Comparison of Cardiovascular Magnetic Resonance and Single-Photon Emission Computed Tomography in Women With Suspected Coronary Artery Disease From the Clinical Evaluation of Magnetic Resonance Imaging in Coronary Heart Disease (CE-MARC) Trial

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Background—Coronary artery disease is the leading cause of death in women, and underdiagnosis contributes to the high mortality. This study compared the sex-specific diagnostic performance of cardiovascular magnetic resonance (CMR) and single-photon emission computed tomography (SPECT).

Methods and Results—A total of 235 women and 393 men with suspected angina underwent CMR, SPECT, and x-ray angiography as part of the Clinical Evaluation of Magnetic Resonance Imaging in Coronary Heart Disease (CE-MARC) study. CMR comprised adenosine stress/rest perfusion, cine imaging, late gadolinium enhancement, and magnetic resonance coronary angiography. Gated adenosine stress/rest SPECT was performed with $^{99m}$Tc-tetrofosmin. For CMR, the sensitivity in women and men was similar (88.7% versus 85.6%; $P=0.57$), as was the specificity (83.5% versus 82.8%; $P=0.86$). For SPECT, the sensitivity was significantly worse in women than in men (50.9% versus 70.8%; $P=0.007$), but the specificities were similar (84.1% versus 81.3%; $P=0.48$). The sensitivity in both the female and male groups was significantly higher with CMR than SPECT ($P<0.0001$ for both), but the specificity was similar ($P=0.77$ and $P=1.00$, respectively). For perfusion-only components, CMR outperformed SPECT in women (area under the curve, 0.90 versus 0.67; $P<0.0001$) and in men (area under the curve, 0.89 versus 0.74; $P<0.0001$). Diagnostic accuracy was similar in both sexes with perfusion CMR ($P=1.00$) but was significantly worse in women with SPECT ($P<0.0001$).

Conclusions—In both sexes, CMR has greater sensitivity than SPECT. Unlike SPECT, there are no significant sex differences in the diagnostic performance of CMR. These findings, plus an absence of ionizing radiation exposure, mean that CMR should be more widely adopted in women with suspected coronary artery disease.


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Key Words: magnetic resonance imaging ■ myocardial ischemia ■ tomography, emission-computed, single-photon ■ women

Coronary artery disease (CAD) remains the leading cause of death in women worldwide. Coronary artery disease is therefore a crucial step in improving outcomes for women, particularly because up to 40% of their initial cardiac events are fatal. However, a lack of awareness of the sex-specific aspects of CAD and the substantial underrepresentation of women in trials limit the evidence base for clinical decision making. Furthermore, physicians need to be aware of the specific strengths and weaknesses of the available noninvasive functional tests in women.

Clinical Perspective on p 1138

There are significant differences in the prevalence, symptoms, and pathophysiology of myocardial ischemia in women compared with men. For example, women have a lower disease prevalence, more atypical symptoms, different cardiac risk factor profiles, and less anatomically obstructive CAD. Data from the Women’s Ischemia Syndrome Evaluation (WISE) study implicated adverse coronary reactivity, microvascular dysfunction, and plaque microembolization as contributing factors.
to a female-specific myocardial ischemia pathophysiology. Moreover, several factors such as lower exercise tolerance, lower ECG voltage, smaller heart size, and breast attenuation artifacts make noninvasive testing in women particularly challenging. The Clinical Evaluation of Magnetic Resonance Imaging in Coronary Heart Disease (CE-MARC) study was the largest prospective evaluation of multiparametric cardiovascular magnetic resonance (CMR) and single-photon emission computed tomography (SPECT) in patients with suspected CAD. A rigorous study design avoided referral bias by mandating that all patients undergo the reference test (coronary angiography) independently of the CMR or SPECT result.

This predefined substudy of CE-MARC compared the sex-specific diagnostic accuracy of multiparametric CMR (rest and stress perfusion, left ventricular [LV] function, coronary MR angiography, and late gadolinium enhancement) with SPECT (rest and stress perfusion, LV function). Additional analyses compared the perfusion-only components of CMR and SPECT and assessed the effects of factors thought to reduce their accuracy in women, namely small heart size, disease pattern, and breast size. The overall aim was to increase the evidence base for appropriate noninvasive imaging test selection in women with suspected CAD.

Methods

Patients

CE-MARC was a prospective study of 752 consecutive patients with suspected angina. Between March 2006 and August 2009, patients were screened and enrolled if they had suspected angina and at least 1 cardiovascular risk factor. All patients were scheduled to undergo SPECT and CMR (in randomized order), followed by x-ray coronary angiography within 4 weeks regardless of the physician’s chosen clinical pathway. Exclusion criteria were as previously published. The study was approved by the local ethics committee and complied with the Declaration of Helsinki (2000). Patients provided written informed consent.

Procedures

The order of CMR and SPECT was randomized by an automated service using stratified permuted blocks to ensure that groups were balanced for age and sex. SPECT, CMR, and x-ray angiogram results were reported in consensus by masked paired readers with >10 years of relevant experience. Arbitration could be sought from a third independent reader with >10 years of experience in their modalities. If there was lack of consensus, arbitration could be sought from a third independent reader with >10 years of relevant experience.

Table 1. Criteria for a Positive CMR

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Method</th>
<th>Positive Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>RWMA</td>
<td>Wall motion in each segment (17-segment model) was visually graded on poststress cine imaging (0=normal, 1=mild to moderate hypokinesis, 2=severe hypokinesis, 3=akinesis, 4=dyskinesis)</td>
<td>Wall motion score ≥1 in ≥2 adjacent segments or score ≥2 in ≥1 segments</td>
</tr>
<tr>
<td>Ischemia</td>
<td>Perfusion in each segment (17-segment model)* was visually graded at rest and then stress (0=normal, 1=equivocal, 2=subendocardial defect, 3=transmural defect, 4=transmural defect and wall thinned)</td>
<td>Decrease in perfusion score ≥2 between rest and stress in any segment or ≥1 in each of 2 adjacent segments†</td>
</tr>
<tr>
<td>Stenosis</td>
<td>Percentage of coronary artery luminal narrowing visually assessed on coronary magnetic resonance angiography</td>
<td>≥70% Stenosis or ≥50% left main stem stenosis</td>
</tr>
<tr>
<td>Infarction</td>
<td>LGE images were visually assessed for hyperenhancement in each segment (17-segment model; 0=None, 1=1%–25%, 2=26%–50%, 3=51%–75%, 4=&gt;75%)</td>
<td>Any score ≥1 in a pattern consistent with myocardial infarction</td>
</tr>
</tbody>
</table>

CMR indicates cardiovascular magnetic resonance; LGE, late gadolinium enhancement; and RWMA, regional wall motion abnormality.

*17-segment model excluding apical cap.
†With the exception of change between normal and equivocal, which was coded as normal.
Table 2. Criteria for a Positive SPECT

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Method</th>
<th>Positive Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reversible or fixed perfusion defect (visual</td>
<td>Perfusion in each segment (17-segment model) was visually graded at</td>
<td>Reversible defect is a decrease in perfusion score between rest and stress ≥2 in</td>
</tr>
<tr>
<td>assessment)</td>
<td>rest and stress (0=normal, 1=mildly reduced, 2=moderately reduced,</td>
<td>any segment or ≥1 in each of 2 adjacent segments*; fixed defect is any fixed score</td>
</tr>
<tr>
<td></td>
<td>3=severely reduced, 4=absent uptake)</td>
<td>≥1</td>
</tr>
<tr>
<td>Reversible or fixed perfusion defect</td>
<td>Using QPS software,† perfusion in each segment (20-segment model) was</td>
<td>SSS ≥4 or SDS &gt;0‡</td>
</tr>
<tr>
<td>(semiautomated assessment)</td>
<td>scored at stress and rest (0=normal, 1=mildly reduced, 2=moderately</td>
<td></td>
</tr>
<tr>
<td></td>
<td>reduced, 3=severely reduced uptake, 4=absent uptake); segmental scores</td>
<td></td>
</tr>
<tr>
<td></td>
<td>were summed to give SSS and SDS (SSS minus SRS)</td>
<td></td>
</tr>
<tr>
<td>RWMA</td>
<td>Wall motion in each segment (17-segment model) was scored after stress</td>
<td>Wall motion score ≥1 in ≥2 adjacent segments or score ≥2 in ≥1 segments</td>
</tr>
<tr>
<td></td>
<td>(0=normal, 1=mild-moderate hypokinesis, 2=severe hypokinesis, 3=</td>
<td></td>
</tr>
<tr>
<td></td>
<td>akinesis, 4=dyskinesis)</td>
<td></td>
</tr>
<tr>
<td>Ancillary findings</td>
<td>Transient ischemic dilatation</td>
<td>Yes (ratio &gt;1.15)</td>
</tr>
<tr>
<td></td>
<td>RV myocardial uptake at stress</td>
<td>Increased</td>
</tr>
</tbody>
</table>

RV indicates right ventricular; RWMA, regional wall motion abnormality; SDS, summed difference score; SPECT, single-photon emission computed tomography; SRS, summed rest score; and SSS, summed stress score.

*With the exception of change between normal and mild, which was coded as normal.
†Quantitative Perfusion SPECT software, Cedars-Sinai Medical Center.
‡Quantitative analysis was only used as an adjunct to, not as a substitute for, visual analysis (overread).

Statistical Analysis

Sensitivity, specificity, positive predictive value, and negative predictive value of SPECT and multiparametric CMR were determined with x-ray angiography used as the reference standard. Corresponding 95% confidence intervals were calculated with the Wilson score method. To compare a single test performance between the male and female groups, sensitivity, specificity, and predictive values were compared by use of Pearson χ² tests. To compare tests head to head in a sex group, sensitivity and specificity values were compared by use of the McNemar test, and predictive values were compared by use of the generalized score statistic.
Perfusion-Only Comparison

To permit direct comparison of perfusion-only CMR and perfusion-only SPECT components for the detection of ischemia using receiver-operating characteristic analysis, summed stress scores from visual assessment (17-segment model excluding apical cap) were calculated for both techniques by summing segmental perfusion scores at stress (excluding those with absent uptake; Tables 1 and 2). Receiver-operating characteristic analyses were used to compare the diagnostic performance (area under the curve [AUC]) of perfusion CMR and perfusion SPECT as either independent curves (for a single method in discrete populations) or paired curves (for the 2 methods in a single population of patients) as appropriate.14 To evaluate the effects of disease pattern, the above analyses were repeated in single-vessel disease and multivessel disease (MVD; ie, 2- to 3-vessel disease) subgroups. For further evaluation, the sensitivity and specificity of perfusion CMR and perfusion SPECT were compared across LV mass tertiles and, in women, on either side of the median bra cup size.

All statistical analysis was undertaken by the Clinical Trials Research Unit (University of Leeds, Leeds, UK) at a 2-sided 5% significance level (SAS 9.2, SAS Institute; Cary, NC).

Results

Study Population

A total of 235 women and 393 men had analyzable results for all 3 investigations, which equated to 83.6% and 83.4%, respectively, of those recruited into the main CE-MARC study (Figure 1). Table 3 summarizes the patient characteristics and their anginal symptoms.15 The prevalence of CAD was significantly lower in women (overall, 23%; 1-vessel disease, 15%; 2-vessel disease, 6%; 3-vessel disease, 2%) than in men (overall, 50%; 1-vessel disease, 24%; 2-vessel disease, 17%; 3-vessel disease, 8%), and women had significantly less MVD than men (P<0.0001).

Detection of CAD

The overall sensitivity of multiparametric CMR to detect significant CAD in the female and male groups was similar (women, 88.7% versus men, 85.6%; P=0.57), as was the specificity (women, 83.5% versus men, 82.8%; P=0.86; Table 4). However, for SPECT, the sensitivity was significantly worse in women compared with men (women, 50.9% versus men, 70.8%; P=0.007), but the specificity was similar (women, 84.1% versus men, 81.3%; P=0.48). For both the female and male groups, sensitivity was significantly higher with multiparametric CMR than SPECT (both P<0.0001), but specificity was similar (P=0.77 for men; P=1.00 for women). Positive and negative predictive values are also shown in Table 4.

On receiver-operating characteristic analysis, perfusion CMR outperformed perfusion SPECT in both the female (AUC, 0.90 versus 0.67; P<0.0001) and male (0.89 versus 0.74; P<0.0001) groups (Figure 2). There was no significant sex discrepancy for the diagnostic accuracy of perfusion CMR in women versus men (AUC: women, 0.90 versus men, 0.89; P=1.00), but for perfusion SPECT, the diagnostic accuracy was worse in women (AUC: women, 0.67 versus men, 0.74; P<0.0001; Figure 2).

Influence of Pattern of Disease

Multiparametric CMR had a greater sensitivity than SPECT to detect single-vessel disease and MVD in both men and women (Table 5). Similarly, on receiver-operating characteristic analysis, perfusion CMR outperformed perfusion SPECT in both single-vessel disease and MVD in both sexes (Figure 3). In single-vessel disease, the diagnostic accuracy was similar in men and women for both perfusion CMR (AUC: men, 0.86 versus women, 0.89; P=0.42) and perfusion SPECT (AUC: men, 0.72 versus women, 0.71; P=0.94). However, in MVD, although perfusion CMR maintained a similar overall diagnostic accuracy between the sexes (AUC: men, 0.92 versus female, 0.89; P=0.64), there was a significantly lower diagnostic accuracy in women with perfusion SPECT (AUC: men, 0.80 versus women, 0.64; P=0.045).

Influence of LV Size

Male hearts were on average 35% larger than female hearts on the basis of CMR-derived LV mass measurements (107±23 versus 79±17 g; P<0.0001). For perfusion CMR, sensitivities...
were similar across all tertiles of LV mass (<84 g, 77.8% versus 84–105 g, 70.8% versus >105 g, 81.8%; \( P = 0.20 \)). For perfusion SPECT, sensitivity significantly differed with LV mass. The poorest performance was in the lowest tertile (<84 g, 50.9% versus 84–105 g, 65.6% versus >105 g, 77.0%; \( P = 0.004 \)). Specificities were similar across all tertiles of LV mass for both perfusion CMR and perfusion SPECT (\( P = 0.17 \) and \( P = 0.19 \), respectively).

**Influence of Bra Cup Size**

The distribution of bra cup size among women was as follows: A/B, \( n=69 \); C, \( n=55 \); D, \( n=46 \); and larger than D, \( n=45 \). The median bra cup size was C. Because of patient preference, bra size data were not available for 20 women. For perfusion CMR, the sensitivity was similar on either side of the median bra cup size (C or smaller, 84.4% versus larger than C, 81.0%; \( P = 0.75 \)), as was the specificity (C or smaller, 86.5% versus larger than C, 91.2%; \( P = 0.62 \)). For perfusion SPECT, sensitivity (C or smaller, 50.0% versus larger than C, 55.0%; \( P = 0.73 \)) and specificity (C or smaller, 83.5% versus larger than C, 92.6%; \( P = 0.078 \)) were also similar on either side of the median.

**Performance of Individual CMR and SPECT Components**

Table 6 summarizes the sensitivity and specificity of individual CMR and SPECT study components in men and women. These values are strongly influenced by CAD prevalence, which differs between men and women.

<table>
<thead>
<tr>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>PPV, %</th>
<th>NPV, %</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>PPV, %</th>
<th>NPV, %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Women (n=235)</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>50.9 (37.9–63.9)</td>
<td>84.1 (78.1–88.7)</td>
<td>48.2 (35.7–61.0)</td>
<td>85.5 (79.6–89.9)</td>
<td>88.7 (77.4–94.7)</td>
<td>83.5 (77.4–88.2)</td>
<td>61.0 (49.9–71.2)</td>
<td>96.2 (92.0–98.2)</td>
</tr>
<tr>
<td><strong>Men (n=393)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>70.8 (64.0–76.7)</td>
<td>81.3 (75.3–86.1)</td>
<td>78.8 (72.2–84.3)</td>
<td>73.9 (67.6–79.2)</td>
<td>85.6 (80.0–89.9)</td>
<td>82.8 (77.0–87.4)</td>
<td>83.1 (77.3–87.6)</td>
<td>85.4 (79.7–89.7)</td>
</tr>
</tbody>
</table>

When sensitivity and specificity of CMR and SPECT were compared in the same patients, the sample size is the \( n \) value given. When the sensitivity and specificity of 1 test in 1 sex are compared with those in the other sex, the sample size is the sum of the relevant \( n \) values. Significant CAD was defined as \( \geq 70\% \) luminal stenosis of a first-order coronary artery or left main stem stenosis \( \geq 50\% \) by quantitative coronary angiography. Values in parentheses are 95% confidence intervals. CAD indicates coronary artery disease; CMR, cardiovascular magnetic resonance; MVD, multivessel disease; NPV, negative predictive value; PPV, positive predictive value; SPECT, single-photon emission computed tomography; and SVD, single-vessel disease.

**Figure 2.** Receiver-operating characteristic (ROC) curves divided by sex. ROC curves generated with summed stress scores (\( n=393 \) men, 235 women). The diagnostic accuracy of stress perfusion cardiovascular magnetic resonance (CMR) was significantly greater than that of single-photon emission computed tomography (SPECT) in both sexes. For CMR, there was no significant difference in the diagnostic accuracy between men and women; with SPECT, there was a sex discrepancy with significantly worse performance in women. AUC indicates area under the curve.
This study represents the largest prospective series of women evaluated by multiparametric or perfusion CMR protocols. The 4 major findings are the following: (1) Multiparametric CMR has significantly greater sensitivity, negative predictive value, and positive predictive value compared with SPECT in women (and men) but similar specificity; (2) there is no sex discrepancy in the overall diagnostic performance of multiparametric or perfusion CMR; (3) both SPECT and the perfusion-only component of SPECT have a significantly inferior diagnostic performance in women compared with men, particularly in MVD; and (4) the lower diagnostic accuracy of perfusion SPECT in women appears to be related to smaller heart size rather than breast attenuation.

Several previous SPECT studies have also shown a significant sex discrepancy in diagnostic performance. For example, Hansen et al.10 (n=283; 107 women) found a lower diagnostic accuracy in women with 201TI SPECT (AUC: women, 0.82 versus men, 0.93; P<0.05), and Iskrandian et al.16 (n=1216; 489 women) found a significantly lower sensitivity in women (women, 84% versus men, 94%; P<0.05). Technetium isotopes improve the diagnostic accuracy of SPECT and are less prone to attenuation artifacts, but even when using 99mTc-sestamibi, Santana-Boado et al.17 (n=163; 63 women) found a lower sensitivity in women than men (women, 85% versus men, 93%; P=0.01). Finally, a systematic review of several SPECT studies with either isotope by the US Agency for Health Care Research and Quality confirmed these findings with a significantly lower mean weighted sensitivity in women.

### Discussion

This study represents the largest prospective series of women evaluated by multiparametric or perfusion CMR protocols. The 4 major findings are the following: (1) Multiparametric CMR has significantly greater sensitivity, negative predictive value, and positive predictive value compared with SPECT in women (and men) but similar specificity; (2) there is no sex discrepancy in the overall diagnostic performance of multiparametric or perfusion CMR; (3) both SPECT and the perfusion-only component of SPECT have a significantly inferior diagnostic performance in women compared with men, particularly in MVD; and (4) the lower diagnostic accuracy of perfusion SPECT in women appears to be related to smaller heart size rather than breast attenuation.

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### Table 5. Sensitivity of Multicomponent CMR and SPECT in Single-Vessel and Multivessel CAD

<table>
<thead>
<tr>
<th>Sex</th>
<th>SPECT (n = 248), %*</th>
<th>Multicomponent CMR (n=248), %*</th>
</tr>
</thead>
<tbody>
<tr>
<td>SVD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>48.6 (33.0–64.4)</td>
<td>85.7 (70.6–93.7)</td>
</tr>
<tr>
<td>Male</td>
<td>65.6 (55.7–74.4)</td>
<td>77.1 (67.7–84.4)</td>
</tr>
<tr>
<td>MVD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>55.6 (33.7–75.4)</td>
<td>94.4 (74.2–99.0)</td>
</tr>
<tr>
<td>Male</td>
<td>75.8 (66.5–83.1)</td>
<td>93.9 (87.4–97.2)</td>
</tr>
</tbody>
</table>

Values in parentheses are 95% confidence intervals. CAD indicates coronary artery disease; CMR, cardiovascular magnetic resonance; MVD, multivessel disease; SPECT, single-photon emission computed tomography; and SVD, single-vessel disease.

*All patients in this table had both SPECT and CMR results and had significant CAD. Therefore, a total of 248 patients are included in this table. CAD was defined as ≥70% luminal stenosis of a first-order coronary artery or left main stem stenosis ≥50% by quantitative coronary angiography.

### Figure 3.

Receiver-operating characteristic (ROC) curves divided by coronary artery disease distribution and sex. ROC curves generated with summed stress scores (n=393 men, 235 women). The diagnostic accuracy of stress perfusion cardiovascular magnetic resonance (CMR) was significantly greater than that of single-photon emission computed tomography (SPECT) in both single-vessel disease (SVD) and multivessel disease (MVD) for both sexes (all P<0.05). In SVD (A and B), the diagnostic accuracy was similar between men and women for both stress perfusion CMR (area under the curve [AUC]: men, 0.86 vs women, 0.89; P=0.42) and SPECT (AUC: men, 0.72 vs women, 0.71; P=0.94). In MVD (C and D), stress perfusion CMR maintained a similar diagnostic accuracy between men and women (AUC: men, 0.92 vs women, 0.90; P=0.94), but SPECT had a significantly lower diagnostic accuracy in women (AUC: men, 0.80 vs women, 0.64; P=0.045).
women than men (women, 86% versus men, 93%; P=0.012) but equal specificity (57% for both sexes). Conversely, however, a recent bivariate meta-analysis of 26 SPECT studies did not find a significant sex discrepancy in diagnostic accuracy; therefore, this remains an area of controversy.

We attempted to explain the potential sex discrepancies seen with SPECT but not CMR by considering the influence of factors such as breast size, heart size, and the distribution of CAD. Despite the perceived problems of breast attenuation with perfusion SPECT, this did not appear to be a significant limiting issue because there was no adverse trend in diagnostic accuracy across bra cup sizes (Figure 4). This may reflect the use of a gated SPECT protocol in CE-MARC, the use of highly experienced interpreters, and the fact that the severity of breast artifacts is not always proportional to breast size; position and density of breast tissue, which can alter with age, are also contributing factors. However, our results suggest that small heart size and MVD are 2 factors that can lead to a poorer diagnostic accuracy with CMR compared with women. In contrast, CMR appears relatively immune to these factors (Figure 5). These findings may be the result of the combined challenge to spatial resolution of balanced ischemia in MVD and the smaller female heart.30,31 The greater spatial resolution of CMR may be sufficient to overcome the difference in heart size between the sexes; therefore, even in the context of MVD, there was no sex discrepancy in its diagnostic accuracy.

These findings are supported by those of Hansen et al.,32 who also found a significant difference in the diagnostic accuracy of SPECT between patients grouped into large and small LV categories (AUC, 0.94 versus 0.73; P<0.01), as well as a significant sex discrepancy in overall diagnostic accuracy (AUC: women, 0.83 versus men, 0.93; P<0.05). Furthermore, when men and women were compared within the same category of LV size, there was no longer a sex discrepancy in diagnostic accuracy, confirming the significance of smaller cardiac size in women as a significant challenge to the limited spatial resolution of SPECT.30 Balanced ischemia poses an additional challenge to spatial resolution in myocardial perfusion imaging, and Chung et al33 found that the sensitivity for identifying perfusion defects in all 3 territories in patients with 3-vessel disease (n=78) was significantly higher for CMR than for SPECT (84.6% versus 55.1%; P<0.001). Therefore, with these factors taken together, it is not surprising that we found that the greatest sex discrepancy in diagnostic accuracy occurred in the assessment of MVD with SPECT (AUC: men, 0.80 versus women, 0.64; P=0.045; Figure 3). In contrast, with the higher spatial resolution of CMR, the diagnostic accuracy in MVD was superior to that of SPECT in both sexes, and there was no significant sex discrepancy (AUC: men, 0.92 versus women, 0.89; P=0.64; Figure 3). The recent Magnetic Resonance Imaging for Myocardial Perfusion Assessment in Coronary Artery Disease Trial II (MR-IMPACT II) study also found a higher diagnostic accuracy for perfusion CMR compared with SPECT in patients with MVD (AUC: 0.80 versus 0.72; P=0.003), but this was not subdivided further into sex-specific results.21

The diagnostic performance of CMR in women in our study was similar to that found in 2 smaller studies in women by Klem et al22 (sensitivity, 84%; specificity, 88%) and Merkle et al23 (sensitivity, 91%; specificity, 91%). These concordant results with different CMR stress perfusion acquisition protocols show the inherent accuracy of this technique in women. However, neither of these previous studies offered a direct comparison with SPECT. Furthermore, previous studies comparing CMR and SPECT in mixed-sex populations have been limited by referral bias or relatively small numbers or have included only a small proportion of women. For example, MR-IMPACT had only 45 patients in its direct comparison arm (at the optimal contrast dose), of which only 13 were women.24 Although the recent MR-IMPACT II study evaluated 123 women and 342 men with CMR, SPECT, and X-ray angiography, 43 patients were excluded because of inadequate image quality, and SPECT studies were gated in only ≈50%; therefore, the patient population available for sex-specific results was comparatively small.21 Despite this limitation, the secondary end points of MR-IMPACT II corroborate our findings, with a higher diagnostic accuracy for perfusion CMR compared with SPECT in both men (AUC, 0.75 versus 0.66; P=0.004) and women (AUC, 0.76 versus 0.63; P=0.033) using a quantitative coronary angiography threshold of ≥50% diameter stenosis.21

The diagnostic performance of SPECT in this substudy and in the main CE-MARC trial is lower than in previous studies (sensitivity range, 63%–93%; specificity range, 10%–90%), although the data lie within the published 95% confidence interval.25,26 The reason is that CE-MARC was a prospective study, deliberately designed to minimize any selection (referral) bias. In contrast, the trials that contribute to the majority of prior SPECT data are all subject to either a pretest selection bias (only patients warranting coronary angiography enrolled) or a posttest selection bias (only positive SPECT cases referred for coronary angiography), leading to overestimation of the true diagnostic accuracy. Prior investigators have proposed bayesian methods to correct for both pretest and posttest referral bias.27–29 When these methods were used to correct the apparent

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**Table 6. Diagnostic Accuracy of Individual CMR and SPECT Components in Men and Women for the Detection of CAD**

<table>
<thead>
<tr>
<th></th>
<th>Sex (n)</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CMR</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV function</td>
<td>Male (393)</td>
<td>49.2 (42.3–56.2)</td>
<td>92.9 (88.5–95.7)</td>
</tr>
<tr>
<td></td>
<td>Female (235)</td>
<td>39.6 (27.6–53.1)</td>
<td>95.1 (90.9–97.4)</td>
</tr>
<tr>
<td>Perfusion</td>
<td>Male (388)</td>
<td>75.4 (68.8–81.0)</td>
<td>92.9 (88.4–95.7)</td>
</tr>
<tr>
<td></td>
<td>Female (229)</td>
<td>81.1 (68.6–89.4)</td>
<td>89.2 (83.8–93.0)</td>
</tr>
<tr>
<td>LGE imaging</td>
<td>Male (392)</td>
<td>41.2 (34.5–48.3)</td>
<td>94.4 (90.3–96.9)</td>
</tr>
<tr>
<td></td>
<td>Female (235)</td>
<td>34.0 (22.7–47.4)</td>
<td>97.8 (94.5–99.1)</td>
</tr>
<tr>
<td>MR angiography</td>
<td>Male (349)</td>
<td>72.3 (65.2–78.4)</td>
<td>90.3 (85.1–93.9)</td>
</tr>
<tr>
<td></td>
<td>Female (208)</td>
<td>66.7 (52.1–78.6)</td>
<td>87.7 (81.8–91.9)</td>
</tr>
<tr>
<td><strong>SPECT</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV function</td>
<td>Male (384)</td>
<td>18.8 (13.9–25.0)</td>
<td>93.8 (89.4–96.4)</td>
</tr>
<tr>
<td></td>
<td>Female (227)</td>
<td>11.8 (5.5–23.4)</td>
<td>98.9 (96.0–99.7)</td>
</tr>
<tr>
<td>Perfusion</td>
<td>Male (392)</td>
<td>74.7 (68.2–80.3)</td>
<td>64.6 (57.8–71.0)</td>
</tr>
<tr>
<td></td>
<td>Female (235)</td>
<td>54.7 (41.5–76.3)</td>
<td>79.1 (72.6–84.1)</td>
</tr>
</tbody>
</table>

Values in parentheses are 95% confidence intervals. CAD was defined as ≥70% luminal stenosis of a first-order coronary artery or left main stem stenosis ≥50% by quantitative coronary angiography. CAD indicates coronary artery disease; CMR, cardiovascular magnetic resonance; LGE, late gadolinium enhancement; LV, left ventricular; MR, magnetic resonance; and SPECT, single-photon emission computed tomography.

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**Figure 3.** The diagnostic accuracy of perfusion CMR compared with SPECT in patients with MVD (AUC: 0.80 versus 0.72; P=0.003), but this was not subdivided further into sex-specific results.21
sensitivity (98%) and specificity (13%) for SPECT in a cohort of 1853 patients, the adjusted values were 65% and 67%, respectively, which are similar to (in fact inferior to) the CE-MARC values for SPECT (sensitivity, 67%; specificity, 83%). In the same study, Miller et al. found that the corrected sensitivity and specificity values for SPECT in the female group (n=477) were 47% and 78%, respectively, almost identical to our values of 51% and 84%, which vindicates the robustness of the prospective study design of the CE-MARC trial.

The lower prevalence of CAD and higher incidence of atypical angina compared with previous studies relate to its prospective, pragmatic real-world design. The overall prevalence of CAD in the main CE-MARC study (39%) and in this substudy (23% in women, 50% in men) is actually far more reflective of a typical hospital outpatient department than the artificially higher prevalence seen in the majority of previous noninvasive imaging studies subject to referral bias. For example, disease prevalence in the aforementioned MR-IMPACT study was 77% and 49% in MR-IMPACT II. Our results are therefore likely to be more generalizable to daily clinical practice and the typical patients seen in cardiology clinics.

Despite the recognized lower diagnostic accuracy in women, the American Heart Association recommends the exercise treadmill test as the first-line investigation in women with a low or intermediate pretest CAD risk, a recommendation that has been vindicated by 2-year outcomes and health-economic evaluation in the recent What is the Optimal Method for Ischemia Evaluation in Women (WOMEN) study. However, a UK National Institute for Health and Clinical Excellence technology appraisal recommended SPECT as a first-line investigation for women with suspected CAD. Our results suggest that in women who require a noninvasive imaging test because of an equivocal exercise treadmill test result, an uninterpretable ECG, or other factors, CMR should be considered over conventional SPECT imaging because of its superior diagnostic performance and lack of ionizing radiation exposure.

Finally, an in-depth discussion of the relative contribution of individual multiparametric CMR protocol components (Table 6) is beyond the scope of this predefined sex substudy. One needs to consider that sensitivity and specificity values are strongly influenced by CAD prevalence, which differs between men and women (50% and 23%, respectively, in this study). The primary analyses of CE-MARC and this sex substudy have included analyses directly comparing the perfusion-only component of CMR with perfusion SPECT. Arguably, MR coronary angiography does not always form part of clinical multiparametric CMR protocols; therefore, its inclusion may be considered to offer CMR an unfair advantage over SPECT, particularly for the detection of angiographically significant CAD. However, secondary analyses performed in the main CE-MARC study found

![Case example 1](http://circ.ahajournals.org/)

Figure 4. Case example 1: A 76-year-old woman had a tight left anterior descending artery stenosis on x-ray coronary angiography (arrow, A). Left ventricular mass (99.7 g) was within the middle tertile for our population. Despite an above-average breast size (bra cup size F) as seen on survey cardiovascular magnetic resonance (CMR) images (arrows, B), both stress perfusion CMR (arrows, C) and single-photon emission computed tomography (SPECT; arrows, D) identified inducible ischemia in the septum and anterior wall concordant with the angiographic findings (only midventricular slices shown). This case illustrates that the perceived problem of breast attenuation with SPECT may not be the limiting issue.

![Case example 2](http://circ.ahajournals.org/)

Figure 5. Case example 2: A 74-year-old woman with previous percutaneous coronary intervention to the left anterior descending artery had diffuse disease in the left circumflex artery with an occluded obtuse marginal branch on x-ray angiography (arrow, A). Her breast size was average (bra cup size C) as seen on cardiovascular magnetic resonance (CMR) survey images (arrows, B). Left ventricular mass (65.4 g) was within the lowest tertile for our population. Stress perfusion CMR identified subtle inducible ischemia in the inferolateral wall (arrows, C) concordant with the angiogram. However, single-photon emission computed tomography (SPECT) did not identify any significant inducible ischemia (D). This case illustrates the difficulties of imaging subjects with small hearts (mostly women) with both perfusion techniques. However, although subtler than in case 1 (Figure 4), CMR is still able to identify inducible ischemia as a result of its greater spatial resolution.
that omitting MR coronary angiography did not impair overall diagnostic accuracy but actually made the positive predictive value of CMR statistically superior to that of SPECT as a result of a reduction in false-positive CMR results.\textsuperscript{11}

**Study Limitations**

Use of quantitative coronary angiography as opposed to fractional flow reserve as the study end point is a limitation common to the majority of imaging studies before the Fractional Flow Reserve Versus Angiography for Multivessel Evaluation (FAME) study, which was published after CE-MARC had recruited.\textsuperscript{33} Although we acknowledge our single-center design as a potential limitation, it also had the advantage of ensuring consistency in both imaging modality protocols. Inevitably, both CMR and SPECT have undergone technological improvements since CE-MARC was designed and reported. Specifically, we did not use attenuation correction for SPECT because this was not the technical standard in most nuclear institutions worldwide, including ours, at the start of recruitment in 2006. In addition, CMR technology has improved since 2006, with evidence of superior diagnostic accuracy with 3.0-T CMR systems and high-resolution image acquisition techniques.\textsuperscript{34,35}

We recognize that self-reported bra cup size is an imperfect measure of breast size, but it is nonetheless a useful pragmatic marker of relative breast volume, which has often been used in clinical studies, including those relating to the accuracy of SPECT in women.\textsuperscript{36} Furthermore, using bra cup size puts the analysis in the context of real-world clinical practice where more sophisticated measures of breast volume are not easily available during the assessment of patients for appropriate diagnostic imaging.

Finally, it should be acknowledged that because of the multiple statistical comparisons within this study, the results with P values close to the 5\% level of significance might be attributable to chance, and these findings should be validated in further studies.

**Conclusions**

This CE-MARC substudy demonstrates that CMR has a superior diagnostic accuracy compared with SPECT in both men and women. Whereas the diagnostic performance of SPECT is significantly worse in women, CMR performs equally well in both sexes. The major challenge for SPECT in women appears to be the smaller heart size rather than breast attenuation artifacts. CMR may be less susceptible to these effects because of its inherent higher spatial resolution, even in the setting of multivessel CAD. These findings support the wider adoption of CMR for the diagnosis and management of CAD in women, particularly in view of the growing concern over the cancer risk associated with medical source ionizing radiation.

**Acknowledgments**

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**Disclosures**

None.

**References**


CLINICAL PERSPECTIVE

The primary outcome analysis of the Clinical Evaluation of Magnetic Resonance Imaging in Coronary Heart Disease (CE-MARC) trial has been described as a landmark study and thus may change the way coronary artery disease is investigated and may be incorporated into future clinical guidelines. These findings are relevant and of interest to all cardiologists and general physicians who are involved in the management of patients with coronary artery disease. However, it is well recognized that there are important sex-specific issues related to the diagnosis and management of coronary artery disease and that women are underrepresented in clinical trials. Despite the widespread use of single-photon emission computed tomography in women with suspected coronary artery disease, there is increasing concern about its diagnostic accuracy, perceived wisdom being that this relates in part to breast attenuation artifacts. This sex-specific analysis of the CE-MARC trial represents the largest prospective series of women evaluated by cardiovascular magnetic resonance compared with single-photon emission computed tomography, all with invasive coronary angiography. In addition to demonstrating superior diagnostic accuracy of cardiovascular magnetic resonance over single-photon emission computed tomography in women, we have provided insight into the reasons. It appears that the diagnostic limitation for single-photon emission computed tomography relates more to its inherent lower spatial resolution than to breast attenuation, as is the current belief.
Comparison of Cardiovascular Magnetic Resonance and Single-Photon Emission Computed Tomography in Women With Suspected Coronary Artery Disease From the Clinical Evaluation of Magnetic Resonance Imaging in Coronary Heart Disease (CE-MARC) Trial

John P. Greenwood, Manish Motwani, Neil Maredia, Julia M. Brown, Colin C. Everett, Jane Nixon, Petra Bijsterveld, Catherine J. Dickinson, Stephen G. Ball and Sven Plein

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