



# Prognostic value of stress cardiac magnetic resonance. A third level hospital experience

Valor pronóstico de la resonancia magnética cardíaca de estrés.  
Una experiencia en hospital de tercer nivel

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**How to cite:** Rebull-  
Isusi JM, Galindo-Uribe  
J, Oseguera MJ, Rosales  
US, Aldaco-Rodríguez  
AR, Palacios GD, et  
al. Prognostic value of  
stress cardiac magnetic  
resonance. A third level  
hospital experience.  
CIU Cardiac Image  
Updated. 2022; 2 (1):  
10-15. [https://dx.doi.  
org/10.35366/105939](https://dx.doi.org/10.35366/105939)

Received: 22/01/2021  
Accepted: 19/04/2021

**ABSTRACT. Introduction:** Evaluating myocardial perfusion in patients with suspected coronary artery disease (CAD) is a widely accepted and recommended practice. In recent years, cardiac magnetic resonance imaging (CMR) with pharmacological stress has proven to be a better diagnostic performance than traditional tools (Echo and SPECT). However, there is limited evidence on the prognostic value of a positive CMR stress result. The present study aimed to determine the prognostic value of CMR and pharmacological stress (dipyridamole) for adverse events. **Material and methods:** This is a historical cohort, conducted between January 2011 and December 2014, which included patients over 18 years of age at the National Institute of Medical Sciences and Nutrition Salvador Zubirán, Mexico City. All underwent stress CMR (dipyridamole) and first-step perfusion evaluation. A 24-month follow-up was performed in search of an adverse event occurrence including death, non-fatal myocardial infarction, stroke, rehospitalization for cardiovascular causes, or heart failure decompensation. **Results:** A total of 97 patients were included, of which 47 were men. Hypertension (82%), dyslipidemia (56%), active smoking (53%) and diabetes (47%) were the most prevalent cardiovascular risk factors. The median age was  $66 \pm 13$  years. 55% of patients had previous CAD. The stress CMR was positive in 33 patients and was associated with a higher proportion of adverse events without statistical significance (54% vs 31%,  $p = 0.1$ ). The primary outcome was observed in 11 patients, with LVEF  $< 55\%$  as predictor (OR: 5.6, 95% CI 1.5-20;  $p = 0.01$ ). **Conclusion:** A positive stress test was not associated with adverse events in CAD intermediate to high-risk population. Nonetheless, more studies are needed to clarify its prognostic value in this clinical scenery. **Keywords:** Myocardial perfusion, magnetic resonance imaging, coronary artery disease, ischemia.

**RESUMEN. Introducción:** La evaluación de la perfusión miocárdica en pacientes con sospecha de enfermedad arterial coronaria (EAC) es una práctica ampliamente aceptada y recomendada. En los últimos años, la resonancia magnética cardíaca (RMC) con estrés farmacológico ha demostrado tener un mejor rendimiento diagnóstico que las herramientas tradicionales (Eco y SPECT). Sin embargo, hay pocas pruebas sobre el valor pronóstico de un resultado positivo de la RMC de estrés. El presente estudio tuvo como objetivo determinar el valor pronóstico de la RMC y el estrés farmacológico (dipiridamol) para los eventos adversos. **Material y métodos:** Se trata de una cohorte histórica, realizada entre enero de 2011 y diciembre de 2014, que incluyó a pacientes mayores de 18 años en el Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Ciudad de México. A todos se les realizó RMC de estrés (dipiridamol) y evaluación de perfusión de primer paso. Se realizó un seguimiento de 24 meses en busca de un evento adverso que incluyera muerte, infarto de miocardio no mortal, accidente cerebrovascular, rehospitalización por causas cardiovasculares o descompensación de la insuficiencia cardíaca. **Resultados:** Se incluyeron 97 pacientes, de los cuales 47 eran hombres. La hipertensión (82%), la dislipidemia (56%), el tabaquismo activo (53%) y la diabetes (47%) fueron los factores de riesgo cardiovascular más prevalentes. La edad media era de  $66 \pm 13$  años. El 55% de los pacientes tenía una EAC previa. La RMC de estrés fue positiva en 33 pacientes y se asoció a una mayor proporción de eventos adversos

sin significación estadística (54% frente a 31%,  $p = 0.1$ ). El resultado primario se observó en 11 pacientes, con una FEVI < 55% como factor predictivo (OR: 5.6; IC del 95%: 1.5-20;  $p = 0.01$ ). **Conclusión:** Una prueba de esfuerzo positiva no se asoció con eventos adversos en la población de riesgo intermedio a alto de EAC. No obstante, se necesitan más estudios para aclarar su valor pronóstico en este escenario clínico.

**Palabras clave:** Perfusión miocárdica, resonancia magnética, enfermedad arterial coronaria, isquemia.

## INTRODUCTION

Ischemic heart disease (IHD) is characterized by myocardial supply-demand mismatch, which is often promoted by exercise, emotional disturbances, and induced or reproducible stress. Still, they also may develop suddenly without apparent underlying cause.<sup>1,2</sup>

IHD risk factors include hypertension, hypercholesterolemia, diabetes, sedentary lifestyle, obesity, smoking, and a family history of IHD at an early age.<sup>3-7</sup> Timely risk factors detection and management may reduce its incidence.

CMR has been widely studied in recent years, demonstrating good diagnostic performance in detecting IHD, superiority to single photon emission computed tomography (SPECT), and comparable to positron emission tomography (PET).<sup>8</sup> In patients with intermediate cardiovascular risk, a positive stress CMR has proven to be an independent risk factor for myocardial infarction and cardiac death.<sup>9</sup> Moreover, recent studies showed that CMR reduces unnecessary coronary angiography (CA) and revascularization with similar events rate compared to a fractional flow reserve guided strategy.<sup>10,11</sup>

2013 ESC guidelines on the management of stable coronary artery disease recommended CMR use in the IHD evaluation.<sup>2</sup> Most studies use regadenoson and adenosine as stress agents. Nevertheless, few studies have evaluated dipyridamole use, an inexpensive and more available agent.

## MATERIAL AND METHODS

**Study type and population:** a historical cohort study was developed at the *Instituto Nacional de Nutrición y Ciencias Médicas Salvador Zubirán* in Mexico City between January 1st, 2011, and December 30th, 2014. Patients over 18 years

old with angina or an equivalent who underwent CMR imaging with dipyridamole were included. A sequential non-probability sampling was performed. Sample size was not determined, and all available studies were included. Patients with severe valvular, pericardial, or aortic disease, and those with known neoplasia or a life expectancy of less than 12 months in their follow-up were excluded.

**CMR protocol:** this study was performed with a 6-hour fasting, without sedation and repeated apneas. T1 sequences were obtained with subsequent 2, 3, 4 cameras and short axes cardiac planes acquisition, following dipyridamole administration (56 mg/kg in 4 minutes). At minute 7, 0.1 mmol/kg of gadolinium was injected to obtain first pass perfusion stress.

**Study variables:** clinical variables were defined according to the Framingham risk scale. In addition, the total number of cardiovascular risk factors was determined by the presence of hypertension, dyslipidemia, diabetes, age (women > 55 years old and men > 45 years old), current or previous smoking history, previous IHD event, or IHD familial history. Laboratory analysis taken within a week prior to the CMR study were used. Basal heart rate, left ventricular ejection fraction (LVEF), wall motion abnormalities (WMA), and perfusion alterations data were obtained from CMR report.

**Statistical analysis:** numerical variables were determined by Kolmogorov-Smirnov test. According to their distribution, mean and standard deviation or median and interquartile range was used. The categorical variables were expressed in frequency and percentage. Bivariate analysis was performed depending on major adverse cardiovascular events (MACE) presence. Numerical variables were analyzed with Student's t-test or Mann-Whitney U.  $\chi^2$  or Fisher's test was used for categorical variables. Survival analysis was determined using Kaplan-

Meier curves and Log Rank test. A two-tailed  $p < 0.05$  was considered significant. All analyzes were performed using SPSS v21 software.

## RESULTS

Ninety-seven patients were included, of which 48% were male. The mean age was  $66 \pm 13$  years.

Hypertension was present in 82%, dyslipidemia in 56%, smoking in 53%, and diabetes in 47% of the individuals. 53 patients had previous IHD. Regarding the lipid profile, the mean cholesterol was  $176 \pm 40$  mg/dL, with median triglycerides of 144 mg/dL. The most common pharmacological treatment used

**Table 1: General characteristics (N = 97).**

Characteristics	n (%)
Age	$66.6 \pm 13.2$
Males	47 (48.5)
Smoking	52 (53.6)
Diabetes mellitus	46 (47.4)
Heart failure	17 (17.5)
Arterial hypertension	80 (82.5)
Dyslipidemia	55 (56.7)
Hypothyroidism	17 (17.5)
Autoimmunity	15 (15.5)
Chronic kidney disease	21 (21.6)
Previous CAD	53 (54.6)
Family history of CAD	38 (39.2)
Framingham score	$0.25 (0.13, 0.41)$
Cholesterol (mg/dL)	$176 \pm 40$
LDLc (mg/dL)	$104 \pm 40$
HDLc (mg/dL)	$46 \pm 14$
Triglycerides	144 (117, 191)
Creatinine serum	1 (1, 1)
Beta blocker	53 (54.6)
Calcium channel blocker	26 (26.8)
ACEi	25 (25.8)
ARB	25 (25.8)
Aspirine	47 (48.5)
Clopidogrel	18 (18.6)
Diuretic	20 (20.6)
Statin	49 (50.5)

CAD = coronary artery disease; LDLc = low density lipoprotein cholesterol; HDLc = high density lipoprotein cholesterol; ACEi = angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor antagonist.

**Table 2: Cardiac magnetic resonance parameters.**

Characteristics	Value
Basal HR (bpm)	$73.8 \pm 15.3$
LVEF (%)	$63.5 \pm 14.1$
Heart failure	3 (3, 4)
WMA at rest	36 (37.1%)
WMA at stress	33 (34%)
Induced perfusion alterations	32 (33%)
Positive study for ischemia	33 (34%)

HR = heart rate; bpm = beats per minute; LVEF = left ventricle ejection fraction; WMA = wall motion abnormalities.

**Table 3: Outcomes.**

Event	n (%)
Fatal arrhythmias	1 (1.0)
New ACS	5 (5.2)
Hospital readmission	10 (10.3)
Heart failure decomposition	1 (1.0)
Emergency revascularization	0
Stroke	1 (1.0)
Death	3 (3.1)
Cumulative events	11 (11.3)

ACS = accurate coronary syndrome.

were beta-blocker, aspirin, and statin. Patient's characteristics are shown in [Table 1](#).

Regarding stress CMR characteristics, the mean initial LVEF was  $63.5 \pm 14\%$ . 33 cases were positive for ischemia, and a third (37%) had WMA. [Table 2](#) displays all CMR parameters.

Mortality was observed in 3% of the population. The most frequent event was hospital readmission. The rest of the outcomes are presented in [Table 3](#).

No difference in sociodemographic characteristics and risk factors was observed between both groups. Patients with MACE showed lower LVEF ( $65\%$  vs  $53\%$ ,  $p < 0.05$ ) and greater use of clopidogrel. A positive stress test was not associated with MACE ( $31\%$  vs  $54\%$ ,  $p = 0.17$ ). Both groups comparison is shown in [Table 4](#).

Table 4: Comparison of groups according to MACE.

Characteristics	No MACE N = 86 n (%)	MACE N = 11 n (%)	P
Age	66.2 ± 13	69.5 ± 14	0.43
Males	42 (49.4)	5 (45.5)	0.80
Smoking	47 (54.7)	5 (45.5)	0.56
Diabetes mellitus	42 (48.8)	4 (36.4)	0.43
Heart failure	16 (18.6)	1 (9.1)	0.68
Arterial hypertension	71 (82.6)	9 (81.8)	1.00
Dyslipidemia	46 (53.5)	9 (81.8)	0.11
Hypothyroidism	16 (18.6)	1 (9.1)	0.68
Autoimmunity	13 (15.3)	2 (18.2)	0.68
Chronic kidney disease	19 (22.1)	2 (18.2)	1.00
Previous CAD	47 (54.7)	6 (64.5)	1.00
Family history of CAD	34 (39.5)	4 (36.4)	1.00
Framingham score	0.23 (0.12, 0.4)	0.4 (0.18, 0.6)	0.19
Cholesterol (mg/dL)	165 (143, 210)	185 (150, 195)	0.76
LDLc (mg/dL)	104.9 ± 38	96.9 ± 52	0.55
HDLc (mg/dL)	46.8 ± 13	46.3 ± 23	0.92
Triglycerides	141 (117, 185)	172 (127, 236)	0.24
Creatinine serum	1 (1, 1)	1 (1, 1)	1.00
Beta blocker	47 (54.7)	6 (54.6)	1.00
Calcium channel blocker	22 (25.6)	4 (36.4)	0.47
ACEi	20 (23.3)	5 (45.5)	0.14
ARB	22 (25.6)	3 (37.3)	1.00
Aspirine	40 (46.5)	7 (63.6)	0.28
Clopidogrel	13 (15.1)	5 (45.5)	0.02
Diuretic	18 (20.9)	2 (18.2)	1.00
Statins	43 (50.0)	6 (54.6)	0.77
LVEF (%)	64.8 ± 13	53.8 ± 18	0.01
Heart failure	3 (3, 4)	3 (2, 4)	0.21
Mobility disturbances at rest	29 (33.7)	7 (63.6)	0.09
WMA at rest	28 (32.6)	5 (45.5)	0.50
Induced WMA	26 (30.2)	6 (54.5)	0.17
Positive study for ischemia	27 (31.4)	6 (54.5)	0.17

MACE = major adverse cardiovascular events; CAD = coronary artery disease; LDLc = low density lipoprotein cholesterol; HDLc = high density lipoprotein cholesterol; ACEi = angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor antagonist; LVEF = left ventricle ejection fraction; WMA = wall motion abnormalities.

Kaplan-Meier curve (Figure 1) shows a favorable prognosis in negative stress CMR patients with an event-free survival at seven years of 91%, compared to 76% in those with a positive test, without statistical significance. There was no difference in patients with and without IHD with a p value of 0.08 for both groups.

## DISCUSSION

The present study is, to our knowledge, the first in evaluating the prognostic performance of CMR stress with dipyridamole in a Mexican population.

Previous studies such as Bodi et al.,<sup>12-14</sup> observed a mean age of 64 ± 11 years, finding a hypertension in 50%, dyslipidemia in 44%, smoking history in 15% and previous coronary artery disease in 23%. These results might differ from ours due to ethnicity differences as their cohort was of Anglo-Saxon descent. Although mean age was similar, our population had a higher prevalence of risk factors, conferring a higher risk for cardiovascular disease. Conversely, the risk factor prevalence found in the present study is not dissimilar to those described in RENASICA II,<sup>15</sup> one of the largest Mexican cohorts published.

Regarding the outcomes, we observed that MACE events occurred in 11.3% of the population, with a mortality of 3.1%. Similar results were found by Bodi et al.,<sup>13</sup> with a MACE occurrence of 9.7%. When we compared patients' characteristics, those with positive events had significantly lower LVEF (65 vs. 53%, p < 0.05) and greater use of clopidogrel. The reduced ejection fraction has already been demonstrated in previous studies as one of the main prognostic factors. Nonetheless, the greater use of clopidogrel in the MACE group could be due to a higher angioplasty rate.

Although our data did not show statistical significance, a higher proportion of MACE was observed in those patients without previous CAD and positive stress-CMR with dipyridamole, suggesting its prognostic value. In agreement with this finding, several studies have demonstrated CMR prognostic value not solely in patients without previous CAD in middle-aged adults but in elderly patients (> 75 years old) as well.<sup>16-18</sup>

Moreover, during an eight-year follow-up of 6,095 patients, Pezel T et al. perceived an annual rate of MACE in 2.4% on those with a negative CMR compared to the 14.6% observed in those with IHD or late gadolinium enhancement. Furthermore, this study demonstrated a good prognostic value in diverse subgroups, including diabetes, obese and non-obese

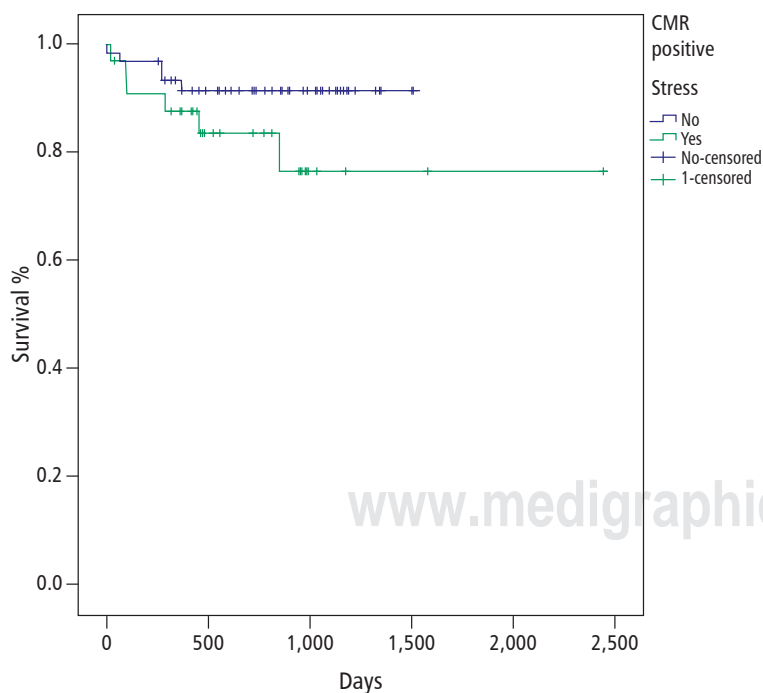
subjects.<sup>18</sup> Thus, the small sample size and rate of patients lost to follow-up of our study, rather than dipyridamole efficacy, might explain the discrepancies observed between our analysis and previous literature. Nonetheless, all studies seem to converge in the good discriminative long-term prognostic value of CMR, which discloses the urgency of prospective studies to discern its value in the assessment and risk stratification in IHD, especially in high-risk individuals who could benefit from improved preventive and therapeutic instruments.

### Limitation of the study

The limitations of the study are the «n» achieved and short-term follow-up, a longer follow-up time would be required to observe results with better statistical significance.

### CONCLUSIONS

A positive stress test was not associated with adverse events in CAD intermediate to high-risk population. Nonetheless, more studies are needed to clarify its prognostic value in this clinical scenery.



**Figure 1:** Kaplan-Meier event-free survival in the total population.

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