**Predictors of poor clinical outcomes in patients with acute myocardial infarction and non-obstructed coronary arteries (MINOCA)**

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**Objective**. To assess the characteristics and prognosis of patients with myocardial infarction and non-obstructed coronary arteries (MINOCA).

**Methods.** MINOCA was defined as acute myocardial infarction (AMI) with angiographic coronary stenosis <50%.Cardiomyopathies and myocarditis were -*a priori-* excluded from the study.Stenosis <30% were considered normal coronary arteries (NCA); stenosis ≥30% but <50% were considered mild coronary artery disease (MCAD).Patients were subdivided in 3 groups: I) NCA (0 vessels; stenosis <30%);II) 1-2 vessels showing MCAD and III) MCAD in 3 vessels or the left main stem (LMS).

**Results**. From January 2006 to December 2014, 7935 consecutive AMI patients were entered into our institutional database;150 (2%) were diagnosed as having MINOCA.At a median follow-up of 7.1 years the composite end-point (cardiovascular death, AMI or acute coronary syndrome, heart failure, stroke) occurred in 23 patients (17.4%).Survival analysis showed no differences between NCA versus MCAD (p=0.781). When assessed by distribution of CAD, group III had a lower event-free survival compared to group I and group II, respectively 54±14%, 83±4% and 90±5% (p=0.001).In a multivariate model, only 3 vessel disease or LMS involvement (HR= 23.5, 95% CI 2.59-173.49, *P*=0.001) and high C-reactive protein at hospital admission (HR=1.47, 95% CI 1.06-2.07, *P=*0.005) were significant predictors of the study composite endpoint.

**Conclusions**. In patients with MINOCA, the presence of NCA or 1-2 vessel MCAD was associated with better long-term clinical outcomes compared with patients with MCAD affecting 3 vessels or the LMS.Increased CRP concentrations on hospital admission were also a marker of worse clinical outcome during follow-up.

**Keywords**: acute myocardial infarction; MINOCA; acute coronary syndrome; C-reactive protein; prognosis.

**1. Introduction**

It has been estimated that 1% to 13% of patients presenting to hospital with an acute myocardial infarction (AMI) have non-obstructed coronary arteries (MINOCA) at coronary angiography [1-4]. Patients with MINOCA represent a rather heterogeneous category of acute coronary syndrome and this may account for the wide variation in the incidence of MINOCA in different series [1-4]. Several pathogenic mechanisms have been suggested to underlie MINOCA but the condition continues to represent a diagnostic and therapeutic challenge for the cardiologist [4,5].

Little is known about the prognosis of MINOCA as few studies have assessed clinical outcome and most of them have included patients with myocarditis and patients with Takotsubo syndrome [4,5]. Moreover, even less prognostic information is available on patients with MINOCA whose etiologic diagnosis remains undefined (“idiopathic” MINOCA), which account for at least 20-25% of MINOCA patients [3,4]. In a recent Position Paper of the European Society of Cardiology (ESC) [5], the following criteria for diagnosis of MINOCA were proposed: 1) AMI according to the III universal definition of AMI [6]; 2) absence of ≥50% stenosis at angiography; 3) exclusion of other clinically overt specific etiologies. The authors subdivided MINOCA patients in two groups: a) normal coronary arteries (stenosis <30%); b) mild coronary atheromatosis (stenosis ≥ 30% but <50%).

The aim of this study is to assess the characteristics and the long-term prognosis of a contemporary cohort of patients with MINOCA.

**2. Methods**

2.1 Participants

The study cohort was derived from 7935 consecutive patients discharged from hospital with the diagnosis of AMI and who were systematically entered in the AMI registry of the Cardiology Department of Perugia University Hospital from 1th January 2006 to 31th December 2014. Patients were identified as having AMI according to the International Classification of Diseases, 10th Revision (ICD-10) codes: I21-I22-I23. We retrospectively analysed this source and selected patients with: (I) diagnosis of AMI; (II) coronary angiography within 48 hours from onset of symptoms; (III) absence of ≥50% coronary stenosis. Following the publication of the III universal definition of AMI, all patients in the database were reclassified in accordance with this definition [6]. 150 patients satisfied all selection criteria and were included in the study (Figure 1). Follow-up was carried out at regular outpatient visits and/or by telephone contact. Full follow-up data were available for 132 patients (88%). The study was approved by the local ethics committee and managed in accordance with Good Clinical Practice and the Declaration of Helsinki [7].

2.2 Data collection

Two researchers (G.C. and M.B.) independently double checked the information available on the database and when discrepancies arose these were discussed with a third senior researcher (I.T.) and sorted out by consensus. The following clinical variables were collected and assessed: a) medical history including hypertension, diabetes mellitus, hyperlipidaemia, smoking and CAD family history, presence of atrial fibrillation, chronic obstructive pulmonary disease (COPD), cerebrovascular disease and prior AMI; b) body mass index (BMI), systolic blood pressure and heart rate at admission; c) ECG, left ventricular ejection fraction (LVEF) at admission; d) blood test results including cardiac troponin and CK-MB peak concentrations, creatinine, haemoglobin, white blood cell count, C-reactive protein (CRP) and uric acid levels.

Patients were subdivided into two groups according to the extent of their CAD, as proposed by the recent ESC position paper on MINOCA [5**]**: patients with normal coronary arteries (NCA) (no stenosis or stenosis <30%) and patients with mild coronary artery disease (MCAD) when stenosis ≥30% but <50% were present. With regard to the distribution of CAD, patients were subdivided into 3 groups: I) 0 vessel disease (absence of stenosis ≥30%); II) 1-2 vessel disease, when MCAD was observed in 1 or 2 major coronary arteries and III) 3-vessel disease, when 3 vessels or the left main stem (LMS) showed MCAD.

2.3 Statistical methods

Continuous variables are expressed as mean (±SD) and categorical variables as percentages. We used chi-square tests and one-way ANOVA for statistical comparisons of clinical characteristics among groups. For the purpose of this study, the endpoint was represented by a composite of major adverse cardiovascular events (MACE) including: cardiovascular death, AMI or acute coronary syndrome (ACS), heart failure leading to hospitalization (HF), stroke. Death was considered as of cardiovascular origin unless obvious non-cardiac causes could be identified. Univariate analyses by Cox proportional hazards models were performed to assess the association between each variable (listed in Table 1) and outcome. Variables associated with the considered outcome with a P-value <0.10 were maintained in the multivariate model along with age and male sex, considered as relevant a priori. Multivariate analyses were performed using a backward-conditional selection procedure. Kaplan–Meier method was used to estimate survival probabilities for the combined endpoint. Differences between survival curves were analysed using the log-rank test. A P-value <0.05 was considered significant. Statistical analyses were performed using SPSS package version 23.0 (Chicago, IL, USA).

**3. Results**

Groups 1, 2 and 3 comprised 91, 45 and 14 patients, respectively. Clinical data are reported in Table 1. Hypertension (92.9% vs. 59.3%; p=0.015) and cerebrovascular disease (14.3% vs. 2.2%; p=0.028) were more frequent in group III compared with group I; family history of CAD was more frequent in group I compared with group II (14.3% vs. 2.2%; p=0.03); all other baseline characteristics were not significantly different among the 3 groups (Table 1, supplementary material).

There were no in-hospital MACE or deaths among the study patients. At follow-up (median 7.1 years, 1.5-10.4; minimum follow-up period 328 days), a total of 23 combined events had occurred (8 cardiovascular deaths, 7 AMI/ACS, 7 hospitalizations for heart failure, and 1 stroke). In group 1, 13 MACE occurred (5 cardiovascular deaths, 3 AMI/ACS, 4 hospitalizations for heart failure, and 1 stroke). In group 2, 4 MACE occurred (1 cardiovascular death, 1 AMI/ACS, 2 hospitalizations for heart failure). In group 3, 6 MACE occurred (2 cardiovascular deaths, 3 AMI/ACS, 1 hospitalization for heart failure). Rate of MACE is shown in the supplementary material section (Figure 1, supplementary material).

There was a non-statistically significant difference between patients who presented with STEMI and those with NSTEMI, with the latter showing more events during follow up (Log-Rank=1.530; p=0.216) (Figure 2A). Furthermore, there were no significant differences regarding MACE when patients with NCA and those with MCAD were compared (Log Rank=1.1; p=0.781) (Figure 2B).

Patients with MCAD affecting 3 vessels or the LMS (group III) had a lower event-free survival (54%± 14%) compared to patients in group I (83%±4%) and group II (90%±5%) (Log Rank= 12.383; p=0.001; Figure 2C). Furthermore, compared with group I, used as reference, group III displayed a strong association with an impaired clinical outcome (HR 3.66, 95% CI 1.40 to 9.65; P =0.009) whereas groups I and II showed similar rates for the combined study endpoint (HR 0.55, 95% CI 0.18 to 1.70; P =0.298). Moreover, as shown in Figure 2D, Kaplan-Meier survival curves revealed a poorer outcome in patients who had a CRP >2 mg/dL at admission (Log Rank= 8.908; p=0.003;).

Univariate analysis showed prior AMI, troponin peak ratio, increased CRP levels, presence of 3-vessel and LMS MCAD to be significant predictors of MACE (Table 2). Multivariate analysis showed only 3 vessels/LMS MCAD (HR 23.5, 95% CI 2.59-173.49, p=0.001) and high CRP concentrations (HR 1.47, 95% CI 1.06-2.07; P=0.005) to be independent predictors of MACE (Table 3).

**4. Discussion**

The present study shows that although patients with MINOCA generally have a more favourable prognosis than patients with AMI triggered by obstructive CAD, the presence of MCAD affecting 3 vessels or the LMS identifies patients with an impaired clinical outcome. Our study also supports a significant prognostic role of increased CRP concentrations at hospital admission in patients with MINOCA.

Interestingly, our findings suggest that the distribution of CAD expressed as number of coronary vessels involved rather than the degree/severity of coronary stenosis, may represent a better risk stratification strategy. Moreover, our study indicates that in MINOCA patients, an accurate assessment of the coronary angiography and the identification of the number of vessels with MCAD could have incremental prognostic value. It can be speculated that the greater the number of vessels involved, albeit without obstructive CAD, the greater the likelihood that one or more plaques can destabilize over time, particularly in the presence of high CRP concentrations [8,9], leading to an acute coronary event. We found that the presence and the distribution of atherosclerotic plaques at angiography appears to provide a better prognostic yield than the sole estimation of the degree of stenosis, probably because the former is easier to be reported and less operator-dependent (i.e. present/absent), whereas the latter is affected by more inter-operator variability. However, given the limitations of coronary angiography to identify non-obstructive plaques, other imaging modalities such as CT (computed tomography) [10,11], IVUS (intravascular ultrasound) [12], OCT (optical coherence tomography) [13], and CMR (cardiovascular magnetic resonance) [14] may offer better diagnostic and risk-stratification options.

It has been suggested that the burden of atherosclerosis is significant in patients with AMI and no obstructive CAD and this is often overlooked by conventional angiography when compared to assessment of stenosis using CT angiography (CTA) [10,11]. In MINOCA patients with documented myocardial scar tissue, as assessed by CMR, Aldrovandi et al. reported CAD -as assessed by CTA- in 84% of cases [10]. Furthermore, Amhadi et al. showed that mortality rates in MINOCA patients were related to the type of atherosclerotic plaques i.e. calcified plaque (1.4%), mixed plaque (3.3%) and non-calcified plaque (9.6%). In a 10-year follow up study, outcomes were impaired in patients with 3-vessel disease compared with those with single-vessel disease (p <0.001) [11]. In our study, patients with 3-vessel/LMS disease had significantly worse outcomes than patients with lesser degrees of CAD. However, prognosis was similar among patients with normal coronaries and patients with MCAD affecting 1-2 vessels.

According to our data, mortality was low in MINOCA patients assessed over a median follow-up of 7 years. This could be due to the use of more strict inclusion criteria in our study and our choice to assess cardiovascular mortality only and not all-cause mortality. In a pooled analysis of 8 studies on the prognosis of MINOCA patients (including Takotsubo and myocarditis) in-hospital and 1-year all-cause mortality were 0.9%, (95% CI, 0.5% -1.3%) and 4.7% (95% CI , 2.6% -6.9%), respectively, substantially lower than in patients with obstructive CAD (in-hospital mortality 3.2%; 1-year mortality 6.7%), but still far from negligible [4] . Of importance, among our patients with MCAD affecting 3 vessels or the LMS, 7-year cardiovascular mortality was in the region of 15%. In a recent study of patients undergoing elective coronary angiography 1-year mortality was higher in patients with 3-vessel non-obstructive CAD (i.e. stenosis >20% but <70%) compared to those with no CAD (stenosis <20%) (HR 1.6; 95% CI, 1.1 – 2.5) [15]. Rossini et al. reported similar results in unselected consecutive patients presenting with ACS. There were no differences in the incidence of MACE between patients with NCA (0% stenosis) and those with mild CAD (>0% and <50% stenosis) at either 30 days (p= 0.50) or long-term follow-up (p= 0.16) [16].

However, available data are biased by a large heterogeneity in defining normal and diseased coronaries [16,17] and often patients with normal troponin or CK-MB were also included [16]. In addition the majority of this studies are affected by significant selection biases, because they are post-hoc analysis from multicentre trials [17] or specific registries [18], whereas others enrolled only selected populations, for instance only STEMI [17] or NSTE-ACS patients [18].

Furthermore, our results may have a practical application, i.e. the high-risk group could probably benefit from standard therapy for secondary prevention as used in obstructive CAD. In fact, in a large MINOCA population from the SWEDEHEART registry, Lindhal et al.[19] demonstrated a beneficial prognostic effect of statins and ACEI/ARB. However, in the same study beta-blockers and double anti-platelet therapy did not significantly improve outcomes, probably due to the large heterogeneity of this MINOCA population [20].

4.1 Limitations

Our study has some limitations. As the current definition of MINOCA requires knowledge of coronary angiographic anatomy, we enrolled only MINOCA patients who underwent coronary angiography but angiographic results were not adjudicated by a core laboratory. The decision to refer patients to angiography was part of the clinical management of patients in the institution and as such it was left to the discretion of the managing physician; this could have resulted in an underestimation of the prevalence of MINOCA in our study, as in other MINOCA studies with a retrospective enrolment design. The relatively low prevalence of MINOCA in our study compared with other reports in the literature [4, 15-18], could also be explained by our more strict inclusion and exclusion criteria. We *-a priori-* excluded patients with myocarditis and Takotsubo syndrome, as these patients were discharged from hospital with different ICD-10 codes. Moreover our detailed evaluation of individual clinical records have allowed for further exclusion of miscoded diseases.

We do not report data on CMR, endomyocardial biopsy or provocative testing to rule out coronary spasm [21] as these tests were not part of a systematic assessment protocol and such information was available in a small number of patients in our database. Our focus was on clinical variables during follow-up. However, it is conceivable that, if CMR had been systematically performed in all MINOCA patients, some other miscoded or misdiagnosed myocarditis (not clinically suspected, as defined by ESC guidelines [22]) could have been discovered [14].

Although baseline characteristics in our patients are similar to those in other MINOCA studies [4,17], we do not report on a matched obstructive CAD control group for comparison, as it was our aim to identify markers of risk within this study population. Pharmacological therapy was left to the discretion of the managing physician and all patients were treated according to ESC guidelines. Given the small number of events in the study our conclusions should be interpreted as hypothesis generating.

**5. Conclusions**

MINOCA is a relatively infrequent AMI presentation compared to ACS with obstructed coronary arteries. Albeit the absence of obstructive CAD portends good long-term prognosis, the number of vessels affected by MCAD has an incremental effect on clinical outcomes. MINOCA patients with MCAD affecting 3 vessels or the LMS appear to have a guarded prognosis. Increased CRP levels also appear to have prognostic value in these patients. Prospective studies are necessary to test the hypotheses generated by our findings.

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**Figure legends**

**Figure 1.** Flow diagram for the selection of patients. AMI, acute myocardial infarction.

**Figure 2.** A,Kaplan–Meier curves for the combined endpoint (MACE) according to STEMI versus NSTEMI presentation. B, Kaplan–Meier curves for the combined endpoint (MACE) according to the presence of <30% stenosis (NCA) versus MCAD (≥30% but <50% stenosis). C,Kaplan–Meier curves for the combined endpoint (MACE) according to the CAD distribution: I) NCA (<30% stenosis); II) 1-2 vessels MCAD; III) 3 vessels/LMS MCAD. D,Kaplan–Meier curves for the combined endpoint (MACE) according to CRP levels > 2 mg/dL versus ≤2 mg/dl.

CRP, C-reactive protein; LMS, left main stem; MCAD, mild coronary artery disease; NCA, normal coronary arteries.

**Table 1**

|  |  |
| --- | --- |
| Total, n | 150 |
| Demographics |  |
| Age (±SD) | 62.6±13 |
| Female (%) | 55.3 |
| BMI (kg/m2) | 25.3±4.7 |
| SBP (mmHg) | 145.7±26.1 |
| HR (bpm) | 73.4±13.3 |
| Medical history, % |  |
| Hypertension | 66 |
| Diabetes mellitus | 11.3 |
| Hyperlipidaemia | 26.7 |
| Smoking | 28 |
| CAD Family history | 9.8 |
| Atrial fibrillation | 9 |
| COPD | 7.3 |
| Cerebrovascular disease (%) | 4 |
| Prior AMI (%) | 4.7 |
| ECG at admission |  |
| ST-elevation (%) | 23.3 |
| LVEF <55% (admission) | 20.7 |
| Blood testings |  |
| Troponin peak (ng/ml) | 0.4±1.0 |
| CK-MB peak (ng/ml) | 1.7±2.8 |
| Creatinine (mg/dl) | 0.7±0.4 |
| Haemoglobin (g/dl) | 12.6±3.8 |
| White blood cells (x103) | 7.1±3.2 |
| CRP (mg/dl) | 1.1±2.6 |
| Uric acid (mg/dl) | 5.5±1.9 |
| Angiographic characteristics |  |
| NCA, n (%) | 91 (61) |
| 1-2 vessels MCAD, n (%) | 45 (30) |
| 3 vessels/LMS MCAD, n (%) (%)(%) | 14 (9) |

Baseline characteristics in the whole cohort. AMI, acute myocardial infarction; BMI, body mass index; bpm, beats per minute; CRP, C-reactive protein; SBP, systolic blood pressure; HR, heart rate; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; LMS, left main stem; LVEF, left ventricular ejection fraction; MCAD, mild coronary artery disease; NCA, normal coronary arteries.**Table 2**

|  |  |  |
| --- | --- | --- |
|  | HR (95%CI) | P value |
| Demographics |  |  |
| Age (per 5 years increment) | 1.01 (0.87-1.18) | 0.212 |
| Male sex | 0.92 (0.40-2.10) | 0.848 |
| BMI (per 5 kg/m2 increment) | 0.01 (0-34.1) | 0.375 |
| SBP (per 15 mmHg increment) | 1.17 (0.95-1.45) | 0.150 |
| HR (per 10 bpm increment) | 1.04 (0.77-1.40) | 0.809 |
| Medical History |  |  |
| Hypertension | 0.97 (0.41-2.28) | 0.939 |
| Diabetes mellitus | 0.290 (0.4-2.15) | 0.226 |
| Hyperlipidaemia | 1.93 (1.40-5.40) | 0.22 |
| Smoking | 1.26 (0.52-3.05) | 0.612 |
| CAD Family history | 0.48 (0.14-1.60) | 0.23 |
| Atrial fibrillation | 0.39 (0.1-2.74) | 0.346 |
| COPD | 1.88 (0.60-6.44) | 0.307 |
| Cerebrovascular disease | 1.49 (0.20-11.42) | 0.699 |
| Prior AMI | 3.04 (0.90-10.22) | 0.073 |
| ECG at admission |  |  |
| ST-elevation | 0.47 (0.14-1.60) | 0.227 |
| LVEF <55% at admission | 1.02 (0.96-1.08) | 0.584 |
| Blood testings |  |  |
| Troponin peak ratio (per 0.06 ng/ml increment) | 0.98 (0.97-1.01) | 0.098 |
| CK-MB peak (per 10 ng/ml increment) | 0.96 (0.91-1.01) | 0.106 |
| Creatinine (per 1 mg/dl increment) | 0.514 (0.16-1.66) | 0.267 |
| Haemoglobin (per 1 g/dl increment) | 0.99 (0.1-2.0) | 0.811 |
| White blood cells (per 1000/mm3 increment) | 1.29 (0.36-4.60) | 0,695 |
| CRP (per 1 mg/dl increment) | 1.20 (0.98-1.28) | 0.087 |
| Uric acid (per 1 mg/dl increment) | 0.99 (0.74-1.33) | 0.962 |
| Angiographic characteristics |  |  |
| NCA | 0.89 (0.39-2.03) | 0.781 |
| 1-2 vessels MCAD | 0.43 (0.15-1.25 | 0.135 |
| 3 vessels/LMS MCAD | 3.05 (1.15-9.1) | 0.009 |

Univariate analysis for the combined endpoint (Major adverse cardiovascular events [MACE]= cardiovascular death, AMI/ACS, heart failure, stroke).

ACS, acute coronary syndrome; AMI, acute myocardial infarction; CRP, C-reactive protein; LMS, left main stem; MCAD, mild coronary artery disease; NCA, normal coronary arteries.

**Table 3**

|  |  |  |
| --- | --- | --- |
|  | HR (95% CI) | P value |
| Age (per 5 years increment) | 0.95 (0.75-1.19) | 0.634 |
| Male sex | 1.70 (0.44-6.53) | 0.439 |
| Prior AMI | 2.20 (0.12-14.07) | 0.187 |
| CRP (per 1 mg/dL increment) | 1.47 (1.06-2.07) | 0.005 |
| Troponin peak ratio (per 0.06 ng/ml increment) | 1.04 (1.01-1.07) | 0.190 |
| 3 vessels/LMS MCAD | 23.5 (2.59-173.49) | 0.001 |

Multivariate Cox model analysis for the combined endpoint (Major adverse cardiovascular events [MACE]= cardiovascular death, AMI/ACS, heart failure, stroke). ACS, acute coronary syndrome; AMI, acute myocardial infarction; CRP, C-reactive protein; LMS, left main stem; MCAD, mild coronary artery disease.