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Clinical effectiveness of a sonographer-led, cardiologist-interpreted stress echocardiography service in the rapid access stable chest pain clinic

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ABSTRACT

Aims: To assess the clinical effectiveness of a sonographer-led, cardiologist-interpreted stress echocardiography (SE) service in a rapid access stable chest pain clinic (RACPC) setting.
Methods and results: Baseline data was collected prospectively on 768 consecutive patients, referred from the RACPC, who underwent SE between May 2014 and May 2015. Retrospective analysis was performed on follow-up data for outcomes. Among 768 patients (mean age 58 years, 57.8% males) with a mean pre-test probability of coronary artery disease (CAD) of 31%, 675 (88%) underwent SE on the same day as the RACPC consultation. Diagnostic tests were obtained in 749 (97.5%) cases with 62 (8.1%) demonstrating inducible ischemia. Coronary angiography was performed in 61 patients of whom 54 demonstrated flow-limiting CAD (positive predictive value: 88.5%). There was no occurrence of serious adverse events. During a mean follow-up period of 2.5 years, 20 first cardiac events were recorded, of which annualised events in the normal SE group were 0.64% versus 5.8% in patients with an abnormal SE (log rank $p < 0.001$).
Conclusion: Sonographer-led SE interpreted by a cardiologist is feasible, safe and efficacious. It impacted on the management of patients with appropriate outcomes and may be a cost-efficient and safer alternative to other non-invasive imaging modalities in the RACPC setting.

1. Introduction

Stress Echocardiography (SE) today is a well-established technique for the evaluation of patients with suspected stable angina [1,2]. Recently, unlike single-photon-emission-tomography (SPECT) which is also widely used, SE has been demonstrated to be more cost-effective than exercise electrocardiography (Ex ECG) for the evaluation of such patients in the setting of rapid-access stable chest pain clinic (RACPC) [3,4]. Such a service can provide both clinical and SE assessments on the same day of patients presenting with stable chest pain. However, despite the ubiquitous availability, proven efficacy and cost-effectiveness of SE, its widespread use has been thwarted in countries where cardiologists perform the procedures - a vast majority of countries. It is perceived that the use of cardiologists' time to perform the test limits its everyday use.

The advent of harmonic imaging and the availability of ultrasound-enhancing agents have greatly improved the yield of diagnostic images [5]. These techniques also have been shown to improve the diagnostic accuracy of SE [5]. The increased number of diagnostic studies and improved efficacy translated into superior cost-effectiveness of contemporary SE compared to exercise electrocardiography (Ex-ECG) [3,4]. Due to improved image quality, sonographers are likely to acquire rapid proficiency in obtaining diagnostic images during SE.

We hypothesised that SE performed in the setting of a RACPC, run by sonographer rather than cardiologist, is likely to provide diagnostic images which can then be rapidly interpreted by the cardiologists. This service will entail the use of cardiologists' time only to interpret the images. Accordingly, we sought to assess whether a sonographer-led SE service where the cardiologists are involved only in interpretation of SE in the setting of a RACPC is feasible, efficacious and safe.

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2. Methods

2.1. Selection and description of participants

Between May 2014 and May 2015, 768 consecutive patients referred for a SE from the RACPC, undertaken by a team of sonographers where baseline data was collected prospectively, were followed-up retrospectively for outcomes as part of a service evaluation. Permission for this service evaluation was granted by the London North West University Healthcare NHS Trust Research and Development department.

Patients referred from the outpatient RACPC for SE included those with new onset stable chest pain, with no dynamic ECG changes at baseline and a pre-test probability of coronary artery disease (CAD) >10% [6]. These patients were fully evaluated by the RACPC prior to referral for SE. Some patients with a pre-test probability of <10% were also referred for a SE from the RACPC because of the presence of other risk factors not included in the standard pre-test probability score i.e. hypertension or strong family history of ischaemic heart disease and clinical concern. Patients also included were those with a previous history of CAD (acute coronary syndrome, coronary revascularisation or flow-limiting CAD on coronary angiography) with stable chest pain. Patients with a previous history of CAD accounted for 9% (70 patients) of the total study population. Pre-test probability was calculated using the National Institute for Health and Care Excellence (NICE) algorithm in the RACPC prior to referring patients for SE [6]. The NICE guidelines [7], use a pre-test risk scoring system calculated for each patient based on age, gender, the type of chest pain (typical, atypical, or non-anginal pain), as well as the presence of risk factors (diabetes, smoking and hyperlipidaemia) [6].

2.2. Stress echocardiography

Patients underwent either treadmill exercise stress echocardiography (ESE) or pharmacological stress echocardiography with dobutamine (DSE). Treadmill exercise was the preferred modality. Dobutamine was used only in cases where exercise was not possible or when both viability and ischaemia had to be evaluated in cases of patients with left ventricular dysfunction (LV) or significant regional wall thickening abnormalities, or if there were non-specific resting ST-T ECG changes and the patient was deemed to have stable symptoms.

During treadmill exercise, images of the LV were obtained at rest in the apical four-, two-, and three-chamber views and the parasternal long-and short-axis views. The standard Bruce or Modified Bruce Protocol was used. End points were significant symptoms, achievement of 85% of age-predicted maximum heart rate, significant or symptomatic tachy- or brady-arrhythmias, ST elevation, > 3 mm ST depression without symptoms, >2 mm ST depression with symptoms, systolic blood pressure rise above 230 mm Hg, development of bundle branch block and patient's request for termination. The same set of images was acquired immediately after peak exercise, within 60–90 s. Baseline and peak images were displayed side by side for analysis.

In patients, unable to exercise and with absence of regional wall thickening abnormalities, dobutamine was administered at 10 μg/kg/min for 3 min and increased by 10 μg/kg/min every 3 min and up to 40 μg/kg/min. If 85% of target heart rate was not reached in absence of significant symptoms atropine sulphate was administered intravenously in bolus doses of 0.3 mg (up to a maximum dose of 1.2 mg). Images were acquired at baseline, intermediate dose and peak stress. In patients with significant resting wall thickening abnormalities-regional or global, with previously known CAD, dobutamine infusion was commenced at 5 μg/kg/min and increased to 10, 15, and then 20 μg/kg/min in 5 min intervals. Thereafter, the dose was increased to 30 and 40 μg/kg/min at 3 min intervals with atropine sulphate administered as described above. Images were obtained at baseline, at low, intermediate dose and at peak stress. End points for dobutamine stress testing include achieving >85% of age predicted maximum heart rate, development of severe ischaemia (severe angina), ST segment elevation, extensive regional wall thickening abnormality (RWTA) or development of intolerable side effects.

In patients where two or more contiguous segments were not visualised adequately during rest or during deep inspiration, intravenous contrast (Sonovue, Bracco, Milan, Italy) was used to opacify the LV cavity and delineate the endocardial borders. Bolus injections of 0.3 ml–0.5 ml were injected through a venous cannula followed by a 0.9% Sodium flush (1 ml–5 ml).

All images were analysed and interpreted together with an expert reader (RS-Consultant Cardiologist).

2.3. Image analyses

The consultant lead (RS) interpreted online digital images qualitatively for the presence, extent and location of regional wall thickening abnormalities (RWTA). A four-point score (1: normal, 2: reduced, 3: absent, 4: systolic thinning) was used. Systolic wall thickening was scored, using a 17-segment LV model. If all 17 segments were normal at baseline and at peak stress having achieved 85% of the age predicted maximum heart rate the stress echo was considered normal. The development of RWTA in any segment at peak stress was considered ischemic. During the dobutamine protocol in patients with resting RWTA, the SE was reported as ischemic in the presence of a biphasic response during low and high doses of dobutamine or deterioration of RWTA. If the SE was terminated before reaching an end point or if the images could not be interpreted, the SE was considered inconclusive.

2.4. Sonographer led stress echocardiography service

The Sonographer-led SE team consisted of two cardiac sonographers. RH, assisted by a second cardiac physiologist, acquired the images and was the main operator for the SE studies performed. RH had British Society Echocardiography (BSE) Adult Transthoracic Echocardiography (TTE) accreditation, Advanced Life Support Accreditation, Intravenous Cannulation and Contrast Administration Certification and one year's stress echocardiography experience (performed 100 studies under the supervision of an expert cardiologist).

Exercise SE was performed by the team of sonographers independent of a cardiology doctor and contrast was administered using a Patient Specific Direction (PSD). Contrast was prescribed by an independent prescriber, usually the nurse in the RACPC who is assessing the patient and administered by the sonographers with the use of a PSD.

Dobutamine SE was performed by the team of sonographers with a cardiology doctor informed in case of medical complications but the doctor was not present in the room.

2.5. Downstream testing

According to local clinical practice, in patients with an inconclusive ESE due to patient inability to reach 85% of age predicted maximum heart rate, a DSE was offered.

2.6. Management after SE

Results of the SE were communicated back to the RACPC on the same day. Patients with a normal SE were discharged back to the care of the general practitioner. Patients with an ischaemic SE were referred back to the RACPC on the same day for optimization of medical management and consideration for coronary angiography.

2.7. Follow-up

Data were collected for cardiac events, i.e., cardiac death, acute coronary syndrome, hospitalisation for heart failure and unplanned revascularisation defined as revascularisation due to persistent chest pain or unstable angina. Data were obtained from electronic hospital records and the hospital stress echocardiography/coronary angiography database. The national mortality database was also searched to obtain information on the occurrence of mortality and acute coronary syndrome.

2.8. Statistical analysis

Categorical variables are expressed as percentages and continuous variables as mean with standard deviation reported. Categorical variables were compared with the used of chi-squared test. Continuous variables were compared with the use of independent *t*-test, Cox regression analysis for the prediction of cardiac events was performed using the pre-test probability of CAD (which included age, gender, type of angina, diabetes mellitus, smoking and hyperlipidaemia). For the purpose of this analysis those with history of CAD (9.1% of pts) were given a pre-test probability of CAD score of 100%. Systemic hypertension which was not included in pre-test probability score and presence of ischaemia on SE were other factors assessed in the Cox regression analysis. A p value < 0.05 was considered statistically significant. Statistical analysis was performed with Statistical Package for the Social Sciences version 24.0 (SPSS Inc., Chicago, Illinois, USA).

3. Results

3.1. Study population

Between May 2014 and May 2015, 768 consecutive patients referred from the RACPC underwent SE, undertaken by a team of sonographers. Of these patients, 675 (88%) had their SE performed on the same day as their consultation in the RACPC. The baseline characteristics of the total study population are shown in Table 1. More than half of the population tested were males, with a quarter of the patients suffering from diabetes mellitus. Almost 10% of patients had a previous history of CAD and pre-test probability of CAD was 31% in patients without a history of CAD.

Table 1
Baseline characteristics of patients.

N	768
Age (years)	58 ± 12
Male	444 (58%)
Hypertension	320 (42%)
Diabetes mellitus	184 (24%)
Smoker	98 (13%)
Hyperlipidaemia	367 (48%)
Pre-test probability of CAD (PRYOR risk)	31% ± 26%
History of CAD	70 (9.1%)

Majority of the patients, 703 (91.5%) underwent ESE. Those who underwent ESE were younger with lower prevalence of systemic hypertension, diabetes mellitus, hyperlipidaemia, history of CAD and had lower pre-test probability of CAD compared to those who underwent DSE. However, rate-pressure product (a measure of myocardial oxygen demand) was higher in the ESE group with greater extent of RWTA but both groups had similar prevalence of patients with ischemia (Table 2).

3.2. Stress echocardiography characteristics

Diagnostic tests were achieved in 749 (97.5%) of patients. Ultrasound contrast agents were used in 725 (94%) of patients. Fig. 1 details the flow of patients from the initial SE through to further requested tests, results of coronary angiography and subsequent management. Of the 768 patients, 62 (8.1%) demonstrated inducible ischemia with a mean number of abnormal segments of 6.1 ± 2.6 (median 6, range 2–12). Of these 62 patients, 61 underwent coronary angiography (CAA) of which 54 patients demonstrated flow-limiting CAD (>50% diameter stenosis of one or more of left main, left anterior descending, left circumflex or right coronary arteries and their major branches). Thus, of the 62 patients with a positive SE with availability of the results of CAA 54 had flow-limiting CAD-a positive predictive value of 88.5%. Patients with myocardial ischemia were older, predominantly males, with greater prevalence of hypertension, hyperlipidaemia, history of CAD, and had higher pre-test probability of CAD (Table 3).

3.3. Safety of stress echocardiography

There were no serious adverse events. There was one episode of transient ST elevation on exercise with back pain and one episode of supraventricular arrhythmia followed by transient ST elevation and chest pain during dobutamine stress. Both patients were stable with no rise in biomarkers but were admitted in view of significant transmural ischemia and underwent urgent coronary angiography.

3.4. Management of patients after coronary angiography following a positive SE

Of the 54 patients with confirmed flow limiting CAD, a total of 38 (70.4%) underwent coronary revascularisation: 21 (39%) percutaneous coronary intervention (PCI) and 17 (32.7%) CABG. The remaining 16 (30.8%) with flow-limiting CAD were managed with medical therapy only.

It needs to be noted that of the 62 patients with ischemia 19 patients were enrolled into the International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial: in the trial, patients with significant ischemic burden (3 or more ischemic segments) first underwent coronary computed tomography angiography (CCTA), and if found to have obstructive CAD corresponding to the ischemic territory, were randomised to interventional versus medical therapy only. Of the 19 patients, 8 were in the medical therapy arm. If the patients had not been in the trial, all 19 patients would have undergone revascularisation, and thus of the 54 patients with ischemia and CAD, 46 (85.2%) would have undergone revascularisation.

Table 2
Stress echocardiogram modality, demography and haemodynamics.

	Exercise stress echo (n = 703)	Dobutamine stress echo (n = 65)	p-Value
Demographics			
Age (years)	57.3 ± 12	67 ± 12	<0.005
Male	409 (58.2%)	35 (53.8%)	0.5
Hypertension	278 (39.5%)	42 (64.6%)	<0.005
Diabetes mellitus	161 (22.9%)	27 (41.5%)	0.001
Smoking	165 (23.5%)	9 (13.8%)	0.08
Hyperlipidaemia	353 (50.2%)	49 (75.4%)	<0.005
History of CAD	54 (7.7%)	16 (24.6%)	<0.005
Risk score (Pryor risk)	30% ± 26	39% ± 27%	0.02
Haemodynamics			
METS	9 ± 2	–	NA
Rate pressure product (mm Hg·bpm)	24,165 ± 3744	21,478.7 ± 3662	<0.005
Positive SE	55 (8.2%)	5 (7.9%)	0.95
Abnormal segments	6 ± 3	4.2 ± 1.4	0.02
Complications	2 (0.28%)	0	

3.5. Follow-up results

During a mean follow-up period of 899 (2.5 yrs) ±104 days, there was 1 cardiac death recorded, 3 acute myocardial infarction (AMI), 2 unplanned revascularisations, 14 admissions with unstable angina and 1 admission with acute heart failure. Time to first event was considered. The number of patients with the first event was 20 (2.6%-annualised rate = 1.04%). Of these, 11 events occurred in 697 (1.6%-annualised rate = 0.64%) patients with normal SE and 9 events occurred in 62 (14.5%-annualised rate = 5.8%) patients with a positive SE (log rank test: $p < 0.001$). Fig. 2 shows the Kaplan-Meier survival curves for the prediction of these events in patients with normal SE versus those with ischemia. Cox regression analysis showed that ischemia on SE and the modified pre-test probability of CAD were independent predictors of cardiac events (Table 4).

4. Discussion

To the best of our knowledge, the present study is the first to address the feasibility, efficacy, safety and prognostic value of performing same day SEs, led by sonographers with images interpreted by the cardiologist, in patients presenting with stable chest pain referred from the RACPC where patients were initially fully clinically evaluated. Diagnostic studies were feasible in almost 98% of patients with interpretable images obtained in 99% of patients. The positive predictive value of SE for the detection of flow-limiting stenosis was nearly 90%, of which the majority underwent revascularisation, the latter suggesting that the test influenced management decision. Over a period of approximately 2.5 years, the outcome of a negative SE was excellent with cardiac event rate of <1%. By contrast those with demonstrable ischemia had an event rate almost 10 times higher compared to those with a normal SE suggesting efficacious risk stratification. Sonographer-led stress echocardiography, where the majority of the patients underwent exercise SE, was safe.

Patients presenting with new-onset suspected stable angina require rapid assessment for CAD [7]. RACPCs are set up in the United Kingdom (UK) for this purpose. It is ideal from the aspects of diagnosis, patient safety and reassurance to have the diagnostic non-invasive test performed the same day as clinic attendance. Patients can therefore be rapidly triaged. A normal test is reassuring and the demonstration of myocardial ischemia will lead to treatment for CAD. With the advent of improved technology, SE, which can be performed at the bedside and at a relatively low cost, is efficacious, can be performed rapidly on the same day as the clinic visit, with real-time interpretation of the test and rapid communication of the results, which can facilitate early triaging of patients [3]. Traditionally SE services have been led by cardiologists with sonographers and nurses in supporting roles [2,8,9]. However, availability of cardiologists to perform SE thus far has limited its widespread use as a one-stop test. Recently in the UK, specialist roles have developed within cardiac physiology, which has helped to facilitate the growth of advanced sonographer led services, such as SE [10–12].

In the present study, the sonographer performing SE was accredited in adult TTE and had undergone training with >100 stress echo studies (exercise and dobutamine with and without contrast) performed under the supervision of an imaging cardiologist. As part of the training

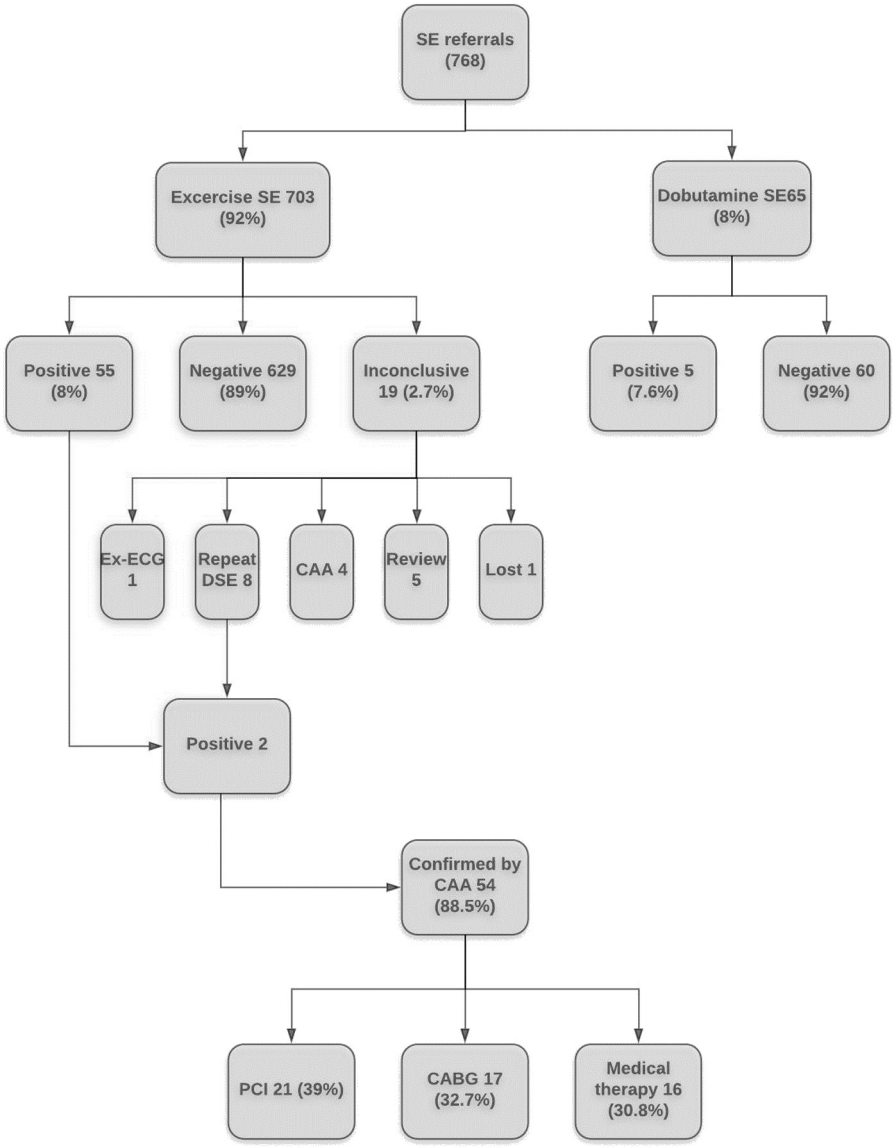

Fig. 1. Flow of patients from initial SE through to further requested tests or discharge. Details the flow of patients from initial SE through to further requested tests, results of subsequent coronary angiography, and subsequent management of patients. SE = Stress echocardiogram CAG = coronary angiogram Ex-ECG = Exercise electrocardiogram CABG = Coronary artery bypass grafting DSE = Dobutamine stress echocardiogram PCI = Percutaneous coronary intervention.

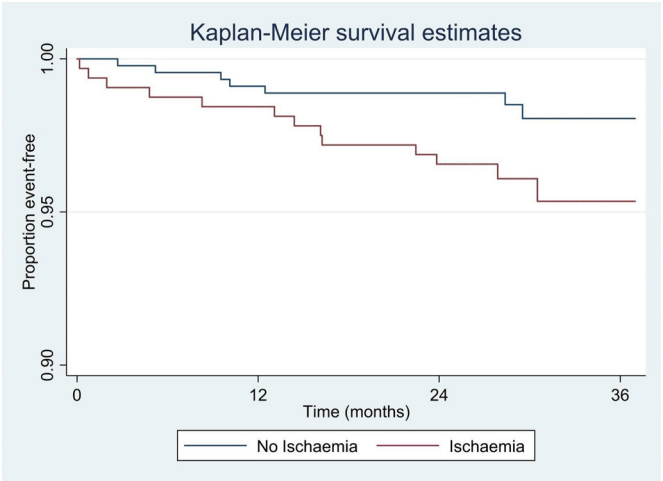

Fig. 2. Kaplan-Meier Survival estimates. The Kaplan-Meier survival curves for the prediction of cardiac events in patients with a normal stress echocardiogram versus those with ischaemia on stress echocardiography.

all reports were interpreted under the supervision of the imaging cardiologist. Furthermore, the sonographer performing the studies had Advanced Life Support (ALS) accreditation and all dobutamine studies were performed with a clinician present in the department, but not at the point of testing. The data from our study showed no serious adverse events in a population in which the majority underwent exercise SE and is comparable to the data from the International stress echo complication registry [8,9]. Our data supported the safety of the service. A very recent study, that assessed the feasibility and safety of physiologist-led SE for the assessment of CAD found no difference in the safety profile of SE (dobutamine and exercise) performed by physiologists (n = 393) and cardiologists (n = 505) [13].

An important factor related to the efficacy of the service is the ability to acquire high quality images leading to the high number of diagnostic studies (almost 98%). This could be in part attributed to the high number of contrast-enhanced studies performed (94%). It has been shown previously, that despite high usage of contrast-enhanced SE, the cost profile of SE strategy was still superior to Ex-ECG. This is because the use of contrast leads to the increased accuracy of the test, and the greater diagnostic certainty, which both reduce unnecessary

downstream cost [3]. In the present study, virtually all patients with demonstrable myocardial ischemia during SE underwent coronary arteriography, of which almost 90% had flow-limiting CAD, leading to revascularisation in the majority as most tested had significant myocardial ischemia. The patients who demonstrated a normal SE had an excellent outcome compared to those with myocardial ischemia, which is in accordance with the literature [1,2,22]. Thus, sonographer-led SE service where cardiologist's role was only to interpret the images, demonstrated that it largely influenced management decision and the outcome data supported the fact that the decision making based on SE was safe and appropriate.

5. Clinical implications

Three international guidelines for the assessment of new onset chest pain all provide advice on how a patient with intermediate risk of CAD should be investigated. Current recommendations by both American Heart Association/American College of Cardiology (AHA/ACC) [14], and European Society of Cardiology (ESC) [15], consider Ex-ECG as the first line investigation in patients typically seen in the RACPC, except those with baseline ECG changes. The NICE guidelines recently (Nov 2016) advocated coronary computed tomography angiography (CCTA) as the first line test in patients with suspected angina [7].

The AHA/ACC/ESC guidelines advocating Ex-ECG are based on previous randomised studies comparing Ex-ECG versus SPECT where Ex-ECG was found to be more cost effective in patients with a pre-test probability of 15–65% [16,17]. However, a very recent study has shown that ESE was more cost-efficient than Ex-ECG in a population where the median pre-test probability of CAD was 34% and this was further affirmed in a longer-term follow-up study [4]. Further retrospective observational studies support the superior cost-profile of SE versus Ex-ECG in patients with and without previous history of CAD [1,3,18].

Two randomised trials (PROMISE and SCOT HEART) which compared management strategies based on CTCA versus functional testing failed to show superior outcome of CTCA [19,20]. Furthermore, safety concerns arising from the use of ionizing radiation particularly in the age group tested (<60 years and >40% female in the present population) and in the very low-risk population (event rate 1.04%/year in our RACPC) typically seen in the RACPC, makes CTCA an unattractive alternative.

ESE has a similar safety profile to Ex-ECG and provides similar physiological exercise data for additional risk stratification but has superior efficacy and cost-benefit profile compared to Ex-ECG [22]. A recent analysis supported SE as the first line investigation in patients presenting at the RACPC [21], taking into account its superior cost-effective profile compared to Ex-ECG and superior safety profile compared to CCTA in the low risk population typically seen in RACPC. The present study further advocates this strategy, as now it can be performed by trained sonographers with cardiologist time being utilised in interpreting the images, an optimal use of a cardiologist time in SE, which can potentially increase the utility of SE in the setting of RACPC.

6. Study limitations

This study was a retrospective analysis, albeit of a prospectively collected data. There was only one reader who interpreted all the SE images which did not address inter-observer variability regarding interpretation of the images. However, the images were acquired by the sonographers and the final report was confirmed by the expert reader as per normal clinic practice. The prevalence of ischemia in this population was around 8% which is low. However, those with a positive SE had a large extent of myocardial ischemia (median: 6 segments) with almost 80% considered for revascularisation, emphasising the need for testing in this population.

7. Conclusion

Sonographer-led SE, interpreted by cardiologist in the RACPC setting, where patients were initially comprehensively clinically evaluated, was highly feasible and safe, allowing rapid communication of the results on the same day in almost 90% of patients, and this translated into same day implementation of a management plan. SE also resulted in appropriate management plan with the majority of the patients with significant ischemia undergoing revascularisation and patients with a negative SE being safely discharged. Given the high volume of referrals to the RACPC, sonographer-led SE may be a cost-efficient and safer alternative to other non-invasive imaging modalities.

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Conflict of interest

Professor Roxy Senior has received speaker fees from Bracco Imaging, Milan, Italy, Lantheus Medical Imaging, Boston, USA and Philips Healthcare, Eindhoven, The Netherlands. All other authors have no conflict of interest to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.01.080.

References

[1] R. Senior, M. Monaghan, H. Becher, J. Mayet, Nihoyannopoulos, Stress echocardiography for the diagnosis and risk stratification of patients with suspected or known coronary artery disease: a critical appraisal. Supported by the British Society of Echocardiography, Heart 91 (4) (2005) 427–436.
[2] R. Sicari, P. Nihoyannopoulos, A. Evangelista, J. Kaprzak, P. Lancellotti, D. Poldermans, J. Voigt, J.L. Zamorano, European Association of Echocardiography, Stress echocardiography expert consensus statement: European Association of Echocardiography (EAE) (a registered branch of the ESC), Eur. J. Echocardiogr. 9 (4) (2008) 415–437.
[3] K. Zacharias, A. Ahmed, B.N. Shah, S. Gurunathan, G. Young, D. Acosta, S. Senior, Relative clinical and economic impact of exercise echocardiography vs. exercise electrocardiography, as first line investigation in patients without known coronary artery disease and new stable angina: a randomized prospective study, Eur. Heart J. Cardiovasc. Imaging 18 (2017) 195–202.
[4] S. Gurunathan, K. Zacharias, M. Akhtar, A. Ahmed, V. Mehta, N. Karogiannis, A. Vamvakidou, R. Khattar, R. Senior, 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, Int. J. Cardiol. 259 (2018) 1–7.
[5] R. Senior, H. Becher, M. Monaghan, L. Agati, J. Zamorano, J.L. Vanoverschelde, P. Nihoyannopoulos, T. Edvardsen, P. Lancellotti, Clinical practice of contrast echocardiography: recommendation by the European Association of Cardiovascular Imaging (EACVI) 2017, Eur. Heart J. Cardiovasc. Imaging 18 (11) (2017) (1205–1205af).
[6] D.B. Pryor, L. Shaw, C.B. McCants, K.L. Lee, D.B. Mark, F.E. Harrell Jr., et al., Value of the history and physical in identifying patients at increased risk for coronary artery disease, Ann. Intern. Med. 118 (2) (1993) 81–90.
[7] National Institute for Health and Care Excellence, Chest pain of recent onset: assessment and diagnosis of recent onset chest pain or discomfort of suspected cardiac origin, Clinical Guideline 95, 2010. www.nice.org.uk/guidance/cg95.
[8] A. Varga, M.A. Garcia, E. Picano, International Stress Echo Complication Registry, Safety of stress echocardiography (from the International Stress Echo Complication Registry), Am. J. Cardiol. 98 (2006) 541–543.
[9] M.I. Geleijnse, B.J. Krenning, A. Nemes, B.M. van Dalen, O.I. Soliman, F.J. Ten Cate, A.F. Schinkel, E. Boersma, M.L. Simoons, Incidence, pathophysiology, and treatment of complications during dobutammine-atropine stress echocardiogrpahy, Circulation 121 (2010) 1756–1767.
[10] R. Wheeler, S. Bhattacharyya, W. Bradlow, et al., A practical guide for performing stress echocardiography in coronary artery disease, ECHO 94 (2016) 9–15.
[11] J. Chambers, G. Lloyd, H.M. Rimington, D. Parkin, A.M. Hayes, G. Baldrock-Apps, A. Topham, Multidisciplinary valve clinics with devolved surveillance: a two-year audit, Br. J. Cardiol. 18 (2011) 231–232.
[12] Strategic Review of Cardiac Physiology Services in England: Final Report. , British Cardiovascular Society, London, UK, 2015.

[13] J.N. Khan, T. Griffiths, T. Fatima, L. Michael, A. Mihai, A. Mustafa, K. Sandhu, R. Butler, S. Duckett, G. Heatlie, Feasibility of physiologist-led stress echocardiography for the assessment of coronary artery disease, Echo Res. Pract. 4 (2) (2017) 29–36.
[14] S.D. Fihn, J.M. Gardin, J. Abrams, K. Berra, J.C. Blankenship, A.P. Dallas, et al., ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons, J. Am. Coll. Cardiol. 2012 (2012) e44–e164.
[15] G. Montalescot, U. Sechtem, S. Achenbach, F. Andreotti, C. Arden, et al., 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology, Eur. Heart J. 34 (2013) 2949–3003.
[16] N.K. Sabharwal, B. Stoykova, A.K. Taneja, A. Lahiri, A randomized trial of exercise treadmill ECG versus stress SPECT myocardial perfusion imaging as an initial diagnostic strategy in stable patients with chest pain and suspected CAD: a cost analysis, J. Nucl. Cardiol. 14 (2007) 174–186.
[17] L.J. Shaw, J.H. Mieres, R.H. Hendel, W.E. Boden, M. Gulati, E. Veledar, et al., WOMEN Trial investigators, Comparative effectiveness of exercise electrocardiography with or without myocardial perfusion single photon emission computed tomography in women with suspected coronary artery disease: results from the what is the optimal method for ischemia evaluation in Women (WOMEN) trial, Circulation 124 (2011) 1239–1249.
[18] T.H. Marwick, L. Shaw, C. Case, C. Vasey, J.D. Thomas, Clinical and economic impact of exercise electrocardiography and exercise echocardiography in clinical practice, Eur. Heart J. 24 (2003) 1153–1163.
[19] P. Douglas, U. Hoffmann, M. Patel, D.B. Mark, H.R. Al-Khalidi, B. Cavanaugh, et al., PROMISE Investigators, Outcomes of anatomical versus functional testing for coronary artery disease, N. Engl. J. Med. 372 (2015) 1291–1300.
[20] SCOT-HEART Investigators, CT coronary angiography in patients with suspected angina due to coronary heart disease (SCOT-HEART): an open label, parallel-group, multicentre trial, Lancet 385 (2015) 2383–2391.
[21] C.J.M. Vrints, R. Senior, F. Crea, U. Sechtem, Assessing suspected angina: requiem for coronary computed tomography angiography or exercise electrocardiogram? Eur. Heart J. 38 (2017) 1792–1800.
[22] R. Chelliah, B. Anantharam, L. Burden, A. Alhajiri, R. Senior, Independent and incremental value of stress echocardiography over clinical and stress electrocardiographic parameters for the prediction of hard cardiac events in new-onset suspected angina with no history of coronary artery disease, Eur. J. Echocardiogr. 11 (2010) 875–882.