JACC: HEART FAILURE VOL. 10, NO. 12, 2022


# Hemodynamically-Guided Management of Heart Failure Across the Ejection Fraction Spectrum

## The GUIDE-HF Trial

Michael R. Zile, MD,[a] Mandeep R. Mehra, MD, MSc,[b] Anique Ducharme, MD, MSc,[c] Samuel F. Sears, PHD,[d] Akshay S. Desai, MD, MPH,[b] Alan Maisel, MD,[e] Sara Paul, DNP,[f] Frank Smart, MD,[g] Gillian Grafton, DO,[h] Sachin Kumar, MD,[i] Tareck O. Nossuli, MD,[j] Nessa Johnson, PhD,[k] John Henderson, MS,[k] Philip B. Adamson, MD,[k] Maria Rosa Costanzo, MD,[l] JoAnn Lindenfeld, MD[m]

## ABSTRACT

**BACKGROUND** Hemodynamically-guided management using an implanted pulmonary artery pressure sensor is indicated to reduce heart failure (HF) hospitalizations in patients with New York Heart Association (NYHA) functional class II-III with a prior HF hospitalization or those with elevated natriuretic peptides.

**OBJECTIVES** The authors sought to evaluate the effect of left ventricular ejection fraction (EF) on treatment outcomes in the GUIDE-HF (Hemodynamic-GUIDEd management of Heart Failure) randomized trial.

**METHODS** The GUIDE-HF randomized arm included 1,000 NYHA functional class II-IV patients (with HF hospitalization within the prior 12 months or elevated natriuretic peptides adjusted for EF and body mass index) implanted with a pulmonary artery pressure sensor, randomized 1:1 to a hemodynamically-guided management group (treatment) or a control group (control). The primary endpoint was the composite of HF hospitalizations, urgent HF visits, and all-cause mortality at 12 months. The authors assessed outcomes by EF in guideline-defined subgroups ≤40%, 41%-49%, and ≥50%, within the trial specified pre-COVID-19 period cohort.

**RESULTS** There were 177 primary events (0.553/patient-year) in the treatment group and 224 events (0.682/patient-year) in the control group (HR: 0.81 [95% CI: 0.66-1.00]; $P = 0.049$); HF hospitalization was lower in the treatment vs control group (HR: 0.72 [95% CI: 0.57-0.92]; $P = 0.0072$). Within each EF subgroup, primary endpoint and HF hospitalization rates were lower in the treatment group (HR <1.0 across the EF spectrum). Event rate reduction by EF in the treatment groups was correlated with reduction in pulmonary artery pressures and medication changes.

**CONCLUSIONS** Hemodynamically-guided HF management decreases HF-related endpoints across the EF spectrum in an expanded patient population of patients with HF. (Hemodynamic-GUIDEd Management of Heart Failure [GUIDE-HF]; NCT03387813) (J Am Coll Cardiol HF 2022;10:931-944) © 2022 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

From the [a]Medical University of South Carolina, RJH Department of Veterans Affairs Medical Center, Charleston, South Carolina, USA; [b]Cardiology Division, Brigham and Women's Hospital, and Harvard Medical School, Boston, Massachusetts, USA; [c]Montreal Heart Institute, Université de Montréal, Montreal, Quebec, Canada; [d]East Carolina University, Greenville, North Carolina, USA; [e]University of California-San Diego, La Jolla, California, USA; [f]Catawba Valley Health System, Conover, North Carolina, USA; [g]Louisiana State University School of Medicine, New Orleans, Louisiana, USA; [h]Henry Ford Hospital, Detroit, Michigan, USA; [i]Memorial Hermann Hospital, Houston, Texas, USA; [j]The Heart Group of Lancaster General Health, Lancaster, Pennsylvania, USA; [k]Abbott, Abbott Park, Illinois, USA; [l]Midwest Cardiovascular Institute, Naperville, Illinois, USA; and the [m]Vanderbilt Heart and Vascular Institute, Nashville, Tennessee, USA.

G. Michael Felker, MD, served as Guest Associate Editor for this paper. Barry Greenberg, MD, served as Guest Editor-in-Chief for this paper.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received June 16, 2022; revised manuscript received August 15, 2022, accepted August 17, 2022.

ISSN 2213-1779 https://doi.org/10.1016/j.jchf.2022.08.012

**ABBREVIATIONS AND ACRONYMS**

**ACE** = angiotensin-converting enzyme

**AE** = adverse event

**ARB** = angiotensin receptor blocker

**ARNI** = angiotensin receptor blocker-neprilysin inhibitor

**EF** = ejection fraction

**FDA** = Food and Drug Administration

**HF** = heart failure

**HFmrEF** = heart failure with mildly reduced ejection fraction

**HFpEF** = heart failure with preserved ejection fraction

**HFrEF** = heart failure with reduced ejection fraction

**MRA** = mineralocorticoid receptor antagonist

**NYHA** = New York Heart Association

**PA** = pulmonary artery

**SAP** = statistical analysis plan

**SGLT2** = sodium-glucose transport protein 2

A fundamental characteristic in symptomatic chronic heart failure (HF), across all ejection fractions (EFs), is the presence of an increase in cardiac filling pressures at rest or during activity.[1,2] Cardiac filling pressures and changes in filling pressure are associated with HF events and cardiovascular mortality.[3-6] Therefore, it might be anticipated that HF management guided by hemodynamic assessment could improve outcomes independent of the EF and that this effect would depend on alterations in filling pressures. This hypothesis has not been previously examined in a broad group of patients with HF, including those with New York Heart Association (NYHA) functional class II-IV with either previous hospitalizations or natriuretic peptide elevations. Recent studies of pharmacologic therapies have shown a nonhomogeneous response, across wide ranges of EF, despite their ability to directly or indirectly reduce filling pressures, suggesting fundamental pathophysiological differences among patients with HF based on EF categories.[7,8] This raises the possibility that the hemodynamic response to a given drug differs at different EF thresholds or that changes in filling pressure result in differential outcomes across the spectrum of EF.

SEE PAGE 945

The recently reported GUIDE-HF (Hemodynamic-GUIDEd management of Heart Failure) randomized trial of patients implanted with a pulmonary artery (PA) pressure sensor supported the decision by the U.S. Food and Drug Administration (FDA) to approve the clinical indication for hemodynamically-guided management to reduce HF hospitalizations in patients with NYHA functional class II-III HF with a prior HF hospitalization or in those with elevated natriuretic peptides.[6,9] The purposes of the current analysis of the GUIDE-HF trial data are to determine whether hemodynamically-guided management of HF patients based on direct measurement of filling pressures is effective in reducing morbidity and mortality across the EF spectrum and to demonstrate that management efficacy is dependent on reduction in filling pressures independent of EF.

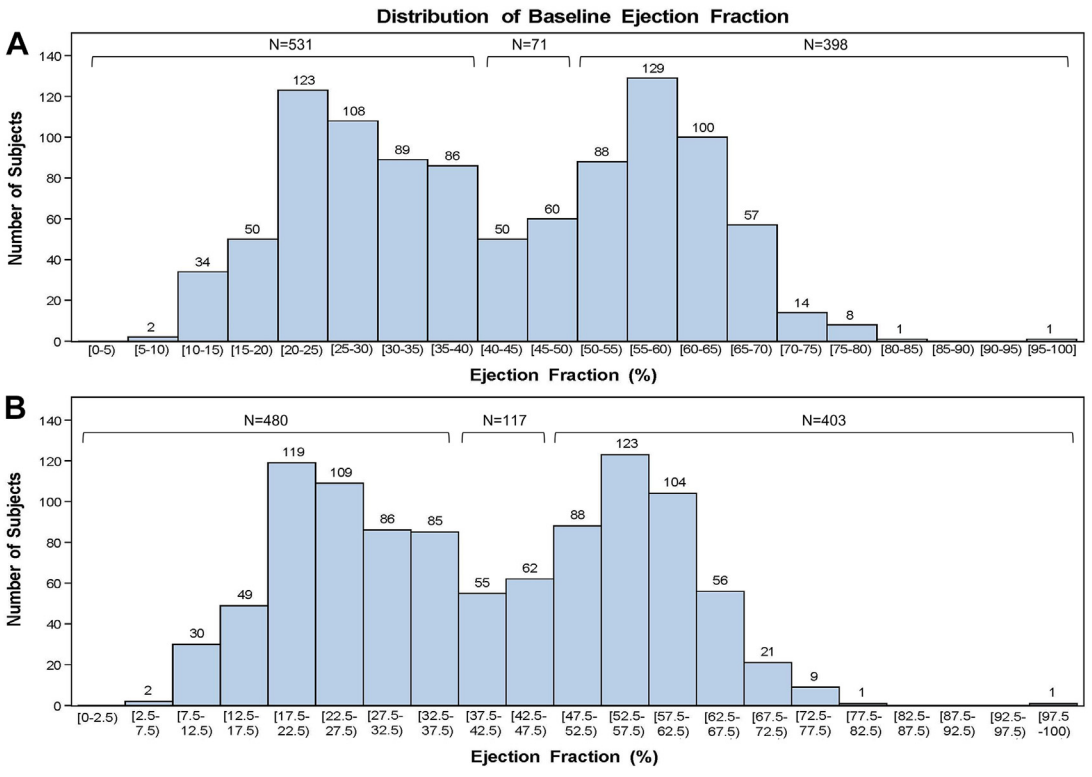
## METHODS

**STUDY DESIGN.** The GUIDE-HF trial design (NCT03387813) has been described in detail through prior publications.[6,9,10] The GUIDE-HF randomized arm compared hemodynamically-guided HF management based on knowledge of PA pressure (treatment group) to clinical HF management without knowledge of PA pressures (control group) in patients with NYHA functional class II-IV HF with either a previous HF hospitalization or elevated B-type natriuretic peptides. The trial protocol was approved by the institutional review boards at each of the 118 participating trial sites in the United States and Canada. Written informed consent was obtained from all patients or their authorized representatives before any study-related procedures were completed. Details regarding the participating centers and trial procedures are published.[6,10] The GUIDE-HF trial was conducted in compliance with the most current version of the World Medical Association Declaration of Helsinki and 21 Code of Federal Regulations Parts 50, 54, 56, and 812 in addition to applicable local laws and regulations. The authors vouch for the completeness and accuracy of the data, analyses, and results.

**PARTICIPANTS.** Eligibility criteria for this analysis were the same as previously published.[6,10] Briefly, patients were ≥18 years old, NYHA functional class II-IV HF, and had a HF hospitalization within 12 months before consent and/or elevated natriuretic peptide levels within 30 days before consent with thresholds prespecified according to each natriuretic peptide type, EF, and body mass index.[10]

**RANDOMIZATION AND MASKING.** After successful implantation of the PA pressure sensor (CardioMEMS HF System, Abbott) patients were randomized 1:1 to the treatment group (PA pressure-guided patient management in addition to guideline-directed medical therapy) or the control group (clinical heart failure management using guideline-directed medical therapy without provider access to PA pressures). Randomization was stratified by site and gender using randomly permuted blocks. The trial was single-blind, with patients blinded to their study group assignment and having no access to their PA pressures. The investigators were aware of patient treatment group assignments to manage patients accordingly but did not have access to PA pressure information in control group patients. To maintain patient blinding, all site-to-patient communication was completed through personnel blinded to the allocation group at each site and each patient was contacted at a minimum frequency of every 2 weeks for months 0-3 and monthly for months 3-12. Patients in both treatment and control groups were instructed to upload daily PA pressures and patient compliance with daily uploads was monitored for both groups by investigators. The specific methods implemented to

**FIGURE 1** Distribution of Baseline EF in Patients Randomized in GUIDE-HF




**(A)** This shows patients in 5 EF unit increments with intervals ending in "0%" or "5%." **(B)** This shows patients 5 EF unit increments with intervals ending in "2.5%" or "7.5%" to avoid the measurement reporting bias seen in clinical practice, which exhibits a preference for values ending in "0" or "5." Data indicate a bimodal distribution. EF = ejection fraction; GUIDE-HF = Hemodynamic-GUIDEd management of Heart Failure randomized trial.

preserve appropriate patient blinding to treatment group assignment were previously described in detail.[6,10]

**OUTCOMES.** The primary endpoint was a composite of all-cause mortality and cumulative HF events (including HF hospitalizations or urgent HF visits requiring intravenous diuretics) at 12 months. A blinded, independent Clinical Events Committee adjudicated whether adverse events (AEs) met definitions for primary endpoint events. PA pressures were measured using the device, and HF medication changes were reported. A blinded, independent Data Safety Monitoring Board advised the sponsor regarding the continuing safety, validity, and scientific merit of the clinical trial.

**STATISTICAL ANALYSIS.** The analysis population of the GUIDE-HF randomized arm included all successfully implanted and randomized patients, and statistical comparisons were between treatment and control groups. Of particular note, the prespecified statistical analysis plan (SAP) was divided into 3 timelines: the overall data for the entire study, data limited to events that occurred before the onset of the COVID-19 pandemic, and data that occurred during COVID-19.[6,9] For the current analysis, only data limited to events that occurred before the onset of the COVID-19 pandemic were included. The rationale for this choice was described in detail in our previous publication[9] in which all data endpoints were analyzed in each of the 3 time periods and the overall results were negatively impacted by the events of the COVID-19 pandemic. All patients in this population were included in the primary endpoint analysis regardless of their duration in the trial, and all effectiveness analyses were performed from the point of randomization in the intent-to-treat population. The distribution of subjects according to EF was assessed in 5 EF increments (such as, 5% EF-10% EF) and defined by midrange EF values (such as, 2.5% EF-

**TABLE 1 Demographics**

| | HFrEF (EF ≤40%) (n = 531) | HFmrEF (EF 41%-49%) (n = 71) | HFpEF (EF ≥50%) (n = 398) |
|---|---|---|---|
| Age, y | 67.2 ± 11.4 (531) | 70.5 ± 12.4 (71) | 71.6 ± 9.7 (398) |
| Female | 29.2 (155/531) | 31.0 (22/71) | 49.7 (198/398) |
| Race | | | |
| White | 73.6 (391/531) | 87.3 (62/71) | 89.2 (355/398) |
| Black | 25.0 (133/531) | 11.3 (8/71) | 9.8 (39/398) |
| Asian | 0.2 (1/531) | 0.0 (0/71) | 0.0 (0/398) |
| American Indian or Alaskan Native | 0.4 (2/531) | 0.0 (0/71) | 0.5 (2/398) |
| Pacific Islanders | 0.0 (0/531) | 0.0 (0/71) | 0.0 (0/398) |
| Other | 0.9 (5/531) | 1.4 (1/71) | 0.8 (3/398) |
| Ethnicity | | | |
| Hispanic | 4.1 (22/531) | 1.4 (1/71) | 2.5 (10/398) |
| Non-Hispanic | 94.7 (503/531) | 97.2 (69/71) | 97.5 (388/398) |
| Unknown | 1.1 (6/531) | 1.4 (1/71) | 0.0 (0/398) |
| Body mass index, kg/m$^2$ | 31.4 ± 7.4 (531) | 32.0 ± 7.2 (71) | 36.3 ± 9.0 (398) |
| NYHA functional class | | | |
| II | 31.6 (168/531) | 32.4 (23/71) | 26.4 (105/398) |
| III | 62.5 (332/531) | 63.4 (45/71) | 68.6 (273/398) |
| IV | 5.8 (31/531) | 4.2 (3/71) | 5.0 (20/398) |
| Medical history | | | |
| Ischemic etiology | 50.5 (268/531) | 42.3 (30/71) | 24.9 (99/398) |
| Previous myocardial infarction | 39.9 (212/531) | 31.0 (22/71) | 17.1 (68/398) |
| Previous percutaneous coronary intervention | 39.5 (210/531) | 31.0 (22/71) | 22.9 (91/398) |
| Previous coronary artery bypass grafting | 29.9 (159/531) | 28.2 (20/71) | 23.1 (92/398) |
| Diabetes | 49.0 (260/531) | 43.7 (31/71) | 53.5 (213/398) |
| Cerebrovascular accident | 15.1 (80/531) | 11.3 (8/71) | 10.8 (43/398) |
| Atrial flutter or fibrillation | 55.6 (295/531) | 59.2 (42/71) | 63.8 (254/398) |
| Vital signs and hemodynamic analyses | | | |
| Heart rate, beats/min | 74.8 ± 12.6 (531) | 75.1 ± 10.6 (71) | 72.7 ± 12.4 (398) |
| Systolic BP, mm Hg | 116.9 ± 17.9 (531) | 120.1 ± 17.3 (71) | 127.1 ± 18.2 (398) |
| Diastolic BP, mm Hg | 69.3 ± 11.0 (531) | 68.9 ± 9.9 (71) | 68.8 ± 10.6 (398) |
| LVEF, % | 25.9 ± 8.3 (531) | 44.9 ± 1.4 (71) | 58.1 ± 6.6 (398) |
| LVEF, >40% | 0.0 (0/531) | 100.0 (71/71) | 100.0 (398/398) |
| PA systolic pressure, mm Hg | 45.1 ± 15.4 (531) | 43.7 ± 13.0 (71) | 45.1 ± 12.8 (398) |
| PA diastolic pressure, mm Hg | 19.3 ± 8.9 (531) | 18.0 ± 6.7 (71) | 18.4 ± 6.3 (398) |
| PA mean pressure, mm Hg | 29.5 ± 10.9 (531) | 28.2 ± 8.0 (71) | 29.2 ± 8.2 (398) |
| Pulmonary capillary wedge pressure, mm Hg | 17.8 ± 9.0 (530) | 15.5 ± 5.3 (71) | 17.3 ± 6.7 (397) |
| Cardiac output, L/min | 4.52 ± 2.46 (531) | 4.55 ± 1.36 (71) | 5.12 ± 1.63 (398) |
| Cardiac index, L/min/m$^2$ | 2.15 ± 1.05 (531) | 2.12 ± 0.53 (71) | 2.36 ± 0.68 (398) |
| Ambulatory hemodynamics during first week | | | |
| PA systolic pressure, mm Hg | 46.1 ± 13.9 (527) | 45.4 ± 14.4 (71) | 46.6 ± 13.8 (398) |
| PA diastolic pressure, mm Hg | 23.1 ± 8.1 (527) | 21.6 ± 7.1 (71) | 22.1 ± 6.8 (398) |
| PA mean pressure, mm Hg | 32.1 ± 10.3 (527) | 31.2 ± 9.9 (71) | 31.7 ± 9.3 (398) |
| Heart rate, beats/min | 80.1 ± 11.8 (527) | 80.8 ± 10.5 (71) | 77.4 ± 11.7 (398) |
| Laboratory analyses | | | |
| Serum creatinine level, μmol/L | 133.2 ± 48.7 (524) | 121.7 ± 40.6 (70) | 129.7 ± 44.5 (396) |
| eGFR, mL/min/1.73 m$^2$ | 55.2 ± 22.0 (523) | 57.9 ± 21.4 (70) | 50.6 ± 19.4 (396) |
| BNP level, pg/mL | 723.8 ± 998.2 (297) | 365.9 ± 569.2 (33) | 268.9 ± 371.1 (187) |
| NT-proBNP level, pg/mL | 3,173 ± 4,129 (209) | 2,115 ± 2,302 (36) | 1,461 ± 1,921 (199) |

*Continued on the next page*

7.5% EF) across the EF spectrum. The analysis was performed to avoid the measurement reporting bias seen in clinical practice, which exhibits a preference for values ending in "0" or "5."

In the prespecified SAP, patients were divided into 2 EF subgroups: ≤40% and >40%. However, subsequent to FDA filing of the SAP, the Heart Failure Collaboratory, the European Guideline Committee, and the American College of Cardiology (ACC)/American Heart Association (AHA)/Heart Failure Society of America (HFSA) Guideline Committee established a "universal definition" for HF based on 3 EF

**TABLE 1 Continued**

| | HFrEF (EF ≤40%) (n = 531) | HFmrEF (EF 41%-49%) (n = 71) | HFpEF (EF ≥50%) (n = 398) |
|---|---|---|---|
| Treatment history | | | |
| Previous CRT | 40.5 (215/531) | 26.8 (19/71) | 17.8 (71/398) |
| Previous implantation of defibrillator | 68.0 (361/531) | 26.8 (19/71) | 9.5 (38/398) |
| Guideline-directed medical therapy | | | |
| ACE inhibitor/ARB/ARNI | 75.1 (399/531) | 63.4 (45/71) | 49.0 (195/398) |
| ARNI | 47.5 (252/531) | 15.5 (11/71) | 5.3 (21/398) |
| Beta-blocker | 95.1 (505/531) | 93.0 (66/71) | 79.1 (315/398) |
| MRA | 51.0 (271/531) | 42.3 (30/71) | 38.2 (152/398) |
| Diuretic | 94.2 (500/531) | 95.8 (68/71) | 96.5 (384/398) |
| Hydralazine | 15.3 (81/531) | 11.3 (8/71) | 18.1 (72/398) |
| Nitrate | 24.1 (128/531) | 15.5 (11/71) | 15.8 (63/398) |
| SGLT2 inhibitors | 1.1 (2/184) | 0.0 (0/22) | 2.3 (2/86) |
| Enrollment type | | | |
| HF hospitalization in y prior only | 34.9 (185/530) | 26.8 (19/71) | 39.4 (157/398) |
| Elevated BNP/NT-proBNP in 30 d prior only | 43.8 (232/530) | 47.9 (34/71) | 44.2 (176/398) |
| HF hospitalization in y prior and elevated BNP/NT-proBNP in 30 d prior | 21.3 (113/530) | 25.4 (18/71) | 16.3 (65/398) |
| Patient-reported outcomes | | | |
| KCCQ-12 at baseline, overall summary score | 57.6 ± 24.2 (527) | 55.0 ± 22.5 (70) | 51.2 ± 23.6 (394) |
| 6-MHW as baseline, m | 252.9 ± 123.0 (509) | 233.7 ± 113.0 (69) | 204.5 ± 115.9 (378) |

Values as mean ± SD (N) or % (n/N).

6-MHW = 6-minute hall walk; ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor blocker-neprilysin inhibitor; BNP = B-type natriuretic peptide; BP = blood pressure; CRT = cardiac resynchronization therapy; eGFR = estimated glomerular filtration rate; HF = heart failure; HFmrEF = heart failure with mildly reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; KCCQ = Kansas City Cardiomyopathy Questionnaire; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide; MRA = mineralocorticoid receptor antagonist; NYHA = New York Heart Association; PA = pulmonary artery; SGLT2 = sodium-glucose transport protein 2.

subgroups.[11] Analysis of the outcome data was performed using the Universal Definition and Classification of Heart Failure-defined subgroups of patients with HF: heart failure with reduced ejection fraction (HFrEF) ≤40%, heart failure with mildly reduced ejection fraction (HFmrEF) 41%-49%, and heart failure with preserved ejection fraction (HFpEF) ≥50%.[11] Analysis of EF was performed in 4 separate categories including: 1) use of the universal definition; 2) use of the prespecified <40 vs ≥40% cut points; 3) use of a commonly used category <50 vs ≥50% cut points; and 4) use of 5% intervals for selected quantifications.

The primary endpoint was analyzed for each subgroup according to EF using the Andersen-Gill extension of the Cox proportional hazards model with robust sandwich estimate of variance. HR and 95% CIs were calculated across the EF spectrum using only the main effects in the Andersen-Gill model with EF as a continuous variable and a presumed linear relationship across the EF spectrum. A covariate for EF and treatment by EF interaction were added to the Andersen-Gill model for interaction testing. PA pressures were analyzed at fixed time points (baseline, 6 months, and 12 months) with treatment groups compared using a 2-sample Student's *t*-test. PA pressure changes from baseline to 6 and 12 months were analyzed as average change from baseline during follow-up, as well as using area under the pressure-time curve (AUC). Comparisons between study groups were made using a general linear model with baseline pressure as a covariate. Medication changes were analyzed during the maintenance phase of study (excluding the first 90 days after randomization, which constituted the optimization phase[10]) and differences in medication rates and changes in medication rates between groups were evaluated using a Wilcoxon rank sum test. Statistical analyses were performed using SAS software, version 9.4 or higher (SAS Institute).

**ROLE OF THE FUNDING SOURCE.** Abbott sponsored the trial, selected the sites, and analyzed the data. The primary endpoint and COVID-19 impact analyses were verified by an independent statistician.

## RESULTS

**OVERALL POPULATION EFFECTIVENESS OUTCOME DATA.** In the pre-COVID-19 patient group, there was a reduction in primary endpoint events with 177 events in 497 patients (0.553 per patient-year) in the treatment group and 224 events in 503 patients (0.682

per patient-year) in the control group (HR: 0.81 [95% CI: 0.66-1.00]; $P = 0.049$). Similarly, HF hospitalizations were reduced with 124 hospitalizations in the treatment group and 176 in the control group (HR: 0.72 [95% CI: 0.57-0.92]; $P = 0.0072$). There were no differences between groups for either urgent HF visits or all-cause mortality.

**EF FREQUENCY DISTRIBUTION ACROSS PATIENTS WITH HF AND DEMOGRAPHICS IN 3 DEFINED EF GROUPS.** There was a bimodal distribution of EFs in the study group with peaks at 20%-25% and 55%-60% (Figure 1). Also, 53% of the patients had an EF ≤40% (HFrEF; n = 531), 7% of the patients had an EF between 41% and 49% (HFmrEF; n = 71), and 40% of the patients had an EF ≥50% (HFpEF; n = 398). The frequency distribution of subjects was similar when examined in 5 EF unit increments both between 5% (Figure 1A) and within 5% (Figure 1B) measurements. Comparing the 3 groups, patients with HFpEF were older, more often White patients, and female, had higher body mass index and blood pressure, less frequent coronary artery disease (CAD), more frequent atrial fibrillation (AF), lower estimated glomerular filtration rate (eGFR), N-terminal pro-B-type natriuretic peptide (NT-proBNP), 6-minute hall walk (6-MHW), and Kansas City Cardiomyopathy Questionnaire (KCCQ-12) compared with HFrEF patients. In patients with HFmrEF, these demographic differences fell in an intermediate range between HFpEF and HFrEF (Table 1).

**EFFICACY OUTCOME DATA.** The event rates for both the primary and HF hospitalization endpoints were lowest in the HFpEF group (primary endpoint: 0.376 and 0.538 events/patient-year for treatment and control groups, respectively; HF hospitalizations: 0.275 and 0.393, respectively), highest in the HFrEF group (primary endpoint: 0.738 and 0.870, respectively; HF hospitalizations: 0.515 and 0.721, respectively), and intermediate in HFmrEF (primary endpoint: 0.564 and 0.661, respectively; HF hospitalizations: 0.436 and 0.534, respectively) (Figures 2 and 3).

In each of the 3 EF groups, there was a reduction in the primary and HF hospitalization event rates in the treatment compared with control groups (Figures 2 and 3); the difference in HF hospitalizations reached statistical significance in the HFrEF subgroup. For each of the 3 EF subgroups (Figure 3), HR point estimates were <1, although some of the 95% upper CIs crossed 1, especially where sample sizes were limited. When EF was divided into 2 prespecified groups, EF ≤40% vs >40% or another commonly used cutoff of <50% vs ≥50%, results were consistent with data presented already in this article. For each endpoint, the treatment by EF interaction was not statistically significant for either the primary endpoint ($P = 0.71$) or HF hospitalizations ($P = 0.95$) (Figure 3).

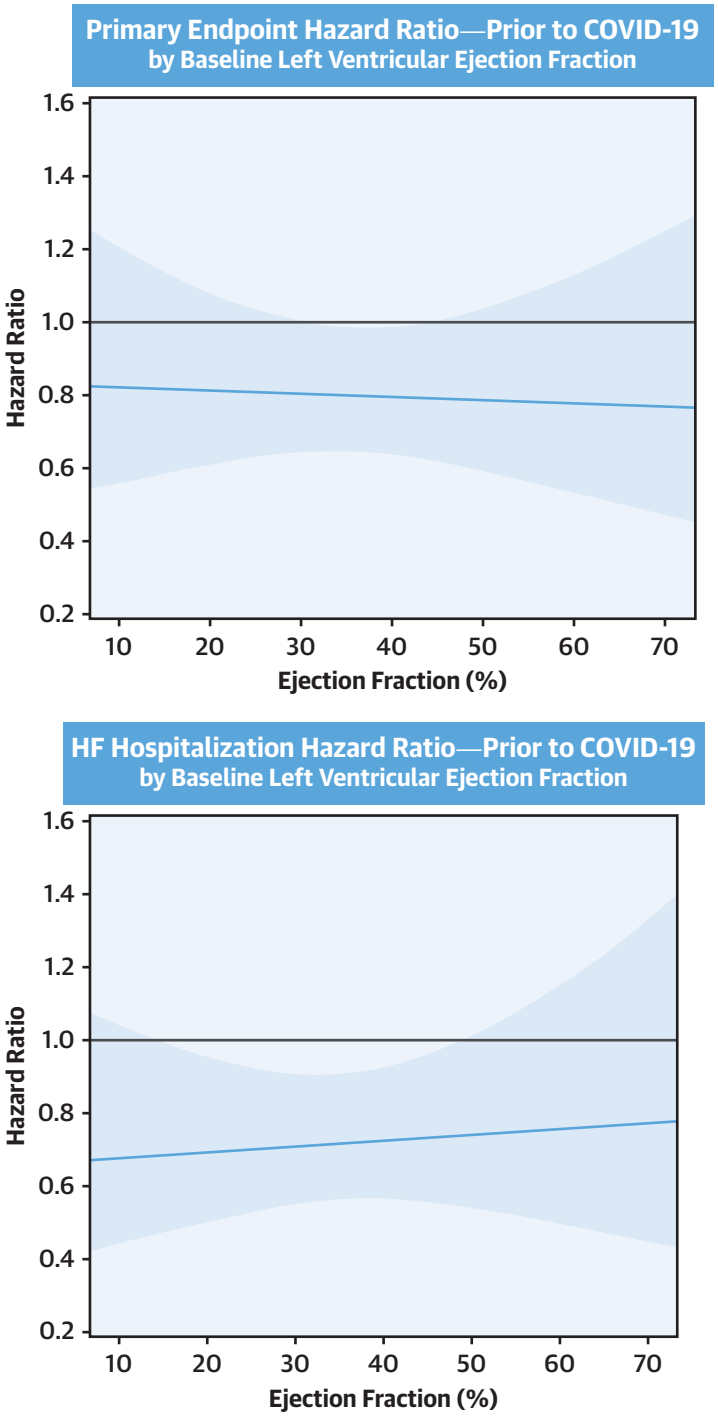
Using EF as a continuous predictor, treatment effect was evaluated across EF values from 5%-80% with HR estimates produced in 5% increments using a linear assumption. The HR point estimate comparing the effects of treatment vs control on the primary and HF hospitalization endpoints remained <1 over the spectrum of EF values (Central Illustration). The upper limit CIs at both the lowest and highest EF ranges did cross 1. The HR and CI for primary and HF endpoints was similar when subjects were examined as individual subgroups dividing the population into 5 EF unit increments both between 5% and within 5% measurements.

**MEDICATION CHANGES.** For data from the pre-COVID-19 period, there were 70% more medication changes in the treatment group compared with the control group with 1.19 changes/patient-month in treatment vs 0.700 changes/patient-month in control ($P < 0.001$). Medication changes were examined in each of 5 drug categories: ACE inhibitor/angiotensin receptor blockers (ARBs)/angiotensin receptor blocker-neprilysin inhibitor (ARNI), beta-blocker, mineralocorticoid receptor antagonists (MRAs), diuretic agents (both loop and thiazide), and all others (Table 2). The most frequent medication changes were diuretics, which occurred in 83.3% of subjects in treatment vs 59.2% in control. The frequency and pattern of medication changes and differences between treatment and control groups were similar across each of the 3 EF groups (Table 2). However, in the treatment group, the frequency with which ACE inhibitor, ARB, ARNI, and beta-blockers were changed was greater in the HFrEF and HFmrEF groups than in the HFpEF group. This is likely based on guideline recommendations present during the study. Changes in diuretic agents were similar in all 3 EF groups.

In addition, the direction in which medications were changed (increase, start, or resume a drug vs decrease, stop, or hold a drug) in treatment vs control are presented in Table 2. In the control and treatment groups, the rates of increase were generally > the rate of decrease in medication with a noticeably greater ratio of increase to decrease in the treatment group. This was particularly true for diuretics. This pattern was similar in each of the 3 EF groups.

**PA PRESSURE MEASUREMENTS.** Baseline pressures were comparable across the 3 EF groups (eg, diastolic PA pressure was 23.1 ± 8.1 mm Hg in ≤40% EF,

**CENTRAL ILLUSTRATION** **HR With 95% CIs Depicting the Effects of Hemodynamically-Guided Treatment vs Usual Care Control on Event Rates**




**Zile MR, et al. J Am Coll Cardiol HF. 2022;10(12):931-944.**

The primary event rates **(top)**, and heart failure (HF) hospitalization event rate **(bottom)** were plotted using baseline ejection fraction (EF). The treatment by EF interaction was not statistically significant for either the primary endpoint ($P = 0.71$) or HF hospitalizations ($P = 0.95$). HR and 95% CIs were calculated across the EF spectrum using only the main effects in the Andersen-Gill model with a presumed linear relationship across the EF spectrum.

**TABLE 2 Medication Changes**

| | Treatment | | | Control | | |
|---|---|---|---|---|---|---|
| | Any Change | Increase/Start/Resume | Decrease/Stop/Hold | Any Change | Increase/Start/Resume | Decrease/Stop/Hold |
| All subjects | (N = 497) | (N = 497) | (N = 497) | (N = 503) | (N = 503) | (N = 503) |
| ACE inhibitor/ARB/ARNI | 28.4 (141) | 21.7 (108) | 19.5 (97) | 23.1 (116) | 15.1 (76) | 16.5 (83) |
| Beta-blocker | 27.6 (137) | 19.5 (97) | 17.9 (89) | 25.6 (129) | 15.9 (80) | 19.5 (98) |
| MRA | 23.1 (115) | 16.1 (80) | 16.9 (84) | 16.7 (84) | 12.3 (62) | 11.1 (56) |
| Diuretic (loop and thiazide) | 83.3 (414) | 76.3 (379) | 58.4 (290) | 59.2 (298) | 51.5 (259) | 42.9 (216) |
| All others | 85.5 (425) | 78.7 (391) | 61.2 (304) | 61.8 (311) | 54.9 (276) | 46.1 (232) |
| Any HF medication | 87.9 (437) | 82.9 (412) | 66.6 (331) | 68.6 (345) | 62.0 (312) | 52.5 (264) |
| HFrEF (EF ≤40%) | (n = 273) | (n = 273) | (n = 273) | (n = 258) | (n = 258) | (n = 258) |
| ACE inhibitor/ARB/ARNI | 34.8 (95) | 28.6 (78) | 22.7 (62) | 25.2 (65) | 18.2 (47) | 18.6 (48) |
| Beta-blocker | 28.2 (77) | 19.4 (53) | 19.4 (53) | 25.6 (66) | 14.7 (38) | 18.2 (47) |
| MRA | 22.3 (61) | 16.8 (46) | 15.4 (42) | 14.3 (37) | 9.3 (24) | 10.5 (27) |
| Diuretic (loop and thiazide) | 81.7 (223) | 74.4 (203) | 55.3 (151) | 55.8 (144) | 47.7 (123) | 39.9 (103) |
| All others | 83.9 (229) | 76.9 (210) | 57.9 (158) | 58.9 (152) | 51.9 (134) | 42.6 (110) |
| Any HF medication | 87.5 (239) | 82.1 (224) | 63.7 (174) | 65.1 (168) | 58.5 (151) | 50.4 (130) |
| HFmrEF (EF 41%-49%) | (n = 35) | (n = 35) | (n = 35) | (n = 36) | (n = 36) | (n = 36) |
| ACE inhibitor/ARB/ARNI | 31.4 (11) | 17.1 (6) | 22.9 (8) | 8.3 (3) | 5.6 (2) | 8.3 (3) |
| Beta-blocker | 31.4 (11) | 22.9 (8) | 17.1 (6) | 13.9 (5) | 11.1 (4) | 11.1 (4) |
| MRA | 20.0 (7) | 11.4 (4) | 17.1 (6) | 13.9 (5) | 13.9 (5) | 11.1 (4) |
| Diuretic (loop and thiazide) | 85.7 (30) | 65.7 (23) | 60.0 (21) | 58.3 (21) | 50.0 (18) | 41.7 (15) |
| All others | 91.4 (32) | 68.6 (24) | 65.7 (23) | 63.9 (23) | 52.8 (19) | 50.0 (18) |
| Any HF medication | 91.4 (32) | 80.0 (28) | 71.4 (25) | 58.3 (21) | 55.6 (20) | 52.8 (19) |
| HFpEF (EF ≥50%) | (n = 189) | (n = 189) | (n = 189) | (n = 209) | (n = 209) | (n = 209) |
| ACE inhibitor/ARB/ARNI | 18.5 (35) | 12.7 (24) | 14.3 (27) | 23.0 (48) | 12.9 (27) | 15.3 (32) |
| Beta-blocker | 25.9 (49) | 19.0 (36) | 15.9 (30) | 27.8 (58) | 18.2 (38) | 22.5 (47) |
| MRA | 24.9 (47) | 15.9 (30) | 19.0 (36) | 20.1 (42) | 15.8 (33) | 12.0 (25) |
| Diuretic (loop and thiazide) | 85.2 (161) | 81.0 (153) | 62.4 (118) | 63.6 (133) | 56.5 (118) | 46.9 (98) |
| All others | 86.8 (164) | 83.1 (157) | 65.1 (123) | 65.1 (136) | 58.9 (123) | 49.8 (104) |
| Any HF medication | 87.8 (166) | 84.7 (160) | 69.8 (132) | 73.7 (154) | 67.5 (141) | 55.0 (115) |

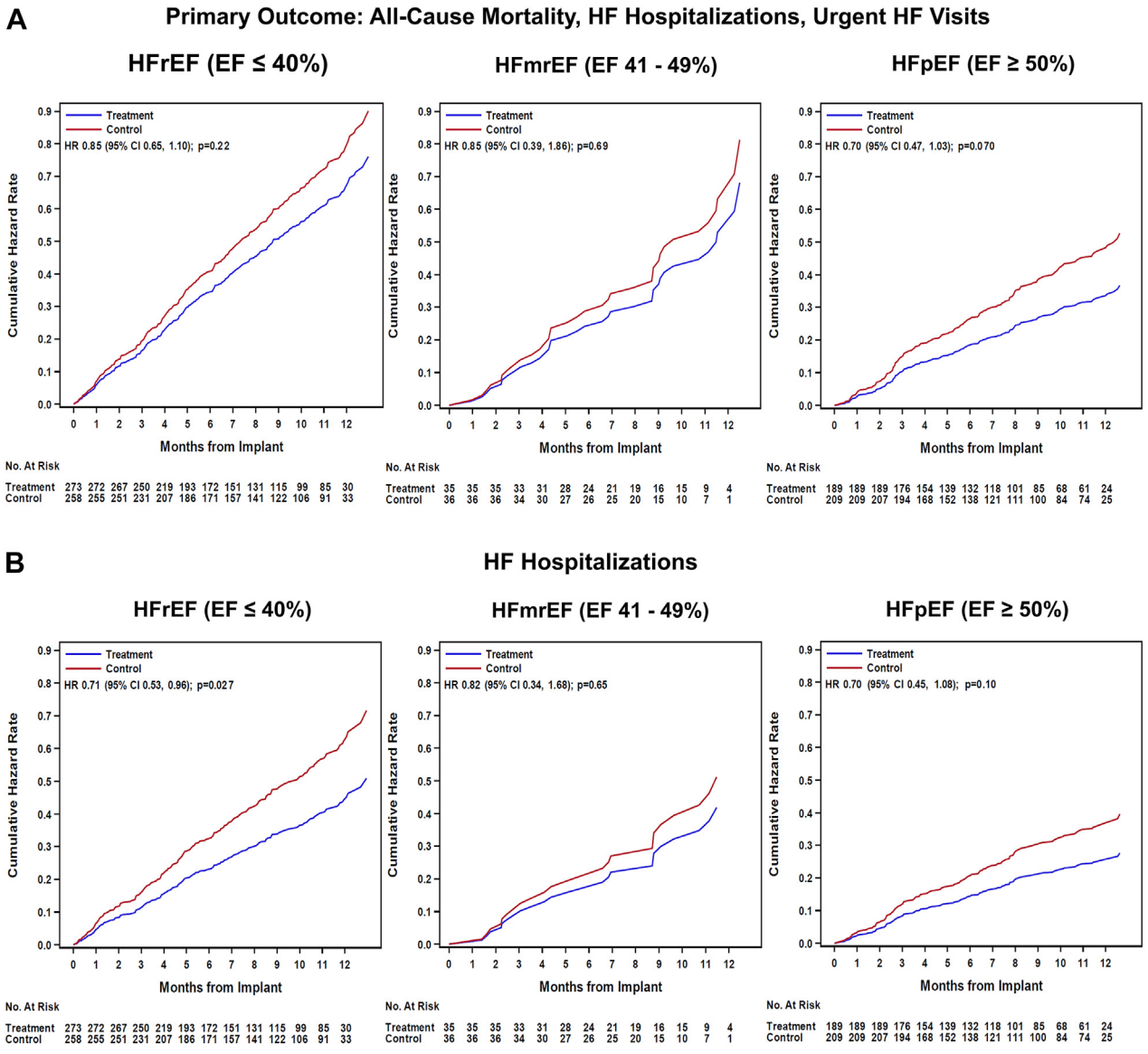
Values are % (n).
EF = ejection fraction; other abbreviations as in Table 1.

21.6 ± 7.1 in 41%-49% EF, and 22.1 ± 6.8 in ≥50% EF groups), with ≤40% EF pressures being higher but not statistically different from the other 2 groups (Table 1, Figure 4). The pattern of pressure changes from 6 weeks before a HF event and after a HF event was comparable across the 3 EF groups (Figure 4), demonstrating a consistent increase in PA pressure preceding a HF event and a decreased PA pressure after discharge. Fewer patients in the treatment group compared with the control group developed this pattern of increasing pressure resulting in a HF hospitalization. This was true across all 3 EF groups.

Changes in PA pressure data across follow-up for subgroups <50% vs ≥50% are plotted in Figure 5. The small sample size and significant variability in the HFmrEF subgroup limited the ability to successfully and meaningfully analyze pressure data in 3 EF groups. Daily AUC for mean PA pressure decreased in both treatment and control groups significantly relative to baseline, with greater reduction in the treatment group in both the HFrEF and HFpEF but without a significant difference between groups (Figure 5) (−620.6 ± 1,330.7 mm Hg-days in HFrEF, −350.8 ± 1,307.2 in HFpEF for treatment vs control −420.3 ± 1,442.8 in HFrEF, −190.9 ± 1,141.3 in HFpEF). Even when analyzed in each of the 3 EF groups, daily mean PA pressure decreased in both treatment and control groups (−641.7 ± 1,294.1 mm Hg-days in HFrEF, −456.6 ± 1,600.0 in HFmrEF, −350.8 ± 1,307.2 in HFpEF groups vs control −400.9 ± 1,489.0 in HFrEF, −556.8 ± 1,068.3 in HFmrEF, −190.9 ± 1,141.3 in HFpEF). Similar data patterns in AUC and mean pressures were seen using PA systolic and diastolic pressures.

**ADVERSE EVENTS.** The AEs rate (as reported by the sites) for hypotension, hypovolemia, hyperkalemia, hypokalemia, and acute kidney injury in each of the 3 EF categories and in both the treatment and control

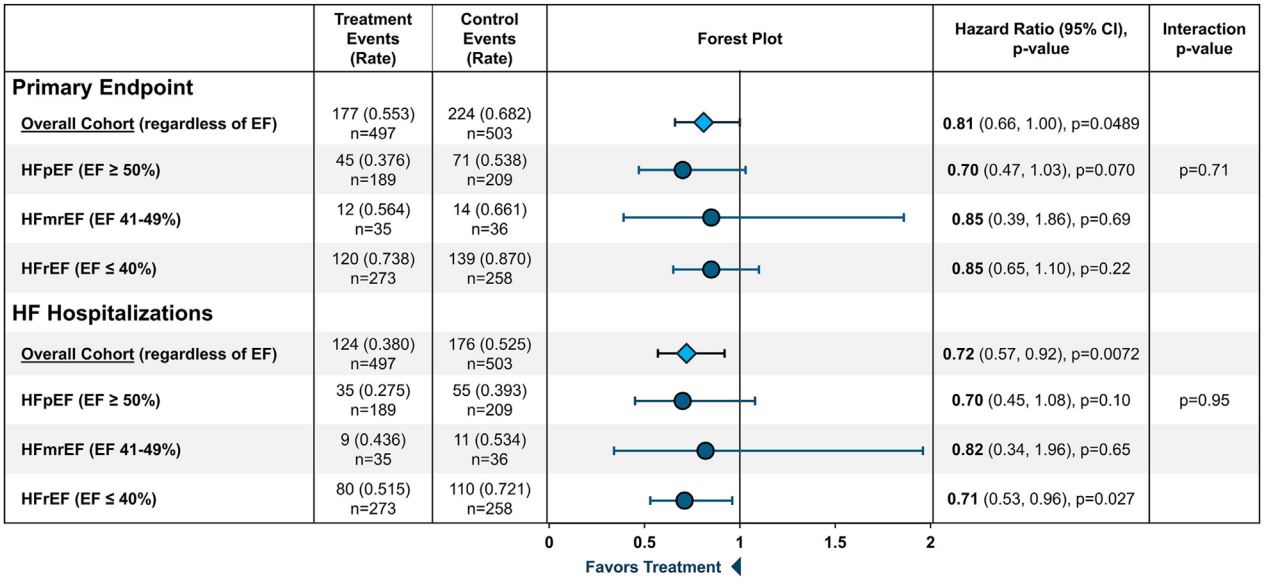
**FIGURE 2** **Effects of Hemodynamically-Guided Management on the GUIDE-HF Trial Endpoints**




**(A)** The primary endpoint was all-cause mortality, HF hospitalizations, and urgent HF visits in 3 EF groups: HFrEF (EF ≤40%), HFmrEF (EF 41%-49%), HFpEF (EF ≥50%). The usual care control group is plotted in **red**, the treatment group in **blue**. Across the EF spectrum, hemodynamically-guided management reduced the primary endpoint. **(B)** Effects of hemodynamically-guided management on the GUIDE-HF trial HF hospitalizations in 3 EF groups: HFrEF (EF ≤40%), HFmrEF (EF 41%-49%), and HFpEF (EF ≥50%). The usual care control group is plotted in **red**, the treatment group in **blue**. Across the EF spectrum, hemodynamically-guided management reduced the HF hospitalizations. HF = heart failure; HFmrEF = heart failure with mildly reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; other abbreviations as in Figure 1.

groups of these 3 EF categories were examined. As shown in Supplemental Table 1, the rate of AEs was quite low for all events in all groups. Given the low AE rate and the small sample size for the HFmrEF group, we presented data for EF <50% and ≥50% in the table. From this analysis we concluded that the rate of AEs that could potentially be related to hemodynamically-guided management was not statistically different between treatment and control and was not different across the EF spectrum.

**FIGURE 3** Forest Plot Depicting the Effects of Hemodynamically-Guided Treatment vs Usual Care Control on Event Rates



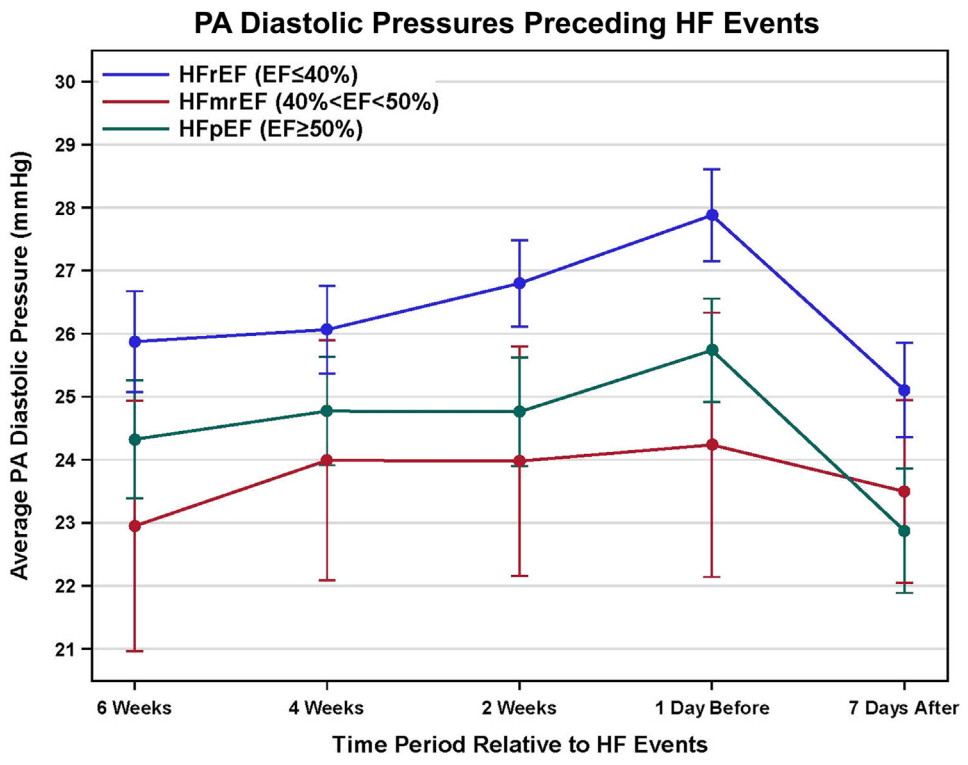

This figure plots HR with 95% CI and *P* value. Primary endpoint and HF hospitalizations for overall patient group, 3 EF groups: HFrEF (EF ≤40%), HFmrEF (EF 41%-49%), and HFpEF (EF ≥50%) are plotted. For each endpoint, an interaction *P* value is presented. Abbreviations as in Figures 1 and 2.

## DISCUSSION

The current analysis of the data from the GUIDE-HF trial provides novel findings with respect to understanding the impact of hemodynamic management across the EF spectrum of HF. First, hemodynamically-guided management of patients with HF based on direct measurement of filling pressures is effective across the EF spectrum in reducing the HF hospitalization endpoint in an expanded patient population of NYHA functional class II-IV HF enrolled with a previous HF hospitalization or increased natriuretic peptides. Second, key changes in medications in response to measured hemodynamics were similar in patients in all EF groups with greater interventions in the treatment group, supporting the contention that observed efficacy is related to changes in filling pressures. Third, baseline pressure, change from baseline pressure, and differences between treatment and control pressures were similar in patients in all EF groups indicating that treatment efficacy is likely independent of the baseline EF.

**EFFECTIVENESS OF MEDICATION TITRATION BASED ON PRESSURE VS EF.** In 3 studies using CardioMEMS-based hemodynamically-guided management,[5,6,12] the most frequent medication change, and in particular, the most frequent medication that was increased in dose or started de novo were diuretics, including both loop and thiazide diuretics.[6,9,13,14] Diuretics were changed in an average of 80%-85% of patients in the treatment arm vs 50%-60% in the control arm with the majority of these changes consisting of an increase in dosage. The use of diuretic agents was similar across the various EF groups and were done at pressures that were increased to a comparable degree in all EF groups. It seems likely that these medication changes and resultant decreases in pressure played a causative role in the resultant reduction in HF events, supporting the role of congestion on HF events. However, these observations stand in contrast to a number of studies that question the value of diuretic use in patients with HF and suggest that the higher the diuretic use, frequency, and dose, the higher the HF hospitalization rate.[15,16] In addition, drugs that lower diuretic use or augment diuresis, such as ARNI and sodium-glucose transport protein 2 (SGLT2) inhibitors, have been found to reduce HF hospitalization.[17-19] It should be noted that studies that show these adverse effects of diuretic agents did not use direct measures of pressure to choose the dose or titrate the regimen of the diuretic. One previous study that tried to account for the degree of volume overload (and thus indirectly the degree of pressure increase) found that increased diuretic use decreased

**FIGURE 4** PA Diastolic Pressures Preceding HF Events in 3 EF Groups

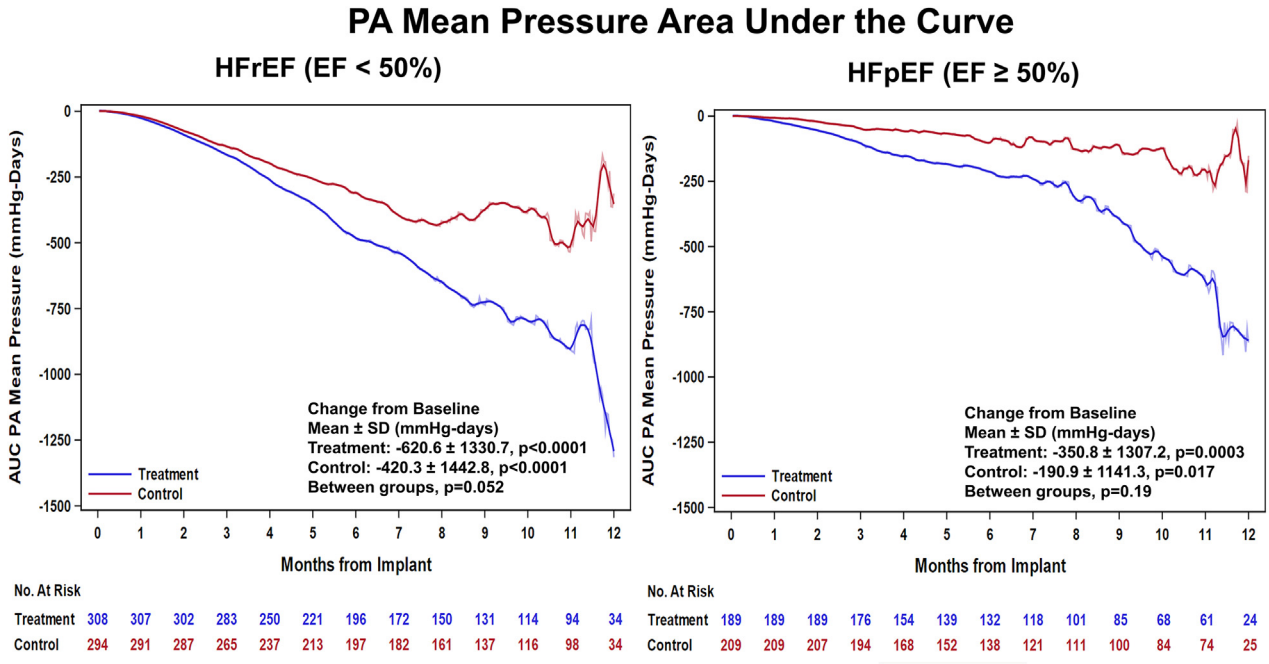



The 3 study groups were HFrEF (EF ≤40%), HFmrEF (EF 41%-49%), and HFpEF (EF ≥50%). Baseline pressures were comparable across the 3 EF groups with ≤40% EF pressures being higher but not statistically different from the other 2 groups. The pattern of pressure changes from 6 weeks before and after HF event was comparable across the 3 EF groups. PA = pulmonary artery; other abbreviations as in Figures 1 and 2.

HF hospitalization in those patients with the most "congestion" (ie, increased pressure), whereas increased diuretic use in those patients with no signs of congestion had an increase in hospitalization rate.[20] Data from the current analysis supports the concept that hemodynamically-guided management with diuretic agents can safely and effectively reduce HF events in patients across the EF spectrum by targeting those at risk for such events while potentially avoiding use in others. It should be acknowledged, however, that the current analysis could not be used to determine which change in drug category, which increase or decrease in drug dose, and which short- or long-term change in therapy was responsible for the decrease in HF events in the treatment group. In general changes in treatment fell into 2 categories: 1) changes in disease-modifying guideline-directed therapy, which were longer term and meant to decrease the "static" high values of pressure; and 2) changes in diuretic agents (and perhaps vasodilators), which were of shorter-term use and meant to decrease "dynamic" increases in pressure that precede the onset of "acute decompensated HF." GUIDE-HF did not prescribe the choices made by the clinicians; rather, clinicians were instructed to "act" on dynamic pressure changes using medication changes they deemed appropriate based on general guidelines provided to lower elevated static pressures during the study. It is likely these approaches led to a larger number of medication changes in ACE inhibitor/ARB/ARNI and beta-blockers in patients with HFrEF and HFmrEF compared with patients with HFpEF. The only supportable conclusions that we can draw is that the clinician choice of medication change in response to measured hemodynamics appears to have been successful in decreasing HF event rates.

**RESPONSE TO TREATMENT ACROSS THE EF SPECTRUM.** It was not a given that hemodynamically-guided management would reduce HF events across the EF spectrum, especially at the extremes of the EF range. For example, 4 categories of pharmacologic therapy, ARB (candesartan), MRA (spironolactone), ARNI

**FIGURE 5** PA Mean Pressure AUC




AUC data during 12-month study follow-up in 2 EF groups: EF <50% and EF ≥50%. The usual care control group is plotted in **red**, the treatment group in **blue**. Daily AUC for mean PA pressure decreased in both treatment and control groups, with significantly greater reduction in the treatment group in each EF group. AUC = area under the curve; other abbreviations as in Figures 2 and 4.

(sacubitril/valsartan), and SGLT2 inhibitors (dapagliflozin, empagliflozin), have been shown to effectively reduce HF events across a wide, but incomplete, range of EFs.[7,8,21,22] In these studies, the efficacy of these drugs appeared to wane at the lowest and highest ranges of EFs. These study results have led to variability in pharmacologic therapy recommendation based on EF despite subsequent FDA approval across a broad range of EFs.[1,2] By contrast, device-based hemodynamically-guided management has demonstrated efficacy across the entire range of EFs based on the use of measured pressures. It is uncertain why the response to HF drugs would differ across EF and differ from hemodynamic-based management. There are, however, several possible but speculative explanations.

There may be both hemodynamic and nonhemodynamic reasons why HF management would result in nonhomogeneous results across EFs. Fundamental differences in left ventricular diastolic pressure-volume relationship (stiffness) between EF groups may play a role. It is possible that variable steepness (shape and position) makes the response to therapy different in each HF subgroup.[23] For example, at lower EFs (with a less steep curve) a larger change in volume is required to achieve a desired change in pressure. Conversely, at higher EFs (with a steeper curve) a smaller change in volume is required to achieve a desired change in pressure. In addition, for similar reasons, it may be more difficult to assess "volume status" in patients with HF at the highest or lowest ranges in EF, especially in an ambulatory setting, even with invasive hemodynamic monitoring because intravascular volume may differ at similar pressures in patients across EFs. Therefore, theoretically, treatment interventions based on pressure could have had variable effect in each EF category; however, data from GUIDE-HF demonstrated that management based on pressure was equally effective across the EF spectrum. Alternatively, patients with HF across an EF spectrum may have a differential rate of complications and comorbidities for selected therapy that limits treatment intensity and limits beneficial effects on outcomes. Finally, trials evaluating new pharmacologic agents specifically attempt to keep medical management constant throughout the study; studies evaluating hemodynamically-guided management take a

completely opposite approach, starting with stable drug therapy but encouraging titration of existing medications and adding evidence-based medications in an attempt to optimize and control PA pressure.

In GUIDE-HF (and CHAMPION [CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in New York Heart Association [NYHA] Class III Heart Failure Patients][24]), drugs and doses were comparable across EFs and complications from these drugs were comparable across EF. Furthermore, patients with HF with higher EF have a greater aggregation of comorbid, nonhemodynamic, noncardiac clinical illnesses that limit measurable effectiveness of cardiovascular-directed drugs. When cardiovascular morbidity and mortality are low in a given HF population, it is more difficult to prove the benefits of a given cardiovascular-directed treatment. Pressure may be the exception to this observation. Another factor to consider is that HFrEF has a high rate of HF hospitalization and HF mortality, which is primarily caused by HF but HFpEF has a lower rate of HF hospitalization and HF mortality so at least the absolute benefit of drugs is less whereas at equivalent rates of congestion there are equal HF hospitalization and mortality (like similar B-type natriuretic peptides [BNPs] have the same mortality in HFrEF and HFpEF).

**STUDY LIMITATIONS.** There was no core laboratory evaluation for EF determination, and, thus, there may be misclassification of EFs within groups. Individual statistics and degree of statistical significance (as measured using a *P* value threshold) may have varied due to differing number of events and patients within the EF categories, however, it is important to note the consistent pattern and point estimates <1. Particularly in the HFmrEF group, and in all EF groups, "significance" was limited by small sample sizes. When HFmrEF was added into the <40% or >50%, the *P* values were more significant. The consistency of the observed patterns supports the conclusions in this analysis. Further, adjusted analyses within the EF subgroups were not performed to account for all baseline differences.

## CONCLUSIONS

Data from the GUIDE-HF trial indicate that hemodynamically-guided HF management decreased the HF event rate across the EF spectrum in an expanded patient population of patients with HF. Furthermore, these data suggest that targeting filling pressures supersedes categories of EF as a fundamental determinant of HF hospitalization risk. It may be for this reason that hemodynamically-guided management reduces event rates across the EF spectrum, whereas medication trials have not because they fundamentally do not primarily target pressure. Although further intervention studies to evaluate specific algorithms for therapeutic intervention across the spectrum of EF may be warranted, the current study demonstrates consistency across the various EF ranges when hemodynamic changes are targeted for medical management.

## FUNDING SUPPORT AND AUTHOR DISCLOSURES

Funding was provided by Abbott. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

**ADDRESS FOR CORRESPONDENCE:** Dr Michael R. Zile, Division of Cardiology, Department of Medicine, Medical University of South Carolina, Thurmond/Gazes, Room 323, 30 Courtenay Drive, Charleston, South Carolina 29425, USA. E-mail: zilem@musc.edu.

## PERSPECTIVES

**COMPETENCY IN MEDICAL KNOWLEDGE:** The effects of medical therapies using 4 classes of drugs, SGLT2 inhibitors, ARNI, MRAs, and ARBs, on cardiovascular morbidity and mortality appear to "trail off" toward a lack of significance in subgroups of patients with HF based on EF.[7,21] This is particularly true in HFpEF subsets especially at EFs >60%-65%. Each of the drugs were studied in trials segmented by EF ranges and with dosages targeted to this highest tolerable dose regardless of EF. In contrast, the hemodynamically-guided management strategy studied in GUIDE-HF was shown to be effective across the EF spectrum with HRs consistently falling below 1, reflecting effectiveness.

**TRANSLATIONAL OUTLOOK:** These data suggest that a strategy targeting filling pressures represents a fundamental determinant of decreasing HF hospitalization risk. It may be for this reason that hemodynamically-guided management reduces event rates across the EF spectrum, whereas medication trials have not because they do not primarily target filling pressure. Would individual medication trials succeed more definitively across all EF ranges if dosages were determined by filling pressures? This remains an intriguing question to answer.

## REFERENCES

**1.** Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2022;79:e263–e421.

**2.** McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2021;42:3599–3726.

**3.** Zile MR, Bennett TD, St John Sutton M, 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.

**4.** Zile MR, Bennett TD, El Hajj S, 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.

**5.** Abraham WT, Stevenson LW, Bourge RC, et al. 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.

**6.** Lindenfeld J, Zile MR, Desai AS, et al. Haemodynamic-guided management of heart failure (GUIDE-HF): a randomised controlled trial. *Lancet*. 2021;398:991–1001.

**7.** Dewan P, Jackson A, Lam CSP, et al. Interactions between left ventricular ejection fraction, sex and effect of neurohumoral modulators in heart failure. *Eur J Heart Fail*. 2020;22:898–901.

**8.** Solomon SD, Vaduganathan M, Claggett BL, et al. Sacubitril/Valsartan across the spectrum of ejection fraction in heart failure. *Circulation*. 2020;141:352–361.

**9.** Zile MR, Desai AS, Costanzo MR, et al. The GUIDE-HF trial of pulmonary artery pressure monitoring in heart failure: impact of the COVID-19 pandemic. *Eur Heart J*. 2022;43(27):2603–2618. https://doi.org/10.1093/eurheartj/ehac114

**10.** Lindenfeld J, Abraham WT, Maisel A, et al. Hemodynamic-GUIDEd management of Heart Failure (GUIDE-HF). *Am Heart J*. 2019;214:18–27.

**11.** Bozkurt B, Coats AJ, Tsutsui H, et al. Universal definition and classification of heart failure: a report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and writing committee of the universal definition of heart failure. *J Card Fail*. 2021;23:352–380.

**12.** Shavelle DM, Desai AS, Abraham WT, 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.

**13.** Adamson PB, Abraham WT, Bourge RC, et al. Wireless pulmonary artery pressure monitoring guides management to reduce decompensation in heart failure with preserved ejection fraction. *Circ Heart Fail*. 2014;7(6):935–944.

**14.** Brinkley DM, Guglin ME, Bennett MK, et al. Pulmonary artery pressure monitoring effectively guides management to reduce heart failure hospitalizations in obesity. *J Am Coll Cardiol HF*. 2021;9:784–794.

**15.** Curtain JP, Campbell RT, Petrie MC, et al. Clinical outcomes related to background diuretic use and new diuretic initiation in patients with HFrEF. *J Am Coll Cardiol HF*. 2022;10(6):415–427.

**16.** Felker GM, O'Connor CM, Braunwald E. Loop diuretics in acute decompensated heart failure: necessary? Evil? A necessary evil? *Circ Heart Fail*. 2009;2:56–62.

**17.** Desai AS, Heywood JT, Rathman L, et al. Early reduction in ambulatory pulmonary artery pressures after initiation of sacubitril/valsartan. *Circ Heart Fail*. 2021;14:e008212.

**18.** Vardeny O, Claggett B, Kachadourian J, et al. Reduced loop diuretic use in patients taking sacubitril/valsartan compared with enalapril: the PARADIGM-HF trial. *Eur J Heart Fail*. 2019;21:337–341.

**19.** Jackson AM, Dewan P, Anand IS, et al. Dapagliflozin and diuretic use in patients with heart failure and reduced ejection fraction in DAPA-HF. *Circulation*. 2020;142:1040–1054.

**20.** Faselis C, Lam PH, Patel S, et al. Loop diuretic prescription and long-term outcomes in heart failure: association modification by congestion. *Am J Med*. 2021;134:797–804.

**21.** Packer M, Butler J, Zannad F, et al. Effect of empagliflozin on worsening heart failure events in patients with heart failure and preserved ejection fraction: EMPEROR-Preserved trial. *Circulation*. 2021;144:1284–1294.

**22.** Packer M, Anker SD, Butler J, et al. Effect of empagliflozin on the clinical stability of patients with heart failure and a reduced ejection fraction: the EMPEROR-Reduced trial. *Circulation*. 2021;143:326–336.

**23.** Aurigemma GP, Zile MR, Gaasch WH. Contractile behavior of the left ventricle in diastolic heart failure: with emphasis on regional systolic function. *Circulation*. 2006;113:296–304.

**24.** Costanzo MR, Stevenson LW, Adamson PB, et al. Interventions linked to decreased heart failure hospitalizations during ambulatory pulmonary artery pressure monitoring. *J Am Coll Cardiol HF*. 2016;4:333–344.

**KEY WORDS** ejection fraction, heart failure, hemodynamics, pulmonary artery pressure

**APPENDIX** For a supplemental table, please see the online version of this paper.


Go to http://www.acc.org/jacc-journals-cme to take the CME/MOC/ECME quiz for this article.