International study of Coronary Microvascular Angina (iCorMicA): a randomised, controlled, multicentre trial and registry

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The primary objective is to determine whether stratified medical therapy guided by an adjunctive interventional diagnostic procedure (IDP) during the invasive management of patients with known or suspected angina but no obstructive CAD improves...

Ethical review	Approved WMO
Status	Pending
Health condition type	Coronary artery disorders
Study type	Interventional

Summary

ID

NL-OMON57361

Source
ToetsingOnline

Brief title
iCorMicA - Stratified medicine in angina

Condition

- Coronary artery disorders

Synonym
coronary vasomotor dysfunction, microcirculatory dysfunction

Research involving
Human

Sponsors and support

Primary sponsor: Glasgow Univeristy

Source(s) of monetary or material Support: Abbott Vascular,Abbott Vascular;NHS Greater Glasgow & Clyde and The University of Glasgow

Intervention

Keyword: angina, ischaemia with no obstructive coronary artery disease (INOCA), microvascular angina, stratified medicine

Outcome measures

Primary outcome

The primary efficacy variable will be the SAQ Summary Score at 12 months, which

will be compared

between the groups using a linear regression model, adjusting for the baseline

score.

Secondary outcome

8.3 Secondary outcomes (detailed)

8.3.1 Feasibility and process

* Rates of enrolment, drop-out, completion of the diagnostic protocol,

* Integrity of blinding in the catheter laboratory and blinding at 1 year

(patient and

attending clinician)

* Loss to follow-up including time-point

8.3.2 Safety

Safety of coronary function tests, as reflected by SAEs related to the

procedure in a multicentre

setting, and those arising during longer term follow-up.

8.3.3 Diagnostic utility

To assess impact of disclosure of the coronary function test results on the diagnosis and the certainty of the diagnosis (diagnostic utility) in a multicentre setting (Appendix 4),

The clinician*s diagnosis i.e. coronary heart disease, angina due to obstructive coronary heart disease, angina due to a disorder of coronary function e.g. microvascular angina, vasospastic angina,

will be assessed for certainty (yes/no vs unlikely/probable in the primary analysis) and frequency (yes/probable vs unlikely/no).

A missed diagnosis of microvascular angina and/or vasospastic angina was defined as the final physician diagnosis of non-cardiac chest pain in the presence of objective abnormalities of coronary artery function.

8.3.4 Clinical utility

To assess impact of disclosure of the coronary function test results on clinical management (including treatment and investigations) (Appendix 2),

Comparison of health status: Rose Angina, Seattle Angina scores (5 components and summary

score), EQ5D health status, Illness perception, Treatment Satisfaction, Diet Questionnaire, Duke
Activity Status Index, International Physical Activity Questionnaire short-form.
Assess changes to medications, and long-term compliance with medications, as measures of the
clinical utility of the overall strategy.
To assess the relationships between baseline cardiovascular risk factors and parameters of coronary
function in medically managed patients.
Healthcare resource utilisation including primary and secondary care costs for tests, procedures and
out-patient visits, and medicines, and iPCQ.

8.3.5 Health status

Quality of life, symptoms and health status will be serially assessed using validated, self-administered questionnaires. The participant will complete health status questionnaires with a
member of the research team (as needed). The EQ5D, Seattle Angina Questionnaire and iCorMicA
Symptom Log will be completed at baseline, 6 and 12 months, and 5- and 10 years where feasible.
The other questionnaires will be completed at baseline and 12 months only. The participant and the
researcher should be blind to treatment group.

Angina symptoms will be assessed with the Seattle Angina Questionnaire

Angina episodes will be adjudicated by a blinded CEC

Quality of life will be assessed using the SAQ and EuroQOL (EQ-5D-5L)

instruments. This is a widely

used standardised instrument for measuring generic health status whereby higher

scores represent

better quality of life [112,113].

Other PROMS: Illness perception (Brief IPQ) [110], functional status (DASI)

[114] assessment of

economic burden of disease (iPCQ) [116] will also be recorded using the

relevant questionnaires. Cardiovascular risk factors and risk scores e.g.

QRisk3, EUROScore (see Section 3.5 - 3.7)

Changes to medications and compliance with medications during follow-up, are

measures of the

clinical utility of the overall strategy

8.3.6 Health outcomes

8.3.6.1 Assessment of adverse events during follow-up

Health outcomes will include death, re-hospitalisation for cardiovascular

events including recurrent

MI, heart failure, stroke or TIA, unstable angina and coronary

revascularisation. Hospital visits for chest pain episodes (emergency department, chest pain clinic) that may not have led to hospital admission will also be documented as a prioritised outcome of interest. Data on health outcomes will be collected after (but not including) the index procedure at baseline. The next assessment will take place at 6 months. Event reporting will be performed prospectively during the study and quality assurance will also take place prospectively.

After Visit 6, electronic case records and record linkage will be the default approach for assessing health outcomes, although contacts (clinic visit, telephone, mail) are an option if electronic health record linkage is not possible. Electronic record linkage will be performed wherever available. In the NHS, the Community Health Index (CHI) number in Scotland and the NHS number in England and Wales will be used. The record linkage plan will be implemented by the Information and Statistics Division (ISD), and Clinical Practice Research Datalink (CPRD) linked to the Information Centre in England at the end of the study (5 years +). These are quality assured systems

made possible by

electronic registration of all deaths and hospitalisations (and their causes)

which have been used

widely, including for research by the trial statistician [129-131].

Participants will be invited to give

permission for life-long electronic case record linkage. In other countries,

similar healthcare and

government records will be linked as source data.

Healthcare resource utilisation will also be assessed by identifying inpatient

visits in secondary care,

procedures, and medicine use [132-135]. Resource use and costs in different

healthcare systems will

be prospectively gathered at 6 and 12 months and again at 5- and 10- years.

These data will be used

to support a health economic analysis.

Study description

Background summary

Ischaemic heart disease (IHD) is a leading global cause of premature disability [1] and death [2]. The
classic cause of IHD is coronary atherosclerosis but evidence is accruing that coronary vascular
dysfunction is also a prevalent, prognostically important cause [3-5]. Approximately half of patients
undergoing coronary angiography for known or suspected angina have non obstructed epicardial
coronary arteries and a vasomotion disorder, including microvascular- and/or vasospastic angina,

may be relevant.
Epicardial artery spasm causes vasospastic angina, first described by Prinzmetal as *variant angina*
[6]. Microvascular spasm and/or impaired coronary vasodilation cause microvascular angina,
formerly known as Cardiac Syndrome X [3]. These vasospastic disorders are diagnosed by coronary
reactivity testing and often co-exist with coronary atherosclerosis [3-5]. Moreover, coronary vascular
dysfunction - whether epicardial or microvascular - can also cause myocardial ischaemia in patients
with obstructive coronary artery disease (CAD) [3-5].
Coronary vasomotion disorders cause a relative supply/demand mismatch of myocardial blood flow
and nutrients relative to their requirements inducing myocardial ischaemia that may be transient,
recurrent and/or chronic. Ischaemia with no obstructive CAD (INOCA) is typically a chronic health
problem that may involve acute and relapsing episodes (acute INOCA) reflecting myocardial blood:
supply mismatch due to a coronary vasomotion disorder [3-20]. Patient factors e.g. emotional stress,
menopause, smoking, and co-morbidity e.g. hypertension, anaemia, and environmental factors e.g.
cold temperature, may be associated trigger factors. When studied using specific tests,
microvascular angina and vasospastic angina are common findings; potentially, 1 in 3 all-comers
undergoing invasive angiography may be affected, including up to 4 in 5 patients with INOCA [10-
15]. These patients are mostly female [10-14] and prognosis [7,8,12-21] and quality of life
[9,12,15,16,12-24] are impaired. Vasospasm may be a primary cause of myocardial infarction (MI)
with no obstructive coronary artery disease (MINOCA) which is a major subtype of type 2 MI.
Although, currently adjunctive tests of coronary function are rarely used in daily practice, emerging
clinical trial evidence provides some support for this approach [4,13-16]. Coronary functional
disorders also occur among patients with obstructive CAD but current diagnostic testing is limited
with an upstream obstructive lesion. The research in this study is focused on patients without
obstructive CAD.
Coronary vascular function can be assessed using an *Interventional Diagnostic Procedure (IDP)* in

the cardiac catheter laboratory. An IDP may also be considered a *Functional Diagnostic Procedure
(FDP)*, complementing anatomical coronary angiography.

Study objective

The primary objective is to determine whether stratified medical therapy guided by an adjunctive
interventional diagnostic procedure (IDP) during the invasive management of patients with known or
suspected angina but no obstructive CAD improves health status as reflected by the Seattle Angina
Questionnaire Summary Score [99].
3.1.1 Stratified medicine for angina
A key tenet of stratified medicine in patients with ischaemic heart disease (IHD) is the prevention of
cardiovascular events through intensive management of cardiovascular risk factors, notably through
lifestyle measures, and prescription of angina therapy linked to the endotype (see management
guideline). The clinical strategy endorses active management of cardiovascular risk factors, including
through repeated evaluation and titration of therapy during follow-up in primary and secondary
care.
Our primary objective aligns with contemporary guidelines from the European Society of Cardiology
[26,117]. Site staff are encouraged to follow lifestyle and pharmacotherapy interventions to achieve
the following goals:
• Hypertension - SBP target value < 130 mmHg, DPB <80 mmHg
• Lipids - The goal of treatment and lifestyle measures is to lower LDL-C to <1.8 mmol/L (<70
mg/dL) or at least to reduce it by 50% if the baseline LDL-C level is 1.8 - 3.5 mmol/L (70 - 135 mg/dL).
• Diabetes - Good control of glycated haemoglobin (HbA1c) to <7.0% based on individual
considerations.
• BMI - The guideline-recommended target BMI is 20 - 25 kg/m2.
• No Smoking- Smoking is a strong and independent risk factor for cardiovascular disease
(CVD) and all smoking, including environmental smoking exposure, must be avoided in all patients
with CVD.
• Physical activity - Moderate-to-vigorous intensity aerobic exercise training >=3 times a
week (30 min).

• Diet - A healthy diet reduces CVD risk. The Dietary Instrument for Nutrition Education (DINE)
questionnaire will be used to assess diet.
Cardiac rehabilitation can be particularly beneficial for patients with a diagnosis of IHD. Study
participants with a diagnosis of IHD should be referred to a cardiac rehabilitation programme which
should help with a comprehensive risk-reduction regimen to support the patient in achieving
lifestyle modifications, compliance with pharmacotherapy and guideline targets for BP, lipids,
smoking, BMI, physical activity and diet

3.2 Secondary objectives - trial
Secondary objectives of this trial are to assess:
* Symptoms
* Health status (including quality of life)
* Change from baseline health status scores in repeat questionnaires at 12 months
* Lifestyle factors: smoking, weight, blood pressure, cardiac rehabilitation attendance
* Physical activity and functional capacity
* Measure coronary microvascular function
* Blinding to treatment group allocation
* Feasibility / process outcomes (cross-over within 30 days of randomisation; loss to follow-up)
* Stratified medicine (intervention group) actively managed to control symptoms and achieve
guideline-directed targets for cardiovascular risk factors
* Major adverse cardiovascular and cerebrovascular events (MACCE)
* Health economics.
* Adjudication of angina episodes as morbid adverse events by a blinded clinical event
committee (CEC). Chest pain and symptoms will be categorised as angina (typical), angina
(equivalent), or non-anginal.

Study design

This trial has a prospective, randomised, double-blind, sham-controlled, parallel group design. All
participants will receive a single adjunctive diagnostic intervention (active or sham), assigned at
random, followed by linked management guided by the group allocation. The trial is designed to
assess the superiority of stratified medicine including guideline-indicated therapy as compared with

standard, angiography-guided management and guideline-indicated therapy according to the
diagnosis in patients with known or suspected INOCA.

The study will be conducted in hospitals in more than one country. The institutions will have the
ability to host the study activities.
If a patient moves home away from the recruiting site they should have the option of being followed
up in an alternative study site if feasible to facilitate participant retention. The arrangements would
be determined by agreement with the relevant sites in the best interests of the participant.

Intervention

The left anterior descending (LAD) coronary artery will in general be the target coronary artery for
measurement of microvascular function. The cardiologists may decide to select the
diagonal/intermediate, circumflex or right coronary artery if the LAD is unattractive e.g. small vessel,
highly tortuous, calcified. If vascular function measurements are normal then in order to mitigate
against a false negative diagnosis, additional measurements may be undertaken in one or more of
the other branches. In this case, the results for each coronary artery should be recorded (multivessel
assessment) and the most abnormal results will be used to inform the clinical diagnosis. If CFR
and/or IMR is abnormal the cardiologist should consider assessing the physiological response to a
standard intracoronary dose of verapamil (below).

Study burden and risks

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Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Age >=18 years.
2. A clinical plan for invasive coronary angiography.
3. Symptoms of angina (typical or atypical) according to the Rose- and/or Seattle Angina questionnaires.
4. Able to comply with study procedures.
5. Able to provide informed consent.

Exclusion criteria

1. A non-coronary primary indication for invasive angiography (e.g. valve disease, heart failure).
2. History of coronary artery bypass surgery.
3. Presence of obstructive disease evident in a main coronary artery (diameter >2.5 mm), i.e. a coronary stenosis >50% and/or a fractional flow reserve (FFR) <=0.80*.

*These patients will enter a follow-up registry.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Active
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-01-2025
Enrollment:	150
Type:	Anticipated

Medical products/devices used

Registration:	No

Ethics review

Approved WMO

Date:	13-03-2025
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
ClinicalTrials.gov	NCT04674449
CCMO	NL82836.091.24