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Clinical validation of an artificial intelligence-based decision support system for diagnosis and risk stratification of heart failure (STRATIFYHF): a protocol for a prospective, multicentre longitudinal study

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ABSTRACT

Introduction Heart failure (HF) is a complex clinical syndrome. Accurate risk stratification and early diagnosis of HF are challenging as its signs and symptoms are non-specific. We propose to address this global challenge by developing the STRATIFYHF artificial intelligence-driven decision support system (DSS), which uses novel analytical methods in determining the risk, diagnosis and prognosis of HF. The primary aim of the present study is to collect prospective clinical data to validate the STRATIFYHF DSS (in terms of diagnostic accuracy, sensitivity and specificity) as a tool to predict the risk, diagnosis and progression of HF. The secondary outcomes are the demographic and clinical predictors of risk, diagnosis and progression of HF.

Methods and analysis STRATIFYHF is a prospective, multicentre, longitudinal study that will recruit up to 1600 individuals (n=800 suspected/at risk of HF and n=800 diagnosed with HF) aged ≥45 years old, with up to 24 months of follow-up observations. Individuals suspected of HF will be divided into two categories based on current definitions and predefined inclusion criteria. All participants will have their medical history recorded, along with data on physical examination (signs and symptoms), blood tests including serum natriuretic peptides levels, ECG and echocardiogram results, as well as demographic, socioeconomic and lifestyle data, and use of complete novel technologies (cardiac output response to stress test and voice recognition biomarkers). All measurements will be recorded at baseline and at 12-month follow-up, with medical history and hospitalisation also recorded at 24-month follow-up. Cardiovascular MRI assessment will be completed in a subset of participants (n=20–40) from eligible clinical centres only at baseline. Each clinical centre will recruit a subset of participants (n=30) who will complete a 6-month home-based monitoring of clinical characteristics and accelerometry (wrist-worn monitor) to determine the feasibility and acceptability of the STRATIFYHF mobile application. Focus groups and semistructured interviews will be conducted with up to 15 healthcare professionals and up to 20 study participants (10 at risk of HF and 10 diagnosed with HF) to explore the

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ STRATIFYHF will recruit patients suspected of or at risk of heart failure and those diagnosed with heart failure from eight clinical centres across Europe and will follow them over multiple time points.
⇒ STRATIFYHF will encompass novel technologies (cardiac output response to stress test and voice recognition) in improving risk stratification and diagnostic strategies for heart failure.
⇒ STRATIFYHF will involve stakeholders (healthcare professionals and patients) prior to the development of the decision support system and acceptability of the mobile app.
⇒ A limitation of STRATIFYHF is that not all participants will have access to the mobile app.

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needs of patients and healthcare professionals prior to the development of the STRATIFYHF DSS and to evaluate the acceptability of this mobile application.

Ethics and dissemination Ethical approval has been granted by the East Midlands - Leicester Central Research Ethics Committee (24/EM/0101). Dissemination activities will include journal publications and presentations at conferences, as well as development of training materials and delivery of focused training on the STRATIFYHF DSS and mobile application. We will develop and propose policy guidelines for integration of the STRATIFYHF DSS and mobile application into the standard of care in the HF care pathway.

Trial registration number NCT06377319.

INTRODUCTION

Heart failure (HF) is a complex clinical syndrome associated with impaired heart function during exertion and often at rest.[1] It is associated with poor prognosis and quality of life, along with high healthcare costs.[1] HF is a global pandemic affecting at least 64.3 million individuals worldwide[2] and 15 million individuals in Europe.[3] The prevalence of HF is ~2% (~15 million people) in the general population and >10% in those over 70 years of age.[4] The incidence of HF is greater in men, but trends suggest women have a higher prevalence starting at 79 years old.[3 5] HF morbidity exhibits an upward trend, shown by a 12% increase in diagnosed cases over the last decade due to prolonged survival rates and ageing population.[3 6]

Accurate prediction of risks, diagnosis and disease progression of HF allows implementation of evidence-based prevention and treatment strategies to reduce HF morbidity and mortality and its burden on healthcare. However, there is strong evidence to suggest that HF is often misdiagnosed or underdiagnosed in the primary care setting.[7 8] General practitioners (GPs) play an influential role in gatekeeping by identifying the signs and symptoms of HF for early diagnosis and accurate referral to specialist care.[9] Clinical guidelines for HF recommend the use of risk stratification models to estimate prognosis; however, these are limited and not implemented in clinical practice.[1]

Patients suspected of HF often present in primary care with signs and symptoms that include breathlessness, oedema and fatigue.[1 10] Early diagnosis is challenging to GPs and is often inaccurate as initial signs and symptoms are non-specific and do not discriminate from other conditions such as obesity and lung disease.[1 11] Currently, GPs rely on patients' medical history, physical examination, blood test (serum natriuretic peptides, NTproBNP [N-terminal pro b-type natriuretic peptide]) and ECG to make clinical decisions on HF.[1 10] Serum natriuretic peptide (NTproBNP) blood test has high sensitivity in ruling out HF[12]; however, its low specificity (65%) results in a high number of false positives.[7 13–16] In cases where the blood test cannot rule out HF, patients are referred to secondary care for an ultrasound of the heart and a specialist review from a consultant cardiologist to confirm or refute a diagnosis. Regrettably, GPs and cardiologists have no access to adequate risk stratification tools to further enhance their clinical judgement on HF. This has resulted in up to two-thirds of HF-suspected patients not having their HF confirmed following echocardiography and specialist review.[17–21] Hence, there is a huge clinical demand for novel risk stratification tools to enhance the early and accurate diagnosis of HF and to predict the risk and progression of HF in primary (GPs) and secondary (cardiologists) care.

STRATIFYHF aims to collect data to develop, validate and implement the first artificial intelligence (AI)-based decision support system (DSS) to assess and predict the risk of development, provide early diagnosis and determine the progression of HF. STRATIFYHF will integrate (1) patient-specific data, that is, demographic, clinical, genetic, lifestyle and socioeconomic data; (2) an AI-based digital patient library and AI-driven algorithms for risk stratification, early diagnosis and disease progression of HF; and (3) a highly innovative multifunctional AI-based DSS and mobile application for informing patient-centred, personalised prevention and treatment strategies for HF. STRATIFYHF has the potential to change the way HF is managed today, thereby improving the quality of life and life expectancy of patients' lives. STRATIFYHF will actively drive innovation in Europe's medical diagnostics industry by providing a new AI DSS for risk stratification, diagnosis and prognosis of HF at primary and secondary care levels. The STRATIFYHF DSS will integrate existing and novel technologies and develop an innovative mobile application for healthcare professionals and patients. Our solution will lead towards an efficient and sustainable healthcare system and will aim to reduce the number of HF-related hospital admissions and deaths, as well as unnecessary referrals from primary to secondary care.

The present study will collect prospective clinical data to validate the STRATIFYHF DSS as a tool to predict the risk, diagnosis and progression of HF in primary and secondary care and to determine the feasibility and acceptability of the mobile application. To achieve this, the aim of the present study is to capture longitudinal observations of the existing tools used to monitor HF along with novel technologies in individuals at risk of HF and those diagnosed with HF.

METHODS AND ANALYSIS

Study design, setting and ethics

This study is a prospective, multicentre longitudinal study (NCT06377319), with a planned start date of 1 October 2024 and an end date of 31 May 2027. The trial sponsor is Coventry University, UK. Ethical approval for the UK sites has been granted by the East Midlands - Leicester Central Research Ethics Committee (24/EM/0101) under protocol version 2.0 on 30 May 2024. Any future amendment will be submitted for HRA (Health Research Authority) and National Health Service (NHS) ethical approval and then published on the trial registry

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(NCT06377319). Eligible patients will be identified by each participating clinical centre and contacted by a member of the study research team. Eight clinical centres (Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne; University Hospitals Coventry and Warwickshire, Coventry; Cambridge University Hospitals NHS Foundation Trust; University Medical Centre Regensburg, Regensburg; Careggi University Hospital, Florence; Institute of Cardiovascular Diseases, Vojvodina, Sremska Kamenica; Julius Centre for Health Sciences and Primary Care, Utrecht; Hospital Universitario Ramón y Cajal, Madrid) will recruit up to 1600 patients (200 patients per centre, ~50% female) within a 24-month recruitment window, with a recruitment target of eight to nine patients per month. Follow-up data will be collected at 12 months and optionally at 24 months.

Sample size

Up to 1600 participants ≥45 years old of age will be recruited for the study. With an anticipated dropout rate of 20% during follow-up assessments, it is estimated that 1600 participants will be sufficient to achieve high specificity and sensitivity. This sample size will also be sufficient to evaluate the accuracy of prediction and diagnosis of different types of HF based on the most recent guidelines[1] (ie, heart failure with reduced ejection fraction (HFrEF), heart failure with mildly reduced ejection fraction (HFmrEF), heart failure with improved ejection fraction (HFimpEF) and heart failure with preserved ejection fraction (HFpEF)), assuming a sensitivity of at least 90%, with a margin of error of 12%, and a prevalence of HFpEF of ~50% in patients with a diagnosis of HF.

Recruitment

The Newcastle upon Tyne Hospitals NHS Foundation Trust, University Hospitals Coventry and Warwickshire, Cambridge University Hospitals NHS Foundation Trust and Julius Centre for Health Sciences and Primary Care, Utrecht will recruit individuals at risk of HF via either primary care (GP practices), direct access echocardiography or secondary care (cardiology department). The University Medical Centre Regensburg, Regensburg; Careggi University Hospital, Florence; Institute of Cardiovascular Diseases, Vojvodina, Sremska Kamenica; and Hospital Universitario Ramón y Cajal, Madrid will recruit individuals already diagnosed with HF from secondary care.

Eligible participants will be sent a participant information sheet. A member of the study research team will contact the participants to see if they are interested in participating in the study. Consent forms will be signed by the participant and countersigned by a member of the study team either prior to the research visit or on the first research visit. A copy of a sample consent form is found in the online supplemental materials file. A recruitment target of eight to nine patients per month is expected from each clinical centre. Recruitment will be completed during the first 24 months and will allow a follow-up period of up to 24 months.

The percentage of recruited patients diagnosed or hospitalised with HF (ie, from secondary care sites) will reflect the current classification of HF (ie, HFrEF: ~40%, ie, 80 patients per centre; HFmrEF: ~20%, ie, 40 patients per centre; HFpEF: ~40%, ie, 80 patients per centre). We will recruit 50% female participants for the at-risk and those diagnosed with HF.

Inclusion and exclusion criteria

Inclusion criteria for patients at risk of HF

Individuals ≥45 years of age at risk of developing HF will be divided into two categories based on current definitions[22]: (1) patients with current or prior symptoms or signs of HF (ie, shortness of breath at rest, paroxysmal nocturnal dyspnoea, orthopnoea and pleural effusion) without structural, biomarker or known genetic markers of heart disease, but with evidence of one of the following: hypertension, type 2 diabetes mellitus, obesity (body mass index ≥30 kg/m^2), known exposure to cardiotoxins (based on cancer treatment) or family history of cardiomyopathy; and (2) patients with current or prior symptoms or signs of HF and with evidence of one of the following: structural heart disease (eg, left ventricular (LV) hypertrophy, chamber enlargement, wall motion abnormality and significant valvular disease), abnormal cardiac function (eg, reduced LV without signs and/or symptoms of HF or right ventricular systolic function, evidence of increased filling pressures or abnormal diastolic function), elevated natriuretic peptide (NTproBNP >400 ng/L) or elevated cardiac troponin on exposure to cardiotoxin. All patients must be willing to visit the clinical research facility and able to provide written informed consent.

Inclusion criteria for patients with confirmed diagnosis of HF

Individuals ≥45 years of age with a confirmed diagnosis of HF according to guidelines (ie, HFrEF, HFmrEF, HFimpEF, HFpEF)[1] or hospitalisation due to HF over the previous 24 months, are willing to visit the clinical research facility and are able to provide written informed consent will be included.

Exclusion criteria for at-risk individuals and patients diagnosed with HF

Participants will be excluded if they meet the following criteria: inability to provide verbal informed consent; presenting with severe symptoms (NTproBNP/BNP (Brain natriuretic peptide) >2000 ng/L, hospitalised); major multimorbidity or other alternative diagnoses (eg, patients with a terminal diagnosis of cancer, patients in receipt of oxygen therapy or with oxygen saturation at rest <92%, severe mental health); recent acute coronary syndrome (within 60 days); severe physical disability preventing independence; scheduled or implanted pacemaker or cardio-defibrillator in the last 3 months; severe renal insufficiency (estimated GFR (Early glomerular filtration rate) ≤15 mL/min/1.73 m^2 or in receipt of

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Table 1 Study timeline, schedule of enrolment and assessments

Assessment	Baseline	Follow-up (months) 12	24
Inclusion/exclusion criteria	✓	–	–
Informed consent	✓	–	–
Medical history	✓	✓	✓
Physical examination/ anthropometrics	✓	✓	–
Electrocardiography	✓	✓	–
Echocardiography	✓	✓	–
Blood sample	✓	✓	–
Exercise stress (CORS) test	✓	✓	–
Questionnaires (quality of life, health economics)	✓	✓	–
Voice recording	✓	✓	–
CMR imaging	✓	–	–
Hospitalisation (and length of stay)	–	✓	✓
Home-based monitoring	✓	–	–
Focus group and interviews	✓	✓	–

CMR, cardiac magnetic resonance; CORS, cardiac output response to stress.

dialysis); present or planned pregnancy, which will limit performance of the cardiac output response to stress (CORS) test; and life expectancy of less than 12 months.

Study assessments

During the first visit, participants will undergo screening to ensure they meet the inclusion/exclusion criteria. Participants will be provided with the opportunity to ask further questions and will then be requested to provide written informed consent, which would be either returned to the post prior to the first appointment or completed at the first research visit. Participants will be informed that they can withdraw from the study at any point without giving reasons and without their medical care being affected. If the participant becomes ineligible at any point during the study, they will be withdrawn. All data will be recorded on standardised case report forms across the eight centres and imported into REDCap.

Eligible participants will attend two visits (ie, baseline and follow-up clinical assessments at month 12) at the clinical research site of the participating clinical centres. Each visit will last approximately 2.5 hours. An additional visit will be arranged in a subset of 20–40 participants per clinical centre who will undergo cardiac magnetic resonance (CMR) imaging assessment. Further monitoring of patient outcomes (eg, hospitalisation) will be performed via examination of medical records and telephone calls to patients. Table 1 provides a summary of the investigations to be completed at the different time points of the study. Participant retention is a key component of this study. Participants will be kept informed throughout the visits, and a follow-up call prior to the 12-month visit will be made to ensure they are happy to continue with the study. Another subset of the first 30 participants per clinical centre (ie, a total of 240 participants) who have provided consent for the mobile application will be invited to undergo daily monitoring of their body weight, blood pressure, ECG and physical activity for 6 months using weighing scale, ambulatory blood pressure monitor, activity diary and a smart watch (Withings ScanWatch 2, France).

Medical history, physical examination, anthropometrics and body composition

After providing informed consent, a review of participants' medical history will be performed, along with a physical examination, including body weight and height, which will be measured using a hospital-based scale and stadiometer. The amount of fat and muscle in the body will be assessed using bioimpedance or other appropriate methods. In case of contraindications, only anthropometrics (weight, height and waist circumference) will be measured. Data on medications, GP visits, admissions, referrals and presentation with new symptoms/complications will be recorded. Medical history will be recorded at baseline and at 12-month and 24-month follow-up. Physical examination and anthropometrics will be completed at baseline and at 12-month follow-up.

Blood samples

A blood sample will be taken from the antecubital vein. The blood sample will be assessed for cardiac biomarkers (serum natriuretic peptides (NTproBNP), troponin, total protein, creatine kinase myocardial band, BNP), lipid profile (total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol), triglycerides, blood profile (erythrocyte, leucocyte and thrombocyte counts, haemoglobin, mean corpuscular volume, mean corpuscular haemoglobin concentration), glucose, HbA1c (glycated hemoglobin), markers of renal function (albumin, urea, creatinine, eGFR [early glomerular filtration rate]), markers of liver function (aspartate aminotransferase, alanine transaminase, gamma-glutamyl transpeptidase, bilirubin), calcium, potassium, sodium, uric acid, markers of inflammation (C reactive protein) and thyroid-stimulating hormone. Blood samples will be collected at baseline and at 12-month follow-up.

Quality-of-life questionnaires

All participants will be asked to complete the Short Form-36 quality-of-life questionnaire.[23] In addition, participants diagnosed with HF will be asked to complete the validated Minnesota Living with Heart Failure questionnaire.[24] The quality-of-life questionnaires will be completed at baseline and at 12-month follow-up.

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Health economics

A health economics analysis will be performed based on the clinical records of participants' use of healthcare facilities related to HF (including visits to GP, cardiology department, rehabilitation and other specialist services), clinical investigations completed and medication use. The health economics analysis will be completed at baseline and at 12-month follow-up.

Cardiovascular function

An ECG will be performed using a standard 12-lead ECG in the supine position. Cardiac autonomic function, that is, heart rate variability, will be assessed using non-invasive methods integrated into the ECG device.

Transthoracic echocardiography, including colour and tissue Doppler, will be performed at rest and in response to Valsalva manoeuvre. Real-time images will be acquired in the standard parasternal (long-axis) and apical (apical four-chamber, apical two-chamber and apical long-axis) views, for which three cardiac cycles will be recorded. Parasternal short-axis views will be acquired at three levels: basal (at the mitral valve level), midpapillary and apical (minimum cavity distal to the papillary muscle level). Parasternal long axis of the right ventricle and right ventricular outflow tract will be monitored. Peak velocity of the LV outflow tract will be recorded from the apical five-chamber view by pulse Doppler, used to calculate pressure gradient. Apical four-chamber view will be used for right ventricular evaluation.

At the Coventry University site only, arterial stiffness, as a measure of arterial function, will be assessed using the non-invasive SphygmoCor device, which allows for both pulse wave analysis and pulse wave velocity to be performed non-invasively using gold standard techniques. The measurement is simple and painless, taking only a few minutes to perform. While the participant is in a comfortable supine position, the researcher will place a tonometer (pencil-like sensor) gently against the wrist, which will record blood pressure signal from the pulse. Cardiovascular function will be recorded at baseline and at 12-month follow-up.

CMR imaging assessment

On the informed consent form, participants will be able to opt in to participate in the CMR imaging assessment. Eligible centres will undertake CMR imaging assessment in a subset of 20–40 eligible participants who have not had CMR imaging assessment over the previous 6 months or have no contraindications to CMR imaging studies as determined by a cardiologist or a qualified radiographer. There will be a subset of 20–40 participants opting in to participate in this part of the study. Participants will undergo cardiac cine imaging to evaluate cardiac morphology and systolic and diastolic functions. These measurements will be taken according to standard imaging protocol of the clinical testing facility. The CMR imaging assessment will be recorded at baseline only.

CORS test

Participants will then be connected to a bioreactance non-invasive cardiac output monitor (NICOM, Starling, Baxter, USA), which we have previously evaluated.[25–28] The method uses four pairs of electrodes placed on the front side of the upper and lower thorax (similar to ECG). Bioreactance is a novel method for continuous non-invasive cardiac function monitoring. It estimates cardiac output by analysing the frequency of relative phase shift of electronic current delivered across the thorax. Measurements will be performed using the protocol we have recently developed,[18 29 30] consisting of three phases: 3 min rest (supine) phase, 3 min challenge (standing) phase and 3 min stress (exercise step test) phase. The CORS test will be completed at baseline and at 12-month follow-up.

Voice recording assessment

Subtle changes in speech pattern have emerged as a tool to risk-stratify, diagnose and monitor cardiovascular conditions.[31] Participants will be seated in a quiet room in the clinical research facility to complete the recording. Participants' voices will be audio-recorded for up to 5 min while they read a standardised text aloud. The recorder will be started just before the patient starts to read the text and will be stopped at the end of the task. The standardised text will be translated to different languages to ensure diversity and inclusion are achieved. The audio file will be transferred to a computer and then processed using a dedicated software available from Praat (https://www.fon.hum.uva.nl/praat/). The software extracts relevant voice features after low-level acoustic features and sudden impulsive noise have been removed using spectral noise gating and voice processing techniques.[32] Extracted voice features are presented in numerical values and will be stored in a password-protected computer for further analysis using machine learning and AI. The voice recording assessment will be recorded at baseline and at 12-month follow-up.

Home-based monitoring

Participants will have the opportunity to opt in to participate in the home-based monitoring. Thirty participants per centre will undertake home-based monitoring of body weight, blood pressure, accelerometry and electrocardiography during 6 months of follow-up. Participants will be selected from the first 30 participants who have opted in to participate in this part of the study. Participants who do not have access to body weight scale or blood pressure monitor at home will be provided the same by the local research team. Accelerometry and electrocardiography will be monitored using a wrist-worn watch (ScanWatch 2, Withings, France).

Focus groups and semistructured interviews

Coventry University and Newcastle University will complete this part of the project. Participants will be able to opt in to participate in the focus groups and

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semistructured interviews. A separate participant information sheet and informed consent for healthcare professionals will be created for this part of the project. Focus groups and semistructured interviews with up to 15 healthcare professionals (50% female) and up to 20 study participants (ie, 10 at risk of HF and 10 diagnosed with HF; 50% female) will be conducted to explore the needs of the participants and healthcare professionals prior to the development of the DSS and to evaluate the acceptability of the mobile application. We expect the focus groups and semistructured interviews to be conducted at baseline and at 6-month and 12-month follow-up.

An online training programme on how to use the DSS will be codesigned with input from healthcare professionals. The training programme will be delivered face-to-face to GPs, cardiologists and nurses by a trained researcher. A stand-alone online training programme will also be made available.

Primary and secondary outcome measures

Outcome measures

For the at-risk population, the primary outcome is the collection of prospective data to determine the diagnostic accuracy (ie, sensitivity and specificity) of the STRATIFYHF DSS in predicting the risk of developing HF within 12 months. The secondary outcome is identification of demographic and clinical predictors of risk, diagnosis and progression of HF. Data to determine the diagnostic accuracy (sensitivity and specificity) of the STRATIFY DSS in predicting risk, diagnosis and progression of HF will include data on medical history, physical examination (signs and symptoms), blood tests including serum natriuretic peptides (NTproBNP), ECG, echocardiogram, CMR imaging assessment, in addition to genetic testing as appropriate (ie, hypertrophic cardiomyopathy), as well as sociodemographic data, including economic and lifestyle data, along with use of novel technologies including CORS test and voice recording assessment.

Data collection storage and monitoring

Data will be collected by the research team at each clinical centre and only individuals authorised by the chief investigator at each site will have access to the data. All data will be processed in accordance with the UK General Data Protection Regulation 2016 and the Data Protection Act 2018, as well as European General Data Protection Regulation 2016 laws. All data will be stored securely and will be pseudonymised with study IDs. The data will be accessible only to authorised project staff and backed up daily with a highly available offsite mirror. The audio recordings for the focus groups and semistructured interviews will be destroyed once they have been transcribed. The audio files for the voice recording assessment will be processed at each clinical centre and then destroyed once analysis has been completed. Data will be archived in accordance with NHS ethics.

Assessment, reporting and documentation of study events

As this is a prospective, multicentre longitudinal study using existing and novel technologies, we do not anticipate adverse events and/or reactions. However, where they occur, the standard clinical operating procedure for the reporting site will be followed. A study report detailing all procedures and events will also be presented by each clinical partner at the end of the project. In case of an adverse event or reaction, this will be reported according to Good Clinical Practice and documented within the official study documentation, with immediate communication to the study steering group, ethical adviser and research ethics committee.

Data analysis methods

The central component of the DSS will be a model constructed using machine learning algorithms based on the acquired medical data. Since patients' data are collected from various clinics, this necessitates the standardisation of observed patient features, value ranges and measurement units, as well as handling of missing values. To address this, we will employ techniques ranging from imputing values based on similarity in the data space to matrix factorisation, with the primary goal of ensuring consistency and coherence of the data set. The training data will be transformed so that each instance represents a specific moment in the time sequence of patient care. The current clinical picture and a summary of previous measurements will serve as independent variables, while the time to diagnosis of HF (a known value, as it is based on retrospective data) will be the target variable.

After the training phase, the model will be able to predict the time to the onset of HF based on the dynamics of changes in the patient's clinical picture. This predicted value will form the basis for risk stratification of HF, enabling the analytical tool to identify patients at the highest risk who require the most urgent care. Additionally, identifying patterns in the sequence of changes in the clinical picture across patient observations will allow the tool to predict disease progression over time, facilitating early interventions and preventing severe complications. For classification and regression modelling, contemporary machine learning algorithms will be used, such as neural networks (deep learning), random forests, support vector machines and gradient boosting.

To ensure transparency in the decision-making process, we will provide explanations for all of the model's predictions, detailing the positive and negative contributions of individual patient features towards or against a specific class (LIME (Local Interpretable Model-agnostic Explanations), Shapley values, etc). This transparency will enable medical experts to validate predictions, thereby enhancing trust in the operation of the entire DSS.

The quality of the predictions will be assessed using cross-validation, ensuring that the tool's recommendations are robust and broadly applicable. The DSS will be evaluated using the data gathered, and different metrics such as sensitivity, specificity, F1 and R2 will be reported.

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Where possible, an independent clinical test set from the University of Florence will be used to independently validate the model's accuracy and reliability.

Patient and public involvement

Patients or the public were involved in the design, or conduct, or reporting or dissemination plans of the research. Patients or the public were involved in the design of the DSS and in the development of the mobile app.

Dissemination policy

The STRATIFYHF project implements a structured synergistic approach to implementing all outreach activities. For dissemination measures, STRATIFYHF commits to open science practices, complying with the Horizon Europe programme. Data will be analysed and published in peer-reviewed journals and presented at national and international conferences. We will create online training materials for healthcare providers interested in STRATIFYHF's approach to an efficient risk stratification and diagnosis of HF in the form of videos from key experts in the project. These will be made freely available on the project website and shared with the Physicians' Academy for Cardiovascular Education. At the end of the study, all participants will be provided with information about the study's major findings. The study will be completed when study participants have completed the proposed research visits.

DISCUSSION

HF is a complex clinical syndrome[1] and diagnosis continues to be highly challenging.[1 11] The limited access to healthcare facilities with sufficient expertise to risk-stratify and diagnose HF has been identified by the World Heart Federation as a top barrier to early diagnosis in current clinical practice.[33] There is therefore a huge clinical demand for novel risk stratification tools that will predict the risk of HF as well as enhance the early and accurate diagnosis and progression of HF in primary (GPs) and secondary (cardiologists) care.[29] STRATIFYHF will shift the current clinical pathway by developing, evaluating and implementing novel, AI-driven risk stratification and diagnostic tools to reduce the burden of HF in primary to secondary care.

Accurate risk stratification and early diagnosis of HF allow the implementation of evidence-based prevention[34] and treatment[1] strategies, reducing HF morbidity and mortality[12] and its burden on healthcare.[1 10 35] Recent advances in risk stratification, diagnosis and prognosis of HF using machine learning and AI have presented some promising findings for improving current challenges.[36–41] The STRATIFYHF DSS and mobile application will revolutionise the current diagnostic tools available for HF and will validate novel technologies to improve the quality of life and life expectancy of patients and reduce the economic burden of HF on healthcare systems worldwide. STRATIFYHF will equip primary and secondary healthcare professionals and patients with novel AI-based technologies (STRATIFYHF DSS and mobile application) that will allow risk stratification, early diagnosis and prediction of disease progression of HF. Such development will lead to prompt initiation of evidence-based prevention[34] and treatment[1] strategies, eliminate the need for patient referrals from primary to secondary care and reduce hospitalisation and mortality rates in HF.

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