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Complete List of Authors:	Koopman, Moniek; University Medical Center Groningen Department of Radiology, Radiology Reijnders, Jorn ; Zuyderland Medical Centre Heerlen, Department of Cardiology Willemsen, Robert ; Maastricht University, Department of Family Medicine van Bruggen, Rykel; Multicenter General Practitioners Organisation 'HuisartsenOrganisatie Oost-Gelderland' Doggen, Carine J.M.; University of Twente, Department of Health Technology & Services Research, Techmed Centre Kietselaer, Bastiaan; Zuyderland Medical Centre Heerlen, Department of Cardiology Oude Wolcherink, Martijn ; University of Twente, Department of Health Technology & Services Research van Ooijen , Peter M A; University Medical Center Groningen , Department of Data Science Center in Health; University Medical Center Groningen, 7. Department of Radiation Oncology Gratama, Jan Willem ; Gelre Hospitals, Department of Radiology Braam, Richard; Gelre Hospitals, Department of Cardiology Oudkerk , Matthijs ; University of Groningen Van der Harst, Pim; University Medical Center Groningen Department of Cardiology, Division Heart and Lungs; University Medical Centre Utrecht Department of Cardiology Dinant, Geert-Jan; Maastricht University, Department of Family Medicine Vliegenthart, Rozemarijn; University Medical Center Groningen Department of Radiology
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Coronary calcium scoring as first-line test to detect and exclude coronary artery disease in patients presenting to the general practitioner with stable chest pain: protocol of the cluster-randomized CONCRETE trial

Moniek Y. Koopman[1] (ORCID 0000-0001-5082-409X), Jorn J.W. Reijnders[2], Robert T.A. Willemsen[3] (ORCID 0000-0002-3538-0264), Rykel van Bruggen[4] (ORCID 0000-0001-8761-8687), Carine J.M. Doggen[5] (ORCID 0000-0003-4766-4333), Bas Kietselaer[2] (ORCID 0000-0002-0096-8594), Martijn J Oude Wolcherink[5], Peter van Ooijen[6,7] (ORCID 0000-0002-8995-1210), Jan Willem C. Gratama[8] (ORCID 0000-0001-7483-4997), Richard Braam[9] (ORCID 0000-0002-3630-7341), Matthijs Oudkerk[10] (ORCID 0000-0003-2800-4110), Pim van der Harst[11,12] (ORCID 0000-0002-2713-686X), Geert-Jan Dinant[3] (ORCID 0000-0001-7411-8325), Rozemarijn Vliegenthart[1] (ORCID 0000-0002-7262-3376).

Affiliations

1. Department of Radiology, University Medical Center Groningen, Groningen, the Netherlands.
2. Department of Cardiology, Zuyderland Medical Center, Sittard-Geleen, the Netherlands
3. Department of Family Medicine, Maastricht University, Maastricht, the Netherlands
4. Multicenter General Practitioners Organisation 'HuisartsenOrganisatie Oost-Gelderland', General Practitioner, Apeldoorn, the Netherlands.
5. Department of Health Technology & Services Research, Techmed Centre, University of Twente, Enschede, the Netherlands.
6. Department of Data Science Center in Health, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands.
7. Department of Radiation Oncology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands
8. Department of Radiology, Gelre Hospital, Apeldoorn, the Netherlands
9. Department of Cardiology, Gelre Hospital, Apeldoorn, the Netherlands.
10. Department of Medical Science, University of Groningen, Groningen, the Netherlands
11. Department of Cardiology, University Medical Centre Utrecht, Utrecht, the Netherlands.
12. Department of Cardiology, Division Heart and Lungs, University Medical Center Groningen, Groningen, the Netherlands

Corresponding author

Prof Dr R Vliegenthart, University of Groningen, Department of Radiology, University Medical Centre Groningen, Hanzeplein 1, 9713 GZ Groningen, the Netherlands. [r.vliegenthart@umcg.nl]

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ABSTRACT

Introduction: Identifying and excluding coronary artery disease (CAD) in patients with atypical angina pectoris (AP) and non-specific thoracic complaints is a challenge for general practitioners (GPs). A diagnostic and prognostic tool could help GPs in determining the likelihood of CAD and guide patient management. Studies in outpatient settings have shown that the computed tomography (CT)-based coronary calcium score (CCS) has high accuracy for diagnosis and exclusion of CAD. However, the CT CCS test has not been tested in a primary care setting. In the CONCRETE study, the impact of direct access of GPs to CT CCS will be investigated. We hypothesize that this will allow for early diagnosis of CAD and treatment, more efficient referral to the cardiologist and a reduction of health care related costs.

Methods and analysis: CONCRETE is a pragmatic multicenter trial with a cluster randomized design, in which direct GP access to the CT CCS test is compared to standard of care. In both arms, at least 40 GP offices, and circa 800 patients with atypical AP and non-specific thoracic complaints will be included. To determine the increase in detection and treatment rate of CAD in GP offices, the cardiovascular risk management registration rate is derived from the GPs electronic registration system. Individual patients' data regarding cardiovascular risk factors, expressed chest pain complaints, quality of life, downstream testing, and CAD diagnosis will be collected through questionnaires and the electronic GP dossier.

Ethics and dissemination: CONCRETE has been approved by the Medical Ethical Committee of the University Medical Center of Groningen. The study is registered in the Netherlands Trial Register (NTR 7475).

STRENGTHS AND LIMITATIONS OF THE STUDY

- CONCRETE determines the efficiency of CT coronary calcium scoring for diagnosing and excluding CAD in non-acute primary care patients with chest pain.
- CONCRETE gives insight into downstream testing and (unnecessary) referral rates of both strategies.

- CONCRETE gives insight into the cost-effectiveness of the CT CCS-based strategy and the standard of care in primary care.
- CONCRETE may initiate a change in primary healthcare policy for non-acute chest pain patients.
- CONCRETE is an implementation study based on the Dutch Healthcare situation in which patients with non-acute chest pain first visit their GP.

INTRODUCTION

Cardiovascular diseases (CVD) have a large impact on mortality, with 17.9 million annual deaths worldwide[1], and coronary artery disease (CAD) as a leading cause.[2] From 2015 to 2040 the number of adults with CAD is expected to increase with about 50% in the Netherlands.[3] CAD is often expressed by chest discomfort;[4] for diagnostic purposes physicians use three core symptoms to describe typicality of chest pain: 1) retrosternal complaints; 2) complaints provoked by exertion, cold, emotional stress or heavy meals; and 3) complaints that are relieved within 15 minutes after discontinuation of exertion or 5 minutes after using sublingual nitro-glycerine.[4] Presence of all three symptoms indicates typical angina pectoris (AP). If two out of three symptoms are present, the chest pain is called atypical AP, and patients presenting with none or one of the three symptoms are determined as having non-specific thoracic complaints.

In the Dutch health care system, the general practitioner (GP) is usually the first physician a patient consults with non-acute chest discomfort. Chest pain is the primary reason to contact the GP in about 4% of the consultations.[5] In only 10-15%, obstructive CAD will eventually be diagnosed as cause of the symptoms.[5] The challenge for the GP is to diagnose CAD based on symptoms, age and sex.[5] Distinguishing life threatening and non-life threatening diseases is essential for the treatment of patients, but may be challenging in particular in case of atypical AP or non-specific thoracic complaints.[5 6] The Dutch College of General Practitioners *(Nederlands Huisartsen Genootschap- NHG)* clinical Standard for Stable AP serves as the guideline for GPs regarding, among others, referral for additional testing and treatment strategies.[5 7] According to the prior clinical Standard the GP could order exercise electrocardiography (ECG).[5] In practice, however, an important part of this heterogeneous group of patients was sent directly to the cardiologist for evaluation.[8] The most recent Standard (as of January 2020) has been adapted to this practice, and recommends that patients with typical and atypical AP be referred to the cardiologist (without first having exercise ECG ordered by the GP).[7] In non-specific thoracic complaints, the GP should consider diseases other than CAD, unless there is reason to regard CAD as a possible cause. A recent Dutch nation-wide analysis

based on data from 2012 shows that 61% of patients who are referred to the cardiologist undergo an exercise ECG, 22% receive no testing, and 19% undergo (also) a non-invasive CAD imaging test, most often an ischemia test.[8] Presently, In the Netherlands, about 105,000 patients are referred to the cardiologist (52% women) each year.[8] Ultimately, only 5% of men and 1% of women have severe obstructive CAD requiring invasive treatment.[8] There is a clinical need in chest pain patients to optimize diagnostic management and referral to the cardiologist. An accurate diagnostic and prognostic tool could help GPs in determining the likelihood of CAD and guide patient management. At this moment the Dutch GP does not have access to advanced imaging tests for CAD, such as computed tomography (CT).

In this paper, we present the rationale, objectives, and study design of the CONCRETE trial. CONCRETE is the abbreviation for 'Coronary calcium scoring as first-line test to detect and exclude coronary artery disease in GP patients with stable chest pain.' In CONCRETE, we investigate the impact of giving GPs direct access to CT coronary calcium scoring for the diagnosis and exclusion of CAD in a pragmatic randomized trial. The coronary calcium score (CCS) is a robust, quantitative measure of coronary calcification based on non-contrast, low-dose ECG-triggered CT with a standardized protocol for scanning and post-processing, with virtually no contra-indications. In outpatient cardiology clinic setting, the CCS has proven to have better diagnostic and prognostic power than exercise ECG.[9-11] The CCS has a negative predictive value of 93-99% for obstructive CAD in symptomatic patients,[12-16] and 99% for major acute cardiovascular events (MACE), with similar prognostic results in men and women.[13 14] The sensitivity of CCS for obstructive CAD is 95-99%.[17-19] The severity of coronary calcification is strongly related to CAD burden,[12 20 21] ischemia,[21] and MACE,[22-24] and allows for early detection of patients with non-obstructive CAD, who can then receive early treatment.[25-28] Research in symptomatic patients undergoing exercise ECG and calcium scoring in an outpatient cardiology setting showed that the CCS can be safely used for patient stratification, with no events after one year in patients with CCS <10 (52% of all patients), and better identification of patients with obstructive CAD and/or subsequent coronary events.[10] Other Dutch studies in

outpatient cardiology setting have confirmed these findings, and indicate that CCS improves diagnostic and prognostic stratification compared to exercise ECG testing.[9 11] A recent Dutch study in 1,551 cardiology outpatients with chest discomfort and low or intermediate CAD probability, showed a CCS 0 in 48%, CCS 1-100 in 32%, CCS 101-400 in 14% and CCS >400 in 6%.[23] Only 3% of patients with CCS 0 had obstructive CAD on CT coronary angiography. During a follow-up of nearly 2 years, the MACE rate was 0.3% in CCS 0, 1% in CCS 1-100, 4% in CCS 101-400 and 7% in CCS >400.[23] A CCS of 0 was found a safe and efficient approach to exclude CAD in patients with low-intermediate pre-test probability, while probability of obstructive CAD increased particularly from a CCS of 100.[9 19 22 29] The CAD consortium recently reported that inclusion of calcium scoring in risk stratification tools improves prediction of CAD probability in chest pain patients undergoing invasive or CT coronary angiography.[30] It remains uncertain whether the diagnostic accuracy of CT CCS is the same in primary care, although prior outpatient studies included mainly low and intermediate probability patients, similar to the risk profile of GP patients. Also, the impact of implementation of calcium scoring in a GP setting on CAD diagnosis and treatment rate is unknown. CONCRETE is an implementation study focusing on the Dutch health care system in which the GP is usually the first physician a patient consults with non-acute chest discomfort. We hypothesize that GP access to the CT CCS test allows for early diagnosis of CAD and treatment, more efficient referral to the cardiologist and a reduction in health care related costs.

OBJECTIVES

The primary objective is to determine the increase in detection and treatment rate of CAD in GP offices with the CT CCS-based strategy, compared to GP offices with the standard of care strategy, in patients presenting with atypical AP and non-specific thoracic complaints. The primary endpoint is the (early) CAD diagnosis registration as expressed by the cardiovascular risk management (CVRM) registration rate.[31] The primary and secondary objectives of the trial are listed in table 1.

Table 1: Primary and secondary objectives of CONCRETE

Primary objective (cluster-based)
1. To determine the increase in detection/treatment rate of CAD in GP offices with the CT CCS-based strategy, compared to GP offices with the standard of care strategy, in patients with atypical AP and non-specific thoracic complaints.
Secondary objectives (patient-based)
1. To establish the diagnostic yield to diagnose obstructive CAD, for both strategies
2. To establish the effectiveness in terms of CAD diagnosis and exclusion of GP referral to the cardiologist for the calcium score cluster as well as the time to (exclusion of) CAD diagnosis
3. To compare downstream diagnostic testing and treatment for both strategies
4. To evaluate whether diagnostic stratification, in particular cut-offs for referral to the cardiologist, can be optimized for the calcium score
5. To estimate the effect of calcium scoring versus the standard of care on quality of life and cardiac complaints after 6, 12, and 24 months
6. To estimate the effect of calcium scoring on reduction of MACE (after 2 years).
7. To derive data on the costs per diagnosis of obstructive and diagnosis of non-obstructive CAD in the setting of calcium score testing versus the standard of care
8. To estimate the cost-utility of implementing the calcium score test in GP setting
9. To develop machine learning tools to evaluate big data on (combinations of) symptoms and family history/risk factors, and relationship to CAD
10. To establish and visualize relationships between (combinations of) symptoms and family history/risk factors and probability of CAD, using innovative techniques for big data analysis; these results will form the input for a risk assessment tool to be developed
Note: all analyses will be analysed by sex. CAD= coronary artery disease. GP= general practitioner. CT CCS= computed tomography coronary calcium score.

METHODS AND ANALYSIS

Study design and setting

CONCRETE is a pragmatic multicenter study with a cluster-randomized design. This type of design is increasingly used in primary care for the evaluation of health care interventions.[32-35] An overview of the study design is provided in Figure 1. From January 2019 onward, GPs are recruited from multi-practice GP organizations in urban and rural regions from the provinces Gelderland, Groningen,

Limburg and Overijssel in the Netherlands. The initial aim was to include 80 GP offices. Through a permutated block randomization scheme (1:1), GP offices are divided into two equally large strategy groups; one group of GP offices refers patients for CT CCS testing and another group of GP offices provides the standard of care (Figure 1). The primary analysis will be performed in the two clusters. After GP office randomization, approximately 800 patients will be included over a period of two years in both diagnostic strategies (Figure 1).

Enrolment of clusters, GP offices (for primary analysis)

GP offices from the collaborating multi-practice GP organizations are included as clusters if they are willing to take part in the trial and provide written informed consent.

Enrolment of patients (for secondary analysis)

For the individual-based analyses, patients with non-acute chest discomfort, either atypical AP or non-specific thoracic complaints (Figure 1), with indication for further diagnostic evaluation as determined by the GP, will be informed about the trial and asked to participate by the GP. Men of 40 years and older, and women of 45 years and older will be included. Exclusion criteria for individual patients are pregnancy, unwillingness to provide written informed consent for the individual level (secondary) outcomes, and prior diagnosis of CAD (percutaneous coronary intervention, coronary artery bypass surgery, myocardial infarct, stable CAD).

Patients receive an information brochure and informed consent form. The signed informed consent form is returned to the GP and sent to the researcher. For a patient, participation comprises agreement to share clinical data from the GP system with the researchers, and filling in questionnaires. The first questionnaire is sent to the patient either digitally or by letter, to be completed prior to the visit to the cardiologist or the CT scan. The diagnostic management executed by the GP (CT CCS or standard of care) does not depend on the signing of the informed consent by the patient; this depends on the cluster to which the GP office is randomized.

CT coronary calcium scoring strategy

The CT CSS is carried out in accordance with the routine procedure of the participating radiology departments, and performed on the routine (single or dual source) CT scanner used for cardiac imaging in these departments. In this way, adherence to common clinical practice and generalizability of results are optimized. In practice, the scan and reconstruction protocol for CCS is rather standardized. In all centers, the CT scan consists of an ECG-synchronized acquisition without intravenous iodine contrast, during breath hold. The entire heart is included in the scan range. Images are commonly acquired around 60% of the cardiac cycle. Tube voltage is 120 kVp and tube current is generally set at around 80 mAs as reference. Images are reconstructed with a slice thickness of 3.0 mm and slice increment of 1.5 or 2.5 mm. The radiation dose is approximately 0.5–1 mSv, which is less than 50% of the annual background radiation dose in the Netherlands.[36 37] The CCS is calculated according to Agatston's method.[38] Patients receive AP medication subscribed by the GP while awaiting the results of the CT CCS test.[7] The GP will be informed of the CT CCS result based on the radiologist report (Figure 1). The report of the radiologist consists of the total CCS and the CCS per coronary artery (right coronary artery, left coronary artery, left anterior descending artery and left circumflex artery) and the MESA (the Multi-Ethnic Study of Atherosclerosis) percentile.[39] CCS results are categorized as CCS of 0 (no CAD), 1-10 (minimal CAD), 11-100 (mild CAD), 101-399 (moderate CAD) and ≥400 (severe CAD), respectively. When no CAD or minimal CAD is found, GPs are advised to stop AP medication and consider other causes for the complaints. In case of mild CAD, continuation of AP medication and inclusion of these patients into CVRM is to be considered.[31] In patients with moderate and severe CAD, AP medication is continued and in addition, the patient will be included into CVRM[31] and referred to the cardiologist. In case of a CCS result above the 75th percentile for age and sex based on MESA percentile,[39] the GP is recommended to classify the patient one CCS category higher than the category matching the absolute score, in view of the premature atherosclerosis and the associated long-term cardiovascular risk (Figure 1).[22 40 41] The categories are based on recent literature from Dutch studies,[9 11 22 42] and on the experience of physicians who have

been applying the CCS for years in practice. The management advice for the CCS categories is based on discussions with cardiologists, GPs and radiologists, and is not obligatory but meant as guidance. The GP discusses the results with the patient. Decisions regarding patient management remain at the discretion of the GP, who takes all available patient information into account.

Standard of care strategy

In this arm, all steps are in agreement with routine standard of care, as determined by the NHG Standard for Stable AP. Thus, patients with atypical AP or with non-specific thoracic complaints in whom the GP wants to exclude CAD as underlying cause, will be referred to the outpatient cardiology clinic. There, evaluation of the patient takes place with additional testing at the discretion of the attending cardiologist in accordance with the guidelines of the European Society of Cardiology (ESC).[42] GPs will be informed of the findings and cardiac diagnosis based on the letter from the cardiologist (Figure 1).

Data collection

The primary endpoint is an increase in (subclinical) CAD diagnosis and treatment in patients in the CT CCS strategy compared with the standard care strategy. The detection and treatment rate of CAD in GP offices is based on the CVRM registration rate. According to the CVRM guideline patients are registered into the CVRM registry when they have high risk of developing CVD and/or are diagnosed with CVD.[31] CVRM registry data are derived from the GP electronic registration system with registration date one year before baseline, at baseline and one and two years after baseline. Individual patient data are collected over a period of two years, using four questionnaires (Table 2) containing questions with regard to experienced chest pain complaints,[43] quality of life (EQ-5D-5L)[44] [45] and heart-related quality of life (HeartQoL).[46] [47] In addition, the cardiovascular risk profile of the patient, and information on downstream testing and CAD diagnosis will be collected through the electronic patient dossier (Table 3).

Table 2: SPIRIT schedule of enrolment, test strategies and assessments

	STUDY PERIOD					
	Enrolment	**Baseline**	**Execution of strategy**	**Post execution strategy**		**Close-out**
Time points	***0***	**0**	**1-2** weeks	**6** months	**12** months	**24** months
Enrolment:						
Eligibility screening by GPs	x					
Informed consent	x					
Test strategies:						
Standard care strategy			x			
CT CCS strategy			x			
Assessment:						
CVRM GPs offices		x			x	x
Risk factors	x					
Chest pain complaints		x				
Quality of life		x		x	x	x
Heart related quality of life		x		x	x	x

Note: GPs=general practitioners, CT CCS = computed tomography coronary calcium score, CVRM= number of patients registered to Cardiovascular risk management.

Table 3: Cardiovascular risk assessment items

General health assessment	
Smoking habits	Tobacco use per day Total number of smoking pack years
Alcohol use	Mean number of glasses per day General behaviour with regard to alcohol use using the 5SH1 test
Family history	Fatal or non-fatal cardiovascular diseases in a first degree family member?
Diabetes Mellitus	Does the patient have diabetes mellitus?
Rheumatoid arthritis	Does the patient have rheumatoid arthritis?
Physical assessment	
Systolic blood pressure	Mean of three blood pressure measurements by general practitioner
Body mass index	Determination of BMI: kilograms/ length^2 (kg/m^2)

Laboratory assessment	
Blood lipids spectrum	- HDL ratio - LDL ratio - Total cholesterol ratio - Total cholesterol-HDL ratio - Triglycerides ratio
Blood glucose level	Fasting glucose ratio
Estimated Glomerular filtration	eGFR ratio

Note: measurements to assess cardiovascular risk of the patients. BMI=body mass index. HDL= High density lipoprotein. LDL= Low density lipoprotein. eGFR= estimated glomerular filtration.

Sample size

We used sample size calculations for cluster randomised trials.[48] In order to detect a 7.5% difference in CVRM registrations between the two clusters, with a power of 80%, a significance level of 5%, and an intra-cluster correlation of 0.01, inclusion of 36 GP offices in each cluster would be necessary, with an estimated total of 20 patients per GP office (10 patients per year per GP office). To anticipate unforeseen circumstances, such as drop out, we initially decided to include 40 GP offices in each strategy group. The calculations are based on the assumption that yearly about 50 patients will consult their GP with atypical AP and non-specific thoracic complaints,[5] with an estimated 10 patients who will be referred for additional evaluation to diagnose or exclude CAD.[6] In the CT CCS strategy a CCS of 0 are expected in 45% of patients, a CCS of 1-10 in 10%, a CCS of 11-100 in 20% and a CCS larger than 100 in 10%, actual percentages will only be known during this study.[23 30 49 50] In the standard care strategy, 27.5% of the patients are expected to be included in CVRM registry for CAD diagnosis/treatment, and 35% of the patients in the CT CCS test strategy. These percentages are based on similar populations from previously published Dutch research.[9 51 52]

COVID-19 pandemic

The trial was stopped due to the COVID-19 pandemic from March until June 2020. However, even after the re-start in July 2020, the inclusion of GP offices and patients was so far (June 2021) severely

slowed due to effects of the COVID-19 pandemic (among others, lower GP consultation rates, procedures to re-start clinical practice in adherence to COVID-19 regulations, and vaccination procedures). The COVID-19 pandemic urged us to realign the patient inclusion rate, sample size and the interdependent calculations of the trial. To reduce the impact of COVID-19 on the progress of CONCRETE, we aim to increase the number of participating GP offices from 80 to 130.

Data analysis

Baseline characteristics will be summarized by means (standard deviation), median (interquartile range) and percentages. The primary outcome is the (early) CAD diagnosis/treatment registration as expressed by the CVRM registration rate at GP office level. The increase for each individual GP office will be calculated by subtracting the percentage of registrations at baseline from the percentages of CAD diagnosis/treatment registrations at follow-up. CVRM registration rate of the two clusters will be compared by using an independent t-test or non-parametric test, depending on distribution. In case of missing data, due for example loss to follow-up, multiple imputations will be used. In the CT CCS strategy, receiver operating characteristic (ROC) analyses will be used to find the optimal CCS and CCS percentile for referral to the cardiologist, by sex.

Follow-up

Patients will be followed for acute myocardial infarction and sudden cardiac death as well as CAD diagnostic procedures, cardiac interventions, and diagnostic/treatment costs, for up to five years; source data about CAD diagnosis, diagnostic procedures and follow-up cardiovascular events will periodically be obtained from the GP electronic dossier. As part of the current grant, follow-up procedures up to 2 years after the inclusion period are covered. A follow-up up to 5 years will be performed if additional funding is secured.

Quality of life

Quality of life (QoL) and HeartQoL will be compared between the strategies.[45 53] Patients fill in both questionnaires prior to the CT CCS or cardiologist referral, and after 6, 12 and 24 months. Multiple linear regression will be performed, to adjust for potential confounders. Analyses will be performed on an intention to treat basis.

Cost-utility

Costs of diagnosis are recorded in this clinical trial and used to calculate the costs per CAD diagnosis (obstructive and non-obstructive) for each strategy. Additionally, costs for events during follow-up are recorded for each strategy. Cost-utility analysis will be performed to reflect the balance between incremental monetary cost and incremental quality adjusted life years (QALY) resulting in an incremental cost-utility ratio (ICUR). A societal perspective will be used and discounting will be applied for costs (4%) and health outcomes (1.5%) according to Dutch guidelines.[54]

A patient-level simulation model using a life-long time horizon will be created to assess the long-term impact of CT CCS access by GPs regarding costs and health outcomes. Due to the late onset of symptoms for CAD and the major impact of cardiovascular events caused by CAD, extrapolating the results to a lifelong time horizon is desired to determine the true impact of CT CCS. Clinical data will be used as input for the simulation model where possible. Bootstrapping is used to determine uncertainty surrounding these input parameters.[55] Model parameters beyond the scope of the clinical trial are supplemented by literature. Expert opinion will be used in case literature yielded inconclusive results. To reflect outcome (ICUR) uncertainty, a probabilistic analysis will be performed using the Monte Carlo approach with 5,000 iterations.[56] Results of the probabilistic analysis will be visualised in a cost-effectiveness plane and cost-effectiveness acceptability curve. Finally, subgroup-specific cost-utility outcomes will be determined for example for age and sex.

Patient and Public Involvement

Patients were involved in the design and reporting of the study. Cardiovascular patients gave input on the information and questionnaires to be provided to patients. Patients are also included in the user committee of the study, that gives input on every aspect of the trial including recruitment and conduct. There is a specific part of the CONCRETE website dedicated to informing patients about the trial and its results.

ETHICS AND DISSEMINATION

CONCRETE has been approved by the Medical Ethical Committees of the University Medical Center of Groningen, under number 2018/404. The study will be conducted according to the principles of the Declaration of Helsinki, Brazil, October 2013,[57] and in accordance with the Dutch Medical Research Involving Human Subjects Act (WMO).[58] Study data will be collected in a pseudonymised fashion and managed using REDCap electronic data capture tools hosted by the University Medical Center Groningen. Pseudonymised CT image data will be stored in the XNAT imaging data archive. We will handle personal data in compliance with the Dutch General Data Protection Regulation (AVG). [59] The study is registered in the Netherlands National Trial Register on https://www.trialregister.nl/ (NTR: 7475). Information on CONCRETE for patients, physicians and researchers is available at the website www.concrete-project.nl. Results will be published in peer-reviewed journals and presented at (inter)national conferences.

DISCUSSION

The CONCRETE study aims to determine whether direct GP access to CT CCS leads to earlier and more cost-effective diagnosis and treatment of CAD in patients with atypical AP or non-specific thoracic complaints, compared to standard of care. To our knowledge CONCRETE is the first study that will test the implementation of CT CCS in primary care, as previous studies have been performed in secondary care settings.[4 11 60 61] Further, the study will assess and optimize sex-specific diagnostic

stratification based on the CCS. In addition, CONCRETE will give insight into the QoL of these patients, downstream testing, (unnecessary) referral rates, and the cost-effectiveness of both strategies. Implementation of CONCRETE findings could initiate a change in healthcare policy for patients with atypical AP and non-specific thoracic complaints.

Inclusion of GP offices and patients started in January 2019; at that time, the standard GP management was to request exercise ECG in patients suspected of CAD. Since January 2020, the standard of care has changed and exercise ECG testing was replaced by referral to the cardiologist.[7] It is expected that the change of the standard care will not influence the study results to a large extent, because a recent survey has shown that in the years before 2020, GPs frequently referred patients with suspected CAD directly to the cardiologist, instead of ordering exercise ECG.[6 62] Furthermore, 61% of the patients referred to the cardiologist received an exercise ECG test as first diagnostic test, and 22% of the referred patients received no diagnostic test at all.[51 63] Thus, the initial diagnostic procedure in referred patients has so far been commonly the same as in primary care. Finally, it is expected that direct referral to the cardiologist can reduce heterogeneity in the referral indications by GPs.

As the study is performed in the Netherlands, health care practice in the standard care strategy is based on the Dutch GP guideline. However, the scope of atypical AP and non-specific thoracic complaints in primary care and the diagnostic use of CT CCS are broader. Only 6 to 11% of chest pain patients will be diagnosed with stable CAD at first GP consultation,[64] but 33% of MACE and cardiovascular mortality patients present first symptoms five years before the events.[65] Prognosis is worse in patients without diagnostic testing to exclude cardiac etiology.[66] Therefore, GPs often refer patients with chest pain to the cardiologist for further work-up, as advanced cardiac imaging is currently not available in primary care. The Dutch National Health Care Institute analysis shows that the majority of GP patient referrals to cardiology outpatient clinics do not have obstructive CAD and only 1-5% of the referred patients need invasive treatment.[52] The high prevalence of a zero CCS in referred patients (~50%) supports this fact.[23] There is a clear need to improve the cost-effectiveness

of GP referrals to secondary care facilities. A drawback of CT CCS is the need for ECG-synchronized cardiac CT scanning, however, cardiac CT is nowadays available in most Dutch hospitals. Although CT CCS to identify individuals with obstructive CAD is not recommended by the ESC guidelines, it does mention the use of CT CCS as risk modifier in the assessment of the overall likelihood of obstructive CAD in low pre-test probability patients.[4] The CCS is a more powerful predictor of obstructive CAD and future events in symptomatic patients than traditional risk factors. [42 64-66] The "power of zero CCS" to exclude clinically relevant CAD has been proven in symptomatic patients. [42 66] GP access to CT CCS could reduce unnecessary referrals, downstream testing and health care costs. However, little is known about the usefulness of CCS in a primary care setting. In particular in primary care, the vast majority of chest pain patients present with atypical chest pain and non-specific thoracic complaints, causing a diagnostic challenge to GPs if CAD as underlying cause cannot be excluded. In addition, the question remains, what CCS cut-off value should be used to decide on the need to refer patients to a cardiologist for additional testing. Finally, CT CCS can be used as biomarker for early treatment of CAD in patients with non-obstructive CAD detected at an early stage.[27 30 67 68] Treatment of early CAD may prevent future MACE or sudden cardiac death, although at this moment this has not yet been proven in randomized clinical trials.

CONCLUSION

CONCRETE is a pragmatic implementation study to determine the effectiveness of direct GP access to CT CCS to diagnose and exclude CAD in patients with atypical AP and non-thoracic complaints, compared with the standard of care. The CONCRETE results are expected to lead to change of GP referral indications for patients with atypical AP and non-specific thoracic complaints and change of reimbursement policies in healthcare.

FIGURE CAPTIONS AND LEGENDS

Figure 1: Flowchart of randomisation, referral and test results

CT CCS: computed tomography coronary calcium scoring, CAD = coronary artery disease, CVRM = Cardiovascular risk management. AP = angina pectoris. *Guidelines indicate stable chest pain patients have to start with medication for AP before undergoing diagnostic testing.[4 7] **With CCS ≥ 75th percentile for age and sex, the GP is advised to consider classifying the patient one CCS category higher.

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AUTHORS' CONTRIBUTIONS

Moniek Y. Koopman: Data curation, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing - original draft. **Jorn Reijnders**: Data curation, Formal analysis, Investigation, Methodology, Writing - original draft. **Robert T.A. Willemsen:** Resources, Conceptualization, Funding acquisition, Methodology, Supervision, Writing - original draft. **Rykel van Bruggen:** Resources, Conceptualization, Methodology, Writing - original draft. **Carine J.M. Doggen**: Methodology, Formal analysis Writing- review & editing. **Bas Kietselaer:** Investigation, Funding acquisition, Resources, Supervision, Writing- review & editing. **Martijn J Oude Wolcherink:** Methodology, Writing- review & editing. **Peter van Ooijen:** Methodology, Writing- review & editing. **Jan Willem C. Gratama:** Investigation, Resources, Writing- review & Editing. **Richard Braam:** Investigation, Resources, Writing- review & editing. **Matthijs Oudkerk:** Conceptualization, Funding acquisition, Writing- review & editing**. Pim van der Harst:** Conceptualization, Funding acquisition, Resources, Supervision, Writing- review & editing. **Geert-Jan Dinant:** Resources, Methodology, Writing- review & editing. **Rozemarijn Vliegenthart:** Conceptualization, Formal analysis, Funding acquisition, Methodology, Project administration, Supervision, Writing - original draft.

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COMPETING INTERESTS

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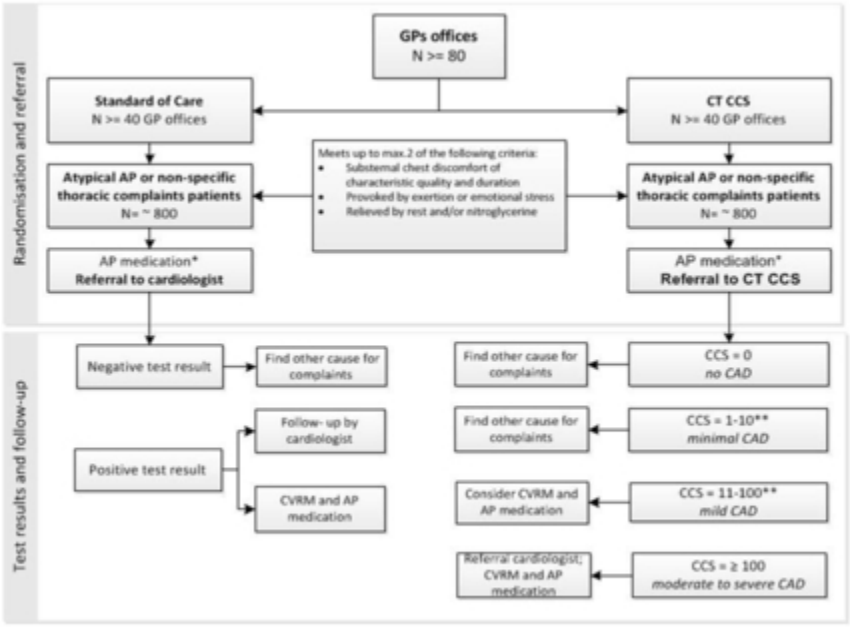

Figure 1: Flowchart of randomisation, referral and test results

20x15mm (600 x 600 DPI)

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Coronary calcium scoring as first-line test to detect and exclude coronary artery disease in patients presenting to the general practitioner with stable chest pain: protocol of the cluster-randomized CONCRETE trial

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Coronary calcium scoring as first-line test to detect and exclude coronary artery disease in patients presenting to the general practitioner with stable chest pain: protocol of the cluster-randomized CONCRETE trial

Moniek Y. Koopman[1] (ORCID 0000-0001-5082-409X), Jorn J.W. Reijnders[2], Robert T.A. Willemsen[3] (ORCID 0000-0002-3538-0264), Rykel van Bruggen[4] (ORCID 0000-0001-8761-8687), Carine J.M. Doggen[5] (ORCID 0000-0003-4766-4333), Bas Kietselaer[2] (ORCID 0000-0002-0096-8594), Martijn J Oude Wolcherink[5], Peter van Ooijen[6,7] (ORCID 0000-0002-8995-1210), Jan Willem C. Gratama[8] (ORCID 0000-0001-7483-4997), Richard Braam[9] (ORCID 0000-0002-3630-7341), Matthijs Oudkerk[10] (ORCID 0000-0003-2800-4110), Pim van der Harst[11,12] (ORCID 0000-0002-2713-686X), Geert-Jan Dinant[3] (ORCID 0000-0001-7411-8325), Rozemarijn Vliegenthart[1] (ORCID 0000-0002-7262-3376).

Affiliations

1. Department of Radiology, University Medical Center Groningen, Groningen, the Netherlands.
2. Department of Cardiology, Zuyderland Medical Center, Sittard-Geleen, the Netherlands
3. Department of Family Medicine, Maastricht University, Maastricht, the Netherlands
4. Multicenter General Practitioners Organisation 'HuisartsenOrganisatie Oost-Gelderland', General Practitioner, Apeldoorn, the Netherlands.
5. Department of Health Technology & Services Research, Techmed Centre, University of Twente, Enschede, the Netherlands.
6. Department of Data Science Center in Health, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands.
7. Department of Radiation Oncology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands
8. Department of Radiology, Gelre Hospital, Apeldoorn, the Netherlands
9. Department of Cardiology, Gelre Hospital, Apeldoorn, the Netherlands.
10. Department of Medical Science, University of Groningen, Groningen, the Netherlands
11. Department of Cardiology, University Medical Centre Utrecht, Utrecht, the Netherlands.
12. Department of Cardiology, Division Heart and Lungs, University Medical Center Groningen, Groningen, the Netherlands

Corresponding author

Prof Dr R Vliegenthart, University of Groningen, Department of Radiology, University Medical Centre Groningen, Hanzeplein 1, 9713 GZ Groningen, the Netherlands. [r.vliegenthart@umcg.nl]

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ABSTRACT

Introduction: Identifying and excluding coronary artery disease (CAD) in patients with atypical angina pectoris (AP) and non-specific thoracic complaints is a challenge for general practitioners (GPs). A diagnostic and prognostic tool could help GPs in determining the likelihood of CAD and guide patient management. Studies in outpatient settings have shown that the computed tomography (CT)-based coronary calcium score (CCS) has high accuracy for diagnosis and exclusion of CAD. However, the CT CCS test has not been tested in a primary care setting. In the CONCRETE study, the impact of direct access of GPs to CT CCS will be investigated. We hypothesize that this will allow for early diagnosis of CAD and treatment, more efficient referral to the cardiologist and a reduction of health care related costs.

Methods and analysis: CONCRETE is a pragmatic multicenter trial with a cluster randomized design, in which direct GP access to the CT CCS test is compared to standard of care. In both arms, at least 40 GP offices, and circa 800 patients with atypical AP and non-specific thoracic complaints will be included. To determine the increase in detection and treatment rate of CAD in GP offices, the cardiovascular risk management registration rate is derived from the GPs electronic registration system. Individual patients' data regarding cardiovascular risk factors, expressed chest pain complaints, quality of life, downstream testing, and CAD diagnosis will be collected through questionnaires and the electronic GP dossier.

Ethics and dissemination: CONCRETE has been approved by the Medical Ethical Committee of the University Medical Center of Groningen. The study is registered in the Netherlands Trial Register (NTR 7475).

STRENGTHS AND LIMITATIONS OF THE STUDY

- CONCRETE determines the efficiency of CT coronary calcium scoring for diagnosing and excluding CAD in primary care patients with stable chest pain.
- CONCRETE gives insight into downstream testing and (unnecessary) referral rates of both strategies.

- CONCRETE gives insight into the cost-effectiveness of the CT CCS-based strategy and the standard of care in primary care.
- CONCRETE may initiate a change in primary healthcare policy for stable chest pain patients.
- CONCRETE is an implementation study based on the Dutch Healthcare situation in which patients with stable chest pain first visit their GP.

INTRODUCTION

Cardiovascular diseases (CVD) have a large impact on mortality, with 17.9 million annual deaths worldwide[1], and coronary artery disease (CAD) as a leading cause.[2] From 2015 to 2040 the number of adults with CAD is expected to increase with about 50% in the Netherlands.[3] CAD is often expressed by chest discomfort;[4] for diagnostic purposes physicians use three core symptoms to describe typicality of chest pain: 1) retrosternal complaints; 2) complaints provoked by exertion, cold, emotional stress or heavy meals; and 3) complaints that are relieved with the rest and/or within 2-15 minutes after using sublingual nitro-glycerine.[4] Presence of all three symptoms indicates typical angina pectoris (AP). If two out of three symptoms are present, the chest pain is called atypical AP, and patients presenting with none or one of the three symptoms are determined as having non-specific thoracic complaints.

In the Dutch health care system, the general practitioner (GP) is usually the first physician a patient consults with chest discomfort. Chest pain is the primary reason to contact the GP in about 4% of the consultations [5] In only 10-15%, obstructive CAD will eventually be diagnosed as cause of the symptoms.[5] The challenge for the GP is to diagnose CAD based on symptoms, age and sex.[5] Distinguishing life threatening and non-life threatening diseases is essential for the treatment of patients, but may be challenging in particular in case of atypical AP or non-specific thoracic complaints.[5 6] The Dutch College of General Practitioners *(Nederlands Huisartsen Genootschap- NHG)* clinical Standard for Stable AP serves as the guideline for GPs regarding, among others, referral for additional testing and treatment strategies.[5 7] According to the prior clinical Standard the GP could order exercise electrocardiography (ECG).[5] However, exercise ECG is known to have suboptimal sensitivity and specificity for CAD. Furthermore, in clinical practice an important part of this heterogeneous group of patients was sent directly to the cardiologist for evaluation.[8] The most recent Standard (as of January 2020) has been adapted to this practice, and recommends that patients with typical and atypical AP be referred to the cardiologist (without first having exercise ECG ordered by the GP).[7] In non-specific thoracic complaints, the GP should consider diseases other than

CAD, unless there is reason to regard CAD as a possible cause. A recent Dutch nation-wide analysis based on data from 2012 shows that 61% of patients who are referred to the cardiologist undergo an exercise ECG, 22% receive no testing, and 19% undergo (also) a non-invasive CAD imaging test, most often an ischemia test.[8] Presently, in the Netherlands, about 105,000 patients are referred to the cardiologist (52% women) each year.[8] Ultimately, only 5% of men and 1% of women have obstructive CAD requiring invasive treatment.[8] There is a clinical need in chest pain patients to optimize diagnostic management and referral to the cardiologist. An accurate diagnostic and prognostic tool could help GPs in determining the likelihood of CAD and guide patient management. At this moment the Dutch GP does not have access to advanced imaging tests for CAD, such as computed tomography (CT). Furthermore, the most commonly performed first test, exercise ECG, apart from suboptimal accuracy for obstructive CAD, cannot detect early stages of CAD. A sensitive test for early diagnosis of CAD, including non-obstructive stages, will allow earlier treatment based on the Dutch guideline for Cardiovascular Risk Management (CVRM).[9] Early treatment could potentially allow a reduction in the incidence of major acute cardiac events (MACE).

In this paper, we present the rationale, objectives, and study design of the CONCRETE trial. CONCRETE is the abbreviation for 'Coronary calcium scoring as first-line test to detect and exclude coronary artery disease in GP patients with stable chest pain.' In CONCRETE, we investigate the impact of giving GPs direct access to CT coronary calcium scoring for the diagnosis and exclusion of CAD in a pragmatic randomized trial. The coronary calcium score (CCS) is a robust, quantitative measure of coronary calcification based on non-contrast, low-dose ECG-triggered CT with a standardized protocol for scanning and post-processing, with virtually no contra-indications. In outpatient cardiology clinic setting, the CCS has proven to have better diagnostic and prognostic power than exercise ECG.[10-12] The CCS has a negative predictive value of 93-99% for obstructive CAD in symptomatic patients,[13-17] and 99% for major acute cardiovascular events (MACE), with similar prognostic results in men and women.[14 15] The sensitivity of CCS for obstructive CAD is 95-99%.[18-20] The severity of coronary calcification is strongly related to CAD burden,[13 21 22] ischemia,[22] and

MACE,[23-25] and allows for early detection of patients with non-obstructive CAD, who can then receive early treatment.[26-29] Research in symptomatic patients undergoing exercise ECG and calcium scoring in an outpatient cardiology setting showed that the CCS can be safely used for patient stratification, with no events after one year in patients with CCS <10 (52% of all patients), and better identification of patients with obstructive CAD and/or subsequent coronary events.[11] Other Dutch studies in outpatient cardiology setting have confirmed these findings, and indicate that CCS improves diagnostic and prognostic stratification compared to exercise ECG testing.[10 12] A recent Dutch study in 1,551 cardiology outpatients with chest discomfort and low or intermediate CAD probability, showed a CCS 0 in 48%, CCS 1-100 in 32%, CCS 101-400 in 14% and CCS >400 in 6%.[24] Only 3% of patients with CCS 0 had obstructive CAD on CT coronary angiography. During a follow-up of nearly 2 years, the MACE rate was 0.3% in CCS 0, 1% in CCS 1-100, 4% in CCS 101-400 and 7% in CCS >400.[24] A CCS of 0 was found a safe and efficient approach to exclude CAD in patients with low-intermediate pre-test probability, while probability of obstructive CAD increased particularly from a CCS of 100.[10 20 23 30] The CAD consortium recently reported that inclusion of calcium scoring in risk stratification tools improves prediction of CAD probability in chest pain patients undergoing invasive or CT coronary angiography.[31] In contrast to exercise ECG, the CT CCS test detects also early stages of CAD. Early detection of CAD combined with early treatment can potentially prevent adverse cardiac events, lower the burden of disease and increase the patient's life expectancy.[3 32] It remains uncertain whether the diagnostic accuracy of CT CCS is the same in primary care, although prior outpatient studies included mainly low and intermediate probability patients, similar to the risk profile of GP patients. Also, the impact of implementation of calcium scoring in a GP setting on CAD diagnosis and treatment rate is unknown. CONCRETE is an implementation study focusing on the Dutch health care system in which the GP is usually the first physician a patient consults with chest discomfort. We hypothesize that GP access to the CT CCS test allows for early diagnosis of CAD and treatment, more efficient referral to the cardiologist and a reduction in health care related costs.

OBJECTIVES

The primary objective is to determine the increase in detection and treatment rate of CAD in GP offices with the CT CCS-based strategy, compared to GP offices with the standard of care strategy, in patients presenting with atypical AP and non-specific thoracic complaints. The primary endpoint is the (early) CAD diagnosis registration as expressed by the cardiovascular risk management (CVRM) registration rate.[9] The primary and secondary objectives of the trial are listed in table 1.

Table 1: Primary and secondary objectives of CONCRETE

Primary objective (cluster-based)
1. To determine the increase in detection/treatment rate of CAD in GP offices with the CT CCS-based strategy, compared to GP offices with the standard of care strategy, in patients with atypical AP and non-specific thoracic complaints.
Secondary objectives (patient-based)
1. To establish the diagnostic yield to diagnose obstructive CAD, for both strategies
2. To establish the effectiveness in terms of CAD diagnosis and exclusion of GP referral to the cardiologist for the calcium score cluster as well as the time to (exclusion of) CAD diagnosis
3. To compare downstream diagnostic testing and treatment for both strategies
4. To evaluate whether diagnostic stratification, in particular cut-offs for referral to the cardiologist, can be optimized for the calcium score
5. To estimate the effect of calcium scoring versus the standard of care on quality of life and cardiac complaints after 6, 12, and 24 months
6. To estimate the effect of calcium scoring on reduction of MACE (after 2 years).
7. To derive data on the costs per diagnosis of obstructive and diagnosis of non-obstructive CAD in the setting of calcium score testing versus the standard of care
8. To estimate the cost-utility of implementing the calcium score test in GP setting
9. To develop machine learning tools to evaluate big data on (combinations of) symptoms and family history/risk factors, and relationship to CAD
10. To establish and visualize relationships between (combinations of) symptoms and family history/risk factors and probability of CAD, using innovative techniques for big data analysis; these results will form the input for a risk assessment tool to be developed
Note: all analyses will be analysed by sex. CAD= coronary artery disease. GP= general practitioner. CT CCS= computed tomography coronary calcium score.

METHODS AND ANALYSIS

Study design and setting

CONCRETE is a pragmatic multicenter study with a cluster-randomized design. This type of design is increasingly used in primary care for the evaluation of health care interventions.[33-36] An overview of the study design is provided in Figure 1. From January 2019 onward, GPs are recruited from multi-practice GP organizations in urban and rural regions from the provinces Gelderland, Groningen, Limburg and Overijssel in the Netherlands. The initial aim was to include 80 GP offices. Through a permutated block randomization scheme (1:1), GP offices are divided into two equally large strategy groups; one group of GP offices refers patients for CT CCS testing and another group of GP offices provides the standard of care (Figure 1). The primary analysis will be performed in the two clusters. After GP office randomization, approximately 800 patients will be included over a period of two years in both diagnostic strategies (Figure 1).

Enrolment of clusters, GP offices (for primary analysis)

GPs and medical staff of the GP offices, from the collaborating multi-practice GP organizations, are informed of the trial through written information (e.g. information brochure, newsletters and website) and verbal information (e.g. presentations during mandatory educational courses and local policy meetings) by the (local) researchers of the trial. Then, every GP office is contacted by the researchers to schedule a face to face appointment in order to discuss the trial and their potential participation. GP offices are included cluster-wise if they are willing to take part in the trial and provide written informed consent. Thereafter, the GP office is randomized into one of the two strategy groups using a computerized randomization scheme and is informed by the researcher by telephone or per email of the randomization outcome. If a GP experiences difficulties in fulfilling the study tasks; a meeting will take place with the researcher to find solutions in order to sustain participation. In case GPs wish to discontinue their participation, collaboration is ended and data of

patients included up to that moment are used in the study, since written consent of the patients was obtained.

Enrolment of patients (for secondary analysis)

For the individual-based analyses, patients with chest discomfort, either atypical AP or non-specific thoracic complaints (Figure 1), with indication for further diagnostic evaluation as determined by the GP, will be informed about the trial and asked to participate by the GP. Men of 40 years and older, and women of 45 years and older will be included. Exclusion criteria for individual patients are pregnancy, unwillingness to provide written informed consent for the individual level (secondary) outcomes, and prior diagnosis of CAD (percutaneous coronary intervention, coronary artery bypass surgery, myocardial infarct, stable CAD).

Patients receive an information brochure and informed consent form. The signed informed consent form is returned to the GP and sent to the researcher. For a patient, participation comprises agreement to share clinical data from the GP system with the researchers, and filling in questionnaires. The first questionnaire is sent to the patient either digitally or by letter, to be completed prior to the visit to the cardiologist or the CT scan. Patients will receive digital reminders to fill in the questionnaires. The diagnostic management executed by the GP (CT CCS or standard of care) does not depend on the signing of the informed consent by the patient; this depends on the cluster to which the GP office is randomized.

CT coronary calcium scoring strategy

The CT CSS is carried out in accordance with the routine procedure of the participating radiology departments, and performed on the routine (single or dual source) CT scanner used for cardiac imaging in these departments. In this way, adherence to common clinical practice and generalizability of results are optimized. In practice, the scan and reconstruction protocol for CCS is rather standardized. In all centers, the CT scan consists of an ECG-synchronized acquisition without

intravenous iodine contrast, during breath hold. The entire heart is included in the scan range. Images are commonly acquired around 60% of the cardiac cycle. Tube voltage is 120 kVp and tube current is generally set at around 80 mAs as reference. Images are reconstructed with a slice thickness of 3.0 mm and slice increment of 1.5 or 2.5 mm. The radiation dose is approximately 0.5–1 mSv, which is less than 50% of the annual background radiation dose in the Netherlands.[37 38] The CCS is calculated according to Agatston's method.[39] Patients receive AP medication subscribed by the GP while awaiting the results of the CT CCS test, the preventive or pre-emptive treatment for stable CAD can be stopped if the diagnosis CAD has been ruled out, as recommended by the NHG Standard for Stable AP.[7] The GP will be informed of the CT CCS result based on the radiologist report (Figure 1). The report of the radiologist consists of the total CCS and the CCS per coronary artery (right coronary artery, left coronary artery, left anterior descending artery and left circumflex artery) and the MESA (the Multi-Ethnic Study of Atherosclerosis) percentile.[40] CCS results are categorized as CCS of 0 (no CAD), 1-10 (minimal CAD), 11-100 (mild CAD), 101-399 (moderate CAD) and ≥400 (severe CAD), respectively. When CCS is 0 or 1-10, GPs are advised to stop AP medication and consider other causes for the complaints. In case of CCS 11-100, continuation of AP medication and inclusion of these patients into CVRM is to be considered.[9] In patients with CCS 101-400 and CCS ≥400, AP medication is continued and in addition, the patient will be included into CVRM [9] and referred to the cardiologist. In case of a CCS result above the 75th percentile for age and sex based on MESA percentile,[40] the GP is recommended to classify the patient one CCS category higher than the category matching the absolute score, in view of the premature atherosclerosis and the associated long-term cardiovascular risk (Figure 1).[41 42]The categories are based on recent literature from Dutch studies,[9 11 22 42] and on the experience of physicians who have been applying the CCS for years in practice. The management advice for the CCS categories is based on discussions with cardiologists, GPs and radiologists, and is not obligatory but meant as guidance. The GP discusses the results with the patient. Decisions regarding patient management remain at the discretion of the GP, who takes all available patient information into account.

Standard of care strategy

In this arm, all steps are in agreement with routine standard of care, as determined by the NHG Standard for Stable AP. Thus, patients with atypical AP or with non-specific thoracic complaints in whom the GP wants to exclude CAD as underlying cause, will be referred to the outpatient cardiology clinic. There, evaluation of the patient takes place with additional testing at the discretion of the attending cardiologist in accordance with the guidelines of the European Society of Cardiology (ESC).[43] GPs will be informed of the findings and cardiac diagnosis based on the letter from the cardiologist (Figure 1).

Data collection

The primary endpoint is an increase in CAD diagnosis and treatment in patients in the CT CCS strategy compared with the standard care strategy. The detection and treatment rate of CAD in GP offices is based on the CVRM registration rate. According to the CVRM guideline patients are registered into the CVRM registry when they have high risk of developing CVD and/or are diagnosed with CVD.[9] CVRM registry data are derived from the GP electronic registration system with registration date one year before baseline, at baseline and one and two years after baseline. Individual patient data are collected over a period of two years, using four questionnaires (Table 2) containing questions with regard to experienced chest pain complaints,[44] quality of life (EQ-5D-5L)[45 46] and heart-related quality of life (HeartQoL).[47 48] In addition, the cardiovascular risk profile of the patient, and information on downstream testing and CAD diagnosis will be collected through the electronic patient dossier (Table 3).

Table 2: SPIRIT schedule of enrolment, test strategies and assessments

	STUDY PERIOD					
	Enrolment	**Baseline**	**Execution of strategy**	**Post execution strategy**		**Close-out**
Time points	***0***	**0**	**1-2** weeks	**6** months	**12** months	**24** months
Enrolment:						

Eligibility screening by GPs	x					
Informed consent	x					
Test strategies:						
Standard care strategy			x			
CT CCS strategy			x			
Assessment:						
CVRM GPs offices		x			x	x
Risk factors	x					
Chest pain complaints		x				
Quality of life		x		x	x	x
Heart related quality of life		x		x	x	x

Note: GPs=general practitioners, CT CCS = computed tomography coronary calcium score, CVRM= number of patients registered to Cardiovascular risk management.

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Table 3: Cardiovascular risk assessment items

General health assessment	
Smoking habits	Tobacco use per day Total number of smoking pack years
Alcohol use	Mean number of glasses per day General behaviour with regard to alcohol use using the 5SH1 test
Family history	Fatal or non-fatal cardiovascular diseases in a first degree family member?
Diabetes Mellitus	Does the patient have diabetes mellitus?
Rheumatoid arthritis	Does the patient have rheumatoid arthritis?
Physical assessment	
Systolic blood pressure	Mean of three blood pressure measurements by general practitioner
Body mass index	Determination of BMI: kilograms/ length^2 (kg/m^2)
Laboratory assessment	
Blood lipids spectrum	- HDL ratio - LDL ratio - Total cholesterol ratio - Total cholesterol-HDL ratio - Triglycerides ratio
Blood glucose level	Fasting glucose ratio

Estimated Glomerular filtration	eGFR ratio

Note: measurements to assess cardiovascular risk of the patients. BMI=body mass index. HDL= High density lipoprotein. LDL= Low density lipoprotein. eGFR= estimated glomerular filtration.

Sample size

We used sample size calculations for cluster randomised trials.[49] In order to detect a 7.5% difference in CVRM registrations between the two clusters, with a power of 80%, a significance level of 5%, and an intra-cluster correlation of 0.01, inclusion of 36 GP offices in each cluster would be necessary, with an estimated total of 20 patients per GP office (10 patients per year per GP office). To anticipate unforeseen circumstances, such as drop out, we initially decided to include 40 GP offices in each strategy group. The calculations are based on the assumption that yearly about 50 patients will consult their GP with atypical AP and non-specific thoracic complaints,[5] with an estimated 10 patients who will be referred for additional evaluation to diagnose or exclude CAD.[6] In the CT CCS strategy a CCS of 0 are expected in 45% of patients, a CCS of 1-10 in 10%, a CCS of 11-100 in 20% and a CCS larger than 100 in 10%, actual percentages will only be known during this study.[24 31 50 51] In the standard care strategy, 27.5% of the patients are expected to be included in CVRM registry for CAD diagnosis/treatment, and 35% of the patients in the CT CCS test strategy. These percentages are based on similar populations from previously published Dutch research.[10 52 53]

COVID-19 pandemic

The trial was stopped due to the COVID-19 pandemic from March until June 2020. However, even after the re-start in July 2020, the inclusion of GP offices and patients was so far (June 2021) severely slowed due to effects of the COVID-19 pandemic (among others, lower GP consultation rates, procedures to re-start clinical practice in adherence to COVID-19 regulations, and vaccination procedures). The COVID-19 pandemic urged us to realign the patient inclusion rate, sample size and the interdependent calculations of the trial. To reduce the impact of COVID-19 on the progress of CONCRETE, we aim to increase the number of participating GP offices from 80 to 130.

Data analysis

Baseline characteristics (including baseline rate of CVRM registration) will be summarized by means (standard deviation), median (interquartile range) and percentages. The primary outcome is the (early) CAD diagnosis/treatment registration as expressed by the CVRM registration rate at GP office level. The increase for each individual GP office will be calculated by subtracting the percentage of registrations at baseline from the percentages of CAD diagnosis/treatment registrations at follow-up. The difference in increase of CVRM registration rate of the two clusters will be compared with an independent t-test or non-parametric test, depending on distribution. A multiple multilevel linear regression will be performed to adjust for potential confounders (differences between GP practices), such as GP practice size and the ratio men/women per practice (characteristics of each practice). In case of missing data, due for example loss to follow-up, multiple imputations will be used.

In the CT CCS strategy, receiver operating characteristic (ROC) analyses will be used to find the optimal CCS and CCS percentile for referral to the cardiologist, by sex and age.

Follow-up

Patients will be followed for acute myocardial infarction and sudden cardiac death as well as CAD diagnostic procedures, cardiac interventions, and diagnostic/treatment costs, for up to five years; source data about CAD diagnosis, diagnostic procedures and follow-up cardiovascular events will periodically be obtained from the GP electronic dossier. As part of the current grant, follow-up procedures up to 2 years after the inclusion period are covered. A follow-up up to 5 years will be performed if additional funding is secured.

Quality of life

Quality of life (QoL) and HeartQoL will be compared between the strategies.[46 54] Patients fill in both questionnaires prior to the CT CCS or cardiologist referral, and after 6, 12 and 24 months. Multiple

linear regression will be performed, to adjust for potential confounders. Analyses will be performed on an intention to treat basis.

Cost-utility

Costs of diagnosis are recorded in this clinical trial and used to calculate the costs per CAD diagnosis (obstructive and non-obstructive) for each strategy. Additionally, costs for events during follow-up are recorded for each strategy. Cost-utility analysis will be performed to reflect the balance between incremental monetary cost and incremental quality adjusted life years (QALY) resulting in an incremental cost-utility ratio (ICUR). A societal perspective will be used and discounting will be applied for costs (4%) and health outcomes (1.5%) according to Dutch guidelines.[55]

A patient-level simulation model using a life-long time horizon will be created to assess the long-term impact of CT CCS access by GPs regarding costs and health outcomes. Due to the late onset of symptoms for CAD and the major impact of cardiovascular events caused by CAD, extrapolating the results to a lifelong time horizon is desired to determine the true impact of CT CCS. Clinical data will be used as input for the simulation model where possible. Bootstrapping is used to determine uncertainty surrounding these input parameters.[56] Model parameters beyond the scope of the clinical trial are supplemented by literature. Expert opinion will be used in case literature yielded inconclusive results. To reflect outcome (ICUR) uncertainty, a probabilistic analysis will be performed using the Monte Carlo approach with 5,000 iterations.[57] Results of the probabilistic analysis will be visualised in a cost-effectiveness plane and cost-effectiveness acceptability curve. Finally, subgroup-specific cost-utility outcomes will be determined for example for age and sex.

Patients and Public Involvement

Patients were involved in the design and reporting of the study. Cardiovascular patients gave input on the information and questionnaires to be provided to patients. Patients are also included in the user committee of the study, that gives input on every aspect of the trial including recruitment and conduct. There is a specific part of the CONCRETE website dedicated to informing patients about the trial and its results.

ETHICS AND DISSEMINATION

CONCRETE has been approved by the Medical Ethical Committees of the University Medical Center of Groningen (UMCG) on November 12th 2018, version 2.0, under number 2018/404. The study will be conducted according to the principles of the Declaration of Helsinki, Brazil, October 2013,[58] and in accordance with the Dutch Medical Research Involving Human Subjects Act (WMO).[59] Study data will be collected in a pseudonymised fashion and managed using REDCap electronic data capture tools hosted by the UMCG. Pseudonymised CT image data will be stored in the XNAT imaging data archive. We will handle personal data in compliance with the Dutch General Data Protection Regulation (AVG). [60] The trial has a Data Management Plan (DMP) not accessible to the public, consisting - among other things - of information regarding metadata, the used software for data management and a platform for storing and sharing data. Monitoring of the data will be performed independently of the sponsor, by a monitor of the monitoring committee of the UMCG using a preconceived plan. The participating (University) Medical Centers are subject to internal audit programs, randomly evaluating scientific studies, independently of the sponsor and investigators. The accredited METc will receive a summary of the progress of the trial once a year and will make the final decision to continue or (prematurely) terminate the trial. In case of (serious) events continuation of the trial will be discussed within the consortium and the accredited METc. However, due to the negligible risk associated with the CT CCS we do not anticipate adverse events due to the implementation of CT calcium scoring in GP setting, nor a premature termination of the study. There is liability insurance for ancillary and post-trial care for those who could have suffered harm from trial participation. The

study is registered in the Netherlands National Trial Register on https://www.trialregister.nl/ (NTR: 7475). Information on CONCRETE for patients, physicians and researchers is available at the website www.concrete-project.nl. Results from the trial will be published in peer-reviewed journals with the consortium members as co-authors and presented at (inter)national conferences. We do not intend to use professional writers. Following FAIR principles (Findability, Accessibility, Interoperability and Reuse of digital assets), data will be made available to third parties, after completion of the trial. Procedures and criteria for sharing of the data will be designed.

DISCUSSION

The CONCRETE study aims to determine whether direct GP access to CT CCS leads to earlier and more cost-effective diagnosis and treatment of CAD in patients with atypical AP or non-specific thoracic complaints, compared to standard of care. To our knowledge CONCRETE is the first study that will test the implementation of CT CCS in primary care, as previous studies have been performed in secondary care settings.[4 12 61 62] Further, the study will assess and optimize sex-specific diagnostic stratification based on the CCS. In addition, CONCRETE will give insight into the QoL of these patients, downstream testing, (unnecessary) referral rates, and the cost-effectiveness of both strategies. Implementation of CONCRETE findings could initiate a change in healthcare policy for patients with atypical AP and non-specific thoracic complaints.

Inclusion of GP offices and patients started in January 2019; at that time, the standard GP management was to request exercise ECG in patients suspected of CAD. Since January 2020, the standard of care has changed and exercise ECG testing was replaced by referral to the cardiologist.[7] It is expected that the change of the standard care will not influence the study results to a large extent, because a recent survey has shown that in the years before 2020, GPs frequently referred patients with suspected CAD directly to the cardiologist, instead of ordering exercise ECG.[6 63] Furthermore, 61% of the patients referred to the cardiologist received an exercise ECG test as first diagnostic test, and 22% of the referred patients received no diagnostic test at all.[52 64] Thus, the initial diagnostic

procedure in referred patients has so far been commonly the same as in primary care. Finally, it is expected that direct referral to the cardiologist can reduce heterogeneity in the referral indications by GPs.

No upper age limit is used in this study. Research has shown that even in older symptomatic patients a CCS 0 can be detected in a sizable proportion (23%).[65] Evidently, these patients can be reassured by the GP. In addition, there are still many older GP patients with undetected, increased cardiovascular risk. In the ROBINSCA screening trial (mean age 64 year) 17% of the women and 31% of the men could benefit from preventive drug therapy, based on an elevated CCS.[66] The results of this study can help to answer the question whether there is an age above which performing a CCS test is no longer of additional value.

The CVRM-registration rate at GP-office level will be used in order to determine if there is an increase in patients within the CVRM registry after the implementation of CCS, in comparison with the standard of care. Although different types of cardiovascular patients are included in the CVRM registry (patients with established cardiovascular disease, patients at high risk for cardiovascular disease resulting from diabetes, chronic kidney disease, or high cardiovascular mortality risk otherwise), [9] the CVRM-registration rate at baseline between the two strategy groups is expected to be similar, as well as the effects of potential new guidelines. The only difference during the trial that can be expected to cause a difference in CVRM registrations between the strategy groups is the application of the CCS in only one of the strategy groups.

The NHG guideline states that patients with typical and atypical AP need to be referred to the cardiologist for a diagnostic evaluation.[7] After careful discussion in the CONCRETE steering committee, we excluded patients with typical AP from inclusion in the present study. Previous research among patients with atypical AP or non-specific chest pain complaints with generally a low- to intermediate PTP, demonstrated that CCS is well suited as gatekeeper to rule out (obstructive) CAD.[67] Research regarding high PTP patients, including typical AP patients, is limited and shows a low prevalence of CCS 0 (12% and 19%), and a relatively high percentage of obstructive CAD in CCS 0 (7%

and 26%).[67] Thus, in this patient category, CCS 0 cannot exclude the presence of obstructive CAD. On the other hand, the use of CT CCS in the lower PTP population, can not only help to safely reassure patients with negligible probability of (obstructive) CAD, but also lead to higher diagnostic yield of patients who are referred to the cardiologist.

As the study is performed in the Netherlands, health care practice in the standard care strategy is based on the Dutch GP guideline. However, the scope of atypical AP and non-specific thoracic complaints in primary care and the diagnostic use of CT CCS are broader. Only 6 to 11% of chest pain patients will be diagnosed with stable CAD at first GP consultation,[68] but 33% of MACE and cardiovascular mortality patients present first symptoms five years before the events.[69] Prognosis is worse in patients without diagnostic testing to exclude cardiac etiology.[70] Therefore, GPs often refer patients with chest pain to the cardiologist for further work-up, as advanced cardiac imaging is currently not available in primary care. The Dutch National Health Care Institute analysis shows that the majority of GP patient referrals to cardiology outpatient clinics do not have obstructive CAD and only 1-5% of the referred patients need invasive treatment.[52] The high prevalence of a zero CCS in referred patients (~50%) supports this fact.[24] There is a clear need to improve the cost-effectiveness of GP referrals to secondary care facilities. A drawback of CT CCS is the need for ECG-synchronized cardiac CT scanning, however, cardiac CT is nowadays available in most Dutch hospitals. Although CT CCS to identify individuals with obstructive CAD is not recommended by the ESC guidelines, it does mention the use of CT CCS as risk modifier in the assessment of the overall likelihood of obstructive CAD in low pre-test probability patients.[4] The CCS is a more powerful predictor of obstructive CAD and future events in symptomatic patients than traditional risk factors. [42 64-66] The “power of zero CCS” to exclude clinically relevant CAD has been proven in symptomatic patients. [42 66] GP access to CT CCS could reduce unnecessary referrals, downstream testing and health care costs. However, little is known about the usefulness of CCS in a primary care setting. In particular in primary care, the vast majority of chest pain patients present with atypical chest pain and non-specific thoracic complaints, causing a diagnostic challenge to GPs if CAD as underlying cause cannot be excluded. In addition, the

question remains, what CCS cut-off value should be used to decide on the need to refer patients to a cardiologist for additional testing. Finally, CT CCS can be used as biomarker for early treatment of CAD in patients with non-obstructive CAD detected at an early stage.[28 31 71 72] Treatment of early CAD may prevent future MACE or sudden cardiac death, although at this moment this has not yet been proven in randomized clinical trials.

CONCLUSION

CONCRETE is a pragmatic implementation study to determine the effectiveness of direct GP access to CT CCS to diagnose and exclude CAD in patients with atypical AP and non-thoracic complaints, compared with the standard of care. The CONCRETE results are expected to lead to change of GP referral indications for patients with atypical AP and non-specific thoracic complaints and change of reimbursement policies in healthcare.

FIGURE CAPTIONS AND LEGENDS

Figure 1: Flowchart of randomisation, referral and test results

CT CCS: computed tomography coronary calcium scoring, CAD = coronary artery disease, CVRM = Cardiovascular risk management. AP = angina pectoris. *Guidelines indicate stable chest pain patients have to start with medication for AP before undergoing diagnostic testing.[5] **With CCS ≥ 75th percentile for age and sex, the GP is advised to consider classifying the patient one CCS category higher.

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AUTHORS' CONTRIBUTIONS

Moniek Y. Koopman: Data curation, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing - original draft. **Jorn Reijnders**: Data curation, Formal analysis, Investigation, Methodology, Writing - original draft. **Robert T.A. Willemsen:** Resources, Conceptualization, Funding acquisition, Methodology, Supervision, Writing - original draft. **Rykel van Bruggen:** Resources, Conceptualization, Methodology, Writing - original draft. **Carine J.M. Doggen**: Methodology, Formal analysis Writing- review & editing. **Bas Kietselaer:** Investigation, Funding acquisition, Resources, Supervision, Writing- review & editing. **Martijn J Oude Wolcherink:** Methodology, Writing- review & editing. **Peter van Ooijen:** Methodology, Writing- review & editing. **Jan Willem C. Gratama:** Investigation, Resources, Writing- review & Editing. **Richard Braam:** Investigation, Resources, Writing- review & editing. **Matthijs Oudkerk:** Conceptualization, Funding acquisition, Writing- review & editing**. Pim van der Harst:** Conceptualization, Funding acquisition, Resources, Supervision, Writing- review & editing. **Geert-Jan Dinant:** Resources, Methodology, Writing- review & editing. **Rozemarijn Vliegenthart:** Conceptualization, Formal analysis, Funding acquisition, Methodology, Project administration, Supervision, Writing - original draft.

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DECLARATION OF INTERESTS

GPs in the control condition receive a 50 euro compensation for the inclusion of 5 patients, to compensate for the time investment to include patients into the study. We expect that this financial compensation will not lead GPs to include patients due to a financial incentive. Vliegenthart is supported by an institutional research grant from Siemens Healthineers. The performance of the trial

and trial results do not result in a conflict of interest of the authors as there are no other competing interests.

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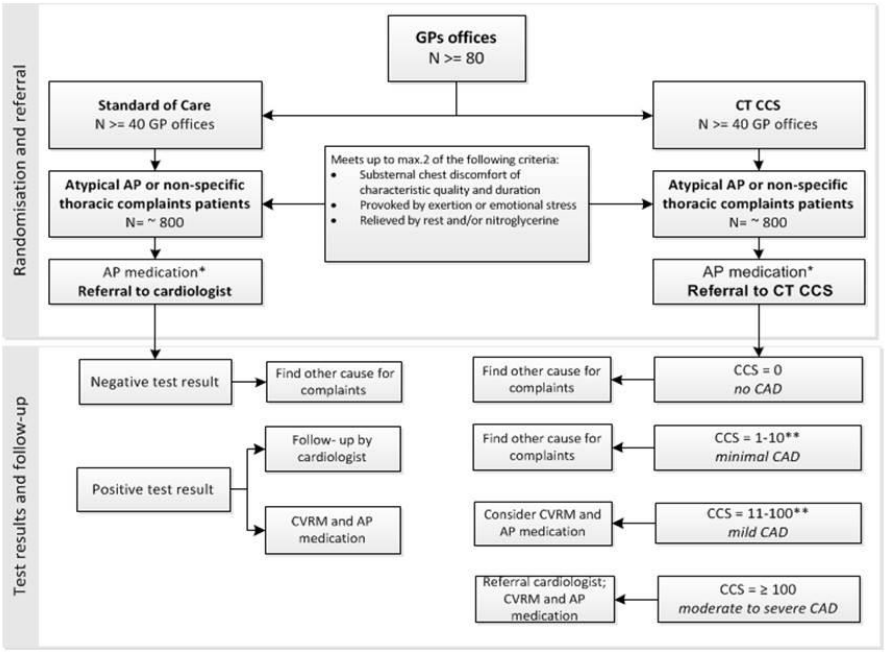

Figure 1: Flowchart of randomisation, referral and test results

20x15mm (1200 x 1200 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents* Date: 15/03/2022

Section/item	Item No	Description	Page Line numbers
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Page: 1 Line numbers: 1-4
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Page: 2 and 16-17 Line numbers: 60- 61 and 357-361
	2b	All items from the World Health Organization Trial Registration Data Set	n/a, the study is registered in the Netherlands Trial Register. This register is described in the manuscript (2a)
Protocol version	3	Date and version identifier	Page: 16 Line numbers: 339-340
Funding	4	Sources and types of financial, material, and other support	Page: 26 Line numbers: 704- 706
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Page: 1 Line numbers: 6 - 31
	5b	Name and contact information for the trial sponsor	Page: 26 Line numbers: 704
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and	Page: 26

		interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Line numbers: 705-706
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Page: 26 Line numbers: 687-701
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Page: 4 – 7 Line numbers: 74 - 157
	6b	Explanation for choice of comparators	Page: 4 – 7 Line numbers: 74 - 157
Objectives	7	Specific objectives or hypotheses	Page: 6 – 7 Line numbers: 148 - 157
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	Page: 8 Line numbers: 161 - 171
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Page: 8 and 27 Line numbers: 162-171 and 717-727
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Page: 8 and 9 Line numbers: 173 - 203
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Page: 9 - 11 Line numbers: 205-244
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	Page: 10 Line numbers: 234-235
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Page: n/a Line numbers: n/a
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Page: n/a Line numbers: n/a
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood	Page: 11 - 12

		pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Line numbers: 246-259
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Page: 11 - 12 Line numbers: 246-259 Table 2 and figure 1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Page: 13 Line numbers: 260-273
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Page: 8 and 13 Line numbers: 173 -179 and 275– 282. *The description of the enrolment of the GPs was limited, therefore we have we added information regarding the enrolment.*
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	Page: 8 Line numbers: 166-167
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	Page: 8 Line numbers: 166 – 167 and 180-182
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Page: 8 and 9 Line numbers: 166-167 and 189-191

Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Page: n/a Line numbers: n/a
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Page: n/a Line numbers: n/a
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Page: 11 and 12 Line numbers: 246-259
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Page: 8 and 9 Line numbers: 182-186 and 200-201.
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Page: 16 Line numbers: 346-348
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Page: 14 Line numbers:284-296
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Page: 14 - 15 Line numbers: 284 - 329
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	Page: 14 Line numbers: 293-294
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Page: 16 Line numbers: 348-351
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	Page: 16 Line numbers: 251-353
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Page: 16 Line numbers: 353-356

Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Page: 16 Line numbers: 350-351
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Page: 16 Line numbers: 339-340
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	Page: 16-17 Line numbers: 357-366
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Page: 8 and 9 Line numbers: 177-180 and 189-191
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Page: n/a Line numbers: n/a
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Page: 16 Line numbers: 339-348
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page: 26-27 Line numbers: 708-714
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Page: 16 Line numbers: 346-348 not explicitly described in the manuscript
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Page: 16 Line numbers: 356-357
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	Page: 17 Line numbers: 361-366
	31b	Authorship eligibility guidelines and any intended use of professional writers	Page: 17 Line numbers: 362-364
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Page: 17

			Line numbers: 364-366
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Not added as a supplement, but can be requested
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Page: n/a Line numbers: n/a

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.