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Pump failure, shock, dyspnea, anxiety, pulmonary edema, arrhythmias, venous thromboembolic disease, drug-related adverse events, and sometimes death—these clinical hallmarks of acute, decompensated heart failure are well known to the emergency physician, cardiologist, hospitalist, and intensivist. With nearly 5 million patients currently diagnosed with heart failure (HF) in the United States—and almost 500,000 new cases identified each year—this country is experiencing, and will continue to witness, a cardiovascular epidemic of staggering proportions.[1] The facts surrounding this debilitating and, more often than not, life-threatening condition are enough to concern even the most confident clinician. Consider the following: The mortality rate of HF not only exceeds most cancers,[1] but this condition is responsible for the debilitation and, eventually, death of more elderly individuals than any other single ailment.

Almost 300,000 patients die from HF or its complications each year, and this disease accounts for more hospitalizations (900,000 annually) and re-hospitalizations than any other illness in patients older than age 65.[1] The financial burden that HF places on the Medicare system is as great as the two most common cancers—breast and lung—combined. In fact, at the 1999 Heart Failure Society of America Third Annual Scientific Assembly, it was estimated that inpatient costs for HF in that year would be $23.1 billion; it was estimated an additional $14.7 billion would be required for outpatient management of this growing patient population.

Although the incidence of HF is increasing at a dramatic pace, and its societal impact is as great as any other chronic illness, surprisingly few articles have been published in the emergency medicine literature outlining a systematic approach to managing patients with this life-threatening condition. This is unfortunate, because the diagnostic and therapeutic landscape for HF is undergoing a dramatic shift. Established therapies that include diuretics, inotropic agents, oxygen, and nitroglycerin are being supplemented by newer approaches that produce more rapid reductions in pulmonary wedge pressures and reduce such complications as

The Clinical Challenge of Heart Failure: Comprehensive, Evidence-Based Management of the Hospitalized Patient With Acute Myocardial Decompensation—Diagnosis, Risk Stratification, and Outcome-Effective Treatment

Part I: Presentation, Differential Diagnosis, Laboratory Examination, and Prophylaxis Against Venous Thromboembolic Disease (VTED)

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deep venous thrombosis (DVT) and pulmonary embolism (PE) in patients at high risk. Considering recent advances in the comprehensive, multi-factorial management of patients with HF—among them, recent approval of nesiritide for treatment of acute, decompensated HF, as well as approval for enoxaparin to prevent DVT in hospitalized patients, including those with New York Heart Association (NYHA) Grade III/IV congestive heart failure (CHF)—there is an urgent need to review current, evidence-based strategies for optimizing outcomes in patients with HF.

Of the two newest strategies introduced for managing patients with HF, nesiritide (B-type natriuretic peptide [BNP]) is the first medication approved by the U.S. Food and Drug Administration (FDA) in more than a decade for treatment of the acutely decompensated patient. The recombinant DNA-manufactured form of endogenously synthesized BNP, nesiritide represents an amplification of the natural compensatory mechanism for neurohormonal and hemodynamic derangements that occur in HF. The results of such studies as the PRECEDENT trial have been strongly supportive of adopting nesiritide as a standard of care for an appropriately selected patient population. In this trial, which evaluated and compared varying doses of nesiritide or dobutamine, patients treated with dobutamine had higher ectopy rates, were more likely to suffer cardiac arrest, and had a higher rate of ventricular tachycardia as compared to nesiritide. Another study, evaluating six-month survival following short-term nesiritide therapy, showed a marked decrease in death rates compared to dobutamine. In short, there is evidence suggesting nesiritide is superior to the most commonly used inotropes for managing patients with HF.

Although augmentation and stabilization of left ventricular (LV) pump function, reduction of arrhythmia risk, and hemodynamic stabilization with pharmacological and/or surgical intervention remain the primary clinical and functional objectives of managing patients with HF, recent attention has been focused on preventing other complications, including venous thromboembolic disease (VTED), especially upon admission to the hospital setting. Not surprisingly, identifying a cost-effective strategy for preventing DVT and/or PE in HF patients has been an area of intense interest, inasmuch as recent consensus guidelines have introduced thromboprophylaxis recommendations with either low molecular weight heparin (LMWH) or unfractionated heparin (UFH) for general medical patients admitted to the hospital with risk factors for VTED; in all such guidelines, HF is cited as one of the principal indications.[2]

Based on such recommendations and other recent studies, there is compelling evidence that in immobilized patients—or those with significant restrictions in ambulation that place them at risk for DVT—who present to the hospital with CHF (NYHA Class III-IV), prophylaxis should be considered mandatory if there are no significant contraindications.[3] Moreover, it should be emphasized that the American College of Chest Physicians (ACCP) guidelines and International Consensus Statement also cite CHF as a risk factor for VTED and emphasize the importance of this risk factor when assessing prophylaxis requirements for hospitalized medical patients.[2,4]

Clinical trials, albeit small, specifically have evaluated patients with HF. The PRINCE (Prevention in Cardiopulmonary Disease with Enoxaparin) study group conducted a randomized, multicenter trial in 665 hospitalized patients with severe cardiopulmonary diseases (332 with respiratory disorders, 333 with NYHA Grade III/IV heart failure).[5] Patients were treated with enoxaparin (a type of LMWH) 40 mg subcutaneously (SC) daily or 5000 IU UFH SC TID for 8-12 days in an open-label study. Efficacy rates were evaluated in 454 patients using an intention-to-treat analysis. Although the rate of VTE was similar in both groups (8.4% in the enoxaparin group vs 10.4% in the UFH group), a subgroup analysis indicated that the incidence of VTE was greater in patients with

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Table 1. Diastolic Heart Failure Etiologies[38]

RESTRICTIVE CARDIOMYOPATHY
• Cardiac amyloidosis
CONSTRICTIVE PERICARDITIS
ISCHEMIC HEART DISEASE
• Post-infarction scarring/remodeling
HYPERTROPIC HEART DISEASE
• Hypertrophic cardiomyopathy
• Chronic hypertenison
• Aortic stenosis
MITRAL OR TRICUSPID STENOSIS

HF than those with respiratory diseases.[5] These and other studies stress the need for a comprehensive approach to the management of HF, i.e., one that includes pharmacological interventions aimed at improvement of LV function and overall functional status, as well as those aimed at preventing complications commonly encountered in hospitalized patients with HF.

Overall, during the past few years, we have witnessed dramatic progress in both our understanding and treatment of HF. With these advances in clear focus, this landmark review will describe both established and recently introduced strategies for diagnostic evaluation of and therapy for patients with HF. Basing recommendations on evidence-based trials, it will outline promising technological advances that are likely to optimize outcomes in this challenging patient population.

— The Editor

Clinical Presentation

From a clinical perspective, HF is characterized by dyspnea, weakness, fatigue, and compromised functional status and results when the myocardium cannot maintain the cardiac output that is required for normal metabolism and venous return. Presentation in the emergency department (ED) is characterized by a continuum that may begin with asymptomatic LV dysfunction; it then may progress to mild symptoms of dyspnea that occur only with significant exertion, or manifest as dyspnea at rest, and eventually terminate with severe LV failure, hypoperfusion, and cardiogenic shock. The acuity of this progression, the spectrum of symptoms, and the level of patient distress are determined by the rapidity at which LV dysfunction occurs. At the critical extreme, in the setting of an acute myocardial infarction (MI), which frequently is characterized by precipitous LV dysfunction, critical loss of myocardial performance results in severe dyspnea, hypotension, and altered mental status. This patient will present in extremis, and has a significant near-term mortality rate.

At the opposite end of the spectrum is the patient with chronic systolic dysfunction. This individual may be a regular or repeat visitor to the ED, and present with symptomatic exacerbation as a result of dietary and/or medication non-compliance, which may lead to edema, orthopnea, and moderate dyspnea on exertion. These patients usually are treated in the ED and hospitalized. However, they occasionally can be discharged home if there is good therapeutic response.

A third category of patients frequently presents to the ED, despite optimal medical care and meticulous medication compliance. These individuals complain of weakness, fatigue, malaise, and a general failure to thrive. Commonly euvolemic, or even dehydrated, their systemic symptoms result from terminal pump dysfunction. At this stage, medical treatment frequently is ineffective. While it is unlikely that this subgroup of patients will succumb in the ED, only invasive therapy (heart transplant, LV assist device, implantable cardiac device, biventricular pacing, and other cardiac devices) can alter what is, inevitably, an unfavorable prognosis.

Heart Failure: Definitions and Categories

The terminology of HF can be confusing. To facilitate accurate communication among health care providers and to orchestrate proper treatment plans, clinicians must be precise with the the broad range of qualifying terms. The descriptor "congestive" HF can be problematic. Loop diuretics may allow patients with HF to avoid congestive symptoms, despite severe LV dysfunction. Consequently, the term "congestive heart failure" describes a clinical state from which a patient with HF may or may not be suffering. Moreover, the terms high and low output, and forward and backward flow HF are best avoided.

Better descriptors are acute or chronic, and systolic or diastolic HF. Finally, some physicians differentiate left- and right-sided HF. Left-sided failure is described as having pulmonary symptoms in the absence of peripheral edema, jugular venous distention (JVD), or hepatojugular reflux (HJR). In contrast, right-sided HF is characterized by peripheral edema, JVD, and HJR, without pulmonary symptoms. Because cardiac architecture, from a mechanical perspective, is a closed system, abnormally elevated cardiac chamber pressures and volumes quickly are reflected into the contralateral system. This distinction should be reserved for patients with flow-limiting lesions (e.g., valvular dysfunction).

Systolic vs. Diastolic HF. In HF, the fundamental abnormality is impaired LV contractility, manifested by a downward shift in the Frank-Starling curve. In a healthy heart, increased preload (i.e., venous return), is associated with improved myocardial contractility (increased inotropicity) and, therefore, an increased stroke volume. This response is lost in HF, and represents the downward shift of the Frank-Starling mechanism. Consequently, any cardiovascular stress (e.g., walking) that increases venous return and cardiac pressures is not met by improved contractility, and ultimately leads to pulmonary congestion and edema.

The Law of LaPlace describes ventricular wall tension as a function of the product of pressure (afterload) and ventricular radius. With increased wall tension as the stimulus, myocardial remodeling occurs. Initially, healthy myocytes hypertrophy. An adverse response results when myocytes die (apoptosis) and become scar tissue. The underlying stimulus for apoptosis is unclear. The end result of remodeling is the determinant for the type of HF.

A normal ejection fraction (EF) is 60%. This means that the heart empties 60% of its blood volume with each cardiac cycle. Systolic dysfunction is defined as an EF no greater than 40%.[6] In

Table 2. Major Etiologies of Heart Failure

CORONARY ARTERY DISEASE
COMPLICATIONS OF MYOCARDIAL INFARCTION
• Acute mitral regurgitation (papillary muscle rupture)
SUSTAINED CARDIAC ARRHYTHMIA
POORLY CONTROLLED HYPERTENSION
VALVULAR RUPTURE OR DISEASE
MYOCARDITIS
POSTPARTUM CARDIOMYOPATHY
ACUTE PULMONARY EMBOLUS
PERICARDIAL DISEASE/TAMPONADE
• Effusion
• Constrictive pericarditis
HYPERKINETIC STATES
• Anemia
• Thyrotoxicosis
• A-V fistula (e.g., dialysis)
INFILTRATIVE DISORDERS

Table 3. Etiologies of Cardiogenic Shock

EXTENSIVE MYOCARDIAL INFARCTION (MI)
MI WITH MECHANICAL COMPLICATIONS
• Ventricular septal defect
• Acute mitral regurgitation
• Myocardial free wall rupture
SEPTIC SHOCK WITH MYOCARDIAL DEPRESSION
PERICARDIAL TAMPONADE
LV OUTFLOW OBSTRUCTION
• Hypertrophic obstructive cardiomyopathy (HOCM)
• Aortic stenosis
MYOCARDITIS
END-STAGE CARDIOMYOPATHY
CARDIAC CONTUSION

systolic HF, the ventricle has difficulty ejecting blood. The underlying pathologic cascade in systolic HF is impaired cardiac contractility, neurohormonal activation, increased intracardiac volume and pressure, and enhanced sensitivity to increased afterload.

In diastolic failure, systolic function is preserved such that the EF may be normal or even supra-normal, but with an abnormal diastolic pressure/volume relationship. The primary pathophysiological abnormality is impaired ventricular relaxation. This results in a left ventricle that has difficulty receiving blood. The decrease in LV compliance from impaired myocardial relaxation necessitates higher atrial pressures to ensure adequate diastolic filling of the left ventricle. The frequency of diastolic dysfunction increases with age.[7] Longstanding hypertension accompanied by the development of LV hypertrophy often are responsible for this syndrome. Coronary artery disease also contributes, as diastolic dysfunction is an early event in the ischemic cascade. Common etiologies for diastolic HF are summarized in Table 1.

As many as 30-50% of HF patients have circulatory congestion on the basis of diastolic dysfunction[8]; treatment for volume overload is the same as it is for systolic dysfunction. However, patients with diastolic dysfunction are preload dependent and the use of excessive diuresis or venodilation may exacerbate the underlying deficit in ventricular filling, which can cause hypotension. Ultimately, after hemodynamics have been stabilized and congestion resolved, treatment of diastolic dysfunction requires consideration of therapy directed at the underlying etiology. Determining the type of HF can be difficult using history and physical findings; consequently, an echocardiogram is necessary.

Clinical Pathophysiology

Our understanding of HF has evolved greatly during the past two decades.[9] The genesis of HF no longer is explained as simple mechanical pump dysfunction. New studies have enabled investigators to discern the pathophysiological forces contributing to the syndrome. Typically, HF is set into motion by some myocardial injury or stressor. Myocardial injury can act directly on the heart tissue (e.g., ischemia/infarction, autoimmune insult, infectious disease, and other causes); it also can result from hemodynamic stress (chronic hypertension or valvular disease) or from arrythmogenic stress (tachycardia-induced cardiomyopathy). Extra-cardiac factors such as severe anemia, thyroid dysfunction, and sepsis can generate supra-normal cardiac work requirements and, as a result, HF. Although most cases of HF are believed to be due to hypertension and/or coronary artery disease, a large number of patients do not have a clearly identifiable precipitating cause for their syndrome. *(See Table 2.)*

Myocardial Injury. The sequence of events that leads to the progression of HF from a triggering insult is reasonably well identified. Myocardial injury activates several endogenous biochemical pathways in an initial attempt to maintain circulatory integrity and adequate arterial pressure. After an initial reduction in cardiac output, compensatory hormonal activation acts to preserve circulatory function. The mechanisms of circulatory preservation include sympathetic nervous system (SNS) activation, and increasing baseline levels of norepinephrine (NE), endothelin (ET, one of the most potent vasoconstrictors), and vasopressin. The renin-angiotensin-aldosterone system (RAAS) also is activated, resulting in elevated levels of angiotensin II and aldosterone. While initially protective to ensure tissue perfusion, these compensatory processes ultimately serve as the driving forces behind the pathology of chronic HF. Other substances implicated in the pathophysiology of HF include inflammatory cytokines such as tumor necrosis factor (TNF) and interleukin-6.[10,11]

Vasodilator peptides also are released by the failing heart. BNP and atrial natriuretic peptide (ANP) are secreted from the ventricles and atria in response to stretch stimulus. These natriuretic peptides promote sodium excretion, decrease vascular resistance, and act to decrease levels of aldosterone. In this regard, the heart functions as an endocrine organ. The natriurectic peptides serve as the endogenous counter-regulatory hormon-

Table 4. Forrester Classification[39]

CLASS	DESCRIPTION	CARDIAC INDEX	PCWP	MORTALITY (%)
I	No congestion/ peripheral hypo-perfusion	2.7	12	2
II	Isolated congestion	2.3	23	10
III	Isolated peripheral hypoperfusion	1.9	12	22
IV	Both congestion and peripheral hypoperfusion	1.7	27	55

Key:
PCWP = Pulmonary capillary wedge pressure

Table 5. Cardiogenic Shock Criteria

- Systolic blood pressure < 90 mmHg (higher if chronically hypertensive)
- Urine output < 0.5 cc/kg/hr
- Evidence of end organ dysfunction:
  - Renal failure
  - Cerebral (confusion)
  - Peripheral hypoperfusion (cool extremities)
- If hemodynamic monitoring is available:
  - PCWP > 18 mmHg and CI < 1.8 L/min/m^2

Key:
PCWP = Pulmonary capillary wedge pressure; CI = Cardiac index

al system to the RAAS, ET, and SNS. These peptides antagonize the compensatory hormones listed above and form the theoretical basis for newer HF diagnostic and therapeutic regimens.

The RAAS promotes salt and water retention. Angiotensin II also acts to promote peripheral vasoconstriction, resulting in increased afterload stress on the heart. Chronic adrenergic activation results in direct myocardial damage, increased vascular resistance, and increased risk of arrhythmias.[9] Chronic elevation of arginine vasopression (AVP), NE, and ET are associated with higher death rates in HF. The combined effects of hormonal activation include sodium and water retention and increased vascular tone. While cardiac output may be maintained, it is at the cost of increased systemic vascular resistance and elevated intra-cardiac pressures. At this stage, the patient may be asymptomatic, but the mechanism already is in place to initiate the secondary pathologic process of cardiac remodeling.

Cardiogenic Shock

Cardiogenic shock (CS) is defined clinically as a state of decreased cardiac output, with evidence of tissue hypoperfusion, despite adequate intravascular volume.[12] The etiology of CS usually is acute coronary ischemic disease; other causes are listed in Table 3. The most common cause of CS is acute myocardial infarction (AMI), and in this setting, CS has an overall mortality of 50-90%. In association with AMI, HF occurs if there is acute impairment of at least 25% of the left ventricle. If LV dysfunction exceeds 40%, CS ensues. However, CS may not occur immediately post-MI. In one large study, the median delay from AMI to clinical development of CS was seven hours.[13]

Symptoms of CS commonly are the result of progressive myocardial dysfunction associated with impaired myocardial perfusion.[12] Because a critical quantity of functioning myocardial tissue is lost in CS, cardiac output is decreased. To compensate for decreased stroke volume, tachycardia develops. The combination of hypotension and tachycardia drastically reduces coronary artery flow by decreasing perfusion pressure and diastolic filling time (the period during which the majority of coronary flow occurs). This may result in further ischemia and myocardial dysfunction. The signs of end organ dysfunction as a result of CS include altered mental status, severe respiratory distress, and decreased urine output. The Forrester classification relates clinical findings to hemodynamic states and mortality. *(See Table 4.)*

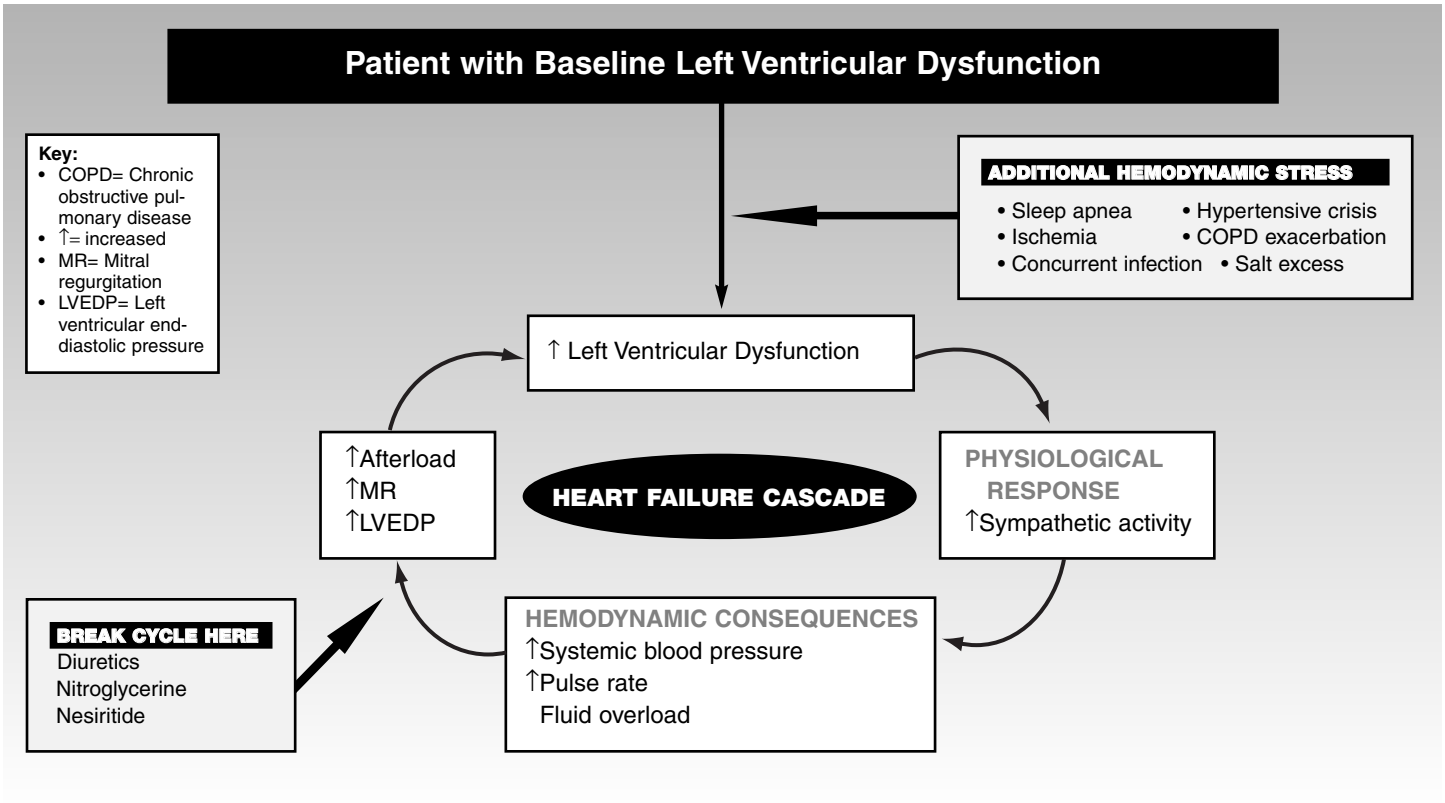
Diagnosis. Patients with CS can present with pulmonary edema as well as end organ hypoperfusion. Typically, they are congested and vasoconstricted. These patients may present with pulmonary rales and cool extremities, and frequently manifest mental obtundation. Although circulatory shock is diagnosed at the bedside, a cardiogenic source is confirmed by documentation of myocardial dysfunction and persistence of shock despite correction of hypoxemia, hypovolemia, and acidosis.[12] Diagnostic criteria for CS are listed in Table 5. The BNP level (BNPL) will be elevated markedly and the chest x-ray (CXR) may show evidence of excess fluid. However, cardiomegaly may be absent in the acute presentation.

Acute Pulmonary Edema

Acute pulmonary edema (APE) is characterized by fluid overload in the lungs. It may be cardiogenic in nature (i.e., secondary to increased LV filling pressures) or non-cardiogenic (i.e., fluid overload from renal failure). The development of APE is best understood as a downward spiral of events resulting in progressive myocardial dysfunction that highlights the failing heart's sensitivity to increased afterload. The spiral starts when an individual with baseline LV dysfunction (diastolic or systolic) experiences an additional myocardial stressor. Filling pressures are increased, the myocardium is unable to compensate, and hence pulmonary congestion and dyspnea result. Catecholamine levels and vascular resistance are increased. This results in increases in blood pressure and afterload, further LV dysfunction, and progressive increases in filling pressures with more pulmonary congestion. A recent report has stressed the importance of diastolic dysfunction in the majority of patients presenting with hypertensive PE.[14]

Diagnosis. APE presents with clinical evidence of pulmonary congestion (tachypnea, rales, and x-ray changes) in the presence of elevated systemic blood pressure. Occasionally, patients with impending PE may have intense dyspnea in the absence of rales or edema. Patients with PE can progress rapidly to respiratory failure, cardiogenic shock, and cardiovascular collapse if the diagnosis is not recognized promptly and the condition is not treated aggressively. The arterial blood pressure often is elevated and serves as the

Figure 1. Pathophysiological Cycle of Acute Decompensated Heart Failure



focus of immediate therapy with vasodilators. Even patients with pronounced systolic dysfunction are capable of having significantly elevated blood pressure in this setting. Peripheral vasoconstriction often is severe, and the extremities are cool. *(See Table 6 for the correlation between physical diagnosis and hemodynamic parameters.)* As with cardiogenic shock, a search for underlying precipitants should be performed.

Decompensated Heart Failure

While a patient suffering from a new anterior infarction presents a clear reason for developing HF, most patients do not have a single, defining insult explaining the development of this syndrome. *(See Figure 1.)* However, most references report that the majority of HF is due to coronary artery disease (chronic ischemia or infarction) or hypertension.

The clinical spectrum of decompensated HF is broad. It includes asymptomatic patients, mildly symptomatic patients with dyspnea, and progresses to cardiogenic shock and acute pulmonary edema. Frequently, the diagnosis of HF has been established, and the presentation is the culmination of increasing congestive symptoms. HF frequently is decompensated due to an additional event superimposed upon the patient's pre-existent pathology. Consequently, the physician should attempt to identify possible reasons for acute decompensation. Common precipitants are listed in Table 7. The results of a recent study of 323 patients are listed in Table 8. These patients were part of a clinical trial, and, therefore, the incidence of non-compliance may have been underestimated.

Myocardial ischemia always should be considered as a possible precipitant of decompensated HF. In a retrospective review of 151 decompensated HF patients seen in the ED, 21 (14%) were found to have elevated cardiac enzymes. In these patients, chest pain occurred in only 30%, and the ECG was diagnostic for acute cardiac ischemia in fewer than 1%.[15] Although controversial, elevated cardiac enzymes in HF patients are associated with an increased in-hospital mortality rate, poor six-month mortality rates, and a higher cardiac transplantation rate.

The NYHA class severity for individuals with HF represents an historical standard for categorizing the clinical severity of HF. This scale is based on the amount of effort required to produce symptoms of dyspnea and exercise intolerance. *(See Table 9.)* NYHA class is directly proportional to survival, with higher classes suffering higher morbidity and mortality rates; however, there is no direct relationship between NYHA and EF. For example, some patients are well-compensated with an EF of only 10%, while others with much higher EFs are profoundly symptomatic. In addition, NYHA class suffers from interobserver variability. The newly available BNP assay correlates with NYHA class, and may provide a more objective measure in the future.[16,17]

Recently, the American College of Cardiology and the American Heart Association, in an effort to include patients who are in the asymptomatic initial stages of HF, published a new classification system. This system recognizes the fact that earlier intervention has the potential for greater morbidity and mortality benefits as compared to therapy in the late stages of disease. *(See Table 10.)*

Table 6. Physical Diagnosis and Hemodynamic Status

WARM EXTREMITIES	DRY (CLEAR LUNGS)	WET (RALES)
(good perfusion)	Normal SVR	Vasodilated (low SVR)
	Lungs without rales	Lungs congested (rales)
	Normal CO	Normal CO
	Ex: Normal hemodynamics	Ex: Septic shock
COLD EXTREMITIES		
(poor perfusion)	Vasoconstricted (high SVR)	Vasoconstricted (high SVR)
	Lungs without rales	Lungs congested (rales)
	Low CO	Low CO
	Ex: Dehydration and HF	Ex: Decompensated HF

Key:
CO = Cardiac output
SVR = Systemic vascular resistance
HF = Heart failure

Table 7. Common Causes of Heart Failure Decompensation

- Acute myocardial ischemia or infarction
- Uncontrolled hypertension
- Obesity
- Superimposed infection
- Atrial fibrillation or other arrythmia
- Excessive alcohol
- Worsening valvular lesion
- Endocrine abnormalities (e.g., diabetes, hyperthyroidism, etc.)
- Negative inotropic medications (e.g., verapamil, nifedipine, etc.)
- Non-steroidal anti-inflammatory drugs
- Treatment and dietary non-compliance

Diagnosis. The majority of patients with decompensated HF will have a history of HF and present to the ED without florid PE or systemic hypoperfusion. They may complain of dyspnea (on exertion, nocturnally, or with recumbency), peripheral edema, cough, weight gain, fatigue, abdominal pain, or generalized weakness. These patients suffer from a progression of their previously compensated HF.

Low Cardiac Output

HF traditionally has been considered a congestive state with an inexorable course characterized by increasing symptoms, frequent hospitalizations, and ultimately, death. With the advent of powerful loop diuretics, vasodilator therapy, ACE inhibitors, and other agents, treatment not only forestalls development of symptoms, but prolongs the quality of life and decreases mortality. Consequently, a relatively new class of HF patient may present to the ED. This patient generally is compliant with medications, meticulous in fluid restriction, and has a long-established course of HF therapy. With progressive ventricular dysfunction, these individuals present with a low cardiac output syndrome, in the absence of clinically detectable systemic or pulmonary congestion. Peripheral perfusion may be compromised, and there is severe fatigue, shortness of breath, and limitation in physical activity on the basis of poor cardiac output. As with decompensated HF, a superimposed precipitant added to the patient's baseline myocardial dysfunction must be considered. In addition, intravascular volume depletion (i.e., secondary to overzealous diuresis) may contribute to clinical deterioration.

Diagnosis. These patients report a history of HF, and already are taking appropriate medications. They may relate a history of overwhelming fatigue, dyspnea on exertion, nausea, malaise, and orthostatic symptoms. These symptoms occur despite meticulous compliance with medications, and in the absence of significant weight gain or congestive findings. They usually are not fluid overloaded, and are generally without pulmonary congestion or extremity edema. These patients will require work-up for a progression of their HF, as well as a search for reversible precipitants of decompensation. These patients represent the "cold and dry" patient in Table 6.

Differential Diagnosis

A number of clinical conditions can mimic the acute presentation of HF. Diagnostic accuracy is required in these patients, as omissions in treatment will prevent an optimal response in HF; moreover, therapy directed against another acute condition could have grave consequences. Because breathlessness is a common presenting symptom, other conditions causing dyspnea should be considered. Acute coronary syndrome always must be excluded as the primary cause of the patient's complaints, and as the underlying etiology of HF exacerbation. Table 11 summarizes diagnoses that must be considered in the differential diagnosis of HF.

As might be expected, the diagnosis of HF can be especially problematic in the patient with co-existing obstructive pulmonary disease. As is the case with acute exacerbation of HF, patients with chronic obstructive pulmonary disease (COPD) may present with acute dyspnea and have abnormal lung sounds. In fact, an exacerbation of HF can result in worsening of COPD and vice versa. The history may provide clues to the cause of the exacerbation. Non-compliance with diuretics, or the presence of fever with increased sputum production, should suggest the presence of HF or pneumonia, respectively. A careful physical examination, searching for findings that permit the clinician to distinguish between HF and COPD, should be performed. Severe hypertension and peripheral vasoconstriction suggest acute HF, even in the presence of audible wheezing in a patient with known COPD. A directed physical exam is necessary, although it is limited in sensitivity and specificity. This includes checking for JVD, HJR, the presence of extra heart sounds, and evaluating peripheral perfusion and extremity edema. The chest x-ray can be of assistance, but it does have limitations.

Ventilation perfusion scan, helical thoracic computed tomography (CT), or pulmonary angiography may be required to confirm the diagnosis. Finally, peripheral edema is a common finding in

Table 8. Precipitants of Decompensated Heart Failure[40]

PRECIPITANT	INCIDENCE
Excess salt	22%
Non-cardiac causes	20%
Anti-arrhythmic agents within 48 hours	15%
New arrhythmia	13%
Calcium blocker use	13%
Inappropriate therapy reduction	10%
Rapid atrial fibrillation	10%
Myocardial ischemia	8%
Medication non-compliance	7%
Myocardial infarction	2%
Uncontrolled hypertension	2%

Table 9. New York Heart Association Class

CLASS	LIMITATIONS	DAILY LIVING SYMPTOMS	BNPL (PG/ML)
I	No limitation	Asymptomatic during usual daily activities	100
II	Slight limitation	Mild symptoms during ordinary daily activities	200
III	Moderate limitation	Symptoms noted with minimal activities	450
IV	Severe limitation	Symptoms present even at rest	>1000

HF, but it is not specific for this condition. It also is found in patients with hypoproteinemic states, hepatic or renal failure, and may be the result of primary venous disease.

Diagnosis. The diagnosis of HF may be difficult when the patient has minimal symptoms and when there is no supporting data from clinical laboratory or echocardiography. With disease progression, the most common ED complaint is a respiratory problem (e.g., dyspnea, orthopnea), although edema, weakness, difficulty sleeping, fatigue, dizziness, cough, or abdominal pain are associated symptoms. When limited to using only history and physical, the diagnosis of HF frequently is in error. In a family practice clinic environment, the diagnosis of HF was correct in only 36% of males, and 18% of females.[18] Misdiagnoses were attributed to obesity, deconditioning, or another dyspneic condition. The diagnosis of HF is more accurate in the ED, but this is probably because symptoms are more acute. Among 250 patients presenting to an urgent care environment with HF, physicians misdiagnosed 30 patients. Of these 30 patients, 15 were overdiagnosed and 15 were underdiagnosed as having HF.[17]

History. In general, a brief history should be elicited from the patient or family with special attention to risk factors, signs, or symptoms of myocardial ischemia, arrhythmia, potential infectious processes and, as appropriate, PE. Once stabilized, the patient and family should be questioned about salt intake, medicine compliance (with attention to financial concerns and side effects), alcohol and drug use, and recent changes in their therapeutic regimen. Clinicians also should evaluate the possibility that iatrogenic, drug-related factors, such as digitalis intoxication, use of nonsteroidal anti-inflammatory drugs, or negative inotropism, may have played a role in exacerbating HF.

Physical Examination. After the ABCs have been addressed, the physical exam should focus initially on murmurs indicative of ventricular outflow tract obstruction, such as those found with aortic stenosis and hypertrophic obstructive cardiomyopathy. These valvular lesions require specialized care and prompt detection inasmuch as administration of nitrates, arterial vasodilators, or diuretics may worsen their clinical status.

Some aspects of the physical exam can narrow the differential diagnosis of HF. The most useful findings for confirming the diagnosis of HF is the presence of elevated JVD or a cardiac third heart sound (S3). All other physical exam parameters have a poorer correlation with HF. *(See Table 12.)*[17]

ECG and Laboratory Evaluation of Heart Failure

The ECG is a pivotal diagnostic tool in patients with suspected HF. ECG changes diagnostic of acute MI or acute ischemia mandate admission to the cardiac intensive care unit. An ECG also can assess cardiac rhythm, suggest the need for evaluation of a possible electrolyte abnormality (e.g., hyperkalemia), and may indicate the presence of potential drug toxicity (e.g., junctional bradycardia with digoxin toxicity). It also can provide prognostic information. In dilated cardiomyopathy, the presence of abnormal Q waves, QRS duration greater than 0.12 ms, or left bundle-branch block, predict an increased five-year mortality rate.[8] Note that in patients with systolic dysfunction, the resting ECG is relatively insensitive and nonspecific in identifying severe underlying coronary disease (i.e., presence or absence of old Q-waves).

Cardiac Monitoring. A period of cardiac monitoring in the ED is necessary for patients with HF. This may help exclude cardiac arrhythmia as the cause of the current exacerbation. Continued monitoring, either on the inpatient unit or in the observation unit may be of utility when indicated by the clinical presentation (i.e., recent palpitations or near-syncope). Aggressive treatment strategies, such as repetitive diuretic dosing, may result in electrolyte abnormalities whose effect can be pro-arrhythmic.

Laboratory. As emphasized, asymptomatic cardiac ischemia can precipitate acute HF, or it may produce decompensation in a previously stable HF patient. Because of CK-MB kinetics, a positive result may diagnose but not exclude acute ischemia. Similarly, troponin T may provide evidence of cardiac injury as long as 10 days prior to presentation, but cannot exclude acute myocardial damage.[15] As compared to AMI in non-HF patients, elevated cardiac ischemia markers in HF may not necessarily represent epicardial coronary artery occlusion. However, cardiac marker elevation is associated with an increased risk of adverse outcome.[19-25] Arterial blood gases routinely are not necessary, and can be limited to the cohort at concurrent risk of CO_2 retention and in those who are severely ill. Other suggested laboratory tests include serum electrolytes.

Testing for specific drug levels (e.g., digoxin) should be guided by the presentation. Alcohol analysis and drug screening may be considered in selected patients. Magnesium levels

Table 10. ACC/AHA Heart Failure Classification[37]

ACC/AHA CLASS	STAGE	PATIENT DESCRIPTION	NYHA CLASS
A	High risk for developing left ventricular dysfunction (LVD)	Hypertension Coronary artery disease Diabetes mellitus Family history of cardiomyopathy	—
B	Asymptomatic LVD	Previous MI LV systolic dysfunction Asymptomatic valvular disease	I
C	Symptomatic LVD	Known structural heart disease Shortness of breath and fatigue Reduced exercise tolerance	II-III
D	Refractory end-stage HF	Marked symptoms at rest despite maximal medical therapy	IV

should be considered when either arrhythmia or severe hypokalemia is present.

B-type Natriuretic Peptide—An Emerging Tool

Natriuretic peptides (NP) are a series of proteins released as a result of volume stimulus. ANP originates from the cardiac atria and increases in response to atrial distension. BNP is stored in ventricular myocardial granules and is released in response to ventricular overload. Lastly, CNP is an endothelially derived NP. These peptides serve as the hormonal counterpoint to the renin-angiotensin-aldosterone system, which produces vasoconstriction, sodium retention, and SNS activation in patients with HF. NPs result in vasodilation, decreased aldosterone levels, inhibition of the renin-angiotensin-aldosterone system, and decreases in SNS activity, therefore modulating the processes known to be at the core of HF pathophysiology.

BNP is cleared by three mechanisms: 1) binding to cell surface clearance receptors with internalization and proteolysis; 2) proteolytic cleavage by neutral endopeptidases; and 3) renal filtration. The elimination half-life of exogenously administered BNP is approximately 18 minutes.

Measuring the BNP level (BNPL) has the potential to improve diagnostic accuracy with suspected HF in the ED in as much as BNPL correlates well with cardiac function and clinical presentation. In one study, in the absence of clinical HF, BNPL was a mean of 38 pg/mL, compared to patients with HF, in whom the mean BNPL was 1076 pg/mL.[17] Accordingly, BNPL is an accurate tool for the diagnosis of HF, and it correlates with NYHA class.[16] *(See Table 9.)*

A BNPL is most useful in patients who present a diagnostic challenge, i.e., those with comorbid conditions that may confound historical and physical findings. In one study, patients whose dyspnea was due to an exacerbation of COPD had a BNPL lower than 100, compared to those with HF-induced dyspnea, in whom the BNPL was in the range of 1000. Another analysis comparing edema in HF and non-HF patients reported similar results.[17]

Studies also suggest that BNP can discern future outcomes. A BNPL greater than 480 predicts higher six-month death and rehospitalization rate due to HF, compared to those with levels less than 230 pg/mL.[26] In addition, the one-year mortality rate is increased markedly if the BNPL exceeds 73, in comparison to those with a lower BNPL.[27] Finally, some data suggest ED disposition can be guided by BNPL. Patients with a BNPL greater than 700 were more likely to require inpatient admission, while those treated successfully as outpatients had BNPL less than 254 pg/mL.[17] While these findings need to be duplicated by other trials, BNPLs have demonstrated a clear trend for having predictive value in making patient dispositions in patients with HF.[26]

The diagnosis of HF is suggested by a suggestive clinical presentation and a BNPL greater than 100 pg/mL. At this cutoff point, the BNPL demonstrates both a sensitivity and specificity of 94%. The positive predictive value is 92%, and the negative predictive value is 96%, for an overall accuracy of 94%. Although this can be a useful test for helping ED physicians confirm the presence or absence of congestive HF,[17] the BNPL also is elevated in some non-HF conditions. It is increased relatively in the elderly, in women, and in those conditions that would be predicted to increase intracardiac pressures, such as dialysis, cirrhosis, primary pulmonary hypertension, possibly hormone replacement therapy, and PE. Finally, this test has a coefficient of variation of about 10%. In the ranges that BNP occurs clinically in the ED, this is insignificant.

Clinical Utility of BNP Assay. Guidelines for incorporating a BNPL into patient management have not yet been accepted uniformly. However, studies suggest a BNPL is useful for excluding the diagnosis of HF when it would be considered in the differential.[17] In these situations, a normal BNPL should prompt consideration of a non-HF diagnosis. Because non-HF conditions can elevate BNPL, the clinical context of a high BNPL must be considered. A positive BNPL should prompt testing to verify the diagnosis and determine the cause of HF (e.g., ECG, CXR, echocardiogram, cardiac stress testing).

Serial BNPLs can be used to monitor adequacy of HF thera-

Table 11. Heart Failure Differential Diagnosis

DYSPNEIC STATES
- Chronic obstructive pulmonary disease exacerbation
- Asthma exacerbation
- Pulmonary embolus
- Acute myocardial infarction
- Physical deconditioning
- Obesity
- Pleural effusions
- Pneumonia/pulmonary infection
- Pneumothorax

FLUID RETENTIVE STATES
- Renal failure/nephrotic syndrome
- Liver failure/cirrhosis
- Portal vein thrombosis
- Hypoproteinemia
- DVT
- Dependent edema

LOW CARDIAC OUTPUT STATES
- Acute myocardial infarction
- Tension pneumothorax
- Pericardial tamponade
- Sepsis

py.[28] In general, levels correlate well with treatment response. Following treatment for HF, a declining BNPL portends a more favorable outcome, whereas a rising BNPL suggests a greater risk of adverse outcome. A rising BNPL indicates a more aggressive treatment strategy may be warranted. Finally, a BNPL 48 hours post-MI is a strong prognostic indicator for the development of HF or death within one year, and appropriate treatment and monitoring strategies should be considered in this group.[29,30]

Changes in BNPL correlate dynamically with pulmonary capillary wedge pressure (PCWP). It has been suggested that levels may be utilized to follow acute responses to treatment. Further research is needed, but BNP appears to be a laboratory surrogate for PCWP.[31] The BNP test takes 15 minutes to perform and it is available as a Clinical Laboratories Improvement Act (CLIA)-defined moderately complex bedside point of care assay.

Radiographic Modalities in Heart Failure

Chest Radiograph. A PA and lateral CXR should be obtained in all patients with suspected HF. Importantly, a negative radiograph does not exclude the diagnosis of abnormal left ventricular function. However, in the acutely dyspneic patient, it may exclude other significant, confounding diagnoses, among them, pneumothorax, infiltrative processes, pneumonia, and others. CXR findings suggesting HF include cardiomegaly, Kerley's lines, increased pulmonary vascularity, and pleural effusions. Because radiographic abnormalities may follow the clinical presentation by hours, therapy should not be withheld waiting for the CXR.

It should be stressed that the CXR has poor sensitivity for cardiomegaly,[32] and the performance technique significantly can impact the interpretation. Supine radiographs, commonly used following endotracheal intubation, have poor sensitivity (67%) and specificity (70%) for detecting pulmonary fluid.[33] Furthermore, in chronic HF, the CXR has unreliable sensitivity, specificity, and predictive value in identifying patients with PCWP greater than 20 mmHg. In addition, both physical and x-ray signs of congestion have poor predictive values for an elevated PCWP in patients with chronic HF. In one study, x-ray evidence of pulmonary congestion was absent in 53% of HF patients with mild to moderately elevated PCWPs (16-29 mmHg) and in 39% of those with markedly elevated PCWP (> 30 mmHg).[34]

Cardiomegaly is a useful finding for diagnosing HF, and a cardiothoracic ratio of 60% is associated with a higher five-year mortality rate.[8] However, the CXR is insensitive for cardiomegaly. In 49 cases of echocardiographically proven cardiomegaly, 22% had cardiothoracic ratios less than 50%.[32] Undetectable cardiomegaly by CXR is explained by intrathoracic cardiac rotation. While cardiomegaly is detected accurately by echocardiography, this modality is not available in all EDs.

Pleural effusions are common in HF, but they easily are missed by CXR. This is of concern in intubated patients, since the supine technique further degrades the diagnostic accuracy for the detection of pleural effusions. In one study, 34 patients with pleural effusions proven by decubitus CXRs, the sensitivity, specificity, and accuracy of the supine CXR was reported as 67%, 70%, and 67%, respectively.[33]

Although a portable CXR is obtained readily in the ED, there are drawbacks to relying upon it for diagnostic purposes. *(See Table 13 for the common findings of HF.)* In 22 "mild" HF patients, only dilated upper lobe vessels were found in more than 60%. The frequency of findings increased with increasing HF severity. In severe HF, CXR abnormalities occurred in at least 67%, except a prominent vena cava in 44%, and Kerley's lines in 11%.[35] The "gold standard" for documenting intrathoracic fluid is unclear, although CT-scanning has been proposed. While CT may offer improved imaging, it is difficult to perform in unstable patients, and cannot be recommended routinely for ED use in HF.

Echocardiography. Echocardiography is the "gold standard" test for confirming the presence of HF. It provides excellent information about contractility, chamber size, valve status, and it can evaluate EF. As the single most important measurement in HF,[36] quantitative determination of EF can establish the diagnosis and determine the type of HF, but there is no predictable association between symptoms and EF. Once the diagnosis of systolic failure is established, repetitive measurements usually are unnecessary. However, if an echocardiogram more than one year prior showed a normal EF, a repeat study may be considered. While echocardiography can be done by portable technique, it is relatively unavailable in real time for most emergency physicians. Knowledge of a patient's EF can impact therapy. Since diastolic HF is relatively pre-load dependent, a less aggressive treatment regimen can avoid hypotension resulting from rapid lowering of preload in this population.

Bioimpedance Monitoring. Bioimpedance monitoring is FDA-approved for non-invasive hemodynamic measurement of cardiac function. The placement of four electrodes, similar to ECG

Table 12. Accuracy of Various Heart Failure Parameters[17]

VARIABLE	SENSITIVITY	SPECIFICITY	ACCURACY
History of HF	62	94	90
Dyspnea	56	53	54
Orthopnea	47	88	72
Rales	56	80	70
S3	20	99	66
JVD	39	94	72
Edema	67	68	68

Table 13. Most Common Portable CXR Findings (Descending Order of Frequency)[35]

1. Dilated upper lobe vessels
2. Cardiomegaly
3. Interstitial edema
4. Enlarged pulmonary artery
5. Pleural effusion
6. Alveolar edema
7. Prominent superior vena cava
8. Kerley's lines

electrodes, allows the calculation of cardiac output, systemic vascular resistance (SVR), and total thoracic fluid content. Output and resistance parameters may be normalized by index, similar to data generated from a Swan-Ganz catheter. While maximizing cardiac output has little effect on mortality, improving SVR with vasodilators results in an acute improvement in dyspnea, and chronically decreases mortality. Determining SVR may permit more aggressive use of vasodilator medication in the acute treatment of decompensated HF. Secondly, bioimpedance measurement of thoracic fluid content correlates with the amount of thoracic fluid noted on CXR. This measurement may be useful for rapid evaluation of suspected HF, or when the chest radiograph is equivocal.

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Physician CME Questions

51. What do endogenous natriuretic peptides do?
    A. Promote sodium excretion
    B. Decrease systemic vascular resistance
    C. Decrease aldosterone levels
    D. All of the above

52. In a primary care environment, the clinical diagnosis of HF in females is correct in what percentage of cases?
    A. 100%
    B. 72%
    C. 50%
    D. 18%

53. Which pair of clinical findings is most specific for diagnosing HF?
    A. Orthopnea and rales
    B. JVD and edema
    C. An S3 and JVD
    D. Dyspnea and orthopnea

54. Which of the following statements regarding BNP is correct?
    A. BNP less than 230 pg/mL is associated with higher six-month death rates.
    B. BNP greater than 700 pg/mL is associated with the need for hospitalization.
    C. BNP greater than 500 pg/mL is associated with mild symptoms (NYHA score of II).

55. Which of the following statements about chest x-rays is true?
    A. They identify 100% of cardiomegaly cases.
    B. They identify more than 80% of pleural effusions.
    C. They may lag clinical findings by hours.
    D. They are more accurate if done portably.

56. Decompensated HF may be precipitated by which of the following?
    A. Calcium blocker usage
    B. Myocardial ischemia
    C. Rapid atrial fibrillation
    D. Uncontrolled hypertension
    E. All of the above

57. Which of the following statements is true regarding heart failure?
    A. Almost 500,000 new cases of HF are identified each year.
    B. HF is the single most expensive diagnosis of the Medicare system.
    C. HF is the most common cause of hospitalization and rehospitalization in patients older than age 65.
    D. The combined inpatient and outpatient costs of HF exceed $35 billion annually in the United States.
    E. All of the above are true.

58. The diagnosis of HF is:
    A. a significant indicator for VTE.
    B. associated always with congestion.
    C. associated always with a low ejection fraction.
    D. best made using clinical criteria.

In Future Issues: **Heart Failure: Part II**

Emergency Medicine Reports

CME Objectives

To help physicians:

- quickly recognize or increase index of suspicion for specific conditions;
- understand the epidemiology, etiology, pathophysiology, and clinical features of the entity discussed;
- be educated about how to correctly perform necessary diagnostic tests;
- take a meaningful patient history that will reveal the most important details about the particular medical problem discussed;
- apply state-of-the-art therapeutic techniques (including the implications of pharmaceutical therapy discussed) to patients with the particular medical pro lems discussed;
- understand the differential diagnosis of the entity discussed;
- understand both likely and rare complications that may occur;
- and provide patients with any necessary discharge instructions.

Emergency Medicine Reports
The Practical Journal for Emergency Physicians

Heart Failure Part I

Diastolic Heart Failure Etiologies

RESTRICTIVE CARDIOMYOPATHY
- Cardiac amyloidosis

CONSTRICTIVE PERICARDITIS

ISCHEMIC HEART DISEASE
- Post-infarction scarring/remodeling

HYPERTROPIC HEART DISEASE
- Hypertrophic cardiomyopathy
- Chronic hypertenison
- Aortic stenosis

MITRAL OR TRICUSPID STENOSIS

Etiologies of Cardiogenic Shock

EXTENSIVE MYOCARDIAL INFARCTION (MI)

MI WITH MECHANICAL COMPLICATIONS
- Ventricular septal defect
- Acute mitral regurgitation
- Myocardial free wall rupture

SEPTIC SHOCK WITH MYOCARDIAL DEPRESSION

PERICARDIAL TAMPONADE

LV OUTFLOW OBSTRUCTION
- Hypertrophic obstructive cardiomyopathy (HOCM)
- Aortic stenosis

MYOCARDITIS

END-STAGE CARDIOMYOPATHY

CARDIAC CONTUSION

Forrester Classification

CLASS	DESCRIPTION	CARDIAC INDEX	PCWP	MORTALIT (%)
I	No congestion/ peripheral hypo-perfusion	2.7	12	2
II	Isolated congestion	2.3	23	10
III	Isolated peripheral hypoperfusion	1.9	12	22
IV	Both congestion and peripheral hypoperfusion	1.7	27	55

Key:
PCWP = Pulmonary capillary wedge pressure

New York Heart Association Class

CLASS	LIMITATIONS	DAILY LIVING SYMPTOMS	BNPL (PG/ML)
I	No limitation	Asymptomatic during usual daily activities	100
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IV	Severe limitation	Symptoms present even at rest	>1000

Cardiogenic Shock Criteria

- Systolic blood pressure < 90 mmHg (higher if chronically hypertensive)
- Urine output < 0.5 cc/kg/hr
- Evidence of end organ dysfunction:
  - Renal failure
  - Cerebral (confusion)
  - Peripheral hypoperfusion (cool extremities)
- If hemodynamic monitoring is available:
  - PCWP > 18 mmHg and CI < 1.8 L/min/m^2

Key:
PCWP = Pulmonary capillary wedge pressure; CI = Cardiac index

Major Etiologies of Heart Failure

CORONARY ARTERY DISEASE

COMPLICATIONS OF MYOCARDIAL INFARCTION
- Acute mitral regurgitation (papillary muscle rupture)

SUSTAINED CARDIAC ARRHYTHMIA

POORLY CONTROLLED HYPERTENSION

VALVULAR RUPTURE OR DISEASE

MYOCARDITIS

POSTPARTUM CARDIOMYOPATHY

ACUTE PULMONARY EMBOLUS

PERICARDIAL DISEASE/TAMPONADE
- Effusion
- Constrictive pericarditis

HYPERKINETIC STATES
- Anemia
- Thyrotoxicosis
- A-V fistula (e.g., dialysis)

INFILTRATIVE DISORDERS

Common Causes of Heart Failure Decompensation

- Acute myocardial ischemia or infarction
- Uncontrolled hypertension
- Obesity
- Superimposed infection
- Atrial fibrillation or other arrythmia
- Excessive alcohol
- Worsening valvular lesion
- Endocrine abnormalities (e.g., diabetes, hyperthyroidism, etc.)
- Negative inotropic medications (e.g., verapamil, nifedipine, etc.)
- Non-steroidal anti-inflammatory drugs
- Treatment and dietary non-compliance

Precipitants of Decompensated Heart Failure

PRECIPITANT	INCIDENCE
Excess salt	22%
Non-cardiac causes	20%
Anti-arrhythmic agents within 48 hours	15%
New arrhythmia	13%
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Heart Failure Differential Diagnosis

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- Asthma exacerbation
- Pulmonary embolus
- Acute myocardial infarction
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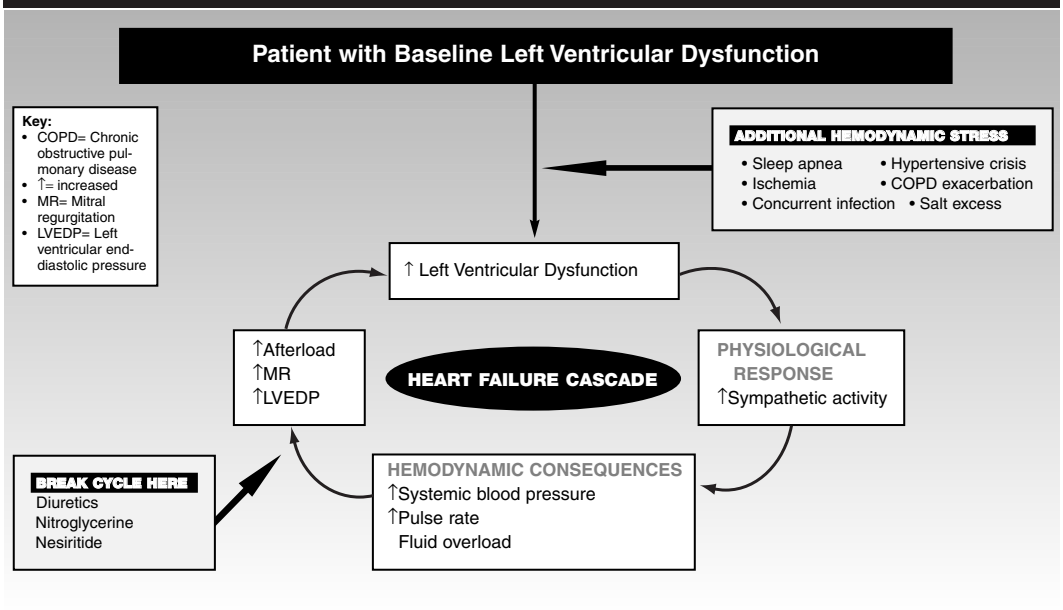
- Portal vein thrombosis
- Hypoproteinemia
- DVT
- Dependent edema

LOW CARDIAC OUTPUT STATES
- Acute myocardial infarction
- Tension pneumothorax
- Pericardial tamponade
- Sepsis

Pathophysiological Cycle of Acute Decompensated Heart Failure



ACC/AHA Heart Failure Classification

ACC/AHA CLASS	STAGE	PATIENT DESCRIPTION	NYHA CLASS
A	High risk for developing left ventricular dysfunction (LVD)	Hypertension Coronary artery disease Diabetes mellitus Family history of cardiomyopathy	—
B	Asymptomatic LVD	Previous MI LV systolic dysfunction Asymptomatic valvular disease	I
C	Symptomatic LVD	Known structural heart disease Shortness of breath and fatigue Reduced exercise tolerance	II-III
D	Refractory end-stage HF	Marked symptoms at rest despite maximal medical therapy	IV

Most Common Portable CXR Findings (Descending Order of Frequency)

1. Dilated upper lobe vessels
2. Cardiomegaly
3. Interstitial edema
4. Enlarged pulmonary artery
5. Pleural effusion
6. Alveolar edema
7. Prominent superior vena cava
8. Kerley's lines

Accuracy of Various Heart Failure Parameters

VARIABLE	SENSITIVITY	SPECIFICITY	ACCURACY
History of HF	62	94	90
Dyspnea	56	53	54
Orthopnea	47	88	72
Rales	56	80	70
S3	20	99	66
JVD	39	94	72
Edema	67	68	68

Physical Diagnosis and Hemodynamic Status

WARM EXTREMITIES	DRY (CLEAR LUNGS)	WET (RALES)
(good perfusion)	Normal SVR	Vasodilated (low SVR)
	Lungs without rales	Lungs congested (rales)
	Normal CO	Normal CO
	Ex: Normal hemodynamics	Ex: Septic shock
COLD EXTREMITIES		
(poor perfusion)	Vasoconstricted (high SVR)	Vasoconstricted (high SVR)
	Lungs without rales	Lungs congested (rales)
	Low CO	Low CO
	Ex: Dehydration and HF	Ex: Decompensated HF

Key:
CO = Cardiac output
SVR = Systemic vascular resistance
HF = Heart failure

Supplement to Emergency Medicine Reports, March 25, 2002: "The Clinical Challenge of Heart Failure: Comprehensive, Evidence-Based Management of the Hospitalized Patient with Acute Myocardial Decompensation—Diagnosis, Risk Stratification, and Outcome-Effective Treatment. Part I." Authors: **W. Frank Peacock, MD**, Emergency Department Clinical Operations Director, The Cleveland Clinic, OH; **Benjamin J. Freda, DO**, Department of Internal Medicine, Cleveland Clinic Foundation, OH.

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DVT Prophylaxis in Patients with Heart Failure: The Evolving Standard of Care for Hospitalized Patients

The Mandate to Prevent Deep Venous Thrombosis (DVT) and Pulmonary Embolism in Patients with Heart Failure

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There is increasing awareness and evidence that seriously ill, hospitalized medical patients, especially those with heart failure, are at increased risk for sustaining deep venous thrombosis (DVT),[1-3] in addition to other complications and sequelae affiliated with left ventricular dysfunction and associated coronary artery disease. Moreover, the potential complications, cost, and morbidity associated with DVT in this patient population can be significant, and may include pulmonary embolism (PE), prolonged hospitalization, and, in some cases, sudden death.[4-10] Overall, it is estimated that as many as 10 million patients hospitalized annually for medical conditions merit screening for and prophylaxis against venous thromboembolic disease (VTED).

Although the consequences of acute coronary artery ischemia and/or thrombosis are well-documented and include a spectrum of life-threatening complications ranging from heart failure to cardiac arrhythmias, the venous "thrombosis crisis" rapidly is becoming a clinical focal point for hospital-based practitioners managing medical patients with serious illnesses. In this regard, it should be stressed that immobilized patients with such conditions as congestive heart failure (CHF), chronic respiratory failure, serious pulmonary and systemic infections, and underlying malignancy are at greater risk for sustaining the morbid sequelae and complications associated with DVT. Accordingly, the threshold for empirical prevention of DVT in this patient population must be balanced against the relatively low risk of serious complications associated with antithrombin-mediated prophylaxis.

Along with the acute management of patients with heart failure, the clinical crisis of thrombosis prevention and management presents a daily challenge to physicians practicing in the hospital environment. In this regard, venous and arterial thromboembolic events are responsible for more than 650,000 deaths in the United States each year. Venous thromboembolism (VTE), in particular, is a common disease that affects more than 2 million people each year, and is associated with such comorbid conditions as impaired left ventricular function. With an incidence in the United States of 1 in 1000, VTE may present as DVT or as PE. Approximately 600,000 patients each year develop PE, and 60,000 deaths due to this disease are reported annually. Unfortunately, these statistics have not changed in three decades despite aggressive diagnostic evaluation, identification of risk factors (See Table 1), evidence-based treatment protocols, and improved prophylaxis, which remains under-utilized in hospitalized medical patients. Moreover, the prevalence of VTE actually may be on the rise due to the aging population and longer survival of cancer patients.

The burden of VTED in hospitalized patients is especially significant, with certain medical conditions (e.g., CHF, respiratory failure, and systemic infection) being associated with an elevated risk for thromboembolic disease. DVT and PE are two manifestations of the same disease process, VTE. Of patients diagnosed with DVT, approximately 30% develop symptomatic PE. The survival rates for those with a diagnosis of VTE are poor. Moreover, the detection of PE frequently is elusive, with the diagnosis being made at autopsy in a large percentage of cases. More than one-third of all deaths from PE occur on the day of presentation. Consequently, emergency practitioners and hospital-based practitioners must recognize patients who are at increased risk of VTE early in their presentations and initiate an appropriate diagnostic evaluation and treatment plan.

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From a clinical perspective, perhaps the most important issue is for hospital-based clinicians to recognize those patient subgroups that are at significant risk for acute DVT, including those with CHF. Although numerous trials have identified specific medical disorders which, when they afflict acutely hospitalized, immobilized patients, increase the risk of acquiring acute DVT (See Table 2), there is no single patient profile that mandates medical prophylaxis against DVT. Rather, the clinician must weigh all of the relevant risk factors (e.g., respiratory status, cardiovascular function, patient age, etc.), and determine, based on clinical judgment, whether the risks of prophylaxis outweigh the risks. When patients with CHF are selected in a systematic way that accounts for all the risks and benefits, DVT prophylaxis will be outcome-effective.

Fortunately, the safety and effectiveness of medical prophylaxis has been analyzed carefully in recent clinical trials. In this regard, a recent landmark study (MEDENOX) has confirmed the effectiveness of at least one low molecular weight heparin (LMWH), enoxaparin in preventing VTED in seriously ill medical patients.[1] Risk-stratification strategies that identify those subgroups of patients with CHF who are most suitable for prophylaxis using enoxaparin will expand awareness of the risks of VTED in this patient population, and make medical prophylaxis against DVT a mandated clinical strategy in a broad range of hospitalized patients.

VTE remains a major cause of mortality and morbidity in hospitalized patients, despite the availability of effective prophylactic agents.[11] Interestingly, studies demonstrate that the majority of patients who suffer a fatal PE have not undergone recent surgery,[12] yet PE rarely is suspected as a cause of death in non-surgical patients[13] and prophylaxis is used infrequently,[14] despite consensus statement recommendations.[15] The burden of VTED in non-surgical populations is significant,[15] with certain medical conditions (e.g., CHF, respiratory failure, and systemic infection) associated with elevated risk for thromboembolic disease. A review of recent studies evaluating risk factors in individual patients will help clarify the need for and value of thromboprophylaxis in clearly defined groups of medical patients.

Burden of Thromboembolic Disease

Compared with surgical populations, far fewer studies have reported the frequency of VTE in medical patients. However, those figures that are available suggest a moderate risk of DVT in general medical patients in the absence of prophylaxis,[16,17] according to the risk categories (low, moderate, high) defined for surgical patients.[18] It should be noted that much higher rates of VTE have been observed in specific groups which, accordingly, should be risk-stratified to receive thromboembolic prophylaxis when indicated.[16,17,19-23] In this regard, a recent study reported that up to one in 20 hospitalized medical patients with multiple problems and severe immobility may suffer a fatal PE.[24] It should be noted, however, that current management practices emphasizing extensive use of thrombolytics, unfractionated heparin (UFH), GP IIb/IIIa inhibitors, LMWH, and antiplatelet agents may contribute to a reduction in the incidence of VTE, including PE.

Table 1. Deep Venous Thrombosis (DVT) Risk Factors for Hospitalized Medical Patients

- Congestive Heart Failure
- Respiratory Failure
- Serious Infection
- Malignancy
- Elderly
- History of DVT
- Immobilization
- Intensive Care Unit Setting
- Hypercoagulability Syndromes
- Inflammatory Rheumatic Disorders

Table 2. Patients with Serious Medical Illnesses Who Should Be Considered for DVT Prophylaxis*

CLASS III-IV CONGESTIVE HEART FAILURE (CHF)

- Ischemic cardiomyopathy
- Non-ischemic cardiomyopathy
- CHF secondary to valvular disease
- Chronic idiopathic cardiomyopathy
- CHF secondary to arrhythmias

SEVERE RESPIRATORY FAILURE

- Acute exacerbations of chronic obstructive pulmonary disease (AE/COPD)
- Adult respiratory distress syndrome
- Community-acquired pneumonia
- Noncardiogenic pulmonary edema
- Pulmonary malignancy
- Interstitial lung disease

SERIOUS INFECTION

- Pneumonia
- Urinary tract infection
- Abdominal infection

ELDERLY PATIENTS

- All hospitalized elderly patients who are immobilized for three days or more and who have serious underlying medical conditions known to be risk factors for DVT should be considered strongly for prophylaxis with enoxaparin.

* Enoxaparin 40 mg subcutaneously QD is indicated providing there are no contraindications and immobilization period of three or more days is anticipated.

In light of the substantial burden of VTE in medical populations, current consensus statements on the prevention of VTE recommend assessment of all hospitalized patients, both medical and surgical, for thromboembolic risk and the use of appropriate prophylaxis. Specific prophylaxis recommendations have been made for patients with stroke and myocardial infarction (MI) by the American College of Chest Physicians (ACCP)[25] and the International Consensus Conference.[20] Prophylaxis also is recommended for other groups of medical patients with clinical risk factors for VTE. However, recommendations are for poorly defined patient groups and vary among consensus documents. For example, recommendations by the UK-based second Thromboembolic Risk Factors (THRIFT II) Consensus Group are based on the individual level of thromboembolic risk assessed for each patient.[26]

Patient Risk Stratification and Prophylaxis

Despite current consensus statement recommendations, surveys show that prophylaxis still is underused in medical settings.[14] Several reasons explain these practice patterns. First, despite epidemiological data demonstrating the prevalence of VTE, many clinicians remain unaware of the level of thromboembolic risk in medical settings. The diversity of medical patients, lack of reliable evidence demonstrating risk levels, and perceived difficulty in assessing individual thromboembolic risk in the presence of multiple risk factors may contribute to the problem. The paucity of data from well-designed trials demonstrating the efficacy of prophylaxis in medical patients provides a further barrier to widespread use. Finally, even those studies that have been published to date are mostly small, involve poorly defined populations, and vary in their end points, undermining confidence in their findings and preventing cross-trial comparisons.

From a clinical, need-to-prophylax perspective, a broad range of medical conditions are associated with an increased risk of VTE. Some of these have been stratified according to the level of risk they confer, although classifications may vary depending on concomitant risk factors.[27] In particular, stroke, MI, malignant disease, and critical care patients are strongly linked to thromboembolic events.

A number of clinical trials have demonstrated a reduction in the frequency of asymptomatic DVT in CHF patients through the use of pharmacological prophylaxis. Some of these studies, illustrate a substantial reduction in the rate of DVT in medical patients as detected by the fibrinogen uptake test, suggesting that prophylaxis with either UFH or LMWH may be of value in these groups.[25] The validity of these findings is questionable, however, because the fibrinogen uptake test has been shown to be a weak predictor of clinically important VTE.[28] Furthermore, while the benefit in high-risk stroke and MI patients appears significant, the evidence in general medical patients is less conclusive. Given the diversity of general medical patients, there is an urgent need for further investigation to assess the potential benefit of anticoagulant treatment in more clearly defined medical populations.

The venous thrombosis risk in non-surgical patients was evaluated in an epidemiological study (PRIME) that also assessed the efficacy and safety profile of enoxaparin. This was a multicenter, randomized, double-blinded comparison of enoxaparin (40 mg) vs. heparin (5000 U TID) in DVT prophylaxis. The 959 patients were expected to be immobilized for more than half of the daytime for the study period of seven days and have at least one additional risk factor (older than age 60, malignancy, obesity, previous VTE event, CHF, paresis, hemiplegia, or severe infection). New

VTE disease occurred in 0.2% of the enoxaparin group and in 1.4% of the heparin groups (P = NS). Bleeding complications were comparable. The investigators concluded that enoxaparin is at least as efficacious as standard heparin in the prophylaxis of venous thrombosis.

MEDENOX Trial

In response to the need for evidence to clarify the role of prophylaxis in specific non-surgical patient subgroups, the MEDENOX (prophylaxis in MEDical patients with ENOXaparin) trial was conducted using the LMWH enoxaparin in clearly identified risk groups. In contrast to previous investigations, the MEDENOX trial included a clearly defined patient population (patients immobilized with severe chest [cardiopulmonary] disease), and was designed to answer questions about the need for prophylaxis in this group of medical patients and to determine the optimal dose of LMWH.[1]

Study Design. The design of the MEDENOX trial included a placebo arm, allowing determination of the thromboembolic risk and the need for prophylaxis in the clearly defined patient group. According to the THRIFT II classification, the population would be expected to be at moderate risk of VTE, since low-risk patients and those with high-risk conditions (e.g., stroke or MI) were excluded.[26] However, the actual risk level for the defined population has not been confirmed in any previous trial. The use of systematic venography to detect DVT provided a reliable and accurate means of assessing prophylactic efficacy.

Inclusionary criteria for MEDENOX were intended to define clearly the risk groups within the general medical population. Patients were considered eligible if they were 40 years of age or older; had been immobilized for fewer than three days; and were hospitalized due to a specific, acute medical condition (i.e., heart failure, respiratory failure, infectious disease, or rheumatic disorder). In this regard, it should be stressed that patients with CHF and/or pulmonary infections have been highlighted in the most recent ACCP consensus statement as a specific target group requiring thromboprophylaxis.[25]

Patients randomized in the MEDENOX trial had a projected hospital stay of at least six days. Patients with respiratory failure were considered eligible provided they did not require respiratory support. The primary exclusion criteria were: pregnancy or possible pregnancy, breastfeeding, stroke, major surgery in the previous three months, contraindications to iodinated contrast media, thrombophilia, serum creatinine greater than 150 mmol/L, intubation, HIV infection, uncontrolled hypertension, conditions conferring risk of hemorrhage, abnormal clotting tests, or hypersensitivity to heparin.

Patients with an acute infectious condition without septic shock, an acute rheumatic disorder, or an active episode of inflammatory bowel disease were considered eligible only if the acute illness was accompanied by at least one additional predefined risk factor for VTE. The risk factors for VTE (age, malignancy, obesity, varicose veins, etc.) closely mirror the clinical risk factors defined by the THRIFT II consensus document,[26] and would be expected to increase the likelihood of a VTE event. The ACCP guidelines[25] and International Consensus Statement[20] also cite these risk factors and emphasize their importance when assessing prophylaxis requirements for medical patients.

Patients in the MEDENOX trial were randomized to receive enoxaparin, 20 or 40 mg subcutaneously, or placebo once daily, beginning within 24 hours of randomization. They were treated for 10 ± 4 days in the hospital and followed up in person or by telephone contact on day 90 (days 83-110). During follow-up, patients were instructed to report any symptoms or signs of VTE or any other clinical event. The primary and secondary efficacy end points for MEDENOX were chosen to allow an objective assessment of the risk of VTE in the study population and the extent of any benefit of prophylaxis. The primary end point was any VTE event between day 1 and day 14. All patients underwent systematic bilateral venography at day 10 ± 4, or earlier if clinical signs of DVT were observed. Venous ultrasonography was performed if venography was not possible. Suspected PE was confirmed by high-probability lung scan, pulmonary angiography, helical computerized tomography, or at autopsy.

The primary safety end points were hemorrhagic events, death, thrombocytopenia, or other adverse event or laboratory abnormalities. As the principal adverse event associated with anticoagulant therapy, hemorrhage was a key safety outcome. Major and minor hemorrhagic events occurring during treatment were recorded. Major hemorrhage was defined as overt hemorrhage associated with a need for transfusion of two or more units of packed red blood cells or whole blood; a decrease in hemoglobin concentration of 20 g/L or more compared with baseline; or retroperitoneal, intracranial, or fatal bleeding. Overt hemorrhage that did not meet the criteria for major hemorrhage was defined as minor. Injection sites were checked daily for hematomas larger than 5 cm in diameter. Full blood counts were performed prior to treatment, and then at three-day intervals.

A total of 1102 patients from 60 centers and nine countries were included in the MEDENOX trial. Overall, the mean age was 73.4 ± 10.5 years, the gender distribution was 50:50, and the mean body mass index was 25.0 ± 6.2 kg/m^2. The mean patient ages, gender distribution, and body mass index were similar in all three treatment groups; there were slightly more males than females in the placebo and enoxaparin 20 mg groups, and more females than males in the enoxaparin 40 mg group, but this difference was not significant. The reasons for hospitalization of randomized patients varied. The majority of patients were hospitalized for acute cardiac failure, respiratory failure, or infectious disease. The frequency of different reasons for hospitalization was similar across all treatment groups. The number of patients in each hospitalization group suggests that a high proportion of acutely ill medical patients have two or more concomitant conditions, each contributing to the overall thromboembolic risk.[1]

For the study population as a whole, the most prevalent risk factor in addition to the underlying illness was advanced age (50.4%), followed by varicose veins (25.4%) and obesity (20.2%). A similar number and proportion of patients in the three treatment groups exhibited each of the separate risk factors. Just more than one-third of patients in each group had chronic cardiac failure, and

about one-half suffered from chronic respiratory insufficiency.

A large percentage of the patients in all three treatment groups had multiple risk factors. Overall, 96.9% of the study population (1068 patients) had at least one additional risk factor for VTE, in addition to their qualifying medical condition (heart failure or acute respiratory failure). Only 31 patients (2.8%) had no additional risk factors, 335 (30.2%) had one risk factor, and 733 (66.7%) had two or more risk factors. This pattern was similar in all treatment groups. The mean number of risk factors per patient was 2.1 ± 1.1, 2.0 ± 1.1, and 2.1 ± 1.1 in the placebo, enoxaparin 20 mg, and enoxaparin 40 mg groups, respectively. Multiple risk factors, therefore, appear to affect a high proportion of patients with acute cardiopulmonary or infectious disease. Risk factors for VTE have a cumulative effect on total risk.

The mean duration of treatment in MEDENOX was approximately seven days, with a standard deviation of three days. Duration of treatment did not differ significantly among the groups. Overall, 16% of patients had fewer than six days' treatment (i.e., less than the planned minimum period), and 26% had more than eight days. No patients were treated for longer than 14 days as per protocol specifications. The continuation of any anticoagulant therapy after the end of the treatment period was left to the individual investigator's judgment. Of the 1102 patients included in the study, 1073 received at least one dose of the study drug and were included in the safety analysis.

Results. Of the 1102 patients enrolled, a total of 866 patients were assessed for primary efficacy at day 14. The incidence of total, proximal, and distal DVT was significantly reduced with enoxaparin 40 mg compared with placebo. By day 14, the incidence of VTE was 14.9% in the placebo group and 5.5% in the enoxaparin 40 mg group, representing a significant 63% relative risk reduction (97% CI: 37-78%; P = 0.0002). A subgroup analysis of enoxaparin-mediated benefits demonstrated a VTE relative risk reduction of 72% in patients with acute heart failure (95% CI, 19-91, P = 0.01); 74% in patients with chronic heart failure (95% CI, 9-93, P = 0.022); and 78% for all patients older than age 75 (95% CI, 49-91, P = 0.0001).[2]

Outcomes in the enoxaparin 20 mg group were not significantly different from placebo. A total of four symptomatic nonfatal PEs occurred, three in the placebo group and one in the enoxaparin 20 mg group. Finally, there was a trend toward mortality reduction with enoxaparin. By day 110, death had occurred in 50 (13.9%), 51 (14.7%), and 41 (11.4%) patients in the placebo, enoxaparin 20 mg, and enoxaparin 40 mg groups, respectively. The 2.5% reduction in overall mortality in the enoxaparin 40 mg group was clinically meaningful but did not reach statistical significance.

By day 110, 798 patients had been assessed for secondary efficacy. The significant reduction in total VTE and proximal and distal DVT observed in the enoxaparin 40 mg group was maintained at the three-month follow-up. Relative risk reduction at three-month follow-up was: all VTE, 59%; and proximal DVT, 66%.[1] Four additional fatal PEs occurred during follow-up, one in the placebo group (three weeks after the treatment period ended), and one and two in the enoxaparin 20 mg and 40 mg groups, respectively (two months after the treatment period ended).

From a clinical safety perspective, there were no significant differences among the groups in the frequency of major or minor hemorrhage, thrombocytopenia, or any other adverse events. Major hemorrhage occurred in 11 patients during the treatment period; the fatal hemorrhage in the enoxaparin 40 mg group was considered unrelated to the study treatment by the investigators. Two additional fatal hemorrhages occurred during follow-up, one in the enoxaparin 20 mg group and one in the enoxaparin 40 mg group, eight and three weeks after discontinuation of the study medication, respectively.

A total of 31 cases of thrombocytopenia occurred during the treatment period (13 cases in the placebo group, 10 in the enoxaparin 20 mg group, and eight in the enoxaparin 40 mg group). Fourteen of them were judged to be probably related to study medication, eight in the placebo group, four in the enoxaparin 20 mg group, and two in the enoxaparin 40 mg group. Remarkably, the three patients who experienced severe thrombocytopenia were in the placebo group.

The PRINCE Study

Other investigations have focused more specifically on patients with heart failure. The PRINCE (Prevention in Cardiopulmonary Disease with Enoxaparin) study group conducted a randomized, multicenter trial in 665 hospitalized patients with severe cardiopulmonary diseases (332 with respiratory disorders, 333 with New York Heart Association [NYHA] Grade III/IV heart failure).[29] Patients were treated with enoxaparin 40 mg subcutaneously (SC) daily or 5000 IU UFH SC TID for 8-12 days in an open-label study. Efficacy rates were evaluated in 454 patients using an intention-to-treat analysis.

Although the rate of VTE was similar in both groups (8.4% in the enoxaparin group vs 10.4% in the UFH group), a subgroup analysis indicated that the incidence of VTE was greater in patients with heart failure than those with respiratory diseases. All patients were included in an adverse event analysis, which indicated that the incidence of adverse events, including bleeding events (1.5% vs 3.6%) and injection site hematomas (7.2% vs 12.6%), occurred more frequently in the UFH group. The authors concluded that enoxaparin 40 mg SC QD was at least as effective and safe as UFH for the prophylaxis of VTE in acutely ill medical patients.

In a further subset analysis,[30] the PRINCE II study group revealed that administration of enoxaparin 40 mg SC QD was at least as effective as UFH 5000 IU SC TID for the prevention of DVT and/or PE in the 333 patients with NYHA Class III/IV heart failure.[31] The incidence of DVT and/or PE was 11/113 (9.7%) in the enoxaparin group and 15/93 (16.1%) in the UFH group (P = 0.014), respectively. Moreover, significantly fewer adverse events occurred in the group prophylaxed with enoxaparin (51.8% vs. 59.7%, P = 0.02).

The PRIME Study Group

The PRIME (Prophylaxis in Internal Medicine with Enoxaparin) study group conducted a randomized, double-blind, multicenter trial to compare the efficacy and safety of enoxaparin 40 mg

SC QD with UFH 5000 IU SC TID for the prevention of VTE in hospitalized medical patients.[31] A total of 959 patients initiated enoxaparin (n = 477) or UFH (n = 482) therapy 24 hours after hospital admission and continued prophylactic therapy for seven days. Demographic characteristics were comparable between the two groups; the mean age of the participants was 74 years (82.7% > 60 years of age). Based on the intent-to-treat analysis, 0.25% of patients in the enoxaparin group and 1.4% of patients in the UFH group developed VTE during the seven-day period (P = 0.1235). The safety analysis found fewer adverse events and fewer major hemorrhagic complications in the enoxaparin group. The results indicated that enoxaparin 40 mg SC QD was at least as effective as 5000 IU UFH SC TID for prophylaxis of immobilized medical patients. Furthermore, the enoxaparin group experienced fewer adverse events than the UFH-treated group.

Pharmacoeconomic Issues and Analysis: Selecting the Optimal, Outcome-Effective Agent for Prevention of DVT in the Hospitalized Patient with Heart Failure

The clinical benefits[3] and cost-effectiveness[32-34] of thromboprophylaxis in most moderate- and high-risk surgical patients already has been established firmly, and attention among hospital-based practitioners has turned to the hospitalized medical patient, especially since the majority of inpatients who suffer a fatal PE have not undergone recent surgery.[11,35-37] There are estimates that up to one in 20 patients who present with multiple problems and severe immobility are suffering a fatal PE.[4,5,38]

A meta-analysis of medical patients who are at moderate risk for VTE has confirmed the benefits of prophylaxis with heparinoids.[6] In this analysis, seven studies combining data from 15,095 patients and comparing heparin (LMWH or UFH) with placebo showed significant reductions of 56% and 58% in the incidence of DVT and clinical PE, respectively. Nine studies comparing LMWH and UFH (4699 patients) revealed no significant difference between LMWH and UFH on the incidence of DVT, clinical PE, or mortality, although LMWH significantly reduced the risk of major hemorrhage compared to UFH (52% risk reduction).[6]

Identifying a cost-effective strategy for preventing DVT and/or PE in patients with heart failure has been an area of intense interest, inasmuch as the most recent ACCP Consensus Conference introduced thromboprophylaxis recommendations (LMWH or UFH) for general medical patients admitted to the hospital with risk factors for VTE, of which heart failure is cited as one of the principal indications.[7]

Enoxaparin vs. UFH. To assess the cost-effectiveness of enoxaparin prophylaxis (40 mg SC QD) compared with UFH (5000 units SC BID) for patients bedridden due to medical illness, a British group performed a pharmacoeconomic evaluation to assess the cost-effectiveness of these two therapeutic options.[39] Because no head-to-head studies comparing enoxaparin vs. UFH prophylaxis in medical patients are available for analysis, this group's comparison was based on the aforementioned meta-analysis that included randomized studies of UFH and LWMH at doses recommended for prophylaxis in medical patients.[6]

Table 3. Exclusionary Criteria for Prophylaxis in Seriously Ill Medical Patients

- Pregnancy or possible pregnancy
- Major surgery in the past three months
- Breast feeding
- Bleeding disorder
- Uncontrolled hypertension
- Conditions conferring risk for hemorrhage
- Abnormal clotting tests
- Hypersensitivity to heparin, LMWHs, or heparin products
- Severe renal failure

The primary end point considered was DVT detected by systematic objective screening, while secondary end points included PE confirmed by lung scan or necropsy and major bleeding.[6] Secondary effectiveness measures included estimated mortality. The authors identified nine trials in 4660 patients that compared LMWH to UFH, and calculated the relative risk of DVT to be 83% (95%, CI 0.56-1.24, P = 0.37) and major bleeding to be 0.48 (95%, CI 0.23-1.00, P = 0.049). Although UFH was not included as a comparator in the MEDENOX trial,[1] it was used in this analysis, as evidence exists that UFH is used for thromboprophylaxis in hospitalized medical patients.[8,9]

To estimate the overall costs of managing VTE, an economic model was used to extrapolate beyond the timescale of the studies, and the best available evidence was used to estimate the clinical manifestations and progression of DVT. Long-term complications up to 15 years also were included. In addition to the drug acquisition costs associated with prophylaxis, other costs of managing VTE also were accounted for, including the costs of radiology and other investigations for suspected DVT and PE, treatment of confirmed cases, management of major bleeding, and management of long-term sequelae of VTE. Results were estimated for a hypothetical cohort of 100 patients.

To evaluate the effect of using enoxaparin vs. no prophylaxis for VTE, both incremental costs and effectiveness were considered, thereby permitting the authors to evaluate whether enoxaparin prophylaxis represented a cost-effective approach to DVT prevention in a medical population. Cost-effectiveness ratios were calculated by dividing the increase in costs estimated in the model [(cost of VTE if patients are given prophylaxis with enoxaparin 40 mg QD) - (cost of VTE if no prophylaxis is given)] by the decrease in the number of events [(number of events related to VTE if no prophylaxis given) - (number of events related to VTE if patients are given prophylaxis with enoxaparin)].[39]

The results of this cost-analytical model indicate that thromboprophylaxis with enoxaparin (enoxaparin 40 mg SC QD) is cost-effective in acutely ill medical patients compared to no prophylaxis. The authors also emphasize that the effectiveness analysis in their model is consistent with the large body of clinical evidence that there is a better risk-to-benefit ratio when using LMWH, rather than UFH, for DVT prevention.[10] Moreover,

compared to thromboprophylaxis with UFH, enoxaparin prophylaxis was found to be cost-neutral.[39]

This landmark pharmacoeconomic evaluation has important clinical implications for the hospital-based practitioner, especially those managing medical patients with serious medical conditions such as heart failure. Inasmuch as: 1) enoxaparin is the only LMWH that carries a formal indication for prophylaxis of DVT that may lead to PE in medical patients who are at risk for thromboembolic complications due to severely restricted mobility during acute illness; 2) the most recent ACCP Consensus Conference statement mandates either LMWH or UFH for thromboprophylaxis in hospitalized, acutely ill medical patients; and 3) the risk of major hemorrhage appears to be lower with LMWH as compared to UFH, enoxaparin prophylaxis (40 mg SC QD) should be considered the preferred strategy of VTE prevention in appropriately selected and screened hospitalized patients with heart failure.

Prevention of VTE in Patients with Heart Failure: Clinical Implications and Adoption of LMWH Prophylaxis Strategies into Clinical Pathways

Based on recent studies, in immobilized patients—or those with significant restrictions in ambulation that place them at risk for DVT—who present to the hospital with CHF (NYHA Classes III-IV), prophylaxis should be considered mandatory if there are no significant contraindications.[25] *(See Table 3.)* It should be added that the ACCP guidelines[26] and International Consensus Statement[20] also cite CHF as a risk factor for VTED and emphasize the importance of this risk factor when assessing prophylaxis requirements for hospitalized medical patients.

The primary efficacy and safety results, as well as the conclusions of the MEDENOX trial can and should be applied directly to clinical practice. First, acutely ill medical patients with Stages III-IV NYHA functional class CHF are at significant risk of VTE. Second, based on the MEDENOX trial, enoxaparin, given once daily subcutaneously at a dose of 40 mg for 6-14 days, reduces the risk of VTE by 63%; and third, the reduction in thromboembolic risk is achieved without increasing the frequency of hemorrhage, thrombocytopenia, or any other adverse event compared with placebo. In addition, the study strongly suggests that a wide range of hospitalized medical patients, in particular those who have heart failure and are elderly, should, if there are no contraindications to the use of anticoagulants, be prophylaxed with enoxaparin 40 mg SC QD upon admission to the hospital to prevent DVT and its associated life-threatening complications. *(See Insert.)*

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Physician CME Questions

To earn CME credits for this supplement to Emergency Medicine Reports*, please refer to the enclosed Scantron form for directions on taking the test and submitting your answers.*

1. Which of the following is a possible, relative contraindication for DVT prophylaxis in seriously ill medical patients?
   A. Stage III-IV NYHA heart failure
   B. Lack of hypersensitivity to heparin or LMWHs
   C. Uncontrolled hypertension
   D. Minor surgery in the past two months

2. Which of the following risk factors is linked to an increased risk for thromboembolic events?
   A. Stroke
   B. Critical care patients
   C. Myocardial infarction
   D. Malignant disease
   E. All of the above

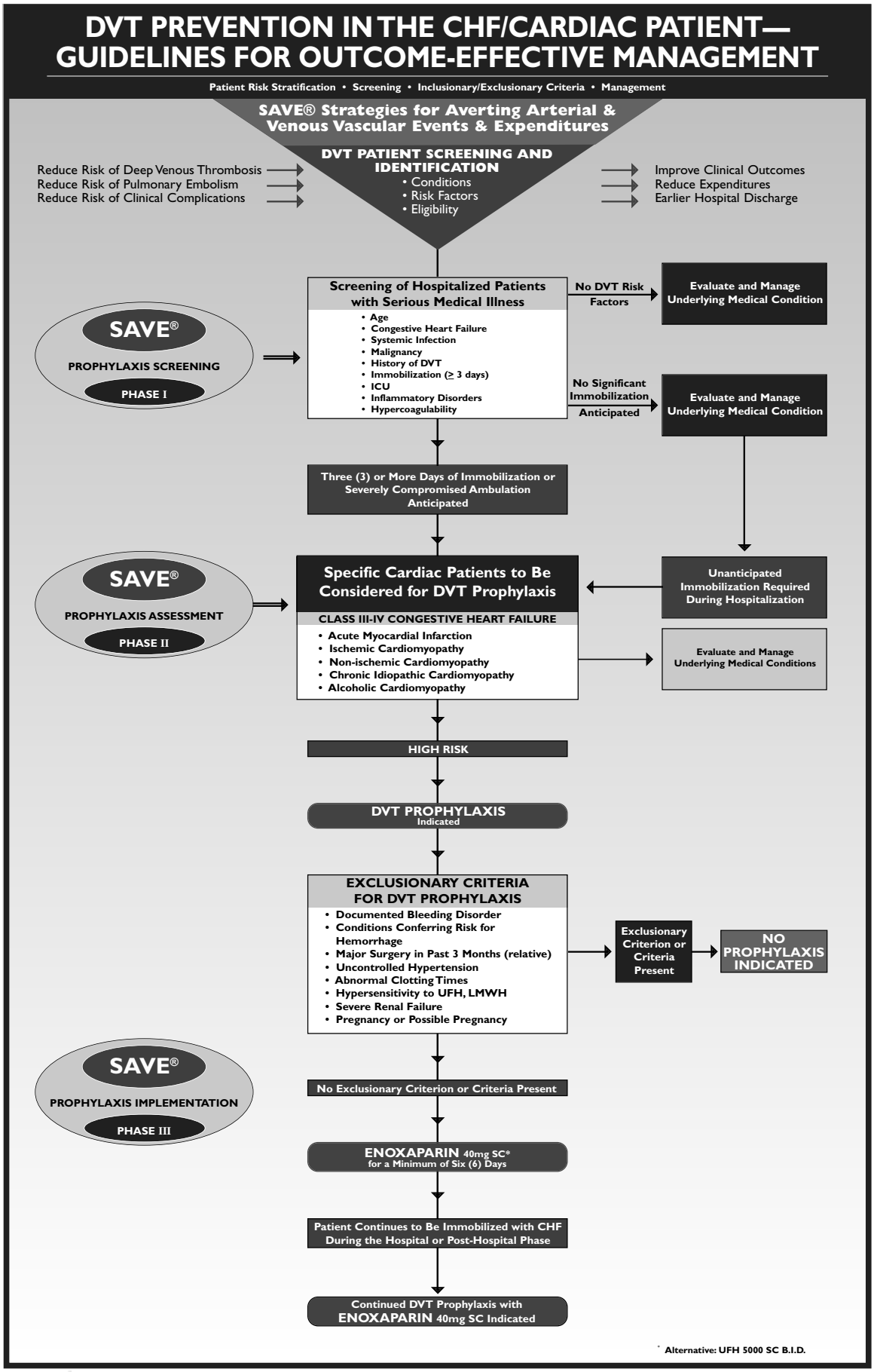
3. In the MEDENOX trial, the relative risk reduction of proximal DVT at three months follow-up was:
   A. 33%.
   B 44%.
   C. 55%.
   D. 66%.
   E. 77%.

4. The primary conclusions of the MEDENOX trial include which of the following?
   A. Acutely ill medical patients with cardiopulmonary or infectious disease are at significant risk of VTE.
   B. Enoxaparin, given once daily at a dose of 40 mg for 6-14 days, reduces the risk of VTE by 63%.
   C. The reduction in thromboembolic risk is achieved without increasing the frequency of hemorrhage, thrombocytopenia, or any other adverse event compared with placebo.
   D. All of the above

Emergency Medicine Reports CME Objectives

To help physicians:

- quickly recognize or increase index of suspicion for specific conditions;
- understand the epidemiology, etiology, pathophysiology, and clinical features of the entity discussed;
- be educated about how to correctly perform necessary diagnostic tests;
- take a meaningful patient history that will reveal the most important details about the particular medical problem discussed;
- apply state-of-the-art therapeutic techniques (including the implications of pharmaceutical therapy discussed) to patients with the particular medical problems discussed;
- understand the differential diagnosis of the entity discussed;
- understand both likely and rare complications that may occur;
- and provide patients with any necessary discharge instructions.


DVT PREVENTION IN THE CHF/CARDIAC PATIENT—
GUIDELINES FOR OUTCOME-EFFECTIVE MANAGEMENT
Patient Risk Stratification • Screening • Inclusionary/Exclusionary Criteria • Management
SAVE® Strategies for Averting Arterial & Venous Vascular Events & Expenditures
DVT PATIENT SCREENING AND IDENTIFICATION
• Conditions
• Risk Factors
• Eligibility
Reduce Risk of Deep Venous Thrombosis
Reduce Risk of Pulmonary Embolism
Reduce Risk of Clinical Complications
Improve Clinical Outcomes
Reduce Expenditures
Earlier Hospital Discharge
SAVE®
PROPHYLAXIS SCREENING
PHASE I
Screening of Hospitalized Patients with Serious Medical Illness
• Age
• Congestive Heart Failure
• Systemic Infection
• Malignancy
• History of DVT
• Immobilization (≥ 3 days)
• ICU
• Inflammatory Disorders
• Hypercoagulability
No DVT Risk Factors
Evaluate and Manage Underlying Medical Condition
No Significant Immobilization Anticipated
Evaluate and Manage Underlying Medical Condition
Three (3) or More Days of Immobilization or Severely Compromised Ambulation Anticipated
SAVE®
PROPHYLAXIS ASSESSMENT
PHASE II
Specific Cardiac Patients to Be Considered for DVT Prophylaxis
CLASS III-IV CONGESTIVE HEART FAILURE
• Acute Myocardial Infarction
• Ischemic Cardiomyopathy
• Non-ischemic Cardiomyopathy
• Chronic Idiopathic Cardiomyopathy
• Alcoholic Cardiomyopathy
Unanticipated Immobilization Required During Hospitalization
Evaluate and Manage Underlying Medical Conditions
HIGH RISK
DVT PROPHYLAXIS Indicated
EXCLUSIONARY CRITERIA FOR DVT PROPHYLAXIS
• Documented Bleeding Disorder
• Conditions Conferring Risk for Hemorrhage
• Major Surgery in Past 3 Months (relative)
• Uncontrolled Hypertension
• Abnormal Clotting Times
• Hypersensitivity to UFH, LMWH
• Severe Renal Failure
• Pregnancy or Possible Pregnancy
Exclusionary Criterion or Criteria Present
NO PROPHYLAXIS INDICATED
SAVE®
PROPHYLAXIS IMPLEMENTATION
PHASE III
No Exclusionary Criterion or Criteria Present
ENOXAPARIN 40mg SC* for a Minimum of Six (6) Days
Patient Continues to Be Immobilized with CHF During the Hospital or Post-Hospital Phase
Continued DVT Prophylaxis with ENOXAPARIN 40mg SC Indicated
* Alternative: UFH 5000 SC B.I.D.