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

Annals of Global Health 2014;80:46-54

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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No funding support was provided for this manuscript.

S.P. has clinical trial support from Thoratec, Inc and consulting fees from XDX, Inc. P.U.G. states that they have no conflicts of interest.

http://dx.doi.org/10.1016/j.aogh.2013.12.005

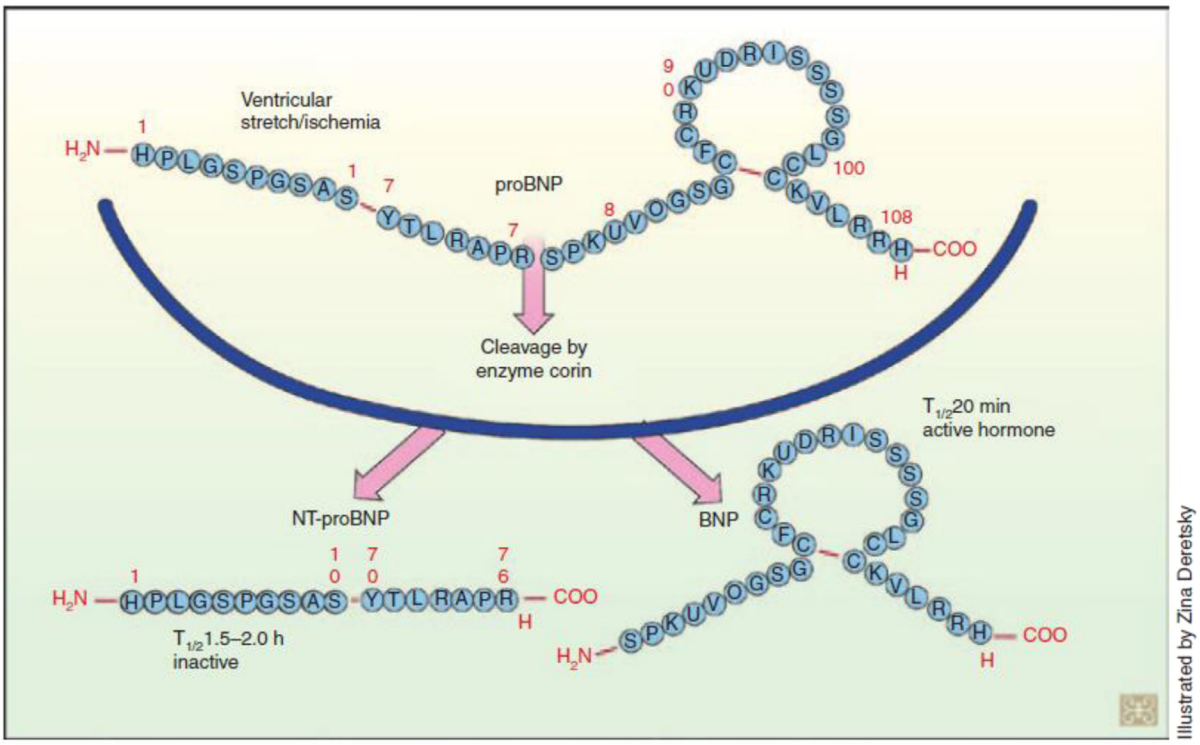

Figure 1. Structure of BNP and NT-pro BNP. Reproduced with permission from Motiwala SR et al.[9]

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]

Table 2. Study Design Overview for Included Trials

	Troughton[14]	STARBRITE[21]	STARS-BNP[15]	TIME-CHF[20]	BATTLESCARRED[22]	PRIMA[23]
N	69	137	220	499	364	345
Marker used	NT-proBNP	BNP	BNP	NT-proBNP	NT-proBNP	NT-proBNP
Randomization	Yes	Yes	Yes	Yes	Yes	Yes
Blinding	No	No	No	Single-blind	Double-blind	Single-blind
Strategy for intervention group	Target NT-proBNP level <200 pmol/L (1692 pg/mL)	Target BNP value chosen at hospital discharge, up-titrate therapy for values >2 × discharge BNP	Target BNP <100 pg/mL	Target NT-proBNP <400 pg/mL is age <75, NT-proBNP <800 pg/mL if age ≥75	Target NT-proBNP <150 pmol/L (1270 pg/mL)	NT-proBNP at discharge from hospital
Strategy for control group	HF score	Congestion score	Usual care, BNP measurement not allowed	Target symptoms <NYHA class II	Usual care or intensive clinical care based on HF score	Usual care
Length of follow-up	9.6 mo	3 mo	15 mo	18 mo	Minimum of 12 mo	Minimum of 12 mo
Primary endpoint	Death + cardiovascular hospitalization + outpatient HF event	Total days alive and out of hospital at 90 d	HF death + HF hospitalization	Death + all-cause hospitalization	All-cause mortality	Days alive and out of hospital
Patient population						
Age (y, mean)	70	61	66	77	76	72
Gender (% male)	76	70	64	66	62*	58
Ejection fraction (%, mean)	27	20	31	30	37	33
HF etiology (% ischemic)	74	44	52	58	71*	N/A

HF, heart failure; NYHA, New York Heart Association.
*Derived from design article[26] since data not presented in final abstract.
Reproduced with permission from Felker GM et al.[16]

prospective, randomized trials were included in this analysis with a total of 1,627 patients (Table 2).

The NT-proBNP-assisted Treatment to Lessen Serial Cardiac Readmissions and Death (BATTLESCARRED) and Can Pro-brain-natriuretic Peptide Guided Therapy of Heart Failure Improve Heart Failure Morbidity and Mortality? (PRIMA) trials included patients with both systolic and diastolic dysfunction. The Strategies for Tailoring Advanced Heart Failure Regimens in the Outpatient Setting (STARBRITE) trial included more younger patients with advanced disease, with the majority having nonischemic cardiomyopathy, whereas the Trial of Intensified vs Standard Medical Therapy in Elderly Patients With Congestive Heart Failure (TIME-CHF) and BATTLESCARRED had primarily older patients with a mean age >75. At baseline, use of evidence-based medications in all of the studies was relatively high, except for β-blockers in one study that was performed before the accepted use of β-blockers in heart failure.[16] Medical therapy was optimized in both the biomarker-guided group as well as in the control group in all of the studies, but was significantly greater in the former with regard to angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, β-blockers, and aldosterone antagonists. Diuretic therapy was unchanged in the intervention group of all of the studies. Of note, none of the studies reported significant differences in hypotension or worsened renal function in the intervention group compared with the control group, however, there was a trend toward increasing creatinine in the biomarker group of the PRIMA trial and a trend toward increase in hypotension in the biomarker arm of the TIME-CHF trial. Regarding all-cause mortality, the point estimate favored biomarker-guided therapy in all of the studies, with an estimated 30% improvement in survival, although these trials individually had mixed outcomes regarding their primary endpoints.[16] This may be due to the greater use of guideline-recommended therapies in the biomarker-guided therapy group. Another theme that emerged from the TIME-CHF and the BATTLESCARRED trials was the greater benefit of biomarker-guided therapy in patients under the age of 75.

The most recent study investigating NT-proBNP–guided care in patients with systolic dysfunction is the ProBNP Outpatient Tailored Chronic Heart Failure Therapy (PROTECT) trial. One hundred fifty-one patients were randomized to either standard heart failure care or standard care at a single, tertiary care center with a goal of reducing NT-proBNP levels to ≤1000 pg/mL. The primary endpoint of total cardiovascular events was significantly reduced in the biomarker-guided therapy group (58 vs 100 events), driven by a reduction in hospitalization and worsening heart failure; quality of life was improved in the biomarker group. Patients in the biomarker-guided arm were seen more frequently (median, 6 vs 5 times), which may have contributed to the difference in events.[17] A large, randomized trial is still needed to investigate a difference in survival, and this question will likely be answered by the Guiding Evidence Based Therapy Using Biomarker Intensified Treatment (GUIDE-IT) trial. This multicenter, randomized controlled trial will compare the use of a biomarker-guided treatment strategy with usual care in patients with left ventricular systolic dysfunction with a primary outcome of time to cardiovascular death or heart failure hospitalization (http://clinicaltrials.gov/ct2/show/NCT01685840).

Natriuretic peptide measurement can provide insight into prognosis in patients with chronic heart failure, and the prognostic value of both baseline values and changes in BNP and norepinephrine (NE) was examined in more than 4000 patients from the Valsartan Heart Failure (Val-HeFT) trial.[18] The incidence of all-cause mortality and first morbid event was significantly higher in patients with elevated baseline BNP and NE levels, and BNP showed a stronger association with morbidity and mortality than NE. Regarding changes in BNP and NE over 4 months, patients with the highest increase in BNP or NE had the highest mortality. Twelve-month data were similar. Therefore, both baseline values and trends in BNP are important predictors of morbidity and mortality.[18] A similar study was done with 1742 patients from the Val-HeFT trial to investigate changes in NT-proBNP over 4 months.[19] The highest all-cause mortality out of the 4 quartiles of patients was in the group with both initial and 4-month NT-proBNP values above the baseline value, as shown in Figure 2.[19]

In patients who are hospitalized with heart failure, those who had a <50% reduction in NT-proBNP had a 57% greater risk for readmission or death compared with those who had a >50% reduction.[20] BNP also has been demonstrated to be a good predictor of 1-year mortality or rehospitalization in patients aged ≥65 from the Organized Program To Initiate Lifesaving Treatment In Hospitalized Patients With Heart Failure (OPTIMIZE-HF) study.[21] The role of biomarker-guided therapy in the inpatient setting still needs to be clarified.[9]

Troponin

Cardiac troponins T and I have been used for the diagnosis of myocardial injury for the past 20 years, and detection is increasing with the development of highly sensitive assays. Cardiac troponin I was found in half of the patients with chronic heart failure, and the presence of troponin I was an independent predictor of death even after adjustment for other factors associated with poor prognosis.[22] Troponin T was also investigated in 136 ambulatory patients with heart failure who were followed for 14 months, and a level >0.02 ng/mL was found in 33 patients. The relative risks for death, hospitalization for heart failure, and myocardial infarction were all significantly higher in these patients.[23] The association of baseline troponin T levels, all-cause mortality, and heart failure hospitalization was studied in the patients with chronic heart failure from the Val-HeFT trial.[24] With a highly

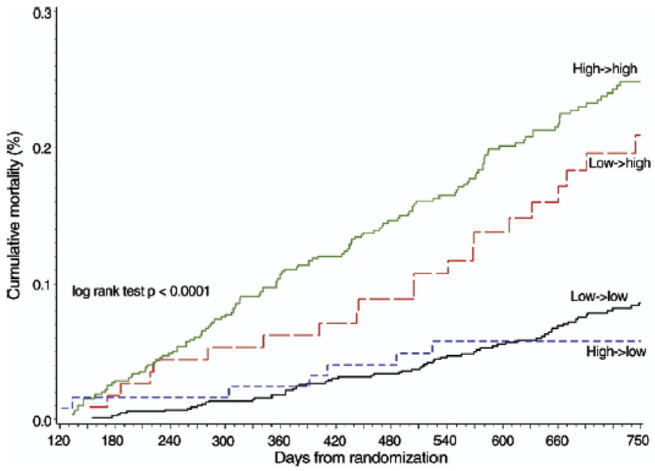

Figure 2. Kaplan-Meier curves for all-cause mortality in the 4 categories of patients. Reproduced with permission from Masson S et al.[19]

sensitive assay, they were able to detect levels of troponin T in 92% of these patients compared with 10% using the standard assay. After baseline variables including BNP levels were adjusted, the presence of elevated troponin T using the highly sensitive assay was associated with an increased risk for death.[24] The possible etiology of troponin elevation is ongoing cardiomyocyte injury in heart failure from myocardial strain or subendocardial ischemia. Apoptosis also may be contributing, but this has not been confirmed. Finally, troponin detected in the bloodstream also may reflect degradation products from proteolysis or turnover of myocardial contractile proteins, which may be secondary to myocardial stretch, oxidative stress, neurohormonal activation, or microvascular ischemia.[25] When combined with the use of BNP, improved risk stratification for these patients may be obtained.[26]

RENAL BIOMARKERS

The term *cardiorenal* syndrome has been used to describe the complex pathophysiology of coexistent heart failure and renal dysfunction. Renal dysfunction is prevalent in patients with heart failure and effects prognosis. In a review of 16 studies examining 80,098 patients with heart failure, 63% had at least mild renal dysfunction, and 20% had moderate to severe dysfunction. A 7% increase in mortality with every 10 mL per minute decrease in estimated glomerular filtration rate was seen.[27] Serum creatinine has been consistently associated with poor prognosis in patients with heart failure including prolonged hospital stay, increased readmissions, and increased 6-month mortality.[28]

Given the important link between these 2 organ systems, 2 biomarkers of renal injury cystatin C (CysC) and neutrophil gelatinase-associated lipocalin (NGAL) have been studied in the context of heart failure. CysC is produced at a constant rate by all nucleated cells and is freely filtered through the glomerulus, reabsorbed, and fully catabolized in the proximal tubule. CysC is unaffected by age, sex, or muscle mass.[10] Compared with creatinine, CysC is a stronger predictor of mortality and cardiovascular events in patients over the age of 65.[29] In acute heart failure, it has been demonstrated that combining CysC with NT-proBNP further improved risk stratification. In addition, in patients with normal creatinine, elevated levels of CysC also were associated with a significantly higher mortality at 1 year.[30]

NGAL is a secretory glycoprotein that was originally identified in mouse kidney cells and human neutrophil granules. NGAL expression in the renal tubules is rapidly induced by acute injury and is detected in the bloodstream soon after acute kidney injury.[10] In a small study of older patients with congestive heart failure, higher levels of NGAL were found to parallel the severity of heart failure symptoms with the highest levels seen in New York Heart Association (NYHA) class IV patients and were associated with a higher mortality.[31] In another study including 150 patients with chronic heart failure, NGAL levels correlated with clinical and neurohormonal deterioration as well as NT-proBNP levels.[32]

Along with creatinine, CysC, and NGAL, serum sodium has been studied extensively in heart failure and hyponatremia portends a poor prognosis.[33] In the OPTIMIZE-HF registry, the relationship between serum sodium on admission and clinical outcomes was analyzed in more than 40,000 patients from 259 hospitals. Patients with hyponatremia (Na < 135 mmol/L) on admission had significantly higher rates of in-hospital and follow up mortality and longer hospital lengths of stay. In addition, for each 3 mmol/L decrease in serum sodium <140 mmol/L at admission, the risk for in-hospital mortality and follow-up mortality increased by 19.5% and 10%, respectively.[34]

Markers of hypertrophy and fibrosis

Soluble ST2 (sST2) is a protein that is formed secondary to myocardial stretch and is associated with cardiac remodeling and fibrosis. sST2 has been found to have prognostic value in patients with acute decompensated

heart failure and the combination of sST2 and NT-proBNP is a superior predictor of death than either alone.[35] Galectin-3 is a marker of fibrosis and inflammation that is elevated in many diseases, including renal and heart failure. Given its lack of specificity, it is not employed for diagnosis of heart failure, but can assist in prognosis.[36] The role of galectin-3 in combination with the natriuretic peptides is being clarified, however, one study showed a loss of predictive value when combined with NT-pro BNP.[37]

MONITORS

Remote telemedical management of heart failure may be an option to further improve outcomes, with the mainstay of telemedicine being the early detection of disease deterioration leading to prompt intervention. Both noninvasive and invasive monitoring tools have been developed from simple portable imaging devices and digital assistants to intracardiac pressure monitoring and use of parameters from implantable cardiac defibrillators.[38] A review from 2011 showed the overall benefit achieved from telemonitoring with regard to all-cause mortality, all-cause hospital admission, and hospital admission related to chronic heart failure.[38] Since this review was released, 2 other trials have been published with negative results. The Telemonitoring to Improve Heart Failure Outcomes (Tele-HF) and Telemedical Interventional Monitoring in Heart Failure (TIM-HF) trials both employed noninvasive monitoring approaches. Tele-HF randomly assigned more than 1600 patients who were recently admitted for heart failure either to telemonitoring with a phone-based interactive voice-response system to allow for daily evaluation of symptoms and weight or to usual care. No significant difference was noted in the primary endpoint of readmission or death from any cause at 180 days.[39] The TIM-HF study also randomized chronic heart failure patients with left ventricular ejection fraction (LVEF) <35% and NYHA class II-III symptoms to usual care or telemonitoring using a wireless Bluetooth device and personal digital assistant that measured 3-lead electrocardiography, blood pressure, and weight, as well as medical telephone support. No significant difference was seen in the primary outcome of mortality between the 2 groups over a mean follow-up of 21.5 months.[40]

Invasive monitoring also has been studied. The Chronicle Offers Management to Patients with Advanced Signs and Symptoms of Heart Failure (COMPASS-HF) study used a device to measure right ventricular pressure in 274 patients with NYHA class III-IV symptoms who were receiving optimal medical therapy. The patients were randomized to device-guided management or the control group. The device was found to be safe, but no significant difference was detected in the number of heart failure-related events.[41] The CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Patients (CHAMPION) study enrolled patients with NYHA class III heart failure (regardless of LVEF, however ~80% had LVEF <40%) and previous hospitalization for heart failure and randomized them to usual care or a wireless implantable hemodynamic monitoring system (W-IHM). The W-IHM involved the implantation of a pulmonary artery pressure sensor and patients in the intervention group had daily measurement of pulmonary artery pressures. All patients were on optimal medications at time of W-IHM implantation, and medications were titrated based on pulmonary artery pressure readings as well as patient symptoms. Patients in the intervention group experienced a 39% reduction in heart failure admissions over 15 months and also benefitted from a greater number of medication changes compared with the usual-care group.[42] However, the W-IHM was not approved by the FDA secondary to the difference in medical therapy between the 2 groups.[43] A new left atrial pressure monitor called the HeartPod has been developed and currently is being investigated in the Left Atrial Pressure Monitoring to Optimize Heart Failure Therapy (LAPTOP HF) trial.[43] Finally, the Diagnostic Outcome in Heart Failure (DOT-HF) trial studied the use of diagnostic features from implantable cardiac defibrillators and cardiac resynchronization therapy such as intrathoracic impedance (using OptiVol) to assist in management of 355 patients with chronic heart failure. Compared with the control arm, patients in the intervention group did not experience a significant reduction in the composite primary endpoint of all-cause mortality and heart failure hospitalization.[44] This trial was terminated early due to enrollment difficulties, and the Optimization of Heart Failure Management using OptiVol Fluid Status Monitoring and CareLink (OptiLink-HF) trial is currently under way to determine if OptiVol monitoring with an automatic alert can reduce mortality and hospitalization.[43]

DISEASE MANAGEMENT STRATEGIES

The definition of *disease management program* is highly variable, and although many definitions have been proposed, a universal definition does not exist. For this reason in 2006, the American Heart Association organized the Disease Management Taxonomy Writing Group.[45] The taxonomy defined the various components of a disease management program, such as patient population, intervention, communication method, and outcome measures and was intended to assist in classification and understanding of the structure of these various programs, which could then subsequently allow for proper investigation of their effectiveness (Fig. 3).[45]

The effectiveness of comprehensive heart failure management programs was previously studied in nonrandomized trials, but showed a reduction in rehospitalization, health care costs, improved functional status and symptoms, and better quality of life compared with

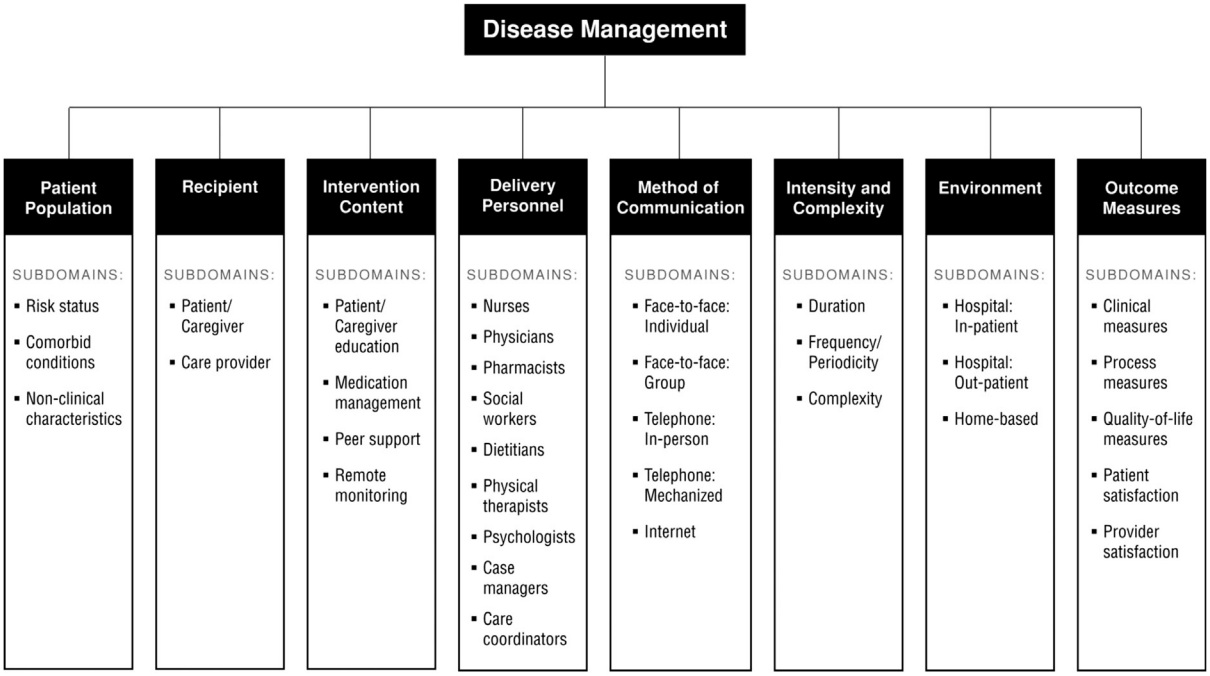

Figure 3. Disease Management Taxonomy. Reproduced with permission from Krumholz et al.[45]

patients receiving standard care.[46,47] The first randomized trial was published in 1995 from a single center and used a nurse-directed multidisciplinary disease management intervention to address risk factors for readmission including dietary and medication noncompliance, failure to recognize exacerbations of heart failure, and inappropriate medication prescribing. They found a 56% reduction in 90-day readmissions for heart failure and a reduction in costs of $460 per patient.[48] One systematic review that included 29 trials with 5039 patients confirmed that management strategies including follow-up by a multidisciplinary team (either in a clinic or nonclinic setting) reduced mortality, heart failure hospitalizations, and all-cause hospitalizations. Programs that focused on self-care reduced heart failure hospitalizations, but did not affect mortality. Programs that used telephone contact and recommended primary care attention in the event of deterioration also reduced heart failure hospitalizations, but did not have an effect on mortality or all-cause hospitalization. Eighteen of the reviewed trials studied cost, and 15 of these showed a reduction in costs with multidisciplinary care.[49]

As noted previously, phone-based interventions were found to have variable results. In a trial with 1069 patients who were randomized to telephone-based disease management or usual care, patients were enrolled for 18 months and all patients were assessed every 6 months by history, physical, 6-minute walk test, and serum chemistry. Patients in the disease management group were found to have a reduction in mortality and an improvement in NYHA class, however, there was no significant change in 6-minute walk data and total health care utilization, including hospitalization.[50] Another phone-based intervention was studied in the Randomized Trial of Phone Intervention in Chronic Heart Failure (DIAL), which included 1518 outpatients with stable chronic heart failure who were randomized to routine care or an intervention that included an explanatory booklet and periodic telephone contact by a specialized nurse over 1 year. The intervention resulted in a lower rate of death or hospitalization compared with the control group, driven by a decrease in rehospitalization.[51] Follow-up of these patients at 1 and 3 years showed the benefit persisted and was again mostly due to a reduction in hospital admissions.[52]

Not all of the published studies have had positive outcomes. The Coordinating Study Evaluating Outcomes of Advising and Counseling in Heart Failure (COACH) trial was a multicenter, randomized trial that evaluated 1023 patients who were enrolled after a heart failure hospitalization and were assigned to a control group (follow-up by a cardiologist), intervention with basic support from a specialized nurse, or intervention with intensive support from a specialized nurse. The basic-support group included additional visits with a heart failure nurse at the clinic, and the intensive group consisted of additional visits with the nurse as well as phone calls, home visits, and multidisciplinary advice sessions with a physical therapist, social worker, and dietitian. The patients were followed for 18 months and the results showed no difference in the primary endpoint of death and heart failure hospitalization.[53]

The most recent meta-analysis from the Cochrane group included 25 randomized trials with 5942 patients and investigated types of disease management strategies

after hospital discharge. The interventions were divided into 3 groups: 1) case management interventions including telephone and home visits, 2) clinic interventions, and 3) multidisciplinary interventions using a team approach. Case management interventions demonstrated a reduction in all-cause mortality after 1 year of follow-up and reduced heart failure readmissions at 6 months. Clinic interventions did not have a significant effect on mortality or readmissions. The multidisciplinary approach reduced heart failure and all-cause readmissions but did not affect mortality; however, only 2 studies investigated this modality.[54]

The variable results of these trials are possibly secondary to differences in program design, but raise doubt as to whether these results can be generalized. Despite published recommendations to guide the structure of a disease management program, it remains difficult to predict efficacy. In addition, many of the details of the intervention are not provided, which further limits reproducibility. The most recent randomized trial of disease management programs, HeartNetCare-HF (HNC), used a well-defined nurse-coordinated disease management program, which incorporated care from nurses, general practitioners, cardiologists, and caregiver training and used standardized questions and written intervention templates.[55] Seven hundred fifteen patients were randomized to either usual care or to HNC before discharge. The patients in the usual-care group underwent standard postdischarge planning with a follow-up appointment 1 to 2 weeks after discharge with either a general practitioner or cardiologist. The HNC group patients were given scales and blood pressure monitors and met with the specialty nurse before discharge. There was no difference in the number of patients who reached the combined primary endpoint of time to death or rehospitalization; however, mortality was reduced in the HNC group. HNC patients also improved more with regard to NYHA class, drug adherence, and physical well-being.[55] This trial provided well-defined interventions, measured health care utilization, and had a well-defined study population, which will ultimately assist in further study of disease management programs.

CONCLUSION

In summary, biomarkers are valuable tools that can assist in diagnosis, management, and determination of prognosis for patients with heart failure. Although the natriuretic peptides are well established and widely used, many new biomarkers are under investigation and may further assist with the care of patients with chronic heart failure. More studies are needed to elucidate the complex disease mechanisms underlying these biomarkers, which would allow this enhanced understanding to then be combined with the technology of cardiac monitoring devices and ultimately lead to new disease management strategies to improve the use of guideline-based therapies and outcomes.

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