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Prognostic value of a negative peak supine bicycle stress echocardiography with or without concomitant ischaemic stress electrocardiographic changes: A cohort study

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Abstract

Background: a negative peak supine bicycle exercise stress echocardiography (ESE) was shown to have a long-term favourable prognostic value. Data on the long-term prognosis of ischaemic electrocardiographic (ISECG) changes in the setting of a negative peak supine bicycle ESE are lacking.

Design: we evaluated the prognostic value of negative peak supine bicycle ESE with or without concomitant ISECG changes in a referral population evaluated for chest pain after an inconclusive first-line work-up including clinical evaluation and exercise ECG stress.

Methods: from 2003 to 2010, patients who underwent a peak supine bicycle ESE and were deemed to be negative were evaluated. Two groups based on concomitant stress ECG tracing were analysed – those with normal stress ECG and those with ISECG changes. The primary endpoint was cumulative incidence of cardiovascular death, hospitalizations for acute coronary syndrome and coronary revascularizations.

Results: a total of 371 patients (mean age 59.1 ± 12.1 years, 49.9% women) were studied. Of those, 141 (38.0%) had concomitant ISECG changes. Mean follow-up was 3.46 ± 1.76 years. The primary endpoint occurred in 3.0% of patients, (2.2% in those with normal stress ECG, and in 4.3% with ISECG changes, $p = 0.251$); with unadjusted hazard ratio for primary endpoint of 2.04 (95%CI 0.62–6.69, $p = 0.239$) in patients with ISECG changes compared to those with normal stress ECG.

Conclusions: in an outpatient population without known CAD evaluated for chest pain after inconclusive first-line work-up, a negative peak supine bicycle ESE confers an excellent prognosis regardless of the nature of concomitant stress ECG abnormalities.

Keywords

Stress electrocardiography, exercise stress echocardiography, ischaemia, prognosis

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Introduction

Exercise treadmill testing (ETT) is currently the preferred test for evaluation of low risk patients with atypical chest pain symptoms[1]. Nonetheless, inconclusive results (due to equivocal ECG changes or discordance between symptoms and test results) limit the diagnostic ability of this noninvasive test.[1] Further testing after an inconclusive ETT can be recommended to improve the

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diagnostic accuracy for detecting obstructive coronary artery disease (CAD) and enhancing risk assessment. Currently, there is no agreement on an efficient subsequent diagnostic test to be used in patients with inconclusive ETT. Peak supine bicycle exercise stress echocardiography (ESE) is a well-validated test that can diagnose the presence of CAD by visualizing stress-induced wall motion abnormalities in patients able to achieve adequate workload with exercise.[2,3] A positive peak supine bicycle ESE is a strong independent predictor of major cardiac events, particularly in patients with an intermediate pre-test probability of CAD.[4] In addition, a negative peak supine bicycle ESE has a long-term favourable prognostic value.[5]

A recent study reported that patients with negative treadmill ESE had excellent long-term outcomes (annualized event rate of 1%), regardless of 'ischaemic'stress electrocardiographic changes (ISECG) results over a median 95-month follow-up period.[6] Another study demonstrated the incremental prognostic value of ISECG[7] when combined to an imaging modality. Therefore, the prognostic value of ISECG in the setting of a normal wall motion response in a stress echocardiographic study is not well defined.

We aimed to evaluate the prognostic value of negative peak supine bicycle ESE, with or without ISECG, in a referral population evaluated for chest pain symptomatology after an inconclusive first-line work-up, including clinical evaluation and ETT.

Methods

This study is a retrospective analysis of a large dataset for evaluation of the prognostic value of simultaneous peak supine bicycle ESE and stress ECG in patients with an inconclusive first-line work-up for chest pain symptomatology, including clinical evaluation and ETT. The study was conducted and reported in accordance with The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[8]

Identification of study cohorts

Using the Modena University Hospital Cardiovascular Echocardiography Laboratory Database, we identified all patients who underwent peak supine bicycle ESE for the evaluation of chest pain between 1 March 2003 and 31 December 2010.

Study inclusion criteria were: age $\geq$18 years, patients who had an inconclusive ETT, patients with a normal or negative for ischaemia peak supine bicycle ESE, patients residing in Modena province, Italy, and those presenting for evaluation of CAD with estimated sufficient functional capacity.[9] Study exclusion criteria were: documented history of cardiovascular diseases, including CAD (defined as prior hospitalization for acute coronary syndrome, coronary revascularization and/or presence of Q waves at the baseline electrocardiogram and/or angiographic evidence of coronary stenosis >50%), congenital heart disease, severe valvular heart disease, dilated cardiomyopathy, or congestive heart failure; patients with left bundle branch block, or abnormal baseline ECG interfering with interpretation (digoxin therapy, left ventricular hypertrophy by voltage with ST-segment or T-wave abnormalities, ST depression $\geq$1 mm at baseline, pre-excitation, or paced rhythm); patients with prognostically relevant extracardiac disease (cancer, end-stage chronic renal disease, severe obstructive pulmonary disease) and patients with poor acoustic windows (two or more left ventricular segments not visualized per American Society of Echocardiography 'ASE' guidelines).[10]

The identified patients were a subgroup of patients all referred to our laboratory after an ETT judged inconclusive by the interpreting physician. Inconclusive results occurred because of equivocal or rapid resolution of ECG changes or discordance between symptoms and test results[11] regardless of the heart rate and exercise capacity reached during the ECG stress test.

During the study period – 1 March 2003 to 31 December 2010 – a total of 1087 patients were referred to the Modena University Hospital Cardiovascular Echocardiography Laboratory for supine bicycle ESE, which were performed by two experienced operators (AB, FB). A total of 371 (34.1%) met the inclusion criteria and were included in the final analysis (Figure 1).

Peak supine bicycle exercise stress echocardiography (ESE)

When possible, peak supine bicycle ESE was performed with patients who were not taking anti-angina therapy. The exercise test was conducted with a variable load supine bicycle ergometer (Ergometrics 900 EL, Ergoline, Bitz, Germany) on a reclining seat at a 50° position to obtain the best echo windows for imaging. After recording a resting 2-dimensional echocardiogram from the standard views, patients pedalled at constant speed beginning at a workload of 25–50 W and increasing by 25 W every 3 minutes.[12] Two-dimensional images were obtained in four standard views (parasternal long-axis, parasternal short-axis, apical 4- and 2-chamber view) using Acuson Sequoia ultrasound systems (Mountain View, California, USA) in the supine position at baseline, at each workload and during recovery phase, and recorded using a quad-screen cine-loop system.

During each stage of exercise and recovery, symptoms (chest pain, shortness of breath, fatigue),

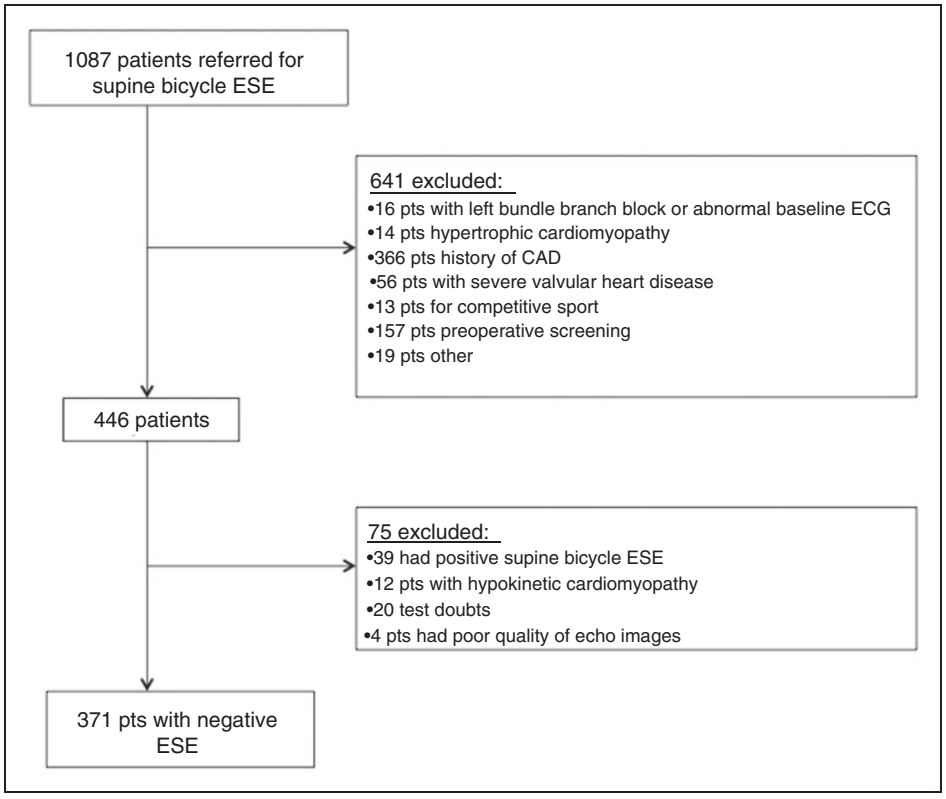

Figure 1. Flowchart of the study population (1 March 2003 to 31 December 2010).

blood pressure (BP), heart rate, cardiac rhythm, a 12-lead ECG and workload were recorded on the computerized database. Tests were supervised by specialist physicians.

Clinical data

Patients' demographics and clinical characteristics including age, gender, cardiac risk factors, cardiovascular medications and co-morbidities data were recorded at the time of supine bicycle ESE. Cardiac risk factors included: current smoking or history of smoking, hypertension (defined as untreated systolic blood pressure (BP) >140 mmHg or diastolic BP >90 mmHg or receiving anti-hypertension medication);[13] diabetes mellitus (defined as fasting glucose ≥120 mg/dl or receiving medication for hyperglycaemia);[14] dyslipidaemia (defined as total cholesterol >210 mg/dl, or LDL >130 mg/dl, or HDL <35 mg/dl or receiving medication for lipid control);[15] and obesity (defined as Body Mass Index ≥30 kg/m^2).

Supine bicycle exercise variables

Exercise variables obtained from the supine bicycle ESE included: exercise time in minutes; peak heart rate (HR) expressed in absolute values (maxHR); and achieved workload in W. Stress ECG at the time of supine bicycle ESE were interpreted as ischaemic (ISECG) if there was an abnormal (ischaemic) ST segment changes (defined as ≥1 mm horizontal or downsloping ST-segment depression or elevation measured 0.08 s after the J-point in ≥2 contiguous leads).[16]

Echocardiographic analysis

Digitized images at baseline and maximal exercise from each workload were interpreted by experienced observers (AB, FB) and utilizing the ASE 16-segment model.[10] Regional wall motion was graded as normal, hypokinetic, akinetic, dyskinetic, or aneurysmal and the wall motion score index (WMSI) was calculated for rest and stress. A negative (normal response) peak supine bicycle ESE was defined as normal or hyperdynamic during peak supine bicycle ESE.

Outcome endpoints

The primary endpoint was the cumulative incidence of cardiac death and hospitalizations for acute coronary syndrome and coronary revascularizations (percutaneous coronary intervention or coronary artery bypass surgery). The secondary endpoint was the composite endpoints of cardiac death and hospitalizations for

acute coronary syndrome, coronary revascularizations, atrial fibrillation and acute heart failure. The diagnoses were derived from hospital discharge codes. In most cases more than one code was reported, but only the first one was considered to classify the cause of hospitalization. Follow-up information for death was obtained from the national death index, where the status of all citizens is steadily updated and is 100% complete.

Death certificates were used to assign the cause of death. To avoid misclassification, cardiac death was classified according to Hinkle and Thaler's criteria.[17] Cardiovascular morbidity requiring hospitalization was assessed using the electronic archives of the health service of Modena province. All public hospitalization records of citizens resident in Modena province are stored in a digital format and may be accessed online after obtaining permission and an access password. This archive allows a nearly complete knowledge of all clinical events requiring hospitalization in Modena province since 1999. If there was uncertainty in adjudicating events from this electronic database, the general practitioners were contacted by phone. In order to allow complete follow-up only residents in Modena province were included in the study. All events were checked by an investigator (FM) blinded to the patient's past medical history and echocardiographic results.

Statistical analysis

Descriptive statistics were shown as percentages for categorical variables or as mean ± standard deviation for continuous variables with a normal distribution. Patients were divided into two groups on the basis of whether or not they had ISECG changes at the time of a negative peak supine bicycle ESE. Comparisons across two groups (those with ISCECG changes and normal stress ECG) were made with the Chi square test for categorical variables and the t-test or Kruskal Wallis test for continuous variables where appropriate. Kaplan-Meier curves were constructed to show survival free from primary and secondary endpoint events in patients with positive versus negative electrocardiographic findings. Time to event was calculated for each patient from date of supine bicycle ESE to the date of cardiac mortality. Survival in the two groups was compared with the log rank test. Cox regression analysis was used to estimate the hazard ratio (HR) and the 95% confidence interval (95%CI) using primary and secondary endpoint events as dependent variables. Patients were censored at the time of first event. Analysis was performed using a backward elimination procedure: variables were deleted from the model when $p > 0.1$ and entered when $p < 0.05$. The following variables were analysed in the Cox model: ISECG changes, age, gender, hypertension, dyslipidaemia, diabetes, smoking, baseline ejection fraction, double product, workload (W) achieved during exercise, and percentage of the age-predicted maximal heart rate achieved.

All analyses were performed using the Statistical Package (SPSS, Version 15.0, Chicago, IL). Differences were considered significant at $p < 0.05$ (2-sided).

Results

Study participants

The overall mean age of patients was 59.1 ± 12.1 years and 49.9% were women. A total of 141 of 371 patients (38.0%) had ISECG changes. Patients with ISECG changes were similar for age, cardiovascular risk factors and rate-slowing medications compared with the group with normal stress ECG (Table 1).

Results of the supine bicycle exercise variables

Exercise variables are shown in Table 2. Typical angina was reported only in 7 (2%) patients. A total of 171 patients (46%) achieved more than 100% of their age-predicted peak HR. There were no statistical significant differences between patients with normal stress ECG and ISECG in terms of achievement of >85% of the age-predicted maximal heart rate or maximal heart rate. Furthermore, no statistical differences were noted in workloads (W) achieved, in maximal systolic or diastolic arterial blood pressure or the rate pressure product (heart beat x arterial pressure). The baseline ejection fraction was comparable in the two groups as well as symptoms (Table 2).

Main outcome analysis

During a mean follow-up of 3.4 ± 1.8 years (median 4 years), there were a total of 11 (3%) patients with primary endpoint event. No patients died or had a ST elevation myocardial infarction; nine patients had unstable angina or non-ST elevation myocardial infarction; and two patients developed stable CAD requiring coronary revascularization (one surgical and one percutaneous). The decision to perform surgery was made by individual cardiologists in charge of the patients. No patient underwent myocardial revascularization within the first 5 months after the exercise stress echocardiographic examination. All patients who underwent coronary revascularizations were older than 60 years. Three patients did not achieve the 85% of age predicted maximal heart rate, five patients achieved a workload of at least 100 W and six patients had ISECG. None of the patients who had cardiac events reported angina during ESE.

Table 1. Baseline characteristics categorized by stress-induced ECG changes (n = 371).

	Normal stress ECG and normal peak supine bicycle ESE N = 230	Stress induced ischaemic ECG (ISECG) and normal peak supine bicycle ESE N = 141	*p*
Age (years)	59 ± 12	59 ± 13	0.5
Age > 65 years, n (%)	74 (32)	44 (31)	0.8
Women, n (%)	110 (48)	75 (53)	0.3
Hypertension, n (%)[a]	120 (57)	79 (59)	0.7
Current smokers, n (%)[a]	22 (11)	15 (11)	0.9
Former smokers, n (%)[a]	14 (7)	8 (6)	
Diabetes mellitus, n (%)[a]	21 (10)	20 (15)	0.2
Dyslipidaemia, n (%)[a]	82 (33)	47 (36)	0.5
Beta blockers, n (%)[a]	45 (23)	31 (23.3)	0.9
Nitrates, n (%)[a]	7 (4)	4 (3)	0.8
Calcium blockers, n (%)[a]	16 (8)	17 (13)	0.2

Continuous data are presented as mean ± SD; categorical data as number of patients and percentage of sample.; [a]Data on risk factors and medications were available in at least 90% of patients.

Table 2. Supine bicycle stress variables categorized by stress-induced ECG changes (n = 371).

	Normal stress ECG and normal peak supine bicycle ESE N = 230	Stress induced ischaemic ECG (ISECG) and normal peak supine bicycle ESE N = 141	*p*
No symptoms, n (%)	198 (86)	125 (89)	0.5
Angina, n (%)	3 (1)	4 (3)	0.3
Atypical chest pain, n (%)	17 (7)	4 (3)	0.06
Dyspnea, n (%)	8 (4)	5 (4)	0.9
Workload achieved (W)	103 ± 31	102 ± 38	0.7
Maximal heart rate achieved (bpm)	134 ± 21	136 ± 20	0.3
Percentage of age-predictedmaximal heart rate (%)	83 ± 12	84 ± 12	0.5
Achieving ≥85% age-predictedmaximal heart rate, n (%)	100 (44)	71 (50)	0.3
Peak systolic arterial pressure (mmHg)	192 ± 27	191 ± 22	0.6
Peak diastolic arterial pressure (mmHg)	88 ± 21	92 ± 22	0.1
Baseline ejection fraction (%)	59 ± 3	59 ± 4	0.4
Peak ejection fraction (%)	69 ± 9	73 ± 7	0.0004
Peak rate pressure product (double product) (mmHg/s)	25,657 ± 5882	25,980 ± 4929	0.6

Continuous data are presented as mean ± SD; categorical data as number of patients and percentage of sample.

Stress ECG and primary endpoints

Five (2%) patients with normal stress ECG results and six patients (4%) with ISECG changes had primary endpoints ($p = 0.3$). Five-year survival free from primary endpoint events was 98% in patients with normal stress ECG and 96% in those with ISECG changes, $p = 0.2$ (Figure 2) with an annual incidence of the primary endpoint of 0.9%/year, (0.6%/year in patients with normal stress ECG and 1.2%/year in patients with ISECG changes). The unadjusted hazard ratio for primary endpoints was 2.04 (95%CI

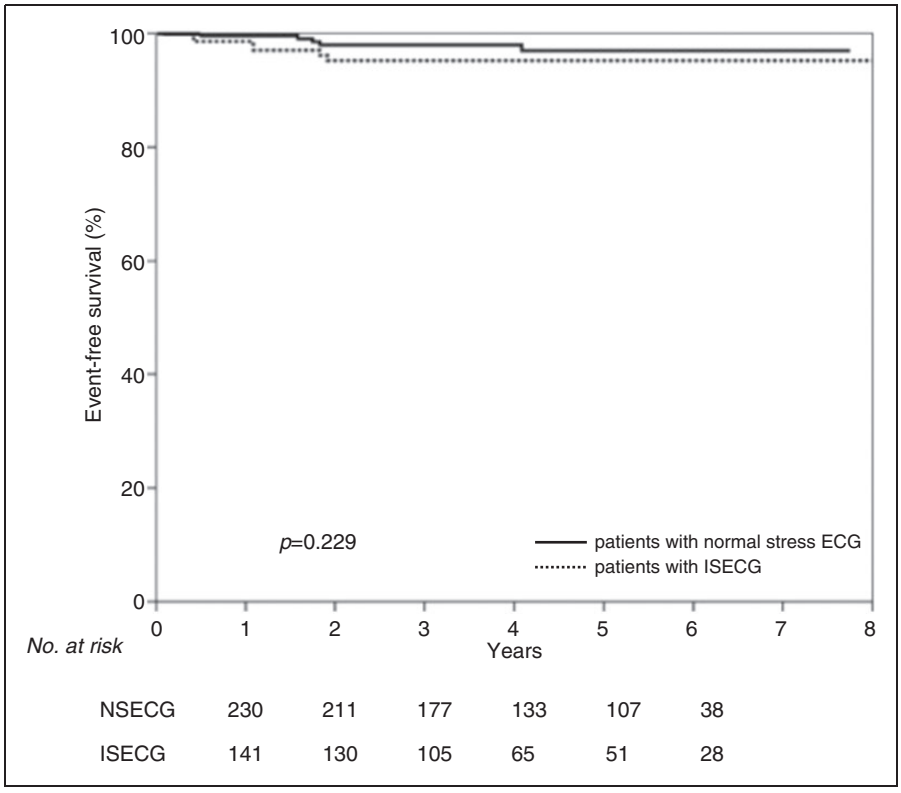

Figure 2. Kaplan–Meier survival curves categorized by stress ECG results at the time of a negative peak supine bicycle ESE, showing survival-free from primary endpoints.

0.62–6.69), $p = 0.2$ in patients with ISECG changes compared to those with normal stress ECG at the end of follow-up.

Multivariate predictors of primary endpoint events

ECG changes were not independent predictors of primary endpoint events after adjusting for age, gender, hypertension, dyslipidaemia, diabetes, smoking, baseline ejection fraction, rate pressure product, workload (W) achieved during exercise and percentage of the age-predicted maximal heart rate achieved. Dyslipidaemia and workload (W) achieved were independent predictors of primary endpoint events at multivariable analysis with adjusted HR of 4.35 (95% CI 1.06–17.9), $p = 0.04$; and 1.02, (95%CI 1.00–1.03), $p = 0.04$, respectively. Exercise stress ECG results at the time of negative peak supine bicycle ESE did not show any added prognostic value. Furthermore, there was no significant interaction between ISECG changes and exercise-induced angina.

Composite endpoints

During a mean follow-up of 3.4 ± 1.8 years, 23 (6%) patients had the composite primary and secondary endpoints. There were no significant differences in the occurrence of composite endpoints between patients with normal stress ECG –13 (6%) – and patients with ISECG changes – 10 (7%), $p = 0.72$ – with an annual incidence of the composite of primary and secondary endpoint events of 1.8%/year, (1.6%/year in patients with normal stress ECG and 2.1%/year in patients with ISECG) (Figure 3). The unadjusted hazard ratio for composite endpoints was 1.17 (95% CI 0.50–2.73), $p = 0.71$ in patients with ISECG changes compared to NSECG results.

Multivariable predictors of composite endpoints

In our patient cohort, ECG changes at the time of a negative supine bicycle ESE were not independent predictors of composite endpoints after adjusting for age, gender, hypertension, dyslipidaemia, diabetes, smoking, baseline ejection fraction, rate pressure product, workload (W) and percentage of the age-predicted maximal heart rate. The only independent predictor of composite endpoints was older age (HR = 1.05, 95%CI 1.00–1.10, $p = 0.03$). We found no significant interaction between ISECG changes and exercise-induced angina ($p = 0.98$). Furthermore, we found no significant interaction between ISECG results and

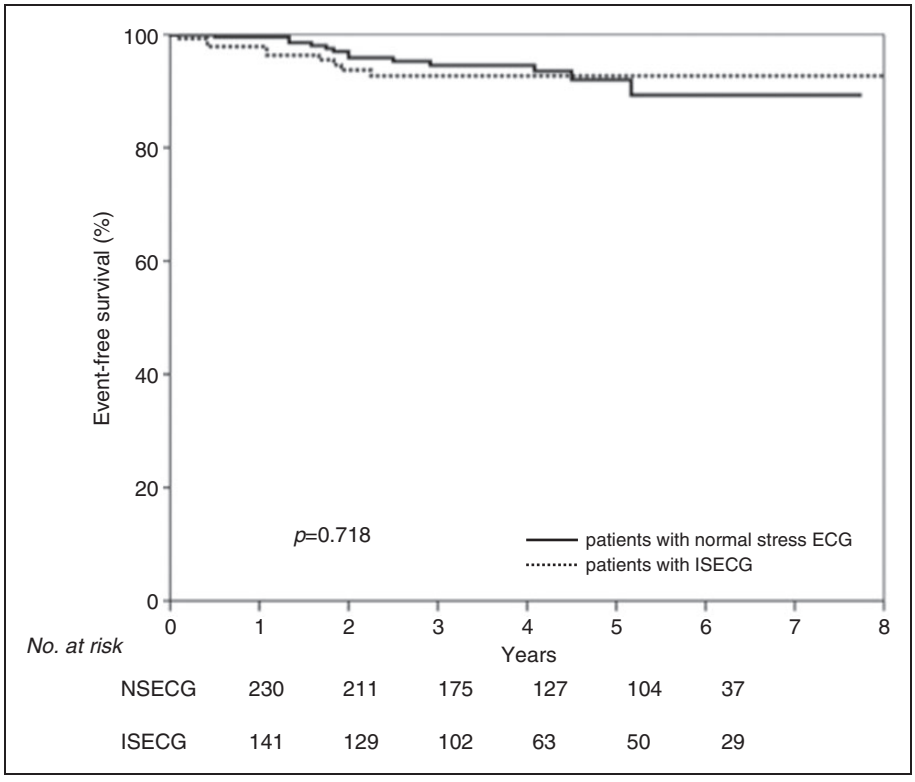

Figure 3. Kaplan–Meier survival curves categorized by stress ECG results at the time of a negative peak supine bicycle ESE, survival-free from composite endpoints.

medical therapy (primary endpoint interaction between any therapy at time of echo × ISECG changes $p = 0.127$.

Discussion

The main finding of our study is that the presence of concomitant ISCEG changes at the time of a negative peak supine bicycle ESE did not change the risk assessment profile and was not an independent prognostic variable in predicting cardiovascular events (primary or composite).

The overall incidence of cardiovascular events (primary endpoint) in this population was 0.9%/year and the secondary composite endpoint was 1.8%/year with a mean follow-up of 3.4 years, consistent with the meta-analysis by Metz et al.[5]

The incidence of primary endpoints was not affected by the presence of ISECG changes. Similar findings for composite endpoints were highlighted.[6,18]

Our findings are in support of previous report by Al-Mallah et al., who studied a high-risk population with substantial incidence of CAD and reported that patients with negative treadmill ESE had excellent long-term outcomes, regardless of stress ISECG changes.[6] Furthermore, our findings were consistent with previous findings in patients undergoing post-exercise treadmill ESE protocols. In a prior study, McCully et al.[18] examined outcomes in 1325 patients with a negative post-exercise treadmill ESE and no history of CAD. They found excellent 3-year outcomes in the study group, with first-year freedom from events of 99.2%. Independent predictors of adverse events were METs achieved, angina, increasing age and echocardiographic left ventricular hypertrophy. Stress-induced ECG abnormalities were not univariate or multivariate predictors of cardiac events in their population.

We believe there are two new aspects of our results when compared to previous reports. First, in our study we had a greater proportion of patients with exercise ECG changes and normal stress echocardiograms (38%) because of a previous inconclusive exercise ECG stress test. Second, we adopted strict exclusion criteria, particularly the exclusion of patients with known CAD. This increased the external validity of our results but at the cost of the low rate of the primary outcome.

Therefore, it is critical that our findings are interpreted within the specific population enrolled. However, we believe that our study cohort is

representative of a typical population undergoing stress testing in laboratories in which a large number of tests are performed. Indeed, because of the increased concern for CAD risk it is common practice that lower risk symptomatic patients seek earlier diagnostic screening.[1] On the other hand, clinicians frequently refer high-risk patients directly to invasive angiography rather than noninvasive testing.[19]

The favourable prognosis associated with a negative ESE despite the concomitant presence of an abnormal stress ECG (reversible downsloping of ST segment) may be surprising. However, it is now clear that the functional capacity and age are more potent cardiovascular mortality predictors.[20] Podrid et al. demonstrated that functional capacity is the strongest predictor of survival in patients with and without known CAD and ischaemic stress-induced ST segment downsloping[21] and stress induced angina.[22] A recent study finds that a rapidly upsloping ST segment during exercise is a common but benign finding in healthy middle-aged subjects.[23]

The ECG represents the bioelectrical activity of the heart. The ST segment represents the early phase of the repolarization.[24] The presence of ST downsloping may be attributed to an ischaemic aetiology (secondary to microvascular disease and/or the epicardial vessels) or to a non-ischaemic aetiology.[25] When the ST segment downsloping is secondary to microvascular disease, the inducible subendocardial ischaemia cannot achieve the critical mass to generate segmental anomalies of the left ventricle wall. It was also reported that endothelial dysfunction could modify the repolarization process through the prolongation of the repolarization phase at the subendocardial level.[26] Indeed, the prognostic value of an ST downsloping associated with a negative ESE depends on the clinical setting.

Limitations and strengths

The relatively limited sample size and number of events represent the most important study limitation of the present study. However, unlike several previous studies of larger cohorts, our report fulfilled good methodological quality criteria[5] based on the presence of complete follow-up for the entire baseline cohort of patients and outcome data obtained by investigators blinded to the test results. Furthermore, hospital records and death certificates were used to ascertain outcomes. The generalizability of our results to other practice settings may be debated because of our stricter inclusion criteria. Therefore, we recognize that in future, larger studies that prospectively evaluate clinical outcomes in patients with negative stress echocardiography (including treadmill, bicycle and pharmacological stress) with concomitant evaluation of stress-induced ECG abnormalities are required.

We included coronary revascularization among the primary endpoint. Nevertheless, it was thought that in the specific setting of patients with normal ESE, coronary revascularization reflects a 'spontaneous' clinical event and by excluding these patients we would miss potential outcomes. However, if we did not include revascularization in the primary endpoints, the results were unchanged, the HR = 1.53 (0.43–5.51), $p = 0.511$ for patients with ISECG compared to patients with normal ECG.

Finally, we did not include the analysis and outcome of patients with positive supine bicycle ESE during the same study period. The reason is that these values are particularly subject to referral bias due to the effect of positive tests on subsequent revascularization and medical management. Consequently, in studies of prognosis, referral bias usually overestimates event rate after a positive test. As clinical decision-making is heavily affected by stress echo result, the value of a positive test result in predicting spontaneous events could not be ascertained in our study as well as in previous studies.

Conclusions

In an outpatient population without previous diagnosis of CAD evaluated for chest pain after inconclusive first-line work-up including clinical evaluation and ETT, a negative peak supine bicycle ESE confers an excellent prognosis regardless of the nature of concomitant stress ECG abnormalities and may be considered a useful 'gatekeeper cardiac imaging test' in daily clinical practice.

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Conflicts of interest

None declared.

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