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REVIEW

Acute heart failure syndromes: Epidemiology, risk stratification and prognostic factors

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Abstract
Acute heart failure syndromes (AHFS) resulting in hospitalization are associated with an extremely high post-discharge mortality and readmission rate. There are several important prognostic factors, which includes blood pressure, body weight, renal function, QRS duration, and presence of coronary artery disease. The epidemiology of AHFS, prognostic factors and therapeutic targets were discussed at the 2008 European Society of Cardiology Working Group on Acute Cardiac Care Meeting held in Versailles, France from 25–28 October 2008. This is a brief summary of the lectures presented on these topics at this meeting.

Key Words: *Acute heart failure, epidemiology, prognosis*

There are several emerging prognostic factors and therapeutic targets, which are essential for the treatment of acute heart failure syndromes (AHFS). The epidemiology of AHFS, prognostic factors and therapeutic targets were discussed at the 2008 European Society of Cardiology Working Group on Acute Cardiac Care Meeting held in Versailles, France from 25–28 October 2008. This is a brief summary of the lectures presented on these topics at this meeting.

Epidemiology

There are approximately 3 million admissions per year with a primary or secondary diagnosis of heart failure (HF) in the United States and similarly in Europe. The post-discharge event rate can be as high as 35% at 60 days and 50% in patients with a systolic blood pressure (SBP) <120 mmHg at the time of admission (1). Improving post-discharge mortality and prevention of readmissions are the most important goals in AHFS. Many different classifications have been proposed for patients with AHFS, but most clinicians agree that AHFS can be classified into three main groups with: (1) worsening chronic HF, (2) acute HF and (3) advanced HF (2,3).

Worsening chronic HF which accounts for 80% of all admissions, acute *de novo* HF accounting for approximately 15% and advanced, end-stage and refractory HF being about 5% (1). Worsening HF requiring hospitalization may be a distinct entity from chronic HF since it requires urgent therapy and (2) in the process there may be myocardial and/or renal injury, which contributes to the progression of HF.

Hospitalizations for HF appear to be the most important predictors for poor prognosis in a population of chronic HF (4). This may be related to the severity of HF, but also to the fact that myocardial and kidney injuries occur immediately and/or during hospitalization (4,5).

Patients presenting with AHFS have a complex cardiac condition representing more than isolated LV dysfunction. Their mean age is 75 years, $>50\%$ are women, more than 60% have clinically significant coronary artery disease (CAD), 70% have history of hypertension, 40% with diabetes, 30% with a history of atrial fibrillation and 30% have severe renal dysfunction (6–8) (Figure 1). These patients present with dyspnea, fatigue, rales and

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Clinical Characteristics of AHFS Patients*

Median Age (years)	75	History of Atrial Fibrillation	30%
Women	>50%	Renal Abnormalities	30%
History of Coronary Artery Disease	60%	SBP >140 mm Hg	50%
History of Hypertension	70%	SBP 90-140 mm Hg	45%
History of Diabetes	40%	SBP <90 mm Hg	5%

*Data on approximately 200,000 patients

Figure 1. Clinical characteristics of AHFS patients.

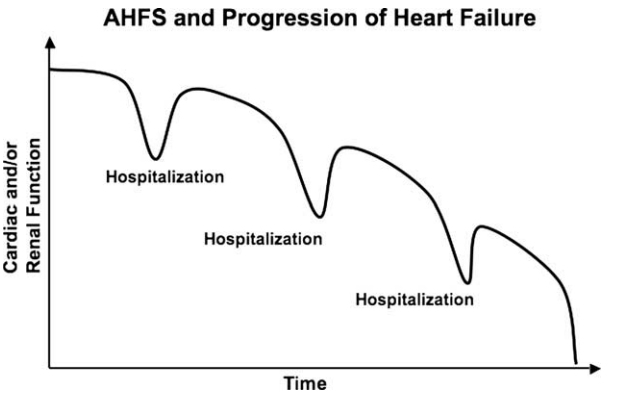

Figure 2. AHFS and progression of heart failure.

peripheral edema. The majority are hypertensive or normotensive. Less than 5–10% are hypotensive (7,9,10). Data from several registries has shown that most patients admitted with worsening HF are not on optimal medical therapy (i.e. only 37–52% are taking a beta-blocker, 51–67% angiotensin converting enzyme inhibitors or angiotension II receptor blockers, and less than half are taking aldosterone blocking agents or digoxin) (6–8).

Data from the OPTIMIZE-HF registry revealed that 60% of patients hospitalized with HF had one or more precipitating factors identified, with pneumonia or pulmonary processes (15%), ischemia (15%) and arrhythmia (14%) being the most common (11).

Pathophysiology

Patients with AHFS have significant cardiac and non-cardiac underlying conditions that contribute to the pathogenesis of AHFS. These factors include CAD (ischemia, hibernating myocardium, and endothelial dysfunction), hypertension, atrial fibrillation, and diabetes mellitus. An episode of acute HF can be defined as a rapid onset, or change in the signs and symptoms of HF requiring urgent treatment and may be due to several pathophysiologic mechanisms (e.g. acute ischemic event, atrial fibrillation with rapid ventricular response, etc.) (12). In addition, non-cardiac conditions may contribute to this picture (e.g. pulmonary embolus, dietary indiscretion, non-compliance with medications, etc.). With each hospitalization there may be myocardial and renal damage, which may worsen a patient's baseline after each hospitalization preventing them from returning to their previous level of function (Figure 2).

It has been recognized that patients with AHFS often have CAD, thus making maintenance of adequate coronary perfusion an important goal (13). The available therapies, which includes inotropes with vasodilatory properties and pure vasodilators may adversely affect those patients by decreasing coronary perfusion. In fact, hypotension related to those agents in patients with CAD has been associated with an increase in post-discharge mortality in spite of the fact that some of these agents were used only for a short period of time (14,15).

Several factors may contribute to myocardial injury in AHFS, particularly in CAD patients, creating the 'perfect storm' including (1) reduced coronary perfusion due to high left and right ventricular diastolic pressures and inotropic stimulation; (2) further activation of neurohormones; and (3) ischemic or hibernating myocardium (12) (Figure 3). Further reducing blood pressure and increasing contractility with inotropes with vasodilatory properties may precipitate cardiac injury. In fact, during both dobutamine and nesiritide therapies, a significant number of patients with AHFS and CAD had a cardiac troponin release (16). Myocardial injury therefore may contribute to the pathophysiology of AHFS and accordingly the goals of care in AHFS should be not only to improve hemodynamics and symptoms, but to salvage myocardium.

Prognosis

Blood pressure

Gheorghiade et al. evaluated the relationship between SBP at admission, clinical profile, and

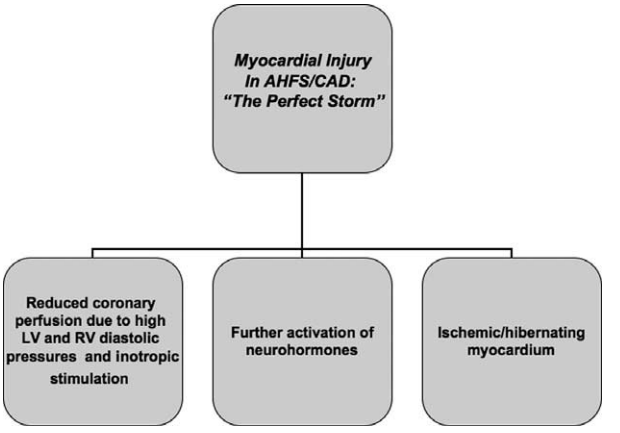

Figure 3. Myocardial injury in AHFS patients with CAD.

outcomes in patients hospitalized with AHFS (10). They found that patients with lower SBP at admission had higher in-hospital and post-discharge mortality rates, while those with higher SBP at admission was associated with lower in-hospital mortality rates: 7.2% (<120 mm Hg), 3.6% (120–139 mm Hg), 2.5% (140–161 mm Hg), and 1.7% (>161 mm Hg) ($P<0.001$) (10). Other groups confirmed their data. However, the rehospitalization rate was the same independent of the SBP and was approximately 30%. Therefore, SBP was determined to be an independent predictor of morbidity and mortality in patients with HF with either reduced or relatively preserved ejection fraction.

Body weight

It is common for congestion to precede hospitalization by several days if not weeks (17,18). However, despite the negative impact of increasing body weight on post-discharge outcomes, more than 50% of patients have little or no weight loss during hospitalization (9). In the EVEREST (Effect of Oral Tolvaptan in Patients Hospitalized for Worsening Heart Failure) trial, an increase in body weight post-discharge has been associated with an increase in hospitalization rate but not mortality. It is interesting however that a reduction in body weight in the tolvaptan group when compared to placebo did not reduce hospitalization rate (19–22). Accordingly, reduction in body weight should not be used as a surrogate endpoint for rehospitalization in response to an investigational agent.

Serum sodium

Hyponatremia is the most common electrolyte abnormality seen in patients admitted with AHFS. In an analysis from the OPTIMIZE-HF registry, the investigators assessed the predictive value of hyponatremia in unselected patients hospitalized for HF (23). The data revealed that the risk of in-hospital death increased by 19.5%, the risk of follow-up mortality by 10%, and the risk of death or rehospitalization by 8% for each 3 mmol/l decrease in admission serum sodium below 140 mmol/l. Data from the evaluation study of congestive heart failure and pulmonary artery catheterization effectiveness (ESCAPE) study revealed that hyponatremia was an independent predictor of mortality, and or rehospitalization in patients admitted for HF despite clinical and hemodynamic improvements that were similar to those in patients without hyponatremia (24).

Despite the common finding of hyponatremia in patients hospitalized for HF, available medical therapies often fail to correct the sodium level. Vasopressin antagonists has been shown to effectively and safely correct hyponatremia, however their effects on clinical outcomes remains to be discovered. It has been observed that independent of fluid restriction, vasopressin antagonists, such as tolvaptan, improved serum sodium and hyponatremia on day 4 and at the end of 30 days of therapy for many conditions, such as chronic HF, cirrhosis, or the syndrome of inappropriate antidiuretic hormone secretion (SIADH) in association with hyponatremia. In retrospect, in hyponatremic patients, representing 8% of the entire patient population, improvement in serum sodium with tolvaptan did not improve outcomes. Although tolvaptan appears to effectively improve serum sodium in hyponatremic patients, this improvement does not translate into improved outcomes (25,26).

Renal function

Klein et al examined the relationships among measures of renal function, including blood urea nitrogen (BUN) and glomerular filtration rate at admission and throughout the hospitalization in patients admitted with AHFS (27). They have shown that higher admission BUN and increasing BUN throughout hospitalization, independent of admission values, were associated with a reduced survival rate. Moreover, baseline BUN is a predictor of post-discharge mortality even in the absence of severe renal failure (28).

In the EVEREST study, approximately 30% of patients had worsening renal function during hospitalization and 25% soon after discharge. The post-discharge worsening renal function was a major independent predictor of mortality (29).

QRS duration

A prolonged QRS duration, a marker of ventricular dyssynchrony, is present in approximately 40% of patients hospitalized with AHFS and reduced LV ejection fraction. The clinical implications and predictive value of the QRS duration were analyzed in a post hoc analysis from the EVEREST trial (30). During a median follow-up of 9.9 months, all-cause mortality was 18.7% for patients with a normal baseline QRS duration and 28.1% for patients with a prolonged baseline QRS duration (hazard ratio [HR], 1.61; 95% confidence interval [CI], 1.38–1.87). The composite of cardiovascular death or hospitalization for heart failure was 32.4% for patients with a baseline QRS duration less than 120 ms and 41.6% for patients with a baseline QRS duration of 120 ms or greater (HR, 1.40; 95% CI: 1.24–1.58) (30). The investigators concluded that a prolonged QRS duration in hospitalized HF patients with reduced systolic function is an independent predictor of high post-discharge morbidity and mortality. The prognostic value of QRS

duration in patients admitted with AHFS, who have preserved systolic function, has not yet been studied.

Coronary artery disease

CAD is common among patients with AHFS and has been shown to be an independent predictor of early post-discharge mortality (1,31–34). Early, in-hospital and post-discharge management of AHFS may be dependent on the extent and severity of CAD and the presence of ischemia and/or stunned/hibernating myocardium, however few studies exist which assess the management of CAD in patients with AHFS (35). Rossi et al. studied the influence of coronary revascularization status on survival in patients with AHFS (36). CAD was associated with higher in-hospital (3.7% versus 2.9%, OR: 1.14, 95% CI: 1.00–1.31) and post-discharge mortality (9.2% versus 6.9%, HR: 1.37, 95% CI: 1.03–1.81) compared to those patients without CAD. Patients with CAD who were not revascularized in the post-discharge phase had increased mortality compared to patients without CAD (10.6% versus 6.9%, HR: 1.56, 95% CI: 1.15–2.11). These associations were similar in patients with both reduced (EF $<40\%$) and preserved (EF $\geq 40\%$) systolic function. Patients with CAD who were revascularized had similar mortality to patients without CAD. Therefore, the investigators concluded that revascularization might confer a survival benefit in this group of patients with AHFS.

Conclusions

Several variables have been identified as predictors of clinical outcomes in AHFS. In addition to those noted, natriuretic peptides, including b-type natriuretic peptide (BNP) and N-terminal pro-BNP may be useful for diagnosis and management of AHFS in the emergency department as well as the assessment of pre-discharge prognosis and therapy effectiveness (37–39). Recently, several statistical models have been devised to help risk stratify patients with AHFS more effectively during hospitalization and post-discharge (40,41). Utilizing data from the OPTIMIZE-HF registry, a scoring system has been devised to help risk stratify patients during hospitalization based on age, heart rate, SBP, sodium, creatinine, HF as primary cause of hospitalization, and presence or absence of systolic dysfunction (40). In addition a clinical model has been developed to predict short-term clinical outcomes in the post-discharge period which incorporates age, creatinine, reactive airway disease, liver disease, SBP, serum sodium, admission weight, and depression (41).

The goals of AHFS treatment remain (1) to improve hemodynamics (pulmonary capillary wedge pressure [PCWP]) without causing myocyte damage (ischemia, necrosis, apoptosis), arrhythmias, hypotension or renal dysfunction realizing that the high PCWP may be the result of specific therapeutic targets (e.g. ST elevation myocardial infarction, atrial fibrillation, hypertension); (2) improve symptoms; (3) achieve euvolemia; and (4) implement life-saving therapies (e.g. ACE inhibitor, beta blockers, implantable cardioverter-defibrillators, etc.). Further research is needed to achieve the most important goals, which are to improve post-discharge mortality and reduce readmissions.

Declaration of interest: Mihai Gheorghiade Disclosures: Consultant: Otsuka, Solvay Pharma, Novartis, Bayer, Sigma Tau, Debiopharm, Medtronic, Merck, Astellas, Cytokinetics, CorThera Inc, Pericor Therapeutics, GlaxoSmithKline, ohnson & Johnson, Abbott, Errekappa Therapeutics, Protein Design Laboratories, Astra Zeneca, Sanofi Aventis. Matthew E. Harrison and Gerasimos S. Flippatos have no conflicts of interest.

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