Heart Failure

Physician-Directed Patient Self-Management of Left Atrial Pressure in Advanced Chronic Heart Failure

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Background—Previous studies suggest that management of ambulatory hemodynamics may improve outcomes in chronic heart failure. We conducted a prospective, observational, first-in-human study of a physician-directed patient self-management system targeting left atrial pressure.

Methods and Results—Forty patients with reduced or preserved left ventricular ejection fraction and a history of New York Heart Association class III or IV heart failure and acute decompensation were implanted with an investigational left atrial pressure monitor, and readings were acquired twice daily. For the first 3 months, patients and clinicians were blinded as to these readings, and treatment continued per usual clinical assessment. Thereafter, left atrial pressure and individualized therapy instructions guided by these pressures were disclosed to the patient. Event-free survival was determined over a median follow-up of 25 months (range 3 to 38 months). Survival without decompensation was 61% at 3 years, and events tended to be less frequent after the first 3 months (hazard ratio 0.16 [95% confidence interval 0.04 to 0.68], \( P = 0.012 \)). Mean daily left atrial pressure fell from 17.6 mm Hg (95% confidence interval 15.8 to 19.4 mm Hg) in the first 3 months to 14.8 mm Hg (95% confidence interval 13.0 to 16.6 mm Hg; \( P = 0.003 \)) during pressure-guided therapy. The frequency of elevated readings (>25 mm Hg) was reduced by 67% \( (P < 0.001) \). There were improvements in New York Heart Association class (\(-0.7 \pm 0.8, P < 0.001\)) and left ventricular ejection fraction (\(7 \pm 10\% , P < 0.001\)). Doses of angiotensin-converting enzyme/angiotensin-receptor blockers and \(\beta\)-blockers were uptitrated by 37% \((P < 0.001)\) and 40% \((P < 0.001)\), respectively, whereas doses of loop diuretics fell by 27% \((P = 0.15)\).

Conclusions—Physician-directed patient self-management of left atrial pressure has the potential to improve hemodynamics, symptoms, and outcomes in advanced heart failure.

Clinical Trial Registration Information—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00547729.

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Key Words: heart failure ■ hemodynamics ■ diuretics ■ self-management ■ left atrium ■ monitoring, physiological

Despite advances in evaluation and management of heart failure, morbidity and mortality remain high, with rehospitalization rates of 20% at 1 month and nearly 50% at 6 months.\(^1\)\(^-\)\(^8\) Approximately 90% of patients admitted to the hospital for heart failure have pulmonary congestion related to elevated left atrial filling pressure (LAP).\(^8\)\(^-\)\(^10\) Recommended methods for detecting congestion in outpatients are insensitive and do not reduce readmission rates.\(^1\)\(^-\)\(^11\)

 Implantable hemodynamic monitoring systems have been developed to guide outpatient heart failure management with the aim of reducing episodes of acute decompensated heart failure.\(^10\)\(^-\)\(^12\) The present report includes the clinical results of the Hemodynamically Guided Home Self-Therapy in Severe Heart Failure Patients (HOMEOSTASIS) trial. Using a per-
manently implanted LAP sensor linked to a physician-directed patient self-management treatment paradigm, this small observational study assessed early safety and clinical outcomes with the goal of generating hypotheses for subsequent randomized trials.

Methods

Patients

HOMEOSTASIS is the first human use of an implanted LAP monitoring system (HeartPOD, St Jude Medical Inc, Minneapolis, Minn) for the management of heart failure (Figure 1). The trial comprised the first 20 patients enrolled in 3 Australian/New Zealand sites and the first 20 patients enrolled in 4 US centers.

Patients were eligible if they had a history of New York Heart Association class III or ambulatory class IV heart failure of at least 6 months, regardless of left ventricular ejection fraction. They were required to have at least 1 episode of acute decompensated heart failure treated with intravenous therapy during the prior year and to be taking maximally tolerated, stable doses of an angiotensin-converting enzyme (ACE) inhibitor or angiotensin-receptor blocker (ARB) and a β-blocker if left ventricular ejection fraction was <40%.

Patients were excluded if they had intractable class IV heart failure, recent acute coronary syndrome, stroke or left-sided cardiac thrombus, creatinine >2.5 mg/dL, or chronic atrial fibrillation. The trial was approved by the US Food and Drug Administration under an Investigational Device Exemption (G050018) and by the institutional review boards associated with each center. All subjects gave written informed consent. Serious adverse events were adjudicated for cause and study relatedness by an independent clinical events committee, and patient safety was assessed periodically by an independent data safety monitoring board.

Study Design

The study was a prospective, observational, open-label registry (Figure 2). Details of the device, protocol, early safety, and LAP sensor performance have been published previously.12 Briefly, after implantation of the LAP sensor lead and subcutaneous antenna (inserted during transeptal cardiac catheterization), patients were seen at 2 and 6 weeks, at 3 months, and every 3 months thereafter. Postprocedure medications included aspirin (150 to 325 mg/d) and clopidogrel 75 mg/d for 6 months. Patients taking warfarin for other indications additionally received aspirin (150 to 325 mg/d). During the first 3 months, known as the “observation period,” patients and clinicians were blinded to LAP readings, and treatment was based on clinical status according to routine clinical assessment and standard guidelines. Patients next entered a 3-month “titration period” during which LAP-guided therapy was initiated with the goal of optimizing LAP trends and clinical status. Thereafter, patients entered the “stability period” for the study duration, during which the intention was to use guided therapy to maintain optimal LAP.

Patients acquired LAP data by placing a handheld patient advisor module (PAM) over the subcutaneous antenna. The PAM powers the sensor by use of radiofrequency telemetry and displays pressure data. The PAM’s reminder function alerted patients to measure resting LAP within scheduled morning and evening time windows before they took their heart failure medications. Patients were encouraged to take additional LAP readings if they had worsening symptoms. At clinic visits, LAP trends and waveform data were uploaded, and treatment orders were downloaded to the PAM.12 There was no facility for remote upload of hemodynamic data.

After 3 months and at the local investigator’s discretion, the PAM was set to display LAP values and to inform patients which medications were due according to the local investigator’s prescription. Such enabling triggered transition from the observation to the titration period. LAP-guided therapy was enabled in 2
Inclusion/Exclusion & Consent
n=40

Implant Study Device & RHC
n=40

Observation Period
Standard therapy without LAP-guidance for 3 months & RHC

Titration Period
LAP-guided therapy rapid drug titration for 3 months

Stability Period
LAP-guided therapy for ≥ 6 months & RHC at 12 months

1st Safety Endpoint at 6 weeks
n=40

12 month follow-up
n=35, 4 deaths, 1 withdrawal

 Longer term follow-up
median 25 months
n= 30, 9 deaths, 1 withdrawal

Figure 2. HOMEOSTASIS trial design. RHC indicates right-sided heart catheterization.

ways. Prescriptions could be adjusted according to overall LAP trends. This type of dosing was called “static therapy.” If further enabled, the PAM displayed physician-directed patient self-management instructions called “dynamic therapy,” which allowed specified treatments to be adjusted by the current LAP value. Dynamic therapy was based on 5 LAP ranges (very low, low, optimal, high, and very high). Local investigators individually adjusted these ranges for each patient. Each range was associated with a prescription for medication dosing, activity level, sodium and fluid intake, or physician contact. Although there were no specific prescribing rules and dynamic prescribing was at the discretion of the local investigator, the general aim was to reduce or eliminate diuretic doses for low or very low LAP and increase diuretic or vasodilator doses for high or very high LAP. Figure 3 is an example of LAP waveforms and trends in 1 subject before and after dynamic therapy was applied.

Data Analysis
Investigators had full access to the study data, which were analyzed on the basis of intention to treat with LAP-guided therapy. Data are presented as mean±SD or 95% confidence intervals (CIs).

The primary safety end point was freedom from major adverse cardiac and neurological events at 6 weeks. Major adverse cardiac and neurological events were defined as the hierarchical composite of cardiovascular-related death, myocardial infarction, systemic thromboembolism, and stroke. Device success was defined as freedom from device failure due to explantation for infection or sensor malfunction sufficient to preclude clinical use. Outcome events were the composite of acute decompensated heart failure that required intravenous heart failure therapy or death due to any cause. Echocardiographic and right-sided heart catheterization parameters were reviewed by observers blinded to the time point. Estimated glomerular filtration rate was calculated with the Modification of Diet in Renal Disease Study equation. Compliance was estimated as the fraction of scheduled LAP readings taken. Target ACE/ARB and β-blocker doses were defined as ≥50% of maximal American Heart Association/American College of Cardiology heart failure guideline doses. LAP control was empirically defined if the frequency of pressures ≥25 mm Hg was <10% for 6 consecutive months.

Time to first events was evaluated by the Kaplan–Meier product-limit method. The effect of LAP-guided treatment was assessed with a modified landmark analysis in which the landmarks were enrollment and transition from the observation to the titration/stability periods. The estimated hazard ratios and CIs were calculated by the Cox regression method. All remaining summary data were generated with generalized linear mixed-effects models that included subjects as the random effect (intercept), whereas study periods and events were fixed effects. Event rates were analyzed as Poisson distributed data; serial measurements of LAP, clinical parameters, and drug dose were treated as normally distributed data; and LAP distributions and drug use frequencies were analyzed as binomially distributed data. All P values and CIs were calculated by the generalized linear mixed-effects model with appropriate distribution assumptions. A 2-tailed P<0.05 was taken to indicate statistical significance.

Results
Patient Characteristics
Enrollment was from March 2005 to May 2007. The database closed on June 30, 2008, with a median follow-up of 25 months (range 3 to 38 months) available in 39 patients (97.5%). One patient withdrew 5.8 months after implantation (see below for details). Before enrollment, all patients were managed by cardiologists, and 87.5% were treated in hospital-based heart failure specialty clinics at trial sites.

Table 1 summarizes patient demographics and laboratory parameters at enrollment. Patients were older, predominantly male, white, and moderately obese. Ischemic cardiomyopathy was the most common cause of heart failure, and comorbidities including diabetes and renal dysfunction (67.5% with estimated glomerular filtration rate <60 mL·min⁻¹·1.73 m⁻²) were frequent. Fifty-five percent had prior cardiac resynchronization therapy and/or an implantable cardioverter defibrillator. The average left ventricular ejection fraction was 32%, which included 9 patients (23%) with preserved left ventricular ejection fraction ≥40%. All patients had compensated heart failure at enrollment. On average, cardiac filling pressures, systemic and pulmonary vascular resistances, and brain natriuretic peptide levels were moderately elevated, whereas cardiac index and exercise capacity were reduced.
Device Success
Study devices were implanted successfully in all subjects. Four patients had device failures due to sensor malfunction; 3 underwent successful implantation of a new sensor lead after 4, 5, and 26 months, respectively. The fourth patient declined lead replacement. A total of 43 sensors were implanted in the 40 patients. At last follow-up, 38 patients (95%) had functioning implants guiding therapy.

Effect on Clinical Outcomes
After implantation, all subjects were free of major adverse cardiac and neurological events at 6 weeks, which achieved the primary safety end point. There were 2 late ischemic strokes. In 1 subject with previous postinfarction ventricular septal defect repair, left ventricular thrombus was present before implantation and after stroke. Although the protocol had been breached at enrollment, a relationship to the study could not be excluded. This is the patient who later withdrew from the trial. The second patient developed a transient VII cranial nerve palsy and confusion. No source of embolus was found on transesophageal echocardiography, and computed tomography did not show cerebral infarction.

The event rate during the 1 year before enrollment was 1.4 events per year (95% CI 1.1 to 1.9 per year). The event rate trended lower during the observation period (0.68 per year [95% CI 0.33 to 1.4 per year]; P=0.054) and was significantly lower during the titration and stability periods (0.28

Figure 3. Top, Examples of LAP and intracardiac electrogram (IEGM) waveforms in a 60-year-old man with ischemic cardiomyopathy and left ventricular ejection fraction of 25%. After it recorded an LAP of 40 mm Hg with v waves >70 mm Hg at 9 AM, the PAM instructed the patient to take furosemide 80 mg and to call the clinic. After 4 hours, LAP returned to near normal at 13 mm Hg. Bottom, Trend plot of same subject showing morning and evening LAP values and 7-day moving average over a 2-year period. LAP control was achieved with the dynamic-therapy patient self-management feature to adjust diuretics and the addition of a long-acting nitrate in the evening. The patient developed transient worsening symptoms when β-blockers were withheld inappropriately.
per year [95% CI 0.18 to 0.45 per year]), which represents 80% \((P<0.001)\) and 59% \((P=0.041)\) reductions compared with the previous year and the observation period, respectively.

Figure 4 shows event-free survival 2 ways: from the time of implantation and with respect to landmarks before and after LAP-guided therapy was initiated. There were 9 deaths (3 during hospital admission for acute decompensated heart failure, 3 due to other cardiac causes, and 3 noncardiac). No deaths were device or study related. There were 22 episodes of acute decompensated heart failure that required intravenous treatment. Altogether, 15 patients had 28 events. Event-free survival was 0.72 at 1 year, 0.69 at 2 years, and 0.61 after 3 years. Event-free survival during the observation period was 0.77 at the mean duration of the landmark \((3.4 \pm 1.0\) months) compared with 0.95 for the titration/stability periods after the same length of follow-up \((hazard ratio 0.16 [95\% CI 0.04 to 0.68], P=0.012)\). There were 2 episodes of uncomplicated dehydration during the titration/stability periods, each of which required a 1-day hospitalization. LAP values of <5 mm Hg were observed before both episodes.

Many clinical parameters improved from baseline to 3 months and later to 12 months, including New York Heart

Table 1. Patient Characteristics at Enrollment \((n=40\) Subjects)

<table>
<thead>
<tr>
<th>Demographics and clinical history</th>
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<tbody>
<tr>
<td>Age, y</td>
<td>66±10 ((47–83))</td>
</tr>
<tr>
<td>Male gender, %</td>
<td>78</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>92±19</td>
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<tr>
<td>Body mass index, kg/m²</td>
<td>32±6</td>
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<tr>
<td>NYHA class at enrollment, median (range)</td>
<td>3.0 ((2–3))</td>
</tr>
<tr>
<td>Prior myocardial infarction, %</td>
<td>73</td>
</tr>
<tr>
<td>Hyperlipidemia, %</td>
<td>88</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>60</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>73</td>
</tr>
<tr>
<td>CRT/ICD/CRT or ICD, %</td>
<td>32.5/45/55</td>
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<table>
<thead>
<tr>
<th>Laboratory testing</th>
<th></th>
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<tbody>
<tr>
<td>BNP, pg/mL</td>
<td>357±346 ((14–1429))</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>1.5±0.4 ((0.7–2.6))</td>
</tr>
<tr>
<td>eGFR, mL \cdot min^{-1} \cdot 1.73 m^{-2}</td>
<td>54±20 ((26–115))</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>13.4±1.5 ((9.1–17.3))</td>
</tr>
<tr>
<td>6-Minute walk, m</td>
<td>342±97 ((23–555))</td>
</tr>
<tr>
<td>V̇Ȯ₂ max, ml \cdot min^{-1} \cdot kg^{-1}</td>
<td>13.8±4.4 ((3.8–23.7))</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>32±12 ((10–60))</td>
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</table>

<table>
<thead>
<tr>
<th>Resting hemodynamics</th>
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<tbody>
<tr>
<td>Heart rate, bpm</td>
<td>65±10 ((45–88))</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>120±21 ((88–165))</td>
</tr>
<tr>
<td>RAP, mean, mm Hg</td>
<td>9±5 ((1–20))</td>
</tr>
<tr>
<td>PAP, systolic, mm Hg</td>
<td>42±13 ((17–64))</td>
</tr>
<tr>
<td>PAP, diastolic, mm Hg</td>
<td>21±9 ((4–38))</td>
</tr>
<tr>
<td>PCWP, mean, mm Hg</td>
<td>19±8 ((4–32))</td>
</tr>
<tr>
<td>LAP by catheter, mean, mm Hg</td>
<td>17±8 ((4–37))</td>
</tr>
<tr>
<td>Cardiac output, L/min</td>
<td>4.5±1.1 ((2.9–7.3))</td>
</tr>
<tr>
<td>Cardiac index, L \cdot min^{-1} \cdot m^{-2}</td>
<td>2.2±0.5 ((1.5–3.2))</td>
</tr>
<tr>
<td>SVRI, dyne \cdot s^{-1} \cdot cm^{-5} \cdot m^{-2}</td>
<td>2878±768 ((1538–4516))</td>
</tr>
<tr>
<td>PVRI, dyne \cdot s^{-1} \cdot cm^{-5} \cdot m^{-2}</td>
<td>367±197 ((79–980))</td>
</tr>
<tr>
<td>SVI, ml/m²</td>
<td>34±8 ((21–55))</td>
</tr>
</tbody>
</table>

NYHA indicates New York Heart Association; CRT, cardiac resynchronization therapy; ICD, implantable cardiac defibrillator; BNP, brain natriuretic peptide; eGFR, estimated glomerular filtration rate; V̇Ȯ₂ max, oxygen uptake; LVEF, left ventricular ejection fraction; RAP, right atrial pressure; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; SVRI, systemic vascular resistance index; PVRI, pulmonary vascular resistance index; and SVI, stroke volume index.

Data are summarized as mean±SD (range) unless otherwise specified.
Table 2. Selected Clinical Parameters in 12-Month Survivors (n=35 Subjects)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>3 Months</th>
<th>12 Months</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA class</td>
<td>2.5±0.5</td>
<td>2.3±0.7</td>
<td>1.8±0.8</td>
<td>&lt;0.001</td>
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<tr>
<td>MLWHFQ score</td>
<td>45±29</td>
<td>NA</td>
<td>36±25</td>
<td>0.011</td>
</tr>
<tr>
<td>BNP, pg/mL</td>
<td>316±296</td>
<td>257±214</td>
<td>303±256</td>
<td>0.21</td>
</tr>
<tr>
<td>eGFR, mL·min⁻¹·1.73 m⁻²</td>
<td>55±20</td>
<td>57±25</td>
<td>54±29</td>
<td>0.46</td>
</tr>
<tr>
<td>6-Minute walk, m</td>
<td>358±82</td>
<td>NA</td>
<td>368±100</td>
<td>0.40</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>33.2±12.7</td>
<td>NA</td>
<td>40.0±14.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>65±11</td>
<td>66±11</td>
<td>64±10</td>
<td>0.42</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>121±21</td>
<td>124±23</td>
<td>127±22</td>
<td>0.23</td>
</tr>
<tr>
<td>PCWP mean, mm Hg</td>
<td>17.7±7.7</td>
<td>14.9±7.0</td>
<td>14.1±7.9</td>
<td>0.013</td>
</tr>
<tr>
<td>Cardiac index, L·min⁻¹·m⁻²</td>
<td>2.2±0.5</td>
<td>2.5±0.6</td>
<td>2.5±0.5</td>
<td>0.010</td>
</tr>
<tr>
<td>SVRI, dyne·s⁻¹·cm⁻⁵·m⁻²</td>
<td>2850±791</td>
<td>2658±823</td>
<td>2672±676</td>
<td>0.34</td>
</tr>
<tr>
<td>PVRI, dyne·s⁻¹·cm⁻⁵·m⁻²</td>
<td>378±206</td>
<td>345±208</td>
<td>316±154</td>
<td>0.33</td>
</tr>
<tr>
<td>SVI, mL/m²</td>
<td>35.3±8.3</td>
<td>38.5±11.0</td>
<td>39.4±6.9</td>
<td>0.013</td>
</tr>
</tbody>
</table>

NYHA indicates New York Heart Association; MLWHFQ, Minnesota Living With Heart Failure Questionnaire quality-of-life score; NA, data not available for study period; BNP, brain natriuretic peptide; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; PCWP, pulmonary capillary wedge pressure; SVRI, systemic vascular resistance index; PVRI, pulmonary vascular resistance index; and SVI, stroke volume index.

Data are summarized as mean±SD. P values are for comparisons across all time points.

Association class, quality-of-life score, ejection fraction, pulmonary capillary wedge pressure, cardiac index, and stroke volume index (Table 2). Corresponding measurements of exercise capacity, brain natriuretic peptide, and estimated glomerular filtration rate remained unchanged. Patients with events had more abnormal baseline brain natriuretic peptide (537±437 vs 262±242 pg/mL, P=0.044), cardiac index (1.9±0.4 vs 2.4±0.5 L·min⁻¹·m⁻², P=0.004), and systemic vascular resistance index (3252±859 versus 2575±576 dyne·s⁻¹·cm⁻⁵·m⁻², P=0.013) than subjects without events.

Effect on LAP

LAP data were available for all study periods for 36 patients (90%). Subjects performed an average of 2.3±0.8 readings per day, which included 42,012 scheduled and 15,473 unscheduled readings. Compliance throughout the study was 78±22% (range 13% to 100%). All subjects had LAP elevations (the maximum LAP per patient averaged 44.3 mm Hg (95% CI 40.1 to 48.5 mm Hg, range 21 to 83 mm Hg).

Figure 5 shows the cumulative frequency distribution of LAP readings across surviving patients. LAP distributions were similar during the observation and titration periods (mean LAP 17.6 mm Hg [95% CI 15.8 to 19.4 mm Hg] and 17.3 mm Hg [95% CI 15.4 to 19.1 mm Hg], respectively; P=0.70). LAP fell during the stability period (14.8 mm Hg [95% CI 13.0 to 16.6 mm Hg], P=0.003) compared with the observation period. During the stability period, the frequency of LAP elevations >20 mm Hg was reduced by 59% compared with the observation period (P<0.001). Even greater relative reductions were seen for higher values of LAP (LAP >25, 67%; LAP >30, 84%; LAP >35, 87%; P<0.001 for all comparisons). The frequency of very-low-pressure readings (<5 mm Hg) did not change (P=0.84). LAP reductions were sustained in patients with at least 2 years of follow-up; mean LAP was 15.3 mm Hg (95% CI 13 to 17.5 mm Hg) and 14.2 mm Hg (95% CI 12.0 to 16.4 mm Hg) at 1 and 2 years, respectively (P=0.035).

LAP was particularly elevated during the 30 days before events (mean LAP 23.0 mm Hg [95% CI 19.8 to 26.1 mm Hg] versus 17.2 mm Hg [14.2 to 20.2 mm Hg] during the intervals between events; P=0.003). Event-free patients had still lower LAP readings (13.2 mm Hg [95% CI 11.9 to 14.5 mm Hg], P<0.001). The maximum LAP within 7 days of an event averaged 36.5 mm Hg (95% CI 32.8 to 40.2 mm Hg), and readings >25 mm Hg were present for 5.2±6.8 consecutive days (range 0 to 22 days). Patients with events were less compliant in taking readings (64±28% versus 87±11%; P=0.001), especially within 7 days of an event (40±35%; P<0.001).

LAP control was achieved for at least 6 consecutive months in 30 (77%) of the 39 patients who remained in the study and for the entire stability period in 22 (56%). There was a single event during LAP control in a patient with poor compliance (23% compliance) during the preceding 30 days. Event rates were lower during LAP control (0.02 per year, 95% CI 0.002 to 0.14 per year) than during periods without LAP control (0.88 per year, 95% CI 0.56 to 1.4 per year), a 98% reduction (P<0.001).

Effect on Medications and Other Therapies

Static therapy was the primary treatment method in 3 patients, whereas dynamic therapy was applied in 33 subjects with daily loop diuretic dosing based on the morning LAP value. In 39% of these patients, a second drug was adjusted according to the LAP level (nitrate at night in 11 patients, metolazone in 2, and spironolactone in 1).

ACE/ARB and β-blocker usage was nearly universal at baseline and throughout the study (Table 3). Dosages of these medications did not change during the observation period, during which target levels of ACE/ARBs were prescribed in
46% of patients, of β-blockers in 54%, and of both drug classes in 27%. During the stability period, ACE/ARB doses increased by 37%, with 59% achieving target; β-blocker doses increased by 40%, with 76% reaching target; and 54% reached target levels for both drug classes (P<0.001). The mean daily dose of loop diuretics trended lower by 27% during the stability period, going from 151±212 to 111±109 mg equivalents of furosemide (P=0.015). During dynamic therapy, diuretic prescriptions were altered on 53% of days, with 24% of morning readings driving lower diuretic doses and 29% raising doses (Table 4). Patients with events were taking 40% less ACE/ARBs (P=0.036), 43% less β-blockers (P=0.001), and 94% more loop diuretics (P=0.11) than patients without events.

LAP waveform morphology initiated referral of 4 patients (10%) for therapeutic procedures. Two patients with acute coronary syndromes, worsening heart failure, and associated giant v waves underwent stenting of stenotic left circumflex coronary arteries. One patient with severe functional mitral regurgitation had investigational percutaneous edge-to-edge mitral valve repair, and 1 patient with coexisting pericardial constriction had surgical pericardial stripping. All patients had sustained symptomatic improvement without subsequent events. LAP averaged 21.0 mm Hg (95% CI 14.2 to 27.8 mm Hg) during the 3 months before intervention and fell to 13.6 mm Hg (95% CI 6.8 to 20.4 mm Hg) for the 6 months after intervention (P=0.043). The frequency of pressure >25 mm Hg decreased by 83% from 0.23 to 0.04 (P=0.001) in these patients.

Discussion
This exploratory, observational study of an investigational implanted LAP sensor coupled with a physician-directed patient self-management treatment paradigm demonstrated the potential for controlling LAP and improving outcomes in patients with advanced chronic heart failure. The sensor was implanted safely without early major adverse cardiovascular or neurological events. After an initial 3-month blinded observation period, LAP measurements guided medication dosing. Although not a true concurrent control, the observation period results served as the basis for comparison of event rates before and after the application of LAP-guided therapy (landmark analysis). There was a lower short-term combined rate of heart failure hospitalization and all-cause mortality after LAP-guided therapy was initiated. Over the course of treatment, patients also had significant improvements in left-sided filling pressures, symptoms, quality of life, and systolic function without deterioration of renal function.

The self-management strategy is analogous to diabetes care in which patients regulate prescribed therapy using objective daily measurements of therapeutic efficacy by glucometer. We aimed to achieve hemodynamic stability by first giving physicians LAP trend and waveform morphology information from twice-daily pressure measurements, which allowed them to individualize patient’s prescriptions as they responded to guided therapy. During the first 3 months, when physicians and patients were blinded to sensor information, elevated LAP measurements consistent with worsening heart failure were relatively frequent despite regular interactions with caregivers and twice-daily computer-initiated reminders to measure pressure and input symptoms. Later, with LAP guiding therapy, there was a 67% reduction in readings.
>25 mm Hg; this effect was sustained beyond 2 years and was associated with a reduction in clinical events. Empirically derived criteria for LAP control were achieved in 77% of patients.

Several mechanisms may be responsible for the observed improvement in left-sided filling pressure. One possibility is that daily knowledge of LAP facilitated uptitration of ACE/ARBs and \( \beta \)-blockers. Although subjects were recruited from heart failure programs and were receiving guideline-based care with maximally tolerated doses, only 27% were taking target doses of both drug classes. The present data suggest that awareness of suboptimal LAP trends followed by more appropriate diuretic dosing may have facilitated uptitration of neurohormonal antagonists, such that 54% of patients were able to tolerate target doses of both major drug classes. In particular, avoidance of dehydration by reducing diuretics when LAP was lower may have aided the advancement of appropriate diuretic dosing.

Lower diuretic dosing was likely achieved by reducing diuretics on the days when LAP was low and by the diuretic-sparing effect of uptitrated neurohormonal antagonists and the increased use of long-acting nitrates at bedtime. Given the association between high diuretic doses and poor outcomes in heart failure, diuretic reduction may contribute to improved outcomes through reduced neurohormonal activation, maintenance of glomerular filtration, and prevention of diuretic refractoriness. One last mechanism includes 4 cases in which detection of pressure waveform morphology indicative of severely abnormal atrial filling and mitral valve function prompted percutaneous or surgical intervention. In these patients, marked clinical and hemodynamic stabilization followed the interventions. This limited experience suggests that long-term outpatient hemodynamic monitoring may guide decision making about revascularization and repair of structural heart disease in selected patients.

Patients with adverse outcomes had higher baseline BNP levels and lower resting cardiac output, consistent with more advanced disease. Compared with patients without events, they also had less favorable LAP profiles, especially during the 30 days before events. Patients with events were prescribed substantially lower doses of ACE/ARBs and \( \beta \)-blockers and took significantly fewer pressure measurements, especially within 30 days of an event. Automated algorithms that detect worsening compliance and hemodynamic control could alert caregivers, allowing time to intervene, possibly by uptitrating neurohormone antagonists before clinical deterioration.

The small study size, lack of a randomized design with a concurrent control group, and observer bias from lack of blinding limit the ability to reach definitive conclusions about the safety and clinical effectiveness of this heart failure management strategy. The event rates in the early months after implantation when physicians and patients were blinded to whether they were in the observation or stability periods were somewhat lower than later on, possibly reflecting this treatment effect. The small sample size precludes statistical analysis of trends. Despite these limitations, the data provide an opportunity to explore the potential benefits and hazards of chronic ambulatory hemodynamic monitoring in heart failure. The following are the main findings of the study:

### Table 3. Pharmacological Profiles

<table>
<thead>
<tr>
<th>Medication</th>
<th>Use</th>
<th>Dose</th>
<th>Use</th>
<th>Dose</th>
<th>Use</th>
<th>Dose</th>
<th>Use</th>
<th>Dose</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE or ARB</td>
<td>0.97</td>
<td>0.38±0.27</td>
<td>0.95</td>
<td>0.38±0.25</td>
<td>0.97</td>
<td>0.52±0.34</td>
<td>0.52</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>( \beta )-blocker</td>
<td>0.92</td>
<td>0.44±0.29</td>
<td>0.92</td>
<td>0.45±0.28</td>
<td>0.97</td>
<td>0.64±0.33</td>
<td>0.24</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Loop diuretic</td>
<td>1.00</td>
<td>0.25±0.31</td>
<td>1.00</td>
<td>0.26±0.35</td>
<td>0.95</td>
<td>0.18±0.18</td>
<td>NC</td>
<td>0.15</td>
<td></td>
</tr>
<tr>
<td>Aldosterone antagonist</td>
<td>0.46</td>
<td>...</td>
<td>0.46</td>
<td>...</td>
<td>0.49</td>
<td>...</td>
<td>0.77</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>Digoxin</td>
<td>0.30</td>
<td>...</td>
<td>0.30</td>
<td>...</td>
<td>0.24</td>
<td>...</td>
<td>0.47</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>Long-acting nitrate</td>
<td>0.19</td>
<td>...</td>
<td>0.30</td>
<td>...</td>
<td>0.62</td>
<td>...</td>
<td>0.003</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>Thiazide diuretic</td>
<td>0.14</td>
<td>...</td>
<td>0.19</td>
<td>...</td>
<td>0.16</td>
<td>...</td>
<td>0.70</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>Hydralazine</td>
<td>0.08</td>
<td>...</td>
<td>0.08</td>
<td>...</td>
<td>0.08</td>
<td>...</td>
<td>1.0</td>
<td>...</td>
<td></td>
</tr>
</tbody>
</table>

Use indicates fraction of cases prescribed medication; dose, fraction of ACC/AHA heart failure guidelines–stated maximum dose (mean±SD); and NC, no convergence.

Data are from patients who entered the stability period (n=37 subjects).

*P for comparison between observation and stability periods.

### Table 4. Dynamic Therapy in Each LAP Range (n=33 Subjects)

<table>
<thead>
<tr>
<th>Dynamic Therapy Range</th>
<th>Very Low</th>
<th>Low</th>
<th>Optimal</th>
<th>High</th>
<th>Very High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean LAP boundaries, mm Hg</td>
<td>≤5</td>
<td>6 to 9</td>
<td>10 to 18</td>
<td>19 to 27</td>
<td>≥28</td>
</tr>
<tr>
<td>Fraction of readings in range</td>
<td>0.05±0.12</td>
<td>0.16±0.22</td>
<td>0.47±0.22</td>
<td>0.26±0.24</td>
<td>0.03±0.07</td>
</tr>
<tr>
<td>Furosemide equivalents, mg</td>
<td>8±21</td>
<td>55±66</td>
<td>112±94</td>
<td>178±151</td>
<td>218±187</td>
</tr>
</tbody>
</table>
to LAP information may not be indicative of a true standard-
therapy control group, particularly if the hazard of experienc-
ing an event is nonlinear, with more events early after
implantation and fewer events later. These deficiencies can
best be overcome in subsequent adequately powered random-
ized controlled trials.

Conclusions

In this small observational study, physician-directed pa-

tient self-management of heart failure with direct LAP
monitoring was associated with improved LAP control,
reduced symptoms, more optimal neurohormonal antago-
nist and diuretic dosing, and a reduction of early clinical
events. The present data indicate that hemodynamic de-
compensation nearly always precedes clinical decompensa-
tion and suggest that outpatient hemodynamic monitor-
ing linked to a self-management therapeutic strategy could
change current management of advanced heart failure and
potentially facilitate more optimal therapy and improved outcomes.

Appendix

The following centers and investigators participated in the HO-
MEOSTASIS trial, providing the study subjects included in this
publication (listed in alphabetic order according to center): Alfred
Hospital, Melbourne, Australia—J. Aw, D. Kaye, H. Krum, T.
Walton; Auckland City Hospital, Auckland, New Zealand—R.
Doughty, J. Stewart; Cedars-Sinai Medical Center, Los Angeles,
Calif—N. Eigler, S. Kar, R. Makkar; P.K. Shah, R. Siegel, J.
Whiting; Christchurch Hospital, Christchurch, New Zealand—J.
Crozier, J. Lainchbury, I. Melton, M. Richards, J. Ritzema-Carter, G.
Roper, R. Troughton; Ohio State University, Columbus, Ohio—
W.T. Abraham (Study Chairman), P. Binkley, C. Bush, G. Cooke, D.
Love, R. Magorien, R. Mehta, B. White; Oklahoma Cardiovascular Re-
search Group, Oklahoma City, Okla—P. Adamson, M. Harvey; 
 Scripps Clinic, La Jolla, Calif—T. Ahern, T. Heywood, A. Johnson,

Data and Safety Monitoring Board—B. Greenberg (Chair), M.
Mehra, J. McAnulty. Clinical Events Committee—M. Klapolz
(Chair), M. Semigran, D. Benditt.

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Drs Kar, Whiting, and Eigler disclose a financial interest in St. Jude
Medical. Drs Abraham, Adamson, Haas, Heywood, Melton and
Troughton report receiving honoraria or consulting fees from St.
Jude Medical and other companies that manufacture devices. The
remaining authors report no conflicts.

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Untreated heart failure: clinical and neuroendocrine effects of introducing 


CLINICAL PERSPECTIVE

Previous studies have suggested that monitoring of ambulatory hemodynamics may improve outcomes in chronic heart failure. We conducted a prospective, observational, first-in-human study of a physician-directed patient self-management system targeting left atrial pressure (LAP). In this study, patients with reduced or preserved left ventricular ejection fractions and a history of New York Heart Association class III to IV heart failure and acute decompensation were implanted with an investigational LAP monitor, and readings were acquired twice daily. For the first 3 months, patients and clinicians were blinded to these readings, and treatment continued per usual clinical assessment. Thereafter, LAP readings and individualized therapy instructions guided by these pressures were displayed to the patient. Event-free survival without decompensation was 61% at 3 years, and events tended to be more favorable after the first 3 months once therapy was being guided by daily LAP readings. Mean daily LAP fell in the first 3 months during pressure-guided therapy. The frequency of elevated readings (>25 mmHg) was reduced significantly during LAP-guided therapy, and there were improvements in New York Heart Association class and left ventricular ejection fraction. Doses of angiotensin-converting enzymes/angiotensin-receptor blockers and β-blockers were uptitrated significantly, by 37% and 40%, respectively, whereas there was a trend to lower doses of loop diuretics. These findings suggest that physician-directed patient self-management of LAP has the potential to improve hemodynamics, symptoms, and outcomes in advanced heart failure. Hemodynamic monitoring may guide more optimal dosing with proven neurohormonal antagonist therapies.
Physician-Directed Patient Self-Management of Left Atrial Pressure in Advanced Chronic Heart Failure


on Behalf of the Hemodynamically Guided Home Self-Therapy in Severe Heart Failure Patients (HOMEOSTASIS) Study Group

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