# Characteristics of patients with recurrent acute myocardial infarction after MINOCA

Giuseppe Ciliberti [a,*], Federico Guerra [a], Carmine Pizzi [b], Marco Merlo [c], Filippo Zilio [d], Francesco Bianco [e], Massimo Mancone [f], Denise Zaffalon [c], Rocco Gioscia [g], Luca Bergamaschi [b], Paolo Compagnucci [a], Matteo Armillotta [b], Michela Casella [a], Angelo Sansonetti [b], Marco Marini [h], Pasquale Paolisso [i], Giulia Stronati [a], Sabina Gallina [j], Antonio Dello Russo [a], Gian Piero Perna [h], Francesco Fedele [f], Roberto Bonmassari [d], Giuseppe De Luca [k], Isabella Tritto [l], Tommaso Piva [h], Gianfranco Sinagra [c], Giuseppe Ambrosio [l], Juan Carlos Kaski [m], Monica Verdoia [g]

[a] *Cardiology and Arrhythmology Clinic, Marche Polytechnic University, Azienda Ospedaliero Universitaria delle Marche, Ancona, Italy*
[b] *Cardiology Unit, IRCCS Azienda Ospedaliera-Universitaria di Bologna; Department of Medical and Surgical Sciences – DIMEC – Alma Mater Studiorum, University of Bologna, Bologna, Italy*
[c] *Cardiovascular Department, Azienda Sanitaria Universitaria Integrata, University of Trieste, Italy*
[d] *Department of Cardiology, S. Chiara Hospital, Trento, Italy*
[e] *Department of Pediatric and Congenital Cardiology and Cardiac Surgery, Azienda Ospedaliero-Universitaria "Ospedali Riuniti", Ancona, Italy*
[f] *Department of Cardiovascular, Respiratory, Nephrology, Anesthesiology and Geriatric Sciences, Sapienza University of Rome, Rome, Italy*
[g] *Ospedale degli Infermi, Biella, Italy*
[h] *Cardiology and Coronary Care Unit, Marche University Hospital, Ancona, Italy*
[i] *Cardiovascular Center Aalst, OLV-Clinic, Aalst, Belgium; Dept. of Advanced Biomedical Sciences, University Federico II, Naples, Italy*
[j] *Department of Neuroscience, Imaging and clinical Sciences, "G. d'Annunzio" University, Chieti, Italy*
[k] *Division of Cardiology, Policlinico AOU G. Martino, and Department of Clinical and Experimental Medicine, Cardiology Unit, University of Messina, Messina, Italy*
[l] *Division of Cardiology, University of Perugia, School of Medicine, Perugia, Italy*
[m] *Molecular and Clinical Sciences, St George's, University of London, London, UK*

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ABSTRACT

***Background:*** Myocardial infarction (MI) with non-obstructed coronary arteries (MINOCA) is an increasingly recognized condition with challenging management. Some MINOCA patients ultimately experience recurrent acute MI (re-AMI) during follow-up; however, clinical and angiographic factors predisposing to re-AMI are still poorly defined.

***Methods:*** In this retrospective multicenter cohort study we enrolled consecutive patients fulfilling diagnostic criteria of MINOCA according to the IV universal definition of myocardial infarction; characteristics of patients experiencing re-AMI during the follow-up were compared to a group of MINOCA patients without re-AMI.

***Results:*** 54 patients (mean age 66 ± 13) experienced a subsequent re-AMI after MINOCA and follow-up was available in 44 (81%). Compared to MINOCA patients without re-AMI ($n = 695$), on first invasive coronary angiography (ICA) MINOCA patients with re-AMI showed less frequent angiographically normal coronaries (37 versus 53%, $p = 0.032$) and had a higher prevalence of atherosclerosis involving 3 vessels or left main stem (17% versus 8%, $p = 0.049$).

Twenty-four patients (44%) with re-AMI underwent a new ICA: 25% had normal coronary arteries, 12.5% had mild luminal irregularities (<30%), 20.8% had moderate coronary atherosclerosis (30–49%), and 41.7% showed obstructive coronary atherosclerosis (≥50% stenosis).

*Abbreviations:* CAD, coronary artery disease; CMR, cardiac magnetic resonance imaging; CVD, cardiovascular disease; ECG, electrocardiogram; ICA, invasive coronary angiography; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; MINOCA, myocardial infarction with non-obstructed coronary arteries.

* Corresponding author at: Cardiology and Arrhythmology Clinic, Marche University Hospital, Via Conca 71, Ancona, Italy.
*E-mail address:* giuseppe.ciliberti@ospedaliriuniti.marche.it (G. Ciliberti).

Among patients undergoing new ICA, atherosclerosis progression was observed in 11 (45.8%), 37.5% received revascularization, only 4.5% had low-density lipoprotein cholesterol (LDL_C) under 55 mg/dL and 33% experienced a new cardiovascular disease (CVD) event (death, AMI, heart failure, stroke) at subsequent follow-up.
***Conclusions:*** In the present study, only a minority of MINOCA patients with re-AMI underwent a repeated ICA, nearly one out of two showed atherosclerosis progression, often requiring revascularization. Recommended LDL-C levels were achieved only in a minority of the cases, indicating a possible underestimation of CVD risk in this population.

## Introduction

Myocardial infarction (MI) with non-obstructed coronary arteries (MINOCA) represents an increasingly recognized condition accounting for 2 to 6% of all MIs,[1,2]

Recently, the fourth universal definition of MI has stated that MINOCA should be diagnosed when there is evidence of a spontaneous acute MI (AMI) and absence of coronary stenosis ≥50% in the main epicardial vessels.[3]However, MINOCA still represents a heterogeneous population, since different definitions, inclusion and exclusion criteria have been adopted in the current literature and significant differences in management are reported.[4–6]In fact, although recent European guidelines state that patients with a final diagnosis of MINOCA "of unknown cause" may be treated according to secondary prevention strategies for obstructive MI,[5] high-quality evidence is scarce, since the current MINOCA criteria were not fully applied in the majority of existing studies[7–10] . Moreover, most recent pharmacological acquirements, as in terms of lipid management, have been seldom tested in MINOCA patients.[11–13]

Indeed, an aggressive lowering of low-density lipoprotein-C < 55 mg/dL, as recommended for coronary artery disease, should be pursued even in MINOCA, but there is limited evidence on the adherence to the recommended LDL-C target and its prognostic impact on the outcome among MINOCA patients.[13]In fact, a proportion of MINOCA patients ultimately go on to experience a subsequent MI but strategies and therapeutic approaches to prevent such events remain unclear.[13–15]Atherosclerosis progression across previously unobstructed coronary arteries can be claimed as a potential cause of MI recurrence, despite its real clinical frequency is still undefined.[16]

In the present study, we aimed to assess the clinical and angiographic characteristics of patients with MINOCA who experienced re-AMI at follow-up, with particular reference to angiographic atherosclerosis progression and LDL-C level at the time of re-AMI.

## Methods

### *Patients*

We retrospectively evaluated characteristics of patients with re-AMI after MINOCA selected as previously reported.[17] Another center only provided data on MINOCA patients who experienced re-AMI at follow-up, selected from January 2017 to October 2021.

Atherosclerosis progression was considered as the development of higher degree of coronary stenosis at subsequent angiography, defined as follows: progression from normal coronaries to mild luminal irregularities (<30% stenosis), moderate (30–49%) or obstructive (>50%) atherosclerosis; progression from mild luminal irregularities (<30% stenosis) to moderate (30–49%) or obstructive (>50%) atherosclerosis; progression from moderate (30–49%) to obstructive (>50%) atherosclerosis.

LDL-C levels at the time of re-AMI were collected for analysis.

MINOCA patients without re-AMI were considered for comparison and were derived from our previous report [17].

The study was approved by the local ethics committee (registration number 7267/17/ON) and managed in accordance to Good Clinical Practice and the Declaration of Helsinki.[18]

### *Statistical methods*

Statistical analysis was performed using SPSS 22.0 statistical package (IBM SPSS Inc., Chicago, Illinois). Categorical data were provided as percentage, whereas continuous data were expressed as mean ± standard deviation. The Chi-Square test was performed for categorical variables, whereas ANOVA was performed for continuous variables if normally distributed, otherwise the test of Mann-Whitney was applied. A *P*-value <0.05 was considered significant.

## Results

Among 735 consecutive patients with a diagnosis of MINOCA, follow-up was completed in 621, and 40 (6.4%) experienced re-AMI. Additionally, 14 consecutive MINOCA patients with re-AMI were included from another center (Table S1).

Among the 54 patients with re-AMI, subsequent follow-up was available in 44 (81.5%). The flowchart for the study design is displayed in Fig. 1.

Baseline characteristics of MINOCA patients with without re-AMI (at the first MINOCA event) are shown in Table 1.

Compared to MINOCA patients without re-AMI ($n = 695$), MINOCA patients with re-AMI showed less frequent angiographically normal coronaries at first invasive coronary angiography (ICA) (37 versus 53.1%, $p = 0.032$) and had a higher prevalence of atherosclerosis involving 3 vessels or left main stem (16.7% versus 7.6%, $p = 0.049$).

Among patients with available follow-up, twenty-four patients (54.5%) with re-AMI underwent a new ICA. Among them, 25% showed normal coronary arteries, 12.5% mild luminal irregularities, 20.8% moderate coronary atherosclerosis, and 41.7% obstructive coronary atherosclerosis (Table 2, Fig. 2).

Among the 24 patients receiving a repeated ICA, atherosclerosis progression was observed in 11 (45.8%), of whom 72.7% underwent coronary revascularization. Among the 9 patients receiving revascularization, all but one showed obstructive CAD on ICA; however, this patient with moderate stenosis showed high-risk plaque features at optical coherence tomography imaging; moreover, one patient with atherosclerosis progression leading to obstructive atherosclerosis was managed conservatively (Table S2; Fig. 3).

Among MINOCA patients with re-AMI receiving a new ICA LDL-C < 55 mg/dL was found only in 4.5%.

The time interval from MINOCA to re-AMI was significantly higher among patients with atherosclerosis progression (1241.7 ± 648.6 versus 387.2 ± 107.4 days, $p = 0.02$).

Among 44 patients with re-AMI and available follow-up, a subsequent new major adverse event [cardiovascular disease (CVD) death, AMI, or stroke] occurred in 8 (18.2%), and among those who underwent repeated ICA ($n = 24$) and revascularization ($n = 9$) a third re-AMI event occurred in 5 (20.8%) and 3 (33.3%), respectively. Complete follow-up data are shown in Supplementary Table S2.

## Discussion

The main findings of the present study are that the majority of MINOCA patients with re-AMI who showed obstructive CAD and/or received revascularization on repeated ICA had atherosclerosis

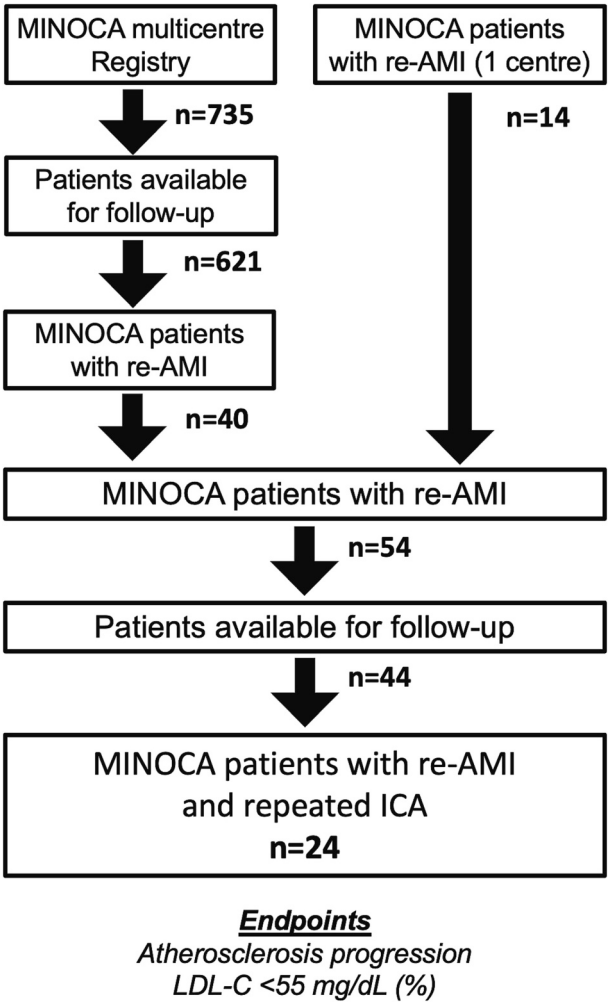


**Fig. 1.** Flow-diagram for the selection of patients.
AMI, acute myocardial infarction; ICA, invasive coronary angiography.

progression and LDL-C levels above the contemporary recommended target (Fig. 3).

To the best of our knowledge, the present is the first study that analyzed the level of LDL-C and detailed angiographic characteristics among MINOCA patients at the time of re-AMI.

*Reinfarction after MINOCA*

According to our findings, at the time of reinfarction, ICA is repeated nearly in half of patients with previous MINOCA. This finding could be explained by the perceived low cardiovascular risk attributed to MINOCA patients, possibly due to the previously known coronary anatomy with absence of epicardial coronary stenosis requiring revascularization.

However, in the present study, the time from MINOCA to re-AMI was significantly higher in patients with atherosclerosis progression, thus we can hypothesize that atherosclerotic coronary narrowing is progressive and there should be enough time to adopt optimal preventive strategies, even in the absence of obstructive disease at first CVD event.[16]

Moreover, since the large majority of patients presented with LDL-C levels above the currently recommended target, it is conceivable that appropriate lipid-lowering treatment is underused in this population.[19,20]It should be also considered that factors other than cholesterol can contribute to destabilizing atherosclerotic plaque, for example inflammation, plaque composition and coronary vasomotion abnormalities.[21–23]

**Table 1**
Baseline characteristics of MINOCA patients with and without re-AMI.

| | MINOCA patients with re-AMI Total, $n = 54$ | MINOCA patients without re-AMI or follow-up Total, $n = 695$ | *P* value |
|---|---|---|---|
| Demographics | | | |
| Age (±SD) | 66 ± 13 | 65 ± 14 | 0.672 |
| Female, (%) | 57.4 | 55.4 | 0.887 |
| Medical history, (%) | | | |
| Hypertension | 71.2 | 61.4 | 0.181 |
| Diabetes mellitus | 19.2 | 15.0 | 0.422 |
| Hyperlipidaemia | 40.4 | 44.4 | 0.662 |
| Smoking | 36 | 31.1 | 0–365 |
| CAD family history | 30.6 | 30.6 | 0.570 |
| AF history | 16.0 | 11.8 | 0.439 |
| Prior AMI | 8.3 | 5.9 | 0.521 |
| COPD | 6.3 | 4.8 | 0.723 |
| Cerebrovascular disease | 12.5 | 5.3 | 0.053 |
| ECG at admission, (%) | | | |
| ST-elevation | 22.2 | 16.1 | 0.252 |
| LVEF <50% (admission), (%) | 29.6 | 24.5 | 0.414 |
| CMR, n (%) | 14.8 | 20.3 | 0.379 |
| Acute complications, (%) | 2.0 | 4.5 | 0.259 |
| Angiographic characteristics, (%) | | | |
| Normal coronaries | 37.0 | 53.1 | **0.032** |
| Moderate atherosclerosis (30–49%) | 38.1 | 38.9 | 1.000 |
| 1–2 vessel (30–49%) | 25.0 | 19.5 | 0.350 |
| 3 vessels/LMS (30–49%) | 16.7 | 7.6 | **0.049** |
| Pharmacological therapy at discharge | | | |
| Aspirin, (%) | 98.1 | 86.8 | 0.09 |
| DAPT, (%) | 64.0 | 54.5 | 0.235 |
| P2Y12-I, (%) | 64.0 | 56.1 | 0.301 |
| Beta-blockers, (%) | 67.1 | 67.3 | 1.000 |
| ACE-I, (%) | 64.8 | 55.5 | 0.200 |
| ARB, (%) | 10.2 | 14.7 | 0.524 |
| Statins, (%) | 79.6 | 78.7 | 1.000 |
| CCBs, (%) | 16.3 | 26.2 | 0.169 |
| Nitrates, (%) | 10.2 | 18.9 | 0.175 |

ACE-I, angiotensin-converting enzyme inhibitors; AF, atrial fibrillation; AMI, acute myocardial infarction; ARB, angiotensin-receptor blockers; CAD, coronary artery disease; CCB, calcium-channel blockers; CMR, cardiac magnetic resonance; COPD, chronic obstructive pulmonary disease; DAPT, dual anti-platelet therapy; LMS, left main stem; LVEF, left ventricular ejection fraction; PE, primary end-point; P2Y12-I, P2Y12-inhibitors.

Accordingly, we previously demonstrated that C reactive protein predicted adverse outcomes in MINOCA patients independently of the extent of coronary atheromatosis,[14] and these findings have been independently confirmed by other studies.[24,25]

Moreover, evidence from recent trials[26–28] suggests that specific anti-inflammatory therapies could significantly improve outcomes among high-risk populations, although available studies do not specifically include MINOCA patients.

*Atherosclerosis progression and lipid targets*

Atherosclerosis progression assumes an increase of coronary plaque burden along with changes in plaque composition, promoting its disruption, thrombus superimposition and acute vessel obstruction.[29]In fact, plaque disruption and coronary thrombus have been demonstrated at autopsy in patients who died of MINOCA,[30,31] and among survivors by intravascular imaging tools as optical coherence tomography, with a prevalence ranging around 40%.[32]

Contributors to coronary atherosclerotic progression are classic cardiovascular risk factors as cholesterol levels,[11] diabetes,[33] smoking habit,[34] systemic arterial hypertension,[35] and unhealthy diet.[36]

For these reasons, intensive treatment of cardiovascular risk factors should be pursued even in MINOCA patients, and lipid management

**Table 2**
Baseline characteristics of MINOCA patients with re-AMI according to the presence of atherosclerosis progression.

| | Total, n = 24 | Atherosclerosis progression, *n* = 11 | No Atherosclerosis progression, *n* = 13 | P value |
|---|---|---|---|---|
| Demographics | | | | |
| Age (±SD) | 61.4 ± 13.2 | 58.8 ± 13.5 | 63.6 ± 13.0 | 0.781 |
| Female, (%) | 50.0 | 36.4 | 61.5 | 0.414 |
| Medical history, (%) | | | | |
| Hypertension | 77.3 | 88.9 | 69.2 | 0.360 |
| Diabetes mellitus | 18.2 | 33.3 | 7.7 | 0.264 |
| Hyperlipidaemia | 54.5 | 44.4 | 61.5 | 0.666 |
| Smoking | 28.6 | 37.5 | 23.1 | 0.631 |
| CAD family history | 40.0 | 42.9 | 38.5 | 1.000 |
| AF history | 23.8 | 37.5 | 15.4 | 0.325 |
| Prior AMI | 15.4 | 14.3 | 15.0 | 1.000 |
| COPD | 5.0 | 0.0 | 7.7 | 1.000 |
| Cerebrovascular disease | 15.0 | 0.0 | 23.1 | 0,521 |
| ECG at admission, (%) | | | | |
| ST-elevation | 12.5 | 18.2 | 7.7 | 0.576 |
| LVEF <50% (admission), (%) | 20.8 | 27.3 | 15.4 | 0.630 |
| LDL-C ≤ 55 mg/dL, (%) | 4.5 | 9.1 | 0.0 | 1.000 |
| Time to re-AMI (days) | 955.1 ± 577.7 | 1241,7 ± 648,6 | 387,2 ± 107,4 | **0.02** |
| Angiographic characteristics, (%) | | | | |
| Normal coronaries | 25.0 | 0.0 | 46.2 | **0.016** |
| Mild luminal irregularities (<30%) | 12.5 | 0.0 | 23.1 | 0.596 |
| Moderate atherosclerosis (30–49%) | 20.8 | 9.1 | 30.7 | 0.649 |
| Obstructive atherosclerosis (>50%) | 41.7 | 90.9 | 0.0 | **<0.0001** |
| PTCA/stenting | 37.5 | 72.7 | 7.7 | **0.002** |
| Intracoronary imaging/ functional assessment, (%) | 25.0 | 18.1 | 30.8 | **1.000** |

AF, atrial fibrillation; AMI, acute myocardial infarction; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; LDL-C; low-density lipoprotein cholesterol;
LVEF, left ventricular ejection fraction; PTCA, percutaneous transluminal coronary angioplasty.

should be mandatory in high-risk population aimed at reducing atherosclerotic risk by substantially lowering LDL-C[11].

Since our study was designed with inclusion and exclusion criteria according to the current universal definition of myocardial infarction,[3] we considered contemporary recommended lipid targets for secondary prevention,[11] thus providing reproducible results which could be useful for clinical practice application.

In fact, European guidelines for the management of dyslipidemias stated that for secondary prevention in very-high-risk patients, an LDL-C reduction of ≥50% from baseline and an LDL-C goal of <55 mg/dL are recommended, whereas for patients who experience a second vascular event within 2 years while taking maximally tolerated statin therapy, an LDL-C goal <40 mg/dL may be considered.[11]

*State-of-the-art and future directions*

So far, there are limited data on MINOCA patients with re-AMI. In 2019 Nordenskiöld et al.[13] analyzed the characteristics of 570 MINOCA patients who experienced a recurrent MI (2.4%/year incidence of recurrent MI), with repeated ICA performed in 60% of cases showing obstructive atherosclerosis in 47%, although without subdivision of patients into those with normal coronary arteries and mild or moderate atherosclerosis and with the possible inclusion of cases of myocarditis or takotsubo syndrome.[15] Other studies showed 1-year re-infarction rate ranging from 1.2% to 3.6% among MINOCA patients,[37–39] but detailed data on clinical and angiographic characteristics at the time of re-AMI were lacking.

We previously observed a lower 1-year rate of re-AMI of 0.9%,[17] probably because of our different strict inclusion and exclusion criteria, focusing on "ischemic" MINOCA and excluding possible other conditions or MINOCA "mimics".[40]Moreover, previous studies were limited because of the heterogeneous population and adoption of different and non-contemporary MINOCA standardized definitions.[2,7–9]

In conclusion, although it is not clear if MINOCA patients may not necessarily benefit from treatments that are effective in MI with obstructive coronary atherosclerosis,[6,41] our observations suggest that patients with re-AMI represent a high-risk group who could possibly benefit from cardiovascular risk factors aggressive management, especially in the presence of unmeet LDL-C targets and evidence of atherosclerosis progression.[12,15] Of course, our data are limited and prospective randomized studies are urgently needed to explore these hypothesis-generating findings.

## Limitations

The present retrospective study is characterized by some limitations. Since the aim of the study was to analyze characteristics of MINOCA patients with re-AMI we included data from one hospital which provided only patients with re-AMI and this could represent a possible selection bias, although the same inclusion and exclusion criteria were applied and the source was a population of MINOCA patients with a likely ischemic etiology.[24]Pharmacological therapy was left to the discretion of the responsible physician, and adherence to medications was only obtained from patients' self-reported data. LDL-C levels were not available at the time of the first MINOCA and for patients with MINOCA without re-AMI. Moreover, information on the proportion of patients with correctly titrated therapy and on-target therapeutic goals even for other cardiovascular risk factors (i.e., diabetes, hypertension) was not collected. Nearly one out of three patients underwent intracoronary imaging or functional assessment, with possible missing of high-risk features. In addition, the small proportion of patients which received cardiovascular magnetic resonance (CMR) in the present study, could represent a further potential limitation, since CMR is required to rule-out MINOCA "mimics" such as myocarditis and other non-ischemic conditions,[5,42] although in previous studies CMR was often non available at all.[13]Furthermore, given the small number of events in the study and a relevant proportion of patients missed at follow-up, our findings should solely be interpreted as hypothesis generating.

## Conclusions

In the present study, MINOCA patients who experienced re-AMI frequently underwent revascularization in the presence of out-of-target LDL-C levels in nearly all cases. It is conceivable that there is a possible cardiovascular risk underestimation in this population, possibly due to the evidence of unobstructed coronary arteries on first ICA. Moreover, these findings raise the concern that all patients with re-AMI after MINOCA should undergo repeated coronary anatomy evaluation. Our data suggest that MINOCA patients with re-AMI are a high-risk population, and deserve appropriate treatment to prevent future

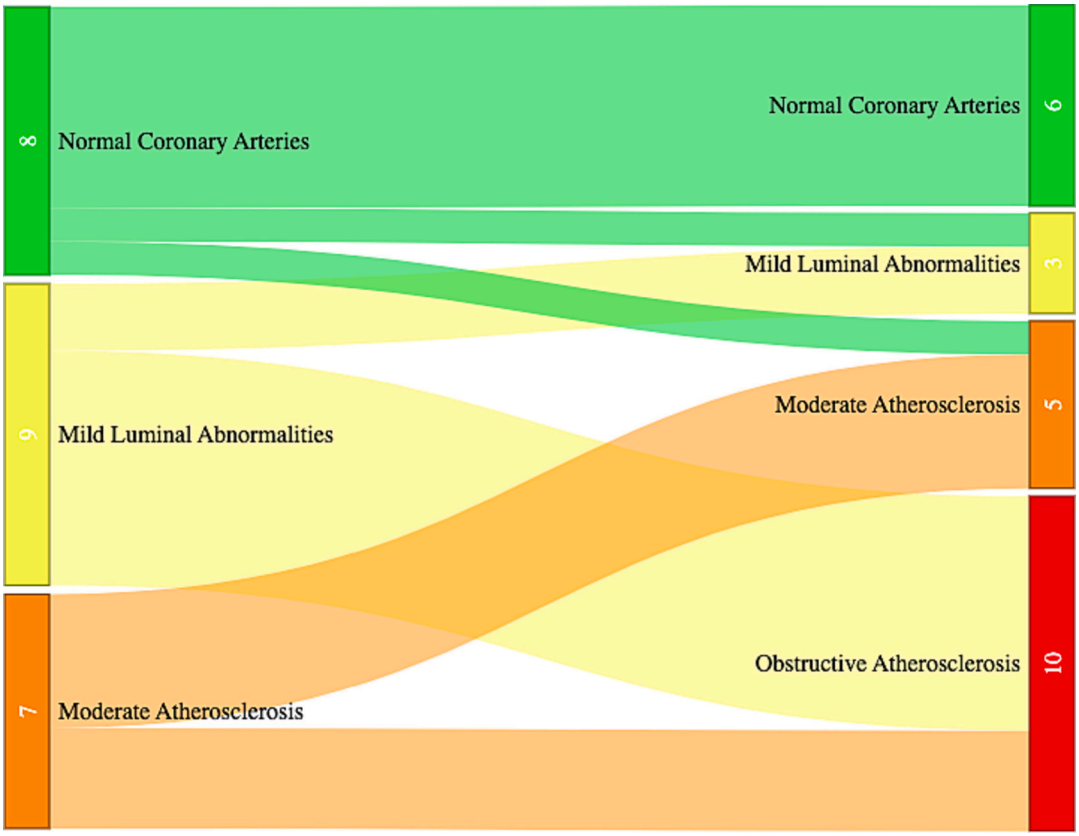


**Fig. 2.** Sankey diagram of the reclassification before and after re-AMI.

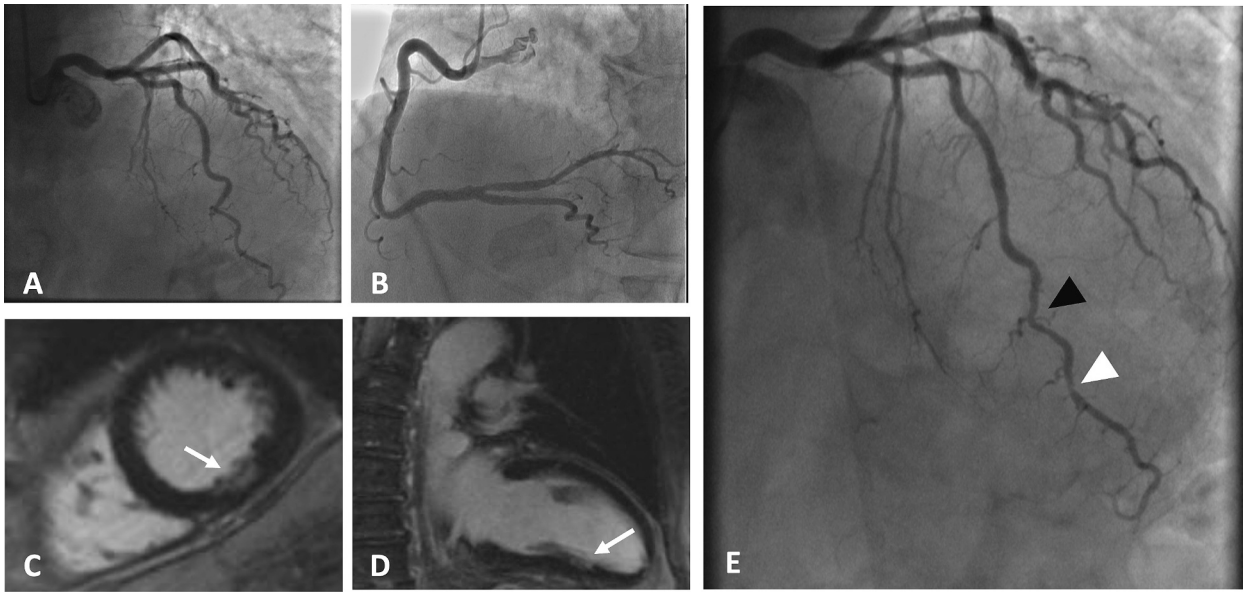


**Fig. 3.** Angiographic details of a patient suffering recurrent AMI after MINOCA. A 70-year old man who experienced non-ST elevation MINOCA with diffuse minimal luminal irregularities (A,B). C,D: Cardiac magnetic resonance showing subendocardial late gadolinium enhancement in the mid portion of left ventricle inferior wall (white arrows). The same patient suffered non-ST elevation re-infarction after nearly 4 years since the first event. In panel E angiographic atherosclerosis progression was noted on mid-distal left anterior descending coronary artery with moderate (30-50%, black arrowhead) and obstructive (>50%) lesions (white arrowhead). LDL-C at the time of re-infarction was 78 mg/dL. The patient was managed conservatively without further events occurring at subsequent follow-up (images courtesy of Dr. Filippo Zilio).

cardiovascular events. Prospective large-scale studies are necessary to assess our generating hypothesis findings.

## Declaration of Competing Interest

None.

## Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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