ORIGINAL ARTICLE

VIA MEDICA

Clinical characteristics and prognosis of myocardial infarction with non-obstructive coronary arteries: A prospective single-center study

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Abstract

Background: *A definition of myocardial infarction with non-obstructive coronary arteries (MINOCA) was published by European Society of Cardiology in 2016. The aim of this study is to analyze the clinical profile and prognosis of these patients in a prospective single-center study and compare it with the literature data.*

Methods: *During a 3-year period, information from every consecutive MINOCA patient was gathered (n = 109). It was then compared with 412 contemporaneous patients with myocardial infarction and obstructive coronary arteries (MIOCA). Univariate and multivariate analyses were performed. Prognosis analysis was adjusted by age and cardiovascular risk factors (CVRF).*

Results: *MINOCA represented 16.9% of the total of patients admitted for myocardial infarction (MI). Compared with MIOCA, they had more psychosocial disorders (22.9% vs. 10.7%; p < 0.01) and more pro-inflammatory conditions (34.9% vs. 14.0%; p < 0.01). Atrial fibrillation was twice as frequent in MINOCA (14.7% vs. 7.3%; p = 0.016). Predictors of MINOCA were as follows: female gender, absence of diabetes, absence of tobacco use, tachycardia, troponin above 10 times the 99th percentile, and pro-inflammatory conditions. Median follow-up was 17.3 ± 9.3 months. Major adverse cardiovascular events (MACE; a composite of a recurrence of acute MI, transient ischemic attack/stroke, or death from cardiovascular cause and death from any cause) occurred in 10.8% of the MINOCA group as compared with 10.7% in the MIOCA group (hazard ratio [HR] 1.19, 95% confidence interval [CI] 0.58–2.45; p = 0.645). Cardiovascular re-admission rates were higher in the MINOCA group: 19.8% vs. 13.9% (HR 1.85; CI 1.06–3.21; p = 0.030).*

Conclusions: *The frequency of MINOCA is high, with fewer CVRF, and it is linked to atrial fibrillation, psychosocial disorders, and pro-inflammatory conditions. Mid-term prognosis is worse than previously thought, with a similar proportion of MACE as compared to MIOCA, and even a higher rate of cardiovascular re-admissions.* (Cardiol J 2022; 29, 5: 798–806)

Key words: myocardial infarction with non-obstructive coronary arteries (MINOCA), prognosis, definition, proinflammatory, atrial fibrillation
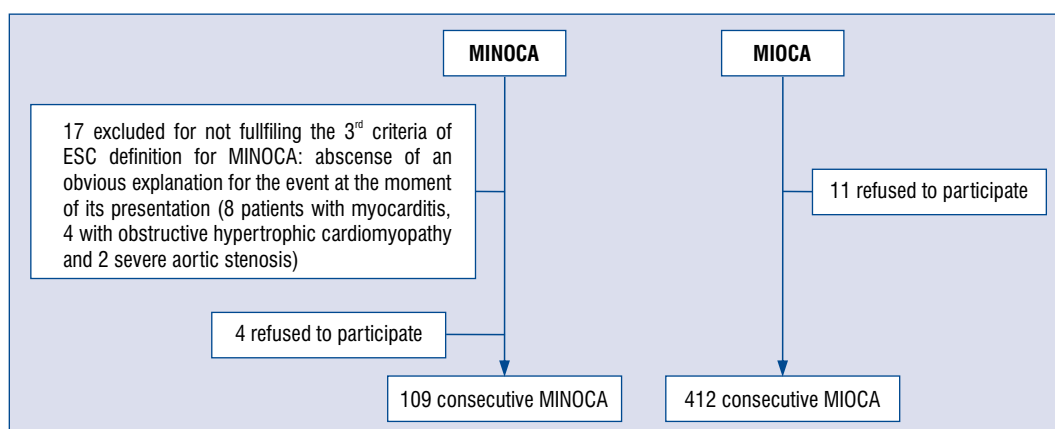
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Figure 1. Formation of the cohorts; MINOCA — myocardial infarction with non-obstructive coronary arteries; MIOCA — myocardial infarction with obstructive coronary arteries; ESC — European Society of Cardiology.

Introduction

Coronary atherosclerosis and its complications play a crucial role [1] in the majority of acute coronary syndromes. Nevertheless, there is a subgroup of patients with acute myocardial infarction (AMI) in which coronariography shows non-obstructive coronary arteries. These patients are denominated under the acronym of MINOCA (myocardial infarction with non-obstructive coronary arteries). In extensive epidemiological studies, they represent between 5% and 14% of all AMIs [2–6]. This entity affects younger patients with fewer cardiovascular risk factors (CVRF), mainly women [3, 6, 7], and in some cases these were related with psychosocial disorders [8, 9]. Its prognosis remains controversial [2–5, 10–14], as well as its optimal treatment [4, 5, 8, 15]. The only solid recommendation is to treat the specific physiopathological mechanism when it can be identified. Clinical conditions predicting major adverse cardiovascular events (MACE, a composite of a recurrence of AMI, transient ischemic attack [TIA]/stroke, or death from cardiovascular cause and death from any cause) and mortality of MINOCA patients are similar to those already known in patients with AMI and obstructive coronary arteries [16].

In daily practice, MINOCA remains a challenge, with low use of evidence-based medicines [5] due to lack of clear information. The main reason for this is the absence of a standard definition, making comparison between the studies impossible [2, 3, 11, 12] due to the heterogeneity of the inclusion criteria [5, 10, 16, 17]. In 2016 the European Society of Cardiology (ESC) published a Position Paper on MINOCA [4]. It defined it

as a "working diagnosis" to start searching the underlying mechanism in each patient. The ESC has clearly and precisely established the criteria for classifying a patient as a MINOCA, which is a remarkable step in this field. This definition is the one used in recent ESC guidelines [18] and consensus documents, including the 4th Universal Definition of Myocardial Infarction [19].

The aim of this prospective single-center study is to analyze the clinical profile, predictors, and prognosis of MINOCA based on the ESC criteria compared to patients with AMI and obstructive coronary arteries.

Methods

A prospective analytical study of cohorts performed in a University General Hospital that covers a population of 220,000 inhabitants.

Population of the study

All consecutive patients admitted for AMI during a 3-year period (from 1st January 2016 to 31st December 2018) were recorded (Fig. 1). Two cohorts were made: one with those who fulfilled the MINOCA criteria (Table 1) and the other one with the remaining AMI patients. MINOCA was defined according to the ESC Position Paper on MINOCA [4]: AMI according to the 3rd Universal Definition of Myocardial Infarction (which equals to type 1 MI in the 4th Universal Definition of Myocardial Infarction) [19, 20]; and coronary arteries without significant angiographic obstruction (less than < 50% of stenosis). In addition to this, there could not be any other obvious explanation for the event at the moment of its presentation.

Table 1. Inclusion and exclusion criteria for myocardial infarction with non-obstructive coronary arteries (MINOCA) according to European Society of Cardiology position paper.

Inclusion criteria
AMI criteria
Positive cardiac biomarker (preferably cardiac troponin) defined as a rise and/or fall in serial levels, with at least one value above the 99th percentile upper reference limit
+
Corroborative clinical evidence of infarction shown by at least one of the following: — Symptoms of ischemia   — New or presumed new significant ST-T changes or new LBBB   — Development of pathological Q waves   — Imaging evidence of new loss of viable myocardium or new RWMA   — Intracoronary thrombus evident on angiography or at autopsy
Non-obstructive coronary arteries on angiography. This includes both patients with: — Normal coronary arteries (no stenosis or < 30%) or   — Mild coronary atheromatosis (stenosis > 30% but < 50%)
Exclusion criteria
Alternative cause for the acute presentation   — Suspected myocarditis at admission   — Suspected pulmonary thromboembolism
Acute myocardial injury   Elevated troponin value above the 99th percentile (with a rise and/or fall of troponin value) but without clinical or electrocardiographic evidence of acute myocardial ischemia

LBBB — left bundle branch block; RWMA — regional wall motion abnormality

This point was confirmed in every case during a thorough review carried out by trained cardiologists. Patients who suited the new definition of myocardial injury [19] were excluded.

As a control group, we used the second cohort consisting of 412 consecutive patients admitted with AMI and obstructive coronary arteries (MIOCA) during the same period.

Based on previous data, around 10% of AMI patients will be MINOCA. Above 400 patients will be sufficient if we assume a rate of events in the first year of 13% in MIOCA and 5% in MINOCA (alpha error of 0.05 and power of 0.80).

All patients provided written informed consent. The study was approved by the institutional review board and followed the tenets of the Declaration of Helsinki.

Variables

Standardized forms were used to set up the database, including demographic information, epidemiological data, and relevant clinical information. Socio-economic aspects that could act as emotional stress modulators were also registered, as well as psychosocial disorders (a compound of previously diagnosed psychiatric disease {According to Diagnostic and Statistical Manual of Mental Disorders, fifth edition, [21]} and/or chronic anxiety treatment) and migraine. Data involving pro-inflammatory conditions were also collected: the presence of active cancer, autoimmune diseases, or the fact that AMI was an intercurrent complication during hospitalization for another pathology. The main laboratory results (Siemens Healthcare Diagnostic, Erlangen, Germany) were peak creatinine kinase, troponin T, and C-reactive protein.

According to current guidelines and previous reports [22], optimal medical treatment at discharge was considered when patients simultaneously received antiplatelets, statins, and angiotensin-converter enzyme inhibitors or angiotensin receptor blockers.

All in-hospital complications and death from any cause were registered. Follow-up analysis included the following: MACE, time to first readmission, and death from any cause. Follow-up data were based on clinical visits, institutional database, or telephone interviews.

Statistical analysis

Continuous variables are presented as means and standard deviations or as medians with interquartile range. Categorical variables are provided with percentages. Pearson χ^2 or Student's t-test and their non-parametric equivalent were used depending on the variable type. A two-sided p value of less than 0.05 was considered statistically significant. Characteristics at admission with a p value < 0.01 in the univariable comparison were included in a logistic regression model (as a block: enter method) to determining the presence of early predictors of MINOCA.

Survival analysis with Kaplan-Meier (using long-rank) was performed for each follow-up event between MINOCAs and AMI-coronary artery disease. Prognosis analysis was developed with multiple Cox regression models adjusted depending on age and CVRF. Odds ratios and hazard ratios (HR) are reported with 95% confidence intervals (CI).

Results

Clinical characteristics and in-hospital evolution

During the recruitment period, 644 consecutive patients were diagnosed with AMI. Coronariography was performed in 521 cases. Among those, 109 fulfilled the 2016 ESC definition of MINOCA, representing 16.9% of the AMI admitted at the hospital. The most common underlying mechanism in MINOCA was stress myocardiopathy (25.9%). In 13.4% plaque disruption was identified, 9.8% had positive vasospasm provocation test, 3.6% presented coronary emboli, and 0.9% coronary dissection. Almost 9% were diagnosed with type 2 AMI. In 30.8% the mechanism remained unclear despite all tests performed. Only 7.1% of the patients initially included in the working diagnosis of MINOCA were finally diagnosed with myocarditis.

Considering that this is the sole hospital for the sanitary population in the area (totaling 220,000), we can estimate an annual incidence of 36.3/MINOCA/year and an annual incidence tax of 0.17 MINOCA per 1000 inhabitants/year.

Table 2 summarizes baseline characteristics of both cohorts. Patients with MINOCA compared to those with MIOCA were more frequently women (51.4% vs. 21.8%; p < 0.001) and with a better cardiovascular risk profile: less diabetes (23.9% vs. 35.6%; p = 0.020) and lower smoking rates (40.3% vs. 65.5%; p < 0.001). Regarding the patients' age, MINOCA patients were non-significantly younger (64.6 ± 14.9 years and 66.7 ± 13.5 years, respectively; p = 0.171).

The prevalence of pro-inflammatory conditions (compound of autoimmune diseases, active cancer, and being AMI a complication intercurrent with hospitalization for another pathology) was higher in the MINOCA group: 34.9% vs. 14.0%; p < 0.001. The relationship was maintained with autoimmune diseases (17.4% vs. 8.0%; p < 0.004) and active cancer (10.1% vs. 3.4%; p < 0.004) on their own.

The atrial fibrillation rate was twice as frequent in the MINOCA group compared to the MIOCA group (14.7% vs. 7.3%; p = 0.016). Psychosocial disorders and migraine were higher in the MINOCA group: 22.9% vs. 10.7% (p = 0.001) and 10.1% vs. 4.1% (p = 0.015), respectively.

The main data regarding hospitalization are shown in Table 3. MINOCA patients had higher heart rate at presentation (89.2 ± 27.1 vs. 79.1 ± ± 17.7; p < 0.001). The main symptom was angina in 73.9% of MINOCA patients as compared with 82.8% in the MIOCA group (p = 0.027). MINOCA patients less frequently had an ischemic electrocardiogram pattern (new or presumed new significant ST-T changes or new left bundle branch block; 61.1% vs. 72.7%; p < 0.020). As Table 2 shows, cardiac necrosis biomarkers were lower in the MINOCA group. Left ventricular dysfunction was present in 33.8% of MINOCA group as compared to 31.5% of the MIOCA group (p = 0.659). None of the MINOCA patients was revascularized; regarding MIOCA group, 93.9% underwent percutaneous coronary intervention and 6.1% had bypass surgery.

In-hospital complications (re-infarction, major bleeding, stroke, cardiorespiratory arrest, pulmonary edema, or shock) occurred in 13.8% of the MINOCA patients and in 17.6% of the MIOCA group (p = 0.335). In-hospital mortality was non-significantly lower in MINOCA patients (0.9% vs. 3.4%; p = 0.167).

At discharge, double antiplatelet treatment was prescribed in 62.0% of MINOCA patients, as compared with 99.7% of the MIOCA patients (p < 0.001). There were also differences in the prescription of beta-blockers (60.2% vs. 86.8%, p < 0.001), angiotensin convertase enzyme inhibitors/angiotensin II receptor antagonists (59.3% vs. 78.2%, p < 0.001), and statins (58.3% vs. 95.7%, p < 0.001). Anticoagulation prescription was higher in the MINOCA group (22.2% vs. 10.1%; p < 0.001).

Predictors of MINOCA at admission

Six characteristics that could be determined at admission had independent association with MINOCA and can be used as early predictors: female gender, absence of diabetes, absence of tobacco use, tachycardia (100 bpm or above), troponin above 10 times 99-percentile (usual laboratory threshold), and the presence of a pro-inflammatory condition (autoimmune diseases, or active cancer, or AMI being a complication during hospitalization for another pathology). Details of the analysis are represented in Table 4.

Prognosis

Median follow-up was 17.3 ± 9.3 months. The time-to-event analysis is summarized in Figure 2. MACE occurred in 10.8% of the MINOCA group as compared with 10.7% in the MIOCA group (HR of 1.19, 95% CI 0.58–2.45; p = 0.645). Regarding individual components, cardiovascular mortality was non-significantly lower in the MINOCA group (2.8% vs. 5.1%; HR 0.54, 95% CI 0.12–2.36). Also, they had a non-significantly higher rate of TIA/ /stroke (3.0% vs. 0.8%; HR 2.89, CI, 0.52–16.13)

Table 2. Demographic profile, cardiovascular risk factors, proinflammatory conditions, and other comorbidities comparing both cohorts.

	MINOCA (n = 109)	MIOCA (n = 412)	p
Basal characteristics			
Age [years]	64.6 ± 14.9	66.7 ± 13.5	0.171
Female gender	56/109 (51.4)	90/412 (21.8)	< 0.001
Cardiovascular risk factors			
Hypertension	67/109 (61.5)	256/412 (62.1)	0.830
Diabetes	26/109 (23.9)	146/412 (35.6)	0.020
Dyslipidemia	49/109 (45.2)	223/412 (54.1)	0.090
Tobacco use	44/109 (40.3)	270/412 (65.5)	< 0.001
Pro-inflammatory conditions	38/109 (34.9)	58/412 (14.0)	< 0.001
Active cancer	11/109 (10.1)	14/412 (3.4)	0.004
Autoimmune diseases	19/109 (17.4)	33/412 (8.0)	0.004
AMI while hospitalization for other pathology	8/109 (7.3)	10/412 (2.4)	0.13
Other comorbidities			
Atrial fibrillation	16/109 (14.7)	30/412 (7.3)	0.016
Psychosocial disorders	25/109 (22.9)	44/412 (10.7)	0.001
Migraine	11/109 (10.1)	17/412 (4.1)	0.015

AMI — acute myocardial infarction; MINOCA — myocardial infarction with non-obstructive coronary arteries; MIOCA — myocardial infarction with obstructive coronary arteries

**Table 3.** Characteristics at admission and in-hospital complications.

	MINOCA (n = 109)	MIOCA (n = 412)	P
At admission			
Heart rate [bpm]	89.2 ± 27.1	79.1 ± 17.7	< 0.001
Systolic arterial pressure [mmHg]	140.7 ± 28.0	143.7 ± 30.1	
ST-segment elevation	26/109 (24.1)	166/412 (40.8)	0.001
ST-segment decrease or inversion of T wave	66/109 (61.1)	295/412 (72.7)	0.020
Laboratory			
Troponin T HS [ng/mL]	743.1 ± 1808.6	2856.2 ± 0	< 0.001
Hemoglobin [g/dL]	13.5 ± 2.1	14.2 ± 1.8	0.003
Creatinine [mg/dL]	1.1 ± 0.9	1.2 ± 1.1	0.467
Echocardiogram			
Left ventricular dysfunction	37/109 (33.8)	130/412 (31.5)	0.659
Severe left ventricular dysfunction	8/109 (7.4)	20/412 (4.5)	0.313
Moderate-severe valve disease	7/109 (6.4)	20/412 (4.8)	0.509
Pulmonary hypertension	5/109 (4.6)	27/412 (6.6)	0.436
In-hospital complications	15/109 (13.8)	72/412 (17.6)	0.335
Reinfarction	3/109 (2.8)	16/412 (3.9)	0.562
Major bleeding	2/109 (1.8)	13/412 (3.2)	0.453
Acute cerebrovascular accident	3/109 (2.8)	7/412 (1.7)	0.487
Cardio-respiratory arrest	0/109 (0.0)	15/412 (3.7)	0.042
Acute pulmonary edema	8/109 (7.3)	24/412 (5.9)	0.579
Cardiogenic shock	5/109 (4.6)	33/412 (8.1)	0.211
Mechanical complications	0/109 (0.0)	2/412 (0.5)	0.463
In-hospital mortality	1/109 (0.9)	14/412 (3.4)	0.167
Duration of hospitalization (days)	8.89 ± 13.1	6.91 ± 6.0	0.025

Severe left ventricle dysfunction is defined as ejection fraction < 30%; MINOCA — myocardial infarction with non-obstructive coronary arteries; MIOCA — myocardial infarction with obstructive coronary arteries

Table 4. Early predictors of myocardial infarction with non-obstructive coronary arteries by multivariable analysis.

	Odds ratio	95% CI	p
Female gender	2.60	1.50–4.51	0.001
Tobacco use	0.49	0.29–0.83	0.008
Diabetes	0.44	0.25–0.76	0.004
Pro-inflammatory conditions	2.32	1.33–4.05	0.003
Tachycardia at admission	2.32	1.27-–4.24	0.006
Troponin T peak > 10×p99	2.53	1.35–4.73	0.004

CI — confidence interval; pro-inflammatory conditions — active cancer, autoimmune diseases or acute myocardial infarction during other pathology hospitalization; 10×p99 — 10 times 99th percentile
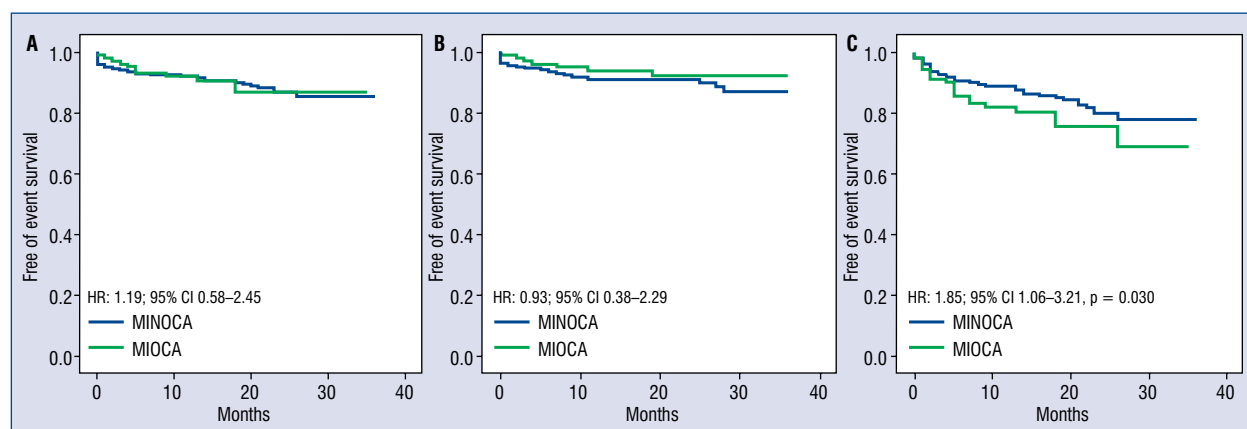
Figure 2. Kaplan-Meyer curves comparing both cohorts: myocardial infarction with non-obstructive coronary arteries (MINOCA) and myocardial infarction with obstructive coronary arteries (MIOCA); **A.** Major adverse cardiovascular events (cardiovascular death, transient ischemic attack/stroke, or re-infarction); **B.** All-cause mortality; **C.** Cardiovascular re-admissions; HR —hazard ratio adjusted by age and cardiovascular risk factors; CI — confidence interval.

and re-infarction (5.9% vs. 4.7%; HR 1.61, 95% CI 0.60–4.29). Cardiovascular re-admission rates were higher in the MINOCA group: 19.8% as compared with 13.9% in the MIOCA group (HR 1.85, 95% CI 1.06–3.21; p = 0.030).

Death from any cause occurred in 6.9% of MINOCA patients as compared with 9.3% in the MIOCA group (HR 0.93, 95% CI 0.38–2.29). The proportion of all-cause re-admission rates tended to be higher in the MINOCA group: 33.7% vs. 32.7% (HR 1.45, 95% CI 0.94–2.25; p = 0.097). Details regarding these analyses are provided in Table 5.

At the 1-year interview, 1.0% of MINOCA patients referred stable angina compared with 2.4% of the MIOCA patients (p = 0.337); at that moment, dyspnea worse than New York Heart Association II was present in 6.1% of the MINOCA vs. 9.6% of the MIOCA group (p = 0.268).

Discussion

The impact of MINOCA on daily clinical practice is high, representing 16.9% of all AMI in which coronariography is performed. This proportion is slightly higher than previously described [2, 3, 10–12] and may be related to the use of new ultra-sensitive troponin assay, even though cases of myocardial injury were not included. Improved early screening techniques and increased awareness are leading to increased MINOCA diagnoses [23].

This job is in line with previous studies by checking that patients with MINOCA are more frequently women [24] and have a better cardiovascular risk profile compared with MIOCA patients [3, 6, 7, 10, 12]. An interesting new point here is that the prevalence of atrial fibrillation is higher in

Table 5. Main findings at 12-month follow-up survival analysis adjusted by age and cardiovascular risk factors (hypertension, dyslipidemia, diabetes, and tobacco).

	MINOCA	MIOCA	HR	95% CI	P
MACE	10.8%	10.7%	1.19	0.58–2.45	0.645
CV re-admission	19.8%	13.9%	1.85	1.06–3.21	0.030
CV mortality	2.8%	5.1%	0.54	0.12–2.36	0.410
Re-infarction	5.9%	4.7%	1.61	0.60–4.29	0.341
TIA or stroke	3.0%	0.8%	2.89	0.52–16.13	0.226
Total mortality	6.9%	9.3%	0.93	0.381–2.29	0.880
Re-admission	33.7%	32.7%	1.45	0.94–2.25	0.097

CI — confidence interval; CV — cardiovascular; HR — hazard ratio; MACE — major adverse cardiovascular events (infarction, TIA/stroke or CV death); MINOCA — myocardial infarction with non-obstructive coronary arteries; MIOCA — myocardial infarction with obstructive coronary arteries; TIA — transient ischemic attack

MINOCA, a fact that could be related to coronary emboli as the physiopathological explanation in some cases.

Also, psychiatric diseases, migraine, and pro-inflammatory conditions are more frequent in the MINOCA group than in MIOCA. Previous studies proposed a connection between psychiatric diseases and MINOCA [25], specifically with takotsubo syndrome [8]. This was also checked in a sub-analysis of our group in which, even after excluding takotsubo syndrome patients from the analysis, MINOCA and psychosocial disorders remained associated [9]. Different mechanisms could explain this association: the most reasonable of which is the impact of emotional stress in sympathetic regulation [26], being catecholamine levels a fundamental player in the endothelial function regulation [27]. Direct catecholamine toxicity on cardiomyocytes has also been proposed [28]. Nociceptive mechanisms of migraine are thought to be in relation with vascular tone dysregulation [29], one of the feasible mechanisms underlying MINOCA.

A higher presence of pro-inflammatory conditions in MINOCA has recently been described [7] and points in the direction of new evidence about the interrelation between the immune system and ischemic heart disease. Some interesting studies have also been published in this field, like the CANTOS trial [30], reflecting the impact of immunomodulator therapies in cardiovascular risk; or the relation between influenza infection and AMI [31]. As for MINOCA, a hypersensitivity-associated AMI has also been described, known as Kounis syndrome [32].

It has been postulated that MINOCA patients have a better prognosis than MIOCA patients [3].

However, given the heterogeneity of the analyzed groups in previous studies, there are significant differences regarding the prognosis (between 3% and 8% of 1-year mortality) [3, 6, 10–12, 33]. One of the latest works [25] described a 1-year mortality of 4.7% while in other specific types of presentation (ST-segment elevation MINOCA) 1-year mortality was 7% [10]. In Spain [6] there was lower mortality at 3-year follow-up in patients with non-ST-segment elevation AMI and non-significant stenosis compared with those with significant stenosis, while in a more recent work [12] the described mortality was similar to those patients with one-vessel disease. Considerable differences in the inclusion criteria of these works should be taken into account.

This prospective study based on the standards of MINOCA definition shows that MINOCA prognosis could be worse than was previously thought. Despite a lower CVFR charge, MINOCA did not differ from MIOCA in terms of MACE events and had a higher number of cardiovascular re-hospitalizations. There was an excess of mortality in the MIOCA group, but, conversely, MINOCA patients had more re-infarction and TIA/stroke during follow-up. MINOCA may encompass milder mechanisms that confer a better prognosis, but could also lead to misdiagnosis in the index episode.

The daily importance of MINOCA is high, not only because of its incidence, but also for all the complex studies it requires for its correct characterization in order to adjust the proper treatment (intravascular imaging, magnetic resonance) [34, 35]. This causes a longer hospitalization and, consequently, an increment in the economic costs. Studies like this one would help to know better

the role of the working diangnosis of MINOCA in the future as well as helping to reveal independent predictors in these patients.

Limitations of the study

Apart from the inherent problems of an observational single-center study, this work has other limitations that must be outlined to provide a correct interpretation of the results: (1) It was conducted in a center with a modest recruitment capacity, so the recruitment period had to be prolonged for three years. This could lead to a reduction in the power of some analyses; (2) We had some financial limitations for performing exhaustive intravascular imaging. That affects the characterization of MINOCA patients whose mechanism was the transient complication of the atheroma plaque [35], and some of them could have been erroneously classified as an unknown mechanism; (3) The same argument applies to magnetic resonance (performed in only 34.3% of MINOCA patients). Despite this, economic restrictions are unfortunately a common factor nowadays, and this can reflect the daily clinical practice for many of hospitals. This improves the applicability of the results presented. Including all consecutive MINOCA patients may mitigate in part this limitation.

Conclusions

MINOCA represents a considerable proportion of all AMIs. Its clinical presentation is very similar to MIOCA, so it reinforces the idea of considering it as a "working diagnosis". These results are in agreement with most previous reports. However, mid-term prognosis may be worse than previously thought.

Patients with MINOCA have lower charge of traditional risk factors, but psychosocial disorders, pro-inflammatory conditions, atrial fibrillation, and migraine are more frequent among them. This study complements the study of MINOCA and provides some new data in this field that could improve the future management of these patients.

Conflict of interest: None declared

References

1. Libby P. Coronary syndromes. Circulation. 2001; 104(3): 365––372, doi: 10.1161/01.cir.104.3.365, indexed in Pubmed: 11457759.
2. Diver DJ, Bier JD, Ferreira PE, et al. Clinical and arteriographic characterization of patients with unstable angina without critical coronary arterial narrowing (from the TIMI-IIIA Trial). Am J Cardiol. 1994; 74(6): 531–537, doi: 10.1016/0002-9149(94)90739-0, indexed in Pubmed: 8074033.
3. Pasupathy S, Air T, Dreyer RP, et al. Systematic review of patients presenting with suspected myocardial infarction and nonobstructive coronary arteries. Circulation. 2015; 131(10): 861–870, doi: 10.1161/CIRCULATIONAHA.114.011201, indexed in Pubmed: 25587100.
4. Agewall S, Beltrame JF, Reynolds HR, et al. ESC working group position paper on myocardial infarction with non-obstructive coronary arteries. Eur Heart J. 2017; 38(3): 143–153, doi: 10.1093/eurheartj/ehw149, indexed in Pubmed: 28158518.
5. Bainey KR, Welsh RC, Alemayehu W, et al. Population-level incidence and outcomes of myocardial infarction with non-obstructive coronary arteries (MINOCA): Insights from the Alberta contemporary acute coronary syndrome patients invasive treatment strategies (COAPT) study. Int J Cardiol. 2018; 264: 12–17, doi: 10.1016/j.ijcard.2018.04.004, indexed in Pubmed: 29655952.
6. Cortell A, Sanchis J, Bodí V, et al. Infarto de miocardio sin elevación del ST con coronarias normales: predictores y pronóstico. Rev Esp Cardiol. 2009; 62(11): 1260–1266, doi: 10.1016/s0300-8932(09)73078-7.
7. Daniel M, Ekenbäck C, Agewall S, et al. Risk factors and markers for acute myocardial infarction with angiographically normal coronary arteries. Am J Cardiol. 2015; 116(6): 838–844, doi: 10.1016/j.amjcard.2015.06.011, indexed in Pubmed: 26251000.
8. Templin C, Ghadri JR, Diekmann J, et al. Clinical features and outcomes of takotsubo (stress) cardiomyopathy. N Engl J Med. 2015; 373(10): 929–938, doi: 10.1056/NEJMoa1406761, indexed in Pubmed: 26332547.
9. Pais JL, Izquierdo Coronel B, Galán Gil D, et al. Psycho-emotional disorders as incoming risk factors for myocardial infarction with non-obstructive coronary arteries. Cardiol J. 2018; 25(1): 24–31, doi: 10.5603/CJ.a2017.0139, indexed in Pubmed: 29240964.
10. Andersson HB, Pedersen F, Engstrøm T, et al. Long-term survival and causes of death in patients with ST-elevation acute coronary syndrome without obstructive coronary artery disease. Eur Heart J. 2018; 39(2): 102–110, doi: 10.1093/eurheartj/ehx491, indexed in Pubmed: 29029035.
11. Rossini R, Capodanno D, Lettieri C, et al. Long-term outcomes of patients with acute coronary syndrome and nonobstructive coronary artery disease. Am J Cardiol. 2013; 112(2): 150–155, doi: 10.1016/j.amjcard.2013.03.006, indexed in Pubmed: 23602693.
12. Redondo-Diéguez A, Gonzalez-Ferreiro R, Abu-Assi E, et al. Pronóstico a largo plazo de pacientes con infarto agudo de miocardio sin elevación del segmento ST y arterias coronarias sin estenosis significativa. Rev Española Cardiol. 2015; 68(9): 777–784, doi: 10.1016/j.recesp.2014.09.021.
13. Scally C, Rudd A, Dawson DK, et al. Persistent long-term structural, functional, and metabolic changes after stress-induced (takotsubo) cardiomyopathy. Circulation. 2018; 137(10): 1039––1048, doi: 10.1161/CIRCULATIONAHA.117.031841, indexed in Pubmed: 29128863.
14. Abdu FA, Liu Lu, Mohammed AQ, et al. Myocardial infarction with non-obstructive coronary arteries (MINOCA) in Chinese

patients: Clinical features, treatment and 1 year follow-up. Int J Cardiol. 2019; 287: 27–31, doi: 10.1016/j.ijcard.2019.02.036, indexed in Pubmed: 30826195.

15. Lindahl B, Baron T, Erlinge D, et al. Medical therapy for secondary prevention and long-term outcome in patients with myocardial infarction with nonobstructive coronary artery disease. Circulation. 2017; 135(16): 1481–1489, doi: 10.1161/circulationaha.116.026336.

16. Nordenskjöld AM, Baron T, Eggers KM, et al. Predictors of adverse outcome in patients with myocardial infarction with nonobstructive coronary artery (MINOCA) disease. Int J Cardiol. 2018; 261: 18–23, doi: 10.1016/j.ijcard.2018.03.056, indexed in Pubmed: 29563017.

17. Rakowski T, De Luca G, Siudak Z, et al. Characteristics of patients presenting with myocardial infarction with non-obstructive coronary arteries (MINOCA) in Poland: data from the ORPKI national registry. J Thromb Thrombolysis. 2019; 47(3): 462–466, doi: 10.1007/s11239-018-1794-z, indexed in Pubmed: 30565147.

18. Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2018; 39(2): 119–177, doi: 10.1093/eurheartj/ehx393, indexed in Pubmed: 28886621.

19. Thygesen K, Alpert JS, Chaitman BR, et al. Fourth Universal Definition of Myocardial Infarction (2018). Circulation. 2018; 1.

20. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. Eur Heart J. 2012; 33(20): 2551–2567.

21. Association AP. Diagnostic and statistical manual of mental disorders (DSM-5®). 2013. https://books.google.com/books?hl=es&lr=&id=-JivBAAAQBAJ&oi=fnd&pg=PT18&ots=ceTS_3JLwa&sig=Kd6JMNVB2iJ0slEyOGW2IRtbUL0 (cited 2019 Sep 8).

22. Iqbal J, Zhang YJ, Holmes D, et al. Optimal medical therapy improves clinical outcomes in patients undergoing revascularization with percutaneous coronary intervention or coronary artery bypass grafting. Circulation. 2015; 131(14): 1269–1277, doi: 10.1161/circulationaha.114.013042.

23. Agüero F, Marrugat J, Elosua R, et al. New myocardial infarction definition affects incidence, mortality, hospitalization rates and prognosis. Eur J Prev Cardiol. 2015; 22(10): 1272–1280, doi: 10.1177/2047487314546988, indexed in Pubmed: 25139771.

24. Gehrie ER, Reynolds HR, Chen AY, et al. Characterization and outcomes of women and men with non-ST-segment elevation myocardial infarction and nonobstructive coronary artery disease: results from the Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines (CRUSADE) quality improvement initiative. Am Heart J. 2009; 158(4): 688–694, doi: 10.1016/j.ahj.2009.08.004, indexed in Pubmed: 19781432.

25. Gu XH, He CJ, Shen L, et al. Association between depression and outcomes in chinese patients with myocardial infarction and non-obstructive coronary arteries. J Am Heart Assoc. 2019; 8(5): e011180, doi: 10.1161/JAHA.118.011180, indexed in Pubmed: 30803294.

26. Ghadri JR, Wittstein IS, Prasad A, et al. International Expert Consensus Document on Takotsubo Syndrome (Part I): Clinical Characteristics, Diagnostic Criteria, and Pathophysiology. Eur Heart J. 2018; 39(22): 2032–2046, doi: 10.1093/eurheartj/ehy076, indexed in Pubmed: 29850871.

27. Spieker LE, Hürlimann D, Ruschitzka F, et al. Mental stress induces prolonged endothelial dysfunction via endothelin-A receptors. Circulation. 2002; 105(24): 2817–2820, doi: 10.1161/01.cir.0000021598.15895.34, indexed in Pubmed: 12070106.

28. Shao Y, Redfors B, Ståhlman M, et al. A mouse model reveals an important role for catecholamine-induced lipotoxicity in the pathogenesis of stress-induced cardiomyopathy. Eur J Heart Fail. 2013; 15(1): 9–22, doi: 10.1093/eurjhf/hfs161, indexed in Pubmed: 23099354.

29. Asghar MS, Hansen AE, Kapijimpanga T, et al. Dilation by CGRP of middle meningeal artery and reversal by sumatriptan in normal volunteers. Neurology. 2010; 75(17): 1520–1526, doi: 10.1212/WNL.0b013e3181f9626a, indexed in Pubmed: 20975053.

30. Ridker PM, Libby P, MacFadyen JG, et al. Modulation of the interleukin-6 signalling pathway and incidence rates of atherosclerotic events and all-cause mortality: analyses from the Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS). Eur Heart J. 2018; 39(38): 3499–3507, doi: 10.1093/eurheartj/ehy310, indexed in Pubmed: 30165610.

31. Kwong JC, Schwartz KL, Campitelli MA, et al. Acute myocardial infarction after laboratory-confirmed influenza infection. N Engl J Med. 2018; 378(4): 345–353, doi: 10.1056/NEJMoa1702090, indexed in Pubmed: 29365305.

32. Kounis NG, Koniari I, Soufras GD, et al. The humble relation of kounis syndrome, MINOCA (myocardial infarction with nonobstructive coronary arteries) and MACE (major adverse cardiac events). Can J Cardiol. 2018; 34(8): 1089.e7, doi: 10.1016/j.cjca.2018.04.024, indexed in Pubmed: 30049360.

33. De Ferrari GM, Fox KAA, White JA, et al. Outcomes among non-ST-segment elevation acute coronary syndromes patients with no angiographically obstructive coronary artery disease: observations from 37,101 patients. Eur Heart J Acute Cardiovasc Care. 2014; 3(1): 37–45, doi: 10.1177/2048872613489315, indexed in Pubmed: 24562802.

34. Prasad A, Lerman A, Rihal CS. Apical ballooning syndrome (Tako-Tsubo or stress cardiomyopathy): a mimic of acute myocardial infarction. Am Heart J. 2008; 155(3): 408–417, doi: 10.1016/j.ahj.2007.11.008, indexed in Pubmed: 18294473.

35. Takahashi T, Okayama H, Matsuda K, et al. Optical coherence tomography-based diagnosis in a patient with ST-elevation myocardial infarction and no obstructive coronary arteries. Int J Cardiol. 2016; 223: 146–148, doi: 10.1016/j.ijcard.2016.08.026, indexed in Pubmed: 27537744.