Sex differences in the performance of cardiac CT compared with functional testing in evaluating stable chest pain: sub-analysis of the multicenter, randomized CRESCENT trial

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ABSTRACT

Background - Cardiac CT represents an alternative diagnostic strategy for women with suspected CAD, with potential benefits in terms of effectiveness and cost-efficiency.

Methods and Results - the CRESCENT trial prospectively randomized 350 patients with stable angina (55% women; 55±10 years), mostly with an intermediate CAD probability, between cardiac CT and functional testing. The tiered cardiac CT protocol included a calcium-scan followed by CT-angiography if the Agatston calcium score was between 1-400. Patients with test specific contraindications were not excluded from study participation. Gender differences were studied as a pre-specified sub-analysis. Enrolled women presented more frequently with atypical chest pain and had a lower pre-test probability of CAD compared to men. Independently of this differences, cardiac CT led in both sexes to a fast final diagnosis as compared functional testing, while the effect was larger in women (p-interaction=0.01). The reduced need for further testing after CT, compared to functional testing, was most evident in women (p-interaction=0.009). However, no gender interaction was observed with respect to changes in angina and quality of life, cumulative diagnostic costs, and applied radiation dose (all p-interactions≥0.097).

Conclusions – Cardiac CT is more efficient in women than men in terms of time to reach the final diagnosis and downstream testing. However, overall clinical outcome showed no significant difference between women and men after one year.

INTRODUCTION

In industrialized countries, coronary artery disease (CAD) is the leading cause of death among women and associated with a worse outcome compared to men [1, 2]. Due to a frequently different presentation of complaints ischemic heart disease is thought to be under-recognized in women [3, 4]. The prevalence of vasospasm and microvascular angina is higher in women, which may partly explain the differences in symptoms between women and men [4]. Conventional first-line non-invasive diagnostic tests are thought to be less accurate in women, further contributing to under-diagnosis, and potentially under-treatment [5, 6]. On the other hand, women have higher rates of indeterminate exercise ECG results, but also more false positive results due to nonspecific ST-T changes. The lower sensitivity of nuclear imaging is thought to result from the smaller size of the female heart, while false-positive diagnoses may be introduced by breast attenuation artifacts [7, 8]. Paradoxically, there appears to be an relative overuse of invasive angiography (ICA) in women, perhaps fueled by the limited confidence in noninvasive tests, resulting in a rather low diagnostic yield for obstructive CAD [9, 10].

Cardiac CT is a non-invasive imaging modality with an excellent diagnostic accuracy for the detection of CAD in both men and women [11]. Recently, three multicenter randomized trials showed that cardiac CT is at least as effective and safe as standard diagnostic testing for patients with suspected CAD [12-14].Given the uncertain diagnostic accuracy of functional tests in women, direct visualization of CAD by cardiac CT may be particularly effective in women.

In this pre-specified sub-analysis of the recently published CRESCENT trial (Calcium imaging and selective CT angiography in comparison to functional testing for suspected coronary artery disease), we investigated whether sex affects the effectiveness and safety of cardiac CT compared to standard functional testing in patients with symptoms suggestive of CAD.

METHODS

Study design and participants

CRESCENT is a multicenter randomized controlled clinical effectiveness trial. From the cardiology outpatient clinics at four hospitals in the Rotterdam region of the Netherlands, 350 patients with stable chest pain and suspected CAD were enrolled in the study. The study design, inclusion and exclusion criteria, and primary results have been reported previously [12]. Briefly, all adult patients with stable chest pain or angina equivalent symptoms potentially caused by obstructive CAD were considered for study participation. Exclusion criteria were a history of known CAD, invasive coronary angi-

ography or stress test performed less than one year ago, or inability or unwillingness to provide informed consent. Renal impairment, contrast allergy, atrial fibrillation, or other test specific contra-indications did not preclude study participation. The study was approved by the medical ethics committees at each participating site and all participants provided informed consent. The CRESCENT trial is registered at the US National Institutes of Health (ClinicalTrials.gov), number NCT01393028.

Randomization and study procedures

Patients were randomized in a 1:2 ratio between standard functional testing as dictated by local caregivers and the investigational CT algorithm. For the CT algorithm, all patients first underwent a calcium scan. Absence of calcium excluded CAD and obviated the need for further testing, except for patients with a high pre-test probability of CAD (>70% by Diamond and Forrester criteria [15]). Patients with a calcium score between 1 and 400, as well as 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. All participating sites had prior experience in performing cardiac CT before initiation of the trial. Image acquisition was performed on a 64-slice or more advanced CT system with radiation minimizing measures depending on local practices and patients characteristics. For the standard arm the functional test was chosen and interpreted by the local physician, based on clinical guidelines [16, 17]. Observed disease by CTA and XECG test results were recorded and compared between both sexes. A heart rate below 85% of the predicted heart rate, and a maximum workload below 100% of the predicted exercise capacity were classified as insufficient. A positive XECG was defined as >1-mm ST deviation. A negative XECG was defined as without >1-mm ST deviation, provided that the target heart rate and workload were achieved. CT scans were classified as negative calcium scan, <50% stenosis on CTA, not high-risk >50% CAD, and high-risk >50% CAD (left main stenosis, three-vessel disease or >50% proximal LAD stenosis).

All patients were contacted after 12 months for ascertainment of trial endpoints and health status measurements. The occurrence and results of downstream procedures (exercise ECG, cardiac CT, stress echocardiography, perfusion imaging, catheter angiography and revascularization) were collected during follow-up. All diagnostic procedures were confirmed through review of the patients' medical records. This pre-specified secondary analysis focused on differences between women and men with regard to the effectiveness and safety of a cardiac CT strategy versus standard functional testing in patients with suspected CAD.

Endpoints

The primary outcome was the clinical effectiveness, defined as the absence of chest pain complaints after one year. Additionally, Seattle Angina Questionnaire (SAQ), EuroQol-5D-5L (EQ-5D) and Short-Form-36 (SF-36) for quality-of-life 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 (PCI or CABG) 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 and invasive angiography to detect CAD after the initial test. The diagnostic costs included all tests performed during one year follow up. Average costs per test were based on a previously published cost analysis [18]. The safety outcomes included the event-free survival using the composite endpoint of all-cause mortality, non-fatal myocardial infarction or major stroke, unstable angina pectoris with objective ischemia and/or requiring revascularization, unplanned cardiac evaluations and late coronary revascularization procedures, defined as more than 90 days after the first presentation in the outpatient clinic. The cumulative radiation dose was defined as radiation exposure from all tests and interventions from the first outpatient clinic visit until 1 year of follow up, including CT, perfusion imaging and catheter angiography, calculated in millisieverts (mSv) using standard methods [19, 20], applying a conversion factor kappa (κ) of 0.017 for cardiac CT scans.

Statistical analysis

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. We used logistic regression to test the interaction between sex and randomization strategy for binary outcomes and linear regression for continuous outcome, as appropriate. Logistic regression variables with more than two outcomes, were transformed into dichotomous variables. For adjusted analysis of sex interaction and randomization strategy on the angina improvement we used multivariable models and controlled for age, cardiac risk factors (hypertension, dyslipidemia, smoking, diabetes and family history of premature CAD), as well as for other covariates that were found to be different between men and women (diastolic blood pressure, type of angina and pre-test probability). While the cumulative diagnostic costs are not normally distributed, costs are presented as means, as it better reflects the overall financial burden of each approach. The probability of event-free survival was calculated by the Kaplan-Meier method for each of the end points, and impact of randomization strategy in man and women was analyzed with the log-rank test. A Cox-proportional hazards model with treatment assignment, sex, as

well as their interaction were used to test the hypothesis that sex interacts with clinical adverse events. A two-sided p-value <0.05 was considered statistically significant. Statistical analysis were made using SPSS (version 21, IBM Corp, Armonk NY, United States of America), according to the intention-to-treat principle.

RESULTS

Study population

There were 192 (55%) women and 158 (45%) men. Women more often presented with atypical chest pain compared to men (58% vs. 46%, p=0.029), and had a lower pre-test probability of CAD, as determined using the Diamond and Forrester criteria (p<0.001). While cardiovascular risk factors were similar between sexes, except for a lower diastolic blood pressure, the Systematic Coronary Risk Evaluation [21] was lower in women (p<0.001) (table 1). Neither for women nor men were there differences in baseline characteristics between the two diagnostic strategies (all p>0.05).

Test results

Women had a median calcium score of 1.0(0-43.5), compared to 17.0(0-143.5) in men (p=0.159). CAD was excluded based on the absence of calcium in 48% of women and 35% of men (p=0.036). In women CT angiography demonstrated obstructive CAD in 7% and 13% of men (p=0.279) The technical test results are summarized in figure 1. There were no significant differences between women and men for the exercise test result, which showed comparable rates of insufficient heart rate or exercise capacity (figure 1). Overall, 41 patients (12%) underwent invasive angiography. In women that underwent CT the revascularization rate was 62% (8/13), compared to 50% (4/8) in the functional test group (p=0.604). For men 81% (13/16) were revascularized after CT, compared to 75% (3/4) after revascularization (p=0.780).

Clinical effectiveness

After one year 40% of women randomized to CT reported no anginal symptoms in comparison to 22% of women in the functional testing group (p=0.026). For men 36% reported no symptoms after CT compared to 30% after functional testing (p=0.466). However, significant interactions by sex on the outcome of resolved angina could not be demonstrated (p-interaction=0.286) (Figure 2). For the Seattle angina questionnaire (SAQ) and the quality of life questionnaires (EQ-5D and SF-36), however, there were no significant differences in improvement between CT and functional testing, neither for women and men (table 2).

Table 1. Baseline characteristics of patients by sex

	Women			Men		
	All women	**Cardiac CT**	**Functional testing**	**All men**	**Cardiac CT**	**Functional testing**
n	192 (55)	133 (55)	59 (55)	158 (45)	109 (45)	49 (45)
Demographics						
Age, years†	56 ± 10	56 ± 10	55 ± 10	54 ± 10	53 ± 10	55 ± 10
Systolic blood pressure (mmHg)†	139 ± 22	139 ± 23	136 ± 20	138 ± 20	137 ± 20	139 ± 21
Diastolic blood pressure (mmHg)†	82 ± 12*	82 ± 11	81 ± 13	87 ± 11*	86 ± 11	88 ± 10
Mean body mass index (kg/m^2)†	28 ± 6	28 ± 6	28 ± 6	28 ± 5	28 ± 5	28 ± 5
Cardiovascular risk factors						
Former or current smoker	65 (34)	43 (32)	22 (37)	55 (35)	39 (36)	16 (33)
Hypertension	95 (49)	68 (51)	27 (46)	85 (54)	56 (51)	29 (59)
Dyslipidemia	104 (54)	70 (53)	34 (58)	91 (58)	59 (54)	32 (65)
Diabetes mellitus	32 (17)	22 (17)	10 (17)	26 (16)	19 (17)	7 (14)
Family history of ischemic heart disease	79 (41)	54 (41)	25 (42)	53 (34)	38 (35)	15 (31)
History of stroke	6 (4)	6 (5)	4 (7)	10 (5)	2 (2)	4 (8)
History of peripheral artery disease	7 (4)	4 (3)	3 (5)	9 (6)	5 (5)	4 (8)
Presenting chest pain symptoms						
Typical angina	40 (21)	29 (22)	11 (19)	41 (26)	28 (26)	13 (27)
Atypical angina	110 (58)*	77 (58)	33 (56)	72 (46)*	49 (45)	23 (47)
non-anginal complaints	40 (21)	26 (20)	14 (24)	42 (27)	30 (28)	12 (25)
None	1 (1)	1 (1)	0	2 (1)	1 (1)	1 (2)
Pre-test probability†	38 ± 28*	39	36	54 ± 28*	53	55
10 years Cardiovascular risk ‡ (SCORE)	7 ± 9*	3 [1-10]	4 [1-10]	12 ± 13*	6 [3-17]	8 [4-18]

Unless otherwise specified, data are numbers of patients, with percentages in parentheses. †Data are means ± standard deviations. ‡ Data are medians, with interquartile ranges in parentheses. *Significant difference between men and women. Diabetes mellitus is defined as plasma glucose >11.0mmol/L or treated with either diet regulation or medication. Dyslipidemia defined as a total cholesterol level >5mmol/L, low-density lipoprotein level >3mmol/L, or on lipid-lowering medication. Hypertension defines as >150mmHg systolic or >90mmHg diastolic or treated. Pretest probability based on Diamond and Forrester criteria [15]. Estimated 10-year risk of cardiovascular death was done using SCORE[21] . SCORE = Systematic Coronary Risk Evaluation.

Diagnostic efficiency

In women additional diagnostic testing over the subsequent year was less often needed after cardiac CT compared to standard care (16% vs. 57%, p<0.001). The reduced need for further testing after CT was significantly better in women compared to men (p-interaction=0.009), in whom the secondary diagnostic testing rate just failed to reach statistical significance (27% vs. 41%, p=0.057)(figure 3). Women had lower downstream diagnostic costs after CT compared to functional testing (one-year mean cumulative costs for women in CT group: €326 ± 470 vs. functional testing: €478 ± 493, p<0.001; men: €421 ± 534 for CT vs. €394 ± 451, p=0.329). However, a sex-specific difference could

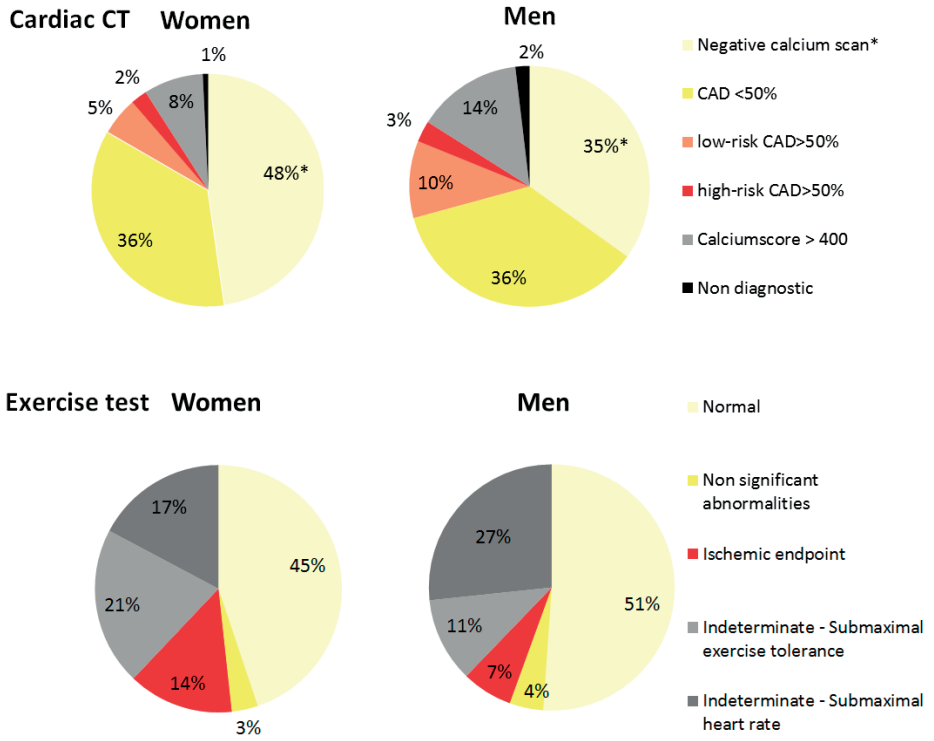

Figure 1. Cardiac CT and exercise test results stratified by sex
CT results based on calcium scan or CTA, classified as absent calcium, calcium score >400, <50% CAD on CTA, and CTA>50% subdivided in high-risk or not (left main stenosis, three-vessel disease or proximal LAD stenosis). A negative calcium scan was more frequent in women (*p=0.036). XECG test results were classified as ischemic (>1 mm ST-deviation in ≥2 leads), non-significant (0.5-1 mm), normal, insufficient heart rate response, or insufficient exercise capacity. No significant XECG result differences were observed between women and men. These technical classifications did not necessarily correspond with clinical interpretations.

not be statistically confirmed (p-interaction=0.120). For women the final diagnosis could be made on the same day in 86% after CT, compared to 44% of women after functional testing (median time to final diagnosis 0(0;0) vs. 10(0;57) days, p<0.001). While the diagnosis was also reached faster in men after cardiac CT (0(0;0) vs. 0(0;29), p=0.011), the improvement was more in women (p-interaction=0.012).

Safety

During an average of 1.2 years of follow-up (median follow up time: 1.2 IQR [1.0;1.7] years) a total of 19 clinical events were recorded, 8 (4%) in women and 11 (7%) in men (p=0.344) (table 3). The event-free survival was 97.7% for women randomized to CT and 91.5% for functional testing (log rank p=0.061). For men randomized to CT the event-

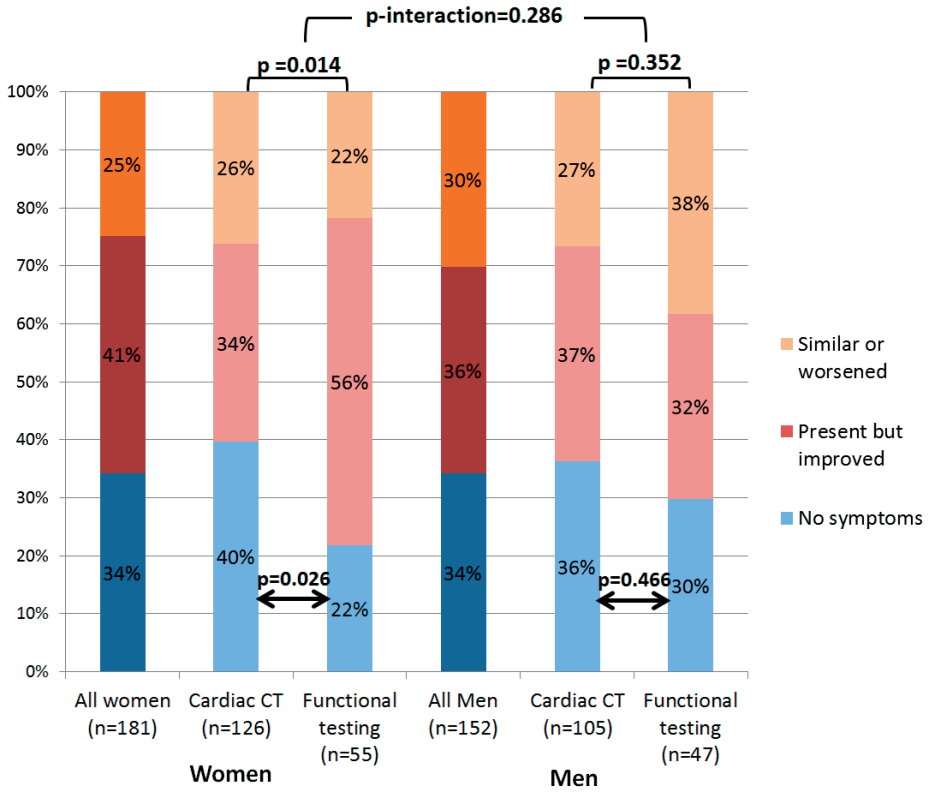

Figure 2. Anginal symptoms
Anginal status at one year, stratified by randomized diagnostic strategy and sex. P-values between the blue stack bars signify differences between the cardiac CT and functional group with regard to the absence of angina symptoms after one year, left part of the graph for women and right for men. P-values above the stacked bars signify differences in the total distribution of anginal complaints between CT and functional testing. Above is the p-interaction signifying the interaction between sex and randomization strategy on anginal symptoms, which was not significant (0.286).

free survival was 95.4% and for functional testing 87.8% (log rank p=0.083) (figure 4). Sex was not a significant predictor of clinical adverse events (p-interaction=0.759).

Radiation exposure

The median radiation dose for the complete cardiac CT examination was 1.7 mSv [0.8;4.7] in women, and 2.6 mSv [1.0;6.8] in men (p=0.179), while the mean doses were 3.7±4.2 mSv in women and 4.6±4.8 mSv in men. Because of the skewed cumulative dose distribution for women in the functional testing group, of whom a minority received relatively high radiation exposure from nuclear imaging and angiography, the median effective dose was 0 mSv [0;12.5], compared to 4.7 mSv [0.9;7.9] in the CT group (p=0.005). Similarly,

Table 2. Questionnaire derived changes in angina and quality of life

	Women			Men			
	Cardiac CT	**Functional testing**	**p-value**	**Cardiac CT**	**Functional testing**	**p-value**	**p-interaction**
Responders (n)	81 (108)	66 (39)		85 (93)	69 (34)		
SAQ	10.3 ± 15.5*	9.9 ± 14.6*	0.874	10.3 ± 12.8*	9.0 ± 12.8*	0.628	0.896
EQ-5D total	0.005 ± 0.331	-0.020 ± 0.384	0.670	-0.017 ± 0.305	-0.016 ± 0.371	0.982	0.743
EQ-5D VAS score	3.4 ± 15.8*	3.9 ± 15.2	0.868	5.9 ± 15.2*	-0.24 ± 16.4	0.063	0.118
SF-36	272 ± 619*	207 ± 672	0.668	369 ± 618*	305 ± 662*	0.685	0.997

Change in questionnaire score after one year. Responders are percentages, with numbers in parentheses. *Significant improvement in score from first outpatient clinic visit to one year follow up. A higher score indicates a better health status. Mean (±SD). P value signifies differences in improvement between CT and functional testing. P-interaction for sex-dependent differences. SAQ; Seattle Angina Questionnaire. EQ-5D total; EuroQol-5D-5L total quality of life score. EQ-5D VAS score; EuroQol-5D-5L quality of life respondent's self-rated health on a vertical, visual analog scale from 0-100 scale; SF-36; Short-Form-36 quality of life questionnaire.

Table 3. Adverse events

	Women			Men		
	All	**Cardiac CT**	**Functional testing**	**All**	**Cardiac CT**	**Functional testing**
All-cause death	0 (0)	0 (0)	0 (0)	2.5 (4)	1.8 (2)	4.1 (2)
Non-fatal myocardial infarction	0.5 (1)	0 (0)	1.7 (1)	0.6 (1)	0.9 (1)	0 (0)
Unstable angina	0.5 (1)	0 (0)	1.7 (1)	0.6 (1)	0.9 (1)	0 (0)
Non-fatal stroke	0.5 (1)	0 (0)	1.7 (1)	0 (0)	0 (0)	0 (0)
Late revascularizations	1 (2)	0.8 (1)	1.7 (1)	1.3 (2)	0.9 (1)	2.0 (1)
Unplanned cardiac evaluations	1.6 (3)	1.5 (2)	1.7 (1)	1.9 (3)	0 (0)	6.1 (3)
All events	**4.2 (8)**	**2.3 (3)**	**8.5 (5)**	**7.0 (11)**	**4.6 (5)**	**12.2 (6)**

Data are percentages, with numbers in parentheses. No significant differences as stratified for sex

Table 4. Cumulative radiation dose

	Cardiac CT	**Functional testing**	**p-value**
Women	Median: 4.7[0.9;7.9] Mean: 5.3 ± 5.5	Median: 0[0;12.5] Mean: 6.3 ± 10.3	0.005
Men	Median: 4.7 [1.1;11.5] Mean: 8.2 ± 11.2	Median: 0[0;14.0] Mean: 5.8 ± 8.1	<0.001
p-value	0.014	0.791	0.097*

Cumulative radiation dose in mSv. *p-interaction value

in men the median cumulative dose was 4.7 mSv [1.1;11.5] in the CT group, compared to 0 mSv [0;14.0] in the functional testing group (p<0.001; p-interaction=0.097)(table 4). If calcium scans had not been included in the decision making, and all patients had

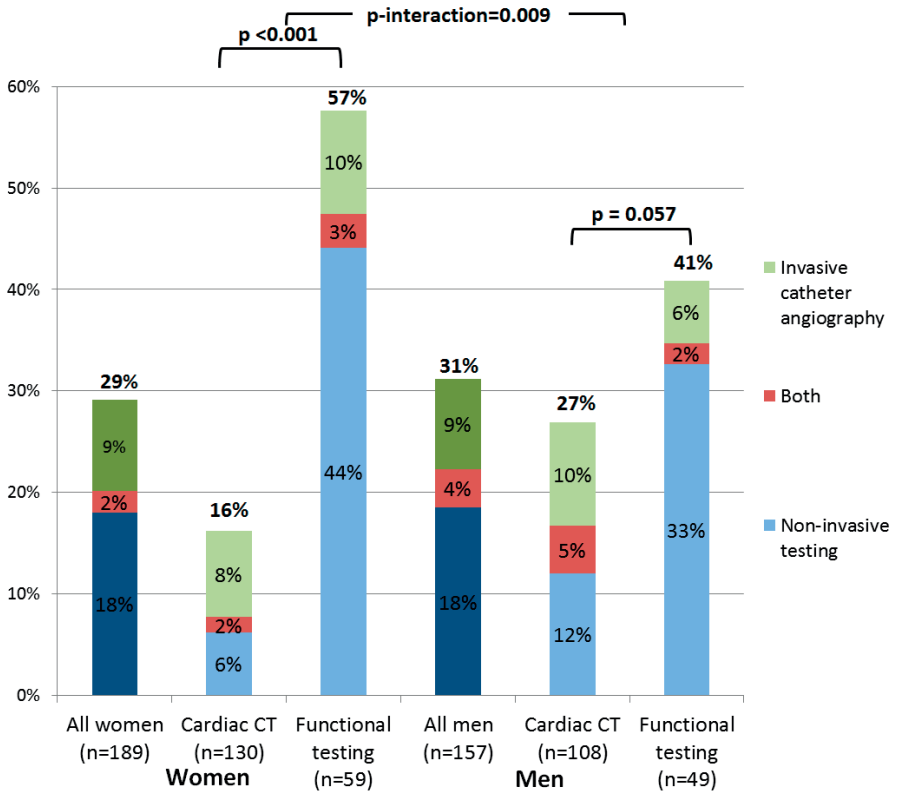

Figure 3. Downstream diagnostic testing stratified by sex
Proportion of patients requiring further non-invasive and/or invasive testing. P-values signify differences in total number of downstream diagnostic testing in the CT arm versus the functional testing arm. P-interaction (0.009) indicates no significant interaction by sex and randomization strategy.

undergone CTA instead, the estimated median radiation exposure from the CT exam might have increased to 4.7 mSv [3.7;10.7] (mean 7.5±8.6 mSv). In women below 60 years (59%), in whom CAD was ruled out based on a negative calcium scan in 71%, the median cumulative radiation dose was 1.1 mSv [0.8;1.5] (mean 1.4±1.3mSv).

DISCUSSION

In this pre-specified sub-analysis of the CRESCENT trial we compared the performance of cardiac CT and functional testing between women and men. Apart from previously described differences in disease prevalence the main findings of our study are that cardiac CT performs well in women with stable chest pain complaints. In women cardiac CT

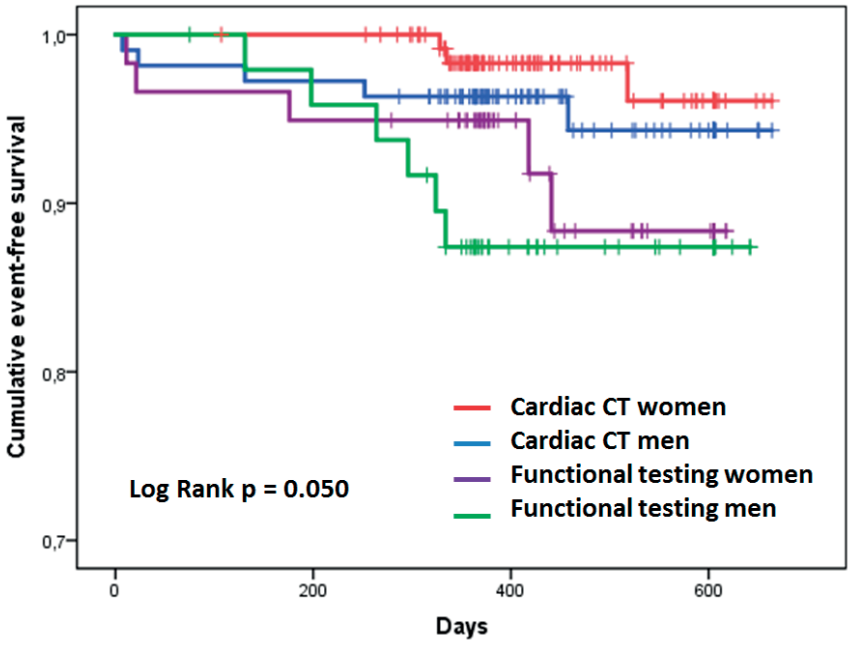

Figure 4. Event-free survival
Kaplan-Meier curves of event-free survival stratified by randomized diagnostic strategy and by sex. There was a difference in event rate between randomization strategy (p=0.011), but not between sexes.

resulted in more resolution of chest pain, a lower need for further testing and diagnostic expenses, however with a higher median radiation exposure. In terms of the need for further testing and time to reach the final diagnosis, women had significantly more benefit from cardiac CT compared to men.

Symptoms and disease prevalence

In concordance with prior observations, women in the CRESCENT trial more often had atypical symptoms (57% vs. 46%, p=0.032) and lower rates of focal, epicardial CAD than men[4]. All trials, including this cohort, had a low CAD prevalence with overestimation of the individual probability of disease by conventional prediction rules for both men and women [13, 14, 22]. In CRESCENT the CAD prevalence was 9% in women, while the predicted probability by the Diamond and Forrester method was 38%. For men the prevalence was 12%, while the predicted probability was 54%. In PROMISE the pre-test probability of CAD was 53% by Diamond & Forrester criteria, while the observed disease prevalence was approximately 9%.

Sex differences in the performance of diagnostic testing

In many centers the routine diagnostic work-up of patients with suspected CAD includes stress testing. The recommended test modality depends on the patient's pre-test probability of CAD, clinical characteristics, technical availability and local expertise. In women, exercise testing is thought to be less helpful due to a lower diagnostic accuracy and high rate of indeterminate test results [7]. In the previously published subanalysis of the PROMISE trial women were less likely to have a positive CTA than a positive exercise ECG or nuclear stress test result, even after adjusting for clinical factors, which may be the result of false-positive stress test results [23]. Interestingly, in the CRESCENT trial no differences were observed between sexes with regard to the exercise tolerance or achieved heart rate during exercise testing, possibly caused by the small population size. Both in women and men cardiac CT reached a final diagnosis faster, requiring fewer additional tests. In 47% of women randomized to functional testing additional testing was ordered by the treating physician, compared to only 8% after cardiac CT. Contrary to PROMISE and SCOT-HEART, in this study cardiac CT was not associated with an increase in the number of cardiac catheterizations in women [13, 14]. The reduced catheterization referral rate after CT may theoretically be explained by the use of the calcium scan, or a higher accuracy by newer CT equipment, but may as well be the result of differences in management following the CT scan, compared to previous studies. Conservative management of low-risk CAD and functional confirmation before revascularization may have avoided premature catheterization referral in CRESCENT, although it is unknown if these treatment practices were different in other pragmatic trials. Alternatively, equivalent catheterization rates may also be explained by a higher referral rate in the control group resulting from different stress test decisions. While in PROMISE more revascularizations and catheterizations were performed after CTA, costs were comparable after 90 days and 3 years[24]. In CRESCENT, women had lower downstream diagnostic costs after CT compared to functional testing.

In women, as well as the cohort as a whole[12], cardiac CT more often resulted in resolved anginal symptoms after one year in comparison to functional testing. 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 reassurance of patients and physicians by the test results. However, for the SAQ and quality of life questionnaires there were no significant differences between CT and functional testing for either sex. Similar equivalidity was found in the PROMISE trial[25], while the PLATFORM trial observed more improvement in QoL scores after CT (including FFR_{CT}), in comparison to a strategy with usual noninvasive testing[26].

Safety

Cardiac CT is in both women and men associated with a higher median cumulative radiation dose, compared to functional testing, however significant interaction by sex could not be demonstrated (p-interaction=0.097). In the functional testing group the cumulative radiation exposure increased because of more nuclear imaging tests (mean 14±2mSv) and invasive angiography (mean 14±14mSv) after the initial functional test. We incorporated the calcium scan into the CT algorithm because of its excellent negative predictive value. By not performing CTA in patients with a negative calcium scan, contrast medium and additional radiation could be avoided in 48% of women. Young women are relatively more vulnerable to radiation exposure, but we observed that with the incorporation of the calcium scan the cumulative radiation dose in this group was very low. While it is possible that severe but non-calcified lesions may be missed if CT angiography is not performed, the clinical course of patients who did not undergo CTA was uneventful over the first 6 months.

Similar to other CT studies in populations with stable CAD the overall event rate was low. While for the entire population cardiac CT was associated with lower event rates [12-14], no significant differences were found between sexes.

Diagnostic management of suspected CAD in women and men

While exercise-ECG has a modest diagnostic performance, especially in women, both American and European guidelines recommend it as the first choice test in patients with a low to intermediate pre-test probability, interpretable resting ECG and ability to exercise[27, 28]. PROMISE and SCOT-HEART, as well as CRESCENT, have demonstrated that cardiac CT is equally or more effective and safe as standard diagnostic testing for patients with suspected CAD [12-14]. This sub analysis underlines the notion that cardiac CT is more efficient in women in terms of less downstream testing and a speedier diagnosis, compared to functional testing.

Limitations

This subgroup analysis was hampered by the small sizes of subgroups, which was particularly relevant for the comparison of the diagnostic yield of ICA as well as some other secondary endpoints. Observed differences in diagnostic performance may reflect in part differences in disease prevalence between men and women. While we performed adjusted analysis to correct for potential confounders, other relevant confounders may have remained unidentified. 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. 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.

Although the study was performed at several sites, appropriateness of extrapolation of our results to other centers will depend on comparability of the clinical setting in terms of current diagnostic care, available technology, cost-accounting systems and therapeutic management practices.

CONCLUSION

Cardiac CT is more efficient in women than men in terms of time to reach the final diagnosis and downstream testing. However, overall clinical outcome showed no significant difference between women and men after one year.

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AD, TG, JA, TB, BK, PM, MO, AL, AN, PF: none declared

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