Sex Differences in the Performance of Cardiac Computed Tomography Compared With Functional Testing in Evaluating Stable Chest Pain

Subanalysis of the Multicenter, Randomized CRESCENT Trial (Calcium Imaging and Selective CT Angiography in Comparison to Functional Testing for Suspected Coronary Artery Disease)

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Background**—**Cardiac computed tomography (CT) represents an alternative diagnostic strategy for women with suspected coronary artery disease, with potential benefits in terms of effectiveness and cost-efficiency.

Methods and Results**—**The CRESCENT trial (Calcium Imaging and Selective CT Angiography in Comparison to Functional Testing for Suspected Coronary Artery Disease) prospectively randomized 350 patients with stable angina (55% women; aged 55±10 years), mostly with an intermediate coronary artery disease 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 and 400. Patients with test-specific contraindications were not excluded from study participation. Sex differences were studied as a prespecified subanalysis. Enrolled women presented more frequently with atypical chest pain and had a lower pretest probability of coronary artery disease compared with men. Independently of these differences, cardiac CT led in both sexes to a fast final diagnosis when compared with functional testing, although the effect was larger in women (P interaction=0.01). The reduced need for further testing after CT, compared with functional testing, was most evident in women (P interaction=0.009). However, no sex 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 in 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 1 year.

Clinical Trial Registration**—**URL: http://www.clinicaltrials.gov. Unique identifier: NCT01393028.

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Key Words: angiography ■ chest pain ■ clinical trial ■ coronary artery disease ■ women

In industrialized countries, coronary artery disease (CAD) is the leading cause of death among women and associated with a worse outcome compared with men.[1,2] Because of 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 noninvasive diagnostic tests are thought to be less accurate in women, further contributing to underdiagnosis and potentially undertreatment.[5,6] On the other hand, women have higher rates of indeterminate exercise ECG results but also more false-positive results because of nonspecific ST-T segment changes. The lower sensitivity of nuclear imaging is thought to result from the smaller size of the female heart, although false-positive diagnoses may be introduced by breast attenuation artifacts.[7,8] Paradoxically, there seems to be a relative overuse

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of invasive coronary 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 computed tomography (CT) is a noninvasive imaging modality with an excellent diagnostic accuracy for the detection of CAD in both men and women.[11] Recently, 3 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 prespecified subanalysis 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 with 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 4 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 angiography or stress test performed <1 year ago, or inability or unwillingness to provide informed consent. Renal impairment, contrast allergy, atrial fibrillation, or other test-specific contraindications 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.

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 pretest 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% pretest probability, underwent contrast-enhanced coronary CT angiography to detect obstructive CAD. Those with CT contraindications, a calcium score >400, or nonconclusive CT angiogram (noninterpretable or intermediate obstructive disease), underwent stress testing or ICA at the discretion of the treating physician. All participating sites had previous experience in performing cardiac CT before the 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 computed tomography angiography (CTA) and exercise-ECG test results was recorded and compared between both sexes. A heart rate <85% of the predicted heart rate and a maximum workload <100% of the predicted exercise capacity were classified as insufficient. A positive exercise-ECG was defined as >1 mm ST deviation. A negative exercise-ECG 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, 3-vessel disease or >50% proximal left anterior descending artery stenosis).

All patients were contacted after 12 months for ascertainment of trial end points 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 prespecified 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.

End Points

The primary outcome was the clinical effectiveness, defined as the absence of chest pain complaints after 1 year. In addition, Seattle Angina Questionnaire, EuroQol-5D-5L, and Short Form 36 for quality-of-life responses were compared between baseline and 1-year follow-up. Prespecified secondary outcomes included the diagnostic yield, defined as the proportion of patients undergoing revascularization (percutaneous coronary intervention or coronary artery bypass grafting) after ICA. Efficiency outcomes included the time to diagnosis, defined as the period from the presentation until the first test that led to the final diagnosis, or the final test that ruled out obstructive CAD. Downstream testing included all noninvasive testing and ICA to detect CAD after the initial test. The diagnostic costs included all tests performed during 1-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 end point of all-cause mortality, nonfatal myocardial infarction or major stroke, unstable angina pectoris with objective ischemia and requiring revascularization, unplanned cardiac evaluations, and late coronary revascularization procedures, defined as >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 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 χ^2 or Fisher 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 >2 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 mellitus, 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 pretest probability). Although 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, and their interaction was used to test the hypothesis that sex interacts with clinical adverse events. A 2-sided P value <0.05 was considered statistically significant. Statistical analysis was made using SPSS (version 21, IBM Corp, Armonk, NY), 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 with men (58% versus 46%; *P*=0.029) and had a lower pretest probability of CAD, as determined using the Diamond and Forrester criteria (*P*<0.001). Although 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 for men were there differences in baseline characteristics between the 2 diagnostic strategies (all *P*>0.05).

Test Results

Women had a median calcium score of 1.0 (0–43.5), compared with 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 ICA. In women who underwent CT, the revascularization rate was 62% (8/13), compared with 50% (4/8) in the functional test group (*P*=0.604). For men, 81% (13/16) were revascularized after CT, compared with 75% (3/4) after revascularization (*P*=0.780).

Clinical Effectiveness

After 1 year, 40% of women randomized to CT reported no anginal symptoms in comparison with 22% of women in the functional testing group (*P*=0.026). For men, 36% reported no symptoms after CT compared with 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 and the quality-of-life questionnaires (EuroQol-5D-5L and Short Form 36), however, there were no significant differences in improvement between CT and functional testing, neither for women nor men (Table 2).

Diagnostic Efficiency

In women, additional diagnostic testing over the subsequent year was less often needed after cardiac CT compared with standard care (16% versus 57%; *P*<0.001). The reduced need for further testing after CT was significantly better in women

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, y*	56±10	56±10	55±10	54±10	53±10	55±10
Systolic blood pressure, mm Hg*	139±22	139±23	136±20	138±20	137±20	139±21
Diastolic blood pressure, mm Hg*	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)
Nonanginal 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)
Pretest probability*	38±28†	39	36	54±28†	53	55
10-y 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. Diabetes mellitus is defined as plasma glucose >11.0 mmol/L or treated with either diet regulation or medication. Dyslipidemia defined as a total cholesterol level >5 mmol/L, low-density lipoprotein level >3 mmol/L, or on lipid-lowering medication. Hypertension defines as >150 mm Hg systolic or >90 mm Hg diastolic or treated. Pretest probability based on Diamond and Forrester criteria.[15] Estimated 10-y risk of cardiovascular death was done using SCORE.[21] CT indicates computed tomography; and SCORE, Systematic Coronary Risk Evaluation.

*Data are means±SD.

†Significant difference between men and women.

‡Data are medians, with interquartile ranges in parentheses.

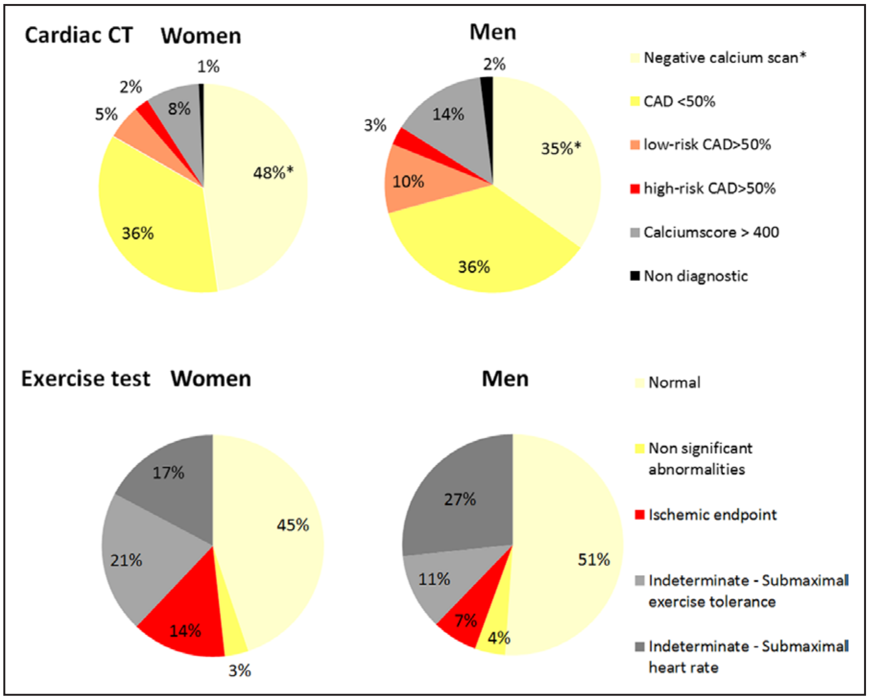

Figure 1. Cardiac computed tomography (CT) and exercise test results stratified by sex. CT results based on calcium scan or computed tomography angiography (CTA), classified as absent calcium, calcium score >400, <50% CAD on CTA, and CTA>50% subdivided in high risk or not (left main stenosis, 3-vessel disease or proximal left anterior descending artery stenosis). A negative calcium scan was more frequent in women (*P=0.036). exercise-ECG test results were classified as ischemic (>1 mm ST deviation in ≥2 leads), nonsignificant (0.5–1 mm), normal, insufficient heart rate response, or insufficient exercise capacity. No significant exercise-ECG result differences were observed between women and men. These technical classifications did not necessarily correspond with clinical interpretations.

compared with men (P interaction=0.009), in whom the secondary diagnostic testing rate just failed to reach statistical significance (27% versus 41%; P=0.057; Figure 3). Women had lower downstream diagnostic costs after CT compared with functional testing (1-year mean cumulative costs for women in CT group: €326±470 versus functional testing: €478±493, P<0.001; men: €421±534 for CT versus €394±451 for functional testing, P=0.329). However, a sex-specific difference could 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 with 44% of women after functional testing (median time to final diagnosis 0 [0;0] versus 10 [0;57] days; P<0.001). While the diagnosis was also reached faster in men after cardiac CT (0 [0;0] versus 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 inter quartile range, [1.0;1.7] years), a total of 19 clinical events were recorded, 8 (4%) in women and 11 (7%)

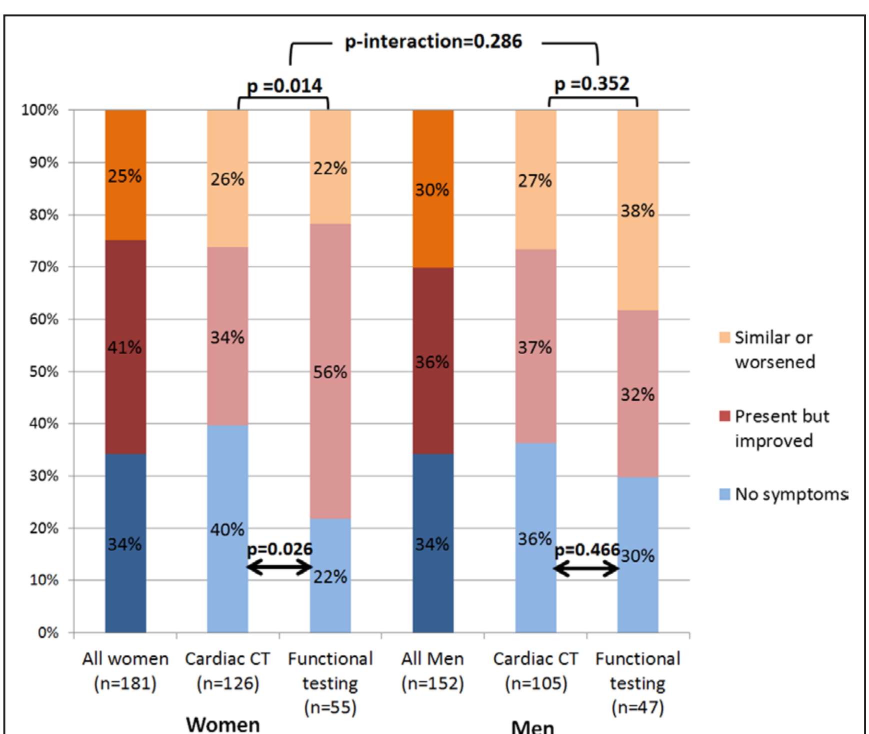

Figure 2. Anginal symptoms. Anginal status at 1 y, stratified by randomized diagnostic strategy and sex. P values between the blue stack bars signify differences between the cardiac computed tomography (CT) and functional group with regard to the absence of angina symptoms after 1 y, left part of the 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).

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 1 y. Responders are percentages, with numbers in parentheses. 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. CT indicates computed tomography; 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 to 100 scale; SAQ, Seattle Angina Questionnaire; and SF-36, Short Form 36 quality-of-life questionnaire.

*Significant improvement in score from first outpatient clinic visit to 1-y follow-up.

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-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), whereas 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 with 4.7 mSv [0.9;7.9] in the CT group (P=0.005). Similarly, in men, the median cumulative dose was 4.7 mSv [1.1;11.5] in the CT group, compared with 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 undergone CTA instead, the estimated median radiation exposure from the CT examination might have increased to 4.7 mSv [3.7;10.7], mean 7.5±8.6 mSv. In women <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±1.3 mSv.

Discussion

In this prespecified subanalysis of the CRESCENT trial, we compared the performance of cardiac CT and functional testing between women and men. Apart from previously described

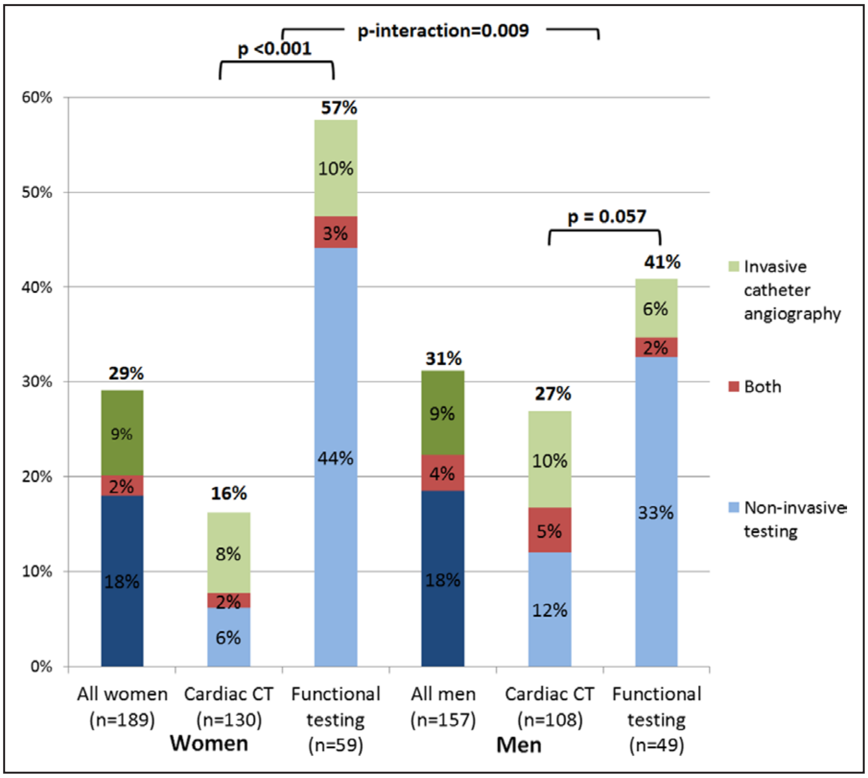

Figure 3. Downstream diagnostic testing stratified by sex. Proportion of patients requiring further noninvasive and invasive testing. *P* values signify differences in total number of downstream diagnostic testing in the computed tomographic (CT) arm vs the functional testing arm. *P* interaction (0.009) indicates no significant interaction by sex and randomization strategy.

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)
Nonfatal 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)
Nonfatal 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. CT indicates computed tomography.

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 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 with men.

Symptoms and Disease Prevalence

In concordance with previous observations, women in the CRESCENT trial more often had atypical symptoms (57% versus 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, whereas the predicted probability by the Diamond and Forrester method was 38%. For men, the prevalence was 12%, whereas the predicted probability was 54%. In PROMISE (Prospective Multicenter Imaging Study for Evaluation of Chest Pain), the pretest probability of CAD was 53% by Diamond and Forrester criteria, whereas the observed disease prevalence was ≈9%.

Sex Differences in the Performance of Diagnostic Testing

In many centers, the routine diagnostic workup of patients with suspected CAD includes stress testing. The recommended test modality depends on the patient's pretest probability of CAD, clinical characteristics, technical availability, and local expertise. In women, exercise testing is thought to be less helpful because of 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

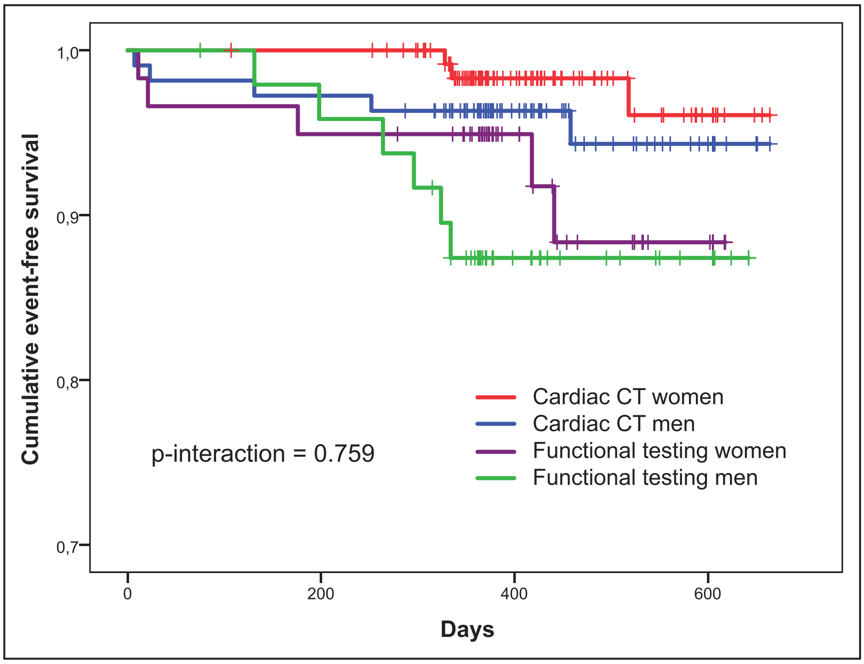

Figure 4. Event-free survival. Kaplan–Meier curves of event-free survival stratified by randomized diagnostic strategy and by sex. There was a difference in event rate between randomization strategy (*P*=0.011) but not between sexes. CT indicates computed tomography.

Table 4. Cumulative Radiation Dose

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

Cumulative radiation dose in mSv.
**P* interaction value.

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 with only 8% after cardiac CT. Contrary to PROMISE and SCOT-HEART (Scottish Computed Tomography Coronary Angiography in Patients With Suspected Angina Due to Coronary Heart Disease), 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 after the CT scan, compared with the previous studies. Conservative management of low-risk CAD and functional confirmation before the 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. Although 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 with functional testing.

In women, as well as the cohort as a whole,[12] cardiac CT more often resulted in resolved anginal symptoms after 1 year in comparison to functional testing. This can be explained by a higher diagnostic performance of CT, followed by more appropriate management of cardiac and noncardiac 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 Seattle Angina Questionnaire 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] whereas the PLATFORM trial observed more improvement in quality of life scores after CT (including fractional flow reserve$_{CT}$), 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 with 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±2 mSv) and ICA (mean 14±14 mSv) 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. Although it is possible that severe but noncalcified 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. Although 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

Although 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 pretest 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 subanalysis underlines the notion that cardiac CT is more efficient in women in terms of less downstream testing and a speedier diagnosis, compared with 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 and some other secondary end points. Observed differences in diagnostic performance may reflect in part differences in disease prevalence between men and women. Although 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.

Conclusions

Cardiac CT is more efficient in women than in 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 1 year.

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References

1. Stramba-Badiale M, Fox KM, Priori SG, Collins P, Daly C, Graham I, Jonsson B, Schenck-Gustafsson K, Tendera M. Cardiovascular diseases in women: a statement from the policy conference of the European Society of Cardiology. *Eur Heart J*. 2006;27:994–1005.
2. Lloyd-Jones D, Adams R, Carnethon M, De Simone G, Ferguson TB, Flegal K, Ford E, Furie K, Go A, Greenlund K, Haase N, Hailpern S, Ho M, Howard V, Kissela B, Kittner S, Lackland D, Lisabeth L, Marelli A, McDermott M, Meigs J, Mozaffarian D, Nichol G, O'Donnell C, Roger V, Rosamond W, Sacco R, Sorlie P, Stafford R, Steinberger J, Thom T, Wasserthiel-Smoller S, Wong N, Wylie-Rosett J, Hong Y; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics–2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation*. 2009;119:480–486. doi: 10.1161/CIRCULATIONAHA.108.191259.
3. Shaw LJ, Bairey Merz CN, Pepine CJ, Reis SE, Bittner V, Kelsey SF, Olson M, Johnson BD, Mankad S, Sharaf BL, Rogers WJ, Wessel TR, Arant CB, Pohost GM, Lerman A, Quyyumi AA, Sopko G; WISE Investigators. Insights from the NHLBI-Sponsored Women's Ischemia Syndrome Evaluation (WISE) Study: Part I: gender differences in traditional and novel risk factors, symptom evaluation, and gender-optimized diagnostic strategies. *J Am Coll Cardiol*. 2006;47(3 suppl):S4–S20. doi: 10.1016/j.jacc.2005.01.072.
4. Douglas PS, Ginsburg GS. The evaluation of chest pain in women. *N Engl J Med*. 1996;334:1311–1315. doi: 10.1056/NEJM199605163342007.
5. Kwok Y, Kim C, Grady D, Segal M, Redberg R. Meta-analysis of exercise testing to detect coronary artery disease in women. *Am J Cardiol*. 1999;83:660–666.
6. Shaw LJ, Mieres JH, Hendel RH, Boden WE, Gulati M, Veledar E, Hachamovitch R, Arrighi JA, Merz CN, Gibbons RJ, Wenger NK, Heller GV; WOMEN Trial Investigators. Comparative effectiveness of exercise electrocardiography with or without myocardial perfusion single photon emission computed tomography in women with suspected coronary artery disease: results from the What Is the Optimal Method for Ischemia Evaluation in Women (WOMEN) trial. *Circulation*. 2011;124:1239–1249. doi: 10.1161/CIRCULATIONAHA.111.029660.
7. Mieres JH, Shaw LJ, Arai A, Budoff MJ, Flamm SD, Hundley WG, Marwick TH, Mosca L, Patel AR, Quinones MA, Redberg RF, Taubert KA, Taylor AJ, Thomas GS, Wenger NK; Cardiac Imaging Committee, Council on Clinical Cardiology, and the Cardiovascular Imaging and Intervention Committee, Council on Cardiovascular Radiology and Intervention, American Heart Association. Role of noninvasive testing in the clinical evaluation of women with suspected coronary artery disease: consensus statement from the Cardiac Imaging Committee, Council on Clinical Cardiology, and the Cardiovascular Imaging and Intervention Committee, Council on Cardiovascular Radiology and Intervention, American Heart Association. *Circulation*. 2005;111:682–696. doi: 10.1161/01.CIR.0000155233.67287.60.
8. Detry JM, Kapita BM, Cosyns J, Sottiaux B, Brasseur LA, Rousseau MF. Diagnostic value of history and maximal exercise electrocardiography in men and women suspected of coronary heart disease. *Circulation*. 1977;56:756–761.
9. Patel H, Rosengren A, Ekman I. Symptoms in acute coronary syndromes: does sex make a difference? *Am Heart J*. 2004;148:27–33. doi: 10.1016/j.ahj.2004.03.005.
10. Shaw LJ, Shaw RE, Merz CN, Brindis RG, Klein LW, Nallamothu B, Douglas PS, Krone RJ, McKay CR, Block PC, Hewitt K, Weintraub WS, Peterson ED; American College of Cardiology-National Cardiovascular Data Registry I. Impact of ethnicity and gender differences on angiographic coronary artery disease prevalence and in-hospital mortality in the American College of Cardiology-National Cardiovascular Data Registry. *Circulation*. 2008;117:1787–1801. doi: 10.1161/CIRCULATIONAHA.107.726562.
11. Dharampal AS, Papadopoulou SL, Rossi A, Weustink AC, Mollet NR, Meijboom WB, Neefjes LA, Nieman K, Boersma E, de Feijter PJ, Krestin GP. Computed tomography coronary angiography accuracy in women and men at low to intermediate risk of coronary artery disease. *Eur Radiol*. 2012;22:2415–2423. doi: 10.1007/s00330-012-2503-5.
12. Lubbers M, Dedic A, Coenen A, Galema T, Akkerhuis J, Bruning T, Krenning B, Musters P, Ouhlous M, Liem A, Niezen A, Hunink M, de Feijter P, Nieman K. Calcium imaging and selective computed tomography angiography in comparison to functional testing for suspected coronary artery disease: the multicentre, randomized CRESCENT trial. *Eur Heart J*. 2016;37:1232–1243. doi: 10.1093/eurheartj/ehv700.
13. Douglas PS, Hoffmann U, Patel MR, Mark DB, Al-Khalidi HR, Cavanaugh B, Cole J, Dolor RJ, Fordyce CB, Huang M, Khan MA, Kosinski AS, Krucoff MW, Malhotra V, Picard MH, Udelson JE, Velazquez EJ, Yow E, Cooper LS, Lee KL; PROMISE Investigators. Outcomes of anatomical versus functional testing for coronary artery disease. *N Engl J Med*. 2015;372:1291–1300. doi: 10.1056/NEJMoa1415516.
14. Investigators S-H. CT coronary angiography in patients with suspected angina due to coronary heart disease (SCOT-HEART): an open-label, parallel-group, multicentre trial. *Lancet*. 2015;385:2383–2391. doi: 10.1016/S0140-6736(15)60291-4.
15. Diamond GA, Forrester JS. Analysis of probability as an aid in the clinical diagnosis of coronary-artery disease. *N Engl J Med*. 1979;300:1350–1358. doi: 10.1056/NEJM197906143002402.
16. Gibbons RJ, Balady GJ, Bricker JT, Chaitman BR, Fletcher GF, Froelicher VF, Mark DB, McCallister BD, Mooss AN, O'Reilly MG, Winters WL, Gibbons RJ, Antman EM, Alpert JS, Faxon DP, Fuster V, Gregoratos G, Hiratzka LF, Jacobs AK, Russell RO, Smith SC; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Committee to Update the 1997 Exercise Testing Guidelines. ACC/AHA 2002 guideline update for exercise testing: summary article. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines). *Circulation*. 2002;106:1883–1892.
17. Hendel RC, Berman DS, Di Carli MF, Heidenreich PA, Henkin RE, Pellikka PA, Pohost GM, Williams KA; American College of Cardiology Foundation Appropriate Use Criteria Task Force; American Society of Nuclear Cardiology; American College of Radiology; American Heart Association; American Society of Echocardiography; Society of Cardiovascular Computed Tomography; Society for Cardiovascular Magnetic Resonance; Society of Nuclear Medicine. ACCF/ASNC/ACR/AHA/ASE/SCCT/SCMR/SNM 2009 appropriate use criteria for cardiac radionuclide imaging: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, the American Society of Nuclear Cardiology, the American College of Radiology, the American Heart Association, the American Society of Echocardiography, the Society of Cardiovascular Computed Tomography, the Society for Cardiovascular Magnetic Resonance, and the Society of Nuclear Medicine. *Circulation*. 2009;119:e561–e587. doi: 10.1161/CIRCULATIONAHA.109.192519.
18. Genders TS, Ferket BS, Dedic A, Galema TW, Mollet NR, de Feyter PJ, Fleischmann KE, Nieman K, Hunink MG. Coronary computed tomography versus exercise testing in patients with stable chest pain: comparative effectiveness and costs. *Int J Cardiol*. 2013;167:1268–1275. doi: 10.1016/j.ijcard.2012.03.151.
19. Gerber TC, Carr JJ, Arai AE, Dixon RL, Ferrari VA, Gomes AS, Heller GV, McCollough CH, McNitt-Gray MF, Mettler FA, Mieres JH, Morin RL, Yester MV. Ionizing radiation in cardiac imaging: a science advisory from the American Heart Association Committee on Cardiac Imaging of the Council on Clinical Cardiology and Committee on Cardiovascular Imaging and Intervention of the Council on Cardiovascular Radiology and Intervention. *Circulation*. 2009;119:1056–1065. doi: 10.1161/CIRCULATIONAHA.108.191650.
20. Mettler FA Jr, Huda W, Yoshizumi TT, Mahesh M. Effective doses in radiology and diagnostic nuclear medicine: a catalog. *Radiology*. 2008;248:254–263. doi: 10.1148/radiol.2481071451.
21. Conroy RM, Pyörälä K, Fitzgerald AP, Sans S, Menotti A, De Backer G, De Bacquer D, Ducimetière P, Jousilahti P, Keil U, Njølstad I, Oganov RG, Thomsen T, Tunstall-Pedoe H, Tverdal A, Wedel H,

Whincup P, Wilhelmsen L, Graham IM; SCORE project group. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. *Eur Heart J*. 2003;24:987–1003. doi: 10.1016/S0195-668X(03)00114-3.
22. Hemal K, Pagidipati NJ, Coles A, Dolor RJ, Mark DB, Pellikka PA, Hoffmann U, Litwin SE, Daubert MA, Shah SH, Ariani K, Bullock-Palmer RP, Martinez B, Lee KL, Douglas PS. Sex differences in demographics, risk factors, presentation, and noninvasive testing in stable outpatients with suspected coronary artery disease: insights from the PROMISE Trial. *JACC Cardiovasc Imaging*. 2016;9:337–346. doi: 10.1016/j.jcmg.2016.02.001.
23. Pagidipati NJ, Hemal K, Coles A, Mark DB, Dolor RJ, Pellikka PA, Hoffmann U, Litwin SE, Udelson J, Daubert MA, Shah SH, Martinez B, Lee KL, Douglas PS. Sex differences in functional and CT angiography testing in patients with suspected coronary artery disease. *J Am Coll Cardiol*. 2016;67:2607–2616. doi: 10.1016/j.jacc.2016.03.523.
24. Mark DB, Federspiel JJ, Cowper PA, Anstrom KJ, Hoffmann U, Patel MR, Davidson-Ray L, Daniels MR, Cooper LS, Knight JD, Lee KL, Douglas PS; PROMISE Investigators. Economic outcomes with anatomical versus functional diagnostic testing for coronary artery disease. *Ann Intern Med*. 2016;165:94–102. doi: 10.7326/M15-2639.
25. Mark DB, Anstrom KJ, Sheng S, Baloch KN, Daniels MR, Hoffmann U, Patel MR, Cooper LS, Lee KL, Douglas PS; PROMISE Investigators. Quality-of-life outcomes with anatomic versus functional diagnostic testing strategies in symptomatic patients with suspected coronary artery disease: results from the PROMISE randomized trial. *Circulation*. 2016;133:1995–2007. doi: 10.1161/CIRCULATIONAHA.115.020259.
26. Hlatky MA, De Bruyne B, Pontone G, Patel MR, Norgaard BL, Byrne RA, Curzen N, Purcell I, Gutberlet M, Rioufol G, Hink U, Schuchlenz HW, Feuchtner G, Gilard M, Andreini D, Jensen JM, Hadamitzky M, Wilk A, Wang F, Rogers C, Douglas PS; PLATFORM Investigators. Quality-of-life and economic outcomes of assessing fractional flow reserve with computed tomography angiography: PLATFORM. *J Am Coll Cardiol*. 2015;66:2315–2323. doi: 10.1016/j.jacc.2015.09.051.
27. Fihn SD, Gardin JM, Abrams J, Berra K, Blankenship JC, Dallas AP, Douglas PS, Foody JM, Gerber TC, Hinderliter AL, King SB III, Kligfield PD, Krumholz HM, Kwong RY, Lim MJ, Linderbaum JA, Mack MJ, Munger MA, Prager RL, Sabik JF, Shaw LJ, Sikkema JD, Smith CR Jr, Smith SC Jr, Spertus JA, Williams SV, Anderson JL; American College of Cardiology Foundation/American Heart Association Task Force. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *Circulation*. 2012;126:e354–e471. doi: 10.1161/CIR.0b013e318277d6a0.
28. Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, Budaj A, Bugiardini R, Crea F, Cuisset T, Di Mario C, Ferreira JR, Gersh BJ, Gitt AK, Hulot JS, Marx N, Opie LH, Pfisterer M, Prescott E, Ruschitzka F, Sabaté M, Senior R, Taggart DP, van der Wall EE, Vrints CJ, Zamorano JL, Achenbach S, Baumgartner H, Bax JJ, Bueno H, Dean V, Deaton C, Erol C, Fagard R, Ferrari R, Hasdai D, Hoes AW, Kirchhof P, Knuuti J, Kolh P, Lancellotti P, Linhart A, Nihoyannopoulos P, Piepoli MF, Ponikowski P, Sirnes PA, Tamargo JL, Tendera M, Torbicki A, Wijns W, Windecker S, Knuuti J, Valgimigli M, Bueno H, Claeys MJ, Donner-Banzhoff N, Erol C, Frank H, Funck-Brentano C, Gaemperli O, Gonzalez-Juanatey JR, Hamilos M, Hasdai D, Husted S, James SK, Kervinen K, Kolh P, Kristensen SD, Lancellotti P, Maggioni AP, Piepoli MF, Pries AR, Romeo F, Rydén L, Simoons ML, Sirnes PA, Steg PG, Timmis A, Wijns W, Windecker S, Yildirir A, Zamorano JL; Task Force Members; ESC Committee for Practice Guidelines; Document Reviewers. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. *Eur Heart J*. 2013;34:2949–3003. doi: 10.1093/eurheartj/eht296.

CLINICAL PERSPECTIVE

Cardiac computed tomography (CT) has the potential to improve the diagnostic workup of suspected coronary artery disease in women. The present subanalysis of the previously published CRESCENT trial (Calcium Imaging and Selective CT Angiography in Comparison to Functional Testing for Suspected Coronary Artery Disease) assessed the effectiveness and safety of a cardiac CT protocol in comparison to functional testing in women. Cardiac CT led in both women and men to a fast final diagnosis as compared to functional testing, while the effect was larger in women (*P* interaction=0.01). After 1 year, the reduced need for further testing after CT was significantly better in women compared with men (*P* interaction=0.009). However, no sex interaction was observed with respect to changes in angina and quality of life, cumulative diagnostic costs, and applied radiation dose (all *P* interaction>0.05). This trial shows that cardiac CT is more efficient in women than in men in terms of time to reach the final diagnosis and downstream testing.

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Marisa Lubbers, Adriaan Coenen, Tobias Bruning, Tjebbe Galema, Jurgen Akkerhuis, Boudewijn Krenning, Paul Musters, Mohamed Ouhlous, Ahno Liem, Andre Niezen, Admir Dedic, Ron van Domburg, Miriam Hunink and Koen Nieman

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