Acute Decompensated Heart Failure
– Treatments and Challenges –

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Acute decompensated heart failure (ADHF) is a major public health problem throughout the world and its importance is continuing to grow. This article reviews the epidemiology of ADHF and the profile of patients suffering from this condition. It describes factors used in assessing prognosis and presents treatment options. Although no currently available treatments have been shown to favorably affect long-term outcomes, there are a variety of strategies and approaches to management that are expected to reduce morbidity and mortality following discharge after ADHF hospitalization. In particular, the clinician is alerted to the need to identify factors that trigger decompensation as well as to optimize treatments for chronic heart failure. The importance of the transition from hospital to the outpatient setting is described. Particular attention should be focused on providing health education to the patient and their family at an appropriate level of medical literacy as well as ensuring early follow-up evaluation after hospital discharge. (Circ J 2012; 76: 532–543)

Key Words: Brain natriuretic peptide; Congestive heart failure; Diuretics; Inotropic agents; Vasodilation

Heart failure has emerged over the past several decades as a major global public health problem, with rising prevalence reported in both industrialized and developing nations alike. In addition to the enormous costs in human suffering and loss of productivity, heart failure has imposed an increasing financial burden on health-care systems throughout the world. Although highly effective treatments including new drug therapies and devices have been developed for patients with chronic heart failure (specifically those with systolic dysfunction), episodes of decompensation that require hospitalization still occur commonly in this population. Hospitalization for decompensation is not only a major driver of heart failure cost but it also augers the onset of a new phase of the disease, which is characterized by a less favorable clinical course. As a result, considerable attention is being focused on managing patients during an episode of acute decompensated heart failure (ADHF) in order to improve both immediate and long-term outcomes. This article presents an overview of current treatment approaches with emphasis on the most pressing issues and challenges that are being faced by clinicians caring for patients with ADHF.

Epidemiology

The overall prevalence of heart failure is increasing throughout the world. There are a variety of reasons for this, including the aging of the population, improved survival in patients following a myocardial infarction (MI) and with other cardiovascular (CV) diseases, and failure to adequately treat risk factors such as hypertension and diabetes. In developing nations, longer life expectancy combined with a sharp increase in CV risk factors has helped drive the heart failure pandemic. Paradoxically, the improved survival of patients with chronic heart failure also adds to the increasing prevalence of this disease. As a consequence of the considerable worldwide growth in the heart failure population, hospitalizations for ADHF have been increasing for many years. In the USA alone, there are approximately 1 million hospitalizations annually that have heart failure as the primary discharge diagnosis, and there is a comparable rate in Europe. While in-hospital mortality and length of stay for ADHF have improved, post-discharge outcomes remain unacceptably poor. In the OPTIMIZE-HF registry that includes data from a representative sampling of US hospitals, 30% of patients discharged after a heart failure hospitalization were readmitted within the first 60–90 days and an additional 9% died during this period. Recognition that hospitalization consumes a large component of the cost of heart failure care and the perception that a substantial number of readmissions are preventable have resulted in changes in reimbursement schedules in the USA, so that hospitals with readmission rates within the first 30 days after discharge that exceed the national average will suffer significant financial penalties.

Registry data from the USA and elsewhere provide insight into the clinical characteristics of patients who are hospitalized due to ADHF. As shown in Table 1, these patients are, in general, elderly, with an average age in the low to mid-70s. In Asia, however, the average age is considerably lower. Approximately half of them are female. Hypertension, coronary artery disease (CAD) and diabetes are common, and...
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one-fourth have atrial fibrillation. Hypertension on admission is more frequent than previously imagined, with systolic pressure averaging between 140 and 150 mmHg. Blood pressure in patients hospitalized with decompensated heart failure in Japan, however, tends to be considerably lower. Patients with evidence of hypotension comprise only a small percentage of those hospitalized with ADHF. As shown in Figure 1, approximately half of the patients admitted with decompensation in the USA have heart failure with preserved ejection fraction (HFpEF) and this percentage is even higher in Japan. Overall 60–90-day post-discharge morbidity and mortality risk, however, does not differ significantly between the HFpEF patients and patients with heart failure and reduced ejection fraction (HFrEF). As shown in Figure 1, patients in the USA who are hospitalized with ADHF are often afflicted by a variety of other medical conditions. A strikingly similar pattern in comorbidities is seen in the patients admitted with ADHF in Japan. Recognizing the presence of comorbidities is extremely important because they can affect both in-hospital and post-discharge outcomes, particularly in HFpEF patients who have a greater likelihood of subsequent re-hospitalization for non-CV causes than do HFrEF patients. Renal dysfunction, in particular, has an important impact on outcomes in ADHF both in hospital and after discharge. At the time of hospital admission, impaired renal function is present in 20–30% of ADHF patients. Moreover, up to 70% of patients hospitalized with ADHF experience an increase in serum creatinine (sCr) levels, and in around 30% it is ≥0.3 mg/dl. As will be discussed, patients with evidence of kidney dysfunction on admission or who develop it during hospitalization are at increased risk for adverse outcomes both during the hospitalization and following discharge. The high prevalence of comorbidities and their impact on outcomes support the notion that attention to these conditions should be an important part of the management of ADHF patients.

Management Issues

The goals of managing ADHF are outlined in Table 2. Although seemingly obvious, the first task is to confirm that the cause is heart failure rather than some other condition. Making the correct diagnosis expeditiously enables prompt initiation of appropriate therapy and, in the author’s experience, this can greatly influence outcomes, particularly length of stay in hospital. Because worsening congestion is the precipitant for most ADHF episodes, diagnosis is based on a constellation of well-described signs and symptoms that reflect the increased intravascular volume (eg, orthopnea, paroxysmal nocturnal dyspnea, exertional dyspnea, neck vein distention, pulmonary

| Table 1. Clinical Characteristics of DHF Patients in the USA and Europe
| Median age (years) | 75 |
| Female (%) | >50 |
| History of CAD (%) | 60 |
| History of hypertension (%) | 70 |
| History of diabetes (%) | 40 |
| History of atrial fibrillation (%) | 30 |
| Renal abnormalities (%) | 30 |
| SBP >140 mmHg (%) | 50 |
| SBP 90–140 mmHg (%) | 45 |
| SBP <90 mmHg (%) | 5 |

DHF, decompensated heart failure; CAD, coronary artery disease; SBP, systolic blood pressure

Figure 1. Distribution of left ventricular ejection fraction (LVEF) in patients hospitalized with decompensated heart failure. The broken line separates patients hospitalized with heart failure with preserved ejection fraction (HFpEF) from those with heart failure with reduced ejection fraction (HFrEF). From reference 18.

Figure 2. Distribution of left ventricular ejection fraction (LVEF) in patients hospitalized with decompensated heart failure. The broken line separates patients hospitalized with heart failure with preserved ejection fraction (HFpEF) from those with heart failure with reduced ejection fraction (HFrEF). From reference 18.
The physical examination in patients with worsening chronic heart failure may differ somewhat from that in patients with new-onset heart failure. Pulmonary findings may be substantially less pronounced when decompensation occurs in the setting of chronic heart failure as a result of compensatory changes within the lungs (eg, lymphatic hypertrophy) of patients with longstanding heart failure that enable them to accommodate high pulmonary artery wedge (PAW) pressures without the usual findings (eg, rales, pleural effusions) of pulmonary congestion. In addition, the time course over which patients decompensate affects their appearance on presentation. Patients with abrupt onset (ie, within days) of worsening heart failure usually manifest less overall fluid retention than patients with more chronic deterioration (eg, over weeks). One notable caveat with the physical examination for the diagnosis of ADHF is that the presence of peripheral edema is neither a sensitive nor specific sign of heart failure. Many patients with ADHF (particularly those with abrupt decompensation) do not have this finding. Alternatively, the presence of edema may be caused by conditions other than heart failure (eg, venous insufficiency, liver disease, drugs etc). Overall, the most valuable physical finding for detecting congestion is the assessment of jugular venous pressure (JVP). There is reasonably good correlation between JVP and PAW pressure and the absence of elevated JVP usually indicates that left-sided filling pressures are not elevated. Thus, careful assessment of the JVP is considered an integral part of the initial evaluation of patients with ADHF.

Confirming Presence and Establishing Etiology of ADHF

Although recognition of ADHF is based predominantly on the history and examination (supplemented by standard lab tests, chest X-ray and electrocardiogram), the diagnosis at the time of presentation is not always apparent. Biomarkers are extremely helpful in deciding whether dyspneic patients are suffering from heart failure or some other condition. In the Breathing Not Properly study, there was considerable uncertainty in the cause of dyspnea in >40% of patients who were being evaluated for this symptom in the emergency room. The level of B-type natriuretic peptide (BNP) in the patients’ blood helped the examining physicians determine whether heart failure was present, and integration of BNP into the diagnostic equation greatly reduced the degree of uncertainty. Patients with BNP <100 pg/ml are unlikely to have heart failure, whereas heart failure is likely in those with levels >500 pg/ml. Levels in between fall into a ‘gray zone’ requiring BNP results to be integrated with other findings to arrive at the correct diagnosis. Exceptions to the diagnostic accuracy of BNP are related to the fact that it may not be elevated until later in the course in patients with flash pulmonary edema, and can remain within the normal range (or be minimally elevated) when left ventricular (LV) wall stress is not elevated, as is the case in patients with mitral stenosis or cardiac tamponade. Isolated right heart failure is usually associated with lower BNP levels than is seen with left heart failure, and HFpEF patients
tend to have lower levels than HFrEF patients.

Establishing the cause of heart failure is a goal that should be approached at the same time as the diagnosis of ADHF is being confirmed. While a discussion of the myriad causes of heart failure is beyond the scope of this review, it is worth emphasizing that management of patients in the acute setting may be strongly influenced by the etiology. For instance, heart failure that is precipitated by uncontrolled hypertension is treated quite differently than if the cause was an acute MI or a valvular lesion such as aortic stenosis.

Assessing Risk

Although a variety of risk factors has been used to predict in-hospital mortality or post-discharge events, the ones listed in Table 3 appear to be the most valuable for determining prognosis. In an analysis of patients hospitalized with ADHF in the ADHERE Registry summarized in Figure 3, Fonarow et al found that a blood urea nitrogen (BUN) level >43 mg/dl was the strongest predictor of in-hospital mortality among measures commonly obtained at the time of hospital admission. By combining this BUN cut-off with systolic blood pressure (SBP) ≥ or < 115 mmHg and sCr levels ≥ or < 2.7 mg/dl they found an approximate 10-fold difference in mortality in hospital between patients with high BUN, low SBP and high sCr compared to those with a low BUN and high SBP. Changes in sCr alone during ADHF hospitalization have also been shown to be highly predictive of the clinical course. Patients whose sCr increases by ≥0.3 mg/dl have higher risk of in-hospital mortality, longer length of stay and higher post-discharge mortality and readmission rates. Similar findings have been reported from Japan.

As noted earlier in this review, SBP at the time of admission for decompensated heart failure can be highly variable. Gheorghide et al reported a stepwise mortality increase during hospitalization in OPTIMIZE-HF patients from the lowest to the highest decile of SBP at the time of admission. The vast majority of patients with ADHF have signs and symptoms of congestion at the time that they are hospitalized. Although treating congestion to relieve symptoms is a goal in and of itself, the degree to which this is successful has been associated with a reduction in subsequent risk of clinical events. Patients discharged from hospital with lower PAW pressure and/or less evidence of congestion are more likely to have a favorable course following discharge. Similarly, serum sodium levels are highly predictive of outcomes both in hospital and after discharge from an ADHF hospitalization. Although a variety of criteria for defining hyponatremia have been proposed, all seem arbitrary because the association between serum sodium levels and mortality is continuous, with risk increasing progressively from milder to more severe levels of hyponatremia.

In addition to their diagnostic value, biomarkers have also proven to be quite useful in assessing prognosis. The natriuretic peptides have been used most commonly for this purpose and there is good evidence that the levels of BNP or N-terminal proBNP measured either on admission or at the time of discharge can distinguish patients at various levels of risk for subsequent events. Circulating cardiac troponins have been traditionally used to evaluate patients with chest pain to detect cardiomyocyte cell death or damage. There is good evidence, however, that circulating troponins are present in a substantial percentage of heart failure patients without ischemia, and the levels measured have been correlated with mortality risk. In patients with ADHF, a positive cardiac troponin test is associated with higher in-hospital mortality, independently of other predictive variables. Although the likelihood of having what has been termed a ‘troponin leak’ in the setting of an episode of ADHF is increased in patients with CAD, patients with non-ischemic cardiomyopathies may also have elevated troponin levels, indicating that factors above and beyond a restriction in coronary flow are involved. Ischemia developing as a result of myocardial oxygen supply/
demand mismatches, adverse effects of neurohormonal agents that are released within the heart, or elevated levels of free oxygen radicals have all been postulated as the cause of the troponin leaks that occur in HF patients in non-acute coronary syndrome settings.\textsuperscript{44} There is evidence that combining troponin-I with BNP levels is helpful in assessing risk in patients hospitalized with decompensated heart failure.\textsuperscript{55}

The importance of defining risk in patients hospitalized with ADHF is based on the presumption that it identifies a group that would benefit from more intensive therapy and/or follow-up, and that such aggressive treatment would improve outcomes. Definitive proof that this is the case, however, is lacking and this hypothesis still requires support from the results of well-designed clinical trials.

**Initial Treatment to Relieve Symptoms and Stabilize Hemodynamics**

**Diuretics and Other Treatments to Reduce Congestion**

Because patients hospitalized with ADHF almost always have symptoms of congestion,\textsuperscript{26} removing excess fluid is required to help them feel better. The total amount that needs to be removed, however, may vary considerably. As noted above, volume overload is often modest in patients with rapid onset of heart failure (within 48h), so that removal of only a few liters of fluid may be sufficient. In contrast, fluid retention can be massive (exceeding 20L in some cases) in patients with a more gradual onset of congestion. Defining the amount of fluid that a patient has retained is important in setting goals for diuresis during hospitalization.\textsuperscript{46,47} The objective is to remove a sufficient amount of fluid to reduce filling pressures and relieve symptoms while avoiding over-diuresis, with its attendant adverse effects on blood pressure and renal function.

Despite concerns about their safety and efficacy,\textsuperscript{48,49} diuretics are the first line of therapy for treating congestion. Loop diuretics are preferred due to their greater potency compared to other diuretics, even when renal function is impaired. In the setting of ADHF, they are usually given i.v. either by bolus injection or continuous infusion. The safety and efficacy of these 2 approaches was recently compared in the DOSE study but no clear-cut advantage of either strategy was detected.\textsuperscript{50} In patients who are refractory to loop diuretics, the addition of a second diuretic agent that acts on another site in the nephron is often effective in promoting diuresis.\textsuperscript{51} Either a thiazide (which can be given i.v.) or metolazone, both of which act on the distal portion of the nephron, can be used for this purpose.

Disadvantages and side-effects of diuretic therapy include electrolyte abnormalities (eg, hypokalemia and hypomagnesia), metabolic disturbances (eg, gout and hyperglycemia), pancreatitis and ototoxicity. Diuretics can overshoot the mark, leading to hypovolemia that may compromise renal blood flow and function, and/or activation of neurohormonal systems that may also cause worsening renal function.

As noted earlier, worsening renal function is common in patients hospitalized with ADHF and is associated with less favorable outcomes.\textsuperscript{22,53} As listed in Table 4, several factors may be involved. All of these should be considered in order to determine the best means of removing excess fluid without adversely affecting renal function. Diuretic agents are often implicated as the cause of worsening renal function and there is evidence that they can do so by further activating the renin-angiotensin system, or (by delivering large quantities of sodium to the distal portion of the nephron) stimulating adenosine release within the kidney.\textsuperscript{52} When worsening renal function is detected by a rise in sCr, diuretic therapy is often discontinued or reduced based on the belief that renal perfusion has been compromised by excessive volume loss. While this scenario may be correct following diuresis that has been too vigorous or extensive, it is unlikely the cause of worsening renal function that occurs early in the hospital course, when sCr rises in most cases.\textsuperscript{22} This temporal association suggests that overly aggressive diuresis is not usually the cause of worsening renal function. In contrast, systemic congestion with high levels of venous pressure have been shown to compromise renal function.\textsuperscript{53,54} This is due to both a reduction in the pressure differential that drives blood through the kidney (determined by the difference between mean arterial pressure and central venous pressure), and the physical impact of congested renal veins on renal epithelial cell function. This pathophysiology indicates that in many cases further diuresis with a goal of relieving renal venous congestion may be indicated, because it would be expected to improve kidney function.\textsuperscript{53}

**Vasodilators**

Vasodilators favorably affect cardiac function by reducing loading conditions on the heart. Nitroglycerin (NTG), a predominant venodilator, can relieve congestive symptoms by reducing cardiac preload.\textsuperscript{56,57} Intravenous NTG is usually initiated at a dose of 20–40μg/min. Based on symptoms and blood pressure the dose can be uptitrated to 200–400μg/min. Its short half-life in minutes allows rapid change in dose in response to the clinical situation. Although NTG improves hemodynamic parameters and can help improve congestive symptoms, there is little evidence from carefully done studies in ADHF patients that it favorably affects outcomes. Nonetheless, it is used frequently, particularly in patients in whom blood pressure is elevated. Side-effects include hypotension, tachycardia, headache and abdominal pain. Tachyphylaxis can occur with extended use and there is some evidence that this occurs within the first 24h.\textsuperscript{58} Although tachyphylaxis can be overcome in the short term by increasing dose, it leads to progressively decreasing NTG efficacy.

Nitroprusside (NP) is a balanced vasodilator drug that relaxes arterial resistance and venous capacitance vessels.\textsuperscript{59,61} By reducing both preload and afterload it can relieve congestion and also improve cardiac output, particularly in patients with high levels of systemic vascular resistance (SVR). It is useful in favorably redistributing total LV stroke volume in patients with either mitral or aortic insufficiency such that regurgitant flow is reduced while forward flow is increased. Similar to NTG, the drug is short acting (with a half life in minutes). Because it is equally effective in relaxing arterial resistance and venous capacitance vessels, an arterial line is

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**Table 4. Factors Associated With Worsening Renal Function in Decompensated Heart Failure**

<table>
<thead>
<tr>
<th>Risk Factors</th>
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<tr>
<td>1. Underlying renal disease due to atherosclerosis, hypertension and/or diabetes</td>
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<td>2. Low cardiac output and reduced renal perfusion</td>
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<tr>
<td>3. Diagnostic or therapeutic agents (eg, contrast, non-steroidal anti-inflammatory drugs)</td>
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<tr>
<td>4. Drugs used to treat heart failure (eg, diuretics, angiotensin enzyme inhibitors, angiotensin receptor blockers)</td>
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<td>5. Neurohormonal activation</td>
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<tr>
<td>6. Tubulo-glomerular feedback caused by intra-renal release of adenosine</td>
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<td>7. Systemic venous congestion</td>
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usually placed so that blood pressure can be monitored. The starting dose is between 0.25–0.50 μg·kg⁻¹·min⁻¹ and the drug can be uptitrated in increments of 0.25 μg·kg⁻¹·min⁻¹ at frequent intervals (eg, 5–15 min) until the desired clinical response is achieved or blood pressure falls to a defined lower limit. Side-effects are similar to those of NTG but also include methemoglobinemia and cyanide toxicity. The latter may occur with prolonged use at high dose and is more likely in patients with renal insufficiency. It may be detected by the smell of almonds on the patients’ breath. Although monitoring serum thiocyanate levels is helpful, close observation of the patient for anorexia, fatigue or mental status changes includ-
ing psychosis, weakness, seizures, tinnitus and hyperreflexia is recommended. One cautionary note is that downtitration of NP should proceed slowly over a period of hours to days in order to avoid rebound vasoconstriction that occurs with abrupt discontinuation. Although NP has been used almost exclusively in the past with a right heart catheter in place, this practice has become less common and is not necessary for safe or effective use of the drug. Studies demonstrating beneficial clinical effects of NP on either symptoms or long-term outcomes in ADHF patients are lacking.

The third i.v. vasodilator that is used in the USA is nesiritide or recombinant human-B type natriuretic peptide (rh-BNP). The drug is predominantly an arterial dilator and is most useful in patients with congestive symptoms in association with elevations of blood pressure. The Vasodilators in the Management of Acute Congestive Heart Failure (VMAC) study compared the effects of nesiritide with both fixed-dose NTG (at 60 μg/min) and placebo on a background of standard therapy including i.v. diuretics in patients with ADHF. The results showed that at 3 h after initiation of therapy, nesiritide caused a greater and more rapid reduction in PAW pressure than either NTG or placebo. Nesiritide was associated with a significantly greater likelihood of relief from dyspnea than placebo. The more recent and much larger Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure Trial (ASCEND-HF) study, however, showed only very modest improvements in dyspnea and no favorable effect on either short-term or post-discharge morbidity and mortality. Hypotension was more common with nesiritide than with placebo but there was no significant adverse effect of the drug on renal function, as had been suggested in an earlier meta-analysis. Nesiritide treatment can be initiated with a lower bolus dose, an approach that may be helpful in hypertensive patients with ADHF. Most clinicians, however, do not use a loading dose and start therapy at the maintenance dose of 0.10 μg · kg⁻¹ · min⁻¹. Although there is some anecdotal evidence that lower doses enhance diuresis while avoiding hypotensive effects, definitive evidence supporting this possibility is lacking.

**Inotropic Agents**

Over the last several years there has been less use of inotropic agents in the USA than in the past based on concerns about adverse effects of this class of drugs on outcomes in patients with ADHF. Nonetheless, judicious use of inotropic agents can be helpful in treating patients with systolic dysfunction who present with evidence of tissue hypoperfusion. Clinical trial results supporting safety and efficacy of any inotropic agent as routine therapy in ADHF, however, are lacking and there is information that they may be associated with less favorable outcomes, particularly in CAD patients.

Dopamine is the least commonly used inotropic agent in the USA. At low dose (3–5 μg · kg⁻¹ · min⁻¹) its predominant effect is to cause renal arterial vasodilation through activation of dopaminergic receptors in the renal vasculature. As shown in Figure 5, the resultant increase in renal blood flow appears to be in excess of any increase in cardiac output that is related to other hemodynamic effects of the drug. While there has been some enthusiasm for use of low-dose dopamine in ADHF patients with rising Cr levels or diuretic resistance, clinical trial evidence confirming the safety and efficacy of this approach is lacking. At doses between 5 and 10 μg · kg⁻¹ · min⁻¹ dopamine acts predominantly to activate the β-1 adrenergic receptor producing inotropic, chronotropic and arterial dilating effects. Above 10 μg · kg⁻¹ · min⁻¹ α-1 adrenergic effects begin to predominate and when the drug is used in this range it can increase or maintain blood pressure by increasing SVR. This effect, however, may be a double-edged sword because high levels of SVR increase LV afterload, which impairs chamber emptying of the dysfunctional left ventricle. Dopamine is short acting and adjustments in dose according to prevailing clinical conditions and blood pressure can be initiated with rapid effects. The drug should be given through a central line because infiltration at a peripheral i.v. site can cause intense vasoconstriction and tissue necrosis due to its α-adrenergic blocking properties at high concentrations. Side-effects of dopamine include tachycardia, arrhythmogenesis and hypotension (when used in β-agonism doses) and provocation of myocardial ischemia in patients with underlying CAD.

Dobutamine is a β-agonist that affects predominantly the β-1 adrenergic receptor. It is usually given in doses ranging between 3 and 10 μg · kg⁻¹ · min⁻¹ but doses up to 20 μg · kg⁻¹ · min⁻¹ are occasionally used. By virtue of its β-agonism dobutamine has inotropic and chronotropic effects that can improve cardiac output by increasing both heart rate and stroke volume. Dobutamine also dilates arterial resistance vessels and should be considered an inovasodilator rather than only an inotropic agent. In addition to increasing cardiac output, the hemodynamic effects include reductions in right ventricular and LV filling pressures, pulmonary artery pressure and SVR. Reductions in blood pressure and increases in heart rate are common and the drug may provoke or worsen cardiac arrhythmias. These properties limit its use in ADHF patients who are already tachycardic or who are having problems with either atrial or ventricular arrhythmias.

Milrinone is a phosphodiesterase inhibitor. By increasing cyclic AMP and GMP concentrations in the heart and blood vessels it has inotropic, chronotropic and vasodilatory effects. Although milrinone can be initiated with a loading dose, most clinicians avoid this approach unless inotropic support is urgently required. The usual approach is to start an i.v. drip at 0.25–0.50 μg · kg⁻¹ · min⁻¹ and uptitrage to a maximum dose of 1.0 μg · kg⁻¹ · min⁻¹ as needed. Milrinone has similar hemodynamic effects to dobutamine. Increases in cardiac output and reduction in pulmonary artery pressure may be somewhat greater with milrinone than with dobutamine. Side-effects are similar between the drugs, although chronotropic and arrhythmogenic effects appear less pronounced with milrinone, while hypotensive effects are somewhat greater. Because the half-life of milrinone is between 1 and 2 h, untoward hemodynamic effects persist for a longer time than with the other inotropic drugs. As with other inotropic agents, there is little support from clinical trials indicating safety and efficacy of milrinone use. In the OPTIME study, ADHF patients did not show long-term benefits when milrinone was added to standard therapy and there was an increased likelihood of hypotension and arrhythmias. Patients with CAD in the OPTIME study were more likely to experience adverse effects with milrinone compared to placebo. Patients in OPTIME, however, were not required to have evidence of low cardiac output or evidence of tissue hypoperfusion, so that the main message is that milrinone should not be routinely used in ADHF patients. Although definitive evidence of beneficial effects in ADHF patients with tissue hypoperfusion is lacking, this is the group in which milrinone (as well as the other inotropic agents) appears to be most effective.

**Alternative Approaches and Advanced Treatment**

Patients with volume overload who fail to respond adequately to the treatment approaches outlined here due to either diuretic
resistance or worsening renal function can also be considered for ultrafiltration or dialysis. Veno-venous ultrafiltration was assessed in the Ultrafiltration vs. Intravenous Diuretics for Patients Hospitalized with Acute Decompensated HF trial (UNLOAD). In that study 200 patients with AHF were randomized to receive ultrafiltration or i.v. diuretics within 24h of hospitalization. Although improvement in dyspnea was similar between the 2 study groups, there was evidence of greater fluid and weight loss after 48h and a reduction in 90-day re-hospitalization rate in patients who underwent ultrafiltration. Further studies are needed to determine the ultimate role of ultrafiltration in patients hospitalized with ADHF.

Additional therapies for such patients and those who have evidence of hemodynamic instability include mechanical circulatory support devices and/or heart transplantation. In-depth discussion of these advanced treatments, however, is beyond the scope of this article and the reader is referred to several excellent reviews on these topics. In addition, patients with end-stage refractory heart failure who are not candidates for advanced therapies should be counseled about end-of-life decisions (eg, resuscitation, deactivating defibrillator devices) and the availability of palliative care services.

Initiating and Optimizing Long-Term Management Therapies

Hospitalization for ADHF augers the onset of a phase of the disease characterized by a generally down-hill clinical course that is associated with high rates of death and re-hospitalization in many patients. Although the ADHF treatment strategies described here can effectively relieve congestive symptoms and restore hemodynamic stability during hospitalization in most cases, there is no convincing evidence that any of these therapies reduce the likelihood of post-discharge events. Thus, there is a need to define strategies that will improve outcomes in this highly vulnerable population. The next several sections address this issue.

Identifying Triggers for Decompensation

A list of triggers that are known to precipitate ADHF is provided in Table 5. Many of these can be easily identified as part of the initial evaluation from the history, physical examination, routine laboratory tests, chest X-ray and electrocardiogram. Recognition that one or more of these triggers or that a comorbid condition precipitated the episode of ADHF provides a compelling rationale for treating or correcting them in order to improve post-discharge outcomes.

Non-compliance to either diet or the medical regimen has been identified as a common and important cause of decompen-
sation. It is also potentially correctable. Patients often consume diets that contain larger amounts of sodium than are optimal for their condition due to the fact that they either were unaware of the adverse effects of doing so or they had not been educated about how to identify the salt content of various foods. In such cases, dietary counseling is indicated. Failure to comply with the medical regimen is commonly recognized as an important contributor or the main precipitant of an episode of ADHF. Medical non-compliance can be a complex multi-factorial problem and defining the cause is essential in devising an effective strategy for dealing with it. Poor discharge planning including failure of the medical team to provide prescriptions for all medications, patient difficulty in obtaining drugs due to cost or insurance restriction, physical infirmity that prevents patients from contacting the pharmacy, obtaining the medications or self-administering the drugs may all be involved. Willful non-compliance from patients who are suspicious about medications or frankly delusional about their conditions may also be a factor. Educating patients and their families about medications, including providing information about what each drug is meant to do, how to recognize various drugs, and the prescribed dosing regimen has been recognized as a critical component of discharge planning. Patients also need to be informed about the side-effects of each drug that they are taking as well as avenues for refilling prescriptions when needed. Providing such education, however, may be limited by poor patient comprehension so that it is extremely important to assess each patient’s level of medical literacy and to educate them about their medications in a manner consistent with their ability to understand what is being taught. Finally, recognizing and addressing social, physical or insurance-related issues that may impede compliance with the medical regimen is an important means of improving outcomes.

Optimizing Medical Therapy

Although drugs used to treat ADHF that are described here have not been shown to improve long-term outcomes, several agents used to treat chronic heart failure have been shown to be effective in reversing maladaptive cardiac remodeling, improving cardiac function, providing symptomatic relief, improving quality of life and reducing morbidity and mortality. In patients with systolic dysfunction, use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, aldosterone receptor antagonists and (in African–American patients) the combination of hydralazine and isosorbide dinitrate have all been shown to improve outcomes significantly. Moreover, evidence that early initiation of these drugs and/or up titration to target doses is beneficial provides a compelling rationale for starting these drugs during hospitalization in appropriate candidates. Inpatients already receiving these drugs, consideration should be given to up titrating or optimizing the dose during the hospitalization whenever possible.

Defining and Correctable Cause of Heart Failure

Hospitalization for decompensated heart failure should be consid-
ered a watershed event in the patient’s clinical course and every effort should be made to favorably alter the natural history in this high-risk group. In addition to assessing the overall management strategy as described here, review of the etiology of cardiac dysfunction is recommended in order to determine if there may be a correctable cause.

CAD is present in a substantial percentage of patients who are hospitalized due to ADHF, and patients with CAD have a higher 60–90-day post-discharge mortality compared to non-

<table>
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<th>Table 5. Triggers for Decompensation</th>
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<tr>
<td>1. Non-compliance to diet and medications</td>
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<tr>
<td>2. Myocardial ischemia</td>
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<tr>
<td>3. Poorly controlled hypertension</td>
</tr>
<tr>
<td>4. Cardiac arrhythmias (particularly atrial fibrillation)</td>
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<tr>
<td>5. Infections</td>
</tr>
<tr>
<td>6. Anemia</td>
</tr>
<tr>
<td>7. Worsening renal function</td>
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<tr>
<td>8. Thyroid abnormalities</td>
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CAD patients. Evidence that CAD patients who are revascularized have similar post-discharge mortality as the no-CAD group suggests that revascularization may confer a survival advantage in this high-risk group. Thus, defining the presence of ischemia and/or stunned myocardium should be considered during the time the patient is hospitalized with ADHF. Whether revascularization improves outcomes in patients with viability detected on non-invasive testing, however, is controversial and there is a strong need for prospective studies designed to determine the potential benefits of assessing and treating CAD in the ADHF population.

Transition From Hospital to Home

The process of transition from the hospital to the outpatient setting (either home or an extended care facility) has been identified as a potential target for improving outcomes and reducing preventable readmissions. This has resulted in the development of a variety of approaches, the goal of which is to improve patient care during this highly vulnerable period. One such approach in the USA, the Hospital to Home (H2H) project, focuses on 3 key aspects of the discharge plan: (1) providing critical education about the patient’s medications at the time of discharge; (2) teaching the patient to recognize the signs of worsening heart failure (and what to do if this occurs); and (3) establishing a follow-up visit with a health-care provider within a short interval of time following hospital discharge. Although a follow-up clinic visit is a critical component in this approach, there is no universal definition for exactly when this should occur nor is it evident that all patients require the same intensity of post-discharge scrutiny. A recent publication using data from an administrative data base of US Medicare patients suggested that a follow-up visit within the 7–10-day post-discharge period was associated with a lower rate of re-hospitalization. Whether this time interval (or even shorter follow-up) is optimal for all patients or only a defined high-risk group is uncertain at this time. There is also evidence that participation in heart failure performance improvement registries is associated with improved use of guideline-recommended heart failure therapies, better conformity with quality measures, and improved outcomes in patients with heart failure.

Disease management programs have been shown to favorably affect the clinical course of heart failure patients. Benefits include improved use of evidence-based therapy, improved symptomatic status and functional capacity, improved quality of life, reduction in hospitalization and decrease in total medical costs. Increased survival has also been suggested by some studies.

Post-Discharge Patient Monitoring to Improve Outcomes

Due to the vulnerability of heart failure patients during the period following discharge, strategies for increased surveillance have emerged as an area of considerable interest. Post-discharge monitoring using a variety of devices measuring physiologic parameters (eg, blood pressure and weight), collecting information about change in symptoms, or the use of biomarkers to help guide subsequent therapy have been studied in high-risk groups. The rationale for the use of devices that track signs and symptoms associated with worsening heart failure or which detect evidence of an increase in filling pressures is that this will lead to the initiation of therapy that will then reduce the likelihood of clinical deterioration, thereby avoiding events such as hospitalization. This approach implies that there are measurable variables that reflect incipient deterioration and that this information can be integrated into a plan for management that could be used to stop this event from occurring. The vast majority of patients hospitalized with ADHF have signs and symptoms of congestion, and evidence from some of the early device studies indicated that increases in filling pressures occur in these patients in the period preceding the clinical episode. More recently, results of the CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients (CHAMPION) trial demonstrated that collection of these data combined with a means of identifying signals that indicate high risk of an event and intervening by altering medical management resulted in a highly significant and clinically relevant reduction in heart failure hospitalizations. Similarly, studies assessing the impact of following changes in biomarkers such as BNP over time on the clinical course of high-risk patients have been conducted. Although the results are not entirely consistent, there is evidence that this approach can be used to alter management in a manner that reduces hospitalization risk.

Conclusion

Hospitalization for ADHF is an important and growing global health problem. Although current treatments are adequate for stabilizing and relieving symptoms in most patients, compelling evidence that any of the current approaches improve outcomes is scarce. More work is needed in developing new approaches for improving in-hospital and post-discharge outcomes. Until this is accomplished, there are recommended strategies for managing patients hospitalized with ADHF. These include identifying correctable conditions, treating comorbidities and preventing events that trigger decompensation. Attention to these issues, optimizing long-term medical therapy, improving the transition from the hospital to the outpatient setting and use of emerging surveillance strategies to help follow patients should help improve outcomes. The magnitude of the problem and the degree of uncertainty about many of the approaches discussed in this review, however, provide a rationale for greatly intensified research efforts about the management of ADHF.

References

Acute Heart Failure


44. Fortuna P, Reis I, Ascencao R, Carneiro AV. Drug therapy for chronic heart failure due to left ventricular systolic dysfunction: II. Diuretics, Rev Port Cardiol 2009; 28: 977–989.


107. Stoyanov N, Paul V. Clinical use of telemonitoring in chronic heart failure: Keeping up with the times or misuse of time? *Curr Heart Fail Rep* 2011 [Epub ahead of print].


