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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-randomised CONCRETE trial

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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 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 COroNary Calcium scoring as first-line Test to deEtect and exclude coronary artery disease in GPs patients with stable chest pain (CONCRETE) study, the impact of direct access of GPs to CT CCS will be investigated. We hypothesise that this will allow for early diagnosis of CAD and treatment, more efficient referral to the cardiologist and a reduction of healthcare-related costs.

Methods and analysis CONCRETE is a pragmatic multicentre trial with a cluster randomised design, in which direct GP access to the CT CCS test is compared with 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 CVRM 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.

Trial registration number NTR 7475; Pre-results.

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; 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 min after using sublingual nitroglycerine.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 healthcare 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. In only 10%–15%, obstructive CAD will eventually be diagnosed as cause of the symptoms. The challenge for the GP is to diagnose CAD based on symptoms, age and sex. 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. 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. According to the prior clinical standard, the GP could order exercise electrocardiogram (ECG). 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. 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). 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 nationwide 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 ischaemia test. Presently, in the Netherlands, about 105,000 patients are referred to the cardiologist (52% women) each year. Ultimately, only 5% of men and 1% of women have obstructive CAD requiring invasive treatment. There is a clinical need in patients with chest pain to optimise 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). 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 CoRoNary Calcium scoring as fIrSt-liNE Test to dEct and exclude coronary artery disease in GPs patients with stable chest pain (CONCRETE) trial. 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 randomised 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 standardised protocol for scanning and postprocessing, with virtually no contraindications. In outpatient cardiology clinic setting, the CCS has proven to have better diagnostic and prognostic power than exercise ECG. The CCS has a negative predictive value of 93%–99% for obstructive CAD in symptomatic patients, with similar prognostic results in men and women. The sensitivity of CCS for obstructive CAD is 95%–99%. The severity of coronary calcification is strongly related to CAD burden, ischaemia and MACE, and allows for early detection of patients with non-obstructive CAD, who can then receive early treatment.

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 1 year in patients with CCS <10 (52% of all patients), and better identification of patients with obstructive CAD and/or subsequent coronary events. Other Dutch studies in outpatient cardiology setting have confirmed these findings, and indicate that CCS improves diagnostic and prognostic stratification compared with exercise ECG testing. A recent Dutch study in 1551 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%. 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. A CCS of 0 was found to have a safe and efficient approach to exclude CAD in patients with low-to-intermediate pretest probability, while probability of obstructive CAD increased particularly from a CCS of 10 to 1–100. The CAD consortium recently reported that inclusion of calcium scoring in risk stratification tools improves prediction of CAD probability in patients with chest pain undergoing invasive or CT coronary angiography. 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. 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 healthcare system in which the GP is usually the first physician a patient consults with chest discomfort. We hypothesise that GP access to the CT CCS test allows for early diagnosis of CAD and treatment, more efficient...
Box 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 with 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 optimised 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, in relationship to CAD.
10. To establish and visualise 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.

All analyses will be analysed by sex.

AP, angina pectoris; CAD, coronary artery disease; CCS, coronary calcium score; CONCRETE, COroNary Calcium scoring as first-End to eEffect and exclude coronary artery disease in GPs patients with stable chest pain; GP, general practitioner; MACE, major acute cardiac event.

referral to the cardiologist and a reduction in healthcare-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 with GP offices with the standard of care strategy, in patients presenting with atypical AP and non-specific thoracic complaints. The primary end point is the (early) CAD diagnosis registration as expressed by the CVRM registration rate.9 The primary and secondary objectives of the trial are listed in box 1.

METHODS AND ANALYSIS
Study design and setting
CONCRETE is a pragmatic multicentre study with a cluster-randomised design. This type of design is increasingly used in primary care for the evaluation of healthcare interventions.32-35 An overview of the study design is provided in figure 1. From January 2019 onward, GPs are recruited from multipractice GP organisations 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 permuted block randomisation 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 randomisation, approximately 800 patients will be included over a period of at least 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 multipractice GP organisations, are informed of the trial through written information (eg, information brochure, newsletters and website) and verbal information (eg, 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 randomised into one of the two strategy groups using a computerised randomisation scheme and is informed by the researcher by telephone or per email of the randomisation 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 randomised.

**CT coronary calcium scoring strategy**

The CT CCS 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 generalisability of results are optimised. In practice, the scan and reconstruction protocol for CCS is rather standardised. In all centres, the CT scan consists of an ECG-synchronised 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 <50% of the annual background radiation dose in the Netherlands. The CCS is calculated according to the method by Agatston et al. 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. 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 Multi-Ethnic Study of Atherosclerosis (MESA) percentile. CCS results are categorised 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.
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. In patients with CCS 101–400 and CCS ≥400, AP medication is continued and in addition, the patient will be included into CVRM and referred to the cardiologist. In case of a CCS result above the 75th percentile for age and sex based on MESA percentile, 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). The categories are based on recent literature from Dutch studies 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). GPs will be informed of the findings and cardiac diagnosis based on the letter from the cardiologist (figure 1).

### Data collection

The primary end point 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. CVRM registry data are derived from the GP electronic registration system with registration date 1 year before baseline, at baseline and 1 and 2 years after baseline. Individual patient data are collected over a period of 2 years, using four questionnaires (table 1) containing questions with regard to experienced chest pain complaints, quality of life (QoL) (EQ-5D-5L) and heart-related QoL (HeartQoL). 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 2).

### Sample size

We used sample size calculations for cluster randomised trials. 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 intraclass 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, with an estimated 10 patients who will be referred for additional evaluation.
to diagnose or exclude CAD. 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 >100 in 10%, actual percentages will only be known during this study. 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.

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 restart 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 summarised by mean (SD), median (IQR) and percentage. 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 of men/women per practice (characteristics of each practice). In case of missing data, due to loss to follow-up, multiple imputations will be used.

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 5 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.

Table 2 Cardiovascular risk assessment items

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<th>Physical assessment</th>
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<td>Blood glucose level</td>
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<td>Estimated glomerular filtration rate (eGFR)</td>
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Measurements to assess cardiovascular risk of the patients. HDL, high-density lipoprotein; LDL, low-density lipoprotein; 5SH1, FiveShot1 questionnaire, that is used to determine alcohol use or possible alcohol abuse.
Quality of life
QoL and HeartQoL will be compared between the strategies. 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 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.

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. 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 5000 iterations. 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 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, which 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 12 November 2018, V.2.0, under number 2018/404. The study will be conducted according to the principles of the Declaration of Helsinki, Brazil, October 2013, and in accordance with the Dutch Medical Research Involving Human Subjects Act (WMO). 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).

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 with 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. Furthermore, the study will assess and optimise 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. 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. 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. 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 sizeable proportion (23%). 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 Risk Or Benifit IN Screening for CArdiovascular disease (ROBINS-CA) screening trial (mean age 64 years), 17% of the women and 31% of the men could benefit from preventive drug therapy, based on an elevated CCS. 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), 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. 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 pre-test probability (PTP) demonstrated that CCS is well suited as gatekeeper to rule out (obstructive) CAD. 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%). 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 help to safely reassure patients with negligible probability of (obstructive) CAD, and lead to higher diagnostic yield of patients who are referred to the cardiologist.

As the study is performed in the Netherlands, healthcare 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%-11% of patients with chest pain will be diagnosed with stable CAD at first GP consultation, but 33% of MACE and cardiovascular mortality patients present first symptoms 5 years before the events. Prognosis is worse in patients without diagnostic testing to exclude cardiac aetiology. 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. The high prevalence of a zero CCS in referred patients (~50%) supports this fact. 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-synchronised 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 pretest probability patients. The CCS is a more powerful predictor of obstructive CAD and future events in symptomatic patients than traditional risk factors. The ‘power of zero CCS’ to exclude clinically relevant CAD has been proven in symptomatic patients. GP access to CT CCS could reduce unnecessary referrals, downstream testing and healthcare costs. However, little is known about the usefulness of CCS in a primary care setting. In particular in primary care, the vast majority of patients with chest pain 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.
early CAD may prevent future MACE or sudden cardiac death, although at this moment this has not yet been proven in randomised 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.

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Contributors
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Competing interests
General practitioners (GPs) in the control condition receive a €500 compensation for the inclusion of five 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. RV 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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Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the ‘Methods and analysis’ section for further details.

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