

CHAPTER

# 25

## *Acute Decompensated Heart Failure : Medical Management*

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### **Introduction**

Acute decompensated heart failure (ADHF) poses unique diagnostic and management challenges. This entity has recently received attention from researchers, clinicians, regulatory agencies, and the pharmaceutical industry. However, there is no consensus on its definition, epidemiology, pathophysiology, appropriate therapeutic options, and directions for future research.

While pharmaceutical innovation has been highly successful in reducing mortality in chronic heart failure, this has not been matched by similar success in acute decompensated heart failure (ADHF). ADHF is the most common reason for hospital admission in patients over the age of 65, and is associated with staggering costs. Furthermore, the prognosis of patients admitted with ADHF remains dismal, associated with high readmission and mortality rates within 6 months after admission. Therefore, it is important to understand current characteristics and clinical care of patients hospitalized with ADHF. Furthermore, an awareness of existing efficacy and safety data with available therapies is essential for optimal patient management. Unfortunately, there is a paucity of controlled clinical trial data to guide treatment, and the few trials conducted have focused primarily on symptom relief and not outcomes. Our

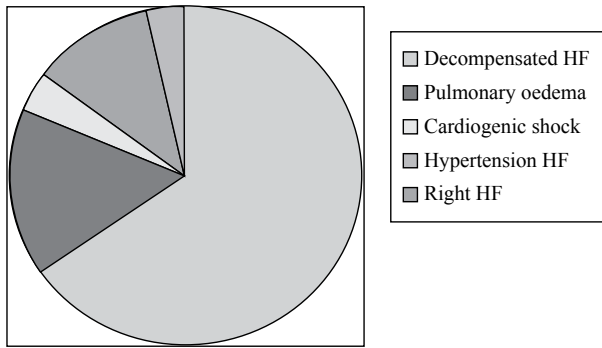
understanding and appropriate patient management of acute decompensated heart failure (ADHF) has continued to evolve.

### **Clinical Profile**

The majority of patients hospitalized with ADHF have evidence of systemic hypertension on admission and commonly have preserved LVEF. Most hospitalized patients have significant volume overload, and congestive symptoms predominate. Patients with severely impaired systolic function, reduced blood pressure, and symptoms resulting from poor end-organ perfusion are in the distinct minority. Natural history studies have shown that ADHF represents a period of high risk for patients, during which their likelihood of death and rehospitalization is significantly greater than for a comparable period of chronic, but stable HF<sup>1</sup>. ADHF is the most common clinical presentation amongst acute heart failure admissions accounting for about two-thirds of cases (Figure 1).<sup>2</sup>

This is a disease entity that is associated with dismal morbidity and mortality. In fact, the in-hospital mortality is close to 5%. The average number of days spent by a patient in the hospital is about 4-6 days. This is a disease associated with marked increase in the incidence of readmission rate --20% at 30 days, and as much as 50% at 6-12 months. The mortality escalates with time in this disease,

**Figure 1**



**Table 1 : Adhere : Clinical Presentation**

| Clinical Presentation     | Incidence |
|---------------------------|-----------|
| Any dyspnea ( % )         | 89        |
| Dyspnea at rest ( % )     | 34        |
| Fatigue ( % )             | 31        |
| Rales ( % )               | 67        |
| Peripheral edema ( % )    | 66        |
| Median BNP ( pcg / ml )   | 838       |
| SBP assessed ( % )        | 99.6      |
| SBP < 90 mm Hg ( % )      | 2         |
| SBP 90-140 mm Hg ( % )    | 48        |
| SBP > 140 mm Hg ( % )     | 50        |
| NYHA class assessed ( % ) | 12        |
| NYHA class II ( % )       | 13        |
| NYHA class III ( % )      | 39        |
| NYHA class IV ( % )       | 46        |

and is noted to be 10% at 30 days, and as much as 20-40% at 6-12 months. Interestingly, in patients presenting with the diagnosis of decompensated heart failure to most emergency departments, 1 in 5, or 21% of these episodes include de novo first-time presentations, while 80% of presentations are recurrent presentations. The rates of hospital readmission rates are certainly extraordinarily high and represent an enormous morbidity and mortality.<sup>3</sup>

ADHF National Registry has shown patients' presentation through the emergency department (Table 1). Ninety per cent will have dyspnea, so the most common reason to go to the hospital is they're short of breath. Fatigue and rales and these

**Table 2 : Precipitating Factors for ADHF**

|   |  |
|---|--|
| Inadequate therapy / noncompliance          | Anemia   |
| Drug resistance / tolerance                 | Complicating conditions                            |
| Adverse drug effects                        | ACS  |
| Negative inotropic properties               | Uncontrolled hypertension                          |
| Salt & water retention                      | Dysrhythmias                                       |
| Adverse interactions                        | Development / exacerbation of valvular dysfunction |
| Deterioration of underlying cardiac disease | Pulmonary embolization                             |
| Excess salt intake                          | Infection  |
| Renal dysfunction                           | Excessive Stress                                   |

other symptoms occur with significant frequency. The 50% have a blood pressure greater than 140, 48% between 90-140. Only 2% present as hypotensive, in other words pressures less than 90. That's important when therapy is started, because vasoactive therapies are not really appropriate in most. Inotropes are not appropriate unless there is hypotension, so only 2% are eligible.

### Precipitating Factors

Precipitating factors should be considered when a patient with ADHF presents ( Table 2 ). Physicians should evaluate through medical history, physical examination, and basic laboratory tests, whether any of these conditions may have led to the decompensation and, when appropriate obtain specifically directed laboratory studies.

### Aim of Management

The key management goals, those should be employed in the management of these patients, include stabilization of the patient, to prevent end-organ dysfunction and to promote prevention of progression of heart failure, and in that regard the appropriate use of neurohormonal antagonism. A key initial goal in stabilizing the patients' symptoms includes improvement in ventricular filling pressures leading to relief from dyspnea, orthopnea, GI symptoms, reduction in mitral and tricuspid regurgitation, reduction in atrial distension and improvement in the balance of

**Table 3 : Recommendations for Hospitalizations**

| Clinical Circumstances      |   |
|-----------------------------|---|
| Hospitalization recommended | Evidence of severely decompensated HF, including: <ul style="list-style-type: none"> <li>• Hypotension</li> <li>• Worsening renal function</li> <li>• Altered mentation</li> </ul> Dyspnea at rest <ul style="list-style-type: none"> <li>• Typically reflected by resting tachypnea</li> <li>• Less commonly reflected by oxygen saturation &lt; 90%</li> </ul> Hemodynamically significant arrhythmia <ul style="list-style-type: none"> <li>• Including new onset of rapid atrial fibrillation</li> </ul> Acute coronary syndromes |

coronary perfusion.

Relief of congestion and volume overload generally is accomplished with sodium and fluid restriction and the use of diuretics. Intravenous vasodilators may be added. Agents to consider for the improvement of hemodynamic parameters include intravenous nitroglycerin, sodium nitroprusside, and nesiritide. The use of inotropes should be severely limited. Discharge evaluation and planning for follow-up are important factors in reducing readmission.

## Diagnosis

The diagnosis of decompensated HF is based primarily on signs and symptoms. When the diagnosis is uncertain, determination of BNP or NT-proBNP concentration should be considered in patients being evaluated for dyspnea who have signs and symptoms compatible with HF. The natriuretic peptide concentration should not be interpreted in isolation, but in the context of all available clinical data bearing on the diagnosis of ADHF. Echocardiography and other necessary procedures should be done.

**Table 4 : Recommendations for Hospitalizations**

| Hospitalizations should be considered | Worsened congestion   |
|---------------------------------------|---|
|                                       | <ul style="list-style-type: none"> <li>• Even without dyspnea</li> <li>• Typically reflected by a weight gain <math>\geq</math> 5 kilograms</li> </ul>  |
|                                       | <b>Signs and symptoms of pulmonary or systemic congestion</b>   |
|                                       | <ul style="list-style-type: none"> <li>• Even in the absence of weight gain</li> </ul>  |
|                                       | <b>Major electrolyte disturbance</b>  |
|                                       | <b>Associated comorbid conditions</b>   |
|                                       | <ul style="list-style-type: none"> <li>• Pneumonia</li> <li>• Pulmonary embolus</li> <li>• Diabetic ketoacidosis</li> <li>• Symptoms suggestive of transient ischemic accident or stroke</li> </ul> |
|                                       | <b>Repeated ICD firings</b>   |
|                                       | <b>Previously undiagnosed HF with symptoms of systemic or pulmonary congestion</b>  |

## Criteria for Hospital Admission

Hospital admission is recommended for patients presenting with ADHF when the clinical circumstances listed in Table 3 and Table 4 are present.<sup>4</sup>

## Monitoring

Patients admitted with ADHF should be carefully monitored and assessed at the stated frequencies shown in Table 5.

The routine invasive hemodynamic monitoring in patients with ADHF is not recommended. Invasive hemodynamic monitoring should be considered in a patient:

- Who is refractory to initial therapy,
- Whose volume status and cardiac filling pressures are unclear,
- Who has clinically significant hypotension (typically systolic blood pressure < 80 mm Hg) or worsening renal function during therapy, or

**Table 5 : Monitoring Recommendations**

| Frequency       | Value                          | Specifics  |
|-----------------|--------------------------------|--|
| At least daily  | <b>Weight</b>                  | Determine after voiding in the morning<br>Account for possible increased food intake due to improved appetite                        |
| At least daily  | <b>Fluid intake and output</b> |  |
| More than daily | <b>Vital signs</b>             | Including orthostatic blood pressure   |
| At least daily  | <b>Signs</b>                   | Edema<br>Ascites<br>Pulmonary rales<br>Hepatomegaly<br>Increased jugular venous pressure<br>Hepatojugular reflux<br>Liver tenderness |
| At least daily  | <b>Symptoms</b>                | Orthopnea<br>Paroxysmal nocturnal dyspnea<br>Nocturnal cough<br>Dyspnea<br>Fatigue   |
| At least daily  | <b>Electrolytes</b>            | Potassium<br>Sodium  |
| At least daily  | <b>Renal function</b>          | BUN<br>Serum creatinine  |

- In whom documentation of an adequate hemodynamic response to the inotropic agent is necessary when chronic outpatient infusion is being considered.

### Risk Classification and Evaluation

A newly identified, validated classification scheme for patients with ADHF uses admission blood urea nitrogen (BUN), creatinine, and systolic blood pressure to assess risk of in-hospital mortality.<sup>5</sup> The new tool is a first for the treatment of acute heart failure, and offers a simple quick way for clinicians

to assess mortality risk upon hospital admission and quickly decide on a treatment strategy. The best single predictor for mortality is high admission levels of BUN ( $\geq 43$  mg/dL [15.35 mmol/L]) followed by low admission systolic blood pressure ( $< 115$  mm Hg) and then by high levels of serum creatinine ( $\geq 2.75$  mg/dL [243.1  $\mu$ mol/L]). Risk groups associated with these groups are presented below.

- High-risk group (all 3 risk factors present)
- Intermediate-risk group 1 (elevated BUN and reduced systolic blood pressure but serum creatinine less than 2.75 mg/dL)
- Intermediate-risk group 2 (elevated BUN only)
- Intermediate-risk group 3 (reduced systolic blood pressure only)
- Low-risk group (none of the 3 risk factors present)

Furthermore, an elevated admission BNP level is a significant independent predictor of In-hospital mortality in ADHF. B-type natriuretic peptide level is predictive of In-hospital mortality in patients with either reduced or preserved LVEF independent of other clinical and laboratory variables. In light of the demonstration of incremental prognostic information, the BNP assay may be considered for inclusion as part of the assessment of patients presenting with an HF. Further research will be necessary to determine whether patients with higher admission BNP will benefit from more intensive monitoring and aggressive treatment strategies.<sup>6</sup>

Patients admitted with ADHF, should undergo evaluation for the precipitating factors like atrial fibrillation or other arrhythmias (e.g., atrial flutter, other supraventricular tachycardia or ventricular tachycardia), exacerbation of hypertension, myocardial ischemia/infarction, exacerbation of pulmonary congestion, anemia, thyroid disease, or significant drug interactions, as well as other less common factors.

## Management

### Diuretic

Patients admitted with ADHF and evidence of fluid overload be treated initially with loop diuretics—usually given intravenously rather than orally. Diuretics be administered at doses needed to produce a rate of diuresis sufficient to achieve optimal volume status with relief of signs and symptoms of congestion (edema, elevated JVP, dyspnea), without inducing an excessively rapid reduction in intravascular volume, which may result in symptomatic hypotension and/or worsening renal function. Careful repeated assessment of signs and symptoms of congestion and changes in body weight is needed, because clinical experience suggests it is difficult to determine that congestion has been adequately treated in many patients. Monitoring of daily weights, intake, and output is necessary to assess clinical efficacy of diuretic therapy. Routine use of a Foley catheter is not required for monitoring volume status. However, placement of a catheter is needed when close monitoring of urine output is warranted.

Careful observation for development of a variety of side effects, including renal dysfunction, electrolyte abnormalities and symptomatic hypotension, is necessary in patients treated with diuretics, especially when used at high doses and in combination. Patients should undergo routine laboratory studies and clinical examination as dictated by their clinical response. Serum potassium and magnesium levels should be monitored at least daily and maintained in the normal range. More frequent monitoring may be necessary when diuresis is rapid. Overly rapid diuresis may be associated with severe muscle cramps, which should be treated with potassium replacement if indicated. Careful observation for the development of renal dysfunction is needed in patients treated with diuretics. Patients with moderate to severe renal dysfunction and evidence of fluid retention should continue to be treated with diuretics. In the presence of severe

fluid overload, renal dysfunction may improve with diuresis.

When congestion fails to improve in response to diuretic therapy, the following options should be considered:

- Sodium and fluid restriction,
- Increased doses of loop diuretic,
- Continuous infusion of a loop diuretic, or
- Addition of a second type of diuretic orally (metolazone or spironolactone) or intravenously (chlorothiazide).

A low-sodium diet (2 g daily) is recommended, as is supplemental oxygen, as needed for hypoxemia. In patients with recurrent or refractory volume overload, stricter sodium restriction may be considered. Fluid restriction (< 2 L/day) is recommended in patients with moderate hyponatremia (serum sodium < 130 mEq/L) and should be considered to assist in treatment of fluid overload in other patients. In patients with severe (serum sodium < 125 mEq/L) or worsening hyponatremia, stricter fluid restriction may be considered.

### Ultrafiltration

The UNLOAD trial conclusively shows that early ultrafiltration safely produces greater weight and fluid loss than intravenous loop diuretics in hypervolemic ADHF patients. Ultrafiltration significantly decreased rehospitalizations for HF and unscheduled medical visits. The cost-effectiveness of ultrafiltration is not established; however, this treatment may have favorable economic implications for patients and payers owing to reduced resource utilization after the index hospitalization. Mechanisms linking different methods of fluid removal to clinical benefit deserve further study.<sup>7</sup>

### Vasodilators

In the absence of symptomatic hypotension, intravenous nitroglycerin, nitroprusside, or nesiritide may be considered as an addition to diuretic therapy

for rapid improvement of congestive symptoms in patients admitted with ADHF. Frequent blood pressure monitoring is recommended with these agents. These agents should be decreased in dosage or discontinued if symptomatic hypotension develops. Reintroduction in increasing doses may be considered once symptomatic hypotension is resolved.

Intravenous vasodilators (intravenous nitroglycerin or nitroprusside) and diuretics are recommended for rapid symptom relief in patients with acute pulmonary edema or severe hypertension.

Intravenous vasodilators (nitroprusside, nitroglycerin, or nesiritide) may be considered in patients with ADHF and advanced HF who have persistent severe HF despite aggressive treatment with diuretics and standard oral therapies.

When added to standard care in patients hospitalized with acutely decompensated CHF, nesiritide improves hemodynamic function and some self-reported symptoms more effectively than intravenous nitroglycerin or placebo.<sup>8</sup>

The results of one recent prospective, randomized, double-blind, placebo-controlled clinical trial indicate that nesiritide therapy does not cause or prevent worsened renal function in patients with ADHF and pre-existing renal dysfunction.<sup>9</sup>

### **Inotropes**

Intravenous inotropes (milrinone or dobutamine) may be considered to relieve symptoms and improve end-organ function in patients with advanced ADHF characterized by LV dilation, reduced LVEF, and diminished peripheral perfusion or end-organ dysfunction (low output syndrome), particularly if these patients have marginal systolic blood pressure (< 90 mm Hg), have symptomatic hypotension despite adequate filling pressure, or are unresponsive to, or intolerant of, intravenous vasodilators.

These agents may be considered in similar patients with evidence of fluid overload if they

respond poorly to intravenous diuretics or manifest diminished or worsening renal function.

When adjunctive therapy is needed in other patients with ADHF, administration of vasodilators should be considered instead of intravenous inotropes (milrinone or dobutamine).

Intravenous inotropes (milrinone or dobutamine) are not recommended unless left heart filling pressures are known to be elevated based on direct measurement or clear clinical signs. Administration of intravenous inotropes (milrinone or dobutamine) in the setting of ADHF should be accompanied by continuous or frequent blood pressure monitoring and continuous monitoring of cardiac rhythm. If symptomatic hypotension or worsening tachyarrhythmias develop during administration of these agents, discontinuation or dose reduction should be considered.

### **Controversy**

The treatment of acute decompensated heart failure remains problematic and most often requires parenteral therapies. Significant concerns have been expressed regarding risks and benefits of individual therapies, especially nesiritide, but few studies have compared the relative safety of varied intravenous therapies on clinical outcomes.

Nesiritide when given with diuretics as currently used in clinical practice do not increase inpatient mortality rates compared with other intravenous treatment regimens for ADHF. In contrast, the use of intravenous Inotrope is consistently associated with a higher hospital mortality rate than was the use of diuretics or diuretics plus vasodilators.<sup>10</sup> Finally, one analysis suggests that nesiritide's adverse effect on worsening of renal function as suggested in retrospective meta-analyses<sup>11</sup> also occurs in clinical practice and may be influenced by nesiritide's characteristics and timing of initiation and perhaps by the intensity of diuretic therapy.

It has been that observed a rapid de-adoption of a drug prescribed for decompensated heart failure after a series of publications brought into question

**Table 6 : Discharge Criteria for Patients with ADHF**

|  |  |
|--|--|
| <b>Recommended for all ADHF patients</b>   | <ul style="list-style-type: none"> <li>• Exacerbating factors addressed</li> <li>• At least near optimal volume status achieved.</li> <li>• Transition from intravenous to oral diuretic successfully completed.</li> <li>• Patient and family education completed.</li> <li>• At least near optimal pharmacologic therapy achieved</li> <li>• Follow-up clinic visit scheduled, usually for 7–10 days</li> </ul>  |
| <b>Should be considered for patients with advanced ADHF or recurrent admissions for ADHF</b> | <ul style="list-style-type: none"> <li>• Oral medication regimen stable for 24 hours</li> <li>• No intravenous vasodilator or inotropic agent for 24 hours</li> <li>• Ambulation before discharge to assess functional capacity after therapy</li> <li>• Plans for postdischarge management (scale present in home, visiting nurse or telephone follow up generally no longer than 3 days after discharge)</li> <li>• Referral for disease management</li> </ul> |

its clinical safety profile. Because intravenous vasoactive therapy use is increasingly driven by nesiritide, the overall use of these therapies also decline. However, among patients on intravenous vasoactive therapy, a higher proportion is prescribed intravenous inotropic drugs. The rate of de-adoption appears to be faster than what has been conventionally described for the adoption of new heart failure medications. Whether the magnitude of these changes can be anticipated or are reproducible in other therapeutic areas remains to be seen.<sup>12</sup>

But the results of one very recent prospective, randomized, double-blind, placebo-controlled clinical trial indicate that nesiritide therapy does not cause or prevent worsened renal function in patients with ADHF and pre-existing renal dysfunction.<sup>9</sup>

These findings all warrant further investigations in controlled clinical trials and may necessitate a

change in clinical practice. Certainly, any ongoing use of nesiritide should reflect a heightened surveillance of renal function. As we await additional trials, especially ASCEND-HF, this analysis of ADHERE supports the use of vasodilator therapy for acute decompensated heart failure, adds to other data which may indicate a need for more judicious application of diuretic therapy, and further reinforces guideline recommendations against the routine use of inotropic support unless indicated by the presence of hypotension or cardiogenic shock.<sup>4</sup>

### Emerging Agents

An unprecedented wealth of pharmacologic innovation may soon transform the management of these challenging patients. Agents that target contractility, such as cardiac myosin activators and novel adenosine triphosphate-dependent transmembrane sodium-potassium pump inhibitors, provide inotropic support without arrhythmogenic increases in cytosolic calcium or side effects of more traditional agents.

Adenosine receptor blockade may improve glomerular filtration and diuresis by exerting a direct beneficial effect on glomerular blood flow while vasopressin antagonists promote free water excretion without compromising renal function and may simultaneously inhibit myocardial remodeling.

Urodilatin, the renally synthesized isoform of atrial natriuretic peptide, may improve pulmonary congestion via vasodilation and enhanced diuresis. Finally, metabolic modulators such as perhexiline may optimize myocardial energy utilization by shifting adenosine triphosphate production from free fatty acids to glucose, a unique and conceptually appealing approach to the management of heart failure.

These advances allow optimism not only for the advancement of our understanding and management of decompensated heart failure syndromes but for the translational research effort in heart failure biology in general.<sup>13</sup>

## Discharge Criteria

It is desirable that criteria in Table 6 be met before a patient with ADHF is discharged from the hospital.

## Key Issues<sup>14</sup>

### Patient characteristics

Unlike clinical trial populations, 'real-life' patients with ADHF are a heterogeneous population: they tend to be relatively old, normo- or hypertensive, and have a high incidence of co-morbidities including diabetes, atrial fibrillation, coronary artery disease, hypertension, and renal dysfunction.

Over 50% of patients have an LVEF > 40%—but patients with preserved systolic function are rarely included in clinical trials.

Renal dysfunction is a common finding and a major predictor of poor prognosis.

### Diagnosis and treatment

Despite the complex physiology underlying presentation, work-up is not always complete and the available diagnostic technology is underutilized.

Congestion is not well treated and warrants greater clinical focus.

Treatment requires a multidisciplinary approach.

Many patients with no apparent clinical indication received positive inotropes, even though these drugs are associated with increased mortality.

### Outcomes and quality of care

Performance on JCAHO quality of care indicators requires substantial improvement.

Many patients receive treatment which affords temporary relief but may ultimately contribute to the high readmission rates.

### Long-term patient management

The implementation of basic life-saving chronic heart failure therapies is not optimal (e.g. beta-blockers).

## Conclusion

Patients admitted with ADHF and evidence of fluid overload be treated initially with loop diuretics. When congestion fails to improve in response to diuretic therapy, adjunctive options should be considered like sodium and fluid restriction, increased doses of loop diuretics, continuous infusion of a loop diuretic and addition of a second type of diuretic.

Ultrafiltration may also be considered as an effective alternative therapy. Ultrafiltration safely produces greater weight and fluid loss than intravenous diuretics.

In the absence of symptomatic hypotension, IV nitroglycerine, nitroprusside or nesiritide may be considered as an addition to diuretic therapy for rapid improvement of congestive symptoms in patients with ADHF.

Intravenous inotropes (milrinone or dobutamine) may be considered to relieve symptoms and improve end-organ function in patients with advanced ADHF characterized by LV dilation, reduced LVEF, and diminished peripheral perfusion or end-organ dysfunction (low output syndrome), particularly if these patients have marginal systolic blood pressure (< 90 mm Hg), have symptomatic hypotension despite adequate filling pressure, or are unresponsive to, or intolerant of, intravenous vasodilators.

## Summary

Acute Decompensated Heart Failure (ADHF) is the most common reason for hospital admission in patients over the age of 65, and is associated with staggering costs. Furthermore, the prognosis of patients admitted with ADHF remains dismal, associated with high readmission and mortality rates within 6 months after admission. Therefore, it is important to understand current characteristics and clinical care of patients hospitalized with ADHF in the context of recently released practice guidelines. Diuretics and vasodilators are the mainstay of therapy. Inotropes are used only in



low output state. Ultrafiltration is the new option to relieve fluid overload. Furthermore, an awareness of existing efficacy and safety data with available therapies is essential for optimal patient management. Unfortunately, there is a paucity of controlled clinical trial data to guide treatment, and the few trials conducted have focused primarily on symptom relief and not outcomes. Our understanding and appropriate patient management of acute decompensated heart failure (ADHF) has continued to evolve. Questions remain regarding existing ADHF therapies, and planned clinical trials may provide valuable insights and assist the clinician in management strategies.

## References

1. Blackledge HM, Tomlinson J, Squire IB. Prognosis for patients newly admitted to hospital with heart failure: survival trends in 12 220 index admissions in Leicestershire 1993–2001. *Heart*. 2003;89:615–620.
2. Nieminen MS, Brutsaert D, Dickstein K, Drexler H, Follath F, Harjola V-P, et al. EuroHeart Failure Survey II (EHFS II): a survey on hospitalized acute heart failure patients: description of population *Eur Heart J* 2006 ; 27: 2725-2736
3. Adams KF, Fonarow GC, Emerman CL. Characteristics and outcomes of patients hospitalized for heart failure in the United States (2001–2003): rationale, design and preliminary observations from the Acute Decompensated Heart Failure National Registry (ADHERE). *Am Heart J* 2005; 49 : 209-216
4. Adams KF, Lindenfeld J, Arnold JMO, Baker DW, Barnard DH, Baughman KL, et al. Executive Summary: HFSA 2006 Comprehensive Heart Failure Practice Guideline. *J Cardiac Failure* 2006;12:10–38.
5. Gregg C, Fonarow G, Kirkwood F, Adams Jr; William T. Abraham; Clyde W. Yancy; W. John Boscardin; for the ADHERE Scientific Advisory Committee, Study Group, and Investigators. Risk Stratification for In-Hospital Mortality in Acutely Decompensated Heart Failure: Classification and Regression Tree Analysis. *JAMA*. 2005;293:5
6. Fonarow GC, Peacock WF, Phillips CO, Givertz MM, Lopatin M, for the ADHERE Scientific Advisory Committee and Investigators. Admission B-Type Natriuretic Peptide Levels and In-hospital Mortality in Acute Decompensated Heart Failure. *J Am Coll Cardiol*. 2007;49(19):1943-1950
7. Costanzo MR, Guglin ME, Saltzberg MT, Jessup ML, Bart BA, Teerlink JR , et.al. Ultrafiltration Versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Heart Failure. *J Am Coll Cardiol*, 2007; 49:675-683.
8. Intravenous Nesiritide vs Nitroglycerin for Treatment of Decompensated Congestive Heart Failure: A Randomized Controlled Trial Publication Committee for the VMAC Investigators *JAMA*. 2002;287:1531-1540.
9. Witteles RM, Kao D, Christopherson D, Matsuda K, Vagelos RH, Schreiber D, and Fowler MB. Impact of Nesiritide on Renal Function in Patients With Acute Decompensated Heart Failure and Pre-Existing Renal Dysfunction: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial. *J Am Coll Cardiol* 2007; 50: 1841-1843.
10. Costanzo MR, Johannes RS, Pine M, Gupta V, Saltzberg M, Hay J, et al. The Safety of Intravenous Diuretics Alone Versus Diuretics Plus Parenteral Vasoactive Therapies in Hospitalized Patients With Acutely Decompensated Heart Failure: A Propensity Score and Instrumental V. *Am Heart J*. 2007;154:267-277.
11. Sackner-Bernstein JD, Skopicki HA, Aaronson KD. Risk of WRF with nesiritide in patients with acutely decompensated heart failure. *Circulation*. 2005;111:1487-1491.
12. Hauptman PJ, Schnitzler MA, Swindle J, Burroughs TE. Use of nesiritide before and after publications suggesting drug-related risks in patients with acute decompensated heart failure. *JAMA* 2006;296:1877-1884.
13. deGoma EM, Vagelos RH, Fowler MB, Ashley EA. Emerging Therapies for the Management of Decompensated Heart Failure. From Bench to Bedside. *J Am Coll Cardiol*. 2006;48:2397-2409.
14. Gheorghade M, Filippatos G. Reassessing treatment of acute heart failure syndromes: the ADHERE registry *Eur Heart J* 2005;7(Suppl B):B13-B19.