ESC European Society of Cardiology

European Heart Journal (2022) **00**, 1–16
https://doi.org/10.1093/eurheartj/ehac114

CLINICAL RESEARCH
Heart failure and cardiomyopathies

The GUIDE-HF trial of pulmonary artery pressure monitoring in heart failure: impact of the COVID-19 pandemic

Michael R. Zile [1]*, Akshay S. Desai [2], Maria Rosa Costanzo [3], Anique Ducharme [4], Alan Maisel [5], Mandeep R. Mehra [2], Sara Paul[6], Samuel F. Sears [7], Frank Smart[8], Christopher Chien [9], Ashrith Guha[10], Jason L. Guichard [11], Shelley Hall[12], Orvar Jonsson[13], Nessa Johnson [14], Poornima Sood[14], John Henderson[14], Philip B. Adamson [14], and JoAnn Lindenfeld [15]

[1]Division of Cardiology, Department of Medicine, RJH Department of Veterans Affairs Medical Center, Medical University of South Carolina, SC, USA; [2]Cardiovascular Division, Brigham and Women's Hospital, and Harvard Medical School, Boston, MA, USA; [3]Advocate Heart Institute, Naperville, IL, USA; [4]Montreal Heart Institute, Université de Montréal, Montreal, QC, Canada; [5]University of California San Diego, La Jolla, CA, USA; [6]Catawba Valley Health System, Conover, NC, USA; [7]East Carolina University, Greenville, NC, USA; [8]School of Medicine, Louisiana State University, New Orleans, LA, USA; [9]Division of Cardiology, University of North Carolina, Chapel Hill, NC, USA; [10]Cardiology, Houston Methodist DeBakey Heart and Vascular Center, Houston, TX, USA; [11]Department of Medicine, Division of Cardiology, Section for Advanced Heart Failure, Pulmonary Hypertension and Mechanical Circulatory Support, Prisma Health-Upstate, Greenville, SC, USA; [12]Baylor University Medical Center, Dallas, TX, USA; [13]Sanford Health, Sioux Falls, SD, USA; [14]Abbott, Abbott Park, IL, USA; and [15]Vanderbilt Heart and Vascular Institute, Nashville, TN, USA

Received 30 July 2021; revised 27 January 2022; accepted 15 February 2022

Abstract

Aims During the coronavirus disease 2019 (COVID-19) pandemic, important changes in heart failure (HF) event rates have been widely reported, but few data address potential causes for these changes; several possibilities were examined in the GUIDE-HF study.

Methods and results From 15 March 2018 to 20 December 2019, patients were randomized to haemodynamic-guided management (treatment) vs. control for 12 months, with a primary endpoint of all-cause mortality plus HF events. Pre-COVID-19, the primary endpoint rate was 0.553 vs. 0.682 events/patient-year in the treatment vs. control group [hazard ratio (HR) 0.81, $P = 0.049$]. Treatment difference was no longer evident during COVID-19 (HR 1.11, $P = 0.526$), with a 21% decrease in the control group (0.536 events/patient-year) and no change in the treatment group (0.597 events/patient-year). Data reflecting provider-, disease-, and patient-dependent factors that might change the primary endpoint rate during COVID-19 were examined. Subject contact frequency was similar in the treatment vs. control group before and during COVID-19. During COVID-19, the monthly rate of medication changes fell 19.2% in the treatment vs. 10.7% in the control group to levels not different between groups ($P = 0.362$). COVID-19 was infrequent and not different between groups. Pulmonary artery pressure area under the curve decreased −98 mmHg-days in the treatment group vs. −100 mmHg-days in the controls ($P = 0.867$). Patient compliance with the study protocol was maintained during COVID-19 in both groups.

Conclusion During COVID-19, the primary event rate decreased in the controls and remained low in the treatment group, resulting in an effacement of group differences that were present pre-COVID-19. These outcomes did not result from changes in provider- or disease-dependent factors; pulmonary artery pressure decreased despite fewer medication changes, suggesting that patient-dependent factors played an important role in these outcomes.

Clinical Trials.gov: NCT03387813

* Corresponding author. Division of Cardiology, Department of Medicine, RJH Department of Veterans Affairs Medical Center, Medical University of South Carolina, Thurmond/Gazes, Room 323, 30 Courtenay Dr, Charleston, SC 29425, USA. Tel: +1 843 792 4799, Fax: +1 843789 6850, Email: zilem@musc.edu

Key questions

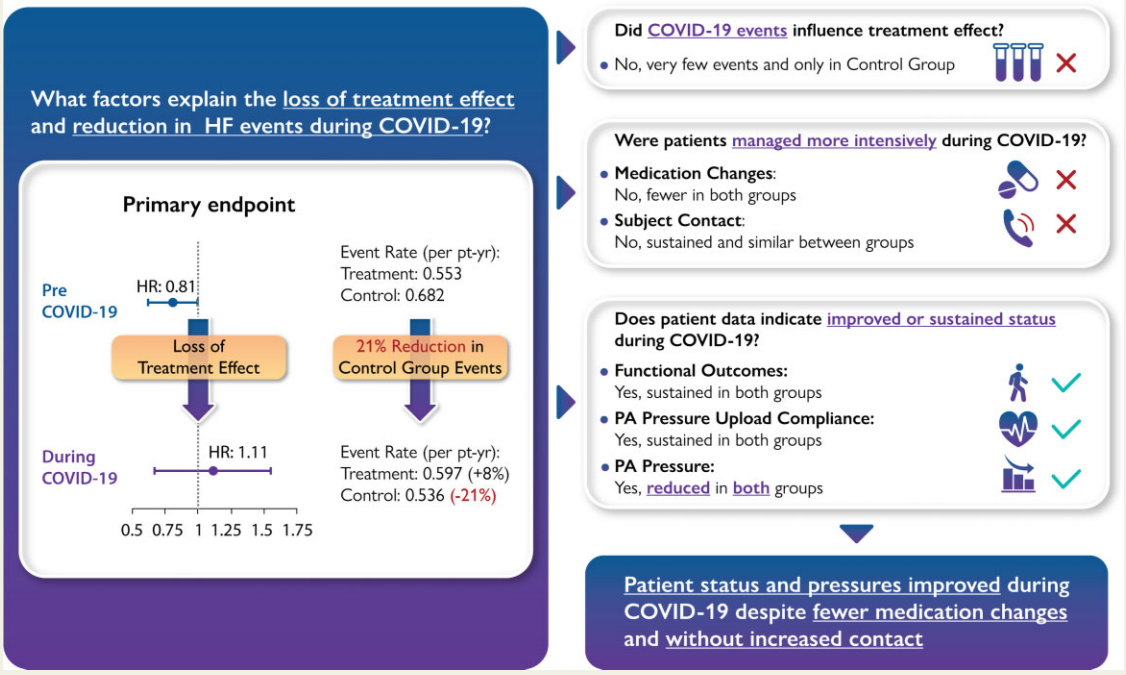
What factors explain the loss of treatment effect and reduction in heart failure events during COVID-19?

Key findings

The treatment effect change was not due to COVID-19-related events. Patient management was sustained but not intensified during COVID-19. Patient status improved during COVID-19 and pulmonary artery pressure reduced in both groups.

Take home message

Patient behaviour probably improved during COVID-19, given that patient status and pulmonary artery pressure improved during COVID-19 despite fewer medication changes and without increased contact from providers.



Structured Grapical Abstract Patient-dependent factors played an important role in the outcomes of GUIDE-HF.

Keywords Heart failure • Haemodynamics • Pulmonary artery pressure • COVID-19

Introduction

During the coronavirus disease 2019 (COVID-19) pandemic, significant changes in the number of cardiovascular events, including heart failure (HF) hospitalizations, have been observed in patients with chronic HF. This was true in the population at large and in randomized clinical trials (RCTs) conducted during the pandemic.[1–10] These changes were unanticipated and have significantly impacted the conduct and outcomes of RCTs. This impact was seen both in the accumulation of endpoint events and in a differential effect between control and intervention groups. The causes of these changes have not been completely defined. Several possibilities can be postulated. These include alterations in provider-dependent, disease-dependent, and patient-dependent factors. Data necessary to examine these factors are not routinely gathered in standard clinical practice.

However, during the conduct of one RCT, the Hemodynamic-GUIDEd management of Heart Failure (GUIDE-HF) trial which used an implantable pulmonary artery (PA) pressure sensor, data that relate to some of these potential factors were systematically collected and are presented in this analysis that follows the publication of the primary results.[11,12] All clinical contacts between enrolled patients and the health management team, changes in medications (examples of provider-dependent factors), patient symptom status [quality of life (QoL) questionnaires], cases of COVID-19 infection (examples of disease-dependent factors), daily haemodynamic data (PA pressures), and patient compliance with the study protocol (examples of patient-dependent factors) were quantified prior to (pre-COVID-19) and after the onset (during COVID-19) of the pandemic.

GUIDE-HF tested the hypothesis that haemodynamically guided management of patients with chronic HF improves health outcomes in New York Heart Association (NYHA) class II–IV HF patients with either elevated brain natriuretic peptide (BNP) or N-terminal pro-BNP (NT-proBNP) and/or a prior HF hospitalization. Following successful implantation of a PA pressure sensor, patients were randomized in a 1:1 ratio into one of two groups: the treatment

group in which management of subjects was based on PA pressure information derived from the CardioMEMS™ HF System, and the control group in which management of subjects was based on usual clinical care (signs, symptoms, weight, etc.) without knowledge of PA pressure information. In follow-up studied pre-COVID-19, the primary event rate was significantly lower in the treatment group compared with the control group. However, during COVID-19, this difference was no longer evident. These results were summarized in our recent publication of the primary results of the GUIDE-HF trial.[12] The purpose of the current analysis was to use data available in the GUIDE-HF study to examine factors that may contribute to loss of the differences in primary events, including HF events, between treatment and control groups during the COVID-19 pandemic (*Structured Graphical Abstract*). These data will enhance our understanding of the effects of the COVID-19 pandemic on the rates of HF events in the community at large and in RCTs in particular. These data will also inform the development and analysis of other RCTs performed during the pandemic era.

Methods

Study design

Details regarding the GUIDE-HF trial design (NCT03387813) have been previously published.[11] The randomized arm of the GUIDE-HF trial compared HF management guided by PA pressures obtained remotely via an implanted sensor with usual clinical HF management in NYHA class II–IV HF patients. The institutional review boards approved the trial protocol at each of the 118 participating trial sites in the USA and Canada. Written informed consent was obtained from all patients or their authorized representatives before any study-related procedures were done. Additional details about the participating centres and trial procedures have already been published. In addition to applicable regional or local laws and regulations, the GUIDE-HF trial was conducted in compliance with the most current version of the World Medical Association Declaration of Helsinki and 21 CFR Parts 50, 54, 56, and 812. The authors vouch for the completeness and accuracy of the data, analyses, and results, and for the fidelity of the trial to the trial protocol.

Participants

Eligibility criteria for this analysis were the same as previously published.[11,12] All of the patients included in the GUIDE-HF study are included in this analysis. Briefly, patients were ≥18 years old, with NYHA class II–IV HF, and had a HF hospitalization within 12 months prior to consent and/or elevated natriuretic peptide levels (BNP or NT-proBNP) within 30 days prior to consent, with thresholds pre-specified for each natriuretic peptide type, ejection fraction, and body mass index.[11]

Randomization and masking

Following successful implantation of the PA pressure sensor (CardioMEMS™, Abbott, Abbott Park, IL, USA), patients were randomly assigned 1:1 to the treatment group (patient management guided by PA pressures in addition to standard-of-care guideline-directed medical therapy) or the control group (standard-of-care patient management using guideline-directed medical therapy without provider access to PA pressures). Randomization was stratified by site and gender using randomly permuted blocks implemented with an electronic case report form (Oracle Clinical). The investigators were aware of the treatment assignments but did not have access to the PA pressures of patients in the control group. Patients were blinded to their study group assignment and had no access to their PA pressures. All patients were instructed to upload daily PA pressures, and investigator monitoring of patients' compliance with daily PA pressure uploads was provided for both groups. Specific methods were implemented to preserve appropriate patient blinding to treatment group assignment: (i) blinded, scripted site-to-patient interactions which were balanced between treatment groups; (ii) prohibiting access of blinded site personnel to PA pressures and treatment group assignments; and (iii) limiting post-implant PA pressures collected during hospitalizations. To maintain patient blinding and balance in site–patient interactions, each site designated blinded personnel for all site–patient communication related to HF management and contacted all patients in both groups at least once every 2 weeks for the first 3 months and then monthly until study completion. Any symptoms reported voluntarily by the patient to blinded personnel were documented, and a scripted response was used when applicable. Access to PA pressures and patient compliance within the Merlin.net website was restricted to unblinded members of the study team at each investigative site.

Follow-up clinical assessments

Following implantation and randomization, patients had follow-up visits for clinical assessments at 6 and 12 months post-implantation including 6-min hall walk (6MHW) tests and QoL measures, including the Kansas City Cardiomyopathy Questionnaire (KCCQ-12) and European Quality of Life–5 Dimensions–5 Level questionnaire (EQ-5D-5L). During COVID-19, follow-up visits were conducted remotely as needed, including QoL and adverse event data, apart from the 6MHW test. Details of the recommended response to elevation of PA pressures have been published.[11,12]

Outcomes

The primary endpoint was a composite of all-cause mortality and cumulative HF events at 12 months. HF events included urgent HF visits requiring i.v. diuretic therapy and hospitalizations for HF. Secondary endpoints at 12 months included the KCCQ-12, EQ-5D-5L, and 6MHW test. PA pressures, circulating natriuretic peptide levels, NYHA class, HF medications, site–patient contacts, and frequency of PA pressure uploads were measured. A blinded, independent Clinical Events Committee adjudicated whether adverse events met definitions for primary endpoint events. A blinded, independent Data Safety Monitoring Board advised the Sponsor regarding the continuing safety, validity, and scientific merit of the clinical trial.

Statistical analysis (including a COVID-19 impact analysis)

The effectiveness analysis population of the GUIDE-HF randomized arm included all randomized patients, and statistical comparisons were between treatment and control groups. All patients in this population were included in the primary endpoint analysis regardless of the duration of their inclusion in the trial, and all effectiveness analyses were performed from the point of randomization in the intent-to-treat population. The primary endpoint was analysed using the Andersen–Gill extension of the Cox proportional hazards model with robust sandwich estimate of variance. Model assumptions were evaluated as an early step in understanding the impact of COVID-19 in this trial. The assumption was assessed for the time period pre-COVID-19 using a censored dataset and methods including residual plots and non-parametric approaches. In addition to graphical visual inspection, linear hypothesis testing was performed by adding a time-varying covariate defined as randomization group-by-log follow-up time to the model as well as tests for non-zero slope of standardized Schoenfeld residuals vs. time. Evidence from these assessments supports the proportional hazards assumption as not violated for the period pre-COVID-19.

The potential impact of COVID-19 on all aspects of clinical trials has been discussed by the Heart Failure Association of the European Society of Cardiology, the European Medicines Agency, the Heart Failure Collaboratory, and the US Food and Drug Administration (FDA).[1,13–16] Sensitivity analyses were performed to assess the impact of the COVID-19 pandemic on the primary and secondary endpoints. To assess the impact of the timing of the COVID-19 pandemic—represented in analyses by the USA national emergency declaration date of 13 March 2020—a pre-specified sensitivity analysis was performed on the primary endpoint and its components in which event rates observed during subject follow-up occurring pre-COVID-19 were evaluated along with the rates observed during subject follow-up occurring during COVID-19 (see Supplementary material online, *Figure S1*). The pre-specified primary COVID-19 impact analysis compared the primary endpoint event rates pre-COVID-19 with those during COVID-19 utilizing a time-varying covariate within the Andersen–Gill model. This methodology allows for evaluation of statistical interaction between the two time periods along with evaluation of the primary endpoint pre-COVID-19. Previous trials impacted by COVID-19 have evaluated endpoints pre-COVID-19 using data censored at the start of the pandemic but without comparison with the period during COVID-19.[1] This pre-specified analysis was described in our 'Statistical Analysis Plan' and was reviewed and approved by the FDA, several months prior to the last patient follow-up and to data analysis. While we acknowledge that different interaction significance thresholds can be used, our statistical analysis plan pre-specified a significance level for all interaction terms at $P < 0.15$ (including the COVID-19 sensitivity analysis). To account for an increased probability of Type II error due to general interaction testing and the unplanned nature of COVID-19, we judged that a significance level of 0.15 is a reasonable threshold for assessing a potential change of treatment effect regarding its relationship to the timing of COVID-19 in this study. Baseline patient demographic data were stratified by order of enrolment between the first 500 vs. the second 500 patients randomized (*Table 1*) to assess whether patients with follow-up completed or nearly completed pre-COVID-19 differed from those with follow-up completed during COVID-19. Medication changes were analysed during the maintenance phase of the study (excluding the first 90 days after randomization), and differences in medication rates and changes in medication rates during COVID-19 between groups were evaluated using a Wilcoxon rank sum test. Site–patient contacts were analysed descriptively during the maintenance phase of the study (excluding the first 90 days after randomization) both for site-initiated blinded contacts and for all subject contact. PA pressures were analysed using a general linear model to analyse pressure at fixed time points (baseline, 6 months, and 12 months) and as an area under the pressure–time curve (AUC; calculated using the trapezoidal rule) of each patient's daily change in PA pressure from their baseline PA pressure.[17–21] Statistical analyses were performed using SAS software, version 9.4 or higher (SAS Institute).

Role of the funding source

Abbott (Abbott Park, IL, USA) sponsored the trial, selected the sites, and analysed the data. The primary endpoint and COVID-19 impact analyses were verified by an independent statistician.

Results

Populations

Patient characteristics were largely similar between populations with follow-up completed or nearly completed pre-COVID-19 to those with follow-up during COVID-19 (*Table 1*). However, the first 500 patients included a greater proportion of NYHA class II patients due to the study design limiting NYHA class II enrolment to 300 patients. The KCCQ-12 score and 6MHW distance were also elevated in the first 500 patients compared with the last 500 subjects.

Effects of COVID-19 on differential event rates in treatment vs. control groups

The COVID-19 sensitivity analysis demonstrated an interaction *P*-value of 0.11 (*Table 2*; Supplementary material online, *Figure S2*), which is lower than the pre-specified interaction *P*-value threshold of 0.15, and we concluded that the null hypothesis of no difference between pre-COVID-19 and during-COVID-19 periods could be rejected and subsequent analyses were merited for the time periods pre-COVID-19 and during COVID-19. There was a significantly lower primary endpoint event rate in the treatment group; 0.553 events/patient-year vs. 0.682 events/patient-year in the control group [hazard ratio (HR) 0.81, 95% confidence interval (CI) 0.66–1.00; $P = 0.049$] for events that occurred pre-COVID-19 (before 13 March 2020). This difference was driven by the reduction in HF events as there were no changes in all-cause mortality (*Table 2*). In contrast, considering only those events that occurred during the COVID-19 pandemic (13 March 2020 and after), there was no significant difference in the primary event rate between groups (HR 1.11, 95% CI 0.80–1.55; $P = 0.53$); the rate remained low at 0.597 events/patient-year in the treatment group but dropped unexpectedly by 21% to 0.536 events/patient-year in the control group (see Supplementary material online, *Figure S2*).

Provider-dependent factors

The number of times patients were contacted in the treatment vs. the control groups before and after the onset of COVID-19 are shown in *Figure 1*. The number of site-initiated (blinded) calls and the number of all subject contacts were similar in the treatment group compared with the control group both before and during COVID-19 (~1 contact/patient-month). Site-initiated calls were made because of an observed change in PA pressures or represented matching calls required by the protocol. All subject contact included site-initiated contacts, subject-initiated contacts, other contact between site and subject (e.g. office visit), and scheduled study follow-up visits. A site-initiated contact was counted only if the patient was successfully reached and acknowledged receipt of instructions. The equivalency of these data demonstrated the degree of compliance and maintenance of blind throughout follow-up in both groups both before and during COVID-19. In addition, there was no evidence of an increase in the number of patient contacts during COVID-19 and no evidence of a differential distribution between groups.

In general, there were frequent changes in medications throughout the GUIDE-HF study in both the treatment and control groups. However, pre-COVID-19, there were nearly twice as many medication changes in the treatment group compared with the control group, with 0.835 changes/patient-month in the treatment group vs. 0.475 changes/patient-month in controls ($P < 0.001$) (*Table 3*). During COVID-19, however, the monthly rate of medication changes fell in both groups, with a 19.2% reduction in the treatment group vs. a 10.7% reduction in controls to levels of medication

Table 1 Demographics stratified by enrolment order: first 500 vs. second 500 randomized

	First 500 subjects ($n = 500$)	Second 500 subjects ($n = 500$)	*P*-value
Age, years	69.4 ± 10.9 (500)	68.9 ± 11.2 (500)	0.66
Female sex	36.8% (184)	38.2% (191)	0.70
Race			
White	82.0% (410)	79.6% (398)	0.38
Black	17.4% (87)	18.6% (93)	0.68
Asian	0.0% (0)	0.2% (1)	1.00
American Indian or Alaskan Native	0.4% (2)	0.4% (2)	1.00
Pacific Islanders	0.0% (0)	0.0% (0)	
Other	0.4% (2)	1.4% (7)	0.18
Ethnicity			
Hispanic	3.6% (18)	3.0% (15)	0.72
Non-Hispanic	95.4% (477)	96.6% (483)	0.42
Unknown	1.0% (5)	0.4% (2)	0.45
Body mass index, kg/m2	32.9 ± 7.7 (500)	33.9 ± 9.0 (500)	0.14
NYHA class			
II	41.2% (206)	18.0% (90)	<0.0001
III	55.0% (275)	75.0% (375)	<0.0001
IV	3.8% (19)	7.0% (35)	0.035
Medical history			
Ischaemic aetiology	42.4% (212)	37.0% (185)	0.093
Previous myocardial infarction	30.6% (153)	29.8% (149)	0.84
Previous percutaneous coronary intervention	33.0% (165)	31.6% (158)	0.69
Previous coronary artery bypass grafting	29.0% (145)	25.2% (126)	0.20
Diabetes	47.0% (235)	53.8% (269)	0.037
Cerebrovascular accident	13.8% (69)	12.4% (62)	0.57
Atrial flutter or fibrillation	61.8% (309)	56.4% (282)	0.094
Vital signs and haemodynamic analyses			
Heart rate, bpm	74.0 ± 12.5 (500)	74.0 ± 12.3 (500)	0.94
Systolic blood pressure, mmHg	121.2 ± 18.4 (500)	121.2 ± 18.8 (500)	0.95
Diastolic blood pressure, mmHg	69.0 ± 11.2 (500)	69.1 ± 10.4 (500)	0.52
Left ventricular ejection fraction, %	39.8 ± 17.2 (500)	40.3 ± 17.0 (500)	0.62
Left ventricular ejection fraction >40%	45.8% (229)	48.0% (240)	0.53
PA systolic pressure, mmHg	44.8 ± 14.7 (500)	45.2 ± 13.9 (500)	0.27
PA diastolic pressure, mmHg	18.9 ± 7.7 (500)	18.8 ± 7.9 (500)	0.97
PA mean pressure, mmHg	29.3 ± 9.8 (500)	29.3 ± 9.7 (500)	0.68
Pulmonary capillary wedge pressure, mmHg	17.5 ± 7.9 (499)	17.3 ± 8.0 (499)	0.58
Cardiac output, L/min	4.74 ± 1.41 (500)	4.78 ± 2.64 (500)	0.18
Cardiac index, L/min/m^2	2.23 ± 0.60 (500)	2.23 ± 1.12 (500)	0.060

Continued

Table 1 *Continued*

	First 500 subjects ($n = 500$)	Second 500 subjects ($n = 500$)	*P*-value
Ambulatory haemodynamics during first week			
PA systolic pressure, mmHg	46.5 ± 14.0 (499)	46.0 ± 13.8 (497)	0.68
PA diastolic pressure, mmHg	23.0 ± 7.7 (499)	22.1 ± 7.4 (497)	0.11
PA mean pressure, mmHg	32.2 ± 10.0 (499)	31.5 ± 9.7 (497)	0.37
Heart rate, bpm	79.5 ± 11.8 (499)	78.7 ± 11.8 (497)	0.23
Laboratory analyses			
Serum creatinine level, μmol/L	130.1 ± 44.2 (493)	131.9 ± 48.8 (497)	0.84
eGFR, mL/min/1.73 m^2	53.7 ± 21.1 (492)	53.4 ± 21.0 (497)	0.82
BNP level, pg/mL	527.8 ± 701.5 (246)	544.2 ± 933.1 (271)	0.95
NT-proBNP level, pg/mL	2179 ± 3292 (232)	2474 ± 3266 (212)	0.88
Treatment history			
Previous cardiac resynchronization therapy	32.8% (164)	28.2% (141)	0.13
Previous implantation of defibrillator	43.4% (217)	40.2% (201)	0.34
Guideline-directed medical therapy			
ACE inhibitor, ARB, or ARNi	62.6% (313)	65.2% (326)	0.43
ARNi	27.0% (135)	29.8% (149)	0.36
Beta-blocker	88.2% (441)	89.0% (445)	0.77
Mineralocorticoid receptor antagonist	43.4% (217)	47.2% (236)	0.25
Loop diuretic	92.4% (462)	94.2% (471)	0.31
Thiazide diuretic	19.6% (98)	12.0% (60)	0.0013
Hydralazine	16.6% (83)	15.6% (78)	0.73
Nitrate	20.0% (100)	20.4% (102)	0.94
SGLT2 inhibitor[a]	0.7% (1)	2.0% (3)	0.62
Enrolment type			
HF hospitalization only	37.2% (186)	35.1% (175)	0.51
Elevated natriuretic peptide level only	41.0% (205)	47.5% (237)	0.042
HF hospitalization and elevated natriuretic peptide level	21.8% (109)	17.4% (87)	0.094
Patient-reported outcomes			
KCCQ-12 at baseline, overall summary score	57.0 ± 23.9 (495)	52.8 ± 23.9 (496)	0.0073
6MHW at baseline, m	241.8 ± 120.1 (481)	222.9 ± 122.4 (475)	0.025

Continuous variables, mean ± SD (sample size); categorial variables, % (sample size).
[a]SGLT2 (sodium–glucose co-transporter 2) inhibitor information was only collected at baseline in 143 patients in the treatment group and 149 patients in the control group.

changes that were closer between groups, with 0.675 changes/patient-month in the treatment group vs. 0.425 changes/patient-month in the control group. In addition, the direction in which medications were changed (increase, start, or resume a drug vs. decrease, stop, temporarily discontinue a drug) in treatment vs. control, pre- vs. during COVID-19 are presented in *Table 4*. In the control and treatment groups, the rates of increase and decrease in medication declined during COVID-19. The ratio of increases to decreases fell during COVID-19, i.e. there were fewer increases relative to decreases. Therefore, during COVID-19, there was no intensification of medical therapy; there was in fact a trend toward a decrease in intensification. The relationship between change in medication data and event rates in each group was considered. The treatment group primary event rate did not rise during COVID-19 despite the fact that the intensity of medical treatment decreased compared with pre-COVID-19. Thus, while the event rate fell in the control group, despite a decrease in management intensity, the treatment group event rate did not rise. In effect, both event rates were 'affected', but the control group effect was larger. Since the lowest event rates in either the treatment or control group pre- or during COVID-19

Table 2 Primary endpoint and components: split into pre- and during COVID-19

Endpoint[a]	Treatment ($n=497$) events (rate[b])	Control ($n=503$) events (rate[b])	Hazard ratio (95% CI), P-value[c]	
Pre-COVID-19 impact analysis: primary endpoint and components[d]				
HF hospitalization + urgent HF visits + death (primary endpoint)	**177 (0.553)**	**224 (0.682)**	**0.81 (0.66–1.00), $P=0.049$**	
HF events (HF Hospitalization + urgent HF visits) (secondary endpoint)	147 (0.450)	199 (0.595)	0.76 (0.61–0.95), $P=0.014$	
Urgent HF visits	23 (0.074)	23 (0.073)	1.02 (0.57–1.82), $P=0.95$	
HF hospitalization	124 (0.380)	176 (0.525)	0.72 (0.57–0.92), $P=0.0072$	
Death	30 (0.110)	25 (0.088)	1.24 (0.73–2.11), $P=0.42$	
All-cause hospitalization[e]	312 (0.976)	355 (1.080)	0.90 (0.77–1.06), $P=0.23$	
During-COVID-19 impact analysis: primary endpoint and components[d]				
				Interaction P-values[f]
HF hospitalization + urgent HF Visits + death (primary endpoint)	**76 (0.597)**	**65 (0.536)**	**1.11 (0.80–1.55), $P=0.53$**	$P=0.11$
HF events (HF hospitalization + urgent HF visits) (secondary endpoint)	66 (0.539)	53 (0.455)	1.19 (0.82–1.70), $P=0.36$	$P=0.036$
Urgent HF visits	5 (0.048)	4 (0.041)	1.19 (0.32–4.45), $P=0.80$	$P=0.83$
HF hospitalization	61 (0.490)	49 (0.414)	1.18 (0.81–1.73), $P=0.38$	$P=0.029$
Death	10 (0.067)	12 (0.085)	0.79 (0.35–1.83), $P=0.59$	$P=0.38$
All-cause hospitalization[e]	108 (0.821)	93 (0.744)	1.10 (0.83–1.47), $P=0.50$	$P=0.24$

[a]Endpoints include Clinical Events Committee-adjudicated heart failure (HF) hospitalizations or urgent HF visits with an admission date after the date of implant hospitalization discharge up to 395 days after the date of implant. All-cause deaths are included from implant date to 395 days after implant date.
[b]Event rate is an annualized rate estimated from the Andersen–Gill model.
[c]Hazard ratio, 95% confidence interval, and *P*-value estimated from the Andersen–Gill model with robust sandwich estimates.
[d]Events and rates represent the time period prior to COVID-19, defined as data collected up to 13 March 2020, or during COVID-19, defined as data collected after 13 March 2020. Contrast comparison hazard ratio, 95% confidence interval, and *P*-value estimated from the Andersen–Gill model with robust sandwich estimates.
[e]All-cause hospitalizations includes all adjudicated hospitalizations.
[f]Interaction *P*-value is a joint test on the interaction term of treatment group by COVID-19 analysis time period.

centred around ~0.55 events/patient-year, it is possible that this is a theoretical 'lowest' possible value in this population.

Disease-dependent factors

An improvement in the disease process itself, i.e. an improvement in HF, or an asymmetric worsening in HF progression in one of the two groups studied could have affected a reduction in cardiovascular events during COVID-19 and the loss of a differential effect of haemodynamically guided management. Progression of disease may be indicated by worsening of the following metrics: QoL scores (KCCQ-12 and EQ-5D-5L) or 6MHW distance; in contrast, regression of disease may be indicated by improvement in these metrics. There were no changes in mean value of KCCQ-12, EQ-5D-5L visual analogue scale (VAS), or 6MHW comparing pre-COVID-19 vs. during COVID-19 in either treatment or control for subjects with follow-up ending pre-COVID-19 vs. follow-up ending during COVID-19 (*Table 5*). *Table 6* delineates the quantification of missing data for each of KCCQ-12, EQ-5D-5L VAS, and 6MHW pre- vs. during COVID-19. The PA pressure data below also support these patterns and conclusions. Therefore, it appears unlikely that progression or regression of disease played a significant role in affecting the outcomes of this study.

A disproportionate change in the number of non-cardiovascular- or COVID-19-related hospitalizations or mortalities could have affected a reduction in cardiovascular events during COVID-19. The Clinical Events Committee adjudicated the causes and COVID-19 relatedness of all hospitalizations and mortalities in GUIDE-HF. There were seven events related or possibly related to COVID-19 during the trial—all occurred in the control group. There were no changes in the proportion of cardiovascular vs. non-cardiovascular events pre-COVID-19 vs. during COVID-19 in either the treatment or the control group. There were no differences in adverse events that could potentially be related to haemodynamically guided management (*Table 7*).

Patient-dependent factors

Patient compliance in obtaining and transmitting daily PA pressure readings was documented throughout follow-up, both before and during COVID-19, to be in the range of 80–90% (*Figure 2*). There

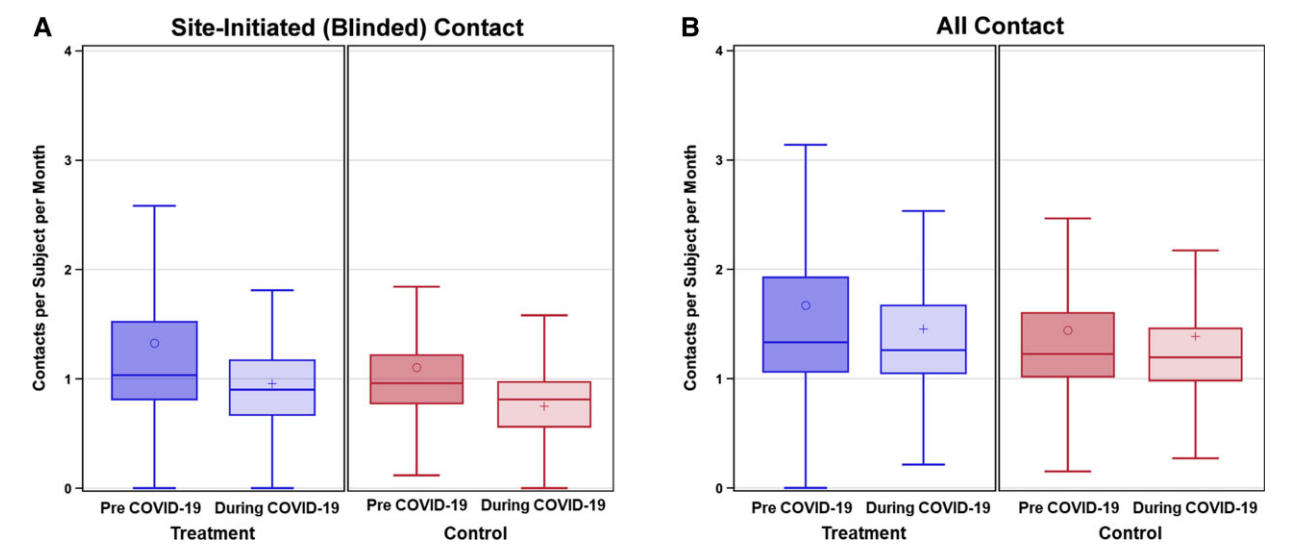


Figure 1 Number of patient contacts in the treatment and control groups before (blue) and after (red) onset of COVID-19. The number of site-initiated (blinded) calls (*A*) and the number of all subject contacts (*B*) were similar in the treatment group compared with the control group both before and during COVID-19. Site-initiated calls consisted of a change in pulmonary artery pressure-induced calls and all matching calls prescribed by the protocol. All subject contact includes site-initiated contacts, subject-initiated contacts, other contact between site and subject (e.g. office visit), and study follow-up visits. Patient contacts shown are after 90 days of follow-up to allow for equivalent comparison of protocol requirements for contact frequency between time periods.

Table 3 Changes in medication in treatment vs. control, before and during COVID-19

	Prior to COVID-19		During COVID-19	
	Med changes [monthly rate][a]	**Subjects with change (%)[b]**	**Med changes [monthly rate][a]**	**Subjects with change (%)[b]**
Treatment		***n* = 465**		***n* = 310**
Angiotensin-converting enzyme inhibitors	55 [0.022]	31 (6.7%)	8 [0.003]	8 (2.6%)
Angiotensin receptor blocker	30 [0.011]	20 (4.3%)	18 [0.011]	13 (4.2%)
Angiotensin receptor–neprilysin inhibitor	78 [0.025]	39 (8.4%)	32 [0.019]	19 (6.1%)
Beta-blockers	152 [0.058]	82 (17.6%)	82 [0.060]	44 (14.2%)
Mineralocorticoid receptor antagonist	145 [0.057]	75 (16.1%)	45 [0.029]	32 (10.3%)
Loop diuretics	1165 [0.429]	256 (55.1%)	539 [0.382]	149 (48.1%)
Thiazide diuretic	506 [0.172]	101 (21.7%)	154 [0.126]	51 (16.5%)
Nitrates	57 [0.019]	30 (6.5%)	22 [0.016]	13 (4.2%)
Vasodilators	61 [0.025]	38 (8.2%)	13 [0.011]	9 (2.9%)
SGLT2 inhibitor	3 [0.001]	3 (0.6%)	5 [0.002]	5 (1.6%)
Calcium channel blockers	33 [0.011]	22 (4.7%)	14 [0.010]	13 (4.2%)
Digoxin	9 [0.002]	5 (1.1%)	4 [0.003]	3 (1.0%)
Sinus node I_f channel inhibitors	6 [0.002]	4 (0.9%)	1 [0.000]	1 (0.3%)
Total	**2300 [0.835]**	**307 (66.0%)**	**937 [0.675]**	**178 (57.4%)**
COVID-19 total reduction (% reduction)			**0.160 [19.2%][c]**	**8.6% (13.0%)[d]**

Continued

Table 3 *Continued*

	Prior to COVID-19		During COVID-19	
	Med changes [monthly rate][a]	Subjects with change (%)[b]	Med changes [monthly rate][a]	Subjects with change (%)[b]
Control		***n* = 463**		***n* = 307**
Angiotensin-converting enzyme inhibitors	24 [0.010]	18 (3.9%)	17 [0.009]	10 (3.3%)
Angiotensin receptor blocker	32 [0.013]	22 (4.8%)	16 [0.011]	10 (3.3%)
Angiotensin receptor–neprilysin inhibitor	52 [0.016]	35 (7.6%)	15 [0.008]	10 (3.3%)
Beta-blockers	128 [0.049]	72 (15.6%)	77 [0.117]	44 (14.3%)
Mineralocorticoid receptor antagonist	94 [0.033]	54 (11.7%)	33 [0.020]	23 (7.5%)
Loop diuretics	631 [0.230]	176 (38.0%)	285 [0.166]	101 (32.9%)
Thiazide diuretic	213 [0.075]	59 (12.7%)	78 [0.057]	29 (9.4%)
Nitrates	37 [0.013]	24 (5.2%)	15 [0.009]	11 (3.6%)
Vasodilators	26 [0.017]	20 (4.3%)	21 [0.011]	12 (3.9%)
SGLT2 inhibitor	1 [0.001]	1 (0.2%)	5 [0.003]	5 (1.6%)
Calcium channel blockers	33 [0.014]	18 (3.9%)	12 [0.010]	9 (2.9%)
Digoxin	13 [0.004]	8 (1.7%)	5 [0.003]	4 (1.3%)
Sinus node I_f channel Inhibitors	1 [0.000]	1 (0.2%)	2 [0.001]	1 (0.3%)
Total	**1285 [0.475]**	**235 (50.8%)**	**581 [0.425]**	**129 (42.0%)**
COVID-19 total reduction (% reduction)			**0.051 [10.7%][c]**	**8.7% (17.2%)[d]**
Medication rate treatment vs. control *P*-value[e]	***P* < 0.0001**		***P* < 0.0001**	
Medication rate change Treatment vs. control *P*-value[f]			***P* = 0.3622**	

SGLT2 = sodium–glucose co-transporter 2.
[a]Total medication changes per category during the maintenance phase of the study (i.e. excluding the changes made during the first 90 days after randomization because of protocol-mandated medication titrations) and average monthly rate of change per category per subject.
[b]Total subjects with a medication change per category and percentage of subjects with a medication change per category.
[c]Absolute reduction of total medication change rate and the percentage reduction of the total medication change rate during COVID-19.
[d]Absolute change in the percentage of total subjects with a medication change and percentage reduction in the percentage of total subjects with a medication change during COVID-19.
[e]*P*-value testing medication rates between treatment and control groups from Wilcoxon rank sum test.
[f]*P*-value testing change in medication rates between treatment and control groups from Wilcoxon rank sum test.

Table 4 **Direction of medication changes (increase vs. decrease) in treatment vs. control, pre- vs. during COVID-19**

	Increase, start, resume	Decrease, stop, hold	Ratio increase/decrease	% change in ratio
Control				
Pre-COVID	0.375	0.273	1.374	
During COVID	0.202	0.178	1.135	−17.4%
Treatment				
Pre-COVID	0.666	0.41	1.624	
During COVID	0.32	0.216	1.481	−8.8%

1. Control and treatment groups, rate of increase and decrease in medication declined during COVID.
2. Ratio of increases to decreases falls during COVID; fewer increases relative to decreases; % Δ Negative #.
During COVID, there is no intensification of medical therapy; there is a decrease in intensification.

Table 5 Disease-dependent factor: quality of life and 6MHW test

Value at 12-month follow-up	Treatment	Control
KCCQ-12 overall summary score		
Follow-up ending prior to COVID-19	62.0 ± 24.0 (140)	62.9 ± 22.2 (140)
Follow-up ending during COVID-19	61.3 ± 24.7 (283)	58.2 ± 24.7 (271)
EQ-5D-5L VAS		
Follow-up ending prior to COVID-19	68.3 ± 20.9 (140)	71.5 ± 18.5 (141)
Follow-up ending during COVID-19	68.8 ± 19.8 (283)	66.4 ± 21.9 (271)
6MHW distance		
Follow-up ending prior to COVID-19	230.4 ± 133.2 (124)	245.1 ± 136.1 (130)
Follow-up ending during COVID-19	246.0 ± 130.0 (171)	230.7 ± 135.3 (168)

Data are presented as the mean ± SD (sample size)

Table 6 Effect of COVID-19 on missing data

Patient-reported outcome	Visit with partially missing data ($n = 942$)	Visit with completely missing data ($n = 942$)	Visit with any missing data ($n = 942$)	Subjects with any missing data ($n = 660$)
KCCQ-12				
Prior to COVID-19	2.2%	2.7%	4.9%	4.7%
During COVID-19	1.2%	5.1%	6.3%	6.1%
EQ-5D-5L				
Prior to COVID-19	0.2%	2.4%	2.7%	2.6%
During COVID-19	0.1%	5.0%	5.1%	4.9%
6MHW				
Prior to COVID-19	NA	11.5%	11.5%	10.2%
During COVID-19	NA	47.7%	47.7%	40.0%

Partially: patient-reported outcome data were incomplete; Completely: patient-reported outcome data were not collected; Any: patient-reported outcome data were incomplete or not collected.

Table 7 Adverse events: potentially related to haemodynamically guided management

Adverse event	Pre-COVID-19				During COVID-19			
	Treatment ($n = 497$)		Control ($n = 503$)		Treatment ($n = 310$)		Control ($N = 307$)	
	Events [rate]	% Subjects	Events [rate]	% Subjects with event	Events [rate]	% Subjects with event	Events [Rate]	% Subjects with Event
Hypotension	15 [4.56]	2.6% (13/497)	11 [3.26]	2.2% (11/503)	0 [0.00]	0.0% (0/310)	2 [1.56]	0.7% (2/307)
Hypovolaemia	8 [2.43]	1.6% (8/497)	3 [0.89]	0.6% (3/503)	1 [0.74]	0.3% (1/310)	2 [1.56]	0.7% (2/307)
Renal failure	23 [7.00]	3.8% (19/497)	22 [6.51]	4.2% (21/503)	3 [2.23]	0.6% (2/310)	14 [10.9]	3.9% (12/307)
Hyperkalaemia	1 [0.30]	0.2% (1/497)	1 [0.30]	0.2% (1/503)	0 [0.00]	0.0% (0/310)	0 [0.0]	0.0% (0/307)
Hypokalaemia	1 [0.30]	0.2% (1/497)	2 [0.59]	0.4% (2/503)	0 [0.00]	0.0% (0/310)	1 [0.78]	0.3% (1/307)

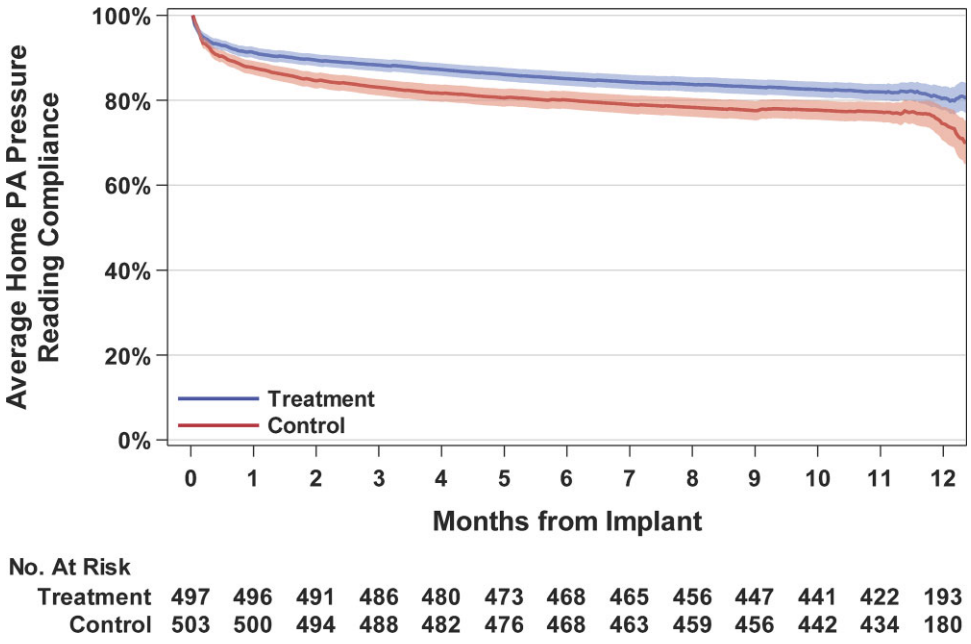


Figure 2 Average patient compliance in obtaining and transmitting daily pulmonary artery (PA) pressure readings. Data demonstrate good subject compliance overall throughout follow-up, both before and during COVID-19 (~80–90%). There was a slight decline in PA pressure reading compliance observed over time (similar to that observed in CHAMPION) with slightly less compliance in the control group, but there were no statistically significant differences between groups at any follow-up time.

was a slight decline in pressure reading compliance observed over time, with non-significant lower compliance in the control group, but there were no clinically relevant changes between the groups over time.

Overall during the total follow-up time period, daily AUC for mean PA pressure decreased in both treatment and control groups, with significantly greater reduction in the treatment group −792.7 ± 1767 mmHg-days vs. control −582.9 ± 1698.1 mmHg-days ($P = 0.0402$) (*Table 8*; Supplementary material online, *Figure S7A*). Pre-COVID-19, a reduction of the AUC was observed in both groups, with significantly greater reduction in the treatment group (−518 ± 1327 mmHg-days vs. control −324 ± 1329 mmHg-days; $P = 0.014$) (*Table 8*; Supplementary material online, *Figure S7B* and Supplementary material online, *Table S2A*). To examine changes in AUC specific to the time period during COVID-19, a new baseline value was established as of COVID-19 onset (13 March 2020) and AUC calculations restarted. During COVID-19, a small reduction of the AUC was observed in both groups; however, there were no significant differences between the treatment and control groups (*Table 8*; Supplementary material online, *Figure S7C* and Supplementary material online, *Table S2B*).

Overall, during the total follow-up time period, daily mean PA pressure decreased in both treatment and control groups, with significantly greater reduction in the treatment group (mean PA pressure decreased from baseline to 12 months by −2.4 ± 5.2 mmHg) vs. the control group (−1.7 ± 5.0 mmHg, $P = 0.033$) (*Table 8*; *Figure 3A*). During the pre-COVID-19 period, a reduction in daily mean PA pressure was observed in both groups, with significantly greater reduction in the treatment group (mean PA pressure decreased from baseline to 12 months by −2.1 ± 4.8 mmHg) vs. the control group (−1.4 ± 4.8 mmHg, $P = 0.016$) (*Table 8*; *Figure 3B*). During COVID, there were small changes in daily mean PA pressure in both groups, with no significant differences between groups (*Table 8*; *Figure 3C*).

Similar data patterns were seen using PA systolic and diastolic pressures (*Table 8*; Supplementary material online, *Figures S4–S6*).

Discussion

Data obtained from the GUIDE-HF trial provided a unique opportunity to examine several factors potentially related to the changes in the primary event rate and the loss of the differential effects on the primary event rate between treatment and control groups that occurred in GUIDE-HF and similar findings that have been observed in other studies performed during the COVID-19 pandemic.[1] These GUIDE-HF data support several novel findings. First, the decrease in the number of primary events, including HF events, that occurred during COVID-19 in GUIDE-HF was not associated with provider-dependent intensification of medical care. Intensification of medical care could have been evident by an increase in the number of times a patient was contacted by the study site team or an increase in the number of medication changes made. Neither occurred during COVID-19; the number of patient contacts was unchanged and the number of medication changes was reduced. Second, there was no evidence that the underlying disease progression common to all patients with HF was modified during COVID-19. Third, there was no evidence that severe COVID-19 infections differentially affected event rates in the two study groups. Fourth, the decrease in the

Table 8 Changes in PA pressures in treatment vs. control groups pre-COVID-19 and during COVID-19

PA pressure mean ± SD, median, [95% CI]	Treatment ($n = 497$)	Pre-COVID-19 Within-group *P*-value	Control ($n = 499$)	Within-group *P*-value	Between-group *P*-value
First week (mmHg)[a]					
Mean	31.8 ± 10.2, 30.9 [30.9–32.7]		31.9 ± 9.6 31.3 [31.1–32.8]		0.88[b]
Systolic	46.3 ± 14.4, 44.7 [45.0–47.6]		46.2 ± 13.3, 44.7 [45.0–47.3]		0.87[b]
Diastolic	22.4 ± 7.8, 21.8 [21.7–23.1]		22.7 ± 7.4, 22.2 [22.1–23.4]		0.48[b]
AUC (mmHg-days)[c]					
Mean	−518.0 ± 1327.0, −312.8 [−635.0 to −401.1]	<0.0001	−324.2 ± 1328.5 −199.5 [−441.1 to −207.4]	<0.0001	0.014[d]
Systolic	−622.8 ± 1738.6, −373.3 [−776.0 to −469.6]	<0.0001	−337.0 ± 1766.2, −231.7 [−492.4 to −181.7]	<0.0001	0.0083[d]
Diastolic	−450.4 ± 1053.1, −272.0 [−543.2 to −357.6]	<0.0001	−331.3 ± 1053.4, −232.2 [−423.9 to −238.6]	<0.0001	0.043[d]
Δ from baseline to 12 months[e]					
Mean	−2.1 ± 4.8, −1.7 [−2.5 to −1.7]	<0.0001	−1.4 ± 4.8, −1.5 [−1.8 to −1.0]	<0.0001	0.016[d]
Systolic	−2.5 ± 6.3, −1.8 [−3.1 to −2.0]	<0.0001	−1.5 ± 6.5, −1.6 [−2.1 to −0.9]	<0.0001	0.0088[d]
Diastolic	−1.8 ± 3.8, −1.4 [−2.1 to −1.5]	<0.0001	−1.4 ± 3.8, −1.3 [−1.7 to −1.1]	<0.0001	0.044[d]
During COVID-19					
PA pressure mean ± SD, median, [95% CI]	**Treatment** ($n = 310$)	Within-group *P*-value[f]	Control ($n = 307$)	Within-group *P*-value[f]	Between-group *P*-value
First week (mmHg)[a]					
Mean	28.2 ± 10.0, 26.8 [27.0–29.3]		29.1 ± 10.6, 28.4 [27.8–30.4]		0.29[b]
Systolic	41.8 ± 14.0, 39.9 [40.2–43.5]		43.2 ± 14.2, 41.3 [41.5–45.0]		0.25[b]
Diastolic	19.2 ± 7.9, 18.3 [18.3–20.1]		19.9 ± 8.6, 20.0 [18.9–21.0]		0.31[b]
AUC (mmHg-days)[c]					
Mean	−98.0 ± 687.6, −21.71 [−178.4 to −17.5]	0.017	−100.7 ± 572.6, −10.1 [−170.8 to −30.6]	0.0050	0.87[d]
Systolic	−127.1 ± 899.3, −34.9 [−232.3 to −21.9]	0.018	−110.6 ± 743.6, −15.7 [−201.6 to −19.6]	0.017	0.64[d]
Diastolic	−70.6 ± 560.1, −5.3 [−136.1 to −5.1]	0.035	−99.8 ± 485.7, −12.5 [−159.3 to −40.4]	0.0011	0.65[d]

Continued

Table 8 *Continued*

PA pressure mean ± SD, median, [95% CI]	Treatment ($n = 497$)	Pre-COVID-19 Within-group *P*-value	Control ($n = 499$)	Within-group *P*-value	Between-group *P*-value
Δ from baseline to 12 months[e]					
Mean	−0.4 ± 3.5, −0.3 [−0.9 to −0.0]	0.030	−0.5 ± 3.5, −0.3 [−0.9 to −0.1]	0.024	0.96[d]
Systolic	−0.6 ± 4.6, −0.4 [−1.1 to −0.0]	0.033	−0.6 ± 4.7, −0.2 [−1.2 to −0.0]	0.034	0.89[d]
Diastolic	−0.3 ± 2.9, −0.1 [−0.7 to 0.0]	0.052	−0.5 ± 2.9, −0.3 [−0.8 to −0.1]	0.0092	0.71[d]

[a]Average of the first week (7 days) of home PA pressure readings post-discharge from the implant hospitalization.
[b]*P*-value testing between groups using *t*-test with unequal variances.
[c]AUC (area under the curve) is the cumulative area between change from baseline pressure and baseline pressure over 12 months of follow-up from implant.
[d]*P*-value testing between-groups general linear model adjusted for baseline PA mean pressure.
[e]Average change is the average pressure difference from baseline over 12 months of follow-up.
[f]Within-group *P*-value testing difference from zero using one-sample *t*-test.

primary event rate during COVID-19 was not associated with worsening haemodynamic abnormalities or the development of more advanced and decompensated HF status. In fact, during COVID-19, the daily measured mean PA pressure and the cumulative change in mean PA pressure (AUC) fell in both the control and treatment groups in a similar manner. Taken together, these data suggest, but do not definitively prove, that changes in patient-dependent factors may be most likely to be responsible for the observed changes in the primary event rate and the loss of the differential effects on the primary event rate between treatment and control groups during COVID-19.

Relationship between medication optimization and measured pressures

After PA sensor implantation, there was a period of medication optimization. Once PA pressures were optimized, patients entered a maintenance phase (typically after ∼3 months) in which further changes in medications were guided by interval changes in pressures. All patients had been followed for at least 3 months at the onset of COVID-19, suggesting that differences in medication optimization alone, particularly as it related to timing of the COVID-19 pandemic, are unlikely to be responsible for loss of group differences during COVID-19. However, the time course of the PA pressure changes over time in each group at each time period do provide some insights. During the pre-COVID-19 period, after ∼5 months of follow-up, pressures in the control group rose while pressures in the treatment group fell. While neither of these directional changes is necessarily 'statistically significant', we interpret these data to suggest that continued 'active haemodynamically guided management', even after the optimization period, resulted in continued declines in pressure in the treatment group pre-COVID-19. This is aligned with the CHAMPION trial, in which the effects of haemodynamically directed management on study outcomes did not diminish after the optimization phase;[18,19,22] rather, the annualized rate of HF hospitalizations continued to fall over a 2-year time period.

However, a different pattern in pressure over time emerged during COVID-19. In both the control and treatment groups, pressures fell continuously during follow-up, with no differentiating pattern emerging in the control vs. treatment group. We interpret these data to suggest that the presence of COVID-19 and changes in behavioural patterns in both the control and treatment groups influenced the outcomes and were not dependent on the optimization period changes.

Effects of COVID-19 pandemic mandates

The COVID-19 pandemic mandated social distancing, business restrictions, mask wearing, and teleworking that may have had several effects on patient-dependent factors that could alter measured outcomes. For example, there has been a significant decrease in the incidence of non-COVID-19-related infectious diseases such as influenza.[23] Influenza and other communicable illnesses are known to increase the rate of cardiovascular events in patients with chronic HF. The effects of these mandates on other patient-dependent factors are not as clear. For example, it appears from some studies that the overall activity level may have decreased, with an associated increase (or constant) calorie consumption leading to weight

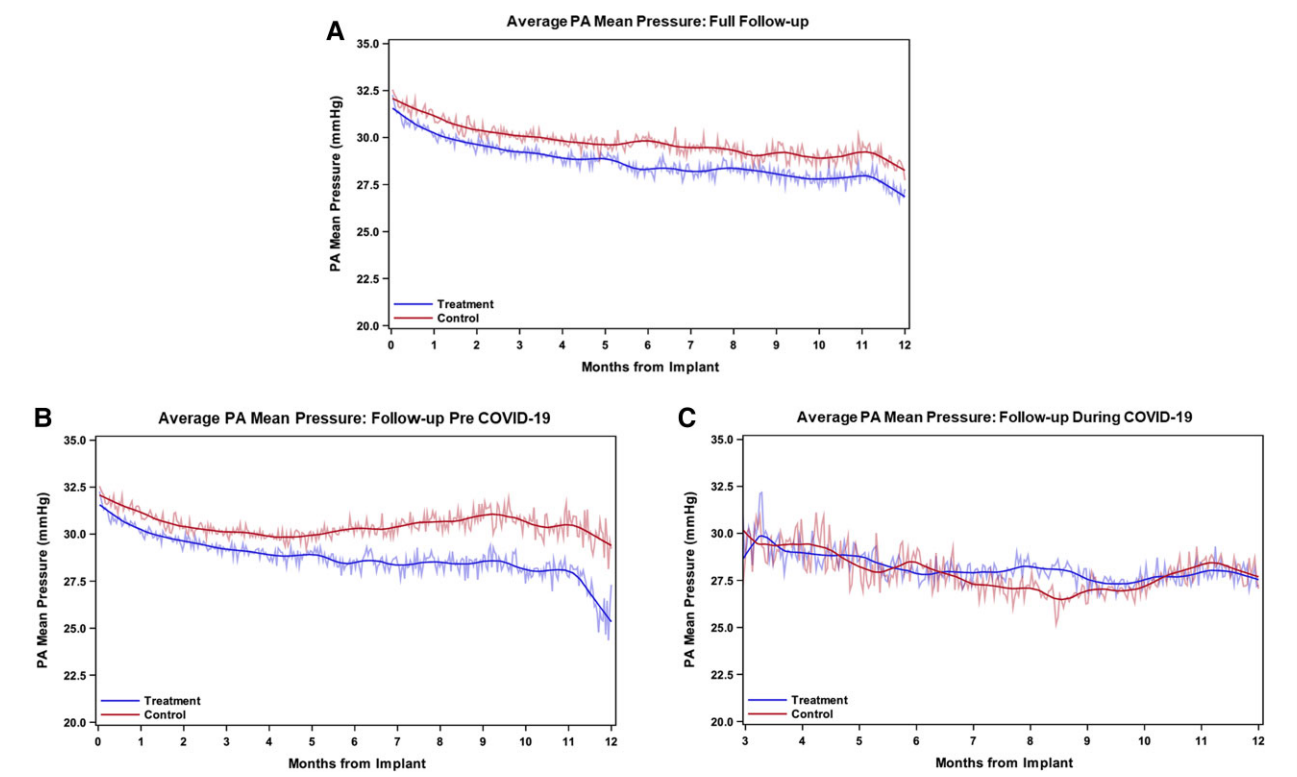


Figure 3 Average daily mean pulmonary artery (PA) pressure data in treatment vs. control groups before and during COVID-19. Baseline values are the average of the first 7 days of home PA pressure readings. The thicker lines represent the trend lines and thin lines represent the raw data. (*A*) Average daily mean PA pressure data in the treatment vs. control groups for the total follow-up period. A reduction in daily mean PA pressure was observed in both groups, with significantly greater reduction in the treatment group (mean PA pressure decreased from baseline to 12 months by -2.4 ± 5.2 mmHg) vs. control (-1.7 ± 5.0 mmHg, $P = 0.033$). (*B*) Average daily mean PA pressure data in the treatment vs. control groups for the pre-COVID-19 follow-up period. A reduction in daily mean PA pressure was observed in both groups, with significantly greater reduction in the treatment group (mean PA pressure decreased from baseline to 12 months by -2.1 ± 4.8 mmHg) vs. control (-1.4 ± 4.8 mmHg, $P = 0.0159$). (*C*) Average daily mean PA pressure data in the treatment vs. control groups for the during COVID follow-up period. During COVID-19 there were negligible changes in daily mean PA pressure in both groups, with no significant differences between groups.

gain.[24,25] In HF patients, particularly those with preserved ejection fraction, weight gain has been associated with disease progression and increased likelihood of cardiovascular events. In contrast, some patients may have increased at-home exercise (using a home gym), increased the number and quality of home-prepared meals rather than commercially prepared meals, and maintained (or decreased) body weight. Diet changes with fewer commercially prepared components would be expected to have a marked decrease in sodium chloride and to reduce filling pressures and blood pressure. Patients may have also been more compliant with their medication regimen while staying at home, thus improving overall outcomes. While social isolation may have decreased the incidence of non-COVID-19-related infectious diseases, it may also have contributed to increased emotional stress, depression, alcohol consumption, and inactivity, all of which may increase activation of the sympathetic nervous system and increased cardiovascular events.[26,27] No clear conclusions can be reached from the data provided by GUIDE-HF with respect to these factors. In contrast, the observed decrease in the primary event rate and the observed decrease in PA pressures support the presence of a change in an incompletely defined set of patient-dependent factors that contributed to these results.

An additional patient-dependent factor postulated to affect the decreases in hospitalization rate is fear-based avoidance of seeking healthcare services, even with extreme symptoms, hoping to avoid exposure to COVID-19. This behaviour may have a direct impact on mortality, in both HF and other acute cardiovascular emergencies such as myocardial infarction. Indeed, dramatic increases in at-home deaths were reported in Italian and US COVID-19 epicentres that were temporally associated with decreased emergent visits for acute myocardial infarction and HF. Increased at-home mortality may be the result of inappropriate healthcare avoidance. Patient reluctance to access outpatient or inpatient clinical care, and patient choice to delay care even when symptomatic, should have resulted in hospitalizations of patients with more advanced disease, more intense and prolonged hospital care, and increased hospital mortality. However, the majority of published studies to date do not support these expected outcomes. Instead, patients admitted with HF during COVID-19 did not have more advanced disease and had similar lengths of stay and in-hospital mortality compared with

pre-COVID-19 time periods.[28–32] Control and treatment subjects in the GUIDE-HF trial did not have an increase in cardiovascular events, including mortality, or worsened haemodynamic decompensation during the COVID-19 pandemic. In fact, disease severity based on haemodynamic assessment improved during the time period that cardiovascular events declined. The intensity of medical management as judged by the number of changes made in medications/patient-month declined in both control and treatment groups. Despite this 'reduction' in treatment intensity, event rates (and PA pressure) declined in the control group and remained unchanged in the treatment group during COVID-19.

Clinical, research, and regulatory issues

Analyses performed in this study were motivated by several clinical, research, and regulatory issues that have arisen during the COVID-19 pandemic. Clinical data reported from centres in the USA, Europe, and Asia showed a decrease in the number of HF hospitalizations when comparing 2019 pre-COVID-19 with 2020 during COVID-19 time periods.[1–10] These percentage reductions have varied from ~25% to 75%, but average ~40%.

Because the COVID-19 pandemic has functionally affected HF epidemiology,[4,5] it has also presented an unpredictable threat to the conduct of clinical trials and interpretation of the results.[13–16] Based on recommendations by the Heart Failure Association of the European Society of Cardiology,[13] the European Medicines Agency,[14] and the US FDA,[15] it has been suggested that the statistical analysis plans for RCTs performed during the pandemic should include a pre-COVID-19 sensitivity analysis, analyse data prior to a date related to the declaration of the COVID-19 pandemic, and prespecify a revised statistical analysis plan before locking the database. These recommendations were followed with pre-specified statistical analyses of the primary endpoints in GUIDE-HF and provide the rationale for the data analysis performed in this study. Since the COVID-19 sensitivity analysis demonstrated an interaction *P*-value of 0.11, which is lower than the pre-specified interaction *P*-value threshold of 0.15, evidence supported a difference between periods pre- and during COVID-19, and subsequent analyses were merited for the time periods prior to and during COVID-19. Given the significant treatment × period interaction and the change in directionality of treatment effect between periods, we also compared the event rate change within each treatment arm pre-COVID-19 and during COVID-19. The change in HR during COVID-19 seems to be largely due to a reduction in the event rate for the control group during COVID-19 compared with the event rate in the control group pre-COVID-19. We acknowledge that the *P*-value, in comparing the event rate pre- vs. during COVID-19 in the control group, was not significant ($P = 0.12$). However, the intent of this study is not to claim significance in the reduction of events within the control group but—given the significant treatment × period interaction for COVID-19—to evaluate what may have changed during COVID-19 to explain the loss of treatment effect during COVID-19. These data will be important to the evaluation of a number of trials that collected endpoints during the pandemic and to those trials that continue to do so. The GUIDE-HF study contains unique data collected during the COVID-19 pandemic which can provide an important perspective regarding patient status during the pandemic, including medications, PA pressures, and subject contact.

Limitations

The GUIDE-HF trial was designed and initiated well before the COVID-19 pandemic. Thus, the data points measured in the GUIDE-HF trial were not designed to comprehensively and specifically answer the question: why did HF event rates change during the COVID-19 pandemic? In retrospect, several patient-dependent measurable factors would have further informed and potentially supported the conclusions presented above. For example, the quantification of dietary composition and quality, activity levels, socioeconomic factors, medication availability and compliance, changes in emotional stress, and many other foreseeable and unforeseeable issues could have contributed to patient-dependent factors that would have helped to explain the outcomes of GUIDE-HF and other trials performed during COVID-19. However, the limitations in this study imposed by the absence of all possible data should not impede our efforts to draw at least hypothesis-generating conclusions from the unique data that were available in the GUIDE-HF trial and interpret these data in light of other published data that may support these conclusions. Furthermore, the GUIDE-HF trial does provide reasonably definitive data that rule out some possible explanations for the changes in event rates seen during the COVID-19 pandemic that would not have been possible to assess without the measurements available in this trial.

Conclusions

In the GUIDE-HF study, during COVID-19, the primary event rate decreased in the control group and remained low in the treatment group, resulting in an effacement of group differences and a loss in the treatment effects that were present pre-COVID-19. These outcomes did not appear to result from changes in provider-dependent or disease-dependent factors. PA pressures decreased despite a reduction in the number of provider-prescribed medication changes in both groups. These data suggest that patient-dependent factors may have played an important role in these outcomes.

Contributors

M.R.Z., A.S.D., and J.L. contributed to study design and writing of the report. M.R.C., A.D., A.M., M.R.M., S.P., S.F.S., F.S., N.J., P.S., and P.B.A. contributed to study design. J.H. contributed to the study design and data analyses. J.L., M.R.C., F.S., C.C., A.G., J.G., S.H., and O.J. contributed to data collection and provision of patients. All authors reviewed the data analyses, contributed to data interpretation and writing of the report, and approved the final version of the submitted report.

Data sharing

No aggregate or patient-level data collected in the trial will be made available to others. The trial protocol that includes the pre-specified statistical analyses is in the Supplementary material.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Acknowledgements

This study was funded by Abbott. We thank the patients, their families, the investigators, and research coordinators for their participation in and dedication to this study.

Conflict of interest: J.L. has received research grants from Astra-Zeneca, Sensible Medical, and Volumetrix, and is a consultant for Abbott, Alleviant Medical, Astra-Zeneca, Boehringer-Ingelheim, Boston Scientific, CVRx, Edwards, Impulse Dynamics, and VWave. A.S.D. has received research grants from Alnylam, Astra-Zeneca, Bayer, and Novartis, is a consultant for Alnylam, Astra-Zeneca, Amgen, Biofourmis, Boston Scientific, Boehringer-Ingelheim, Cytokinetics, DalCor Pharma, Lexicon, Merck, Novartis, Relypsa, and Regeneron, and has received personal fees from Lupin Pharma and Sun Pharma. M.R.M. is a consultant for Medtronic, Janssen, Portola, Bayer, Triple Gene, and Baim Institute for Clinical Research, has served on advisory boards for Abbott and Mesoblast, has served on the Clinical Events Committee for GUIDE-HF through the Baim Institute for Clinical Research, and has stock in NuPulseCV, Leviticus, and FineHeart. S.F.S. has received research grants from Medtronic and Zoll, is a consultant for Abbott, Medtronic, and Milestone Pharmaceutical, and has received personal fees from Medtronic and Zoll. F.S. has received research grants from Amgen and is a consultant for Abbott. M.R.Z., A.D., A.M., S.P., M.R.C., and C.C. are consultants for Abbott. O.J. has received personal fees from Astra-Zeneca. S.H. is a consultant for Abbott, Abiomed, CareDx, Natera, and Medtronic, has received personal fees from CareDx and Novartis, and has served on advisory boards for Abbott, Abiomed, and Medtronic. A.G. has received personal fees from Abbott. N.J., P.S., J.H., and P.B.A. are employees of Abbott. All other authors declare no competing interests.

References

1. Ponikowski P, Kirwan BA, Anker SD, McDonagh T, Dorobantu M, Drozdz J, *et al.* Ferric carboxymaltose for iron deficiency at discharge after acute heart failure: a multicentre, double-blind, randomised, controlled trial. *Lancet* 2020;**396**: 1895–1904.
2. DeFilippis EM, Reza N, Donald E, Givertz MM, Lindenfeld J, Jessup M. Considerations for heart failure care during the COVID-19 pandemic. *JACC Heart Fail* 2020;**8**: 681–691.
3. Cox ZL, Lai P, Lindenfeld J. Decreases in acute heart failure hospitalizations during COVID-19. *Eur J Heart Fail* 2020;**22**:1045–1046.
4. Mafham MM, Spata E, Goldacre R, Gair D, Curnow P, Bray M, *et al.* COVID-19 pandemic and admission rates for and management of acute coronary syndromes in England. *Lancet* 2020;**396**:381–389.
5. Sokolski M, Gajewski P, Zymlinski R, Biegus J, Ten Berg JM, Bor W, *et al.* Impact of coronavirus disease 2019 (COVID-19) outbreak on acute admissions at the emergency and cardiology departments across Europe. *Am J Med* 2021;**134**:482–489.
6. Toner L, Koshy AN, Ko J, Driscoll A, Farouque O. Clinical characteristics and trends in heart failure hospitalizations: an Australian experience during the COVID-19 lockdown. *JACC Heart Fail* 2020;**8**:872–875.
7. Cannatà A, Bromage DI, Rind IA, Gregorio C, Bannister C, Albarjas M, *et al.* Temporal trends in decompensated heart failure and outcomes during COVID-19: a multisite report from heart failure referral centres in London. *Eur J Heart Fail* 2020;**22**:2219–2224.
8. Charman SJ, Velicki L, Okwose NC, Harwood A, McGregor G, Ristic A, *et al.* Insights into heart failure hospitalizations, management, and services during and beyond COVID-19. *ESC Heart Fail* 2021;**8**:175–182.
9. Hall ME, Vaduganathan M, Khan MS, Papadimitriou L, Long RC, Hernandez GA, *et al.* Reductions in heart failure hospitalizations during the COVID-19 pandemic. *J Card Fail* 2020;**26**:462–463.
10. Rao VN, Kelsey MD, Kelsey AM, Russell SD, Mentz RJ, Patel MR, *et al.* Acute cardiovascular hospitalizations and illness severity before and during the COVID-19 pandemic. *Clin Cardiol* 2021;**44**:656–664.
11. Lindenfeld J, Abraham WT, Maisel A, Zile M, Smart F, Costanzo MR, *et al.* Hemodynamic-GUIDEd management of Heart Failure (GUIDE-HF). *Am Heart J* 2019;**214**:18–27.
12. Lindenfeld J, Zile MR, Desai AS, Bhatt K, Ducharme A, Horstmanshof D, *et al.* Haemodynamic-guided management of heart failure (GUIDE-HF): a randomised controlled trial. *Lancet* 2021;**398**:991–1001.
13. Anker SD, Butler J, Khan MS, Abraham WT, Bauersachs J, Bocchi E, *et al.* Conducting clinical trials in heart failure during (and after) the COVID-19 pandemic: an Expert Consensus Position Paper from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). *Eur Heart J* 2020; **41**: 2109–2117.
14. European Medicines Agency. Guidance on the management of clinical trials during the COVID-19 (coronavirus) pandemic. April 2, 2021 (version 4). https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/guidanceclinicaltrials_covid19_en.pdf (22 April 2021).
15. US Food and Drug Administration. FDA guidance of conduct of clinical trials of medical products during COVID-19 public health emergency. March 2020 (Updated January 27, 2021). https://www.fda.gov/media/136238/download (17 February 2021).
16. Psotka MA, Abraham WT, Fiuzat M, Filippatos G, Lindenfeld J, Ahmad T, *et al.* Conduct of clinical trials in the era of COVID-19: JACC scientific expert panel. *J Am Coll Cardiol* 2020;**76**:2368–2378.
17. Zile MR, Adamson PB, Cho YK, Bennett TD, Bourge RC, Aaron MF, *et al.* Hemodynamic factors associated with acute decompensated heart failure: part 1—insights into pathophysiology. *J Card Fail* 2011;**17**:282–291.
18. Abraham WT, Adamson PB, Bourge RC, Aaron MF, Costanzo MR, Stevenson LW, *et al.* Wireless pulmonary artery haemodynamic monitoring in chronic heart failure: a randomised controlled trial. *Lancet* 2011;**377**:658–666.
19. Abraham WT, Stevenson LW, Bourge RC, Lindenfeld JA, Bauman JG, Adamson PB. Sustained efficacy of pulmonary artery pressure to guide adjustment of chronic heart failure therapy: complete follow-up results from the CHAMPION randomised trial. *Lancet* 2016;**387**:453–461.
20. Zile MR, Bennett TD, St John Sutton M, Cho YK, Adamson PB, Aaron MF, *et al.* Transition from chronic compensated to acute decompensated heart failure: pathophysiological insights obtained from continuous monitoring of intracardiac pressures. *Circulation* 2008;**118**:1433–1441.
21. Zile MR, Bennett TD, El Hajj S, Kueffer FJ, Baicu CF, Abraham WT, *et al.* Intracardiac pressures measured using an implantable hemodynamic monitor: relationship to mortality in patients with chronic heart failure. *Circ Heart Fail* 2017;**10**: e003594.
22. Shavelle DM, Desai AS, Abraham WT, Bourge RC, Raval N, Rathman LD, *et al.* Lower rates of heart failure and all-cause hospitalizations during pulmonary artery pressure-guided therapy for ambulatory heart failure: one-year outcomes from the CardioMEMS post-approval study. *Circ Heart Fail* 2020;**13**:e006863.
23. Zile MR, Koehler J, Sarkar S, Butler J. Prediction of worsening heart failure events and all-cause mortality using an individualized risk stratification strategy. *ESC Heart Fail* 2020;**7**:4277–4289.
24. Boehmer JP, Hariharan R, Devecchi FG, Smith AL, Molon G, Capucci A, *et al.* A multisensor algorithm predicts heart failure events in patients with implanted devices: results from the MultiSENSE study. *JACC Heart Fail* 2017;**5**:216–225.
25. Olsen SJ, Azziz-Baumgartner E, Budd AP, Brammer L, Sullivan S, Pineda RF, *et al.* Decreased influenza activity during the COVID-19 pandemic—United States, Australia, Chile, and South Africa, 2020. *MMWR Morb Mortal Wkly Rep* 2020;**69**: 1305–1309.
26. Sassone B, Mandini S, Grazzi G, Mazzoni G, Myers J, Pasanisi G. Impact of COVID-19 pandemic on physical activity in patients with implantable cardioverter-defibrillators. *J Cardiopulm Rehabil Prev* 2020;**40**:285–286.
27. Tison GH, Avram R, Kuhar P, Abreau S, Marcus GM, Pletcher MJ, *et al.* Worldwide effect of COVID-19 on physical activity: a descriptive study. *Ann Intern Med* 2020; **173**:767–770.
28. Cousino MK, Pasquali SK, Romano JC, Norris MD, Yu S, Reichle G, *et al.* Impact of the COVID-19 pandemic on CHD care and emotional wellbeing. *Cardiol Young* 2021; **31**:822–828.
29. Cleland JGF, Pellicori P. To master heart failure, first master congestion. *Lancet* 2021; **398**:935–936.
30. Severino P, D'Amato A, Saglietto A, D'Ascenzo F, Marini C, Schiavone M. Reduction in heart failure hospitalization rate during coronavirus disease 19 pandemic outbreak. *ESC Heart Failure* 2020;**7**:4182–4188.
31. Basso C, Leone O, Rizzo S, De Gaspari M, van der Wal AC, Aubry MC, *et al.* Pathological features of COVID-19-associated myocardial injury: a multicentre cardiovascular pathology study. *Eur Heart J* 2020;**41**:3827–3835.
32. Fauvel C, Weizman O, Trimaille A, Mika D, Pommier T, Pace N, *et al.* Pulmonary embolism in COVID-19 patients: a French multicentre cohort study. *Eur Heart J* 2020;**41**:3058–3068.