





Real-world performance and accuracy of stress echocardiography: the EVAREST observational multi-centre study

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Received 15 March 2021; editorial decision 22 April 2021; accepted 4 May 2021; online publish-ahead-of-print 20 June 2021

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Aims

Stress echocardiography is widely used to identify obstructive coronary artery disease (CAD). High accuracy is reported in expert hands but is dependent on operator training and image quality. The EVAREST study provides UK-wide data to evaluate real-world performance and accuracy of stress echocardiography.

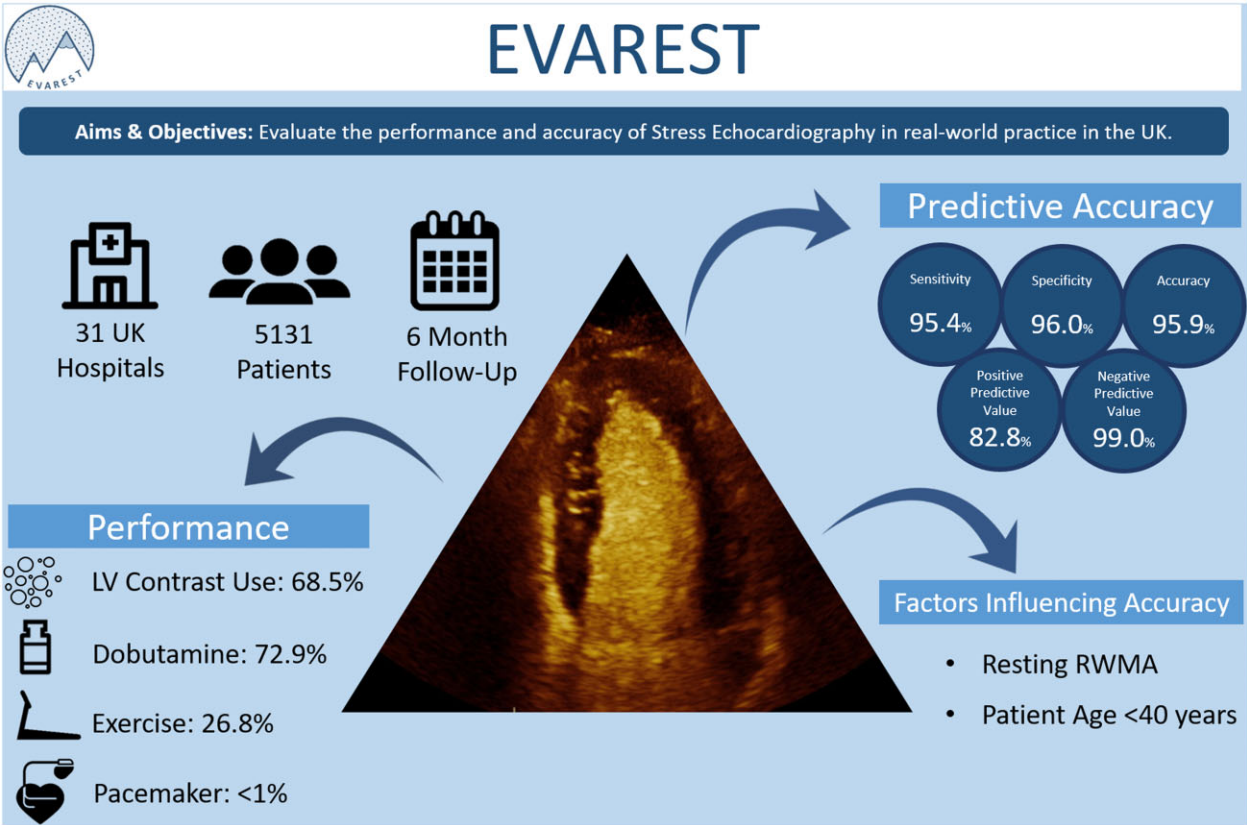
Methods and results

Participants undergoing stress echocardiography for CAD were recruited from 31 hospitals. Participants were followed up through health records which underwent expert adjudication. Cardiac outcome was defined as anatomically or functionally significant stenosis on angiography, revascularization, medical management of ischaemia, acute coronary syndrome, or cardiac-related death within 6 months. A total of 5131 patients (55% male) participated with a median age of 65 years (interquartile range 57–74). 72.9% of studies used dobutamine and 68.5% were contrast studies. Inducible ischaemia was present in 19.3% of scans. Sensitivity and specificity for prediction of a cardiac outcome were 95.4% and 96.0%, respectively, with an accuracy of 95.9%. Sub-group analysis revealed high levels of predictive accuracy across a wide range of patient and protocol sub-groups, with the presence of a resting regional wall motion abnormality significantly reducing the performance of both dobutamine ($P < 0.01$) and exercise ($P < 0.05$) stress echocardiography. Overall accuracy remained consistently high across all participating hospitals.

Conclusion

Stress echocardiography has high accuracy across UK-based hospitals and thus indicates stress echocardiography is being delivered effectively in real-world practice, reinforcing its role as a first-line investigation in the assessment of patients with stable chest pain.

Graphical Abstract



Keywords

Stress echocardiography • Coronary artery disease • Ischaemic heart disease • Accuracy

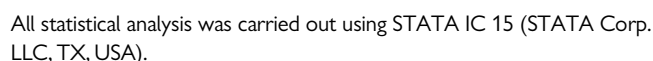


Figure 1 shows patient recruitment from 31 hospitals. The broad geographical distribution of this research network and hospital characteristics are shown in the [Supplementary data](#) online ([Supplementary data](#) online, [Figure S2](#)). Of those recruited, 32 were identified as screening failures and 46 were excluded from the analysis as their stress echocardiogram was not performed. A further 97 patients were excluded as their stress echocardiogram was inconclusive or abandoned. Of the 5354 patients who were followed up, 223 were excluded. Therefore, a total of 5131 patients were included in the analysis.

disease. Pre-existing CAD was present in 1868 (36.7%) participants, with 867 (17.2%) participants having previously suffered a myocardial infarction.

Dobutamine was the most common stressor accounting for 3739 (72.9%) of tests, while exercise was used in 1375 (26.8%) studies. Of those undergoing exercise stress echocardiography, 918 (66.8%) underwent treadmill stress, whilst 454 (33.0%) underwent bicycle ergometer stress, mode of stress was not recorded for 3 (0.2%) patients. Seventeen patients (0.2%) underwent a pacemaker-mediated study. [Supplementary data](#) online, [Table S1](#) shows a higher prevalence of cardiovascular risk factors in those undergoing dobutamine stress echocardiograms, compared to those having exercise studies. Left ventricular (LV) contrast was used in 3510 (68.5%) of studies, with more frequent use in dobutamine stress echocardiograms compared to exercise stress (76.1% vs. 47.8%). Increased age and BMI were independently associated with contrast use in multivariate regression analysis ([Supplementary data](#) online, [Table S2](#)).

Six-month outcome data were analysed to determine the predictive accuracy of stress echocardiography. *Figure 2A* demonstrates time-related events up to 6 months after stress echocardiography. A positive stress echocardiogram was significantly associated with cardiac outcome (adjusted HR 123.9, 95% CI 88.8–172.8; $P < 0.0001$).

Overall sensitivity for all types of stress echocardiography and patient was 95.4% with a specificity of 96.0%. Positive predictive value and negative predictive value were 82.8% and 99.0%, respectively. Overall accuracy was 95.9%. No significant difference in predictive ability was observed between dobutamine and exercise stress echocardiography ($P = 0.533$). Table 2 shows the sensitivity, specificity, and accuracy for stress echocardiography when separated by sub-group according to patient characteristic and type of stressor. The presence of a resting regional wall motion abnormality was associated with a significant reduction in overall predictive accuracy in both exercise stress echocardiography ($P < 0.05$) and dobutamine stress echocardiography ($P < 0.01$). The presence of left bundle branch block (LBBB), which is more common in those with resting wall motion abnormalities, also reduced sensitivity, specificity, and accuracy during dobutamine stress echocardiography. However, there was no statistically significant difference in predictive performance ($P = 0.366$). The presence of atrial fibrillation selectively reduced sensitivity of dobutamine stress echocardiography but overall predictive ability did not change ($P = 0.728$). Sensitivity was higher for both dobutamine and exercise stress echocardiography in those with the previous coronary artery bypass graft surgery but specificity was lower resulting in no overall change in predictive ability for either dobutamine ($P = 0.813$) or exercise stress echocardiography ($P = 0.982$). Increased BMI $> 40 \text{ kg/m}^2$ did not significantly impact overall performance ($P = 0.402$); however, sensitivity was higher during dobutamine stress echocardiography in those patients with a BMI of $< 40 \text{ kg/m}^2$. Overall predictive ability was significantly greater ($P < 0.0001$) in patients aged < 40 years. Sub-group analysis was carried out on patients undergoing stress echocardiography prior to surgery. No significant differences ($P = 0.562$) in predictive accuracy were observed in this group of patients.

Table 3 reports the accuracy of stress echocardiography related to contrast use. No statistically significant differences in overall accuracy were observed between contrast and non-contrast stress echocardiograms ($P=0.813$). A significant ($P<0.05$) reduction in predictive accuracy was observed with non-contrast exercise

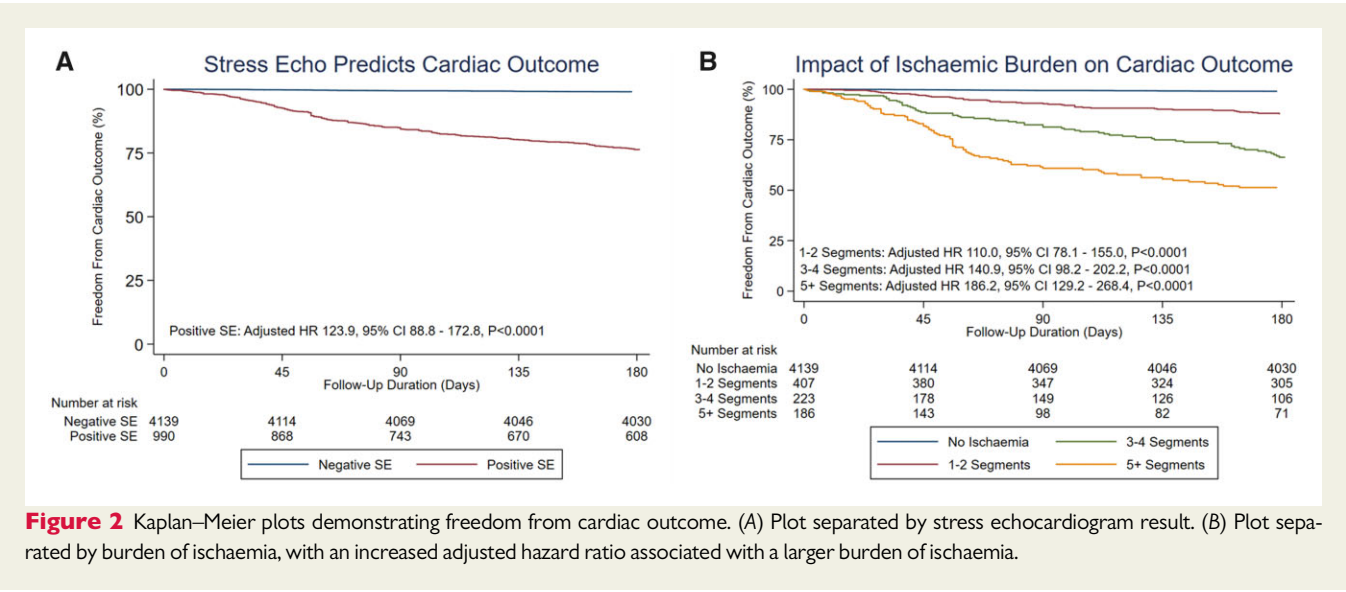


Figure 2 Kaplan–Meier plots demonstrating freedom from cardiac outcome. (A) Plot separated by stress echocardiogram result. (B) Plot separated by burden of ischaemia, with an increased adjusted hazard ratio associated with a larger burden of ischaemia.

Table 2 Diagnostic performance of dobutamine and exercise stress echocardiography

	N		Sensitivity (%)		Specificity (%)		Accuracy (%)		P-value	
	DSE	ESE	DSE	ESE	DSE	ESE	DSE	ESE	DSE	ESE
Overall	3739	1375	95.6	94.4	96.0	96.0	96.0	95.8	.	.
Normal resting wall motion	3168	1238	96.4	94.0	96.6	96.9	96.6	96.5	0.002	0.048
Resting RWMA	564	134	94.2	95.9	91.5	84.7	92.6	88.8		
Normal conduction	3641	1347	95.7	94.8	96.1	96.0	96.0	95.8	0.366	.
LBBB	60	17	90.9	.	91.8	.	91.7	.		
RBBB	38	11		
Sinus rhythm	2314	808	93.9	92.9	96.5	97.3	96.1	96.7	0.728	.
Atrial fibrillation	131	14	90.9	.	97.2	.	96.2			
No previous CABG	3400	1307	95.5	93.6	96.1	96.2	96.0	95.9	0.813	0.982
Previous CABG	316	67	96.2	100.0	94.8	89.7	95.3	94.0		
BMI < 40 kg/m ²	3246	1307	96.1	94.7	96.0	96.2	96.1	95.9	0.402	.
BMI > 40 kg/m ²	182	30	92.9	.	94.8	.	94.5	.		
Age < 40 years	74	61	100.0	100.0	98.6	98.3	98.6	98.4	0.000	0.001
Age > 40 years	3651	1313	95.7	94.4	96.0	95.9	95.9	95.7		
Indication: ischaemia	3642	1360	95.7	94.4	96.1	96.1	96.0	95.8	0.562	.
Indication: pre-operative/pre-transplant	97	15	94.4	.	93.7	.	93.8	.		

Diagnostic performance of stress echocardiography, overall and by patient sub-group. Values are presented for dobutamine stress echocardiography (DSE) and exercise stress echocardiography (ESE). P-values for χ^2 comparison of AUROCs between sub-groups. NB. . indicates that fewer than 50 patients were in this sub-group, therefore values not calculated.

BMI, body mass index; CABG, coronary artery bypass graft surgery; LBBB, left bundle branch block; RBBB, right bundle branch block; RWMA, regional wall motion abnormalities.

segments (IQR 3–7 segments) compared with four segments (IQR 2–6 segments), respectively. No significant difference ($P = 0.118$) in ischaemic burden was observed between LAD, LCx, and RCA disease. Univariate logistic regression demonstrated that LAD ischaemia was significantly associated with ischaemia in the LAD territory (OR 4.9, 95% CI 1.9–13.0; $P < 0.001$) whilst RCA ischaemia was significantly associated with RCA territory ischaemia (OR 2.4, 95% CI 1.3–4.3; $P < 0.01$). However, stress echocardiography lacked the precision to

detect LCx disease, with no significant association with LCx ischaemia (OR 1.5, 95% CI 0.8–2.8; $P = 0.156$).

Discussion

This study provides contemporary, real-world data on the use, and accuracy of stress echocardiography in clinical practice across a

Benefits of stress echocardiography include a lack of ionizing radiation, which complicates other cardiac imaging modalities. However, image quality can be adversely affected by patient body habitus, making interpretation challenging. One study reports up to one in three patients may have sub-optimal images.²⁷ This can be overcome with LV contrast agents.²⁸ We observed a high use of LV contrast, at 68.5% of studies; known to increase diagnostic accuracy.²⁸ Patients receiving contrast tended to have an elevated BMI and older age, matching known factors likely to increase the requirement for contrast use.²⁸ Our findings demonstrate contrast-enhanced stress echocardiography has a high predictive accuracy, even in the sub-group of patients with a BMI >40 kg/m².

Accuracy was mainly affected by non-procedural factors, specifically, pre-existing regional wall motion abnormalities, which are recognized as complicating identification of new wall motion abnormalities²⁹ as well as resulting in a higher risk of adverse events.^{21,30} The reduction in accuracy in those with regional wall motion abnormalities may reflect an impact of dobutamine on post-systolic shortening,³¹ which could disguise a lack of segmental contractile function, leading to misdiagnosis on visual assessment.

We have demonstrated the ability of stress echocardiography to accurately detect flow-limiting coronary disease in the LAD and RCA; however, no significant association was observed between ischaemia detected the LCx territory and LCx coronary disease. This lack of association between LCx ischaemia and corresponding disease on angiography may be explained by the termination of the stress echocardiogram following the development of ischaemia in a different territory with a lower coronary flow reserve. Once ischaemia has been documented, especially in dobutamine stress echocardiography, the test is typically terminated and may therefore mask an ischaemic response in another territory with significant stenosis.

Since stress echocardiography relies on the qualitative assessment of wall motion, accurate interpretation is dependent on operator experience.³² One obstacle to a more widespread use of stress echocardiography may be lack of trained operators to confidently and accurately interpret the test. In the future, this obstacle may be overcome by the incorporation of artificial intelligence (AI) tools into the clinic capable of performing a quantitative assessment of stress images.^{33–35} Increased consistency and confidence in reporting by the use of AI could broaden the range of personnel who could perform stress echocardiograms.

Acute coronary events or cardiac-related deaths that occur after a negative stress echocardiogram remain a concern. However, this study shows similar rates of 1–2% of patients having acute events over 6 months in both the negative and positive stress echocardiogram cohorts. Recent trials have shown an early invasive strategy has a similar impact on longer-term event rates as a medical management-based approach,^{13,24} which may reflect the evolving nature of the underlying pathology and emergence of new disease. As CAD progresses over time, accuracy for stress echocardiography to predict longer-term outcomes is likely to vary and subsequent analysis with longer-term follow-up will be of interest.

The present study reveals over half of patients who have positive functional imaging do not go on to have further investigation or intervention. The number of ischaemic segments was lower in this group consistent with accepted clinical decision making to manage medically those with lower ischaemic burden.¹⁴ This study confirms a striking

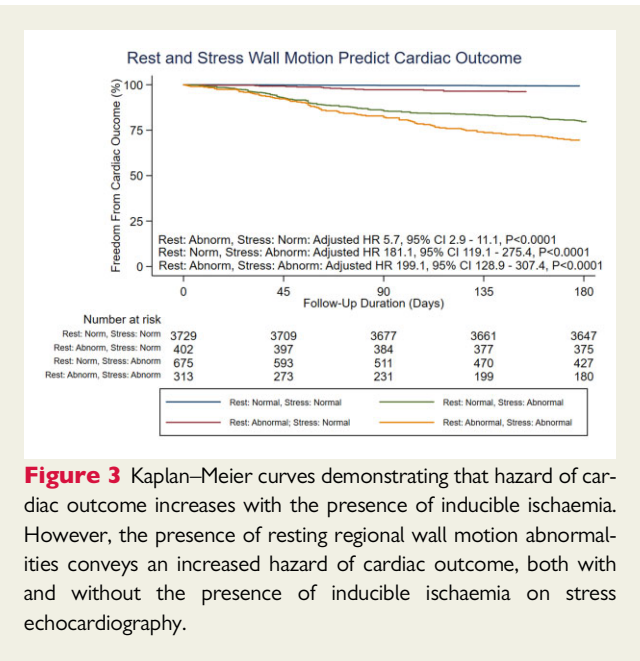


Figure 3 Kaplan–Meier curves demonstrating that hazard of cardiac outcome increases with the presence of inducible ischaemia. However, the presence of resting regional wall motion abnormalities conveys an increased hazard of cardiac outcome, both with and without the presence of inducible ischaemia on stress echocardiography.

graded association between the degree of ischaemia assessed by the clinician and the likelihood of cardiac outcome over the next 6 months. Reassuringly, outcome at 6 months in the medically managed positive stress echocardiogram population was comparable to other arms of clinical care. The recently published ISCHEMIA study would support the medical management of stable ischaemic heart disease patients with preserved ventricular function and no evidence of heart failure or LMS disease, even if they have a large burden of ischaemia.¹³ Long-term follow-up of this study will investigate whether revascularization reduces the incidence of myocardial infarction in the longer term in patients with significant ischaemia.

The study has limitations. Firstly, by using real-world data, angiographic confirmation of obstructive or non-obstructive coronary disease was not available for all patients. Instead, patients were allocated to outcome based on clinical history during a 6-month period, using criteria developed for handling outcomes in this setting.^{36,37} Therefore, patients with obstructive coronary disease who had a negative stress echocardiogram but then remained well for the next 6 months could have been misclassified from an anatomical perspective in analysis. Arguably, this outcome was clinically acceptable and the statistical misclassification bias is minimized by related misclassification in patients with positive stress echocardiogram who did not undergo further investigation. Secondly, patients who underwent angiography were judged based on the degree of stenosis in their epicardial arteries assessed by the operating clinician rather than an independent review of the angiogram. Thirdly, this meant potential causes of non-obstructive ischaemia, such as microvascular disease, may have been misclassified in outcome allocation as a false positive stress echocardiogram. Fourthly, not all sites started recruiting at the same time and therefore some sites contributed more proportionally to the dataset. Reanalysis at future time points beyond 6 months and with more patients from each site providing outcome data will be of interest. Finally, due to the nature of the consent process, there may

