REVIEW

Management of Chronic Heart Failure: Biomarkers, Monitors, and Disease Management Programs

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ABSTRACT

Background: The management of patients with heart failure has been evolving given the complex nature of the disease and the increasing number of patients.

Findings: Biomarkers, and in particular the natriuretic peptides, have been studied to assist with diagnosis, chronic management, and prognosis in patients with heart failure. Several new biomarkers are emerging and may be used individually or in combination with the natriuretic peptides. The use of cardiac monitoring devices and disease management programs is being established to assist in the care of patients with chronic heart failure. Interventions using phone calls, telemedicine devices, intracardiac pressure monitors, and implantable cardioverter defibrillators have been investigated.

Conclusions: The combination of biomarkers, monitoring devices, and disease management programs shows promise for improving care in this challenging patient population.

Keywords: biomarkers, cardiac monitors, disease management programs, heart failure, natriuretic peptides

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INTRODUCTION

Heart failure is a growing pandemic affecting approximately 5.8 million people in the United States alone with 670,000 new cases diagnosed each year.[1] Even with the development of several new therapies, approximately 30% of patients with chronic heart failure are readmitted within 2 to 3 months.[2] Heart failure is a complex syndrome, and both diagnosis and treatment therefore can be challenging. Furthermore, although several evidence-based therapies exist, achieving an appropriate regimen and target doses of medications can be difficult, resulting in significant variability in treatment practices especially in older patients and patients with renal dysfunction.[3] Use of guideline-recommended therapies has been linked to an improvement in survival that only starts to plateau after 4 to 5 therapies have been initiated.[4] Biomarkers, intracardiac monitors, and disease management programs are 3 important tools that can improve the routine use of guideline-based therapies and ultimately lead to an improvement in clinical outcomes. The objective of this review is to provide a foundation on the natriuretic peptides, discuss some newer biomarkers, review some of the intracardiac monitors that have been developed, and finally to elucidate the data on disease management programs.

BIOMARKERS

The term *biomarker* was initially used in 1989 as a Medical Subject Heading (MeSH) term, and the definition was standardized in 2001 by the National Institutes of Health as "a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention."[5,6] Three criteria for a useful biomarker were previously defined as follows: 1) to provide accurate and repeated measurements with short turnaround times and reasonable cost, 2) to provide additional information beyond what can be ascertained from a thorough clinical assessment, and 3) to use results to aid in making clinical decisions.[7] This review focuses on established biomarkers, as well as some emerging biomarkers.

NATRIURETIC PEPTIDES

BNP was discovered in 1988, and was initially called brain natriuretic peptide as it was isolated from porcine

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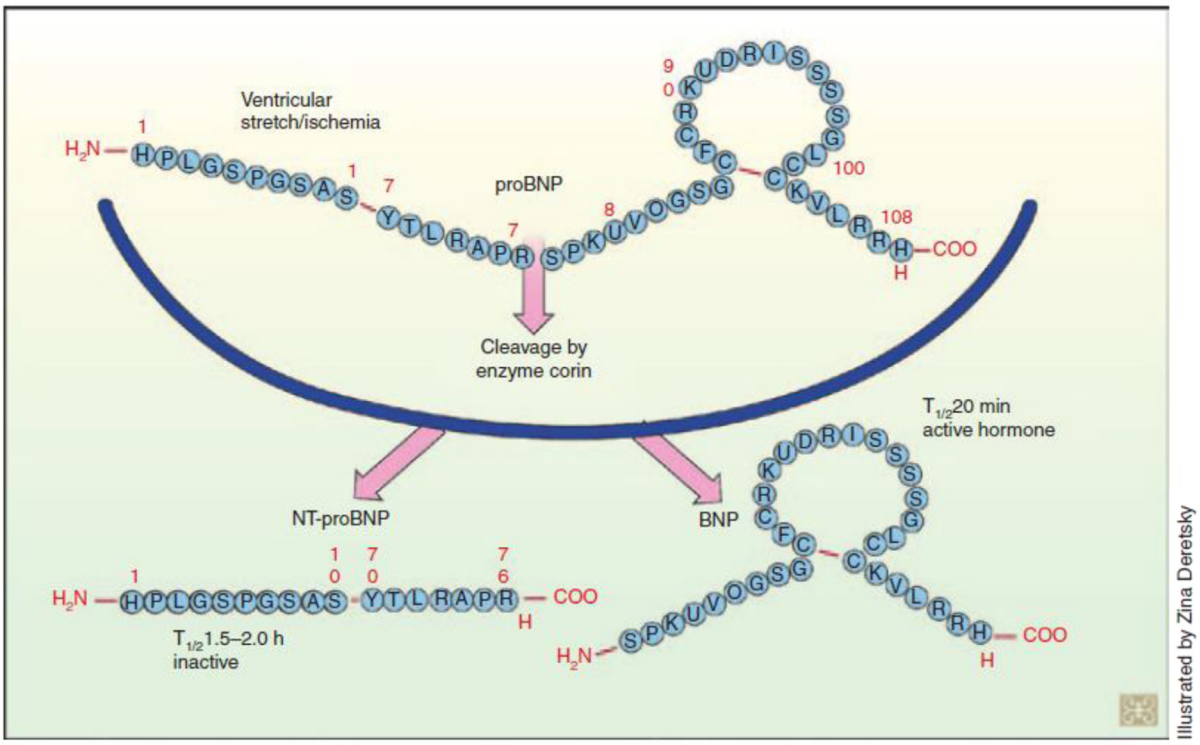

Figure 1. Structure of BNP and NT-pro BNP. Reproduced with permission from Motiwala SR et al.[9]

brain tissue. Once the primary source was found to be ventricular cardiac myocytes, the name was changed.[8] BNP is 32 amino acids in length and is one of 2 products of the cleavage of the prohormone BNP, with the second product being NT-proBNP (Fig. 1).[9] When BNP is in the bloodstream, it binds to NP receptor A, leading to activation of the cGMP-dependent cascade resulting in diuresis, vasodilation, inhibition of renin and aldosterone production, and inhibition of cardiac and vascular cell myocyte growth. It is ultimately removed from the bloodstream by either binding to the NP clearance receptor type C or degradation by neutral endopeptidase and renal filtration.[8] Although BNP and NT-proBNP are similar, they have important differences. For instance, NT-proBNP has a longer half-life than BNP, and the former also is more sensitive to renal function regarding its clearance.[8] Table 1 highlights other features of BNP and NT-proBNP.[10] In addition, both BNP and NT-proBNP values tend to increase with age, are higher in women, and are lower in obese individuals.[11,12]

The Breathing Not Properly study, a landmark clinical trial, established the importance of BNP in the diagnosis of acute heart failure and led to its widespread use. In this study, BNP was measured in 1586 patients presenting to the emergency department (ED) with acute dyspnea. The clinical diagnosis of heart failure was made by 2 independent cardiologists, who were blinded to the BNP results. The final diagnosis of dyspnea due to heart failure occurred in 47% of the patients. BNP levels were more accurate than any other physical exam or historical finding with an odds ratio of 29.60.[13] Similar findings were reported in the Pro-BNP Investigation of Dyspnea in the Emergency Department (PRIDE) study using NT-proBNP in 600 patients with cut-points differing with age (> or <50).[14] Finally, BNP measured in the ED for patients presenting with acute dyspnea also was found to decrease time to discharge and total hospital cost.[15]

Natriuretic peptides may be useful to guide heart failure management. Several small, randomized trials have compared a treatment strategy of optimizing medical therapy with the guidance of natriuretic peptides compared with usual care, but these trials have not been adequately powered to find a mortality benefit. A meta-analysis on the available data with a primary endpoint of all-cause mortality was previously performed.[16] Six

Table 1. Comparison of BNP and NT-proBNP

	BNP	NT-proBNP
Amino acids	32	76
Molecular weight (kDa)	3.5	8.5
Half-life (min)	20	60-120
Hormonal activity	Yes	No
Clearance	Renal, NPR-C	Renal
Removal by hemodialysis	~30%	~10%
Clinical range (pg/mL)	0-5000	0-35,000
Approved cutoff value for heart failure diagnosis in normal renal function	100	Age <50 y: 450 Age >50 y: 900

NPR-C, neutral endopeptidase clearance receptors.
Adapted from Iwanaga Y et al.[10]