Johnson, CL, Krasner, S, Woodward, W, Mao, E, McCourt, A, Dockerill, C, Balkhausen, K, Chandrasekaran, B, Kardos, A, Sabharwal, N, Firoozan, S, Sarwar, R, Senior, R, Sharma, R, Wong, K, Augustine, DX, Paton, M, O'Driscoll, J, Oxborough, D, Pearce, K, Robinson, S, Willis, J, Leeson, P and EVAREST/BSE-NSTEP Investigators,

Changes in Coronary Disease Management Decisions in Real World Practice between 2015 and 2023: Insights from the Evarest/BSE-NSTEP observational study

CHANGES IN CORONARY DISEASE MANAGEMENT DECISIONS IN REAL WORLD PRACTICE BETWEEN 2015 AND 2023: INSIGHTS FROM THE EVAREST/BSE-NSTEP OBSERVATIONAL STUDY

Casey L Johnson[1], Samuel Krasner[1], William Woodward[1,2], Emma Mao[1], Annabelle McCourt[1], Cameron Dockerill[1,3], Katrin Balkhausen[4], Badrinathan Chandrasekaran[5], Attila Kardos[6], Nikant Sabharwal[7], Soroosh Firoozan[8], Rizwan Sarwar[7], Roxy Senior[9], Rajan Sharma[10], Kenneth Wong[11], Daniel X Augustine[12], Maria Paton[13], Jamie O'Driscoll[10,14], David Oxborough[15], Keith Pearce[16], Shaun Robinson[17], James Willis[12], and Paul Leeson[1].

On behalf of the EVAREST/BSE-NSTEP Investigators

[1] Cardiovascular Clinical Research Facility, Division of Cardiovascular Medicine, University of Oxford, Oxford, United Kingdom

[2] Barts and the London School of Medicine and Dentistry, Queen Mary University of London, London, United Kingdom

[3] Kings College London, London, United Kingdom

[4] Royal Berkshire Hospital, Reading, United Kingdom

[5] Great Western Hospital, Swindon, United Kingdom

[6]Department of Cardiology, Translational Cardiovascular Research Group, Milton Keynes University Hospital NHS Foundation Trust, Milton Keynes, and Faculty of Medicine and Health Sciences, University of Buckingham, Buckingham, United Kingdom

[7]Oxford University Hospitals NHS Foundation Trust, Oxford, United Kingdom

[8]Wycombe Hospital, High Wycombe, United Kingdom

[9]Northwick Park Hospital, London, United Kingdom

[10]St George's University Hospitals NHS Foundation Trust, Tooting, United Kingdom

[11]Lancashire Cardiac Centre, Blackpool Teaching Hospitals NHS Foundation Trust, Blackpool, United Kingdom

[12]Royal United Hospitals, Bath, United Kingdom

[13]University of Leeds, Leeds, United Kingdom

[14]Diabetes Research Centre, College of Life Sciences, University of Leicester, Leicester, United Kingdom

[15]Liverpool John Moores University, Liverpool, United Kingdom

[16]Machester University NHS Foundation Trust, Manchester, United Kingdom

[17]Imperial Healthcare NHS Trust, London, United Kingdom

Correspondence to:
Professor Paul Leeson
Cardiovascular Clinical Research Facility
John Radcliffe Hospital, Oxford, OX3 9DU United Kingdom

Paul.leeson@cardiov.ox.ac.uk

Abstract

Aims – To assess the real world impact of updated clinical guidelines and literature on the management of patients undergoing stress echocardiography for the assessment of inducible ischaemia across a national health service.

Methods and Results – A total of 13,819 patients from 32 UK hospitals, referred for stress echocardiography between 2015-2023, were analysed across two phases: phase 1 (2015-2020) and phase 2 (2020-2023). Follow-up data for one year was available for 4,920 participants through NHS Digital. Patients in phase 2 were younger, and presented with a higher cardiovascular risk profile, although sex distribution remained similar across phases. There was an observed reduction in invasive angiography referrals within one year following a positive stress echocardiogram ($p<0.01$), which appeared to be attributed to changes in management of patients with moderate ischaemia (3-4 segments; $p<0.01$). For those who did receive invasive assessment, there were no changes in intervention rate ($p=0.27$), regardless of ischaemic burden. This trend was most evident in centres performing a higher volume of stress echocardiograms.

Conclusion – Coronary disease management pathways have changed within the UK and fewer patients with moderate ischaemia are undergoing invasive coronary angiography. However, coronary intervention rates are unchanged, suggesting stress echocardiography is being used to improve patient selection for invasive procedures, while minimising unnecessary referrals. Future

work will assess if this reduction in angiography referrals is maintained long term, and if there are any effects on patient outcomes.

INTRODUCTION

For many years, referral for invasive coronary angiography was common for patients with evidence of more than mild cardiac ischaemia on functional imaging to ensure patients received the opportunity to have revascularisation. However, contradicting evidence from randomised studies have led to recent debate over the appropriate investigation and treatment steps in the care pathway for coronary disease.

Several studies have indicated risk of death, myocardial infarction, or other cardiac events may not be reduced by an initial invasive strategy in all patients in the non-acute setting (1-6), and the ORBITA trial found limited symptomatic benefit of an invasive approach, with no improvement in exercise capacity (7-10). However, ORBITA-2 trial demonstrated improved patient-reported symptom scores for those who received coronary intervention (11), and outcome benefits were also evident in long term follow up of the ISCHEMIA study (12) consistent with a recent metanalysis (13).

To take account of this emerging data, guidelines have evolved to focus on better selection of high-risk patients for revascularisation, preferring an initial medical management strategy in those with lower ischaemic burden. Referral for invasive angiography is reserved for when guideline-directed medical therapy fails to relieve symptoms (14-16). Prior to these recent updates, referral of patients for invasive coronary angiography after diagnosis of coronary artery disease was entrained in medical practice, and patients understood this as ‘the best’ way to manage their disease (17-19). Whether patients and medical staff would adopt recent guideline updates therefore remained unclear.

Stress echocardiography has been used as a first line test for patients with chest pain for decades (20-25). The Echocardiography Value and Accuracy at Rest and Stress (EVAREST) studied the care pathway of up to 18,000 patients undergoing stress echocardiography across 32 UK hospitals between 2015 and 2023. Recruitment spanned the time that key randomised trials and updated guidelines on cardiovascular disease management were published. As such, the study is uniquely placed to provide insight into whether there have been temporal changes in management decisions for patients presenting with coronary disease in the UK.

METHODS

Study Design

The EVAREST study is a multi-centre observational study evaluating the use, accuracy, and performance of stress echocardiography in real-world practice. From 2020-2023, the study incorporated the British Society of Echocardiography National Review of Stress Echocardiography Practice (BSE-NSTEP). Full methodology and six-month outcome results from the first phase of the study have been previously reported (26). The study is registered at ClinicalTrials.gov (NCT03674255), and ethical approval was provided by the Health Research Authority South Central Berkshire Research Ethics Committee (Ethics Reference: 14/SC/1437). The study design predates common widespread use of patient and public involvement, but patient and public feedback was received via the National Institute for Health and Care Research survey of research participants following the conclusion of the study. Written informed consent was obtained from all patients and the study was conducted in accordance with the Declaration of Helsinki principles.

Participants

Participants were recruited in two phases with the first recruitment phase running from March 2015 to March 2020 and included patients who were referred for stress echocardiography to assess inducible ischaemia. Recruitment restarted after the initial period of the COVID pandemic and then ran from October 2020 to September 2023, but was expanded to include patients referred to stress echocardiography for any clinical reason. However, only patients referred to stress echocardiography to assess inducible ischaemia were included in this analysis. As there was variation in participating centres between the two phases, only participants recruited at 26 sites that were recruiting centres during both phases of the study were included in this analysis. A subgroup of participants provided consent to link their details with follow up outcome data provided by NHS England.

Data Collection

Participant demographics and stress echocardiogram procedure details were collected by the local study teams and entered into an electronic database (Castor EDC, Amsterdam, Netherlands). Annual stress echocardiography volume was self-reported by each hospital. Hospital capacity as measured by number of beds was retrieved from NHS England (27). This work uses data provided by patients and collected by the NHS as part of their care and support via NHS Digital Data Access Request Service. Hospital admission data was collected from the Hospital Episode Statistics Admitted Patient Care database. Data collected included date and reason for admission, and any procedures undertaken during admission such as invasive coronary angiography, percutaneous coronary intervention, and coronary artery bypass grafting. Reasons for admission were defined by International Classification of Disease-10th revision coding (ICD-10), and interventions and/or procedures were defined by OPCS Classification of Interventions and Procedures-4th revision coding (OPCS 4.10) which is the procedural classification used within the NHS in the UK. Data on subsequent diagnostic imaging including invasive coronary angiography was obtained from the Diagnostic Imaging Dataset held by NHS England. Imaging data submitted to NHS England are coded using the Systematized Nomenclature of Medicine-Clinical Terms (SNOMED-CT). Mortality data including date and cause of death were obtained from the Civil Registrations of Death database provided by NHS England. Details of codes used in this analysis are provided as supplementary material.

Statistical Analysis

Patient demographics and stress echocardiogram procedural details are reported using standard approaches. Variations in hospital size, measured via annual stress echocardiography volume and hospital bed capacity, were separated into quartiles for comparison. Descriptive statistics were investigated as frequencies and medians [interquartile range (IQR)]. Comparison of discrete data between recruitment phases was conducted using Pearson's χ^2 tests. Stress echocardiogram result (positive or negative) was reported as the result from the clinician responsible for each participant's care. Kaplan-Meier time-to-event curves and Log-Rank tests were used to assess differences in rates of invasive coronary angiography, and percutaneous coronary intervention. Additionally, differences in invasive angiography referrals between recruitment phases were examined according to ischaemic burden (mild: 1-2 ischaemic segments, moderate: 3-4 ischaemic segments or severe: ≥5 ischaemic segments). Participants with missing data were included in the study, and missing data points were not interpolated. Censored datapoints were included in all time-to-event analysis to account for any death during the follow up period. Covariates of age, sex, and demographic variables that were statistically significant between recruitment phases were included in multivariate Cox proportional hazard models. The generated Cox models were used to estimate the hazard ratio (HR) of temporal recruitment phase as a primary predictor for downstream interventions. Hospital annual stress echocardiogram volume and size (total bed capacity) were included as interaction terms within each Cox model. Sensitivity analyses were conducted via iterative removal of covariates to assess the robustness and reliability of the Cox models. All statistical analysis was carried out using R Statistical Software (v4.4.0, R Core Team 2024), and time-to-event analysis was conducted using the survminer package.

RESULTS

Study population

Between March 2015 and September 2023, 17,656 patients were recruited into the EVAREST study of which data for 13,819 participants was available for the temporal analysis (7,332 in phase 1 and 6,487 in phase 2). Follow up data was received from NHS Digital for a subgroup of 4,920 participants (2,451 in phase 1 and 2,469 in phase 2). Participant inclusion and exclusion for this analysis is described in Figure 1.

Patient Demographics and Stress Echocardiography Characteristics (Entire Cohort)

Full patient demographics are provided in Table 1. Median age was similar between phase 1 and phase 2, 66 (IQR 57-73) and 65 (IQR 57-74) years respectively. Patient sex was also consistent across both phases (56.3% vs 57.6%) but patients recruited in phase 2 had a higher incidence of hypertension (48.3% vs 53.4%), hypercholesterolaemia (39.9% vs 47.9%) and diabetes (18.2% vs 22.7%) (all $p<0.001$). The percentage of patients reporting current smoking practices remained consistent but there was an increase of ex-smokers (49.7% vs 54.4%) ($p<0.001$). There was a decrease in peripheral vascular disease in phase 2 (2.9% vs 1.5%) as well as a decrease in previous PCI (31.2% vs 20.5%) (both $p<0.001$). There were no significant changes in percentage of previous MI, CABG, and presence of resting regional wall motion abnormalities between phases.

Stress echocardiogram positivity was similar between phases at 19.0%. While dobutamine remained the most common stressor used between phases, there was a decrease from 69.7% in phase 1 to 60.5% in phase 2 ($p<0.001$). This saw a corresponding increase in the use of exercise stress from 30.2% to 38.7% between phases ($p<0.001$). There was also a marginal increase in the use of pacemaker stress (0.2% vs 0.6%, $p<0.001$). Within dobutamine stress echocardiograms, there was a decrease in the use of atropine (49.5% vs 45.9%, $p<0.001$). The use of contrast increased (71.9% vs 82.4%, $p<0.001$) with a related increase in the use of Luminity as a contrast agent (5.4% vs 16.9%, $p<0.001$). Patient demographics and stress echocardiogram procedural details separated by stress echocardiogram outcome are provided in supplementary materials.

Patient Demographics and Stress Echocardiography Characteristics (NHS Digital subgroup)

The NHS Digital subgroup had similar demographics, medical history and stress echocardiography practice as the overall cohort except for a marginally higher stress echocardiogram positivity rate in phase 2 (18.3% vs 21.2%, $p<0.05$) despite a lower prevalence of resting regional wall motion abnormalities (16.2% vs 12.7%, $p<0.001$). Comorbidity was similar to the overall cohort with the exception of less hypertension in phase 2 (58.0% vs 52.8%), peripheral vascular disease (3.2% vs 1.6%), and a higher rate of current smokers (8.3% vs 15.1%) (all $p<0.001$) (Table 1).

Participant Management

Time-to-event analysis within the NHS Digital subgroup is provided in Figure 2, showing no difference in invasive angiography referral rate between groups in the total subgroup analysis (Fig. 2A), but a decrease in referral to invasive coronary angiography within one year for participants with a positive stress echocardiogram result in phase 2 compared to phase 1 ($p<0.01$, Fig. 2B). Analysis of invasive angiography referral rate according to ischaemic burden demonstrated the main reduction in referral rates was seen in participants with moderate ischaemia with no significant difference in participants with mild or severe ischaemia ($p<0.01$) (Fig. 2C-E).

As reported in Table 2, there was a reduced hazard ratio for invasive angiography in phase 2 participants within the whole NHS Digital subgroup analysis, HR 0.77 (95% CI 0.66 to 0.91, $p<0.01$) and in those with a positive stress echocardiogram, HR 0.75 (95% CI 0.62 to 0.92, $p<0.01$) after covariate adjustment. There was no significant difference in the number of percutaneous coronary intervention performed in those with a positive stress echocardiogram ($p=0.27$), regardless of ischaemic burden. As shown in Table 3, hospitals with an annual stress echocardiography volume of <400 had a relative increase in the proportion of invasive angiogram referrals from phase 1 to phase 2 (14.4% vs. 21.5%), resulting in an inverse association between hazard ratio for invasive angiography and volume of stress echocardiograms performed in a centre following a positive stress echocardiogram, HR 0.71 (95% CI 0.64 to 0.79, p<0.001) (Table 2).

DISCUSSION

This study provides real world data on the changing management pathways of patients who are referred for stress echocardiography for the assessment of myocardial ischaemia. This study benefits from having a large patient population from a wide range of recruiting centres across the UK, increasing the diversity of the data and generalisability of the results. There is an overall reduction in the referral to invasive coronary angiography following a positive stress echocardiogram, presumably in favour of medical therapy. The observed reduction in angiography referrals appears to be driven by a shift in management in patients with moderate (3-4 segments) myocardial ischaemia.

These findings support recent clinical trial results which reported no additional short-term risk from an initial medical management strategy in patients with stable chest pain (6, 7, 10). This data also supports recommendations in the updated 2024 ESC guidelines suggesting that patients receive medical therapy following confirmation of diagnosis with first line testing. Invasive angiography and possible revascularisation are then suggested for patients who are categorised as high risk following diagnostic testing, or who continue to have symptoms despite optimal medical therapy (16). While it has been reported that invasive coronary angiography use is reduced with the use of non-invasive CT angiography for chest pain (28), the current study would suggest this is a function of using an imaging test rather than providing information on anatomy or function. Patients included in this analysis did not undergo CT angiography prior to the stress echocardiogram and there is no evidence patients were being referred for CT angiography instead of invasive angiography after the test. This may be due to issues with access to CT angiography in the United Kingdom (29). Thus, the reduction in angiography referrals observed is more likely to be attributed to change in decisions about management approach.

Why hospitals performing a low volume of stress echocardiograms, i.e. <400 per year, did not appear to demonstrate this drop in referral pattern needs further consideration. Large volume centres may more rapidly adapt practice to include guideline updates or there may be differences in patient referral patterns or disease severity between centres that were not captured within the datasets available in this analysis. Alternatively, previously reported data from the EVAREST study illustrating associations of ischaemic burden and outcomes(26) may have also influenced patient management workflow at participating centres. Nevertheless, this pattern appears consistent when using different metrics of centre size such as hospital bed number.

Interestingly, rates of percutaneous coronary intervention remain consistent across phases, and this likely reflects the use of coronary intervention largely in those identified with severe ischaemia, in whom referral rates have remained consistent. (1, 10). Therefore, while this analysis reveals a shift in current practice, it also provides evidence that a more selective approach for use of angiography is not reducing the rate of intervention within patients with coronary disease (30, 31). An analysis of five-year outcomes for a subgroup of the EVAREST cohort has recently been published indicating that a positive stress echocardiogram, and degree of ischaemic burden, is associated with an increased risk of both all cause and cardiac-related mortality, as well as myocardial infarction, and predicts the need for revascularisation (32). As this analysis relied on outcomes over five years this primarily reflects outcomes of the referral practice in the first phase of EVAREST. Future long term follow up, up to ten years, will provide an opportunity to investigate whether outcomes remain similar in the second phase of EVAREST.

There are limitations to this analysis. Firstly, due to the nature of the data collection, there are no results on patient symptoms throughout the management period. Some studies have shown that patient-reported symptoms and quality of life are improved with an invasive management strategy even when a reduction in mortality and adverse events is not identified (6, 11). However, this improvement in symptoms appears inconsistent (7) and some investigators have attributed this to a placebo effect (33). Secondly, the time horizon used in this analysis is limited to one year. Most patients referred for an elective coronary angiogram following their stress echocardiogram will be seen within this timeframe and this appears appropriate to account for further investigational testing such as invasive angiography. However, any invasive angiography performed more than one year following uncontrolled symptoms with an initial medical management strategy may be unaccounted for. Thirdly, the study was focused on an evaluation of real world practice and it is possible associations may differ if other stress echocardiography protocols were applied in practice that used additional measures that may improve predictive accuracy such as heart rate reserve. Fourthly, it should be noted that data received from the data request service from NHS Digital has inherent limitations. If no outcome data was received after supplying NHS Digital with participant identifiers for data linkage, it was assumed that this participant had no follow up outcomes or events within the requested timeframe. This could however, also mean that the participant had follow up data, but was not able to be retrieved by NHS Digital for unknown reasons. Fifthly, while sites remained consistent for the temporal analysis, not all sites began recruiting at the same time and had varying recruitment rates. Therefore, some sites contributed more proportionally to the dataset. Finally, due to the nature of the prospective consented study design, there may be a selection bias amongst those enrolled towards those with an interest in research participation.

CONCLUSION

This study provides real world evidence of a change in coronary disease management decisions within the NHS. Since 2020, there has been a small but significant reduction in the number of patients who are referred for invasive angiography after a positive stress echocardiogram. This can be attributed to a reduced referral to invasive angiography in patients with moderate ischaemia, while those with mild and severe disease have not experienced significant changes in their management pathways. Interestingly, rates of use of percutaneous coronary intervention did not change over the recruitment period suggesting a better selection of patients for angiography. These results should be considered in the context of the sample size and time horizon, and future work will aim to further confirm these management changes, and establish what effect, if any, this has on patient outcomes long term.

Contributor and Guarantor Information

PL was responsible for conceptualization of the analysis. PL, KB, BC, AK, NS, SF, RSa, RSe, RSh, KW, DXA, MP, JOD, DO, KP, SR, and JW developed the overarching research study design. PL assisted with funding acquisition. WW, CD, CLJ, AM, EM, and SK provided project administration and data curation. WW, CD, CLJ, AM, SK, DXA, JW, MP, PL, RSe, JOD, RS, and all EVAREST/BSE-NSTEP investigators provided investigation for the study. SK supported data analysis and visualisation. CLJ, and PL wrote and edited the original manuscript draft. All authors reviewed and edited the manuscript. PL accepts the responsibility of guarantor and senior author for this manuscript. All BSE-NSTEP/EVAREST Investigators conducted investigations for the purposes of the study.

Copyright/License for Publication

The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, a worldwide licence to the Publishers and its licensees in perpetuity, in all forms, formats and media (whether known now or created in the future), to i) publish, reproduce, distribute, display and store the Contribution, ii) translate the Contribution into other languages, create adaptations, reprints, include within collections and create summaries, extracts and/or, abstracts of the Contribution, iii) create any other derivative work(s) based on the Contribution, iv) to exploit all subsidiary rights in the Contribution, v) the inclusion of electronic links from the Contribution to third party material where-ever it may be located; and, vi) licence any third party to do any or all of the above.

Competing Interests

All authors have completed the Unified Competing Interest form (available on request from the corresponding author) and declare: AK has received an educational grant from Lantheus Medical Imaging and honoraria from Bracco, and Tom-Tec-Phillips. KW is a member of the British Cardiovascular Society Guidelines and Practice Committee (unpaid role). RSenior has received honoraria from Bracco, Lantheus Medical Imaging, and GE Healthcare. PL is a shareholder and founder of Ultromics Ltd, and has received personal consultancy fees from Ultromics Ltd. PL is an inventor on patents in the field of echocardiography. All other authors have no conflicts of interest to declare.

Funding

This work was supported by National Institute for Health Research Health Education England Healthcare Science Research Fellowship [NIHR-HCS-P13-04–001]; Cardiovascular Clinical Research Facility, University of Oxford; Ultromics Ltd.; Lantheus Medical Imaging Inc. and National Institute for Health Research Oxford Biomedical Research Centre, University of Oxford. The funders of the study had no role in study design, data collection, analysis, interpretation, or writing of the report.

Data Availability Statement

Data on patient demographics and stress echocardiogram procedures will be made available upon reasonable request. Outcome data collected via NHS Digital is not available for sharing.

Transparency Statement

The guarantor affirms that this manuscript is an honest, accurate, and transparent account of the study analysis being reported. No important aspects of the study have been omitted.

Figure Legends:

Figure 1: **Figure 1:** CONSORT Diagram illustrating participant recruitment

Figure 2: **Figure 2:** Kaplan-Meier analysis of freedom from invasive coronary angiogram total NHS Digital subgroup (A), those with a positive stress echocardiogram (B), and according to ischaemic burden of mild, moderate, severe (C-E)

REFERENCES

1. Boden WE, O'Rourke RA, Teo KK, Hartigan PM, Maron DJ, Kostuk WJ, et al. Optimal Medical Therapy with or without PCI for Stable Coronary Disease. New England Journal of Medicine. 2007;356(15):1503-16.
2. A Randomized Trial of Therapies for Type 2 Diabetes and Coronary Artery Disease. New England Journal of Medicine. 2009;360(24):2503-15.
3. Weintraub WS. Role of Big Data in Cardiovascular Research. Journal of the American Heart Association. 2019;8(14):e012791.
4. Perera D, Clayton T, O’Kane PD, Greenwood JP, Weerackody R, Ryan M, et al. Percutaneous Revascularization for Ischemic Left Ventricular Dysfunction. New England Journal of Medicine. 2022;387(15):1351-60.

5. Frye Rl Fau - August P, August P Fau - Brooks MM, Brooks Mm Fau - Hardison RM, Hardison Rm Fau - Kelsey SF, Kelsey Sf Fau - MacGregor JM, MacGregor Jm Fau - Orchard TJ, et al. A randomized trial of therapies for type 2 diabetes and coronary artery disease. New England Journal of Medicine. 2009;360(1533-4406 (Electronic)).
6. Shah R, Nayyar M, Le FK, Labroo A, Nasr A, Rashid A, et al. A meta-analysis of optimal medical therapy with or without percutaneous coronary intervention in patients with stable coronary artery disease. Coronary Artery Disease. 2022;33(2):91-7.
7. Al-Lamee R, Thompson D, Dehbi H-M, Sen S, Tang K, Davies J, et al. Percutaneous coronary intervention in stable angina (ORBITA): a double-blind, randomised controlled trial. The Lancet. 2018;391(10115):31-40.
8. Brown DL, Redberg RF. Last nail in the coffin for PCI in stable angina? The Lancet. 2018;391(10115):3-4.
9. Jackson M, Zaman A. ORBITA: What Goes Around, Comes Around... Or Does It? (1756-1485 (Electronic)).
10. Maron DJ, Hochman JS, Reynolds HR, Bangalore S, O'Brien SM, Boden WE, et al. Initial Invasive or Conservative Strategy for Stable Coronary Disease. New England Journal of Medicine. 2020;382(15):1395-407.
11. Rajkumar CA, Foley MJ, Ahmed-Jushuf F, Nowbar AN, Simader FA, Davies JR, et al. A Placebo-Controlled Trial of Percutaneous Coronary Intervention for Stable Angina. New England Journal of Medicine. 2023;389(25):2319-30.
12. Hochman JA-O, Anthopolos R, Reynolds HA-O, Bangalore SA-O, Xu Y, O'Brien SM, et al. Survival After Invasive or Conservative Management of Stable Coronary Disease. Circulation. 2023;147(1524-4539 (Electronic)).
13. Navarese EP, Lansky AJ, Kereiakes DJ, Kubica J, Gurbel PA, Gorog DA, et al. Cardiac mortality in patients randomised to elective coronary revascularisation plus medical therapy or medical therapy alone: a systematic review and meta-analysis. European Heart Journal. 2021;42(45)(1522-9645 (Electronic)).
14. Virani SS, Newby LK, Arnold SV, Bittner V, Brewer LC, Demeter SH, et al. 2023 AHA/ACC/ACCP/ASPC/NLA/PCNA Guideline for the Management of Patients With Chronic Coronary Disease: A Report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. Circulation. 2023;148(9):e9-e119.
15. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes: The Task Force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC). European Heart Journal. 2019;41(3):407-77.
16. Vrints C, Andreotti F, Koskinas KC, Rossello X, Adamo M, Ainslie J, et al. 2024 ESC Guidelines for the management of chronic coronary syndromes: Developed by the task force for the management of chronic coronary syndromes of the European Society of Cardiology (ESC) Endorsed by the European Association for Cardio-Thoracic Surgery (EACTS). European Heart Journal. 2024.
17. Members TF, Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, 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. European Heart Journal. 2013;34(38):2949-3003.
18. Neumann F-J, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. European Heart Journal. 2018;40(2):87-165.
19. Iqbal J, Gunn J, Serruys PW. Coronary stents: historical development, current status and future directions. British Medical Bulletin. 2013;106(1):193-211.

20. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes: The Task Force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC). European Heart Journal. 2020;41(3):407-77.
21. Recent-onset chest pain of suspected cardiac origin: assessment and diagnosis; Clinical Guidance CG95. National Institute for Health and Care Excellence (NICE); 2016 30 November 2016.
22. Gulati M Fau - Levy PD, Levy Pd Fau - Mukherjee D, Mukherjee D Fau - Amsterdam E, Amsterdam E Fau - Bhatt DL, Bhatt Dl Fau - Birtcher KK, Birtcher Kk Fau - Blankstein R, et al. 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR Guideline for the Evaluation and Diagnosis of Chest Pain: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. (1524-4539 (Electronic)).
23. Steeds RP, Wheeler R, Bhattacharyya S, Reiken J, Nihoyannopoulos P, Senior R, et al. Stress echocardiography in coronary artery disease: a practical guideline from the British Society of Echocardiography. Echo Research & Practice. 2019;6(2):G17-G33.
24. Ihekwaba U, Johnson N, Choi JS, Savarese G, Orsini N, Khoo J, et al. Long-term prognostic value of contemporary stress echocardiography in patients with suspected or known coronary artery disease: systematic review and meta-analysis. Heart. 2024:heartjnl-2024-324534.
25. Johnson CL, Woodward W, McCourt A, Dockerill C, Krasner S, Monaghan M, et al. Real world hospital costs following stress echocardiography in the UK: a costing study from the EVAREST/BSE-NSTEP multi-centre study. Echo Research & Practice. 2023;10(1):8.
26. Woodward W, Dockerill C, McCourt A, Upton R, O'Driscoll J, Balkhausen K, et al. Real-world performance and accuracy of stress echocardiography: the EVAREST observational multi-centre study. Eur Heart J Cardiovasc Imaging. 2022;23(5):689-98.
27. England N. [Excel Document]. [Available from: https://www.england.nhs.uk/statistics/wp-content/uploads/sites/2/2019/11/Beds-Open-Overnight-Web_File-Final-Q1-201920.xlsx.
28. Weir-McCall JR, Williams MC, Shah ASV, Roditi G, Rudd JHF, Newby DE, et al. National Trends in Coronary Artery Disease Imaging: Associations With Health Care Outcomes and Costs. JACC: Cardiovascular Imaging. 2023;16(5):659-71.
29. Dreisbach JG, Nicol ED, Roobottom CA, Padley S, Roditi G. Challenges in delivering computed tomography coronary angiography as the first-line test for stable chest pain. Heart. 2018;104(11):921-7.
30. Lopez-Sendon J, Moreno R, Tamargo J. ISCHEMIA Trial: Key Questions and Answers. European Cardiology Review. 2021;16:e34(1758-3764 (Electronic)).
31. Montone RA, Ford TJ, Galli M, Rinaldi R, Bland A, Morrow A, et al. Stratified medicine for acute and chronic coronary syndromes: A patient-tailored approach. Progress in Cardiovascular Diseases. 2024.
32. Woodward W, Johnson CL, Krasner S, O'Driscoll J, McCourt A, Dockerill C, et al. Long-term outcomes after stress echocardiography in real-world practice: a 5-year follow-up of the UK EVAREST study. European Heart Journal - Cardiovascular Imaging. 2024;26(2):187-96.
33. Rajkumar CA, Nijjer SS, Cole GD, Al-Lamee R, Francis DP. 'Faith Healing' and 'Subtraction Anxiety' in Unblinded Trials of Procedures. Circulation: Cardiovascular Quality and Outcomes. 2018;11(3):e004665.

Table 1: Participant Demographics

	Phase 1 Total Cohort (n=7332)	Phase 2 Total Cohort (n=6487)	p-value*	Phase 1 NHS Digital subgroup (n=2451)	Phase 2 NHS Digital subgroup (n=2469)	p-value**
Participant Demographics						
Male (%)	4126/7332 (56.3)	3739/6486 (57.6)	0.10	1440/2451 (58.8)	1429/2469 (57.9)	0.53
Median age (years) (IQR)	66 (57-73)	65 (57-74)	0.20	67 (59-74)	65 (56-73)	**<0.001**
Median BMI (kg/m2) (IQR)	28.2 (25.0-31.9)	28.1 (25-31.6)	0.87	27.9 (24.9-31.5)	28.1 (24.9-31.9)	**<0.05**
Positivity Rate (%)	1394/7332 (19.0)	1231/6487 (19.0)	0.96	448/2451 (18.3)	523/2469 (21.2)	**<0.05**
Current smoker (%)	860/7045 (12.2)	744/6285 (11.8)	0.63	203/2541 (8.3)	374/2469 (15.1)	**<0.001**
Ex-smoker (%)	2687/7045 (38.1)	2125/6285 (33.8)	**<0.001**	1025/2451 (41.8)	786/2469 (31.8)	**<0.001**
Non-smoker (%)	3498/7045 (49.7)	3416/6285 (54.4)	**<0.001**	1144/2451 (46.7)	1242/2469 (50.3)	**<0.05**
Hypertension (%)	3346/6931 (48.3)	3445/6455 (53.4)	**<0.001**	1332/2295 (58.0)	1301/2466 (52.8)	**<0.001**
Hypercholesterolaemia (%)	2767/6931 (39.9)	3090/6455 (47.9)	**<0.001**	1064/2295 (46.4)	1187/2466 (48.1)	0.22
Diabetes mellitus (%)	1331/7332 (18.2)	1463/6455 (22.7)	**<0.001**	506/2451 (20.6)	525/2466 (21.3)	0.57
Peripheral vascular disease (%)	204/6931 (2.9)	99/6453 (1.5)	**<0.001**	74/2295 (3.2)	40/2467 (1.6)	**<0.001**
Previous MI (%)	1243/7214 (17.2)	1121/6453 (17.4)	0.83	445/2423 (18.4)	472/2467 (19.1)	0.49
Previous PCI (%)	2256/7228 (31.2)	1323/6453 (20.5)	**<0.001**	835/2425 (34.4)	548/2467 (22.2)	**<0.001**
Precious CABG (%)	529/7241 (7.3)	441/6453 (6.8)	0.28	178/2429 (7.3)	156/2467 (6.3)	0.16
Resting RWMA (%)	1080/7328 (14.7)	916/6449 (14.2)	0.37	397/2449 (16.2)	313/2467 (12.7)	**<0.001**
Stress Echocardiogram Details						
Exercise (%)	2211/7330 (30.2)	2508/6480 (38.7)	**<0.001**	778/2451 (31.7)	982/2469 (39.8)	**<0.001**
Pacemaker (%)	11/7332 (0.2)	39/6480 (0.6)	**<0.001**	7/2451 (0.3)	18/2469 (0.7)	**<0.05**
Dobutamine (%)	5108/7330 (69.7)	3919/6480 (60.5)	**<0.001**	1665/2451 (67.9)	1464/2469 (59.3)	**<0.001**
Atropine use in DSE (%)	2518/5091 (49.5)	1773/3859 (45.9)	**<0.001**	734/1665 (44.1)	689/1464 (47.1)	0.10
Contrast used	5258/7309 (71.9)	5279/6407 (82.4)	**<0.001**	1961/2440 (80.4)	1907/2444 (78.0)	**<0.05**
SonoVue (%)	4847/7309 (66.3)	4193/6407 (65.4)	0.07	1729/2440 (70.9)	1668/2444 (68.2)	<0.05
Luminity (%)	393/7309 (5.4)	1080/6407 (16.9)	**<0.001**	220/2440 (9.0)	236/2444 (9.7)	0.44
Other (e.g. Optison) (%)	18/7309 (0.2)	6/6407 (0.1)	**0.031**	12/2440 (0.5)	3/2444 (0.1)	**<0.05**

***p*-value comparison between recruitment phases (overall cohort)

**p-value comparison between recruitment phases (NHS Digital subgroup)

	Total Subgroup			Positive Stress Echocardiogram		
Variable	**HR**	**95% CI**	***P*-value**	**HR**	**95% CI**	***P*-value**
Recruitment Phase (Phase 2)	0.77	0.65-0.91	**<0.01**	0.75	0.62-0.92	**<0.01**
Age	0.99	0.99-1.00	0.08	0.99	0.98-1.00	**<0.05**
Sex (male)	1.16	0.97-1.38	0.10	1.16	0.94-1.42	0.17
SE Outcome (Positive)	17.38	14.29-21.15	**<0.001**	--	--	--
Current Smoker	0.90	0.70-1.16	0.41	0.87	0.65-1.16	0.35
Hypertension	1.19	1.00-1.41	**<0.01**	1.16	0.95-1.41	0.14
Previous Peripheral Vascular Disease	0.91	0.56-1.48	0.71	1.11	0.67-1.84	0.69
Previous PCI	0.79	0.66-0.96	**<0.05**	0.73	0.59-0.90	**<0.01**
Baseline RWMA	1.21	1.00-1.46	**<0.05**	1.12	0.91-1.37	0.29
Hospital Demographics						
SE Per Year (per quartile)	0.75	0.68-0.81	**<0.001**	0.71	0.64-0.79	**<0.001**
Bed Number (per quartile)	1.10	1.00-1.21	**<0.05**	1.12	1.00-1.25	0.06

Table 2: Multivariate Cox regression analysis of invasive coronary angiography in NHS Digital subgroup

Table 3: Invasive angiography referrals relative to hospital volume and capacity in NHS Digital subgroup

	Total Angiograms (%)*	Angiogram Phase 1 (%)*	Angiogram Phase 2 (%)*
Stress Echocardiography Volume			
<400	137 (17.3)	68 (14.4)	69 (21.5)
400-599	116 (10.5)	72 (12.4)	44 (8.4)
600-850	102 (13.0)	44 (13.5)	58 (12.6)
>850	264 (11.8)	145 (13.5)	119 (10.2)
Hospital Capacity (number of beds)			
<600	194 (14.9)	104 (14.3)	90 (15.8)
600-799	84 (12.0)	74 (14.5)	10 (5.3)
800-1000	155 (10.4)	35 (10.0)	120 (10.6)
>1000	186 (12.9)	116 (13.5)	70 (12.2)

* as percentage of recruitment contribution

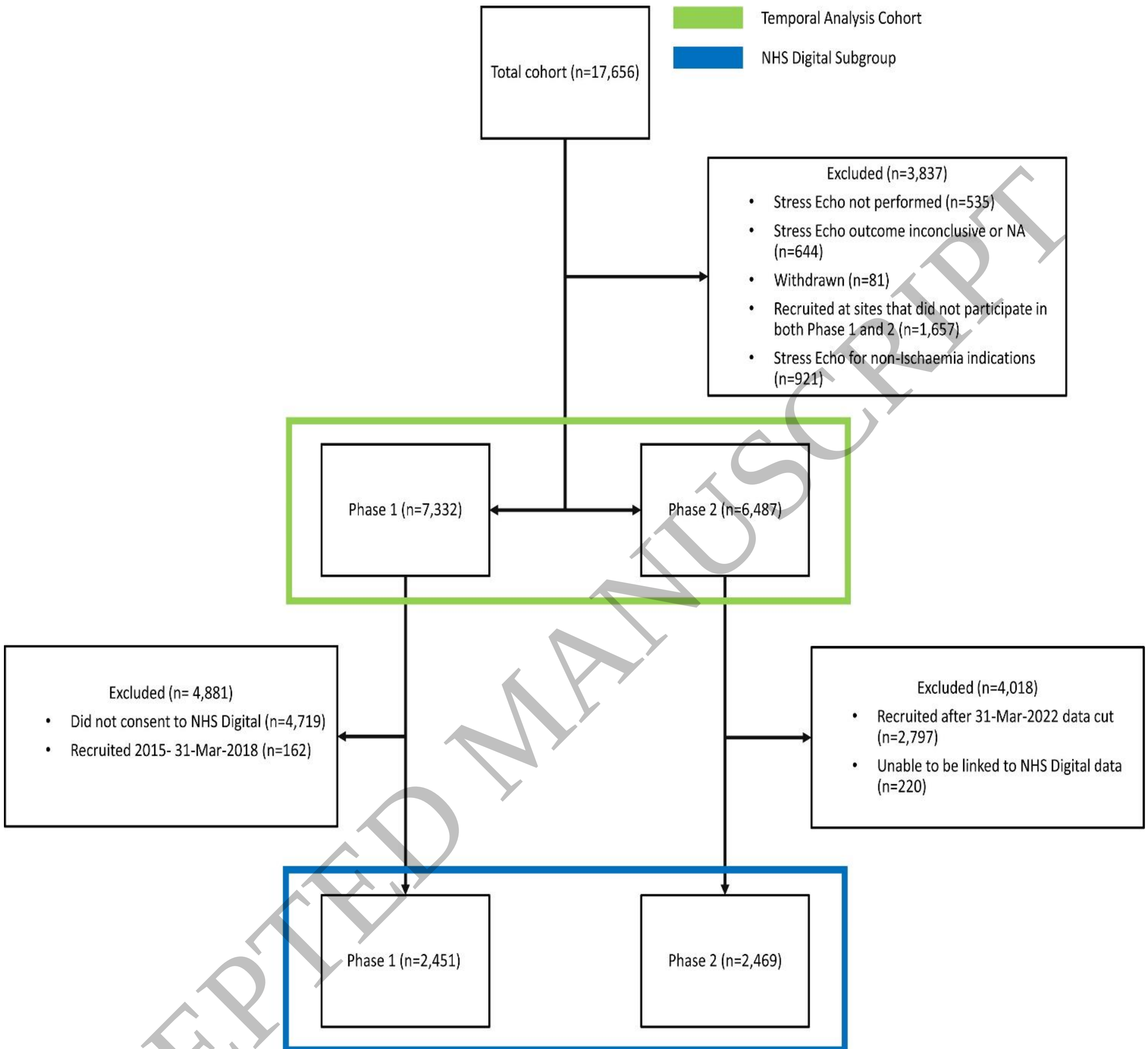


Figure 1
316x237 mm (x DPI)

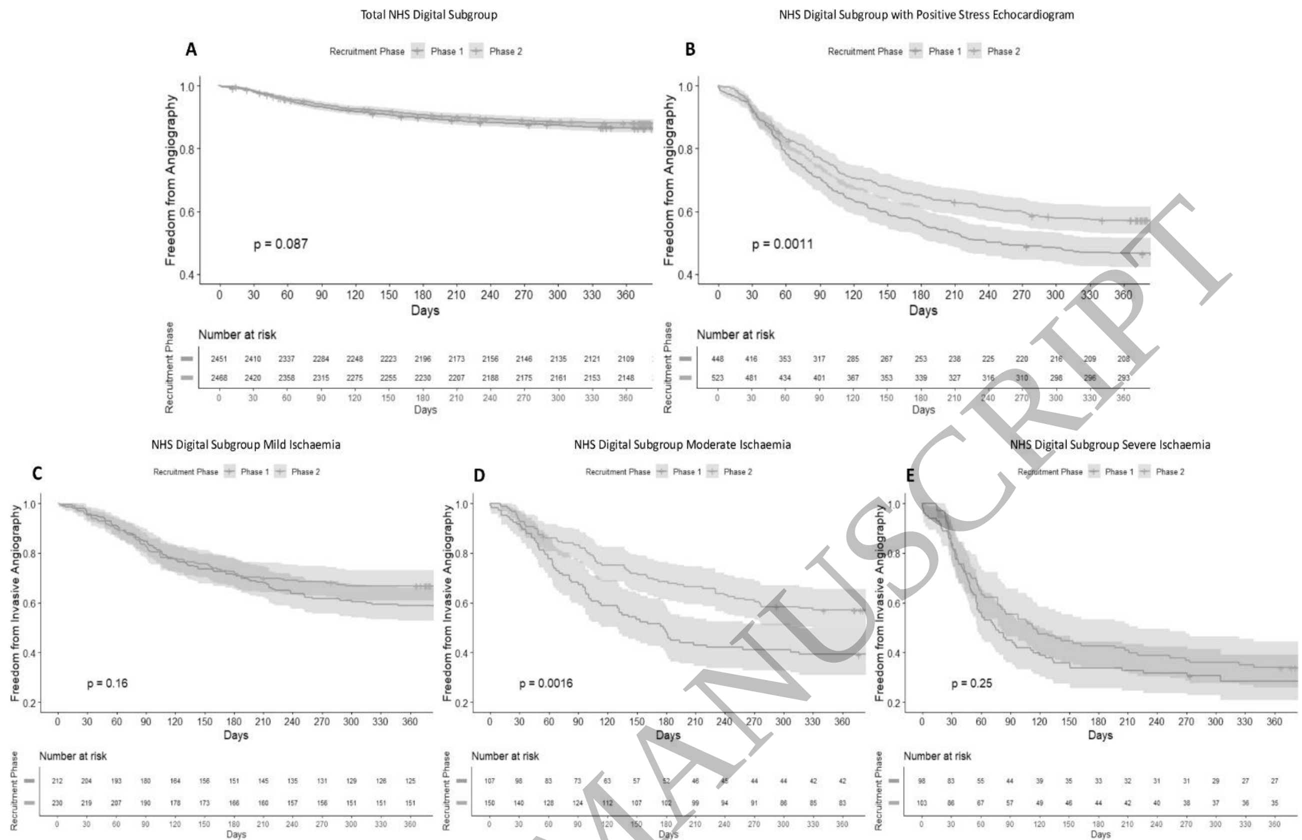
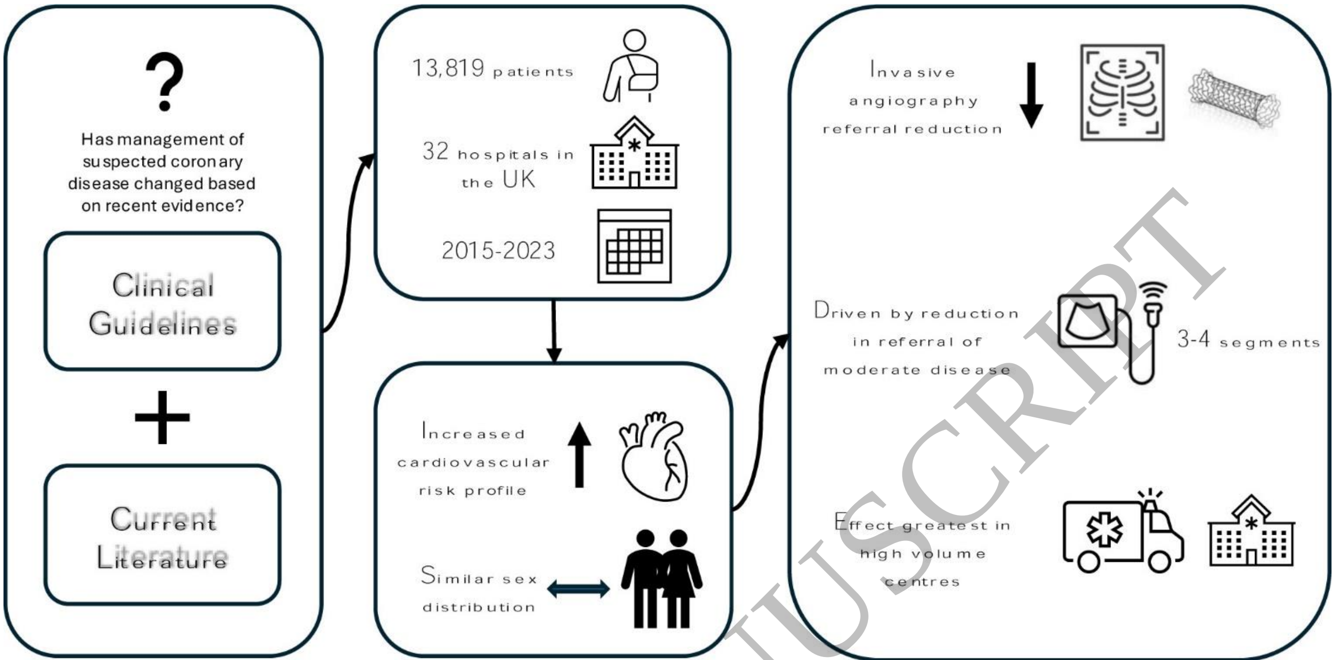


Figure 2
432x258 mm (x DPI)



Graphical Abstract
176x87 mm (x DPI)

EVAREST/BSE-NSTEP Investigators:

Abraheem Abraheem[18], Sanjay Banypersad[19], Sadie Bennett[19], Henry Boardman[7], Christopher Boos[20], Sudantha Bulugahapitiya[21], Jeremy Butts[22], Duncan Coles[23], Joanna d'Arcy[7], Jacob Easaw[12], Sarah Fairbairn[24], Patrick Gibson[25], Haytham Hamdan[26], Shahnaz Jamil-Copley[27], Gajen Kanaganayagam[28], Guy Lloyd[29], Ioannis Moukas[30], Tom Mwambingu[31], Thuraia Nageh[32], Antonis Pantazis[33], Alexandros Papachristidis[34], Ronak Rajani[35], Muhammad Amer Rasheed[36], Naveed A. Razvi[37], Sushma Rekhraj[27], Joban Sehmi[38], Azeem Sheikh[22] David P. Ripley[39], Kathleen Rose[40], Michaela Scheuermann-Freestone[41], Rebecca Schofield[42], Ayyaz Sultan[26], Spiros Zidros[43]

[17]Department of Cardiology, Tameside and Glossop Integrated Care NHS Foundation Trust, Ashton-under-Lyne, UK.

[18]Department of Cardiology, Royal Blackburn Hospital, East Lancashire Hospitals NHS Trust, Burnley, UK.

[19]Department of Cardiology, Heart & Lung Centre, Royal Stoke University Hospital, University Hospitals of North Midlands NHS Foundation Trust, Stoke, UK.

[20]Department of Cardiology, Poole Hospital NHS Foundation Trust, Poole, UK.

[21]Department of Cardiology, Bradford Royal Infirmary Hospital, Bradford Teaching Hospitals NHS Foundation Trust, Bradford, UK.

[22]Department of Cardiology, the Calderdale Royal Hospital and Huddersfield Royal Infirmary, Calderdale and Huddersfield NHS Foundation Trust, Calderdale, UK.

[23]Department of Cardiology, Broomfield Hospital, Mid and South Essex NHS Foundation Trust, Broomfield, UK.

[24]Bristol Heart Institute, University Hospitals Bristol and Weston NHS Foundation Trust, Bristol, UK.

[25]Royal Infirmary Edinburgh and Western General Hospital, NHS Lothian, UK.

[26]Department of Cardiology, Wrightington, Wigan and Leigh NHS Foundation Trust, Wigan, UK.

[27]Department of Cardiology, Nottingham University Hospitals NHS Trust, Nottingham, UK.

[28]Department of Cardiology, West Middlesex University Hospital, Chelsea and Westminster Hospital NHS Foundation Trust, London, UK.

[29]University College London, Barts Health NHS Trust, UK.

[30]Department of Cardiology, Warrington and Halton Teaching Hospitals NHS Foundation Trust, Warrington, UK.

[31]Department of Cardiology, The Mid Yorkshire Hospitals NHS Trust, Pinderfields, UK.

[32]Department of Cardiology, Southend University Hospital, Mid and South Essex NHS Foundation Trust, Southend-on-Sea, UK.

[33]Department of Cardiology, North Middlesex University Hospital NHS Trust, London, UK.

[34]Department of Cardiology, King's College Hospital NHS Foundation Trust, London, UK.

[35]Department of Cardiology, Guy's and St Thomas' NHS Foundation Trust, London, UK.

[36]Department of Cardiology, Yeovil District Hospital, Somerset NHS Foundation Trust, Yeovil, UK.

[37]Department of Cardiology, East Suffolk and North Essex NHS Foundation Trust, Ipswich, UK.

[38]West Hertfordshire Hospitals NHS Trust, UK.

[39]Department of Cardiology, Northumbria Healthcare NHS Foundation Trust, North Tyneside, UK.

[40]Department of Cardiology, Northampton General Hospital NHS Trust, Northampton, UK.

[41]Department of Cardiology, Hampshire Hospitals NHS Foundation Trust, Basingstoke, UK.

[42]Department of Cardiology, North West Anglia NHS Foundation Trust, Peterborough, UK.

[43]Department of Cardiology, Bedford Hospital, Bedfordshire Hospitals NHS Foundation Trust, Bedford, UK.