Clinical research

Impact of gender on risk stratification by exercise and dobutamine stress echocardiography: long-term mortality in 4234 women and 6898 men

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Aims

Prior research is limited with regard to the diagnostic and prognostic accuracy of commonplace cardiac imaging modalities in women. The aim of this study was to examine 5-year mortality in 4234 women and 6898 men undergoing exercise or dobutamine stress echocardiography at three hospitals.

Methods and results

Univariable and multivariable Cox proportional hazards models were used to estimate time to cardiac death in this multi-centre, observational registry. Of the 11 132 patients, women had a greater frequency of cardiac risk factors ($P < 0.0001$). However, men more often had a history of coronary disease including a greater frequency of echocardiographic wall motion abnormalities ($P < 0.0001$). During 5 years of follow-up, 103 women and 226 men died from ischaemic heart disease ($P < 0.0001$). Echocardiographic estimates of left ventricular function ($P < 0.0001$) and the extent of ischaemic wall motion abnormalities ($P < 0.0001$) were highly predictive of cardiac death. Risk-adjusted 5-year survival was 99.4, 97.6, and 95% for exercising women with no, single, and multi-vessel ischaemia ($P < 0.0001$). For women undergoing dobutamine stress, 5-year survival was 95, 89, and 86.6% for those with 0, 1, and 2–3 vessel ischaemia ($P < 0.0001$). Exercising men had a 2.0-fold higher risk at every level of worsening ischaemia ($P < 0.0001$). Significantly worsening cardiac survival was noted for the 1568 men undergoing dobutamine stress echocardiography ($P < 0.0001$); no ischaemia was associated with 92% 5-year survival as compared with death rates of ≥16% for men with ischaemia on dobutamine stress echocardiography ($P < 0.0001$).

Conclusion

Echocardiographic measures of inducible wall motion abnormalities and global and regional left ventricular function are highly predictive of long-term outcome for women and men alike.

KEYWORDS

Prognosis; Gender; Echocardiography; Ventricular function; Exercise testing

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Introduction

Cardiovascular disease is the leading cause of death for women in western society. Despite advances in the diagnosis and management of coronary artery disease, nearly 250,000 female lives are claimed each year with a lifetime risk of cardiovascular disease of 25% for a 40-year-old woman. The marked reduction in case fatality rates for cardiovascular disease noted for men (35–50% reduction) has not been realized to the same extent for women. Accurate non-invasive assessment may be the first step towards improving the outcome for women at risk. Previous research using non-invasive cardiac testing has noted limitations when applied to female subsets of the population. Several prior reports, examining near-term prognosis (on average 3 years) and using combined endpoints, have revealed promising results with regard to the prognostic value of stress echocardiography in women. Despite this evidence in smaller series, evidence is lacking as to its predictive value for cardiac mortality. The purpose of the current project was to evaluate the prognostic value of exercise and dobutamine stress echocardiography in a large observational cohort of symptomatic women and men consecutively tested at three hospitals.

Methods

Patient entry criteria

This series included a total of 11,132 unselected consecutively tested patients with known or suspected coronary artery disease undergoing stress echocardiography. As this was a consecutive series, no referrals to stress echocardiography were excluded. Patients were enrolled at the following institutions: the Cleveland Clinic Foundation, University of Indiana, and Asheville Cardiology Associates (Asheville, NC). Portions of this patient series have previously been published. Informed consent was obtained from all patients, and patient follow-up approval was obtained by the institutional review boards.

Exercise testing procedures

Exercise testing was performed using the Bruce or modified Bruce protocol. Standards for the conductance of testing and termination of exercise were consistent with the current ACC/AHA guidelines for exercise testing. Generally, patients exercised until the point of volitional fatigue unless marked electrocardiographic abnormalities, haemodynamic instability, chronotropic incompetence, ventricular tachycardia or fibrillation, or disabling chest pain symptoms occurred. The Duke treadmill score was calculated using the following equation:

\[
\text{Duke treadmill score} = \text{exercise time} - (5 \times 5T \text{ segment changes}) - (4 \times \text{chest pain index})[\text{limiting: chest pain is the main reason for exercise discontinuation}] - (1 \text{ non-limiting}, 2 \text{-limiting})^{16,17}
\]

A low-risk Duke treadmill score was defined by a score ≥5, intermediate-risk scores ranged from ≥-11 to <4, and high-risk scores ≤-11.

Dobutamine stress testing

In patients who were unable to exercise, dobutamine was infused using a standard incremental dosing protocol from 5 to 40 μg/kg/min, during which time the patient remained under continuous clinical, electrocardiographic, and echocardiographic monitoring. Endpoints of the test included completion of the final stage, severe ischaemia (severe angina, >2 mm ST depression, extensive wall motion abnormalities), hypertension (systolic blood pressure >220 mmHg), hypotension (drop in systolic blood pressure of >20 mmHg), arrhythmias, or side effects intolerable to the patient. Atropine (1 mg iv) was used in patients who failed to attain 85% of age-predicted maximal heart rate at peak dose.

Echocardiographic procedures

Echocardiographic imaging acquisition protocols have been reported previously. However, in brief, the rest, stress, and immediate post-stress images were performed using standard equipment and imaging planes, ensuring that the same imaging planes were employed for each image. The detection of inducible changes with exercise was facilitated by digital image processing, but images were also stored on videotape. Interpretations were completed without knowledge of the patient’s clinical history, exercise test, or angiographic data. The results of the exercise echocardiogram were made available to the overseeing physician and influenced post-test management decisions.

Resting left ventricular function was assessed categorically as normal or abnormal, and further qualitative assessment was used to classify resting wall motion as showing normal, mild, moderate, or severely reduced function. In a qualitative assessment, we compared this estimation with catheterization-defined ejection fraction in 185 women and 646 men; mean catheterization ejection fractions were 58 ± 11, 45 ± 11, 39 ± 11, and 30 ± 10%, for normal, mildly, moderately, and severely depressed function (P < 0.0001), respectively, but did not differ by gender (P = 0.15).

We employed previously described standard criteria for interpreting the stress echocardiogram. Studies were considered abnormal if any wall motion abnormalities were noted on either the rest or immediate post-exercise images; with an exception—if an abnormality included either the basal inferior or septal wall, involvement of an adjacent abnormal segment was required to define an abnormality. Markers of infarction included documentation of akinesis or dyskinesis on the resting images. New or worsening wall motion abnormalities noted in the immediate post-exercise images were used to signify myocardial ischaemia. In order to define the extent of infarction or ischaemia, myocardial segments were combined into vascular territories including one, two, and three vascular territories. For the echocardiogram, the left anterior descending territory included the apex, anteroseptal, septal, and anterior walls. For the left circumflex, the lateral wall was used and for the right coronary artery, the inferior and basal septal walls were identified as the risk area. Finally, abnormalities noted on the posterior wall were attributed to either the circumflex or right coronary artery vascular territory; isolated posterior wall abnormalities were ascribed to the left circumflex vascular territory. Thus, the extent of ischaemia was defined for echocardiography using the number of vascular territories with new or worsening wall motion abnormalities, ranging from no to three vascular territories.
Follow-up procedures

To determine the occurrence of major cardiac events, medical records were reviewed, and contact with the patient’s primary care physician was undertaken in order to more clearly discern each patient’s outcome status. If these steps resulted in ambiguity, the patient or a family member was queried by telephone follow-up, which involved a scripted interview that was completed by an experienced research assistant or nurse. Following a thorough review of each patient’s current health status, the investigator at each site reviewed the occurrence of cardiovascular death or non-fatal myocardial infarction. All events were reviewed while blinded to the patient’s past medical history and echocardiographic results. The median follow-up time was 4.8 years (25th to 75th percentile 3.4–6.3 years). A total of 2.7% of patients was lost to follow-up but did not differ in their clinical history and stress testing results from those included in the survival analysis.

Data collection for hospitalization and clinical events

We collected data on major adverse events including death as well as hospitalization for acute myocardial infarction or coronary revascularization procedure. The date of each hospitalization was documented. Additionally, each patient’s medical record was queried for the date of any coronary revascularization procedure including percutaneous coronary interventions (PCIs) or coronary bypass graft (CABG) surgery. The use of and time to cardiac catheterization in the post-test time period was recorded for each patient. Although not available in all patients, significant coronary disease was defined as ≥70% stenosis, assessed visually. The number of vessels with ≥70% stenosis was used to define the number of vessels with disease at coronary angiography. Also, the occurrence and date of all-cause death was documented for each patient. For an event occurrence, confirmation of the occurrence and date were obtained from the patient’s medical record, death certificate, and/or referring physician. All events were confirmed by an experienced physician who was blinded to all clinical, exercise, and imaging data. A cardiac death was defined as having occurred within 24 h of an acute myocardial infarction, from an ischaemic cardiomyopathy, or following sudden cardiac death.

Statistical analysis

Continuous variables were expressed as mean and standard deviation, and compared by Student’s t-test or analysis of variance techniques. Categorical variables were recorded as frequency or percentiles, and compared by the χ² test. P < 0.05 was considered statistically significant.

Cox proportional hazards models

The primary endpoint for this analysis was time to cardiac death. Patients undergoing coronary revascularization procedures were followed but censored at the time of their procedure. Univariable and multivariable Cox proportional hazards models were used to assess time to cardiac death. For exercising patients, candidate variables included the Duke treadmill score, resting left ventricular function, the extent of echocardiographic ischaemia post-stress, and relevant clinical variables (age, gender, diabetes, and hypertension). Similarly, for dobutamine stress imaging, we evaluated the relationship of gender, age, diabetes, peak rate pressure product, resting left ventricular function, and ischaemia extent using Cox regression modelling techniques.

All death rates were derived from the Cox proportional hazards survival curves. Risk-adjusted models [including significant (i.e. univariable P < 0.05) historical and risk factor variables] were devised to control for underlying risk differences between women and men. Cox models were stratified by gender for the calculation of separate survival plots for exercise and dobutamine stress imaging.

To prevent model overfitting, we included one variable for every 10 clinical outcomes. Various regression diagnostics were performed including visual inspection of the survival curves, plotting of partial residuals over time, and inspection of the hazard ratios over time. The final multivariable model included all significant estimators of time to cardiac death with P < 0.20. From the Cox proportional hazards model, risk-adjusted rates of cardiac death were determined from the survival curves. In order to assess whether there was a differential prognostic value for ischaemia in women and men, a first-order test for interaction (gender by ischaemia extent) was used for both exercise and dobutamine stress imaging. From this interaction, a relative risk (95% confidence interval) for men vs. women by ischaemia extent was calculated. A stepwise Cox regression model was also applied in order to define independent significant predictors of cardiac mortality. The probability value for removal was P < 0.10. The incremental value of ischaemia extent was defined using a Δχ² that may be calculated as:

full multivariable model – (full model – ischaemia)

full multivariable model

= % contribution to estimating cardiac mortality.

In a post hoc calculation, the available statistical power was sufficient to detect differences in 5-year cardiac survival for women (β ≥ 0.90, two-tailed α = 0.05) and to detect a differential prognostic value for inducible ischaemia in women and men (β ≥ 0.90, two-tailed α = 0.05).

Overall and 90-day cardiac catheterization rates were calculated based upon univariable Cox proportional hazards model of time to the procedure.

Meta-analysis

Using prior published reports, we derived a 2 × 2 frequency table of cardiac death or myocardial infarction by low- and high-risk echocardiographic or single photon emission computed tomography (SPECT) scan results. We calculated a relative risk ratio (95% confidence interval) for each study as well as a summary ratio using a random effects model (www.meta-analysis.com, date accessed: 15 April 2004). A Forest plot was used to chart the relative risk ratio data.

Results

Clinical history (Table 1)

Women were, on average, older, with a greater frequency of cardiac risk factors. However, men more often had a history of coronary disease including a
greater frequency of prior myocardial infarction, and more often typical or atypical chest pain symptoms.

**Exercise testing results (Table 2)**

Women exercised, on average, for 5.6 min compared with 6.9 min for men \( (P < 0.0001) \). Exertional symptoms were common and reported in approximately one-third of patients. Men had a greater frequency of \( \geq 1.0 \) ST segment depression \( (\text{for men: } 28 \text{ vs. } 24\%, P < 0.0001) \). Interestingly, more men \( (56\%) \) had a low-risk Duke treadmill score, in part related to greater exercise ability compared with women \( (42\%, P < 0.0001) \).

**Echocardiographic results (Table 3)**

Based upon a qualitative estimate of left ventricular function, women were more likely to have a normal left ventricular ejection fraction \( (P < 0.0001) \); 91% of exercising and 73% of dobutamine stress women had normal ventricular function \( (P < 0.0001) \). For women undergoing an exercise test, 1 and 2–3 vessel ischaemia was recorded in 12 and 7%, and for men in 15 and 8% \( (P < 0.0001) \). For the 1183 women undergoing dobutamine stress imaging, only 6% had multi-vessel ischaemia compared with 10% of men \( (P < 0.0001) \).

**Cardiac catheterization results**

Overall catheterization rates were 8 and 29% for women undergoing exercise and dobutamine stress echocardiography, respectively \( (P < 0.0001) \). Higher catheterization rates were noted for women undergoing dobutamine stress; nearly half of those women with single and multi-vessel ischaemia were referred to coronary angiography \( (P < 0.0001) \). Approximately 10% of women were referred to coronary angiography within the first year of follow-up. By 90 days post-testing, only 1.3% of women without inducible ischaemia were referred to cardiac catheterization \( (P < 0.0001) \). Of the women referred to coronary angiography with ischaemia, the available results reveal that 78% of exercising and 83% of dobutamine stress women had at least one \( \geq 70\% \) stenosis at catheterization \( (\text{Figure 1}) \). Of the women with multi-vessel ischaemia, 55 and 63% of exercise and dobutamine stress patients, respectively, had multi-vessel disease at angiography. A similar pattern of resource utilization and disease frequency was also noted for male patients.

**Unadjusted cardiac mortality**

During the 5 years of follow-up, 103 women and 226 men died from coronary artery disease \( (P < 0.0001) \). During follow-up of exercising patients, 5 and 4% of women underwent PCI or CABG surgery, respectively. Significantly higher rates of coronary revascularization were noted for exercising male patients \( (\text{PCI } 8\% \text{ and CABG } 8\%, P < 0.0001) \). By comparison, of those undergoing dobutamine stress imaging, a total of 5 and 12% of

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**Table 1** Clinical characteristics of the stress testing cohort by gender

<table>
<thead>
<tr>
<th></th>
<th>Exercise echocardiography</th>
<th>Dobutamine stress echocardiography</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Women ((n = 3051))</td>
<td>Men ((n = 5330))</td>
</tr>
<tr>
<td>Age, years ((\text{mean } \pm \text{ standard deviation}))</td>
<td>61 ± 13</td>
<td>60 ± 13</td>
</tr>
<tr>
<td>Age &gt; 55 years, %</td>
<td>64</td>
<td>65</td>
</tr>
<tr>
<td>Risk factors, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>Hypertension</td>
<td>33</td>
<td>24</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>14</td>
<td>10</td>
</tr>
<tr>
<td>Known coronary artery disease, %</td>
<td>19</td>
<td>28</td>
</tr>
<tr>
<td>Prior myocardial infarction, %</td>
<td>21</td>
<td>32</td>
</tr>
<tr>
<td>Catheterization-defined disease, %</td>
<td>(n = 215)</td>
<td>(n = 753)</td>
</tr>
<tr>
<td>No stenosis &gt;70%</td>
<td>37</td>
<td>27</td>
</tr>
<tr>
<td>1 vessel</td>
<td>21</td>
<td>20</td>
</tr>
<tr>
<td>2 vessel</td>
<td>18</td>
<td>21</td>
</tr>
<tr>
<td>3 vessel</td>
<td>25</td>
<td>32</td>
</tr>
</tbody>
</table>

\(^{a}\)Age > 55 years was used to denote women who were post-menopause.

**Table 2** Additional exercise test parameters in the 5330 men and 3051 women

<table>
<thead>
<tr>
<th></th>
<th>Men ((n = 5330))</th>
<th>Women ((n = 3051))</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duke treadmill score ((\text{mean } \pm \text{ standard deviation}))</td>
<td>4.8 ± 6</td>
<td>3.2 ± 5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Risk groups, %</td>
<td>Low</td>
<td>56</td>
<td>42</td>
</tr>
<tr>
<td></td>
<td>Intermediate</td>
<td>31</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>13</td>
<td>13</td>
</tr>
</tbody>
</table>
women vs. 6 and 18% of men underwent post-test PCI and CABG, respectively (P < 0.0001).

At 5 years, cumulative cardiac death rates were 7 and 11% for the 1183 women and 1568 men, respectively, undergoing dobutamine stress echocardiography (P = 0.007), indicating that men had a 45% (95% confidence interval 11–91%) increased risk of death. However, at 5 years, 2.7% of 3051 exercising women and 3.4% of 5330 men died of coronary artery disease (P = 0.34).
Multivariable Cox proportional hazard model for exercising women and men (Table 4)

Significant predictors of cardiac death for the 8381 women and men undergoing exercise testing included age (P < 0.0001), hypertension (P = 0.012), and diabetes (P = 0.032) as historical factors, and the Duke treadmill score (P < 0.0001). In this multivariable model, gender was not a significant estimator of cardiac death (P = 0.46).

From the echocardiographic examination, estimates of left ventricular function (P < 0.0001) and the extent of ischaemia (P < 0.0001) noted during peak exercise were highly predictive of cardiac death during follow-up. Risk-adjusted death rates ranged from 2 to 11.7% for women and 3 to 13.0% for men by normal to severely depressed left ventricular function, respectively (P < 0.0001). In a step-wise Cox proportional hazards analysis, age, the Duke treadmill score, resting left ventricular function, and ischaemia extent were the greatest estimators of time to cardiac death (all P < 0.0001). Using an added value analysis, the stress echocardiographic parameters provided incremental predictive information above and beyond resting ventricular function (Δχ² = 12.7%) and the Duke treadmill score (Δχ² = 14.6%).

Multivariable Cox proportional hazard model of dobutamine stress imaging results (Table 5)

Significant clinical predictors of cardiac death included age (P < 0.0001) and diabetes (P < 0.0001). In this multivariable model, when controlling for other clinical and stress imaging parameters, gender did not retain statistical significance in predicting cardiac mortality (P = 0.20).

Similar to exercising patients, estimates of left ventricular function were associated with higher cardiac death rates (P < 0.0001). The relative risk of cardiac death was elevated 1.43-fold (95% confidence interval 1.24–1.65) per strata for exercising patients with mild, moderate, to severely depressed left ventricular function (P < 0.0001). Risk-adjusted death rates ranged from 5 to 15.5% for women and 5.7 to 18.6% for men by normal to severely depressed left ventricular function, respectively (P < 0.0001). In this multivariable proportional hazards model, ischaemia extent (relative risk 1.27 per vascular territory, 95% confidence interval 1.07–1.52, P = 0.0008) was highly predictive of time to cardiac death.

Tests for gender interaction and ischaemia extent of 5-year cardiac survival

Although gender was not a multivariable estimator of death for either exercising or dobutamine stress imaging patients, male patients, in a combined model including both exercise and dobutamine stress, exhibited statistically worse survival at every amount of inducible ischaemia (2.0-fold higher risk, 95% confidence interval 1.6–2.5). This first-order interaction between male gender and ischaemia was significant for both exercise (P < 0.0001) and dobutamine stress (P < 0.0001). In general, these results revealed that while gender per se was not predictive of outcome, overall survival was differential in women and men by the extent of ischaemia.

Furthermore, in a subset model examining patients without ischaemia, there was no statistical difference between cardiac survival for women and men. Thus, these results reveal that, although no sex-specific differences could be elucidated, the differential survival is related to a greater worsening outcome for men by the extent of their ischaemic burden.

Cox proportional hazard risk-adjusted survival curves by ischaemia extent and gender

Using a risk-adjusted (controlling for clinical and stress parameters as noted in Table 4 for exercise and Table 5 for dobutamine stress) Cox model, 5-year time to cardiac death is reported in Figure 2 for 3051 and 1183 women undergoing exercise and dobutamine stress echocardiography, respectively. In general, women undergoing an exercise test had significantly higher survival (P < 0.0001). At 5 years, risk-adjusted survival was 99.4, 97.6, and 95% for women with no, single, and multiple vascular
territories with ischaemia, respectively ($P < 0.0001$). For women undergoing dobutamine stress, 5-year survival was $95, 89, \text{ and } 86.6\%$ for those with no, one, and two or three vessel ischaemia, respectively ($P < 0.0001$).

For the women, 5-year risk-adjusted survival by the extent of ischaemia varied considerably by age (Table 6). For women $\geq 55$ years of age, risk-adjusted 5-year survival ranged from $94 \text{ to } 97\%$ for those exercising and from $76 \text{ to } 92\%$ for those undergoing dobutamine stress by the extent of ischaemia ($P < 0.0001 \text{ and } P = 0.003$). For younger women, significantly higher 5-year survival was noted.

For men, cardiac death at 5 years was reported in $1.1, 2.4, \text{ and } 4.5\%$ with no, one, and two or three vascular territories with exertional ischaemia, respectively (Figure 3, $P < 0.0001$). For the 1568 men undergoing dobutamine stress echocardiography, no ischaemia was associated with a 92% survival as compared with cumulative cardiac death rates of $\geq 16\%$ for men with ischaemia on dobutamine stress echocardiography ($P < 0.0001$).

**Discussion**

Although the diagnostic accuracy of some functional tests is diminished in women, recent reports have noted an enhanced ability to risk-stratify female and male patients who undergo echocardiographic or SPECT imaging.$^{9-14,21,22,24-30}$ Several smaller series have examined prognosis in women undergoing stress echocardiography with an average of 3 years of follow-up and
often using combined endpoints.9–12 Our current report differs from previous ones in that we examined long-term cardiac mortality obtained from a large observational, multi-centre registry including 4234 intermediate-risk, symptomatic women. The current results reveal that risk stratification is effective for women and men alike but that due to a greater underlying disease burden for men, overall survival is significantly diminished when compared with their female counterparts.

Although our estimates of outcome reinforce prior smaller series, the current statistically powered sample reveals for the first time the estimation of cardiovascular death by the extent of echocardiographic ischaemia in a large sample of 4234 women and 6898 men. A review of evidence (Figure 4) reveals that with this larger sample, there is enhanced precision (i.e. narrow confidence intervals) when compared with smaller series.9–12,22,28,29 In this large observational registry of 11 132 patients, qualitative estimates of left ventricular function as well as stress-induced wall motion abnormalities were highly predictive of time to cardiac death for both women and men. This is consistent with a prior report by Sicari and colleagues31 from the Echo Persantine International Cooperative (EPIC) Study Group: Echo Dobutamine International Cooperative (EDIC) multi-centre study group noting Kaplan–Meier survival rates of 92% for negative and 71% for positive pharmacological stress imaging.31 Similar results were previously reported by Cortigiani et al.,11 Dodi et al.,10 and Heupler et al.24 In a recent report from the Mayo Clinic in 2476 exercising women, death or myocardial infarction-free survival was approximately 97% for women with no inducible wall motion abnormalities compared with 88% for those with a wall motion score index \( \geq 1.25 \) (defined as the sum of segmental scores/number of segments visualized with new or worsening abnormalities).9 The current results provide additional insight into the long-term predictive value of testing a female patient population. Although prior reports have focused on exercising women, we included a large cohort of women incapable of performing maximal levels of stress. This segment of the population is growing and risk stratification information may be particularly helpful for the older, post-menopausal woman where functional disability is common. In this population referred to echocardiography, measurements of the extent of myocardial ischaemia provide important guidance as to a patient’s likelihood of dying within 5 years. For women undergoing an exercise test, 5-year death rates increased from 0.6 to 4.3% for no to multi-vessel ischaemia. Thus, for those exercising women, the annual risk of dying is approximately 1 per 1000 if the results are negative and increases to 1 per 100 for those with high-risk ischaemia. For women undergoing dobutamine stress echocardiography, 5-year death rates increased from 5 to 13.4% for no to three vascular territories with ischaemia. That is, for women with significant functional disability who undergo dobutamine stress echocardiography, the yearly risk of cardiac death increases from 1 per 100 to 3–5 per 100 for negative to high-risk ischaemia. In addition, resting ventricular function was also a strong estimator of time to cardiac death. The male patients in this series had decrementally and proportionally worsening cardiac survival by the extent of ischaemia and systolic dysfunction.

**Comparative prognostic value of other cardiac imaging modalities in women**

Similar to reports using exercise echocardiography,9–12 several large female samples have been reported for Tc-99m sestamibi (rest and exercise) and dual isotope myocardial perfusion SPECT.22,25–30 These results reveal that there is an added incremental prognostic value of myocardial perfusion data compared with clinical and exercise variables in women.22,25,29 From a recent multi-centre registry of 3402 women with stable chest pain symptoms, risk stratification was similar by gender.22 Similar to the scoring system applied in the current analysis, 3-year survival ranged from 98.5 to 85% for no to three vascular territories with ischaemia.22 When these data are compiled and compared with the ever-growing body of evidence on the prognostic value of stress echocardiography in women, the results reveal similar risk stratification.9–12 The summary relative risk ratio is elevated 16.3-fold for stress echocardiography and 9.0-fold for stress SPECT imaging in women;9–12,22,28,29 both results revealed a highly accurate test in diverse samples of at-risk women.

Thus, it appears that measurements of the extent of myocardial ischaemia, derived from echocardiography or SPECT, provide information as to the risk of dying both in the near- (i.e. up to 3 years) and long-term (i.e. at 5 years) for symptomatic women. This important finding indicated that, contrary to the prior limitations noted in older diagnostic series, a woman’s risk of major adverse cardiac events may be estimated during stress imaging and used to guide management. Increasingly, as these results are applied globally to the large

### Table 6 Risk-adjusted 5-year cardiac survival for women <55 and ≥55 years of age

<table>
<thead>
<tr>
<th>Risk-adjusted 5-year survival estimate (%)</th>
<th>Age &lt;55 years</th>
<th>Age ≥55 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise (P &lt; 0.0001)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n = 910</td>
<td>n = 2141</td>
<td></td>
</tr>
<tr>
<td>No ischaemia</td>
<td>99</td>
<td>97</td>
</tr>
<tr>
<td>1 vessel ischaemia</td>
<td>98</td>
<td>96</td>
</tr>
<tr>
<td>2–3 vessel ischaemia</td>
<td>97</td>
<td>94</td>
</tr>
<tr>
<td>Dobutamine (P = 0.003)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n = 258</td>
<td>n = 925</td>
<td></td>
</tr>
<tr>
<td>No ischaemia</td>
<td>97</td>
<td>92</td>
</tr>
<tr>
<td>1 vessel ischaemia</td>
<td>92</td>
<td>84</td>
</tr>
<tr>
<td>2 vessel ischaemia</td>
<td>88</td>
<td>76</td>
</tr>
</tbody>
</table>

Risk adjustment includes use of a multivariable Cox model with covariate adjustment as specified in Table 4 for exercising and Table 5 for dobutamine stress imaging.
cohort of at-risk women who undergo cardiac imaging every year, a more aggressive pattern of testing and intervention may initiate reductions in case fatality rates for women (which have not been previously realized to the same extent as for their male counterparts). A synthesis of evidence for both echocardiography and SPECT imaging in women would yield the following: (i) in the setting of normal stress perfusion or wall motion (i.e. no ischaemia), for exercising women, mortality rates are in the range 0.1–0.4% annually, (ii) for women undergoing pharmacological stress, mortality rates are higher but approximately 1% per year, and (iii) multi-vessel ischaemia is associated with the worst survival, with expected death rates from 1% (for exercising women) to 3–5% (for pharmacological stress) per year. A similar application of risk stratification results, regardless of imaging modality, can provide enhanced assimilation and understanding of information upon which to guide the intensity of post-test management for women presenting for evaluation of suspected myocardial ischaemia.

Study limitations

Despite the inclusion of a diverse, large multi-centre registry of 11 132 patients, there are several notable challenges and limitations with the current series including a limited myocardial model for interpretation of inducible wall motion abnormalities. We employed a three-territory myocardial model where only the extent of wall motion abnormalities was examined on the rest and stress echocardiographic imaging. We also did not score the severity of inducible wall motion changes. A more detailed 17-segment model would provide enhanced defining of diverse risk subsets. We also did not employ contrast enhancement, in this series, which could have improved endocardial border delineation and left ventricular opacification in particular for obese patients and those with lung disease. Finally, the extent and severity of coronary disease at angiography was not available in all patients (Figure 1).

Conclusions

Prior research has been limited with regard to the prognostic accuracy of commonplace cardiac imaging modalities in women. The purpose of the current report was to examine 5-year mortality in 4234 women and 6898 men undergoing exercise and dobutamine stress echocardiography at three hospitals. In general, the women in this series were lower risk with greater cardiac survival rates compared with men. However, qualitative measures of rest left ventricular function as well as parameters obtained during stress testing may enhance insight into the long-term mortality risk for women. Using multivariable modelling techniques, gender did not add prognostic information after considering historical and echocardiographic parameters. In conclusion, echocardiographic measures of inducible wall motion abnormalities and left ventricular function are highly predictive of long-term outcome for women and men, alike.

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