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Stratified Medical Therapy Using Invasive Coronary Function Testing in Angina

The CorMicA Trial

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ABSTRACT

BACKGROUND Patients with angina symptoms and/or signs of ischemia but no obstructive coronary artery disease (INOCA) pose a diagnostic and therapeutic challenge.

OBJECTIVES The purpose of this study was to test whether an interventional diagnostic procedure (IDP) linked to stratified medicine improves health status in patients with INOCA.

METHODS The authors conducted a randomized, controlled, blinded clinical trial of stratified medical therapy versus standard care in patients with angina. Patients with angina undergoing invasive coronary angiography (standard care) were recruited. Patients without obstructive CAD were immediately randomized 1:1 to the intervention group (stratified medical therapy) or the control group (standard care, IDP sham procedure). The IDP consisted of guidewire-based assessment of coronary flow reserve, index of microcirculatory resistance, fractional flow reserve, followed by vasoreactivity testing with acetylcholine. The primary endpoint was the mean difference in angina severity at 6 months (assessed by the Seattle Angina Questionnaire summary score).

RESULTS A total of 391 patients were enrolled between November 25, 2016, and November 12, 2017. Coronary angiography revealed obstructive disease in 206 (53.7%). One hundred fifty-one (39%) patients without angiographically obstructive CAD were randomized (n = 76 intervention group; n = 75 blinded control group). The intervention resulted in a mean improvement of 11.7 U in the Seattle Angina Questionnaire summary score at 6 months (95% confidence interval [CI]: 5.0 to 18.4; p = 0.001). In addition, the intervention led to improvements in the mean quality-of-life score (EQ-5D index 0.10 U; 95% CI: 0.01 to 0.18; p = 0.024) and visual analogue score (14.5 U; 95% CI: 7.8 to 21.3; p < 0.001). There were no differences in major adverse cardiac events at the 6-month follow-up (2.6% controls vs. 2.6% intervention; p = 1.00).

CONCLUSIONS Coronary angiography often fails to identify patients with vasospastic and/or microvascular angina. Stratified medical therapy, including an IDP with linked medical therapy, is routinely feasible and improves angina in patients with no obstructive CAD. (CORonary MICrovascular Angina [CorMicA]; NCT03193294) (J Am Coll Cardiol 2018;72:2841–55) © 2018 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

ACh = acetylcholine

CAD = coronary artery disease

CFR = coronary flow reserve

FFR = fractional flow reserve

IDP = interventional diagnostic procedure

IMR = index of microcirculatory resistance

INOCA = ischemia but no obstructive coronary artery disease

MVA = microvascular angina

SAQ = Seattle Angina Questionnaire

VSA = vasospastic angina

Coronary angiography is routinely performed for the investigation of angina. It is the reference test for identifying obstructive coronary artery disease (CAD). In Europe and the United States, approximately 4 million elective coronary angiograms are performed each year (1,2). Up to one-half of all patients undergoing elective coronary angiography for the investigation of known or suspected angina have no obstructive epicardial CAD (2). This large, undifferentiated subgroup includes patients with microvascular angina (MVA) and/or vasospastic angina (VSA). These conditions are associated with high morbidity (3), impaired quality of life (4), and considerable health resource utilization (5).

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Invasive coronary angiography has a spatial resolution of 0.3 mm and is thus insensitive in visualizing the resistance arterioles (diameter 0.1 mm) that largely govern myocardial blood flow (6). The rationale for adjunctive testing of coronary vascular function during coronary angiography in patients with no obstructive CAD is 3-fold. First, normal angiography does not exclude a disorder of coronary vascular function. Coronary angiography may be considered incomplete without specifically assessing coronary vasomotion or the microcirculation (7). Second, coronary function testing enables individualized management of this undifferentiated population. Stratified medical therapy is the identification of key subgroups of patients (endotypes) within an undifferentiated, heterogeneous population; these endotypes (MVA, VSA, both, or none) are distinguishable by distinct mechanisms of disease and/or responses to therapy (8). For example, discrimination of epicardial coronary artery vasospasm (VSA) from coronary microvascular dysfunction (MVA) permits specific and distinct treatment (Online Appendix) (9). Third, demonstration of coronary microvascular dysfunction or VSA provides prognostic information to patients and their physicians (10).

Practice guideline recommendations are based on the weakest evidence (Level of Evidence: C) reflecting a lack of randomized controlled trials (11). In clinical practice, adoption of coronary function testing in angina with no obstructive CAD approximates zero in part because there is no evidence that a diagnostic strategy linked to therapy improves patient well-being. Considering the gap in evidence, we hypothesized that stratified medicine, including an interventional diagnostic procedure (IDP) with linked medical therapy, is routinely feasible and improves angina in patients with no obstructive CAD (**Figure 1**).

METHODS

STUDY DESIGN AND PARTICIPANTS. The BHF CorMicA (British Heart Foundation Coronary Microvascular Angina) study is a parallel-group, randomized, sham-controlled trial with blinded outcome assessment. We screened elective, adult referrals to 2 large regional hospitals (Golden Jubilee National Hospital and Hairmyres Hospital) providing invasive cardiac services to all patients in the West of Scotland (population 2.5 million). The study design of this pilot study has been published previously (12), and the protocol is available in the Online Appendix. Outpatients undergoing clinically indicated, elective diagnostic coronary angiography as standard of care for the investigation of angina (definite or probable as defined by Rose angina questionnaire) were screened and invited to participate (**Figure 2**) (13). Exclusion criteria included a noncoronary indication for invasive angiography (e.g., valve disease) and inability to give informed consent. Following informed consent, demonstration of obstructive CAD (≥50% diameter stenosis and/or fractional flow reserve [FFR] ≤0.80) during coronary angiography was also an exclusion criterion. Patients who provided informed consent but who did not proceed into the randomized trial (e.g., obstructive CAD) entered a registry for ancillary studies.

Following provision of written informed consent, participants were enrolled on the cardiology ward prior to coronary angiography. The diagnosis and management strategy from the interventional cardiologist was recorded on a questionnaire administered by independent research staff (Online Appendix). This was performed at 3 time points on the day of enrollment: at baseline (before angiography), before randomization (after angiography), and finally, after randomization. The diagnoses (e.g., disorder of

agreements with companies that have commercial interests in the diagnosis and treatment of angina, including Abbott Vascular, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Menarini Pharmaceuticals, Opsens, Philips, and Siemens Healthcare. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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FIGURE 1 Stratified Medical Therapy Guided by an IDP in Patients With Angina but No Obstructive CAD

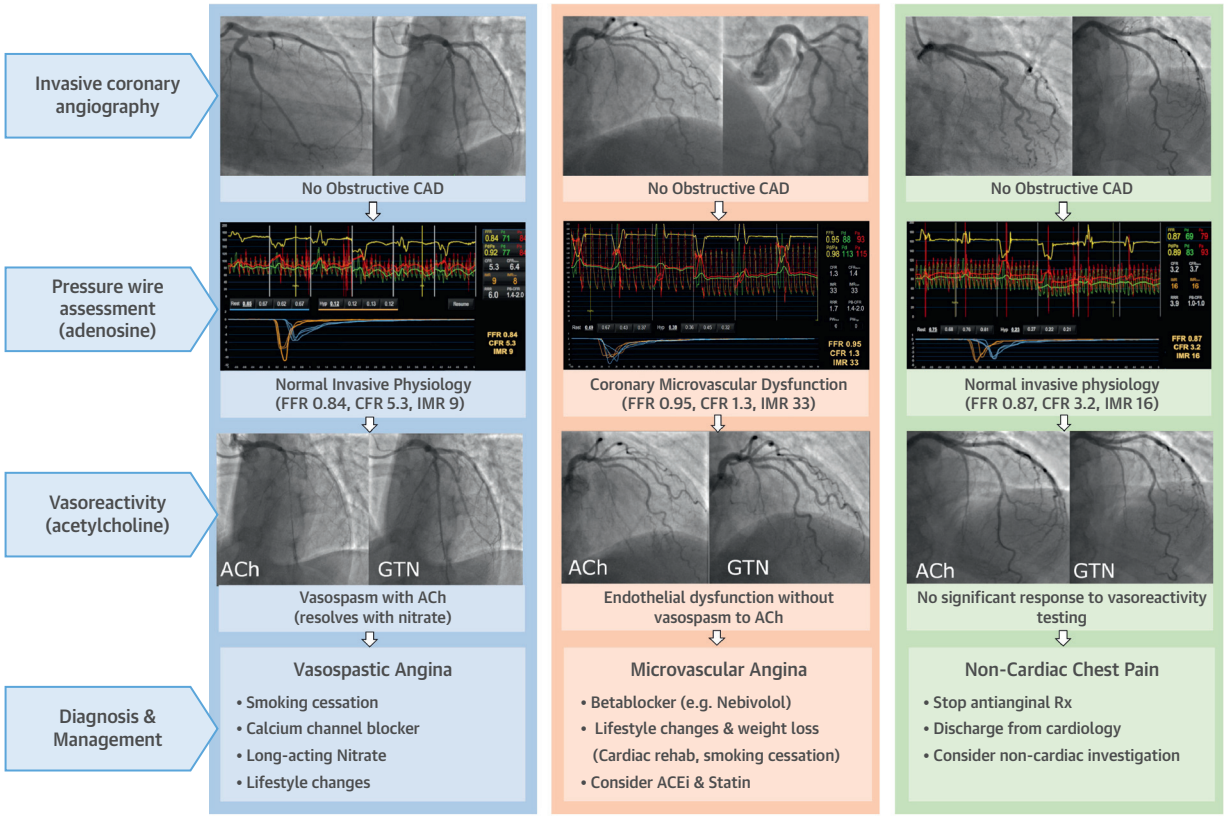
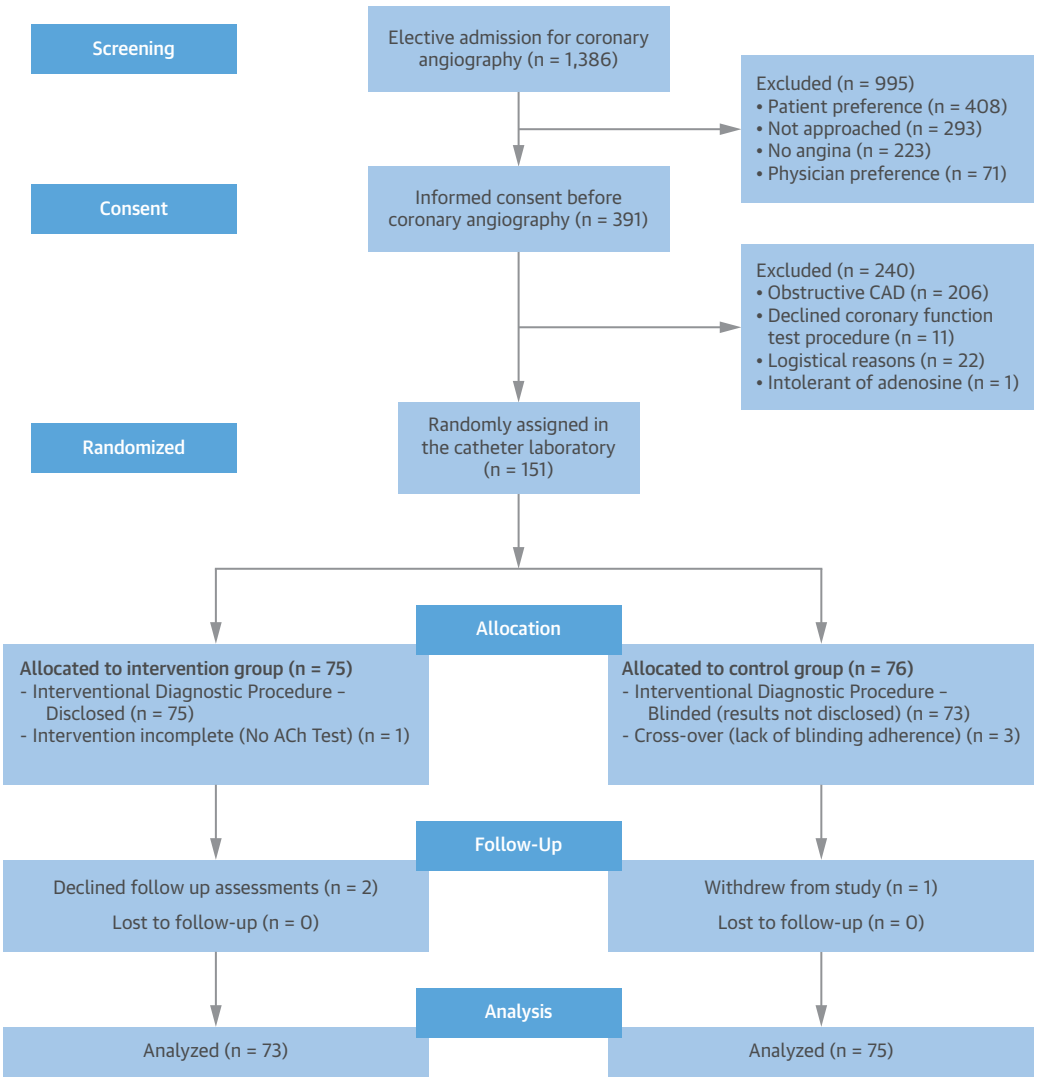


Figure illustrating 3 cases with similar baseline angiograms showing no obstructive epicardial coronary artery disease. Each case undergoes the IDP, which reveals distinct diagnoses (endotypes) with different therapy guided by the IDP results. The **blue figure** shows a typical case of VSA with preserved microvascular function. The patient was previously on a beta-blocker, and this was substituted for a calcium-channel blocker with smoking cessation counselling. The **orange case** has proven microvascular dysfunction but no severe vasospasm. There were abnormalities in both microcirculatory resistance (IMR) and coronary vasodilator reserve (CFR). The patient has a diagnosis of microvascular angina and had cessation of long-acting nitrate medication with up titration of beta-blocker. The patient underwent cardiac rehabilitation classes to assist in weight loss and identify relevant lifestyle factors implicated in the condition. The final patient **(green)** presented with anginal symptoms but no objective abnormality in coronary function. The patient was diagnosed with noncardiac chest pain, reassured, and discharged from cardiology. ACEI = angiotensin-converting enzyme inhibitor; ACh = acetylcholine; CAD = coronary artery disease; CFR = coronary flow reserve; FFR = fractional flow reserve; GTN = glyceryl trinitrate; IDP = interventional diagnostic procedure; IMR = index of microcirculatory resistance; VSA = vasospastic angina.

coronary artery function or noncardiac chest pain) were assessed for certainty (yes/no vs. unlikely/probable) and frequency (yes/probable vs. unlikely/no) based on this physician questionnaire. The West of Scotland Research Ethics Committee approved the study (REC 1 reference 16/WS/0192).

RANDOMIZATION, GROUPS, AND MASKING. After recruitment, patients were randomly assigned (1:1) to the intervention (IDP plus medical therapy stratified according to IDP results) or blinded control (IDP performed but results not disclosed [sham procedure]; standard care medical therapy according to physician preference). In other words, all participants underwent the IDP. The results were disclosed to the attending cardiologist in the intervention group and were not disclosed in the control group. In the intervention group, the cardiologist could reappraise the diagnosis based on coronary angiography and could change the diagnosis with linked therapy decisions. In the control group, management was guided by coronary angiography and all of the other available medical information, but not the IDP results. Written guidance informed by practice guidelines was provided to physicians in both groups, allowing treatment based on the physician's working diagnosis. This included using results of the IDP if available (Online Appendix, Guidance on Therapy) (11). Trained staff in the catheter laboratory used a web-based randomization tool to immediately randomize the patient after the index coronary

FIGURE 2 Trial Profile (CONSORT)



Trial profile according to CONSORT requirements. The total number of patients randomized was 151 with analysis according to intention-to-treat. There was 98% completion of the primary efficacy endpoint assessment. Abbreviations as in Figure 1.

angiography revealed no obstructive CAD (Robertson Centre for Biostatistics, University of Glasgow). The randomization sequence involved block lengths randomized in blocks of length 4, that is, every 20 allocations consists of 4 blocks, 2 of length 4 and 2 of length 6, in a random order. Patients were considered to be randomized as soon as the allocation was assigned on the web-based portal.

BLINDING AND ADHERENCE. Patients in the control arm had their IDP performed in the same way as those in the intervention group except that the results were not disclosed to the treating cardiologist. This control procedure had blinding implemented by obscuring the hemodynamic monitor from the clinicians, nurses, and patients such that it was impossible for them to observe the results of the IDP. Complete blinding was ensured through the assistance of a second cardiologist (T.F., D.Collison) who supervised the coronary function and vasoreactivity testing protocol. The treating cardiologist was invited to leave the room for the duration of the diagnostic procedure. For this reason, it was not possible to blind the cardiologist to the patient's randomization allocation. The cardiologist and the patient were blinded to the diagnostic findings in the control group. Pharmacological tests were performed in an

identical fashion in both groups. Adherence to monitoring and blinding was prospectively recorded by the research staff. The outcome assessors and statisticians were blinded to treatment group allocation.

INVASIVE CORONARY ARTERY FUNCTION TESTING (IDP). Invasive coronary angiography was performed via the radial artery in line with standard care at the participating hospitals, and coronary function tests were performed as an adjunctive procedure. The IDP was focused on a single major coronary artery on practical grounds to curtail the duration of the additional procedure time required. The left anterior descending coronary artery was the pre-specified target vessel; however, if technical factors precluded guidewire-based assessment of this artery (e.g., tortuous anatomy), then the left circumflex or right coronary artery was selected. Full details of the diagnostic procedure is in the Online Appendix. In brief, this involved passing a pressure wire via a guiding catheter (typically into the left anterior descending coronary artery) for 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 μg/kg/min). Incremental concentrations of acetylcholine (ACh) (10^{-6}, 10^{-5}, 10^{-4} mol/l) were then sequentially infused during 2-min periods, followed by vasospasm provocation testing (ACh bolus, 100 μg for left coronary artery or 50 μg right), and finally 300 μg of glyceryl trinitrate.

DEFINITIONS OF ENDOTYPES. In the intervention arm, the IDP was used to stratify patients into groups (endotypes: MVA, VSA, both, or none). Diagnosis of a clinical endotype was linked to guideline-based management. A diagnosis of VSA required that 3 conditions be satisfied during ACh testing: 1) clinically significant epicardial vasoconstriction (≥90%); 2) reproduction of the usual chest pain; and 3) ischemic ECG changes (14). MVA was defined according to standardized COVADIS (Coronary Vasomotion Disorders International Study Group) diagnostic criteria: symptoms of myocardial ischemia, unobstructed coronary arteries, and proven coronary microvascular dysfunction (any of abnormal IMR, CFR or microvascular spasm to ACh; see Online Appendix for definitions) (7). Diagnosis of coronary microvascular spasm required provocation and reproduction of anginal symptoms, ischemic ECG shifts, but no epicardial spasm during ACh testing (14). A diagnosis of noncardiac chest pain required no obstructive epicardial CAD (FFR >0.80) and normal invasive coronary artery function (CFR >2.0, IMR <25, and negative ACh testing).

LINKED MEDICAL THERAPY. After randomization and completion of the diagnostic intervention, research staff invited the cardiologist to consider the new findings and re-evaluate the diagnosis and treatment plan initially made based on angiography alone. The attending cardiologist in both groups was provided with written management guidance informed by practice guidelines to facilitate personalized treatment that was specifically aligned to their final diagnosis (Online Appendix) (11). Standardized letters were sent to the general practitioner with advice on tailoring and optimizing treatment (including nonpharmacological and lifestyle measures) in line with the final diagnosis. Standard care for patients in the control arm consisted of guideline-directed medical therapy and antianginal therapies according to the preference of the patient's usual cardiologist. The attending cardiologist had discretion over the final treatment decisions in both groups.

QUESTIONNAIRES AND FOLLOW-UP. The Seattle Angina Questionnaire (SAQ) is a self-administered, disease-specific measure of angina severity that is valid, reproducible, and sensitive to change (15). 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) (15). The Seattle Angina Questionnaire summary score (SAQSS) averages the domains of angina limitation, frequency, and quality of life to provide an overall metric of angina severity (16).

Health status was serially assessed using validated, self-administered questionnaires for quality of life using the EuroQOL (EQ-5D-5L). This is a widely used standardized instrument for measuring generic health status, whereby higher scores represent better quality of life (scaled from −0.59 to 1.00) (17). We also recorded the Brief Illness Perception Questionnaire, (B-IPQ) (18), screening for depression and anxiety (PHQ-4) (19), and the Treatment Satisfaction Questionnaire (TSQM-9) (20). At 6 months, patients' anginal symptoms were assessed using the same questionnaires.

ROLE OF THE FUNDING SOURCE. The funder of the study had no role in study design, data collection,

TABLE 1 Baseline Demographic and Clinical Characteristics for the Randomized Population Overall, and By Randomized Treatment Group

	Randomized		
	All Patients (N = 151)	**Control (n = 76)**	**Intervention (n = 75)**
Age, yrs	61.0 (53.0, 68.0)	60.0 (53.0, 68.0)	62.0 (53.5, 69.0)
Female	111 (73.5)	58 (76.3)	53 (70.7)
BMI, kg/m^2	29.7 (25.6, 34.7)	29.7 (25.6, 34.0)	29.6 (25.7, 34.8)
Current smoker	27 (17.9)	14 (18.4)	13 (17.3)
Previous myocardial infarction	24 (15.9)	13 (17.1)	11 (14.7)
Previous stroke or TIA	20 (13.2)	13 (17.1)	7 (9.3)
Diabetes mellitus	29 (19.2)	15 (19.7)	14 (18.7)
Dyslipidemia	120 (79.5)	61 (80.3)	59 (78.7)
Family history of CVD	105 (69.5)	51 (67.1)	54 (72.0)
Predicted 10-year CHD risk*	18.6 (10.6, 31.4)	18.1 (9.7, 27.9)	19.0 (11.9, 38.9)
Aspirin	131 (86.8)	67 (88.2)	64 (85.3)
Beta-blocker	101 (66.9)	51 (67.1)	50 (66.7)
Calcium-channel blocker	52 (34.4)	28 (36.8)	24 (32.0)
Nitrates	71 (47.0)	38 (50.0)	33 (44.0)
Statin	126 (83.4)	66 (86.8)	60 (80.0)
Nicorandil	26 (17.2)	15 (19.7)	11 (14.7)
ACE inhibitor or angiotensin receptor blocker	68 (45.0)	35 (46.1)	33 (44.0)
Total cholesterol, mmol/l	3.55 ± 0.98	3.57 ± 1.06	3.52 ± 0.90
HDL cholesterol, mmol/l	1.2 ± 0.4	1.2 ± 0.3	1.2 ± 0.4
Baseline patient Rose Angina Questionnaire			
Definite (typical) angina	97 (64.2)	42 (55.3)	55 (73.3)
Probable (atypical) angina	54 (35.8)	34 (44.7)	20 (26.7)
Nonanginal	0 (0.0)	0 (0.0)	0 (0.0)
Seattle Angina Questionnaire			
Angina summary score	50.8 ± 18.1	49.0 ± 17.2	52.6 ± 18.9
Angina limitation	52.1 ± 24.4	52.4 ± 24.3	51.9 ± 24.7
Angina stability	44.7 ± 24.4	41.4 ± 25.3	48.0 ± 23.2
Angina frequency	59.3 ± 23.5	54.9 ± 21.3	63.7 ± 25.0
Angina treatment satisfaction	81.9 ± 19.5	81.9 ± 20.0	81.8 ± 19.1
Angina quality of life	40.9 ± 21.7	39.7 ± 21.7	42.1 ± 21.9
Quality of life (EQ-5D-5L)			
Index Score	0.60 ± 0.29	0.58 ± 0.30	0.62 ± 0.28
VAS score	66.3 ± 20.5	67.9 ± 21.1	64.6 ± 19.8
Stress electrocardiograph			
Performed	95 (62.9)	46 (60.5)	49 (65.3)
Normal	13 (13.7)	6 (13.0)	7 (14.3)
Inconclusive	37 (39.0)	18 (39.1)	19 (38.8)
Abnormal	45 (47.4)	22 (47.8)	23 (46.9)
Radionuclide myocardial perfusion			
Performed	58 (38.4)	30 (39.5)	28 (37.3)
Negative or inconclusive	28 (48.3)	17 (56.7)	11 (39.3)
Abnormal	30 (51.7)	13 (43.3)	17 (60.7)

Values are median (Q1, Q3), n (%), or mean ± SD. *ASSIGN (36) – risk score.

ACE = angiotensin-converting enzyme; BMI = body mass index; CHD = coronary heart disease; CVD = cardiovascular disease; HDL = high-density lipoprotein; TIA = transient ischemic attack; VAS = Visual Analogue Scale.

analysis, interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

OUTCOMES. Primary efficacy endpoint. The primary outcome was angina severity according to the SAQSS (16).

Secondary efficacy endpoints. Five key secondary endpoints were pre-specified.

1. Diagnostic utility (frequency, certainty and change in diagnosis, missed diagnosis).
2. Clinical utility (impact of the stratified intervention on patient management including preventative therapy, antianginal therapy, downstream investigations, and onward referral to another specialty).
3. Health status (change from baseline by repeat of validated questionnaires at 6 months).
4. Feasibility of the stratified medical therapy intervention (protocol completion, blinding, crossover).
5. Safety of the IDP.

STATISTICAL METHODS. To detect a mean group difference of change in SAQSS of 9 U, we calculated that a sample size of 70 patients per group gave 80% power to detect a between-group difference in SAQSS. This calculation assumed a 2-tailed 5% significance level. This projected calculation assumed an SD of 19 U and was consistent with other studies, for example, the observed difference in the change in SAQ frequency score with ranolazine (9.4; p = 0.027) versus placebo in patients with a reduced CFR (21).

A missed diagnosis of MVA and/or VSA was defined as the final physician diagnosis of noncardiac chest pain in the presence of objective abnormalities of coronary artery function. The effect size of changes in diagnosis and treatment (diagnostic and clinical utility) according to the physician questionnaire was quantified using risk ratios. Health status change from baseline was analyzed as per the primary outcome incorporating baseline score in a regression model. Safety, feasibility, and adverse events were recorded by blinded research staff and passed to the independent safety and clinical events committee (from Aberdeen Royal Infirmary: Dr. Andrew Hannah, Dr. Andrew Stewart, Dr. Francis G. Dunn) to adjudicate all serious adverse events in the study in line with a pre-defined charter. Major adverse cardiac and cerebrovascular events were cardiovascular death, nonfatal myocardial infarction, hospitalization for heart failure, nonfatal stroke or transient ischemic attack, and resuscitated cardiac arrest. Specific definitions for each entity are listed in the clinical events committee document (Online Appendix).

The study population comprised all of the participants who had provided informed consent, and no patients were excluded. There were no interim

analyses, and the trial enrollment was considered complete after the pre-specified recruitment target was met. Data are reported as mean ± SD, median (25th, 75th percentile), or frequency and percentage. Continuous outcome measures recorded at baseline and 6 months were 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 was estimated as the interaction term from this model. Categorical outcomes were compared between randomized groups using Fisher exact tests with additional calculation of relative risk estimation of effect size. We performed 2-tailed analysis and considered a p value ≤0.05 to be significant. Statistical analyses were performed using R version 3.4.1 (R Foundation, Vienna, Austria).

RESULTS

Between November 25, 2016, and November 12, 2017, we enrolled 391 (28%) of 1,386 screened patients who had been electively referred for invasive coronary angiography with suspected angina (Figure 2). Coronary angiography revealed obstructive CAD in 206 (53.7%) patients, and 151 (83%) of 181 patients with no obstructive CAD were randomized (n = 76 intervention group; n = 75 blinded-control group). The left anterior descending was the target artery in 88% (n = 132), the right coronary artery in 12 (8%), and circumflex in 6 (4%). Within the randomized population, 74 (49%) underwent FFR assessment of CAD as part of standard care. A total of 34 potentially eligible patients were not randomized for logistical and other reasons (Figure 2).

Table 1 shows the characteristics of the patients who provided informed consent. The study participants were mostly female (n = 111; 73.5%) and the median age in the study was 61 years. There was a high prevalence of cardiovascular risk factors and preventive medicines in keeping with an elevated 10-year risk of coronary heart disease events (median 18.6%). In the randomized population, antianginal therapies were commonly prescribed beta-blockers (n = 101; 66.9%), long-acting nitrates (n = 71; 47.0%) and calcium-channel blockers (n = 52; 34.4%). At baseline, the majority of subjects had daily/weekly angina (SAQ frequency score ≤60), with mild-to-moderate angina limitation (SAQ limitation mean 52.1 ± 24.4). Many patients who underwent noninvasive stress testing had evidence of ischemia (positive exercise test 45 [47.4%], positive myocardial perfusion 30 [51.7%]) (Table 1). The mean exercise time was 6.3 ± 2.6 min of the standard Bruce protocol.

TABLE 2 Procedural Characteristics

	Control (n = 76)	Intervention (n = 75)
Procedure time, min	60 (50, 65)	55 (50, 65)
Angiographically normal	18 (23.7)	16 (21.3)
Obstructive CAD*	0 (0.0)	1 (1.3)
Gensini score†	0 (0, 0)	0 (0, 1)
Invasive physiology		
LVEDP, mm Hg	9.00 (7.00, 12.00)	9.00 (6.00, 12.00)
Left anterior descending target artery	63 (83)	69 (92)
Resting transit time, s	0.79 (0.54, 1.15)	0.75 (0.49, 1.02)
Hyperemic transit time, s	0.26 (0.21, 0.38)	0.27 (0.20, 0.38)
FFR	0.89 (0.84, 0.92)	0.87 (0.83, 0.92)
Index of microcirculatory resistance	18.8 (14.9, 29.2)	19.8 (14.8, 29.2)
Coronary flow reserve	2.75 (1.98, 3.48)	2.22 (1.70, 3.30)
Endothelial dysfunction	39 (51.3)	31 (41.9)
Endotypes		
MVA	35 (46.1)	43 (57.3)
VSA	13 (17.1)	12 (16.0)
Mixed MVA/VSA	17 (22.4)	14 (18.7)
Normal coronary artery function	11 (14.5)	6 (8.0)

Values are median (Q1, Q3) or n (%). *FFR abnormal (≤0.80) on physiological testing. †Gensini angiographic score is a metric of angiographic disease severity incorporating lesion severity and location. There were no significant differences between the procedural characteristics of the randomized groups.

CAD = coronary artery disease; FFR = fractional flow reserve; LVEDP = left ventricular end-diastolic pressure; MVA = microvascular angina; VSA = vasospastic angina.

Procedural characteristics are shown in Table 2. The left anterior descending was the target artery in 132 (86.8%), right coronary in 12 (7.9%), and circumflex in 7 (4.6%). Across all randomized patients, the median FFR was 0.88 (interquartile range: 0.84 to 0.92). The median procedure time was 60 ± 14 min. The underlying abnormalities revealed by the IDP in the entire randomized population included: isolated MVA in 78 (51.7%), isolated VSA in 25 (16.6%), mixed (both) in 31 (20.5%), and noncardiac chest pain in 17 (11.3%).

PRIMARY OUTCOME. A total of 148 (98%) subjects completed the primary outcome assessment (SAQ) at 6 months. One (0.6%) of the randomized participants formally withdrew from the study. Details and group allocation of nonresponders is outlined in the study diagram (Figure 2). For the SAQSS, the intervention resulted in an improvement of 11.68 U (95% confidence interval [CI]: 4.99 to 18.37; p = 0.001). This was driven by reduced angina limitation (14.50 U; 95% CI: 7.32 to 21.67; p < 0.001), reduced angina frequency (9.29; 95% CI: 0.49 to 18.09; p = 0.04), and improved

TABLE 3 Primary Outcome and Changes in Health Status at 6 Months

	Control (n = 75)		Intervention (n = 73)		Intervention Effect*		
	6 Months	Change From Baseline	6 Months	Change From Baseline	Estimate	95% CI	p Value
Primary efficacy endpoint—Seattle Angina Questionnaire							
Angina summary score	51.8 ± 26.1	3.1 ± 21.3	67.5 ± 23.0	14.4 ± 20.1	11.68	4.99 to 18.37	0.001
Angina limitation	50.9 ± 31.2	−1.6 ± 22.1	65.4 ± 27.7	12.6 ± 22.5	14.50	7.32 to 21.67	<0.001
Angina stability	46.3 ± 25.9	5.0 ± 37.2	57.2 ± 24.1	8.9 ± 33.4	4.31	−6.88 to 15.49	0.452
Angina frequency	55.9 ± 30.3	1.6 ± 27.1	74.5 ± 22.2	10.1 ± 27.5)	9.29	0.49 to 18.09	0.040
Treatment satisfaction	71.9 ± 23.6	−9.9 ± 25.8	83.9 ± 18.9	2.1 ± 19.0	12.05	4.73 to 19.37	0.002
SAQ quality of life	48.8 ± 28.2	9.3 ± 27.5	61.9 ± 27.9	19.5 ± 23.7	10.48	2.18 to 18.79	0.015
Secondary efficacy endpoints—health status							
Quality of life (EQ-5D-5L)							
Index score	0.5 ± 0.4	−0.07 ± 0.27	0.66 ± 0.28	0.02 ± 0.24	0.10	0.01 to 0.18	0.024
VAS score	59.2 ± 24.7	−9.1 ± 20.4	70.4 ± 20.4	5.4 ± 21.7	14.54	7.77 to 21.31	<0.001
Illness perception (B-IPQ)†	44.7 ± 16.3	1.7 ± 15.8	38.6 ± 16.5	−6.5 ± 13.5	−8.34	−13.06 to −3.62	0.001
Psychological distress (PHQ4)	4.8 ± 4.5	−0.1 ± 3.8	3.5 ± 3.7	−0.1 ± 3.4	−0.10	−1.27 to 1.06	0.862
Treatment satisfaction							
Effectiveness	58.8 ± 24.5	−1.1 ± 28.5	68.0 ± 18.7	10.7 ± 22.5	10.73	2.37 to 19.09	0.013
Convenience	68.8 ± 26.0	−5.5 ± 21.8	77.8 ± 20.2	9.3 ± 21.7	14.34	7.30 to 21.37	<0.001
Global satisfaction	54.3 ± 27.0	−4.0 ± 29.2	65.7 ± 24.0	13.1 ± 27.9	16.47	7.28 to 25.66	0.001

Values are mean ± SD unless otherwise indicated. *Adjusted mean difference at 6 months (intervention − control). Seattle Angina Questionnaire (SAQ): lower scores represent worse angina symptoms. †Illness perception: a lower score reflects a less threatening view of the illness. Patient Health Questionnaire-4 (PHQ4) is a 4-item brief screening tool for anxiety and depression, higher scores indicate more psychological distress. VAS is a visual analogue score of EQ-5D validated quality of life tool, higher scores indicate better quality of life. B-IPQ = Brief Illness Perception Questionnaire.

angina-related quality of life (10.48; 95% CI: 2.18 to 18.79; p = 0.015). The individual components of the primary outcome are shown in Table 3 and Figure 3.

SECONDARY OUTCOMES. Health status. Quality of life (as assessed by the EQ-5D-5L instrument) at 6 months was higher in the intervention arm (index 0.10; 95% CI: 0.01 to 0.18; p = 0.024, visual analogue

TABLE 4 Secondary Endpoints: Diagnostic Utility, Clinical Utility and Clinical Events

	Control (n = 76)	Intervention (n = 75)	RR	95% CI	p Value
Diagnostic Utility					
Baseline (pre-randomization)					
Diagnosis: disorder of coronary function	35 (46.1)	35 (46.7)			
Diagnosis: noncardiac	49 (64.5)	45 (60.0)			
Post-randomization					
Diagnosis: disorder of coronary function	35 (46.1)	66 (88.0)	1.91	1.48–2.47	<0.001
Diagnostic certainty	14 (18.4)	62 (82.7)	4.49	2.76–7.28	<0.001
Change (no to yes/yes to no)	0 (0.0)	39 (52.0)	80.0	5.00–1,278	<0.001
Diagnosis: noncardiac	49 (64.5)	12 (16.0)	0.25	0.14–0.42	<0.001
Diagnostic certainty	15 (19.7)	47 (62.7)	3.18	1.95–5.16	<0.001
Change (no to yes/yes to no)	0 (0.0)	35 (46.6)	71.9	4.49–1,151	<0.001
Missed diagnosis MVA/VSA	27 (35.5)	2 (2.7)	0.08	0.02–0.30	<0.001
Clinical utility					
Include preventative therapy	57 (75.0)	63 (85.1)	1.12	0.95–1.32	0.154
Include angina therapy	37 (48.7)	65 (87.8)	1.78	1.39–2.28	<0.001
Change angina therapy for functional coronary disorder	23 (30.3)	64 (86.5)	2.82	1.98–4.02	<0.001
Referral to another specialty	13 (17.6)	8 (10.7)	0.62	0.27–1.41	0.248
Referral for additional cardiovascular tests	0 (0.0)	2 (2.7)	5.06	0.25–103.8	0.292
Referral for additional noncardiovascular tests	1 (1.3)	6 (8.0)	6.08	0.75–49.3	0.063
Clinical events (6 months)					
Major adverse cardiac and cerebrovascular events	2 (2.6)	2 (2.6)	1.01	0.14–7.39	1.000

Values are n (%) unless otherwise indicated.
CI = confidence interval; MVA = microvascular angina; RR = relative risk; VSA = vasospastic angina.

score 14.5; 95% CI: 7.8 to 21.3; $p < 0.001$). Illness perception (Brief Illness Perception Questionnaire, whereby a lower score reflects a less threatening view of illness) was significantly reduced in the intervention arm (treatment effect 8.34; 95% CI: −13.06 to −3.62; $p = 0.001$). Psychological distress levels between the groups were not different and relatively unchanged from baseline (treatment effect −0.1; 95% CI: −1.27 to 1.06; $p = 0.862$). Change in treatment satisfaction (Treatment Satisfaction Questionnaire for Medication-9) was enhanced in all 3 domains of effectiveness (treatment effect 10.7; 95% CI: 2.4 to 19.1; $p = 0.013$) and convenience (treatment effect 14.3; 95% CI: 7.3 to 21.4; $p < 0.001$). Overall satisfaction (16.5; 95% CI: 7.3 to 25.7; $p = 0.001$) was also higher amongst those randomized to the intervention group (Table 3).

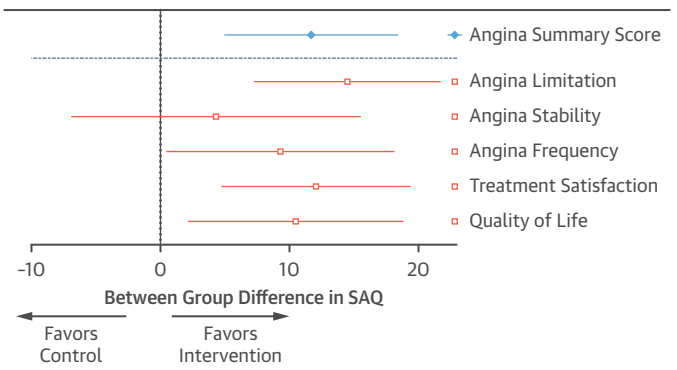
FEASIBILITY AND BLINDING. The IDP was successfully completed in 145 (96%) subjects. Five (4%) subjects had the vasoreactivity testing protocol terminated by the cardiologist due to transient bradycardia with ACh. Blinding was achieved in all but 3 patients (2.0% crossover) due to the attending cardiologist not complying with the blinding procedure.

DIAGNOSTIC UTILITY (TABLE 4). Before randomization, the attending clinician considered a possible diagnosis of angina due to a disorder of coronary artery function in 35 (46.1%) control subjects and 35 (46.7%) intervention subjects. After randomization, the frequency of diagnosis (angina due to a disorder of coronary artery function) increased in patients in the intervention arm but not in the control subjects (88.0% vs. 46.1%; relative risk [RR] 1.91; 95% CI: 1.48 to 2.47; $p < 0.001$). Frequency of possible noncardiac chest pain diagnosis was similar before randomization; however, after randomization, the noncardiac diagnosis was significantly less common in the intervention arm compared with control (16% vs. 64.5%; RR: 0.25; 95% CI: 0.14 to 0.42; $p < 0.001$). In the intervention arm, treating cardiologists had increased certainty in making diagnoses of angina due to a disorder of coronary artery function (RR: 4.49; 95% CI: 2.76 to 7.28; $p < 0.001$) and of noncardiac chest pain (RR: 3.18; 95% CI: 1.95 to 5.16; $p < 0.001$). Overall, a missed diagnosis of MVA and/or VSA occurred in 2 (2.7%) cases in the intervention arm and 27 (35.5%) cases in the control arm (RR: 0.08; 95% CI: 0.02 to 0.30; $p < 0.001$).

CLINICAL UTILITY. In the intervention arm, physicians were more inclined to include antianginal therapy (87.8% vs. 48.7%; RR: 1.78; 95% CI: 1.39 to 2.28; $p < 0.001$). Additionally, in the intervention arm, physicians were more likely to tailor angina therapy specifically to treat a disorder of coronary artery function (86.5% vs. 30.3%; RR: 2.82; 95% CI: 1.98 to 4.02; $p < 0.001$). At 6 months, patients in the intervention arm were more likely to be taking calcium-channel blockers (50.7% vs. 21.1%; RR: 2.41; 95% CI: 1.48 to 3.93; $p = 0.001$). In addition, secondary prevention therapies including angiotensin-converting enzyme (ACE) inhibitors (or equivalent) and statins were also more frequently prescribed in the intervention group (ACE inhibitors 58.7% vs. 36.8%; RR: 1.59; 95% CI: 1.12 to 2.26; $p = 0.009$; and statins 88.0% vs. 53.9%; RR: 1.63; 95% CI: 1.30 to 2.04; $p < 0.001$). Other medical treatments taken at 6 months were similar between the groups (Online Appendix). There were no differences in physician inclination toward referral to another specialty or planned downstream investigations at the time of invasive coronary angiography.

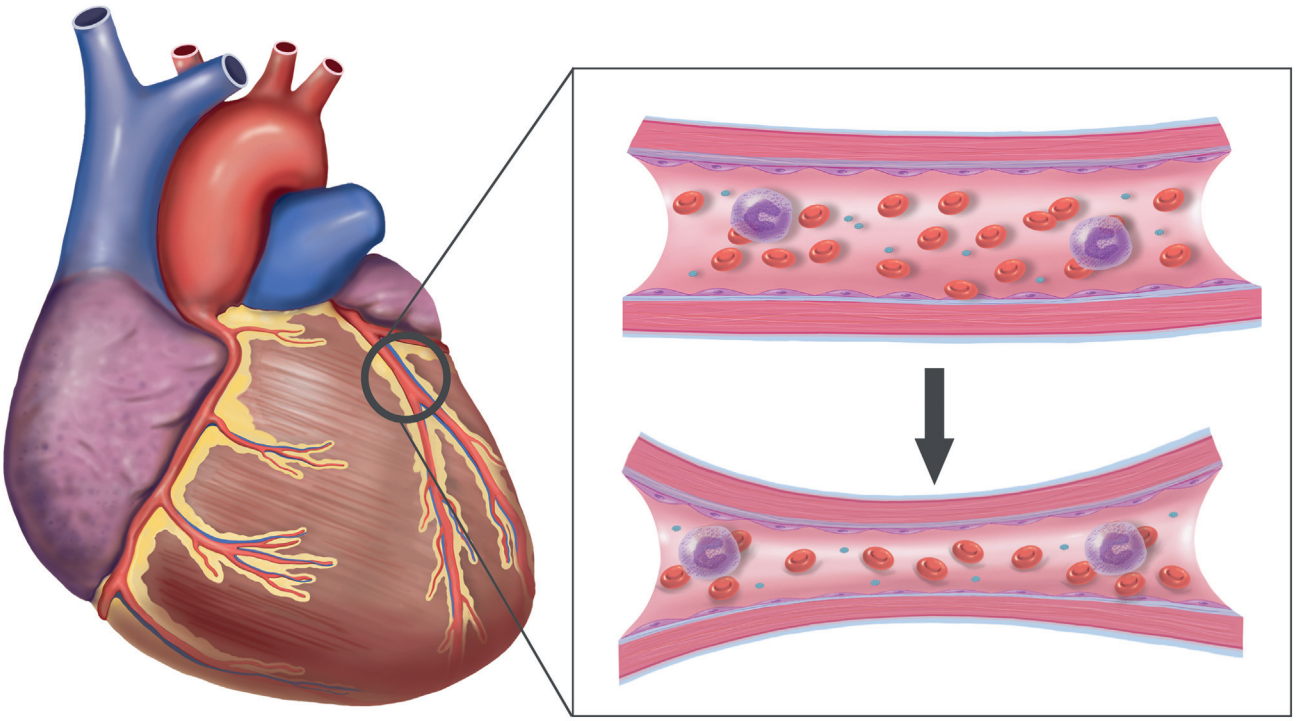
CLINICAL EVENTS AND SAFETY AND ADVERSE EVENTS. Adverse events related to the interventional diagnostic procedure. No serious adverse events occurred secondary to the IDP. One patient developed persistent atrial fibrillation, but was successfully cardioverted to sinus rhythm using intravenous amiodarone. Oral anticoagulation was prescribed in view of underlying risk factor profile (age, hypertension, diabetes). Hospitalization was not prolonged, and the patient was discharged on the day of the procedure. There were 8 (5.3%) other patients who experienced adverse events in association with

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; $p < 0.001$).

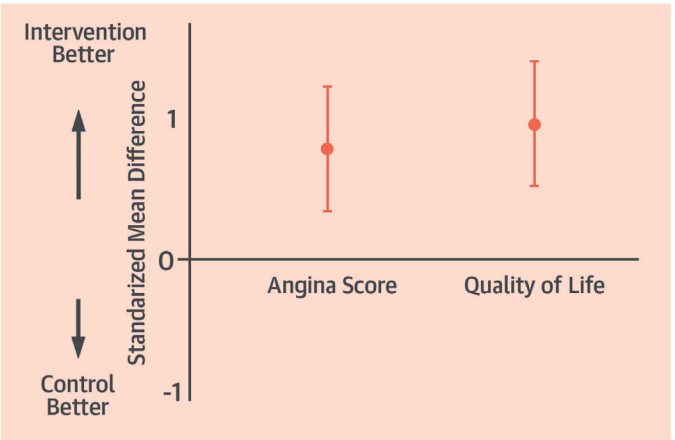
CENTRAL ILLUSTRATION **Invasive Coronary Function Testing in Angina: Study Design and Results**



Stratified Medicine in Patients with INOCA:

- Microvascular Angina
- Vasopastic Angina
- Non-Cardiac Chest Pain

Improved Angina and Quality of Life



Ford, T.J. et al. J Am Coll Cardiol. 2018;72(23):2841–55.

Stratified medical therapy guided by an interventional diagnostic procedure (IDP) improves health status of patients with symptoms and/or signs of angina but no obstructive coronary artery disease (INOCA).

the IDP (paroxysmal atrial fibrillation temporally related to acetylcholine administration). All resolved within 30 min without treatment or thromboembolic sequelae. Transient bradycardia and sinus pauses during acetylcholine were common physiological responses and did not constitute an adverse event (Online Appendix).

SAE FOLLOWING THE PROCEDURE. Vital status at 6 months was obtained for all (100%) participants. At the 6-month follow-up study assessment, 2 (2.6%) of 76 patients in the control group and 2 (2.6%) of 75 in the intervention group experienced cardiac death, nonfatal myocardial infarction, stroke, or heart failure hospitalization (4 [2.6%]) major adverse

cardiac and cerebrovascular events at 6 months (**Table 3**).

DISCUSSION

We implemented stratified medicine using an interventional diagnostic procedure with linked therapy as a routine adjunct to elective invasive coronary angiography in patients with known or suspected angina. The intervention led to improvements in patient outcomes, including reduction in angina severity and better quality of life (**Central Illustration**). In addition, we have shown the IDP to be feasible and safe, with clear diagnostic and clinical utility.

Over a 12-month period, participants were enrolled at 2 hospitals that together provide invasive cardiac services to approximately one-half of the population of Scotland. For the primary efficacy endpoint, 6-month difference in angina severity using linear regression, the overall treatment effect of the intervention was an increase of almost 12 U in the angina summary score (95% CI: 4.99 to 18.37; $p = 0.001$). The difference in angina frequency at 6 months is consistent with 1 grade in the Canadian Cardiovascular Society classification. The treatment effect on angina frequency was an increase of approximately 9 U (95% CI: 0.49 to 18.09; $p = 0.04$). Overall, this is similar to that observed with ranolazine compared with placebo in patients with MVA and reduced CFR (21). The change is greater than the minimum clinically important difference of 8 points for the SAQ angina limitation, frequency, and quality-of-life domains and 5 points for SAQ treatment satisfaction (22). In addition, the intervention arm reported objective improvement in quality of life (improved EQ-5D-5L index of 0.1 U compared with control), which was both statistically and clinically significant. The proposed minimum clinically important mean difference of this index in the United Kingdom is 0.08 U (23).

The relative improvement in angina in the intervention arm is clear; however, the mechanism is more nuanced. Indeed, it may be related to medical therapy, better engagement, or better informed patients who felt as if their concerns were being heard. In a pilot study of this size, there is insufficient power to provide a stratified analysis of treatment effect by these variables, and such a post hoc analysis may be misleading. We propose that some of the benefit seen in the intervention arm relates to tailored therapy. In the IDP group at 6-month follow-up, secondary prevention statin use was more common in the intervention arm versus control subjects (88% vs. 53.9%; RR 1.63, 95% CI: 1.30 to 2.04; $p < 0.001$). ACE inhibitor/angiotensin-receptor blocker use was also more common in the intervention arm (58.7% vs. 36.7%; RR: 1.59; 95% CI: 1.12 to 2.26; $p = 0.009$) (Online Appendix). Improvements in health status may in part relate to these agents with disease-modifying properties with plausible benefits on microcirculatory and endothelial function (24,25). We observed that clinicians were almost 3 times more inclined to tailor therapy for a disorder of coronary artery function than control subjects (RR: 2.82; 95% CI: 1.98 to 4.02; $p < 0.001$). We noted patients were almost 2.5 times more likely to take calcium-channel blockers at 6 months in the intervention arm (50.7% vs. 21.1%; RR: 2.41; 95% CI: 1.48 to 3.93; $p = 0.001$). Identifying endotypes may be helpful in personalizing treatment; for example, the poor nitrate response or tolerance seen in MVA contrasts with patients with VSA, in whom nitrates are a cornerstone of therapy and beta-blockers are relatively contraindicated (11). All 3 domains of treatment satisfaction recorded at 6 months showed significant improvements in the randomized cohort when compared with the control group, which suggests that stratified therapy was also more acceptable to patients.

After diagnosis and treatment, angina symptoms in most studies (SAQ scores) tend to naturally improve with time (26). We noted a distinct lack of improvement in the control group that was quite striking compared with other contemporary studies in similar populations with no obstructive CAD (26). Between-group differences may be partly explained by failure of "natural" improvement in the control group. Reasons for this are not immediately clear, but diagnostic uncertainty and illness perception are potentially relevant. Indeed, beyond pharmacotherapy, we noted significantly enhanced illness perception (lower scores at 6 months) amongst the intervention arm representing 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. The disclosure of the IDP changed the diagnosis in around one-half of subjects, whereas clinicians in the intervention arm were over 4 times more certain regarding a diagnosis of a functional coronary artery disorder (RR: 4.49; 95% CI: 2.76 to 7.28; $p < 0.001$). Patients randomized to the intervention were 4 times less likely to be diagnosed with noncardiac chest pain (RR: 0.25; 95% CI: 0.14 to 0.42; $p < 0.001$). These findings indicate that the intervention has an incremental diagnostic value over standard care using coronary angiography.

It is impossible to distinguish between the beneficial impact of a definitive diagnosis on symptoms and

the benefits achieved from the IDP aligned to tailored medical therapy. The effect of having a diagnosis would presumably motivate patients to modify lifestyle and increase drug compliance to a much greater extent than those in the control group, who did not have the benefit of receiving a correct diagnosis. Longitudinal studies of other cardiovascular diseases have shown that illness perception is an important predictor of longer-term outcomes, including disability and returning to work (27). A new diagnosis of angina may increase use of nonpharmacological therapies, including cardiac rehabilitation, which may benefit patients with ischemic heart disease (28). We are assessing lifestyle factors and longer-term events according to randomized group at 12 months. In our cohort, the median body mass index was 30 kg/m^2 (obese), and we acknowledge the clinical significance of body weight as a potential therapeutic target.

Overall, the diagnostic intervention revealed abnormalities of coronary vascular function that substantiated a clinical diagnosis in 134 (88.7%) patients in the randomized study population. This is a strikingly high proportion of patients that is in keeping with previous studies of patients with angina but no obstructive CAD (64% to 77%) (29,30). The largest European cohort of patients with angina and no obstructive CAD undergoing ACh provocation testing disclosed a high prevalence of epicardial spasm (26%) and microvascular spasm (33%), which is similar to our population (37% and 34%, respectively) (30). Importantly, the diagnostic accuracy of intracoronary ACh for diagnosing coronary spasm during invasive coronary angiography alone is excellent (sensitivity 90%, specificity 99%) (31). We used a reference definition of microvascular spasm (14) during ACh but did not specifically measure the coronary blood flow response to this agonist. Measurement of coronary blood flow using Doppler is a technically demanding procedure that is useful for mechanistic research but is not readily implemented in a pragmatic clinical trial such as CorMicA. Our median procedure time of 60 min, taking into account the angiogram, re-evaluation of eligibility, randomization online, and IDP, is similar to the duration of single-vessel percutaneous coronary intervention.

We showed routine feasibility of the IDP demonstrated by the high rate of protocol completion, preservation of blinding, and lack of cross-overs. In terms of safety, atrial fibrillation occurred in 1 in 20 patients, and this was self-limiting in all but 1 patient. Transient bradycardias reflected expected physiological responses. These are important sequelae, but in the setting of the cardiac catheter laboratory patient safety was optimized and ensured. Our study provides preliminary evidence that the IDP can be safely administered during routine practice, but more data are needed.

Our study has several strengths. First, we screened and enrolled patients in a routine care setting prior to undergoing clinically-indicated elective coronary angiography. We purposely did not impose restrictive eligibility criteria, such as a requirement for inducible ischemia on noninvasive testing, because some patients with a propensity to vasospastic chest pain syndromes may have normal findings from pharmacological and exercise stress testing. Second, we designed a stratified medical therapy intervention, combining a novel interventional diagnostic procedure with linked pharmacological and non-pharmacological therapy, in the context of a randomized, controlled trial, including patient-reported outcome measures and clinician questionnaires. This trial represents an advance for the many observational research studies that have been undertaken in patients with angina and "*normal coronary arteries*" during the past 3 or more decades. Third, we designed an interventional diagnostic strategy that included a focused set of measurements derived from different techniques that would permit the clinician to diagnose (rule-in, rule-out) the distinct endotypes. Our method allowed assessment of the effects of a stratified medical therapy approach within the context of a randomized, controlled, clinical trial. Fourth, the IDP was performed immediately after randomization in all of the trial participants. Coronary function tests were performed but not disclosed, which represented a true sham procedure and hence more effective control comparator. Finally, informed consent was obtained before coronary angiography, therefore the presence of CAD, if any, was unknown. Consequently, the study population included patients in whom coronary angiography subsequently disclosed obstructive CAD. These patients were ineligible for randomization and therefore entered a registry. The registry provided an opportunity to compare clinical characteristics, symptom burden, and quality of life at baseline between the participants in the registry (mainly obstructive CAD) and randomized population (no obstructive CAD), respectively.

STUDY LIMITATIONS. Our study has 4 potential limitations. First, we adopted binary cutoffs for the IDP test results in line with guidelines and established diagnostic thresholds. The optimal prognostic thresholds for these parameters of ischemia (e.g., CFR/IMR/ACh-responses) are part of a continuum. It is possible that indeterminate (gray zone or

borderline) test results may be misclassified (30). Nevertheless, we adopted a stringent approach using unambiguous reference thresholds for disease classification (e.g., CFR cutoff 2.0 rather than 2.5). The classification of MVA and VSA align with recent international standardized diagnostic criteria (13,14). Intravascular imaging does not provide information on coronary vascular function, but may have provided additional insights into vascular structure, such as atherosclerosis not revealed by the angiogram (32).

Second, we assessed patient-reported outcome measures. While unquestionably important, these measures are susceptible to bias given that the patient and cardiologist were not blinded to group allocation. Because of the nature of the intervention, a double-blind study design was not feasible. Our study may have been strengthened by recording more information on lifestyle factors and obtaining objective measures of exercise capacity, for example, cardiopulmonary exercise testing. On the other hand, we wished to avoid overburdening the patients with questionnaires and test procedures. The SAQ is a validated patient-reported outcome measure for angina. Although this questionnaire was derived from a predominantly male cohort with obstructive CAD, this tool has been clinically validated in women (predicts 12-month mortality and rehospitalization) (33,34). Angina severity derived from this tool correlates with physiological metrics of coronary microvascular dysfunction but also exercise stress test metrics (21,35). Our study provides "real-world" insights into the equal importance of tailored medical therapy combined with improved diagnostic certainty on patient-reported outcomes. Long-term data, a health economic analysis, and a larger multicenter trial will be needed to assess the value of the stratified intervention to patients and health care providers, and the potential for impact on clinical practice.

Third, critics may argue that improvement in angina could be achieved without a complex assessment of coronary function. A simple and pragmatic approach would be to treat all patients with possible angina and nonobstructive CAD with an additional antianginal therapy for 6 months as a therapeutic trial. As scientists and clinicians, we would take a different view. We believe that a person-centered approach to care is key. Avoiding unnecessary medicines and optimizing therapy to a specific diagnosis will benefit patients and health care providers. Furthermore, stratifying this group of undifferentiated patients in the clinic will pave the way for new insights into mechanisms and disease-modifying therapy.

Finally, a considerable proportion of patients undergoing invasive coronary angiography were not enrolled, with the most common reason being patient preference (n = 408 [29%] of 1,386). A minority (n = 295 [21%]) of patients were not approached due to logistical reasons (**Figure 2**). It is conceivable that the total number of patients with obstructive CAD would differ if all patients that were screened participated in the study. Our study provides evidence of the clinical value of assessing coronary vascular function in patients with symptoms and/or signs of ischemia but no obstructive coronary artery disease and highlights the limitations of anatomical coronary artery imaging (i.e., invasive coronary angiography and computed tomography coronary angiography). These tests have limited sensitivity for diagnosing disorders of coronary vascular function. Anatomical imaging with computed tomography coronary angiography leads to small but significant deteriorations in angina limitation, frequency, and quality of life compared to standard care, notably in patients with no obstructive CAD (26). This is an important consideration for women with angina, in whom coronary dysfunction without obstructive CAD is much more common.

CONCLUSIONS

We found that a strategy of adjunctive invasive testing for disorders of coronary function with linked therapy led to a reduction in angina severity and better quality of life compared with standard care. Stratified medicine represents a new treatment approach for patients with angina and no obstructive CAD, and more research seems warranted.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Vasoreactivity testing with ACh and measurement of coronary flow reserve and microcirculatory resistance can be used to guide medication therapy in patients with angina who have no obstructive epicardial coronary disease.

TRANSLATIONAL OUTLOOK: Prospective studies are needed to compare the safety and efficacy of various pharmacological and nonpharmacological regimens for patients with microvascular dysfunction and vasospastic causes of angina stratified by direct assessments of flow reserve and vascular resistance.

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APPENDIX For an expanded Methods section, please see the online version of this paper.