Precision medicine versus standard of care for patients with myocardial infarction with non-obstructive coronary arteries (MINOCA): rationale and design of the multicentre, randomised PROMISE trial

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KEYWORDS

- ACS/NSTE-ACS
- miscellaneous
- NSTEMI

Abstract

Myocardial infarction with non-obstructive coronary arteries (MINOCA) represents about 6-8% of patients presenting with myocardial infarction (MI), and it is associated with a significant risk of mortality, rehospitalisation, and angina burden, with high associated socioeconomic costs. It is important to note that multiple mechanisms may be responsible for MINOCA. However, to date, there are few prospective clinical trials on MINOCA and the treatment of these patients is still not defined, most likely because of the multiple underlying pathogenic mechanisms. The PROMISE trial is a randomised, multicentre, prospective, superiority, phase IV trial that will include 180 MINOCA patients randomised 1:1 to a "precision-medicine approach", consisting of a comprehensive diagnostic workup and pharmacological treatment specific for the underlying cause, versus a "standard of care" approach, consisting of routine diagnostic workup and standard medical treatment for acute coronary syndrome. The aim of this study is to evaluate if the "precision-medicine approach" will improve the angina status, evaluated using the Seattle Angina Questionnaire summary score, at 12 months (primary endpoint). Secondary endpoints include the rate of major adverse cardiovascular events at 12-month follow-up, the related primary and secondary healthcare costs, and the ability of cardiac magnetic resonance to evaluate the different mechanisms of MINOCA. Of importance, the results derived from this trial may pave the way for a new pathophysiology-driven approach with cause-target therapies personalised for the mechanisms of MINOCA (ClinicalTrials.gov: NCT05122780).

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Abbreviations

ACEi	angiotensin-converting enzyme inhibitors
ACh	acetylcholine
ARBs	angiotensin receptor blockers
CAD	coronary artery disease
CAG	coronary angiography
CCB	calcium channel blockers
CEE	contrast-enhanced echocardiography
CMR	cardiac magnetic resonance
CRP	C-reactive protein
DAPT	dual antiplatelet therapy
ECG	electrocardiogram
ET-1	endothelin-1
INOCA	ischaemia with no obstructive coronary artery disease
MACE	major adverse cardiovascular events
MI	myocardial infarction
MICAD	myocardial infarction and obstructive coronary artery disease
MINOCA	myocardial infarction with non-obstructive coronary arteries
MiRNA	microRNA
NPY	neuropeptide Y
OCT	optical coherence tomography
PE	plaque erosion
PR	plaque rupture
SAE	serious adverse events
SAQ	Seattle Angina Questionnaire
SAQSS	Seattle Angina Questionnaire summary score
SCAD	spontaneous coronary artery dissection
SD	standard deviation
TOE	transoesophageal echocardiography
TTE	transthoracic echocardiography
TTS	Takotsubo syndrome
sCD40L	soluble CD40-ligand

Introduction

Myocardial infarction with non-obstructive coronary arteries (MINOCA) represents about 6-8% of all patients presenting with acute myocardial infarction (MI) referred for coronary angiography (CAG)[1]. MINOCA is defined by the evidence of MI with normal or near normal coronary arteries in the absence of a specific alternate diagnosis for the clinical presentation (i.e., sepsis, myocarditis, pulmonary embolism and Takotsubo syndrome [TTS]). Notably, there are a variety of causes underlying MINOCA, including coronary plaque rupture (PR)/erosion (PE), epicardial or microvascular spasm, spontaneous coronary artery dissection (SCAD) and coronary microembolism[2-4]. Atherosclerotic plaque disruption (including PR and PE) can be identified in up to 40% of MINOCA patients[2]. The use of intracoronary imaging, and specifically optical coherence tomography (OCT), thanks to its high resolution (up to 10-15 µm), has demonstrated a higher diagnostic accuracy than conventional angiography alone for the detection of PR/PE or SCAD, especially when angiographically non-obstructive lesions are present[2]. Furthermore, coronary vasomotor disorders (including epicardial or microvascular spasm) are another frequent aetiology of MINOCA which can be elicited by performing intracoronary provocation testing with acetylcholine (ACh) at the time of CAG[5,6]. Therefore, MINOCA should not be considered as a single entity but a heterogeneous working diagnosis that requires a comprehensive evaluation to elucidate the potential underlying cause[1-8]. It is important to note that MINOCA is also associated with a significant risk of mortality, rehospitalisation, disability and angina burden, portending high socioeconomic costs[9].

To date, however, there are few prospective clinical trials in this population and a treatment algorithm for MINOCA has still not been defined, likely because of the multiple underlying pathogenic mechanisms.

Upon this background, we designed the "PROgnostic Value of Precision Medicine in Patients With Myocardial Infarction and Non-obStructive Coronary artEries" (PROMISE) trial (ClinicalTrials.gov: NCT05122780). Of importance, the PROMISE trial aims to further refine the treatment algorithm for MINOCA patients and to test the prognostic value of a targeted therapeutic approach.

Methods

STUDY DESIGN

The PROMISE study is a randomised, multicentre, prospective, open-label, superiority, phase IV trial comparing a "precision-medicine approach" versus "standard of care approach", with the aim of improving the prognosis and/or the quality of life of patients presenting with MINOCA. Enrolled patients will be randomised 1:1 to either (1) a "precision-medicine approach", consisting of a comprehensive diagnostic workup aimed at elucidating the pathophysiological mechanism and consequently a tailored pharmacological approach or (2) a "standard of care" approach, consisting of the standard diagnostic algorithm and therapy for MI. Patients will be enrolled in at least 3 sites in Italy. The respective local ethical committees approved the protocol. The study will be conducted according to the Declaration of Helsinki (1964, and its amendments and clarifications) and EU Directives 2001/20/EC and 2005/28/EC. The International Conference on Harmonisation-Good Clinical Practice will be used as guidance.

STUDY POPULATION, INCLUSION AND EXCLUSION CRITERIA

The study will include 180 patients aged ≥18 years and hospitalised for MINOCA. General inclusion and exclusion criteria are depicted in **Table 1**. Acute MI will be defined based on the Fourth Universal Definition of MI Criteria **(Supplementary Appendix 1)**[10].

INFORMED CONSENT

All patients must give informed consent prior to enrolment in the study and before any activity related to experimentation. If the patient is unable to provide written informed consent because of an acute setting, an initial verbal consent from the patient can be obtained. If a patient is providing verbal consent, an impartial

Table 1. Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
– Ability to give informed consent to the study	– Inability or limited capacity to give informed consent to the study
– Age ≥18 years – MINOCA diagnosis, defined as: – Acute MI* – Evidence of non-obstructive coronary artery disease on CAG (i.e., no coronary artery stenosis >50%) – No specific alternate diagnosis for the clinical presentation	– Age <18 years – Pregnant and breast-feeding women or patients considering becoming pregnant during the study period – Alternate diagnosis for the clinical presentation – Contraindication to contrast-enhanced CMR (e.g., severe renal dysfunction [glomerular filtration rate <30 mL/min]) or non-CMR-compatible pacemaker/defibrillator – Contraindication to drugs administered: e.g., a history of hypersensitivity to drugs administered or its excipients, significant renal and/or hepatic disease – Patients with comorbidities having an expected survival <1 year will be excluded

*definition based on the Fourth Universal Definition of Myocardial Infarction Criteria. CAG: coronary angiography; CMR: cardiac magnetic resonance; MI: myocardial infarction; MINOCA: myocardial infarction with non-obstructive coronary arteries

witness must be present during the entire informed consent discussion. Where a patient has initially consented verbally, written consent should be sought from the patient as soon as the patient is capable of signing the consent form.

RANDOMISATION

Patients are deemed enrolled into the trial after randomisation and treatment assignment using a web-based randomisation tool, available 24/7 at any of the enrolling sites. After informed consent has been obtained and the index CAG has been performed, revealing non-obstructive CAD, the operator will record the suspected diagnosis at that moment, and patients will be immediately randomised to the "precision-medicine approach" or the "standard of care" approach.

TREATMENT

Figure 1 depicts the flowchart of the study.

In the "precision-medicine approach" arm, patients will undergo a comprehensive diagnostic workup consisting of:

– CAG and ventriculography
– OCT (suggested in all cases if technically feasible, in particular if coronary PR/PE is suspected) at the time of CAG
– intracoronary ACh provocative test (to assess for the presence of coronary vasospasm) at the time of CAG (performed in all patients, unless clinically contraindicated [i.e., haemodynamic instability, sustained ventricular arrhythmias])

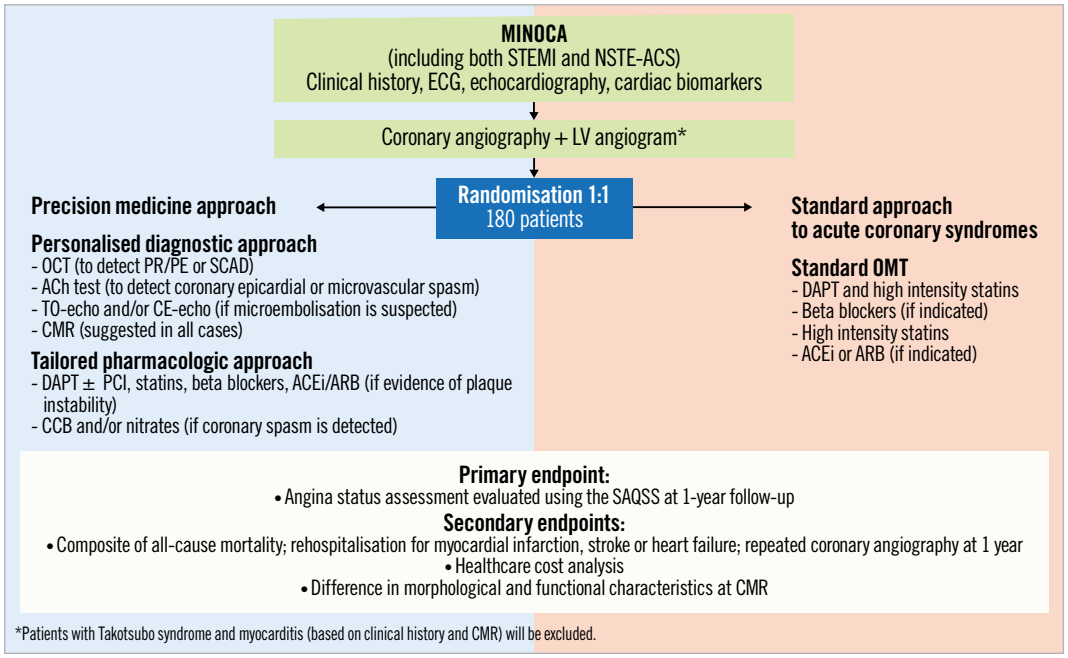

Figure 1. *Study flowchart. ACEi: angiotensin-converting enzymes inhibitors; ACh: acetylcholine; ACS: acute coronary syndrome; ARB: angiotensin receptor blockers; CCB: calcium channel blockers; CE: contrast enhanced; CMR: cardiac magnetic resonance; DAPT: dual antiplatelet therapy; ECG: electrocardiogram; LV: left ventricle; MINOCA: myocardial infarction with non-obstructive coronary arteries; NSTE: non-ST-segment elevation; OCT: optical coherence tomography; OMT: optimal medical therapy; PCI: percutaneous coronary intervention; PE: plaque erosion; PR: plaque rupture; SAQSS: Seattle Angina Questionnaire summary score; SCAD: spontaneous coronary artery dissection; STEMI: ST-segment elevation myocardial infarction; TO: transoesophageal*

– transoesophageal echocardiography (TOE) and/or contrast-enhanced echocardiography (CEE; if distal/microvascular embolisation is suspected based on the presence of risk factors of thromboembolism, such as atrial fibrillation, mechanical valves, thrombophilic disorders, etc.) during the index hospitalisation
– blood sampling for circulating biomarkers and microRNA (miRNA) expression profile at the time of CAG or within 12 hours
– transthoracic echocardiography (TTE) in all patients during the index hospitalisation
– cardiac magnetic resonance (CMR) in all cases during the index hospitalisation (time frame: from day 3 to day 7 following the acute coronary event)

Further details on diagnostic workup are reported in **Supplementary Appendix 3-Supplementary Appendix 7**.

Afterwards, a targeted pharmacological treatment specific for the underlying cause will be established **(Figure 2)**, consisting of:

– dual antiplatelet therapy (DAPT) (acetylsalicylic acid and a $P2Y_{12}$ receptor inhibitor [i.e., clopidogrel])±stent implantation if required **(Supplementary Appendix 2)**, statins, beta blockers, angiotensin-converting enzyme inhibitors (ACEi)/angiotensin receptor blockers (ARBs) (in case of evidence of PR/PE)
– calcium channel blockers (CCBs) and/or nitrates (in case of documentation of coronary vasospasm)
– anticoagulation (in case of coronary embolism)

Conversely, in the "standard approach" arm, patients will undergo a routine diagnostic workup consisting of:

– CAG and ventriculography without additional diagnostic tests (neither intracoronary imaging nor functional testing)
– TTE in all patients during the index hospitalisation
– CMR only if clinically indicated (e.g., suspected myocarditis or TTS)

Afterwards, a standard medical treatment will be established, consisting of:

– DAPT in all patients
– beta blockers, if clinically indicated **(Supplementary Appendix 2)**
– high intensity statins in all patients
– ACEi/ARBs, if clinically indicated **(Supplementary Appendix 2)**.

FOLLOW-UP

Patients will be followed up for 12 months after the index procedure. This will include a phone interview at 3 (90±5 days), 6 (180±5 days) and 9 months (270±5 days) as well as a clinical visit at 12 months (365±5 days) aiming to collect vital status, the incidence of rehospitalisation for MI, stroke, heart failure, repeated coronary angiography, the ongoing medical therapy, the occurrence of adverse events and the Seattle Angina Questionnaire (SAQ) summary score (SAQSS)[11] at 12 months.

During each follow-up visit, the occurrence of adverse events and serious adverse events (SAE) (e.g., adverse effects of the

Pathogenic mechanisms	Definition	Treatment
Plaque rupture/erosion	– Plaque rupture: presence of fibrous cap discontinuity with a clear communication between the lumen and the inner core of a coronary plaque. – Plaque erosion: presence of attached thrombus overlying an intact plaque, luminal surface irregularity at the culprit lesion without thrombus or attenuation of underlying plaque by thrombus without superficial lipid or calcification immediately proximal or distal to the site of thrombus.	– DAPT±PCI (if evidence of unstable plaque) – ACEi/ARB (if clinically indicated) – Statins – Beta blockers (if clinically indicated)
Spontaneous coronary artery dissection	Defined as a separation of the coronary artery wall not iatrogenic or related to trauma (intimal tears, intraluminal thrombi, false lumens, and intramural haematoma observed at OCT analysis).	– SAPT or DAPT±PCI (if recurrent ischaemia, haemodynamic instability, ventricular arrhythmias or left main dissection) – Beta blockers
Epicardial spasm	Defined by the presence of chest pain, ischaemic ECG changes and >90% coronary vasoconstriction in any epicardial vessel during intracoronary provocative test with ACh.	– CCB (first choice) – Nitrates – Consider statins
Microvascular spasm	Defined by the presence of chest pain, ischaemic ECG changes and <90% coronary vasoconstriction in any epicardial vessel during intracoronary provocative test with ACh.	– CCB
Coronary embolism/thrombus	Abrupt filling defect of a distal coronary artery branch in the presence of thrombophilic disorder, AF, mechanical valves, LV thrombus.	– Treatment of the underlying condition (if possible) – Anticoagulants

Figure 2. *Detailed description of the different pharmacological approaches according to the specific aetiology underlying MINOCA. ACEi: angiotensin-converting enzymes inhibitors; ACh: acetylcholine; AF: atrial fibrillation; ARB: angiotensin receptor blockers; CCB: calcium channel blockers; DAPT: dual antiplatelet therapy; ECG: electrocardiogram; LV: left ventricle; MINOCA: Myocardial Infarction with Non-Obstructive Coronary Arteries; OCT: optical coherence tomography; PCI: percutaneous coronary intervention; SAPT: single antiplatelet therapy*

drugs administered, such as bleeding) will be recorded and monitored **(Supplementary Appendix 8-Supplementary Appendix 9)**.

ENDPOINTS

The primary endpoint is the angina status evaluated using the SAQSS at 12-month follow-up.

The secondary endpoints include:

1. rates of major adverse cardiovascular events (MACE; defined as the composite of all-cause mortality, rehospitalisation for MI, stroke, heart failure and repeated CAG) at 12-month follow-up
2. related primary (including costs for tests, procedures and outpatient visits or medicines) and secondary (evaluated as mean quality-adjusted life year [QALY] gained and as the incremental cost-effectiveness ratio [ICER] expressed as the cost per QALY) healthcare costs and socioeconomic burden
3. the ability of CMR in evaluating the different mechanisms of MINOCA as well as their prognostic value.

EXPLORATORY ANALYSIS

The exploratory analysis includes:

1. the correlation of different circulating biomarkers (endothelin-1 [ET-1], neuropeptide Y [NPY], C-reactive protein [CRP], soluble CD40-ligand [sCD40L] and miRNA [miR-16, miR-26a, miR-145, miR-222, miR-155-5p, miR-483-5p and miR-451]) with the different pathophysiological mechanisms and clinical outcomes in MINOCA
2. in the "precision-medicine approach" arm, both the suspected diagnosis at the time of randomisation (e.g., after diagnostic CAG) and after randomisation (following the additional diagnostic tests) will be collected, to assess the frequency, certainty and change in diagnosis and/or potentially missed diagnosis (diagnostic utility).

In particular, we will assess if miRNA and circulating biomarkers could correlate with different causes of MINOCA, possibly paving the way for future clinical studies to explore their use as diagnostic and stratification tools in clinical practice **(Supplementary Appendix 10)**.

STATISTICAL CONSIDERATION

In order to detect a mean group difference of change in SAQSS of 9 U, we calculated that a sample size of 70 patients per group (140 patients in total) gave 80% power to detect a between-group difference in SAQSS. This calculation assumed a 2-tailed 5% significance level. This projected calculation assumed a standard deviation (SD) of 19 U and was consistent with previous studies[12]. However, we extended the sample size to 180 patients to avoid any reduction of statistical power if patients were lost to follow-up or had poor compliance to medical therapy.

STATISTICAL ANALYSIS

The analysis will consider the time to first event and time to each event. There will be no interim analyses, and the trial enrolment will be considered complete after the prespecified recruitment target is met. Data will be reported as mean±SD, median (25th, 75th percentile), or frequency and percentage. Continuous outcome measures recorded at baseline and 12 months will be compared between randomised groups using a mixed effects linear regression model, including a random effect for patients, and fixed effects for timepoints (baseline or follow-up), randomised groups and their interaction. The baseline-adjusted intervention effect will be estimated as the interaction term from this model. Categorical outcomes will be compared between randomised groups using Fisher's exact tests with additional calculation of relative risk estimation of effect size. We will perform a 2-tailed analysis and consider a p-value ≤0.05 to be significant. Statistical analyses will be performed using SPSS (IBM) software.

Discussion

Several studies have demonstrated that MINOCA patients have a 1-year mortality and rehospitalisation rate similar to those patients with acute MI and obstructive coronary artery disease (MICAD)[13]. Furthermore, approximately 25% of patients with MINOCA will experience angina in the subsequent 12 months, which is at least as high as that reported in patients with MICAD, with a significant impact on quality of life and healthcare related costs[14]. Angina symptoms also have relevant socioeconomic consequences, as patients with angina without evidence of coronary artery disease (CAD) have the same increased probability of a future disability pension and premature exit from the workforce as patients with obstructive CAD[15]. Therefore, as a potentially modifiable condition, angina status could be an ideal target to both improve patient symptoms and reduce healthcare costs. This is of crucial importance, because MINOCA patients are usually younger than patients with MICAD. However, less attention has been paid to quality of life outcomes in this population, and whether a pharmacological approach may have an impact on angina burden has never been investigated.

Therefore, a comprehensive evaluation and a multimodal assessment aimed at uncovering the aetiology of MINOCA should be pursued in order to implement a tailored therapeutic approach targeted to the specific underlying cause. Indeed, precision medicine may be particularly important in MINOCA patients because of the multiple causes underlying this condition[4-8]. In addition, such an approach has already proven its effectiveness in patients with stable angina and/or signs of ischaemia with no obstructive coronary artery disease (INOCA) in the landmark coronary microvascular angina (CorMicA) trial, where a strategy of adjunctive invasive testing for disorders of coronary function in these patients linked to stratified medical therapy led to an improvement in patient outcomes, including a reduction in angina severity and better quality of life[12,16].

Similarly, the identification of functional alterations of coronary circulation is relevant in the clinical setting of MINOCA. Indeed, we previously demonstrated that MINOCA patients with a positive test result (epicardial or microvascular spasm) had a significantly higher occurrence of cardiovascular events, thus

identifying a high-risk subset of patients that may need a more aggressive therapy and a closer follow-up[17,18].

Of note, despite the management of MICAD having well-established evidence-based guidelines, the management of MINOCA still has limited evidence-based literature. Indeed, the current guidelines do not specifically address the issue of acute and long-term management of patients with MINOCA. Moreover, the effects of secondary preventive treatments proven beneficial in patients with MICAD are unknown in MINOCA patients, with few prospective trials exploring this field. In particular, the "Randomized Evaluation of Beta Blocker and ACEI/ARBs treatment of MINOCA patients" (MINOCA-BAT) clinical trial aims to determine whether beta blockers and/or ACEi/ARBs may reduce the composite endpoint of all-cause mortality, readmission for MI, ischaemic stroke or heart failure in MINOCA patients (ClinicalTrials.gov: NCT03686696)[19]. Similarly, the "Stratified Medicine of Eplerenone in Acute MI/Injury" (StratMed-MINOCA) clinical trial aims to evaluate if a stratified medicine approach, with early risk stratification by coronary microvascular dysfunction (defined as an index of microvascular resistance ≥25), coupled with mineralocorticoid antagonist therapy (i.e., eplerenone) may limit myocardial damage, defined as changes in N-terminal prohormone of brain natriuretic peptide (ClinicalTrials.gov: NCT05198791). Furthermore, the results of a large observational study of MINOCA patients from the SWEDEHEART registry have shown a significantly lower rate of cardiovascular events associated with the use of statins and ACEi/ARBs, and a trend for a lower event rate with the use of beta blockers, while DAPT, a cornerstone of therapy for MICAD patients, failed to improve prognoses. However, an important limitation of this study is the heterogeneous nature of the MINOCA cohort and the difficulty in discerning the mechanism leading to MI[20,21].

Moreover, information about cardiac structure and function as well as the plasma biochemical profile associated with the different causes of MINOCA is scarce. Beyond its role in differential diagnosis, CMR may help in the morphological and functional cardiac characterisation as well as in the prognostic stratification[22-24].

Finally, the biochemical profile of patients with MINOCA is still unidentified and whether a unique profile associated with specific pathophysiological mechanisms exists remains unknown. ET-1 and NPY are endogenous vasoactive substances regulating coronary vasomotion, with higher levels circulating in patients with coronary microvascular and epicardial spasm[25,26]. Elevated plasma levels of soluble CD40L and CRP, two inflammatory biomarkers associated with inflammation and thrombus formation, have been described in patients with MI due to acute plaque destabilisation[27]. Recent findings have shown that levels of specific circulating miRNA may have a close association with specific pathophysiological mechanisms of MI[28]. Particularly, a unique signature, comprising the upregulation of miR-16 and miR-26a and the downregulation of miR-1 and miR-133, has been reported to characterise coronary microvascular spasm, whereas miR-145 and miR-222 may help to identify patients with epicardial spasm[29]. Finally, a recent study identified miR-155-5p, miR-483-5p and miR-451a as novel biomarkers for the early identification of PR[30]. However, the role of circulating plasma biomarkers and miRNA in MINOCA patients has never been investigated.

Limitations

Given the trial design, both physicians and patients cannot be blinded to treatment allocation and, therefore, will know the allocated treatment arm.

Conclusions

In conclusion, the "one-size-fits-all" approach used for MICAD treatment may not apply uniformly to all MINOCA patients, and instead the approach should be "personalised" depending on the underlying pathophysiological mechanism responsible for the clinical presentation.

Thus, the next key step in the management of MINOCA is to demonstrate the benefits of tailored therapies on cardiovascular and quality of life outcomes. With this prospectively designed trial, we will test the prognostic value of a targeted therapeutic approach based on the identification of the underlying cause. Moreover, the results deriving from this trial may pave the way for a new pathophysiology-driven approach with cause-targeted therapies personalised for the mechanisms of MINOCA.

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Conflict of interest statement

L. Testa has served as an advisory board member and proctor for Abbott Vascular. The other authors have no conflicts of interest to declare.

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Supplementary data

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Supplementary data

Supplementary Appendix 1. Study population, inclusion and exclusion criteria.

Acute myocardial infarction (MI) will be defined based on the Fourth Universal Definition of MI Criteria, and in particular on clinical evidence of acute myocardial ischaemia, detection of rise and fall of serum troponin I levels with at least 1 value exceeding the 99th percentile upper limit and at least 1 of the following: 1) symptoms of myocardial ischaemia; 2) new ischaemic electrocardiographic (ECG) changes (ST-segment and/or T wave abnormalities); 3) development of pathological Q waves; 4) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology[10].

Exclusion criteria comprise an alternate diagnosis for the clinical presentation, in particular non-ischaemic causes of myocardial injury (such as sepsis, pulmonary embolism, valvular heart disease, hypertrophic cardiomyopathy, Takotsubo syndrome and myocarditis) that will be excluded prior to inclusion. For women of childbearing potential, the use of a highly effective contraceptive measure will be required in order to be included in the study.

Supplementary Appendix 2. Treatment.

In the "precision-medicine approach" arm, stent implantation will be considered if plaque rupture (PR) or plaque erosion (PE) at optical coherence tomography (OCT) analysis has been identified as the pathophysiological mechanism of MINOCA and in case of spontaneous coronary artery dissection (SCAD) for those patients with ongoing or recurrent ischaemia, haemodynamic instability, ventricular arrhythmias, or dissections involving the left main. In any case, the decision to proceed with percutaneous coronary intervention is at the operators' discretion. Patients with SCAD will be treated with single antiplatelet therapy (SAPT) or dual antiplatelet therapy (DAPT) according to the clinicians' discretion; DAPT will be the choice in case of PCI.

In the "standard approach" arm, treatment with beta blockers and angiotensin converting enzymes inhibitors (ACEi)/angiotensin receptor blockers (ARBs) will be considered in all patients as long-term therapy if not contraindicated (especially in case of left ventricle ejection fraction <40% and/or signs or symptoms of heart failure).

Pharmacological strategies will be started after the coronary angiography and during the index hospitalisation. All the procedures will be done by cardiologists with experience in the specific field. All enrolling centres already have a high proficiency in performing all the procedures required

for this study. Given the trial design, both physicians and patients cannot be blinded to treatment allocation, and both will know the allocated treatment arm.

Supplementary Appendix 3. Echocardiographic assessment.

All patients will undergo a comprehensive transthoracic echocardiographic (TTE) evaluation during hospital admission using a standard ultrasound machine (Artida; Toshiba) and all images will be digitally saved in raw data format to magneto optical discs for offline analysis performed by experienced echocardiographers. TTE will be used to calculate left and right ventricular and atrial dimensions (assessed by M-mode and two-dimensional [2D] images), ejection time, stroke volume, left ventricular (LV) systolic function (calculated using the modified Simpson's biplane method), right ventricular systolic function, transmitral flow Doppler spectra, mitral and tricuspidal valve annulus tissue Doppler spectra, inferior vena cava, aorta and pulmonary artery diameters and Doppler spectra, according to the recommendations of the European Association for Cardiovascular Imaging (EACVI).

Similarly, in patients with suspected distal/microvascular embolisation, a transoesophageal echocardiogram (TOE) will be performed during hospital admission to detect a hidden cardioembolic source (e.g., left atrial thrombus) using 2D and three-dimensional (3D) images and pulsed Doppler spectra of the left atrial appendage according to the EACVI recommendations on cardiovascular imaging for the detection of embolic sources. Philips Healthcare System machines will be used, and all images will be digitally saved in raw data format to magneto optical discs for offline analysis performed by experienced echocardiographers. Moreover, in case of suspect cardioembolic source coming from the LV (e.g., LV thrombus), contrast echocardiography with the injection of a 0.3 ml solution of SONOVUE through a large peripheral vein will be performed.

Supplementary Appendix 4. Coronary angiography and ventriculography.

Coronary angiography will be performed through a radial or femoral approach within 90 minutes from hospital admission in patients presenting with persistent ST-segment elevation, and within 48 hours in patients presenting with non-ST-segment elevation. Unfractionated heparin (initial weight-adjusted intravenous bolus of 60 IU/kg, with repeat boluses to achieve an activated clotting time of 250 to 300 seconds) will be administered in all patients. To fully expose all segments of the coronary arteries, at least 2 perpendicular projections for the right coronary artery (RCA) and 4 projections for the left coronary artery (LCA) will be taken. Left ventriculography will be performed at time of coronary angiography to assess the invasive measurement of LV end-diastolic

pressure (LVEDP), a surrogate measure of LV preload and LV diastolic operating compliance, along with the detection of global and regional LV wall motion abnormalities.

Non-obstructive coronary artery disease will be defined as any lesions ≥50% in any major epicardial vessel. In case of epicardial coronary artery stenosis ranging from 30 to 49%, a quantitative coronary analysis (QCA) can be performed at the operator's discretion. Moreover, in order not to miss any alternative diagnoses, an independent analysis of coronary angiography and left ventriculography will be performed at the end of the study by 2 independent cardiologists blinded to patients' diagnosis and group allocation.

Supplementary Appendix 5. Optical coherence tomography (OCT).

Optical coherence tomography will be performed at the time of coronary angiography in all patients randomised to the "precision-medicine approach" to detect images suggestive of PR/PE or SCAD. A 0.014-inch guidewire will be placed distally in the target vessel. The target vessel will be defined as the vessel with suspected angiographic images of plaque instability or with non-obstructive atherosclerotic lesions. In case of completely normal coronary arteries, the left anterior descending artery will be chosen reflecting its subtended myocardial mass and coronary dominance. Frequency domain OCT (FD-OCT) images will be acquired using a commercially available system (C7 System; LightLab Imaging/St Jude Medical) connected to an OCT catheter (C7 Dragonfly; LightLab Imaging/St Jude Medical), which will be advanced distally. The FD-OCT run will be performed using the integrated automated pullback device at 20 mm/s. During image acquisition, coronary blood flow will be replaced by continuous flushing of contrast media directly from the guiding catheter at a rate of 4 ml/s with a power injector to create a virtually blood-free environment. OCT analysis and definition of PR/PE and/or SCAD will be performed according to the most recent OCT consensus document recommendations.

Supplementary Appendix 6. Intracoronary acetylcholine (ACh) provocative test.

An intracoronary acetylcholine provocative test was performed at the time of coronary angiography in all patients randomised to the "precision-medicine approach". When a radial approach is chosen, long sheaths will be used to prevent radial spasm and prophylactic use of calcium channel blockers (CCBs) will be avoided. A fasting period >12 h will be requested in all patients when feasible. ACh will be administered with a slow-rate manual infusion over a period of 3 minutes and a "stepwise approach", with a 2–3 minute interval between injections (20-50-100-200 mcg into the LCA or 20–50 μg into the RCA). Coronary angiography will be performed 1 min after each injection of these

agents and/or when chest pain and/or ischaemic ECG shifts are observed. The decision of testing the LCA or RCA first with the provocative test will be left to the discretion of the physicians; both the LCA and RCA will be tested if the first test is negative. Angiographic responses during the provocative test are assessed in multiple orthogonal views to detect the most severe narrowing and analysed by visual assessment. The test will be considered positive for epicardial coronary spasm in the presence of these three components: 1) focal or diffuse epicardial coronary diameter reduction ≥90% in comparison with the relaxed state following intracoronary nitroglycerine administration given to relieve the spasm; 2) reproduction of the patient's symptoms; and 3) ischaemic ECG shifts. Microvascular spasm will be diagnosed when typical ischaemic ST-segment changes and angina develops in the absence of epicardial coronary constriction (<90% diameter reduction). Patients who experience no angina, spasm, or ST-segment shifts are considered to have a negative test response (normal coronary vasoreactivity). Similarly, patients who experience ischaemic ECG shifts without angina or patients with chest pain without ischaemic ECG shifts are considered to have a negative test response.

Supplementary Appendix 7. Cardiac magnetic resonance (CMR).

CMR will be performed during the hospital stay using a 1.5 Tesla system equipped with a 32-channel cardiac coil. A conventional CMR including cine, T2-weighted, first pass perfusion, and conventional breath-held late gadolinium enhancement (LGE) will be performed. Cardiac chamber size and function will be assessed according to the European association of cardiovascular imaging (EACVI) recommendations. Defect of perfusion will be assessed in first pass perfusion sequences. Myocardial tissue characterisation will be assessed by T2-weighted and LGE sequences to detect the presence and extent of myocardial and pericardial inflammation/oedema and myocardial scar/fibrosis.

Supplementary Appendix 8. Adverse events and serious adverse events/reactions (SAEs/SARs) assessment.

An adverse event will be defined according to Article 2 of Directive 2001/20/EC as any untoward medical occurrence in a patient or clinical trial subject who has been administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of a medicinal product, whether or not it is considered related to the medicinal product.

An adverse reaction will be defined according to Article 2(n) of Directive 2001/20/EC as all untoward and unintended responses to an investigational medicinal product related to any dose administered. The definition implies a reasonable possibility of a causal relationship between the event and the investigational medicinal product (IMP).

SAEs/SARs will be defined according to Article 2 of Directive 2001/20/EC as any untoward medical occurrence or effect that, at any dose, results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect. These characteristics/consequences have to be considered at the time of the event. For example, regarding a life-threatening event, this refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. Some medical events may jeopardise the subject or may require an intervention to prevent one of the above characteristics/consequences. Such events (herein after referred to as "important medical events") will also be considered as "serious" in accordance with the definition. Medical and scientific judgement will be exercised in deciding whether an event is "serious" in accordance with these criteria. In particular, in case of bleeding, these will be defined according to the Bleeding Academic Research Consortium (BARC) classification and will be recorded as "adverse events" or "SAEs" according to the above definitions.

Reports of SAEs will be immediately notified to the principal investigator of the coordinating centre (Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome) regardless of the attribution by the investigator of a causal relationship with the product under study.

The causal relationship with the product under study will be defined as:
• related: after careful evaluation, a safe relationship emerges with the use of the product under study
• not related: due to causes not related to the product under study.

Immediate reporting should allow the appropriate measures to be taken to address potential new risks in the clinical trial.

Supplementary Appendix 9. Monitoring.

Initiation visits before the start of the trial, visits during and at the end of the trial (close-out visit) are provided for each centre. Regular telephone conferences between the clinical trial units (CTUs)/contract research organizations (CROs) will ensure the harmonisation of procedures. Monitoring will be carried out by the respective CTUs at the sites or by the CRO delegated for this purpose. All data and source documents will be made accessible to the monitors, and any questions posed during monitoring can be answered by any participant. To reduce the risk of detection and performance bias, the Seattle Angina Questionnaire (SAQ) will be completed by the patients and, afterwards, a team of 2 cardiologists blinded to group allocation and belonging to an external cardiology unit will submit and collate the questionnaires from the study participants.

The Data Monitoring Committee (DMC) will consist of an independent group of 3 experts consisting of a clinical cardiologist expert in cardiovascular emergencies, an interventional cardiologist, and a clinical cardiologist expert in biostatistics. The DMC is responsible for monitoring the safety of participants and the conduct of the trial. The DMC provides recommendations on the advisability of continuing the trial or of adopting protocol changes necessary to maintain the safety of enrolled patients. The initial DMC meeting will occur at the start of the trial and will convene once annually, to examine the accumulated safety and enrolment data, review study progress, and discuss all the factors that might impact continuation of the study as designed.

Supplementary Appendix 10. Circulating biomarkers and microRNA (miRNA) assay.

A 42 mL sample of venous blood will be collected at the time of coronary angiography or within 12 hours from coronary angiography for circulating biomarkers and miRNA expression profile assay. Peripheral blood mononuclear cells (PBMC) will be isolated from ethylenediamine tetraacetic acid (EDTA) blood by density gradient centrifugation. Serum and PBMC expression levels for deregulated miRNAs will be performed on the same samples to test circulating levels of miR-16, miR-26a, miR-145, miR-222, miR-155-5p, miR-483-5p, miR-45 using the serum microRNA microarray commercial kit. Biochemical profile for evaluating the expression of endothelin-1 (ET-1) and neuropeptide Y (NPY), C-reactive protein (CRP), soluble CD40 ligand (sCD40L) will performed on plasma and serum samples at baseline using ELISA immunoassay and results will be expressed in picograms per millilitre (pg/mL).

Moreover, circulating ET-1, NPY and sCD40L will be assessed through ELISA immunoassay and results will be expressed in picograms per millilitre (pg/mL). Blood sampling will be processed and

analysed in the research laboratory of the Department of Cardiovascular Science. Biological aliquots will be preserved at XBiogem Biobank at Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome. Coded plasma, serum and PBMC samples from patients enrolled in the other centres (Centro Cardiologico Monzino IRCCS and IRCCS Policlinico San Donato) will be collected and stored with a shared and unique protocol in order to guarantee procedure standardisation and will be shipped to our centre for the analysis.