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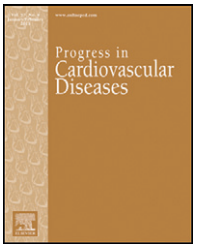

Contemporary Treatment of Acute Heart Failure

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ARTICLE INFO

Keywords:
Acute heart failure
Treatment
Investigational agent

ABSTRACT

Heart failure (HF) is a rapidly growing global pandemic. A consequence of the increased prevalence of HF has been an increase in hospitalizations due to acute HF (AHF) in the United States and in many other countries around the world. Despite advances in treatment, morbidity and mortality rates in the post-discharge period after an AHF admission remain unacceptably high. The occurrence of an AHF episode poses a major clinical challenge since current therapeutic options are limited to providing mostly short-term symptomatic relief. Diuretics to relieve congestion, inotropic agents to maintain tissue perfusion and vasodilators to reduce the load on the heart are the primary drug approaches for treating AHF. Determining the most effective way of using these agents has been the focus of several recently completed studies, but success in altering outcomes has proved to be elusive. Results from studies using new experimental agents such as ularitide and serelaxin, however, have been promising and ongoing. Phase 3 clinical trials will determine their role in the therapeutic regimen. This manuscript reviews aspects of medical therapy of AHF for which new insights are available and describes pathophysiologic abnormalities that appear to be amenable to treatment with both currently available therapies and novel agents that are being developed.

Heart failure (HF) is a major and growing global public health problem.[1] The worldwide aging of the population and better immediate outcomes in patients experiencing acute coronary syndromes are important contributors to the increase in HF prevalence.[2,3] In developing countries, reduced mortality from other chronic conditions (e.g. infectious diseases) along with a substantial increase in risk factors (e.g. diabetes and obesity) for cardiovascular (CV) disease has also contributed to the increase in HF prevalence.[4,5] A consequence of the growth in HF prevalence has been a substantial increase in HF-related hospitalizations.[6] For instance, in the United States (U.S.) where there are estimated to be approximately 6 million patients with HF, there are more than 1 million hospitalizations attributable to HF as the primary cause and several million additional hospitalizations include HF as a secondary diagnosis,[7,8] thus making HF now the most common cause of hospitalization among patients 65 years of age or older in the U.S.[9,10]

The development of acute HF (AHF) is an important event in the patient's natural history as it augers in a phase of the disease that is characterized by substantial increases in the likelihood of repeat hospitalization and/or death[7,8] (Fig 1). It is estimated that nearly 2/3 of the costs for HF are consumed by hospitalizations and their aftercare[9–11] and the overall burden

Statement of Conflict of Interest: see page 376.

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http://dx.doi.org/10.1016/j.pcad.2015.12.005
0033-0620/

Abbreviations and Acronyms
AHF = acute heart failure
BNP = brain natriuretic peptide
BP = blood pressure
cAMP = cyclic adenosine monophosphate
cGMP = cyclic guanosine monophosphate
CV = cardiovascular
EF = ejection fraction
HF = heart failure
HTN = hypertension
IV = intravenous or intravenously
LOS = length of stay
NT-BNP = N-terminal brain natriuretic peptide

on the healthcare system of caring for patients during and after an AHF episode is substantial.

Over the last 50 years there has been progress in AHF management. In-hospital mortality has been reduced and length of stay (LOS) is now less than 5 days in most patients hospitalized for AHF in the U.S.[10,11] However, current therapeutic options have little impact on post-discharge outcomes. Consequently, the likelihood of post-discharge re-hospitalization is substantial with 30 day and 1-year re-admission rates in the range of 25% and 67%, respectively.[10,11] Moreover, the likelihood of death in the year after an AHF hospitalization is in excess of 30%, and this unacceptably high level has not significantly changed over the past several years.[11,12] (Fig 2). In this context, it is worthwhile reflecting on current management practices for patients who experience an episode of AHF in order to see if they can be employed more effectively in order to favorably affect outcomes. It is clear that successful management of AHF patients involves not only use of medical therapies but also strategies for transitioning the patient from the hospital to the outpatient setting.[13] While the importance of detailed planning and coordinating the transition of the patient from the hospital to the out-patient setting has quite appropriately received increased emphasis over the past years, the focus of this review will be on current approaches to the medical management of patients hospitalized with AHF, including an overview of experimental therapies that have shown promise for the treatment of AHF.

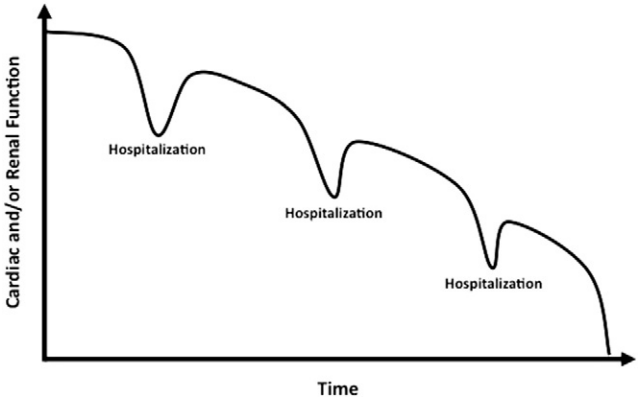

Fig 1 – Progression of heart failure. With each hospitalization for acute heart failure, there is substantial myocardial and/or renal damage leading to an overall decline in function.

The AHF population

AHF can be defined as either the rapid onset of signs and symptoms of HF or their gradual worsening to the point where intensification of therapy involving the use of intravenous agents is required. In patients with pre-existing HF, there is often a clear precipitant or trigger, including arrhythmia, acute coronary syndrome, infection, worsening hypertension (HTN), medication non-adherence, etc. to which the patient's deterioration can be attributed.[14] Hospitalization for AHF is skewed toward a more elderly population with a mean age of 79 years old and there is a slightly higher incidence of men than women.[11,15] Approximately half of the patients hospitalized with AHF have preserved ejection fraction (EF).[16] Patients with AHF often times have many co-morbidities including coronary artery disease, atrial fibrillation, HTN and renal disease that complicate management.[16–18] Most AHF patients present with signs and symptoms of volume overload, including dyspnea and other congestive symptoms, elevated jugular venous pressure, and elevated levels of biomarkers that indicate increased load on the heart [e.g. brain natriuretic peptide (BNP) or N-terminal (NT)pro-BNP] or evidence of end organ injury (e.g. troponins and creatinine elevation) or both.[16–18]

Current treatments

Current treatments of patients with AHF have focused on stabilizing hemodynamics and relieving symptoms. While right heart catheterization is not commonly performed during an AHF hospitalization, it is possible to characterize the hemodynamic status of patients according to whether they have elevated filling pressures (i.e. are they wet or dry?) and whether cardiac output is impaired or normal (i.e. are they cold and hypoperfused or warm and normally perfused?) (Fig 3). Clinical evaluation alone, however, may not be definitive and use of a variety of tests including biomarkers is used to assess the presence and severity of HF in patients presenting with a complex of signs and symptoms that cannot be definitively attributed to AHF. Based on the overall clinical assessment that synthesizes information from the history, physical examination, chest X-ray, laboratory results and other tests, a diagnosis of AHF or an alternative cause of the patient's signs and symptoms is made. In the case of AHF, therapeutic interventions designed to reduce congestion and influence preload, afterload and/or myocardial contractility are selected. Treatment is then tailored to enhance the likelihood of correcting the hemodynamic alterations and relieving the symptoms that resulted in the patient's hospitalization (Fig 4).

Diuretics and other approaches for relieving congestion

Most patients who present with AHF are congested. In some, volume overload occurs over a relatively short period of time