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Scientific Update™

The Clinical Roadmap to Acute Heart Failure: Ascending to New Heights

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By GORDON MOE, MD

Heart failure (HF) is now recognized as a major and escalating public health problem in industrialized countries with aging populations. In the United States, hospitalizations for HF increased markedly, from 377,000 in 1979, to 999,000 in 2000.[1,2] Acute decompensated heart failure (ADHF) or acute worsening of chronic HF, represents three-quarters of hospitalizations due to HF.[3] Unfortunately, compared to other acute cardiovascular (CV) conditions, clinical trial evidence that supports the management of patients with ADHF is still relatively scarce. This issue of *Cardiology Scientific Update* reviews the clinical roadmap to the management of patients with ADHF, including the use of natriuretic peptides based on current evidence, as well as the background information and rationale underlying the largest clinical trial in ADHF.

Pathophysiology of acute decompensated heart failure

Heart failure is a multisystem disorder characterized by abnormalities in cardiac and skeletal muscle and renal function, stimulation of the sympathetic nervous system, and a complex pattern of neurohormonal changes. Some of the mechanisms that may mediate the progression of HF are shown in Table 1. Increasing evidence suggests that the development of renal dysfunction or worsening of renal function while being treated for HF, ie, the cardiorenal syndrome, is associated with a poor prognosis.[4,5] Data from the Acute Decompensated Heart Failure National Registry (ADHERE) database, which enrolled unselected patients admitted to the hospital for ADHF, demonstrate that impaired renal function is common in HF patients and may be a key cause of the cascade involving fluid retention, decompensation, and eventual hospital admission.[5]

The natriuretic peptide family consists of the atrial natriuretic peptide (ANP), B-type or brain natriuretic peptide (BNP), and 3 other structurally similar peptides, including C-type natriuretic peptide (CNP) mostly of central nervous system and endothelial origin, and urodilatin from the kidney.[6-8] Among the natriuretic peptides, BNP, and the amino-terminal fragment of the BNP prohormone, NT-proBNP, have evolved to be useful biomarkers of cardiac function, as well as for prognosis in HF and other CV disorders. Several large-scale studies have established a close association between blood levels of BNP and NT-proBNP, and the diagnosis of symptomatic HF,[9-13] as well as an independent prediction of mortality and subsequent HF events.[14-18] In an international pooled analysis of 1,256 patients (the International Collaborative of NT-proBNP Study), among those with an adjudicated diagnosis of ADHF, a presenting NT-proBNP concentration >5180 pg/mL was strongly predictive of death by 76 days (Table 2).[14]

The demonstration of unprocessed BNP (1-108) in advanced human HF[19] has led to the speculation that there may be a deficiency in natriuretic peptide-processing to the biologically-active peptide in this setting and that this may contribute to disease progression by decreasing the compensatory actions of the natriuretic peptides. Although elevated levels of BNP are consistently associated with adverse outcomes in HF populations of mixed severity, a recent report within a relatively small, but homogeneous population of patients with advanced HF, demonstrated that nonsurvivors (when compared with survivors) had lower BNP levels (point-of-care assay).[20] It is, therefore, possible that a subpopulation of persons with advanced HF and a low BNP level may actually be in a "BNP-deficient" state. These observations also raise the intriguing possibility that these patients may particularly benefit from therapy using exogenous administration of BNP.

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Table 1: Mechanisms underlying the progression of heart failure

- Sustained neurohormonal stimulation (sympathetic and the renin-angiotensin-aldosterone system)
- Inflammation/oxidative stress at the cardiac, systemic and peripheral muscular system
- Hypoxemia and structural abnormalities of cardiomyofibroblasts (apoptosis, necrosis, and activation of matrix metalloproteinases)
- Abnormalities in arterial and peripheral baroreceptors
- Pulmonary and ventilatory abnormalities

Table 2: Independent predictors of 76-day mortality among those with ADHF

Predictor	Odds ratio	95% CI	P-value
NT-proBNP >5180 pg/ml	5.2	2.2–8.1	<0.001
Troponin T > 0.03 ng/mL	3.4	1.6–5.2	<0.001
Hemoglobin	0.92	0.87–0.97	0.006

Current therapies for acute HF

The goals of therapy of patients with ADHF include:

- relieving symptoms
- stabilizing the condition and reducing the risk for rehospitalization
- initiating treatments that will hopefully retard or reverse disease progression
- improving long-term survival
- limiting significant adverse effects (arrhythmia, renal failure).

A list of agents or approaches that have been developed for the management of ADHF is shown in Table 3 and a management algorithm from the 2007 update of the Canadian Cardiovascular Society Consensus Conference in the management of HF is shown in Figure 1.

Table 3: Agents or approaches developed for treatment of acute heart failure

Volume reduction/decongestion
- Diuretics
- Vasopressin antagonists*
- Ultrafiltration
- CPAP

Inotropic agents
- Milrinone
- Levosimendan*
- Dobutamine

Vasodilators
- Nitroglycerin
- Nesiritide

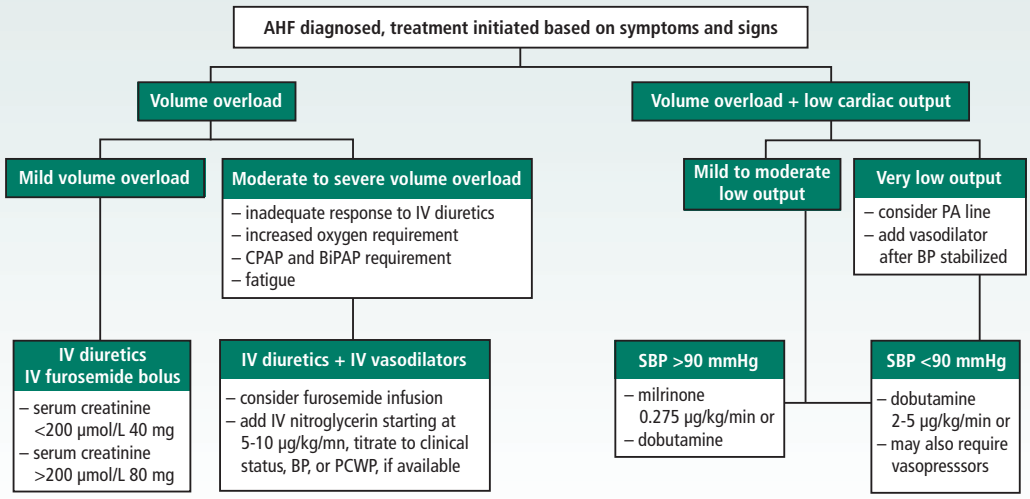
*Not yet approved in Canada

Volume reduction

The most commonly used agents are the loop diuretics. Although diuretics are effective in providing symptomatic relief and should be the first-line treatment for patients experiencing symptoms from fluid overload, there is no evidence that diuretics are effective in improving outcomes in HF. Furthermore, high doses of diuretics may cause neurohormonal activation, aggravate systemic vasoconstriction, and are associated with worsening renal function,[21-23] which may, in turn, be related to increased mortality.[23] Hemodynamic improvements with diuretics may be attenuated and relief of symptoms may be incomplete (diuretic resistance), thereby, increasing the risk of rehospitalization.[24]

Vasopressin antagonists can increase renal water excretion and have been evaluated for the management of HF. In the recently completed Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) study, tolvaptan, an oral, nonpeptide, selective vasopressin V_2-receptor antagonist, was found to produce a greater improvement than placebo in a composite of changes in global clinical status based

Figure 1: Treatment algorithm for acute heart failure (AHF)[26]



on a visual analog scale and body weight in patients hospitalized for HF.[25] However, it had no effect on long-term mortality or HF-related morbidity.[26]

Veno-venous ultrafiltration has recently been used to relieve congestion in patients with severe HF and volume overload. In the Ultrafiltration vs IV Diuretics for Patients Hospitalized for Acute Decompensated CHF (UNLOAD) trial, 200 patients hospitalized for HF with hypervolemia were randomized to ultrafiltration or intravenous diuretics.[27] Primary endpoints were weight loss and dyspnea assessment at 48 hours following randomization. At 48 hours, weight (5.0±3.1 kg vs. 3.1±3.5 kg, P=0.001) and net fluid loss (4.6 vs. 3.3 litre, P=0.001) were greater in the ultrafiltration group. Dyspnea scores were similar. At 90 days, the ultrafiltration group had fewer patients rehospitalized for HF, rehospitalization days, and unscheduled visits. Although these results are promising, patients who are candidates for ultrafiltration are required to have adequate systemic perfusion and renal function and be able to tolerate anticoagulation with appropriate local nephrology support.

Although recent data have suggested that judicious use of noninvasive ventilation, including continuous positive airway pressure (CPAP) and bilevel positive airway pressure (BiBAP), may obviate the need for intubations in up to 75% of cases,[28,29] the recently presented preliminary results (at the European Society of Cardiology Congress 2007) of the 3CPO Trial in acute pulmonary edema demonstrated that treatment with noninvasive ventilation was not associated with differences in mortality compared with standard oxygen therapy (the primary endpoint), despite improvements in early physiologic parameters (eg, oxygen saturation and respiratory distress with noninvasive ventilation).

Inotropes

Inotropes are frequently required in patients with ADHF who have low systemic pressures because of their augmentative effects on hemodynamic parameters, namely cardiac output. The use of dobutamine is supported by small studies documenting improved hemodynamics in patients with ADHF.[30] The only randomized controlled study of adequate sample size – the Outcome of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-HF) – examined milrinone in 951 patients with ADHF, but with preserved systolic blood pressure.[31] The use of milrinone was associated with an excess in adverse events driven by increased systemic hypotension and atrial fibrillation.

The calcium sensitizer, levosimendan, was shown to improve hemodynamics (primary endpoint) and 180-day mortality over dobutamine in 203 patients with severe low output HF in the Levosimendan Infusion versus DObutamine (LIDO) study. However, in the subsequent Survival of Patients with Acute Heart Failure in Need of Intravenous Inotropic Support (SURVIVE) study of 1327 patients, designed to assess 180-day mortality as the primary endpoint,[32] levosimendan was no better than dobutamine. In the Randomized Evaluation of Levosimendan (REVIVE-2) trial, presented at the American Heart Association 2006 meeting, levosimendan improved symptoms better than placebo in 600 patients, but there were more adverse events in the actively-treated group.

Vasodilator therapy

Vasodilators rapidly improve resting hemodynamics, reduce ventricular filling pressures, and reduce myocardial oxygen consumption. Vasodilators can also decrease systemic vascular resistance, decrease ventricular workload, increase stroke volume, and improve cardiac output.[33] Nitroglycerin (NTG) is a vasodilator commonly used to relieve pulmonary congestion. While it is an effective vasodilator, frequent dose titrations of intravenous (IV) NTG are often necessary to produce the desired hemodynamic effects and symptomatic relief, and doses >150 µg/min may be necessary to sufficiently decrease filling pressures and alleviate symptoms.[34] Because IV NTG requires frequent dose titration and may cause dose-dependent hypotension, patients with ADHF treated with IV NTG are often required to be monitored in an intensive care unit or "step-down" settings.

Given the biologic effects of the natriuretic peptides, it is not surprising that exogenous administration of these peptides has been explored as a strategy to treat patients with HF.[35,36] Two synthetic natriuretic peptides have been developed for use in HF[35,37]: recombinant human BNP (nesiritide) and ANP (carperitide). Nesiritide is approved in Canada and several countries for treatment of ADHF. When administered intravenously to patients with HF, nesiritide rapidly decreased cardiac filling pressures[38,39] and improved self-reported symptoms.[38] The use of nesiritide will be discussed in the remainder of this *Cardiology Scientific Update*.

Recent trials of novel therapies

Heart failure is a clinical syndrome that is associated with heterogeneous groups of conditions. As shown in Table 4, 3 commonly-encountered clinical scenarios include:

- chronic, moderate to severe HF
- cardiac surgery in HF patients
- ADHF.

Table 4: Three commonly-encountered clinical scenarios in patients with HF

Characteristic	Chronic HF	Post CABG	ADHF
Mortality course	Linear	Early, less late	Early and Late
Hormonal activation	Stable,	Predictable	Prior acute
Inflammation	Mild, stable	Acute	Acute
Vasoconstriction	Somewhat	Yes, but can also be iatrogenic	Yes
Evidence for β-blocker use	Yes	Somewhat	No
Decline in renal function	Linear	Yes, acute	Yes, acute

All of these scenarios differ from that of standard "stable chronic HF" in their pathophysiology and the same treatments may have different effects on the different clinical scenarios. Nesiritide, a recombinant human BNP, induces vasodilatation, diuresis, and inhibits neurohormones[40,41] and, therefore, should potentially be of benefit in the above clinical scenarios.

Advanced chronic heart failure

The Follow-up Serial Infusions of Nesiritide for the Management of Patients with Advanced Heart Failure (FUSION II) Trial evaluated the efficacy and safety of serial infusions of nesiritide compared to placebo, in patients with advanced (stage D) HF.[42]

In the pilot, open-label FUSION I trial, the adjunctive administration of nesiritide with standard therapy for patients with advanced HF, was demonstrated to have a neutral effect on outcomes, with no evidence of increased risk. Within a prespecified subset of high-risk patients, a potential signal of benefit on a combined endpoint of mortality and CV hospitalization was identified.[43]

FUSION II was a randomized, double-blind, placebo-controlled trial using a 2:1 nesiritide:placebo randomization, with nesiritide patients randomly assigned to receive usual care plus nesiritide, either once or twice weekly. Placebo patients received usual care only. The trial was conducted over 3 months, with a 3-month follow-up period. The primary endpoint was a composite of all-cause mortality and CV, renal, or cardiorenal hospitalization. A total of 911 patients were randomized to placebo (n = 306) or nesiritide (n = 605) and the results were presented at the American College of Cardiology 2007 scientific meeting. The composite primary endpoint through week 12 was identical in the placebo and nesiritide arms (37%). On the other hand, treatment with nesiritide was not associated with increased mortality or deterioration in renal function, a concern that has been raised with this drug.[44,45]

The high risk post-CABG surgery patient

The Nesiritide Administered Peri-Anesthesia in Patients Undergoing Cardiac Surgery (NAPA) trial was a prospective, multicentre, double-blind, exploratory study that randomly assigned patients with ejection fraction (EF) ≤40% who were undergoing coronary artery bypass graft (CABG) surgery with anticipated use of cardiopulmonary bypass (CPB) to receive nesiritide or placebo for 24 to 96 hours after induction of anesthesia.[46] Postoperative renal function, hemodynamics, and drug use (primary endpoints) were assessed in patients who underwent CABG using CPB. Mortality and safety (secondary endpoints) were assessed in all patients who received the study drug.

Of 303 randomized patients, 279 received the study drug and 272 underwent CABG using CPB. Compared with placebo, nesiritide was associated with a significantly attenuated peak increase in serum creatinine and a smaller fall in glomerular filtration rate during the hospital stay or by study day 14, and a greater urine output during the initial 24 hr after surgery. In addition, nesiritide-treated patients had a shorter hospital stay (p=0.043) and lower 180-day mortality (p=0.046).

Acute decompensated heart failure

The Vasodilation in the Management of Acute CHF (VMAC) was the first large, multicentre, double-blind, randomized controlled trial to evaluate the hemodynamic and clinical effects of a natriuretic peptide compared to another IV vasodilating agent, both against the background of standard care, in the management of patients with ADHF.[38] A total of 489 inpatients with dyspnea at rest from ADHF, including 246 who received pulmonary artery catheterization, were randomized to IV nesiritide (n=204), IV NTG (n=143), or placebo (n = 142), added to standard medications for 3 hours, followed by nesiritide (n=278) or NTG (n=216) added to standard medication for 24 hours. The primary outcome was the change in pulmonary capillary wedge pressure (PCWP) among catheterized patients and patient self-evaluation of dyspnea at 3 hours after initiation of study drug among all patients. Secondary outcomes included comparisons of hemodynamic and clinical effects between nesiritide and NTG at 24 hours

Results of the primary outcomes are shown in Figure 2 and 3. At 3 hours, the mean ± (SD) decrease in PCWP from baseline was -5.8±6.5 mm Hg for nesiritide (vs. placebo, P<0.001; vs. NTG, (P=0.03), -3.8±5.3 mm Hg for NTG (vs. placebo, P=.09), and -2±4.2 mm Hg for placebo. At 3 hours, nesiritide resulted in improvement in dyspnea compared with placebo (P=0.03), but there was no significant difference in dyspnea or global clinical status with nesiritide compared with NTG. At 24 hours, the reduction in PCWP was greater in the nesiritide group (-8.2 mm Hg) than in the NTG group (-6.3 mm Hg), but patients reported no signifi-

Figure 2: Primary endpoint of VMAC: pulmonary capillary wedge pressure through 3 hours

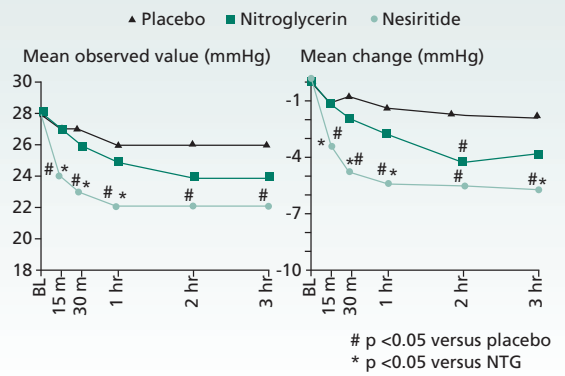
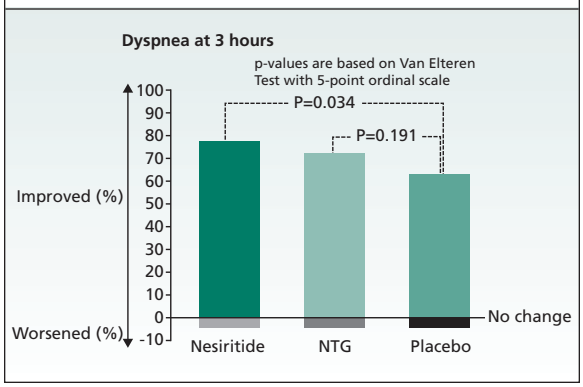


Figure 3: Primary endpoint of VMAC: dyspnea at 3 hours



cant differences in dyspnea and only modest improvement in global clinical status.

Subsequent to the publication of VMAC, 2 pooled analyses of a randomized controlled trial of nesiritide raised concerns regarding a potential for nesiritide to increase the risk of death and worsening renal function in patients with ADHF.[44,45] However, there are important limitations to these analyses, including the unavailability of the primary data, the use of a single arbitrary definition of worsened renal function (one chosen by the Food and Drug Administration [FDA] medical reviewers), the inability to identify and adjust for baseline differences in the treatment groups, and limited information on events or interventions that occurred after the treatment periods. A properly conducted outcome trial with a large enough sample size was, therefore, needed to address the issue of safety.

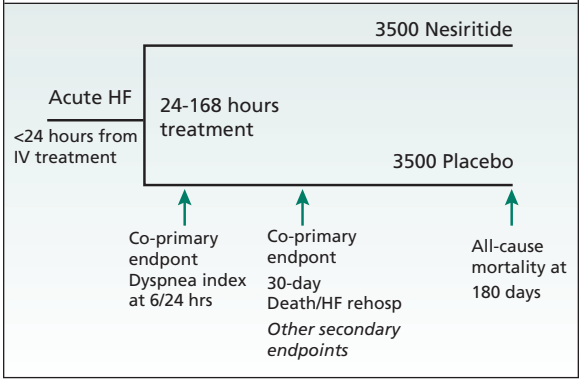
ASCEND-HF: Looking to the future

Based on information to date discussed above, the following questions remained unanswered regarding the role of nesiritide in the management of HF:

- Does nesiritide reduce HF rehospitalization?
- Does it reduce mortality?
- Is it safe?

In 2005, an Expert Panel, convened and chaired by Dr. Eugene Braunwald at the request of the sponsor, provided guidance and counsel on the ongoing and planned clinical development program for nesiritide. The panel endorsed the sponsor's plan to conduct a large trial of clinical outcomes to further assess the benefits and risks of nesiritide compared to standard therapy. The panel also recommended that the trial should include patients presenting to a hospital with ADHF and severe dyspnea and be adequately powered to detect at least a 15% reduction in the combined risk of mortality and cardiorenal morbidities at 30 to 90 days and mortality at 180 days. The trial should also evaluate the effects of nesiritide on renal function, pharmacogenomic parameters, and changes in symptoms. The Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF) is,

Figure 4: ASCEND-HF study design



therefore, a study that is based on the guiding principles that include academic independence, a large and efficient study design with meaningful endpoints, the enrollment of patients with HF with real world experience (standard of care), and substudies that would help advance the knowledge of ADHF.

The primary objectives of ASCEND-HF are to assess if nesiritide compared to placebo:

- reduces risk for HF rehospitalization and/or all-cause mortality through 30 days;
- improves self-assessed dyspnea at 6 and 24 hours;

The secondary objectives are to assess whether nesiritide improves:

- well-being at 6 and 24 hrs
- other clinically meaningful outcomes through day 30
  - number of days alive outside of hospital
  - CV rehospitalization/CV death

To be enrolled into ASCEND-HF, the patients must have all of the following:

- dyspnea at rest or with minimal activity
- one of the following clinical signs
  - respiratory rate >20
  - pulmonary congestion/edema with crackles more than one-third above lung bases
- one of the following objective findings
  - pulmonary congestion on chest radiograph
  - BNP ≥400 pg/mL or NT-proBNP ≥1000 pg/mL
  - PCWP >20 mmHg
  - ejection fraction <40%

The study design is summarized in Figure 4. Importantly, ASCEND-HF will help promote the best standard of care worldwide through the review of evidence and guidelines, development of monographs, as well as the continuous monitoring of the standard of care through the course of the trial. In addition, ancillary studies on biomarkers and pharmacogenomics, respiratory parameters (only in Canada), and climate/environment globally will contribute to the overall understanding of the disease mechanisms of ADHF. Finally, the Canadian health economic substudy and registry will provide information on the management of ADHF in Canada. ASCEND-HF will involve >800 sites in 40 countries.

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