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
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.8,10

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 criteria15). Patients with a calcium score between 1 and 400, as well as patients without calcium but >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 were 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.13 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 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 χ2 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 multi-variable 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 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 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 compared with men (P = 0.036). Although cardiovascular risk factors were similar between sexes, except for a lower diastolic blood pressure, the Systematic Coronary Risk Evaluation 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).

**Table 1. Baseline Characteristics of Patients by Sex**

<table>
<thead>
<tr>
<th></th>
<th>Women All</th>
<th>Women Cardiac CT</th>
<th>Women Functional Testing</th>
<th>Men All</th>
<th>Men Cardiac CT</th>
<th>Men Functional Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>192 (55)</td>
<td>133 (55)</td>
<td>59 (55)</td>
<td>158 (45)</td>
<td>109 (45)</td>
<td>49 (45)</td>
</tr>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y*</td>
<td>56±10</td>
<td>56±10</td>
<td>55±10</td>
<td>54±10</td>
<td>53±10</td>
<td>55±10</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg*</td>
<td>139±22</td>
<td>139±23</td>
<td>136±20</td>
<td>138±20</td>
<td>137±20</td>
<td>139±21</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg*</td>
<td>82±12†</td>
<td>82±11</td>
<td>81±13</td>
<td>87±11†</td>
<td>86±11</td>
<td>88±10</td>
</tr>
<tr>
<td>Mean body mass index, kg/m²**</td>
<td>28±6</td>
<td>28±6</td>
<td>28±6</td>
<td>28±5</td>
<td>28±5</td>
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<tr>
<td><strong>Cardiovascular risk factors</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Former or current smoker</td>
<td>65 (34)</td>
<td>43 (32)</td>
<td>22 (37)</td>
<td>55 (35)</td>
<td>39 (36)</td>
<td>16 (33)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>95 (49)</td>
<td>68 (51)</td>
<td>27 (46)</td>
<td>85 (54)</td>
<td>56 (51)</td>
<td>29 (59)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>104 (54)</td>
<td>70 (53)</td>
<td>34 (58)</td>
<td>91 (58)</td>
<td>59 (54)</td>
<td>32 (65)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>32 (17)</td>
<td>22 (17)</td>
<td>10 (17)</td>
<td>26 (16)</td>
<td>19 (17)</td>
<td>7 (14)</td>
</tr>
<tr>
<td>Family history of ischemic heart disease</td>
<td>79 (41)</td>
<td>54 (41)</td>
<td>25 (42)</td>
<td>53 (34)</td>
<td>38 (35)</td>
<td>15 (31)</td>
</tr>
<tr>
<td>History of stroke</td>
<td>6 (4)</td>
<td>6 (5)</td>
<td>4 (7)</td>
<td>10 (5)</td>
<td>2 (2)</td>
<td>4 (8)</td>
</tr>
<tr>
<td>History of peripheral artery disease</td>
<td>7 (4)</td>
<td>4 (3)</td>
<td>3 (5)</td>
<td>9 (6)</td>
<td>5 (5)</td>
<td>4 (8)</td>
</tr>
<tr>
<td><strong>Presenting chest pain symptoms</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Typical angina</td>
<td>40 (21)</td>
<td>29 (22)</td>
<td>11 (19)</td>
<td>41 (26)</td>
<td>28 (26)</td>
<td>13 (27)</td>
</tr>
<tr>
<td>Atypical angina</td>
<td>110 (58)†</td>
<td>77 (58)</td>
<td>33 (56)</td>
<td>72 (46)†</td>
<td>49 (45)</td>
<td>23 (47)</td>
</tr>
<tr>
<td>Nonanginal complaints</td>
<td>40 (21)</td>
<td>26 (20)</td>
<td>14 (24)</td>
<td>42 (27)</td>
<td>30 (28)</td>
<td>12 (25)</td>
</tr>
<tr>
<td>None</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>0</td>
<td>2 (1)</td>
<td>1 (1)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Pretest probability*</td>
<td>38±28†</td>
<td>39</td>
<td>36</td>
<td>54±28†</td>
<td>53</td>
<td>55</td>
</tr>
</tbody>
</table>

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 >5.0 mmol/L, low-density lipoprotein level >3.0 mmol/L, or on lipid-lowering medication. Hypertension defines as >150 mmHg systolic or >90 mmHg diastolic or treated. Pretest probability based on Diamond and Forrester criteria. Estimated 10-y risk of cardiovascular death was done using SCORE. 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.
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: 1.0–1.7 years), a total of 19 clinical events were recorded, 8 (4%) in women and 11 (7%)
Sex Differences in Performance of Cardiac CT 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

Table 2. Questionnaire Derived Changes in Angina and Quality of Life

<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th></th>
<th></th>
<th>Men</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cardiac CT</td>
<td>Functional Testing</td>
<td>P Value</td>
<td>Cardiac CT</td>
<td>Functional Testing</td>
<td>P Value</td>
</tr>
<tr>
<td>Responders (n)</td>
<td>81 (108)</td>
<td>66 (39)</td>
<td>85 (93)</td>
<td>69 (34)</td>
<td>6.28</td>
<td>0.896</td>
</tr>
<tr>
<td>SAQ</td>
<td>10.3±15.5*</td>
<td>9.9±14.6*</td>
<td>0.874</td>
<td>10.3±12.8*</td>
<td>9.9±12.9*</td>
<td>0.628</td>
</tr>
<tr>
<td>EQ-5D total</td>
<td>3.4±15.8*</td>
<td>3.9±15.2</td>
<td>0.868</td>
<td>5.9±15.2*</td>
<td>369±618*</td>
<td>0.668</td>
</tr>
<tr>
<td>SF-36</td>
<td>272±619*</td>
<td>207±672</td>
<td>0.668</td>
<td>369±618*</td>
<td>305±662*</td>
<td>0.685</td>
</tr>
</tbody>
</table>

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.

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.
Sex Differences in Performance of Cardiac CT

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. 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. 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, women had significantly more benefit from cardiac CT compared with men.

Table 3. Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th></th>
<th>Men</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
<td>Cardiac CT</td>
<td>Functional Testing</td>
<td>All</td>
</tr>
<tr>
<td>All-cause death</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2.5 (4)</td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>0.5 (1)</td>
<td>0 (0)</td>
<td>1.7 (1)</td>
<td>0.6 (1)</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>0.5 (1)</td>
<td>0 (0)</td>
<td>1.7 (1)</td>
<td>0.6 (1)</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>0.5 (1)</td>
<td>0 (0)</td>
<td>1.7 (1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Late revascularizations</td>
<td>1 (2)</td>
<td>0.8 (1)</td>
<td>1.7 (1)</td>
<td>1.3 (2)</td>
</tr>
<tr>
<td>Unplanned cardiac evaluations</td>
<td>1.6 (3)</td>
<td>1.5 (2)</td>
<td>1.7 (1)</td>
<td>1.9 (3)</td>
</tr>
<tr>
<td>All events</td>
<td>4.2 (8)</td>
<td>2.3 (3)</td>
<td>8.5 (5)</td>
<td>7.0 (11)</td>
</tr>
</tbody>
</table>

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

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.
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.\textsuperscript{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. Conservatory 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.\textsuperscript{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,\textsuperscript{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 equivalency was found in the PROMISE trial,\textsuperscript{25} whereas the PLATFORM trial observed more improvement in quality of life scores after CT (including fractional flow reserve\textsubscript{cath}), in comparison to a strategy with usual noninvasive testing.\textsuperscript{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,\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.

---

**Table 4. Cumulative Radiation Dose**

<table>
<thead>
<tr>
<th></th>
<th>Cardiac CT</th>
<th>Functional Testing</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>4.7 [0.9;7.9]</td>
<td>Median: 0 [0;12.5]</td>
<td>0.005</td>
</tr>
<tr>
<td>Mean</td>
<td>5.3±5.5</td>
<td>Mean: 6.3±10.3</td>
<td></td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>4.7 [1.1;11.5]</td>
<td>Median: 0 [0;14.0]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean</td>
<td>8.2±11.2</td>
<td>Mean: 5.8±5.1</td>
<td></td>
</tr>
</tbody>
</table>

Cumulative radiation dose in mSv.

* $P$ interaction value.


Acknowledgments

We thank all participating patients and medical personnel who made this study possible.

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References


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.
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)

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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