RESEARCH

Does stress echocardiography still have a role in the rapid access chest pain clinic post NICE CG95?

Victoria Pettemerides MBBS BSc MRCP[1], Thomas Turner[2], Conor Steele[2] and **Anita Macnab MBchB FRCP[1]**

[1]Manchester University Foundation Trust, North West Heart Centre, Wythenshawe Hospital, Manchester, UK
[2]University of Manchester Faculty of Biology, Medicine and Health, Manchester, UK

Correspondence should be addressed to V Pettemerides: victoria.pettemerides@mft.nhs.uk

Abstract

Introduction: The 2016 NICE clinical guideline 95 (CG95) demoted functional imaging to a second-line test following computed tomography coronary angiography (CTCA). Many cardiac CT services in the UK require substantial investment and growth to implement this. Chest pain services like ours are likely to continue to use stress testing for the foreseeable future. We share service evaluation data from our department to show that a negative stress echocardiogram can continue to be used for chest pain assessment.
Methods: 1815 patients were referred to rapid access chest pain clinic (RACPC) between June 2013 and March 2015. 802 patients had stress echocardiography as the initial investigation. 446 patients had normal resting left ventricular (LV) systolic function and a negative stress echocardiogram. At least 24 months after discharge, a survey was carried out to detect major adverse cardiovascular events (MACE) (cardiac death, myocardial infarction, admission to hospital for heart failure or angina, coronary artery disease at angiography, revascularisation by angioplasty or coronary artery bypass grafting) within 2 years.
Results: Overall, 351 patients were successfully followed up. The mean Diamond-Forrester (D-F) score and QRISK2 suggested a high pre-test probability (PTP) of coronary artery disease (CAD). There were nine deaths (eight non-cardiac deaths and one cardiac death). MACE occurred in four patients with a mean time of 17.5 months (11.6–23.7 months). The annual event rate was 0.6%.
Conclusion: A negative stress echocardiogram can reliably reassure patients and clinicians even in high PTP populations with suspected stable angina. It can continue to be used to assess stable chest pain post CG95.

Key Words

- stable chest pain
- coronary artery disease
- exercise echocardiography
- dobutamine stress echocardiography,

Introduction

In patients with suspected stable angina, it is important to not only make a diagnosis but also to assess risk and prognosis in order to guide management. There is a wealth of evidence demonstrating the value of functional imaging, especially myocardial perfusion imaging and stress echocardiography in this setting (1, 2, 3, 4, 5, 6), and this underpins both European and American guidelines (7, 8). Up until 2016 in the United Kingdom, functional imaging was also recommended by the National Institute of Clinical Excellence (NICE) as the initial investigation for patients presenting with suspected coronary artery disease (CAD) and an intermediate pre-test probability (PTP).

https://erp.bioscientifica.com
https://doi.org/10.1530/ERP-18-0082

As a result, functional imaging modalities have been widely utilised in clinical practice. Yet in the updated 2016 clinical guideline (CG95), NICE has removed the use of PTP assessment and demoted functional imaging to a second-line investigation behind anatomical assessment with computed tomography coronary angiography (CTCA), which is recommended in all patients with suspected angina unless the test is not feasible. This is yet to be mirrored by European or American guidelines in which CTCA is recommended only as an alternative to stress testing.

In 2015 national data collected by the British Society of Cardiovascular Imaging (BSCI) showed that only 101 centres in the United Kingdom were performing CTCA (9). It was estimated that the change in NICE guidance in 2016 would require a 700% national increase in CTCA delivery and the BSCI acknowledged that alternative methods of assessment such as stress echocardiography would need to be utilised for some years to come. A recent survey of UK consultant cardiologists found that only a quarter felt their practice reflected CG95 (10). We ourselves are a tertiary centre with a high-volume chest pain service and a stress echo infrastructure which has been developed to meet growing demands since 2010. Three years on from NICE CG95 2016 recommendations, our CTCA service has reached capacity and is still only able to scan the low PTP patients coming through the rapid access chest pain clinic (RACPC) as per the 2010 recommendations of CG95. Being NICE non-compliant causes anxieties amongst both clinicians and managers but pathways cannot change without substantial investment in equipment and staffing. Like many other regions in the United Kingdom, we are likely to continue to serve our chest pain patients with functional imaging for some years to come. Here, we present data for our chest pain patients who were discharged following a negative stress echocardiogram with no knowledge of their coronary anatomy.

Methods

Patient selection

All patients attending our RACPC between 1st June 2013 and 31st March 2015 were identified. Patients with a history of prior CAD were excluded. Demographic data, risk factors, symptom score and risk score including modified Diamond–Forrester (11) and QRISK 2 (12) score were entered into the hospital electronic database prospectively at the time of assessment in RACPC. Patients who had stress echocardiography as an initial investigation were selected and any with abnormal LV systolic function at rest or ischaemia detected on stress echocardiogram were excluded. Resting global LV systolic function was assessed visually as normal, mildly, moderately or severely reduced. Any resting wall motion abnormality was recorded. Ischaemia was defined as >1 segment of hypokinesia, akinesia or dyskinesia or cavity dilatation during stress echocardiography. All patients with less than normal global resting function or resting wall motion abnormality were excluded. All patients with ischaemia detected on stress echocardiogram were excluded. The final selected cohort were discharged from RACPC with a diagnosis of non-cardiac chest pain. Follow-up took place 24 months following discharge of the last patient in the cohort to determine major adverse cardiovascular events (MACE).

Stress echocardiography

Stress echocardiography was carried out in accordance with British Society of Echocardiography guidelines (13). Exercise stress echocardiography (ESE) was performed using a semi-supine bicycle using a standard linear exercise protocol with 25 Watt load increase every 2 min, while the patient maintained a steady cadence at 60–70 rpm. Dobutamine stress echo (DSE) was performed using a standard 3-min incremental protocol starting at a dose of 5 µg/kg/min up to a maximum of 40 µg/kg/min. Atropine and hand-grip augmentation was used, as required, commencing at the 30 µg/kg/min stage. Stress echocardiography was considered complete if target heart rate was reached or BSE termination criteria were met. Transpulmonary contrast agents were used if two or more myocardial segments were not well visualised at initial assessment. Standard views (A4Ch, A2Ch, A3Ch, PLAX, PSAX) were acquired. Target heart rate was calculated as $0.85 \times (220 - \text{age})$. Images were taken at baseline, intermediate and target heart rate for the exercise stress echo group and at baseline, low dose, intermediate and target heart rate in the dobutamine group. Images were interpreted by an experienced imaging consultant.

Follow-up

The audit was considered part of service evaluation and therefore ethical approval was not required. At the time of the first clinic visit permission was sought from the patients about contact in the future. Follow-up occurred at

https://erp.bioscientifica.com
https://doi.org/10.1530/ERP-18-0082

least 24 months after discharge and used several methods. The first was a standardised telephone questionnaire using contact details from the hospital electronic record or via the general practitioners (GP). If the patient could not be contacted, hospital and GP records were accessed. If the patient had died, medical records or post mortem reports were reviewed to establish the cause of death. All patients who could not be contacted and had no admissions recorded in our own hospital had to be excluded from follow-up because we could not assume that they were event-free. In our region there were seven other acute trusts and four other cardiac catheter laboratories at the time of the study that they could have been admitted to.

The primary end point as defined by major adverse cardiac event (cardiac death, myocardial infarction, admission to hospital for heart failure or angina, CAD detected at angiography or revascularisation by either angioplasty or CABG) within 2 years following discharge was determined. Death from any cause was also documented. If more than one event occurred, the first event was recorded as the MACE event.

Statistical analysis

Data were analysed using IBM SPSS Statistics for Mac, version 23.0 (IBM Corporation Group). Independent *t*-tests were used for continuous variable and categorical variables were tested with chi-square test or Fisher's exact test as appropriate. *P* values <0.05 were deemed statistically significant.

Results

Overall, 1815 patients without prior coronary arterial disease were referred to our RACPC between 1st June 2013 and 31st March 2015. A total of 802 patients were investigated by stress echocardiography as first line. 446 patients met inclusion criteria but 21% of patients were lost to follow-up giving a total number of 351 patients (204 ESE and 147 DSE).

Table 1 shows the demographics of the cohort split into the two types of stress echo. Those in the DSE group were significantly older (*P*=0.014), with higher QRisk2 scores and had a higher BMI. There were also more females in this group. The mean DF score in both DSE and ESE groups correlated with a 'high' PTP. In our unit, we also calculate the background QRisk2 score (12). The mean score was 20.2 (±13.2), which equates to a high-risk group. 52% of patients had a pre-test diagnosis of typical angina as per the CG95 symptom score assessment (1=non-anginal pain, 2=atypical angina and 3=typical angina). This was significantly higher in the exercise echo group.

Total all-cause mortality was 2.6% (nine patients: five from DSE group, four from ESE group). Only one of these deaths was due to a cardiac cause. Other causes included pulmonary embolus, malignancy, pneumonia and intracerebral bleeds. MACE occurred in four patients consisting of one cardiac death, two admissions for myocardial infarction (one ST elevation infarct with primary percutaneous coronary intervention,

Table 1 Patient demographics.

	Investigation		*P* value	Total cohort (351)
	ESE (*n* = 204)	DSE (*n* = 147)		
Age (years)	62.1 ± 10.4	65.2 ± 12.7	0.014	63.4 ± 11.5
Male	86 (42%)	45 (31%)	0.033	131 (37%)
QRISK2 (%)	17.9 ± 10.4	23.3 ± 15.8	<0.001	20.2 ± 13.2
All-cause mortality	4 (2%)	5 (3.4%)	0.133	9 (2.6%)
D-F score	64.5 ± 28.7	62.8 ± 30.1	0.607	63.8 ± 28.6
BMI	28.3 ± 4.9	30.4 ± 6.9	0.002	29.1 ± 5.9
Symptom score				
1	45	66	<0.001	111 (32%)
2	31	26	0.85	57 (16%)
3	128	55	0.005	183 (52%)
Risk factors				
Diabetes mellitus	46 (23%)	32 (22%)	0.771	78 (22.2%)
Hypertension	82 (40%)	69 (47%)	0.230	151 (43%)
Smoking	44 (22%)	46 (31%)	0.112	90 (25.6%)
Hyperlipidaemia	23 (11%)	14 (10%)	0.725	37 (10.5%)
Family history	78 (38%)	52 (35%)	0.654	130 (37%)

QRISK2: <10% = low, 10–20% = intermediate, >20% high. Symptom score 1 = non-angina pain, 2 = atypical pain, 3 = typical angina. D-F score % likelihood CAD: <10% = very low, 10–29% = low, 30–60% = medium, 61–90% = high.

https://erp.bioscientifica.com
https://doi.org/10.1530/ERP-18-0082

Table 2 Profile MACE and non-MACE at 24 months.

	Patients without MACE (n = 347)	Patients with MACE (n = 4)
Mean age (years)	63.3 ± 11.5	66.8 ± 12.0
Gender (male)	128 (37%)	3 (75%)
Hypertension (%)	43.5	0.0
Diabetes (%)	22.5	0.0
Hyperlipidaemia (%)	10.4	25.0
Family history (%)	36.9	50.0
Smoking (%)	25.6	25.0
Mean BMI	29.2 ± 5.9	27.1 ± 8.1
Mean QRISK2 (%)	20.2 ± 13.3	20.8 ± 5.3
Symptom score 3 (typical angina) (%)	51.9	75.0
DF score	63.6 ± 28.7	82.5 ± 14.5

one non-ST elevation infarct requiring coronary artery bypass grafting) and one patient with CAD detected on elective angiography requiring revascularisation. Three of these occurred in the ESE cohort and one in the DSE cohort. Mean time to MACE was 17.5 months (532.8 days ± 165.7). Table 2 shows the characteristic of patients with MACE. In our cohort, a negative stress echocardiogram correlated with an annual event rate of 0.57%. Two other patients were also electively investigated for ongoing symptoms and were found to have normal coronary arteries at angiography.

Discussion

Our audit has shown that a negative stress echocardiogram is associated with a very low annual event rate even in patients with a high PTP. While this is not a new finding, it is important in view of the 2016 NICE CG95 which recommends CTCA as the initial investigation in all patients with suspected CAD. Cardiac CT services across the United Kingdom are not able to meet this demand. The BSCI and Royal College of Radiologists latest press release in November 2018, estimated a 43% shortfall in CTCA provision (14). We have presented our data to demonstrate the practice in a high-volume tertiary centre and reassure other practitioners who are not able to implement CG95, of the prognostic value of a negative stress echocardiogram.

Historically, a negative stress echocardiogram confers an excellent prognosis (15, 16, 17, 18). One study has demonstrated a 0.4% rate per person-year of cardiac death and non-fatal myocardial infarction in low PTP patients, 0.6% in intermediate patients and 0.8% in high PTP patients (19). Our audit included additional endpoints such as admission to hospital for heart failure or angina and the detection of significant CAD diagnosed at angiography. Even with this broader MACE definition, our data show a low annual event rate, despite a high PTP cohort. The role of stress echo in assessing prognosis has been demonstrated in a similar contemporary audit where MACE was defined by cardiac death, myocardial infarction, revascularisation and cerebrovascular accident (20). They demonstrated a 1% annual event rate, which may in part be explained by the inclusion of cerebrovascular accident as a primary endpoint. This study also included patients with impaired resting LV function and known CAD, which we have excluded in ours; yet, multivariate analysis showed that a positive stress echo was the only predictor of MACE at 12 months.

The mean PTP in our audit, using both QRISK2 and modified D-F score reflected a high pre-test probability. It is in this group that the use of CTCA is not understood and this underpins the European and American guidelines. The 2013 European Society of Cardiology guideline recommends functional testing in patients with an intermediate risk score (15–85%) and CTCA as an alternative only in those with a PTP score of 15–50% (7). The American guidelines also recommend a PTP assessment and reserve CTCA as an alternative to exercise stress testing if exercise is not possible in low-to-intermediate groups (8). NICE however has removed the use of PTP testing and instead recommend that assessment of likelihood of CAD is determined using symptom score (21). Those with typical or atypical symptoms should have CTCA while those with non-cardiac pain and a normal 12 lead ECG require no further testing. Yet, 60% of recently surveyed UK cardiologists did not agree with the removal of a PTP assessment and only 25.5% felt that their practice conformed to CG95 (10). It is not known if this is due to preference or availability of CTCA. In the same survey, 71% would use CTCA for the low-to-intermediate probability groups and only 37% would use it for intermediate–to-high probability patients perhaps reflecting the lack of evidence available in this population. The large multicentre randomised trial PROMISE (Prospective Multicentre Imaging Study for the Evaluation of Chest Pain, n = 10003) (22) looked at low-intermediate PTP patients and did not find CTCA superior to functional testing, (predominantly nuclear stress testing). The large UK trial (SCOT-HEART, n = 4146) (23) did include intermediate–to-high PTP patients and showed the CTCA strategy to be superior to standard care, but this was mainly ECG testing which has limitations and is regarded as inferior to functional imaging (24).

https://erp.bioscientifica.com
https://doi.org/10.1530/ERP-18-0082

NICE updated the 2016 CG95 with an additional recommendation for computed tomography-fractional flow reserve (CT-FFR) to determine the need for an invasive treatment strategy (25). At a cost of £700 per study in addition to the cost of the original CTCA compared to a stress echocardiogram tariff of £177, this does raise concerns about the cost effectiveness with this approach. In addition, the survey of UK cardiologists (10) suggests that when a degree of stenosis is identified, invasive angiography is the preferred downstream test which has a high cost and a small but significant procedural risk.

It is argued that direct visualisation of coronary anatomy has prognostic implications for primary prevention and cost effectiveness (26). One of the recognised benefits of CTCA is the identification of atherosclerosis in individuals who may have had a negative functional imaging test. Budoff argues that clinicians may view a negative stress test as the end of the matter and discharge patients without any primary prevention. On the other hand, detection of atherosclerosis by CTCA prompts the clinician to commence statin and aspirin therapy as appropriate. The mortality benefit seen from a CTCA strategy in the SCOT-HEART trial may have been achieved by the preventative therapies recommended with the finding of underlying atheroma. In our own institution we calculate the QRISK2 score in patients attending RACPC and recommend primary prevention for our patients in line with NICE guidance. Two hundred seventy-seven patients (78%) had a QRISK2 >10% and therefore received recommendation to commence statin therapy.

Limitations

The main limitation to this audit is the proportion of patients lost to follow up (21%). The reason for this is the method of follow-up which was direct telephone communication with patients and therefore relied on having the correct contact details on electronic records. If patients could not be directly contacted, GPs were contacted both for up to date patient details and history of MACE. In some circumstances the patient and GP contact details were not available or patients had moved address or changed GP. We also searched our Electronic Patient Record. This however would not have included all events as patients may have attended other hospitals with MACE. In our region, there were seven other acute trusts and four other cardiac catheter laboratories at the time of the study that they could have been admitted to. If no event was identified on our system, these patients could not be included in the follow-up.

Our audit includes a high proportion of patients undergoing DSE. ESE is recognised as being a more physiological mode of ischaemia testing and provides additional information about exercise capacity, heart rate and blood pressure. ESE has the added value of demonstrating LV systolic function during exercise, which is one of the most important prognostic variables in patients with CAD (27). In the population that we serve, we find that around 30% of patients are unable to exercise due to lung disease, arthritis and peripheral vasculopathy. In this audit, a larger proportion than would be expected (40.6%) were referred for DSE rather than ESE. This may reflect the higher proportion of females and a higher BMI in the DSE group, which is more likely to be associated with poor image quality and inability to exercise adequately on the bike.

Conclusion

The purpose of this audit is to reassure clinicians and patients of the value of functional imaging in the assessment of stable chest pain post NICE 2016 CG95. The guideline recommends that CTCA is used to document coronary artery anatomy in individuals with atypical or typical symptoms and demotes functional imaging to a second-line investigation. However, 3 years on from the published guideline, there is still a significant short fall in CTCA provision with no prospect of meeting the sheer scale of the demand across the United Kingdom for the foreseeable future. There are no data that shows a CTCA strategy is superior to a functional imaging strategy in intermediate to high PTP patients in the assessment of stable chest pain. Moreover, stress echocardiography is radiation free, low cost, well established and easily accessible (28). It is our belief that stress echocardiography should and will continue to play an important role in the assessment of stable chest pain in patients attending RACPCs.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding
This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

https://erp.bioscientifica.com
https://doi.org/10.1530/ERP-18-0082

References

1 Heijenbrok-Kal MH, Fleischmann KE & Hunink MGM. Stress echocardiography, stress single-photon-emission computed tomography and electron beam computed tomography for the assessment of coronary artery disease: a meta-analysis of diagnostic performance. *American Heart Journal* 2007 **154** 415–423. (https://doi.org/10.1016/j.ahj.2007.04.061)

2 de Jong MC, Genders TSS, van Geuns RJ, Moelker A & Hunink MGM. Diagnostic performance of stress myocardial perfusion imaging for coronary artery disease: a systematic review and meta-analysis. *European Radiology* 2012 **22** 1881–1895. (https://doi.org/10.1007/s00330-012-2434-1)

3 Marwick TH, Case C, Vasey C, Allen S, Short L & Thomas JD. Prediction of mortality by exercise echocardiography A strategy for combination with the duke treadmill score. *Circulation* 2001 **103** 2566–2571. (https://doi.org/10.1161/01.CIR.103.21.2566)

4 Marwick TH, Mehta R, Arheart K & Lauer MS. Use of exercise echocardiography for prognostic evaluation of patients With known or suspected coronary artery disease. *Journal of the American College of Cardiology* 1997 **30** 83–90. (https://doi.org/10.1016/S0735-1097(97)00148-4)

5 Fleischmann KE, Hunink MGM, Kuntz KM & Douglas PS. Exercise echocardiography or exercise SPECT imaging? A meta-analysis of diagnostic test performance. *JAMA* 1998 **280** 913–920. (https://doi.org/10.1001/jama.280.10.913)

6 Metz LD, Beattie M, Hom R, Redberg RF, Grady D & Fleischmann KE. The prognostic value of normal exercise myocardial perfusion imaging and exercise echocardiography A meta-analysis. *Journal of the American College of Cardiology* 2007 **49** 227–237. (https://doi.org/10.1016/j.jacc.2006.08.048)

7 Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, Budaj A, Bugiardini R, Crea F, Cuisset T, Di Mario C, *et al*. ESC guidelines on the management of stable coronary artery disease. *European Heart Journal* 2013 **34** 2949–3003. (https://doi.org/10.1093/eurheartj/eht296)

8 Fihn SD, Gardin JM, Abrams J, Berra K, Blankenship JC, Dallas AP, Douglas PS, Foody JM, Gerber TC, Hinderliter AL, *et al*. ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease writing committee members. *Journal of the American College of Cardiology* 2012 **60** e44–e164. (https://doi.org/10.1016/j.jacc.2012.07.013)

9 British Society of Cardiovascular Imaging & British Society of Cardiac Computed Tomography. Projected requirement for CTCA following updated NICE GG95 guidelines. Glasgow, UK: BSCI/BSCCT, 2016. (available at: http://www.bsci.org.uk/standards-guidelines/nice-cg95-update-2016?id=178)

10 Fyyaz S, Papachristidis A & Byrne J. Opinions on the expanding role of CTCA in patients with stable chest pain and beyond: a UK survey. *British Journal of Cardiology* 2018 **25** 107–109. (https://doi.org/10.5837/bjc.2018.019)

11 Diamond GA & Forrester JS. Analysis of probability as an aid in the clinical diagnosis of coronary-artery disease. *New England Journal of Medicine* 1979 **300** 1350–1358. (https://doi.org/10.1056/NEJM197906143002402)

12 Hippisley-Cox J, Coupland C, Vinogradova Y, Robson J, Minhas R, Sheikh A & Brindle P. Predicting cardiovascular risk in England and Wales: prospective derivation and validation of QRISK2. *BMJ* 2008 **336** 1475–1482. (https://doi.org/10.1136/bmj.39609.449676.25)

13 Becher H, Chambers J, Fox K, Jones R, Leech GJ, Masani N, Monaghan M, More R, Nihoyannopoulos P, Rimington H, *et al*. BSE procedure guidelines for the clinical application of stress echocardiography, recommendations for performance and interpretation of stress echocardiography: a report of the British Society of Echocardiography Policy Committee. *Heart* 2004 **90** (Supplement 6) vi23–vi30. (https://doi.org/10.1136/hrt.2004.047985)

14 British Society of Cardiovascular Imaging & The Royal College of Radiologists. Coronary CT provision 2018. Glasgow, UK: BSCI/RCR, 2018. (available at: http://www.bsci.org.uk/standards-guidelines/coronary-cta-provision)

15 Senior R, Monaghan M, Becher H, Mayet J, Nihoyannopoulos P & British Society of Echocardiography. 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* 2005 **91** 427–436. (https://doi.org/10.1136/hrt.2004.044396)

16 Sicari R, Pasanisi E, Venneri L, Landi P, Cortigiani L, Picano E, Echo Persantine International Cooperative (EPIC) Study Group & Echo Dobutamine International Cooperative (EDIC) Study Group. Stress echo results predict mortality: a large-scale multicenter prospective international study. *Journal of the American College of Cardiology* 2003 **41** 589–595. (https://doi.org/10.1016/S0735-1097(02)02863-2)

17 Metz LD, Beattie M, Hom R, Redberg RF, Grady D & Fleischmann KE. The prognostic value of normal exercise myocardial perfusion imaging and exercise echocardiography A meta-analysis. *Journal of the American College of Cardiology* 2007 **49** 227–237. (https://doi.org/10.1016/j.jacc.2006.08.048)

18 Chung G, Krishnamani R & Senior R. Prognostic value of normal stress echocardiogram in patients with suspected coronary artery disease – a British general hospital experience. *International Journal of Cardiology* 2004 **94** 181–186. (https://doi.org/10.1016/j.ijcard.2003.03.020)

19 Mccully RB, Roger VL, Mahoney DW, Karon BL, Oh JK, Miller FA, Seward JB & Pellikka PA. Outcome after normal exercise echocardiography and predictors of subsequent cardiac events: follow-up of 1325 patients. *Journal of the American College of Cardiology* 1998 **31** 144–149. (https://doi.org/10.1016/S0735-1097(97)00427-0)

20 Papachristidis A, Roper D, Cassar Demarco D, Tsironis I, Papitsas M, Byrne J, Alfakih K & Monaghan MJ. The prognostic role of stress echocardiography in a contemporary population and the clinical significance of limited apical ischaemia. *Echo Research and Practice* 2016 **3** 105–113. (https://doi.org/10.1530/ERP-16-0033)

21 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 (update). NICE guideline CG95: methods, evidence and recommendations (final version). London, UK: NICE, 2016. (available at: https://www.nice.org.uk/guidance/cg95/evidence/full-guideline-245282221)

22 Douglas PS, Hoffmann U, Lee KL, Mark DB, Al-Khalidi HR, Anstrom K, Dolor RJ, Kosinski A, Krucoff MW, Mudrick DW, *et al*. PROspective Multicenter Imaging Study for Evaluation of chest pain: rationale and design of the PROMISE trial. *American Heart Journal* 2014 **167** 796.e1–803.e1. (https://doi.org/10.1016/j.ahj.2014.03.003)

23 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* 2015 **385** 2383–2391. (https://doi.org/10.1016/S0140-6736(15)60291-4)

24 Gianrossi R, Detrano R, Mulvihill D, Lehmann K, Dubach P, Colombo A, McArthur D & Froelicher V. Exercise-induced ST depression in the diagnosis of coronary artery disease A meta-analysis. *Circulation* 1989 **80** 87–98. (https://doi.org/10.1161/01.CIR.80.1.87)

25 National Institute for Health and Care Excellence. HeartFlow FFRCT for estimating fractional flow reserve from coronary CT angiography. Medical technologies guidance [MTG32]. London, UK: NICE, 2017.

(available at: https://www.nice.org.uk/guidance/mtg32/chapter/1-Recommendations)
26 Budoff MJ. The 2016 National Institute for Health and Care Excellence guidelines for chest pain: better outcomes with cardiac CT. *Heart* 2018 **104** 186–187. (https://doi.org/10.1136/heartjnl-2017-311776)
27 Upton MT, Rerych SK, Newman GE, Port S, Cobb FR & Jones RH. Detecting abnormalities in left ventricular function during exercise before angina and ST-segment depression. *Circulation* 1980 **62** 341–349. (https://doi.org/10.1161/01.CIR.62.2.341)
28 Bhattacharyya S, Chehab O, Khattar R, Lloyd G & Senior R. Stress echocardiography in clinical practice: a United Kingdom National Health Service Survey on behalf of the British Society of Echocardiography. *European Heart Journal: Cardiovascular Imaging* 2014 **15** 158–163. (https://doi.org/10.1093/ehjci/jet082)

Received in final form 12 March 2019
Accepted 20 March 2019
Accepted Manuscript published online 20 March 2019

https://erp.bioscientifica.com
https://doi.org/10.1530/ERP-18-0082