StAndardizing the Management of patients with coronary miCROvascular dysfunction: the SAMCRO trial

Version number 1 of March, 2023

Signature page, approval of Study Protocol

I, the undersigned, have read and understand the protocol and agree that it contains all necessary information for conducting the study for my position in the study and I agree to conduct the trial as set out in this study protocol, the current version of the World Medical Declaration of Helsinki, ICH-GCP guidelines and the local legally applicable requirements.

Study Principal Investigator

_____ _____

Date: Gianluca Campo, MD

Investigator Statement

I, the undersigned, have read and understand the protocol and agree that it contains all necessary information for conducting the study for my position in the study and I agree to conduct the trial as set out in this study protocol, the current version of the World Medical Declaration of Helsinki, ICH-GCP guidelines and the local legally applicable requirements.

Site: _____

Address: _____

Principal Investigator: _____

_____ _____

Date: Signature

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1 STUDY SYNOPSIS

Study Title	Standardizing the Management of patients with Coronary Microvascular Dysfunction: the SAMCRO trial
Protocol version	V1
Date	March, 2023
Study Sponsors	Consorzio Futuro in Ricerca, Ferrara, Italy
Study Principal Investigator	Gianluca Campo, MD
Study Objectives	The primary efficacy objective is to determine whether a multidomain lifestyle intervention improves angina status and quality of life in ANOCA patients as compared to current standard of care.
Study design	The SAMCRO is an all comers, prospective, randomized, multicenter, open-label study with blinded adjudicated evaluation of outcomes (PROBE). The diagnosis of ANOCA will be confirmed with coronary artery angiography and with the invasive assessment of coronary microvascular dysfunction (CMD) and coronary vasomotion. At least 120 ANOCA patients with invasively confirmed CMD will be randomized to i) multi-domain lifestyle intervention (experimental arm) vs. ii) standard of care (control arm). All patients will undergo follow-up visits at 6, 12, 24, 36, 48 and 60 months. The study endpoints will be the improvement of angina status and quality of life as assessed by validated questionnaires at one year. All participants in the multi-domain lifestyle group will receive five different kinds of intervention: i) dietary counselling, ii) strict management of CV and metabolic risk factors, iii) tailoring of medical therapy on the basis of the invasive assessment of CMD and coronary vasomotion, iv) exercise training and v) psychological intervention. Patients randomized to the control group will be managed according to current guidelines. The angina status will be assessed by the Seattle Angina Questionnaire (SAQ). Quality of life will be assessed using the EuroQoL (EQ5D-5L). Anxiety and depression will be assessed using the Beck Depression Inventory (BDI).
Study arms	EXPERIMENTAL ARM: MULTI-DOMAIN LIFESTILE INTERVENTION Patients will receive five different kinds of intervention: i) strict management of CV and metabolic risk factors, ii) tailoring of medical therapy on the basis of the invasive assessment of CMD and coronary vasomotion, iii) dietary counselling, iv) exercise training v) psychological counselling CONTROL ARM: STANDARD OF CARE Patients randomized to the control group will be managed according to current

	guidelines.
Number of participants	120
Trial Location	Coordinating Center: Cardiology Unit, Azienda Ospedaliero Universitaria di Ferrara Partecipating centers: See List of the partecipating centers
Inclusion criteria	i) Patient admitted to hospital for CCS with clinical symptom of angina and with indication for coronary artery angiography, AND ii) Absence of obstructive coronary artery disease, iii) Invasive diagnosis of coronary microvascular dysfunction
Exclusion criteria	I. Planned coronary revascularization, II. Co-morbidity reducing life expectancy to less than 1 year, III. Any factor precluding 1-year follow-up, IV. Prior Coronary Artery Bypass Graft (CABG) surgery, V. Presence of a chronic total occlusion (CTO)
Primary endpoint	• Seattle Angina Questionnaire (SAQ) summary score
Secondary efficacy endpoints	• SAQ angina frequency domain • SAQ angina stability domain • SAQ treatment satisfaction domain • SAQ physical limitation domain • SAQ quality of life domain • EQ-5D descriptive system: mobility domain • EQ-5D descriptive system: self-care domain • EQ-5D descriptive system: usual activities domain • EQ-5D descriptive system: pain/discomfort domain • EQ-5D descriptive system: anxiety/depression domain • EQ visual analogue scale (EQ-VAS) • Beck Depression Inventory (BDI) • Compliance to the multi-domain lifestyle intervention • All-cause death • Cardiovascular death • Hospital admission for any cause
Assessment Schedule	Pre-eligibility screening, inclusion, randomization, 6-month, 12-month, 24-month, 36-month, 48-month, 60-month
Study Duration	Enrollment: 12-18 months Follow-up: 5-year from the last patient
Clinical Event	A blinded Clinical Event Adjudication Committee will adjudicate adverse events.

Adjudication Committee	
Data and Safety Monitoring Board	An independent Data and Safety Monitoring Board will advise the Steering Committee on the safety aspects and overall progress of the study.
Statistical Considerations	Based on previous studies, we suppose that our intervention will be related to a mean group difference of change in SAQSS of 10 U. We calculated that a sample size of 60 patients per group gave 80% power to detect a between-group difference in SAQSS. This calculation assumed a 2-tailed 5% significance level and a standard deviation of SAQSS values around 20 U.

2 BACKGROUND

2.1 Definition and prevalence of angina without obstructive coronary artery disease (ANOCA)

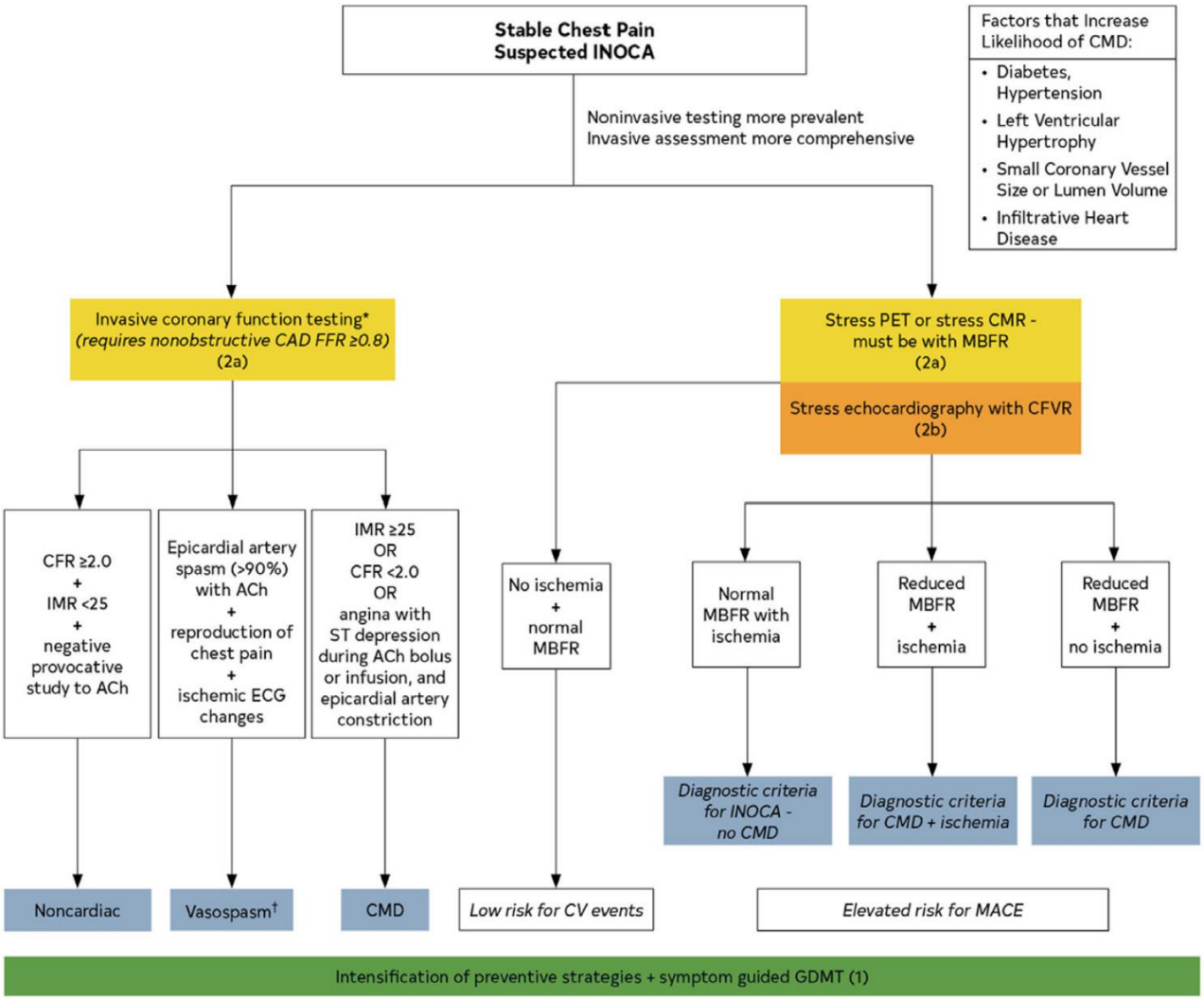
Chest pain is the principal symptom complained by patients with coronary artery disease. However, nearly half of the patients with effort angina have non-obstructive coronary artery disease defined as the absence of >50% of stenosis in an epicardial coronary artery [1]. Patients with effort angina are referred to the interventional cardiologist in case of typical symptoms [2] in presence of a positive ischemia test as abnormal stress electrocardiogram or abnormal cardiac stress imaging test [3]. The terms "angina with no obstructive coronary artery disease" or ANOCA is typically used to define patients with symptoms of angina in absence of epicardial disease. In this case it is of paramount importance to evaluate for the presence of coronary microvascular disfunction (CMD). The Coronary Vasomotor Disorder International Study group (COVADIS) provided the diagnostic criteria for CMD [4]:

- Symptoms of myocardial ischemia
- No obstructive coronary artery disease (stenosis<50% or fractional flow reserve (FFR) > 0.80)
- Objective evidence of myocardial ischemia (not mandatory)
- Evidence of impaired coronary microvascular function.

Classical cardiovascular risk factors (hypertension, diabetes, hyperlipidemia, obesity and menopause) may contribute to a chronic inflammation status triggering endothelial dysfunction and boosting CMD [3]. At rest, the myocardium extracts 75% of the blood oxygen and any increase in oxygen consumption determines increased oxygen demand, which leads to an increase in myocardial blood flow (MBF) [5]. MBF is mainly regulated by microcirculation [4]. MBF can be defined as the amount of flow through the coronary vessels expressed as blood by microcirculation, or the amount of flow through the coronary flow per gram of myocardium [5]. The prevalence of ANOCA has increased over the past decade as a result of growing recognition of this as a clinically important diagnosis apart from obstructive CAD. Based on the ACC National Cardiovascular Data Registry, it has been estimated that approximately 3-4 million individuals annually experience signs and symptoms of ischemia without obstructive CAD; this estimate; however, reflects only those patients referred for invasive angiography. Through numerous large, multicenter observational trials, there was a striking female-predominance of ANOCA as compared to individuals with obstructive CAD. This mirrors previous findings suggesting that ≈50% of women undergoing annual coronary angiograms will lack angiographic evidence of obstructive CAD, as compared with 7%-17% of men undergoing angiography. Once CMD is defined it is of paramount importance to optimize medical therapy with the goal of treating cardiovascular risk factors that fuel endothelial dysfunction. As a matter of fact, having non-obstructive CAD is not benign and portends an intermediate prognosis, with a MACE risk that is higher than those with minimal to no atherosclerosis [7]. However, the false perception of the fact that these patients are a low-risk category, carry to a low treatment of ANOCA patients, which feeds a vicious circle whereby the failure to reduce cardiovascular risk factors leads to a maintenance and aggravation of anginal symptoms. Symptoms persistence leads to a substantial limitation of daily activities and therefore to a significant deterioration in the quality of life (QOL) [8].

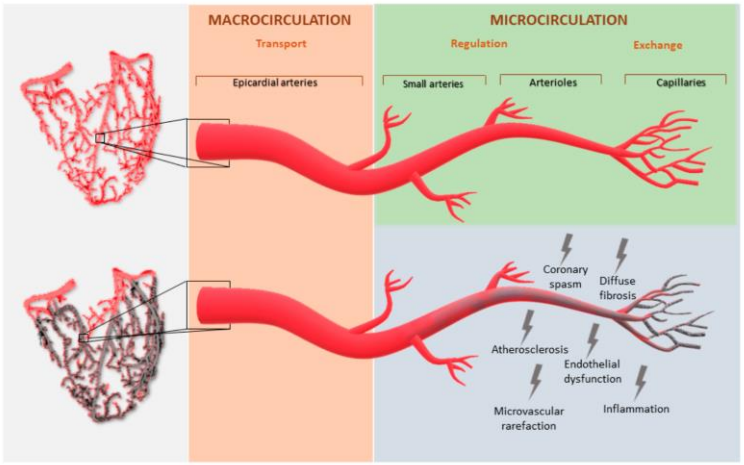
2.2 Invasive diagnosis of coronary microvascular dysfunction

The diagnosis of INOCA can be evaluated invasively or non-invasively. The 2021 ACC/AHA Chest Pain Guideline recommend patients with stable chest pain and suspected ANOCA should be evaluated with invasive coronary function or non-invasive stress PET MPI or stress CMR with myocardial blood flow reserve to enhance diagnosis and risk stratification.



Comprehensive diagnostic assessment for ANOCA ideally requires invasive angiography with functional coronary angiography and coronary reactivity testing, and its use is associated with sustained improvement of angina and better quality of life, as demonstrated by the CorMicA trial. Invasive testing for ANOCA generally begins with coronary angiography followed by coronary function testing (CFT), to evaluate for significant stenoses and microvascular angina using fractional flow reserve (FFR) and CFR, respectively. FFR estimates the severity of epicardial stenosis by measuring the distal coronary pressure (Pd) and aortic pressure (Pa) measured during maximal flow, with FFR being the ratio of Pd to Pa. An abnormal FFR is defined as ≤0.80. CFR and the Index of Microcirculatory Resistance (IMR) are then used to evaluate

microvascular angina. CFR - the ratio of hyperemic coronary blood flow to resting flow - reflects the ability of the coronary circulation to augment blood flow from rest. CFR is calculated using thermodilution in which a saline bolus is injected, and the resting mean transit time divided by hyperemic mean transit time; an abnormal CFR is defined as ≤2. Also, IMR is assessed using thermodilution and is a product of the distal coronary pressure at maximal hyperemia and the hyperemia mean transit time. IMR greater than or equal to 25 is suggestive of CMD. CFT is also used to evaluate for vasospasms using acetylcholine, adenosine, and sodium nitroprusside to trigger reproducible chest pain, ischemic changes on ECG, or an epicardial arterial diameter. Microvascular spasm is diagnosed with the exclusion of 90% reduction in diameter.



Coronary Vasomotion Disorders International Study Group proposed the following diagnostic algorithm for vasospasms:

i. exclude obstructive lesions with FFR and angiography
ii. evaluate for microvascular resistance with CFR and IMR
iii. confirm vasospasms with vasoreactivity test with acetylcholine.

This protocol classifies patients into ANOCA subtypes including:

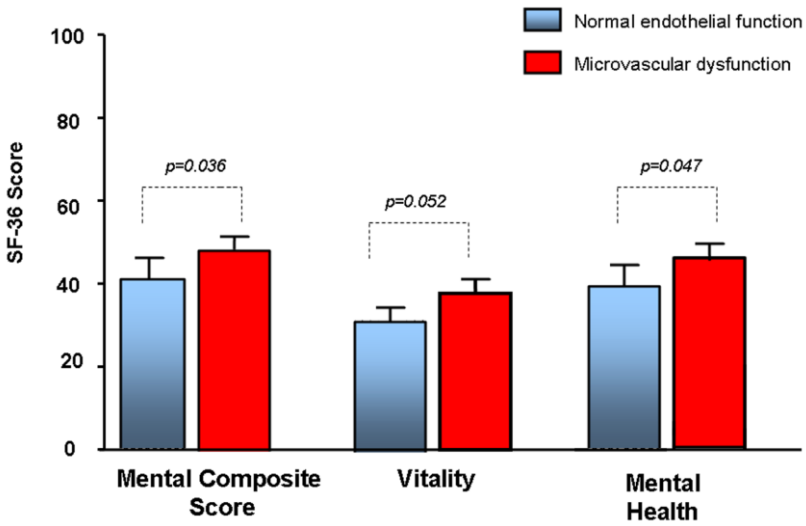
1. coronary microvascular dysfunction
2. coronary vasospasm (epicardial and/or microvascular)
3. mixed forms of coronary microvascular dysfunction and vasospasm

All ANOCA subtypes are associated with an increased rate of MI and cardiac death.

2.3 ANOCA and quality of life

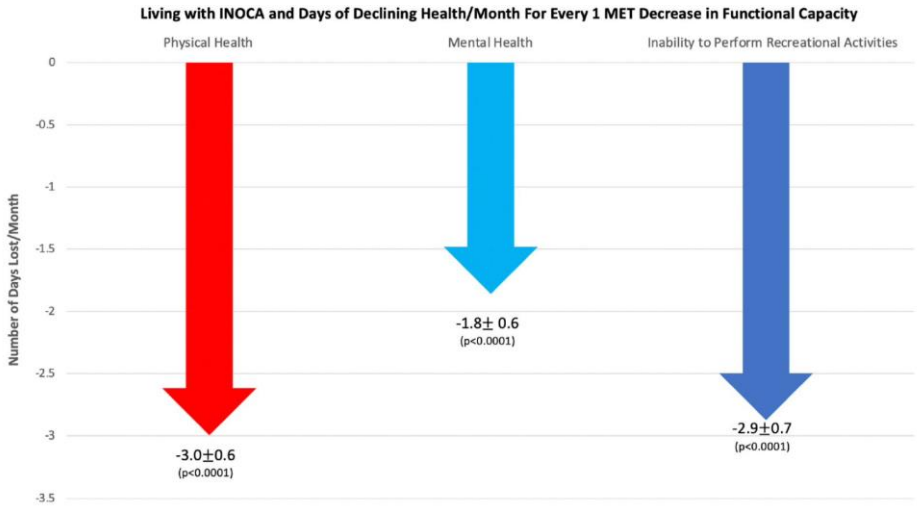
Chronic coronary artery disease (CAD) adversely affects both quality and length of life [9]. A common approach used to measure QOL in cardiovascular clinical trials involves assessing 3 core domains: disease-specific symptoms (eg, angina), physical functioning (eg, ability to perform activities reflecting incremental workloads), and emotional/psychological well-being (eg, anxiety, depression, hedonic adaptation) [9]. A sub-analysis of the ISCHEMIA trial showed that in patients with chronic CAD an improvement in QOL has been seen if an early invasive strategy was chosen when symptoms were more accentuated at the baseline [10]. For patients with ANOCA the problem is even more pronounced. Since immediate treatment of the cause of anginal pain is not possible, these patients often do not benefit even from an early invasive diagnosis strategy [11-12] and usually represent a cost for healthcare considering repeated evaluations for diagnostic and therapeutic uncertainty [11-12]. ANOCA patients have also poor QOL, functional disability and limitations in activities of daily living [13-14]. Reriani et al. evaluated 457 ANOCA patients showing that QOL (tested with SF-36 survey) with respect to measures of mental well-being during long-term follow-up is

better in those patients who were assessed, diagnosed and received treatment for microvascular endothelial dysfunction compared with those who are found to have normal endothelial function [13]. The current study suggests that assessment and treatment of microvascular angina may improve their QOL compared to patients without microvascular angina, however, is not randomized and did not clearly prove that a tailored treatment in ANOCA patients with microvascular disfunction may improve QOL compared to those who do not receive this treatment but always with microvascular dysfunction.



2.4 ANOCA and depression

Gulati et. al recently reported the association between ischemia with no obstructive coronary arteries (INOCA) and self-reported physical, social and mental health through a survey of all members (n=1579) of the INOCA international patient support group [8]. From their results, INOCA patients reported symptoms of chest pain, pressure, or discomfort in 92.9%. Most respondents (40.4%) had experienced INOCA symptoms for at least 1 to 5 years, with almost half of them experiencing symptoms between 1 and 10 years before the diagnosis of INOCA was made (after multiple consultations), and 77.8% who had been told their symptoms were not cardiac [8]. Estimated functional capacity was higher prior to compared to after symptom onset, with an adverse impact of symptoms on their home life (80.5%), social life (80.1%), mental health (70.4%), outlook on life (69.7%), sex life (55.9%), and their partner relationship (53.9%). Approximately three-quarters reduced their work hours or stopped work completely, 47.5% retired early, and 38.4% applied for disability [8].



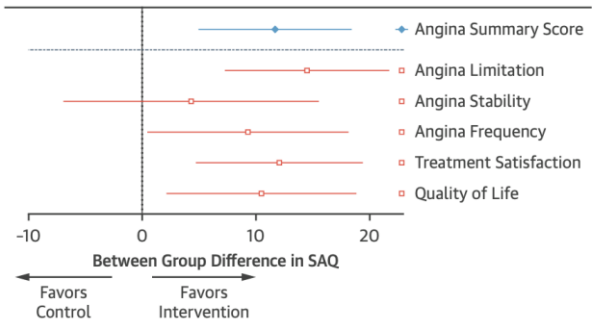
A fact that should not be underestimated is that at the time of the survey, most of the respondents living with INOCA reported their health as being fair (32.7%) or poor (19.2%). Mental health was adversely impacted in 70.4% of those surveyed, with almost the same number reporting that INOCA had negatively

affected their outlook on life. Psychological stress, which includes anxiety, depression, anger and personality disturbances, can be quite common in patients with CAD, including those with INOCA. Psychological stress can induce endothelial dysfunction and be an underlying cause of INOCA, particularly coronary microvascular dysfunction and vasospasm. ANOCA symptoms are associated with adverse physical, mental and social health quality of life. Increased patient awareness and physician recognition through data from randomized trials is crucial for the National Health Service. To improve diagnosis and treatment strategy and to develop evidence-based guidelines for this tricky cardiovascular disorder is clearly on demand. To date, data regarding multidomain lifestyle intervention are lacking from literature. Beyond the development of strict guidelines for a pharmacological approach, a game changer in ANOCA patients' management could stand in the slavish control of each cardiovascular risk factor, which contributes through different and specific mechanisms to worsen these patients' prognosis and quality of life.

2.5 CORMICA trial

The CorMicA trial is a parallel-group, randomized, sham-controlled trial with blinded outcome assessment that evaluated if an interventional diagnostic procedure with linked medical therapy, was routinely feasible and improves angina in patients with ANOCA [15]. The invasive assessment of CMD included: assessment of coronary flow reserve (CFR) (abnormal <2.0), the index of microcirculatory resistance (IMR) (abnormal ≥25), and FFR (abnormal ≤0.80) during intravenous infusion of adenosine (140 mg/kg/min) and vasospasm provocation testing through incremental concentrations of acetylcholine (ACh) (10^6, 10^5, 10^4 mol/l) sequentially infused during 2-min periods [15]. Patients with ANOCA were randomized in a 1:1 fashion to the interventional group (stratified medical therapy) or the control group (standard of care, sham procedure). Seventy-five patients received the invasive assessment of CMD and compared to the standard of care arm ANOCA patients treated with optimized medical therapy showed at 6 month a reduction in angina severity and better quality of life [15].

FIGURE 3 Primary Efficacy Outcome: Treatment Difference in the 6-Month SAQ Summary Score



Forest plot of mean treatment difference in angina summary score (95% CI) and breakdown of the Seattle Angina Questionnaire (SAQ) score domains. The angina summary score is the mean of 3 angina domains (limitation, frequency, and overall quality of life). The angina summary score was adjusted for baseline variation using a regression model. The overall difference at 6 months was 11.7 U (95% confidence interval: 5.0 to 18.4; $p < 0.001$).

The mechanism of improvement in outcome is not so clear and as author underlined might be related to a better knowledge of the patient himself of his own disease and not only to the tailored treatment [15]. The CORMICA trial is not powered enough to differentiate between the improvement in QOL given by the knowledge of the diagnosis and the treatment. Statins and ACE-inhibitors were more prescribed in the interventional group compared to the other, however with not a complete penetration (88% vs. 53.9%; RR 1.63, 95% CI: 1.30 to 2.04; $p < 0.001$ for statins and 58.7% vs. 36.7%; RR: 1.59; 95% CI: 1.12 to 2.26; $p= 0.009$ for ACE inhibitors) [15]. This study clearly shows that diagnostic uncertainty and illness perception are at the basis of the discomfort of ANOCA patients: an increase in illness perception (lower scores at 6 months) amongst the intervention arm might be seen as a less threatening view of illness. Angina reduction

and improved quality-of-life scores could therefore be, in part, related to a better patient understanding of the disease [15].

2.6 Limitations of available evidence

Current evidence is focused on four main topics:

I. Incidence, prevalence of ANOCA condition and contributing factors;
II. Diagnosis (invasive or non invasive) of ANOCA;
III. Prognostic implications in terms of quality of life and outcome of ANOCA diagnosis;
IV. Medical treatment based on ANOCA diagnosis and subtypes.

Each single point has been analyzed and many data are currently available. The general overview suggestes that ANOCA is a mixed and complex condition where multiple factors are involved and resulting in poor outcome. **The missing piece of the puzzle is the integration of this information and how to translate them in daily practice to effectively modify prognosis of ANOCA patients.** Current investigation are mainly focused on medical treatments. CorMicA trial showed that the correct diagnosis and classification of the ANOCA endotype is crucial. But at the moment, the most important (and only) change in treatment is the selection of beta-blocker vs calcium-channel blocker based on the presence or not of positive vasoreactivity test. No data investigated how improve physical limitation, depression and overall quality of life beyond the medical treatment. In different subsent of patients, worthy studies showed that a multi-domain lifestyle intervention can significanly improve the effect of medical treatments. This data is missing for ANOCA patients.

3 HYPOTHESIS

Angina affects millions of people worldwide, being the most common symptom of myocardial ischemia. The most frequent cause of angina is obstructive coronary artery disease. Anyway, in up to 40% of cases, angina derives from coronary microvascular dysfunction (CMD) and/or coronary vasomotor dysfunction which well characterize the so-called angina with no obstructive coronary artery disease (ANOCA) patients. In the last years, the major advancements have been in the diagnostic workflow. Some studies showed that to achieve the correct diagnosis may improve the management and the quality of life of the ANOCA patients. Anyway, most of the studies were focused on single pharmacological approach (beta-blockers vs. calcium channel blockers). No prior studies tried to investigate a broader approach targeting the numerous pathological correlates behind ANOCA condition. The hypothesis of the "Standardizing the Management of patients with Coronary Microvascular Dysfunction (SAMCRO)" trial is to investigate if a multidomain lifestyle intervention improves angina status and quality of life in ANOCA patients as compared to current standard of care. The SAMCRO is an all comers, prospective, randomized, multicenter, open-label study with blinded adjudicated evaluation of outcomes (PROBE). The diagnosis of ANOCA will be confirmed with coronary artery angiography and with the invasive assessment of coronary microvascular dysfunction (CMD) and coronary vasomotion. At least 120 ANOCA patients with invasively confirmed CMD will be randomized to i) multi-domain lifestyle intervention (experimental arm) vs. ii) standard of care (control arm). All patients will undergo follow-up visits at 6, 12, 24, 36, 48 and 60 months. The study endpoints will be the improvement of angina status and quality of life as assessed by validated questionnaires at one year. All participants in the multi-domain lifestyle group will receive five different kinds of intervention: i) dietary counselling, ii) strict management of CV and metabolic risk factors, iii) tailoring of medical therapy on the basis of the invasive assessment of CMD and coronary vasomotion, iv) exercise training and v) psychological intervention. Patients randomized to the control group will be managed according to current guidelines. The angina status will be assessed by the Seattle Angina Questionnaire (SAQ). Quality of life will be assessed using the EuroQoL (EQ5D-5L). Anxiety and depression will be assessed using the Beck Depression Inventory (BDI).

4 STUDY ENDPOINTS

4.1 Primary efficacy endpoint

- Seattle Angina Questionnaire (SAQ) summary score

4.2 Secondary efficacy endpoints

- SAQ angina frequency domain
- SAQ angina stability domain
- SAQ treatment satisfaction domain
- SAQ physical limitation domain
- SAQ quality of life domain
- EQ-5D descriptive system: mobility domain
- EQ-5D descriptive system: self-care domain
- EQ-5D descriptive system: usual activities domain
- EQ-5D descriptive system: pain/discomfort domain
- EQ-5D descriptive system: anxiety/depression domain
- EQ visual analogue scale (EQ-VAS)
- Beck Depression Inventory (BDI)
- Compliance to the multi-domain lifestyle intervention
- All-cause death
- Cardiovascular death
- Hospital admission for any cause

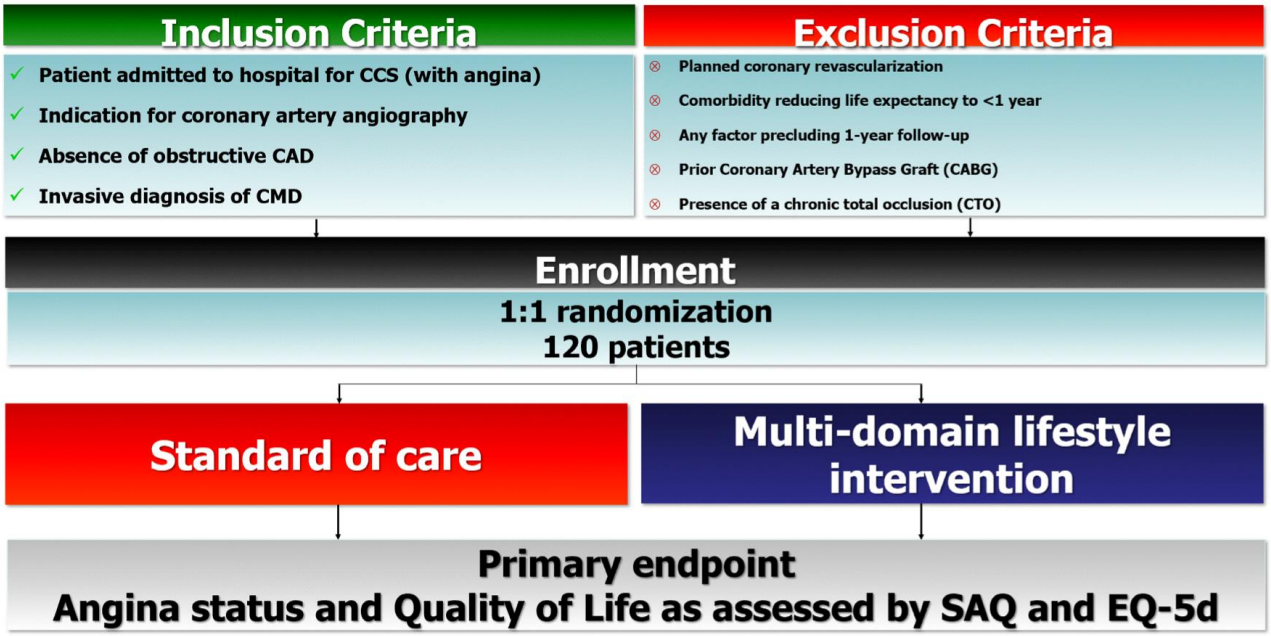
5 STUDY DESIGN, SCREENING, INCLUSION AND RANDOMIZATION

5.1 Study design

The " Standardizing the Management of patients with Coronary Microvascular Dysfunction (SAMCRO) " trial is an all comers, prospective, randomized, multicenter, open-label study with blinded adjudicated evaluation of endpoints (PROBE).

- GENERAL OVERVIEW OF THE STUDY

All patients undergoing coronary artery angiography (CAA) because of chronic coronary syndrome (CCS) will be screened for eligibility. Patient's eligibility must be assessed after the exclusion of epicardial coronary artery disease and then the invasive assessment of coronary microvascular dysfunction (CMD) and coronary vasomotion. CMD must be assessed by invasive measurement of coronary flow reserve (CFR) and index of microcirculatory resistance (IMR). Coronary vasomotion must be assessed by acetylcholine test (ACh test). Written informed consent must be obtained prior to randomization (after CMD and coronary vasomotion test). Patients with angina and absence of obstructive coronary artery disease (ANOCA) plus documented CMD (see below for the definition) are eligible for inclusion.



During inclusion visit (BASELINE), clinical, laboratory and treatment information will be collected and reported in the electronic case report form (eCRF). Baseline questionnaire to assess angina status, quality of life, and depression will be collected. Randomization will be performed centrally using an internet-based system. Patients will be randomized to:

i) multi-domain lifestyle intervention (experimental arm) vs.

ii) standard of care (control arm).

The procedures related to randomization arm are described below.

All patients will undergo follow-up visits at 6, 12, 24, 36, 48, 60 months. During follow-up visits, clinical

status, laboratory data, and compliance to medical therapy will be recorded and questionnaires to assess angina status and quality of life will be repeated. All patients will receive blood withdrawal at baseline and at follow-up visits. The study endpoints will be the improvement of angina status and quality of life as assessed by validated questionnaires (see detailed description below) at one year.

5.2 Screening of the patients

All patients undergoing coronary artery angiography with a diagnosis of stable coronary artery disease will be considered eligible for trial enrollment. In case of absence of epicardial coronary artery disease, coronary physiology assessment will be performed according to standard clinical practice, including acetylcholine test. If coronary physiology assessment discloses the presence of CMD, patients will be asked for the enrollment.

5.3 Study discussion and informed consent

All patients undergoing coronary artery angiography with a diagnosis of suspected stable coronary artery will be informed that they might be candidate for the enrollment in SAMCRO trial. Only in case of absence of epicardial coronary artery disease and documented CMD by invasive coronary physiology patients will be asked for enrollment in the SAMCRO trial. Before any study procedure, the patient must confirm its acceptation by signing the written informed consent.

5.4 Randomization

Randomization will be performed after the signature of the informed consent. Randomization will be performed centrally using an internet-based system. The patient identification number (Patient ID) and the treatment allocation will be assigned by the central randomization system. Treatment allocation will be assigned according to a computer-generated randomization list stratified by center. Randomization will be stratified according to sex (male vs. female), IMR value (less than 45 vs. equal or more than 45), ACh test result (positive vs. negative) and center.

Patients will be randomized to the following:

- EXPERIMENTAL ARM: MULTI-DOMAIN LIFESTILE INTERVENTION
- CONTROL ARM: STANDARD OF CARE

All patients who are randomized are irrevocably in the study, whether or not they are subsequently found to be eligible, or actually receiving the allocated treatment. Therefore, all patients must be followed until the prespecified study end date.

5.5 Study Timeline

The Table summarize the main steps and phases of the study.

BASELINE	From 0 to 6 months	6-MONTH	From 6 to 12 months	1, 2, 3, 4, 5-YEAR
ALL: Assessment of inc/exc criteria	EXPERIMENTAL INTERVENTION: Medical therapy optimization	ALL: Clinical visit and assessment of compliance with therapy. Medical Therapy optimization	EXPERIMENTAL INTERVENTION: Exercise intervention	ALL: Clinical visit and assessment of compliance with therapy. Medical Therapy optimization
ALL: Signature of the informed consent	EXPERIMENTAL INTERVENTION: Dietary counselling	ALL: Seattle Angina Questionnaire (SAQ)		ALL: Seattle Angina Questionnaire (SAQ)
ALL: Assessment of baseline characteristics	EXPERIMENTAL INTERVENTION: Psychotherapy counselling	ALL : EQ-5D-5L questionnaire		ALL : EQ-5D-5L questionnaire
ALL: Seattle Angina Questionnaire (SAQ)	EXPERIMENTAL INTERVENTION: Exercise intervention	ALL: Beck Depression Inventory (BDI)		ALL: Beck Depression Inventory (BDI)
ALL : EQ-5D-5L questionnaire	EXPERIMENTAL INTERVENTION: Strict CV risk factor control			
ALL: Beck Depression Inventory (BDI)				
ALL: RANDOMIZATION				
CONTROL ARM: face-to-face session to promote a heart-healthy lifestyle in terms of diet, smoking cessation, stress management and physical activity. Medical therapy optimization				

5.6 Measures to minimize/avoid bias

The trial is open label. The investigators in charge of follow-up visits and questionnaire collections will be different from investigators in charge of recruitment, baseline questionnaires collection and randomization procedure. The investigators in charge of follow-up procedures will be completely blinded to the randomization, as well as patient identifying information. Regarding clinical outcomes, an independent Clinical Event Committee (CEC) will adjudicate all endpoints. The CEC members and the CEC management team will be completely blinded to the randomization, as well as patient identifying information. Other measures to avoid or minimize bias introduced by the open-label design will include intent-to-treat principles of analysis and use of objective measures for endpoint classification.

6 STUDY POPULATION

6.1 Inclusion criteria

i) Patient admitted to hospital for CCS with indication for coronary artery angiography,

AND

ii) absence of obstructive coronary artery disease at invasive coronary artery angiography,

iii) Coronary microvascular dysfunction as identified by invasive coronary physiology.

6.2 Exclusion criteria

i) Planned coronary revascularization,

ii) Co-morbidity reducing life expectancy to less than 1 year,

iii) Any factor precluding 1-year follow-up,

iv) Prior Coronary Artery Bypass Graft (CABG) surgery,

v) Presence of a chronic total occlusion (CTO).

7 STUDY PROCEDURES

7.1 Diagnosis of ANOCA and coronary microvascular dysfunction

In agreement with consensus document (COVADIS) [4], ANOCA will be defined in presence of:

- Symptoms of myocardial ischemia
- No obstructive coronary artery disease (stenosis<50%)
- Negative troponin
- Objective evidence of myocardial ischemia (not mandatory)

The diagnosis of ANOCA is based on clinical history, tests performed before clinical admission to hospital and invasive coronary artery angiography. The current protocol requires to integrated clinical diagnosis of ANOCA with the documentation of coronary microvascular dysfunction (CMD). Only patients satisfying criteria for ANOCA and CMD can be considered for randomization.

For the present purpose, CMD diagnosis is based on invasive coronary physiology and it is defined as:

- Fractional flow reserve (FFR) value >0.80

AND

- Coronary flow reserve (CFR) <2

AND/OR

- Index of microcirculatory resistance (IMR) >25

AND/OR

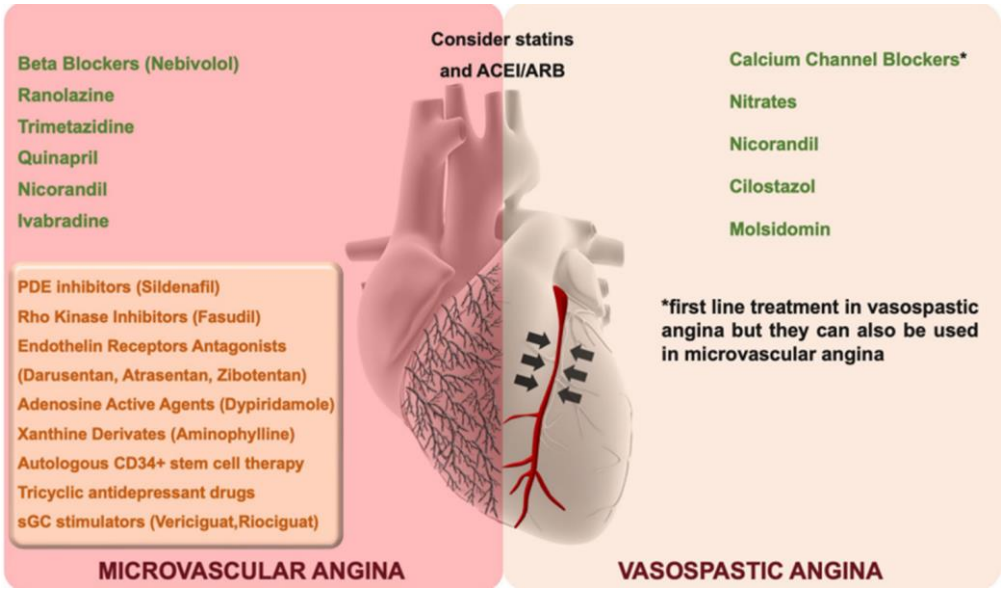
- Positive vasoreactivity test with Ach

7.2 Experimental arm: general description

All participants in the multi-domain lifestyle group will receive five different kinds of intervention:

i) strict management of CV and metabolic risk factors,
ii) tailoring of medical therapy on the basis of the invasive assessment of CMD and coronary vasomotion,
iii) exercise training
iv) dietary counselling,
v) psychological intervention.

Intensive management of CV and metabolic risk factors is based on guidelines with aims to improve blood pressure, to reduce cholesterol, to optimize glucose metabolism, and finally to cease smoking. At all study visits, study physicians will measure blood pressure and supervise the patient's blood pressure diary. In addition, laboratory data and body weight will be controlled. All patients will be treated with high-potency statin (if tolerated) and ezetimibe. Smokers will be supported promptly with dedicated smoking cessation programs.



Tailoring of the medical therapy will be based on the findings of invasive assessment of CMD and coronary vasomotion. Ranolazine will be prescribed at the highest tolerated dose. In presence of negative ACh test, nebivolol will be prescribed at the highest tolerated dose, otherwise verapamil or diltiazem will be administered at the highest tolerated dose. Long-acting nitrates and dihydropyridine calcium-channel blockers will be administered based on patient's symptoms and Ach test outcome. Compliance with medical therapy will be assessed at any study visits and monthly by phone call.

7.3 Experimental arm: exercise intervention

The exercise intervention consists of an early, tailored, mixed program. Briefly, the exercise intervention provides six supervised physical activity sessions (at 1, 2, 3, 6, 9 and 12 months) and a series of exercises to be performed at home from the Otago Exercise Program, along with recommending at least 20 minutes of moderate walking. During the supervised sessions, each patient performs calisthenics exercises for ≈5 min, followed by the 1-kilometre treadmill walking test (1k-TWT). Based on the results of the treadmill-walking practices, patients are then encouraged to replicate similar walking sessions at home and outdoors, autonomously. The home program is periodically adjusted during the subsequent visits. A detailed description of the exercise intervention is reported elsewhere [17-21]. The present exercise intervention showed in previous studies to be safe and effective in improving physical performance in patients with CAD. In addition, the mixed structure including supervised sessions and home-based exercises guarantees high rate of compliance overtime. The Figure below summarizes the main steps of the exercise intervention.

First supervised session	Home-based sessions	Subsequent supervised session
Pre-test: • measure of blood pressure • positioning RS100 Polar heart rate monitor to constantly evaluate heart rate • Calisthenics exercises	• 30 to 60 min of continuous moderate walking a day, at least 3 to 4 and preferably 7 days a week • Calisthenics exercises[b]	Pre-test: • Measure of blood pressure • Positioning RS100 Polar heart rate monitor to constantly evaluate heart rate. • Calisthenics exercises[b]
Start: walking on the level at 2.0 km/h		Start: walking at an updated intensity estabilished according to reached results in the previous activity session
Every 30 s: increases of 0.3 km/h up to reach a walking speed corresponding to a perceived exertion of 11–13 on the Borg scale for 1 km[a].		Every 30 s: increases of 0.3 km/h up to reach a walking speed corresponding to a perceived exertion of 11–13 on the Borg scale for 1 km[a].
Post-test: • Measure of blood pressure. • Counselling on physical activity and daily activities, such as gardening, or household work.		Post-test: • Measure of blood pressure • Counselling on physical activity and daily activities, such as gardening, or household work.

7.4 Experimental arm: diet

The dietary intervention includes individual counselling with a nutritionist. In addition, at any study visits, study physicians assess the body weight, the compliance with diet instructions and stress the importance to follow a Mediterranean diet. Dietary counselling will be provided by an experienced nutrition professional. Participants will attend, at inclusion, an individual face-to-face interview (60-90 minutes), where personal dietary goals and patient's daily diet will be agreed. The Mediterranean diet will be promoted as the healthiest type, and the following specific suggestions will be given: (i) to use olive oil as the main fat for cooking and dressing, (ii) to have at least 2 seasonal, fresh vegetable servings a day, (iii) moderate consumption of fresh fruit, (iv) consumption of fish at least 2 times per week, (v) favoring legumes to meat (strong limitation in the use of red meat) [16]. In addition, advice regarding food preparation is given, e.g., favoring cooking to frying and limiting the use of salt and sugar. A few examples of healthy meals (including information on ingredients and recipes) will be provided.

7.5 Experimental arm: psychological counselling

The psychotherapeutic intervention is aimed at four areas related to depression in CAD:

1. coping with illness, including feelings of being defeated, feelings of insecurity and loss of role gratification
2. dealing with emotions, including coping with dejection and lack of energy
3. change of lifestyle
4. shaping of social relationships and unconscious relationship patterns.

Patients randomized to the experimental arm will receive two sessions of individual, supportive–expressive psychotherapy during the first month after the randomization. Based on the feedback, the psychotherapist can schedule a third individual session in the second month after the randomization. The psychotherapy session aims to analyze illness perception and to enhance patients' capability to cope with anxiety, anger and chronic stress. The session will be based on core principles of cognitive behavioral therapy (e.g., systematic problem analysis, cognitive reframing, and action planning, including "homeworks").

7.6 Control arm: general description

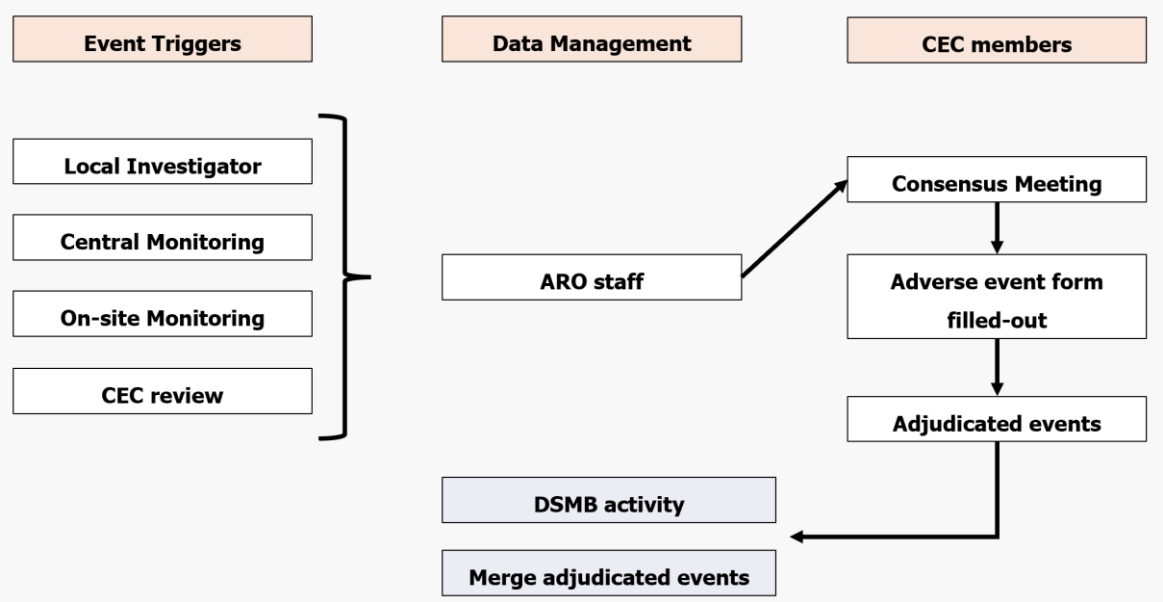
Patients randomized to the control group will be managed according to current guidelines. Briefly, important suggestions for a heart-healthy lifestyle are provided in terms of diet, smoking cessation, stress management and physical activity. Medical therapy will be optimized at the inclusion visit. Additional recommendations and tailoring of the medical therapy will be performed at the follow-up visits.

7.7 Study collection of adverse events

All adverse events must be reported by the study investigators. The Academic Research Organization will collect the source document of all adverse events. Adverse events will be adjudicated by the Clinical Event Committee (CEC).

7.8 Adjudication of clinical events

A committee consisting of clinicians who are blinded to treatment allocation will adjudicate all adverse events. The functioning rules and the membership of the Adjudication Committee are detailed in the Adjudication Committee Charter before the start of the trial. The adjudication results will be binding for the final analysis.



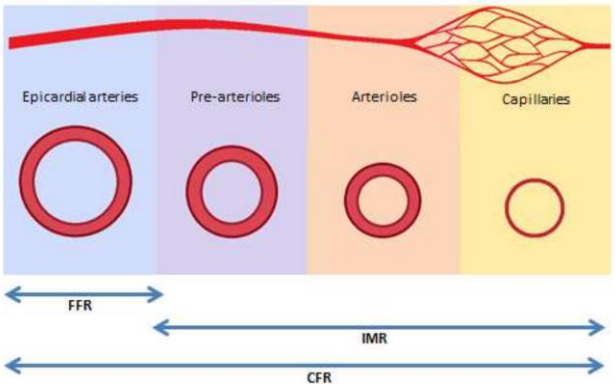
8 STUDY DEFINITIONS

8.1 Invasive assessment of coronary microvascular dysfunction

A comprehensive assessment of microvascular function includes testing the two main mechanisms of microvascular dysfunction:

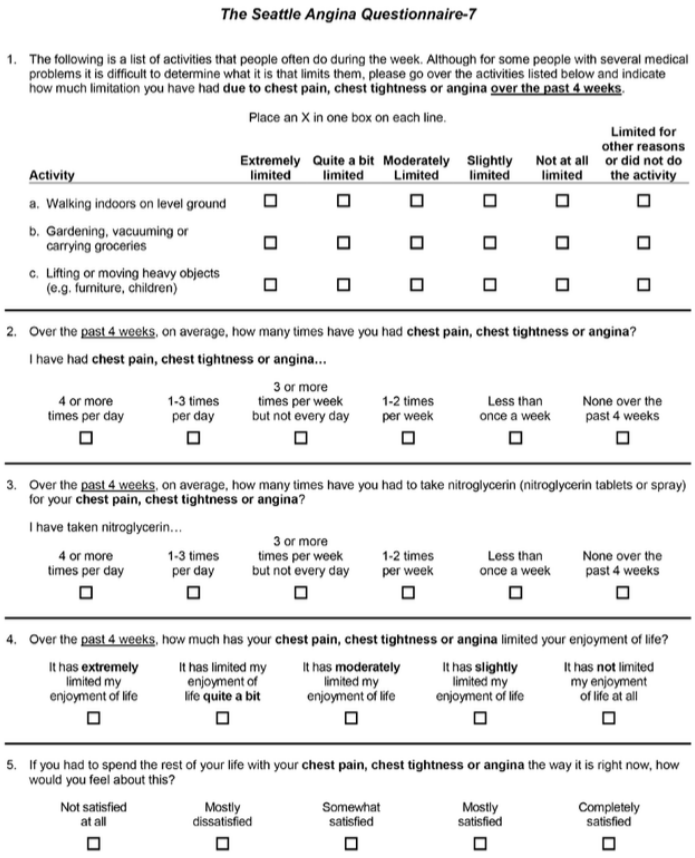
a. impaired endothelium-independent microvascular vasodilatation, which is measured by coronary flow reserve (CFR) and by index of microvascular resistance (IMR), and
b. impaired endothelium-dependent dysfunction, which evaluates the induction of epicardial or microvascular spasm after intracoronary injection of acetylcholine.

Both CFR and IMR are measured using intravenous vasodilators, such as adenosine. In normal conditions, coronary blood flow increases 3–4 times in response to increased myocardial oxygen requirements. CFR is the ability of coronary blood flow to match the metabolic demand and it is measured as the ratio of maximal flow after adenosine induced hyperemia to resting absolute myocardial blood flow. CFR reflects the combined vasodilator capacity of epicardial and microvascular coronary arteries. Hence, its interpretation needs assessment of FFR, which estimates the severity of epicardial stenosis. Microvascular resistance, expressed as index of microcirculatory resistance (IMR) is measured by thermodilution in a hyperemic condition. FFR, CFR and IMR can be measured in a single solution with PressureWire X (Abbott Vascular) with the bolus thermodilution technique. In patients with high FFR (>0.80), CFR is determined mainly by the status of the microvascular system. Hence, measurements of CFR and IMR in patients with high FFR are used to assess microvascular function, allowing more accurate risk stratification. In these patients, values of CFR < 2.0 or IMR >25 units indicate an abnormal microvascular function. Endothelium-dependent dysfunction is assessed using intracoronary acetylcholine infusion. In normal endothelium, acetylcholine induces vasodilatation at both epicardial and microcirculation levels by stimulating NO synthesis. In a dysfunctional endothelium or in impaired smooth muscle cell function, acetylcholine triggers paradoxical arteriolar vasoconstriction. In patients with CMD, acetylcholine infusion may trigger epicardial and/or microvascular spasm with angina symptoms, with or without ECG changes. Provocation of coronary artery spasm is performed with an intracoronary injection of ACh. Acetylcholine chloride is injected in incremental doses of 20, 50, and 100 µg into the left coronary artery (LCA) over 2 minutes, with at least a 3-minute interval between injections. Coronary arteriography is performed when either ST-segment changes or chest pain (or both) occur, or after 1 minute following the completion of each injection. During the study, arterial blood pressure and standard 12-lead ECG are continuously monitored.



8.2 Seattle Angina Questionnaire

Originally written in 1992 and published in 1994, the Seattle Angina Questionnaire (SAQ) is a 19-item self-administered, disease-specific patient-reported outcome with 5 domains: physical limitation, anginal stability, anginal frequency, treatment satisfaction, and disease perception/quality of life [22]. The SAQ serves as a 'standardized history' that can overcome some of the challenges in over- and under-recognizing angina and its impact on patients' lives [22]. To make the SAQ more feasible to use in clinical care, the original 19-item SAQ was shortened to 7 items in 2014, which captures the angina frequency, physical limitation, and quality of life domains. A summary score was also introduced that averages these three domains. All SAQ domain scores and the summary score range from 0 to 100 with higher scores indicating less angina, fewer functional limitations, and better quality of life: 0 to 24 represents poor health status, 25 to 49 as fair, 50 to 74 as good, and 75 to 100 as excellent [22]. SAQ scores have been strongly and independently associated with the risk of subsequent death, hospitalization, myocardial infarction, and costs [22].



The Seattle Angina Questionnaire-7

1. The following is a list of activities that people often do during the week. Although for some people with several medical problems it is difficult to determine what it is that limits them, please go over the activities listed below and indicate how much limitation you have had **due to chest pain, chest tightness or angina** over the past 4 weeks.

Place an X in one box on each line.

Activity	Extremely limited	Quite a bit limited	Moderately Limited	Slightly limited	Not at all limited	Limited for other reasons or did not do the activity
a. Walking indoors on level ground	☐	☐	☐	☐	☐	☐
b. Gardening, vacuuming or carrying groceries	☐	☐	☐	☐	☐	☐
c. Lifting or moving heavy objects (e.g. furniture, children)	☐	☐	☐	☐	☐	☐

2. Over the past 4 weeks, on average, how many times have you had **chest pain, chest tightness or angina**?

I have had **chest pain, chest tightness or angina...**

4 or more times per day	1-3 times per day	3 or more times per week but not every day	1-2 times per week	Less than once a week	None over the past 4 weeks
☐	☐	☐	☐	☐	☐

3. Over the past 4 weeks, on average, how many times have you had to take nitroglycerin (nitroglycerin tablets or spray) for your **chest pain, chest tightness or angina**?

I have taken nitroglycerin...

4 or more times per day	1-3 times per day	3 or more times per week but not every day	1-2 times per week	Less than once a week	None over the past 4 weeks
☐	☐	☐	☐	☐	☐

4. Over the past 4 weeks, how much has your **chest pain, chest tightness or angina** limited your enjoyment of life?

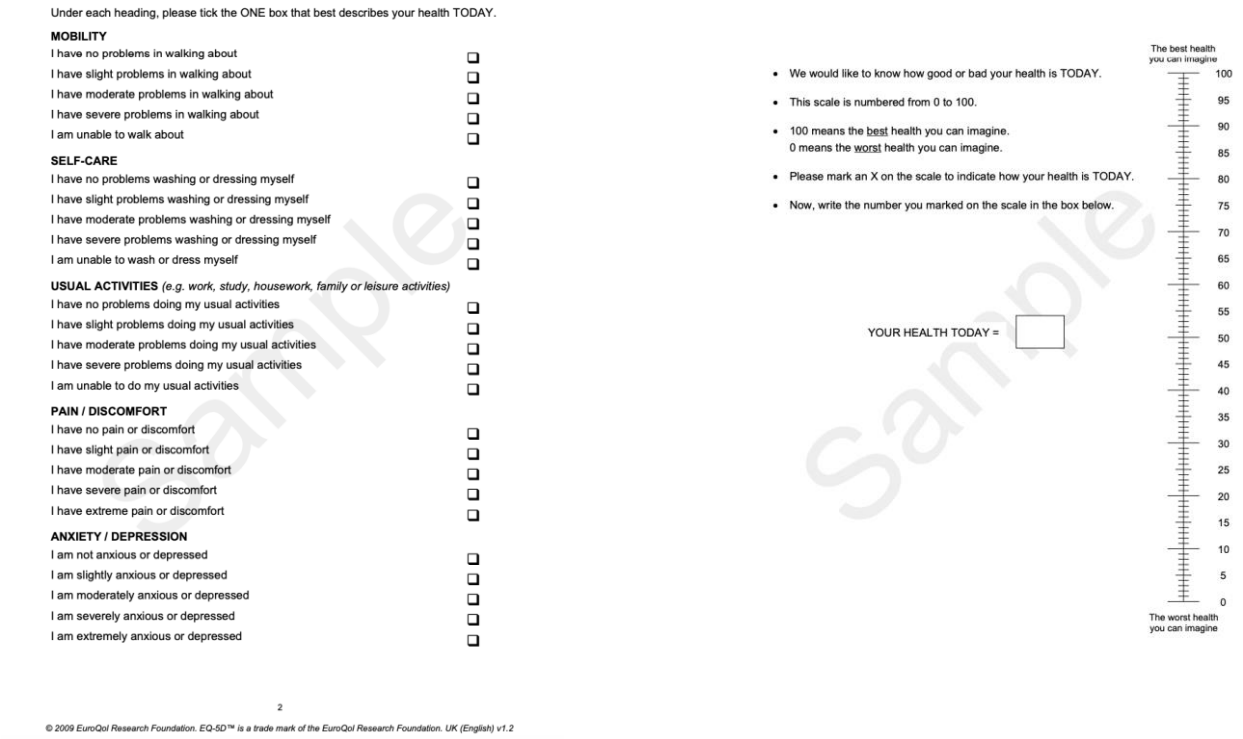
It has **extremely** limited my enjoyment of life	It has limited my enjoyment of life **quite a bit**	It has **moderately** limited my enjoyment of life	It has **slightly** limited my enjoyment of life	It has **not** limited my enjoyment of life at all
☐	☐	☐	☐	☐

5. If you had to spend the rest of your life with your **chest pain, chest tightness or angina** the way it is right now, how would you feel about this?

Not satisfied at all	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Completely satisfied
☐	☐	☐	☐	☐

8.3 EQ-5D-5L

The EQ-5D-5L essentially consists of 2 pages: the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS). The descriptive system comprises five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems and extreme problems. The patient is asked to indicate his/her health state by ticking the box next to the most appropriate statement in each of the five dimensions. This decision results in a 1-digit number that expresses the level selected for that dimension. The digits for the five dimensions can be combined into a 5-digit number that describes the patient's health state [23].



Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY
- I have no problems in walking about ❑
- I have slight problems in walking about ❑
- I have moderate problems in walking about ❑
- I have severe problems in walking about ❑
- I am unable to walk about ❑

SELF-CARE
- I have no problems washing or dressing myself ❑
- I have slight problems washing or dressing myself ❑
- I have moderate problems washing or dressing myself ❑
- I have severe problems washing or dressing myself ❑
- I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*
- I have no problems doing my usual activities ❑
- I have slight problems doing my usual activities ❑
- I have moderate problems doing my usual activities ❑
- I have severe problems doing my usual activities ❑
- I am unable to do my usual activities ❑

PAIN / DISCOMFORT
- I have no pain or discomfort ❑
- I have slight pain or discomfort ❑
- I have moderate pain or discomfort ❑
- I have severe pain or discomfort ❑
- I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION
- I am not anxious or depressed ❑
- I am slightly anxious or depressed ❑
- I am moderately anxious or depressed ❑
- I am severely anxious or depressed ❑
- I am extremely anxious or depressed ❑

2

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Please mark an X on the scale to indicate how your health is TODAY.
- Now, write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐

The best health you can imagine
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
The worst health you can imagine

8.4 Beck Depression Inventory (BDI)

The Beck Depression Inventory questionnaire was created by Aaron T. Beck [24]. It is a 21-question multiple-choice self-report inventory, and it is one of the most widely used psychometric tests for measuring the severity of depression. Its development marked a shift among mental health professionals, who had until then, viewed depression from a psychodynamic perspective, instead of it being rooted in the patient's own thoughts. The original BDI, first published in 1961, consisted of twenty-one questions about how the subject has been feeling in the last week. Each question had a set of at least four possible responses, ranging in intensity. For example:

- (0) I do not feel sad.
- (1) I feel sad.
- (2) I am sad all the time and I can't snap out of it.
- (3) I am so sad or unhappy that I can't stand it.

When the test is scored, a value of 0 to 3 is assigned for each answer and then the total score is compared to a key to determine the depression's severity. The standard cut-off scores were as follows:

- 0–9: indicates minimal depression
- 10–19: indicates mild depression
- 20–29: indicates moderate depression
- ≥30: indicates severe depression.

Higher total scores indicate more severe depressive symptoms.

1.
0 I do not feel sad.
1 I feel sad
2 I am sad all the time and I can't snap out of it.
3 I am so sad and unhappy that I can't stand it.

2.
0 I am not particularly discouraged about the future.
1 I feel discouraged about the future.
2 I feel I have nothing to look forward to.
3 I feel the future is hopeless and that things cannot improve.

3.
0 I do not feel like a failure.
1 I feel I have failed more than the average person.
2 As I look back on my life, all I can see is a lot of failures.
3 I feel I am a complete failure as a person.

4.
0 I get as much satisfaction out of things as I used to.
1 I don't enjoy things the way I used to.
2 I don't get real satisfaction out of anything anymore.
3 I am dissatisfied or bored with everything.

5.
0 I don't feel particularly guilty.
1 I feel guilty a good part of the time.
2 I feel quite guilty most of the time.
3 I feel guilty all of the time.

6.
0 I don't feel I am being punished.
1 I feel I may be punished.
2 I expect to be punished.
3 I feel I am being punished.

7.
0 I don't feel disappointed in myself.
1 I am disappointed in myself.
2 I am disgusted with myself.
3 I hate myself.

8.
0 I don't feel I am any worse than anybody else.
1 I am critical of myself for my weaknesses or mistakes.
2 I blame myself all the time for my faults.
3 I blame myself for everything bad that happens.

9.
0 I don't have any thoughts of killing myself.
1 I have thoughts of killing myself, but I would not carry them out.
2 I would like to kill myself.
3 I would kill myself if I had the chance.

10.
0 I don't cry any more than usual.
1 I cry more now than I used to.
2 I cry all the time now.
3 I used to be able to cry, but now I can't cry even though I want to.

11.
0 I am no more irritated by things than I ever was.
1 I am slightly more irritated now than usual.
2 I am quite annoyed or irritated a good deal of the time.
3 I feel irritated all the time.

12.
0 I have not lost interest in other people.
1 I am less interested in other people than I used to be.
2 I have lost most of my interest in other people.
3 I have lost all of my interest in other people.

13.
0 I make decisions about as well as I ever could.
1 I put off making decisions more than I used to.
2 I have greater difficulty in making decisions more than I used to.
3 I can't make decisions at all anymore.

14.
0 I don't feel that I look any worse than I used to.
1 I am worried that I am looking old or unattractive.
2 I feel there are permanent changes in my appearance that make me look unattractive
3 I believe that I look ugly.

15.
0 I can work about as well as before.
1 It takes an extra effort to get started at doing something.
2 I have to push myself very hard to do anything.
3 I can't do any work at all.

16.
0 I can sleep as well as usual.
1 I don't sleep as well as I used to.
2 I wake up 1-2 hours earlier than usual and find it hard to get back to sleep.
3 I wake up several hours earlier than I used to and cannot get back to sleep.

17.
0 I don't get more tired than usual.
1 I get tired more easily than I used to.
2 I get tired from doing almost anything.
3 I am too tired to do anything.

18.
0 My appetite is no worse than usual.
1 My appetite is not as good as it used to be.
2 My appetite is much worse now.
3 I have no appetite at all anymore.

19.
0 I haven't lost much weight, if any, lately.
1 I have lost more than five pounds.
2 I have lost more than ten pounds.
3 I have lost more than fifteen pounds.

20.
0 I am no more worried about my health than usual.
1 I am worried about physical problems like aches, pains, upset stomach, or constipation.
2 I am very worried about physical problems and it's hard to think of much else.
3 I am so worried about my physical problems that I cannot think of anything else.

21.
0 I have not noticed any recent change in my interest in sex.
1 I am less interested in sex than I used to be.
2 I have almost no interest in sex.
3 I have lost interest in sex completely.

8.5 Clinical endpoints

Clinical adverse events of interest (cardiovascular death, all cause death and hospitalization) are defined in agreement with the consensus documents of the Academic Research Consortium**.**

9 STATISTICAL ANALYSIS PLAN

A detailed Statistical Analysis Plan will be finalized before the end of the recruitment. Briefly, data will be reported as mean (SD), median (25th, 75th percentile), or frequency and percentage. Continuous outcome measures recorded at baseline, 6-month and 12-month will be compared between randomized groups using a mixed effects linear regression model, including a random effect for patients, and fixed effects for time point (baseline or follow-up), randomized group, and their interaction. The baseline-adjusted intervention effect will be estimated as the interaction term from this model. Categorical outcomes will be compared between randomized groups using Fisher exact tests with additional calculation of relative risk estimation of effect size. We will perform 2-tailed analysis and we will consider a p value less than 0.05 to be significant.

9.1 Determination of sample size

Based on previous studies, we suppose that our intervention will be related to a mean group difference of change in SAQSS of 10 U. We calculated that a sample size of 60 patients per group gave 80% power to detect a between-group difference in SAQSS. This calculation assumed a 2-tailed 5% significance level and a standard deviation of SAQSS values around 20 U.

10 ETHICAL AND REGULATORY STANDARDS

10.1 Good Clinical Practice

The procedures set out in this protocol are designed to ensure that the investigator abides by the principles of the Declaration of Helsinki and Good Clinical Practice Guidelines (ICH-GCP) in the latest version, in the conduct, evaluation, and documentation of the study. A copy of these documents will be provided to each center. The study will be carried out according to local legal requirements and international regulations.

10.2 Informed Consent of the Patient

Patients who meet all inclusion criteria and none of the exclusion criteria are deemed eligible. Before being enrolled into the clinical study, the patient must provide written consent to participate in the study after the nature, scope and possible consequences of the clinical study have been explained both orally and in writing. All patients who signed informed consent must be listed on the Screening Log.

10.3 Approval of the Study Protocol

Before the start of the study, the study protocol and the informed consent form used at the site and other appropriate documents must be submitted and approved by the local Ethics Committee or Institutional Review Board and the appropriate regulatory authorities according to local legal requirements. Documentation of Ethics Committee/IRB approvals will be required before sites are activated to randomize.

10.4 Maintenance of Records

The Investigator agrees to obtain a correctly completed informed consent form for each patient included in the study. The investigator will maintain a personal list of patient numbers and patient names to allow records to be found later. The Investigator must maintain all study records, patient files and other source data for the maximum period permitted by the hospital, institution, or private practice. However national regulations should be considered, and the longest time allowed by these rules would be counted. For trials conducted in the European Community, the Investigator is required to arrange for the retention of patient identification codes for at least 15 years after the completion or discontinuation of the trial.

10.5 Confidentiality

All patient names will remain confidential. Patients will be identified throughout documentation and evaluation by the number assigned to them by the study. Patients will be assured that all findings will be stored on the computer and handled with the strictest confidence. The Investigator agrees to maintain the confidentiality of the study protocol.

11 ADMINISTRATIVE RULES

11.1 Curriculum vitae

An updated copy of the curriculum vitae for each Investigator and co-Investigator will be provided prior to the beginning of the study.

11.2 Confidentiality agreement

All goods, materials, information (oral or written) and unpublished documentation provided to the Investigators (or any company acting on their behalf), inclusive of this protocol and the patient case report forms are the exclusive property of the Cardiovascular Department of the University of Ferrara. They may not be given or disclosed by the Investigator or by any person within his authority, either in part or in totality, to any unauthorized person without the prior written formal consent. It is specified that the submission of this protocol and other necessary documentation to the ERC or a like body (IRB, CCPPRB...) is expressly permitted, the Ethics Committee members having the same obligation of confidentiality. The Investigator shall consider as confidential and shall take all necessary measures to ensure that there is no breach of confidentiality in respect of all information accumulated, acquired or deduced in the course of the trial, other than that information to be disclosed by law.

11.3 Record retention in investigating center(s)

The Investigator must maintain all study records, patient files, and other source data for the maximum period of time permitted by the hospital, institution, or private practice. National regulations, however, should be considered and the longest time allowed by these rules would be counted. For trials conducted in the European Community, the Investigator is required to arrange for the retention of patient identification codes for at least 15 years after the completion or discontinuation of the trial.

12 OWNERSHIP OF DATA AND USE OF THE STUDY RESULTS

The Sponsor has ownership of all data and results collected during this study. The full publication rights of the study data reside solely with the Principal Investigator.

13 PUBLICATIONS

All study presentations and/or publication of the results will be based on clean, checked and validated data in order to ensure the accuracy of the results. Publication of the main findings of this study will be made based on the contributions of individuals to the overall study. All the trial participants (investigators and committee members) make a prior delegation of responsibility for primary presentation and/or primary publication of the results to the Steering Committee.

14 STUDY ADMINISTRATIVE INFORMATION

14.1 ADDRESS LIST

14.1.1 Study Committees

A detailed list of the Study Committees and of the members is reported in the Appendix A

14.1.2 Sponsor

Consorzio Futuro in Ricerca
Via Saragat, 1 - Blocco B - 1° Piano - 44122 Ferrara
Tel 0532-762404
E-mail cfr@unife.it - PEC cieffeerre@pec.it
C.F. / P. IVA 01268750385

14.1.3 Principal Investigator

Gianluca Campo
UO di Cardiologia, Azienda Ospedaliero Universitaria di Ferrara
Via Aldo Moro 8, 44124, Cona (FE), Italy

14.1.4 Academic Research Organization

Cardiology Unit, University Hospital of Ferrara
Via Aldo Moro 8, 44124, Cona (FE), Italy

14.2 INSURANCE

Subjects who participate in this study will be insured against study related injury according to local regulatory requirements. A copy of the certificate is filed in each investigator site file and in the trial master file.

14.3 FUNDING AND SUPPORT

A detailed list of economic support is reported in the Appendix B

15 REFERENCES

1. Jespersen L, Hvelplund A, Abildstrøm SZ, Pedersen F, Galatius S, Madsen JK, Jørgensen E, Kelbæk H, Prescott E. Stable angina pectoris with no obstructive coronary artery disease is associated with increased risks of major adverse cardiovascular events. Eur Heart J. 2012 Mar;33(6):734-44.
2. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, Prescott E, Storey RF, Deaton C, Cuisset T, Agewall S, Dickstein K, Edvardsen T, Escaned J, Gersh BJ, Svitil P, Gilard M, Hasdai D, Hatala R, Mahfoud F, Masip J, Muneretto C, Valgimigli M, Achenbach S, Bax JJ; ESC Scientific Document Group. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J. 2020 Jan 14;41(3):407-477.
3. Mehta PK, Huang J, Levit RD, Malas W, Waheed N, Bairey Merz CN. Ischemia and no obstructive coronary arteries (INOCA): A narrative review. Atherosclerosis. 2022 Dec;363:8-21.
4. Ong P, Camici PG, Beltrame JF, *et al*. International standardization of diagnostic criteria for microvascular angina. *Int J Cardiol* 2018;250:16–20.
5. Tonet E, Pompei G, Faragasso E, Cossu A, Pavasini R, Passarini G, Tebaldi M, Campo G. Coronary Microvascular Dysfunction: PET, CMR and CT Assessment. J Clin Med. 2021 Apr 23;10(9):1848.
6. Perera D, Berry C, Hoole SP, Sinha A, Rahman H, Morris PD, Kharbanda RK, Petraco R, Channon K; UK Coronary Microvascular Dysfunction Working Group. Invasive coronary physiology in patients with angina and non-obstructive coronary artery disease: a consensus document from the coronary microvascular dysfunction workstream of the British Heart Foundation/National Institute for Health Research Partnership. Heart. 2022 Dec 22;109(2):88-95.
7. P.K.Mehta,B.D.Johnson,T.S.Kenkre,W.Eteiba,B.Sharaf,C.J.Pepine,S.E.Reis, W.J. Rogers, S.F. Kelsey, D.V. Thompson, et al., Sudden cardiac death in women with suspected ischemic heart disease, preserved ejection fraction, and No obstructive coronary artery disease: a report from the Women's ischemia syndrome evaluation study, J. Am. Heart Assoc. 6 (2017)
8. Gulati M, Khan N, George M, Berry C, Chieffo A, Camici PG, Crea F, Kaski JC, Marzilli M, Merz CNB. Ischemia with no obstructive coronary artery disease (INOCA): A patient self-report quality of life survey from INOCA international. Int J Cardiol. 2023 Jan 15;371:28-39.
9. Mark DB. Assessing quality-of-life outcomes in cardiovascular clinical re- search. *Nat Rev Cardiol.* 2016;13:286–308.
10. Mark DB, Spertus JA, Bigelow R, Anderson S, Daniels MR, Anstrom KJ, Baloch KN, Cohen DJ, Held C, Goodman SG, Bangalore S, Cyr D, Reynolds HR, Alexander KP, Rosenberg Y, Stone GW, Maron DJ, Hochman JS; ISCHEMIA Research Group. Comprehensive Quality-of-Life Outcomes With Invasive Versus Conservative Management of Chronic Coronary Disease in ISCHEMIA. Circulation. 2022 Apr 26;145(17):1294-1307.
11. Bairey Merz CN, Shaw LJ. Stable angina in women: lessons from the national heart, lung and blood Institute-sponsored women's ischemia syndrome evaluation. *J Cardiovasc Med* 2011;12:85–7.

12. Shaw LJ, Bairey Merz CN, Pepine CJ, *et al*. Insights from the NHLBI-Sponsored women's ischemia syndrome evaluation (wise) study: part I: gender differences in traditional and novel risk factors, symptom evaluation, and gender-optimized diagnostic strategies. *J Am Coll Cardiol* 2006;47–S4–20.
13. Reriani M, Flammer AJ, Duhé J, Li J, Gulati R, Rihal CS, Lennon R, Tilford JM, Prasad A, Lerman LO, Lerman A. Coronary endothelial function testing may improve long-term quality of life in subjects with microvascular coronary endothelial dysfunction. Open Heart. 2019 Feb 2;6(1):e000870.
14. Kemp HG, Kronmal RA, Vlietstra RE, *et al*. Seven year survival of patients with normal or near normal coronary arteriograms: a CASS registry study. *J Am Coll Cardiol* 1986;7:479–83.
15. Ford TJ, Stanley B, Good R, Rocchiccioli P, McEntegart M, Watkins S, Eteiba H, Shaukat A, Lindsay M, Robertson K, Hood S, McGeoch R, McDade R, Yii E, Sidik N, McCartney P, Corcoran D, Collison D, Rush C, McConnachie A, Touyz RM, Oldroyd KG, Berry C. Stratified Medical Therapy Using Invasive Coronary Function Testing in Angina: The CorMicA Trial. J Am Coll Cardiol. 2018 Dec 11;72(23 Pt A):2841-2855.
16. Martínez-González MA, Salas-Salvadó J, Estruch R, Corella D, Fitó M, Ros E. (2015) Benefits of the Mediterranean Diet: Insights From the PREDIMED Study. Prog Cardiovasc Dis. 58:50-60.
17. Raisi A, Piva T, Myers J, Zerbini V, Mandini S, Zappaterra T, Mazzoni G, Tonet E, Pavasini R, Campo G, Grazzi G, Visintin EP. Experience and Perceptions among Older Outpatients after Myocardial Infarction following an Exercise Intervention: A Qualitative Analysis from the PIpELINe Trial. Int J Environ Res Public Health. 2023 Jan 26;20(3):2196.
18. Mazzoni G, Raisi A, Myers J, Arena R, Kaminsky L, Zerbini V, Lordi R, Chiaranda G, Mandini S, Sella G, Tonet E, Campo G, Grazzi G. Promotion and maintenance of physically active lifestyle in older outpatients 2 years after acute coronary syndrome. Aging Clin Exp Res. 2022 May;34(5):1065-1072.
19. Campo G, Tonet E, Chiaranda G, Sella G, Maietti E, Bugani G, Vitali F, Serenelli M, Mazzoni G, Ruggiero R, Villani G, Biscaglia S, Pavasini R, Rubboli A, Campana R, Caglioni S, Volpato S, Myers J, Grazzi G. Exercise intervention improves quality of life in older adults after myocardial infarction: randomised clinical trial. Heart. 2020 Nov;106(21):1658-1664.
20. Campo G, Tonet E, Chiaranda G, Sella G, Maietti E, Mazzoni G, Biscaglia S, Pavasini R, Myers J, Grazzi G. Exercise Intervention to Improve Functional Capacity in Older Adults After Acute Coronary Syndrome. J Am Coll Cardiol. 2019 Dec 10;74(23):2948-2950.
21. Tonet E, Maietti E, Chiaranda G, Vitali F, Serenelli M, Bugani G, Mazzoni G, Ruggiero R, Myers J, Villani GQ, Corvi U, Pasanisi G, Biscaglia S, Pavasini R, Lucchi GR, Sella G, Ferrari R, Volpato S, Campo G, Grazzi G. Physical activity intervention for elderly patients with reduced physical performance after acute coronary syndrome (HULK study): rationale and design of a randomized clinical trial. BMC Cardiovasc Disord. 2018 May 21;18(1):98.
22. Thomas M, Jones PG, Arnold SV, Spertus JA. Interpretation of the Seattle Angina Questionnaire as an Outcome Measure in Clinical Trials and Clinical Care: A Review. JAMA Cardiol. 2021 May 1;6(5):593-599.
23. Brooks RG. 28 Years of the EuroQol Group – An Overview

24. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry 1961;4:561–71.