

Evaluation of Clinical Management and Follow-up of Patients with Severe Myocardial Ischemia Detected by Gated-SPECT

Evaluación del manejo clínico y seguimiento de pacientes con isquemia miocárdica grave detectada mediante SPECT gatillado

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ABSTRACT

Background: Ischemic heart disease (IHD) is one of the leading causes of death and disability. Many studies have shown that patients with angina and severe myocardial ischemia, as evidenced by functional studies, have an unfavorable clinical course, with a higher risk of cardiovascular events and mortality.

Objectives: The primary aim of this study was to analyze the management adopted by treating physicians (invasive vs. conservative) in patients with a left ventricular mass ischemic burden (IB) $\geq 10\%$ on a gated-SPECT (single-photon emission computed tomography) myocardial perfusion study, and to explore whether higher ischemia values (15% cutoff point) significantly influence this decision. The secondary goal was to identify clinical and/or functional variables associated with the decision to implement an initial invasive strategy and to compare the incidence of cardiovascular events (acute myocardial infarction, unstable angina, rehospitalization due to cardiovascular causes, heart failure, arrhythmias, and cardiovascular death) between patients treated medically and those undergoing revascularization during long-term follow-up.

Methods: A retrospective, observational, single-center study was conducted including consecutive patients referred for a gated-SPECT myocardial perfusion study (n=142) between January 2021 and December 2024. Patients with an IB $\geq 10\%$ were selected and divided into two cohorts: 1) IB $\geq 16\%$ (n=50, 32.2%) and 2) IB between 10 to 15% (n=92, 64.8%)

Results: The proportion of patients managed with an initial invasive strategy was higher in the group with IB $\geq 16\%$ (84% vs. 68.4%, p=0.044). Major cardiovascular events occurred in 16 patients (11.4%); 9 (9.8%) had an IB between 10–15% and 7 (14%) in the group with IB $\geq 16\%$. Among all patients who experienced events, 11 (68.5%) had previously undergone revascularization: 9 via PCI (81%) and 2 via CABG (18%). The mean time between revascularization and the event was 8.3 months (range: 1 day–21 months), with 5 events occurring within the first month after the procedure.

Conclusion: The presence of severe myocardial ischemia with a left ventricular mass IB $\geq 16\%$ was associated with a higher indication for coronary angiography and revascularization. The incidence of major events during follow-up was low, limiting the ability to draw prognostic conclusions and highlighting the need for additional studies with a larger number of patients and longer follow-up.

Key words: Myocardial perfusion - Gated-SPECT - Ischemic burden - Coronary artery disease

RESUMEN

Introducción: La cardiopatía isquémica (CI) es una de las principales causas de muerte y discapacidad. Diversos estudios han demostrado que los pacientes con angina e isquemia miocárdica grave evidenciada mediante estudios funcionales presentan una evolución clínica desfavorable, con mayor riesgo de eventos cardiovasculares y mortalidad.

Objetivos: Analizar la conducta adoptada por los médicos tratantes (invasiva vs conservadora) en pacientes con un monto isquémico (MI) igual o superior al 10% de la masa del ventrículo izquierdo en un estudio de perfusión miocárdica (PM) con SPECT (tomografía computarizada por emisión de fotón único) gatillado, así como explorar si valores de isquemia mayores (punto de corte en 15%) influyen significativamente en esta decisión.

Identificar variables clínicas y/o funcionales que se asocian con la decisión de adoptar una estrategia invasiva inicial.

Comparar la incidencia de eventos cardiovasculares (infarto agudo de miocardio, angina inestable, reinternación por causa cardiovascular, insuficiencia cardíaca, arritmias y muerte de causa cardiovascular) en el seguimiento a largo plazo en los pacientes tratados médicamente y aquellos sometidos a revascularización.

Material y métodos: Estudio retrospectivo, observacional y unicéntrico. Se seleccionaron pacientes consecutivos entre enero de 2021 y diciembre de 2024 derivados para la realización de estudio de PM con SPECT gatillado, con MI mayor o igual a 10% (n=142),

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dividiéndolos en dos cohortes: 1) MI $\geq 16\%$ (n=50, el 35,2%) y 2) MI 10-15% (n=92, el 64,8%).

Resultados: La proporción de pacientes estudiados con estrategia invasiva inicial fue mayor en el grupo con MI $\geq 16\%$ (84 % vs 68,4 %, p=0,044). Se registraron eventos cardiovasculares mayores en 16 pacientes (11,4 %), 9 (7%) en el grupo con MI entre 10–15 % y 7 (5%) en el grupo con MI $\geq 16\%$; p= 0,476. Del total de pacientes con eventos, 11 (68,5%) habían sido revascularizados previamente: 9 mediante angioplastia y 2 mediante cirugía. El tiempo medio entre la revascularización y el evento fue de 8,3 meses (rango: 1 día–21 meses), con 5 eventos dentro del primer mes posterior a la intervención.

Conclusión: La presencia de isquemia miocárdica grave con un monto isquémico $\geq 16\%$ de la masa del VI se asoció a mayor indicación de cinecoronariografía y revascularización. La incidencia de eventos mayores durante el seguimiento fue baja, lo que limita la posibilidad de establecer conclusiones pronósticas y resalta la necesidad de estudios adicionales con mayor número de pacientes y seguimiento prolongado.

Palabras clave: Perfusión miocárdica - SPECT gatillado - Monto isquémico - Enfermedad coronaria

INTRODUCTION

Ischemic heart disease (IHD) is one of the leading causes of death and disability. (1) According to data from the Pan American Health Organization (PAHO), approximately 73.6 deaths per 100 000 inhabitants are recorded annually. (2)

The primary goals of IHD treatment are to improve symptoms, quality of life, and prognosis. In addition to optimal medical therapy (OMT) and control of cardiovascular risk factors (CVRF), myocardial revascularization, whether through percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), represents another therapeutic strategy in selected patients. (3,4)

Several studies have shown that patients with angina and severe myocardial ischemia, as evidenced by functional tests, have an unfavorable clinical course, with an increased risk of cardiovascular events and mortality. (5,6) Consequently, in clinical practice, these patients are classified as “high clinical risk”, leading to a medical decision favoring an initial invasive strategy in many cases.

Classic studies such as that of Hachamovitch et al. (7) demonstrated a benefit from revascularization in patients with myocardial ischemic burden (IB) $\geq 10\%$. However, other clinical studies, -the most recent of which was the ISCHEMIA trial (8)- did not demonstrate a significant reduction of events in patients with moderate to severe ischemia when comparing an initial invasive strategy vs. OMT. These findings imply a shift in the interpretation of IB and, in clinical practice, its value within the decision-making process is being reevaluated.

Furthermore, contemporary registries have shown that the classic threshold for high-risk ischemia may shift toward 14–15% values in populations treated with current medical therapies. (9).

In this context, the objectives: of the present study were:

Primary objective

To analyze the approach adopted by treating physicians (invasive vs. conservative) in patients with a left ventricular mass IB $\geq 10\%$ on a gated-SPECT myocardial perfusion (MP) study, and to determine whether

higher ischemia values (cutoff point at 15%) significantly influence this decision.

Secondary objectives

To identify clinical and/or functional variables associated with the decision to perform an initial invasive strategy, and to compare the incidence of cardiovascular events (acute myocardial infarction, unstable angina, readmission for cardiovascular causes, heart failure, arrhythmias, and cardiovascular death) during long-term follow-up between patients treated medically and those who underwent revascularization.

METHODS

Study Population

A retrospective, observational, single-center study was conducted, including consecutive patients referred for a gated-SPECT MP study between January 2021 and December 2024.

Inclusion criteria: IB $\geq 10\%$ established on the SPECT study

Exclusion criteria: Inability to conduct long-term follow-up due to loss of contact via telephone or electronic records through the City of Buenos Aires hospital management system (SIGEHOS).

For the analysis, the cohort was stratified into two subgroups based on the IB:

- Ischemia 10–15%
- Ischemia $\geq 16\%$

Follow-up was conducted via telephone contact and review of electronic medical records through SIGEHOS, with a median follow-up of 18 months. Symptoms were assessed, and cardiovascular events were recorded based on the treating cardiologist's interpretation in the medical record, including acute myocardial infarction, unstable angina, readmission for cardiovascular causes, heart failure, arrhythmias, and death from cardiovascular causes. Patients were registered as either being referred to invasive testing with coronary angiography (CA) or continuing with medical therapy alone. For those undergoing CA, the occurrence of subsequent revascularization (PCI or CABG) was documented. Coronary angiography without lesions was defined as studies reported “without angiographically significant lesions” or with previously treated vessels that were found to be patent.

Acquisition protocol for gated-SPECT MP study

A one-day protocol was performed using technetium-99m methoxyisobutylisonitrile (99mTc-MIBI) during stress and

at rest with a Philips Brightview XCT 882482 gamma camera. Images were acquired 30 to 45 minutes after an intravenous injection at rest, and 15 to 20 minutes after maximum exercise. The administered activity was 8–12 mCi for the first injection (at rest or during stress) and 24–36 mCi for the second injection (during stress or at rest), in accordance with the guidelines of the American Society of Nuclear Cardiology (ASNC). (10) Patients who performed exercise did so to the point of symptom onset, according to the Astrand protocol on a cycle ergometer. (11) In patients who received pharmacological stress testing, dipyridamole was administered intravenously at a dose of 0.56 mg/kg over a 4-minute period, with the radiotracer injected 3 minutes after injection, in accordance with the ASNC guidelines.

Image Analysis and Quantification

SPECT analysis was performed according to the left ventricular 17-segment model of the American Heart Association (12). Segments were scored from 0 to 4 based on tracer activity in each segment. Perfusion quantification was achieved using the sum of the stress score (SSS), the rest score (SSR) and the differential score (SD). The ischemic and necrotic volumes were estimated by dividing the differential and rest scores, respectively, by 68 for the 17-segment model. Severe myocardial ischemia was defined as a left ventricular (LV) mass IB $\geq$ than 10%. (7,9) The analysis was performed visually by three independent observers (OM / JH / LB), and in the event of disagreement, a consensus was reached.

Ventricular dysfunction based on left ventricular ejection fraction (LVEF), was classified as mild (49–54%), moderate (35–48%), and severe ($<35\%$). Ventricular dilation was defined as an end-systolic volume (ESV) $>45\text{mL/m}^2$ and/or an end-diastolic volume (EDV) $>70\text{mL/m}^2$. (13). Transient ischemic dilation (TID), defined as a stress/rest volume ratio ≥ 1.22 , was also analyzed. (14)

Statistical Analysis

Categorical variables were expressed as absolute frequencies and percentages and were compared between groups using the chi-square test and the test for difference in proportions. When the expected value in any of the cells was less than 5, the continuity correction or Fisher's exact test was used, as appropriate.

Continuous variables were expressed as mean $\pm$ standard deviation or median and interquartile range (IQR), depending on data distribution. Continuous variables were compared using Student's t-test or the Mann-Whitney test, as appropriate.

To identify independent variables associated with the behavior of treating physicians, a multivariate logistic regression analysis was performed, which included the variables identified in the univariate analysis.

A p-value <0.05 was considered statistically significant. Statistical calculations were performed using Epi Info™.

Ethical Considerations

This study was approved by the Institutional Ethics Committee, and patients' personal data were protected.

All procedures were conducted in accordance with the ethical principles established in the Declaration of Helsinki. (15)

RESULTS

A total of 3051 patients, of whom 177 (5.8%) had severe myocardial ischemia were analyzed, and 142 (80%) met the inclusion criteria for the final analysis. Median IB was 14% (IQR: 11.5–17%). Ninety-two patients (64.8%) had an IB between 10% and 15%, and 50 patients (35.2%) an IB $\geq 16\%$.

Baseline and stress test clinical characteristics are presented in Tables 1 and 2. In the gated-SPECT MP study, 6 patients (4.2%) showed increased ESV, and 7 (5%) increased EDV. The decrease in LVEF was mild in 28 patients (20.1%), moderate in 28 (20.1%), and severe in 10 (7.1%). Transient ischemic left ventricular dilation (TID) was detected in 14 patients (10%), and a post-stress decline in LVEF was observed in 22 (15.7%). The comparison between the two IB groups revealed no statistically significant differences.

Of 142 patients analyzed, 105 (73.9%) underwent CA at the discretion of the treating physician. The proportion of patients studied was higher in the IB $\geq 16\%$ group than in the IB 10–15% group (84% vs. 68.4%, $p=0.044$). (Figure 1). No statistically significant associations predicting the indication for CA were identified. However, a trend toward a higher rate of indication was observed in symptomatic patients (OR 2.18; 95% CI 0.98–4.86; $p=0.056$). (Figure 2)

In the angiographic analysis, 19 patients (18.1%) had no significant lesions.

Fifty-six patients (53.3%) of those studied with CA underwent revascularization via PCI or CABG. The revascularization rate was significantly higher in the group with IB $\geq 16\%$ than in the group with IB 10–15% (65% vs. 32.6%, $p=0.001$).

Among the 142 patients, 80 (56.3%) were initially symptomatic; of these, 65 patients (81.2%) were referred for an initial invasive strategy (OR 2.22; 95% CI 1.03 to 4.79; $p=0.004$). Among them, 34 (52.3%) underwent revascularization and 21 remained asymptomatic after revascularization (OR 2.24; 95% CI 0.83–6.03; $p=0.282$).

Over a median follow-up of 18 months, major cardiovascular events were recorded in 16 patients (11.4%); 9 out of the 92 patients with IB between 10–15% (9.8%) and 7 out of the 50 patients with IB $\geq 16\%$ (14%), $p=0.476$. Patients who underwent revascularization had a higher event rate compared with those in the non-invasive arm (19.6% vs. 4.3%; OR 5.43; 95% CI 1.75–16.8; $p=0.015$). Events occurred with a median time between revascularization and the event of 8.3 months (range: 1 day–21 months) nearly half of the time (5/11 events), and they took place within the first month following the procedure, which could be linked to periprocedural complications.

DISCUSSION

This study analyzed the therapeutic approach adopted by treating physicians in the presence of severe myocardial ischemia ($\geq 10\%$ of LV mass) assessed by gated-SPECT MP study, and clinical outcomes were

Table 1. Population characteristics

	IB ≤15% (n=92)	IB ≥16% (n=50)	p
Baseline variables	n (%)	n (%)	
Male sex	78 (84.8)	44 (88)	0.784
Smoking	25 (27.8)	8 (16)	0.194
Former smokers	37 (40.2)	29 (58)	0.064
Hypertension	69 (75)	35 (70)	0.656
Diabetes mellitus	32 (34.8)	17 (34)	1
Dyslipidemia	48 (52.2)	32 (64)	0.237
Family history	6 (6.5)	2 (4)	0.809
Kidney Failure	1 (1.1)	1 (2)	1
HIV	6 (6.5)	3 (6)	1
Autoimmune disease	4 (4.3)	1 (2)	0.803
Previous AMI	41 (44.6)	17 (34)	0.296
Previous PCI	35 (38)	14 (28)	0.308
Previous CAGB	15 (16.3)	6 (12)	0.658
ACEI	35 (38)	21 (42)	0.778
Beta-blockers	72 (78.3)	39 (78)	1
Calcium channel blockers	9 (9.7)	4 (8)	0.962
Aspirin	70 (76.1)	42 (84)	0.374
IIB IIIA inhibitors	20 (21.7)	13 (26)	0.714
Statins	66 (71.7)	34 (68)	0.784
Nitrites	8 (8.6)	2 (4)	0.483

ACEI: angiotensin-converting enzyme inhibitors; AMI: acute myocardial infarction; CAGB: coronary artery bypass grafting; HIV: human immunodeficiency virus; IB: ischemic burden; MP: myocardial perfusion; PCI: percutaneous coronary intervention.

Table 2. Data from the myocardial perfusion study

	IB ≤15% (n=92)	IB ≥16% (n=50)	p
Stress characteristics	n (%)	n (%)	
Type of physical stress	68 (73.9)	44 (88)	0.080
Angina during exertion	12 (13)	11 (22)	0.252
Shortness of breath on exertion	11 (11.9)	3 (6)	0.399
ST-segment depression	12 (13)	12 (24)	0.152
ST-segment depression and angina	4 (4.3)	7 (14)	0.084
Arrhythmias	12 (13)	7 (14)	1

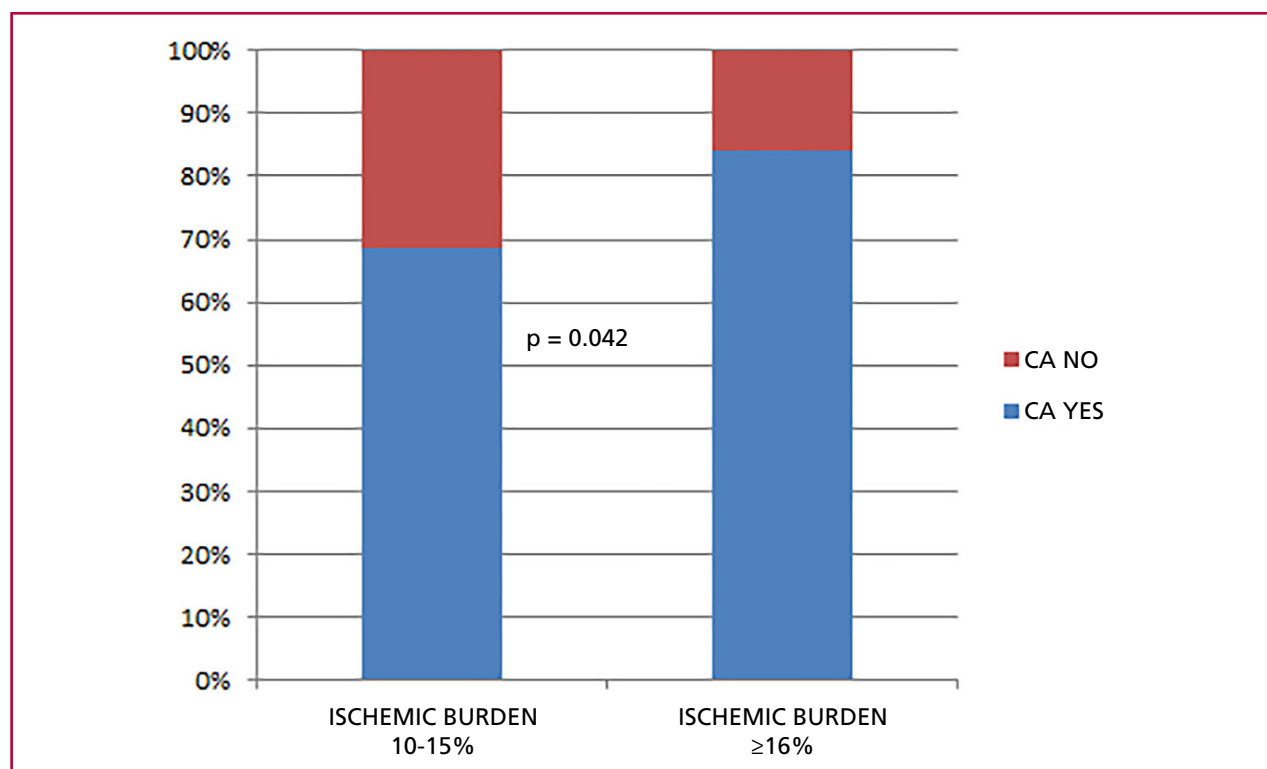
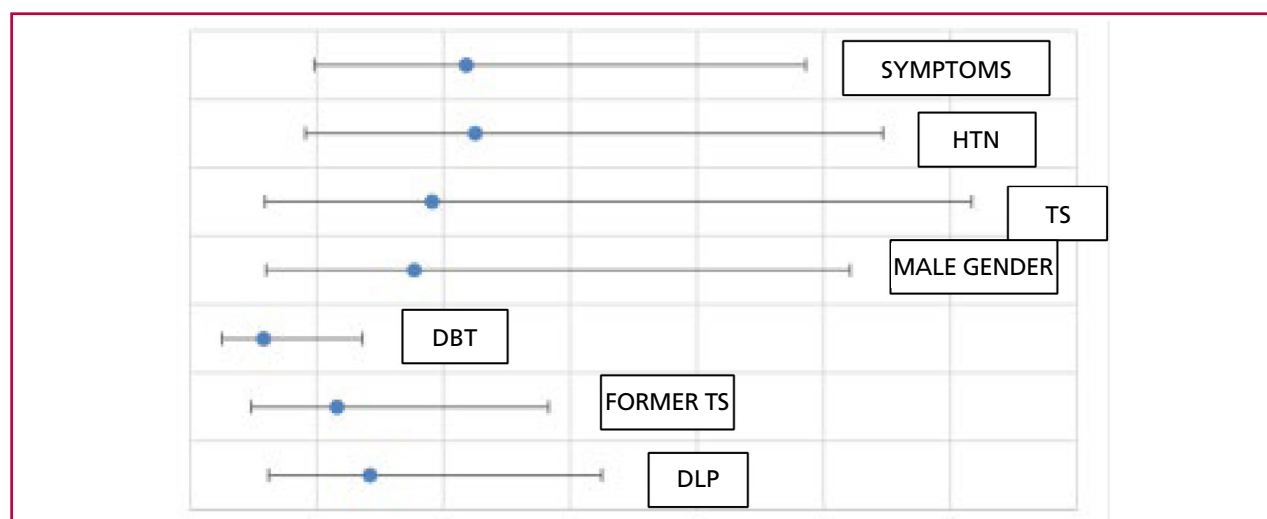
IB: ischemic burden

compared according to the chosen strategy (invasive vs. conservative). Our results provide insight into current clinical practice and its agreement with evidence derived from major clinical trials on stable coronary artery disease.

In this cohort, the prevalence of severe myocardial ischemia was 5.8%, a figure comparable to that reported in other series, where it ranges from 5–10%. (7) Median IB was 14%, similar to the threshold used in studies such as COURAGE (nuclear substudy) and

ISCHEMIA to define high risk. (8,16) In our population, although the presence of severe ischemia was rare, its detection was clinically relevant due to its association with a greater indication for invasive testing and a higher revascularization rate.

We observed a trend in decision-making related to the extent of ischemia and the choice of invasive procedures: patients with IB ≥16% were more frequently referred for diagnostic coronary angiography (84% vs. 68.4%, $p=0.044$) and for revascularization

Fig. 1. Coronary angiography (CA) based on ischemic burden in the perfusión study**Fig. 2.** Multivariate analysis of other predictor variables of initial invasive strategy- OR and 95% CI

DBT: diabetes; DLP: dyslipidemia; HTN: hypertension; TS: tobacco smoking

(65% vs. 32.6%, $p=0.001$) compared with those with IB 10–15%.

Another point worth noting is that clinical decisions were not based exclusively on the findings of the MP study. Symptoms, especially the presence of angina or equivalent symptoms, played a significant role in the indication for CA, as reflected in the observed

trend toward greater intervention in symptomatic patients.

The ISCHEMIA study evaluated whether an initial invasive strategy in patients with moderate-severe ischemia provided additional benefit compared with OMT. In the medium term, the invasive strategy did not significantly reduce major cardiovascular

events or overall mortality, although it did improve symptoms and quality of life in the most symptomatic patients. In our population, we observed partial similarities: while IB was a factor for indicating CA and revascularization, the presence of symptoms also played an important role in decision-making. However, when we conducted a methodological analysis of the ISCHEMIA trial, we identified some differences with our population. First, patients with LVEF <30%, who are potential candidates for revascularization in the presence of myocardial viability, were excluded. On the other hand, 34% of the patients were symptomatic, unlike our cohort, in which symptomatic patients predominated at the time of the study (56.3%). Furthermore, 26% of the patients assigned to OMT were crossed over to an invasive strategy. Another aspect to consider is that in the ISCHEMIA study there was no stratification by IB, but by a general classification of ischemia based on various criteria, including even patients with positive exercise testing without imaging, which prevented quantification of the actual IB. Conversely, in our population, only patients with ischemia $\geq 10\%$ -objectively measured by gated-SPECT MP study- were included.

On the other hand, the PROMISE study provided a complementary perspective by showing that the use of anatomical angiotomography studies as an initial diagnostic tool in symptomatic patients with suspected coronary artery disease does not necessarily lead to better clinical outcomes compared with noninvasive studies. (17) In our series, all the patients included were evaluated by gated-SPECT MP study, and a significant subgroup (18.1%) had coronary arteries without angiographically significant lesions, which could reflect the presence of microvascular disease.

Regarding clinical outcomes, the incidence of major cardiovascular events was relatively low during follow-up (11.4%), which limits the ability to draw conclusions about the prognostic impact of the different strategies. However, it is noteworthy that most events (68.5%) occurred in patients who had previously undergone revascularization, and that nearly half occurred within the first month following the procedure, which likely reflects the anatomical and clinical complexity of these cases.

The absence of a significant reduction in events in the invasively treated group is consistent with the ISCHEMIA trial findings, which demonstrated that an initial invasive strategy did not reduce major events in stable patients with moderate or severe ischemia, although it was associated with symptom improvement in certain subgroups. In our cohort, symptomatic improvement was more common in patients with previous revascularization, although this did not reach statistical significance, possibly due to the sample size in the subgroup analysis.

Recently, results from the ISCHEMIA-EXTENDED study, with a follow-up of up to 7 years, showed a trend toward lower cardiovascular mortality in the

invasive arm, which reopens the debate on the long-term impact of these strategies. (18) As previously noted, although our study was not designed to evaluate mortality as a primary endpoint, the incidence of major events was low and no significant differences were observed between the groups based on initial treatment.

In turn, the COURAGE study had raised similar questions years earlier, showing that in patients with stable coronary artery disease, PCI plus OMT did not offer greater benefit in preventing major events compared with OMT alone. (19) Our observation that 60% of patients with severe ischemia were not revascularized suggests that, in clinical practice, physicians have already come to recognize that revascularization does not always alter the prognosis, reserving it for more symptomatic subgroups or those with high-risk anatomical disease.

Based on our observations and in line with the results of some previous studies (7, 18, 20), the classic definition of severe ischemia ($>10\%$ of LV) may not constitute an optimal cutoff point for guiding therapeutic management. As previously mentioned, in our study, treating physicians tended to recommend an invasive strategy for patients with IB $\geq 16\%$, which could suggest the need to review and validate higher cutoff points for defining severe ischemia in gated-SPECT MP studies, this threshold probably being a more appropriate value when selecting an invasive strategy in current clinical practice.

Our results highlight the importance of contextualizing the information derived from gated-SPECT MP studies within a comprehensive clinical framework, considering that a high IB is associated with a stronger indication for revascularization, that there is a subgroup with angiographically normal coronary arteries that may be due to microvascular disease, and that symptoms remain a key determinant in decision-making. (21) However, the low number of recorded events calls for caution in interpreting the prognostic implications and highlights the need for larger studies with longer follow-up.

Limitations

This is a retrospective, observational, single-center study. The short follow-up period may underestimate the actual incidence of events. Twenty percent of patients were lost to follow-up.

CONCLUSION

In this population, the presence of severe myocardial ischemia with left ventricular mass IB $\geq 16\%$ was associated with a higher indication for coronary angiography and revascularization. Our findings reflect that in clinical practice, therapeutic decisions tend to be individualized, considering both the IB and the patient's clinical presentation. The incidence of major events during follow-up was low, which limits the ability to draw prognostic conclusions and highlights the need

for additional studies with a larger number of patients and prolonged follow-up.

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Conflicts of interest

None declared.

(See authors' conflict of interests forms on the web).

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