Stratified Medicine in Angina with No Obstructive Coronary Artery Disease on Computed Tomography Coronary Angiography

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Abstract

Introduction

Angina and no obstructive coronary artery disease (ANOCA) is increasingly recognised as part of a spectrum of conditions underlying chronic coronary syndromes, reflected in changes in recent ischaemic heart disease (IHD) guidelines. A considerable proportion of patients referred for coronary angiography have unobstructed coronary arteries. In patients referred for computed tomography coronary angiography (CTCA), who are typically a lower risk population, the proportion of patients with unobstructed artery may be as high as 75%. Although anatomical tests such as CTCA enable confirmation or exclusion of an obstructive coronary artery disease (CAD) diagnosis, conditions such as microvascular or vasospastic angina (endotypes of ANOCA) are systematically overlooked and underdiagnosed. Patients with ANOCA endure a substantial symptom burden and prior studies have shown that they have increased long-term risk of cardiovascular events. Contemporary international guidelines have identified ANOCA as an area of unmet need.

The rationale for this study was to characterise the prevalence, clinical significance and management of ANOCA in ambulatory patients referred for the investigation of angina. The specific questions were, firstly, what is the prevalence of coronary microvascular dysfunction in a relatively unselected population of patients with a history of stable angina and no obstructive coronary arteries, as revealed by CTCA. Secondly, does a clinical strategy of stratified medicine, involving tests of coronary microvascular function and coronary spasm to define endotypes and linked therapy, improve wellbeing. Finally, does this strategy improve the burden of cardiovascular risk factors.

Methods

The overall objective was to undertake a prospective observational study with a nested multicentre, randomised, sham-controlled, clinical trial with blind outcome assessments.

Patients referred for clinically-indicated CTCA for the investigation of suspected coronary artery disease were screened in 3 regional centres. Following informed consent, they were enrolled before CTCA and remained eligible if obstructive disease was excluded. Chest symptoms were assessed using the Rose Angina and Seattle Angina Questionnaires (SAQ).

Invasive angiography involving adjunctive coronary vascular function tests was undertaken to assess for endotypes defined by guideline criteria. The interventional diagnostic procedure (IDP) protocol involved measurement of fractional flow reserve (FFR), coronary flow reserve (CFR) and index of microvascular resistance (IMR) using a diagnostic guidewire followed by intra-coronary infusion of incremental doses of acetylcholine (0.182 μg/ml, 1.82 μg/ml, 18.2 μg/ml) sequentially infused (2 ml/minute) to assess for microvascular and/or coronary spasm. Participants were randomised to stratified medicine (Intervention group) or angiography-guided usual care (Control group, blinded). The primary outcome was the mean within-individual change in SAQ Summary Score during follow-up. Patient reported outcome measures included the 5-level EQ-5D health-related quality of life questionnaire, the Brief Illness Perception Questionnaire (BIPQ), the Patient Health Questionnaire-4 (PHQ-4), the Duke Activity Status Index (DASI) and the Treatment Satisfaction Questionnaire for Medication (TSQM-9). Cardiovascular risk factors (modifiable and non-modifiable), including body mass index, blood pressure, lipids and cigarette smoking, were measured at baseline and at the final visit, intended for 12 months post-randomisation.

Results

In summary, the main findings of this study are:

1) ANOCA was prevalent and occurred in three quarters of outpatients with suspected angina and no obstructive coronary artery disease on CTCA.

2) Stratified medicine guided by an IDP to evaluate coronary microvascular function changed the initial diagnosis in 68.7% of patients in the intervention group and improved the attending cardiologist's certainty of the diagnosis.

3) Stratified medicine increased the frequency of a diagnosis of microvascular and/or vasospastic angina.

4) Stratified medicine increased the frequency of prescription of angina therapy for disorders of coronary function.

5) Stratified medicine improved blood pressure and treatment satisfaction but did not improve angina or health-related quality of life or other modifiable cardiovascular risk factors. However, medical management was disrupted by the pandemic.

Conclusion

ANOCA endotypes are common in outpatients with angina and no obstructive coronary artery disease, as defined by CTCA. There is a substantial health burden in this population, with one in four patients having an unplanned episode of hospital care for chest pain. However, a routine invasive strategy with medical management led by the standard care clinicians during a pandemic did not improve health status. Further clinical trials of patients stratified by endotype should improve our understanding of this condition and clarify effective treatment strategies.

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Publications

Ang DTY, **Sidik NP**, Morrow AJ, Sykes R, McEntegart MB, Berry C. *Interventional Diagnostic Procedure: a Practical Guide for the Assessment of Coronary Vascular Function*. J Vis Exp. 2002 Mar 15; (181).

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Berry C, **Sidik N**, Pereira AC, Ford TJ, Touyz RM, Kaski JC, Hainsworth AH. *Small-Vessel Disease in the Heart and Brain: Current Knowledge, Unmet Therapeutic Need, and Future Directions*. J Am Heart Assoc. 2019 Feb 5;8(3):e011104.

Presentations

A ‘Simple Case’ of Stable Angina & PCI

COVADIS (Coronary Vasomotor Disorders International Study Group) Summit IX (Virtual)

24th September 2021

Precision Medicine: A Case Study

Royal College of Physicians and Surgeons Glasgow (RCPSG) Interactive Cardiology Conference 2021 (Virtual)

31st March 2021

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

EuroPCR 2023 Late Breaking Session

18th May 2023

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I am grateful to my predecessor, Dr Thomas Ford, and the current research fellows in our team who have contributed to this work, as well as the cardiologists, radiologists and catheter laboratory staff who facilitated the enrolment of patients and execution of the study protocol. I am indebted to the British Heart Foundation for funding this body of work.

Finally, I would like to thank the patients who volunteered to take part in this study, without whom it would not have been possible.

Author's Declaration

The work presented in this thesis was performed during my BHF Clinical Research Fellowship at the Glasgow Cardiovascular Research Centre, College of Medicine and Veterinary Life Sciences, University of Glasgow. I performed screening of all the patients, and recruitment of 226 of the 250 patients who participated in the study. I performed most of the invasive coronary procedures and was present for all, and completed all the case report forms. I conducted approximately half of the 12-month in-person clinical follow ups and completed all the data entry for the 6-month and 12-month follow ups.

The blinded endpoint analyses were performed by Ms Bethany Stanley under the supervision of Dr Robin Young and Prof Alex McConnachie at the Robertson Centre for Biostatistics.

I declare that, except where reference is made to the contribution of others, this thesis is a result of my own work, written entirely by myself and has not been submitted for any other degree at the University of Glasgow or any other institution.

Novalia Purnama Sidik, October 2023.

Definitions/Abbreviations

ACE	angiotensin-converting enzyme
ACh	acetylcholine
ANOCA	angina with no obstructive coronary artery disease
ANOVA	analysis of variance
AUC	area under the curve
BIPQ	Brief Illness Perception Questionnaire
BMI	body mass index
CABG	coronary artery bypass graft
CAD	coronary artery disease
CCS	Canadian Cardiovascular Society
CFR	coronary flow reserve
CI	confidence interval
CMD	coronary microvascular dysfunction
CMR	cardiac magnetic resonance imaging
CONSORT	Consolidated Standards of Reporting Trials
COPD	chronic obstructive pulmonary disease
CorCMR	Coronary Microvascular Angina Cardiovascular Magnetic Resonance Imaging trial
CorCTCA	Coronary Microvascular Angina and CT coronary angiography trial
CorMicA	Coronary Microvascular Angina Stratified Medicine trial
COVADIS	Coronary Vasomotion Disorders International Study Group
COVID	coronavirus disease
CRP	C-reactive protein
CTCA	computed tomography coronary angiography
CVD	cardiovascular disease
DALY	disability-adjusted life-year
DASI	Duke Activity Status Index
ECG	electrocardiograph/electrocardiogram
EDHF	endothelium-derived hyperpolarising factor
EQ-5D-5L	5 Level EuroQoL 5-Domain
ESC	European Society of Cardiology
ET	endothelin
ETT	exercise tolerance test
FFR	fractional flow reserve
GCP	Good Clinical Practice
GTN	glyceryl trinitrate
HDL	high-density lipoprotein
HRT	hormone replacement therapy
hs	high sensitivity
IDP	interventional diagnostic procedure
IHD	ischaemic heart disease
IMR	index of microvascular resistance
INOCA	ischaemia and no obstructive coronary artery disease

IPAQ-SF	International Physical Activity Questionnaire – Short Form
IQR	interquartile range
ISCHEMIA	International Study of Comparative Health Effectiveness with Medical and Invasive Approaches trial
IV	intravenous
LAD	left anterior descending artery
LDL	low-density lipoprotein
LV	left ventricular
LVEDP	left ventricular end diastolic pressure
MACE	major adverse cardiovascular events
MBF	myocardial blood flow
MI	myocardial infarction
MINOCA	myocardial infarction and no obstructive coronary artery disease
MPR	myocardial perfusion reserve
MPR_{ENDO}	subendocardial myocardial perfusion reserve
MPS	myocardial perfusion scintigraphy
MVA	microvascular angina
NHS	National Health Service
NO	nitric oxide
NT-proBNP	NT-proB-type Natriuretic Peptide
NYHA	New York Heart Association
PCI	percutaneous coronary intervention
PET	positron emission tomography
PGI2	prostacyclin
PHQ-4	Patient Health Questionnaire-4
PRIZE	Precision Medicine with Zibotentan in Microvascular Angina trial
Q1	25th percentile
Q3	75th percentile
QCA	quantitative coronary analysis
RCA	right coronary artery
RRR	resistance reserve ratio
SAQ	Seattle Angina Questionnaire
SAQSS	Seattle Angina Questionnaire Summary Score
SCOT-HEART	Scottish CT Coronary Angiography in Patients with Suspected Angina due to Coronary Heart Disease trial
SD	standard deviation
SIMD	Scottish Index of Multiple Deprivation
SL	sublingual
STROBE	Strengthening the reporting of observational studies in epidemiology
TIA	transient ischaemic attack
TIMI	Thrombolysis in Myocardial Infarction
TSQM-9	Abbreviated Treatment Satisfaction Questionnaire for Medication
TXA	thromboxane
VAS	visual analogue scale
VSA	vasospastic angina

VSMC	vascular smooth muscle cells
WISE	Women's Ischemia Syndrome Evaluation study

1 Introduction

1.1 Ischaemic heart disease

1.1.1 Epidemiology

Ischaemic heart disease (IHD) is a leading global cause of premature morbidity and mortality[1,2]. In many countries, the increase in life expectancies and improvements in IHD mortality have plateaued[1,2]. Global disability-adjusted life-years (DALYs) due to IHD was estimated at 17 million in 2017, with a 17.5% increase between 2007 and 2017[2]. Sex-based differences also exist, with less apparent improvement in mortality in younger women[3].

Epicardial coronary artery disease (CAD) and ischaemia with no obstructive coronary arteries (INOCA) exhibit sex associations. Of those individuals affected by obstructive CAD, most are men[4] whereas of those individuals diagnosed with angina with no obstructive coronary artery disease (ANOCA), most are women[5]. Obstructive CAD also associates with age, occurring in men at a younger age than in women, who typically experience obstructive CAD after the menopause. This age dependency is less clear-cut in INOCA/ANOCA. The latter includes a spectrum of coronary vasomotion disorders which may be structural and/or functional and involve the coronary artery and/or its microcirculation[6,7]. The proportions of patients with lumen stenosis <50% in any major coronary arteries is approximately 45% in women and 30% in men[8-10]. One in two women with suspected angina has non-obstructive CAD compared to one in three men. Myocardial infarction and no obstructive coronary artery disease (MINOCA) is also more common in women than in men. Among MINOCA patients, coronary microvascular spasm may account for at least 16% of cases[11].

1.1.2 Angina and unobstructed coronary arteries

Each year in the United Kingdom, there are more than 20,000 new cases of angina[3], and approximately 240,000 invasive coronary angiograms are performed[12]. However, obstructive CAD is only detected in 40-50% of these cases[8,12-15]. The factors associated with a low-yield from invasive angiography are multifactorial[8,13-15], and the possible underlying conditions behind INOCA include: 1) increased demand for oxygen consumption (e.g. aortic stenosis), 2) reduced oxygen supply (e.g. anaemia), 3) microvascular angina (due to coronary

microvascular and endothelial dysfunction)[16], and 4) vasospastic angina (due to endothelial dysfunction). The prevalence of coronary vascular dysfunction is uncertain but it may occur in approximately one third to half of patients with a 'negative' angiogram[17-19]. It is a chronic condition, although patients may present with symptoms acutely, and recurrently.

The term "coronary microvascular dysfunction" (CMD) was proposed in 2007 to unify the multitude of terminologies used to describe this condition[20], the most commonly used being "syndrome X"[21]. Today, CMD has gained more recognition as a clinical entity and a sub-classification according to the clinical context exists: 1) Type 1: primary CMD in the absence of underlying myocardial disease or obstructive CAD, 2) Type 2: CMD in the presence of myocardial disease (e.g. hypertrophic cardiomyopathy, 3) Type 3: CMD in the presence of obstructive epicardial CAD, 4) Type 4: iatrogenic CMD secondary to coronary revascularisation, and 5) Type 5: CMD following cardiac transplantation. For the purposes of this work, CMD refers to Type 1/primary CMD.

In addition to CMD, coronary vasospasm also makes up a significant proportion of ANOCA endotypes. Vasospastic angina was first described over half a decade ago, and historical terms such as Prinzmetal angina had been used to describe it. Coronary vasospasm is caused by exaggerated vasoconstriction of the coronary arteries causing myocardial ischaemia and angina, and can occur in the epicardial coronary arteries (causing vasospastic angina) or in the microvasculature (leading to microvascular spasm, a subtype of CMD)[18].

1.1.2.1 Natural history and prognosis

Despite the apparently reassuring findings, patients with angina who subsequently undergo coronary angiography that rules out obstructive CAD have an increased long-term risk of cardiovascular events[8]. Several studies performed in the last two decades have suggested that ANOCA is associated with high symptomatic burden and an increased risk of adverse cardiac events[8,22,23].

Many patients with ANOCA have persistence or worsening of symptoms, as well as further presentation to healthcare services for repeat evaluation. In a natural history study of 155 patients with CMD[24], at a mean follow-up of 37 months,

angina symptoms were unchanged in 33% and worsened in 14% of patients. Hospital readmission for recurrent chest pain occurred in 58% and 22% underwent at least one further coronary angiography. In the CIAO-ISCHEMIA study, another natural history study of patients with INOCA, angina symptoms were unchanged in 43% and worsened in 14%[25].

The Women's Ischemia Syndrome Evaluation (WISE) study, a prospective cohort study of women undergoing coronary angiography for suspected angina, has provided considerable data on ANOCA. In particular, it described significant rates of major adverse cardiovascular events (MACE) at 10 years even in women with no or non-obstructive CAD (6.7% and 12.8% respectively)[9]. The biggest predictor of adverse outcome was persistent angina at 1-year follow up. Furthermore, in patients enrolled in the invasive coronary function substudies, increased risk of MACE was associated with abnormal CFR[26] and with abnormal endothelial-dependent vasodilatory function[27].

A Danish case control study of 11223 patients with stable angina reported increased MACE rates in patients with no or non-obstructive CAD compared to asymptomatic, healthy subjects (hazard ratio of 1.52 and 1.85 respectively)[8]. This increased risk is evident in both men and women.

A Swiss cohort study of 718 patients with ANOCA followed up over a mean of 11 years showed that patients with CMD had increased risk of MACE (a four- to five-fold increase risk compared to patients without CMD)[28]. Patients with concurrent endothelial dysfunction were at particularly high risk.

A German observational study of 847 patients with ANOCA showed that patients with heightened vasoreactivity (abnormal acetylcholine results, including epicardial vasospasm and microvascular spasm) had higher rates of recurrent angina and higher burden of angina according to the Seattle Angina Questionnaire (SAQ)[29]. Patients with epicardial vasospasm in the study were shown to have an increased risk of non-fatal myocardial infarction and were more likely to undergo repeat coronary angiography. Irrespective of response to acetylcholine, patients with ANOCA had low rates of all-cause deaths and cardiovascular deaths.

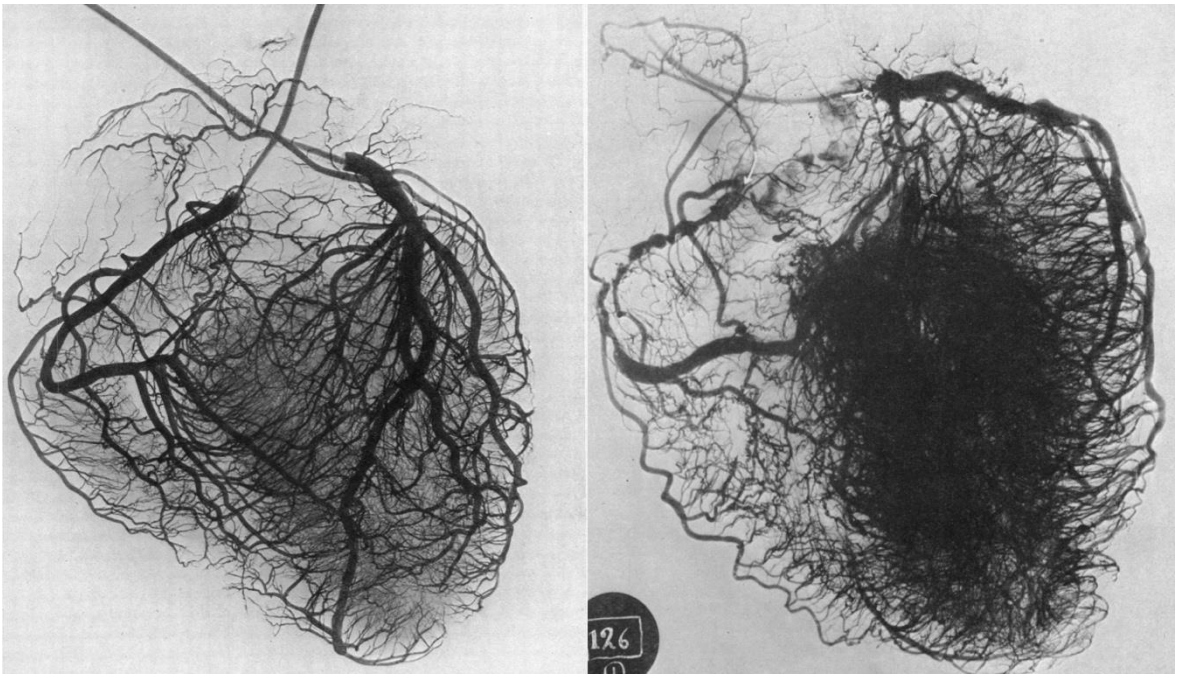
The data on mortality in the ANOCA population is less robust. Most studies looking at long-term outcomes of patients with ANOCA have shown low mortality in this patient population. For instance, the previously mentioned German study observed a 1.1% annual rate of all-cause mortality[29], and a U.S study of women with ANOCA reported a similar annual rate of all-cause mortality of 1.2%[30]. Others, such as the WISE study[31], have reported higher rates of mortality.

Although mortality data in patients with ANOCA is equivocal, there is significant associated morbidity due to the impact on quality of life and risk of cardiovascular events. ANOCA is not a "benign syndrome", as traditionally viewed. Recent practice guidelines have identified ANOCA as a problem of unmet need[32,33].

1.1.2.2 Coronary microcirculation

During the 1960s Professor William Fulton, a cardiologist based in Stobhill Hospital, Glasgow, demonstrated the existence of coronary micro-anastomoses using a patho-anatomical imaging technique[34] (Figure 1-1). The technique developed by Prof Fulton involved submission of an explanted human heart within a saline bath, coronary artery intubation, and infusion of a bismuth microsalt solution at physiological levels of blood pressure. X-ray images were then obtained and use of a stereoscope provides a 3-dimensional impression of the coronary circulation and microvessels. These microvessels can be as small as 30 μm, as compared to epicardial vessels which can be over 500 μm, and are too small to be visible angiographically.

Figure 1-1 - Post-mortem angiogram using bismuth solution with stereoangiography showing the coronary microcirculation.
Reproduced with permission from Prof. Colin Berry, University of Glasgow.



The coronary microcirculation plays an important role in regulating myocardial perfusion. Structural abnormalities and dysfunction in the microcirculation can lead to myocardial perfusion abnormalities and angina[7,35,36], even if in absence of epicardial CAD.

1.1.2.3 Pathophysiology of coronary microvascular dysfunction

As described previously, CMD can cause ischaemia in the absence of obstructive CAD. The mechanisms are incompletely understood, but are believed to involve both structural and functional abnormalities.

Amongst several similar animal models, a study of Ossabaw pigs with metabolic syndrome demonstrated hypertrophic inward remodelling of the coronary microvessels and reduced capillary density within the myocardium[37]. The microvessels exhibited decreased luminal diameter and thicker walls, with reduced collagen: elastin ratio and reduced stiffness. This leads to decreased coronary flow and myocardial ischaemia, even in the absence of an epicardial stenosis.

Endothelial dysfunction involves the reduction of endothelial cell capacity to release nitric oxide (NO; a vasoactive agent that cause arterial relaxation, which is also synthesised by nitric oxide synthase), evidenced by an impairment of endothelium-dependent relaxation[38]. Other vasoactive factors released by

endothelial cells include vasoconstrictive factors such as endothelin-1 (ET-1) and thromboxane (TXA_2), and vasodilatory factors such as prostacyclin (PGI_2) and endothelium-derived hyperpolarising factor (EDHF). These vasoactive factors play important roles in the regulation of vascular tone. In endothelial dysfunction, there is a decrease in endothelium-dependent vasodilation and an increase in vasoconstrictor responses to ET-1 and TXA_2[39]. In particular, ET-1 is a highly potent vasoconstrictor via its receptors (ET_A and ET_B) on vascular smooth muscle cells (VSMCs). ET_A receptors mediate vasoconstriction[40-42]. ET_B receptors are located on VSMCs and endothelial cells, and have NO-dependent vasodilator effects in healthy blood vessels[43,44], or vasoconstrictor effects if NO is deficient[42,45,46]. ET-1 enhances coronary vascular tone *in vivo* via ET_A-activation[47-49], contributing to coronary endothelial dysfunction[47]. Patients with angina and normal coronary angiograms were observed to have increased circulating plasma ET-1 concentrations and shorter time to onset of angina during exercise[50]. Higher circulating ET-1 concentration has also been associated with lower coronary flow reserve (CFR) on multivariate analysis[51].

Abnormal coronary vasoconstriction can also be caused by increased alpha-adrenergic activation from increased sympathetic activity[52] and adipocyte- and perivascular adipose tissue-derived adipokines such as leptin[53]. These adipokines are potent pro-inflammatory factors that may increase ET-1 production. Increased perivascular adipose tissue increases the production of these adipokines, thereby contributing to endothelial dysfunction in patients with metabolic syndrome. This group of patients also exhibit increased angiotensin II-induced vasoconstriction through the activation of the renin-angiotensin-aldosterone system.

1.1.2.4 Endotypes of coronary microvascular dysfunction

The definitive diagnosis of CMD is based on physiology indices derived from the invasive assessment of the coronary microcirculation during cardiac catheterisation. Measurements of Index of Microvascular Resistance (IMR), Coronary Flow Reserve (CFR), and Resistance Reserve Ratio (RRR) are typically obtained during coronary function testing, which typically includes the induction of hyperaemia with adenosine. Coronary function testing also encompasses vasospasm provocation testing with acetylcholine.

Just as the pathophysiology of CMD can be subdivided into structural abnormalities and functional abnormalities, its clinical manifestations can also be divided into endotypes. That is, a subgroup of individuals with a condition defined by specific pathophysiological mechanisms and/or therapy responses. Abnormalities in coronary microvascular responses to adenosine is predominantly endothelium-independent, whereas coronary endothelial dysfunction confers abnormal responses to acetylcholine.

Structural, endothelium-independent abnormalities in the coronary microcirculation generally lead to microvascular angina. Increased microvascular resistance, which is a measure of microvascular function independent of resting haemodynamics, is reflected by a raised IMR. Reduced coronary vasorelaxation, which is the inability to increase coronary flow above twice the resting flow, is reflected by a reduced CFR. Reduced microvasodilator capacity, which the vasodilator capacity of the microcirculation to change from baseline to hyperaemia, is reflected by a reduced RRR. A raised IMR reflects microvascular angina endotype with underlying structural abnormalities, whilst a reduced CFR and RRR are endotypes of microvascular angina with functional abnormalities.

Endothelial dysfunction can be observed in the microcirculation as well as in the epicardial coronary arteries, which can be provoked by intracoronary acetylcholine. Endothelial dysfunction in the microcirculation is angiographically demonstrated by reduced flow in the epicardial coronary arteries without any reduction in the epicardial vessel diameter. A reduction in coronary blood flow is usually accompanied by anginal symptoms and ischaemic electrocardiographic (ECG) changes. This would be consistent with microvascular spasm, an endotype of microvascular angina due to functional abnormalities.

Endothelial dysfunction in the epicardial arteries is diagnosed angiographically by a reduction in the epicardial vessel diameter of >90%, which similarly is usually accompanied by anginal symptoms and ischaemic ECG changes. This would be consistent with a diagnosis of vasospastic angina.

1.1.2.5 Patient subgroups and risk factors

There have been numerous studies on the association between CMD and metabolic syndrome, a syndrome that encompasses diabetes, hypertension, obesity and dyslipidaemia, each of which has been shown to induce or accelerate CMD. Diabetes is associated with CMD, with evidence of reduced myocardial blood flow and microvascular rarefaction in animal models[54]. Hypertension causes inward remodelling of microvessels and microvascular rarefaction, therefore increasing microvascular resistance[55]. Obesity induces perivascular adipose tissue accumulation, which in turn leads to inflammation and endothelial dysfunction as described previously[56]. Hypercholesterolemia causes impaired endothelium-dependent vasodilation in the microcirculation[57] and is also associated with a pro-inflammatory mechanism.

Numerous studies have demonstrated sex-based differences in clinical characteristics and outcomes in ischaemic heart disease. Although women have less extensive epicardial CAD, they have a higher symptomatic burden compared to men. Most recently, the ISCHEMIA (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches) trial illustrated that although women in the trial had less severe ischaemia on nuclear myocardial perfusion stress tests and less extensive CAD on computed tomography coronary angiography (CTCA), they had more angina as assessed by the Seattle Angina Questionnaire, and more dyspnoea as assessed by the New York Heart Association Functional Classification[58]. ANOCA, MINOCA, Takotsubo cardiomyopathy and spontaneous coronary artery dissection form a group of cardiovascular disorders which has a largely unexplained higher prevalence in women. Possible factors contributing to the sex-based differences in symptoms include less evidence-based therapy in women (including mechanistically untargeted therapy and also under-prescription of evidence-based therapy), and concomitant CMD. Furthermore, sex-specific cardiovascular risk factors such as gestational diabetes, preeclampsia and polycystic ovarian syndrome, confer additional susceptibilities to the development of CAD[59]. Overall, women are notoriously under-represented in cardiovascular trials, and most trials are not adequately powered to perform secondary analyses on sex differences in outcomes. Further study is required to investigate and address this issue.

1.1.2.6 Comparisons between ANOCA and obstructive CAD

As discussed previously, there are differences in the clinical presentation of ANOCA compared to obstructive CAD. Gender differences are evident, with a higher prevalence of ANOCA in women than in men[60], while the opposite is true for obstructive CAD. ANOCA also has a younger age of onset than angina due to obstructive CAD.

Patients with ANOCA are less likely to have a positive functional test than those with obstructive CAD. In obstructive CAD, ischaemia is detected in myocardial segments that correspond with an epicardial coronary territory. In contrast, ischaemia in patients with INOCA is often heterogenous and diffuse and undetectable on conventional stress tests[61]. These functional tests will be discussed in greater detail in the following section.

In theory, patients with obstructive CAD should have a higher prevalence of typical angina and less atypical angina presentation. In a multicentre registry looking at patients with angina undergoing CTCA, patients with obstructive CAD (defined as stenosis >70%) have a three-fold likelihood of having typical angina than atypical angina[62]. ANOCA studies, on the other hand, reported a prevalence of typical angina that is approximately half of atypical angina[5,63]. This is likely to be explained by the pathophysiology of the condition, but the higher proportion of women, who classically present with more atypical symptoms, in the ANOCA population may be a factor in this observation.

Response to conventional antianginal therapy (which will be discussed in greater detail in the following section) is less predictable in the ANOCA population compared to patients with obstructive CAD. Whereas the ISCHEMIA[64] and ORBITA[65] trials have shown clear improvement in anginal symptoms with optimal medical therapy in patients with obstructive CAD, no similar large randomised controlled trials in ANOCA patients exist and the current data based on smaller studies are equivocal.

1.1.2.7 Treatment

There is a paucity of data for evidence-based CMD treatment, with no data from large randomised controlled trials comparing therapies, and with most available

data obtained from cohort studies. Clinical guideline recommendations are limited. However, CMD is increasingly recognised as a cause of IHD morbidity and mortality, and clinicians should be prepared to initiate therapy targeted at CMD.

Cardiovascular risk factors are prevalent in patients with ANOCA. Management of modifiable cardiovascular risk factors should be essential, and not just adjunctive, components of therapy[66]. As described previously, diabetes, hypertension and dyslipidaemia are risk factors of CMD and all attempts should be made to ensure that they are well-controlled. Lifestyle changes like smoking cessation and regular exercise should be advised[67].

Statin therapy is recommended in all patients with CMD, even in the absence of atherosclerosis, unless there is a contraindication[68]. Statins have inhibitory effects on vascular inflammation and enhance vascular NO bioavailability. Several small randomised trials and case-control studies have shown that statins improve exercise tolerance[69], quality of life, exercise-induced reversible perfusion defects[70], and endothelial function[71].

Beta-blockers are reasonable when the predominant symptom is effort-related, and beta-blockers treatment has been shown to improve symptoms[68,72]. They induce endothelium-dependent vasodilation, reduce adrenergic tone, and reduce myocardial oxygen demand. They should however be avoided in endothelial dysfunction (microvascular spasm) and coronary spasm (vasospastic angina), in which calcium-channel blockers should be the first-line treatment.

When symptoms persist despite first-line treatment with beta-blockers, calcium-channel blockers and nitrates could be helpful although they have shown conflicting results in clinical trials[72]. In theory, they induce vasodilation to improve angina. Calcium-channel blockers are the first-line treatment recommended by the 2019 European Society of Cardiology (ESC) gudelines[67] for vasospastic angina and microvascular spasm.

Although angiotensin-converting enzyme (ACE) do not have anti-anginal effects, ACE inhibitors may improve microvascular function[73,74] by counteracting the vasoconstrictor and pro-oxidant effects of angiotensin II. ACE inhibitors improve

endothelial dysfunction[69] and ACE inhibition and mineralocorticoid receptor blockade have been shown to improve CFR in patients with diabetes[75,76].

Prior studies have reported symptomatic improvement from hormone replacement therapy (HRT) with oestrogen[77]. This improvement is likely mediated by improvement in endothelial function. However, there is insufficient evidence that HRT is beneficial in primary and secondary prevention of IHD, and guidelines recommend that HRT is not prescribed routinely for women with IHD[78].

1.2 Diagnostic testing in ANOCA

1.2.1 Non-invasive testing

1.2.1.1 CTCA and current clinical guidelines

Diagnostic imaging using CTCA is guideline-recommended and widely adopted as a first-line test for the assessment of stable chest pain in patients with no prior history of coronary artery disease[79-82]. The changes in guidelines were made following recent randomised controlled trials[4,83,84]. The Scottish Computed Tomography of the Heart (SCOT-HEART) trial reported that among patients referred to a cardiology chest pain clinic with suspected stable angina, CTCA added to standard care clarified the diagnosis of CHD and altered subsequent management[4]. CTCA-guided management added to standard care reduced the rate of death from IHD or nonfatal myocardial infarction (MI) at 5 years[85]. However, anginal symptoms and quality life at 6 weeks and 6 months were worse in the CTCA-guided group compared to the control group who received standard care[86]. One explanation could be that in the CTCA group, in patients who had microvascular angina and/or vasospastic angina, exclusion of angina due to obstructive CAD resulted in discontinuation of angina therapy by protocol which in turn led to a deterioration in anginal symptoms and quality of life. None of the landmark CTCA trials involved systematic evaluation of non-flow-limiting CAD and coronary vasomotion[4,83,84,86-88], hence the prevalence of coronary vasomotion disorders in the majority of patients with angina is unknown.

1.2.1.2 Functional testing

Approximately 40-50% of patients with angina undergoing elective coronary angiography have non-obstructive CAD[15]. Although this patient population is heterogeneous, many may have CMD[89]. A significant proportion may be falsely reassured that their symptoms are not cardiac in nature, or have their treatment discontinued despite persistent symptoms.

According to the Coronary Vasomotion Disorders International Study Group (COVADIS) standardised diagnostic criteria, for the diagnosis of definitive microvascular angina, the following criteria have to be met: 1) symptoms consistent with angina, 2) absence of obstructive CAD, 3) objective evidence of myocardial ischaemia, and 4) evidence of abnormal coronary microvascular function (defined as abnormal CFR, abnormal IMR, microvascular spasm, or coronary slow flow phenomenon)[90]. As such, prior to coronary angiography, patients should be investigated for evidence of myocardial ischaemia. This is in keeping with current clinical guidelines for the investigation of stable CAD, which recommend that patients with an intermediate pre-test probability should undergo non-invasive testing[33].

The diagnosis of CMD requires, firstly, the exclusion of obstructive CAD as a cause of the anginal symptoms. With recent guidelines placing emphasis on CTCA as a first-line investigation for patients presenting with suspected angina[79], fewer patients are having to undergo invasive coronary angiography. In patients in whom obstructive CAD has been excluded on CTCA, persistent symptoms suggestive of angina should prompt clinicians to consider CMD as a potential mechanism for ischaemia and proceed to functional testing.

The treadmill exercise tolerance test (ETT) remains the most accessible and inexpensive form of functional testing. However, no specific features that may be diagnostic of CMD have been identified and ETT may be unremarkable, although many patients experience exercise-limiting angina with or without ST-depression[91]. A negative treadmill stress test does not exclude the possibility of CMD especially in individuals with non-exercise dependent endothelial dysfunction.

On stress echocardiography, with or without contrast, only 20-30% of patients exhibit transient perfusion defects. CMD may not produce echocardiographically detectable dysfunction despite the occurrence of symptoms, ECG changes, and perfusion abnormalities[61]. Sensitivity of stress echocardiography is higher if perfusion in a sizeable territory of an epicardial artery or a major branch is significantly decreased. Heterogeneous CMD distributed within the myocardium, which is common in CMD, is likely to be missed. Diffuse, mild involvement across the myocardium may also fail to produce an area of localised reduction.

Transthoracic Doppler echocardiography has been used to evaluate flow in the left anterior descending artery (LAD). Coronary flow velocity is measured at baseline and at maximal hyperaemia, the difference of which is a marker of dilatation of the coronary microvasculature in response to adenosine, and representative of CFR[92]. This test requires a high frequency transducer and highly sensitive and dedicated equipment, and is significantly dependent on acoustic window. As with most other stress tests, there may be false negatives as CMD can be patchy and heterogeneous.

Nuclear perfusion scans may show relative overall reduction in thallium or technetium uptake and reduced washout in CMD, but overall sensitivity is low[93,94].

Stress myocardial perfusion positron emission tomography (PET) has been shown to be reliable in quantifying myocardial blood flow (MBF)[95], which has good correlation with invasively measured CFR. Stress perfusion PET remains the current reference standard for non-invasive quantification of myocardial ischaemia, with or without obstructive CAD. Abnormalities of MBF on PET have been shown to be prevalent in patients with ANOCA[96,97]. Unfortunately, cardiovascular PET is not widely available.

Stress cardiovascular magnetic resonance imaging (CMR) is an alternative to PET, is more widely available and does not involve ionising radiation. Stress perfusion CMR can be used to measure MBF and myocardial perfusion reserve (MPR), both of which correlate with CFR. An additional benefit to CMR is the simultaneous assessment of left ventricular function and myocardial tissue characterisation. On stress perfusion CMR, CMD tends to exhibit reversible perfusion defects with

subendocardial and circumferential distribution not necessarily corresponding with the territory of a coronary artery. This is in contrast to the pattern of CMD seen in patients with obstructive epicardial CAD, where the transmural and segmental perfusion defects would correspond with the distribution of an epicardial coronary artery.

Although non-invasive diagnostic tests (anatomical or stress) do not provide information that permits reliable differentiation between obstructive CAD and CMD, quantitative myocardial stress perfusion imaging tests can provide some useful information in the assessment of patients with angina. For example, Kotecha et al[98] showed that quantitative myocardial perfusion mapping using automatically generated pixelwise myocardial perfusion maps by CMR improves the detection of global ischaemia, which is not dissimilar to the heterogenous ischaemia found in CMD. Rahman et al[99] found that quantitative myocardial perfusion indices derived using 3.0T stress perfusion CMR, MPR_{ENDO} and MPR had the highest accuracy (area under the curve [AUC]: 0.90 and 0.88).

In patients without obstructive CAD on CTCA, the presence of anginal symptoms and objective evidence of myocardial ischaemia should be sufficient for the clinician to consider CMD as a likely cause of the patient's symptoms[90]. Invasive coronary angiography, with its associated risks and complications, could be avoided in these patients.

However, non-invasive diagnostic stress tests lack sensitivity and specificity for spasm of the microcirculation and coronary arteries, which are prevalent pathophysiological causes of ANOCA. Conventional stress testing with echocardiogram and ECG have limited diagnostic accuracy for identifying occult coronary abnormalities that may cause angina in patients with non-obstructive CAD[100], and a normal or negative stress test does not rule out CMD. The 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes now recommend that transthoracic Doppler of the LAD, CMR and PET may be considered for non-invasive assessment of CFR[67] (class IIb, level of evidence B). In patients who are known to have no obstructive CAD, invasive coronary function testing is advised with a higher class of recommendation (class IIa, level of evidence B). Comprehensive invasive coronary testing remains essential to

gaining important diagnostic information. The level of evidence of these recommendations, however, reflect the lack of robust, unequivocal evidence.

1.2.2 Invasive testing

1.2.2.1 Invasive assessment of coronary function

The invasive diagnosis of coronary vascular disorders requires assessment for increased propensity to vasoconstriction as well as assessment for impaired vasorelaxation.

Impaired CFR (which reflects the vasodilator capacity of the coronary circulation), even in the absence of obstructive CAD, is prognostically important[101]. CFR was originally measured invasively using Doppler within a coronary artery[102]. After the introduction of fractional flow reserve (FFR), De Bruyne showed that the same temperature sensitive guidewire could be used to measure CFR using thermodilution in an animal model[103]. A year later, Pijls validated the technique in humans[104].

Ng et al showed that IMR was more reproducible with less variability and, unlike CFR, was independent of resting haemodynamic status[105]. With the guidewire in the distal third of a major coronary artery, IMR is calculated during peak hyperaemia as the product of distal coronary pressure and transit time (using a 3ml bolus of intracoronary saline). By using thermodilution, the mean transit time (T*mn*) of room-temperature saline injected down a coronary artery can be determined and is inversely proportional to absolute coronary flow (F) [T*mn* $\propto$ *1/F]*. True microvascular resistance (TMR) equals distal perfusion pressure divided by flow (TMR = distal coronary pressure (Pd)/F). Assuming that vascular volume is constant at maximum hyperaemia, IMR = Pd * T*mn*.[106] Using a porcine model, Fearon et al compared the TMR with IMR with use of an ultrasound doppler probe and microspheres to induce microvascular dysfunction. The investigators found a reasonable correlation between IMR and TMR ($r = 0.54$ $p<0.0001$)[107].

IMR overestimates microvascular resistance in the presence of an epicardial artery stenosis. Therefore in the presence of an epicardial stenosis, collateral flow must be considered, and the IMR equation is as follows:

IMR = Pa*Tmn*(Pd-Pw/Pa-Pw)

where Pa is the hyperaemic aortic pressure, Pd the hyperaemic distal pressure beyond a stenosis and Pw the coronary wedge pressure. Practically, Pw requires a balloon inflation before assessing the distal pressure without antegrade flow.[107] Yong et al described a linear mathematical formula to overcome this limitation, allowing adjustment of IMR for the pressure drop related to epicardial stenosis (FFR) without assessing Pw[108].

The normal values for IMR and CFR have been challenging to define. The normal range of IMR is considered to be <25, based on three studies evaluating IMR in different populations.[109-112] The only healthy population used to validate IMR was 20 subjects who underwent IMR testing prior to ablation for supraventricular rhythm disturbance. In this study, Solberg et al noted the upper limit of the estimated 95% percentile for IMR in 20 healthy controls to be 27 (95% CI 21 – 34). The authors stated that if a larger cohort of controls was used this upper limit would likely be reduced (potentially closer to 25 as used in this thesis and in the wider literature). In the other studies, authors defined control individuals as patients with 'atypical chest pain' and/or a negative exercise treadmill test and smooth normal epicardial coronary arteries on coronary angiography. This has limitations as patients might have unrecognised microvascular dysfunction. One study of 1096 patients suggested vessel specific cut-offs with left anterior descending coronary artery IMR of <22 based on values above this exceeding the 75th percentile.[113]

For the purpose of this thesis, the literature consensus cut offs for IMR (25) and CFR (2)[114,115] have been adopted with the caveat that dichotomisation of any continuous variable has inherent limitations.

In summary, IMR is a quantitative invasive marker of structural microvascular dysfunction whereas CFR is a functional marker of the vasodilator capacity of the entire coronary circulation[106]. These metrics provide complementary information on coronary artery and microvascular function predominantly assessing endothelial independent pathways.[116] Pharmacological testing with intra-coronary acetylcholine completes the assessment for coronary vasomotion specifically assessing functional propensity to vasospasm of the microvessels or

epicardial coronary artery. In healthy endothelium, acetylcholine (ACh) stimulates abluminal release of nitric oxide mediating vascular smooth muscle relaxation and increased blood flow.[117] At very high doses or in patients with hypercontraction of vascular smooth muscle cells (VSMCs) and/or endothelial dysfunction, ACh stimulates vasoconstriction with epicardial vasospasm[118] and/or microvascular vasospasm[119] inducing ischaemia.

1.2.2.2 Stratified medicine in CorMicA

The Coronary Microvascular Angina (CorMicA) trial[5] has provided new insights into the prevalence of microvascular angina and vasospastic angina in patients selected for invasive coronary angiography. Three hundred and ninety-one patients referred for clinically-indicated coronary angiography in a regional centre were prospectively recruited during a 12-month period. Almost half of this population (n=185 (47%)) had no obstructive CAD. One hundred and fifty-one entered the randomised trial and those with obstructive CAD (n=206 (53%)) entered a registry. CorMicA involved a 1:1 randomised, blinded, sham-controlled, parallel-group, clinical trial of stratified medicine versus standard angiography-guided management. Stratified medicine is the identification of key subgroups of patients (endotypes) within a heterogeneous population; these endotypes being distinguishable by distinct mechanisms of disease and/or responses to therapy[120]. Compared to standard care, the stratified intervention changed the initial diagnosis based on coronary angiography in half of the participants in the intervention group and was associated with directionally consistent improvements in angina, quality of life and treatment satisfaction at 6-months. CorMicA was positioned down-stream in the care pathway in patients selected for invasive management. Whether or not endotypes, such as microvascular angina and/or vasospastic angina, might be common and clinically relevant in a population of patients presenting with stable angina in the outpatient clinic setting is unknown.

The CorMicA trial highlighted the potential for stratified medicine to benefit patients with angina. The strategy is now supported by a Class IIA practice guideline recommendation from the ESC[82].

1.3 Conclusion

1.3.1 Summary

Approximately half of patients presenting with angina have unobstructed coronary arteries, and the proportion of patients with ANOCA is uncertain but felt to be significant. These patients have traditionally been underdiagnosed and undertreated. In recent years, ANOCA has been gaining more awareness in academic and clinical practice. Yet there is still a lack of evidence in this field, especially with regards to treatment.

1.3.2 Rationale

The current study aims to build upon the data from CorMicA in a distinct population. It is a randomised controlled trial assessing whether stratified medicine is informative and clinically useful in patients with angina and no obstructive CAD, as determined by CTCA. As such, this study is positioned upstream to CorMicA in the standard care pathway, and should more accurately reflect the true prevalence of CMD in ambulatory patients with known or suspected angina through the recruitment of a relatively unselected population. It is designed as an oversampling of underrepresented cases to identify novel subgroups of patients in this population.

1.3.3 Ethical challenges

The premise of the study is based on performing invasive coronary angiography with coronary function testing on patients without obstructive CAD. Exposing patients to procedural-related risks and complications as part of a research procedure poses an ethical challenge, especially in patients who would normally have had no further investigation in the diagnostic pathway.

However, studies have shown that approximately 50% of patients with angina undergoing invasive coronary angiography have no obstructive CAD[8,12-15], and yet they have an increased long-term risk of cardiovascular events[8] and have high symptomatic burden[22,23]. In contemporary practice, most of these patients would have been reassured that their symptoms were non-cardiac, sometimes erroneously, despite natural history studies showing a high rate of persistence

and/or worsening of symptoms[24,25]. This under-diagnosed and under-treated patient population reflects a gap in knowledge and appropriate clinical care.

The study design presents an added ethical challenge. Following randomisation, half of the patients undergoing coronary function testing would not have the results disclosed to them or their treating physicians. To mitigate this, the results were disclosed at the second follow up time point (i.e., when the patients attended for the in-person follow up) after all the follow up data had been collected.

1.3.4 Hypothesis

We hypothesise that clarification of ANOCA diagnosis to rule-in or rule-out disease endotypes, increasing the certainty of the diagnosis, will help clinicians make informed therapy decisions, and that stratified medicine will improve patient wellbeing and healthcare resource utilisation.

We aim to assess the prevalence of ANOCA disease endotypes in patients with angina and no obstructive CAD as classified by CTCA, and to assess the effect of stratified medicine on diagnosis, treatment and well-being.

2 Methods

2.1 Study design

This is a prospective observational study with a nested multicentre, randomised, sham-controlled, clinical trial with blinding extending to the diagnostic tests, clinical care teams and outcome assessments.

2.1.1 Aims, objectives and outcomes

2.1.1.1 Aims

The aim of the observational study is to assess the prevalence of coronary vasomotion disorders and its disease endotypes in patients with angina in whom obstructive coronary artery disease (CAD) has been excluded by computed tomography coronary angiography (CTCA). Disease endotypes are prospectively assessed using an interventional diagnostic procedure (IDP) including coronary vascular function testing during invasive angiography.

The aim of the randomised trial is to assess the effect of IDP-guided stratified medicine on diagnosis, treatment and well-being. The participants are randomised into 2 groups: the intervention group (IDP disclosed, stratified medicine) or the control group (IDP not disclosed/sham, standard angiography-guided management).

We hypothesise that in this patient population, microvascular angina and vasospastic angina are prevalent, and that the clarification of diagnosis will lead to changes in treatment and therefore improved patient well-being and healthcare resource utilisation.

2.1.1.2 Primary objective of the observational study

The primary objective of the observational, diagnostic study is to prospectively determine the prevalence of coronary vasomotion disease endotypes in a population of patients with ANOCA. It reflects the reclassification of the initial diagnosis based on the results of the IDP. It is determined by the diagnosis of the following diagnostic groups and endotypes:

1. Angina due to obstructive CAD (fractional flow reserve [FFR] ≤0.80);

2. Microvascular angina (coronary flow reserve [CFR] <2.0 and/or index of microvascular resistance [IMR] >25);
3. Microvascular angina due to microvascular spasm (based on acetylcholine testing);
4. Vasospastic angina (based on acetylcholine testing);
5. Non-coronary aetiology (normal coronary function).

2.1.1.3 Primary objective of the randomised trial

The primary objective of the nested randomised controlled trial is to determine whether IDP-guided stratified medicine, including disclosure of the coronary function findings with linked changes in management, leads to patient benefits. The primary outcome is the within-subject change at 6 months from baseline for the domains of the Seattle Angina Questionnaire (SAQ).

2.1.1.4 Secondary objectives

1. Determine whether IDP-guided stratified medicine leads to changes in diagnosis and certainty of the diagnosis;
2. Determine whether IDP-guided stratified medicine leads to changes in clinical management;
3. Determine the prevalence of obstructive CAD at the time of invasive coronary angiography in this patient population in whom obstructive CAD has been excluded by CTCA;
4. Compare health status using the SAQ, the EuroQoL 5-domain (EQ-5D-5L) health-related quality of life questionnaire, the Brief Illness Perception Questionnaire (BIPQ), the Patient Health Questionnaire-4 (PHQ-4) for anxiety and depression, and the Treatment Satisfaction Questionnaire for Medication (TSQM-9) between the intervention and control groups at baseline and during follow-up (at 6 and 12 months);
5. Compare functional status and physical activity levels using the Duke Activity Status Index (DASI) and the International Physical Activity Questionnaire – Short Form (IPAQ-SF) between the intervention and control groups at baseline and during follow-up (at 6 and 12 months);

6. Compare longer-term health outcomes and resource utilisation including episodes of care and prescriptions between the intervention and control groups using electronic record linkage.

2.1.1.5 Primary outcomes

The primary outcome of the observational study was the prevalence of disease endotypes as diagnosed using coronary vascular function testing in this population.

The primary outcome of the randomised trial was the within-individual change in angina severity according to the SAQ Summary Score at follow-up from baseline.

2.1.1.6 Secondary outcomes

The pre-specified secondary endpoints include:

1. Diagnostic utility (frequency, certainty and change in diagnosis, missed diagnosis)

2. Clinical utility (impact of the stratified intervention on patient management)

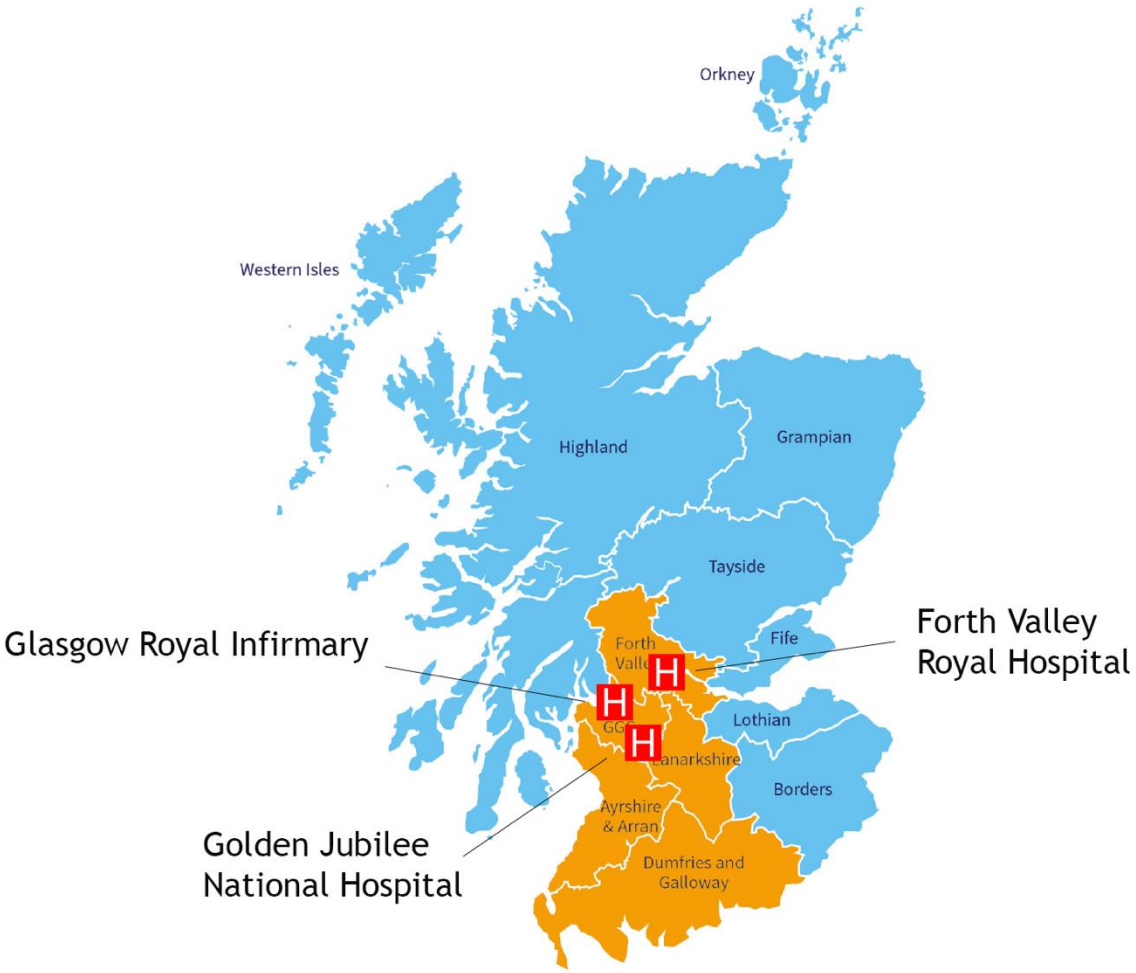
3. Heath status (change from baseline by repeat of validated questionnaires)

2.1.2 Setting

2.1.2.1 Hospitals and catchment area

Electronic health records for outpatients referred for guideline-indicated assessment of coronary artery disease by CTCA at the NHS Golden Jubilee hospital, Glasgow Royal Infirmary, and Forth Valley Royal Hospital in Scotland were screened prospectively[67,79-81]. The geographies included socially diverse populations from urban and rural communities (Figure 2-1). Eligible subjects had anginal symptoms and were referred by their attending cardiologists for clinically indicated CTCA in line with contemporary practice guidelines[79-82].

Figure 2-1- Map of Scotland showing the catchment area of the population included in the study



2.1.2.2 CTCA

2.1.2.2.1 CT scanners and acquisition protocols

Prior to undergoing CTCA, patients were pre-prepared by administration of oral beta-blockers e.g. metoprolol 50 mg, bisoprolol 2.5 mg, if possible, to achieve heart rate control (target 60 beats per minute). Additional intravenous beta-blockers were administered immediately before the scan if the patient's heart rate remained above 60 beats per minute. Sublingual glyceryl trinitrate (GTN) was also administered prior to the scan.

CTCAs were performed on the GE Discovery CT750 HD scanner (a 64-detector-row system), the Canon Aquilion Prime SP scanner (a 80-detector-row system), or the Philips Ingenuity 128 scanner (a 64-detector-row system).

Prospective step-and-shoot acquisition in diastolic phase during a single breath-hold was used whenever the heart rate allowed. Scan timing was determined

with a test bolus or bolus tracking. Retrospective helical scan or “dose padding” modes were available at the discretion of the supervising clinician for higher heart rates. “Padded” scans were performed using a phase tolerance of 5% to allow image optimisation and phases of 70%, 75% and 80% were assessed. Retrospective scans were reconstructed at 40% and 75% with additional phases added at the discretion of the supervising clinician. Tube mAs and kVp material were selected according to the patient’s BMI and habitus. Omnipaque 350 contrast material followed by saline chase was injected to standard local protocol, with flow rate and volume varying according to tube kVp.

2.1.2.2.2 CT scan radiation dose

The dose indices recorded by the radiographers is the Dose Length Product (DLP) measured in mGy.cm. This takes into account the dose per slice and the length of the scan and stochastic risk for a cardiac CT. To convert the mean DLP into an effective dose, a conversion factor (in mSv/mGycm) was used. We utilised a conversion factor of 0.027 mSv/mGycm (which is the coefficient factor for CT chest)[121] to obtain an estimated effective dose in mSv.

2.1.3 Eligibility criteria

To mitigate the possibility of bias through knowledge of the CTCA findings, the decision to enrol patients was made before the CTCA. Patients referred for CTCA were invited to give informed consent and complete the Rose Angina[122] and Seattle Angina Questionnaires[123]. The participants’ responses disclosed in these questionnaires were assessed against the eligibility criteria to confirm a history of anginal symptoms. Participants who reported symptoms of angina and fulfilled the eligibility criteria were invited to complete the other health questionnaires before CTCA. By completing the questionnaires before CTCA, the participants were unaware of the imaging results which therefore cannot influence the patients’ responses.

CTCA was performed during usual care and acquired according to a standard protocol. Where preliminary non-contrast scans were acquired, CT coronary calcium score was estimated according to local practice. Oral and/or intravenous beta-blocker therapy (if required for heart rate control) and

sublingual glyceryl trinitrate (GTN) were given immediately prior to CTCA in line with local standards of care. The CTCA was of sufficient diagnostic quality to substantiate a conclusive radiology report whereby disease severity in an epicardial coronary artery with a diameter >2.5 mm is classified by the reporting clinician as absent or present, and if present whether the disease is obstructive i.e. >70% severity, potentially obstructive >50-70% circumferential with plaque extending for ≥2 coronary segments, intermediate >50-70% plaque but not circumferential plaque extending for severity, or non-obstructive CAD (≤50%). This classification aligns with contemporary trials[4,83-85,87,88]. Overall disease severity was categorised using the CAD-RADS reporting system for stable chest pain[124].

Participants without obstructive CAD on CTCA continued in the study. They were invited to attend on a different date for elective coronary angiography with adjunctive tests of coronary function. These procedures were performed in a single reference centre (Golden Jubilee National Hospital). During the angiogram, participants with either obstructive CAD or who were eligible but for other reasons e.g. logistical, are not randomised continued in a follow-up registry. The Research Ethics Committee and Research and Development Management Office have approved the protocol.

2.1.3.1 Inclusion criteria

1. Age ≥18 years.
2. Symptoms of angina or angina-equivalent informed by the Rose Angina questionnaire.
3. Intermediate or no obstructive coronary disease i.e. no coronary stenosis >70% in an artery >2.5 mm, as revealed by CTCA.

2.1.3.2 Exclusion criteria

1. Non-coronary aetiology of angina, e.g. anaemia, aortic stenosis, hypertrophic obstructive cardiomyopathy.
2. Obstructive coronary disease evident in an artery (diameter >2.5 mm), i.e. >50 - 70% circumferential plaque extending for ≥2 coronary segments, or a stenosis >70% as revealed by CTCA.

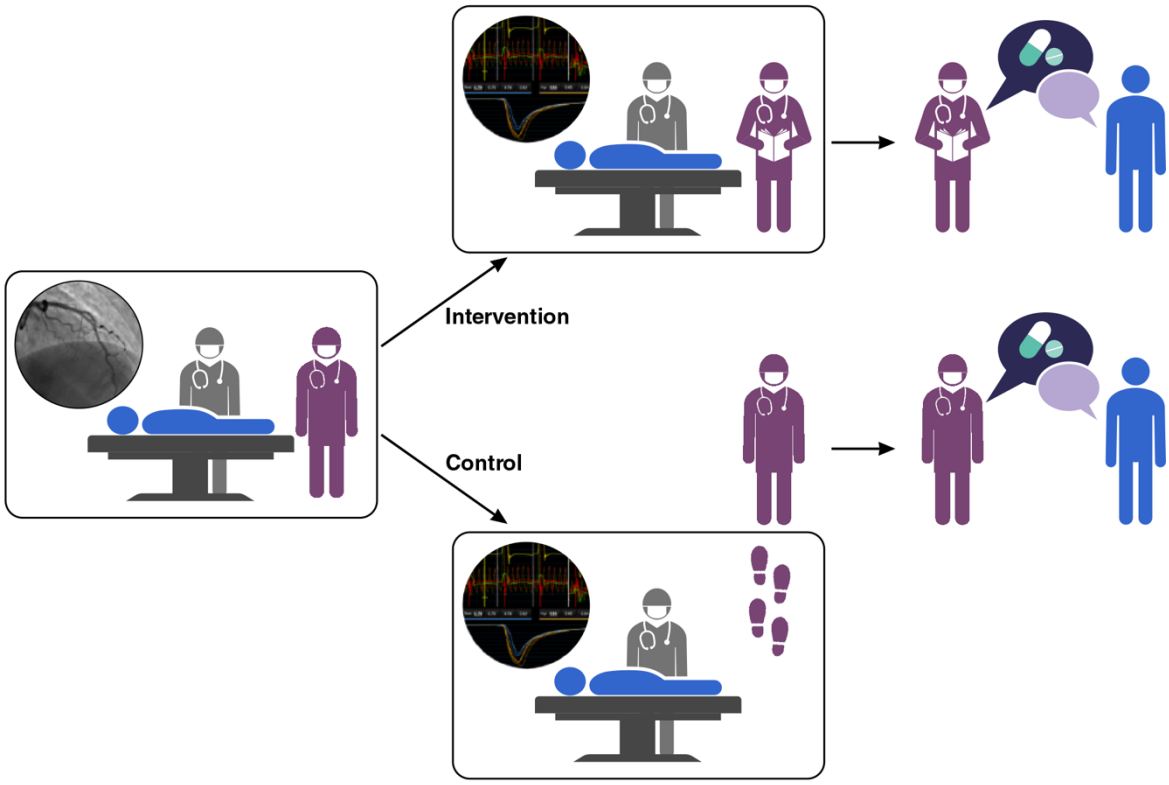
3. Lack of informed consent.
4. Exclusion for the randomised study only: Flow-limiting coronary disease defined by FFR≤0.80 in an artery with a diameter of more than 2.5mm.

2.1.4 Randomisation and implementation

The treatment plan was serially recorded by the attending cardiologist before and after coronary angiography but before randomisation in the catheter laboratory. The non-invasive CTCA findings were re-evaluated using invasive coronary angiography and guidewire-based FFR in any major coronary artery with CAD >50% of the reference vessel diameter. Participants who have flow-limiting CAD were considered for revascularisation by percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) surgery, as appropriate.

Patients (Figure 2-2, blue image) who had unobstructed coronary arteries by FFR criteria (FFR>0.80) were eligible for random assignment. Patients with obstructive coronary artery disease (FFR≤0.80) were not randomly assigned 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, randomisation was undertaken immediately after the angiogram and completion of FFR testing and before coronary function testing. Two cardiologists (Figure 2-2, black image) were in the catheter laboratory, including the research cardiologist who was unblinded. The randomisation involved whether the invasive cardiologist was provided with the results from the functional testing in the cardiac catheter laboratory by the research cardiologist.

Figure 2-2 – Blinding procedure in the catheter laboratory



A web-based randomisation 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 randomisation 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 CTCA indicated coronary artery disease, and sex.

In the control group, the coronary function measurements were acquired by the research cardiologist. The haemodynamic 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 2-2, footstep image) and returned when the coronary function tests had been acquired by the research cardiologist. The invasive cardiologist remained blinded 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 randomisation 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 protocolised interventions specified for each post-invasive diagnosis, and these protocols were identical between the 2 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 randomised group allocation.

2.1.5 Coronary function testing

The stratified medicine protocol[5] is supported by contemporary practice guidelines[82]. On practical grounds, the IDP was performed in a single major coronary artery to curtail the duration of the procedure. The left anterior descending (LAD) coronary artery was usually be the target vessel since it supplies the greatest amount of ventricular mass. The decision was at the discretion of the interventional cardiologist. If the IDP test results are normal and clinical suspicion remains high then additional arteries may be assessed, in line with clinical judgement.

The IDP involved a coronary thermodilution technique. A pressure- and temperature-sensitive diagnostic coronary guidewire was advanced into a major coronary artery (typically into the LAD) 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).

Incremental concentrations of acetylcholine (0.182 microgram/ml, 1.82 microgram/ml, 18.2 microgram/ml) were sequentially infused during 2-minute periods, followed by vasospasm provocation testing (acetylcholine bolus, 100 µg for left coronary artery or 50 µg right) and finally a 300 µg of glyceryl trinitrate. An angiogram was acquired at the end of each period.

2.1.5.1 Diagnostic guidewire test using thermodilution technique

Intra-arterial nitrate was administered during coronary angiography and to facilitate guidewire manipulation. Short-acting GTN (approximately 200 micrograms) was used instead of the longer-acting isosorbide dinitrate.

A PressureWire™ X Guidewire (Abbott Vascular, USA) and the Coroventis software (Coroventis Research, Sweden) were used for the diagnostic guidewire test.

The diagnostic guidewire approach provided information on:

1. Flow-limiting CAD (FFR, normal >0.80)
2. Vasodilator capacity of a coronary artery and its microcirculation (CFR, normal >2.5; grey-zone 2.0-2.5)
3. Vasodilator capacity of the microcirculation only (RRR< normal >2.0)
4. Microvascular resistance (IMR, normal >25)

We achieved hyperaemia with IV adenosine (140 µg/kg/min) for the coronary pressure/flow relationship to be linear. The LAD was preferred as it supplies more myocardium than any other coronary artery and coronary function measures may vary due to differences in heart muscle subtended by individual coronary arteries.

2.1.5.2 Pharmacological coronary reactivity testing using acetylcholine

Coronary reactivity testing with acetylcholine will provide information on the vasodilator capacity of the coronary artery and its microcirculation, and their propensity to spasm. A clinical response is reflected by concomitant symptoms and changes on the electrocardiogram (ECG) and angiogram. More specifically, the physiological responses include the occurrence of symptoms (i.e. chest

pain), ECG changes (i.e. ST-segment deviation), and abnormalities on the coronary angiogram, including a reduction in coronary artery diameter when measured by quantitative coronary analysis (QCA) or assessed visually, transient impairment in antegrade coronary flow, and a reduced blush. Endothelial dysfunction is diagnosed with a constrictor response to acetylcholine in the absence of chest symptoms and ECG changes.

Sequential infusions of increasing concentration of acetylcholine (0.182 microgram/ml, 1.82 microgram/ml, 18.2 microgram/ml) were administered using an automated infusion pump at 2ml/min for 2 minutes each. At the completion of each infusion, a 12-lead ECG and a coronary angiogram were acquired, along with confirmation of the presence or absence of symptoms with the patient.

Next, vasospasm provocation testing using an acetylcholine bolus (100 µg for left coronary artery or 50 µg for the right coronary artery) was performed. Finally, 300 µg of intracoronary glyceryl trinitrate was administered. A 12-lead ECG and coronary angiogram were acquired at the end of each period, as well as documentation of any resulting symptoms.

2.1.6 Endotypes

2.1.6.1 Definitions

The coronary function results were used by the cardiologist to assess for endotypes according to diagnostic criteria defined in guidelines[67,90,125] (Table 2-1). In the intervention group, the tests were used to stratify patients into sub-groups (endotypes: microvascular angina, vasospastic angina, both, or, non-cardiac chest pain). The diagnosis of a clinical endotype was linked to guideline management[67].

Table 2-1 - Endotypes according to guideline-defined diagnostic criteria

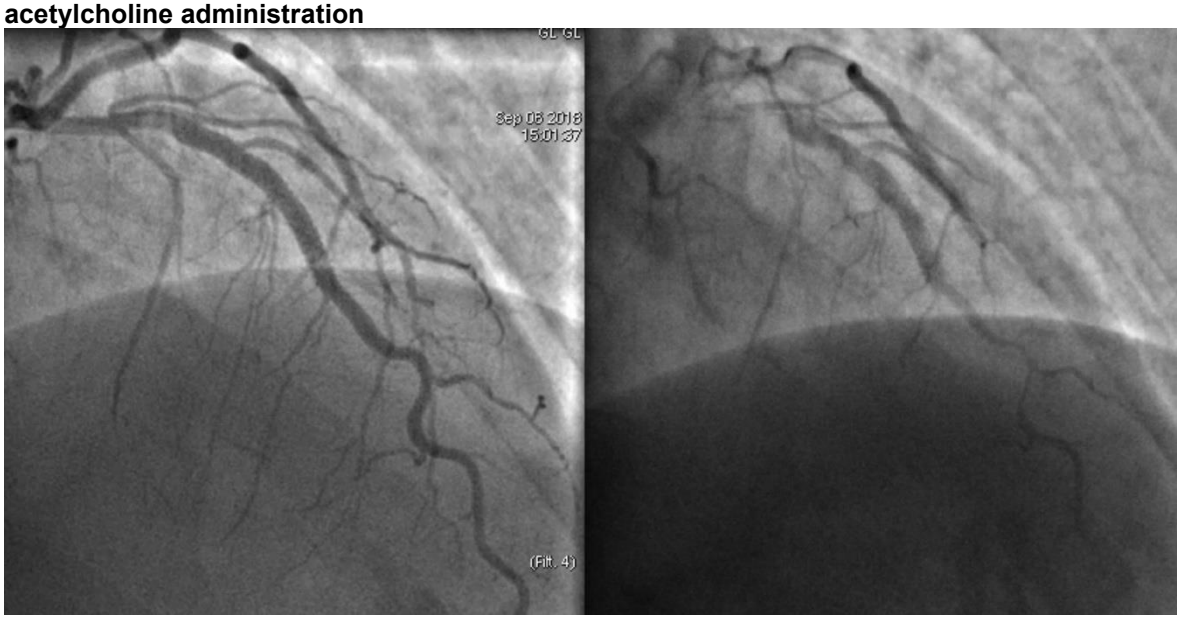
Diagnostic group		Outcome definitions
Microvascular angina	Increased microvascular resistance	IMR ≥ 25
	Reduced coronary vasorelaxation	CFR < 2

	Reduced microvasodilator capacity	RRR < 2 *This reflects the vasodilator capacity of the microcirculation to change from baseline to hyperaemia*
	Microvascular spasm	Angina with typical ischaemic ECG changes and epicardial coronary constriction <90% reduction in epicardial coronary artery diameter during ACh infusion. *This represents increased microvascular constriction.*
Vasospastic angina	Epicardial spasm	Epicardial coronary artery spasm (>90% reduction in coronary diameter) with symptoms and ST segment changes following intracoronary ACh in comparison with baseline resting condition following intracoronary GTN administration in any epicardial coronary artery segment.
Endothelial dysfunction	<u>Normal endothelial function</u>: %Δ >20% luminal vasodilation <u>Mild endothelial dysfunction</u>: %Δ ≤20% vasodilation - >20% vasoconstriction <u>Severe endothelial dysfunction</u>: %Δ ≥20% luminal vasoconstriction ** %Δ = percentage change from baseline in coronary lumen diameter, in response to the 2-minute infusion of intracoronary ACh*	
Obstructive epicardial stenosis	FFR ≤ 0.80	
Non-cardiac	FFR > 0.80 CFR ≥ 2 RRR ≥ 2 IMR < 25 No functional angina / spasm during ACh infusion	

IMR = index of microvascular resistance; CFR = coronary flow reserve; RRR = resistance reserve ratio; ECG = electrocardiogram; ACh = acetylcholine.

A diagnosis of vasospastic angina required that three conditions occur during acetylcholine testing: (i) clinically significant (≥90%) epicardial vasoconstriction (Figure 2-2), (ii) reproduction of the usual chest pain and, (iii) ischaemic ECG changes[125].

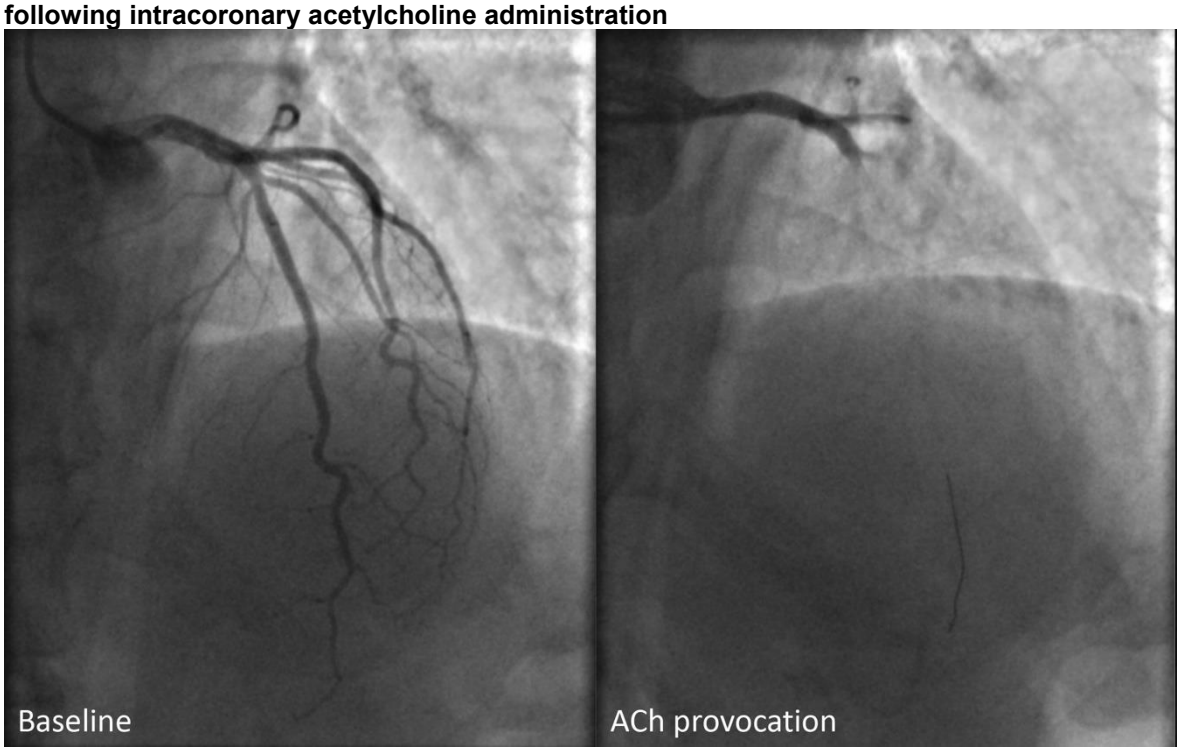
Figure 2-3 - Coronary angiogram showing focal vasospasm following intracoronary acetylcholine administration



Microvascular angina was defined according to the Coronary Vasomotion Disorders International Study Group (COVADIS) criteria[90]: symptoms of myocardial ischaemia, unobstructed coronary arteries and evidence of coronary microvascular dysfunction (any of abnormal IMR, CFR [Figure 2-3] or microvascular spasm to acetylcholine). A diagnosis of coronary microvascular spasm required provocation and reproduction of anginal symptoms, ischaemic ECG shifts, but no epicardial spasm during acetylcholine testing[90] (Figure 2-4).

Figure 2-4 - Abnormal CFR and IMR consistent with coronary microvascular dysfunction

Figure 2-5 - Coronary angiogram showing TIMI 0 flow in left anterior descending artery following intracoronary acetylcholine administration



A diagnosis of non-cardiac chest pain required no obstructive epicardial coronary artery disease (FFR>0.80) and an absence of evidence of any functional coronary disorder (CFR>2.0, IMR<25, and negative acetylcholine testing).

2.1.6.2 Adjudication of diagnosis

An independent panel of three clinicians adjudicated each case to finalise the diagnosis without pre-existing knowledge of the diagnosis made at the time of the IDP. The adjudicated process is performed systematically with a review of clinical history and complete IDP findings, including angiographic reviews.

2.1.7 Stratified medicine in intervention group

After randomisation 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 coronary angiography. The blinded cardiologist was provided with written guidance on prescription of evidence-based medical therapy and non-pharmacological (lifestyle) measures to control cardiovascular risk factors according to guideline targets[67]. Referral for cardiac rehabilitation was prioritised for patients with a new diagnosis of ischaemic heart disease. Standardised guidance letters were sent to the general practitioner and attending cardiologist with advice on tailoring and optimising

treatment. Standard care for participants in the control arm consisted of guideline-directed medical therapy. The attending cardiologist had discretion over the final treatment decisions in both groups.

2.1.8 Questionnaires

The Seattle Angina Questionnaire (SAQ) is a 19-item, self-administered, disease-specific measure of angina severity that is valid, reproducible and sensitive to change[123]. The SAQ quantifies patients' physical limitations caused by angina, the frequency of anginal episodes, 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 (SAQ-SS) averages the domains of angina limitation, frequency and quality of life to provide an overall metric of angina severity[123].

Health status was serially assessed using validated, self-administered questionnaires for quality of life using the 5-level version of the EuroQoL-5D (EQ-5D-5L). This is a widely used standardised instrument for measuring generic health status whereby higher scores represent better health-related quality of life (from −0.59 – 1.00 scale)[126,127]. We also recorded the Brief Illness Perception Questionnaire (B-IPQ)[128], screening for depression and anxiety (PHQ–4)[129] and the Treatment Satisfaction Questionnaire for Medication (TSQM-9)[130].

2.1.9 Follow up

The reporting timepoints were baseline, 6- and 12- months. However, the COVID-19 pandemic disrupted implementation of the protocol. Elective medical care was deferred, social restrictions were imposed, research staff were redeployed to clinical services and research activities in the hospitals were suspended for prolonged periods of varying durations. The study assessments were performed whenever feasible.

Follow-up assessments for adverse events were performed by site research staff who were blind to the baseline data and randomised group. Although the

research team included staff members who participated in the IDP, the coronary function test results were kept separately during follow up. This was upheld until all follow up data had been collected, at which point unblinding took place and the patients and their GP were informed of the IDP results.

At 6 months, patients were sent health status questionnaires, same as those completed at baseline. These were returned by post to the research team. At 12 months, patients were invited to return in person for a review to complete the same health status questionnaires as well as for clinical assessment and blood tests. Impact of the COVID-19 pandemic on the follow up timeline is discussed in the next section.

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 randomised group. The committee was independent of the investigators, funder and sponsor.

2.1.9.1 Impact of COVID-19 pandemic

Due to the restrictions placed on clinical research during the COVID-19 pandemic, there were multiple challenges to delivering this protocol and, notably, delays in obtaining follow up data. These restrictions impacted face-to-face consultations the most, and many patients were unable to be reviewed at the 12-month time point as originally planned. These patients were asked to return their completed PROMS by post to provide the following:

- Health status assessment (SAQ, EQ-5D-5L, BIPQ, PHQ-4, TSQM-9, DASI, IPAQ-SF)
- Drug therapy

These patients were requested to attend in person once the restrictions were lifted to provide the following:

- Weight, height and waist circumference
- Lifestyle factors (diet, smoking, weight, exercise)
- Adverse events evaluation and reporting (including for health economics)

- Blood samples (30 ml) for central laboratory test of cholesterol and lipid profile, hs-troponin, hs-CRP and NT-proBNP.

2.2 Statistical analysis

2.2.1 Sample size calculation

The primary analysis is the between-group comparison of the reclassification rate using logistic regression, adjusted for baseline characteristics associated with the likelihood of reclassification of the initial diagnosis. Pre-specified baseline characteristics include sex and smoking status. If this is not possible due to small numbers, logistic regression with fewer adjustment variables or Fisher's Exact test will be used as appropriate. A sample size of 115 per group will have 80% power to detect a between group difference of 15%, or 90% power to detect a difference of 20%, in the proportion of patients whose diagnosis is reclassified. To allow for any missing data, 250 patients will be randomised. If the coronary function test results are disclosed in the usual care group (operator preference), the plan before disclosure will be recorded.

If SAQ scores at 6 months can 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. This is a small difference but we anticipate that not all patients will have their therapy changed following disclosure of the IDP result. Using the coronary function data for the control (non-disclosure) group, we will carry out focused analyses of the sub-group of patients whose therapy might have been altered based on abnormal results. For example, if therapy would be altered in 50% of patients, the study will have 80% power to detect a difference in SAQ score of 0.60 SD units for these patients; if therapy is altered in 30% of patients, there will be 80% power to detect a between-group difference of 0.74 SD units. We anticipate loss-to-follow-up ≤15% of the participants. The sample size is suggested to be sufficiently large to limit imprecision and be clinically meaningful.

2.2.2 Statistical analysis of primary and secondary endpoints

Statistical analyses were performed according to a pre-specified Statistical Analysis Plan determined prior to database lock 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 summarised descriptively for the randomised population and each treatment group using counts and percentages for categorical variables and mean, standard deviation (SD), or median, 25th and 75th percentiles (Q1, Q3 respectively), depending on the distribution of the data. Categorical outcomes were compared between randomised groups using Fisher's Exact Test and continuous outcomes were compared between randomised 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 occurred out-with the pre-specified 6- and 12- month timepoints. The revised follow-up time-windows for the statistical analyses were 4 to 9 months, 9 to 18 months and greater than 18 months. If multiple visits occurred within a time-period then continuous data were averaged and the most recent response for categorical measures were adopted.

Primary and secondary continuous outcome measures recorded during baseline and follow-up visit windows were analysed and compared between randomised groups using a linear mixed-effects model, based on the lme4 package in R. The study utilised 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 randomised group, visit time-window (baseline, 4 to 9 months, 9 to 18 months or greater than 18 months), and adjustment variables age, sex, SIMD quintile and Rose Angina questionnaire result at baseline. 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. The intervention group effect estimate (between treatment group mean difference), 95% confidence interval (CI) and p-value are reported for outcomes at each follow-up time-window. 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 group treatment effect estimate and 95% CI back-transformed (between treatment group geometric mean difference).

2.3 Trial management and governance

The study was conducted according to observational (STROBE)[131], GCP[132] and CONSORT[133] guidelines. The study was coordinated by the Study Management Group that included those individuals responsible for the day-to-day management of the study including the Chief Investigator, Co-Investigators, Research Nurse and others as considered appropriate. The role of this group was to facilitate the progress of the study, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the study itself.

Clinical events identified as potentially relevant to the designated secondary health outcomes were assessed by a CEC. The CEC was independent of both the investigators and the funder/sponsor and is blinded regarding any information relating to the randomisation group. Study Monitoring is conducted by monitors on behalf of the Sponsor (NHS Golden Jubilee National Hospital). During monitoring assessments, informed consent forms and source clinical data were reviewed, as appropriate.

3 Patients with angina and no obstructive coronary artery disease on CT coronary angiography

3.1 Abstract

3.1.1 Objectives

To prospectively determine the prevalence of coronary vasomotion disease endotypes in a population of patients with angina with no obstructive coronary artery disease on computed tomography coronary angiography (CTCA).

3.1.2 Methods

Prospective cohort study at 3 regional centres of patients with angina referred for clinically-indicated CTCA showing no obstructive coronary artery disease. Enrolled patients underwent invasive angiography involving adjunctive coronary vascular function tests to assess for endotypes defined by guideline criteria.

3.1.3 Results

Between August 31, 2017 and September 9, 2020, 1552 outpatient patients referred for CTCA were screened. After CTCA, 250 (77.6%) of 322 eligible patients underwent invasive management. Nineteen (7.6%) patients were excluded due to obstructive coronary artery disease by angiography or FFR (≤0.80). Two hundred and thirty-one patients (92.4%) were randomised (n=115 Intervention group; n=116 Control group): mean age 55.7 years, 149 (64.5%) women, and 4.2% predicted 10-year likelihood of a coronary heart disease event. One hundred and twenty-seven (55.0%) patients had microvascular angina, 27 (11.7%) had vasospastic angina and 17 (7.4%) had both. Sixty patients (26.0%) had non-cardiac chest pain.

3.1.4 Conclusion

Angina with no obstructive coronary artery disease (ANOCA) occurred in three quarters of outpatients with suspected angina and no obstructive coronary artery disease. These patients may be overlooked by anatomical tests such as CTCA.

3.2 Introduction

Angina with no obstructive coronary artery disease (ANOCA), including microvascular angina and vasospastic angina, is caused by supply-demand

impairments of myocardial perfusion,[7,35,36] the pathophysiology includes a continuum of atherosclerosis and vasomotion disorders, and management is described in guidelines[67].

Following randomised trials[4,83,84,87,88], computed tomography coronary angiography (CTCA) is recommended as a first-line diagnostic test in patients with stable chest pain and no prior history of coronary heart disease[67,79]. SCOT-HEART reported that among patients referred to a chest pain clinic with suspected stable angina, CTCA added to standard care clarified the diagnosis of coronary heart disease and altered subsequent management[4]. At 5 years, CTCA-guided management reduced the rate of death from coronary heart disease or nonfatal myocardial infarction (MI)[85].

Stratified medicine is the identification of key subgroups of patients (endotypes) within a heterogeneous population; these endotypes being distinguishable by distinct mechanisms of disease and/or responses to therapy[120]. In the CorMicA trial, stratified medicine disclosed patients with ANOCA in a population undergoing invasive management for the investigation of suspected angina. The strategy is supported by a Class IIA guideline recommendation[67,134].

In the outpatient setting, the prevalence and management of ANOCA endotypes is uncertain. The aim of this prospective observational study was to investigate the prevalence of ANOCA endotypes in outpatients with suspected angina referred for CTCA. We hypothesised that ANOCA endotypes are prevalent.

3.3 Methods

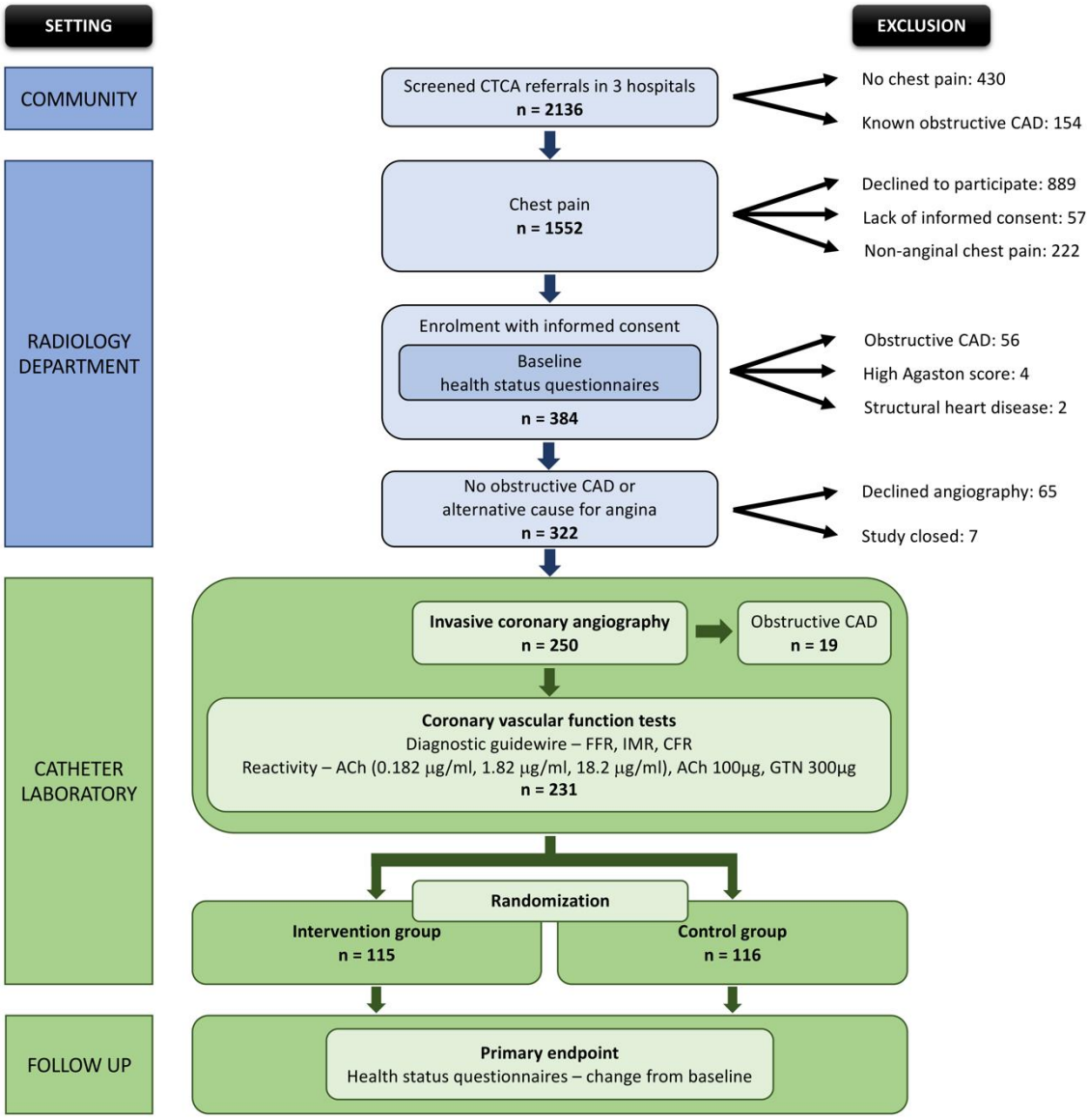
Full details of study methods are outlined in Chapter 2.

3.4 Results

3.4.1 Study population

Between August 31, 2017 and September 9, 2020, 1552 outpatients referred for the non-invasive assessment of coronary artery disease by CTCA were prospectively screened (Figure 3-1).

Figure 3-1 - Schematic study design: flow diagram



Two hundred and fifty (77.6%) of 322 eligible patients provided informed consent and subsequently underwent invasive management between October 6, 2017 and December 12, 2020. Nineteen (7.6%) of these patients were excluded during invasive management because of obstructive coronary artery disease by angiography or fractional flow reserve (≤0.80), which had been underestimated on CTCA.

3.4.2 Baseline characteristics

Two hundred and thirty-one patients (92.4%) with unobstructed coronary arteries were randomised (n=115 Intervention group; n=116 Control group) for a nested randomised controlled trial. The mean age at enrolment was 55.7 ± 8.5 years

(Table 3-1). The patients were mostly women (n = 149, 64.5%) and the predicted 10-year risk of a coronary heart disease event (based on the SCORE2 risk prediction algorithm[135]) was low (mean 4.2%). Despite that, cardiovascular risk factors were prevalent in this population. Half of the patients either were current smokers (47 [20.3%]) or had previously smoked 70 [30.3%]), 108 (46.8%) patients had hypertension, 133 (57.6%) patients dyslipidaemia, and 135 (58.4%) patients a family history of premature coronary artery disease. Obesity was common, with 113 (48.9%) patients having a body mass index (BMI) of ≥30 kg/m^2. The mean BMI was 30.8 ± 6.0 kg/m^2 and mean waist circumference was 95.9 ± 14.4 cm. Thirty-five (15.2%) patients had previously undergone coronary angiography (median 1.0, range [1.0, 4.0]) procedures, and 8 (3.5%) patients had had a previous myocardial infarction. Medicines for the prevention and treatment of angina were commonly prescribed – aspirin in 142 (61.5%) patients, statin 146 (63.2%), beta-blocker 144 (62.3%), calcium-channel blocker 58 (25.1%) and long-acting nitrate 36 (15.6%).

Table 3-1 - Baseline demographic and clinical characteristics for the randomised population

	Randomised		
	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			
Non smoker	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%)
Dyslipidaemia	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)

	Randomised		
	All (N=231)	**Intervention (N=115)**	**Control (N=116)**
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]
Cholesterol and lipid profile			
Total cholesterol, mmol/L	5.1 (1.1)	5.0 (1.1)	5.1 (1.2)
HDL cholesterol, mmol/L	1.3 [1.1, 1.6]	1.4 [1.1, 1.7]	1.3 [1.1, 1.6]
LDL cholesterol, mmol/L	2.8 (1.0)	2.8 (0.9)	2.8 (1.1)
Triglyceride, mmol/L	1.5 [1.1, 2.2]	1.5 [1.0, 2.1]	1.6 [1.2, 2.3]
HbA1c, mmol/mol	36.0 [34.0, 40.0]	36.5 [34.0, 39.2]	36.0 [34.0, 40.0]
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%)
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]
VAS score	70.0 [55.0, 80.0]	70.0 [60.0, 80.0]	70.0 [50.0, 80.0]
Stress electrocardiograph			
Performed	174	85	89

	Randomised		
	All (N=231)	**Intervention (N=115)**	**Control (N=116)**
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%)

Values are mean (SD), median [Q1, Q3] or n (%). *SCORE2 or SCORE2-Older Persons (≥70 years)
TIA = transient ischemic attack; BMI = body mass index; CVD = cardiovascular disease; HDL = high-density lipoprotein; LDL = low-density lipoprotein; ACE = angiotensin-converting enzyme; NYHA = New York Heart Association; VAS = visual analogue scale.

Half of the patients (48.9%) described atypical chest pain according to the Rose Angina Questionnaire. One hundred and sixty-four (71.0%) patients reported rest pain. Patients reported a median duration of 18 (9.0, 36.0) months of symptoms.

Most patients (75.3%) had undergone treadmill exercise tolerance testing prior to CTCA, 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.

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 (CCS) class I-II angina, with a mean SAQ summary score of (SAQSS) 54.8 ± 20.3.

3.4.3 CTCA

Most of the 250 CTCAs performed were of good to excellent quality, as assessed using a Likert scale by the reporting clinician (Table 3-2). One scan was deemed of poor quality but adequate for diagnostic purposes. However, the extent of CAD had been underestimated on CTCA and the patient was diagnosed with obstructive CAD on invasive coronary angiography. The procedural details for the CTCAs are shown in Table 3-2.

Table 3-2 - CTCA procedural characteristics

	Randomised population	

	All (N=231)	Intervention (N=115)	Control (N=116)	Obstructive CAD (N=19)
Scan quality				
Excellent	20 (8.7%)	8 (7.0%)	12 (10.3%)	0 (0.0%)
Good	161 (69.7%)	84 (73.0%)	77 (66.4%)	13 (68.4%)
Moderate	50 (21.6%)	23 (20.0%)	27 (23.3%)	5 (26.3%)
Poor	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.3%)
Non-diagnostic	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Acquisition sequence				
Prospective	212 (91.8%)	103 (89.6%)	109 (94.0%)	19 (100.0%)
Retrospective	19 (8.2%)	12 (10.4%)	7 (6.0%)	0 (0.0%)
Dose Length Product (mGy*cm)	172 [122, 29]	172 [116, 300]	170 [125, 270]	189 [158, 342]
Radiation dose (mSv)	4.6 [3.3, 7.8]	4.6 [3.1, 8.1]	4.6 [3.4, 7.3]	5.1 [4.3, 9.2]
Total contrast (ml)	105 (24)	107 (26)	104 (22)	112 (27)
Heart rhythm during scan				
Sinus	227 (98.3%)	113 (98.3%)	114 (98.3%)	19 (100.0%)
Atrial fibrillation	1 (0.4%)	0 (0.0%)	1 (0.9%)	0 (0.0%)
Ectopic	2 (0.9%)	1 (0.9%)	1 (0.9%)	0 (0.0%)
Paced	1 (0.4%)	1 (0.9%)	0 (0.0%)	0 (0.0%)
Heart rate during scan				
Mean (beats/min)	56.8 (7.4)	57.1 (7.3)	56.4 (7.5)	55.8 (6.3)
Range (beats/min)	2.0 [1.0, 4.0]	2.0 [1.0, 4.0]	2.0 [1.0, 4.0]	1.0 [1.0, 2.0]
IV metoprolol administered (mg)	20.0 [0.0, 40.0]	20.0 [8.5, 40.0]	20.0 [0.0, 42.5]	0.0 [0.0, 37.5]
SL GTN administered	229 (99.1%)	114 (99.1%)	115 (99.1%)	18 (94.7%)
Calcium (Agatston) score (HU)	1.5 [0.0, 55.2]	1.0 [0.0, 49.2]	2.0 [0.0, 56.8]	127.0 [49.5, 206.0]
Myocardial bridging	15 (6.5%)	7 (6.1%)	8 (6.9%)	0 (0.0%)
Normal coronary arteries	87 (37.7%)	44 (38.3%)	43 (37.1%)	0 (0.0%)

Values are mean (SD), median [Q1, Q3] or n (%).
There were no statistically significant differences between the procedural characteristics of the randomised groups.
IV = intravenous; SL = sublingual; GTN = glyceryl trinitrate.

Following standard practice, IV metoprolol was frequently administered (median 20.0 mg) to achieve an adequately low heart rate (mean heart rate in the randomised population was 56.8 ± 7.4 beats/minute). Sublingual glyceryl trinitrate was given in all but 2 patients who reported side effects and declined administration.

Normal coronary arteries were reported in 87 (37.7%) patients. Fifteen (6.5%) patients were reported to have myocardial bridging in the absence of obstructive CAD.

3.4.4 IDP

The interventional diagnostic procedure involving coronary function tests were successfully completed in 230 (99.6%) patients. Blinding in the control group was achieved in all 116 patients.

Invasive management is described in Table 3-3. The left anterior descending coronary artery was evaluated in 223 (96.5%) patients. The mean fractional flow reserve was 0.88 consistent with non-obstructive coronary artery disease. Approximately a third of the patients (74 patients, 32.0%) had angiographically normal coronary arteries, and 30 (13.0%) were noted to have myocardial bridging.

Table 3-3 Invasive management and diagnostic results

	Randomised		
	All (N=231)	**Intervention (N=115)**	**Control (N=116)**
Left anterior descending target artery	223 (96.5%)	112 (97.4%)	111 (95.7%)
Angiographically normal	74 (32.0%)	41 (35.7%)	33 (28.4%)
Invasive physiology			
LVEDP (mmHg)	7.0 [5.0, 10.0]	7.0 [4.0, 10.0]	8.0 [5.0, 10.0]
Resting transit time (seconds)	1.1 (0.5)	1.1 (0.5)	1.1 (0.5)
Hyperaemic transit time (seconds)	0.3 [0.2, 0.4]	0.3 [0.2, 0.4]	0.3 [0.2, 0.4]
FFR	0.88 (0.05)	0.88 (0.04)	0.88 (0.05)
IMR	20.0 [14.0, 28.0]	19.0 [14.0, 30.0]	21.0 [15.0, 30.0]
CFR	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%)
Endotypes			
MVA	127 (55.0%)	66 (57.4%)	61 (52.6%)
VSA	27 (11.7%)	15 (13.0%)	12 (10.3%)
Mixed MVA and VSA	17 (7.4%)	7 (6.1%)	10 (8.6%)
Normal coronary function	60 (26.0%)	27 (23.5%)	33 (28.4%)

	Randomised		
	All (N=231)	**Intervention (N=115)**	**Control (N=116)**
Values are mean (SD), median [Q1, Q3] or n (%). There were no statistically significant differences between the procedural characteristics of the randomised groups. LVEDP = left ventricular end diastolic pressure; FFR = fractional flow reserve; IMR = index of microvascular resistance; CFR = coronary flow reserve; MVA = microvascular angina; VSA = vasospastic angina.			

Compared to CTCA (Table 3-4), the median estimated effective radiation dose for IDP was lower (3.6 mSv vs 4.6 mSv). The total contrast used was higher in IDP (150 ± 37 ml) than in CTCA (105 ± 24 ml). Myocardial bridging was identified more frequently during IDP (13.0%) than on CTCA (6.5%) and more patients were reported as having normal coronary arteries on CTCA (87 [37.7%]) than during IDP (74 [32.0%]).

Table 3-4 - Comparison between CTCA and IDP

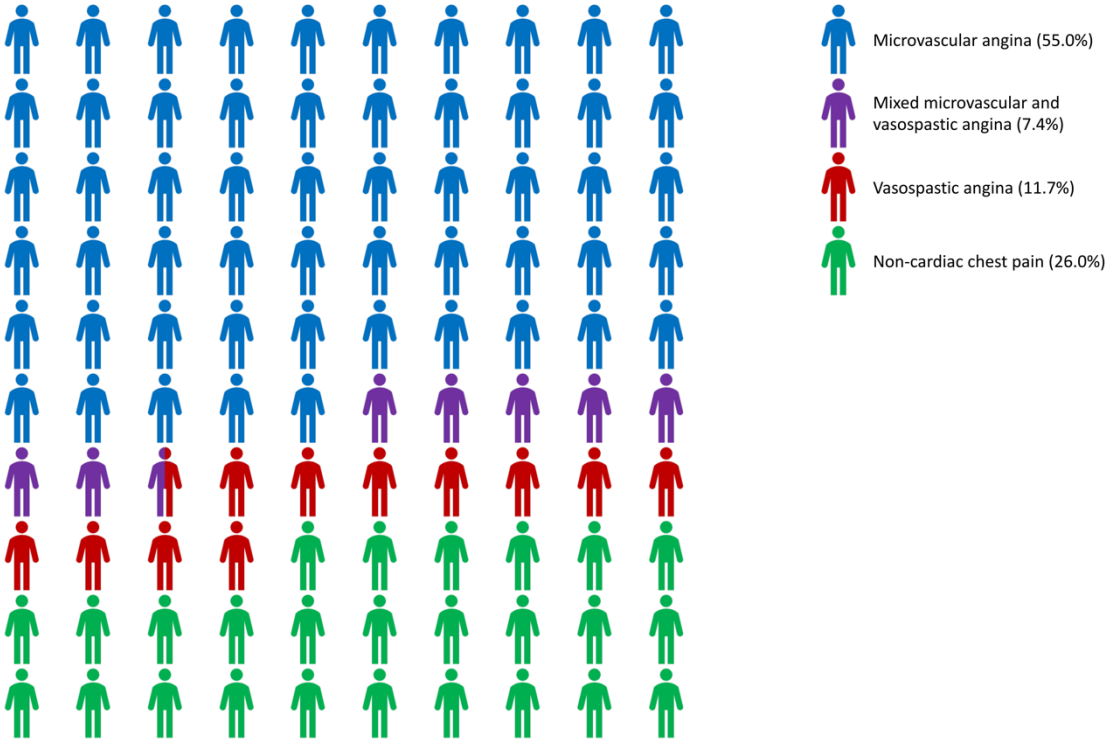
	Randomised population (N=231)	
	CTCA	IDP
Dose Length Product (mGy*cm)	172 [122, 29]	-
Dose Area Product (cGycm2)	-	22.60 [14.32, 34.16]
Radiation dose* (mSv)	4.6 [3.3, 7.8]	3.6 [2.3, 5.5]
Total contrast (ml)	105 (24)	150 (37)
Myocardial bridging	15 (6.5%)	30 (13.0%)
Normal coronary arteries	87 (37.7%)	74 (32.0%)
Values are mean (SD), median [Q1, Q3] or n (%). *Conversion for CTCA radiation from Dose Length Product (mGy*cm) to estimated effective dose (mSv) has been described in detail in Chapter 2. Conversion for IDP from total Dose Area Product (Gycm2) to estimated effective dose (mSv) is performed by multiplying the total DAP by the coefficient value of 0.16 mSv/Gycm2[121]. CTCA = computed tomography coronary angiography; IDP = interventional diagnostic procedure.		

3.4.5 ANOCA: disease endotypes

3.4.5.1 Prevalence of disease endotypes

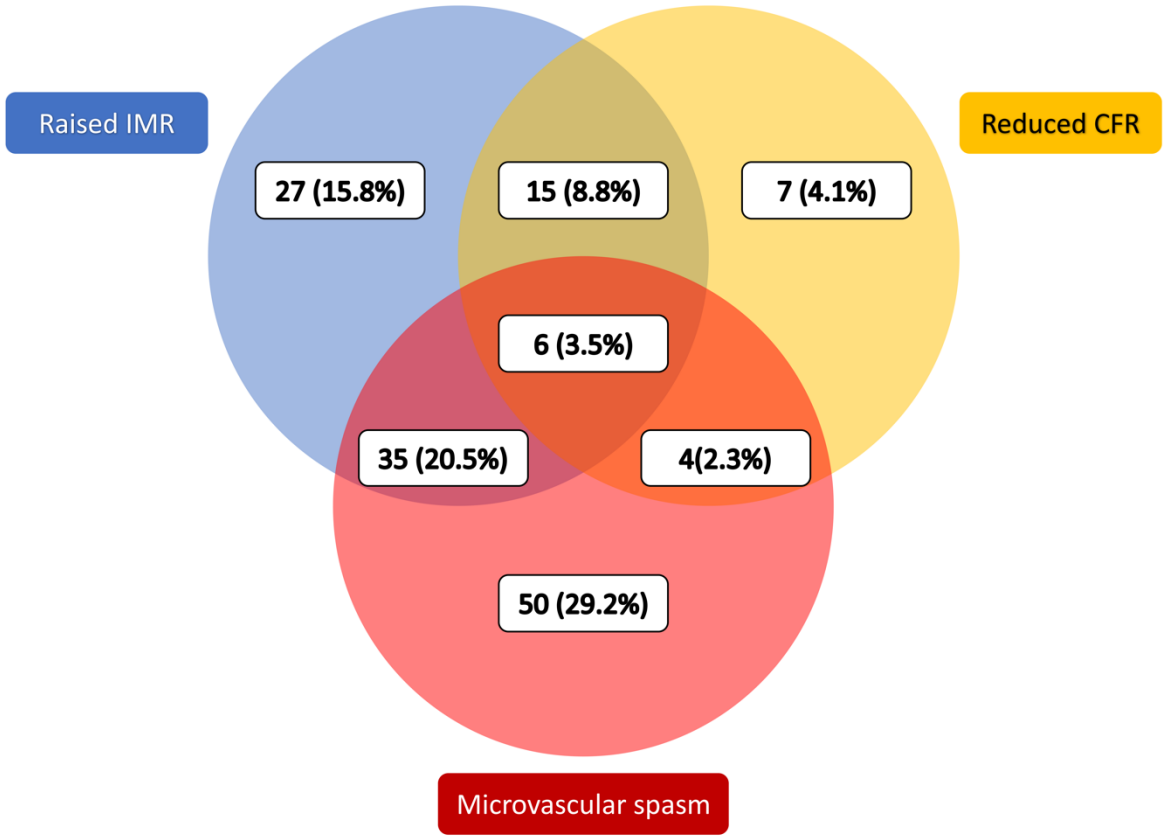
In the randomised population, 127 (55.0%) had microvascular angina, 27 (11.7%) had vasospastic angina and 17 (7.4%) patients had both microvascular and vasospastic angina (Figure 3-2). Sixty (26.0%) patients had non-cardiac chest pain.

Figure 3-2 - Prevalence of ANOCA endotypes



Of the 171 patients with invasive evidence of coronary microvascular dysfunction, 34 (19.9%) had either CFR<2 or IMR≥25, 15 (8.8%) had both, 89 (52.0%) had either CFR<2 or IMR≥25 and microvascular spasm to acetylcholine, and 6 (3.5%) had all three findings. Figure 3-3 shows the breakdown of endotypes within the ANOCA population.

Figure 3-3 - Breakdown of ANOCA endotypes



3.4.5.2 Differences between disease endotypes

Stratifying the baseline data according to the final diagnosis confirmed by the IDP revealed some differences between the endotypes (Table 3-5). The prevalence of menopause was higher in the female patients with ANOCA (92.9%) than those with non-cardiac chest pain (73.0%, p = 0.017). There were no other statistically significant differences in the clinical characteristics of the study population.

Table 3-5 - Patient characteristics, categorised by endotype

	ANOCA (N=171)	MVA (N=127)	VSA (N=27)	Mixed MVA and VSA (N=17)	Non-cardiac chest pain (N=60)	p-value
Age, years	56.2 (7.9)	57.0 (7.6)	53.0 (8.9)	55.5 (7.1)	54.0 (10.1)	p=0.045
Female	112 (65.6%)	89 (70.1%)	16 (59.3%)	7 (41.2%)	37 (61.7%)	p=0.098
Post-menopausal	104 (92.9%) [n=112]	83 (93.3%) [n=89]	14 (87.5%) [n=16]	7 (100.0%) [n=7]	27 (73.0%) [n=37]	p=0.017
BMI, kg/m^2	31.0 (5.9)	30.8 (6.2)	31.4 (5.3)	31.3 (5.0)	30.3 (6.1)	p=0.829
Smoking history						
Non smoker	82 (48.0%)	67 (52.8%)	7 (25.9%)	8 (47.1%)	32 (53.3%)	p=0.069
Ex-smoker	50 (29.2%)	34 (26.8%)	13 (48.1%)	3 (17.6%)	20 (33.3%)	

	ANOCA (N=171)	MVA (N=127)	VSA (N=27)	Mixed MVA and VSA (N=17)	Non-cardiac chest pain (N=60)	p-value
Current smoker	39 (22.8%)	26 (20.5%)	7 (25.9%)	6 (35.3%)	8 (13.3%)	
Previous stroke or TIA	9 (5.3%)	8 (6.3%)	1 (3.7%)	0 (0.0%)	4 (6.7%)	p=0.698
Hypertension	83 (48.5%)	61 (48.0%)	12 (44.4%)	10 (58.8%)	25 (41.7%)	p=0.624
Diabetes mellitus	20 (11.7%)	16 (12.6%)	3 (11.1%)	1 (5.9%)	6 (10.0%)	p=0.846
Dyslipidaemia	101 (59.1%)	78 (61.4%)	12 (44.4%)	11 (64.7%)	32 (53.3%)	p=0.325
Family history of CVD	104 (60.8%)	76 (59.8%)	17 (63.0%)	11 (64.7%)	31 (61.7%)	p=0.628
Typical angina	93 (54.4%)	66 (52.0%)	16 (59.3%)	11 (64.7%)	25 (41.7%)	p=0.250
Rest pain	119 (69.9%)	85 (64.6%)	24 (88.9%)	10 (58.8%)	45 (75.0%)	p=0.065
Stress electrocardiograph						
Normal	31 (18.1%)	22 (17.3%)	6 (22.2%)	3 (17.6%)	15 (25.0%)	p=0.595
Inconclusive	87 (50.9%)	63 (49.6%)	13 (48.1%)	11 (64.7%)	28 (46.7%)	
Abnormal	8 (4.7%)	5 (3.9%)	3 (11.1%)	0 (0.0%)	4 (6.7%)	
Angiographic characteristics						
Angiographically normal	49 (28.7%)	39 (30.7%)	7 (25.9%)	3 (17.6%)	25 (41.7%)	p=0.192
Myocardial bridging	22 (12.9%)	8 (6.3%)	11 (40.7%)	3 (17.6%)	8 (13.3%)	p<0.001
LVEDP (mmHg)	7.8 (4.0)	7.3 (3.8)	8.9 (4.4)	9.3 (3.8)	7.6 (4.0)	p=0.115

Values are mean (SD) or n (%).
ANOCA = angina with no obstructive coronary artery disease; MVA = microvascular angina; VSA = vasospastic angina; BMI = body mass index; TIA = transient ischemic attack; CVD = cardiovascular disease; LVEDP = left ventricular end diastolic pressure.

Angiographically, myocardial bridging was more prevalent in patients with VSA (11 patients [40.7%]) than in those with MVA (8 [6.3%]) or non-cardiac chest pain (8 [13.3%], p < 0.001). In patients with MVA, the mean IMR was 26.8 ± 13.5 and the mean CFR was 3.3 ± 1.6 (Table 3-6). The IMR is higher than in those without MVA (p<0.001) and the CFR is lower (p < 0.001). Microvascular spasm was most frequently provoked by an infusion of 18.2 mcg/ml acetylcholine, while epicardial vasospasm was most frequently provoked by an administration of 100 mcg acetylcholine bolus.

Table 3-6 - Invasive evaluation of randomised population, categorised by endotype

	MVA (N=127)	VSA (N=27)	Mixed MVA and VSA (N=17)	Non-cardiac chest pain (N=60)	p-value
Resting transit time (seconds)	1.1 (0.5)	0.9 (0.4)	1.2 (0.5)	1.0 (0.4)	p=0.011
Resting Pd/Pa	0.9 (0.0)	0.9 (0.0)	0.9 (0.0)	0.9 (0.0)	p=0.690

	MVA (N=127)	VSA (N=27)	Mixed MVA and VSA (N=17)	Non-cardiac chest pain (N=60)	p-value
Hyperaemic transit time (seconds)	0.4 (0.2)	0.2 (0.1)	0.5 (0.3)	0.2 (0.1)	p<0.001
FFR	0.88 (0.05)	0.88 (0.05)	0.87 (0.05)	0.87 (0.04)	p=0.332
IMR	27.1 (12.6)	16.0 (5.1)	32.4 (21.7)	15.6 (4.6)	p<0.001
IMR ≥ 25	73 (57.5%)	0 (0.0%)	11 (64.7%)	0 (0.0%)	p<0.001
CFR	3.32 (1.66)	4.06 (1.34)	2.91 (1.25)	4.71 (1.67)	p<0.001
CFR < 2.0	27 (21.3%)	0 (0.0%)	5 (29.4%)	0 (0.0%)	p<0.001
RRR	3.94 (1.88)	5.05 (1.93)	3.42 (1.39)	5.49 (1.90)	p<0.001
RRR < 2.0	12 (9.4%)	0 (0.0%)	2 (11.8%)	0 (0.0%)	p=0.012
Microvascular spasm					
ACh 0.182 mcg/ml	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	p<0.001
ACh 1.82 mcg/ml	10 (7.9%)	0 (0.0%)	4 (23.5%)	0 (0.0%)	
ACh 18.2 mcg/ml	61 (48.4%)	0 (0.0%)	6 (35.3%)	0 (0.0%)	
100 mcg ACh bolus	5 (4.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Epicardial vasospasm					
ACh 0.182 mcg/ml	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	p<0.001
ACh 1.82 mcg/ml	0 (0.0%)	1 (3.7%)	0 (0.0%)	0 (0.0%)	
ACh 18.2 mcg/ml	0 (0.0%)	8 (29.6%)	2 (11.8%)	0 (0.0%)	
100 mcg ACh bolus	0 (0.0%)	18 (66.7%)	15 (88.2%)	0 (0.0%)	

Values are mean (SD), median [Q1, Q3] or n (%).
MVA = microvascular angina; VSA = vasospastic angina; FFR = fractional flow reserve; IMR = index of microvascular resistance; CFR = coronary flow reserve; ACh = acetylcholine.

Baseline Seattle Angina Questionnaire (SAQ) results identified differences in the symptom burden between patients with ANOCA and those with non-cardiac chest pain (Table 3-7). Overall, the SAQSS was lower in patients with MVA (53.8 ± 21.0), VSA (45.4 ± 17.1) and mixed MVA and VSA (57.7 ± 18.5) than in patients with non-cardiac chest pain (60.7 ± 18.9, p = 0.011). This is mostly driven by corresponding lower SAQ physical limitation score (p = 0.014) and lower SAQ angina stability score (p = 0.022). There were no other differences in quality of life, psychological distress, treatment satisfaction or functional capacity as revealed by the health status questionnaires.

Table 3-7 - Health status questionnaire results at baseline, categorised by endotype

	MVA (N=127)	VSA (N=27)	Mixed MVA and VSA (N=17)	Non-cardiac chest pain (N=60)	p-value
SAQ					
Physical limitation domain score	55.5 (26.8)	42.0 (22.0)	57.6 (27.3)	62.5 (27.1)	p=0.014

	MVA (N=127)	VSA (N=27)	Mixed MVA and VSA (N=17)	Non-cardiac chest pain (N=60)	p-value
Angina stability domain score	47.8 (21.5)	39.8 (23.3)	55.9 (20.8)	54.7 (26.3)	p=0.022
Angina frequency domain score	62.4 (25.6)	59.3 (28.0)	62.9 (22.3)	71.0 (19.7)	p=0.144
Treatment satisfaction domain score	79.8 (18.1)	80.4 (15.8)	86.8 (16.7)	84.0 (18.8)	p=0.142
Quality of life domain score	44.1 (23.4)	35.0 (19.3)	52.5 (20.6)	48.3 (22.4)	p=0.037
Summary score	53.8 (21.0)	45.4 (17.1)	57.7 (18.5)	60.7 (18.9)	p=0.011
EQ-5D-5L					
Utility index score	0.61 (0.29)	0.56 (0.27)	0.69 (0.25)	0.64 (0.32)	p=0.187
Visual analogue scale	66.4 (20.0)	64.6 (16.7)	69.2 (14.5)	71.9 (19.2)	p=0.188
PHQ-4					
Anxiety domain score	1.8 (2.1)	2.0 (2.0)	1.6 (2.1)	2.0 (2.1)	p=0.785
Depression domain score	1.7 (2.1)	2.2 (1.9)	1.4 (1.7)	1.5 (2.0)	p=0.288
Total score	3.6 (4.0)	4.2 (3.8)	3.0 (3.4)	3.5 (3.8)	p=0.624
TSQM-9					
Effectiveness domain score	61.5 (19.1)	67.0 (16.9)	63.2 (19.1)	64.7 (20.2)	p=0.691
Convenience domain score	75.8 (19.2)	70.9 (18.8)	81.6 (13.8)	74.8 (20.4)	p=0.380
Global satisfaction domain score	61.8 (24.3)	63.9 (19.5)	69.2 (13.6)	67.7 (22.3)	p=0.493
BIPQ - Total score	48.8 (10.8)	53.1 (6.4)	47.7 (11.4)	47.7 (11.7)	p=0.288
DASI					
Total score	28.44 (16.57)	23.02 (15.49)	29.64 (17.98)	31.53 (16.28)	p=0.155
VO_2 peak (mL/kg/min)	21.83 (7.12)	19.50 (6.66)	22.35 (7.73)	23.16 (7.00)	p=0.155
IPAQ - level of activity					
Inactive	63 (50.0%)	13 (48.1%)	6 (35.3%)	27 (47.4%)	p=0.282
Minimally active	26 (20.6%)	9 (33.3%)	4 (23.5%)	19 (33.3%)	
HEPA active	37 (29.4%)	5 (18.5%)	7 (41.2%)	11 (19.3%)	

Values are mean (SD) or n (%).
SAQ = Seattle Angina Questionnaire; EQ-5D-5L = EuroQol-5D 5-level version; VAS = visual analogue score; PHQ-4 = Patient Health Questionnaire-4; TSQM-9 = abbreviated Treatment Satisfaction Questionnaire for Medication; BIPQ = Brief Illness Perception Questionnaire; DASI = Duke Activity Score Index; IPAQ = International Physical Activity Questionnaire – Short Form; HEPA = health-enhancing physical activity.

3.4.5.3 Comparison with patients with obstructive CAD

Nineteen patients were found to have obstructive CAD on invasive angiography and were excluded from the randomised controlled trial (Figure 3-4). They were entered into a registry and baseline information was recorded. Of the 19 patients, 12 had angiographically obstructive CAD by visual assessment and 7 had functionally obstructive CAD by pressure-wire assessment. One patient had triple vessel disease and subsequently had a coronary artery bypass graft (CABG) surgery, 12 patients had PCI, and 6 had medical therapy either due to a lack of target for intervention (e.g. diffuse atherosclerosis) or suboptimal medical therapy at presentation.

Figure 3-4 - Study profile showing registry patients

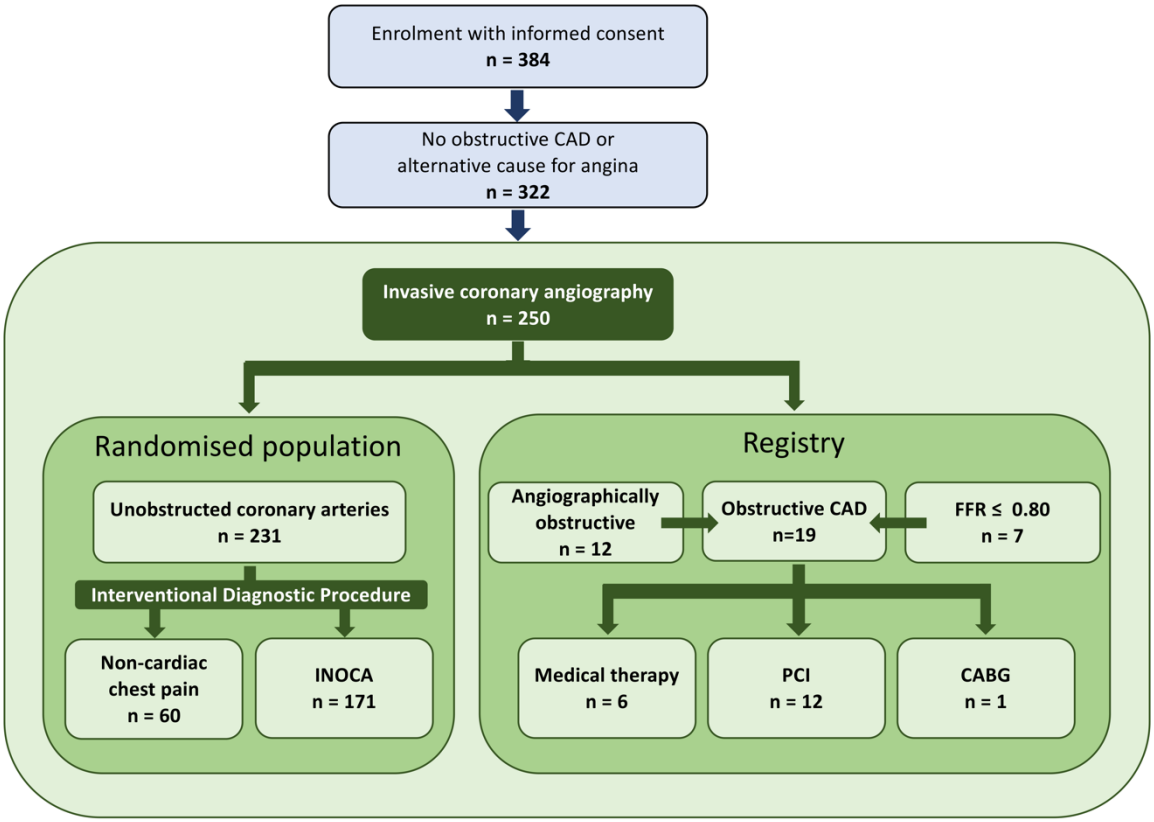


Table 3-8 shows the baseline characteristics of patients with ANOCA and those with obstructive CAD (Table 3-8). Although the diastolic blood pressure is higher in the obstructive CAD patients (82.8 ± 14.4 mmHg) than in the ANOCA patients (75.3 ± 11.6 mmHg, p = 0.010), there was no statistical difference in the systolic blood pressure between the two groups (136.5 ± 21.0 mmHg in the ANOCA population vs 141.3 ± 22.1 mmHg in the obstructive CAD population, p = 0.354). Patients with obstructive CAD were more likely to have had previous coronary

angiography (21.1% vs 18.7%, p = 0.033). There were no other differences in the prevalence of cardiovascular risk factors between the two groups.

Baseline therapy and symptom burden were both similar between the two groups.

Table 3-8 - Baseline characteristics by diagnosis (ANOCA vs obstructive CAD)

	Obstructive CAD (N=19)	ANOCA (N=171)	p-value
Age, years	54.2 (11.5)	56.0 (8.5)	p=0.398
Female	7 (36.8%)	105 (61.4%)	p=1.000
BMI, kg/m^2	31.8 (5.8)	30.8 (6.0)	p=0.500
BMI ≥ 30 kg/m^2	11	83 (48.5%)	p=0.617
Waist circumference, cm	98.6 (15.8)	96.2 (13.7)	p=0.484
Smoking status			
Non smoker	8 (42.1%)	88 (51.5%)	p=0.685
Ex-smoker	5 (26.3%)	52 (30.4%)	
Current smoker	6 (31.6%)	31 (18.1%)	
Previous coronary angiogram	4 (21.1%)	32 (18.7%)	p=0.033
Previous myocardial infarction	0 (0.0%)	8 (4.7%)	p=0.148
Previous stroke or TIA	2 (10.5%)	12 (7.0%)	p=0.636
Hypertension	12 (63.2%)	79 (46.2%)	p=0.811
Diabetes mellitus	4 (21.1%)	24 (14.0%)	p=1.000
Dyslipidaemia	14 (73.7%)	103 (60.2%)	p=0.329
Family history of CVD	10 (52.6%)	95 (55.6%)	p=0.629
Chronic obstructive pulmonary disease	3 (15.8%)	18 (10.5%)	p=0.447
Systolic blood pressure, mmHg	141.3 (22.1)	136.5 (21.0)	p=0.354
Diastolic blood pressure, mmHg	82.8 (14.4)	75.3 (11.6)	p=0.010
Charlson comorbidity index score	1.5 (1.2)	1.6 (1.1)	p=0.589
Cholesterol and lipid profile			
Total cholesterol, mmol/L	5.0 (1.4)	5.1 (1.1)	p=0.877
HDL cholesterol, mmol/L	1.3 (0.3)	1.4 (0.4)	p=0.114
LDL cholesterol, mmol/L	3.0 (1.3)	2.8 (1.0)	p=0.459
Triglyceride, mmol/L	1.8 (0.9)	1.8 (1.0)	p=0.877
HbA1c, mmol/mol	43.8 (15.1)	38.9 (9.8)	p=0.059
Preventive therapy			
Aspirin	14 (73.7%)	101 (59.1%)	p=0.136
Statin	14 (73.7%)	107 (62.6%)	p=0.804
ACE inhibitor or angiotensin receptor blocker	6 (31.6%)	45 (26.3%)	p=0.595
Angina medication			

	Obstructive CAD (N=19)	ANOCA (N=171)	p-value
Beta-blocker	10 (52.6%)	104 (60.8%)	p=0.327
Calcium-channel blocker	7 (36.8%)	45 (26.3%)	p=0.785
Nitrates	5 (26.3%)	26 (15.2%)	p=0.510
Nicorandil	0 (0.0%)	13 (7.6%)	p=0.369
NYHA class			
I	5 (26.3%)	47 (27.5%)	p=0.087
II	13 (68.4%)	115 (67.3%)	
III	1 (5.3%)	9 (5.3%)	
Patient Rose Angina Questionnaire			
Definite (typical) angina	12 (63.2%)	91 (53.2%)	p=1.000
Probable (atypical) angina	7 (36.8%)	80 (46.8%)	
Non-anginal pain	0 (0.0%)	0 (0.0%)	
Seattle Angina Questionnaire			
Angina summary score	57.0 (20.1)	53.6 (22.2)	p=0.549
Angina limitation	58.7 (26.5)	53.5 (26.5)	p=0.438
Angina stability	54.0 (20.9)	47.4 (21.9)	p=0.213
Angina frequency	62.6 (22.1)	61.9 (25.6)	p=0.909
Angina treatment satisfaction	80.4 (12.8)	80.6 (17.6)	p=0.957
Angina quality of life	44.1 (18.6)	43.5 (22.8)	p=0.917
Stress electrocardiograph			
Performed	14 (73.7%)	130 (76.0%)	p=0.448
Normal	4 (28.6%)	31 (23.8%)	p=0.746
Inconclusive	7 (50.0%)	91 (70.0%)	
Abnormal	2 (14.3%)	8 (6.2%)	

Values are mean (SD), median [Q1, Q3] or n (%). *SCORE2 or SCORE2-Older Persons (≥70 years)
CAD = coronary artery disease; ANOCA = angina and no obstructive coronary artery disease; TIA = transient ischemic attack; BMI = body mass index; CVD = cardiovascular disease; HDL = high-density lipoprotein; LDL = low-density lipoprotein; ACE = angiotensin-converting enzyme; NYHA = New York Heart Association.

3.4.6 Procedure-related events

Two patients received coronary 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 and one patient received intravenous amiodarone and remained in hospital overnight.

3.5 Discussion

In this study of outpatients with suspected angina and no obstructive coronary artery disease, an IDP consisting of invasive coronary angiography, diagnostic guidewire test and coronary reactivity testing with acetylcholine was performed to investigate the prevalence of ANOCA. The main findings were: 1) 74.0% of patients with angina and no obstructive CAD identified on CTCA had ANOCA, and 2) microvascular angina and vasospastic angina are prevalent and can co-exist but differ in certain patient characteristics.

ANOCA is common in patients with angina and no obstructive CAD on CTCA

Almost three quarters of this ambulatory population had microvascular angina and/or vasospastic angina that had not been diagnosed based on CTCA-guided management. This is consistent with observations in the CorMicA trial[5], which included patients with angina referred for invasive coronary angiography, downstream in the care pathway. In this study, 74.3% of patients with ANOCA had isolated microvascular angina, 15.8% had vasospastic angina, and 10.0% had mixed microvascular and vasospastic angina.

In the SCOT-HEART trial, anginal symptoms and quality of life[86] improved less in the CTCA-guided group. The prevalence of coronary microvascular dysfunction in this population was unknown since the protocol did not include quantitative non-invasive tests of myocardial ischaemia and/or invasive coronary function tests. One explanation could be that in the CTCA 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 CTCA-guided management have involved assessments of coronary vasomotion[4,83,84,86-88], and the prevalence of clinical endotypes of ANOCA in patients with angina (or ischaemic symptoms) and no obstructive coronary artery disease is unknown. This study is designed to answer this question and has confirmed the high prevalence of ANOCA in a similar patient population, suggesting that there is a significant proportion of patients who would not be adequately managed with a CTCA to exclude obstructive CAD.

Differences in patient characteristics

Most striking is that compared to patients with non-cardiac chest pain, patients with ANOCA, especially those with vasospastic angina, have a higher burden of angina as revealed by their SAQ scores. The CorMicA trial had also reported that the angina burden in the ANOCA cohort in their randomised population is comparable to the obstructive CAD cohort in their registry[5]. Although complications of invasive management were uncommon, two patients (0.8%) had a coronary artery dissection necessitating percutaneous coronary intervention, calling into question the safety of a routine invasive strategy. Given that patients with ANOCA have greater symptom burden, this study would suggest that only patients identified as having more significant angina be referred onwards for invasive coronary angiography +/- coronary function testing.

Surprisingly, there is no statistical difference in the sex distribution between patients with ANOCA and those with non-cardiac chest pain. ANOCA has long been viewed as a "woman's problem"[136] and our findings suggest that this notion might need reconsideration. Certainly, a systematic review[137] of patients presenting with suspected myocardial infarction and non-obstructive coronary arteries (MINOCA) showed that although these patients were more likely to be female compared to patients with myocardial infarction due to obstructive CAD, 60% of the patients with MINOCA were men.

In the female population, the prevalence of menopause was noted to be higher in patients with microvascular angina than those with vasospastic angina and non-cardiac chest pain. There were no other statistically significant differences in the clinical characteristics of the study population, including their cardiac risk factor profile and non-invasive investigations. It has been observed that women with microvascular angina are often menopausal[138]. Oestrogen deficiency may be a trigger but the question if oestrogen replacement therapy is a therapeutic option for these patients remains to be answered.

In the ANOCA population, myocardial bridging was observed more frequently in patients with vasospastic angina. The diagnosis of vasospastic angina requires the administration of acetylcholine, which is not readily available in most catheter laboratories in the country. The correlation between myocardial

bridging and vasospastic angina suggests that it might be practical to trial empirical treatment for vasospastic angina in ANOCA cases where myocardial bridging was found on coronary angiography.

Comparisons with obstructive CAD

In our study, patients with ANOCA have similar prevalence of cardiovascular risk factors as patients with CAD. This is consistent with findings from other studies[137]. Furthermore, at baseline, there was no difference in their angina burden as revealed by their SAQ scores. With comparable risk factor profile and symptom burden to obstructive CAD, ANOCA remains an under-recognised area of unmet need.

Strengths and limitations

This study has several strengths. Firstly, enrolment across three regional centres providing care to most of the west of Scotland (population 3 million) over a wide and diverse geographic area with an all-comer approach ensures the generalisability of these findings. Secondly, invasive characterisation of ANOCA endotypes by the IDP was performed using established internationally-standardised diagnostic criteria[90,125]. Thirdly, it builds upon a pilot study[5] with a larger sample size and a patient population that is higher in the care pathway.

There are some limitations to this study. Firstly, the threshold parameters for coronary microvascular indices (CFR/IMR/response to acetylcholine) reflect a physiological continuum but binary cut-offs had been adopted for the IDP test results. Although imperfect, these values are in line with diagnostic thresholds. Secondly, it is impossible to provide healthy controls to validate the findings of the IDP and the subsequent diagnoses. We recognise that abnormal coronary microvascular function may not cause or correspond with angina symptoms and therefore the observed abnormal IDP results may be incidental findings. The prevalence of abnormal coronary microvascular function in normal, asymptomatic patients (healthy controls) is unknown. To minimise false positives in the study, an independent adjudication panel reviewed each case to finalise the diagnosis.

Conclusion

Anatomical tests such as CTCA and invasive coronary angiography are unable to detect coronary microvascular disease. ANOCA endotypes are very common in outpatients with angina and no obstructive coronary artery disease on CTCA, and the clinical implication is that missed diagnoses, potentially leading to suboptimal management, occurred in three quarters of patients in this pathway.

4 Effect of stratified medicine guided by the Interventional Diagnostic Procedure on diagnosis and treatment

4.1 Abstract

4.1.1 Objectives

To investigate the reclassification of the initial diagnosis (of coronary vasomotion endotypes) based on the results of the interventional diagnostic procedure (IDP) and the corresponding change in management.

4.1.2 Methods

Patients with angina and unobstructed coronary arteries on computed tomography coronary angiography (CTCA) underwent an IDP as part of the study. They were randomised 1:1 to the intervention group (stratified medicine informed by the coronary function tests) or blinded control group (angiography-guided management. The attending cardiologist completed a questionnaire detailing the diagnosis, related certainty, and management plan before the IDP and again following the IDP (with the results in the intervention group, and without in the control group).

4.1.3 Results

Following the IDP, the frequency of a diagnosis of angina due to a coronary vasomotor disorder increased from approximately 50% in the intervention group (to 76.5%) but not in the control group (49.1%). The clinician's certainty of diagnosis improved in the intervention group compared to baseline, which was significantly higher than in the control group ($p < 0.001$). In the intervention group, prescription of antianginal therapy for disorders of coronary function increased post- versus pre-randomization (76.5% vs 41.4%, $p < 0.001$). Prescription of preventative therapy was similar in the intervention and control groups.

4.1.4 Conclusion

Stratified medicine involving the IDP increased the diagnosis of ANOCA by 27.8% in the intervention group. This is accompanied by an improvement in certainty of diagnosis – 88.7% of clinicians were certain of the diagnosis compared to 15.7%

before the IDP. Prescription of antianginal therapy increased in the intervention group.

4.2 Introduction

Angina with no obstructive coronary artery disease (ANOCA), including microvascular angina and vasospastic angina, is part of a diverse spectrum of chronic coronary syndrome. Tests are now available for the evaluation of coronary microvascular function and the management of ANOCA has been described in guidelines[67], but the underdiagnosis and resulting undertreatment of these conditions in contemporary practice remain[139,140].

The CorMicA trial showed that stratified medicine, including an interventional diagnostic procedure (IDP) with linked medical therapy, is feasible and increases the diagnosis of ANOCA endotypes[5]. This was also observed in this study, as described in Chapter 3. It suggested that a personalised approach guided by the IDP can help optimise treatment strategy and improve symptom burden and quality of life.

The first step towards establishing the effect of stratified medicine on patient well-being and long-term prognosis is identifying and appropriately diagnosing patients with ANOCA. Having demonstrated the prevalence of ANOCA endotypes in outpatients with suspected angina referred for CTCA, this study aimed to assess the effect of stratified medicine guided by invasive coronary function tests on the management of this patient population.

4.3 Methods

Full details of study methods are outlined in Chapter 2.

4.4 Results

4.4.1 Feasibility and blinding

The invasive coronary function tests were successfully completed in 230 (99.6%) patients. Blinding in the control group was achieved in all 116 patients.

4.4.2 Diagnostic utility

Prior to randomisation, 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 4-1). Following randomisation, the frequency of this diagnosis increased in the intervention group (76.5%) but not in the control group. The frequency of a non-cardiac chest pain diagnosis was similar between the groups prior to randomisation (51.3% vs 50.9%) but was less common in the intervention group after randomisation (23.5% vs 50.9%, $p < 0.001$). Following randomisation, the clinician's certainty of diagnosis improved in the intervention group (102 [88.7%]) compared to 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 (Figure 4-1) occurred in 3 (2.6%) patients in the intervention group and 75 (64.7%) patients in the control group ($p < 0.001$).

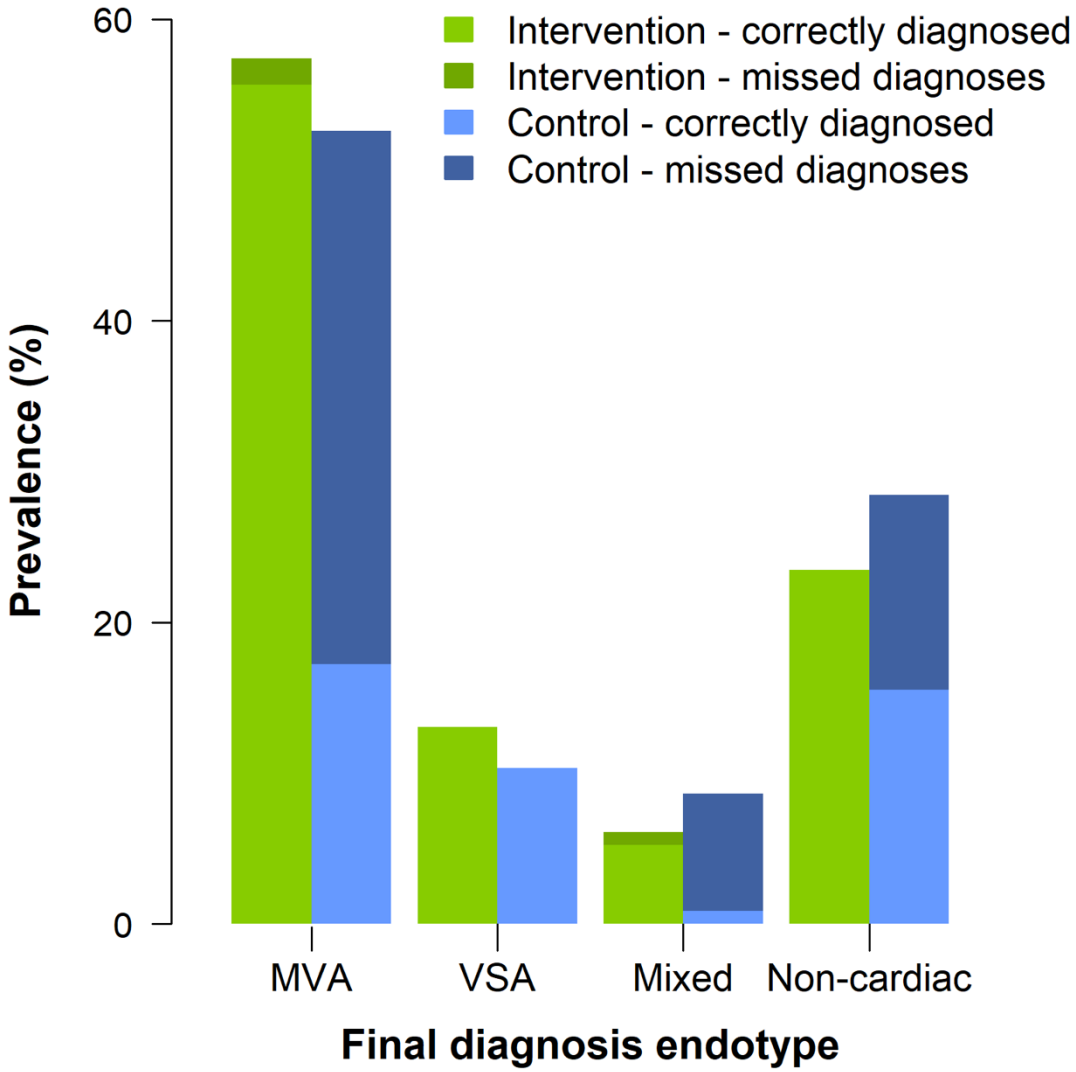
Table 4-1 - Diagnostic utility: change in diagnosis and certainty of diagnosis

	Randomised		
	Intervention (N=115)	**Control (N=116)**	**p-value**
Baseline			
Diagnosis of MVA	41 (35.7%)	40 (34.5%)	p=0.891
Diagnosis of VSA	3 (2.6%)	6 (5.2%)	p=0.499
Diagnosis of Mixed (MVA & VSA)	7 (6.1%)	9 (7.8%)	p=0.796
Diagnosis of non-cardiac chest pain	59 (51.3%)	59 (50.9%)	p=1.000
Certainty of diagnosis			
Possibly	8 (7.0%)	7 (6.0%)	p=0.943
Probably	89 (77.4%)	89 (76.7%)	
Certain	18 (15.7%)	20 (17.2%)	
Post-randomisation			
MVA			
Diagnosis of MVA	64 (55.7%)	40 (34.5%)	p=0.001
Change in diagnosis	47 (40.9%)	0 (0%)	-
VSA			
Diagnosis of VSA	17 (14.8%)	6 (5.2%)	p=0.016
Change in diagnosis	20 (17.4%)	0 (0%)	-
Mixed (MVA & VSA)			
Diagnosis of Mixed (MVA & VSA)	7 (6.1%)	9 (7.8%)	p=0.796
Change in diagnosis	14 (12.2%)	0 (0%)	-
Non-cardiac chest pain			

	Randomised		
	Intervention (N=115)	**Control (N=116)**	**p-value**
Diagnosis of non-cardiac chest pain	27 (23.5%)	59 (50.9%)	p<0.001
Change in diagnosis	60 (52.2%)	0 (0%)	-
Missed diagnosis	3 (2.6%)	75 (64.7%)	p<0.001
Certainty of diagnosis			
Possibly	0 (0.0%)	7 (6.0%)	p<0.001
Probably	13 (11.3%)	89 (76.7%)	
Certain	102 (88.7%)	20 (17.2%)	

Values are n (%) unless otherwise specified. P-values are from the Fisher's Exact test or the Mann-Whitney U test for continuous variables.
MVA = microvascular angina; VSA = vasospastic angina.

Figure 4-1 - Prevalence of missed diagnosis, by randomised group and diagnosis



4.4.3 Clinical utility

In the intervention group, prescription of antianginal therapy for disorders of coronary function increased post- versus pre-randomisation (76.5% vs 41.4%, p <

0.001 (Table 4-2). 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) at their final follow-up visit (median of 608 [389, 829] days post-randomisation) (Table 4-3). There was no difference in the frequency of preventative therapy prescription. Compared to 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.

Table 4-2 - Clinical utility: change in therapy and management plan

	Randomised		
	Intervention (N=115)	**Control (N=116)**	**p-value**
Preventative therapy	92 (80.0%)	88 (75.9%)	0.526
Standard angina therapy	0 (0.0%)	13 (11.2%)	<0.001
Angina therapy for MVA/VSA	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

Values are n (%) unless otherwise specified. P-values are from the Fisher's Exact test or the Mann-Whitney U test for continuous variables.
MVA = microvascular angina; VSA = vasospastic angina.

Table 4-3 - Cardiovascular therapy at follow up

	Intervention		**Control**		**Estimate (95% CI), p-value**
	At baseline (N=115)	**At follow up (N=91)**	**At baseline (N=116)**	**At follow up (N=95)**	
Preventive therapy					
Aspirin	74 (64.3%)	45 (49.5%)	68 (58.6%)	48 (50.5%)	p=1.000
Statin	76 (66.1%)	74 (81.3%)	70 (60.3%)	68 (71.6%)	p=0.122
ACE inhibitor or angiotensin receptor blocker	33 (28.7%)	44 (48.4%)	35 (30.2%)	33 (34.7%)	p=0.103
Angina medication					
Beta-blocker	67 (58.3%)	28 (30.8%)	77 (66.4%)	50 (52.6%)	p=0.002
Calcium-channel blocker	27 (23.5%)	48 (52.7%)	31 (26.7%)	24 (25.3%)	p<0.001
Nitrates	18 (15.7%)	25 (27.5%)	18 (15.5%)	13 (13.7%)	p=0.029
Nicorandil	7 (6.1%)	15 (16.5%)	7 (6.0%)	7 (7.4%)	p=0.072

Values are 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.

4.5 Discussion

Stratified medicine guided by an IDP to evaluate coronary microvascular function changed the initial diagnosis in 79 (68.7%) of patients in the intervention group and improved the attending cardiologist's certainty of the diagnosis. It also led to an increase in the frequency of a diagnosis of microvascular and/or vasospastic angina in the intervention group (from 48.7% to 76.5%), which was not observed in the control group (49.1%). The frequency of prescription of angina therapy for disorders of coronary function increased in the intervention group and was higher in the intervention group (76.5%) than in the control group (41.4%).

The underlying pathology of myocardial ischaemic syndromes includes both obstructive disease in the epicardial coronary arteries, disorders of the coronary microvasculature, and coronary spasm, yet diagnostic and therapeutic resources have traditionally focused on anatomically obstructive epicardial coronary disease. The underdiagnosis and undertreatment of patients with ANOCA[139,140] is an issue that needs to be addressed. Research in recent years[5,19,35,141,142] have shed light onto the importance of the recognition of ANOCA as a possible diagnosis in patients with chest symptoms and subsequent consensus guidelines[67,134] have reflected this. This study strengthens this argument by highlighting the high prevalence of ANOCA endotypes in a low-risk population of patients with suspected angina, patients who in all likelihood would have been labelled as having non-cardiac chest pain in contemporary practice. The adoption of the IDP allows clinicians to make a more informed and accurate diagnosis with a higher degree of certainty, which is the first step in a more patient-focused management.

There was an increase in frequency of prescription of angina therapy, predominantly calcium-channel blockers and long-acting nitrates. These are angina medications that have traditionally been used for patients with coronary microvascular disease due to their vasodilatory effects, although there have been conflicting results in clinical trials[72]. Of note, there was a reduction in the frequency of beta-blocker prescription, which may reflect the high prevalence of microvascular spasm in the MVA cohort in addition to VSA. Whereas the

effectiveness of medical therapy for obstructive CAD has been validated[65,143], the effect of these angina medications on symptomatic relief in patients with ANOCA requires further research.

In conclusion, stratified medicine guided by an IDP increases the frequency of diagnosis of ANOCA endotypes and the level of diagnostic certainty, with a corresponding increase in the prescription of anginal therapy specifically for coronary microvascular disease. Further research in required to determine their effects on symptom burden and long-term prognosis.

5 Effect of stratified medicine guided by the Interventional Diagnostic Procedure on patient well being

5.1 Abstract

5.1.1 Objectives

To assess whether stratified medicine guided by an interventional diagnostic procedure (IDP) investigating the prevalence of angina and no obstructive coronary artery disease (ANOCA) improves health status in patients with angina referred for computed tomography coronary angiography (CTCA)

5.1.2 Methods

A prospective, multi-centre, sham-controlled, blinded, randomised trial of stratified medicine was undertaken (NCT03477890). Patients undergoing CTCA for the investigation of suspected coronary artery disease in whom obstructive coronary artery disease were excluded were eligible for the study. Enrolled patients underwent an IDP. They were randomised 1:1 to the intervention group (stratified medicine informed by the coronary function tests) or blinded control group (angiography-guided management.

The primary outcome was the mean within-individual change in SAQ Summary Score (SAQSS) during follow-up. Patient reported outcome measures included the 5-level EQ-5D health-related (EQ-5D-5L) quality of life questionnaire, the Brief Illness Perception Questionnaire (BIPQ), the Patient Health Questionnaire-4 (PHQ-4), the Duke Activity Status Index (DASI) and the Treatment Satisfaction Questionnaire for Medication (TSQM-9).

5.1.3 Results

Patients were randomised between October 6, 2017 and December 10, 2020. Follow up continued until May 27, 2022. The median follow-up duration was 19.9 (12.6, 26.9) months. 111 patients (48.1%) participated in the study during the pandemic.

Baseline SAQSS were similar in both groups (55.5 $\pm$ 19.9 in the Intervention Group and 54.1 $\pm$ 20.7 in the Control Group). At 4 – 9 months and 9 – 18 months, the SAQSS in the Intervention vs. Control groups were 59.2 $\pm$ 24.2 (a change of 2.3 $\pm$ 16.2 from baseline) vs. 60.4 $\pm$ 23.9 (a change of 4.6 $\pm$ 16.4 from baseline)

and 63.7 ± 23.5 (a change of 4.7 ± 14.7 from baseline) vs. 66.0 ± 19.3 (a change of 7.9 ± 17.1 from baseline), respectively, and not different between the groups (p=0.36). Treatment satisfaction for convenience was higher in the intervention group at 9 to 18 months (82.6 ± 17.2 vs 73.3 ± 21.4, p = 0.002) and for global satisfaction at 9 to 18 months (69.9 ± 22.8 vs 61.7 ± 26.9, p=0.013). Most patients (75.3%) did not comply with the timelines of the protocol during the pandemic.

5.1.4 Conclusion

Despite identifying patients with microvascular and/or vasospastic angina, stratified medicine, consisting of an interventional diagnostic procedure with linked medical therapy, did not improve angina in patients with no obstructive coronary artery disease.

5.2 Introduction

Angina and no obstructive coronary artery disease (ANOCA) is increasingly recognised as part of a spectrum of conditions underlying chronic coronary syndromes, reflected in changes in recent ischaemic heart disease (IHD) guidelines[67,134]. A significant proportion of patients referred for coronary angiography have unobstructed coronary arteries[12,14,15]. In patients referred for computed tomography coronary angiography (CTCA), who are traditionally a lower risk population, the proportion of patients with unobstructed artery is as high as 75%[4]. The Scottish Computed Tomography of the Heart (SCOT-HEART) trial reported that among outpatients referred for suspected stable angina, CTCA added to standard care clarified the diagnosis of coronary heart disease and altered subsequent management[4]. However, compared with standard care, anginal symptoms and quality of life at 6 weeks and 6 months were worse in the CTCA-guided group[86]. Despite this, CTCA is the recommended first line test for the assessment of stable chest pain in patients with no history of coronary artery disease (CAD)[80,81].

Stratified medicine is the identification of key subgroups of patients (endotypes) within a heterogeneous population; these endotypes being distinguishable by distinct mechanisms of disease and/or responses to therapy[120]. The CorMicA trial

identified that stratified medicine benefitted patients with angina undergoing invasive management, and the strategy is supported by a Class IIA guideline recommendation[67,134].

CorMicA was positioned downstream in the patient care pathway. The prevalence and management of ANOCA endotypes in patients undergoing initial investigation for suspected angina (in this case, a CTCA) have been demonstrated in this study, as described in Chapters 3 and 4. The next step is firstly, to assess the effect of stratified medicine guided by invasive coronary function tests on the burden of angina reflected by the Seattle Angina Questionnaire (SAQ) and health-related quality of life and, secondly, to assess the effect of the intervention on cardiovascular risk factors. We hypothesised that compared to angiography-guided management, stratified medicine improves patient wellbeing.

5.3 Methods

Full details of study methods are outlined in Chapter 2.

5.4 Results

5.4.1 Study population

Between August 31, 2017 and September 9, 2020, 1552 outpatients referred for the non-invasive assessment of coronary artery disease by CTCA were prospectively screened, of whom 322 were eligible and 250 (77.6%) provided informed consent and subsequently underwent invasive management (Figure 3-1). Nineteen (7.6%) of these patients were excluded when obstructive coronary artery disease was identified by angiography or fractional flow reserve (≤0.80).

Two hundred and thirty-one patients (92.4%) were randomised (n=115 Intervention group; n=116 Control group).

The baseline characteristics (Table 3-1) and the prevalence of disease endotypes are described in detail in Chapter 3. In summary, in the randomised population, 127 (55.0%) had microvascular angina, 27 (11.7%) had vasospastic angina and 17

(7.4%) patients had both microvascular and vasospastic angina (Figure 3-2). Sixty (26.0%) patients had non-cardiac chest pain.

5.4.2 Primary outcome of the clinical trial

Follow-up was undertaken between October 6, 2017 and May 27, 2022. The median follow-up duration was 19.9 (12.6, 26.9) months and 111 patients (48.1%) participated during the pandemic. In the randomised population, 217 (93.9%) patients provided one response during follow-up and 167 (72.3%) patients provided two or more responses (Table 5-2).

Table 5-1 - Time from study enrolment to follow up

	Randomised		
	Intervention (N=115)	**Control (N=116)**	**p-value**
Provided 1st follow up response (*questionnaires*)	92 (80.0%)	89 (76.7%)	p=0.632
Time to 1st follow up response (days)	212 (191, 271) [152, 639]	209 (190, 241) [142, 1109]	p=0.613
Provided 1st follow up response within 182 (+ 14) days	29 (25.2%)	28 (24.1%)	p=0.880
Completed 2nd follow up (*in-person visit*)	91 (79.1%)	95 (81.9%)	p=0.622
Time to 2nd follow up (days)	581 (388, 800) [236, 1510]	684 (390, 844) [227, 1105]	p=0.508
Completed 2nd follow up within 365 (+ 14) days	19 (16.5%)	21 (18.1%)	p=0.862
Provided 3rd follow up response (*questionnaires*)	9 (7.8%)	3 (2.6%)	p=0.083
Time to 3rd follow up response (days)	719 [442, 812]	733 [732, 1077]	p=0.209
Follow up undertaken during COVID-19 pandemic*	57 (49.6%)	54 (46.6%)	p=0.787

Values are median (Q1, Q3) [min, max] or n (%). Between-group p-value is from the Fisher's Exact test for categorical variables or the Mann-Whitney U test for continuous variables.
*Defined as randomisation or any follow-up post March 16, 2020.

Table 5-3 shows the follow up responses according to the revised follow-up time-windows of 4 to 9 months, 9 to 18 months and greater than 18 months.

Table 5-2 - Follow-up responses for primary outcome assessment

	Intervention (N=115)	**Control (N=116)**	**Between group p-value**
4 - 9 months	70 (60.9%)	70 (60.3%)	p=1.000
9 - < 18 months	66 (57.4%)	64 (55.2%)	p=0.791
≥ 18 months	53 (46.1%)	52 (44.8%)	p=0.895

There was no difference in the SAQSS between the randomised groups (Table 5-4). Baseline SAQSS were similar in both groups (55.5 ± 19.9 in the intervention

group and 54.1 ± 20.7 in the control group). At 4 – 9 months, the SAQSS in the intervention versus 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), at 9 – 18 months, 63.7 ± 23.5 (a change of 4.7 ± 14.7 from baseline) versus 66.0 ± 19.3 (a change of 7.9 ± 17.1 from baseline) and at ≥ 18 months, 52.9 ± 21.7 (a change of 1.1 ± 17.7 from baseline) versus 54.8 ± 24.5 (a change of 5.0 ± 16.5 from baseline).

Table 5-3 - Primary outcome - Seattle Angina Questionnaire

	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					
4 - 9 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
9 - <18 months	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
≥ 18 months	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					
4 - 9 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
9 - <18 months	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
≥ 18 months	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					
4 - 9 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
9 - <18 months	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
≥ 18 months	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					
4 - 9 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
9 - <18 months	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

	Intervention (N=115)		Control (N=116)		Estimate (95% CI), p-value
	At follow up	Change from baseline	At follow up	Change from baseline	
≥ 18 months	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
Angina treatment satisfaction					
4 - 9 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
9 - <18 months	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
≥ 18 months	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					
4 - 9 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
9 - <18 months	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
≥ 18 months	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 treatment group on outcome regardless of timepoint. Seattle Angina Questionnaire (SAQ): lower scores represent worse angina symptoms.

Across three timepoints, there was no difference in the within-patient change from baseline in the SAQSS between the intervention group and the control group (overall p = 0.360). 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).

5.4.3 Secondary outcomes

Treatment satisfaction for convenience was significantly higher in the intervention group at 9 to 18 months (9.27; 3.27 - 15.27; p = 0.002) and for global satisfaction at 9 to 18 months (9.24; 1.97 - 16.52; p=0.013) but not for effectiveness (67.3 ± 21.8 vs 64.1 ± 23.7, p = 0.168) (Table 5-5). 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, as assessed by BIPQ (p = 0.124), or psychological distress levels (PHQ4, p = 0.827).

Table 5-4 - Secondary outcomes - changes in health status

	Intervention (N=115)		Control (N=116)		Estimate (95% CI), p-value
	At follow up	**Change from baseline**	**At follow up**	**Change from baseline**	
Quality of Life (EQ5D-5L) Utility Index score					
4 - 9 months	0.61 (0.30)	-0.02 (0.24)	0.62 (0.29)	-0.02 (0.21)	-0.01 (-0.08, 0.06), p=0.778
9 - <18 months	0.64 (0.27)	-0.03 (0.27)	0.62 (0.27)	-0.03 (0.23)	0.00 (-0.07, 0.07), p=0.998
≥ 18 months	0.55 (0.31)	-0.02 (0.19)	0.54 (0.31)	-0.03 (0.21)	0.00 (-0.07, 0.08), p=0.964
					Overall p-value = 0.992
Quality of Life (EQ-5D-5L) VAS score					
4 - 9 months	64.3 (22.4)	-5.8 (18.5)	63.7 (19.7)	-4.9 (16.3)	-0.56 (-5.81, 4.68), p=0.834
9 - <18 months	66.6 (18.1)	-3.0 (16.8)	63.0 (21.1)	-4.9 (16.4)	2.27 (-3.19, 7.73), p=0.415
≥ 18 months	60.4 (20.4)	-6.3 (21.1)	59.6 (21.2)	-6.7 (17.7)	-0.72 (-6.87, 5.42), p=0.818
					Overall p-value = 0.822
Illness Perception (BIPQ)					
4 - 9 months	49.3 (11.1)	2.7 (8.6)	48.0 (10.6)	-0.9 (10.5)	2.72 (-0.25, 5.69), p=0.073
9 - <18 months	49.5 (11.9)	2.2 (8.6)	48.3 (9.7)	-0.1 (10.7)	0.82 (-2.34, 3.98), p=0.611
≥ 18 months	49.6 (13.9)	-1.9 (7.8)	52.0 (10.3)	1.2 (11.7)	-1.95 (-5.41, 1.50), p=0.267
					Overall p-value = 0.124
Psychological Distress (PHQ-4)					
4 - 9 months	3.6 (3.9)	0.4 (3.3)	4.2 (4.1)	0.9 (3.0)	-0.42 (-1.38, 0.54), p=0.391
9 - <18 months	3.8 (4.1)	1.2 (3.2)	4.4 (3.9)	1.0 (3.0)	0.05 (-0.93, 1.03), p=0.925
≥ 18 months	5.4 (4.3)	0.7 (2.8)	5.1 (4.0)	0.9 (4.2)	0.02 (-1.07, 1.11), p=0.968
					Overall p-value = 0.827
Treatment Satisfaction (TSQM-9) – Effectiveness					
4 - 9 months	65.4 (23.3)	2.7 (22.8)	61.9 (22.5)	-2.3 (22.3)	4.58 (-1.84, 11.00), p=0.162

	Intervention (N=115)		Control (N=116)		Estimate (95% CI), p-value
	At follow up	**Change from baseline**	**At follow up**	**Change from baseline**	
9 - <18 months	67.3 (21.8)	5.4 (21.9)	64.1 (23.7)	0.3 (24.3)	4.65 (-1.96, 11.26), p=0.168
≥ 18 months	61.7 (19.8)	1.3 (22.8)	58.3 (19.1)	-5.2 (22.2)	5.74 (-1.85, 13.33), p=0.138
					Overall p-value = 0.192
Treatment Satisfaction (TSQM-9) – Convenience					
4 - 9 months	78.4 (19.3)	3.1 (20.1)	73.1 (21.3)	-1.2 (21.1)	4.80 (-1.00, 10.60), p=0.104
9 - <18 months	82.6 (17.2)	6.5 (19.0)	73.3 (21.4)	-3.7 (21.3)	**9.27 (3.27, 15.27), p=0.002**
≥ 18 months	72.6 (16.6)	-0.4 (19.3)	75.1 (19.7)	-0.3 (20.5)	0.05 (-6.78, 6.89), p=0.988
					Overall p-value = 0.013
Treatment Satisfaction (TSQM-9) – Global satisfaction					
4 - 9 months	63.4 (25.8)	-0.6 (24.0)	60.7 (26.0)	-3.3 (26.5)	2.80 (-4.20, 9.80), p=0.433
9 - <18 months	69.9 (22.8)	7.4 (25.3)	61.7 (26.9)	-2.8 (24.2)	**9.24 (1.97, 16.52), p=0.013**
≥ 18 months	60.4 (22.2)	-1.9 (27.9)	63.6 (18.7)	-5.0 (21.9)	1.74 (-6.41, 9.89), p=0.675
					Overall p-value = 0.095
Functional capacity (DASI) – VO_2 peak (mL/kg/min)					
4 - 9 months	22.10 (7.19)	-0.41 (5.24)	21.29 (6.93)	-0.51 (4.86)	0.07 (-3.34, 3.48), p=0.970
9 - <18 months	23.03 (6.79)	-0.33 (5.19)	21.52 (6.32)	-0.74 (4.35)	1.34 (-2.20, 4.89), p=0.458
≥ 18 months	20.32 (7.04)	-0.68 (4.53)	20.38 (7.49)	-0.19 (5.69)	-1.16 (-5.11, 2.79), p=0.565
					Overall p-value = 0.786

Values are mean (SD) unless otherwise stated.
Estimate (95% CI) is the intervention group adjusted mean difference.
EQ-5D-5L = EuroQol-5D 5-level version; VAS = visual analogue score (validated quality of life tool, higher scores indicate better quality of life); PHQ-4 = Patient Health Questionnaire-4 (higher scores indicate more psychological distress); TSQM-9 = abbreviated Treatment Satisfaction Questionnaire for Medication; BIPQ = Brief Illness Perception Questionnaire (a lower score reflects a less threatening view of the illness); DASI = Duke Activity Score Index.

Cardiovascular risk factors are described in Table 5-6. At follow up, systolic blood pressure was lower in the intervention group (135.0 mmHg) compared to the control group (140.6 mmHg), with a statistically significant reduction compared to baseline (-5.59 [-10.99, -0.19]; p=0.044). Body mass index, waist

circumference, current smoking and blood lipids were not different between the groups (Table 5-6).

Table 5-5 - Cardiovascular risk factors by randomised group at baseline and follow up (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, mmol/L	5.0 (1.1)	5.0 (1.2)	5.1 (1.2)	5.0 (1.1)	0.02 (-0.30, 0.35), p=0.890
Total cholesterol <5.17 mmol/L (<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, mmol/L	1.4 [1.1, 1.7]	1.4 [1.1, 1.8]	1.3 [1.1, 1.6]	1.3 [1.1, 1.6]	1.5% (-3.6%, 6.9%), p=0.572†
LDL cholesterol*, mmol/L	2.8 (0.9)	2.7 (1.1)	2.8 (1.2)	2.7 (1.0)	0.00 (-0.28, 0.29), p=0.973
LDL cholesterol <2.6 mmol/L (100 mg/dL)	38 (43.2%)	45 (51.1%)	41 (44.6%)	50 (54.3%)	0.87 (0.45, 1.69), p=0.684
LDL cholesterol <1.4 mmol/L (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, mmol/L	1.4 [1.0, 1.9]	1.6 [1.2, 2.2]	1.7 [1.2, 2.3]	1.8 [1.3, 2.6]	2.3% (-8.5%, 14.4%), p=0.688†
Triglyceride <1.7 mmol/L (150 mg/dL)	58 (65.2%)	49 (55.1%)	45 (48.9%)	45 (48.9%)	0.96 (0.48, 1.92), p=0.912
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‡

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.
†SCORE2 or SCORE2-Older Persons (≥70 years)
‡Data analysed on a log-scale; Intervention effect estimate (95% CI) reported as percentage difference between groups.

At follow up, compliance with non-pharmacological measures was assessed subjectively (Table 5-7). 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). In the intervention group, 37.8% of patients reported an increase in weight, compared to 43.6% in the control group (p = 0.687). Expectedly, there was a statistical difference between patients' self-reported compliance with cardiac rehabilitation in the intervention group (27.8%) and the control group (5.3%) due to the higher frequency of cardiac rehabilitation referral in the intervention group. However, rate of compliance is notably low.

Table 5-6 - Patients' self-reported compliance with management at follow up

	Randomised			
	All (N=186)	**Intervention (N=91)**	**Control (N=95)**	**p-value**
Compliance with healthy diet	88 (47.8%)	43 (47.8%)	45 (47.9%)	p=0.884
Compliance with exercise	104 (56.5%)	54 (60.0%)	50 (53.2%)	p=0.464
Increase in weight	75 (40.8%)	34 (37.8%)	41 (43.6%)	p=0.687
Compliance with cardiac rehabilitation programme	30 (16.3%)	25 (27.8%)	5 (5.3%)	p=0.003

Values are n (%). Between-group p-value is from the Fisher's Exact test for categorical variables or the Mann-Whitney U test for continuous variables.

5.4.4 Feasibility and blinding

The invasive coronary function tests were successfully completed in 230 (99.6%) patients. Blinding in the control group was achieved in all 116 patients.

5.4.5 Post-discharge clinical outcomes

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

Clinical events are described in Table 5-8. Approximately one in five patients experienced an unplanned episode of secondary care for chest pain, with or without hospitalization (Figure 5-1). 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. There were no cardiovascular deaths (Table 5-9).

Table 5-7 - Secondary outcomes: clinical events

	Randomised		
	Intervention (N=115)	**Control (N=116)**	**p-value**
Peri-procedural serious adverse events	2 (1.7%)	6 (5.2%)	p=0.280
Atrial fibrillation	1 (0.9%)	3 (2.6%)	p=1.000
Spontaneously resolving atrial fibrillation	1 (0.9%)	2 (1.7%)	
Atrial fibrillation requiring admission	0 (0.0%)	1 (0.9%)	
Coronary dissection	0 (0.0%)	2 (1.7%)	p=0.212
Nausea and vomiting	1 (0.9%)	0 (0.0%)	p=1.000
Ventricular tachycardia	0 (0.0%)	1 (0.9%)	p=1.000
Major adverse cardiac and cerebrovascular events	16 (13.9%)	11 (9.5%)	0.314
Mortality			
All cause death	2 (1.7%)	1 (0.9%)	p=0.622
Cardiovascular death	0 (0.0%)	0 (0.0%)	-
Non-cardiovascular death	2 (100.0%)	1 (100.0%)	-
Non-fatal MI	2 (1.7%)	2 (1.7%)	p=1.000
Cerebrovascular event	0 (0.0%)	0 (0.0%)	-
Hospitalisation with angina (unstable or other)	15 (13.0%)	9 (7.8%)	p=0.203
Unplanned episode of hospital care for chest pain*	27 (23.5%)	23 (19.8%)	p=0.526
Number of unplanned episodes of hospital care for chest pain			
0	88 (76.5%)	93 (80.2%)	p=0.124
1	22 (19.1%)	13 (11.2%)	
≥2	5 (4.3%)	10 (8.6%)	
Median (IQR) [Min, Max]	1 (1, 1) [1, 8]	1 (1, 2) [1, 13]	p=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.
MVA = microvascular angina; VSA = vasospastic angina.
*Chest pain attendance not necessarily leading to admission or overnight stay.

Figure 5-1 - Kaplan-Meier survival plot of time from study enrolment until 1st unplanned episode of hospital care for chest pain, by randomised treatment group.
Solid line presents the survival probability estimate and the shaded area covers the area between the upper and lower 95% confidence interval. The p-value presented is from the log-rank test comparing the survival curve of each randomised treatment group.

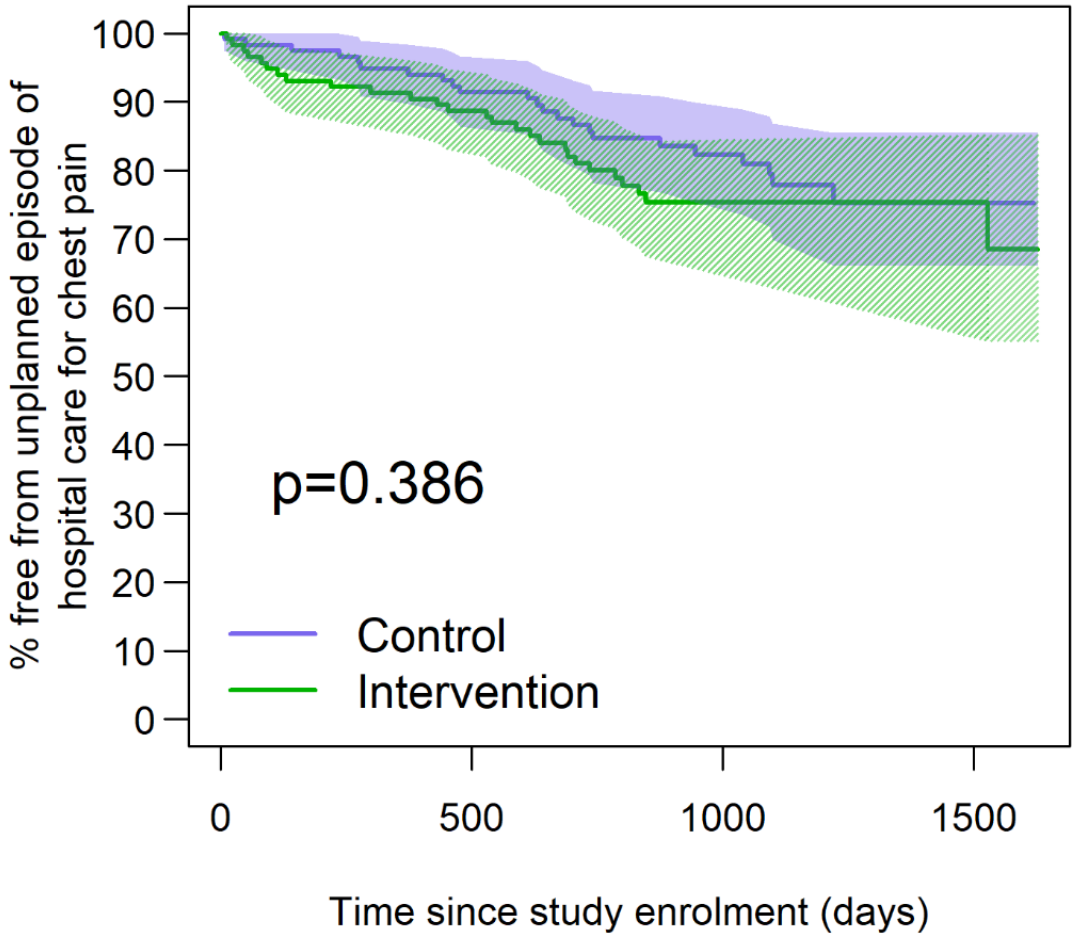


Table 5-8 - Deaths, cause of death and time of death post-enrolment

Age	Sex	Randomisation group	Diagnosis	Cause of death	Time from randomisation to death (months)
61	Female	Intervention	Microvascular angina	Metastatic pancreatic cancer	32
64	Female	Intervention	Microvascular angina	Metastatic pancreatic cancer	26
54	Female	Control	Microvascular angina	COVID-related chest sepsis	32

5.4.6 Impact of COVID-19

In the randomised 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 hospitalised, and one (0.4%) patient died from COVID-19.

The timeline of healthcare and social restrictions during the pandemic is shown in Table 5-1. Between 16 March 2020 and 1 July 2021, in-person clinical research visits at the NHS Golden Jubilee hospital were prohibited. Almost half of the

patients (n=111, 48.1%) participated in the study during the pandemic (Table 5-2). Four in five patients re-attended during follow-up, but four in five of these patients attended out-with the timeline of the protocol, some considerably.

5.5 Discussion

Stratified medicine using invasive coronary function tests and linked medical therapy improved systolic blood pressure and treatment satisfaction but did not improve angina or health-related quality of life.

The potential explanations for the lack of improvement in angina and quality of life include true lack of efficacy, population characteristics, deferral of medical management to the usual care clinicians rather than the research team, the effect of the pandemic, and the lack of effective, disease-modifying medical therapy.

The population in this study included ambulatory outpatients. Their overall burden of angina was less than in the CorMicA population which included patients downstream in the care pathway who had been selected for invasive management. For example, in this study, compared to in CorMicA, the SAQSS were 54.8 (20.3) vs. 50.8 (18.1) and the angina frequency scores were 64.2 (24.5) vs. 59.3 (23.5), respectively. In the CorMicA trial, stratified medicine improved angina and quality of life at 6-[5] and 12- months[144]. In CorMicA, the improvements in angina and quality of life were associated with improvements in cardiovascular risk factors and participation in cardiac rehabilitation.

In this trial, stratified medicine reduced systolic blood pressure, but other cardiovascular risk factors were not different between the groups. The effect on stratified medicine on systolic blood pressure may be explained by enhanced prescription of blood pressure lowering therapy (notably angiotensin converting enzyme inhibitors and calcium channel blockers) in the intervention group (Table 4-3) and also a rise in blood pressure (2.9 mmHg) in the control group (Table 5-6).

The post-randomisation treatment plan was implemented by the blinded clinicians in primary and secondary care rather than the clinical research

physicians. Treatment changes for individual patients were at the discretion of the usual care clinicians. This design minimised bias that occurs with an open-label design when unblinded research staff implement medical care which potentially leads to more intensive treatment in the intervention group and undertreatment of the control group. On the other hand, patients with a new diagnosis of angina should benefit from a shared care plan involving cardiac rehabilitation and sequential outpatient episodes of care to initiate angina medication and preventive therapy, assess the response (including side-effects), optimise the medication to relieve symptoms and mitigate cardiovascular risk factors. This care plan may last months. In the current study, even though differences in medication occurred between the groups, the approach was not successful. Given the breadth of responsibilities held by attending clinicians, they may not have the capacity to implement medical care in this way, and this was obvious during the COVID-19 pandemic.

Our hypothesis was that stratified medicine involving intensive medical therapy would improve modifiable risk factors, such as body mass index, hyperlipidaemia and cigarette smoking. Most of the patients participated in this study during the COVID-19 pandemic which imposed unprecedented disruption in society, including restrictions on access to primary[145,146] and secondary medical care, reduced adherence with medication[147], reduced control of cardiovascular risk factors[148,149] and unfavourable changes in social behaviours[150]. During the pandemic, globally, deferred medical management and reduced access to cardiovascular care became the norm, undermining the feasibility of medical management in the community[151]. Angina management typically involves serial outpatient clinic visits to assess the patient's response to therapy and optimize the treatment. 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 (Table 4-2). However, the efficacy of the intervention is dependent on the doctor-patient relationship, which clearly was undermined during the pandemic. Patients with a new diagnosis of ischaemic heart disease should be referred for cardiac rehabilitation[67,134], to facilitate personalise care, including the use of angina medication, dose, and nonpharmacological measures to improve cardiovascular risk factors. Again, cardiac rehabilitation was disrupted during the pandemic. On

the other hand, the results may have been the same had the pandemic not occurred.

Compared to the CorMicA trial[5], more patients in our study presented with atypical chest pain (48.9% vs 35.8%) and fewer patients had an abnormal exercise tolerance test (5.7% vs 47.4%). These differences in population characteristics, notably the low prevalence of ischaemia on non-invasive testing, may also partly explain why this population were less responsive to angina management. The population in the current study were upstream in the care pathway and less selected as compared to the patients in CorMicA who had been selected for invasive management downstream in the care pathway.

In the SCOT-HEART trial, anginal symptoms and quality of life[86] improved less in the CTCA-guided group. The prevalence of coronary microvascular dysfunction in this population was unknown since the protocol did not include quantitative non-invasive tests of myocardial ischaemia and or invasive coronary function tests. Several factors may be relevant. One explanation could be that in the CTA 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 CTCA-guided management have involved assessments of coronary vasomotion[4,83,84,86-88], and the prevalence of clinical endotypes of ANOCA in patients with angina (or ischaemic symptoms) and no obstructive coronary artery disease is unknown.

Considering the clinical implications of our findings, firstly, ANOCA endotypes are common in outpatients with angina and no obstructive coronary artery disease, as defined by CTCA. Missed diagnoses, potentially leading to suboptimal management, occurred in two thirds of patients in this pathway. Secondly, a routine invasive strategy with medical management led by the standard care clinicians during a pandemic did not improve health status, although blood pressure, treatment satisfaction improved and the need for onward investigations were reduced. Although complications of invasive management were uncommon, two patients (0.8%) had a coronary artery dissection necessitating percutaneous coronary intervention, which suggests that clinicians should not routinely adopt an invasive strategy (Table 5-8). Nonetheless, 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.

Non-invasive, functional imaging of myocardial blood flow is an alternative option for assessing microvascular function in patients with suspected ANOCA.[152] This is currently being investigated in the Coronary Microvascular Angina Cardiac Magnetic Resonance Imaging (CorCMR) trial (ClinicalTrials.gov Identifier: NCT04805814). However, vasospastic angina due to coronary spasm can only be accurately assessed by invasive acetylcholine testing. Therefore, based on the results of our study, in ambulatory patients with suspected ANOCA after CTCA, non-invasive functional imaging of myocardial blood flow should be considered. Invasive management with acetylcholine testing should be considered when non-invasive imaging is not available or when patients have ongoing refractory symptoms.

Finally, the medical management of ANOCA involves antianginal medications that are mainly repurposed therapy for coronary heart disease. Future developments in disease-modifying therapy are urgently needed.[35,152,153]

Strength and limitations

To our knowledge, our study is the first to prospectively quantify the prevalence of coronary microvascular dysfunction and ANOCA endotypes in a chest pain population undergoing coronary CTCA. Novel aspects of the design included multicentre recruitment, use of validated questionnaires, invasive coronary function testing (including the use of acetylcholine) in a single reference centre, a sham-control procedure, blinding, and stratified medical therapy.

The main limitation of our study was that it was delivered during the COVID-19 pandemic, which impeded the implementation of the protocol and personalised medical management of outpatients who participated in this study. Information on contacts between patients and community healthcare staff was not available.

Conclusions

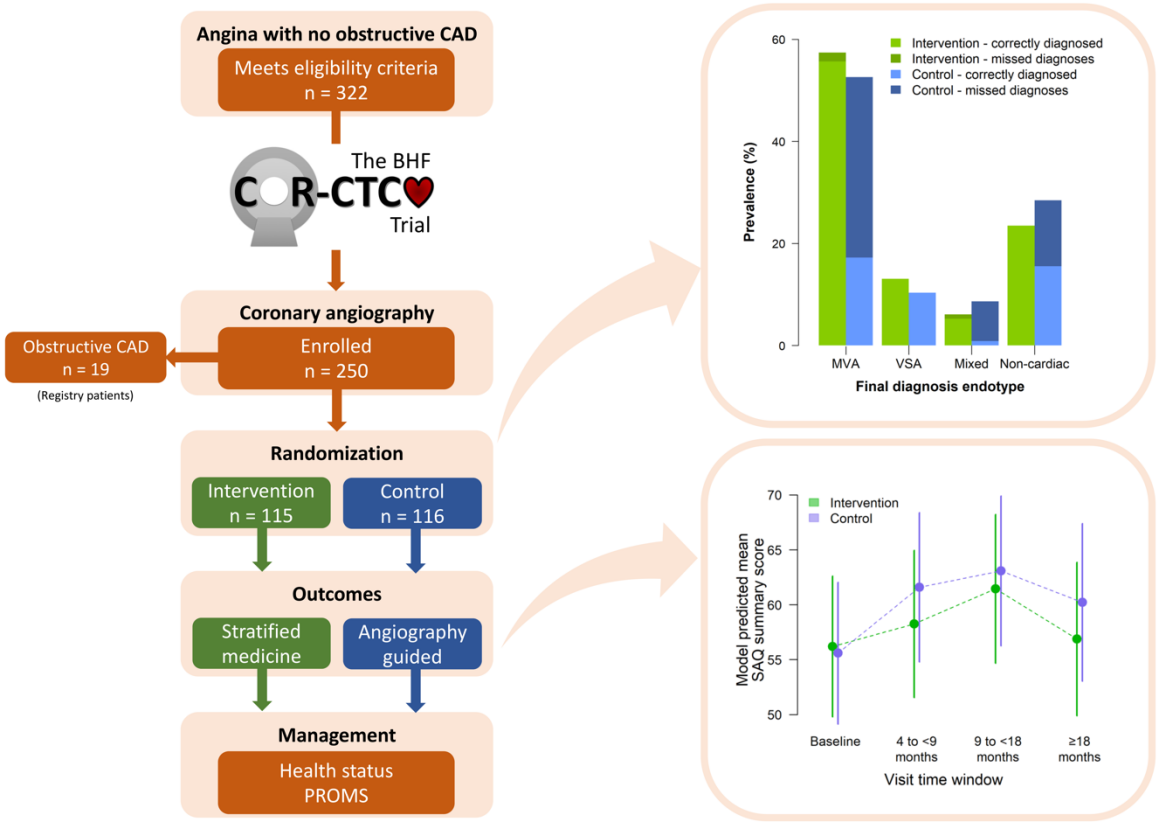
Stratified medicine improved blood pressure and treatment satisfaction but did not improve angina or health-related quality of life. However, medical management was disrupted by the pandemic.

6 Discussion

6.1 Main findings

In this study of outpatients with suspected angina and no obstructive coronary artery disease, endotypes of angina and no obstructive coronary artery disease (ANOCA) were disclosed in three quarters of the population, most of whom were women. A missed diagnosis occurred in almost two thirds of the control group. Stratified medicine using invasive coronary function tests and linked medical therapy improved systolic blood pressure and treatment satisfaction but did not improve angina or health-related quality of life. Fewer referrals for additional investigations occurred in the intervention group. The main findings of the study are illustrated in Figure 7-1.

Figure 6-1 - Central illustration: main study findings



6.2 Study design

This is a randomised controlled trial with single blinding. The interventional cardiologists performing the interventional diagnostic procedure (IDP) were not blinded to the treatment allocation. No special measures were taken to blind the patients' referring cardiologists and primary care physicians. Although they were not explicitly informed of the treatment allocation, it was possible for them to infer from the changes in clinical management which group the patients

had been randomised to. The rationale behind this design was to facilitate cooperation between primary, secondary and tertiary care for optimisation of the patients' medical therapy. Unfortunately, due to NHS constraints exacerbated by the COVID-19 pandemic, most patients had little contact with the healthcare service during the follow up period. There were few changes made to their medical therapy irrespective of their anginal symptoms. The study protocol did not mandate any "check-ins" by the research team during the follow up period, which would have been helpful in identifying patients whose antianginal treatment should be modified or uptitrated. It is unclear how significant a role this played in the neutral outcome of the study.

The study eligibility criteria did not require patients to have had prior functional testing. Although three-quarters of the randomised population had a functional test (in the form of an exercise treadmill test) prior to undergoing computed tomography coronary angiography (CTCA), only 5.7% (10 patients) had a positive test. This small number is expected from a patient cohort who had been referred for CTCA instead of conventional coronary angiography (i.e., a non-invasive anatomical test instead of an invasive procedure). However, it does question whether all the patients with abnormal coronary function test do in fact have microvascular and/or vasospastic angina, and whether these physiological abnormalities in the catheter laboratory correlate with real-life symptoms. Without a true normal control group, which is almost impossible to achieve given the invasive nature of the study, the closest solution would be to include a positive functional test in the inclusion criteria. This would however exclude patients with "false negative" stress tests, which is common in coronary microvascular dysfunction (CMD).

The IDP adopted in the study utilised bolus thermodilution for the measurement of CFR and IMR. Continuous thermodilution has been shown to be more reproducible than bolus thermodilution[154], and would have been the preferred choice. However, it requires a specialised catheter for saline infusion, which exceeded the study budget.

6.3 Prevalence of ANOCA endotypes

Three quarters of the patients had microvascular angina and/or vasospastic angina that had not been diagnosed based on CTCA-guided management. This prevalence is higher than studies using non-invasive imaging, such as Rb82 cardiac positron emission tomography-CT[155] (42%) and related systematic reviews (41% - 43%[156,157], but consistent with studies using invasive testing[5]. The difference between approaches can be explained by the diagnostic gap for vasospastic angina using non-invasive imaging, and case selection through the use of validated questionnaires for angina. Furthermore, as described previously, non-invasive imaging tests are susceptible to false negatives, such as in patchy heterogenous ischaemia that is common in CMD.

The study showed no statistical difference in the sex distribution between patients with ANOCA and those with non-cardiac chest pain. This could be due to sex differences in behaviour towards study participation. Women are more risk averse than men and therefore less likely to take part in research studies, especially one that involves an invasive procedure. Middle-aged women are also more likely to be care-givers than men in the same age group, and will have more considerations to take into account that may hinder commitment to study participation.

An important finding is the correlation between myocardial bridging and epicardial vasospasm. Current practice recommends betablockers for the treatment of angina associated with myocardial bridging to reduce heart rate and myocardial contractility. Betablockers could however worsen vasospasm. Based on our findings, we suggest that in patients with known myocardial bridging and persistent angina on betablockers, it should be stopped and replaced with a calcium channel blocker.

6.4 Health status

This study showed that despite increasing the diagnosis of CMD and the certainty of diagnosis, stratified medicine guided by an IDP did not improve angina or quality of life. There are a few potential causes for this finding.

True lack of efficacy

It is clearly possible that the intervention did not improve well-being because the intervention in itself is not effective. Diagnosing patients with ANOCA endotypes does not improve their angina. However, this observation is an inadequate explanation – the mechanism behind the lack of efficacy is not clear. Two important questions arise: Did it not improve well-being because of misdiagnosis? Or did it not improve well-being because the medication prescribed did not work?

Population characteristics

Compared to the CorMicA population[5], the patients in this study have a lower burden of angina with a lower SAQSS, more patients presented with atypical chest pain, and fewer patients had an abnormal exercise tolerance test. There is a possibility that these patients' symptoms were not due to CMD, in which case treatment for CMD would have not improved their symptoms.

Deferral of medical management to the usual care clinicians

In real-life clinical practice with constraints on time and resources, it is sometimes not feasible for the patients' primary and secondary care team to optimise medication over multiple appointments and months. As shown in this study, most patients' medications were unchanged 12 months post-randomisation, despite persistent angina. Although they have been diagnosed with ANOCA, they remain under-treated.

Effect of the pandemic

The previous point is accentuated with restrictions to primary and secondary care and reduced patient compliance[145-150,158]. The effect of the COVID-19 pandemic has been discussed in detail in Section 5.5.

Lack of effective, disease-modifying medical therapy

As outlined in the Introduction, there is a lack of data for evidence-based CMD treatment, with no data from large randomised controlled trials comparing therapies, and with most available data obtained from cohort studies. Clinical guideline recommendations are also limited.

6.5 Implications for routine practice

Current guidelines for the diagnosis and management of chronic coronary syndromes recommend that non-invasive assessment of CFR[67] be considered in patients with possible CMD (class IIb, level of evidence B). In patients who are known to have no obstructive CAD, invasive coronary function testing is advised with a higher class of recommendation (class IIa, level of evidence B). The level of evidence of these recommendations, reflect the lack of robust, unequivocal evidence. These guidelines were put in place following the CorMicA trial, which demonstrated symptom and quality of life improvement with invasive coronary function tests and linked medical therapy in patients with ANOCA.

In light of the findings of this study, although tests for possible CMD should still be considered, routine testing cannot be recommended, especially for invasive coronary function testing, which carries risks of complications. Patient selection should be an important part of the assessment. The patient population in this study represents a low-risk population, as reflected by their SCORE2 10-year cardiovascular risk, with a relatively low angina burden. Our findings do not support routinely performing invasive coronary function testing in this patient population.

6.6 Future directions

Overall, ANOCA endotypes are common in outpatients with angina and no obstructive coronary artery disease, as defined by CTCA. There is a substantial health burden in this population. 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. However, a routine invasive strategy with medical management led by the standard care clinicians during a pandemic did not improve health status. Further clinical trials of patients stratified by

endotype should improve our understanding of this condition and also allow us to develop more effective treatment strategies.

The lack of evidence-based antianginal therapy for this patient population also needs to be addressed by large randomised trials. Although the patients diagnosed with ANOCA in the intervention group had been prescribed angina medications specific to coronary microvascular dysfunction, this treatment is empirical because of the incomplete understanding of the underlying causes and a lack of evidence[91]. Studies adopting personalised medicine identifying patient characteristics that can predict response to specific therapies are desperately needed.

Although there has been increasing awareness of coronary vasomotion disorders in recent years, there is still an unmet need for effective management strategies to improve these patients' health and well-being.

7 Appendices

Research ethics approval

WoSRES
West of Scotland Research Ethics Service

NHS Greater Glasgow and Clyde

Professor Colin Berry
Honorary Consultant Physician and Cardiologist
University of Glasgow
Institute of Cardiovascular and Medical Sciences
BHF Glasgow Cardiovascular Research Centre
126 University Place, University of Glasgow
G12 8TA

West of Scotland REC 1
Research Ethics
Clinical Research and Development
West Glasgow Ambulatory Care Hospital
Dalnair Street
Glasgow
G3 8SJ
(Formerly Yorkhill Childrens Hospital)

Date 01 August 2017
Direct line 0141 232 1807
E-mail WoSREC1@ggc.scot.nhs.uk

Dear Professor Berry

Study title:	**The conundrum of angina in patients without obstructive coronary disease as revealed by CT coronary angiography: an observational cohort study involving coronary function tests and a nested randomised trial**
REC reference:	**17/WS/0121**
IRAS project ID:	**227553**

Thank you for your letter of 15 July 2017, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information was considered in correspondence by a Sub-Committee of the REC. A list of the Sub-Committee members is attached.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to make a request to postpone publication, please contact hra.studyregistration@nhs.net outlining the reasons for your request.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for NHS permission for research is available in the Integrated Research Application System, www.hra.nhs.uk or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database within 6 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to request a deferral for study registration within the required timeframe, they should contact hra.studyregistration@nhs.net. The expectation is that all clinical trials will be registered, however, in exceptional circumstances non registration may be permissible with prior agreement from the HRA. Guidance on where to register is provided on the HRA website.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS sites (If applicable)

The Committee has not yet completed any site-specific assessment (SSA) for the non-NHS research site(s) taking part in this study. The favourable opinion does not therefore apply to any non-NHS site at present. We will write to you again as soon as an SSA application(s) has been reviewed. In the meantime no study procedures should be initiated at non-NHS sites.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Covering letter on headed paper [Cover letter]		21 May 2017
GP/consultant information sheets or letters [Track Changes]	1.1	15 July 2017
Letter from funder [Funder letter]		16 March 2017
Letter from statistician		17 October 2016
Other [Radiation Protection Assessment]		15 May 2017
Other [ScreenShot of Authorisations]		
Other [Confirmation email that Margaret is happy with the final version of the form]		22 May 2017
Participant consent form [PISICF - Clean]	1.1	15 July 2017
Participant consent form [PISICF - Track Changes]	1.1	15 July 2017
Participant information sheet (PIS) [PISICF - Clean]	1.1	15 July 2017
Participant information sheet (PIS) [PISICF - Track Changes]	1.1	15 July 2017
REC Application Form [REC_Form_22052017]		22 May 2017
Referee's report or other scientific critique report [Response to review]		
Research protocol or project proposal [Clean]	1.1	15 July 2017
Research protocol or project proposal [Track Changes]	1.1	15 July 2017
Response to Request for Further Information [Cover Letter]		15 July 2017
Summary CV for Chief Investigator (CI) [CV - CI]	2017	27 April 2017
Summary CV for student [CV - Clinical PhD student]		
Summary CV for supervisor (student research) [CV - Co-Supervisor]		
Validated questionnaire [Questionnaires - Combined]		

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website: http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

17/WS/0121	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project.

Yours sincerely

On behalf of
Dr Malcolm Booth
Chair

Enclosures:	*List of names and professions of members who were present at the meeting and those who submitted written comments*
	"After ethical review – guidance for researchers"
Copy to:	*Dr Catherine Sinclair, NHS National Waiting Times Centre Board*

West of Scotland REC 1

Attendance at Sub-Committee of the REC meeting on 24 July 2017

Committee Members:

Name	*Profession*	*Present*	*Notes*
Dr Malcolm Booth	Consultant in Anaesthesia and Intensive Care (Chair)	Yes	Chair of Meeting
Dr Peter Hutchison	GP (Vice Chair)	Yes	
Dr Colin Petrie	Physician and Cardiologist	Yes	

Also in attendance:

Name	*Position (or reason for attending)*
Mrs Abibat Adewumi-Ogunjobi	Acting REC Manager

Patient information leaflet

Golden Jubilee National Hospital

NHS National Waiting Times Centre

Participant Information Sheet / Consent Form (Version 1.6.1)

Title: A study of whether tests and treatment of coronary function improve well-being of patients with angina and unobstructed heart arteries on CT.

Full title: The conundrum of angina in patients without obstructive coronary disease as revealed by CT coronary angiography (CorCTCA): an observational cohort study involving coronary function tests and a nested randomised trial.

Introduction

You are invited to take part in a research study of a new way to assess and treat patients with symptoms due to known or suspected narrowing of the blood vessels that supply blood to the heart.

Before you decide to take part, it is important for you to understand why the research is being done and what it will involve. If there is anything that is unclear or if you would like more information, please feel free to ask at any point. Take time to decide whether or not you wish to take part and talk to others about the study if you wish.

Why have I been invited?

You have been invited because you have known or suspected angina and have been referred for a CT scan to obtain pictures of the blood vessels that supply blood to your heart. Angina is a chest symptom that occurs when there is not enough supply of blood to the heart.

The CT angiogram that you are soon to have, can reveal a blockage in the larger vessels that supply the heart. If a blockage is seen, this will explain your angina symptoms. If the scan does not reveal any blockages, and given that you have angina-like chest symptoms, a coronary angiogram is still often performed during standard care. This is because a CT scan may not show the small vessels in the heart or provide information on the function of the blood vessels. Small blood vessel problems cannot be detected by the CT scan, and as a result, the cause of the chest symptoms would be missed. Currently, coronary angiography is not routine if the CT scan is normal, but patients with persistent symptoms and a normal CT scan may eventually be referred for an angiogram.

What is the purpose of the study?

The purpose of this study is to

a) Reassess mild - moderate narrowings revealed by a CT scan in patients with chest symptoms

b) Assess the function of the small blood vessels in the heart

c) Determine what proportion of patients with anginal chest symptoms but without blockages in their heart arteries have abnormal small vessel function

d) Determine whether treatment linked to the results of these tests improves health and well-being and NHS costs.

The results will help answer whether or not a larger study should be performed in the future. Currently, standard care based on the angiogram does not involve tests of small vessel function in the heart. The angiogram can only show us the large blood vessels that supply the heart. It is not known whether routine use of additional tests of small blood vessel function during standard care would be beneficial. However, a recent British Heart Foundation-funded study that was undertaken in our hospital has shown that treatment guided by the results of these tests improves wellbeing.

We would like to:

a) Invite you to take part in this study.

b) Gather information on the function of the heart arteries at the time of the angiogram

c) Obtain a blood sample at the start of the study and urine and blood sample during follow up (at 12 months)

d) Have you complete a health status using questionnaires at the start of the study and during follow-up contacts

e) Obtain information on well-being and treatment in the longer term from NHS or government records (but without contacting you)

f) Undertake additional analyses of the angiograms for research purposes e.g. to develop new tests of heart and blood vessel function

The angiogram, which is part of the study, involves a small catheter (a thin hollow tube about 2-3 mm in size) passed through a blood vessel in the wrist (or sometimes the groin) under local anaesthetic. This is the most accurate method of evaluating the heart arteries. With X-ray guidance, the catheter is advanced to the opening of the heart arteries and a small amount of radio-opaque dye is injected into the arteries to produce images.

The tests at the time of the angiogram involve using a thin wire with a pressure & temperature sensor at the tip. The wire is identical to a standard coronary wire used in angioplasty, except that the sensor is connected to a monitor. The doctor may have already decided to use this wire to assess the main blood vessels (fractional flow reserve, FFR test) in your heart as part of standard care. The same wire can be used in the artery to measure small vessel function with saline injections (without being moved into the small vessels). The final step would be to give you a chemical called acetylcholine (which is found naturally in the body) to assess the function of the blood vessels and take some extra pictures.

If there is a blockage on your angiogram you would not be eligible for the main study. Instead, we would like to be able to record your wellbeing and medications in the future by checking electronic records held by the NHS and government agencies, but without the need to contact you for this. Your care would not be affected. Only if you continue in the study will tests of small vessel function be performed. In one half of the participants, the results will be available to guide management whereas in the other half of participants, the results would not be disclosed ('Usual Care group'). Doctors in the 'Disclosed group' would have the results to guide their decisions. In the Usual Care group, the decisions would be made in the normal way. We favour this approach because we do not know if treatment informed by these tests would make any difference to health and wellbeing.

Do I have to take part?

No, it is up to you to decide whether or not to take part. If you do decide to take part you will be offered this information sheet to keep and be asked to sign a consent form. You are still free to withdraw at any time without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect your care.

What is the procedure that is being tested?

Blood vessel function in the heart will be measured with a thin wire and then a test of blood vessel relaxation with acetylcholine. Normally, small vessel function is not measured during an angiogram so the measurements would be in addition to usual care. The measurements last about 10 - 15 min. The cardiologist will usually make the measurements in one artery, but they may wish to obtain further measurements in other arteries if felt to be appropriate. By taking part in this study, the angiogram might take 15 minutes longer. Before the measurement is made, you will be assigned into one of two groups, the 'Disclosed group' or the 'Usual care' group.

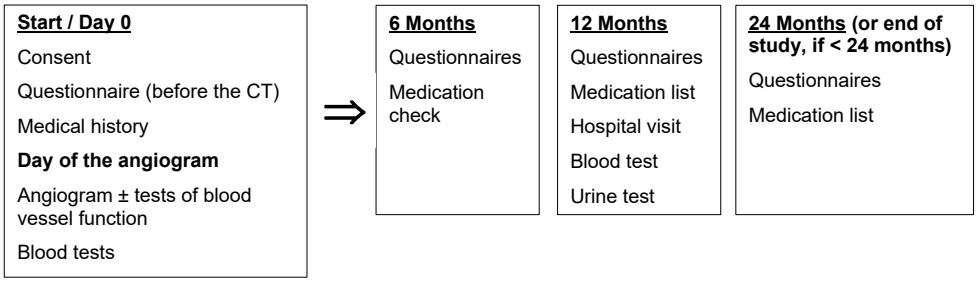
What will happen to me if I take part?

Once you have read this information sheet, you will have the opportunity to discuss the project, including with your family, friends or other staff in the department. If you agree to take part, you should then give written informed consent before you know the result of the CT scan. Information on your medical history will be gathered from NHS records. You will be given an appointment to attend for the coronary angiogram at the Golden Jubilee hospital. If a blockage is found at the time of this angiogram, you will receive standard care at the time e.g. a stent to open the blockage, and you would continue with the follow-up only (no additional contact).

On the day of the angiogram, you will have the opportunity to ask questions. If the angiogram does not reveal a blockage then you would be assigned (by equal chance) to the 'Disclosed Group' or

the 'Usual Care group. The study tests will then be performed. The blood vessel will be briefly relaxed by giving a drug called adenosine. The adenosine is given through a drip in a vein in your arm for up to 2 minutes. Next, the acetylcholine is given in 3 doses into the heart blood vessel, each for up to 2 minutes. If a clear result is obtained, then the next dose(s) would not be needed.

Flow diagram of the study



Guidance for your doctor

If you are assigned to the Disclosed Group, your doctor will be given a letter with information about the final diagnosis and guidance for treatment. If the tests are normal your doctor may stop the angina medication and refer for other tests. If you are in the Usual Care group, then your doctors will follow standard care based on the results of the angiogram.

Possible side effects

The angiogram and procedure: The angiogram usually lasts 30 minutes. There is a small risk of a blood vessel damage that might cause a heart attack (about 1 in 1000) or bleeding (about 1 in 100), which would be treated at the time e.g. with a stent. Adenosine can cause a feeling of chest tightness but this only lasts for the time the adenosine is being given. Otherwise, adenosine is well tolerated. The positioning of the thin wire will require some extra angiogram pictures. Rarely (approximately 1 in 1000), the wire may cause damage and a stent would be needed. Rarely, the acetylcholine medication used to assess the function of your heart artery can cause chest symptoms. This is quickly and easily reversible using the same medicine as the angina spray that you may have previously used under the tongue. During the procedure, you will receive a small additional amount of radiation which should not be harmful to you. The extra dose will be generally equivalent to an x-ray of your lower back. The actual dose is equivalent to 12 months of background radiation representing an additional risk of lifetime cancer of about 1 in 9,500. If you are in the Usual Care Group, your treatment will continue in the usual way without informing you or your doctor of the additional test results. This is an important part of the study as doctors do not know whether decisions guided by the results of the tests makes any difference wellbeing.

Study assessments

There is only one follow-up visit to the hospital (i.e. the clinical research unit) at 1 year. Your costs for travel will be reimbursed. There is a telephone call and mail contact at 6 months and 24 months (or when the study ends). You do not need to visit the hospital at these times. There is longer term follow-up by checking health records but you will not be contacted.

Blood test: We would also like to obtain a blood sample at the start of the study and after 1 year. Our aim is to identify blood markers of abnormal heart artery function – this could allow better identification of patients before invasive procedures. We would like to draw about 30 millilitres (~3 tablespoons) of blood during the angiogram procedure. Blood will be taken from the catheter used for this procedure so no additional needle insertion would be needed. We may prepare DNA and RNA from these cells to examine whether the genetic make-up has any connection with blood vessel function in the heart. Small blood samples will be stored in a freezer to be analysed at a later stage, particularly when new markers of disease will have been developed by us or by other scientists. Further approval will be required by the ethics committee for future studies with any of your samples.

Questionnaire: We would also like you to complete some questionnaires about your health and wellbeing and treatment at the start of the study and up to 3 times at 6, 12 and 24 months (or end of the study). These forms normally take less than 10 minutes and include questions about your symptoms, medications and short "tick-box" questionnaire about your well-being.

Urine test: At 12 months to assess for levels of medications in the urine and also to assess for small chemicals that might be related to blood vessel function in the heart.

Angiograms: The images from the CT scan and coronary angiogram may be useful to develop new tests of heart and blood vessel health. We would like to undertake additional assessments with the images (identifiers removed) including with collaborators in the UK and abroad.

We also wish to link the study information with your other test results in the NHS through access to NHS Safe Havens, which hold de-identified clinical information.

What are the benefits of taking part?

You may not benefit directly from taking part. You will be helping us to find new ways to diagnose and treat patients with chest pain.

Is there any long term follow up?

We would like to obtain follow-up information on your well-being, NHS visits and treatment on up to 3 occasions (6, 12 and 24 months (or end of the study). If we cannot reach you by telephone or by post we would like to contact your General Practitioner. We will contact you at the end of the first year and we will invite you to the hospital in order to obtain a blood test. In the longer-term, we would like to obtain information on your future wellbeing and treatment. We would like to obtain this information by linking with records held by the NHS or on Government records (e.g. Registrar General). We would also like to obtain information on your treatment (medication). We can obtain this information through confidential electronic record linkage. We will not contact you for this.

What if something goes wrong?

We understand that this may be a stressful time and in the unlikely event of a problem we can be contacted and help support you by liaising with your GP for additional care. Furthermore, if you are still unsatisfied, the normal NHS complaints mechanisms will be available to you.

Will my taking part in this study be kept confidential?

Yes. All information that is collected about you during the course of the research will be kept confidential. Any information, including medical images, about you that leaves the hospital will have your name and address removed so that you cannot be recognised from it. Your personal information will be kept on file and securely stored in the University of Glasgow and in the NHS. All test results will be labelled with a code and not with any personal details so that all analyses will be carried out anonymously. All information which is collected about you during the course or the research will be kept strictly confidential. Your name and address will be removed from any information which leaves the hospital so that you cannot be identified.

Involvement of your General Practitioner

Your GP will be informed about your involvement with the research study. Specifically, we will be providing guidance on your drug therapy and management after the angiogram.

Who is funding the research? The British Heart Foundation & University of Glasgow.

Who has reviewed the study? The NHS Research Ethics Committee.

Further Information?

If you have any questions or concerns relating to the study please do get in touch with Dr Novalia Sidik or Prof Colin Berry in the Cardiology Department, Golden Jubilee National Hospital, Tel: 0141 951 5180. If you wish advice from a member of staff who is independent of this study please contact: Ms. Joanne Kelly, Senior Research Nurse: 0141 951 5000.

Patient consent form

Golden Jubilee National Hospital

NHS National Waiting Times Centre

CONSENT FORM Version 1.6.1

Title

"A study of whether tests & treatment of coronary function improve well-being of patients with angina and unobstructed heart arteries on CT**"**

Full title

"The conundrum of angina in patients without obstructive coronary disease as revealed by CT coronary angiography (CorCTCA): an observational cohort study involving coronary function tests and a nested randomised trial"

Name of Researcher: Professor Colin Berry

Please initial box

1. I confirm that I have read and understood the information sheet for the above study and have had the opportunity to ask questions. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. I understand that any data collected before my decision to withdraw will be retained for use in the research study. ☐
3. I understand that whilst my medical information will be treated with full confidentiality, the medical records may be reviewed and recorded by responsible individuals from the research team or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. ☐
4. I understand that the blood samples will be retained for future research, and that further approval will be sought from an Ethics Committee for future studies. ☐
5. I agree to follow-up information being collected on my future wellbeing and treatment from NHS and Government health records. ☐
6. If not enrolled in the main study, I agree to take part in the follow-up registry. ☐
7. I agree to take part in the above study and my GP will be informed of my participation. ☐
8. I agree to being contacted in the future the case of a future study that may be relevant ☐
9. I agree to the angiograms and coronary function tests being used for additional research. ☐

_____	_____	_____
Name of Patient	Date	Signature
_____	_____	_____
Researcher	Date	Signature

1 for patient; 1 for researcher; 1 to be kept with hospital notes

Patient health status questionnaires

Rose Angina Questionnaire[1]

Please circle response

Part A

(a) Have you ever had any pain or discomfort in your chest?
1. Yes
2. No

(b) Do you get this pain or discomfort when you walk uphill or hurry?
1. Yes
2. No

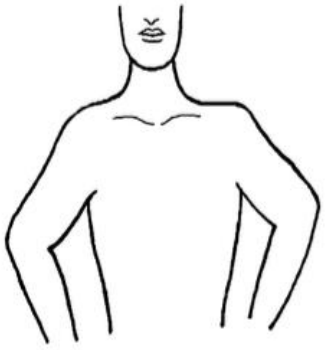
(c) Do you get it when you walk at an ordinary pace on the level?
1. Yes
2. No

(d) When you get any pain or discomfort in your chest what do you do?
1. Stop
2. Slow down
3. Continue at the same pace

(e) Does it go away when you stand still?
1. Yes
2. No

(f) How soon?
1. 10 minutes or less
2. More than 10 minutes

(g) Where do you get this pain or discomfort? Mark the place(s) with an X on the diagram.



Part B

Have you ever had a severe pain across the front of your chest lasting for half an hour or more?
1. Yes
2. No

1 Rose G, McCartney P, Reid DD. Self-administration of a questionnaire on chest pain and intermittent claudication. *Br J Prev Soc Med* 1977; 31: 42-48.

The Seattle Angina Questionnaire

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

Place an x in one box on each line

Activity	Extremely Limited	Quite a bit Limited	Moderately Limited	Slightly Limited	Not Limited at all	Limited for other reasons or did not do the activity
Dressing yourself	☐	☐	☐	☐	☐	☐
Walking indoors on level ground	☐	☐	☐	☐	☐	☐
Showering or bathing	☐	☐	☐	☐	☐	☐
Climbing a hill or a flight of stairs without stopping	☐	☐	☐	☐	☐	☐
Gardening, vacuuming, or carrying groceries	☐	☐	☐	☐	☐	☐
Walking more than a hundred yards at a brisk pace	☐	☐	☐	☐	☐	☐
Running or jogging	☐	☐	☐	☐	☐	☐
Lifting or moving heavy objects such as furniture, or lifting children	☐	☐	☐	☐	☐	☐
Participating in strenuous sports (e.g. swimming, tennis)	☐	☐	☐	☐	☐	☐

2. Compared with 4 weeks ago, how often do you have **chest pain**, **chest tightness**, or **anginal attacks** when doing your **most strenuous** activities?

I have **chest pain**, **chest tightness**, or **anginal attacks**...

Much more often	**Slightly more** often	About **the same**	**Slightly less** often	**Much less** often	I have had **no chest pain** over the last 4 weeks
☐	☐	☐	☐	☐	☐

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

I have had **chest pain**, **chest tightness**, or **anginal attacks**...

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

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

I have taken GTN...

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

5. How bothersome is it for you to take your pills for **chest pain**, **chest tightness** or **anginal attacks** as prescribed?

Extremely bothersome	**Quite a bit** bothersome	**Moderately** bothersome	**Slightly** bothersome	**Not** bothersome at all	My doctor has **not prescribed** pills
☐	☐	☐	☐	☐	☐

6. How satisfied are you that everything possible is being done to treat your **chest pain**, **chest tightness**, or **anginal attacks**?

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

7. How satisfied are you with the explanations your doctor has given you about your **chest pain**, **chest tightness**, or **anginal attacks**?

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

8. Overall, how satisfied are you with the current treatment of your **chest pain**, **chest tightness**, or **anginal attacks**?

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

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

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

10. If you had to spend the rest of your life with your **chest pain**, **chest tightness**, or **anginal attacks** the way it is at the moment, how would you feel about this?

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

11. How often do you think or worry that you may have a heart attack or die suddenly?

I think or worry about it **all the time**	I **often** think or worry about it	I **occasionally** think or worry about it	I **rarely** think or worry about it	I **never** think or worry about it
☐	☐	☐	☐	☐

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

MOBILITY

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

SELF-CARE

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

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

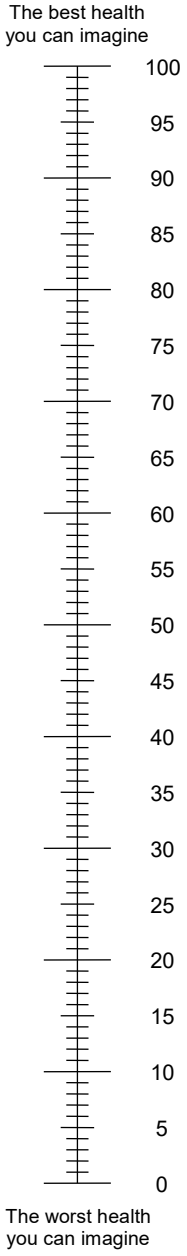
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

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

YOUR HEALTH TODAY = ☐



PHQ-4				
Over the last 2 weeks, how often have you been bothered by the following problems? *(Use "✓" to indicate your answer)*	Not at all	Several days	More than half the days	Nearly every day
1. Feeling nervous, anxious or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Little interest or pleasure in doing things	0	1	2	3
4. Feeling down, depressed, or hopeless	0	1	2	3

(*For office coding: Total Score T*____ = ____ + ____ + ____)

Study ID…….

Treatment satisfaction questionnaire – TSQM 9[1])

1. **How satisfied or dissatisfied are you with the ability of the medication to prevent or treat your condition?**
□1 Extremely Dissatisfied
□2 Very Dissatisfied
□3 Dissatisfied
□4 Somewhat Satisfied
□5 Satisfied
□6 Very Satisfied
□7 Extremely Satisfied

2. **How satisfied or dissatisfied are you with the way the medication relieves your symptoms?**
□1 Extremely Dissatisfied
□2 Very Dissatisfied
□3 Dissatisfied
□4 Somewhat Satisfied
□5 Satisfied
□6 Very Satisfied
□7 Extremely Satisfied

3. **How satisfied or dissatisfied are you with the amount of time it takes the medication to start working?**
□1 Extremely Dissatisfied
□2 Very Dissatisfied
□3 Dissatisfied
□4 Somewhat Satisfied
□5 Satisfied
□6 Very Satisfied
□7 Extremely Satisfied

4. **How easy or difficult is it to use the medication in its current form?**
□**1 Extremely Difficult**
□2 Very Difficult
□3 Difficult
□4 Somewhat Easy
□5 Easy
□6 Very Easy
□7 Extremely Easy

1. Bharmal M, Payne K, Atkinson MJ, Desrosiers MP, Morisky DE, Gemmen E. Validation of an abbreviated Treatment Satisfaction Questionnaire for Medication (TSQM-9) among patients on antihypertensive medications. Health Qual Life Outcomes 2009;7:36.

Study ID…….

5. How easy or difficult is it to plan when you will use the medication each time?
□1 Extremely Difficult
□2 Very Difficult
□3 Difficult
□4 Somewhat Easy
□5 Easy
□6 Very Easy
□7 Extremely Easy

6. **How convenient or inconvenient is it to take the medication as instructed?**
□1 Extremely Inconvenient
□2 Very Inconvenient
□3 Inconvenient
□4 Somewhat Convenient
□5 Convenient
□6 Very Convenient
□7 Extremely Convenient

7**. Overall, how confident are you that taking this medication is a good thing for you?**
□1 Not at All Confident
□2 A Little Confident
□3 Somewhat Confident
□4 Very Confident
□5 Extremely Confident

8. **How certain are you that the good things about your medication outweigh the bad things?**
□1 Not at All Certain
□2 A Little Certain
□3 Somewhat Certain
□4 Very Certain
□5 Extremely Certain

9. **Taking all things into account, how satisfied or dissatisfied are you with this medication?**
□1 Extremely Dissatisfied
□2 Very Dissatisfied
□3 Dissatisfied
□4 Somewhat Satisfied
□5 Satisfied
□6 Very Satisfied
□7 Extremely Satisfied

1. Bharmal M, Payne K, Atkinson MJ, Desrosiers MP, Morisky DE, Gemmen E**.** Validation of an abbreviated Treatment Satisfaction Questionnaire for Medication (TSQM-9) among patients on antihypertensive medications. Health Qual Life Outcomes 2009;7:36**.**

The Brief Illness Perception Questionnaire

For the following questions, please circle the number that best corresponds to your views:

How much does your illness affect your life?										
0 no affect at all	1	2	3	4	5	6	7	8	9	10 severely affects my life
How long do you think your illness will continue?										
0 a very short time	1	2	3	4	5	6	7	8	9	10 forever
How much control do you feel you have over your illness?										
0 absolutely no control	1	2	3	4	5	6	7	8	9	10 extreme amount of control
How much do you think your treatment can help your illness?										
0 not at all	1	2	3	4	5	6	7	8	9	10 extremely helpful
How much do you experience symptoms from your illness?										
0 no symptoms at all	1	2	3	4	5	6	7	8	9	10 many severe symptoms
How concerned are you about your illness?										
0 not at all concerned	1	2	3	4	5	6	7	8	9	10 extremely concerned
How well do you feel you understand your illness?										
0 don't understand at all	1	2	3	4	5	6	7	8	9	10 understand very clearly
How much does your illness affect you emotionally? (e.g. does it make you angry, scared, upset or depressed?										
0 not at all affected emotionally	1	2	3	4	5	6	7	8	9	10 extremely affected emotionally

Please list in rank-order the three most important factors that you believe caused <u>your illness</u>. *The most important causes for me:-*

1. _____

2. _____

3. _____

DUKE ACTIVITY STATUS INDEX

Name: _____ Hosp No: _____

Date: _____

Can You: (please circle yes or no)

1. Take care of yourself, that is, eat dress, bathe or use the toilet?	Yes/No
2. Walk indoors, such as around your house?	Yes/No
3. Walk a block or two on level ground?	Yes/No
4. Climb a flight of stairs or walk up a hill?	Yes/No
5. Run a short distance?	Yes/No
6. Do light work around the house like dusting or washing dishes?	Yes/No
7. Do moderate work around the house like vacuuming, sweeping floors or carrying groceries?	Yes/No
8. Do heavy work around the house like scrubbing floors or lifting or moving heavy furniture?	Yes/No
9. Do yard work like raking leaves, weeding or pushing a power mower?	Yes/No
10. Have sexual relations?	Yes/No
11. Participate in moderate recreational activities like golf, bowling, Dancing, doubles tennis or throwing a baseball or football?	Yes/No
12. Participate in strenuous sports like swimming, singles tennis Football, basketball or skiing?	Yes/No

Score=_____

Estimated VO_2peak=_____[METS]

INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE (August 2002) – Short (7 days)

Think about all the **vigorous** activities that you did in the **last 7 days**. **Vigorous** physical activities refer to activities that take hard physical effort and make you breathe much harder than normal. Think *only* about those physical activities that you did for at least 10 minutes at a time.

1. During the **last 7 days**, on how many days did you do **vigorous** physical activities like heavy lifting, digging, aerobics, or fast bicycling?

   _____ **days per week**

   ☐ No vigorous physical activities → ***Skip to question 3***

2. How much time did you usually spend doing **vigorous** physical activities on one of those days?

   _____ **hours per day**

   _____ **minutes per day**

Think about all the **moderate** activities that you did in the **last 7 days**. **Moderate** activities refer to activities that take moderate physical effort and make you breathe somewhat harder than normal. Think only about those physical activities that you did for at least 10 minutes at a time.

3. During the **last 7 days**, on how many days did you do **moderate** physical activities like carrying light loads, bicycling at a regular pace, or doubles tennis? Do not include walking.

   _____ **days per week**

   ☐ No moderate physical activities → ***Skip to question 5***

4. How much time did you usually spend doing **moderate** physical activities on one of those days?

   _____ **hours per day**

   _____ **minutes per day**

Think about the time you spent **walking** in the **last 7 days**. This includes at work and at home, walking to travel from place to place, and any other walking that you have done solely for recreation, sport, exercise, or leisure.

5. During the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time?

   _____ **days per week**

   ☐ No walking → ***Skip to question 7***

6. How much time did you usually spend **walking** on one of those days?

   _____ **hours per day**

   _____ **minutes per day**

The last question is about the time you spent **sitting** on weekdays during the **last 7 days**. Include time spent at work, at home, while doing course work and during leisure time. This may include time spent sitting at a desk, visiting friends, reading, or sitting or lying down to watch television.

7. During the **last 7 days**, how much time did you spend **sitting** on a **week day**?

   _____ **hours per day**

   _____ **minutes per day**

This is the end of the questionnaire, thank you for participating.

Clinician questionnaire

Cor-CTCA Clinician Questionnaire

Clinician: _____

Date: _____

What is your assessment of the patient's symptoms?	Typical ☐	Atypical ☐	Non-anginal ☐

DIAGNOSIS PRE CTCA				
Likelihood of CAD	Not ☐	Unlikely ☐	Probably ☐	Very ☐
Likelihood of angina due to obstructive CAD (ie >70% stenosis in main branch or >50% in LMS)	Not ☐	Unlikely ☐	Probably ☐	Very ☐
Likelihood of microvascular angina	Not ☐	Unlikely ☐	Probably ☐	Very ☐
Likelihood of vasospastic angina	Not ☐	Unlikely ☐	Probably ☐	Very ☐
Likelihood of a non-cardiac chest pain	Not ☐	Unlikely ☐	Probably ☐	Very ☐

DIAGNOSIS POST CTCA				
Likelihood of CAD	Not ☐	Unlikely ☐	Probably ☐	Very ☐
Likelihood of angina due to obstructive CAD (ie >70% stenosis in main branch or >50% in LMS)	Not ☐	Unlikely ☐	Probably ☐	Very ☐
Likelihood of microvascular angina	Not ☐	Unlikely ☐	Probably ☐	Very ☐
Likelihood of vasospastic angina	Not ☐	Unlikely ☐	Probably ☐	Very ☐
Likelihood of a non-cardiac chest pain	Not ☐	Unlikely ☐	Probably ☐	Very ☐

MANAGEMENT POST CTCA		
Will the treatment plan change?	Yes ☐	No ☐
If yes, in what way?	Medication ☐	Angio/PCI ☐ CABG ☐
Should preventive therapy be included?	Yes ☐	No ☐
Should angina therapy be included?	Yes ☐	No ☐
If yes, will you change the angina therapy?	Yes ☐	No ☐
If yes, is this for a disorder of coronary fx?	Yes ☐	No ☐
Do you plan additional diagnostic test?	Yes ☐	No ☐
If yes, is it a cardiovascular test?	☐ Echocardiogram ☐ CT scan ☐ MRI ☐ Nuclear ☐ Ambulatory ECG ☐ Ambulatory BP ☐ Angiogram	
If yes, is it a non-cardiovascular test?	☐ Ultrasound ☐ CT scan ☐ MRI ☐ Endoscopy ☐ Other	
Will you discharge the patient?	Yes ☐	No ☐
Will you refer to a different specialty?	Yes ☐	No ☐
If yes, which?		

DIAGNOSIS POST CORONARY ANGIOGRAM (BEFORE RANDOMISATION)				
Likelihood of CAD	Not ☐	Unlikely ☐	Probably ☐	Very ☐
Likelihood of angina due to obstructive CAD (ie >70% stenosis in main branch or >50% in LMS)	Not ☐	Unlikely ☐	Probably ☐	Very ☐
Likelihood of microvascular angina	Not ☐	Unlikely ☐	Probably ☐	Very ☐
Likelihood of vasospastic angina	Not ☐	Unlikely ☐	Probably ☐	Very ☐
Likelihood of a non-cardiac chest pain	Not ☐	Unlikely ☐	Probably ☐	Very ☐

MANAGEMENT POST CORONARY ANGIOGRAM (BEFORE RANDOMISATION)			
Will the treatment plan change?	Yes ☐	No ☐	
If yes, in what way?	Medication ☐	Angio/PCI ☐	CABG ☐
Should preventive therapy be included?	Yes ☐	No ☐	
Should angina therapy be included?	Yes ☐	No ☐	
If yes, will you change the angina therapy?	Yes ☐	No ☐	
If yes, is this for a disorder of coronary fx?	Yes ☐	No ☐	
Do you plan additional diagnostic test?	Yes ☐	No ☐	
If yes, is it a cardiovascular test?	☐ Echocardiogram ☐ CT scan ☐ MRI ☐ Nuclear ☐ Ambulatory ECG ☐ Ambulatory BP ☐ Angiogram		
If yes, is it a non-cardiovascular test?	☐ Ultrasound ☐ CT scan ☐ MRI ☐ Endoscopy ☐ Other		
Will you discharge the patient?	Yes ☐	No ☐	
Will you refer to a different specialty?	Yes ☐	No ☐	
If yes, which?			

DIAGNOSIS POST RANDOMISATION (DISCLOSED GROUP)				
Likelihood of CAD	Not ☐	Unlikely ☐	Probably ☐	Very ☐
Likelihood of angina due to obstructive CAD (ie >70% stenosis in main branch or >50% in LMS)	Not ☐	Unlikely ☐	Probably ☐	Very ☐
Likelihood of microvascular angina	Not ☐	Unlikely ☐	Probably ☐	Very ☐
Likelihood of vasospastic angina	Not ☐	Unlikely ☐	Probably ☐	Very ☐
Likelihood of a non-cardiac chest pain	Not ☐	Unlikely ☐	Probably ☐	Very ☐

MANAGEMENT POST RANDOMISATION (DISCLOSED GROUP)			
Will the treatment plan change?	Yes ☐	No ☐	
If yes, in what way?	Medication ☐	Angio/PCI ☐	CABG ☐
Should preventive therapy be included?	Yes ☐	No ☐	
Should angina therapy be included?	Yes ☐	No ☐	
If yes, will you change the angina therapy?	Yes ☐	No ☐	
If yes, is this for a disorder of coronary fx?	Yes ☐	No ☐	
Do you plan additional diagnostic test?	Yes ☐	No ☐	
If yes, is it a cardiovascular test?	☐ Echocardiogram ☐ CT scan ☐ MRI ☐ Nuclear ☐ Ambulatory ECG ☐ Ambulatory BP ☐ Angiogram		
If yes, is it a non-cardiovascular test?	☐ Ultrasound ☐ CT scan ☐ MRI ☐ Endoscopy ☐ Other		
Will you discharge the patient?	Yes ☐	No ☐	
Will you refer to a different specialty?	Yes ☐	No ☐	
If yes, which?			

6-month follow up letter to patients

Golden Jubilee National Hospital
NHS National Waiting Times Centre

***Title**: A study of whether tests and treatment of coronary function improve well-being of patients with angina and unobstructed heart arteries on CT.*

Full title: The conundrum of angina in patients without obstructive coronary disease as revealed by CT coronary angiography (CorCTCA): an observational cohort study involving coronary function tests and a nested randomised trial.

Dear <Insert Patient Name>,

We would be most grateful if you could kindly complete the attached questionnaire which is approximately six months after your coronary angiogram and enrolment in the CorCTCA study. This questionnaire is a vital part of the research process and we take this opportunity to thank you once again for your assistance in completing the questions and returning this via the stamped addressed envelope.

Please list the medications that you take on a daily basis in the space below.

Please write **today's date - …….**

Medicine	Dose	Medicine	Dose

We are most grateful for your participation in this study. If you have any questions or concerns relating to the study please do get in touch with me on the details below.

Kind regards,

Dr Novalia Sidik (Clinical research fellow for Prof Colin Berry)
Department of Cardiology, Golden Jubilee National Hospital, Tel: 0141 951 5180.

Discharge guidance document for primary care physicians

NHS Golden Jubilee National Hospital

Golden Jubilee Research Institute
Patients at the heart of progress

Cor-CTCA Study- Discharge guidance framework for GPs

Diagnosis – Microvascular angina

We have produced this brief guidance document to assist in managing microvascular angina based on the 2013 ESC guidelines & 2007 SIGN guidelines.[1,2]

Pharmacological management

- Calcium antagonists (e.g. **Verapamil** 40mg **BD** uptitrated weekly according to response)
  - Or Beta-blockers (e.g. **Carvedilol** 6.25mg **BD** uptitrated weekly or to response)
- **Aspirin, Statin** or **ACEi** may be reasonable (depending on patient characteristics)
- Short-acting PRN nitrate (e.g. **Sublingual GTN**)
- **Nicorandil** if refractory symptoms (e.g. 5mg BD uptitrated weekly according to response)
- Xanthine inhibitors (aminophylline) – if refractory to all above

Non Pharmacological lifestyle & risk factor control

- **Smoking** "Smoking is a strong and independent risk factor for CVD and all smoking, including environmental smoking exposure, must be avoided in all patients with CVD"
- **Diet** "A healthy diet reduces CVD risk... Energy intake should be limited to the amount of energy needed to maintain (or obtain) a healthy weight—that is, a BMI <25 kg/m2."
- **Exercise** "moderate-to-vigorous intensity aerobic exercise training ≥3 times a week" (30 min)
- **Weight** "Weight reduction in overweight and obese people is recommended in order to achieve favourable effects on BP, dyslipidaemia and glucose metabolism"
- **Lipids** – "The goals of treatment are LDL-C below 1.8 mmol/L"
- **Hypertension** – "SBP/DBP to values within the range 130–139/80–85 mmHg"
- **Diabetes** "good control of glycated haemoglobin (HbA1c) to <7.0%...based on individual considerations."
- **Psychosocial** "Patients should be assessed for psychosocial distress and appropriate care offered… Refer for psychotherapy, medication or collaborative care in the case of clinically significant symptoms of depression, anxiety and hostility."
- **Cardiac rehabilitation** "A comprehensive risk-reduction regimen, integrated into comprehensive cardiac rehabilitation, is recommended to patients with CAD."

1. Task Force M, Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, et al. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. European heart journal. 2013;34(38):2949-3003.
2. SIGN. Guideline No. 96 - Management of stable angina. Edinburgh: Scottish Intercollegiate Guidelines Network (SIGN); 2007.

Version 1.4 April 2018

NHS Golden Jubilee National Hospital

Golden Jubilee Research Institute
Patients at the heart of progress

Cor-CTCA Study- Discharge guidance framework for GPs

Diagnosis – Vasospastic angina

We have produced this brief guidance document to assist in managing vasospastic angina based on the 2013 ESC guidelines & 2007 SIGN guidelines.[1,2]

Pharmacological management

- Non-dihydropyridine calcium channel blocker (e.g. **Verapamil** initially 40mg BD increasing at weekly intervals as tolerated up to 240-360mg daily)
- +/- **Long-acting nitrates** if symptoms ongoing (scheduled to cover the period of the day in which ischaemic episodes most frequently occur, in order to prevent nitrate tolerance.
- β-Blockers should be avoided.
- **Statin** therapy may be reasonable

Non Pharmacological lifestyle & risk factor control

- **Specific to vasospastic angina** – "exclude cocaine/amphetamine use"
- **Smoking** "Smoking is a strong and independent risk factor for CVD and all smoking, including environmental smoking exposure, must be avoided in all patients with CVD"
- **Diet** "A healthy diet reduces CVD risk... Energy intake should be limited to the amount of energy needed to maintain (or obtain) a healthy weight—that is, a BMI <25 kg/m2."
- **Exercise** "moderate-to-vigorous intensity aerobic exercise training ≥3 times a week" (30 min)
- **Weight** "Weight reduction in overweight and obese people is recommended in order to achieve favourable effects on BP, dyslipidaemia and glucose metabolism"
- **Lipids** – "The goals of treatment are LDL-C below 1.8 mmol/L"
- **Hypertension** – "SBP/DBP to values within the range 130–139/80–85 mmHg"
- **Diabetes** "good control of glycated haemoglobin (HbA1c) to <7.0%...based on individual considerations."
- **Psychosocial** "Patients should be assessed for psychosocial distress and appropriate care offered… Refer for psychotherapy, medication or collaborative care in the case of clinically significant symptoms of depression, anxiety and hostility."
- **Cardiac rehabilitation** "A comprehensive risk-reduction regimen, integrated into comprehensive cardiac rehabilitation, is recommended to patients with CAD."

1. Task Force M, Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, et al. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. European heart journal. 2013;34(38):2949-3003.
2. SIGN. Guideline No. 96 - Management of stable angina. Edinburgh: Scottish Intercollegiate Guidelines Network (SIGN); 2007.

Version 1.4 April 2018

Clinical Event Committee charter document

Clinical Event Committee Charter

Version No: 1.0

Study Title:	The conundrum of angina in patients without obstructive coronary disease as revealed by CT coronary angiography (Cor-CTCA): an observational cohort study involving coronary function tests and a nested randomised trial.
Short Title:	CorCTCA
Chief Investigator:	Professor Colin Berry
CEC Chairman	Dr Andrew Hannah
Co-Sponsors:	Golden Jubilee National Hospital
Sponsor Ref:	16/CARD/25
REC No.:	17/WS/0121
Protocol version:	1.5
ClinicalTrials.gov identifier:	NCT03193294

1. Introduction

Angina is form of chest pain that is due to a lack of blood to the heart muscle. Angina is commonly triggered by stress and exertion, and is a common health problem worldwide. The diagnosis and treatment of angina is usually focused on detection of blockages in heart arteries, and relief of this problem with drugs, stents or bypass surgery. However, about one third of all invasive angiograms that are performed in patients with angina do not reveal any blockages. Many of such patients may have symptoms due to narrowings in the very small micro vessels (too small to be seen on an angiogram).

The purpose of the CorCTCA study is to undertake a diagnostic study to determine the prevalence of microvascular or vasospastic angina in patients without obstructive artery disease (CAD) as revealed by a CT coronary angiogram for the investigation of known or suspected CAD. A second objective is to determine the clinical significance of disclosure of these test results on the initial diagnosis, treatment and longer term outcome of the participants.

2. Purpose

The purpose of this charter is to delineate the roles, responsibilities and procedures for the adjudication of cardiovascular events occurring in the CorCTCA study.

3. **Composition of the Clinical Event Committee (CEC)**

The CEC consists of at least 3 cardiovascular physicians who have expertise in the diagnosis and treatment of cardiovascular disorders and in the medical aspects of clinical trials.

All members of the committee will be experienced in clinical research with relevant prior training e.g. Good Clinical Practice.

CEC member	**Affiliation**	**Contact details**
Dr David Carrick (Chair)	University Hospital Hairmyres, UK	David.carrick@lanarkshire.scot.nhs.uk
Dr Ross McGeoch	University Hospital Hairmyres, UK	Ross.mcgeoch@lanarkshire.scot.nhs.uk
Dr David Corcoran	Queen Elizabeth University Hospital, UK	David.corcoran@ggc.scot.nhs.uk
Dr Ninian Lang	Queen Elizabeth University Hospital, UK	Ninian.lang@glasgow.ac.uk

In the event that a CEC member is unable to continue participation, the CEC Chairman will recommend a replacement to the Sponsor. The Sponsor has the final decision as to the replacement.

4. Roles and Responsibilities

The role of the CEC in the CorCTCA study is:

- To provide independent and unbiased review of clinical endpoint events which occur during the trial.
- To ensure unified and unambiguous events evaluation practices across the trial, through application of standardised event criteria, per protocol specifications.
- To compensate for regional diversity in medical practice in the area of event evaluation and classification, thereby reducing the impact of this diversity.

4.1. CEC Chairman

The CEC Chairman will be responsible for:

- Acting as the primary liaison between the CEC and the Sponsor
- Proposal of CEC members
- The overall conduct of the CEC
- Developing the CEC Charter

4.2. CEC members

CEC members will be responsible for:

- Reading and understanding the content of the CEC charter
- Reviewing the relevant de-identified clinical data about a subject identified as having experienced a suspected event of interest requiring adjudication
- Adjudicating pre-specified clinical events of interest in keeping with the study definitions outlined in this charter
- Completion of adjudication forms
- Timely submission of adjudication decisions
- Communicating with the CEC Chairman about needs when necessary
- Attending scheduled CEC meetings throughout the study

5. Clinical Events to be reviewed

The CorCTCA study will use electronic data capture. The identification of potential endpoints, uploading of source documents, completion of endpoint forms, collation of endpoint packages will be facilitated by the CEC Coordinator (Dr Novalia Sidik, University of Glasgow) and supported by clinical research staff at the sites.

6. Identification of potential endpoints

Potential endpoint events requiring review by the CEC will be identified following review of all SAEs by the Chief Investigator (CI) or a designated representative approved by the Sponsor.

SAE reports for each potential endpoint event will be reviewed by the CEC. Where the report contains sufficient information to allow adjudication of the event, the event will be classified. Where additional information is required before adjudication can take place this will be requested from the site.

Site teams will complete the required Case Report Forms for the event type and upload the required source data (detailed in Section 9) for these events and/or submit to the Sponsor and CEC directly.

The CEC will re-review the SAE report provided by the local investigator and relevant source clinical data provided to adjudicate on the cause of the event. The SAE record and source documents (detailed in Section 9) are expected to contain sufficient information to adjudicate on the cause(s) of the event.

The CEC will review and classify all reported instances of Major Adverse Cardiac Events (MACE) and all Major Adverse Cardiovascular and Cardiac Events (MACCE) and additional events to facilitate the assessment of efficacy and safety. This will include the review and classification of:

1. All causes of death
2. Stroke / Transient Ischaemic Attack
3. Non-fatal Myocardial infarction (MI) (i.e. any recurrent MI after index hospitalisation)
4. Heart Failure requiring hospitalisation
5. MI associated with revascularisation procedures (types 4 and 5).
6. Failed medical management - defined as cardiac MACE or coronary revascularisation.
7. Unstable angina requiring hospitalisation
8. Serious adverse events

7. Endpoint Definitions

Endpoint definitions will align with the 2014 ACC/AHA Key Data Elements and Definitions for Cardiovascular Endpoint Events in Clinical Trials Hicks KA, et al. [1]and the "Fourth Universal Definition of Myocardial Infarction" (Thygesen et al Eur Heart J 2019)[2] for diagnosis of myocardial infarction.

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[1] Hicks KA, Tcheng JE, Bozkurt B, Chaitman BR, Cutlip DE, Farb A, Fonarow GC, Jacobs JP, Jaff MR, Lichtman JH, Limacher MC, Mahaffey KW, Mehran R, Nissen SE, Smith EE, Targum SL, 2014 ACC/AHA Key Data Elements and Definitions for Cardiovascular Endpoint Events in Clinical Trials, *Journal of the American College of Cardiology* (2015), doi: 10.1016/j.jacc.2014.12.018.

[2] Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, White HD; ESC Scientific Document Group . Fourth universal definition of myocardial infarction (2018). Eur Heart J. 2019 Jan 14;40(3):237-269. doi: 10.1093/eurheartj/ehy462. PubMed PMID: 30165617.

Each event will usually be adjudicated on the basis of application of the endpoint definitions below. However, the clinical likelihood that a suspected event has occurred will be individually assessed even in the absence of fulfilment of all of the criteria specified in the event-definition, recognizing that information may at times be difficult to interpret (e.g. the exact measurement of ECG changes may be imprecise) or unavailable. The CEC will discuss such cases at a full CEC meeting and adjudicate them using their clinical expertise and the totality of the evidence before arriving at a classification decision that is based on full consensus**.**

7.1. Deaths

In cases where a patient experiences an event and later dies due to that event, the event causing death and the death will be considered as separate events only if they are separated by a change in calendar day. If the event causing death and the death occur on the same calendar day, death will be the only event classified.

7.1.1. Cardiovascular deaths

Cardiovascular death includes death resulting from an acute myocardial infarction, sudden cardiac death, death due to heart failure, death due to stroke and death due to other cardiovascular causes as follows:

7.1.1.1. Death due to Acute Myocardial Infarction refers to a death usually occurring up to 30 days after a documented acute myocardial infarction (verified either by the diagnostic criteria outlined below for acute myocardial infarction, above, or by autopsy findings showing recent myocardial infarction or recent coronary thrombus) due to the myocardial infarction or its immediate consequences (e.g. progressive heart failure) and where there is no conclusive evidence of another cause of death.
If death occurs before biochemical confirmation of myocardial necrosis can be obtained, adjudication should be based on clinical presentation and other (e.g. ECG, angiographic, autopsy) evidence.
NOTE: This category will include sudden cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischaemia, and accompanied by presumably new ST elevation*, or new left bundle branch block*, or evidence of fresh thrombus in a coronary artery by coronary angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood (i.e. myocardial infarction Type 3 – see section 4.2.1, below).
*If ECG tracings are not available for review, the CEC may adjudicate on the basis of reported new ECG changes that have been clearly documented in the case records or in the case report form.

Death resulting from a procedure to treat an acute myocardial infarction [percutaneous coronary intervention (PCI), coronary artery bypass graft surgery (CABG)], or to treat a complication resulting from acute myocardial infarction, should also be considered death due to acute myocardial infarction.

Death resulting from a procedure to treat myocardial ischaemia (angina) or death due to an acute myocardial infarction that occurs as a direct consequence of a cardiovascular investigation/procedure/operation that was not undertaken to treat an acute myocardial infarction or its complications should be considered as a death due to other cardiovascular causes.

7.1.1.2. **Sudden Cardiac Death** refers to a death that occurs unexpectedly in a previously stable patient. The cause of death should not be due to another adjudicated cause (e.g. acute myocardial infarction Type 3 – see section 4.2.1 below).

The following deaths should be included.
a. Death witnessed and instantaneous without new or worsening symptoms
b. Death witnessed within 60 minutes of the onset of new or worsening symptoms unless a cause other than cardiac is obvious.

c. Death witnessed and attributed to an identified arrhythmia (e.g., captured on an ECG recording, witnessed on a monitor), or unwitnessed but found on implantable cardioverter-defibrillator review.

d. Death in patients resuscitated from cardiac arrest in the absence of pre-existing circulatory failure or other causes of death, including acute myocardial infarction, and who die (without identification of a non-cardiac aetiology) within 72 hours or without gaining consciousness; similar patients who died during an attempted resuscitation.
e. Type 3 MI ~ Cardiac death with symptoms suggestive of myocardial ischaemia and presumed new ischaemic ECG changes or new LBBB, but death occurring before blood samples could be obtained, before cardiac biomarker could rise, or in rare cases cardiac biomarkers were not collected.
f. Unwitnessed death without any other cause of death identified (information regarding the patient's clinical status in the 24 hours preceding death should be provided, if available)

7.1.1.3. **Death due to Heart Failure** refers to a death occurring in the context of clinically worsening symptoms and/or signs of heart failure without evidence of another cause of death (e.g. acute myocardial infarction).

Death due to heart failure should include sudden death occurring during an admission for worsening heart failure as well as death from progressive heart failure or cardiogenic shock following implantation of a mechanical assist device.
New or worsening signs and/or symptoms of heart failure include any of the following:
a. New or increasing symptoms and/or signs of heart failure requiring the initiation of, or an increase in, treatment directed at heart failure or occurring in a patient already receiving maximal therapy for heart failure
Note: If time does not allow for the initiation of, or an increase in, treatment directed at heart failure or if the circumstances were such that doing so would have been inappropriate (e.g. patient refusal), the CEC will adjudicate on clinical presentation and, if available, investigative evidence.

b. Heart failure symptoms or signs requiring continuous intravenous therapy (i.e. at least once daily bolus administration or continuous maintenance infusion)
c. Confinement to bed predominantly due to heart failure symptoms.
d. Pulmonary oedema sufficient to cause tachypnoea and distress **not** occurring in the context of an acute myocardial infarction, worsening renal function (that is not wholly explained by worsening heart failure/cardiac function) or as the consequence of an arrhythmia occurring in the absence of worsening heart failure.
e. Cardiogenic shock **not** occurring in the context of an acute myocardial infarction or as the consequence of an arrhythmia occurring in the absence of worsening heart failure.
Cardiogenic shock is defined as systolic blood pressure (SBP) < 90 mm Hg for greater than 1 hour, not responsive to fluid resuscitation and/or heart rate correction, and felt to be secondary to cardiac dysfunction and associated with at least one of the following signs of hypoperfusion:

- Cool, clammy skin **or**
- Oliguria (urine output < 30 mL/hour) **or**
- Altered sensorium **or**
- Cardiac index < 2.2 L/min/m^2

Cardiogenic shock can also be defined if SBP < 90 mm Hg and increases to ≥ 90 mm Hg in less than 1 hour with positive inotropic or vasopressor agents alone and/or with mechanical support.

7.1.1.4. **Death due to Stroke** refers to death after a documented stroke (verified by the diagnostic criteria outlined below for stroke or by typical post mortem findings) that is either a direct consequence of the stroke or a complication of the stroke and where there is no conclusive evidence of another cause of death.

NOTE: In cases of early death where confirmation of the diagnosis cannot be obtained, the CEC may adjudicate based on clinical presentation alone.
Death due to a stroke reported to occur as a direct consequence of a cardiovascular investigation/procedure/operation will be classified as death due to other cardiovascular cause.

Death due to subdural or extradural haemorrhages will be adjudicated (based on clinical signs and symptoms as well as neuroimaging and/or autopsy) and classified separately.

7.1.1.5. Death due to cardiovascular procedures

Death due to cardiovascular procedures refers to death caused by the immediate complications of a cardiac procedure.

7.1.1.6. Death due to Other Cardiovascular Causes refers to a cardiovascular death not included in the above categories but with a specific known cause [e.g. pulmonary embolism or peripheral arterial disease)

7.1.2. Non-cardiovascular deaths

A non-cardiovascular death is defined as any death with a specific cause that is not thought to be due to a cardiovascular cause. There should be unequivocal and documented evidence of a non-cardiovascular cause of death.

7.1.3. Undetermined cause of death

This refers to any death not attributable to one of the above categories of cardiovascular death or to a non-cardiovascular cause (e.g. due to lack of information such as a case where the only information available is "patient died"). It is expected that every effort will be made to provide the adjudicating committee with enough information to attribute deaths to either a cardiovascular or non-cardiovascular cause so that the use of this category is kept to a minimal number of patients.

7.2. Non-fatal Cardiovascular Events

Date of onset: For purposes of classification, when classifying events that are a cause of hospitalisation, the date of admission will be used as the onset date. In cases where the stated date of admission differs from the date the patient first presented to hospital with the event (e.g. because of a period of observation in an emergency department, medical assessment unit or equivalent), the date of initial

presentation to hospital will be used (provided that the patient had not been discharged from hospital in the interim).
For events where an admission date is not applicable (or not available), the date of onset as stated by the investigator will be used.

7.2.1. Acute myocardial infarction

Note on biomarker elevations:
For cardiac biomarkers, laboratories should report an upper reference limit (URL). If the 99th percentile of the upper reference limit (URL) from the respective laboratory performing the assay is not available, then the URL for myocardial necrosis from the laboratory should be used. If the 99th percentile of the URL or the URL for myocardial necrosis is not available, the MI decision limit for the particular laboratory should be used as the URL.

Diagnosis of spontaneous or PCI/CABG-related acute myocardial infarction:
Note: this applies to post randomisation acute myocardial infarction not the index myocardial infarction
A rise and/or fall of cardiac biomarkers (troponin or CK-MB) should usually be detected wherever possible with at least one value above the upper reference limit (URL) together with clinical evidence of new myocardial ischaemia with at least one of the following:
Clinical symptoms and/or signs consistent with new ischaemia
ECG evidence of acute myocardial ischaemia or new left bundle branch block (LBBB) (Table, below).
Development of new pathological Q waves on the ECG (see Table 2, below)
Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
Autopsy evidence of acute myocardial infarction

Specific clinical classification of different types of myocardial infarction from Universal Definition of Myocardial Infarction (Thygesen et al Eur Heart J 2019)

Myocardial infarctions will be clinically classified as:
Type 1
Spontaneous myocardial infarction related to ischaemia due to a primary coronary event such as plaque erosion and/or rupture, fissuring, or dissection.
Type 2
Myocardial infarction secondary to ischaemia due to either increased oxygen demand or decreased supply, e.g. anaemia, arrhythmias, hypertension, hypotension. coronary artery spasm, coronary embolism.

Type 3

Sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischaemia, accompanied by presumably new ST elevation, or new LBBB, or evidence of fresh thrombus in a coronary artery by angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.

Type 4a: Myocardial infarction related to percutaneous coronary intervention (PCI)

Myocardial infarction associated with PCI is arbitrarily defined by elevation of cTn values >5 x 99th percentile URL in patients with normal baseline values (≤99th percentile URL) or a rise of cTn values >20% if the baseline values are elevated and are stable or falling. **In addition**, **either** (i) symptoms suggestive of myocardial ischaemia, or (ii) new ischaemic ECG changes or new LBBB, or (iii) angiographic loss of patency of a major coronary artery or a side branch or persistent slow or no-flow or embolisation, or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required.

Type 4b: Myocardial infarction related to stent thrombosis

Myocardial infarction associated with stent thrombosis is detected by coronary angiography or autopsy in the setting of myocardial ischaemia and with a rise and/or fall of cardiac biomarkers values with at least one value above the 99th percentile URL.

Type 5: Myocardial infarction related to coronary artery bypass grafting (CABG)

Myocardial infarction associated with CABG is arbitrarily defined by elevation of cardiac biomarker values >10 x 99th percentile URL in patients with normal baseline cTn values (≤99th percentile URL). In addition, either (i) new pathological Q waves or new LBBB, or (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

ECG manifestations of acute myocardial injury (troponin elevation in the absence of myocardial infarction)

From the 4th Universal Definition of Myocardial Infarction (Thygesen et al Eur Heart J 2019)

ST elevation

New ST elevation at the J-point in two anatomically contiguous leads with the cut-off points: ≥ 0.2 mV in men (> 0.25 mV in men < 40 years) or ≥ 0.15 mV in women in leads V2-V3 and/or ≥ 0.1 mV in other leads.

ST depression and T wave changes

New horizontal or down-sloping ST depression ≥ 0.05 mV in two contiguous leads; and/or new T wave inversion ≥ 0.1 mV in two contiguous leads.

The above ECG criteria illustrate patterns consistent with myocardial ischaemia. In patients with abnormal biomarkers, it is recognized that lesser ECG abnormalities may represent an ischemic response and may be accepted under the category of abnormal ECG findings.

ECG changes associated with prior myocardial infarction

From Universal Definition of Myocardial Infarction (Thygesen et al Eur Heart J 2019)

- Any Q-wave in leads V2-V3 ≥ 0.02 seconds or QS complex in leads V2 and V3
- Q-wave ≥ 0.03 seconds and ≥ 0.1 mV deep or QS complex in leads I, II, aVL, aVF, or V4-V6 in any two leads of a contiguous lead grouping (I, aVL, V6; V4-V6; II, III, and aVF) [a]
- R wave ≥0.04 sec in V1–V2 and R/S ≥1 with a concordant positive T wave in absence of conduction defect.

[a]The same criteria are used for supplemental leads V7–V9.

7.2.2. Heart Failure

7.2.2(a) Heart failure complicating the index acute myocardial infarction

For the diagnosis of heart failure complicating the index acute MI, the following criteria must be fulfilled at a time-point between the completion of the primary percutaneous coronary interventional procedure used to treat the qualifying MI and discharge from hospital at the end of the index admission:

There should be:

1. Clinical manifestations of new or worsening heart failure including at least one of the following:
    - New or worsening dyspnoea on exertion
    - New or worsening dyspnoea at rest
    - New or worsening fatigue/decreased exercise tolerance
    - New or worsening orthopnoea
    - New or worsening PND (paroxysmal nocturnal dyspnoea)
    - New or worsening lower limb or sacral oedema
    - New or worsening pulmonary crackles/crepitations
    - New or worsening elevation of JVP (jugular venous pressure)
    - New or worsening third heart sound or gallop rhythm

And

2. Investigative evidence of structural or functional heart disease (<u>if available</u>) with at least one of the following:
    - Radiological evidence of pulmonary oedema/congestion or cardiomegaly.

- Imaging (e.g. echocardiography, cardiac magnetic resonance imaging, radionuclide ventriculography) evidence of an abnormality (e.g. left ventricular systolic dysfunction, significant valvular heart disease, left ventricular hypertrophy).
- Elevation of BNP or NT-proBNP levels.
- Other investigative evidence of structural or functional heart disease (e.g. evidence obtained from pulmonary artery catheterisation).

And

3. Need for new/increased therapy***** specifically <u>for the treatment of heart failure</u>

Including at least one of the following:

- New or increased oral therapy for the treatment of heart failure
  (See note on oral therapy, below)
- Initiation of intravenous diuretic, inotrope, vasodilator or other recognised intravenous heart failure treatment or up-titration of such intravenous therapy if already receiving it
- Mechanical or surgical intervention (e.g. mechanical or non-invasive ventilation, mechanical circulatory support, heart transplantation, ventricular pacing to improve cardiac function), or the use of ultrafiltration, hemofiltration, dialysis or other mechanical or surgical intervention that is specifically directed at treatment of heart failure.

<u>Note on oral therapy</u>: In general, for an event to qualify as **heart failure complicating the index acute MI** on the basis of oral heart failure therapy (i.e. in cases where none of the non-pharmacological treatment modalities listed above have been utilised), the new or increased oral therapy should include oral diuretics. However, in special cases, other new or increased oral therapy (e.g. hydralazine/long acting nitrate, aldosterone antagonist) may be accepted provided that the adjudication committee is satisfied that:

a) the new or increased oral therapy was primarily directed at treating clinical manifestations of new or worsening heart failure (rather than, for example, initiation or up-titration of heart failure therapy as part of the routine optimisation of medical therapy)
   and
b) the totality of the evidence indicates that heart failure, rather than any other disease process, was the primary cause of the clinical presentation.

*****If time does not allow for the initiation of, or an increase in, treatment directed at heart failure or if the circumstances were such that doing so would have been inappropriate (e.g. patient refusal), the CEC will adjudicate on clinical presentation and, if available, investigative evidence.

And

The CEC should be satisfied that heart failure was the primary disease process accounting for the clinical presentation.

7.2.2(b) Heart failure requiring hospitalisation

For the diagnosis of heart failure requiring hospitalisation, there should be emergency/unplanned admission to a hospital setting (emergency room, observation or inpatient unit) that results in at least one overnight stay (i.e. a date change) with fulfilment of the following criteria:

There should be:

4. Clinical manifestations of new or worsening heart failure including at least one of the following:
- New or worsening dyspnoea on exertion
- New or worsening dyspnoea at rest
- New or worsening fatigue/decreased exercise tolerance
- New or worsening orthopnoea
- New or worsening PND (paroxysmal nocturnal dyspnoea)
- New or worsening lower limb or sacral oedema
- New or worsening pulmonary crackles/crepitations
- New or worsening elevation of JVP (jugular venous pressure)
- New or worsening third heart sound or gallop rhythm

And

5. Investigative evidence of structural or functional heart disease (<u>if available</u>) with at least one of the following:
- Radiological evidence of pulmonary oedema/congestion or cardiomegaly.
- Imaging (e.g. echocardiography, cardiac magnetic resonance imaging, radionuclide ventriculography) evidence of an abnormality (e.g. left ventricular systolic dysfunction, significant valvular heart disease, left ventricular hypertrophy).
- Elevation of BNP or NT-proBNP levels.
- Other investigative evidence of structural or functional heart disease (e.g. evidence obtained from pulmonary artery catheterisation).

And

6. Need for new/increased therapy***** specifically <u>for the treatment of heart failure</u>

Including at least one of the following:
- New or increased oral therapy for the treatment of heart failure
  (See note on oral therapy, below)
- Initiation of intravenous diuretic, inotrope, vasodilator or other recognised intravenous heart failure treatment or up-titration of such intravenous therapy if already receiving it

- Mechanical or surgical intervention (e.g. mechanical or non-invasive ventilation, mechanical circulatory support, heart transplantation, ventricular pacing to improve cardiac function), or the use of ultrafiltration, hemofiltration, dialysis or other mechanical or surgical intervention that is specifically directed at treatment of heart failure.

Note on oral therapy: In general, for an event to qualify as **heart failure requiring hospitalisation** on the basis of oral heart failure therapy (i.e. in cases where none of the non-pharmacological treatment modalities listed above have been utilised), the new or increased oral therapy should include oral diuretics. However, in special cases, other new or increased oral therapy (e.g. hydralazine/long acting nitrate, aldosterone antagonist) may be accepted provided that the adjudication committee is satisfied that:

c) the new or increased oral therapy was primarily directed at treating clinical manifestations of new or worsening heart failure (rather than, for example, initiation or up-titration of heart failure therapy as part of the routine optimisation of medical therapy)
and

d) the totality of the evidence indicates that heart failure, rather than any other disease process, was the primary cause of the clinical presentation.

*****If time does not allow for the initiation of, or an increase in, treatment directed at heart failure or if the circumstances were such that doing so would have been inappropriate (e.g. patient refusal), the CEC will adjudicate on clinical presentation and, if available, investigative evidence.

And

The CEC should be satisfied that heart failure was the primary disease process accounting for the clinical presentation.

7.2.3. Bleeding

BARC bleeding is defined as:

Type 2 – not for CEC review

Any overt, actionable sign of haemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria: (1) requiring nonsurgical, medical intervention by a healthcare professional, (2) leading to hospitalization or increased level of care, or (3) prompting evaluation

Type 3

- **Type 3a**

Overt bleeding plus haemoglobin drop of 3 to <5 g/dL* (provided haemoglobin drop is related to bleed)

Any transfusion with overt bleeding

- **Type 3b**

Overt bleeding plus haemoglobin drop ≥5 g/dL* (provided haemoglobin drop is related to bleed)

Cardiac tamponade

Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/haemorrhoid)

Bleeding requiring intravenous vasoactive agents

- **Type 3c**

Intracranial haemorrhage (does not include microbleeds or haemorrhagic transformation, does include intraspinal)

Subcategories confirmed by autopsy or imaging or lumbar puncture

Intraocular bleed compromising vision

Type 4: CABG-related bleeding

Perioperative intracranial bleeding within 48 h

Reoperation after closure of sternotomy for the purpose of controlling bleeding

Transfusion of ≥5 U whole blood or packed red blood cells within a 48-h period†

Chest tube output ≥2L within a 24-h period

Type 5: Fatal bleeding

- **5a** Probable fatal bleeding: no autopsy or imaging confirmation but clinically suspicious
- **5b** Definite fatal bleeding: overt bleeding or autopsy or imaging confirmation.

7.2.4. Stroke

Stroke is defined as an acute episode of neurological dysfunction caused by focal or global brain, spinal cord, or retinal vascular injury.

A For the diagnosis of stroke, the following 4 criteria should usually be fulfilled:

1. Rapid onset* of a focal/global neurological deficit with at least one of the following:

- Change in level of consciousness
- Hemiplegia
- Hemiparesis
- Numbness or sensory loss affecting one side of the body
- Dysphasia/aphasia
- Hemianopia (loss of half of the field of vision of one or both eyes)
- Complete/partial loss of vision of one eye

- Other new neurological sign(s)/symptom(s) consistent with stroke

*If the mode of onset is uncertain, a diagnosis of stroke may be made provided that there is no plausible non-stroke cause for the clinical presentation.

2. Duration of a focal/global neurological deficit ≥ 24 hours

or

< 24 hours if

(i) this is because of at least one of the following therapeutic interventions:

(a) pharmacologic i.e. thrombolytic drug administration.

(b) non-pharmacologic i.e. neurointerventional procedure (e.g. intracranial angioplasty).

or

(ii) brain imaging available clearly documenting a new haemorrhage or infarct.

or

(iii) the neurological deficit results in death

3. No other readily identifiable non-stroke cause for the clinical presentation (e.g. brain tumour, hypoglycaemia, peripheral lesion).

4. Confirmation of the diagnosis by at least one of the following**:

a) neurology or neurosurgical specialist.

b) brain imaging procedure (at least one of the following):

(i) CT scan.

(ii) MRI scan.

(iii) cerebral vessel angiography.

c) lumbar puncture (i.e. spinal fluid analysis diagnostic of intracranial haemorrhage).

****If a stroke is reported but evidence of confirmation of the diagnosis by the methods outlined above is absent, the event will be discussed at a full CEC meeting. In such cases, the event may be adjudicated as a stroke on the basis of the clinical presentation alone but full CEC consensus will be mandatory.

B If the acute neurological deficit represents a worsening of a previous deficit, this worsened deficit must have:

Persisted for more than one week

Or < one week if

(i) this is because of at least one of the following therapeutic interventions:

(a) pharmacologic i.e. thrombolytic drug administration.

(b non-pharmacologic i.e. neurointerventional procedure (e.g. intracranial angioplasty).

or

(ii) brain imaging available clearly documenting an appropriate new CT/MRI finding.

or

(iii) the neurological deficit results in death

Strokes will be further sub-classified as:

- **Ischaemic (non-haemorrhagic) stroke**

(i.e. caused by an infarction of central nervous system tissue)

or

- **Haemorrhagic stroke*****

(i.e. caused by non-traumatic intraparenchymal, intraventricular or subarachnoid hemorrhage)

or

- **Stroke type (i.e. haemorrhagic or ischaemic) unknown** (i.e. when imaging/other investigations are unavailable or inconclusive).

***Subdural and extradural haemorrhages will be adjudicated (based on clinical signs and symptoms as well as neuroimaging and/or autopsy) and classified separately by the CEC

7.2.5. Transient Ischaemic Attack

- Transient ischaemic attack (TIA) is any focal neurological deficit consistent with a cerebrovascular event with sudden onset, as defined above, that resolves within 24 hours.

7.3 Major Adverse Cardiac Events (Cardiac MACE)

Defined as 'cardiac death, non-fatal MI or hospitalisation for heart failure'. The cardiac MACE will be considered for all MIs and also for MACE with spontaneous MI only (i.e. not Type 4 or Type 5 MI).

7.4 Failed medical management

Defined as cardiac MACE or coronary revascularisation.

7.5 Hospitalisation for unstable angina

For the diagnosis of hospitalisation due to unstable angina there should be emergency/unplanned admission to a hospital setting (emergency room, observation or inpatient unit) that results in at least one overnight stay (i.e. a date change) with fulfilment of the following criteria:

There should be:

1. Cardiac ischaemic-type symptoms at rest (chest pain or equivalent) or an accelerating pattern of angina (e.g. exercise-related ischaemic-type symptoms increasing in frequency and/or severity, decreasing threshold for onset of exercise related ischaemic type symptoms) but without the fulfilment of the above diagnostic criteria for acute myocardial infarction.

and

2 The need for treatment with parenteral (intravenous, intra-arterial, buccal, transcutaneous or subcutaneous) anti-ischemic/antithrombotic therapy and/or coronary revascularization.

and

3a ECG manifestations of acute myocardial ischaemia (New ST-T changes meeting the criteria for acute myocardial ischaemia - as outlined in Table 1, section 5.2.1).

or

3b Angiographically significant coronary artery disease thought to be responsible for the patient's presentation. [If both invasive and CT angiographic imaging of the coronary arteries were performed, the results of the invasive coronary angiogram should take preference.]

and

4 The CEC should be satisfied that unstable angina was the primary reason for hospitalisation.

Hospitalisation for other angina*

For the diagnosis of hospitalisation for other angina, there should be emergency/unplanned admission to a hospital setting (emergency room, observation or inpatient unit) that results in at least one overnight stay (i.e. a date change) with fulfilment of the following criteria:

There should be:

1 Typical cardiac ischaemic-type symptoms but without the fulfilment of the above diagnostic criteria for acute myocardial infarction or unstable angina.

and

2 The need for treatment with new or increased anti-anginal therapy (excluding sublingual nitrate therapy).

and

3a Investigations undertaken in view of the event (e.g. exercise ECG or stress myocardial perfusion scan) showing evidence of reversible myocardial ischaemia.

or

3b Coronary angiography showing angiographically significant coronary disease thought to be responsible for the patient's presentation. [If both invasive and CT angiographic imaging of the coronary arteries were performed, the results of the invasive coronary angiogram should take preference.]

and

4 The CEC should be satisfied that angina was the primary reason hospitalisation.

Hospitalisation for other chest pain*

There should be:

- Emergency/unplanned admission to a hospital setting (emergency room, observation or inpatient unit) that results in at least one overnight stay i.e. a date change) due to chest pain but where the definitions (above) of acute myocardial infarction, hospitalisation for unstable angina or hospitalisation for other angina are not met.
- The CEC should be satisfied that chest pain was the primary reason for hospitalisation.

*These events are not study cardiovascular events of interest but the definitions provided for these events will be used by the CEC to categorise reported myocardial infarction, angina and chest pain events that do not meet the study definition of acute myocardial infarction or hospitalisation for unstable angina.

Adverse Event (do not require CEC review)

An adverse event (also referred to as an adverse experience) can be any unfavourable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a drug or study protocol. This does not include a judgment about causality or relationship to the drug.

Serious Adverse Event

A serious adverse event (SAE) is defined as an untoward occurrence that:

(a) results in death;

(b) is life-threatening;

(c) requires hospitalisation or prolongation of existing hospitalisation;

(d) results in persistent or significant disability or incapacity;

(e) consists of a congenital anomaly or birth defect; or

(f) is otherwise considered medically significant by the investigator.

NB An SAE occurring to a research participant should be reported to the Research Ethics Committee (University or NHS) that approved the study when in the opinion of the PI the event was:

- Related – that is, it resulted from administration of any of the research procedures, AND
- Unexpected – that is, the type of event is not listed in the protocol as an expected occurrence.

8. Adjudication process

8.1. Review of potential endpoints

Reviewers will be provided with SAE reports by the site research staff. Reviewers will also be able to request additional information if required.

For the first 10 reported events requiring adjudication, the events will be reviewed at a CEC meeting with at least 2 members present. The purpose of this initial committee review will be to ensure that all committee members are applying the endpoint definitions as described in this charter and that members are aligned in their applications of the definitions to the classifications of events. In this review of the initial 10 events, full consensus will be required for each final classification decision.

8.1.1. Phase 1 CEC review

Each SAE report for a potential endpoint event will be reviewed independently by two CEC members. Reports will be allocated for review in a manner that ensures that events are distributed to the members on an even basis.

On confirmation in the electronic system that an SAE report ready for review, an email notification will be sent to 2 members of CEC indicating that an event available for adjudication. On receipt of the email notification the reviewer will complete the review and adjudication in a timely manner. The CEC member will:

- Review the details of the event by accessing the SAE Report
- Classify the event according to the EP definitions as detailed in this charter.

- Complete the EP Adjudication Form.

If the reviewer is unable to classify the event and considers that additional information is required before a classification decision can be made this option should be selected on the review form. An email notification will be forwarded to the site advising that additional information is required. When new information becomes available, it will be re-submitted to the two adjudicators initially assigned the event. In instances where it is confirmed that efforts to obtain requested information have been unsuccessful (e.g. because the study site has indicated that the information is not available), classification of the event will be deferred pending review by the CEC Chairman or discussion at a scheduled CEC meeting.

If the reviewer is able to classify the event the adjudication form should be completed, saved and submitted. An automatic email notification will be forwarded to the EP Office advising that an event has been classified.

If the two reviewers are in agreement the adjudication decision will be accepted and the endpoint classified. If 2 different classifications are given, or if one or both of the reviewers are unable to reach a decision or request that the case is referred to the CEC Chairman, the case will be forwarded to the CEC Chairman for review and classification.

8.1.2. Phase 2 - review by CEC Chairman

If the CEC Chairman is able to classify the event the adjudication form should be completed with the Type of Event, saved and submitted.

If the CEC Chairman is unable to arrive at a classification verdict for an event because of incomplete or inadequate information and it is felt that such information may be obtainable (i.e. the study site has not indicated that the information required is unavailable), the Chairman will detail the precise information/documentation that is needed to achieve classification and this will be requested. If the CEC Chairman is unable to classify the event it will be referred to the full committee for review and classification

8.1.3. Phase 3- review by full CEC

The CEC will convene as required. In general, these will be face- to- face meetings, however, if for some reason a face- to- face meeting is not possible, a meeting by teleconference may substitute.

The frequency of meetings depends on the quantity of clinical events received by the CEC. A meeting may be cancelled if there is no business for discussion or cases to be reviewed by full committee.

The primary objective of CEC meetings is the **Phase 3 review** and classification of those events for which a final classification decision has not been achieved by the Phase 1 or Phase 2 review process already outlined above. Phase 3 review of an event constitutes the discussion and adjudication of the event by the CEC as a group.

If the CEC are unable to arrive at a classification verdict for an event because of incomplete or inadequate information and it is felt that such information may be obtainable (i.e. the study site has not indicated that the information required is unavailable), the Chairman will detail the precise information/documentation that is needed to achieve classification and this will be requested from the site by the EP Office. Adjudication of the event will be deferred and reviewed subsequently at a CEC meeting when the information requested has been made available (or, when, despite best efforts, it is confirmed that the information will not be obtainable).

8.1.4. Adjudication timelines

The CEC members will make every effort to review events and to enter their classification decisions onto the electronic Adjudication Form within 2 to 4 weeks from the time that the event data is received. To facilitate the prompt adjudication of events, it is expected that adverse event data received by the CEC will be as clean and complete as possible and that any CEC data-queries are resolved in a timely fashion.

If necessary, the above timelines may be amended as the study progresses, if the CEC and the other relevant parties agree on a new schedule of event turn-around time.

9. Information to be provided to CEC

Information to be provided for event classification will include:

- Subject study identification number and event details
- Serious Adverse Event form
- Supportive source documentation where requested following initial Phase 1 SAE review

Source Documentation

The following de-identified source documents (if available) will be provided to the CEC to facilitate the review and adjudication of events if requested:

Death

- Hospital Discharge Summary/Death Summary *
- Autopsy Report
- Death Certificate

*Or the clinical equivalent if the above unavailable

Acute Myocardial Infarction

- Hospital Discharge Summary*
- ECGs
    - Pre-Randomisation/Screening- Trial ECG available via electronic system
    - Baseline (prior to event but post-randomization)- Trial ECG available via electronic system
    - During Event
    - Post-Event
- Relevant Procedure/Operation Reports
- Relevant Laboratory Reports (e.g. that document the cardiac enzyme/marker measurements provided – peak values and pre-procedure and post-procedure values, where applicable)
- Reports for other investigations taken:
    - PCI Report
    - CABG Report
    - Coronary Angiography Report
    - Echocardiogram Report
    - Exercise ECG Report
    - Stress Myocardial Perfusion Scan Report
    - Other investigation report undertaken to test for presence of reversible myocardial ischaemia

*Or the clinical equivalent if the above unavailable.

Stroke/TIA

- Hospital Discharge Summary*
- Neurology Consultation Report(s)
- Reports for other investigations undertaken:
    - CT Brain Scan Report
    - MRI Brain Scan Report-Trial scan available via electronic system if event during index admission
    - Cerebral Angiography Report
    - Lumbar Puncture Report

*Or the clinical equivalent if the above unavailable.

Heart failure complicating the index acute myocardial infarction

- Hospital Discharge Summary*
- Clinical note entry in the medical record
- Prescription of diuretic therapy
- Chest X-Ray Report

- Echocardiogram Report
- Relevant Laboratory Reports (e.g. for peak BNP/NT-proBNP)
- Reports for other investigations undertaken:
    - Cardiac Magnetic Resonance Imaging
    - Radionuclide Ventriculogram Scan
    - Pulmonary Artery Catherization

*Or the clinical equivalent if the above unavailable

Heart Failure requiring hospitalisation

- Hospital Discharge Summary*
- Chest X-Ray Report
- Echocardiogram Report
- Relevant Laboratory Reports (e.g. for peak BNP/NT-proBNP)
- Reports for other investigations undertaken:
    - Cardiac Magnetic Resonance Imaging
    - Radionuclide Ventriculogram Scan
    - Pulmonary Artery Catherization

*Or the clinical equivalent if the above unavailable

Bleeding (BARC types 3-5)

- Hospital discharge summary*
- Haemoglobin measurements throughout admission

***** *Or the clinical equivalent if the above unavailable

10. Document History

Version	**Date**	**Reason for change**
1.0	29.11.2019	Initial creation

Approvals:

The following CEC and Sponsor representatives have approved this Charter:

Name	Role	Signature	Date
Professor Colin Berry	Chief Investigator		
Dr David Carrick	CEC Chairman		
Dr Ross McGeoch	CEC Member		
Dr David Corcoran	CEC Member		
Dr Ninian Lang	CEC Member		
Dr Catherine Sinclair	Sponsor Representative		

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