Version History

V1.0		Proposal uploaded

Lay Summary

Heart failure (HF) is the inability of the heart to pump an effective amount of blood to supply the other organs leading to progressive deterioration of the body and significant breathlessness, either during light exercise or at rest. HF is a serious global problem and it is considered as one of the most aggressive killers worldwide. It is estimated that, to date, more than 38 million people suffer of HF, which affects approximately 2% of the general population and up to 10% of the elderly.

The COVID-19 pandemic is a global public health emergency that has dramatically affected all healthcare systems. During the pandemic, a prompt reconfiguration of healthcare services, including cessation of routine, face-to-face treatment, and follow-up of many cardiovascular (CV) conditions, was necessary to accommodate the overwhelming influx of patients with COVID-19. Also, community care has been affected by the pandemic and had to adapt to the extreme scenario.

Throughout the first wave of the pandemic, we observed a significant decline in admission rates for decompensated HF. Furthermore, patients presenting in hospital, despite being lower in number, were sicker compared to pre-pandemic data. This was then paralleled by an increased mortality when compared with the previous year. **The increased HF mortality during the peak of the COVID-19 pandemic necessitates further research, to understand the underlying reasons for it, so that it can be mitigated against in future.**

To address these questions, we will analyse linked data from four key national datasets, namely the Clinical Practice Research Datalink (CPRD), the National Heart Failure Audit (NHFA), Hospital Episode Statistics (HES), and the Office for National Statistics (ONS). Using complementary, national databases we will link information on approximately 100,000 patients over three years to examine the impact of the COVID-19 pandemic on the epidemiology and treatment of HF at a national level, both in the hospital sector and the community. Using these methods, we aim to establish the epidemiology of HF during COVID-1; examine its management both in hospital and in primary care; investigate the changes of hospitalization rates and patient characteristics and characterize the factors which were associated with adverse outcomes.

The results will provide a comprehensive description of HF epidemiology and management during the COVID-19 pandemic. We expect to confirm the changes observed locally in our pilot data at a national level. Specifically, we anticipate that HF admissions will initially decrease and then normalise after the release of the lockdown measures. Patients admitted to hospital will be sicker and overall mortality will increase as a result of changes in primary care management during the COVID-19 pandemic. Inpatient management will also be different during the COVID-19 pandemic, including

a shorter length of stay, less frequent management on a cardiology ward, fewer people accessing specialist care, and optimization of medical therapy will be worse.
The findings of this analysis, on the epidemiology of HF, the quality of its care, and outcomes, at a national level, will be pivotal to understanding the changes that occurred to HF care during COVID-19. The ultimate aim is to ascertain the best approaches to caring for patients with HF to improve outcomes in the future when the health-care system is stressed.

Background & pilot data

Heart failure (HF) affects approximately 2% of the general population and up to 10% of people aged >65 years [1-4], is associated with a high morbidity and mortality[5,6], and consumes over 2% of the entire NHS budget[7]. As both incidence and prevalence increase with age, there has been a substantial increase in its prevalence over the last decade, due to the ageing population and longer survival after the onset of cardiovascular (CV) disease[1]. However, there has also been a lot of good news for HF patients. Evidence-based pharmacological therapy (optimal medical therapy; OMT) and device implantation have reduced the mortality associated with chronic HF over the last 25 years. For HF with reduced ejection fraction (HFrEF), these treatments may have increased life expectancy two to three fold[8-14]. Pathways have been developed and endorsed by national guidelines to allow rapid access to specialist care for the institution of OMT by specialist multidisciplinary HF teams (MDT)[15].

Hospitalisation for worsening HF is associated with a poor prognosis, whether it is due to decompensation of known chronic HF or a new presentation of incident HF. HF should be promptly investigated and treated to reduce risk. Pre-COVID-19, in-hospital mortality rates for acute decompensated HF in the National HF Audit (NHFA) for England & Wales hovered around 10%, and more than 30% of patients discharged after an acute admission died within a year [16]. Patients with decompensated HF require dedicated and specialised multi-professional care to mitigate adverse outcomes. For acute HF, service transformation over the last ten years has also led to better management of those admitted with HF, with improved access to specialist cardiology care and improved outcomes. This translates to better community care after discharge as hospital-based HF and community-based services are increasingly integrated.

The SARS-CoV2 pandemic is a global public health emergency that has dramatically affected all healthcare systems. Rapid reconfiguration of secondary care services, including cessation of routine, face-to-face treatment and follow-up of many cardiovascular (CV) conditions, was necessary to accommodate the overwhelming influx of patients with COVID-19. Community care also had to adapt during periods of lock-down by the conversion of most General Practice (GP) consultations to virtual rather than face-to-face. During this period, admission rates for various medical conditions significantly declined [17-21]. Admission rates for CV diseases, including acute coronary syndromes, similarly dramatically reduced[22].

For patients with HF, who are at the end of the continuum of CV diseases, many specialist HF staff were redeployed, and specialist wards were reconfigured for COVID-19 care. We described a significant decline in admission rates for decompensated HF during the peak of the pandemic[17,23]. Using local NHFA data, we demonstrated a significant decline in admission rates for acute HF to our tertiary centre

in London, compared to previous years. Patients presenting to hospital were generally sicker with more advanced symptoms compared to previous years, including higher New York Heart Association (NYHA) class, lower left ventricular ejection fraction (LVEF) and more peripheral oedema. Furthermore, patients were more frequently managed in medical wards rather than in cardiology, and the length of hospital stay was shorter compared to 2019. Although these trends returned to normal after the peak of the pandemic, we were the first to report that mortality in these patients was significant higher compared to previous years, using Hospital Episode Statistic (HES) data (Fig 2)[23].

Throughout the pandemic, HF patients may have elected to stay at home and avoid visits to their GP, hospital-based clinics and elective hospital admission, following public messaging, national lockdown and healthcare system reconfiguration. For patients with chronic HF, NHS Trusts either paused their routine follow-up completely or resorted to remote telephone clinics. In primary care most appointments were converted to virtual. However, it is not known if changes in HF incidence, prevalence and aetiology over these months also contributed to this observation. In terms of in-patient mortality, changes in specialist healthcare provision during the pandemic might also have partially contributed to the observed increase in in-hospital mortality for HF[17,23].

The increased HF mortality during the peak of the SARS-CoV2 pandemic necessitates further research to understand the underlying reasons so that they can be mitigated in future. The objective of this project is to elucidate the impact of the SARS-CoV2 pandemic on the epidemiology and treatment of HF at a national level, both in the hospital sector and the community, in order to provide a comprehensive evaluation of the whole HF spectrum across both primary and secondary care. It is anticipated that, as a result, we will provide insights into the most important treatments for HF and their association with outcomes so that strategies to maintain them in future public health emergencies can be designed.

Aims and Hypoteses

Specific aims are as follows:

1. Establish the incidence and prevalence of HF during COVID-19;
2. Examine the aetiology of incident HF, including post-ischaemic HF due to late-presenting or missed myocardial infarction;
3. Examine the management of patients with HF in primary care and changes during the pandemic;
4. Analyse the time-to-optimization of medical and device therapy for patients with *de novo* HF, and its prognostic impact;
5. Investigate admission rates and baseline characteristics of patients with HF;
6. Evaluate outcomes of both incident and prevalent HF managed in primary care, as well as after acute admission with decompensated HF;
7. Analyse the effectiveness of remote device monitoring in patients with implantable cardioverted defibrillators (ICD) and cardiac resynchronization therapy (CRT);
8. Characterise demographic variables and factors associated with adverse outcomes;
9. Evaluate the impact of vaccination against influenza, pneumococcal pneumonia and COVID-19 on HF hospitalisations.

Methods

Study design & data linkage

We will compare events of interest pre-COVID-19 (1st January 2018 – 31st December 2019), peri-COVID-19 (1st January 2020 – 31st December 2021) and post-COVID-19 (1st January 2022 – 31st December 2022). [1,24,25].

1. Incidence and prevalence of HF

The incidence and prevalence of HF will be determined for each of the time frames: pre-, peri- and post-COVID-19

Incident HF will be defined as the first record of HF in primary care or hospital admission records from any diagnostic position [1]. For incidence calculations, we will exclude all individuals who have a diagnosis of HF before the study start date of 1st January 2019. Incidence will be calculated as the 1st diagnosis of HF from either database in the time frame expressed as a percentage of the total population at risk without HF. We will calculate prevalence by considering all patients ever diagnosed with HF (numerator) among patients alive, aged 16 years or older, and registered with a GP during a standard time period (denominator) on July 31st in each year.

Aetiology of HF will be ascertained for both ischaemic and non-ischaemic HF. Ischaemic HF will be defined as the first record of HF in primary care or hospital admission records in patients with ischaemic heart disease or acute myocardial infarction (AMI). Non-ischaemic HF will be defined as the first record of HF in primary care or hospital admission records in patients without history of ischaemic heart disease or AMI.

Quality of care for both incident and prevalent HF cases will be assessed in those patients reduced left ventricular ejection fraction (HFrEF) within each allocated the time frame. For those with HFrEF we will determine the proportion having “essential diagnostic tests” i.e. NT-proBNP/BNP, serum creatinine, and FBC as diagnostic quality indicators. We will also record the average daily dose of angiotensin converting enzyme inhibitor (ACEI), angiotensin receptor blocker (ARB), beta-blocker (BB) and mineralocorticoid receptor antagonist (MRA) during each time frame, as quality of care treatment indicators. We will also determine the invasive vs. non-invasive strategy for patients with AMI and for those with chronic ischemic heart disease and the average time-to-optimization of medical therapy for those with incident HF.

Outcomes for both incident and prevalent HF in each of the three time periods will be determined by linkage to HES for hospitalisations (all cause, cardiovascular and HF) and to ONS for mortality (all cause and cardiovascular) at the end of each time frame (for incident and prevalent HF) and 1-year mortality for incident cases. We will examine the association between the above Quality of Care Indicators, and mortality and readmission rates.

2. Quality of Care and Outcomes for Hospitalised patients

A granular examination of quality of care for patients hospitalised for HF during the pre-, peri- and post-COVID-19 periods will be determined by analysis of the NHFA data.

The following quality of care metrics will be used:

1. Length of hospital stay;
2. Proportion of hospitalised patients undergoing specialist care for HF;
3. Differences of place of care (proportion of patients in cardiology vs. other medical wards as main place of care for HF);
4. Medical treatment of HFrEF (single treatment with ACEI, BB and MRA, and the combination of all three medicines, and diuretic management);
5. Device implantation and activation with CRT ± ICD for HFrEF;
6. Follow-up arrangements (proportion followed up in Cardiology and HF specialist nurse clinics);
7. Vaccination rates for influenza, pneumococcus and COVID-19, and their effects on patients with HF.

Outcomes for HF in each of the three time periods will be determined by linkage to HES for hospitalisations (all cause, cardiovascular and HF) at 1-year and the ONS for mortality (all cause and cardiovascular). Mortality during the admission, and 30-day and 1-year mortality post-admission for survivors to discharge will be derived. We will analyse the association between the above quality of care metrics and outcomes.

Statistical analysis

Comparisons between the time-period groups will be made by the analysis of variance (ANOVA) test on continuous variables, using the Brown–Forsythe statistic when the assumption of equal variances do not hold, or by the non-parametric Mann-Whitney test when necessary. Chi-square or Fisher's exact tests will be used for discrete variables. Continuous variables will be reported as mean (standard deviation) or median (interquartile range), as appropriate. Categorical variables will be reported as number (percentage).

Incidence rates of HF hospitalizations will be calculated by dividing the number of cumulative events by the total catchment areas. Incidence-rate ratios (IRR) comparing the different period analysed will be calculated using Poisson regression to model the number of heart failure hospitalizations per week[17]. Hospitalization trends will be compared using a quadratic term, or a higher degree to obtain the best fitting of the curve, for the different cohorts and compared by means of the extra-sum-of-square F test[23].

Cumulative incidence curves for the composite of all-cause mortality and HF hospitalization will be estimated and compared between groups by means of the Log-rank test. Cumulative incidence curves for the secondary endpoints will be estimated and compared considering competing risks of death for other causes, and the appropriate statistical test suitable for competing risks[27]. Univariable and cause-specific multivariable Cox models will be estimated, and variables will be selected on each specific outcome from univariable analyses (i.e. those with a p value <=0.1) in a full-model approach, to assess prognostic significance of the parameter analysed. A variable-per-event ratio of 10 will be used. Time to optimization of medical or device therapy will be considered as time-dependent variables in the Cox models.

All analyses will be conducted using STATA statistics software, and 'R' (R Foundation for Statistical Computing, Vienna, Austria. https://www.r-project.org/). All statistical analyses will be reported following indications present in "Strengthening the Reporting of Observational Studies in Epidemiology" (STROBE) guidelines[28].

Sensitivity analyses will be conducted to examine the impact of case identification restricted to diagnosis recorded in primary or in secondary care or referred for

specialist assessment or echocardiography. A further sensitivity analysis will include only patients with complete covariate data to assess the effect of missingness. Furthermore, we will repeat the primary analysis relaxing the assumption of independence of individuals within a GP practice, by calculating cluster-robust standard errors to take account of any differences between practices with respect to patient management and diagnosis. Moreover, predefined subgroup analysis for patients who will and will not receive specific vaccines will be also performed.

Plan for addressing confounding
This study has all the limitations of observational data, including potential bias as a result of unmeasured confounding factors, and the observed effect may be due to unrecorded variables. Therefore, we can only report associations, rather than causal relationships, and any results must be interpreted with caution. However, we will use a propensity-score matching or an inverse probability weighting to potentially overcome these limitations and to adjust for different baseline characteristics. Furthermore, avoiding overfitting, we will include all available covariates in the Cox regression analysis. This strategy will provide statistically reliable results, adjusted for possible confounders[29,30].

Plan for addressing missing data
Missing data in outcome measures and other covariates will be addressed using multiple imputation according to the approaches suggested by Carpenter and Kenward, depending on the amount of missing data[31].

Expected value of results
In-hospital mortality due to acute HF increased during the first COVID-19 surge. The continued global spread of COVID-19 and the threat of further surges in the UK mandate urgent research to underpin our strategic response. Studies to date have been limited to investigating the impact of COVID-19 on in-hospital management or, at best, short follow-up after discharge [17,23,32-35]. This project is expected to provide a comprehensive account of all such changes in patients with de novo or pre-existing HF, both in the community and in hospital. Finally, this project will be the first to analyse the impact of vaccination against SARS-CoV2, compared with usual seasonal vaccines, on patients with HF. A thorough analysis of the epidemiology and management of HF, and associations with outcomes, at a national level, will be pivotal to tailoring future changes in care. The ultimate aim is to ascertain the best approaches to caring for patients with HF to improve outcomes.

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Data

	NHS England (TRE)	**Wales**
Primary Care	**GDPPR:** General Practice Extraction Service (GPES) Data for Pandemic Planning and Research	WLGP: Wales Longitudinal General Practice
Secondary care	HES: Hospital Episode Statistics: ● Admitted Patient Care ● Adult Critical Care ● Outpatients ● Accident & Emergency/ Emergency Care Data Set ● SUS: Secondary Uses Service ● Uncurated Low Latency Hospital Data (tbc)	● PEDW (Patient Episode Database for Wales) ● CCDS (Critical Care Dataset) ● OPDW(Outpatient Dataset for Wales) ● OPRD (Outpatient Referral Dataset) ● EDDS (Emergency Department DataSet)
COVID-19	● SGSS (Pillar 1, 2 – positive results only) ● Pillar 2 Antigen (positive and negative) ● Pillar 3 Antibody (positive and negative) ● COVID-19 Vaccination events, ● COVID-19 Vaccination adverse reactions ● COVID-19 SARI-Watch	● PATD (COVID-19 testing positive and negative results (Pillar 1, 2, 3)) ● CVVD (COVID-19 Vaccination Data) ● CVSP (Shielded People) ● CTTP (Test, Trace & Protect)
Deaths	● Civil registry deaths	● ADDD (Annual District Death Daily) ● ADDE (ONS mortality data) ● CDDS (Consolidated Death Data Source)
NCOR CVD Audits	● SSNAP: Sentinel Stroke National Audit Programme ● NICOR – MINAP: Myocardial Ischaemia National Audit Project ● NICOR – PCI: Percutaneous Coronary Interventions	● SSNAP: Sentinel Stroke National Audit Programme ● NICOR – MINAP: Myocardial Ischaemia National Audit Project ● NICOR – PCI: Percutaneous Coronary Interventions

	● NICOR – NHFA: National Heart Failure Audit ● NICOR – NACSA: National Adult Cardiac Surgery Audit ● NICOR – NACRM: National Audit of Cardiac Rhythm Management ● NICOR – CHD: National Congenital Heart Disease Audit ● NICOR – TAVI: Transcatheter Aortic Valve Implantation	● NICOR – NHFA: National Heart Failure Audit ● NICOR – NACSA: National Adult Cardiac Surgery Audit ● NICOR – NACRM: National Audit of Cardiac Rhythm Management ● NICOR – CHD: National Congenital Heart Disease Audit ● NICOR – TAVI: Transcatheter Aortic Valve Implantation
NVR	● NVR – National Vascular Registry Audit	● NVR – National Vascular Registry Audit
Prescribing/ Dispensing	● NHS BSA Dispensed Medicines ● Secondary care prescribed medicines	● WLGP (Wales Longitudinal General Practice) ● WDDS (Wales Dispensing Dataset)
Other		● (WRRS) Wales Results Reporting Service ● (WDSD) Welsh Demographic Service Dataset ● (WASD) Welsh Ambulance Service Dataset