Optimizing Treatment of Chronic Decompensated Heart Failure in the Outpatient Setting

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Chronic decompensated heart failure (HF) is costly to manage because of frequent episodes of acute decompensation that result in hospitalization. Patients with chronic decompensated HF may have inadequate hemodynamic responses or limited tolerance of oral HF medications and therefore may require parenteral administration of vasoactive agents. Intermittent infusions of inotropic agents are no longer recommended, but preliminary data suggest that intermittent nesiritide may be a safe and effective adjunct to oral drug therapy for select patients at risk for further episodes of decompensation. In other patients, nonpharmacologic approaches used in combination with drug therapy may help improve functional status and reduce mortality.
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Heart failure (HF) is a major public health problem that affects an estimated 5 million people in the United States, with 550,000 cases newly diagnosed each year.[1] HF is listed as the primary diagnosis in nearly 1 million hospital discharges and accounts for an estimated 3.8 million outpatient visits each year.[1,2] With the aging of the American population, these numbers are expected to increase significantly in the coming decades.[3]

Because of its chronic nature, HF adversely impacts quality of life and substantially increases mortality. At any given time, 30% to 40% of patients with HF are classified as New York Heart Association (NYHA) functional class III or IV, with symptoms at rest or during mild exertion.[4] Patients with HF are at a 6- to 9-times-higher risk of sudden cardiac death than the general population, and high mortality rates are present in this population throughout the course of disease.[1] In a retrospective population-based study, 34% of men and 32% of women died within 1 year of their first hospital admission for HF.[5] Similarly, the Framingham Heart Study found that 59% of men and 45% of women with a diagnosis of HF in the 1990s died within 5 years.[6]

Each year, more than 40,000 patients with HF progress to the end stage of disease.[7] These patients have persisting symptoms while at rest or with minimal exertion, and are often unable to perform most activities of daily living.[4] In this setting, medical treatment is often insufficient for preventing recurrent episodes of acute decompensation, and as a result, patients typically require repeated or prolonged hospitalizations for intensive management. Elderly patients are particularly susceptible to hospital readmissions.

According to the National Hospital Discharge Survey, HF is the largest single cause of hospital admissions and readmissions in persons older than 65 years.[8] Readmission rates of 29% to 47% at 3 to 6 months have been reported in elderly patients with HF.[9–11] Moreover, readmission rates of up to 21% have been reported in this patient population within 2 to 4 weeks of discharge.[12–14] Although recent therapeutic advances have reduced mortality rates, hospital admissions are still on the increase. In 2001, the number of hospitalizations for HF was more than 2.5 times higher than it was in 1979.[1]

In addition to high morbidity and mortality, HF is associated with a substantial economic burden. The total annual cost of HF is estimated at $28.8 billion, which includes $26.7 billion in direct medical costs and $2.1 billion in indirect costs associated with lost productivity resulting from premature mortality.[1] Hospitalization and other inpatient care, such as nursing home care, account for nearly 65% of the direct medical cost. Of note, about 75% of the costs associated with hospitalization accumulate within the first 48 hours of admission.[15] These data indicate that acute decompensated HF is the primary driver of costs in the management of HF.

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The Centers for Medicare & Medicaid Services provide financial incentives to encourage efficient inpatient treatment of acute decompensated HF and limit early readmissions.[16] Hospitals are reimbursed based on the diagnosis but receive no additional payment for patients readmitted within 30 days under the same diagnosis-related group code. Consequently, health care facilities are under economic pressure to shorten hospital lengths of stay while preventing 30-day readmissions. By reducing hospitalization rates as well as limiting 30-day readmission rates, it should be possible to significantly reduce the economic cost of treating HF.

Patients with symptomatic HF who are at high risk for repeated hospital admissions have recently been described as having "chronic decompensated HF."[17] These patients are suitable targets for novel therapies that reduce the need for hospitalization, improve quality of life, and possibly provide a survival advantage. This review will describe strategies to improve the management of chronic decompensated HF in the outpatient setting in order to prevent hospital admissions and reduce the overall costs of treating HF.

Pharmacologic Treatment of Patients With Chronic Decompensated HF

Traditional Therapies

Oral diuretics, β-blockers, and angiotensin-converting enzyme (ACE) inhibitors are recommended for routine use in patients with mild to moderate HF.[4] Diuretics reduce volume overload and effectively reduce symptoms caused by fluid retention, but there is little evidence that they improve outcomes in patients with HF. β-Blockers and ACE inhibitors reduce neurohormonal activation, thereby decreasing the additional tissue damage and remodeling mediated by catecholamines, angiotensin II, and aldosterone.

Multiple studies with a variety of different drug classes, including β-blockers, ACE inhibitors, and, more recently, angiotensin II receptor blockers and aldosterone antagonists, show that suppressing neurohormonal activation reduces mortality and HF hospitalizations.[18–23] In patients with chronic decompensated HF, however, these oral agents are effective but not always adequate to achieve and maintain the hemodynamic responses necessary for symptom control.[4] Neurohormonal mechanisms become increasingly

important for maintaining hemodynamic stability as HF progresses, and consequently, blocking neurohormones can lead to hypotension, renal insufficiency, and even worsening HF in those with chronic decompensated HF.[4] As a result, patients with decompensated HF may tolerate only small doses of these neurohormonal antagonists, if they tolerate them at all.

Intravenous therapies are often required to maintain hemodynamic and clinical stability in patients with chronic decompensated HF. Intermittent infusions of inotropic agents have been used to supplement the effects of oral drugs. Although effective in improving hemodynamics and providing symptom relief over the short term, inotropes also increase heart rate, raise myocardial oxygen demand, worsen ischemia, and promote arrhythmias.[24–26] Inotropic agents also may adversely increase neurohormonal and cytokine levels.[27] It is difficult to advocate intermittent use of these drugs when long-term administration has been shown to increase mortality.[28,29]

In the only placebo-controlled trial of intermittent intravenous inotropic therapy published to date, 19 patients with chronic decompensated HF were randomly assigned to receive dobutamine or placebo for a 24-hour period every 2 to 3 weeks for 6 months.[30] The study showed that intermittent intravenous dobutamine had no effect on the need for hospitalization or on survival. According to current American College of Cardiology/American Heart Association guidelines, intermittent infusions of inotropic agents are not useful or effective and may even be harmful in patients with chronic decompensated HF.[4]

Inadequate efficacy, difficult dosing regimens, and frequent adverse effects have limited the use of older peripheral vasodilators, such as nitroglycerin and nitroprusside, in outpatient treatment of chronic decompensated HF.

Nesiritide

Nesiritide is a recombinant human B-type natriuretic peptide that is identical to the endogenous hormone secreted by the ventricular myocardium in response to increased wall stress and volume overload. Nesiritide produces a combination of beneficial hemodynamic, neurohormonal, and renal effects in patients with HF. Because nesiritide exerts no direct inotropic action on the myocardium, the hemodynamic improvements reflect a balanced vasodilation that leads to reductions in both preload and afterload. Nesiritide also has been shown to reduce plasma concentrations of neurohormones, including norepinephrine and aldosterone,[31] while increasing urine volume and urine sodium excretion.[32]

Nesiritide is well established in the management of hospitalized patients with acute decompensated HF. Clinical trials show that nesiritide compares favorably to standard agents such as nitroglycerin and dobutamine.[33] In the Vasodilation in the Management of Acute Congestive heart failure (VMAC) trial, nesiritide was significantly more effective than nitroglycerin and placebo in improving pulmonary capillary wedge pressure (PCWP) and other hemodynamic parameters in patients with decompensated HF and dyspnea at rest.[34] Moreover, nesiritide significantly improved both dyspnea ($P = 0.027$) and global clinical status ($P = 0.013$) at 24 hours compared with nitroglycerin.[35] Outcomes at 30 days and 6 months did not differ between nesiritide and nitroglycerin.[34] The Prospective Randomized Evaluation of Cardiac Ectopy with Dobutamine or Nesiritide Therapy (PRECEDENT) trial showed that nesiritide and dobutamine were similarly effective in improving the signs and symptoms of congestive HF in patients with acute decompensation, but unlike dobutamine, nesiritide did not increase ventricular ectopy.[26]

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Renal insufficiency is a frequent comorbid condition in patients with chronic HF.[5] In the VMAC trial, nesiritide-induced reductions in PCWP were similar both in patients who had HF with renal insufficiency (serum creatinine level ≥ 2 mg/dL) and those with normal renal function (serum creatinine level < 2 mg/dL).[36] By 24 hours, 83% of patients with renal insufficiency reported improvements in dyspnea. Overall, nesiritide was well tolerated by both groups of patients, and renal function was preserved. These findings indicate that nesiritide is a safe and effective option for patients with HF and comorbid renal disease.

Nesiritide possesses several properties and characteristics that make it an appropriate agent to use in the outpatient setting. Nesiritide does not have inotropic or chronotropic effects, nor is it proarrhythmic.[26,33,37,38] The most common adverse event seen with nesiritide in clinical trials was dose-related hypotension. At the clinically recommended dose of 0.01 μg/kg/min, the

incidence of hypotension with nesiritide was 11%, which is not significantly different from the rates observed in all control patients (10%) or those treated with nitroglycerin (12%).[39] The hypotension was usually asymptomatic or mild and typically responded to temporary discontinuation of the nesiritide infusion, with treatment reinitiated at a lower dose after resolution of the hypotension. Some symptomatic patients required intervention with a small-volume crystalloid infusion.[39]

Nesiritide was significantly more effective than nitroglycerin and placebo in improving pulmonary capillary wedge pressure and other hemodynamic parameters in patients with decompensated HF and dyspnea at rest.

Recent data support the safety and feasibility of nesiritide for the treatment of chronic decompensated HF in the outpatient setting. The Follow-Up Serial Infusions of Nesiritide (FUSION)-I study was a multicenter, randomized, open-label, 12-week evaluation of 210 patients with decompensated HF who had had class III/IV disease for at least 60 days and had received 2 or more intravenous treatments for acute decompensated HF within the preceding 12-month period, at least 1 of which was within 5 to 30 days of enrollment.[40] All patients were receiving optimal oral medications for HF.

Patients were randomly assigned to receive either usual care or usual care plus intermittent nesiritide infusions on an outpatient basis. Nesiritide was infused as a bolus dose of 1 or 2 μg/kg, followed by a steady dose of 0.005 or 0.01 μg/kg/min, respectively, for 4 to 6 hours. The infusions were administered twice weekly to biweekly, depending on hydration status and HF symptoms. Patients receiving usual care alone were allowed to receive inotropic agents if the investigator deemed these agents necessary to alleviate symptoms.

A total of 1645 nesiritide infusions were administered; only 11 infusions (<1%) were discontinued because of an adverse event, most commonly asymptomatic hypotension (n = 4) and symptomatic hypotension (n = 2) (Table 1).[40] Overall, the treatment groups had a similar frequency of adverse events during the 12-week study, and each group reported improvements in quality of life at weeks 4, 8, and 12 as measured by the Minnesota Living With Heart Failure questionnaire. Clinical outcomes did not differ significantly between the nesiritide and usual-care groups. However, in a prospectively defined, higher-risk subgroup (ie, patients with at least 4 of 7 prognostic factors for hospitalization and death), nesiritide significantly reduced the incidence of all-cause death and hospitalization (52% vs 78%; P = .038) and provided significantly more days alive and out of the hospital (77 vs 67 days; P = .027). Nesiritide also produced acute reductions in both aldosterone and endothelin levels.[40]

Based on the strong findings in the FUSION-I trial, another larger trial,[40] FUSION-II, has been developed and enrollment is now under way. FUSION-II is a randomized double-blind study involving 900 patients with HF at high risk for rehospitalization. Based on FUSION-I, high-risk patients with HF in the outpatient clinical setting will be randomized to 1 of 4 treatment arms and will receive serial administration of either placebo or nesiritide infusions (0.01 μg/kg/min) once or twice weekly for 12 weeks, followed by a 12-week follow-up. In addition to monitoring efficacy and safety, FUSION-II will control for increased counseling and education that is typical of disease management clinics.

Finally, the safety and efficacy of nesiritide in the outpatient treatment of chronic decompensated HF has been evaluated in several

Table 1
Nesiritide Infusion Tolerability: Results From the First Follow-Up Serial Infusions of Nesiritide (FUSION)-I Trial

	Nesiritide Dose (μg/kg/min)		All Patients Receiving Nesiritide (N = 141)
	0.005 (n = 72)	0.01 (n = 69)	
Total number of infusions	819	826	1645
Infusions completed, n (%)	814 (99)	814 (99)	1628 (99)
Infusions stopped because of adverse event, n (%)	4 (< 1)	7 (< 1)	11 (< 1)
Infusions stopped for administrative reasons, n (%)	1 (< 1)	5 (< 1)	6 (< 1)
Patients with infusion stopped because of adverse event, n (%)	4 (6)	5 (7)	9 (6)

Adapted with permission from Yancy et al.[40]

Table 2
Clinical Experience With Nesiritide in Outpatient Treatment of Heart Failure

Reference	Design	Patients	Nesiritide Dose	Findings
Altschul et al[41,42]	RCA	65 patients with NYHA class III/IV HF receiving maximum standard care with poor quality of life	2-μg/kg bolus followed by 0.01-μg/kg/min infusion for 4 h 1–3 times/wk for a mean of 33 wk (range, 4 to 77 wk)	Nesiritide reduced hospital days by 94% when compared with the 1-year period before treatment; NYHA functional class improved in 89% of patients, and oral diuretic use declined in 45% of patients.
Beck et al[43]	RCA	28 HF patients receiving optimal oral therapy	2-μg/kg bolus followed by 0.01-μg/kg/min infusion for 4–6 h 1–2 times/wk; mean of 16 treatments per patient	Symptomatic hypotension occurred during 10 (2.2%) of 449 treatments; 9 episodes resolved with discontinuation of nesiritide, and 1 episode required fluid infusion; there were no recurrences with subsequent nesiritide therapy.
Bhaskaran et al[44]	OL	14 patients with NYHA class III/IV HF with persisting volume overload despite maximum standard therapy	2-μg/kg bolus followed by 0.01- to 0.03-μg/kg/min infusion for 6 h once weekly for 12 wk	Nesiritide significantly improved hemodynamics, LVEF, and NYHA functional class. Nesiritide significantly reduced arrhythmias, use of diuretics, and use of IV inotropic agents and significantly improved parameters of renal function.
Squires & Vora[45]	OL	30 patients with NYHA class IIIb/IV HF receiving outpatient inotropic therapy*	2-μg/kg bolus followed by 0.01-μg/kg/min infusion for 4 h twice weekly for 3 mo	Nesiritide significantly improved quality of life associated with physical functioning; no significant differences in hemodynamics were observed on switching from inotropic therapy to nesiritide.
Mulki et al[46]	CC	16 patients with HF with previous HF admissions, persisting volume overload, receiving maximal medical therapy	2-μg/kg bolus followed by 0.01-μg/kg/min infusion for 4 h for a mean of 30 wk (range, 3 to 58 wk)	No recurrent admissions were observed during the follow-up period. Nesiritide significantly improved diuresis, improved functional class and hemodynamics, with favorable safety profile.

RCA, retrospective chart analysis; HF, heart failure; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; OL, open-label; CC, case-controlled study.
*Patients either continued existing inotropic therapy with milrinone and/or dobutamine (n = 16) or were switched to nesiritide (n = 14).

smaller, single-center studies (Table 2).[41–46] Data from FUSION-I and those of several smaller studies support the treatment of symptomatic patients with decompensated HF with nesiritide in an outpatient setting. Further investigation, including definitive trials of nesiritide in patients with chronic decompensated HF, is necessary.

Investigational Agents

Tezosentan. Tezosentan is a dual-endothelin (A/B) receptor antagonist that reduces PCWP and improves cardiac index in patients with acute decompensated HF.[47] When infused at doses of 50 or 100 mg/h, tezosentan improved hemodynamic parameters but not clinical outcomes. In a recent study of patients with HF hospitalized with dyspnea at rest, tezosentan given in doses of 5 or 25 mg/h produced dose-dependent hemodynamic improvement, with effects peaking at 3 hours.[48] However, urine output declined at the higher dose, and endothelin levels increased at both doses. At a dose of 1 mg/h, the improvement in hemodynamics occurred gradually and

reached statistical significance at 24 hours, continuing after the infusion was stopped. A trend toward improvement in subjective dyspnea scores and worsening HF events was observed mainly in patients treated with the 1-mg/h dose. Until this agent is evaluated further, the use of tezosentan in the outpatient setting would be extremely premature.

Levosimendan. Levosimendan is a calcium sensitizer that increases the sensitivity of cardiac myofilaments to calcium.[49,50] This agent also inhibits phosphodiesterase type III and has potassium-channel agonist properties. In the Levosimendan Infusion versus Dobutamine (LIDO) trial, levosimendan was compared with dobutamine in 203 hospitalized patients with low-output HF.[51] Levosimendan was administered at a loading dose of 24 μg/kg over 10 minutes and then infused continuously at a dose of 0.1 μg/kg/min for 24 hours; dobutamine was infused continuously at a dose of 5 μg/kg/min, without a loading dose. Infusion rates were doubled after 2 hours in patients with inadequate responses.

Levosimendan produced hemodynamic improvement (defined as a $\geq$ 30% increase in cardiac output and $\geq$ 25% decrease in PCWP at 24 hours) in significantly more patients than did dobutamine (28% vs 15%; $P < .05$). This advantage was accompanied by a reduction in all-cause mortality at 180 days in the levosimendan group as compared with the dobutamine group (mortality rate, 26% vs 38%; $P < .05$).[51] However, in other clinical studies of levosimendan for the treatment of acute decompensated HF, improvements in dyspnea and fatigue have not been consistently seen.[49] After a 24-hour infusion, active metabolites of levosimendan substantially increase heart rate, although this agent is generally well tolerated. Cardiac rate/rhythm disorders and headache are the most frequent adverse events.[49] Limited data preclude the use of levosimendan in the outpatient setting.

Nonpharmacologic Treatment of Patients With Chronic Decompensated HF

Mechanical Devices

Left ventricular assist devices (LVADs) can improve survival and increase quality of life in patients who are ineligible for cardiac transplantation. In the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) study, 129 patients with end-stage HF who were ineligible for transplantation were randomly assigned to receive an LVAD or optimal medical management.[52] The use of an LVAD significantly reduced all-cause mortality by 48% and improved quality of life at 1 year, but the frequency of serious adverse events was increased by 2.35 times (95% confidence interval [CI], 1.86–2.95) compared with optimal medical care alone. Infection, bleeding, and device malfunction were the most common serious adverse events.

Cardiac resynchronization through simultaneous pacing of the right and left ventricles may be useful in patients with ventricular dyssynchrony.[53,54] Clinical studies demonstrate that cardiac resynchronization improves functional status, exercise capacity, and quality of life and may also improve cardiac structure and function and lower neurohormonal levels.[53–55] In a meta-analysis of 4 randomized trials involving 1634 patients, cardiac resynchronization significantly reduced death from progressive HF by 51% (odds ratio [OR], 0.49; 95% CI, 0.25–0.93) and hospitalizations for HF by 29% (OR, 0.71; 95% CI, 0.53–0.96) relative to controls.[56]

When preliminary data from a fifth large, randomized, controlled study were included in the meta-analysis, cardiac resynchronization was found to also significantly reduce all-cause mortality by 26% (OR, 0.74; 95% CI, 0.56–0.97).[57] The recently completed Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial found that cardiac resynchronization with a pacemaker decreases the combined risk of death from any cause or first hospitalization and, when combined with an implantable defibrillator, significantly reduces mortality.[58] However, analysis of these trials suggests that cardiac resynchronization therapy does not improve functional capacity or well-being in a large percentage of patients.[53] Moreover, the magnitude of the observed benefits in these trials appears to differ, suggesting a large degree of heterogeneity of trial results.

Surgery

Cardiac transplantation to date has been considered one of the best options for patients with end-stage HF that is unresponsive to medical management, but its use is limited by organ availability and the advanced age and comorbidities of many patients with HF.[59,60] At present, cardiac transplantation is available to no more that 2500 patients annually in the United States. A variety of other surgical procedures exist for the treatment of advanced HF, depending on disease etiology and anatomic dysfunction. These procedures include coronary revascularization, mitral valve repair or replacement, cardiomyoplasty, and left ventricular volume reduction.[61]

The National Institutes of Health is currently sponsoring the Surgical

Treatments for Ischemic Heart Failure (STICH) trial, which will compare several surgical procedures with medical therapy for HF management.[62] Better understanding of the role and timing of surgical procedures and of patient selection should change the face of management options for advanced HF.

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The HF Clinic

Most HF care is delivered in an outpatient setting, but a gap exists between the services that can be offered in most physicians' offices and those provided routinely during a hospital stay. The concept of the HF clinic has been created in an effort to address this gap as well the escalating costs of repeated hospitalizations, many of which occur within a capitated reimbursement structure.[63] Typically, the HF clinic provides a multidisciplinary program with primary involvement of a nurse, cardiologist, and ancillary staff.

The structure of the clinic varies depending on the needs and resources available to each institution or practice, but in general, it offers a variety of services that may include patient and physician education, drug titration protocols, outpatient administration of intravenous agents, nurse telemanagement, telephone triage, critical pathway and guideline development, rehabilitation and exercise training, heart transplant evaluation, and participation in clinical research. The benefits of this model have been established in case-control and randomized trials, which show that patients treated in HF clinics have improved symptoms, better quality of life, greater exercise tolerance, and fewer hospitalizations.[64] Moreover, a reduction in the cost of managing HF has been attributed to the HF clinic.

Conclusions

Chronic decompensated HF affects a significant number of persons and is costly to manage, principally because of frequent episodes of acute decompensation. Because they have inadequate hemodynamic responses to oral HF medications or may have limited tolerance of them, patients with chronic decompensated HF may require parenteral administra-

Main Points

- Patients with chronic decompensated heart failure (HF) are in need of therapies that reduce the need for hospitalization and the associated costs, improve quality of life, and possibly provide a survival advantage. In this population, oral agents, such as β-blockers, ACE inhibitors, angiotensin II receptor blockers, and aldosterone antagonists, are effective but not always adequate for symptom control, and intravenous inotropic agents may even be harmful.
- Nesiritide, a recombinant human B-type natriuretic peptide, has been shown to improve pulmonary capillary wedge pressure and dyspnea, and to be safe for use in patients with chronic HF and comorbid renal disease. Its most common adverse event is dose-related hypotension.
- Data from the Follow-Up Serial Infusions of Nesiritide (FUSION)-I study support the safety and feasibility of nesiritide for the treatment of chronic decompensated HF in the outpatient setting: nesiritide infusions added to usual care significantly reduced the incidence of all-cause death and hospitalization in a high-risk subgroup. FUSION-II, currently under way, will further explore the efficacy and safety of nesiritide in comparison with placebo in high-risk patients.
- Tezosentan, a dual-endothelin (A/B) receptor antagonist, and levosimendan, a calcium sensitizer, have both been shown to produce hemodynamic improvement in patients with HF; however, more data are needed before they can be recommended for use in the outpatient setting.
- Studies demonstrate that cardiac resynchronization with mechanical devices improves functional status, exercise capacity, and quality of life and may also improve cardiac structure and function and lower neurohormonal levels, although findings among studies have differed significantly, with outcomes regarding functional capacity and well-being not as encouraging.
- A multidisciplinary treatment program offered through an HF clinic has been shown to be a beneficial and cost-effective way to bridge the gap to outpatient management of HF.

tion of vasoactive agents. Intermittent infusions of inotropic drugs may improve short-term hemodynamics, but these agents are no longer recommended because of an increased risk of adverse events and mortality.

Preliminary data suggest that intermittent nesiritide infusions may be a safe and effective adjunct to oral pharmacotherapy. The hemodynamic benefits with nesiritide are similar to those obtained with intermittent administration of inotropic agents and result in improved quality of life. Nesiritide is generally well tolerated, although symptomatic hypotension, which tends to be transitory and easily managed, may occur occasionally. In select patients, a combination of pharmacologic and nonpharmacologic therapies can reduce mortality and improve functional status. As data are generated in the Acute Decompensated Heart Failure National Registry (ADHERE) database, further advances and refinements in the management of chronic decompensated HF may become apparent. ■

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