Calcium imaging and selective CT angiography in comparison to functional testing for suspected coronary artery disease: the multicenter, randomized CRESCENT trial

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ABSTRACT

Aims To compare the effectiveness and safety of a cardiac CT algorithm with functional-testing in patients with symptoms suggestive of coronary artery disease (CAD).

Methods and Results Between April 2011 and July 2013 350 patients with stable angina, referred to the outpatient clinic of four Dutch hospitals, were prospectively randomized between cardiac CT and functional-testing (2:1 ratio). The tiered cardiac CT protocol included a calcium scan followed by CT angiography if the Agatston calcium score was between 1 and 400. Patients with test specific contra-indications were not excluded from study participation. By one year, fewer patients randomized to cardiac CT reported anginal complaints (p=0.012). The cumulative radiation dose was slightly higher in the CT group (6.6±8.7mSv versus 6.1±9.3mSv; p<0.0001). After 1.2 years, event-free survival was 96.7% for patients randomized to CT and 89.8% for patients randomized to functional-testing (p=0.011). After CT the final diagnosis was established sooner (p<0.0001), and additional downstream testing was required less frequently (25% vs 53%, p<0.0001), resulting in lower cumulative diagnostic costs (€369 versus €440; p<0.0001).

Conclusion For patients with suspected stable CAD, a tiered cardiac CT protocol offers an effective and safe alternative to functional-testing. Incorporating the calcium scan into the diagnostic workup was safe and lowered diagnostic expenses and radiation exposure.

INTRODUCTION

Diagnostic testing of coronary artery disease (CAD) is annually performed in 20 million patients worldwide.(1) Despite concerns about accuracy (2), exercise ECG remains the first performed test in many parts of the world,(3-5) while stress imaging is reserved for patients with a higher probability of disease.(3) Cardiac CT has emerged as an alternative diagnostic test for CAD, characterized by an excellent negative predictive value for confident exclusion of CAD. Recently, two large randomized studies reported on the value of coronary CT angiography for evaluation of stable angina (6, 7). In the Computed Tomography versus Exercise Testing in Suspected Coronary Artery Disease (CRESCENT) randomized-controlled trial we assessed the effectiveness and safety of a tiered cardiac CT protocol, consisting of a calcium scan and selective performance of CT angiography, in comparison to functional-testing.

METHODS

Study Design

The CRESCENT trial is a pragmatic randomized-controlled trial comparing the clinical effectiveness of a tiered cardiac CT approach and a standard diagnostic workup using functional-testing. At four hospitals in the Rotterdam region of the Netherlands, 350 patients with stable chest pain, who had been referred for evaluation of suspected CAD, were prospectively enrolled. The study was approved by the medical ethics committees of the central coordinating centre and participating sites. The CRESCENT trial is registered at the US National Institutes of Health (ClinicalTrials.gov), number NCT01393028.

Study participants

Patients aged 18 years or older with stable chest pain or angina equivalent symptoms potentially caused by obstructive CAD were study eligible. Exclusion criteria were known CAD or invasive angiography or stress test performed within the last year. Renal impairment, contrast allergy, atrial fibrillation, or other test specific contra-indications did not preclude study participation.

Study procedures

Participants who consented in writing were randomly assigned to CT or functional-testing in a 2:1 ratio because of the established performance of the standard protocol. After the standard outpatient clinic visit, 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 subsequent testing was performed at the recruiting center.

Patients were contacted after one year for ascertainment of trial endpoints and health status measurements (questionnaires). Performance and results of downstream diagnostic and therapeutic procedures were collected. All procedures were confirmed through review of medical records.

Cardiac CT strategy

For the CT algorithm, detailed in figure 2, all patients first underwent a calcium scan. Absence of calcium excluded CAD and required no further testing, except for patients with a high pre-test probability of CAD (>70% by Diamond and Forrester criteria (8)). Patients with a calcium score between 1 and 400 (and patients without calcium but a >70% pre-test probability), underwent contrast-enhanced coronary CT angiography to detect obstructive CAD. Those with CT contra-indications, a calcium score >400, or non-conclusive CT angiogram (non-interpretable or intermediate obstructive disease), underwent stress testing or invasive angiography at the discretion of the treating physician. CT angiography results were classified as normal or CAD<50%, low-risk CAD>50%, or high-risk CAD. High-risk CAD was defined as left main stenosis, three-vessel disease or proximal LAD stenosis (>50%). All recruiting sites had previous cardiac CT experience, and were equipped with 64-slice or more advanced CT technology, with radiation minimizing measures depending on local practices and patients characteristics.

Functional-test strategy

Most patients randomized to standard care underwent a symptom-limited exercise ECG. The target heart rate was defined as 85% of the maximum predicted heart rate based on age. Based on exercise tolerance, ST-segment changes and symptoms the Duke Treadmill Score (DTS) was calculated to assist further management. Myocardial perfusion imaging or stress echocardiography were performed in case of contraindications to exercise ECG, or non-interpretable or equivocal results. All functional- imaging tests were interpreted for the presence of inducible ischemia, and assessed risk of adverse outcome applying established criteria for each respective test.(9, 10)

Both CT and functional tests were performed and interpreted by local physicians, who also made the subsequent clinical management decisions. 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.

Outcomes

The primary outcome was the clinical effectiveness, defined as the absence of chest pain complaints after one year. Additionally, SAQ, SF-36 and EQ-5D questionnaire responses were compared between baseline and one year follow-up. Pre-specified secondary outcomes included the diagnostic yield, defined as the proportion of patients undergoing

revascularization after invasive angiography. Efficiency outcomes included the time to diagnosis, defined as the period from presentation 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 testing (exercise-ECG, cardiac CT, stress echocardiography and perfusion imaging) and invasive angiography to detect CAD after the initial test. The diagnostic costs included all tests performed until one year. Average costs per test were based on a previously published cost analyses.(11) Based on the frequency of tests performed in each group, a formula for calculation of the overall downstream procedural costs was constructed, which allows recalculation using alternative procedural charges.

Survival analysis was based on a composite endpoint of all-cause mortality, non-fatal myocardial infarction, major stroke, unstable angina pectoris with objective ischemia and/or requiring revascularization, unplanned cardiac evaluations and late coronary revascularization procedures. Nonfatal myocardial infarction was defined as biomarker elevations in a concordant clinical context. Late revascularizations were defined as performed beyond 90 days. Unplanned cardiac evaluations were defined as non-elective hospital visits and admissions for acute complaints suspected to be of a cardiovascular nature. Events were counted once for each patient in the hierarchical order listed above. Each suspected clinical endpoint and a random 10%-sample of the remaining patients were reviewed by two external, independent reviewers, blinded to randomization, with discordance resolved by a third reviewer.

The cumulative effective radiation dose (mSv) included all tests and interventions involving roentgen. For cardiac CT a conversion factor of 0.017 was used. For SPECT and catheterization conversion factors of 0.0085mSv/millibecquerel and 0.24mSv/Gy*cm^2 were used.(12, 13)

Statistical analyses

Insufficient funding prevented us from testing the original endpoint, which was the proportion of patients undergoing catheter angiography followed by revascularization and required 1128 patients to demonstrate an 8%-points difference (alpha 0.05; power 0.80). For the alternative endpoint, 294 patients were required to demonstrate an 8%-points difference in reported chest pain (alpha significance level 0.05; power 0.80). The secondary power analysis was performed shortly after patient recruitment had started.

Continuous data are presented as means±SD or medians with interquartile ranges. Groups were compared using an independent-sample t-test or Mann-Whitney U-test for continuous variables, and chi-square or Fisher's exact-test for categorical variables. Differences in the SAQ-questionnaire mean scores between baseline and follow-up were analysed with a paired-t-test. The probability of event-free survival was estimated by Kaplan-Meier survival analysis with comparisons performed with the 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 April 2011 and July 2013, 463 eligible patients were approached, of whom 93 (20%) declined participation and 20 (4%) were unable to provide written consent. Of the 350 enrolled patients, 242 were randomly assigned to CT and 108 to standard care based on functional-testing. All patients were included in the intention-to-treat analysis (figure 1). Overall, 293 of 350 participants (84%) had complete one-year follow-up. The original records for hospital visits and events were available in 347 of 350 (99%) patients. The mean age was 55±8 years, 55% were women, and most had an intermediate probability of CAD. While there were no significant differences in baseline characteristics, the estimated cardiovascular risk (SCORE) appeared slightly higher in the functional-testing group (table 1) (14). In 28 patients (8%) a final diagnosis of obstructive CAD was made by invasive angiography.

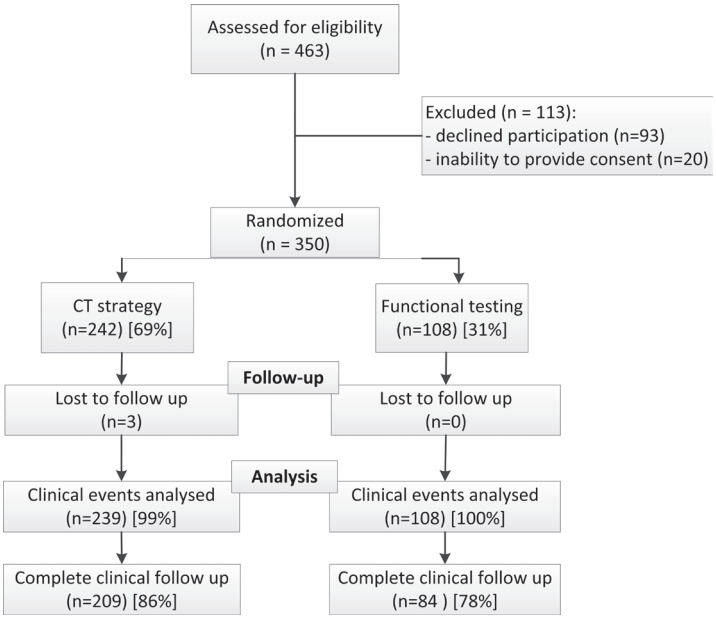


Figure 1. Patient flow diagram with disposition by randomized arm. Complete clinical follow-up defined as both clinical event information and questionnaires available at one year.

Table 1. Patient characteristics

	Cardiac CT (n=242)	Functional testing (n=108)
Mean age (years)	55±10	55±10
Female sex (%)	55	56
Systolic/diastolic blood pressure (mmHg)	138/84	138/84
Median body-mass index	28±5	28±5
History (%)		
Coronary disease	0	0
Stroke	3.3	7.4
Peripheral artery disease	3.7	6.5
Atrial fibrillation	0.4	1.9
Renal impairment*	3.7	4.6
Renal failure*	1.7	1.9
Cardiac risk factors (%)		
Current/past smoker	34	36
Hypertension	52	52
Dyslipidaemia	54	61
Diabetes mellitus	17	16
Family history of ischemic heart disease	38	37
Presenting chest pain symptoms (%)		
Typical angina	24	23
Atypical angina	53	51
Non-anginal complaints	23	24
Pre-test probability (%)**	45±29	45±29
Median cardiovascular risk (SCORE*)**	4.0(2.0;13.8)	6.0(2.0;12.0)
Baseline medications (%)		
ACE inhibitor or AT II blocker	23	25
Beta-blocker	23	30
Calcium channel blocker	11	17
Aspirin or other antiplatelet agent	29	29
Statin or other lipid lowering medication	47	49
Vitamin K antagonists	3	7
Nitrates, oral or sublingual	7	12
Diuretics	11	9

Patient characteristics presented as mean±SD, percentage or median and interquartile range. There are no significant differences between both groups. Dyslipidaemia: total cholesterol >5mmol/L, low-density lipoprotein >3mmol/L, or on lipid-lowering medication. *Renal impairment: GFR<90 ml/min/1.73m^2; renal failure: GFR <30 ml/min/1.73m^2 **Diamond and Forrester criteria(8, 14). ***Estimated annual risk of cardiovascular death by Systematic Coronary Risk Evaluation.(14)

Test results

In the functional testing group exercise ECG could not be performed in five patients (5%) because of left bundle branch block (n=2) or the inability to exercise (n=3). The exercise ECG was considered abnormal in 11%. In 50% of patients, including those with contra-indications to exercise ECG, further testing was required by myocardial perfusion imaging (29%), stress echocardiography (7%), cardiac CT (6%) and invasive angiography (11%).

In the CT group, the median calcium score was 4.0(0-61), and 100 patients had no detectable calcium. In 26 (11%) the calcium score was high (>400), for most of whom clinicians ordered further testing: nuclear imaging (n=8), stress echocardiography (n=3), exercise ECG (n=6), and invasive angiography (n=13). While CT angiography was indicated for 117 patients, one scan was inappropriately performed in a patient with a high calcium score, while the scan was not performed in 9 patients (8%) with renal failure (n=4), severe contrast allergy (n=4), or anxiety (n=1). Significant stenosis was absent in 75% of patients, 17% had >50% low-risk CAD, 6% had high-risk CAD, and 3% of the scans were non-diagnostic (figure 2).

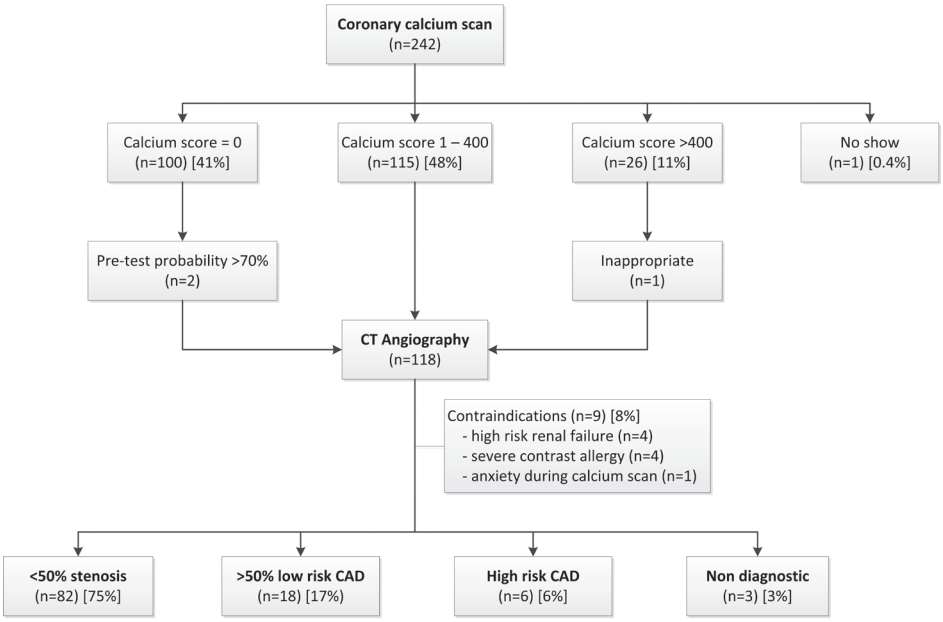


Figure 2. Cardiac CT algorithm and results. Coronary calcium by Agatston method. Pre-test probability of coronary disease (CAD) by Diamond and Forrester criteria(8). High-risk CAD defined as left main stenosis, three-vessel disease or proximal LAD stenosis (all >50%).

Clinical effectiveness

After one year fewer patients randomized to CT reported anginal symptoms in comparison to the functional-testing group (39% vs 25%, p=0.012), although the proportion of patients with similar or worsened symptoms was comparable (26% vs 29%, p=0.595) (figure 3). For the SAQ-subscales, the CT group had a lower angina frequency at one year follow-up (p=0.012). Other SAQ-subscales showed a statistically non-significant trend toward more improvement over one year for the CT group (table 2). Quality-of-life improvement, measured with the five dimensions of the EQ-5D-questionnaire did not differ between the groups (p=0.759)(appendix 1). The mean VAS scale increased in the CT group from 67.6 into 72.5, and in the functional-testing group from mean 66.8 to 69.4 (p=0.237). All SF-36-subscales were similar between both groups (appendix 2).

The diagnostic yield of invasive angiography, i.e. catheterizations followed by a revascularization procedure, was 72% after CT, compared to 58% in the functional-testing group (p=0.469)(table 3). The prevalence of >50% coronary disease was similar between groups (8.8% CT, 6.5% functional-testing; p=0.384), as well as the proportion of high-risk CAD (4% and 3%, respectively (p=0.703), and the proportion undergoing revascularization (table 3).

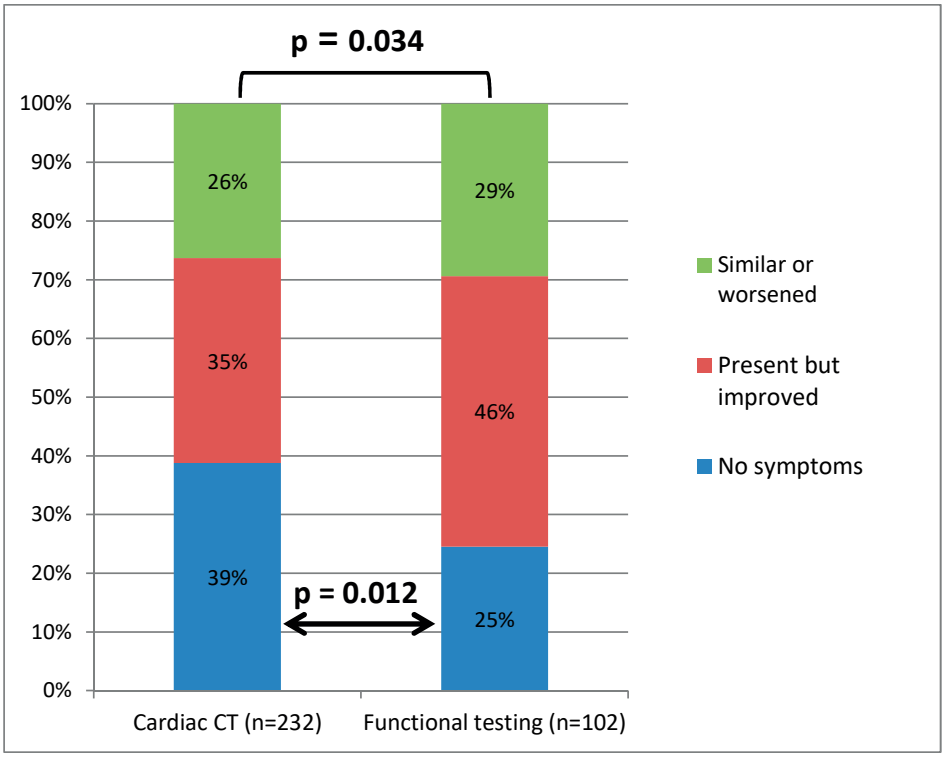


Figure 3. Angina status one year after randomization.

Table 2. SAQ results and subgroups at baseline (BL) and one-year follow-up (FU). The Seattle angina questionnaire consists of 17 questions. For every question points can be scored on an incremental scale. Every question contributes to one of the five SAQ-subscales. Scores are shown as means. A higher score indicates better angina health state.

	Cardiac CT			Functional-testing			Improvement		
	BL	FU	p-value	BL	FU	p-value	CT	FT	p-value
Physical limitations	37.3	39.7	<0.0001	37.0	38.8	0.09	2.30	1.80	0.630
Angina stability	3.1	4.1	<0.0001	3.0	3.9	<0.0001	0.93	0.95	0.948
Anginal frequency	9.2	10.9	<0.0001	9.6	10.6	<0.0001	1.68	1.05	0.012
Treatment satisfaction	17.2	17.8	0.070	17.0	17.2	0.731	0.63	0.23	0.598
Disease perception	3.3	4.1	<0.0001	3.3	4.0	0.001	0.86	0.62	0.209
Total SAQ	64.7	75.0	<0.0001	63.6	73.1	<0.0001	10.28	9.47	0.668

Table 3. Diagnostic yield defined as proportion of invasive angiograms followed by revascularization

	Cardiac CT (n=239)	Functional-testing (n=108)	p-value
Invasive angiography	29 (12.1%)	12 (11.1%)	0.843
No CAD>50%	8 (3.3%)	5 (4.6%)	0.384
Low-risk CAD>50%	12 (5.0%)	4 (3.7%)	0.635
High-risk CAD>50%	9 (3.8%)	3 (2.8%)	0.703
Revascularization	21 (8.8%)	7 (6.5%)	0.384
Percutaneous coronary intervention	15 (6.2%)	7 (6.5%)	0.703
Coronary bypass graft surgery	6 (2.5%)	0 (0%)	0.092
Diagnostic yield	21/29 (72%)	7/12 (58%)	0.469
Days to revascularization	31 (18-67)	46 (30-198)	0.243
Late revascularization(>90 days)	3 (1.2%)	3 (2.8%)	0.144

Table 4. Adverse events

	Cardiac CT (n=239)	Functional testing (n=108)	p-value
All-cause death	2 (1%)	2 (2%)	0.413
Non-fatal myocardial infarction	1 (0%)	1 (1%)	0.564
Unstable angina	1 (0%)	1 (1%)	0.564
Non-fatal stroke	0 (0%)	1 (1%)	0.137
Late revascularizations	2 (1%)	2 (2%)	0.413
Unplanned cardiac evaluations	2 (1%)	4 (4%)	0.058
Acute chest pain at emergency department	1 (0%)	3 (3%)	0.057
Palpitations at emergency department	1 (0%)	1 (1%)	0.564
Total adverse events	8 (3%)	11 (10%)	0.004

Diagnostic efficiency

For most patients the final clinical diagnosis was achieved on the same day in both groups, but more often in the cardiac CT group: median duration until final diagnosis 0(0;0) days by CT and 0(0;44) by functional-testing (p<0.0001). Overall, 25% of patients randomized to CT underwent another test after the baseline test, compared to 53% in the functional-testing group (p<0.0001)(figure 4). Invasive angiography was similarly frequent after CT (12%) and functional-testing (11%, p=0.775). Although index testing costs were higher, cumulative diagnostic expenses were 16% lower for CT €369 versus €440, p<0.0001) (appendix 3).

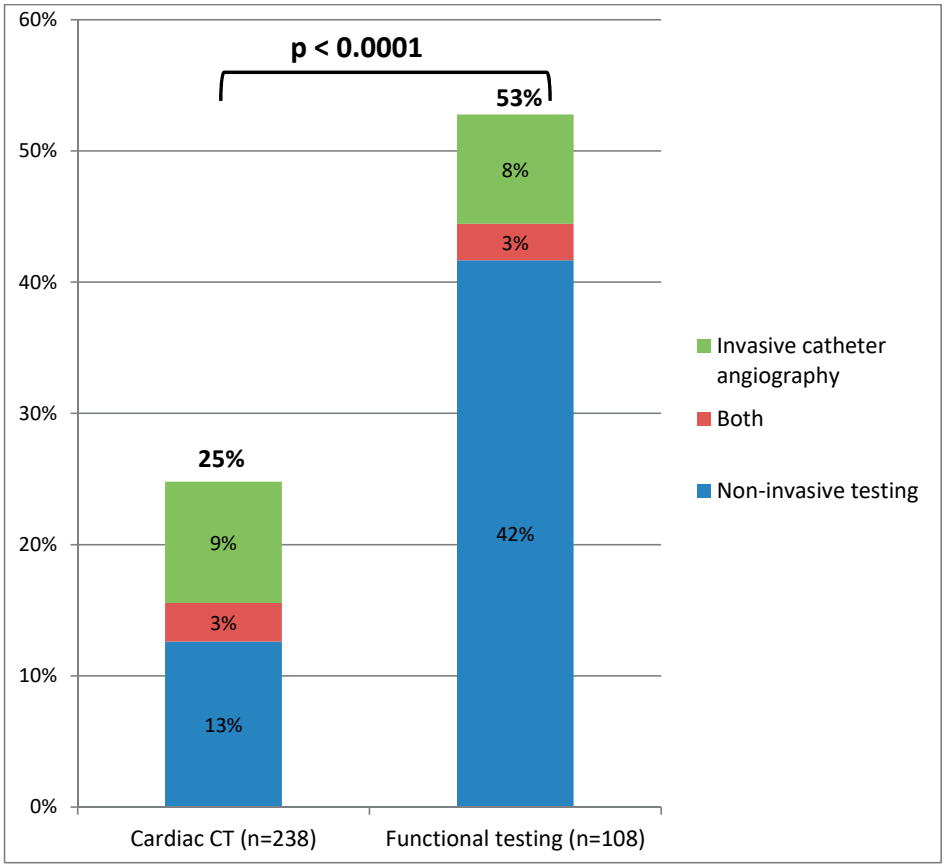
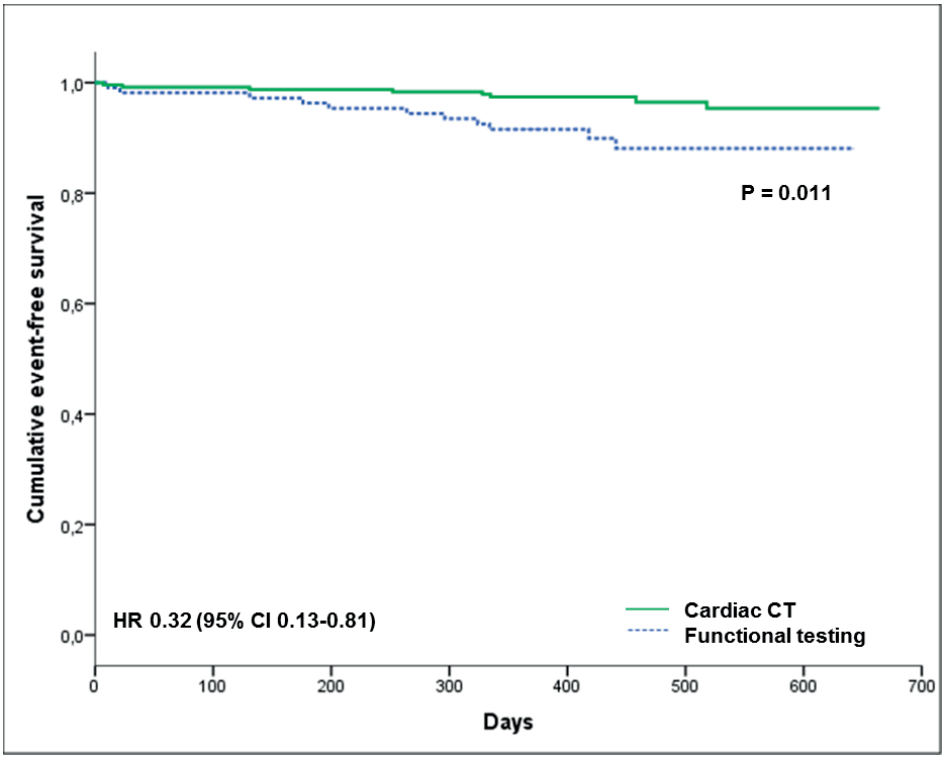


Figure 4. Downstream testing. Proportion of patients requiring further non-invasive and/or invasive testing.

Safety

Observed clinical events (19) included four deaths, two nonfatal infarctions, two cases of unstable angina requiring revascularization, one nonfatal major stroke, four late re-vascularizations and six other unplanned cardiac evaluations, reported in 347 patients



Number at risk

Days	0	100	200	300	400	500	600	664
Functional	108	104	101	98	58	42	33	0
Cardiac CT	239	236	234	228	137	89	69	0

Figure 5. Kaplan-Meier curves of event-free survival. Events counted once per patient in the hierarchical order of all-cause mortality, non-fatal myocardial infarction, major stroke, unstable angina with objective ischemia and/or requiring revascularization, unplanned cardiac evaluations and late revascularizations.

(table 4). The unplanned evaluations in the emergency department included two cases of palpitations and four cases of acute chest pain, four (3.7%) in the standard care group and two after CT (0.8%, p=0.058). At an average follow-up of 446 days (1.2 years), event-free survival was 96.7% for patients randomized to CT and 89.8% for patients randomized to standard care (p=0.011)(figure 5). The hazard ratio for adverse events was 0.32 (95%CI 0.13-0.81) for the CT group compared with the standard care group (p=0.015).

Cumulative radiation dose

All but one patients in the CT group (99.6%), but only 46 of 108 (43%) patients assigned to standard evaluation received radiation exposure from an imaging test. Hence, the cumulative radiation dose was higher in the CT group (6.6 ± 8.7mSv) compared to the

standard care group (6.1 ± 9.3mSv, p<0.0001). The mean radiation dose from only the calcium score scan was 1.3 ± 1.1mSv, for a complete cardiac CT examination 4.1 ± 4.4mSv, for myocardial perfusion scintigraphy 14.0 ± 2.3mSv and for invasive angiography 14.0 ± 14.3mSv.

Calcium scan based rule out of coronary disease

In 98 patients (39%) CAD was ruled out based on a zero calcium score. During follow-up none of these patients underwent further testing, and no adverse events occurred. Anginal symptoms were reported less frequently after a zero calcium scan, compared to when CAD was ruled out based on CT angiography or functional-testing (p=0.042). Only 2 patients (2%) without calcium had a >70% pre-test probability of CAD. CT angiography revealed single-vessel disease in one of these, eventually treated by stenting when symptoms persisted despite medical treatment.

DISCUSSION

This prospective, multicentre, randomized trial was designed to assess whether a tiered cardiac CT protocol based on calcium imaging and selective performance of CT angiography would be effective and safe for the management of suspected CAD, in comparison to functional-testing. To improve the overall applicability patients with test-specific contra-indications were not excluded from study participation, and data were evaluated by an intention-to-diagnose approach. After cardiac CT more patients reported complete relief of anginal symptoms after one year. Fewer adverse events occurred in the CT group. The cumulative radiation exposure was nearly 10% higher. Cardiac CT was more often able to confidently rule out CAD. Therefore the final diagnosis was reached faster, requiring fewer additional tests, and subsequently lower diagnostic expenses.

Diagnostic management of suspected coronary artery disease

Because prospective outcome data are sparse, diagnostic testing recommendations for stable CAD are predominantly based on technical performance studies, registry data and expert opinion, with discordant recommendations between guidelines.(3-5) In many centres the routine non-invasive diagnostic approach consists of stress testing, with the applied test modality depending on pre-test probability, patient characteristics, local availability and expertise. The exercise-ECG is the most widely available and least expensive functional test, but has a modest diagnostic performance. Although functional imaging more accurately detects angiographic CAD, its superiority over the exercise ECG has not been convincingly demonstrated in prospective clinical trials.(15)

Performance and safety

While the negative predictive value and ability to exclude CAD are high, coronary CT angiography has a tendency to overestimate both the angiographic and hemodynamic severity of CAD, which may necessitate further functional-testing for management decisions. Because the prevalence of obstructive CAD is low in real-world populations with stable chest pain symptoms, cardiac CT could be an efficient and cost-effective first-line test (6, 8, 15, 16). In our study cardiac CT allowed immediate exclusion of CAD in 75% of patients, compared to 47% in the functional-testing group. While CT angiography does not assess the hemodynamic severity, excluding high-risk angiographic CAD often allows for reassured medical treatment without further testing required at that moment. While there was a notable numerical difference in the proportion of catheterizations followed by revascularization in favour of patients randomized to CT (72 vs 58%), this result did not reach statistical significance, and it is not possible to conclude whether this higher diagnostic yield affected clinical outcome. The proportion of patients with complete relief of angina was higher after CT. While this can be explained by a higher diagnostic performance of CT followed by more appropriate management of cardiac as well as non-cardiac conditions, perceived symptoms and further need for diagnostic tests may also be affected by differences in experienced reassurance of patients and physicians by the test results.

Importantly, cardiac CT appears a safe strategy. The total adverse event rate was in fact lower in the CT group, although these results should be considered of an explorative nature given the population size and inclusion of softer endpoints. No statistically significant difference in the occurrence of death or myocardial infarction could be demonstrated between the two groups. The use of X-rays represents a drawback of CT, although by applying the calcium scan, contemporary CT equipment and dose reducing techniques, the cumulative exposure exceeded doses in the functional-testing group by no more than 10%.

Diagnostic efficiency

In this population with a relatively low CAD prevalence, the cardiac CT strategy achieved a conclusive diagnostic result much faster than functional-testing. In the functional-imaging group, further testing was required twice more frequent. Contrary to our expectations, cardiac CT did not increase the rate of referral to invasive angiography. Despite higher initial costs, after one year the CT approach was less expensive, decreasing overall diagnostic costs by 16% as calculated within our cost accounting system. Appendix 3 contains a formula for calculation of the overall downstream procedural costs based on frequency of performed tests, which allows recalculation using alternative procedural charges.

Calcium imaging to rule out CAD

Calcium imaging is still mostly used for risk stratification in asymptomatic individuals. While data from high-risk symptomatic populations suggest a non-negligible rate of obstructive CAD in the absence of detectable calcium, (17) registry data from more representative lower-risk cohorts have repeatedly demonstrated that severe CAD is rare and no more than 1% of patients with a negative calcium scan ultimately undergo PCI or bypass graft surgery.(18, 19) Given the excellent negative predictive value of the calcium scan, perhaps better than any other test, we decided its incorporation was justified in the CT algorithm, thereby avoiding contrast medium in 39% of patients, as well as an overall reduction in radiation exposure and costs in the CT group. Although groups are small, our results show no indication that implementation of the calcium scan in patients with a low-intermediate probability is unsafe.

CRESCENT in light of recently published trials

Recently two randomized controlled trials were published that examined whether CCTA would be more clinically effective than standard care. The pragmatic PROMISE trial randomized an impressive 10,003 patients between CT angiography and functional testing (67% nuclear imaging) for evaluation of suspected CAD, and reported no difference in adverse cardiac events after two years.(6) Although more patients underwent invasive angiography within the first 90 days, CT was associated with fewer invasive angiograms without obstructive CAD. Differences between our study and PROMISE include the use of calcium imaging in the CT strategy, and less frequent use of functional imaging in the control group (27% in CRESCENT vs approximately 90% in PROMISE).

In the SCOT-HEART trial, the addition of CCTA to standard care was investigated in 4146 patients with stable angina.(7) The investigators demonstrated improved certainty, but no effect on frequency of the diagnosis of angina due to coronary heart disease if CCTA was included in the diagnostic evaluation. After 1.7 years there was a close to statistically significant 38% reduction in the composite endpoint of death related to coronary heart disease and myocardial infarction (p=0.0527). The design of SCOT-HEART differs from our study, or PROMISE, for the fact that CT did not replace functional testing, but was added to a standard care protocol with XECG for most.

The low prevalence of CAD and the generally benign clinical outcome of patients with stable chest complaints in these studies, has raised questions concerning the need for advanced and expensive imaging tests. In this respect our randomized trial, albeit much smaller in population size, adds to the evidence from PROMISE and SCOT-HEART by demonstrating that a tiered approach including calcium imaging can mitigate the potential risks and costs of cardiac CT, while achieving at least comparable performance in comparison to a functional test approach without predominance of stress imaging.

Contrary to previous trials we did not exclude patients based on contraindications to specific test, thereby widening the applicability of our results.

In all these trials with a relatively low CAD prevalence, the individual probability of disease was overestimated by conventional prediction rules.(6, 7) Depending on the criteria the disease prevalence in CRESCENT was 8%, while the predicted probability by the Diamond and Forrester method was 45%. Similarly, in PROMISE the average probability was 53%, while the observed disease prevalence was 8.8%. In 2013, which was after the study had started, the new ESC guidelines recommended a different prediction rule(3, 20). Retrospective implementation of these Genders criteria lowered the pre-test probability of CAD from 45% to 37%, but still substantially overestimating the true observed disease burden.

In line with contemporary guidelines(3), in the CRESCENT trial patients with angiographically significant, but otherwise low-risk CAD on CT angiography were often treated medically before considering further testing or revascularization. This relatively conservative approach may have affected the downstream use of stress imaging, invasive angiography and revascularization procedures in comparison to previous trials.

Limitations

Although it was not possible to blind caregivers and patients to the test results, participants were treated by multiple physicians without direct involvement in the study. Although our trial demonstrated benefit of cardiac CT on several aspects, the modest population prevented us from drawing firm conclusions on some of the other endpoints. The follow up rate of clinical questionnaires (SAQ, EQ-5D, SF-36) was slightly higher for the CT group (86% vs 78%, p=0.06), which may have influenced results. We compared cardiac CT to a functional strategy starting with exercise ECG in the majority of patients. Performance of the functional approach might have been different if stress imaging techniques had been applied more frequently. In addition, outcome of the diagnostic strategy is indirectly measured, based on the assumed benefit of therapeutic choices based on those test results. Although the study was performed at several sites, appropriateness of extrapolation of our results to other centres will depend on comparability of the clinical setting in terms of current diagnostic care, available technology, cost-accounting systems and therapeutic management attitudes. Further research is necessary to establish the value of cardiac CT in terms of hard endpoints and in comparison to other diagnostic strategies.

CONCLUSION

In the workup of suspected, stable coronary artery disease, cardiac CT represents a safe and effective diagnostic strategy in comparison to functional testing, with potential benefits in terms of cost-efficiency.

APPENDICES

Appendix 1. EQ-5D results. VAS scale is the respondent's self-rated health on a vertical, visual analog scale where the endpoints are labelled best and worst imaginable health state. A higher score indicates a better health state. Mean (± SD). P value of the improvement in the reported quality of life scale at one year follow-up between the CT and functional-testing group.

	Baseline		One year follow-up		p-value
	Cardiac CT (n=219)	Functional testing (n=93)	Cardiac CT (n=208)	Functional testing (n=85)	
Mobility					0.325
No problems walking about	116 (53%)	53 (57%)	132 (63%)	47 (55%)	
Slight problems walking about	40 (18%)	18 (19%)	39 (19%)	25 (29%)	
Some problems walking about	43 (20%)	16 (17%)	21 (10%)	9 (11%)	
A lot of problems walking about	20 (9%)	6 (6%)	12 (6%)	4 (5%)	
Confined to bed	0 (0%)	0 (0%)	4 (2%)	0 (0%)	
Self-care					0.911
No problems with self-care	189 (86%)	79 (85%)	190 (91%)	74 (87%)	
Slight problems washing or dressing	20 (9%)	7 (8%)	7 (3%)	8 (9%)	
Some problems washing or dressing	7 (3%)	5 (5%)	8 (4%)	2 (2%)	
A lot of problems washing or dressing	2 (1%)	2 (2%)	3 (1%)	1 (1%)	
Unable to wash or dress	1 (0%)	0 (0%)	0 (0%)	0 (0%)	
Usual activities					0.670
No problems with usual activities	96 (44%)	43 (46%)	118 (57%)	40 (47%)	
Slight problems with usual activities	70 (32%)	21 (23%)	54 (26%)	26 (31%)	
Some problems with usual activities	42 (19%)	18 (19%)	24 (12%)	16 (19%)	
A lot of problems with usual activities	9 (4%)	11 (12%)	8 (4%)	2 (2%)	
Unable to perform usual activities	1 (0%)	0 (0%)	3 (1%)	1 (1%)	
Pain/discomfort					0.736
No pain or discomfort	43 (20%)	21 (23%)	74 (36%)	29 (34%)	
Slight pain or discomfort	97 (44%)	37 (40%)	87 (42%)	30 (35%)	
Moderate pain or discomfort	62 (28%)	27 (29%)	36 (17%)	20 (24%)	
A lot of pain or discomfort	14 (6%)	6 (6%)	8 (4%)	6 (7%)	
Extreme pain or discomfort	1 (0%)	2 (2%)	3 (1%)	0 (0%)	
Anxiety/depression					0.623
Not anxious or depressed	110 (50%)	41 (44%)	118 (57%)	45 (53%)	
Slightly anxious or depressed	76 (35%)	32 (34%)	63 (30%)	26 (31%)	
Moderately anxious or depressed	26 (12%)	15 (16%)	14 (7%)	10 (12%)	
Very anxious or depressed	6 (3%)	4 (4%)	9 (4%)	3 (4%)	
Extremely anxious or depressed	0 (0%)	1 (1%)	4 (2%)	1 (1%)	
Total EQoL					0.759
VAS scale	67.6 (±16.9)	66.8 (±19.5)	72.5 (±17.6)	69.4 (±19.1)	0.237

Appendix 2. Short Form 36 results. SF-36 quality-of-life questionnaire subdivided into eight subscales. A higher score indicates a better health state. Mean (±SD). P-values for change in SF-36 subscale scores from baseline to follow-up between the CT and functional-testing group.

	Baseline		One year follow-up		
	Cardiac CT (n=219)	Functional testing (n=93)	Cardiac CT (n=208)	Functional testing (n=85)	p-value
Physical functioning	668 (±256)	640 (± 258)	717(±278)	775 (±223)	0.699
Role limitations due to physical health	194 (±168)	210 (± 177)	278(±163)	256 (±160)	0.136
Role limitations due to emotional problems	195 (±125)	196 (±121)	216(±119)	209 (±117)	0.941
Energy/fatigue	201 (±81)	190 (±91)	220 (±90)	219 (±80)	0.991
Emotional well being	337 (±92)	334 (±94)	347(±100)	359 (±82)	0.941
Social functioning	140 (±49)	140 (±53)	154 (±51)	162 (±43)	0.962
Pain	122 (±42)	123 (±45)	147 (±52)	152 (±47)	0.391
General health	218 (±86)	208 (±90)	223 (±95)	218 (±96)	0.209

Appendix 3. Downstream diagnostic costs

Total costs	Cardiac CT	Functional testing	p value
Mean (SD)	369 (± 501)	440 (± 474)	p<0.0001
Median (25th, 75 percentile)	270 (64, 270)	159 (106, 651)	
Cost estimates (euros)[1]			
Exercise tolerance test	106		
Coronary calcium score	64		
CT coronary angiography	206		
Stress echocardiography	105		
Single photon emission CT	545		
Catheter-based coronary angiography	1,394		

Appendix 3. Shows the cost estimates for diagnostic testing, based on Genders et al. (11) and the downstream procedural costs for standard care compared with CT. Results are shown in euros.
Formula for the calculation of the total diagnostic costs of a workup of patients with suspected CAD with functional-testing and the comprehensive cardiac CT workup:

- **Costs in functional-testing group** = (0.94 * € exercise ECG) + (0.29 * € SPECT) + (0.06 * € CCTA) + (0.07 * € Stress echo) + (0.11 * € Cath)
- **Costs in CT group** = (1 * € CAC-score) + (0.46 * € CCTA) + (0.07 * € SPECT) + (0.05 * € exercise ECG) + (0.01 * € Stress echo) + (0.12 * € Cath)

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