Haemodynamic-guided management of heart failure (GUIDE-HF): a randomised controlled trial

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Summary

Background Previous studies have suggested that haemodynamic-guided management using an implantable pulmonary artery pressure monitor reduces heart failure hospitalisations in patients with moderately symptomatic (New York Heart Association [NYHA] functional class III) chronic heart failure and a hospitalisation in the past year, irrespective of ejection fraction. It is unclear if these benefits extend to patients with mild (NYHA functional class II) or severe (NYHA functional class IV) symptoms of heart failure or to patients with elevated natriuretic peptides without a recent heart failure hospitalisation. This trial was designed to evaluate whether haemodynamic-guided management using remote pulmonary artery pressure monitoring could reduce heart failure events and mortality in patients with heart failure across the spectrum of symptom severity (NYHA funational class II–IV), including those with elevated natriuretic peptides but without a recent heart failure hospitalisation.

Methods The randomised arm of the haemodynamic-GUIDEed management of Heart Failure (GUIDE-HF) trial was a multicentre, single-blind study at 118 centres in the USA and Canada. Following successful implantation of a pulmonary artery pressure monitor, patients with all ejection fractions, NYHA functional class II–IV chronic heart failure, and either a recent heart failure hospitalisation or elevated natriuretic peptides (based on a-priori thresholds) were randomly assigned (1:1) to either haemodynamic-guided heart failure management based on pulmonary artery pressure or a usual care control group. Patients were masked to their study group assignment. Investigators were aware of treatment assignment but did not have access to pulmonary artery pressure data for control patients. The primary endpoint was a composite of all-cause mortality and total heart failure events (heart failure hospitalisations and urgent heart failure hospital visits) at 12 months assessed in all randomly assigned patients. Safety was assessed in all patients. A pre-COVID-19 impact analysis for the primary and secondary outcomes was prespecified. This study is registered with ClinicalTrials.gov, NCT03387813.

Findings Between March 15, 2018, and Dec 20, 2019, 1022 patients were enrolled, with 1000 patients implanted successfully, and follow-up was completed on Jan 8, 2021. There were 253 primary endpoint events (0·563 per patient-year) among 497 patients in the haemodynamic-guided management group (treatment group) and 289 (0·640 per patient-year) in 503 patients in the control group (hazard ratio [HR] 0·88, 95% CI 0·74–1·05; p=0·16). A prespecified COVID-19 sensitivity analysis using a time-dependent variable to compare events before COVID-19 and during the pandemic suggested a treatment interaction ($p_{interaction}$=0·11) due to a change in the primary endpoint event rate during the pandemic phase of the trial, warranting a pre-COVID-19 impact analysis. In the pre-COVID-19 impact analysis, there were 177 primary events (0·553 per patient-year) in the intervention group and 224 events (0·682 per patient-year) in the control group (HR 0·81, 95% CI 0·66–1·00; p=0·049). This difference in primary events almost disappeared during COVID-19, with a 21% decrease in the control group (0·536 per patient-year) relative to pre-COVID-19, virtually no change in the treatment group (0·597 per patient-year), and no difference between groups (HR 1·11, 95% CI 0·80–1·55; p=0·53). The cumulative incidence of heart failure events was not reduced by haemodynamic-guided management (0·85, 0·70–1·03; p=0·096) in the overall study analysis but was significantly decreased in the pre-COVID-19 impact analysis (0·76, 0·61–0·95; p=0·014). 1014 (99%) of 1022 patients had freedom from device or system-related complications.

Interpretation Haemodynamic-guided management of heart failure did not result in a lower composite endpoint rate of mortality and total heart failure events compared with the control group in the overall study analysis. However, a pre-COVID-19 impact analysis indicated a possible benefit of haemodynamic-guided management on the primary outcome in the pre-COVID-19 period, primarily driven by a lower heart failure hospitalisation rate compared with the control group.

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Research in context

Evidence before this study

We searched PubMed for articles published in English or with English abstracts, and completed trials recorded in ClinicalTrials.gov from inception up to May 25, 2021, with the heading terms "heart failure" and "pulmonary artery pressure sensor" and either supplementary term "mortality" or "heart failure hospitalization". Our search identified only one previous randomised trial (CHAMPION) with additional prospective registries, administrative claims datasets, and a post-approval study. The CHAMPION trial randomly assigned 550 patients with New York Heart Association (NYHA) functional class III heart failure—irrespective of left ventricular ejection fraction—and a heart failure hospitalisation in the previous 12 months, and showed a significant 28% reduction in heart failure hospitalisation at 6 months, with 99% of patients free from device or system-related complications. The study was not powered for mortality. To our knowledge, no previous study has evaluated the effect of haemodynamic-guided management with a pulmonary artery pressure sensor on mortality, and no previous study of haemodynamic monitoring included patients with NYHA functional class II or IV heart failure or used elevated natriuretic peptides alone as an enrolment criterion. Additionally, to our knowledge, no study has evaluated the effect of the COVID-19 pandemic on the benefits of pulmonary artery pressure-guided management in patients with heart failure. These data have implications for the effects of COVID-19 on heart failure outcomes and follow-up and outcomes for ongoing clinical trials.

Added value of this study

Heart failure hospitalisations and mortality remain high in patients with NYHA functional class II–IV heart failure. To our

knowledge, GUIDE-HF is the first randomised clinical trial to evaluate the benefits of pulmonary artery pressure-guided management in patients with NYHA functional class II and IV heart failure or in patients with heart failure with elevated natriuretic peptides but no previous heart failure hospitalisations. The overall study analysis did not show a benefit on the primary outcome of mortality and heart failure events. However, a pre-COVID-19 impact analysis showed an overall benefit for the primary endpoint, driven by a reduction in heart failure hospitalisations almost identical to that observed in CHAMPION. We found no apparent benefit on all-cause mortality at 12 months. Pulmonary artery pressure sensor monitoring was safe. Compared with pre-COVID-19, heart failure events during the COVID-19 pandemic were not different in the pulmonary artery pressure-guided group but decreased in the control group, with a concomitant large decrease in pulmonary artery pressure and medication changes in the control group narrowing the difference present before the pandemic and possibly explaining the reduction in heart failure hospitalisations.

Implications of all the available evidence

The results of the GUIDE-HF trial, when adjusted for the effects of the COVID-19 pandemic, support the recommendation for haemodynamic-guided management using a pulmonary artery pressure sensor in patients with chronic NYHA functional class II–IV heart failure and either a previous heart failure hospitalisation or elevated natriuretic peptides. Clinical trials during the COVID-19 pandemic should plan for sensitivity analyses regarding the effect of COVID-19.

Introduction

Worsening congestion in patients with heart failure with preserved ejection fraction and patients with heart failure with reduced ejection fraction results in dyspnoea, oedema, and fatigue, which are the most common symptoms leading to admission to hospital for heart failure.[1,2] Current clinical management to prevent worsening congestion and admission to hospital in such patients relies primarily on frequent assessment using either in-person, telephone, or virtual encounters, but despite close clinical evaluation, the rate of heart failure hospitalisations remains high.[3] Symptoms of congestion are predicted by increasing pulmonary artery pressure, which can be longitudinally tracked by implantable devices.[4–6] Data obtained using these devices have shown that elevations in pulmonary artery pressure begin days to weeks before heart failure decompensation, and therefore provide a window of opportunity for medical intervention to reduce pulmonary artery pressure, thus improving congestive symptoms and limiting the need for treatment in hospital.[6,7]

The CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients (CHAMPION) trial showed that haemodynamic-guided management informed by ambulatory data from a wireless pulmonary artery pressure sensor reduced heart failure events compared with usual care in patients with New York Heart Association (NYHA) functional class III heart failure symptoms and a heart failure hospitalisation in the previous 12 months.[5] Subsequent secondary and post-hoc evaluations of data from CHAMPION, prospective registries, and administrative claims datasets support the benefits of haemodynamic-guided management in reducing heart failure hospitalisations, improving health-related quality of life, and even reducing mortality.[8–13]

These encouraging observations suggest that the benefits of haemodynamic-guided heart failure management in recently hospitalised, high-risk patients with moderately severe (NYHA functional class III) symptoms shown in CHAMPION[5] might extend to a broader

population with heart failure. The haemodynamic-GUIDEed management of Heart Failure (GUIDE-HF) trial was designed to evaluate whether haemodynamic-guided management using remote pulmonary artery pressure monitoring could reduce heart failure hospitalisations and mortality in patients with heart failure across the spectrum of symptom severity (NYHA funational class II–IV), including those with elevated natriuretic peptides but without a recent heart failure hospitalisation.[14]

Methods

Study design and participants

The GUIDE-HF trial included a randomised arm (n=1000, completed) and a single-arm, observational study (n=2600, ongoing). In this Article, we present the primary results of the randomised arm, which compared heart failure management guided by pulmonary artery pressure obtained remotely via an implanted sensor to standard-of-care heart failure management using guideline-recommended medical therapy. Details regarding the GUIDE-HF trial design have been published previously.[14] The trial statistical analysis plan is provided in the appendix (pp 35–50). The protocol and statistical analysis plan were approved by the US Food and Drug Administration (FDA), Health Canada, and the institutional review boards at each of the 118 participating trial sites. The trial was sponsored by Abbott and done in accordance with the Declaration of Helsinki and local and national regulations.

The study enrolled patients with NYHA functional class II–IV heart failure, regardless of left ventricular ejection fraction, with a heart failure hospitalisation within the 12 months before study consent or elevated natriuretic peptides (B-type natriuretic peptide [BNP] or N-terminal pro-BNP [NT-proBNP]) within 30 days before study consent.[14] Prespecified thresholds defined BNP values ≥250 pg/mL or NT-proBNP values ≥1000 pg/mL as elevated, with threshold corrections for left ventricular ejection fraction and body-mass index (available in the appendix p 4), but not for atrial fibrillation. Patients likely to receive a heart transplant or left ventricular assist device in the next 12 months, patients with American College of Cardiology/American Heart Association stage D heart failure, and those who required inotropes within the past 6 months were excluded. Written informed consent was obtained from all patients or their authorised representatives before any study-related procedures were done. Full inclusion and exclusion criteria are provided in the appendix (pp 13–14) and were published previously.[14]

Randomisation and masking

After successful pulmonary artery pressure sensor implantation (CardioMEMS; Abbott, Abbott Park, IL, USA) patients were randomly assigned (1:1) to the treatment group (pulmonary artery pressure-guided

patient management and standard-of-care guideline-recommended medical therapy) or the control group (standard-of-care guideline-recommended medical therapy only). Randomisation was performed via a computer-generated schedule stratified by site and sex using randomly permuted block sizes of 2 and 4.

Patients were masked to their study group assignment. Investigators were aware of treatment assignment but did not have access to pulmonary artery pressure data for control patients. To maintain patient masking and ensure balanced contact between groups, each site designated masked personnel for all site-to-patient communication related to heart failure management and sites contacted all patients in both treatment groups using a masked caller and scripted language at least once every 2 weeks for the first 3 months, and then once per month until study completion. Clinical symptoms or concerns discovered during the scripted calls were referred to the investigator for management in both treatment and control patients. Standard heart failure management could incorporate typical data including daily weights, symptoms, and other diagnostics from implantable therapy devices, if available. Patient contacts generated by knowledge of pulmonary artery pressure were communicated to the treatment group through a masked caller using scripted language. All patients were
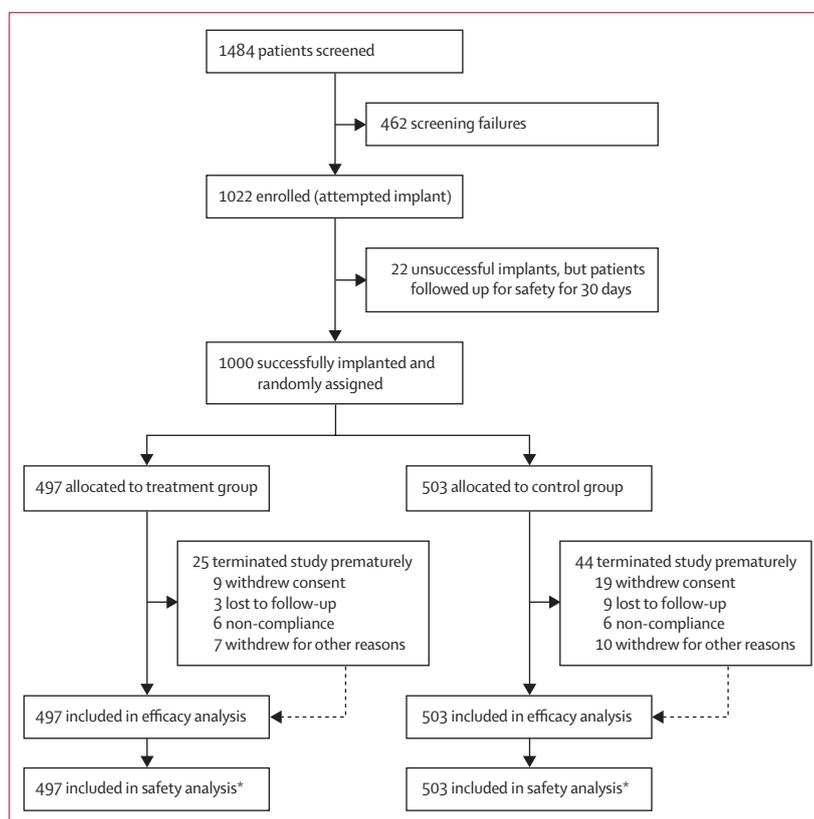
See **Online** for appendix

Figure 1: Trial profile
*22 unsuccessful implants in safety analysis (1022 total patients included in safety analysis).

instructed to upload pulmonary artery pressure data daily. Adherence to daily pulmonary artery pressure uploads was visible to site staff and monitored for both groups, whereas pulmonary artery data were only visible to sites for the treatment group. Poor adherence was addressed through a scripted communication by a masked caller reminding patients to upload pulmonary artery pressure data.

Procedures
After implantation of the CardioMEMS pressure sensor and random assignment, patients were treated either with standard-of-care heart failure management using guideline-recommended medical therapy (control group) or haemodynamic-guided care in addition to guideline-recommended medical therapy (treatment group). Details of the recommended response to elevation of pulmonary artery pressure are outlined in the appendix (pp 5–6). Briefly, titration of diuretics was recommended if pulmonary artery pressure provided evidence of excess intravascular volume, and titration of vasodilators was recommended if elevated vascular resistance was evident. Adverse events and endpoint data were collected throughout the follow-up period. All patients had follow-up visits for clinical assessments at 6 months and 12 months post-implantation, including quality-of-life, safety, and functional assessments. During the COVID-19 pandemic, follow-up visits according to the protocol schedule were done remotely as needed.

Outcomes
The primary endpoint was a composite of all-cause mortality and total heart failure events (heart failure hospitalisations and urgent heart failure hospital visits defined as emergency department or hospital outpatient observation visits requiring intravenous diuretic therapy) at 12 months. Secondary effectiveness endpoints were cumulative heart failure events at 12 months post-implantation, health status at 6 months and 12 months, as assessed by the EuroQol 5 Dimension 5 Level (EQ-5D-5L) questionnaire and the Kansas City Cardiomyopathy Questionnaire (KCCQ-12), functional status at 6 months and 12 months assessed by the 6-min hall walk (6MHW) test, and individual components of the primary endpoint at 12 months. Freedom from device-related or system-related complications at 12 months was the safety endpoint. Details regarding all endpoints in this study were previously described.[14]

Statistical analysis
The efficacy analysis population included all patients who were randomly assigned, regardless of their duration in the trial, and statistical comparisons were between the treatment group and the control group. We analysed the primary endpoint using the Andersen-Gill extension of the Cox proportional hazards model with robust sandwich estimate of variance, as described previously.[14] The assumptions of the Andersen-Gill model were evaluated and were not found to be violated. The sample size estimated to provide approximately 80% power at the 2·5% significance level was 1000 successfully implanted

	Treatment group (n=497)	Control group (n=503)
Age, years	71 (64–76)	70 (64–77)
Sex		
Female	187 (38%)	188 (37%)
Male	310 (62%)	315 (63%)
Race		
White	403 (81%)	404 (80%)
Black	86 (17%)	93 (18%)
Asian	0	1 (<1%)
American Indian or Alaskan Native	1 (<1%)	1 (<1%)
Pacific Islander	0	0
Other	7 (1%)	4 (1%)
Ethnicity		
Hispanic	16 (3%)	17 (3%)
Non-Hispanic	477 (96%)	483 (96%)
Unknown	4 (1%)	3 (1%)
Body-mass index, kg/m²	31·6 (26·8–37·7)	32·6 (28·0–39·0)
New York Heart Association functional class		
II	146 (29%)	150 (30%)
III	322 (65%)	328 (65%)
IV	29 (6%)	25 (5%)
Medical history		
Ischaemic cause	207 (42%)	190 (38%)
Previous myocardial infarction	144 (29%)	158 (31%)
Previous percutaneous coronary intervention	165 (33%)	158 (31%)
Previous coronary artery bypass grafting	135 (27%)	136 (27%)
Diabetes	243 (49%)	261 (52%)
Cerebrovascular accident	66 (13%)	65 (13%)
Atrial flutter or fibrillation	300 (60%)	291 (58%)
Vital signs and haemodynamic analyses		
Heart rate, beats per min	72 (65–82)	72 (65–82)
Systolic blood pressure, mm Hg	120 (108–132)	120 (108–132)
Diastolic blood pressure, mm Hg	68 (60–76)	68 (61–76)
Left ventricular ejection fraction, %	38 (25–55)	40 (25–55)
Left ventricular ejection fraction >40%	224 (45%)	245 (49%)
Left ventricular ejection fraction >50%	154 (31%)	167 (33%)
Pulmonary artery systolic pressure, mm Hg	44 (35–52)	42 (35–53)
Pulmonary artery diastolic pressure, mm Hg	18 (14–23)	18 (13–24)
Pulmonary artery mean pressure, mm Hg	28 (22–35)	29 (22–35)
Pulmonary capillary wedge pressure, mm Hg	16 (11–23)	17 (12–22)
Cardiac output, L/min	4·5 (3·8–5·5)	4·6 (3·7–5·5)
Cardiac index, L/min per m²	2·1 (1·8–2·6)	2·1 (1·7–2·5)
Ambulatory haemodynamics during the first week		
Pulmonary artery systolic pressure, mm Hg	45 (36–54)	45 (37–55)
Pulmonary artery diastolic pressure, mm Hg	22 (17–27)	22 (18–27)
Pulmonary artery mean pressure, mm Hg	31 (25–38)	31 (26–38)
Heart rate, beats per min	78 (70–87)	78 (71–86)
		(Table 1 continues on next page)

and randomly assigned patients (500 per treatment group).[14] The individual components of the primary endpoint and secondary endpoint of heart failure events were evaluated using the Andersen-Gill model. All-cause mortality at 12 months was evaluated using a Cox proportional hazards model with randomised group as a covariate, and Kaplan-Meier estimates of freedom from all-cause mortality were plotted. Prespecified subgroup analyses for the primary endpoint included: ejection fraction, age, sex, race, ethnicity, NYHA functional class III, cause of heart failure, and device implant history (cardiac resynchronisation therapy and implantable cardioverter-defibrillator). Non-prespecified subgroups included NYHA functional class II, IV, and II/III and qualification category (previous heart failure hospitalisation vs natriuretic peptides). Specific data for anticoagulants, pacemakers, and baseline heart rhythm were not collected. For the other secondary endpoints, longitudinal changes in quality of life (KCCQ-12 and EQ-5D-5L) and functional status (6MHW) were analysed using a paired t-test procedure. Pulmonary artery pressure was analysed using a linear mixed model to investigate pressure at fixed timepoints (baseline, 6 months, and 12 months) and as an area under the pressure–time curve (AUC) of each patient's daily change in pulmonary artery pressure from baseline calculated using the trapezoidal rule. Site-to-patient contacts and frequency of pulmonary artery pressure uploads were analysed descriptively. The safety endpoint of freedom from device-related or system-related complications was analysed including all patients with an attempted device implantation. Hypothesis tests were two-tailed at the 5% significance level and not adjusted for multiplicity. Interaction tests used a 15% significance level specified in the statistical analysis plan and suggested by the FDA. Additional details regarding the statistical design of the study were published previously[14] and the statistical analysis plan is available in the appendix (pp 35–50).

The COVID-19 pandemic occurred during the follow-up period of this study, but after all patients had been enrolled for at least 3 months. The potential effect of COVID-19 on all aspects of clinical trials has been discussed by the Heart Failure Association of the European Society of Cardiology (ESC-HFA), the European Medicines Agency (EMA), the Heart Failure Collaboratory (HFC), and the FDA.[15–18] Based on these advisements, the statistical analysis plan was updated to include COVID-19 sensitivity analyses and approved by the FDA on Aug 28, 2020, before the last follow-up visit on Jan 8, 2021. Events reviewed by the Clinical Events Committee that occurred on or after Feb 1, 2020, were adjudicated for COVID-19 relatedness. Additionally, the effect of the COVID-19 pandemic—represented by the US national emergency declaration date[19] of March 13, 2020—on the primary endpoint and components was evaluated through prespecified COVID-19 impact analyses with a 15% interaction significance level. The pre-COVID impact analysis included

	Treatment group (n=497)	Control group (n=503)
(Continued from previous page)		
Laboratory analyses		
Serum creatinine, µmol/L	121·1 (97·2–150·3)	123·8 (97·2–159·1)
Estimated glomerular filtration rate, ml/min per 1·73 m²	51·3 (39·3–65·3)	48·9 (38·1–64·8)
B-type natriuretic peptide, pg/mL	267·0 (133·0–612·0)	292·0 (139·5–586·5)
N-terminal pro-B-type natriuretic peptide, pg/mL	1480 (686–2743)	1274 (661–2318)
Treatment history		
Previous cardiac resynchronisation therapy	142 (29%)	163 (32%)
Previous implantation of defibrillator	213 (43%)	205 (41%)
Guideline-recommended medical therapy		
Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker or angiotensin receptor-neprilysin inhibitor	319 (64%)	320 (64%)
Angiotensin receptor-neprilysin inhibitor	145 (29%)	139 (28%)
β blocker	444 (89%)	442 (88%)
Mineralocorticoid receptor antagonist	237 (48%)	216 (43%)
Diuretic	474 (95%)	478 (95%)
Hydralazine	81 (16%)	80 (16%)
Nitrate	99 (20%)	103 (20%)
SGLT2 inhibitor	2 (<1%)	2 (<1%)
Enrolment criteria		
Heart failure hospitalisation in the previous year	170 (34%)	191 (38%)
Elevated natriuretic peptides in the previous 30 days	230 (46%)	212 (42%)
Heart failure hospitalisation in the previous year and elevated natriuretic peptides in the previous 30 days	97 (20%)	99 (20%)

Data are median (IQR) or n (%). Data on pulmonary capillary wedge pressure were available for 495 patients in the treatment group. Data on ambulatory haemodynamics during the first week were available for 499 patients in the control group. Data on serum creatinine and estimated glomerular filtration rate were available for 495 patients in the treatment group and 495 patients in the control group. Data on B-type natriuretic peptide were available for 261 patients in the treatment group and 256 patients in the control group. Data on N-terminal pro-B-type natriuretic peptide were available for 219 patients in the treatment group and 225 patients in the control group. Data on SGLT2 inhibitors were available for 152 patients in the treatment group and 140 patients in the control group. One control group patient did not meet any of the enrolment criteria.

Table 1: Baseline characteristics

all primary endpoints up to March 13, 2020. The primary COVID-19 impact analysis evaluated the primary endpoint both before and during the COVID-19 pandemic using a time-varying covariate and treatment interaction within the Andersen-Gill model with robust variance estimates. To better understand the effect of the COVID-19 pandemic on factors affecting heart failure, the mean pulmonary artery pressure AUC, heart failure medication changes, and patient compliance in uploading data were evaluated both before and during the COVID-19 pandemic. To examine changes in mean pulmonary artery pressure AUC specific to the time period during COVID-19, the baseline value was reset as of the COVID-19 pandemic onset (March 13, 2020) and AUC calculations were restarted.

A masked, independent clinical events committee adjudicated whether events met prespecified definitions

	Treatment group events* (event rate per patient-year†)	Control group events‡ (event rate per patient-year†)	HR (95% CI)	p value
Overall primary endpoint analysis and components				
Heart failure hospitalisations and urgent heart failure visits and death (primary endpoint)	253 (0·563)	289 (0·640)	0·88 (0·74–1·05)	0·16
Heart failure events (heart failure hospitalisations plus urgent heart failure hospital visits; secondary endpoint)	213 (0·474)	252 (0·557)	0·85 (0·70–1·03)	0·096
Urgent heart failure hospital visits	28 (0·065)	27 (0·063)	1·04 (0·61–1·77)	0·89
Heart failure hospitalisations	185 (0·410)	225 (0·497)	0·83 (0·68–1·01)	0·064
Death	40 (0·094)	37 (0·086)	1·09 (0·70–1·70)	0·71
Pre-COVID-19 impact analysis—primary endpoint and components§				
Heart failure hospitalisations plus urgent heart failure hospital visits plus death (primary endpoint)	177 (0·553)	224 (0·682)	0·81 (0·66–1·00)	0·049
Heart failure events (heart failure hospitalisations plus urgent heart failure hospital visits; secondary endpoint)	147 (0·450)	199 (0·595)	0·76 (0·61–0·95)	0·014
Urgent heart failure hospital visits	23 (0·074)	23 (0·073)	1·02 (0·57–1·82)	0·95
Heart failure hospitalisations	124 (0·380)	176 (0·525)	0·72 (0·57–0·92)	0·0072
Death	30 (0·110)	25 (0·088)	1·24 (0·73–2·11)	0·42

Endpoints include clinical events committee-adjudicated heart failure hospitalisations or urgent heart failure visits with an admission date after the date of implant hospitalisation discharge through to 395 days after the date of implant. All-cause deaths are included from implant date to 395 days after implant date. HR, 95% CIs, and p values were estimated from the Andersen-Gill model with robust sandwich estimates. HR=hazard ratio. *n=497. †Event rate is an annualised rate estimated from the Andersen-Gill model. ‡n=503. §Events and rates represent the time period before COVID-19, defined as data collected through to March 13, 2020.

Table 2: Primary outcomes and components

for primary and safety endpoints. A masked, independent data safety monitoring board regularly reviewed accumulating trial data and advised the sponsor regarding the continuing safety, validity, and scientific merit of the trial. Statistical analyses were done using SAS, version 9.4 or higher. The study is registered with ClinicalTrials.gov, NCT03387813.

Role of the funding source

The funder of the study participated in study design, data collection, data analysis, data interpretation, and writing of the report. The raw data were transferred to a statistician independent of the sponsor who verified the accuracy of the primary endpoint and pre-COVID-19 impact analyses to JL.

Results

Between March 15, 2018, and Dec 20, 2019, 1484 patients were screened, of whom 1022 were enrolled, including 1007 patients at 114 sites in the USA and 15 patients at four sites in Canada (figure 1). 22 patients had unsuccessful implants and were followed up for 30 days for safety outcomes. After successful implantation of

the CardioMEMS device, 1000 patients were randomly assigned to treatment (n=497) or control (n=503). At trial closure (Jan 8, 2021) fatal and non-fatal outcomes up to 12 months were known for all patients, except for 25 treatment group patients and 44 control group patients who withdrew from the study before 12 months (figure 1). However, outcomes in these patients were known up to the withdrawal date and included in the endpoint analyses. Time to withdrawal did not differ between the treatment group and control group (appendix p 21). Patient characteristics and medications at baseline were similar between the study groups (table 1). Overall, 296 (30%) of 1000 patients from the entire cohort were NYHA functional class II, 650 (65%) were NYHA functional class III, and 54 (5%) were NYHA functional class IV. Enrolment was based on a previous heart failure hospitalisation in 361 (36%) of 1000 patients, on elevated natriuretic peptides alone in 442 (44%) patients, and both in 196 (20%) patients. As of the US COVID-19 national emergency date of March 13, 2020, 72% of the total follow-up days had been completed (appendix p 22).

In the overall analysis, 253 primary endpoint events (0·563 per patient-year) occurred in the treatment group and 289 events (0·640 per patient-year) in the control group (hazard ratio [HR] 0·88, 95% CI 0·74–1·05; p=0·16; table 2; figure 2A). There were 185 heart failure hospitalisations in the treatment group and 225 in the control group (HR 0·83, 95% CI 0·68–1·01; p=0·064; table 2; figure 2B). There were no significant differences in either urgent heart failure hospital visits or mortality between the treatment and control group in the overall analysis (table 2). Adjudicated causes of death are provided in the appendix (p 26).

The prespecified COVID-19 sensitivity analysis suggested an effect of COVID-19 on the primary endpoint (appendix p 27), warranting an analysis of all endpoints before the US national emergency declaration date of March 13, 2020 (pre-COVID-19 impact analysis). In the pre-COVID-19 impact analysis, there was a reduction in primary endpoint events with 177 events (0·553 per patient-year) in the treatment group and 224 events (0·682 per patient-year) in the control group (HR 0·81, 95% CI 0·66–1·00; p=0·049; table 2; figure 2C). Similarly, heart failure hospitalisations were reduced with 124 hospitalisations in the treatment group and 176 in the control group (HR 0·72, 95% CI 0·57–0·92; p=0·0072; table 2; figure 2D). As in the overall analysis, we found no differences between groups for either urgent heart failure hospital visits or all-cause mortality before COVID-19 (table 2). These pre-COVID-19 impact analysis results were consistent across sensitivity analyses examining the effect of different onset dates for the COVID-19 pandemic (appendix pp 23, 28).

Subgroup analyses for the primary endpoint for the overall analysis and the pre-COVID-19 impact analysis are presented in figure 3 and the appendix (p 24), respectively. In the overall analysis, the primary endpoint HR was
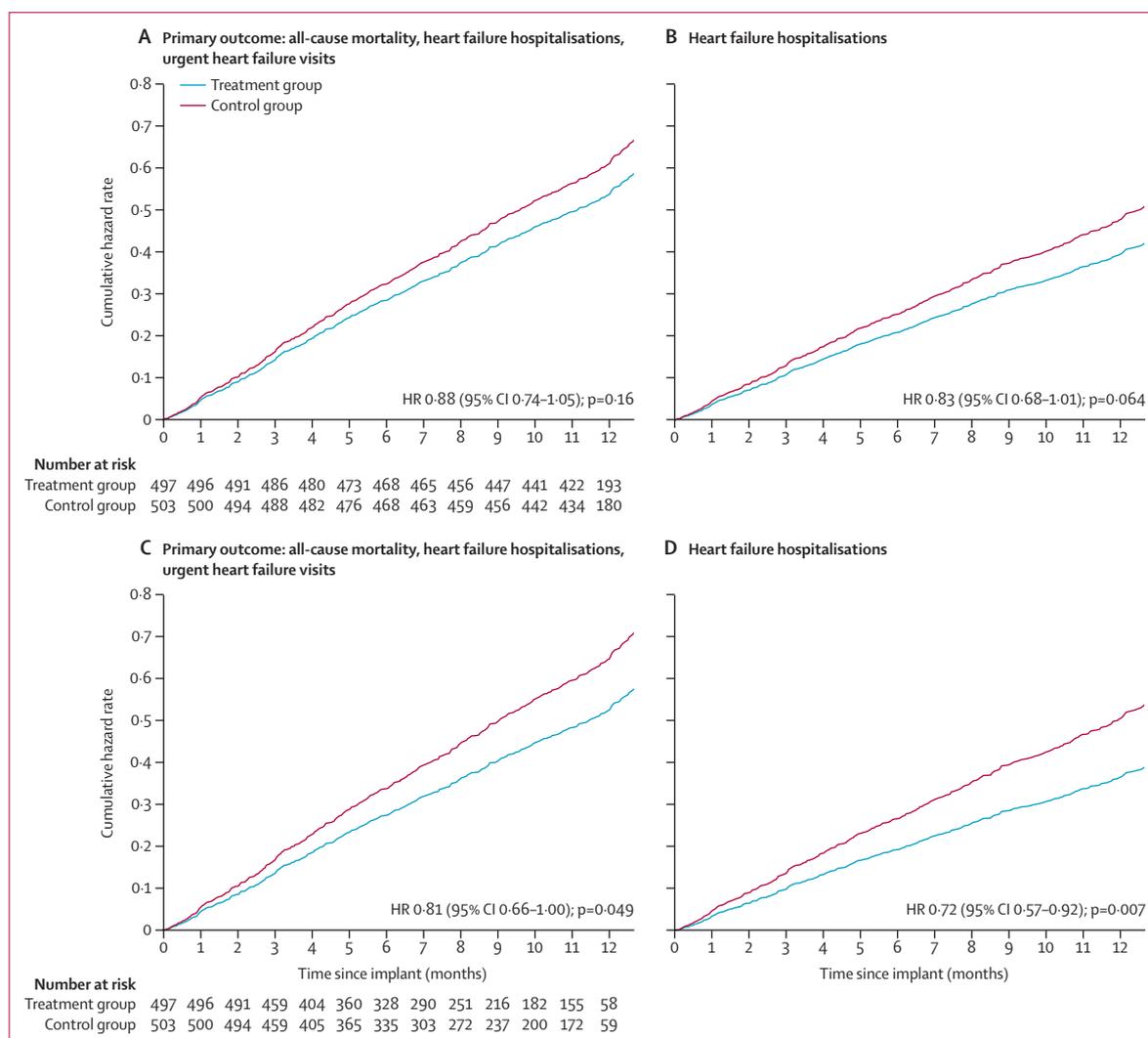
Figure 2: **Cumulative hazard rate curves and 95% CIs for the primary composite endpoint and heart failure hospitalisations**
(A) Overall analysis—primary outcome of all-cause mortality, heart failure hospitalisations, and urgent heart failure hospital visits. (B) Overall analysis—heart failure hospitalisations. (C) Pre-COVID-19 impact analysis—primary outcome of all-cause mortality, heart failure hospitalisations, and urgent heart failure visits. (D) Pre-COVID-19 impact analysis—heart failure hospitalisations. HR=hazard ratio.

consistent for most subgroups (figure 3). Subgroup interactions for the primary outcome were suggested for NYHA functional class (greater treatment effect in NYHA functional class II or III compared with class IV), race (greater treatment effect in Black patients), and sex (greater treatment effect in women). Despite noticeably lower event rates in certain subgroups, including patients qualifying via elevated BNP or NT-proBNP, heart failure with preserved ejection fraction, women, and NYHA functional class II, we observed a consistent HR for the primary endpoint (figure 3; appendix p 24). The effect of haemodynamic-guided management in subgroups was consistent for the pre-COVID-19 impact analysis except for sex, which did not show an interaction in the pre-COVID-19 analysis.

For the secondary endpoint of heart failure events, there were 213 total heart failure events in the treatment group and 252 total heart failure events in the control group in the overall analysis (HR 0·85, 95% CI 0·70–1·03; p=0·096; table 2, figure 2C). In the pre-COVID-19 impact analysis there were 147 total heart failure events in the treatment group and 199 in the control group (0·76, 0·61–0·95; p=0·014; table 2; figure 2D). The paired analyses for the secondary endpoints of KCCQ-12, EQ-5D-5L, and 6MHW at 6 months and 12 months are presented in the appendix (p 29). In both the overall analysis and the pre-COVID-19 impact analysis, the KCCQ-12 and EQ-5D-5L scores improved in both the treatment and control groups at 6 months, with no significant difference between groups. There was also no treatment effect when KCCQ-12 was analysed in 5-point increments (appendix p 30). We found no difference in the 6MHW
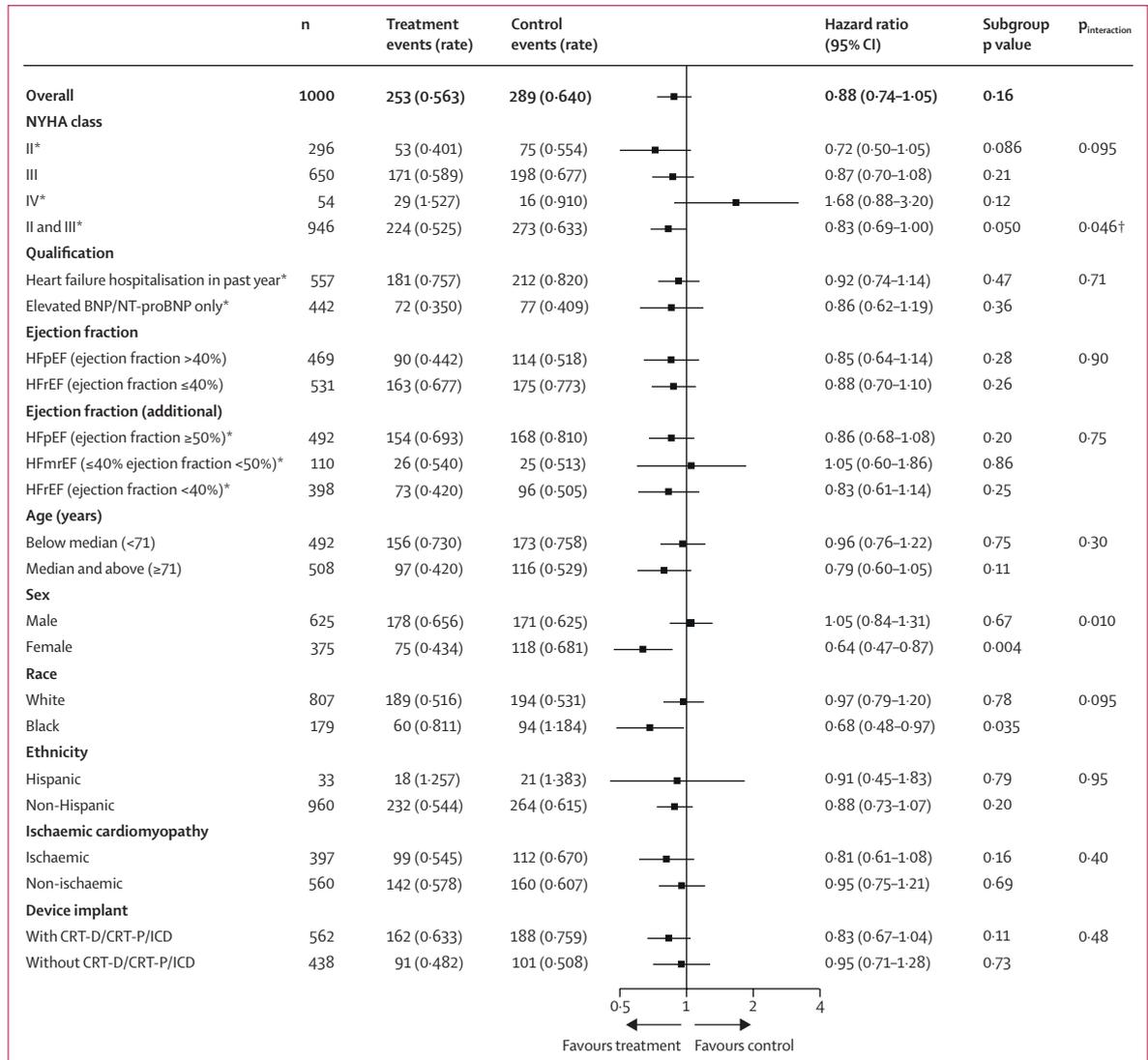
	n	Treatment events (rate)	Control events (rate)		Hazard ratio (95% CI)	Subgroup p value	p interaction
Overall	1000	253 (0·563)	289 (0·640)		0·88 (0·74–1·05)	0·16	
NYHA class							
II*	296	53 (0·401)	75 (0·554)		0·72 (0·50–1·05)	0·086	0·095
III	650	171 (0·589)	198 (0·677)		0·87 (0·70–1·08)	0·21	
IV*	54	29 (1·527)	16 (0·910)		1·68 (0·88–3·20)	0·12	
II and III*	946	224 (0·525)	273 (0·633)		0·83 (0·69–1·00)	0·050	0·046†
Qualification							
Heart failure hospitalisation in past year*	557	181 (0·757)	212 (0·820)		0·92 (0·74–1·14)	0·47	0·71
Elevated BNP/NT-proBNP only*	442	72 (0·350)	77 (0·409)		0·86 (0·62–1·19)	0·36	
Ejection fraction							
HFpEF (ejection fraction >40%)	469	90 (0·442)	114 (0·518)		0·85 (0·64–1·14)	0·28	0·90
HFrEF (ejection fraction ≤40%)	531	163 (0·677)	175 (0·773)		0·88 (0·70–1·10)	0·26	
Ejection fraction (additional)							
HFpEF (ejection fraction ≥50%)*	492	154 (0·693)	168 (0·810)		0·86 (0·68–1·08)	0·20	0·75
HFmrEF (≤40% ejection fraction <50%)*	110	26 (0·540)	25 (0·513)		1·05 (0·60–1·86)	0·86	
HFrEF (ejection fraction <40%)*	398	73 (0·420)	96 (0·505)		0·83 (0·61–1·14)	0·25	
Age (years)							
Below median (<71)	492	156 (0·730)	173 (0·758)		0·96 (0·76–1·22)	0·75	0·30
Median and above (≥71)	508	97 (0·420)	116 (0·529)		0·79 (0·60–1·05)	0·11	
Sex							
Male	625	178 (0·656)	171 (0·625)		1·05 (0·84–1·31)	0·67	0·010
Female	375	75 (0·434)	118 (0·681)		0·64 (0·47–0·87)	0·004	
Race							
White	807	189 (0·516)	194 (0·531)		0·97 (0·79–1·20)	0·78	0·095
Black	179	60 (0·811)	94 (1·184)		0·68 (0·48–0·97)	0·035	
Ethnicity							
Hispanic	33	18 (1·257)	21 (1·383)		0·91 (0·45–1·83)	0·79	0·95
Non-Hispanic	960	232 (0·544)	264 (0·615)		0·88 (0·73–1·07)	0·20	
Ischaemic cardiomyopathy							
Ischaemic	397	99 (0·545)	112 (0·670)		0·81 (0·61–1·08)	0·16	0·40
Non-ischaemic	560	142 (0·578)	160 (0·607)		0·95 (0·75–1·21)	0·69	
Device implant							
With CRT-D/CRT-P/ICD	562	162 (0·633)	188 (0·759)		0·83 (0·67–1·04)	0·11	0·48
Without CRT-D/CRT-P/ICD	438	91 (0·482)	101 (0·508)		0·95 (0·71–1·28)	0·73	

0·5 1 2 4

← Favours treatment   Favours control →

Figure 3: **Primary endpoint within subgroups—overall analysis**
NYHA=New York Heart Association. BNP=B-type natriuretic peptide. NT-proBNP=N-terminal pro B-type natriuretic peptide. HFpEF=heart failure with preserved ejection fraction. HFrEF=heart failure with reduced ejection fraction. HFmrEF=heart failure with mid-range ejection fraction. CRT-D=cardiac resynchronisation therapy with defibrillator device. CRT-P=cardiac resynchronisation therapy with pacemaker device. ICD=implantable cardioverter defibriliator. *Non-prespecified subgroup. †Interaction p value testing randomisation group by NYHA functional class II and III versus class IV.

distance within or between groups for the overall analysis or the pre-COVID-19 impact analysis (appendix p 29). The number of 6MHW tests was substantially reduced after the onset of COVID-19 because of an inability to do the test remotely.

A significantly lower AUC for mean pulmonary artery pressure was observed for the treatment group compared with the control group in the overall analysis (figure 4), with a mean pulmonary artery pressure AUC of –792·7 mm Hg-days (SD 1767.0) in the treatment group and –582·9 mm Hg-days (1698·1) in the control group (p=0·040). The pre-COVID-19 analysis also showed a lower mean pulmonary artery pressure AUC in the treatment group (–518·0 mm Hg-days, SD 1327·0)

compared with the control group (–324·2 mm Hg-days, 1328·5; p=0·014 between groups), but with a gradually widening difference over time favouring the treatment group (appendix p 25). Baseline and 12-month guideline-recommended medical therapy for all patients in treatment and control groups are described in the appendix (p 31) and by left ventricular ejection fractions (appendix p 32), with no substantial differences between groups. SGLT2 inhibitor use increased in both patients with heart failure with reduced ejection fraction and patients with heart failure with preserved ejection fraction in both groups.

In the pre-COVID-19 impact analysis, we found a significant difference in the primary endpoint rate

between the treatment group (0·553 per patient-year) and control group (0·682 per patient-year; p=0·049). This difference almost disappeared during COVID-19, with a 21% decrease in the control group (0·536 per patient-year) relative to pre-COVID-19, virtually no change in the treatment group (0·597 per patient-year) relative to pre-COVID-19, and no difference between groups (p=0·53; appendix p 27). We found frequent changes in medications throughout the GUIDE-HF study in both the treatment group and control group. However, more medication changes were made in the treatment group (1·031 changes per month per patient) compared with the control group (0·608 changes per month per patient) across overall follow-up. Patient compliance in obtaining and transmitting daily pulmonary artery pressure readings were documented throughout follow-up to be between 80–90% in both groups.

The median contact frequency throughout the trial was compliant with the minimum per protocol in both groups (appendix p 33). The safety endpoint (analysis cohort including unsuccessful implants) showed a 99% (1014 of 1022 patients) freedom from device-related or system-related complications (appendix p 34).

The overall incidence of investigator-reported adverse events, serious adverse events, and adverse events leading to study discontinuation were similar in both groups in the overall study analysis and in the pre-COVID-19 impact analysis. Serious adverse events occurred in 282 (57%) of 497 patients in the treatment group and 268 (53%) of 503 patients in the control group, with similar results pre-COVID-19.

Discussion

In the GUIDE-HF trial of patients with chronic heart failure across a broad range of left ventricular ejection fractions, with NYHA functional class II–IV symptoms and either a recent heart failure hospitalisation or elevated natriuretic peptides, haemodynamic-guided management did not reduce the combined endpoint of all-cause mortality, heart failure hospitalisations, and urgent heart failure hospital visits despite significant reductions in pulmonary artery pressure during study follow-up compared with the control group. We found no significant between-group differences in the prespecified secondary endpoints of total heart failure events, health-related quality of life (KCCQ-12 and EQ-5D-5L), or functional capacity (6MHW).

However, the COVID-19 pandemic had an important effect on the trial, with heart failure event rates remaining low in the treatment group during COVID-19, but decreasing substantially in the control group after the declaration of a national emergency in the USA on March 13, 2020. Around 28% of the total follow-up time in the study occurred during the height of the pandemic in the USA. A prespecified pre-COVID-19 impact analysis evaluating event rates during the time period before the pandemic showed a significantly lower primary composite
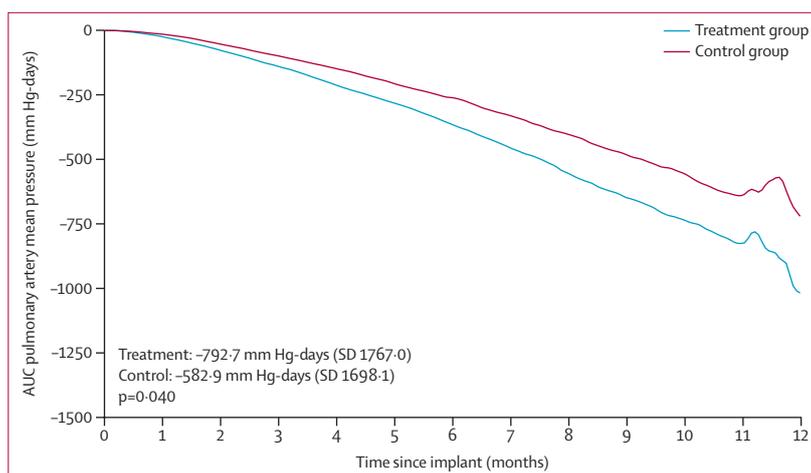
Figure 4: **Mean pulmonary artery pressure change from baseline—overall analysis**
AUC=area under the pressure–time curve.

endpoint rate in the treatment group compared with the control group, principally attributable to a lower rate of total heart failure events. The treatment effect observed in the pre-COVID-19 impact analysis was present even when varying the date of onset of the pandemic. No effect of haemodynamic-guided therapy was observed on quality of life or functional capacity.

Our analysis of the impact of the COVID-19 pandemic on GUIDE-HF is endorsed by the guidance proposed by the ESC-HFA, EMA, HFC, and FDA.[15–18,20] Indeed, the effect of the COVID-19 pandemic in this trial evokes the AFFIRM-AHF trial,[20] in which a neutral overall effect of randomised treatment on the primary composite endpoint of total heart failure hospitalisations and cardiovascular death in the primary statistical analysis masked the potentially significant treatment benefit when evaluated through a COVID-19 sensitivity analysis. A reduction in heart failure events during the COVID-19 pandemic has been reported in the general population with heart failure, overlapping with a portion of the follow-up time in GUIDE-HF.[20–25] Results from GUIDE-HF provide insights into the causes of a reduction in heart failure events during the pandemic and how these affect this trial and will likely affect other trials. We showed that the primary endpoint events were reduced significantly in the control group during COVID-19, thus narrowing the treatment difference observed in the pre-COVID-19 impact analysis. The differences in the mean pulmonary artery pressure AUC between the treatment group and control group similarly appeared greater in the pre-COVID-19 analysis than in the overall analysis. Several factors could explain the considerable loss of benefit of haemodynamic-guided management during the COVID-19 pandemic, including improved patient compliance with medical and dietary regimens, reduced respiratory infections, altered health-care provider behaviour, changes in disease progression due to COVID-19, or other as yet unknown effects of a

major pandemic. However, the data suggest that clinical trials designed to improve heart failure events are likely to be significantly affected by the COVID-19 pandemic, as observed in AFFIRM-AHF and the present study.

Our primary endpoint results were consistent across nearly all subgroups, including those defined by left ventricular ejection fraction, sex, previous heart failure hospitalisation, and race, with the possible exception of patients with NYHA class IV heart failure. However, a treatment effect was observed in patients with mild to moderate (NYHA functional class II–III) heart failure. When aggregated, these data support the observations from other trials[20–25] that the onset of the COVID-19 pandemic might have obscured the true benefit of the intervention, which in GUIDE-HF was the reduction in heart failure events in a broad population of patients with chronic heart failure who were receiving haemodynamic-guided therapy. Although event rates were lower for patients with heart failure with preserved ejection fraction compared with patients with heart failure with reduced ejection fraction, for patients with NYHA functional class II heart failure compared with patients with NYHA functional class III heart failure, and for those enrolled with elevated natriuretic peptides versus a recent heart failure hospitalisation, the magnitude of the treatment effect was consistent across these groups. The potential subgroup interaction for sex differed in direction from that observed in the CHAMPION trial and showed a significant treatment effect in women.[5,9] Patients with NYHA functional class IV heart failure did not appear to benefit from haemodynamic-guided management although this subgroup included only 54 patients and the trial might have lacked the ability to show a difference in this small patient cohort. However, the results in these patients were similar to those reported in a previous trial that evaluated haemodynamic management of heart failure.[4]

The observed treatment effect in this study was largely accounted for by a reduction in heart failure hospitalisation similar to that observed in previous trials.[5,8–13] The observed reduction in heart failure hospitalisations was identical to the 28% decrease reported for patients with NYHA functional class III heart failure in the CHAMPION trial[5,9] and consistent with reports of other observational studies, including the CardioMEMS US Post-Approval Study,[13] and clinical trials reporting the benefits of haemodynamic-guided monitoring.[12] Mortality was not affected in our study and was consistent with other trials that primarily included patients with NYHA functional class II and III heart failure.[26,27] We observed reductions in pulmonary artery pressure and heart failure hospitalisations, both of which have been previously associated with a reduction in mortality.[10,11] Demonstration of mortality benefits might require larger patient numbers or a longer follow-up duration.[11,14] The inclusion of patients with severe heart failure (NYHA functional class IV) who did not appear to benefit from haemodynamic-guided management might

have attenuated the mortality signal in our trial. Over half of the 54 patients with NYHA functional class IV symptoms were enrolled within the last 3 months of the trial, resulting in a particularly truncated follow-up period for this group. The frequent patient contacts and home confinement during the pandemic in both groups might have affected patient compliance with diet and medications.

Despite significant reductions in pulmonary artery pressure and total heart failure events in the pre-COVID-19 analysis, we found no benefit of haemodynamic-guided therapy on quality of life or functional capacity as measured in this trial. Missing data due to the difficulty of completing 6MHW tests and quality-of-life questionnaires remotely during the pandemic probably undermined the power of these analyses. In other much larger studies of medical therapies, the mean change in KCCQ-12 scores has been small (<3 points)[26,28] and could not be shown in trials with the same interventions but fewer patients and shorter follow-up, similar to the numbers of patients and follow-up time in GUIDE-HF.[29,30] It is possible that the high frequency of patient–provider contacts in both groups led to an improvement in quality of life, possibly with an exaggerated beneficial effect during COVID-19, thus decreasing the ability to show a difference due to haemodynamic-guided management. Limitations of this study include the masking of the patients to their treatment assignment, the 12-month duration of follow-up, and the effects of the COVID-19 pandemic in limiting data collection, particularly for secondary endpoints.

In conclusion, haemodynamic-guided management across the spectrum of ejection fraction and symptom severity was safe but did not reduce a composite of mortality and total heart failure events. However, in a pre-COVID-19 impact analysis, a benefit of haemodynamic-guided management on the primary outcome, driven by a decrease in heart failure hospitalisations, was shown. These data affirm and expand the evidence base supporting the benefits of haemodynamic-guided management in patients with chronic heart failure and suggest that such an intervention might be applicable to a broader range of patients, including those with mild to moderate heart failure and those with elevated natriuretic peptides and no previous heart failure hospitalisation.

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