Invasive Endotyping in Patients with Angina and No Obstructive Coronary Artery Disease: A Randomized Controlled Trial

Short title: The CorCTA trial.

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Contributors: CB conceived of and designed the study. NS wrote the first draft and made revisions with CB. BS, RS, AJM, CPB, MMcD, TJF, GR, AH, DS, JB, JA, AMA, RY, DC, RMcG, DC, NL, MMcE, AMcC edited the manuscript and/or supported the development and implementation of the study protocol.

Abstract

Background: We investigated the utility of invasive coronary function testing to diagnose the cause of angina in patients with no obstructive coronary arteries (ANOCA).

Methods: Outpatients referred for coronary computed tomography angiography (cCTA) in three hospitals in the United Kingdom were prospectively screened. Following cCTA, patients with unobstructed coronary arteries and who consented underwent invasive endotyping. The diagnostic assessments included coronary angiography, fractional flow reserve (patient excluded if ≤0.80), and for those without obstructive coronary artery disease, coronary flow reserve (abnormal <2.0), index of microvascular resistance (abnormal ≥25), and intra-coronary infusion of acetylcholine (0.182μg/ml, 1.82μg/ml, 18.2μg/ml; 2 ml/minute for 2 minutes) to assess for microvascular and/or coronary spasm. Participants were randomized to disclosure of the results of the coronary function tests to the invasive cardiologist (intervention group) or non-disclosure (control group, blinded). In the control group, a diagnosis of vasomotor angina was based on medical history, noninvasive tests and coronary angiography. The primary outcome was the between-group difference in the reclassification rate of the initial diagnosis based on cCTA versus the final diagnosis after invasive endotyping. The Seattle Angina Questionnaire summary score (SAQSS) and Treatment Satisfaction Questionnaire for Medication (TSQM-9) were secondary outcomes.

Results: 250 (77.6%) of 322 eligible patients underwent invasive endotyping; 19(7.6%) had obstructive coronary disease, 127(55.0%) had microvascular angina, 27(11.7%) had vasospastic angina, 17(7.4%) had both and 60 (26.0%) had no abnormality.

231 patients (mean age, 55.7 years, 64.5% women) were randomized and followed-up (median duration 19.9 (12.6,26.9) months). The clinician diagnosed vasomotor angina in 51(44.3%) patients in the intervention group and 55(47.4%) patients in the control group. Following

randomization, patients in the intervention group were four-fold (odds ratio (95% CI) 4.05; 2.32 to 7.24; p<0.001) more likely to be diagnosed with a coronary vasomotor disorder; the frequency of this diagnosis increased to 76.5%. The frequency of normal coronary function (i.e., no vasomotor disorder) was not different between the groups before randomization (51.3% vs 50.9%) but was reduced in the intervention group after randomization (23.5% vs 50.9%, p<0.001).

At 6- and 12 months, the SAQSS in the intervention vs. control groups were 59.2±24.2 (2.3±16.2 change from baseline) vs. 60.4±23.9 (4.6±16.4 change) and 63.7±23.5 (4.7±14.7 change) vs. 66.0±19.3 (7.9±17.1 change), respectively, and not different between groups (global p=0.36). Compared with the control group, global treatment satisfaction was higher in the intervention group at 12 months (69.9±22.8 vs 61.7±26.9, p=0.013).

Conclusions: For patients with ANOCA, a diagnosis informed by invasive functional assessment had no effect on long-term angina burden, whereas treatment satisfaction was improved.

Trial Registration: NCT03477890

Keywords: coronary computed tomography angiography, angina and no obstructive coronary artery disease, microvascular angina, vasospastic angina, stratified medicine.

Non-standard Abbreviations and Acronyms

ACE - Angiotensin-converting enzyme;

ANOCA - Angina and no obstructive coronary arteries

ANOVA - Analysis of variance

BIPQ - Brief Illness Perception Questionnaire

BMI - Body mass index

CAD-RADS - Coronary Artery Disease - Reporting and Data System

CVD - Cardiovascular disease

cCTA - Coronary computed tomography angiography

CFR – Coronary flow reserve

CorCMR - Coronary-Cardiovascular Magnetic Resonance

CorMicA - CORonary MICrovascular Angina

COVID-19 – Coronavirus disease-19

COVADIS - Coronary Vasomotion Disorders International Study Group

ECG – Electrocardiogram

EQ-5D-5L – EuroQuol 5-dimensions 5-level

FFR – Fractional flow reserve

HDL - High-density lipoprotein;

IMR – Index of microvascular resistance

INOCA - ischemia with no obstructive coronary arteries

LDL - low-density lipoprotein

MET - metabolic equivalent of task

NHS – National Health Service

NYHA - New York Heart Association

PHQ–4 - Patient Health Questionnaire-4

SAQSS - Seattle Angina Questionnaire Summary Score

SCOT-HEART - Scottish Computed Tomography of the Heart

TIA - Transient ischemic attack.

TSQM-9 - Treatment Satisfaction Questionnaire for Medication

VLDL - Very low-density lipoprotein

Clinical Perspective

What is new?

- Two hundred and fifty outpatients referred with angina and no obstructive coronary disease (ANOCA) defined by coronary computed tomography angiography (cCTA) and invasive coronary angiography underwent invasive assessment of coronary spasm and microvascular function.
- Approximately two-thirds of this population had microvascular angina and/or vasospastic angina undiagnosed by cCTA and randomized disclosure of the findings to the invasive cardiologist increased the likelihood of a diagnosis of microvascular and/or vasospastic angina by four-fold and halved the frequency of a diagnosis of normal coronary function.
- During follow-up, compared with the control group, treatment satisfaction improved in the intervention group, but angina symptoms were not different.

What are the clinical implications?

- Coronary microvascular dysfunction and epicardial coronary artery spasm were common findings in a population of patients with ANOCA defined by cCTA.
- Invasive endotyping clarified the cause of chest pain in patients without obstructive coronary disease and improved treatment satisfaction, but not angina burden.

Background

Angina with no obstructive coronary arteries (ANOCA), including microvascular angina and vasospastic angina, is caused by supply-demand mismatch of myocardial perfusion.[1-3] A diagnosis of myocardial ischemia with no obstructive coronary arteries (INOCA) is established based on findings from noninvasive stress testing. The pathophysiology of these conditions includes a continuum of coronary vasomotion disorders with or without atherosclerosis, and management is described in guidelines[4,5].

Among patients with chest pain without obstructive coronary artery disease who underwent invasive coronary evaluation, we aimed to assess whether a final diagnosis informed by invasive functional coronary assessment of the true endotype versus no functional assessments, with endotype specific-treatment algorithms applied to all patients, affected angina burden and treatment satisfaction. Our specific aims were, first, to characterize the prevalence of ANOCA endotypes in an outpatient population with suspected angina referred for coronary computed tomography angiography (cCTA), second, to assess the reclassification effect on the final diagnosis of coronary endotype classification based on disclosure of the invasive coronary functional assessments to the invasive cardiologist and, finally, to assess the effect of the intervention on health status. We hypothesized that coronary vasomotor endotypes were prevalent in this ANOCA population and, compared with angiography-guided management, management guided by invasive endotyping would improve patient wellbeing.

Methods

Study design

This was a prospective, multicenter, randomized, controlled, blinded trial[6]. The study was

approved by the West of Scotland Research Ethics Committee (reference 17/WS/0121).

Data sharing availability

The anonymized data are available from the corresponding author upon reasonable request.

Population

Potential participants were prospectively identified by referral for cCTA, invited to participate, and consented before the CTA scan. Only after the cCTA results became available was eligibility for randomization determined.

Electronic health records for outpatients referred for assessment of coronary artery disease by cCTA at three hospitals in Scotland (National Health Service (NHS) Golden Jubilee hospital, Glasgow Royal Infirmary, and Forth Valley Royal Hospital) were screened prospectively[4,7-9]. The cCTA indication was 'suspected angina'. Potentially eligible patients provided written informed consent for research and then completed the Rose Angina[10] and Seattle Angina Questionnaires[11].

Eligibility criteria

The inclusion criteria were age ≥18 years; symptoms of angina or angina-equivalent informed by the Rose Angina questionnaire; and no obstructive coronary artery disease i.e., no stenosis >70% in an artery >2.5 mm, as revealed by cCTA.

The exclusion criteria were a health problem that would explain the angina, e.g., anemia, moderate-severe aortic stenosis, hypertrophic obstructive cardiomyopathy; obstructive disease evident in a coronary artery (diameter >2.5 mm), i.e., >50 - 70% circumferential plaque extending for ≥2 coronary segments, or a stenosis >70% as revealed by cCTA; and lack of informed consent.

Patients with angina who fulfilled the eligibility criteria attended a reference center (NHS Golden

Jubilee) for invasive endotyping.

Invasive Assessment of Coronary Endotype

The diagnostic evaluation was undertaken by an invasive cardiologist independent of the treating clinicians. The diagnosis, related certainty, and management plan were serially documented by the invasive cardiologist before and after coronary angiography but before randomization. Adjunctive coronary function tests were then undertaken in a major coronary artery with no stenosis >50% of the reference vessel diameter. Patients with flow-limiting coronary artery disease (FFR ≤0.80) and/or obstructive disease (>50 - 70% circumferential plaque extending for ≥2 coronary segments or a stenosis >70%) were ineligible for randomization and, therefore, were excluded.

Randomization, Groups and Blinding

Patients (Figure 1, blue image) who had unobstructed coronary arteries by FFR criteria (FFR>0.80) were eligible for randomization. Patients with obstructive coronary artery disease (FFR ≤0.80) were not randomized and therefore entered a registry. Patients received intravenous midazolam for conscious sedation and the protocol was identical for all patients who, therefore, were blinded. To mitigate bias, randomization was undertaken immediately after the angiogram and completion of FFR testing, and before coronary function testing. There were two cardiologists (Figure 1, black image) in the catheter laboratory including the research cardiologist who was unblinded. The randomization involved whether the invasive cardiologist was provided with the results from the functional testing in the cardiac catheter laboratory by the research cardiologist.

A web-based randomization tool assigned the patients 1:1 to the intervention group (invasive cardiologist to get results of coronary function testing) or the blinded control group (angiography-guided diagnosis; coronary function tests performed but results not disclosed (patient and invasive cardiologist blinded)). The randomization sequence involved permuted blocks of length 4 or 6

(every 20 allocations consists of 4 blocks, 2 of length 4 and 2 of length 6, in a random order), stratified by recruiting site, whether the cCTA indicated coronary artery disease, and sex.

In the control group, the coronary function measurements were acquired by the research cardiologist. The hemodynamic monitor was obscured from the clinical staff and the patient such that it was impossible to observe the test results. During this time, the invasive cardiologist exited the catheter laboratory (Figure 1, footstep image) and returned when the coronary function tests had been acquired by the research cardiologist. The invasive cardiologist remained blind to the coronary function results in the control group which were not disclosed. The final diagnosis was guided by medical history and angiogram only.

In the intervention group, the research and invasive cardiologists remained in the catheter laboratory and acquired the microvascular function data (white chart image). The invasive cardiologist then established the final diagnosis taking account of the results of the coronary function tests.

The invasive cardiologist revised the final post- invasive diagnostic procedure diagnosis in the medical record for all patients, in both randomization groups, including half of the population informed by functional testing and half not informed. This final post-procedure diagnosis, excluding the data from the invasive evaluations for either group, was then available to all clinicians managing the patients, with protocolized interventions specified for each post-invasive diagnosis and these protocols were identical between the two groups for each endotype after the invasive procedure. The treating clinicians remained blinded as to whether the post-invasive procedure diagnosis was or was not informed by results of invasive functional testing for endotypes according to the randomized group allocated for the patient. The clinical outcome assessors were blinded to randomized group allocation.

Coronary Function Testing

The diagnostic protocol[12] for the assessment of coronary endotype involved guidewire-based thermodilution followed by intracoronary infusion of acetylcholine[4]. A pressure- and temperature-sensitive guidewire (PressureWire™ X, Abbott Cardiovascular, MN) was advanced into a major coronary artery (typically the left anterior descending) for assessment of coronary flow reserve (CFR; abnormal <2.0), the index of microcirculatory resistance (IMR; abnormal ≥25) and fractional flow reserve (FFR, abnormal ≤0.80) during intravenous infusion of adenosine (140 μg/kg/min).

Next, incremental concentrations of acetylcholine (0.182 μg/ml, 1.82 μg/ml, 18.2 μg/ml) were sequentially infused using a programmable pump at 2 ml/minute for 2-minute periods, followed by vasospasm testing by manual, bolus infusion of 100 μg into the left coronary artery or 50 μg of acetylcholine into the right coronary artery. Finally, a bolus dose of 300 μg of glyceryl trinitrate was infused into this artery. An angiogram was acquired at the end of each test period.

Definitions of endotypes

The coronary function results were used by the research cardiologist to define the true endotype documented in the research database according to diagnostic criteria defined in guidelines[4,13,14]. In the intervention group, these findings were used to revise the final diagnosis and stratify patients into sub-groups (endotypes: microvascular angina, vasospastic angina, both, and normal test results). In the control group, the coronary function results were not used to revise the final diagnosis.

A diagnosis of vasospastic angina required that three conditions occur during acetylcholine testing: (i) clinically significant epicardial vasoconstriction (≥90%) (ii) reproduction of the usual chest pain and (iii) ischemic changes on the electrocardiogram (ECG) [14]. Microvascular angina was defined

according to the Coronary Vasomotion Disorders International Study Group (COVADIS) criteria[13]: symptoms of myocardial ischemia, unobstructed coronary arteries, and evidence of microvascular dysfunction (any of abnormal CFR, IMR or microvascular spasm to acetylcholine). Definitive microvascular angina was diagnosed if all four criteria were present. Suspected microvascular angina was diagnosed if symptoms of ischemia are present (criteria-1) with no obstructive coronary artery disease (criteria-2) but only (a) objective evidence of myocardial ischemia (criteria-3), or (b) evidence of impaired coronary microvascular function (criteria-4) alone. A diagnosis of microvascular spasm required provocation and reproduction of anginal symptoms, ischemic ECG shifts, but no epicardial spasm during acetylcholine testing[13]. Normal test results denoted no obstructive epicardial coronary artery disease (FFR>0.80) and no coronary vascular dysfunction (CFR>2.0, IMR<25, and negative acetylcholine testing).

Medical management

The intervention group involved acquisition and disclosure of invasive coronary function testing. The unblinded invasive cardiologist became aware of the invasive coronary function testing results and they could then reclassify the initial diagnosis based on these test results to establish a final diagnosis.

In the control group, the invasive tests were acquired but not disclosed. The final diagnosis and related treatment were guided by the angiogram only. The same endotypes, including microvascular angina and vasospastic angina, could be empirically diagnosed but without access to the coronary function test results.

At the end of the procedure, following determination of the final diagnosis, the cardiologist selected a pre-specified medical management plan customized for each endotype (Supplement). This plan was provided for the endotype regardless of the randomized group. The plan involved

medical therapy and non-pharmacological (lifestyle) measures to control cardiovascular risk factors according to guideline targets[4]. This information was also provided to the primary and secondary care staff with responsibilities for ongoing care.

The patient's caring clinician was encouraged to titrate medications to address persistent symptoms during the follow-up period. The treatment plan was led by the blinded usual care teams rather than the research team and medication changes were at the discretion of the usual care clinicians. Standardized letters with customized medical management guidelines were sent to the general practitioner and cardiologist with advice on treatment optimization to relieve anginal symptoms. Standard care for patients in the control group consisted of guideline-directed medical therapy. Referral for cardiac rehabilitation was prioritized for patients with a new diagnosis of ischemic heart disease.

Outcome assessments

The Seattle Angina Questionnaire (SAQ) is a self-administered, disease-specific measure of angina severity that is valid, reproducible, and sensitive to change[11]. The SAQ quantifies patients' physical limitations caused by angina, the frequency of and recent changes in their symptoms, their satisfaction with treatment, and the degree to which they perceive their disease to affect their quality of life. Each scale is transformed to a score of 0 to 100, where higher scores indicate better function (e.g., less physical limitation, less angina, and better quality of life). The summary score (SAQSS, scale 0 – 100; a higher value reflects less angina burden) averages the domains of angina limitation, frequency, and quality of life to provide a measure of angina severity[11].

Health status was serially assessed using validated, self-administered questionnaires for quality of life using the EuroQoL (EQ-5D-5L). This is a standardized instrument for measuring generic health status whereby higher scores represent better health-related quality of life (on a scale from

-0.59 to 1.00)[15,16]. Other recorded health status measures include the Brief Illness Perception Questionnaire (BIPQ)[17], Patient Health Questionnaire-4 (PHQ-4) screening for depression and anxiety[18] and the Treatment Satisfaction Questionnaire for Medication (TSQM-9)[19] which includes 9 questions covering 3 domains (effectiveness, convenience, and global satisfaction) and a scale from 0 to 100, with higher scores representing higher satisfaction in that domain.

The reporting timepoints were baseline, six and twelve months, with the latter scheduled as an in-person visit to the clinical research facility. However, the COVID-19 pandemic disrupted implementation of the protocol. Elective medical care was deferred, social restrictions were imposed, healthcare and research staff were redeployed and research activities in the hospitals were repeatedly suspended for prolonged periods (Supplement, Table S1).

Primary Outcome

The primary outcome was the between-group difference in the reclassification rate of the initial diagnosis based on cCTA versus the final diagnosis after invasive endotyping.

The pre-specified secondary outcomes included:

1. The proportion of patients in whom the certainty of diagnosis changed after invasive assessment.

2. The proportion of patients in whom management was changed after invasive management.

3. Change in health status (including angina severity according to the SAQSS, TSMQ-9, EQ-5D-5L, BIPQ and PHQ-4) from baseline using repeated validated questionnaires.

Adjudicated adverse events

Follow-up assessments for adverse events were performed by research staff who were blind to the

baseline data and randomized groups. The contacts involved in-person visits, telephone follow-up, or review of electronic health records. Clinical events identified as potentially relevant were assessed by a Clinical Event Committee according to a pre-specified charter. This committee was also blind to the baseline data and randomized groups. The committee was independent of the investigators, funder, and sponsor.

Statistical analyses

The design involved a diagnostic study of coronary endotypes and a nested, randomized, controlled trial of the effects of disclosure of the coronary function tests.

Statistical analyses of primary outcome

We assessed the between-group difference in the reclassification rate of the initial diagnosis based on the cCTA versus the final diagnosis after the invasive procedure involving coronary function tests in a major coronary artery using logistic regression, adjusted for baseline factors associated with the likelihood of reclassification of the initial diagnosis. Considering the proportion of patients whose diagnosis would be reclassified by disclosure of the coronary function test results in the intervention group, or not (control group), 115 patients per group would have 80% power to detect a between group difference of 15%, or 90% power to detect a difference of 20%. To allow for any missing data, the study aimed to randomize 250 patients.

Statistical analyses of secondary outcomes

Considering the diagnostic study (the prevalence of microvascular or vasospastic angina), with a sample size of 250, the 95% confidence interval (CI) of the estimate will have a width of no more than ±6.2%.

If six-month outcomes could be obtained from 180 patients (72%), the trial will have 80% power

to detect a mean between-group difference in within-subject change in SAQ scores of 0.42 standard deviation (SD) units.

Statistical analyses were conducted at the data center (Clinical Trials Unit, Robertson Centre for Biostatistics, University of Glasgow) according to a pre-specified Statistical Analysis Plan and the intention-to-treat principle. The analyses were conducted using R Studio and R version 4.0.0 (R Foundation for Statistical Computing, Vienna, Austria).

Data were summarized descriptively for the randomized population and each treatment group using counts and percentages for categorical variables and mean, SD, or median, 25^{th} and 75^{th} percentiles (Q1, Q3 respectively), depending on the distribution of the data. Categorical outcomes were compared between randomized groups using Fisher's Exact Test and continuous outcomes were compared between randomized groups using the Wilcoxon Mann-Whitney test (for data with a skewed distribution) or Student's T-test (for Normal distributed data). A 2-tailed analysis was performed and a p-value of < 0.05 was taken to be statistically significant.

Due to the COVID-19 pandemic, most follow-up contacts did not occur in line with the planned 6- and 12- month visit schedule. Consequently, for statistical analysis, the follow-up visits were assigned to time windows, and denoted as follows: "6 months" (4 to 8 months), "1 year" (9 to 17 months) and "long term" (18 months and longer). If multiple visits occurred within a time-period, then continuous data were averaged and the most recent response for categorical measures was adopted.

Continuous outcome measures recorded during baseline and follow-up visit windows were analyzed and compared between randomized groups using a linear mixed-effects model, based on the Linear Mixed-Effects Models using 'Eigen' and S4 (lme4) package in R[20]. The study utilized a linear mixed-effects model rather than traditional repeated measures methods such as analysis of variance (ANOVA) since the former allows better handling of missing data. Each model included

a random effect for patient and fixed effects for randomized group, visit time-window (baseline, 6 months, 1 year, or long term), and adjustment variables age, sex, social deprivation (using the Scottish Index of Multiple Deprivation quintile for quantification) and Rose Angina questionnaire result at baseline. Two models were fitted. Model 1 included only those terms listed above. Model 2 additionally included fixed effects to estimate the between-group difference within each follow-up time-window (3 binary indicators, formed by multiplying the treatment group indicator, with each of the 6-month, 1-year, and long-term time-window indicators). The coefficients for these added terms were taken as intervention effect estimates (between treatment group mean differences) and are reported with 95% CIs and p-values. In addition, a global p-value for any intervention effects was derived using a likelihood ratio test, comparing Model 1 with Model 2. For outcomes collected at a single follow-up visit, a linear regression model was used for continuous measures and a logistic regression model for categorical measures, adjusted for the baseline outcome value and adjustment variables previously mentioned. To check that modelling assumptions had been satisfied, plots of model residuals were assessed for constant variance and a Normal distribution. A log-transformation was applied to outcomes with a log-normal distribution and the intervention treatment effect estimate and 95% CI back-transformed (between treatment group geometric mean ratio).

A Kaplan-Meier survival plot was used to present an estimate of the probability of an unplanned episode of hospital care for chest pain, across time and by randomized group. The solid line presents the survival probability estimate and the shaded area covers the area between the upper and lower 95% CIs. The p-value is derived from the log-rank test comparing the survival curve of each randomized treatment group. The number of patients at risk in each randomized group are presented beneath the x-axis of the plot.

Data integrity

Colin Berry and Novalia Sidik had full access to the data in the study and took responsibility for its integrity and the data analysis. Beth Stanley and Alex McConnachie take responsibility for the statistical analyses.

Results

Study population

Between August 31, 2017, and September 9, 2020, 2136 patients who had been referred for cCTA were screened. Of these, 1552 had been referred for assessment of chest pain. Three hundred and eighty-four patients provided written informed consent for research prior to undergoing cCTA, and 322 of these patients were found to have no obstructive coronary artery disease or alternative cause for angina identified on cCTA (Figure 2), meeting the eligibility criteria. Seventy-two patients were not enrolled for logistical and other reasons. Two hundred and fifty (77.6%) patients attended for invasive coronary angiography and coronary function testing after a median of 79.5 days (43.0, 137.8). Nineteen (7.6%) of these patients were then excluded when obstructive coronary artery disease was identified by angiography or fractional flow reserve (≤0.80).

Randomized population

Two hundred and thirty-one patients (92.4%) were randomized (n=115 intervention group; n=116 control group): mean age 55.7 years (Table 1). Most patients were women (n = 149, 64.5%) and the predicted 10-year risk of a coronary heart disease event was low (mean 4.2%). Thirty-five (15.2%) patients had previously undergone coronary angiography (median 1.0, range [1.0, 4.0] procedures), and medicines for the prevention and treatment of angina were commonly prescribed (Table 1).

At baseline, the mean SAQ angina frequency score was 64.2 ± 24.5, corresponding with weekly/monthly angina (SAQ frequency score 31-60 indicates weekly angina, 61-99 indicates monthly angina). The mean SAQ angina limitation score was 55.8 ± 26.8, corresponding with mild to moderate angina limitation. Overall, the angina burden of the patient population was consistent with Canadian Cardiovascular Society class I-II angina, with a mean SAQ summary score of 54.8 ± 20.3.

Half of the patients (48.9%) described atypical chest pain according to the Rose Angina Questionnaire. Most patients (75.3%) had undergone treadmill exercise tolerance testing prior to cCTA, with a mean exercise time of 7.1 ± 2.5 minutes on the Bruce protocol. Only 10 (5.7%) patients had an abnormal (positive) result, and 123 (70.7%) patients had an inconclusive result.

Invasive Endotyping and Findings

Invasive management is described in Table 2. The left anterior descending coronary artery was evaluated in 223 (96.5%) patients. The invasive coronary function tests were successfully completed in 230 (99.6%) patients and the true endotypes are described in Table 2. Blinding in the control group was achieved in all 116 patients. The mean fractional flow reserve was 0.88 consistent with non-obstructive coronary artery disease.

Of the 231 randomized patients, 127 (55.0%) had microvascular angina, 27 (11.7%) had vasospastic angina and 17 (7.4%) patients had both microvascular and vasospastic angina. Sixty (26.0%) patients had normal coronary function test results. The prevalence of microvascular angina according to the distribution of diagnostic criteria is described in the Supplement (Table S2).

Primary outcome

Prior to randomization, the clinician considered a possible diagnosis of angina due to a coronary

vasomotor disorder in 51 (44.3%) patients in the intervention group and 55 (47.4%) patients in the control group (Table 3 and Figure 3). Following randomization, patients in the intervention group were four-fold (odds ratio (95% CI) 4.05; 2.32 to 7.24; p<0.001) more likely to be diagnosed with a coronary vasomotor disorder and the frequency of this diagnosis increased to 76.5%. The frequency of a diagnosis of normal coronary function (i.e., no microvascular dysfunction or vasospastic process) was not different between the groups prior to randomization (51.3% vs 50.9%) but was reduced in the intervention group after randomization (23.5% vs 50.9%, p<0.001). In the control group, 83 patients had a final post-randomization diagnosis of microvascular and/or vasospastic angina (Tables 2 and 3). Of these, 42 were misdiagnosed with normal coronary function (n=41) or coronary artery disease (n=1) and 41 were correctly diagnosed with microvascular angina and/or vasospastic angina (Supplement, Table S3).

Following randomization, the clinician's certainty of diagnosis (Table 3) improved in the intervention group (102 [88.7%]) compared with baseline (18 [15.7%]). This was significantly higher than in the control group (20 [17.2%], p<0.001). Overall, a missed diagnosis of microvascular and/or vasospastic angina occurred in 3 (2.6%) patients in the intervention group and 75 (64.7%) patients in the control group (p<0.001 [Supplement, Figure S1]).

Secondary outcomes

Follow up continued until 27 May 2022, representing a median period of 19.9 months (IQR 12.6 – 26.9). One hundred and fifty-three (66.2%) patients were randomized and/or completed follow-up after March 16, 2020, during the COVID-19 pandemic. In the randomized population (n=231), 217 (93.9%) patients provided one response during follow-up and 167 (72.3%) patients provided two or more responses (Table 4). Seventy (60%) of each randomized patient group returned a SAQSS for the 6-month outcome.

There was no difference in the SAQSS between the randomized groups at 6 months or further time points (Table 4, Supplement Figure S2). At 6 months, the SAQSS in the intervention and controls groups were 59.2 ± 24.2 (a change of 2.3 ± 16.2 from baseline) versus 60.4 ± 23.9 (a change of 4.6 ± 16.4 from baseline), with an overall p=0.360 (Table 4). This was consistent across all SAQ domains, including angina limitation (p=0.862), angina stability (p=0.537), angina frequency (p=0.122), treatment satisfaction (p=0.172), and quality of life (p=0.479). When categorized by symptom severity at baseline, there was no difference in the SAQSS outcome between the randomized groups (Supplement).

At one year, treatment satisfaction for the convenience domain of TSQM-9 increased by 6.5 points over baseline in the intervention group, and decreased by 3.7 points in the control group, an adjusted between-group difference of 9.3 points (95% CI; 3.3 - 15.3; p=0.002). For the global satisfaction domain, the between-group difference was 9.2 points (2.0 - 16.5; p=0.013) (Supplement, Table S4). Health-related quality of life (as assessed by the EQ-5D-5L instrument) was not different between the groups (utility index score p=0.992; visual analogue score p=0.822). There were no differences in illness perception (BIPQ, p=0.124), or psychological distress levels (PHQ-4, p=0.827).

Medical management

In the intervention group, in keeping with the higher proportions of patients diagnosed with ANOCA endotypes, the cardiologist recommended prescription of antianginal medical therapy for disorders of coronary function increased post- versus pre- randomization (76.5% vs 41.4%, p<0.001 [Supplement, Table S5]). At the final follow-up visit, patients in the intervention group were more frequently prescribed calcium-channel blockers (52.7% vs 25.3%, p<0.001) and long-acting nitrates (27.5% vs 13.7%, p=0.029), and less frequently prescribed beta-blockers (30.8% vs 52.6%, p=0.002) (median of 608 [389, 829] days post-randomization). More patients in the

intervention group were prescribed preventative therapy (i.e., statin with or without antiplatelet therapy) but the differences were not statistically significant. Compared with the control group, fewer referrals for additional investigations, including cardiovascular (0% vs 6.0%, p=0.014) and non-cardiovascular (3.5% vs 17.2%, p=0.001) tests, were requested.

At follow up, compliance with non-pharmacological management was also assessed (Supplement, Table S6). In the intervention group, 37.8% of patients reported an increase in weight, compared with 43.6% in the control group (p=0.687). Self-reported compliance with cardiac rehabilitation was higher in the intervention group (27.8%) than in the control group (5.3%) (p=0.003). There was no difference between the intervention and control groups in patients' self-reported compliance with a healthy diet, regular exercise, and weight maintenance. Only 47.8% of patients reported consuming a healthy diet (47.8% of intervention group vs 47.9% of control group, p=0.884), and 56.5% reported regular exercise (60.0% of intervention group vs 53.2% of control group, p=0.464).

Cardiovascular risk factors

Cardiovascular risk factors are described in Table 5. At follow up, systolic blood pressure was lower in the intervention group (135.0 mmHg) compared with the control group (140.6 mmHg), with a statistically significant difference in change compared with baseline (-5.59; -10.99 to -0.19; p=0.044). More patients in the intervention group had a systolic blood pressure <130 mmHg at follow-up (39 (43.3%) vs. 30 (32.3%); 1.97 (1.00, 3.90); p=0.051). Body mass index, waist circumference, current smoking and blood lipids were not different between the groups (Table 5).

Clinical outcomes

Procedure-related events

Two patients received stents for a catheter-induced coronary artery dissection without other complications. Atrial fibrillation occurred in four (1.7%) patients during acetylcholine administration. The atrial fibrillation resolved spontaneously in three patients whereas one patient received intravenous amiodarone and remained in hospital overnight.

Post-discharge clinical outcomes

Vital status and episodes of secondary care were obtained for all patients by verification of electronic health records. Hospitalizations and deaths were adjudicated by a blinded clinical events committee.

Clinical events are described in Table 3. Approximately one in five patients experienced an unplanned episode of secondary care for chest pain, with or without hospitalization (Supplement, Figure S3). Two patients in each group experienced a non-fatal myocardial infarction. Three patients died for a non-cardiovascular reason, including two deaths in the intervention group and one death in the control group (Supplement, Table S7).

Impact of COVID-19

In the randomized population, 168 (72.7%) patients had a laboratory test for SARS-CoV-2 infection. Fifty-eight (25.1%) patients tested positive for SARS-CoV-2, six (2.6%) patients were hospitalized, and one (0.4%) patient died from COVID-19.

The timeline of healthcare and social restrictions during the pandemic is shown in Supplement Table S1. During the COVID-19 pandemic (16 March 2020 - 1 July 2021), in-person clinical

research visits at the NHS Golden Jubilee hospital were prohibited. One hundred and fifty-three (66.2%) patients were randomized and/or completed follow-up after March 16, 2020 (Supplement Table S8). Overall, 174 (75.3%) of 231 randomized patients had a follow-up contact that occurred out with a one-month time-period representing a protocol deviation consistent with deferred medical management. Four in five patients re-attended for an in-person visit, but four in five of these patients attended out with the timeline of the protocol, some considerably.

Discussion

In this randomized, controlled trial, disclosure of invasive coronary function tests undertaken in outpatients with suspected ANOCA improved diagnosing the cause of angina. In this population, microvascular angina and coronary spasm were common and, in general, angina severity was mild. The intervention was associated with improvements in treatment satisfaction but not angina. In the control group, endotypes were commonly missed and more patients were referred for onward investigations.

Novel design features included multicenter recruitment, use of validated questionnaires, invasive coronary function testing (including acetylcholine) performed in a single reference center, randomization before coronary function testing, a control procedure, blinding, and stratified medical therapy. The study was delivered during the COVID-19 pandemic.

In the control group, most (72.3%) patients who had a true endotype of microvascular angina or vasospastic angina were misdiagnosed based on cCTA-guided management (Table 3). In fact, about half (41 of 83 patients), were diagnosed as having normal coronary function. This misdiagnosis rate is higher than prior noninvasive imaging studies, such as rubidium-82 myocardial perfusion positron emission tomography-CT[21] (42%) and systematic reviews (41% - 43%[22,23]), but consistent with invasive testing[12]. This difference highlights the diagnostic gap for

vasospastic angina using noninvasive imaging.

Stratified medicine is the identification of key subgroups of patients (strata) within a heterogeneous population; these patient strata being distinguishable by distinct mechanisms of disease and/or responses to therapy (endotype)[24]. In this outpatient population, stratified medicine did not improve angina or quality of life. The explanations include population characteristics (including mostly mild angina), deferral of medical management to the usual care clinicians, inadequate cardiac rehabilitation, the COVID-19 pandemic, and the lack of effective, disease-modifying medical therapy for ANOCA. When medical management is disrupted, as was the case during the pandemic, patients' angina symptoms and health-related quality of life may not improve. Furthermore, non-disclosure of the coronary function test results to the caring clinicians may have limited a more precise targeting of treatment. Therefore, a 'bias to the null' effect of the blinding (Type 2 error) cannot be discounted.

In the CORonary MICrovascular Angina (CorMicA) trial, which tested whether invasive coronary function testing with linked therapy improves health status in patients with ANOCA, stratified medicine improved angina and quality of life at 6-[12] and 12- months[25], in association with improvements in cardiovascular risk factors and participation in cardiac rehabilitation. The CorMicA trial population[12,25] was downstream in the care pathway having been selected for invasive management. In contrast, the population in the current study included ambulatory outpatients upstream in the care pathway. Compared with CorMicA[12], the SAQ summary scores in the current study were 54.8 (20.3) vs. 50.8 (18.1), respectively, and a higher score represents a lower burden of angina. More patients reported atypical chest pain (48.9% vs 35.8%) and fewer patients had an abnormal exercise tolerance test (5.7% vs 47.4%). These differences may partly explain why this population was less responsive to angina management. Our study involved an "upstream" strategy of routinely performing invasive testing in a heterogeneous group of patients

to characterize the prevalence of endotypes of ANOCA. However, many of these patients had minimal symptoms.

In this trial, stratified medicine reduced systolic blood pressure and the proportion of patients with systolic hypertension (systolic >130 mmHg). The effect on systolic blood pressure may be explained by enhanced prescription of angina medication with blood pressure lowering effects in the intervention group (Supplement, Table S5) and a rise in blood pressure (2.9 mmHg) in the control group (Table 5). The intervention improved compliance with cardiac rehabilitation (Table S6).

Medical management was implemented by blinded clinicians in primary and secondary care. This design minimized bias that occurs with an open-label design when unblinded research staff implement medical care which may be more intensive in the intervention group than in the control group. The design of our study mitigated this bias. On the other hand, patients with a new diagnosis of angina should receive a shared care plan involving active medical management[4,5] and cardiac rehabilitation.

Our hypothesis was that stratified medicine using mechanistically targeted medical therapy would improve modifiable risk factors, such as blood pressure, body mass index, hyperlipidemia, and cigarette smoking. However, most of the patients participated during the COVID-19 pandemic which caused restrictions on access to primary[26,27] and secondary medical care, reduced adherence with medication[28], reduced control of cardiovascular risk factors[29,30] and enhanced unfavorable social behaviors[31]. During the pandemic, reduced access undermined the feasibility of medical management in the community[32]. In this study, stratified medicine changed the diagnosis for microvascular angina (40.9%) and vasospastic angina (17.4%) and more patients in the intervention group had medication changed for these conditions (Supplement Table S5).

In the Scottish Computed Tomography of the Heart (SCOT-HEART) trial, which evaluated cCTA

as an alternative to standard care in the investigation of low- to intermediate-risk patients with chest pain, anginal symptoms and quality of life improved less in the cCTA-guided group[33]. The prevalence of coronary microvascular dysfunction in the SCOT-HEART population is unknown. In the cCTA group, in patients who had microvascular angina and/or vasospastic angina, discontinuation of angina therapy by protocol may have caused a deterioration in anginal symptoms and health-related quality of life. None of the landmark trials of cCTA-guided management have involved assessments of coronary vasomotion[33-38], and prior to our study, the prevalence of coronary vasomotor endotypes in patients with angina (or ischemic symptoms) and no obstructive coronary artery disease was unknown. Furthermore, one in fifteen patients categorized by cCTA as having no obstructive coronary disease had flow-limiting disease identified during invasive management. Noninvasive FFR-CT may have identified these individuals.

Considering clinical implications, first, endotypes of coronary vasomotor dysfunction were common and underdiagnosed in outpatients with ANOCA, as defined by cCTA. Second, routine invasive coronary function testing led to improvements in diagnosing the cause of angina and related treatment satisfaction and reduced referrals for onward investigations but did not improve angina burden which was mild overall. Two patients (0.8%) had a coronary artery dissection during the index diagnostic procedure necessitating percutaneous coronary intervention. Therefore, a selective rather than routine invasive strategy involving patients with refractory symptoms would seem most appropriate.

One in ten patients experienced a major adverse cardiovascular event and one in four patients had an unplanned episode of hospital care for chest pain indicating a substantial health burden in this population. Our findings reaffirm that women are more commonly affected by ANOCA, with implications for quality of life and morbidity. Women are under-represented in cardiovascular

trials, but this is not the case in ANOCA.

Noninvasive, functional imaging of myocardial blood flow is an alternative option for patients with suspected INOCA[39]. This is being investigated in the Coronary Microvascular Angina Cardiovascular Magnetic Resonance Imaging (CorCMR) trial (ClinicalTrials.gov: NCT04805814). However, angina due to coronary spasm can only be accurately assessed by invasive acetylcholine testing. This should be considered for patients with refractory symptoms or when myocardial perfusion imaging is not available.

Finally, the medical management of ANOCA involves repurposing antianginal medications. Clinical trials to identify disease-modifying therapy for ANOCA endotypes are needed[1,39,40].

Limitations

During prospective screening, many patients declined to participate since invasive management post-cCTA was not standard care. The COVID-19 pandemic impeded implementation of the protocol and personalized patient care. In the randomized population, 217 (93.9%) patients provided at least one SAQ response during follow-up however 40% of participants in each group did not return a SAQ response at 6-months. Noninvasive stress tests involved treadmill exercise electrocardiography[41] rather than imaging. Coronary function testing was undertaken in a single artery, however, microvascular function may differ between coronary arteries within the same patient. Although the absence of an abnormality on coronary function testing makes cardiac chest pain unlikely this condition remains possible, and an abnormality of one or more coronary function assessments may not confirm a causal cardiac etiology.

Conclusions

Three quarters of this outpatient population with ANOCA had evidence of coronary microvascular

dysfunction and/or epicardial coronary spasm and angina severity was generally mild. Invasive endotyping improved diagnosing the cause of angina and related treatment satisfaction and reduced referrals for onward investigations but did not improve wellbeing. Medical management was disrupted by the pandemic.

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Disclosures

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Supplemental Materials

Expanded Methods; Expanded Results; Tables S1 – 8; Figures S1 – 3; Appendix

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Figure Legends

Figure 1. Blinding procedures in the catheter laboratory.

Figure 2. Flow diagram of the clinical trial.

Figure 3. Bar chart of diagnoses at sequential timepoints: post-cCTA/pre-angiogram (initial diagnosis by noninvasive angiography), post-angiogram / pre-randomization (diagnosis by invasive angiography), and post-physiology, post-randomization (intervention group, single column, green; coronary function tests were acquired in the control group but not disclosed in the control group). The true endotypes in all patients are also displayed. Colors: intervention group – green, control group – blue.

Tables

Table 1. Baseline Demographic and Clinical Characteristics for the Randomized Population.

	Randomized		
	All (N=231)	**Intervention (N=115)**	**Control (N=116)**
Age, years	55.7 (8.5)	55.9 (7.8)	55.4 (9.1)
Female	149 (64.5%)	74 (64.3%)	75 (64.7%)
BMI, kg/m^2	30.8 (6.0)	30.8 (6.5)	30.7 (5.5)
BMI ≥ 30 kg/m^2	113 (48.9%)	53 (46.1%)	60 (51.7%)
Waist circumference, cm	95.9 (14.4)	95.3 (14.5)	96.6 (14.3)
Smoking status			
Nonsmoker	114 (49.4%)	55 (47.8%)	59 (50.9%)
Ex-smoker	70 (30.3%)	35 (30.4%)	35 (30.2%)
Current smoker	47 (20.3%)	25 (21.7%)	22 (19.0%)
Previous coronary angiogram	35 (15.2%)	16 (13.9%)	19 (16.4%)
Previous myocardial infarction	8 (3.5%)	4 (3.5%)	4 (3.4%)
Previous stroke or TIA	13 (5.6%)	4 (3.5%)	9 (7.8%)
Hypertension	108 (46.8%)	47 (40.9%)	61 (52.6%)
Diabetes mellitus	26 (11.3%)	12 (10.4%)	14 (12.1%)
Dyslipidemia	133 (57.6%)	65 (56.5%)	68 (58.6%)
Family history of CVD	135 (58.4%)	67 (58.3%)	68 (58.6%)
Chronic obstructive pulmonary disease	26 (11.3%)	17 (14.8%)	9 (7.8%)
Systolic blood pressure, mmHg	137.1 (21.1)	135.8 (20.2)	138.4 (22.0)
Diastolic blood pressure, mmHg	75.2 (11.7)	74.2 (11.2)	76.2 (12.1)
Charlson comorbidity index score	1.5 (1.1)	1.6 (1.1)	1.5 (1.1)
Predicted 10-year CVD risk*	4.0 [2.3, 5.5]	3.9 [2.2, 5.8]	4.1 [2.4, 5.5]
Preventive therapy			
Aspirin	142 (61.5%)	74 (64.3%)	68 (58.6%)
Statin	146 (63.2%)	76 (66.1%)	70 (60.3%)
ACE inhibitor or angiotensin receptor blocker	68 (29.4%)	33 (28.7%)	35 (30.2%)
Angina medication			
Beta-blocker	144 (62.3%)	67 (58.3%)	77 (66.4%)
Calcium-channel blocker	58 (25.1%)	27 (23.5%)	31 (26.7%)
Nitrates	36 (15.6%)	18 (15.7%)	18 (15.5%)
Nicorandil	14 (6.1%)	7 (6.1%)	7 (6.0%)
Cholesterol and lipid profile			
Total cholesterol, mg/dL	91.3 (20.5)	90.0 (20.0)	92.5 (21.0)

	Randomized		
	All (N=231)	**Intervention (N=115)**	**Control (N=116)**
HDL cholesterol, mg/dL	23.5 [19.8, 28.9]	24.3 [19.8, 30.1]	23.4 [19.8, 28.8]
LDL cholesterol, mg/dL	50.6 (18.6)	49.8 (16.9)	51.3 (20.1)
Triglyceride, mg/dL	27.8 [19.1, 39.6]	26.3 [18.0, 37.8]	29.5 [21.2, 41.4]
HbA1c, %	5.5 [5.3, 5.8]	5.5 [5.3, 5.7]	5.4 [5.3, 5.8]
NYHA class			
I	54 (23.4%)	32 (27.8%)	22 (19.0%)
II	163 (70.6%)	77 (67.0%)	86 (74.1%)
III	14 (6.1%)	6 (5.2%)	8 (6.9%)
Patient Rose Angina Questionnaire			
Definite (typical) angina	118 (51.1%)	63 (54.8%)	55 (47.4%)
Probable (atypical) angina	113 (48.9%)	52 (45.2%)	61 (52.6%)
Non-anginal pain	0 (0.0%)	0 (0.0%)	0 (0.0%)
Seattle Angina Questionnaire			
Angina summary score	54.8 (20.3)	55.5 (19.9)	54.1 (20.7)
Angina limitation	55.8 (26.8)	56.0 (26.5)	55.5 (27.3)
Angina stability	49.2 (23.3)	46.7 (23.4)	51.8 (23.0)
Angina frequency	64.2 (24.5)	65.6 (25.2)	62.9 (23.8)
Angina treatment satisfaction	81.5 (18.0)	80.2 (18.0)	82.7 (17.9)
Angina quality of life	44.7 (22.8)	45.6 (22.3)	43.9 (23.3)
Quality of life (EQ5D-5L)			
Index score	0.72 [0.43, 0.80]	0.72 [0.49, 0.80]	0.70 [0.42, 0.82]
Visual analogue scale score	70.0 [55.0, 80.0]	70.0 [60.0, 80.0]	70.0 [50.0, 80.0]
Treadmill exercise electrocardiography			
Performed	174	85	89
Symptoms elicited during testing			
Limiting angina	30 (18.4%)	15 (18.8%)	15 (18.1%)
Non-limiting angina	53 (32.5%)	28 (35.0%)	25 (30.1%)
Breathlessness	30 (18.4%)	15 (18.8%)	15 (18.1%)
Pre-syncope	1 (0.6%)	0	1 (1.2%)
Fatigue	59 (36.2%)	28 (35.0%)	31 (37.3%)
Exercise duration, minutes	7.1 [5.7, 9.0]	7.2 [5.5, 9.0]	7.1 [5.7, 9.0]
METs	9.3 [7.0, 10.2]	9.3 [7.0, 10.2]	9.4 [7.0, 10.1]
Duke treadmill score	3.5 [0.0, 6.5]	3.5 [-1.1, 6.2]	3.6 [0.2, 6.6]
Result			
Normal	41 (23.6%)	17 (20.0%)	24 (27.0%)
Inconclusive	123 (70.7%)	63 (74.1%)	60 (67.4%)
Abnormal	10 (5.7%)	5 (5.9%)	5 (5.6%)
Coronary CTA			
Absence of atherosclerosis	87 (37.7%)	44 (38.3%)	43 (37.1%)

	Randomized		
	All (N=231)	**Intervention (N=115)**	**Control (N=116)**
CAD-RADS score	1.0 [0.0, 2.0]	1.0 [0.0, 2.0]	1.0 [0.0, 2.0]
Calcium score, Agatston Units	54.3 (124.8)	53.5 (117.0)	55.1 (132.9)

Values are mean (SD), median [Q1, Q3] or n (%). *SCORE2 or SCORE2-Older Persons (≥70 years)
ACE = angiotensin-converting enzyme; BMI = body mass index; CAD-RADS = Coronary Artery Disease - Reporting and Data System (minimum vessel diameter for inclusion is 1.5 mm); coronary CTA = computed tomography angiography; CVD = cardiovascular disease; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MET = metabolic equivalent of task; NYHA = New York Heart Association; TIA = transient ischemic attack.

Table 2. Invasive Coronary Endotyping.

	Randomized		
	All (N=231)	**Intervention (N=115)**	**Control (N=116)**
Coronary function test performed in the left anterior descending artery	223 (96.5%)	112 (97.4%)	111 (95.7%)
Angiographically normal	74 (32.0%)	41 (35.7%)	33 (28.4%)
Gensini score†	0.0 [0.0, 4.8]	0.0 [0.0, 3.0]	2.5 [0.0, 5.1]
Invasive physiology			
LV end-diastolic pressure (mmHg)	7.0 [5.0, 10.0]	7.0 [4.0, 10.0]	8.0 [5.0, 10.0]
Fractional flow reserve	0.88 (0.05)	0.88 (0.04)	0.88 (0.05)
Index of microvascular resistance	20.0 [14.0, 30.0]	19.0 [14.0, 30.0]	21.0 [15.0, 30.0]
Coronary flow reserve	3.50 [2.50, 4.60]	3.50 [2.60, 4.65]	3.50 [2.40, 4.45]
Microvascular spasm	96 (41.7%)	51 (44.3%)	45 (39.1%)
Epicardial vasospasm	44 (19.0%)	22 (19.1%)	22 (19.0%)
Post-cCTA, pre-angiogram endotype			
CAD/Obstructive CAD	30 (13.0%)	16 (13.9%)	14 (12.1%)
Microvascular angina	73 (31.6%)	33 (28.7%)	40 (34.5%)
Vasospastic angina	6 (2.6%)	2 (1.7%)	4 (3.4%)
Microvascular- and vasospastic angina	0 (0%)	0 (0%)	0 (0%)
Normal coronary function	122 (52.8%)	64 (55.7%)	58 (50.0%)
Post-angiogram, pre-randomization endotype			
CAD/Obstructive CAD	7 (3.0%)	5 (4.3%)	2 (1.7%)
Microvascular angina	81 (35.1%)	41 (35.7%)	40 (34.5%)
Vasospastic angina	9 (3.9%)	3 (2.6%)	6 (5.2%)
Microvascular- and vasospastic angina	16 (6.9%)	7 (6.1%)	9 (7.8%)
Normal coronary function	118 (51.1%)	59 (51.3%)	59 (50.9%)
Post-coronary function test, post-randomization, endotype			
CAD/Obstructive CAD	0 (0%)	0 (0%)	0 (0%)
Microvascular angina	127 (55.0%)	66 (57.4%)	61 (52.6%)
Vasospastic angina	27 (11.7%)	15 (13.0%)	12 (10.3%)
Microvascular- and vasospastic angina	17 (7.4%)	7 (6.1%)	10 (8.6%)
Normal coronary function	60 (26.0%)	27 (23.5%)	33 (28.4%)
*Procedure details**			
Contrast media volume, ml	150 [130, 170]	150 [121, 170]	150 [130, 170]
Angiography screening duration, s	413 [292, 561]	394 [281, 520]	433 [305, 580]
Radiation dose, $cGycm^2$	2260 [1432, 3416]	2159 [1455, 3412]	2325 [1352, 3417]

Values are mean (SD), median [Q1, Q3] or n (%). CAD = coronary artery disease, LV = left ventricular
†Gensini angiographic score is a metric of angiographic disease severity incorporating lesion severity and location.
*There were no statistically significant differences between the procedural characteristics of the randomized groups - contrast media volume (p=0.768), angiography screening duration (p=0.249) and radiation dose (p=0.780).

6 **Table 3.** Primary and Secondary Outcomes: Diagnostic Utility, Clinical Utility and Clinical Events.

		Randomized		
		Intervention (N=115)	**Control (N=116)**	**p-value**
Diagnostic Utility				
Baseline, pre-randomization				
Diagnosis of microvascular angina		41 (35.7%)	40 (34.5%)	0.891
Diagnosis of vasospastic angina		3 (2.6%)	6 (5.2%)	0.499
Diagnosis of microvascular angina & vasospastic angina		7 (6.1%)	9 (7.8%)	0.796
Diagnosis of non-cardiac chest pain		59 (51.3%)	59 (50.9%)	1.000
Diagnosis of obstructive coronary artery disease*		5 (4.3%)	2 (1.7%)	0.280
Certainty of diagnosis	Possibly Probably Certain	8 (7.0%) 89 (77.4%) 18 (15.7%)	7 (6.0%) 89 (76.7%) 20 (17.2%)	0.943
Post-randomization, final diagnosis				
Microvascular angina				
Final diagnosis of microvascular angina		64 (55.7%)	40 (34.5%)	**0.001**
Change in diagnosis		47 (40.9%)	0 (0%)	-
Vasospastic angina				
Final diagnosis of vasospastic angina		17 (14.8%)	6 (5.2%)	**0.016**
Change in diagnosis		20 (17.4%)	0 (0%)	-
Mixed (microvascular angina & vasospastic angina)				
Final diagnosis of microvascular angina & vasospastic angina		7 (6.1%)	9 (7.8%)	0.796
Change in diagnosis		14 (12.2%)	0 (0%)	-
Non-cardiac chest pain				
Final diagnosis of non-cardiac chest pain		27 (23.5%)	59 (50.9%)	**<0.001**
Change in diagnosis		60 (52.2%)	0 (0%)	**-**
Missed diagnosis (all)		3 (2.6%)	75 (64.7%)	**<0.001**
Missed diagnosis (microvascular angina and/or vasospastic angina)		3/88 (3.4%)	60/83 (72.3%)	**<0.001**
Certainty of diagnosis	Possibly Probably Certain	0 (0.0%) 13 (11.3%) 102 (88.7%)	7 (6.0%) 89 (76.7%) 20 (17.2%)	**<0.001**
Clinical Utility				
Preventative therapy		92 (80.0%)	88 (75.9%)	0.526
Standard angina therapy		0 (0.0%)	13 (11.2%)	**<0.001**
Therapy for microvascular angina & vasospastic angina		88 (76.5%)	48 (41.4%)	**<0.001**
Stopping medication		7 (6.1%)	11 (9.5%)	0.463
Additional cardiovascular tests		0 (0.0%)	7 (6.0%)	**0.014**
Additional non-cardiovascular tests		4 (3.5%)	20 (17.2%)	**0.001**
Clinical Events				
Major adverse cardiac and cerebrovascular events		16 (13.9%)	11 (9.5%)	0.314
All cause death		2 (1.7%)	1 (0.9%)	0.622

		Randomized		
		Intervention (N=115)	**Control (N=116)**	**p-value**
Cardiovascular death		0 (0.0%)	0 (0.0%)	-
Non-cardiovascular death		2 (100.0%)	1 (100.0%)	-
Non-fatal myocardial infarction		2 (1.7%)	2 (1.7%)	1.000
Cerebrovascular event		0 (0.0%)	0 (0.0%)	-
Hospitalisation with angina (unstable or other)		15 (13.0%)	9 (7.8%)	0.203
Unplanned episode of hospital care for chest pain§		27 (23.5%)	23 (19.8%)	0.526
Number of unplanned episodes of hospital care for chest pain	0 1 ≥2	88 (76.5%) 22 (19.1%) 5 (4.3%)	93 (80.2%) 13 (11.2%) 10 (8.6%)	0.124
	Median (IQR) [Min, Max]	1 (1, 1) [1, 8]	1 (1, 2) [1, 13]	0.075

Values are n (%) unless otherwise specified. P-values are from the Fisher's Exact test or the Mann-Whitney U test for continuous variables. * = Fractional flow reserve >0.80 and therefore eligible for randomization although clinician opinion of most likely diagnosis was obstructive coronary artery disease; § = Chest pain attendance not necessarily leading to admission or overnight stay.

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Table 4. Seattle Angina Questionnaire Results.

	Intervention (N=115)		**Control (N=116)**		**Between group p-value**
Follow-up response					
6 months	70 (60.9%)		70 (60.3%)		p=1.000
1 year	66 (57.4%)		64 (55.2%)		p=0.791
Long term	53 (46.1%)		52 (44.8%)		p=0.895
	Intervention (N=115)		**Control (N=116)**		**Estimate (95% CI), p-value**
	At follow up	**Change from baseline**	**At follow up**	**Change from baseline**	
Angina summary score					
6 months	59.2 (24.2)	2.3 (16.2)	60.4 (23.9)	4.6 (16.4)	-3.76 (-8.79, 1.27), p=0.143
1 year	63.7 (23.5)	4.7 (14.7)	66.0 (19.3)	7.9 (17.1)	-2.06 (-7.27, 3.14), p=0.437
Long term	52.9 (21.7)	1.1 (17.7)	54.8 (24.5)	5.0 (16.5)	-3.75 (-9.55, 2.04), p=0.204
					Overall p-value = 0.360
Angina limitation					
6 months	60.0 (28.6)	4.6 (17.3)	58.2 (27.5)	0.6 (18.1)	0.64 (-5.08, 6.36), p=0.826
1 year	62.0 (27.0)	4.2 (20.3)	63.8 (26.5)	3.4 (18.4)	-0.27 (-6.21, 5.68), p=0.930
Long term	50.5 (28.5)	-3.0 (20.9)	53.6 (28.2)	1.1 (16.6)	-2.48 (-9.06, 4.10), p=0.460
					Overall p-value = 0.862
Angina stability					
6 months	50.0 (26.1)	3.3 (35.6)	49.8 (18.1)	-1.6 (25.9)	0.26 (-7.13, 7.65), p=0.945
1 year	51.5 (23.8)	5.3 (34.9)	52.3 (22.6)	0.4 (29.0)	-0.85 (-8.48, 6.79), p=0.828
Long term	48.3 (18.7)	2.2 (26.4)	42.5 (18.4)	-10.0 (30.6)	6.38 (-2.14, 14.90), p=0.142
					Overall p-value = 0.537
Angina frequency					
6 months	67.0 (26.4)	0.3 (29.2)	71.4 (26.6)	8.7 (23.3)	-7.15 (-14.05, -0.26), p=0.042
1 year	72.9 (25.6)	2.3 (21.4)	77.7 (20.5)	11.9 (21.4)	-5.71 (-12.83, 1.41), p=0.116
Long term	64.4 (26.1)	3.4 (27.3)	64.3 (26.8)	8.0 (27.0)	-3.78 (-11.72, 4.15), p=0.350
					Overall p-value = 0.122

	Intervention (N=115)		Control (N=116)		Estimate (95% CI), p-value
	At follow up	Change from baseline	At follow up	Change from baseline	
Angina treatment satisfaction					
6 months	79.6 (19.6)	-0.5 (20.8)	74.1 (23.2)	-6.6 (20.3)	4.86 (-0.76, 10.49), p=0.090
1 year	81.8 (18.6)	2.0 (21.2)	79.7 (20.4)	-4.4 (20.6)	4.11 (-1.68, 9.90), p=0.164
Long term	77.8 (17.3)	-1.2 (17.8)	75.2 (22.6)	-7.3 (20.8)	4.34 (-2.15, 10.83), p=0.190
					Overall p-value = 0.172
Angina quality of life					
6 months	51.4 (28.3)	3.5 (23.7)	50.8 (25.4)	5.9 (20.6)	-3.06 (-9.31, 3.19), p=0.337
1 year	57.1 (25.6)	8.1 (19.9)	57.0 (22.5)	9.9 (23.4)	-0.14 (-6.60, 6.31), p=0.965
Long term	44.5 (22.5)	4.1 (22.2)	48.7 (28.0)	8.3 (22.9)	-5.06 (-12.30, 2.18), p=0.170
					Overall p-value = 0.479

Values are n (%) or mean (SD) unless otherwise stated. Between-group p-value is from the Fisher's Exact test. Estimate (95% CI) is the intervention group adjusted mean difference at the specified timepoint. Overall p-value presents whether any effect of randomized group on outcome regardless of timepoint. Seattle Angina Questionnaire (SAQ): lower scores represent worse angina symptoms. Follow up time windows: 6 months (4-8 months), 1 year (9-17 months), long term (≥18months).

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Table 5. Cardiovascular Risk Factors by Randomized Group at Baseline and Follow-Up Visits (intervention group - 581 (388, 800) days; control group - 684 (390, 844) days).

	Intervention (N=115)		**Control (N=116)**		**Estimate (95% CI), p-value**
	At baseline	**At follow up**	**At baseline**	**At follow up**	
Systolic blood pressure, mmHg	137.0 (20.4)	135.0 (17.9)	137.7 (20.9)	140.6 (21.5)	**-5.59 (-10.99, -0.19), p=0.044**
Systolic blood pressure <130 mmHg	32 (35.6%)	39 (43.3%)	32 (34.4%)	30 (32.3%)	1.97 (1.00, 3.90), p=0.051
BMI, kg/m^2	30.8 (6.6)	30.9 (6.5)	31.0 (5.4)	31.2 (5.5)	-0.21 (-0.93, 0.51), p=0.570
BMI <30 kg/m^2	50 (55.6%)	46 (51.1%)	43 (45.7%)	45 (47.9%)	1.22 (0.50, 2.97), p=0.660
Waist circumference, cm	94.8 (14.6)	96.7 (15.9)	96.5 (13.6)	98.7 (12.7)	-0.59 (-3.57, 2.40), p=0.700
Current smoker	17 (18.9%)	17 (18.9%)	16 (17.0%)	15 (16.0%)	1.42 (0.41, 4.92), p=0.579
Total cholesterol, mg/dL	90.0 (20.0)	90.5 (22.5)	92.5 (21.0)	90.4 (20.7)	0.41 (-5.4, 6.2), p=0.890
<200 mg/dL	62 (53.9%)	52 (58.4%)	54 (55.2%)	59 (63.4%)	0.84 (0.42, 1.66), p=0.612
HDL cholesterol, mg/dL	24.3 [19.8, 30.1]	24.3 [20.7, 31.5]	23.4 [19.8, 28.8]	23.9 [19.8, 29.2]	1.5% (-3.6%, 6.9%), p=0.572†
LDL cholesterol*, mg/dL	49.8 (16.9)	48.5 (18.9)	51.3 (20.1)	48.5 (18.3)	0.09 (-4.97, 5.15), p=0.973
<100 mg/dL	38 (43.2%)	45 (51.1%)	41 (44.6%)	50 (54.3%)	0.87 (0.45, 1.69), p=0.684
<55 mg/dL	7 (8.0%)	8 (9.1%)	8 (8.7%)	6 (6.5%)	1.67 (0.49, 5.73), p=0.415
Triglyceride, mg/dL	26.3 [18.0, 37.8]	28.4 [22.3, 40.0]	29.5 [21.2, 41.4]	31.9 [23.2, 46.1]	2.3% (-8.5%, 14.4%), p=0.688†
<150 mg/dL	58 (65.2%)	49 (55.1%)	45 (48.9%)	45 (48.9%)	0.96 (0.48, 1.92), p=0.912
Typical angina¶	63 (54.8%)	55 (59.8%)	55 (47.4%)	46 (52.3%)	1.32 (0.65, 2.68), p=0.441
Atypical angina¶	52 (45.2%)	37 (40.2%)	61 (52.6%)	42 (47.7%)	
Predicted 10-year cardiovascular risk‡ (%)	3.9 [2.3, 5.8]	4.1 [2.5, 5.4]	4.1 [2.4, 5.5]	4.2 [2.6, 6.0]	-4.8% (-12.6%, 3.7%), p=0.265†

Cardiovascular risk factors were recorded at baseline and at one follow-up visit only. Values are mean (SD), median [Q1, Q3] or n (% with data recorded at baseline and follow up) unless otherwise stated. Estimate (95% CI) is the intervention group adjusted mean difference for continuous outcomes or adjusted odds ratio for binary outcomes.
*LDL-c was calculated at follow-up using the Friedewald equation: LDL-c = Total cholesterol – (HDL-c + VLDL-c) where VLDL-c = (Triglycerides / 2.2), with all measured in mmol/L and converted to mg/dl = 18 × mmol/l.
‡SCORE2 or SCORE2-Older Persons (≥70 years).
†Data analyzed on a log-scale; Intervention effect estimate (95% CI) reported as percentage difference between groups.
¶As defined by the Rose Angina Questionnaire. Odds ratio presented for Typical angina with Atypical angina as the reference group.

Figures

Figure 1.

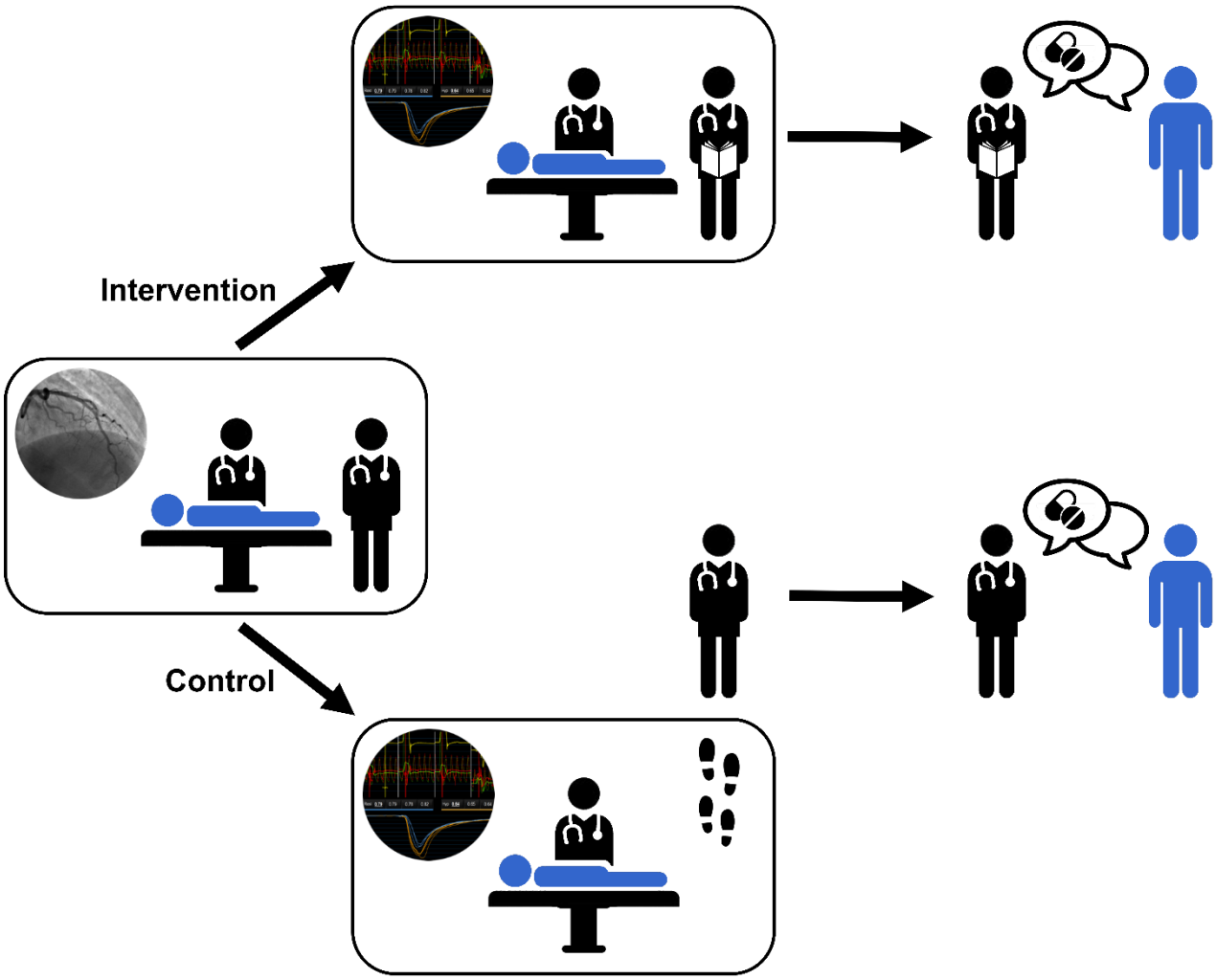


Figure 2.

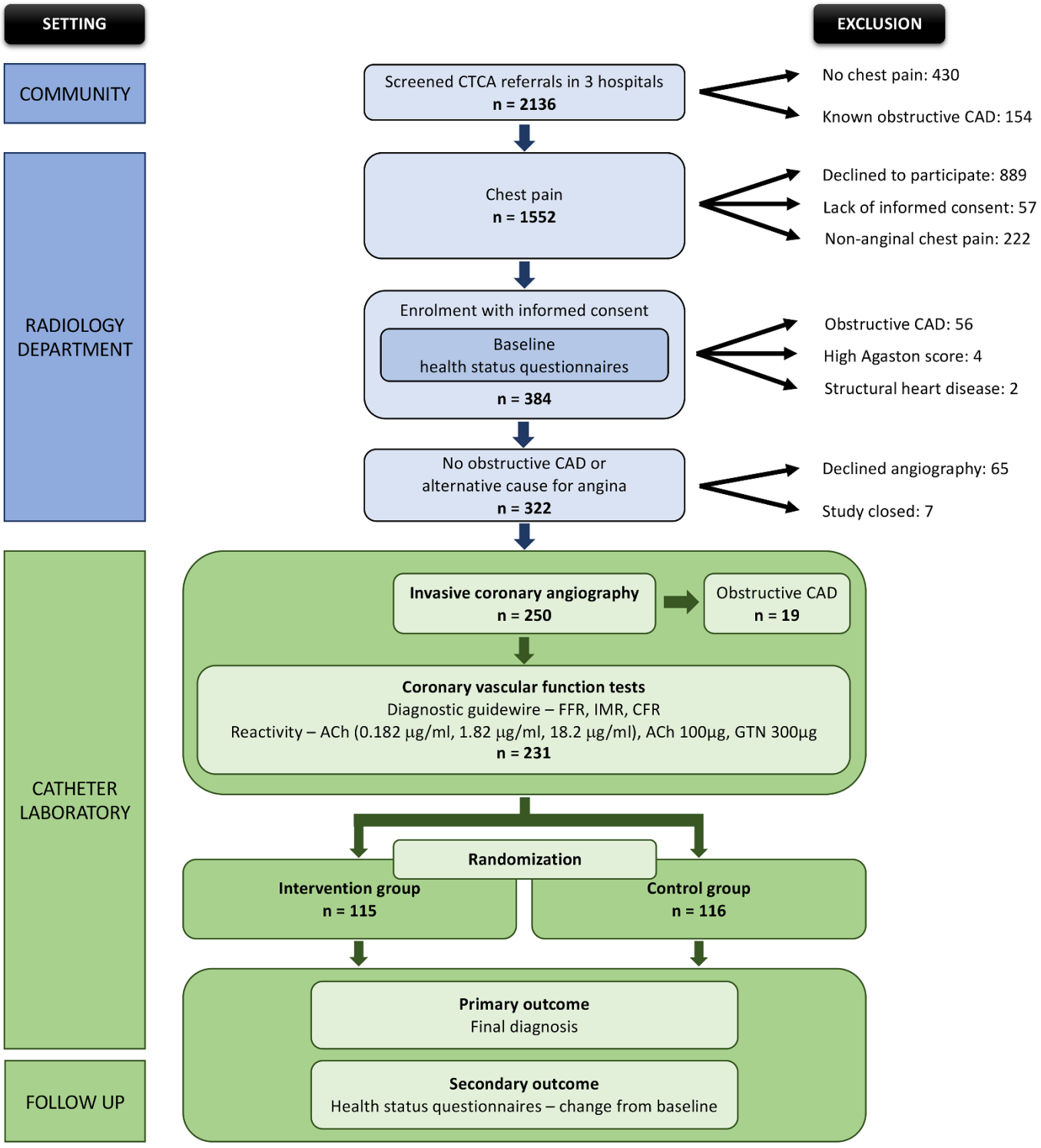
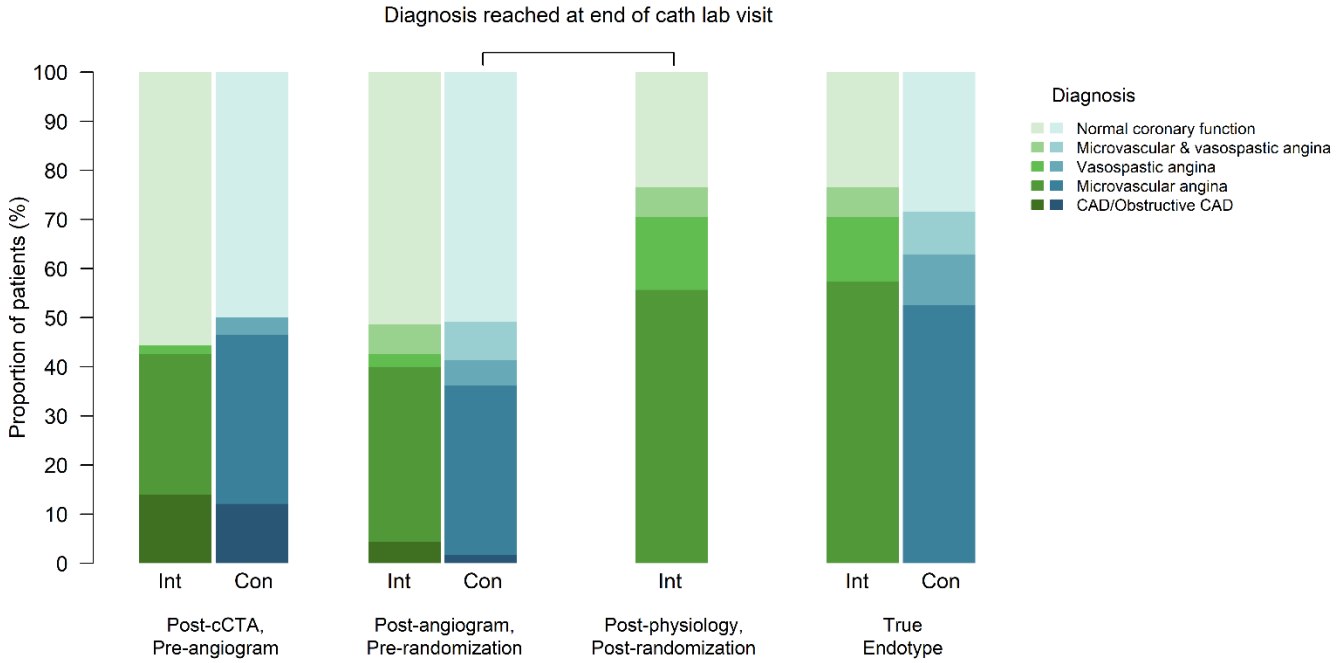

SETTING
EXCLUSION
COMMUNITY
RADIOLOGY DEPARTMENT
CATHETER LABORATORY
FOLLOW UP
Screened CTCA referrals in 3 hospitals
n = 2136
No chest pain: 430
Known obstructive CAD: 154
Chest pain
n = 1552
Declined to participate: 889
Lack of informed consent: 57
Non-anginal chest pain: 222
Enrolment with informed consent
Baseline health status questionnaires
n = 384
Obstructive CAD: 56
High Agaston score: 4
Structural heart disease: 2
No obstructive CAD or alternative cause for angina
n = 322
Declined angiography: 65
Study closed: 7
Invasive coronary angiography
n = 250
Obstructive CAD
n = 19
Coronary vascular function tests
Diagnostic guidewire – FFR, IMR, CFR
Reactivity – ACh (0.182 µg/ml, 1.82 µg/ml, 18.2 µg/ml), ACh 100µg, GTN 300µg
n = 231
Randomization
Intervention group
n = 115
Control group
n = 116
Primary outcome
Final diagnosis
Secondary outcome
Health status questionnaires – change from baseline

Figure 3.


Diagnosis reached at end of cath lab visit
Proportion of patients (%)
100
90
80
70
60
50
40
30
20
10
0
Int
Con
Post-cCTA,
Pre-angiogram
Int
Con
Post-angiogram,
Pre-randomization
Int
Post-physiology,
Post-randomization
Int
Con
True
Endotype
Diagnosis
Normal coronary function
Microvascular & vasospastic angina
Vasospastic angina
Microvascular angina
CAD/Obstructive CAD