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ORIGINAL ARTICLE
Vascular and cardiac imaging

Comparative effectiveness of exercise electrocardiography versus exercise echocardiography in women presenting with suspected coronary artery disease: a randomized study

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Aims There is a paucity of randomized diagnostic studies in women with suspected coronary artery disease (CAD). This study sought to assess the relative value of exercise stress echocardiography (ESE) compared with exercise electrocardiography (Ex-ECG) in women with CAD.

Methods and results Accordingly, 416 women with no prior CAD and intermediate probability of CAD (mean pre-test probability 41%), were randomized to undergo either Ex-ECG or ESE. The primary endpoints were the positive predictive value (PPV) for the detection of significant CAD and downstream resource utilization. The PPV of ESE and Ex-ECG were 33% and 30% ($P = 0.87$), respectively for the detection of CAD. There were similar clinic visits (36 vs. 29, $P = 0.44$) and emergency visits with chest pain (28 vs. 25, $P = 0.55$) in the Ex-ECG and ESE arms, respectively. At 2.9 years, cardiac events were 6 Ex-ECG vs. 3 ESE, $P = 0.31$. Although initial diagnosis costs were higher for ESE, more women underwent further CAD testing in the Ex-ECG arm compared to the ESE arm (37 vs. 17, $P = 0.003$). Overall, there was higher downstream resource utilization (hospital attendances and investigations) in the Ex-ECG arm ($P = 0.002$). Using National Health Service tariffs 2020/21 (British pounds) the cumulative diagnostic costs were 7.4% lower for Ex-ECG compared with ESE, but this finding is sensitive to the cost differential between ESE and Ex-ECG.

Conclusion In intermediate-risk women who are able to exercise, Ex-ECG had similar efficacy to an ESE strategy, with higher resource utilization whilst providing cost savings.

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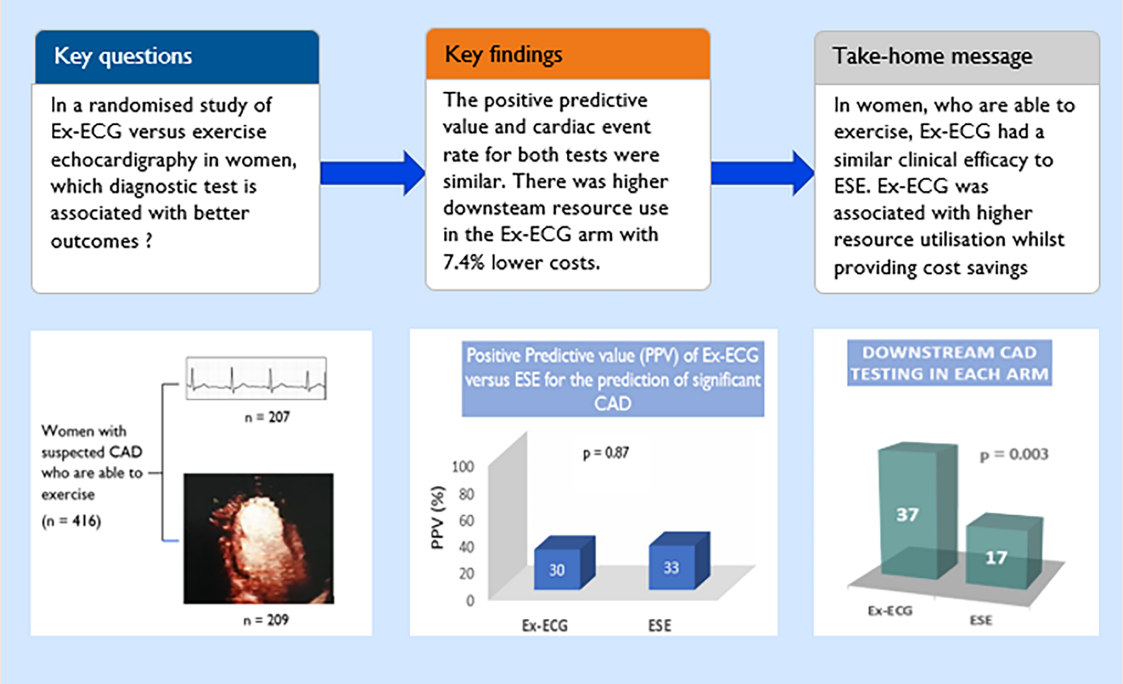
Graphical Abstract



Ex-ECG – Exercise Electrocardiography, ESE – Exercise Stress Echocardiography, CAD – Coronary Artery Disease, PPV - Positive Predictive value

Randomized controlled trial comparing diagnostic accuracy, efficacy, resource utilization, and costs based on an initial exercise echocardiography strategy vs. an exercise electrocardiography strategy in women with suspected angina.

Keywords Stress echocardiography • Exercise electrocardiography • Randomized study • Coronary artery disease

Introduction

Cardiovascular disease accounts for half of all deaths in women in Europe[1] representing a huge healthcare burden. Resource consumption patterns in women are characterized by more frequent angina diagnoses, more clinic visits and hospitalizations, higher myocardial infarction mortality, and higher heart failure rates as compared with men.[2,3] There is a lack of effective, evidence-based diagnostic testing strategies, and under-representation of women in cardiovascular clinical trials.[4] For example, in the recently concluded ISCHEMIA trial, only 23% of study participants were women.[5]

Non-invasive testing offers the opportunity to identify women with coronary artery disease (CAD) and establish early preventative and therapeutic interventions, thus improving outcomes in women. However, although physicians may choose from a wide range of diagnostic modalities, the accuracy, and limitations of stress testing in women remain an area of significant confusion. There is clearly a need for specific, evidence-based diagnostic testing algorithms for the early identification of at-risk women.

Treadmill testing with exercise electrocardiography (Ex-ECG) has been well evaluated in women with numerous reports and meta-analyses.[6,7] Evidence suggests reduced diagnostic accuracy in women compared with men.[6] Despite this, the ACC/AHA exercise testing guidelines recommend that women should undergo Ex-ECG if they are at an intermediate pre-test risk of CAD on the basis of symptoms and risk factors, have a normal resting ECG, and are capable of maximal exercise.[8] Although Ex-ECG is recommended as an initial diagnostic test by current guidelines, only one randomized study supports this strategy in women with suspected CAD.[9]

Stress echocardiography is an effective and accurate means of detecting ischaemic heart disease and risk-stratifying symptomatic women with an intermediate to high pre-test likelihood of CAD.[10–12] Exercise stress echocardiography (ESE) provides incremental value over clinical variables for risk stratification in subjects with suspected or known coronary heart disease compared with Ex-ECG.[10] The superior risk stratification of ESE over Ex-ECG, has also been demonstrated in a randomized study and was associated with cost savings.[13,14]

To our knowledge, there has only been one randomized study assessing health outcomes for diagnostic tests in women, with evidence largely extrapolated from non-randomized studies or large meta-analyses.[9] Further comparative effectiveness evidence for exercise ECG compared with higher-cost imaging options, will further guide decision-making, and has been advocated.[8]

The objective of this study was to compare the diagnostic accuracy, health benefit, and costs associated with an initial ESE strategy compared to an initial Ex-ECG strategy, in intermediate-risk women presenting with chest pain or equivalent symptoms suggestive of ischaemic heart disease, without a prior history of CAD. The primary hypothesis of the study was that the improved accuracy of ESE for the diagnosis of CAD would lead to lower health resource utilization in patients assigned to ESE, than patients assigned to Ex-ECG, due to a combination of reduced downstream testing and reduced unscheduled hospital attendances.

Methods

Study design

This study was an open-label, randomized controlled comparative effectiveness trial between Ex-ECG and ESE in women referred for the evaluation of chest pain or anginal equivalent symptoms with intermediate pre-test risk for CAD, as defined by NICE guidelines for chronic stable angina.[15] The primary aims of the study were to compare the positive predictive value (PPV) of each test for the detection of obstructive CAD and to compare downstream resource utilization (follow-up investigations, clinic visits, and hospitalization). The secondary objectives were to determine major cardiac adverse events (MACE) [death, non-fatal acute myocardial infarction (AMI), late revascularization, and hospitalization for heart failure] for both diagnostic strategies. The tertiary aim was to compare diagnostic costs including follow-up costs for the two strategies.

The study was approved by the London City and East Research Ethics Committee. Once written informed consent was obtained, patients were randomized to either Ex-ECG alone or in conjunction with SE. Permuted block randomization (1:1) was performed using statistical software-generated codes in sealed, opaque sequentially numbered envelopes to conceal allocation. These were stored in a locked office and only opened after patient consent was completed by the trial coordinators. After randomly assigned testing, all clinical decisions were made by the managing physicians based on all available data, including the results of randomized testing and there was no pre-specified management algorithm. The trial was monitored by our institutional review board and was registered at ClinicalTrials.gov (NCT02346565).

Study patients

Consecutive women referred to our Rapid Access Chest Pain Clinic with chest pain or angina equivalent symptoms, for whom non-invasive testing was requested for clinical management, were screened from June 2015 to April 2018. Patients with no known CAD were potentially eligible if there was an intermediate pre-test probability (PTP) of significant CAD. Exclusion criteria were as follows: (i) electrocardiogram abnormalities such as bundle branch block, pacemaker, left ventricular hypertrophy, or resting ST-T wave changes; (ii) persistent or crescendo chest pain; (iii) functional testing or cardiac catheterization within the previous 6 months; (iv) history of severe valvular disease or heart failure, (v) severe hypertension, and (vi) women with difficulty undergoing daily activities, who would be considered to have functional limitation.

Exercise electrocardiography

Exercise electrocardiographies were performed by experienced cardiac physiologists and interpreted by the primary physician (cardiac specialist nurse or cardiology middle-grade doctor) as per standard clinical practice. Treadmill testing used the standard Bruce protocol. Endpoints were fatigue, severe ischaemia (severe chest pain, $\geq$ 2 mm horizontal or downsloping ST depression), severe hypertension (systolic BP $\geq$ 220 mmHg), hypotension (systolic BP $\leq$ 90 mmHg), pre-syncope, or significant arrhythmia. Patients who achieved an adequate workload and achieved 85% of the target heart rate, without any symptoms, haemodynamic compromise, or ECG changes were considered to have a negative test. Patients who developed significant chest pain, hypotension, an arrhythmia, or $\geq$1 mm planar or downsloping ST depression in two or more leads of the same territory, during exercise or in recovery, were considered to have a positive test. All other patients were considered to have an inconclusive test.

Instead of an arbitrary definition, the adequate workload was defined according to the AHA/ACC guidelines with age-specific criteria to avoid inappropriately labelling tests as inconclusive (*Figure 1*).[16]

Exercise stress echocardiography

All ESE studies were performed using treadmill exercise as previously described.[17] Parasternal long axis, short axis, and apical 4-chamber, 2-chamber, and 3-chamber images were obtained at rest and peak stress (iE33 Philips Medical Systems, Eindhoven, the Netherlands). In patients in whom the endocardial borders of $\geq$2 contiguous segments were not visualized during deep breathing, the ultrasound contrast agent Sonovue (Bracco, Milan, Italy) was administered by intravenous bolus injection (0.3 mL) and flushed with saline. The final SE result was based on the interpretation of the expert cardiologist (R.S.) as performed routinely. Online images were interpreted qualitatively for the presence, extent, and location of regional wall motion abnormalities (WMA) by the consultant lead (R.S.) as per routine clinical practice. Systolic wall thickening and endocardial WMA were assessed using a 17-segment left-ventricle model. The stress echocardiogram was considered negative if all segments were normal at baseline and at peak stress having

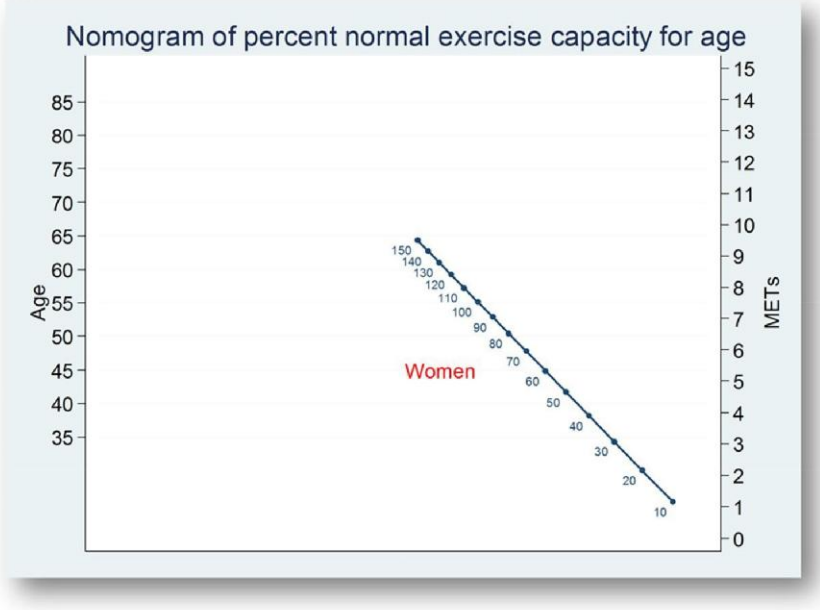


Figure 1 Nomogram of the predicted exercise capacity for age in asymptomatic women.[16]

achieved 85% of the age-predicted target heart rate at an adequate workload. Patients with evidence of WMAs at rest or who developed regional WMAs at peak stress were deemed to have a positive stress echocardiogram. Patients with uninterpretable images or patients that failed to achieve the target heart rate were considered to have inconclusive tests.

Coronary angiography

Standard techniques were used for performing angiography. Coronary artery disease was defined as $\geq$ 70% luminal diameter narrowing in one or more epicardial coronary arteries or their major branches.

Ascertainment of events during follow-up

Patients were contacted by telephone at 6, 12, 24, and 36 months following randomization to determine the occurrence of the study's primary and secondary endpoints. Experienced research personnel utilized a scripted interview for ascertainment of clinical events. Where patients could not be contacted directly and for further information regarding health resource utilization (including data on further diagnostic testing, specialist referral, and casualty attendances), computerized records from all hospitals in the pan-London area were reviewed and general practitioners contacted. The data collectors were blinded to randomization assignment.

Costs

Diagnostic costs were a tertiary end point. The initial diagnostic costs were defined as the sum of all investigations performed up to and including the point when the diagnosis or presumed absence of CAD was deemed established. These included a diagnostic CA, a negative functional test, or a decision not to proceed with any further tests. Costs were calculated in British pounds using the NHS payments tariff 2020/21.[18] Resource use data were collected for all patients on an intention to treat (ITT) and a per-protocol basis.

Statistical analysis

A power calculation performed by an independent statistician, based on the results of a previous study in our institution,[13] suggested that 186 patients would have to be randomized into each study arm for the study to show a difference in the primary outcome (PPV) with a 5% significance level with a margin of the inferiority of 10% and 80% power. We envisaged a drop-out rate of approximately 10%, and possible initial crossover of patients and therefore, we aimed to recruit 210 patients in each arm of the study.

Continuous variables are shown as mean $\pm$ SD, and categorical variables are shown as proportions. Comparison of continuous data was made by the independent *t*-test and by the Mann–Whitney non-parametric test, for data not following a normal distribution. To compare the proportion of categorical variables, Pearson's χ^2 test was used. Index and follow-up procedural costs were summarized as mean (SD) and median [interquartile range (IQR)] and compared with the Mann–Whitney U-test. For all statistical tests, a *P* value of <0.05 was considered significant. Statistical analyses were performed using SPSS Statistics version 21.0 (IBM Software). Outcomes were assessed by ITT (including all recruited participants according to the original group assignment).

Results

Study population

A total of 416 women were recruited into the study with 207 women randomized to Ex-ECG and 209 to ESE. The study flow diagram is

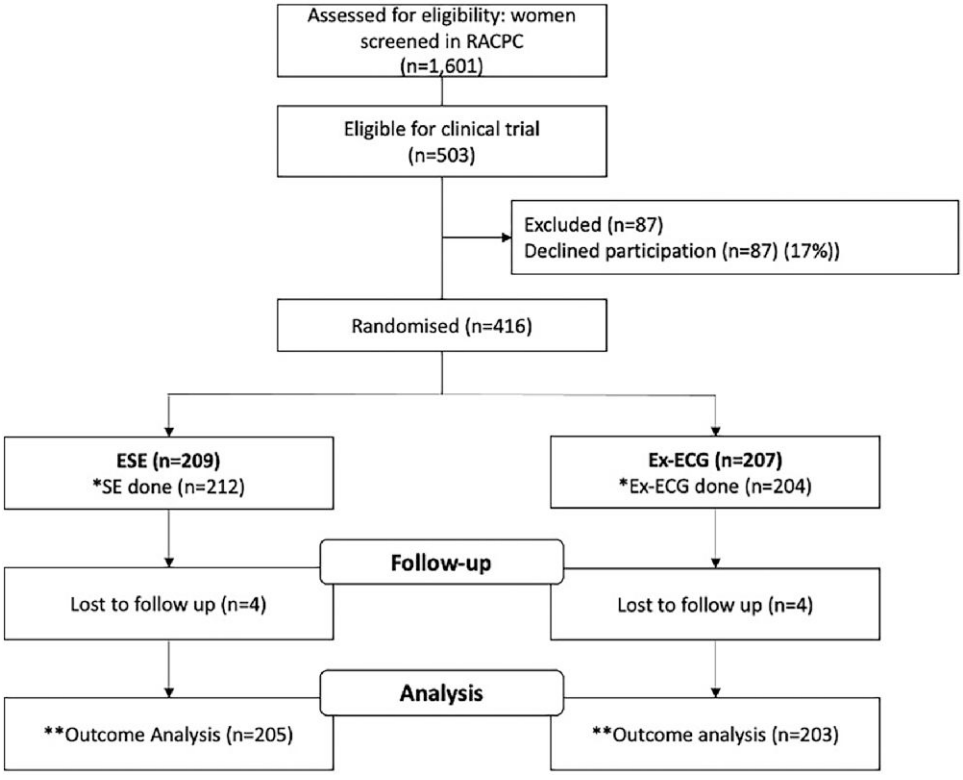


Figure 2 Flow diagram of eligible and randomized patients. Women are screened from the Rapid-Access Chest Pain Clinic. *In the exercise electrocardiography arm, of the 207 patients randomized three preferred to undergo exercise stress echocardiography. Consequently, 204 underwent exercise electrocardiography and whilst 209 were randomized to the exercise stress echocardiography arm, 212 underwent exercise stress echocardiography (per protocol). **Outcome (downstream resource utilization and events) analysis was based on the final randomized patients (intention to treat). ESE, exercise stress echocardiography; Ex-ECG, exercise electrocardiography.

Table 1 Baseline characteristics of study population

Demographics	Total (416)	Ex-ECG (207)	ESE (209)	*P* value
Age	58.4 (8.9)	58.3	58.5	0.49
Ethnicity				
Caucasian	137	67	70	0.81
Asian	213	107	106	0.84
Black	35	14	21	0.23
Other	30	16	14	0.68
Risk factors				
Hypertension	180 (43)	81 (40)	99 (47)	0.32
High cholesterol	202 (48)	98 (48)	104 (49)	0.61
Diabetes mellitus	91 (22)	45 (22)	46 (22)	0.87
Smoker	64 (15)	34 (17)	30 (14)	0.73
FHx	170 (41)	89 (44)	81 (38)	0.30
Chest pain				
Typical	138 (33)	70 (34)	68 (32)	0.86
Atypical	221 (53)	104(50)	117 (56)	0.20
Non-cardiac	57 (14)	32 (16)	25 (12)	0.30
PTP				
NICE	41 (27)	42 (29)	40 (26)	0.71
ESC	14.7 (12.5)	14.5 (12.2)	14.8 (13)	0.13

shown in *Figure 2*. The mean age was 58 ± 9 years, 180 were hypertensive (43%), 91 were diabetic (22%), 201 had hypercholesterolaemia (48%), and the mean PTP for CAD was 41 ± 27%. There were no significant differences in baseline characteristics between the two groups (*Table 1*). Thus, the trial population had ethnic diversity and a high burden of vascular risk factors.

Among women undergoing Ex-ECG, 148 (72.5%) were negative, 45 were inconclusive (22.1%), and 11 (5.4%) were positive. Among the ESE group, 200 (94.3%) were negative and 12 (5.7%) were positive. There were no inconclusive ESE tests (*Figure 3*). There were 43 women with an inconclusive Ex-ECG, who received an ESE; two women declined further testing. No patients in either arm had serious complications from non-invasive imaging. Ultrasound contrast agent was administered in 98.6% of women in the ESE arm.

Outcomes

Of the 416 women recruited into the study, eight were lost to follow-up, four in each arm. Four hundred and eight (98.1%) women were followed up for 2.9 ± 0.88 years.

A total of nine primary endpoints were confirmed, including four AMIs, one death, one late revascularization, and three heart failure hospitalizations. The event rate was 0.75%/year in the entire cohort. The pre-specified, combined endpoint of death, NFMI, late revascularization, and heart failure hospitalization occurred in six in the Ex-ECG arm and three in the ESE arm (*Table 2*). The observed MACE rate was 2.9% in the Ex-ECG arm and 1.4% in the ESE arm ($P = 0.30$ by log-rank test).

Angiography and revascularization

Within 4 months after randomization and as a direct consequence of the initial test, 10 women in the Ex-ECG arm and 12 in the ESE arm underwent coronary angiography; one woman with a positive Ex-ECG declined coronary angiography. There were three women with positive Ex-ECG and four with positive ESE who had flow-limiting disease on angiography giving a PPV of 30% and 33%, respectively ($P = 0.87$). Two women with inconclusive Ex-ECGs underwent coronary angiography following the ESE, both of which showed flow-limiting disease. Nine women underwent early revascularization—five in the Ex-ECG arm and four in the ESE arm.

Downstream resource utilization

Hospital attendances and cardiac imaging-resource utilization are shown in *Table 3*. By randomization, there were no significant differences in clinic attendances (36 vs. 29, $P = 0.44$) and emergency attendances with chest pain (28 vs. 25, $P = 0.55$) in the Ex-ECG and ESE groups, respectively. However, following the initial diagnosis, more women underwent further functional and anatomical testing in the Ex-ECG arm (37 vs. 17, $P = 0.001$). Five patients in the Ex-ECG arm and six women in the ESE arm underwent late coronary angiography. Overall, more patients in the Ex-ECG arm had clinical attendances at hospital and non-invasive cardiac investigations than those in the ESE arm (101 vs. 71, $P = 0.002$).

Cost analysis

The ITT analysis indicated that the mean initial diagnostic cost to either confirm or refute the diagnosis of CAD was significantly lower for Ex-ECG compared with ESE group (£243.43 vs. £274.91, $P < 0.005$), due to the higher index testing costs for ESE (£199 for ESE and £124 for Ex-ECG). Downstream investigations were more frequent in the Ex-ECG group, incurring higher costs than in the ESE group. Overall diagnostic costs (initial plus downstream) were on average 7.4% lower for the Ex-ECG compared with the ESE group (*Table 4*). This lower mean overall cost of Ex-ECG was also observed in the per-protocol analysis.

Discussion

In symptomatic women with an intermediate PTP of significant CAD and preserved functional capacity, there was no significant difference in the PPV for the detection of obstructive CAD between an initial ESE strategy and an initial Ex-ECG strategy. However, downstream resource utilization was significantly higher with an initial Ex-ECG strategy.

Although inconclusive results from initial Ex-ECG testing created a need for more follow-up testing, the higher index test costs for ESE meant that the initial mean diagnostic cost of Ex-ECG was lower. Based on payment tariffs in the British National Health Service 2020/21, the cumulative costs (initial diagnosis and downstream) were 7.4% less in the Ex-ECG arm than the ESE arm. If the differential in costs between the Ex-ECG and ESE procedures was less, however, the balance would tip in favour of ESE. Furthermore, societal costs including time off work for further diagnostic tests, transport costs, etc. were not captured as part of this study. It is likely that the cost savings related to SE are underestimated here, which would favour ESE as the test of choice. Reduced hospital attendances and diagnostic tests are also likely to favour ESE, in terms of quality of life for patients. There was no significant difference in MACE outcomes between the two strategies.

Initial testing with Ex-ECG is recommended by AHA/ACC guidelines in women with suspected angina and no prior history of CAD who can exercise and have no resting ECG changes.[8] These guidelines are mainly based on observational studies, and the WOMEN study comparing Ex-ECG to single photon emission computerized tomography, where Ex-ECG was found to be more cost-effective in this low-risk population.[9]

To date, the evidence base for stress echocardiography in women with suspected CAD has been limited, with the preponderance of evidence derived from observational registries supporting the superiority of ESE over standard Ex-ECG alone. Our findings represent the first

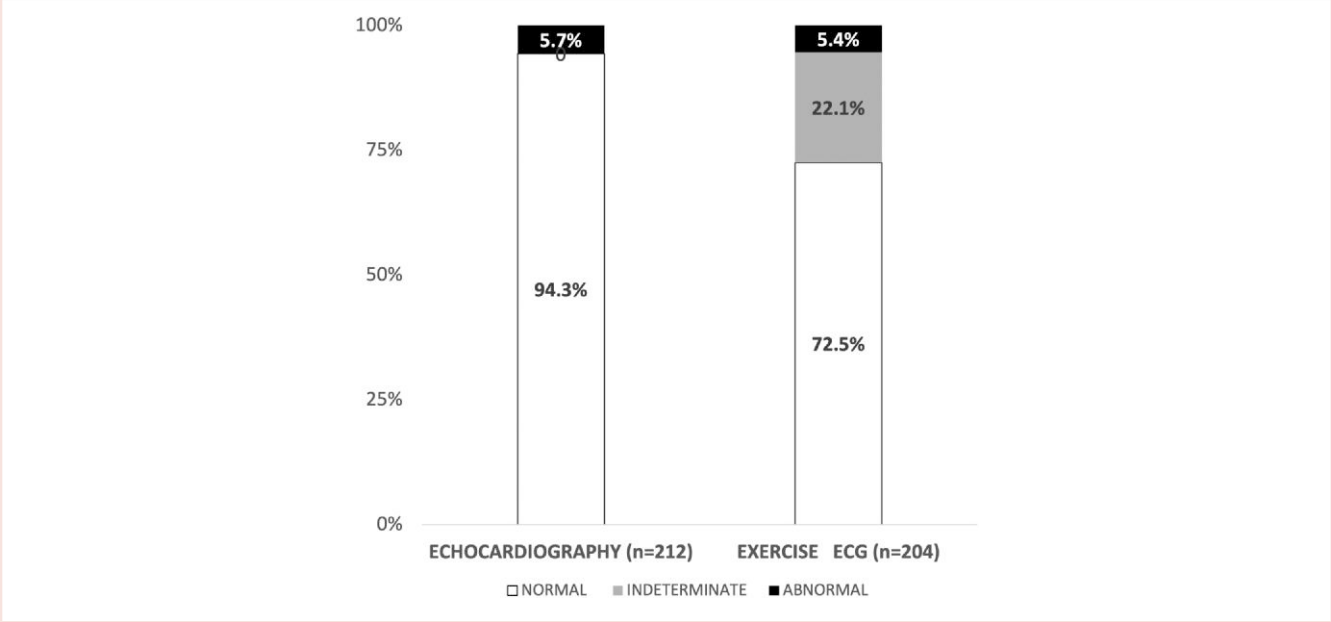


Figure 3 Index test outcome based on tests actually performed in each arm (per protocol). This demonstrates that more patients in the exercise electrocardiography arm had inconclusive tests, in comparison to the exercise stress echocardiography arm.

Table 2 Cardiovascular events and invasive procedures according to randomization

Outcome	Total	Ex-ECG ($n = 203$)	ESE ($n = 205$)	*P* value
Cardiovascular events				
All MACE	9	6	3	0.31
All-cause death	1	1	0	
Non-fatal myocardial infarction	4	3	1	0.31
Late revasc	1	1	0	
Heart failure hospitalization	3	1	2	0.57
Coronary angiography and intervention				
Cardiac catheterization	33	16	18	0.88
Coronary revascularization	9	5	4	0.73

Table 3 Downstream resource utilization according to randomization arm

Resource	Total	ESE ($n = 205$)	Exercise ECG ($n = 203$)	*P* value
Clinical				
Hospitalization with chest pain	53	25	28	0.55
Clinics	65	29	36	0.44
Subsequent imaging				
CTCA	8	4	4	
SE	29	7	22	
Ex-ECG	4	0	4	
SPECT	2	0	2	
Late coronary angiography	11	6	5	
Total downstream testing	43	17	37	0.001

randomized trial evidence comparing the effectiveness of standard treadmill Ex-ECG and ESE for women presenting for the evaluation of suspected CAD, without a previous history of CAD. To our knowledge, this is only the second randomized study in women of non-invasive testing for suspected angina.

Notably, the event rate in this population was low despite the intermediate risk based on PTP, as were the rates of abnormal functional tests. It is evident from the study that the pre-test risk of CAD in women is overestimated. It has been revealed that PTP scores based on both the NICE and ESC guidelines overestimate PTP, with the UK NICE risk score model overestimating risk further compared with the ESC model. It is now known that the prevalence of obstructive CAD in the population tested is only approximately 12% and is much lower in females.[19] The recent ACC/AHA guideline uses a CAD consortium-based PTP of CAD, reflecting the very low prevalence of obstructive CAD in the contemporary population. Additionally, on enrolment, the participants were expected to have a minimum functional status which may explain the low event rate. Other studies have shown similarly low event rates.[9,20]

As demonstrated in a PROMISE sub-study, despite the higher risk factor burden in women, they are less likely to have a positive stress test,[21] and in our study, only 6% of functional testing was abnormal. An observation from the PROMISE study was that more women were referred for imaging stress tests instead of Ex-ECG—a persistent pattern of testing that fails to consider the randomized controlled trial evidence.

Table 4 Resource utilization based on randomization assignment, on an intention-to-treat and a per-protocol basis

			Initial diagnostic costs (all investigations up to point of diagnosis or presumed absence of CAD		Follow-up/downstream costs		Initial diagnostic and follow-up costs	
Analysis	Group	*n*	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)
Intention to treat	Ex-ECG	207	243.43 (317.74)	124.00 (124–323)	57.96 (214.41)	0	301.39 (368.27)	124.00 (124–323)
	ESE	208	274.91 (309.12)	199.00 (199–199)	50.41 (231.54)	0	325.32 (376.13)	199.00 (199–199)
	MWU		$P < 0.001$		$P < 0.001$		$P < 0.001$	
Per protocol	Ex-ECG	204	243.71 (320.13)	124.00 (124–323)	58.81 (215.87)	0	302.52 (370.91)	124.00 (124–323)
	ESE	211	274.18 (306.90)	199.00 (199–199)	49.69 (229.96)	0	323.88 (373.58)	199.00 (199–199)
	MWU		$P < 0.001$		$P = 0.019$		$P < 0.001$	

PROCEDURE and tariff code**	**UNIT COSTS (£) 2020/21**
EY50Z: Complex Echocardiogram (ESE)	199
EY51Z: Electrocardiogram Monitoring or Stress Test (Ex-ECG)	124
RN20Z: Myocardial Perfusion Scan (SPECT)	338
EY43C: Standard Cardiac Catheterization (Coronary Angiogram)	1322
RD28Z: Complex CT Scan (Coronary Angiogram)	290

IQR, interquartile range; MWU, Mann–Whitney U-test; SD, standard deviation.

Overall, following the initial diagnosis, there was a low rate of subsequent testing—approximately 10% of women underwent follow-up testing. The rate of follow-up testing, as was the initial proportion of inconclusive Ex-ECGs was reassuringly comparable to the WOMEN study.

Clinical implications

For intermediate-risk women capable of performing exercise, either Ex-ECG without imaging or ESE are justifiable first-line tests in this low-risk population. These findings are in contrast to a randomized study in an unselected population in our group, in which ESE was associated with better diagnostic performance and significant cost savings, which clearly favours ESE as the first-line test over Ex-ECG in this population.[14]

However, due to the substantially lower inconclusive tests with ESE and higher subsequent testing with Ex-ECG, which may be less assuring for patients and physicians alike, clinicians may prefer using ESE as the initial test in the female population.

Nevertheless, in centres without expertise in ESE, a first-line Ex-ECG strategy is a safe and cost-effective option with health outcomes similar to ESE. A caveat is: For the results of this study to be replicated in clinical practice, it is crucial that the same methodology is used particularly when defining an adequate workload for exercise testing. It is likely that by using age-specific workload criteria, we significantly reduced the number of tests labelled 'inconclusive' whilst at the same time ensuring a low MACE event rate in the Ex-ECG strategy.

Limitations and strengths

This study was conducted in a single centre and a multi-centre study in theory would have provided a stronger evidence base. However, we would assert that since our centre has renown and expertise in stress echocardiography, and ESE was not superior to Ex-ECG, this may be regarded as strong evidence that Ex-ECG is not inferior to ESE as a frontline non-invasive test in women with suspected CAD.

We observed few MACE events during follow-up, and longer follow-up and larger sample sizes are necessary to discern differences in low-risk patients. The study was not powered for clinical outcomes. Furthermore, we assumed in this study that those with a negative test had no evidence of obstructive CAD, and so no further testing was conducted. However, the decision not to test further in patients with a negative test in both arms was a clinical decision, based on the typicality of chest pain, risk factors, exercise capacity, and symptoms on exercise. Furthermore, a recent study showed non-obstructive CAD has a very low event rate for AMI similar to no evidence of atherosclerosis.[22] In this study, the incidence of AMI and all-cause death was only 0.42%/year. Thus, the post-test probability of obstructive CAD in such patients is likely to be very low. Another limitation is that the power of the study associated with the PPV was insufficient since ESE did not perform as well as expected in this all-female population. This is in contrast to non-randomized studies where there is a clear difference in PPV between Ex-ECG and ESE. These findings reflect a contemporary population where the prevalence of obstructive CAD is low, compounded with the higher prevalence of ischaemia with non-obstructive coronary arteries in women associated with abnormal functional testing, than in males. This is likely to have reduced the PPV of ESE. Almost two-thirds (62%) of women referred for coronary angiography and enrolled in the National Heart, Lung, and Blood Institute-sponsored Women's Ischaemia Syndrome Evaluation, did not have a significant obstructive stenosis.[23]

There were some important strengths to this study. A high percentage of eligible patients agreed to participate in the study (over 80%) making this cohort representative of the general population. Furthermore, the population analysed consisted of ethnic minorities of low socioeconomic status, who remain understudied.[24] To replicate real-world practice, a pragmatic approach was taken where decision-making was made by clinicians instead of strict algorithms. This study was also conducted in an experienced centre for stress echocardiography, using cutting-edge techniques with high contrast use providing this modality with the greatest chance of success. Rigorous definitions were given for test outcomes to minimize tests being labelled as inconclusive, with no clinical impact.

Conclusion

Among women who are capable of exercise at the time of planned diagnostic testing and with no previous history of CAD, our data support

either an initial Ex-ECG testing strategy without imaging or ESE as the first-line test. The clinical and health-economic implications of this trial are important and may help to further inform clinical practice guideline development.

Clinical competencies

In patients with suspected CAD, an initial Ex-ECG strategy is as efficacious as ESE and with a better cost profile. However, ESE demonstrated better downstream resource utilization. Thus, the study supports either an initial Ex-ECG strategy or ESE as the first-line test.

Translational outlook

A larger multi-centre randomized study powered to show differences in outcome with these two diagnostic test-determined management strategies, needs to be performed.

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Data availability

No new data were generated in support of the article.

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