

openheart The safety, efficacy and cost-effectiveness of stress echocardiography in patients with high pretest probability of coronary artery disease

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To cite:

Papachristidis A, Demarco DC, Roper D, *et al*. The safety, efficacy and cost-effectiveness of stress echocardiography in patients with high pretest probability of coronary artery disease. *Open Heart* 2017;**0**:e000605. doi:10.1136/openhrt-2017-000605

Received 1 February 2017

Revised 5 May 2017

Accepted 9 May 2017

ABSTRACT

Objective In this study, we assess the clinical and cost-effectiveness of stress echocardiography (SE), as well as the place of SE in patients with high pretest probability (PTP) of coronary artery disease (CAD).

Methods We investigated 257 patients with no history of CAD, who underwent SE, and they had a PTP risk score >61% (high PTP). According to the National Institute for Health and Care Excellence guidance (NICE CG95, 2010), these patients should be investigated directly with an invasive coronary angiogram (ICA). We investigated those patients with SE initially and then with ICA when appropriate. Follow-up data with regard to Major Adverse Cardiac and Cerebrovascular Events (MACCE, defined as cardiovascular mortality, cerebrovascular accident (CVA), myocardial infarction (MI) and late revascularisation for acute coronary syndrome/unstable angina) were recorded for a period of 12 months following the SE. The tariff for SE and ICA is £300 and £1400, respectively.

Results 106 patients had a positive SE (41.2%) and 61 of them (57.5%) had further investigation with ICA. 15 (24.6%) of these patients were revascularised. The average cost per patient for investigations was £654.09. If NICE guidance had been followed, the cost would have been significantly higher at £1400 ($p < 0.001$). Overall, 5 MACCE (2.0%) were recorded; 4 (3.8%) in the group of positive SE (2 CVAs and 2 MIs) and 1 (0.7%) in the group of negative SE (1 CVA). There was no MI and no need for revascularisation in the negative SE group.

Conclusion Our approach to investigate patients who present with de novo chest pain and high PTP, with SE initially and subsequently with ICA when appropriate, reduces the cost significantly (£745.91 per patient) with a very low rate of MACCE. However, this study is underpowered to assess safety of SE.

INTRODUCTION

Coronary artery disease (CAD) is a leading cause of death in developed countries. Patients presenting with new onset chest pain can be investigated by numerous diagnostic imaging modalities. National and international guidelines are available to assist cardiologists in selecting the most appropriate

and most cost effective investigations. The UK National Institute for Health and Care Excellence (NICE) and the European Society of Cardiology (ESC) published guidelines in 2010¹ and 2013,² respectively, recommending the assessment of pretest probability (PTP) risk score (RS) before deciding the choice of investigation. For patients with high PTP (RS >61%), NICE recommended an invasive coronary angiogram (ICA). ESC is providing a different calculation of PTP RS, and they recommend a functional imaging test, such as stress echocardiography (SE), for patients with PTP 15%–85% or PTP >85% under certain circumstances.² When we refer to high PTP in our study, we mean a calculated RS >61% based on NICE scoring algorithm.¹ UK NICE have just published an update guideline,³ recommending not to use their PTP RS. They instead recommend CT coronary angiography (CTCA) as the sole modality of investigation for all patients with new onset chest pain and typical or atypical angina or non-anginal chest pain but abnormal ECG. In this short report, we assess the clinical and cost-effectiveness as well as the place of SE in patients with new onset chest pain and high PTP of CAD.

METHODS

We investigated 594 consecutive patients who underwent SE for de novo chest pain in our centre within a calendar year. These patients did not have any history of CAD or previous coronary revascularisation. We calculated the PTP based on the UK NICE guidance.¹ Two hundred fifty-seven patients had a RS >61% suggestive of high PTP of CAD. According to this guideline, the patients with a high PTP (RS >61%) should be investigated directly with an ICA. In our Institution, these



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KEY MESSAGES

What is already known about this subject?

► National Institute for Health and Care Excellence (NICE) suggested in 2010 (CG 95, 2010) that patients with recent onset chest pain and high pretest probability (PTP) of coronary artery disease should be investigated initially with an invasive coronary angiogram. Now they released an update guideline (CG 95, 2010, upd. 2016) and they recommend to stratify these patients based on the typicality of chest pain and they suggest a CT coronary angiogram (CTCA) as a first-line investigation. However, the European Society of Cardiology (ESC) recommend a non-invasive imaging test, like stress echocardiography (SE), as initial investigation.

What does this study add?

► We investigated patients with new onset chest pain and high PTP who were referred to our center, with a SE initially and subsequently with an invasive coronary angiogram if appropriate. Based on our approach the average cost per patient for investigations (SE + ICA) was £654.09. If NICE guidance (CG95, 2010) had been followed, the cost would have been significantly higher at £1400 ($p < 0.001$). Our strategy reduced the cost of investigations by £745.91 per patient.

How might this impact on clinical practice?

► NICE have just dramatically changed their guideline on stable chest pain which was published 6 years ago. SE is not considered first-line investigation in high pretest probability patients according to previous and updated NICE guidelines. However, it is recommended by ESC. The question for cardiology departments in the UK with established or recently expanded functional imaging services, is whether to downsize these departments and expand cardiac CT instead. Our data from a high-volume UK tertiary centre demonstrate that SE remains a safe and low-cost modality to investigate these patients. Hence, UK hospitals with an established functional imaging test service may choose to continue investigating these patients with functional imaging tests, based on the ESC guidelines.

patients were investigated with a SE initially which is consistent with the ESC guidelines.² Using the ESC RS for these 257 patients, the PTP was 15%–85% and ESC recommends a non-invasive test, such as SE, as first-line investigation.² There were only two patients with ESC RS >85%, and it was considered appropriate to be investigated with a SE as well, for risk stratification as per ESC guidance.² Following the SE, our patients were further investigated with ICA as appropriate, based on clinical judgement and patient's preference.

For the dobutamine SE (DSE), we used the standard 3 min stages protocol with incremental dobutamine doses of 5, 10, 20, 30 and 40 $\mu\text{g}/\text{kg}/\text{min}$. The target heart rate was calculated based on the formula: $220 - \text{patient's age in years}$. The test was terminated when 85% of maximal predicted heart rate (HR) was reached or there was evidence of inducible ischaemia in two or more segments. Intravenous atropine was given up to a maximum dose of 1200 μg if target HR was not achieved on dobutamine alone. Standard apical (four-chamber, two-chamber and three-chamber) and parasternal long-axis and short-axis

images were acquired at baseline, low dose, intermediate dose and at peak heart rates. For the exercise SE (ESE), we used the Bruce treadmill exercise protocol, aiming to reach the maximum predicted heart rate. The standard images were acquired at rest and immediately postpeak exercise. Ultrasound contrast agent was administered intravenously if more than two myocardial segments were not visible on the baseline images.

We present the outcome and the cost-effectiveness of SE in this group of patients. Follow-up data with regard to Major Adverse Cardiac and Cerebrovascular Events (MACCE, defined as cardiovascular mortality, cerebrovascular accident (CVA), documented myocardial infarction (MI) and any late revascularisation for acute coronary syndrome/unstable angina) were recorded for a fixed period of 12 months following the SE. The tariff for SE and ICA in the UK is £300 and £1400, respectively. We summed the costs of all investigations (SE plus ICA) in our cohort, and the total cost was divided by the number of patients to calculate the average cost. If our cohort had been investigated with ICA first, based on NICE guidance, the cost per patient would have been £1400, which is the cost of the ICA. The costs of the two strategies were compared with the Wilcoxon signed rank test, and a p value < 0.05 was considered statistically significant.

RESULTS

Two hundred and ten individuals (81.7%) of the 257 high PTP patients had a DSE, whereas 47 (18.3%) had an ESE. There were no submaximal tests ($< 85\%$ of the maximum predicted heart rate). There were no major adverse events. Two patients developed hypotension at

Table 1 Baseline characteristics

	Total population (n=257)
Age	67.6 \pm 10.6
Gender (male)	150 (58.4%)
Dobutamine stress echo	210 (81.7%)
Diabetes	80 (31.1%)
Smoking	36 (14%)
Hyperlipidaemia	174 (67.7%)
Hypertension	188 (73.2%)
Family history of CAD	57 (22.2%)
NICE PTP score	83.2% \pm 10.8%
Ejection fraction	3 (0.8%)
Normal	214 (93.8%)
Mildly impaired	13 (5.1%)
Moderately impaired	1 (0.4%)
Severely impaired	2 (0.8%)
Positive SE	106 (41.2%)
Invasive coronary angiogram	65 (25.3%)
Revascularisation	15 (5.8%)
MACCE	5 (2.0%)

CAD, coronary artery disease; MACCE, major adverse cardiac and cerebrovascular event; NICE, National Institute for Health and Care Excellence; PTP, pretest probability.

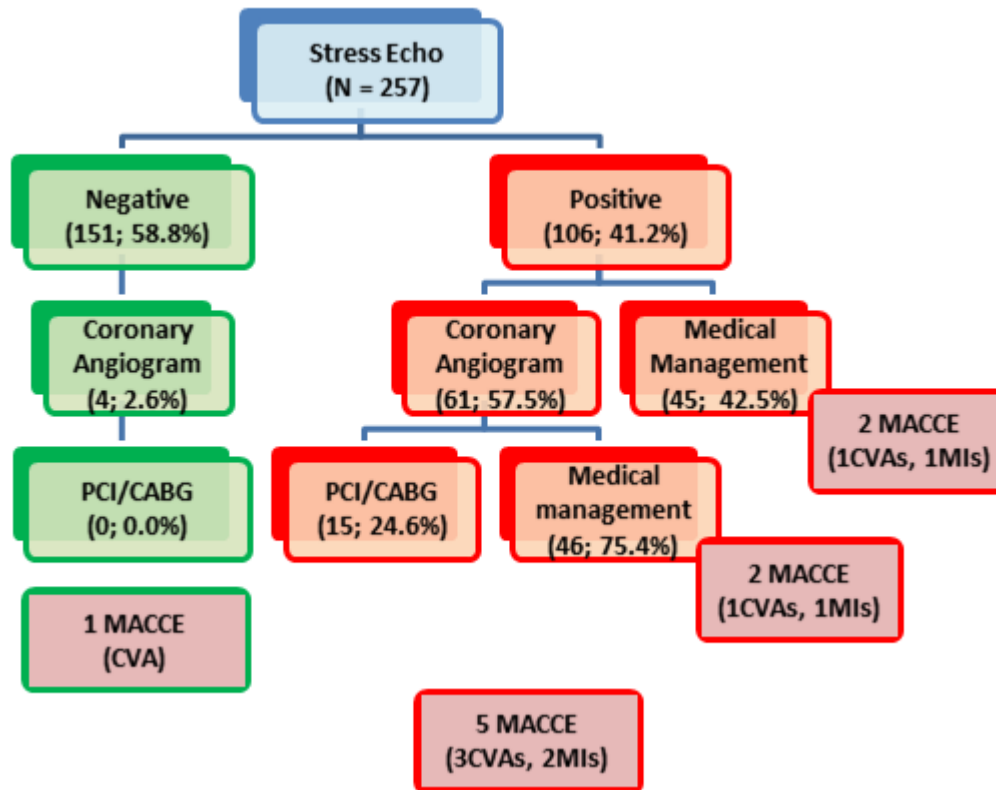


Figure 1 Flow-chart showing the management of patients based on our approach according to ESC guidance. CABG, coronary artery bypass grafting; CVA, cerebrovascular accident; MACCE, major adverse cardiac and cerebrovascular event; MI, myocardial infarction; PCI, percutaneous coronary intervention.

peak stage of DSE, and one patient developed atrial fibrillation. The baseline characteristics are shown in [table 1](#). The mean age was 67.6 ± 10.6 years and 150 (58.4%) were men. The management of patients is presented in [figure 1](#). Sixty-one patients had a positive SE and were clinically judged to need further investigation with ICA (61/257=23.7%). Fifteen of these patients (24.6%) were revascularised with either percutaneous coronary intervention (PCI, 11; 18%) or coronary artery by-pass grafting (4; 6.7%). From the remaining 46 patients who were not revascularised, seven had a Fractional Flow Reserve (FFR) study which was negative (FFR >0.8) or borderline (FFR 0.79), and a decision was made for medical management, based on lack of evidence that revascularisation favours better outcome.^{4,5} Thirty-two patients had no more than mild coronary artery stenosis. Interestingly, 16 of these patients had only apical ischaemia on SE, a finding that may be related to microvascular disease.⁶ The ICA findings of the remaining seven patients were (1) significant right coronary artery (RCA) disease which was a small vessel, (2) moderate disease on proximal and distal left anterior descending artery (LAD), (3) moderate ostial LAD disease, (4) moderate RCA disease, (5) moderate to severe very distal LAD lesion, (6) diffuse atheroma and mild to moderate disease in the distal LAD and (7) proximal LAD disease, not suitable for PCI and turned down for coronary artery bypass graft due to comorbidities. In the above cases (1–6), the angiographic findings and

clinical symptoms were not considered severe enough to warrant revascularisation.

We calculated the average cost per patient for investigations (SE+ICA) as described in the ‘Methods’, and this was found to be £654.09. If NICE guidance had been followed the cost would have been significantly higher at £1400 ($p < 0.001$). Therefore, our strategy reduced the cost of investigations by £745.91 per patient.

None of the patients had any other test apart from SE before the coronary angiogram. There was one patient who had a SPECT scan following the ICA. This test has not been counted in the cost analysis, as it was not performed as part of the screening process before ICA, but afterwards. Therefore, it does not fall in the scope of this study to compare the costs of ‘imaging first’ vs ‘invasive first’ strategies.

Overall, five MACCE (2.0%) were recorded; four (3.8%) in the group of positive SE (two CVAs and two MIs) and one (0.7%) in the group of negative SE (1 CVA). There was no MI and no need for revascularisation in the negative SE group.

DISCUSSION

Our approach to investigate patients who present with new onset chest pain, and high PTP, with SE initially as per the ESC guidelines, and subsequently with ICA if needed, was safe and reduced cost significantly (£745.91 per patient)

compared to the 2010 NICE guidelines strategy. Our results are very similar to the recent Clinical Evaluation of Magnetic Resonance Imaging in Coronary Heart Disease 2⁷ clinical trial, which demonstrated in 1202 patients with new onset chest pain and moderate PTP (RS=49.5%) that cardiac magnetic resonance and myocardial perfusion scintigraphy guided care significantly reduced the need for ICA compared to NICE guideline-directed care, with no difference in MACCE.

NICE have just dramatically changed their guideline on stable chest pain which was published 6 years ago, and at the time, there was also a dramatic departure from the previous standard of care, the exercise ECG. NICE is striving to find the most cost-effective strategy to investigate patients with new onset chest pain. In the UK, there are at least 49 centres which perform CTCA, based on a recent radiation dose audit, conducted by the British Society of Cardiovascular Imaging/British Society of Cardiac CT.⁸ Another audit on SE revealed that 120 out of 198 echocardiography departments in the UK perform SE.⁹ The question for cardiology departments with established or recently expanded functional imaging services, is whether to downsize these departments and expand cardiac CT instead.

The reason for the expansion of the role of CTCA in the new NICE guidelines is likely to be the results from the Prospective Multicentre Imaging Study for Evaluation of Chest Pain trial,¹⁰ which demonstrated that in 10003 patients with new onset chest pain and moderate PTP (RS=53%), CTCA and imaging functional tests have the same outcome. A further major study, Scottish CT of the Heart,¹¹ demonstrated in 4146 patients, that the addition of CTCA to standard of care which was the exercise ECG, improves the diagnosis in 25% of patients. Neither of these two major studies compared CTCA with functional imaging tests in patients with high PTP. Furthermore, ESC guidelines² recommend CTCA in patients with low-intermediate PTP (15%–50%) but not in higher PTP patients. Hence, UK hospitals with an established functional imaging test service may choose to continue to investigate these patients with functional imaging tests based on the ESC guidelines.

The imaging first strategy can reduce the cost of investigations as shown by our data, but it has also some downsides. SE has good accuracy, and the sensitivity of exercise and DSE has been reported to be 81%–84%.¹² This practically means that some false-negative tests are expected and some patients who are having CAD can go undiagnosed, which will not be missed with an invasive first strategy. CTCA has been reported to have a sensitivity of 81% (95% CI: 72% - 89%) and a negative predictive value of 96.5% (95% CI: 94.7% - 98.3%).¹³ The high negative predictive value of CTCA renders this modality a useful tool to rule out CAD. However, the use of CTCA as recommended in the recent NICE guidance,³ has received significant criticism.¹⁴ In any event, it has to be acknowledged that for patients with high PTP a negative non-invasive test may not reduce the post-test probability

in such a degree to rule out CAD.¹⁵ On the other hand, non-invasive tests have significantly lower rate of complications, are more widely available and can reduce the time to diagnosis of CAD.

The aim of this study was to compare the cost of an imaging first approach, in particular SE, with the cost of the previous NICE recommendation,¹ which was an invasive first strategy. In the interim, NICE have changed their recommendation³ and suggest CTCA as initial investigation. One may argue that the findings of our study may sound out of date, but actually our piece of work endorses the new guidelines that starting with a non-invasive test in high PTP patients is cost efficient without significant risks.

This is an observational single-centre study with inherent limitations and bias. It demonstrates a cost reduction when patients with high PTP of CAD are investigated with SE initially instead of ICA. The follow-up period is relatively short with few events recorded, rendering our study underpowered to assess the safety and efficacy of SE. This study has not been designed to answer the question how stress echo compares with CTCA or with other methods of functional imaging; therefore, comparisons between modalities cannot be made.

CONCLUSION

Our data demonstrate that SE remains a low-cost and readily available modality to investigate patients with new onset chest pain and high PTP of CAD. SE can reduce the cost of investigations substantially in this group of patients, but certain conclusions about SE's efficacy and safety cannot be drawn based on the results of our study. The data do not show a clear signal of harm, but the possibility cannot be ruled out.

Contributors AP collected data, performed statistical analysis and interpretation of results and wrote the manuscript. DCD collected data and revised the manuscript. DR collected data and revised the manuscript. IT collected data and revised the manuscript. MP collected data and revised the manuscript. JB revised the manuscript and provided expert opinion throughout. KA conceived the idea for the project and revised the manuscript. MJM conceived the idea for the project, revised the manuscript and provided expert opinion throughout.

Funding This study was supported in part by a National Institute for Health Research Biomedical Research Centre award to Guy's & St Thomas' Hospital and King's College London in partnership with King's College Hospital (Grant Code: IS-BRC-1215-20006)

Competing interests None declared.

Patient consent Detail has been removed from this case description/these case descriptions to ensure anonymity. The editors and reviewers have seen the detailed information available and are satisfied that the information backs up the case the authors are making.

Provenance and peer review Not commissioned; externally peer reviewed.

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