INTRODUCTION

Heart failure is usually a progressive condition that begins with risk factors for cardiac dysfunction, proceeds to asymptomatic changes in cardiac structure and function, and then evolves into clinically overt heart failure, disability, and death[1].

Heart failure is primarily a condition of the elderly and thus the widely recognized "aging of the population" also contributes to the increasing incidence of HF. The incidence of HF approaches 10 per 1000 population after age 65[4], and approximately 80% of patients hospitalized with HF are more than 65 years old. Approximately 1 to 2% of the population in developed countries has heart failure, with the prevalence rising up to 10% or more among persons 70 years of age or older. At least half the patients with heart failure have a low ejection fraction (EF) (EF < 40%)[2].

Heart failure is the leading cause of hospitalization in Medicare-eligible adults. Despite the mortality risk decreased by about 5%, patients with heart failure still have a threefold higher mortality compared with age-matched patients without heart failure, heart failure remains a lethal condition in the community, with an estimated annual mortality of approximately 21% in men 17%in women[3].

In the last decades, the field of management of cardiovascular diseases (CVD) has moved forward

impressively, offering large numbers of patients and subjects at risk for acute and chronic diseases of the heart and vessels a better survival, decreased morbidity and an improved quality of life[4].

Medical therapies, such as angiotensin converting enzyme inhibitors, beta blockers, and spironolactone, have led to marked improvements in both symptom control and overall survival in patients with heart failure (HF). Implanted devices, such as cardioverter-defibrillators (ICDs) and pacemakers, can also be beneficial. ICDs are recommended for primary and secondary prevention of sudden cardiac death in selected patients with ischemic and nonischemic cardiomyopathy. In addition, some patients with HF benefit from simultaneous pacing of both ventricles (biventricular or BiV pacing) or of one ventricle in patients with bundle branch block. This approach is referred to as cardiac resynchronization therapy (CRT). CRT can be achieved with a device designed only for pacing or can be incorporated into a combination device with an ICD[4].

The rationale for cardiac resynchronization therapy (CRT) is based upon the observation that the presence of a bundle branch block or other intraventricular conduction delay can worsen heart failure due to systolic dysfunction by causing ventricular dyssynchrony. Consistent with the concept that left ventricular dyssynchrony exacerbates ventricular dysfunction is the observation that a variety of hemodynamic benefits as well as improved clinical outcomes follow the correction of

dyssynchrony with CRT. Mechanisms of benefit from CRT include improvement in left ventricular systolic function as well as reverse ventricular remodeling manifest as reductions in left ventricular chamber size and measures of mitral regurgitation[5].

In recent years the role of biomarkers, which are specific analytical tests on enzymes, hormones, and other biological substances mostly derived from the blood has become increasingly important and has expanded exponentially. In the field of heart failure, accounting for a growing number of affected and hospitalized patients in the Western world, major diagnostic and therapeutic advances have led to earlier identification and improved clinical outcome. However, the prognosis of a substantial number of HF patients is still adverse. Selection of earlier and more effective therapies may improve outcome in those patients. The clinical application of established biomarkers in HF holds promise to meet those needs. In recent years, biomarker evaluation, particularly testing of circulating B-type natriuretic peptides has become an integral part of acute and chronic HF management, after thousands of papers published, a decade of clinical experience and incorporation in international guidelines[6].

AIM OF THE WORK

The aim of this study is to find out whether an early change in BNP after implantation of CRT can predict the clinical response.

HEART FALUIRE

The definition of heart failure (HF) is hampered by the wide variability of the clinical symptoms and signs, and of their etiologies. Many attempts have been made to come up with a general set of criteria that describe heart failure. These criteria include clinical, epidemiological, pathophysiological, and exercise-related criteria derived from patient's response to therapy[7].

Some historical definitions of heart failure: Descriptions of heart failure exist from ancient Egypt, Greece, and India, and the Romans were known to use the foxglove as medicine.[8]

In 1933 Thomas Lewis first defined heart failure as "A condition in which the heart fails to discharge its contents adequately".[8]

1950 Paul Wood defined heart failure as "A state in which the heart fails to maintain an adequate circulation for the needs of the body despite a satisfactory filling pressure"[8].

1980 E Braunwald defined heart failure as "A pathophysiological state in which an abnormality of cardiac function is responsible for the failure of the heart to pump blood at a rate commensurate with the requirements of the metabolizing tissues"[8].

1983 H Denolin, H Kuhn, H P Kray enbuehl, F Loogen, A Reale, defined heart failure as "the state of any heart disease in which, despite adequate ventricular filling, the heart's output is decreased or in which the heart is unable to pump blood at a

rate adequate for satisfying the requirements of the tissues with function parameters remaining within normal limits"[8].

1985 Philip Poole-Wilson defined heart failure "A clinical syndrome caused by an abnormality of the heart and recognized by a characteristic pattern of haemodynamic, renal, neural and hormonal responses".[8]

1987 Peter Harris defined heart failure as "syndrome which arises when the heart is chronically unable to maintain an appropriate blood pressure without support"[8].

1988 Jay Cohn defined heart failure as "A syndrome in which cardiac dysfunction is associated with reduced exercise tolerance, a high incidence of ventricular arrhythmias and shortened life expectancy"[8].

In 2008 European society of cardiology (ESC) defined heart failure as a clinical syndrome in which patients may have the following features[9]:

- Symptoms typical of heart failure (breathlessness at rest or on exercise, fatigue, tiredness, Ankle swelling) and
- Signs typical of heart failure (tachycardia, tachypnoea, pulmonary rales, pleural effusion, Raised jugular venous pressure, peripheral edema, hepatomegaly) and
- Objective evidence of a structural or functional abnormality of the heart at rest: (cardiomegaly, third heart sound, cardiac murmurs, abnormality on the echocardiogram, raised natriuretic peptide concentration).(9)

In 2009 American College of Cardiology Foundation / American Heart Association (ACC/AHA) defined heart failure as a complex clinical syndrome from any structural or functional cardiac disorders that impairs the ability of ventricle to fill or eject blood. The cardinal manifestations of HF are dyspnea and fatigue, which may limit exercise tolerance, and fluid retention, which may lead to pulmonary congestion and peripheral edema. Both abnormalities can impair the functional capacity and quality of life of affected individuals, but they do not necessarily dominate the clinical picture at the same time. Some patients have exercise intolerance but little evidence of fluid retention, whereas others complain primarily of edema and report few symptoms of dyspnea or fatigue. Because not all patients have volume overload at the time of initial or subsequent evaluation, the term "heart failure" is preferred over the older term "congestive heart failure"[10].

Prevalence, incidence, and prognosis of heart failure

Generally speaking, the prevalence of heart failure can be estimated at 1-2%in the western world and the incidence approaches 5-10 per 1000 persons per year. Estimates of the occurrence of heart failure in the developing world are largely absent .[11].Heart failure is primarily a condition of the elderly [12]and thus the widely recognized "aging of the population" also contributes to the increasing incidence of HF. The incidence of HF approaches 10 per 1000 population after age 65 (13)and approximately 80% of patients hospitalized with HF are more than 65 years old[14].

The median age for patients who have HF in the United States is 75 year (half of all HF cases occur in the 6% of the population 75 years of age or older). Therefore, it is not surprising that the incidence and prevalence of HF will increase proportionately as the population ages. Heart failure is already the most costly cardiovascular disorder in the United States, and it is the leading cause of hospital admission among Medicare beneficiaries. The estimated direct and indirect cost of HF in the United States for 2009 is $37.2 billion[15].

Persons younger than 50 years are hardly ever found to have heart failure, but in those older than 50 years the prevalence and incidence increase progressively with age. In a recent US population-based study the prevalence of heart failure was 2.2% increasing from 0.7% in persons aged 45 through 54 years to 8.4% for those aged 75 years or older[16].

Data from the Rotterdam study suggested that the prevalence of heart failure being 1% in age group 55–64 years, 3% in age group 65–74 years, 7% in age group 75–84 years, and over 10% in those aged >85 years.(17) Data result selected residents of Olmsted County, Minnesota, aged 45 years or older from June 1997 through September 2000. Suggested that the prevalence of asymptomatic systolic heart failure was 6 % and the presence of any left ventricular dysfunction (systolic or diastolic) was associated with an increased risk of developing overt HF, and diastolic dysfunction was predictive of all-cause death[16].

Among patients with symptomatic heart failure the prevalence of systolic dysfunction was 45%.(17) Gender is also

an important factor affecting HF prevalence. The third National Health and Nutrition Examination Survey, conducted from 1988 to 1994, estimated that the number of Americans with HF was 4.7 million, of which 2.3 million were men and 2.4 million were women[18].

In USA approximately 5 million patients HF, and over 550 000 patients are diagnosed with HF for the first time each year. The disorder is the primary reason for 12 to 15 million office visits and 6.5 million hospital days each year. From 1990 to 1999, the annual number of hospitalizations has increased from approximately 810 000 to over 1 million for HF as a primary diagnosis and from 2.4 to 3.6 million for HF as a primary or secondary diagnosis[19].

Prognosis:

1. Mortality

In the Helsinki Ageing Study, four-year mortality in individuals free of congestive heart failure (CHF) was 30%.[20] Of those with CHF, the mortality rate was 43% among subjects with preserved systolic function (PSF) and 54%in those with reduced systolic function (46% in patients with any CHF). In the Cardiovascular Health Study (CHS), the 6.4-year mortality rate in subjects without CHF was 16% compared to 45% in those with CHF. The mortality rate in subjects without CHF and with PSF was 25 deaths per 1,000 patient-years. This rate rose to 87 in subjects with CHF and PSF, 115 in those with CHF and borderline systolic function, and 154 per 1,000 patient-years in subjects with CHF and reduced systolic function[21].

Patients with CHF in the Framingham Heart Study with reduced LV systolic function had an annual mortality rate of 18.9% compared to 4.1% in age and gender-matched controls (over 6.2 years). In patients with PSF, the annual mortality rate was 8.7% compared to 3% in their matched controls.[22] In an adjusted analysis, patients with both types of CHF had four times the risk of death of their age- and gender-matched controls. The median survival in patients with reduced systolic function was 4.3 years, and it was 7.1 years in those with HF-PSF. It was reported that survival decreases as left ventricle (LV) systolic function decreases in a graded way[23].

The IN-CHF registry has also reported one-year outcome data for out-patients with CHF. One-year mortality was 18.8% in patients with an LVEF <35%, 8.9% in patients with an LVEF> 45%, and11.5% in patients with an LVEF between 35% and 45%[24].

2. Hospital Admissions

Population-based studies. The risk of hospitalization was quantified in the Olmsted County incident case study .Of patients with reduced LV systolic function, 10% were never hospitalized, 41% were hospitalized once, and 49%were hospitalized-2 times, for CHF, over five years. Patients with reduced systolic function had significantly more hospitalizations[25].

In the IN-CHF registry, one-year rates of hospitalization for any cause, for a cardiovascular reason, or for worsening CHF were, respectively, 27.1% in patients with LVEF <35%, 18.4% inpatients LVEF> 45%, 19.5% in patients with an LVEF between 35% and 45%[24].

It is clear that both types of CHF have a grim prognosis. Philbin et al. showed that the six-month rate of death or readmission was 50% in patients with PSF and 52% in those with reduced systolic function[26].

The Cardiovascular Health Study (CHS) also reported the risk of nonfatal MI and stroke.[21] In subjects with no CHF and PSF these rates were 10.9 and 12.5, respectively, per 1,000 patient-years at risk. The rates increased to 23.3 and 27.5 in patients with CHF and PSF, 37.7 and 50.7 in those with CHF and borderline systolic function, but fell again to 19.4 and 45.2, respectively, per 1,000 patient-years, in subjects with CHF and reduced systolic function[27].

Table (1): Clinical Classifications of Heart Failure Severity.

NYHA Functional Classification		ACC–AHA Stages of Heart Failure	
Class I	No limitation of physical activity; ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea	Stage A	At high risk for heart failure; no identified structural or functional abnormality; no signs or symptoms
Class II	Slight limitation of physical activity; comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea	Stage B	Developed structural heart disease that is strongly associated with the development of heart failure but without signs or symptoms
Class III	Marked limitation of physical activity; comfortable at rest, but less than ordinary activity results in fatigue, palpitation, or dyspnea	Stage C	Symptomatic heart failure associated with underlying structural heart disease
Class IV	Unable to carry on any physical activity without discomfort; symptoms present at rest; if any physical activity is undertaken, discomfort is increased	Stage D	Advanced structural heart disease and marked symptoms of heart failure at rest despite maximal medical therapy

ACC American College of Cardiology; AHA American Heart Association. Hunt SA et al. Circulation 2005; 1 12:1825–1852. The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th ed. Little Brown & Co; 1994. pp 253–256.

Symptoms and Signs of Heart Failure

According to Framingham Criteria for Congestive Heart Failure the diagnosis of HF requires the simultaneous presence of at least 2 major criteria or 1 major criterion in conjunction with 2 minor criteria [28]:

Major criteria:

- Paroxysmal nocturnal dyspnea
- Neck vein distention
- Rales
- Radiographic cardiomegaly (increasing heart size on chest radiography)
- Acute pulmonary edema
- S3 gallop
- Increased central venous pressure (>16 cm H2O at right atrium)
- Hepatojugular reflux
- Weight loss >4.5 kg in 5 days in response to treatment.

Minor criteria:

- Bilateral ankle edema
- Nocturnal cough
- Dyspnea on ordinary exertion
- Hepatomegaly

- Pleural effusion
- Decrease in vital capacity by one third from maximum recorded
- Tachycardia (heart rate>120 beats/min.)

The Framingham Heart Study criteria are 100% sensitive and 78% specific for identifying persons with definite congestive heart failure

Diagnosis of systolic heart failure

According to ESC guideline systolic heart failure was defined [29]:

1. Typical symptoms and signs of heart failure (dyspnea, orthopnea, S3, rales, jugular vein distension…) and,
2. Objective evidence of structural or functional abnormality of the heart (dilated LV, impaired LVEF < 45%).

General Principles of Treatment

Goals of therapy

The goals of HF therapy are clinical improvement followed by stabilization and ultimately a reduction in risk of morbidity (including the rate of hospitalization) and mortality [30, 31, 32]:

1- Components of therapy:

- Correction of systemic factors (eg, thyroid dysfunction, infection, uncontrolled diabetes), as well as comorbidities such as chronic obstructive pulmonary disease and sleep apnea.

- Lifestyle modification: There have been no randomized trials to document the benefits of lifestyle modification, all of which are based upon observational studies and physiologic rationale.
- Cessation of smoking.
- Restriction of alcohol consumption.
- Salt restriction to approximately 2 to 3 g (or less) of sodium per day to minimize fluid accumulation.
- Weight reduction in obese subjects with goal of being within 10 percent of ideal body weight.
- Daily weight monitoring to detect fluid accumulation before it becomes symptomatic.
- Review of drugs that may contribute to HF (eg, nonsteroidal anti-inflammatory drugs, antiarrhythmic drugs, calcium channel blockers, thiazolidinediones).
- Pneumococcal vaccination and annual influenza vaccination.
- Pharmacologic therapy to relieve symptoms (including the risk of hospitalization), slow the progression of the HF, and improve patient survival. It will be discussed in more depth below.
- Two types of devices are recommended in selected patients with HF:

    1. An implantable cardioverter-defibrillator (ICD) for secondary prevention of sudden cardiac death (SCD) and for primary prevention in selected patients[33].

2. Cardiac resynchronization therapy (CRT) with biventricular pacing can improve symptoms and survival in selected patients who are in sinus rhythm and have a reduced left ventricular ejection fraction, and a prolonged QRS duration. Most patients who satisfy criteria for CRT implantation are also candidates for an ICD and receive a combined device. CRT will be discussed in more detail separately[34].

2- Pharmacologic Therapy of HF

The goals of pharmacologic therapy are to improve symptoms (including risk of hospitalization), slow or reverse deterioration in myocardial function, and reduce mortality. While the initial goal is to alleviate symptoms, drug therapy should be titrated as tolerated to target ranges for optimum clinical benefit.

A number of drugs are recommended in HF for symptom relief and improvement in outcome [30,31,32]:

- Improvement in symptoms can be achieved by digoxin, diuretics, beta blockers, angiotensin converting enzyme (ACE) inhibitors, and angiotensin II receptor blockers (ARBs).
- Prolongation of patient survival has been documented with beta blockers, ACE inhibitors, ARBs, hydralazine plus nitrate, and aldosterone antagonists.

It's recommended that following sequence of drugs in the typical patient, with allowance for variations depending upon clinical response[30,31]: