: regional wall motion abnormalities on transthoracic echocardiography.

231

232 A single vessel disease not including left main or proximal LAD, was present in 8  
 233 patients (classified as CA- above). 4 were CMR+ and 4 CMR-. No revascularization was  
 234 performed on these 4 CMR- patients with single vessel disease. Of the 4 CMR+ patients with  
 235 single vessel disease (and not including left main or proximal LAD), 1 percutaneous  
 236 revascularization was performed on a 80% right coronary artery stenosis. Therefore, if CAD

237 was defined as the presence of at least one 75% stenosis, including stenosis without any  
238 prognostic value according to Felker, sensitivity of CMR for detecting CAD would have been  
239 changed from 96% to 90% (95% CI: 80% to 96%) and specificity from 85% to 86 % (95%  
240 CI: 81% to 90%). However, with this new definition, neither the sensitivity of CMR for  
241 detecting patients requiring revascularization(100%), nor the costs saved by the alternative  
242 strategy would have changed.

243 CMR provided a diagnosis of MINOCA for 33/305(11%) patients, i.e. an ischemic  
244 scar was present in CMR but CA did not show any coronary stenosis.

#### 245 *Cost savings and complications avoided through the alternative strategy*

246 If the “alternative strategy” had been applied (CMR performed on all patients, and CA  
247 only for CMR<sup>+</sup>patients), CA would have been performed on only 89 patients (52 CA+CMR<sup>+</sup>  
248 and 37 CA-CMR<sup>+</sup>). 216/305(71%) CAs would have been avoided. Using a 1.5%  
249 complication rate for CA, the alternative strategy based on CMR would avoid 1 complication  
250 every 94 patients investigated for LVEF reduction. We also calculated the cost difference of  
251 the two approaches : the "current practice", with the number of CMRs and CAs observed in  
252 the initial population of 604 patients evaluated for reduced LVEF (400 with CMR and CA,  
253 202 with CA alone and 2 with CMR alone), and on the other side the "alternative strategy"  
254 (CA performed only in the 29% CMR<sup>+</sup>patients). This alternative strategy would have saved  
255 €3,320 /patient in France and \$8,482 /patient in the USA.

256 Thus, for every 100 patients investigated for LVEF reduction, this alternative diagnostic  
257 strategy would have avoided 1,065 major complication, associated with savings of €332,000  
258 in France and \$848,200 in the USA.

#### 259 *Additional value of CMR over ECG and TTE*

260 The diagnostic value of the ECG and wall motion abnormalities on TTE for predicting CA+  
261 patients, are shown in Table 2. The net reclassification improvement of CMR, compared to

262 the combination of electrocardiogram and regional wall motion abnormalities on TTE, was  
263 0,62(respectively 0,15 and 0,47 for the reclassification of the CA<sup>+</sup> and CA<sup>-</sup> patients).

#### 264 ***Additional findings on CMR***

265 CMR revealed diverse non-ischemic etiologies for LVEF reduction in 72 patients:  
266 myocarditis in 23, LV noncompaction (not reported by TTE) in 20, LV hypertrophy (not  
267 reported by TTE) in 11, left intraventricular dyssynchrony (not reported by TTE) in 9,  
268 Takotsubo cardiomyopathy in 8, and Chagas disease in 1. CMR also influenced care in  
269 14/305(5%) patients: 12 LV apical thrombi not detected by TTE received anticoagulation, 1  
270 atrial septal defect was referred for percutaneous closure, and 1 patient with constrictive  
271 pericarditis underwent surgery. Finally, CMR reported the absence of myocardial viability in  
272 the stenosis territory in 31/52(60%) of CA + patients, thus avoiding revascularization.

273

#### 274 **Discussion**

275 This multicenter study suggests that the use of CMR as a guide in the decision-making  
276 process of the need for CA in patients with unexplained systolic dysfunction (alternative  
277 strategy) may be superior to current practice with near-systematic CA.

278 It reliably identifies patients with significant CAD according to Felker's criteria(96%  
279 sensitivity), especially those requiring revascularization(100% sensitivity), while reducing the  
280 number of CAs performed(-71%), resulting in substantial savings. Furthermore, this strategy  
281 allows to identify some etiologies responsible for the LV systolic dysfunction including  
282 amongst others, MINOCA, and occasional access to additional information guiding care (e.g.,  
283 apical thrombi not identified by TTE).

284 The most important initial fear of using the “alternative strategy” (CA performed only  
285 for CMR<sup>+</sup> patients) was to be unable to diagnose all patients with significant CAD requiring  
286 revascularization. In our study all the patients requiring revascularization were identified.

287 This seems to suggest that hibernation alone can rarely be responsible for a severe  
288 LVEF reduction without at least 1 segment showing necrosis, even subendocardial. Besides  
289 myocardial hibernation animal models failed to significantly reduce LVEF without causing  
290 some necrosis[26,27].

### 291 ***Imaging and diagnostic strategy***

292 Current guidelines state that in the absence of angina, CA should be considered on  
293 patients suitable for revascularization, with LVEF dysfunction, intermediate to high pre-test  
294 probability of CAD, and after a positive non-invasive stress test[3,4]. Our study suggests that  
295 CAD is difficult to predict with basic tests, which is underlined by the high net  
296 reclassification improvement of CMR compared to the combination of electrocardiogram and  
297 TTE. Furthermore the diagnostic performance of stress imaging is questionable when LVEF  
298 is reduced, whether with single-photon emission computed tomography[28] or stress  
299 TTE[29]. About coronary computed tomography angiography, its low specificity (50%) for  
300 identification of hemodynamically significant CAD[30] would lead to perform many  
301 unnecessary CAs if used as a first-line screening test in these patients, over the average age of  
302 60, and 23% diabetic. Above the economic impact, this would lead to multiply iodine contrast  
303 injections, while 20% of these patients with heart failure have a Glomerular Filtration Rate  
304 <30 mL/min/1,73m<sup>2</sup>[31]. Coronary computed tomography angiography may be relevant for  
305 low cardiovascular risk patients; however, it will be less efficient than CMR in diagnosing  
306 MINOCA.

### 307 ***CMR and ischemic cardiomyopathy***

308 CMR reclassified 11% of the cardiomyopathies as MINOCA, instead of “idiopathic dilated  
309 cardiomyopathies”, which is close to the ratio observed in post-mortem or CMR  
310 studies[7,8,10]. This can lead to modify the treatment, introducing aspirin and statins, or in  
311 some cases, to raise the hypothesis of a coronary artery spasm.

312 CMR allowed the detection of apical thrombi, 25% of which had been missed by TTE,  
313 a similar proportion reported by Srichai[32]. This helped prevent cardioembolic events  
314 introducing an anticoagulant therapy.

315 Lastly, CMR prevented futile revascularization in 60% of CA<sup>+</sup> patients, by reporting  
316 the absence of myocardial viability in the territory of the stenosis, since revascularization  
317 presents no benefit in this situation[33].

### 318 *Limitations*

319 Even if this study was sizable, its main limitation was its retrospective design and the  
320 not blind initial reading of CA and CMR. However, we assessed this risk with a new blind  
321 reading of CMR and CA, and the suitable agreement between the first real-life reading and  
322 the new blind reading was reassuring.

323 A selection bias may have arisen due to the exclusion of 202 patients without CMR  
324 and 2 without CA. However, these patients were similar to those included in the study (Table  
325 S1). The non-completion of the second examination (majority CMR) was mainly due to  
326 heterogeneous practices between cardiologists, especially in the early years of the study when  
327 CMR was not easily accessible.

328 The rate of significant CAD(18%) was lower than in previous studies[7,8](21%-44%)  
329 but in our study we excluded obvious etiologies for systolic dysfunction, including typical  
330 angina, which was not the case in others.

331 The mean age of our population with reduced LVEF was 60.2 years, lower than in  
332 some large epidemiological studies (66 years in the MAGGIC meta-analysis in 41,972  
333 patients[34]). This may have under-represented the number of CAD.

334 During this study, FFR was not systematic, and therefore the accuracy of the decision  
335 to perform revascularization may be questioned.



336 **Conclusion**

337 An “alternative strategy” using CMR as a screening tool for performing CA seems  
338 reliable, more informative, and less expensive than a strategy using CA as a first-line  
339 investigation for CAD screening in patients with an unexplained reduction in LVEF. Further  
340 studies are needed, and a prospective multicenter study has been launched to confirm these  
341 results (“Prospective Multicentric Study for the Diagnostic Performance of Cardiac  
342 Magnetic Resonance imaging used first for the diagnosis of Coronary artery disease as the  
343 etiology of left ventricular dysfunction”; CAMAREC trial; Clinical Trial Registration  
344 No.NCT03231189).

345

346 **Declarations**

347 *Funding*

348 The funders had no role in study design, data collection and analysis, decision to publish, or  
349 preparation of the manuscript

350 *Competing interests*

351 The authors declare that they have no competing interests.

352

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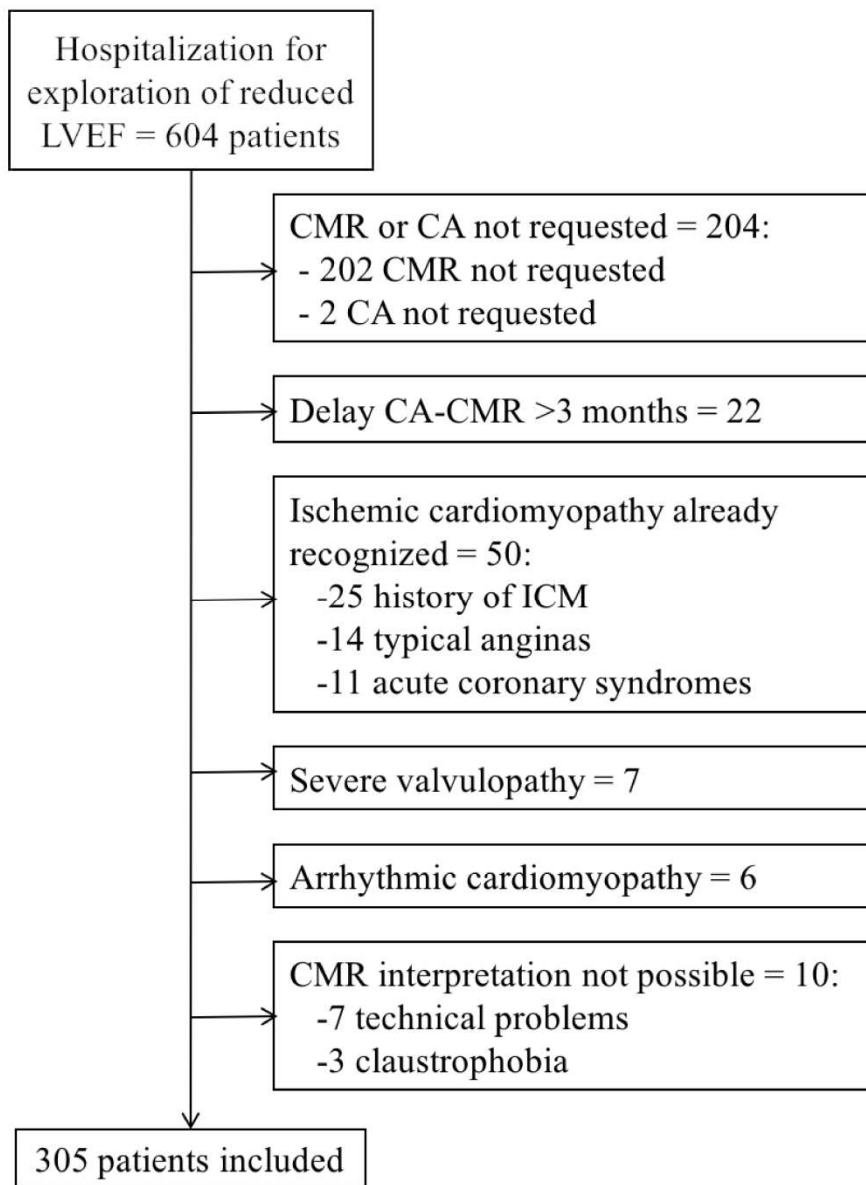
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458

459 **FIGURE LEGENDS**



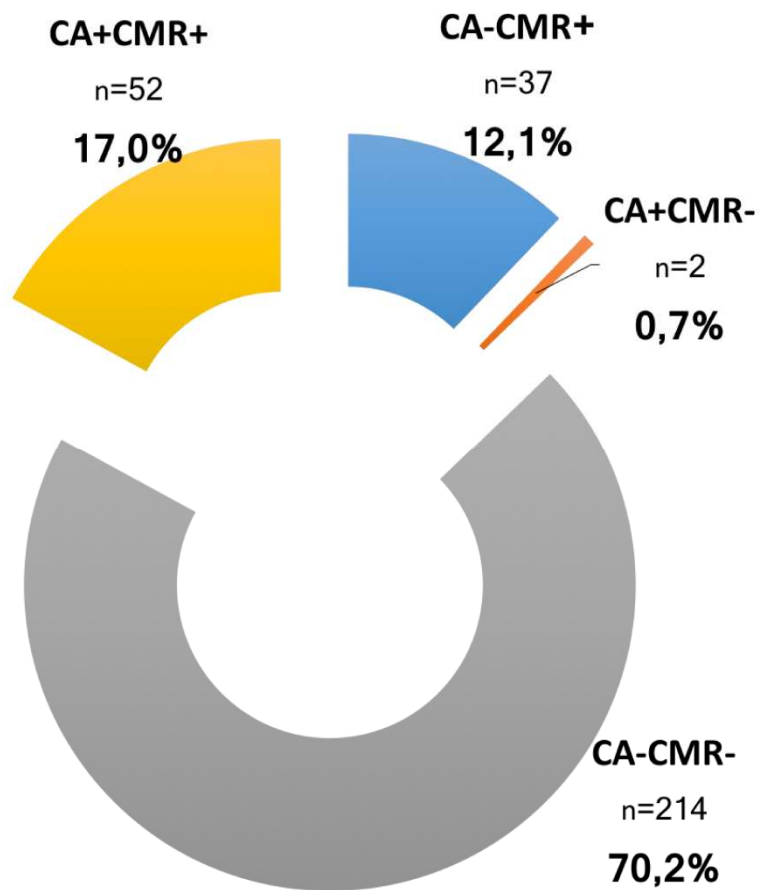
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461 **FIGURE 1.** Flowchart of patient selection

462 CA: coronary angiography; CMR: cardiovascular magnetic resonance imaging; LVEF: left

463 ventricular ejection fraction

464



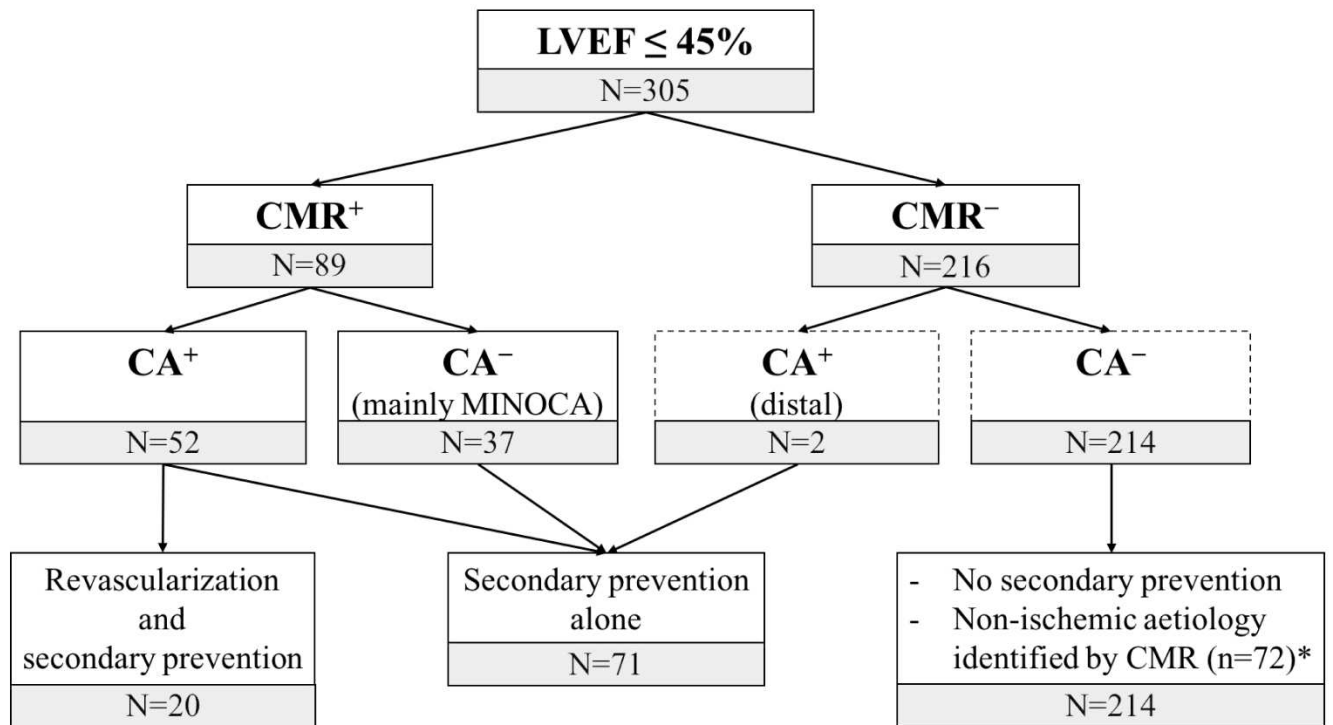
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466 **FIGURE 2.** Patient distribution according to CA and CMR results

467 CA: coronary angiography; CA<sup>+</sup>: significant coronary stenosis; CA<sup>-</sup>: non-significant coronary

468 stenosis; CMR: cardiovascular magnetic resonance imaging; CMR<sup>+</sup>: subendocardial

469 enhancement; CMR<sup>-</sup>: no subendocardial enhancement



470

471 **FIGURE 3.** Flowchart of patient classification and alternative strategy simulation

472 Dashed boxes: CA would not be performed if the alternative strategy were applied.

473 CA: coronary angiography; CA<sup>-</sup>: no significant coronary stenosis; CA<sup>+</sup>: significant stenosis;

474 CMR: cardiovascular magnetic resonance imaging; CMR<sup>-</sup>: no subendocardial enhancement;

475 CMR<sup>+</sup>: subendocardial enhancement; LVEF: left ventricular ejection fraction; MINOCA:

476 myocardial infarction with non-obstructive coronary arteries

477 \* 23myocarditis, 20LV noncompaction (not reported by TTE), 11LV hypertrophy (not

478 reported by TTE), 9left intraventricular dyssynchrony (not reported by TTE), 8Takotsubo

479 cardiomyopathy, 1Chagas disease.