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Cost-effectiveness of a management strategy based on exercise echocardiography versus exercise electrocardiography in patients presenting with suspected angina during long term follow up: A randomized study

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ABSTRACT

Introduction: Exercise ECG (Ex-ECG) is advocated by guidelines for patients with low - intermediate probability of coronary artery disease (CAD). However, there are no randomized studies comparing Ex-ECG with exercise stress echocardiography (ESE) evaluating long term cost-effectiveness of each management strategy.
Methods: Accordingly, 385 patients with no prior CAD and low-intermediate probability of CAD (mean pre-test probability 34%), were randomized to undergo either Ex-ECG (194 patients) or ESE (191 patients). The primary endpoint was clinical effectiveness defined as the positive predictive value (PPV) for the detection of CAD of each test. Cost-effectiveness was derived using the cumulative costs incurred by each diagnostic strategy during a mean of follow up of 3.0 years.
Results: The PPV of ESE and Ex-ECG were 100% and 64% ($p = 0.04$) respectively for the detection of CAD. There were fewer clinic (31 vs 59, $p < 0.01$) and emergency visits (14 vs 30, $p = 0.01$) and lower number of hospital bed days (8 vs 29, $p < 0.01$) in the ESE arm, with fewer patients undergoing coronary angiography (13.4% vs 6.3%, $p = 0.02$). The overall cumulative mean costs per patient were £796 for Ex-ECG and £631 for ESE respectively ($p = 0.04$) equating to a >20% reduction in cost with an ESE strategy with no difference in the combined end-point of death, myocardial infarction, unplanned revascularization and hospitalization for chest pain between ESE and Ex-ECG (3.2% vs 3.7%, $p = 0.38$).
Conclusion: In patients with low to intermediate pretest probability of CAD and suspected angina, an ESE management strategy is cost-effective when compared with Ex-ECG during long term follow up.

1. Introduction

New onset stable chest pain is a widespread clinical problem accounting for 4 million stress tests performed annually in ambulatory patients with no previous diagnosis of coronary artery disease in the US [1]. Recently there has been marked expansion in diagnostic strategies available in patients with suspected stable angina. Nevertheless, increasing constraints on healthcare expenditure in ageing populations, have necessitated the need for more cost effective approaches in the diagnosis and management of CAD. The above factors have called for more robust evidence for the efficacy of cardiovascular imaging leading to a paradigm shift away from test performance, to a focus on clinical outcomes induced by change in the management as a consequence of the test result, as well as cost effectiveness [2–4].

Previously there were few randomized studies assessing health outcomes for diagnostic tests, with evidence largely derived from non-randomized studies or large meta-analyses [2–4]. Consequently little consensus exists among clinicians on which strategy provides best outcomes for patients. Notably, only 1% of over 700 recommendations for cardiovascular imaging in the ACC/AHA guidelines are on the basis of Level of Evidence: A [5].

Because of its simplicity and widespread availability, exercise electrocardiography (Ex-ECG) remains a useful option in patients with suspected CAD. For patients with low-intermediate pretest probability of coronary artery disease (CAD) who can exercise with no resting ECG abnormalities, evaluation with Ex-ECG is a class I recommendation for USA [2] and European guidelines [4], whereas U.K. guidelines recommend against its use [3]. Despite NICE recommendations and in keeping

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with USA and European guidelines, Ex-ECG continues to be used as first line investigation in the UK probably because of its perceived higher feasibility and superior cost profile compared with other non-invasive tests [6]. Meta-analyses have confirmed the superiority of stress echocardiography (SE) to stress ECG for the diagnosis of CAD. SE provides incremental prognostic value for the prediction of hard cardiac events in chest pain patients without a previous history of CAD-over and above clinical, ECG, and stress ECG data [7,8]. However, the superior diagnostic and prognostic accuracy is attended with greater cost, and the cost implications of these alternative investigation strategies need to be scrutinised in a randomized study.

Guidelines in favour of Ex-ECG are reliant on randomized studies where single-photon-computerized-tomography (SPECT) was the stress imaging modality of choice, and from older meta-analyses [9–12].

The objective of the study was to compare the diagnostic accuracy, costs and health benefit associated with Exercise SE (ESE) compared to Ex-ECG. Health benefits are defined as, reduced mortality, fewer NFMI, and fewer late revascularisations. The initial results including test characteristics and cost-to-diagnosis have been published previously [13]. However in comparative studies, it is vital to examine long term health outcomes and cumulative healthcare costs to guide clinical decision making.

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 (including unnecessary coronary angiography) and reduced unscheduled hospital attendances.

2. Methods

2.1. Study design

The trial design has been published previously [13]. Consecutive patients who were seen in our Rapid Access Chest Pain Clinic (RACPC) from February 2013 to March 2014 were randomized to undergo either Ex-ECG or ESE. Patients were eligible for the trial if they [1] were referred for evaluation of possible CAD [2] had a normal resting ECG [3] had intermediate pre-test probability (PTP) of CAD (according to NICE guidelines) [4] moderate physical functioning and [5] no known history of CAD. The study was approved by the UK ethics committee.

Exclusion criteria included patients with unstable angina, prior history of CAD and those with very low PTP. Consenting patients were randomized using a random number generator algorithm incorporated into a Microsoft Access Database. All patients were analysed on an intention to treat basis.

Following the test, all subsequent management decisions were taken by the RACPC healthcare professional after the results of stress testing were made available. Generally, patients with a low post-test risk were discharged from clinic and patients with a high post-test risk were referred for invasive angiography. Patients with an intermediate risk were considered for further investigation at the discretion of the attending physician.

2.2. Exercise ECG

Ex-ECGs were performed and interpreted by experienced cardiac physiologists and the RACPC healthcare professional (cardiac specialist nurse or cardiology middle grade doctor) as per standard clinical practice. Patients underwent treadmill exercise using the standard Bruce protocol. Endpoints were fatigue, severe ischaemia (severe chest pain, ≥2 mm horizontal or downsloping ST depression), severe hypertension (systolic BP ≥ 220 mm Hg), hypotension (systolic BP ≤ 90 mm Hg), pre-syncope, or significant arrhythmia. Patients who achieved a work-load of ≥9 METS or achieved 85% of target heart rate, without any symptoms, haemodynamic compromise, or ECG changes were considered to have a negative test [14]. Patients, who developed significant chest pain, hypotension, an arrhythmia, or ≥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.

2.3. Exercise stress echocardiography

All ESE studies were performed using treadmill exercise as described above. 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 ≥2 contiguous segments were not visualised, 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 (RS) as performed routinely. Online images were interpreted qualitatively for the presence, extent, and location of regional wall motion abnormalities (WMA) by the consultant lead (RS) as per routine clinical practice. The reviewer thus had no knowledge that images were from a patient in the study. Systolic wall thickening and endocardial wall motion were assessed according to a four-point score (1: Normal; 2: Hypokinetic; 3: Akinetic; 4: Dyskinetic motion) using a 17-segment left-ventricle model. The stress echocardiogram was considered negative if all segments were normal at baseline and peak stress having achieved 85% of age-predicted target heart rate at a workload of at least 7 Mets [15]. 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 inconclusive.

2.4. Coronary angiography

Standard techniques were used for performing angiography. Images were analysed using a visual quantitative scoring system, with CAD defined as ≥50% luminal diameter narrowing in one or more epicardial coronary arteries or their major branches. The cut-off value of 50% was used as it has been previously shown to be prognostic [16].

2.5. Follow up

Data on outcomes were collected by means of a postal questionnaire at 6, 12, 24 and 36 months after the clinic appointment, and at the conclusion of the study. Patients consented to be approached for follow-up as part of the study protocol. Patients who did not respond to the postal questionnaire were contacted via telephone. Where patients could not be contacted directly and for further information regarding health resource utilization, computerized records from all hospitals in the pan-London area were reviewed and general practitioners were contacted. A national mortality database was used to identify deceased patients. Follow-up assessment was performed by a research nurse, who was blinded to the study group. Follow-up time was calculated from the day of the initial test to either the date of an event or the date follow-up contact or database search was performed up to 1st August 2016.

2.6. Study endpoints

The primary endpoint was clinical effectiveness defined as the positive predictive value for the detection of CAD of each test in this population. Cost effectiveness was evaluated as the cumulative cost of each diagnostic strategy with respect to its clinical effectiveness. Costs were derived from 'Unit costs of Health and Social Care 2015' and data from the UK NHS resource tariff of 2015–16 [17,18]. Resource consumption data covered emergency department visits, days in hospital, specialist clinic review, coronary angiography and coronary revascularization procedures. All patients were censored for costs following a revascularization procedure or hard event (death or NFMI), since subsequent costs would be related to the hard event and not the original testing strategy.

Secondary endpoints included a composite of all cause mortality, non-fatal MI (NFMI), late revascularization and hospitalization with chest pain, with patients censored at the time of the hard event or at the last follow-up. NFMI was defined by the standard criteria of ischaemic chest pain associated with an elevation of cardiac enzymes with or without electrocardiographic changes. Late revascularization was defined as any revascularization procedure occurring after 6 months. For patients with multiple events, only the first event was considered.

Further endpoints were repeat clinic attendance for chest pain, referral for diagnostic angiography following the index test and time to diagnosis.

2.7. Statistical analysis

A power calculation performed by an independent statistician based on the results of a previous retrospective study [19], suggested that 190 patients would have to be randomized into each study arm for the study to show a difference in the primary endpoint (positive predictive value) for the detection of CAD with a 5% significance level and 80% power. Continuous data are presented as means ± SD or medians with inter-quartile ranges. Groups were compared using an independent sample *t*-test or Mann–Whitney *U* test for continuous variables, and ×2 or Fisher's exact test for categorical variables. The

Table 1
Baseline characteristics of study population.

Number of patients	Ex-ECG	ESE	*P* value
	194	191	
Age	54 ± 11	55 ± 11	0.3
Male (%)	66	70	0.4
Cardiac risk factors (%)			
Smoking	18	14	0.4
Diabetes	17	14	0.4
Hypercholesterolaemia	37	35	0.7
Hypertension	31	40	0.1
Family history of CAD	27	24	0.5
PTP of CAD (%)	34 ± 23	35 ± 25	0.6