Comprehensive Cardiac CT with Myocardial Perfusion Imaging versus Functional Testing in Suspected Coronary Artery Disease: the multicenter, randomized CRESCENT-II trial

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ABSTRACT

Objectives: To assess the effectiveness, efficiency and safety of a tiered, comprehensive cardiac CT protocol in comparison to functional-testing.

Background: While CT angiography accurately rules out coronary artery disease (CAD), incorporation of CT myocardial perfusion imaging as part of a tiered diagnostic approach could improve the clinical value and efficiency of cardiac CT in the diagnostic workup of patients with angina pectoris.

Methods: Between July 2013 and November 2015 268 patients (mean age 58 years; 49% female) with stable angina (mean pretest-probability 54%) were prospectively randomized between cardiac CT and standard guideline-directed functional-testing (95% exercise-ECG). The tiered cardiac CT protocol included a calcium scan, followed by CT-angiography if calcium was detected. Patients with ≥50% stenosis on CT-angiography underwent CT-myocardial perfusion imaging.

Results: By six months, the primary endpoint, the rate of invasive coronary angiograms without an ESC class-I indication for revascularization, was lower in the CT group than the functional-testing group (2/130 (1.5%) vs. 10/138 (7.2%), p=0.035), while the proportion of invasive angiograms with a revascularization indication was higher (88% vs 50%, p=0.017). The median duration until the final diagnosis was 0(0;0) days in the CT group and 0(0;17) in the functional-testing group (p<0.001). Overall, 13% of patients randomized to CT required further testing, compared to 37% in the functional-testing group (p<0.001). The adverse event rate was similar (3% vs 3%, p=1.000), though the median cumulative radiation dose was higher for the CT group (3.1mSv [IQR: 1.6;7.8] vs 0mSv [0;7.1], p<0.001).

Conclusions: In patients with suspected stable CAD, a tiered cardiac CT protocol with dynamic perfusion imaging offers a fast and efficient alternative to functional-testing.

Clinical Trial: US National Institutes of Health (ClinicalTrials.gov): NCT02291484

INTRODUCTION

Coronary computed tomography angiography (1) has become an established, reliable diagnostic test in the management of coronary artery disease (CAD). Two large randomized studies demonstrated that coronary CTA performs at least equally well as functional tests for the evaluation of stable angina(2,3). In the CRESCENT-I trial we found that incorporation of a calcium scan in a tiered CT strategy is safe and effective(4). Although coronary CTA effectively rules out coronary disease, it is limited in its ability to assess the hemodynamic importance of angiographic lesions. Because anatomical lesion severity is a poor predictor of hemodynamic significance, functional evaluation of intermediate stenoses is recommended for therapeutic decision-making(5,6). The performance of myocardial perfusion imaging (MPI) by CT has been validated in a large number of studies(6-11). A comprehensive cardiac CT examination, combining CTA and CT-MPI, could provide all essential information for clinical decision-making in CAD, and avoid invasive coronary angiography (ICA) in patients without hemodynamically significant CAD(7-9,12).

In the Comprehensive Cardiac CT versus Exercise Testing in Suspected Coronary Artery Disease (CRESCENT-II) randomized-controlled trial we assessed the effectiveness, efficiency and safety of a tiered cardiac CT protocol, consisting of a calcium scan with selective performance of CTA and CT-MPI, in comparison to functional-testing.

METHODS

Study design

The CRESCENT-II trial is a pragmatic randomized-controlled trial comparing the effectiveness, efficiency and safety of a comprehensive, tiered cardiac CT approach with a standard diagnostic workup using functional-testing. At four hospitals in the Netherlands, 268 patients referred with stable chest pain and suspected CAD were prospectively enrolled. Medical ethics committees at each of the sites approved the study. The CRESCENT-II trial is registered at the US National Institutes of Health (ClinicalTrials.gov): NCT02291484.

Study participants

Patients ≥18 years with chest pain symptoms suspicious of obstructive CAD, and CAD probability >10% were study eligible(13). Exclusion criteria were prior myocardial infarction or revascularization procedure, renal failure (eGFR<60ml/min/1.73m^2), iodine allergy, contra-indications to adenosine or known pregnancy.

Study procedures

After an outpatient clinic assessment, participants provided written informed consent and were randomly assigned to either the CT group or the functional-testing group. All participants filled out the Seattle Angina Questionnaire(SAQ), EuroQol-5D-5L(EQ-5D) and Short-Form-36(SF-36) for quality-of-life assessment, and a cost questionnaire. All testing was performed at the recruiting center. For ascertainment of trial endpoints at six months, results of downstream diagnostic and therapeutic procedures were collected from the medical records, and patients completed again the questionnaires for ascertainment of angina complaints, quality of life and health status.

Cardiac CT strategy

In the CT group all patients first underwent a non-contrast-enhanced calcium scan (Somatom Definition Flash and Force, Siemens Healthineers, Forchheim, Germany). In patients with a low-intermediate probability of CAD (10-80% by Diamond and Forrester) (13), the absence of calcium excluded obstructive CAD and obviated the need for further testing. Patients with a zero calcium score but >80% pre-test probability, and all patients with a positive calcium score (>0) underwent contrast-enhanced coronary CTA.

All patients received sublingual nitroglycerin before CTA studies. If indicated (HR>65/min) and clinically acceptable, beta-blockers were administrated. The prospective electrocardiographically triggered axial scan mode was used, with an exposure window during diastole and/or systole depending on the heart rate. Tube current and tube voltage were selected semi-automatically on the basis of body size. A test bolus acquisition was performed using 15-ml of contrast medium followed by a 40-ml saline chaser. For the CT angiogram, a contrast bolus of 50-60 ml (depending on iodine concentration) was injected to achieve an iodine delivery rate of 2.2-g/s, followed by a 40-ml saline bolus chaser. Images were reconstructed with a medium-smooth kernel (B26, Bv40), slice thickness of 0.5-mm, and an increment of 0.3-mm. The CTA was immediately assessed, and all patients with >50% stenosis underwent an adenosine-stress dynamic myocardial perfusion CT scan (CT-MPI) during the same session. All recruiting sites had previous cardiac CT experience.

Dynamic CT myocardial perfusion imaging

Detailed descriptions of the dynamic myocardial perfusion imaging protocol were published previously (8,11). In brief, CT perfusion started 10 minutes after CTA for wash-out of contrast media. Myocardial hyperemia was achieved by adenosine infusion (≥3 minutes, 140µg/kg/min) over a second venflon. To avoid interference with adenosine patients abstained from caffeine-containing beverages 24-hours prior to their appointment. A 50-ml contrast bolus (Ultravist, 370mgI/ml; Bayer, Germany) and 40 ml saline were injected at 6ml/s. Using an alternating table positions (shuttle mode) for complete

myocardial coverage, systolic images were acquired every second heart cycle while the patient maintained a 35-s inspiratory breath hold.

The following scan parameters were used for the second-generation dual-source scanner: 2×64×0.6-mm collimation, 280-ms gantry rotation time, 75-ms temporal resolution, 100-kV and 300-mA or 80-kV and 370-mA tube voltage and current per rotation, and shuttle-mode with 73-mm total z-axis coverage; for the third-generation dual-source scanner: 2×96×0.6-mm collimation, 250-ms gantry rotation time, 66-ms temporal resolution, 80-kV tube voltage and 300-mA current (Care-kV as a reference), and 102-mm shuttle-mode z-axis coverage.

From a series of 12-15 consecutive datasets, myocardial attenuation was plotted against time. A parametric deconvolution technique based on a 2-compartment model was used to fit the time-attenuation curves (Volume Perfusion CT body, Siemens). Myocardial blood flow (MBF, ml/100ml/min) was computed by dividing the convoluted maximal slope of the myocardial time-attenuation curve by the maximum arterial input function (aorta). By calculating MBF on a per-voxel basis, 3D-MBF maps were reconstructed with a slice thickness of 3.0-mm and an increment of 1.5-mm, which were used for interpretation of hypoperfusion in relation to angiographic obstructions (figure 1). Patients without (substantial) myocardial ischemia were treated medically. Patients with substantial myocardial ischemia (visually ≥10% LV) were referred for invasive angiography, in accordance with international guidelines(5).

Functional test strategy

The functional-testing strategy was selected by the treating physicians in accordance with international guidelines(5). Most underwent a symptom-limited exercise-ECG, with a target heart rate defined as 85% of the age-defined maximum-predicted heart rate. The main diagnostic ECG criterion for ischemia consists of a horizontal or down-sloping ST-segment depression ≥0.1mV, persisting for at least 0.06–0.08s after the J-point, in one or more ECG leads. SPECT MPI or stress echocardiography were performed in case of contraindications to exercise-ECG, or non-interpretable or equivocal results. Criteria for the presence of ischemia were reversible perfusion defects on SPECT MPI (≥10% ischemia, based on a segment difference score of 7 or higher) or the presence of new wall motion abnormalities on echocardiography. All functional imaging tests were interpreted for the presence of inducible ischemia and risk of adverse outcome, applying established criteria for each respective test (14,15).

Interpretation of CT and functional test results, using all available clinical data, as well as subsequent clinical management decisions, were performed by local physicians. Patients considered to be at high risk based on test results and clinical interpretation, or those with refractory symptoms despite optimal medical treatment, were generally referred to invasive coronary angiography.

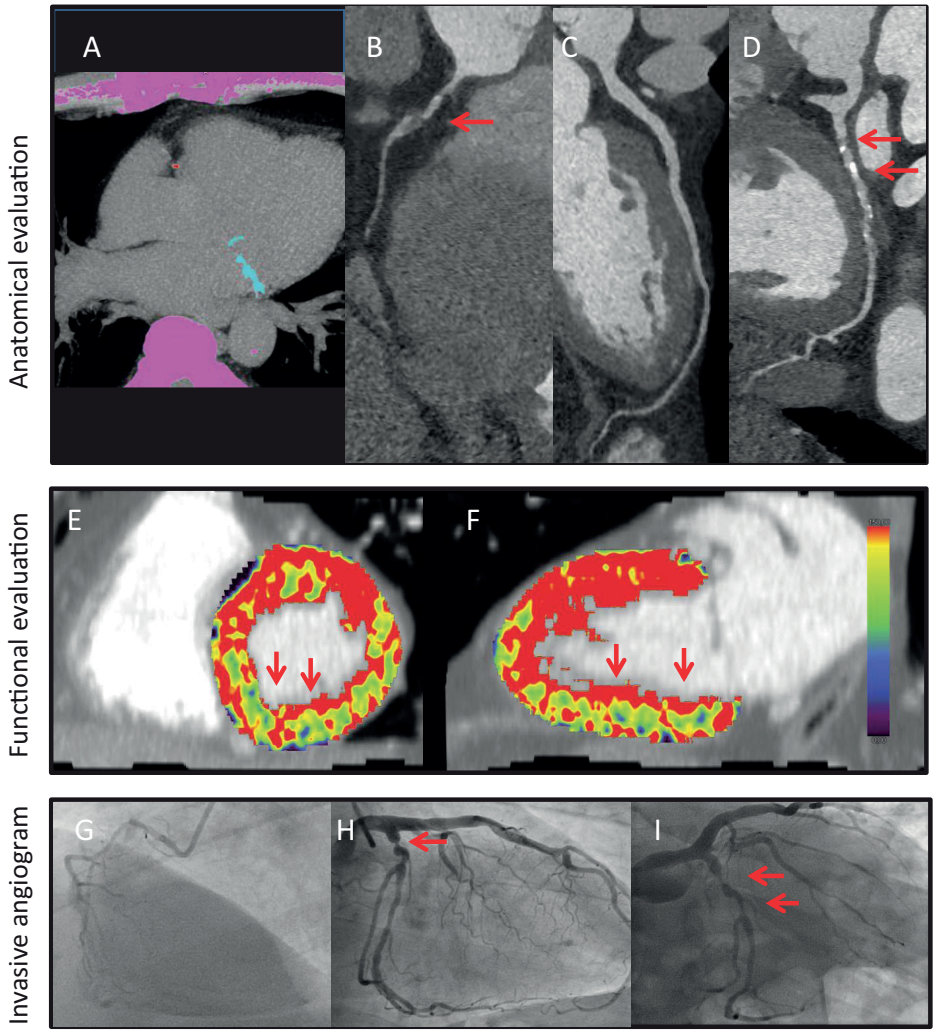

Figure 1. Case example of the comprehensive cardiac CT protocol. 52-years-old man with atypical angina, randomized to cardiac CT. Agatston score: 338.6 (A). CT-angiography: diffuse narrowing (50-70%) in the proximal, small RCA (arrow)(B), normal LAD (C), two 50-70% stenoses in the Cx(D). CT-MPI: low myocardial blood flow (0.55-0.73ml/min/g) in inferior wall (green-blue, arrows)(E,F). Invasive angiography: confirmed Cx lesions (H-I) were percutaneously treated(H-I), RCA regarded too small for revascularization(G).

Outcomes

The primary outcome was the *negative invasive angiography rate*, defined as the number of angiograms without a class I indication for revascularization based on ESC guidelines(16), as a proportion of the total number of patients. Class I indication for re-vascularization were: left main >50% with objective ischemia, proximal LAD >50% with ischemia, two or three-vessel disease with impaired LV function and ischemia, proven

large area of ischemia (>10% LV), >50% stenosis with limiting angina unresponsive to optimal medical treatment(16). An external, independent reviewer reassessed revascularization criteria, irrespective of clinical decisions by the treating physician.

Pre-specified secondary outcomes included the *positive yield of invasive coronary angiography*: proportion of invasive angiograms leading to a class I revascularization indication. Clinical effectiveness was defined by persistent or recurrent *anginal symptoms* and quality of life at 6 months. Efficiency outcomes included *time to diagnosis* from first outpatient visit until the first test that led to the final diagnosis, or the final test that ruled out obstructive CAD. *Downstream testing* included all non-invasive tests and invasive angiography to diagnose CAD after the initial test. *Diagnostic costs* included all tests to diagnose CAD over the first six months. Costs per test were based on previously published cost analyses(17).

Major adverse events included death, non-fatal myocardial infarction, unstable angina, urgent revascularization and stroke. For the survival analysis, events were counted once for each patient in the hierarchical order listed above. The *cumulative effective radiation dose* (mSv) included all tests and interventions applying radiation. For cardiac CT a conversion factor of 0.017 was used. For SPECT and invasive angiography conversion factors of 0.0085mSv/millibecquerel and 0.24mSv/Gy*cm^2 were used(18,19).

Statistical analyses

Based on registry data, an angiography without class I indication for revascularization rate of 1.2% in the CT group and 10.9% in the control group were predicted(20). For 80% power at a two-sided p-value of 0.05 at least 250 patients were required to detect a similar difference in invasive angiograms without a class I revascularization indication. Continuous data are presented as means±SD or medians with interquartile ranges. Groups were compared by independent-sample t-test or Mann-Whitney U-test for continuous variables, and chi-square or Fisher's exact-test for categorical variables. The invasive angiography without class I indication for revascularization rate was compared using a Fisher exact test. The event-free survival probability was estimated by Kaplan-Meier survival analysis and log-rank statistic. A Cox-proportional hazards model was employed to estimate the relative hazard of events by randomized test strategy, deriving hazard ratios and 95% confidence intervals (CIs). A two-sided p-value of <0.05 was considered statistically significant. Statistical analyses were performed using SPSS (version 21, IBM Corp, Armonk NY, USA), according to the intention-to-treat principle.

RESULTS

Study population

Between July 2013 and November 2015, out of 352 potential candidates 268 patients (age 58±11years, 49% women) could be enrolled and randomized between cardiac CT (138) and functional-testing (138) (table 1; figure 2). All patients were included in the intention-to-treat analysis. Pre-test CAD probability was 54±30% based on Diamond&Forrester(13). Invasive angiography demonstrated >50% CAD in 28 patients (8%). At 6-months follow-up original records of hospital visits and events were available in 266 of 268 (99%) patients.

Table 1. Patient characteristics

	Cardiac CT (n=130)	**Functional testing (n=138)**
Mean age (years)	58±11	58±11
Female sex (%)	49	56
Systolic/diastolic blood pressure (mmHg)	136±19/84±11	137±18/83±9
Median body-mass index	28±5	28±5
History (%)		
Transient ischemic attack or stroke	6	7
Peripheral artery disease	2	4
Cardiac risk factors (%)		
Current or past smoker	33	42
Hypertension	52	52
Dyslipidemia	38	40
Diabetes mellitus	18	18
Family history of ischemic heart disease	36	38
Presenting chest pain symptoms (%)		
Typical angina	38	36
Atypical angina	45	51
Non-anginal complaints	18	14
Pre-test probability – Diamond&Forrester (%)(13)	56±30	53±30

Patient characteristics as mean±SD, percentage, or median and interquartile range. No significant differences between both groups. Hypertension: systolic >150mmHg, diastolic >90mmHg, or medication. Dyslipidemia: total cholesterol>5mmol/L, low-density lipoprotein>3mmol/L, or medication. Diabetes mellitus: plasma glucose>11.0mmol/L, or medication.

Test results

In the functional-testing group the first test was exercise-ECG in 131 (95%) and nuclear imaging in 7 patients (5%), with a result interpreted as positive in 12 (9%), negative in 77 (56%), inconclusive in 47/138 (34%), while 2 patients did not undergo their scheduled

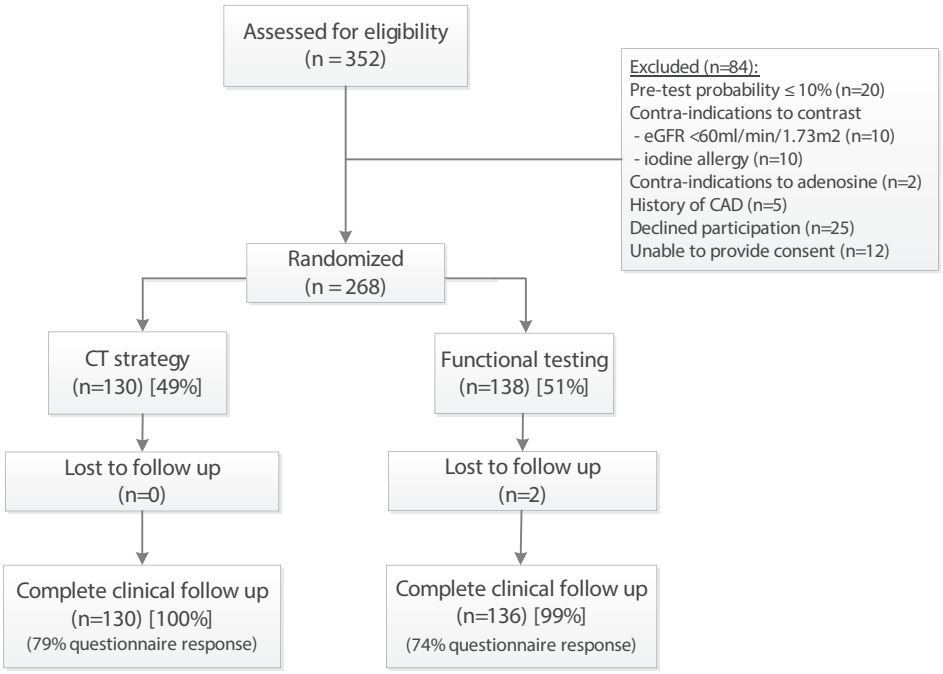

Figure 2. Enrolment, randomization, follow-up. Patient flow diagram with disposition by randomized arm. Complete clinical follow-up: clinical events at 6-months. Questionnaire response at 6 months: SAQ, EQ-5D and SF-36 questionnaires.

examination. Additional testing, and multiple tests in some patients, included: SPECT-MPI (n=24), stress echocardiography (n=4), cardiac CT (n=11), exercise-ECG (n=1) and invasive angiography (n=20)(figure 3). Of 20 patients undergoing invasive angiograms, 10 required revascularization.

In the CT group, the median calcium score was 5 (0-146), and 50 (39%) patients had no detectable calcium. CT-angiography was performed in 79 (61%) patients with a positive calcium scan, and 5 patients with a zero calcium score but >80% pre-test probability. Out of 29 patients with >50% stenosis, 19 (66%) showed myocardial ischemia on perfusion imaging (figure 3). Concordant ischemia was demonstrated by CT-MPI in 7/12 (58%) vessels of patients with three-vessel disease (n=4), 3/4 (75%) with left main or proximal left anterior descending coronary disease, and 13/25 (52%) vessels of patients with other one- or two-vessel disease (n=21) by CT-angiography. Concordant ischemia was demonstrated by CT-MPI in 11/12 (92%) patients with >70% maximum stenosis and 8/17 (47%) patients with 50-70% maximum stenosis by CT angiography. Of 19 patients with myocardial ischemia, 14 underwent invasive angiography, and 13 were revascularized. Two patients with a normal CT-MPI later underwent PCI because of insufficient symptomatic relief, one in the setting of unstable angina.

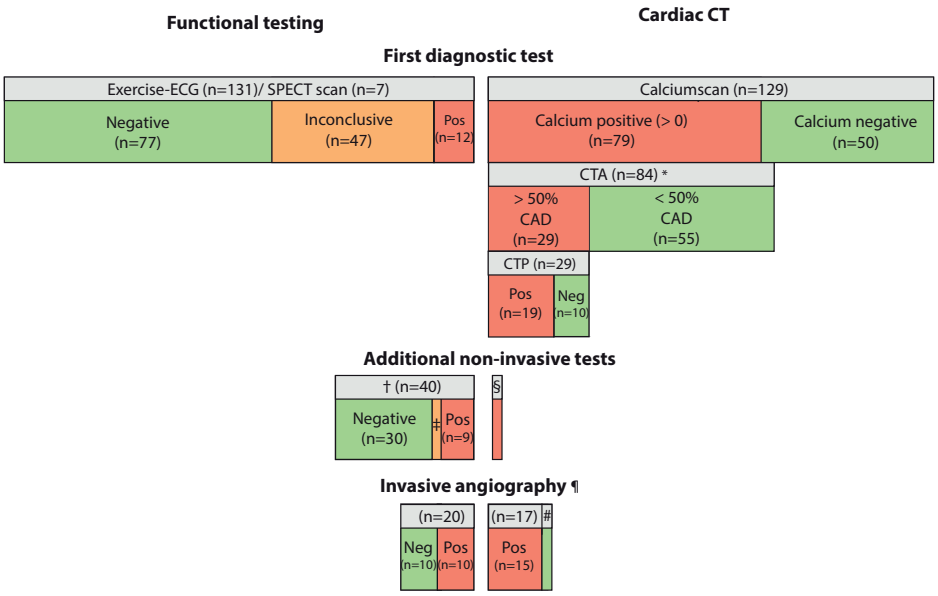

Figure 3. Flowchart of diagnostic testing. Flowchart showing the first and additional diagnostic tests and their outcome, per randomization arm.
* Including 5 patients without calcium but high pretest probability
(>80 by Diamond & Forrester).
† SPECT-MPI (n=24), CTA (n=11), stress echocardiography (n=4), exercise-ECG (n=1).
‡ Inconclusive SPECT-MPI scan (n=1).
§ Positive SPECT-MPI (n=1).
¶ Independent review of class I indication for revascularization, based on the 2010 ESC guidelines.
# Invasive angiography without class I indication for revascularization (n=2).

Table 2. Diagnostic yield of invasive angiography

	Cardiac CT (n=130)	Functional testing (n=138)	p-value
Invasive angiograms	17 (13.1%)	20 (14.5%)	0.860
Class I indication for revascularization[1]	15 (11.5%)	10 (7.2%)	0.294
Left main >50% with objective ischemia	1	1	
Proximal LAD >50% with ischemia	4	0	
2 or 3-vessel disease with impaired LV function and ischemia	1	2	
Proven large area of ischemia (≥10% of LV)	6	2	
Any stenosis >50% with limiting anginal symptoms unresponsive to OMT	3	5	
Without class I indication	2	10	0.035
Positive diagnostic yield of invasive angiography	15/17 (88.2%)	10/20 (50.0%)	0.017

1. Cardiac catheterizations with class I indication for revascularization(16). OMT: optimal medical treatment

Diagnostic effectiveness

Fewer invasive angiograms without class I indication for revascularization were observed in the CT group (2/130, 1.5%), compared to the functional-testing group (10/138, 7.2%, p=0.035)(table 2). At a comparable rate of invasive angiograms (p=0.860), the positive yield was higher after CT (15/17, 88%), compared to functional-testing (10/20, 50%; p=0.017). The independently assigned class I revascularization indications were concordant with the clinically performed revascularization procedures.

Diagnostic efficiency

In both groups the majority of patients reached the final clinical diagnosis the same day at the outpatient clinic, though most frequently in the cardiac CT group (87% vs. 64% of functional-testing group, p<0.001)(figure 4). Further testing was needed in 13% of patients randomized to CT, compared to 37% after functional-testing (p<0.001)(figure 5). Although index testing costs were higher for CT, the mean cumulative diagnostic expenses were comparable for CT €435 [range: €64- €2439] and functional-testing €450 [range: €106- €2015] (p=0.827).

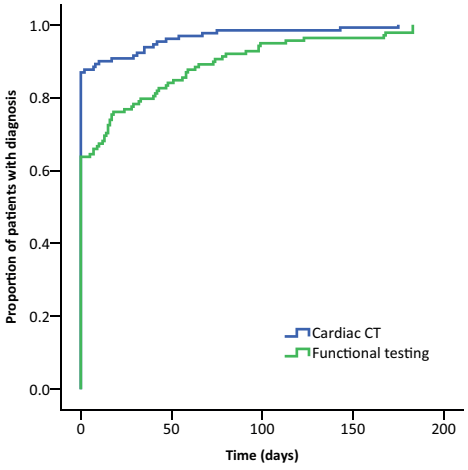

Figure 4. Time to diagnosis. Proportion of patients with a diagnosis plotted against time. P<0.001.

Anginal symptoms and quality of life

After six months 38% of patients in the CT group reported absent anginal symptoms, in comparison to 28% in the functional-testing group (p=0.118). In both groups comparable improvements in SAQ-subscales were observed (appendix 1). Quality-of-life improvement by EQ-5D-questionnaire did not differ (p=0.245)(appendix 2). The improvement in QoL-VAS scale for CT was from 66.8 to 73.7 (p<0.001) compared to 68.9 to 72.4 (p=0.042) for functional testing, this numerical difference failed to reach statistical significance (p=0.168)(appendix 3).

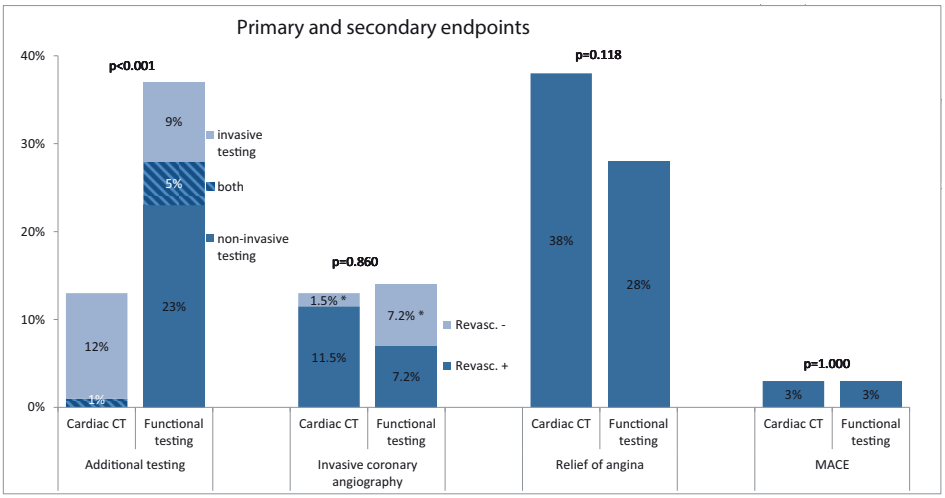

Figure 5. Primary and secondary outcomes. Additional tests after the first diagnostic test, divided into non-invasive, invasive or both. Invasive angiography: followed by revascularization (+), or no revascularization (-). Angiography without class I indication for revascularization rate was the primary endpoint and was significantly different (*) between CT and functional testing (1.5% vs 7.5%, p=0.035). Relief of angina at 6 months. MACE: death, myocardial infarction and stroke.

Safety

After an average follow up of 250±95 days (8±3 months) three non-cardiac deaths, four nonfatal infarctions, and one case of unstable angina requiring revascularization, were observed in 266 patients (CT 4 vs. functional 4 events, p=1.000). Event-free survival was similar (CT 96.9% vs. functional 97.1%, p=0.929) with an adverse event hazard ratio of 1.07 (95%CI 0.27-4.26) for CT compared to standard care (p=0.929).

No adverse events occurred in the 45 patients (35%) in whom CAD was ruled out based on a zero calcium score. One patient later presented with acute chest pain and ECG changes, though biomarkers were negative and invasive angiography revealed no abnormalities. Amongst the five patients without calcium, but >80% pre-test probability, CT-angiography revealed single-vessel CAD with ischemia on CT-MPI in one case.

In the functional-test group only 51 patients (37%) were exposed to radiation, which resulted in a lower median cumulative dose (CT 3.1mSv [1.6;7.8] vs 0mSv [0;7.1], p<0.001). The mean dose of the cardiac CT exam was 5.6±6.3mSv. The mean dose was 1.3±0.7mSv for the calcium scan, 3.5±3.0mSv for CT-angiography, and 10.6±6.3mSv for CT-MPI.

DISCUSSION

In this multicenter randomized clinical trial, a comprehensive cardiac CT examination that involved a stepwise performance of a calcium scan, CT-angiography and CT myocardial perfusion imaging, was compared to the current standard of functional-testing for suspected CAD. The main findings are that a tiered cardiac CT protocol improves the efficiency of invasive angiography without increasing overall catheterization rates. The combined CT protocol achieved a diagnosis faster, and removed the need for additional noninvasive testing.

Diagnostic management of stable angina

While there are many noninvasive techniques for diagnosing CAD, the low diagnostic yield of invasive angiography suggests lack of effectiveness by current diagnostic practices(21). Although stress imaging is more sensitive to the detection of angiographic CAD, without evident clinical outcome benefit(22), the ACC/AHA guidelines maintain exercise ECG as the first-choice test in suitable patients with a low-intermediate CAD probability(23). CT-angiography is a relatively new diagnostic option with a high sensitivity for the detection of CAD. In a very large cohort the PROMISE trial demonstrated equivalent clinical outcome for CT-angiography and stress testing(2). Meta-analyses, however, indicate that CT-angiography may increase catheterization and revascularization rates, of which clinical benefit remains yet unproven(24,25). Functional tests can differentiate patients more likely to benefit from revascularization, although the prospective evidence for this is stronger for fractional flow reserve than noninvasive functional tests. In SCOT-HEART, which demonstrated improved outcome from CT-angiography, cardiac CT was combined with an exercise ECG in the majority of patients(3,26). This supports the idea that both anatomical and functional information are required for therapeutic decisions that affect clinical outcome. Another observation from these trials is the low, but often overestimated CAD prevalence, as well as a low adverse event rate in real-world populations with stable chest pain(2-4), fueling a paradoxical debate on the value of extensive testing in low-risk populations(27).

Comprehensive cardiac CT protocol

The objective of the CRESCENT-II trial was to test a tiered comprehensive cardiac CT protocol that would allow safe rule-out of CAD by relatively simple means, while at the same time incorporating functional measures of CAD for well-informed decisions and avoidance of premature invasive procedures. Calcium imaging in symptomatic patients is controversial due to the possibility of non-calcified obstructions. Supported by CONFIRM and other registries in real-world populations(28-32), and the low CAD prevalence in recent trials (2-4), we concluded that triage by calcium imaging in lower-risk patients

would be a safe opportunity to reduce radiation exposure and save resources. Similar to CRESCENT the present study suggest an uneventful intermediate-term outcome when CAD is excluded based on a negative calcium scan(4). Restriction to patients with detectable calcium or a high CAD probability increased the positive yield of CT-angiography to more than a third.

While there are multiple more established stress imaging techniques, CT-MPI may have practical advantages, as it can be performed in conjunction with CT-angiography, and allows for a comprehensive assessment of anatomy and function. Contrary to CRESCENT(4), the addition of CT-MPI virtually removed the need for a separate functional test after CT (1% in CRESCENT-II vs 16% in CRESCENT).

Overall, cardiac CT increased the diagnostic yield of invasive angiography (88% vs 50%, p=0.017), but without affecting the overall catheterization rate. All except one patients referred for invasive angiography after a positive CT-angiogram and CT-MPI (19/29) required revascularization. CRESCENT-II was not large enough to assess differences in adverse events, or in a statistically significant manner reproduce the symptomatic relief after CT, as observed in the previous trial(4).

While anatomical imaging as the first step appears to be most efficient in our cohort with a low prevalence of CAD and no history of CAD, this may be different in population with a history or truly high prevalence of CAD.

Safety

The use of contemporary CT technology, and restricting CT-MPI to the highest-risk patients, resulted in a median overall effective dose of 3.1mSv (including diagnostic tests after cardiac CT), compared to a median cumulative dose of 10.0mSv in PROMISE, and a 4.1mSv median dose for CT-angiography alone in SCOT-HEART.

In patients with a low CAD probability, often younger and female, calcium imaging and new CT technology lowered doses in those most vulnerable to radiation exposure. However, radiation exposure was lowest in the functional-testing group, of whom most underwent exercise testing without nuclear imaging.

Future outlook

As scanner and data processing technology further develop, the comfort of use and radiation exposure of dynamic CT-MPI will likely improve. Apart from dynamic CT-MPI, and well-known established functional modalities, several other CT-based functional assessment techniques have emerged. Static myocardial perfusion imaging (7,12,33), potentially with dual-energy protocols, or hybrid systems that combine CT with PET or SPECT, also offer functional interpretation in conjunction with CT-angiography. CTA based FFR (CT-FFR) computes coronary flow parameters from conventional CT angiograms(34,35). While CT-FFR is not a direct physiological measurement, and relies on

sufficient CT quality, the lack of additional testing and radiation exposure are obvious advantages. The PLATFORM study demonstrated how CTA combined with CT-FFR can improve the diagnostic yield of invasive angiography(36). The few direct comparisons published to date suggest a comparable and partially complementary performance of CT-MPI and CT-FFR (37-39).

Limitations

Although this study allowed several relevant observations, the cohort size does not permit conclusive results in terms of clinical outcome. Similar to other pragmatic diagnostic trials, the CRESCENT-II trial did not apply a predefined management protocol. While blinding of caregivers and patients was not possible, participants were treated by multiple physicians without direct involvement in the study. We designed a specific CT algorithm, and compared performance with a control group that mostly underwent exercise ECG. While the use of exercise ECG is supported by guidelines and part of standard practice in many parts of the world, extrapolation of the results may not be possible to settings with substantially different diagnostic as well as therapeutic practices. More stress imaging would be expected to improve diagnostic accuracy, but could also increase cost(22). Although dynamic CT-MPI was validated in multiple studies, the technique requires specific CT equipment and is not yet widely practices. Implementation of the tiered algorithm requires scheduling flexibility and immediate reading, which can pose practical challenges.

CONCLUSION

In patients with stable angina and a typically low CAD prevalence the challenge is to accurately rule out CAD in the majority by relative simple means, while comprehensively assessing those who may benefit from revascularization. A tiered, comprehensive cardiac CT protocol, including dynamic perfusion imaging, appears to be a fast and efficient alternative to standard functional-testing in these patients.

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ROLE OF THE FUNDER/SPONSOR

The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

CONFLICT OF INTEREST

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Appendix 1. Seattle Angina Questionnaire results

	Cardiac CT		
	Baseline	**Follow-up**	**p-value**
Physical limitations	71.8 ± 23.2	81.4 ± 21.9	<0.001
Angina stability	49.2 ± 27.5	77.6 ± 23.9	<0.001
Anginal frequency	71.9 ± 13.9	90.5 ± 12.0	<0.001
Treatment satisfaction	81.9 ± 15.4	81.2 ± 16.2	0.720
Quality of life	55.8 ± 29.6	77.5 ± 28.2	<0.001
Total SAQ	324.8 ±403.7	403.7 ±78.1	<0.001

	Functional testing		
	Baseline	**Follow-up**	**p-value**
Physical limitations	67.9 ± 26.3	78.4 ± 23.0	<0.001
Angina stability	47.2 ± 24.3	71.2 ± 23.9	<0.001
Anginal frequency	71.7 ± 17.4	87.4 ± 13.6	<0.001
Treatment satisfaction	78.4 ± 18.9	75.9 ± 17.1	0.245
Quality of life	55.4 ± 26.9	73.3 ± 26.4	<0.001
Total SAQ	317.1 ± 78.0	378.0 ±83.3	<0.001

	Improvement from baseline to follow-up		
	Cardiac CT	**Functional testing**	**p-value**
Physical limitations	9.6 ± 23.2	10.5 ±24.3	0.782
Angina stability	28.4 ± 32.0	24.0 ±30.2	0.325
Anginal frequency	18.6 ± 15.4	15.7 ±18.8	0.225
Treatment satisfaction	-0.7 ± 19.6	-2.4 ±21.5	0.538
Quality of life	21.7 ± 31.9	17.9 ±28.7	0.373
Total SAQ	78.9 ± 81.5	60.9 ±87.0	0.121

SAQ results and subgroups at baseline and six months follow-up. The Seattle angina questionnaire consists of 17 questions. For every question points can be scored on an incremental scale from 0-100. Every question contributes to one of the five SAQ-subscales. Scores are shown as means ±SD. A higher score indicates better angina health state.

Appendix 2. EQ-5D results

	Cardiac CT		
	BL	**FU**	**p-value**
Total EQ-5D score	0.711±0.243	0.818± 0.134	<0.001
VAS scale	66.8±16.9	73.7±13.6	<0.001

	Functional testing		
	BL	**FU**	**p-value**
Total EQ-5D score	0.736±0.213	0.805±0.165	0.003
VAS scale	68.9±17.7	72.4±15.5	0.042

	Improvement		
	CT	**FT**	**p-value**
Total EQ-5D score	0.107±0.240	0.069±0.223	0.245
VAS scale	6.8±16.6	3.5±16.9	0.168

Total EQ-5D quality of life score at baseline (BL) and 6-months follow up (FU). The EQ-5D questionnaire consists of 5 questions, questioning problems with mobility, self-care, usual activities, pain and anxiety. Combined this creates the total EQ-5D score between 0 (worst QoL) and 1 (best QoL). The last question is the VAS scale, it is the respondent's self-rated health on a vertical, visual analog scale where the endpoints are labelled best and worst imaginable health state, ranging from 0-100. A higher score indicates a better health state. Scores are shown as means ± SD.

Appendix 3. Short Form 36 results

	Cardiac CT		
	BL	**FU**	**p-value**
Physical functioning	653 ± 238	756 ± 229	<0.001
Role limitations due to physical health	211 ± 178	275 ± 169	0.001
Role limitations due to emotional problems	214 ± 122	223 ± 115	0.499
Energy/fatigue	203 ± 78	237 ± 77	<0.001
Emotional well being	351 ± 90	369 ± 90	0.038
Social functioning	111 ± 23	105 ± 20	0.046
Pain	122 ± 41	151 ± 45	<0.001
General health	197 ± 60	211 ± 70	0.079

	Functional testing		
	BL	**FU**	**p-value**
Physical functioning	634 ± 242	708 ± 242	0.001
Role limitations due to physical health	221 ± 173	266 ± 168	0.002
Role limitations due to emotional problems	191 ± 128	215 ± 127	0.070
Energy/fatigue	210 ± 77	223 ± 75	0.090
Emotional well being	352 ± 84	356 ± 95	0.665
Social functioning	108 ± 24	110 ± 24	0.659
Pain	125 ± 42	149 ± 45	<0.001
General health	208 ± 67	221 ± 73	0.154

	Improvement		
	CT	**FT**	**p-value**
Physical functioning	103 ± 211	75 ± 222	0.365
Role limitations due to physical health	64 ± 180	45 ± 138	0.426
Role limitations due to emotional problems	9 ± 133	25 ± 133	0.412
Energy/fatigue	34 ± 81	12 ± 70	0.052
Emotional well being	18 ± 86	4 ± 81	0.227
Social functioning	- 6 ± 29	2 ± 35	0.108
Pain	29 ± 48	23 ± 51	0.449
General health	14 ± 77	13 ± 86	0.225

SF-36 quality of life scores at baseline (BL) and 6-months follow up (FU). SF-36 quality-of-life questionnaire subdivided into eight subscales. A higher score indicates a better health state. Scores are shown as means ± SD.

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