Risk stratification of CAD with SPECT-MPI in women with known estrogen status

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Objective. **To compare exercise tolerance testing (ETT) with gated single photon emission computed tomography-myocardial perfusion imaging (SPECT-MPI) risk stratification in women with an intermediate to high CAD pretest risk and known estrogen status (ES).**

Background. **SPECT-MPI is an effective test for risk stratifying patients with stable angina. However in women, the current guidelines recommend the exercise tolerance testing (ETT) as first line test. Further, the relationship of stress imaging to ES, an independent risk indicator for CAD, is unknown.**

Methods. **2,194 women with an intermediate to high CAD pre-test risk were referred for a clinically indicated ETT with gated SPECT-MPI. Duke treadmill scores (DTS) and summed stress score (SSS) were calculated. SSS were classified as normal (SSS < 3), mildly abnormal (SSS 4-8), or moderate-severely abnormal (SSS > 8). The ES was assessed as premenopausal, postmenopausal on hormone replacement therapy (HRT) as ES+ while postmenopausal not on HRT were ES−. An annualized cardiac event rate of a composite of cardiac death, unstable angina (UA) leading to hospitalization, non-fatal myocardial infarction, or late coronary revascularization was calculated for all the groups.**

Results. **The annualized cardiac event rate was 1.3% PPY, 2.1% PPY, and 3.2% PPY for low, intermediate, and high risk DTS ($P = .2$). Patients with intermediate DTS and mildly abnormal or moderate-severely abnormal gated SPECT-MPI had a significantly higher cardiac event rates (5.3% PPY and 10.8% PPY, respectively) than those with a normal gated SPECT-MPI (1.2%, PPY, $P = .01$). This was also demonstrated on further Cox-regression analysis. Risk stratification of SPECT-MPI over DTS was independent of ES.**

Conclusion. **Gated SPECT-MPI provides risk stratification beyond standard exercise stress testing for women with suspected coronary artery disease, especially in patients with intermediate DTS and is independent of ES. (J Nucl Cardiol 2012;19:330–7.)**

Key Words: Coronary artery disease risk stratification · gated SPECT-MPI · estrogen status

INTRODUCTION

Coronary artery disease (CAD) is the leading cause of mortality in women, with more than 200,000 deaths per year in the United States.[1] This may be partly due to the absence of effective risk stratification strategies to assess symptomatic women for CAD.[2] Current American College of Cardiology/American Heart Association (ACC/AHA) guidelines recommend standard exercise tolerance test (ETT) as the first line diagnostic tool to evaluate symptomatic women.[3] However, this recommendation is not supported by prospective randomized trials.[4,5] According to a meta-analysis, ETT in women was associated with only moderate diagnostic accuracy (sensitivity of 62% and specificity 69%).[6] Gated myocardial perfusion imaging with single photon emission computed tomography (SPECT-MPI) has been shown to be an effective risk stratifying modality for CAD.[7-9] Previous studies have demonstrated that stress SPECT-MPI offers independent prognostic information for cardiac events in both men and women.[10,11] However, outcomes data for exercise with gated SPECT MPI are limited in women.

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Previous studies have reported that estrogen status (ES) is an independent risk factor for CAD events.[12] An estrogen positive status (premenopausal or positive hormone replacement therapy; HRT) is associated with a lower risk of cardiac events compared with an estrogen negative status (postmenopausal and not on HRT).[13,14] To date, ES has not been evaluated in conjunction with SPECT-MPI risk stratification.

The purpose of the primary objective of this study was to compare risk stratification with ETT alone versus combined ETT-gated SPECT-MPI in symptomatic women with no known CAD, and with respect to ES.

METHODS

Study Design

Women with chest pain and no known history of CAD, who were referred for exercise gated SPECT-MPI study, were identified from a single center nuclear cardiology database from 1996 to 2006. Of these, there were 2,334 patients who were classified as intermediate or high pretest likelihood for CAD based on the ACC/AHA guidelines[3] (Table 4 in Appendix). Patients with known history of CAD, or electrocardiogram (ECG) with Q wave, left bundle branch block, Wolf Parkinson White (WPW) pattern and pacemaker rhythms were excluded. The Hartford Hospital Institutional Review Board approved the study.

The primary end-point of this study was a composite of cardiac events, defined as cardiac death or non-fatal myocardial infarction (MI) by ECG criteria or by positive cardiac biomarkers, unstable angina (UA) leading to hospitalization and late (longer than three months after the indexed gated SPECT-MPI) revascularization by angioplasty or coronary artery bypass grafting (CABG).

Stress Testing Protocol

Exercise was performed in accordance with the ACC/AHA guidelines.[3] The Bruce protocol was the preferred method of stress testing.[15]

Gated SPECT-MPI acquisition and processing protocols. Radiopharmaceutical dosing, image acquisition, and processing were performed within guidelines of the American Society of Nuclear Cardiology.[16]

ECG Interpretation and calculation of Duke treadmill score (DTS). An exercise ECG was considered abnormal if there was ≥1 mm of horizontal or down-sloping ST-segment depression occurring 80 ms past the J-point, or if there was a change of >1 mm in a segment with a baseline abnormality of <0.5 mm deviation 60 to 80 milliseconds from the isoelectric line. A threshold of 1.5 mm ST segment depression was also considered when up-sloping ST-segment depression was noted. A DTS was calculated by inserting the patients' parameters into a formula previously published. DTS results were classified using the following classification criteria: low (≥5), intermediate (+4 to −10), and high cardiovascular risk (≤−11).[17]

Image Interpretation

All gated SPECT-MPI images were interpreted by a consensus agreement of 2 or more experienced nuclear cardiologists without knowledge of patient's clinical history. For assessment of myocardial perfusion, the left ventricle was divided according to the ASNC/ACC/AHA recommended 17-segment model.[18] All segments were scored for regional perfusion using a 5-point scale (0 = normal to 4 = absent photon activity). A summed stress score (SSS) and a summed rest score (SRS) was calculated by adding the segment scores at stress and rest, respectively. Based on the SSS, perfusion images were classified as normal (SSS 0-3), mildly abnormal (SSS 4-8), or moderate-severely abnormal (SSS ≥ 9). An image was classified as abnormal if the SSS ≥ 4.[19,20] Based on previous studies from our laboratory there was no significant intra-observer variability.[21]

Estrogen Status

Postmenopausal women receiving HRT and premenopausal women were categorized as estrogen positive (ES+), while postmenopausal women not receiving HRT were categorized as estrogen negative (ES−). Patients who had undergone hysterectomy without oophorectomy were considered (ES+) if they were less than 50 years of age and without symptoms of menopause. Patients who under went a hysterectomy/oophorectomy were considered (ES−).[12-14]

Follow-Up

Patient follow-up was performed by mailed questionnaires. In the absence of a response, scripted telephone interviews and evaluation of the hospital database was performed. Cardiac events were confirmed by reviews of death certificates, hospital charts, physician records, and appropriate laboratory test results. Individuals blinded to the patient's test results performed a confirmation of events.

Statistical Analysis

SPSS 15.0 statistical software package was used to compare data, with chi-square used to compare frequencies of dichotomous variables, and Student's *t* test was used to compare means of continuous variables. Patient demographics and clinical characteristics were expressed as mean values with standard deviations (mean ± SD) or as proportions. Univariate analysis was used to examine the association between the end-points of interest: composite of cardiac events with collected covariates. All the covariates with a P value of ≤.20 upon univariate analysis were entered in to the multivariate Cox proportional hazards regression model as potential confounders. A P value <.05 was considered significant in the multivariate analysis. To compare the risk stratification benefit with ETT alone versus ETT-gated SPECT-MPI, an annualized event rate of a composite outcome of cardiac events [cardiac death, non-fatal MI, UA requiring hospitalization, or need for late (>90 days) revascularization] was calculated. Adjusted hazard ratios (HR) and 95% confidence intervals (CI) were calculated for all the independent predictors. Kaplan-Meier analysis was

used to construct event-free survival curves and assess cardiac event free survival.

RESULTS

Clinical Characteristics

A total of 2,334 patients without CAD and intermediate or high pretest CAD likelihood, referred for exercise gated SPECT-MPI study, were included for analysis.

Follow-up was successfully obtained in 2,194 of the 2,334 patients (94%), with a mean follow-up duration 2.4 ± 1.2 years. There were 85 cardiac events (excluding early revascularization, 48 patients). These included 5 (5.8%) cardiac deaths, 21 (24%) non-fatal MIs, 20 episodes of UA requiring hospitalization (23%) and 39 (45%) late revascularizations. Late revascularization procedures included 24 percutaneous coronary interventions (PCI) and 15 coronary artery bypass grafting (CABG) surgeries.

Patients were categorized into two groups (Table 1), based on the presence or the absence of cardiac events. The mean age of the study group was 63 ± 10 years. Nearly half of the study group had a history of hypertension and hypercholesterolemia (48% and 41%, respectively), as the predominant cardiac risk factors, followed by smoking history and Type II diabetes mellitus. In general, cardiac medication use was infrequent. On univariate analysis hypertension, smoking history, Type II diabetes mellitus, beta-blocker use were more common in women with a cardiac event (Tables 2, 3).

Risk Stratification with ETT Alone Using DTS

DTSs were calculated for all the study subjects (Table 1). The majority of patients were in the low 1,062 (48%) and intermediate 1,106 (50.4%) DTS group. The high DTS group accounted for a small proportion of patients 26 (2%) (Table 1). The annualized cardiac event rate was compared in the low, intermediate, and high DTS groups (Figure 1). Overall, the event rate in all the DTS categories was low reflecting a relatively healthy population. There was no statistically significant difference in annualized cardiac event rate between low, intermediate, and high DTS groups ($P = .2$).

Table 1. Univariate predictors of the composite annualized cardiac event

Variables	N (%) Total = 2,194	No cardiac events N = 2,109 (%)	Cardiac events N = 85 (%)	$P < .05$
Risk factors				
Race: Caucasian	1,563 (71)	1,504 (71)	57 (67)	.15
Age (years)	63 ± 6	62 ± 8	64 ± 10	.20
Hypertension	1,048 (48)	995 (47)	53 (62)	**.01**
Hypercholesterolemia	895 (41)	857 (41)	38 (45)	.2
Type II diabetes	356 (16)	326 (15)	30 (35)	**.02**
Smoking history	594 (27)	517 (25)	32 (28)	**.01**
Medications				
Statins	479 (22)	465 (22)	14 (16)	.14
Aspirin	694 (32)	655 (31)	39 (46)	.06
Beta-blocker	521 (24)	489 (23)	32 (38)	**.04**
ACE/ARB	403 (18)	382 (18)	21 (5)	.08
Duke treadmill scores				
DTS (low)	1,060 (48)	951 (45)	30 (35)	.20
DTS (intermediate)	1,101 (50)	1,127 (53)	53 (62)	.19
DTS (high)	36 (2)	34 (2)	2 (2)	.19
Sum stress scores				
SSS (<4)	2,032 (92)	1,965 (93)	67 (79)	**.01**
SSS (4-8)	127 (6)	116 (6)	11 (1)	**.01**
SSS (>8)	34 (1)	29 (1)	7 (8)	**.01**
Estrogen negative	1,158 (53)	1,107 (52.5)	51 (60)	.10

Analysis of all the clinical variables used for multivariate model to determine independent predictors of ACCER in women undergoing ETT and gated SPECT-MPI.
CAD, Coronary artery disease; *ACE*, angiotensin converting enzyme inhibitor; *ARB*, angiotensin receptor blocker; *DTS*, Duke treadmill score; *SSS*, summed stress score.
Bold values are <0.05 and are significant univariate predictors.

Table 2. The multivariate independent predictors from Cox regression analysis of having a cardiac event in this population

Variables	*P* value	Odds ratio	Odds ratio 95% CI
SSS abn > 3	.01	2.5	1.5-4.4
SSS 4-8 vs SSS 0-3	.02	1.9	1.01-3.8
SSS > 8 vs >SSS 0-3	.01	4.5	2.05-10.1

Table 3. ES when stratified by MPI as a multivariate independent predictor cardiac event

Variable	*P* value	Odds ratio	Odds ratio 95% CI
ES+ N-MPI vs ES− N-MPI	.02	0.58	0.35-0.96
ES− abn-MPI vs ES− N-MPI	.01	3.5	1.3-9.4
ES+ abn-MPI vs ES− N-MPI	.01	4.1	1.67-10.1
Age	.20	2.58	0.90-5.6
HTN	.10	1.5	0.60-3.60
DM	.09	2.8	0.92-6.3
Aspirin	.08	0.70	0.40-1.2

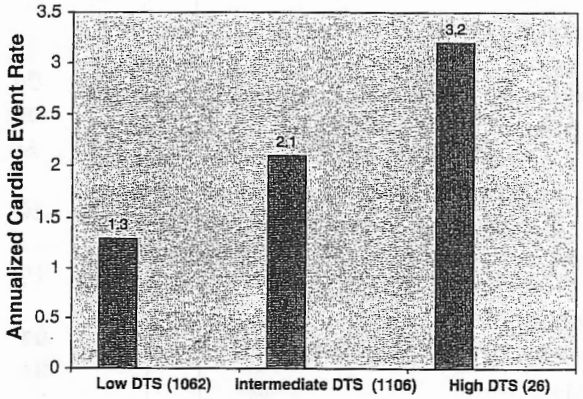

Figure 1. Crude annualized event rate and DTS value = 0.2.

Risk stratification with ETT combined with gated SPECT MPI. The DTS risk categories were further classified according to gated SPECT-MPI SSS (normal, mildly abnormal, moderate-severely abnormal) and compared to subsequent cardiac events (Figure 2). There was no additional risk stratification in the low DTS group with MPI. In the intermediate DTS category, patients with a normal gated SPECT-MPI had a low crude annualized cardiac event rate (1.5% per person year, PPY). There was no statistically significant difference between this group compared to ACER (2.1% PPY) in all patients with intermediate DTS ($P = .07$).

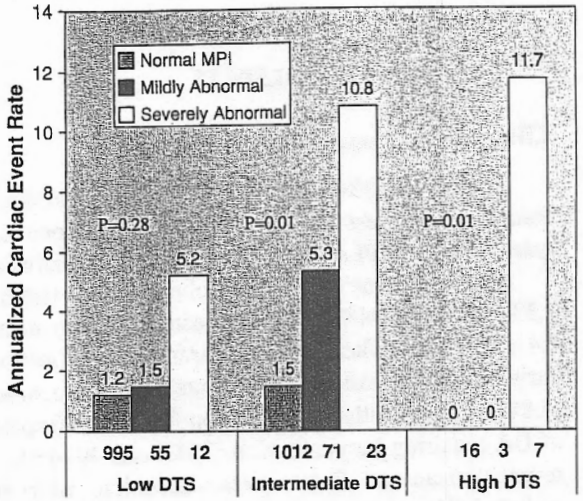

Figure 2. Risk stratification of DTS with SPECT-MPI. Risk stratification of DTS with gated SPECT-MPI. *DTS,* Duke treadmill score. Normal gated SPECT-MPI = SSS < 4; mildly abnormal gated SPECT-MPI = SSS 4-8; moderate-severely abnormal gated SPECT-MPI = SSS > 8.

In contrast, patients with mildly or moderate-severely abnormal studies were further risk stratified with significantly higher annualized cardiac event rates (5.3% PPY and 10.8% PPY, respectively, $P < .001$) when compared to with normal gated SPECT-MPI. Although there were few patients in the high DTS group, the event-free survival was significantly better in normal gated SPECT-MPI versus moderate-severely abnormal gated SPECT-MPI groups ($P = .01$). In our population 48 patients underwent early revascularization. Of these 36 were in the high DTS group.

Multivariable analysis was performed with cox-multiple regression (Figure 3). Abnormal gated SPECT-MPI (SSS > 3) was found to be a statistically significant independent predictor of cardiac events with a HR 2.5 (95% CI 1.5-4.4). Upon further stratification of gated SPECT-MPI into mildly abnormal (SSS 4-8) and moderate-severely abnormal (SSS > 8) and cox regression analysis, the risk of having composite cardiac event was nearly 2-fold greater in mildly abnormal (SSS 4-8) than those with a normal gated SPECT-MPI (HR 1.9, 95% CI 1.01-3.8). The moderate-severely abnormal MPI group

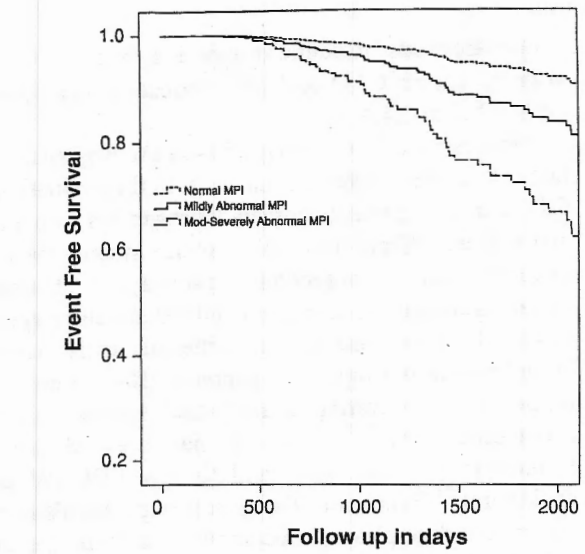

Figure 3. Cox regression analysis showing KM curves of ACCER with SPECT MPI. Cox regression analysis showing KM curves of annualized cumulative cardiac event rate with SPECT-MPI. Normal gated SPECT-MPI = SSS < 4; mildly abnormal gated SPECT-MPI = SSS 4-8; moderate-severely abnormal gated SPECT-MPI = SSS > 8.

had a 4.5 times the risk of reaching the composite cardiac event endpoint compared to normal MPI group. (HR 4.5, 95% CI 2.05-10.1).

ES and Risk Stratification with MPI

The definition of ES was determined using previously published criteria and as specified in "Methods."[12-14] Of 2,194 patients, 470 (21.4%) were premenopausal, 1,158 (52.8%) were postmenopausal not on HRT, and 566 (25.8%) were postmenopausal on HRT. The ACER across all the three groups was statistically higher with worsening severity of SSS score (Figure 4).

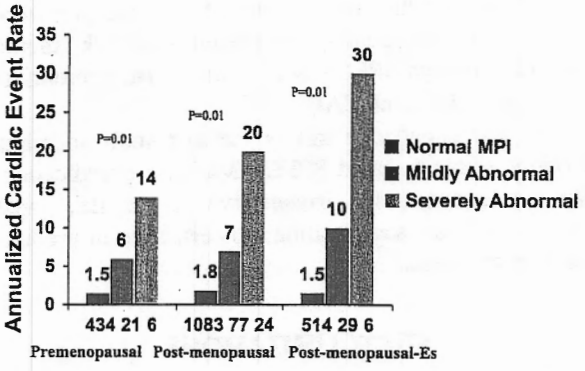

Figure 4. Risk stratification of patients based on varying ES with MPI. Risk stratification of women with MPI based on ES; *MPI*, Myocardial perfusion imaging.

To further evaluate cardiac event over time patients were grouped as being estrogen positive (ES+) and estrogen negative (ES−) as described in "Methods" and as has been done in previous studies looking at estrogen as a marker of risk stratification for CAD.[12-14]

Thus, 1,036 (47.2%) patients were included in the estrogen positive (ES+) and 1,158 (52.8%) patients were classified as estrogen negative (ES−) (Figure 5).

Patients with abnormal MPI had worse survival regardless of ES. Compared to (ES−), gated SPECT-MPI normal patients, patients with (ES+) and gated SPECT-MPI abnormal had four times higher the risk of a cardiac event with a HR 4.1 (95% CI 1.67-10.1). Similarly, patients with (ES−) and abnormal gated SPECT-MPI had 3.5 times the hazard of the composite cardiac event (95% CI 1.3-9.4). Patients with (ES+) and normal gated SPECT-MPI had 42% decreased hazard of composite cardiac event (95% CI 0.35-0.96).

DISCUSSION

This study was conducted to examine the value of gated SPECT-MPI in addition to ETT in women with

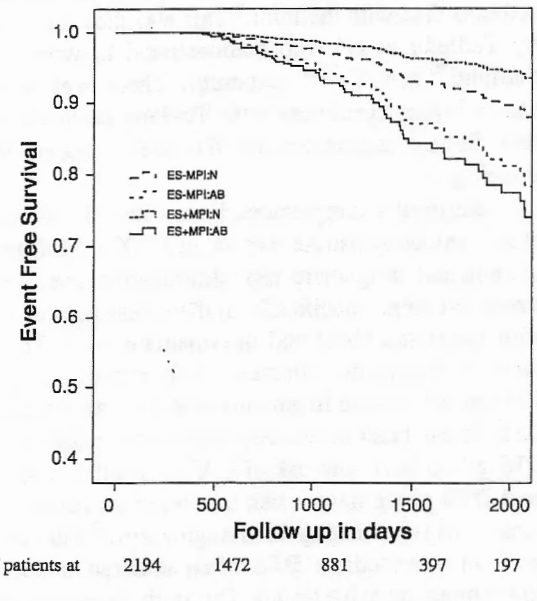

Figure 5. Cox regression analysis showing KM curves of ACCER with varying ES and MPI. Cox regression analysis showing risk stratification of patients with varying ES with respect to MPI. *ES−MPI:N*, Estrogen negative MPI normal; ES−MPI:AB, estrogen negative MPI abnormal; ES+MPI:N, estrogen positive MPI normal; ES+MPI:AB, estrogen negative MPI abnormal.

known estrogen states. We found that gated SPECT-MPI offers incremental risk stratification beyond the ETT results alone, and is independent of ES in women. CAD remains the largest major cause of mortality among women in the United States.[1] Early identification of CAD in women may lead to more successful therapies and potentially improved cardiac outcomes.[2]

Current ACC/AHA guidelines recommend ETT as the initial test for all the symptomatic women undergoing evaluation for CAD, despite no randomized trials to effectively support this strategy.[3,4] The accuracy of ETT to diagnose CAD in women is influenced by many factors.[5] In a meta-analysis that assessed 3,874 women, ECG stress testing demonstrated only a moderate sensitivity and specificity of 62% and 69%, respectively, and was less accurate in women than in men.[6]

SPECT-MPI has been validated by previous studies in terms of its diagnostic efficacy for detecting CAD in women. Amanullah et al studied adenosine Tc-99m sestamibi SPECT in a large consecutive series of female patients, and found it to be accurate for the diagnosis of CAD in women, irrespective of the presenting symptoms or the pretest probability. The overall sensitivity, specificity, and overall predictive accuracy of adenosine sestamibi SPECT for detecting CAD were 93%, 78%, 88%, respectively..[7] Technetium-99m (Tc^{99m}) sestamibi is particularly suited for imaging female patients because of its higher energy and reduced breast attenuation artifacts than with thallium.[8] This was shown in the study by Taillefer et al[9] who demonstrated in women using $thallium^{201}$ and Tc^{99m} sestamibi. There was a significantly higher specificity with Tc-99m sestamibi, which was further augmented by the use of gated SPECT imaging.

Our results complement the results of Hachamovitch et al[11] and demonstrate that gated SPECT-MPI provides incremental prognostic risk stratification over exercise stress test alone specifically in the assessment of women with suspected CAD and intermediate DTS. There has been a diagnostic dilemma with regards to further downstream testing in patients who have an intermediate DTS. It has been previously shown that patients in low DTS group have low risk of CAD.[17] Further, patients in high DTS group have a risk that warrants further downstream invasive testing with angiogram.[17] Patients who have an intermediate DTS often undergo unnecessary downstream invasive testing. Our study demonstrates that patients with intermediate DTS and normal MPI have a low annualized cardiac event rate thus avoiding invasive downstream testing. In our study, it was not possible to predict the severity of DTS before patients undergo ETT and thus it is not possible to select out a population who would most benefit from gated SPECT-MPI. Further studies are needed to define an approach for all the women with no known CAD and intermediate to high pretest probability of CAD.

Hormonal effects are hypothesized to play an important role in the differences that exist in the evaluation of CAD between men and women. Estrogen has both direct and indirect effects on cardiovascular system via both genomic and non-genomic pathways.[23] Estrogen increases arterial vasodilatation, inhibits cellular response to vascular injury, and prevents atherosclerosis. Arterial vasodilatation is a rapid non-genomic effect of estrogen primarily by activating nitric oxide synthase in the endothelial cells.[22,23] Estrogen has been shown to increase HDL ''good lipid'' and decrease LDL and total cholesterol.[24] Continuous estrogen therapy has also been shown to reduce plasma concentration of fibrinogen and anticoagulants antithrombin and protein S.[24] Hypoestrogenemia plays a key role in endothelial micro-vascular dysfunction and symptomatic response to atherosclerotic plaque burden and myocardial ischemia.[23] Estrogens as well as androgens have also been hypothesized to affect the ST segment and the QT interval.[14]

ES has been shown to be an independent marker of cardiac outcomes in women.[12,13] Estrogen positive status was shown to be associated with more favorable outcome and fewer cardiac events in a cohort of symptomatic women with no known CAD.[14] Women Health Initiative study (WHI) demonstrated increased cardiac events in women on HRT.[26] Recent data on further analysis of this database suggests that there may be a ''timing of HRT'' concept. It has been shown that women started early (50-59) and continued for a longer time may actually extract benefit from HRT with respect to CAD.[25] Thus, the exact effect of HRT on cardiac events in women is still not well understood. Our results show that irrespective of ES or HRT there is risk stratification of CAD in women with SPECT-MPI if they have an intermediate or high pretest probability of CAD. Thus, all the women even if they are premenopausal and traditionally considered low risk should probably undergo SPECT-MPI if they have appropriate pretest probability of CAD.

To our knowledge this is the first study to relate hormone status to gated SPECT-MPI risk stratification. We demonstrated that irrespective of the ES, gated SPECT-MPI risk stratification was effective in predicting cardiac events.

STUDY LIMITATIONS

This was a single center retrospective study, involving patients undergoing ETT and gated SPECT-MPI in a continuous manner, rather than being subjected

to both testing procedures separately (ETT vs ETT-gated SPECT-MPI). This was a relatively healthy population thus our annualized event rate was relatively low. There were 48 patients who had early revascularization (PCI/CABG <90 days). All these patients had a high pretest probability. 36 patients had high DTS score and 12 patients had intermediate DTS. This explains the low numbers in the high risk DTS group and thus based on our data we cannot suggest the appropriate downstream risk stratification in patients with high risk DTS. We also excluded patients with revascularization within 90 days. Also there is a trend for worse outcomes for women with estrogen negative status, which may be apparent on longer follow-up. Thus, the results of this study are limited to short-term follow-up. The lack of risk stratification in patients with low risk DTS score may be due to inadequate sample size in the low DTS patient population.

CONCLUSION

Gated SPECT-MPI provides risk stratification beyond exercise testing alone, in women with an intermediate to high pre-test likelihood of CAD and an intermediate DTS, independent of ES.

Conflict of interest

The authors do not have any conflict of interest to disclose.

APPENDIX

See Table 4.

Table 4. Pretest probability of CAD by age, and symptoms in women

	Typical/definite angina pectoris	Atypical/probable angina pectoris	Non-anginal chest pain	Asymptomatic
30–39	Intermediate	Very low	Very low	Very low
40–49	Intermediate	Low	Very low	Very low
50–59	Intermediate	Intermediate	Low	Very low
60–69	High	Intermediate	Intermediate	Low

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