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2013 ACCF/AHA Guidelines for the Management of Heart Failure: Expanded Use of Natriuretic Peptides and Aldosterone Antagonists

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Heart failure (HF) is a complex clinical syndrome characterized by impaired cardiac function that results in inadequate systemic perfusion that fails to meet the body's metabolic demands. [1] It may result from disorders of the myocardium, heart valves, or great vessels, but the most common cause of HF is due to impaired left ventricular function.[1, 2] There is a wide spectrum of left ventricular functional abnormalities, ranging from patients with normal left ventricular size and preserved ejection fraction (EF) to patients with severe dilatation and reduced ejection fraction. [2] Ejection fraction determines and is related to prognosis and response to therapies.[2] The current American College of Cardiology Foundation/American Heart Association (ACCF/AHA) guideline defines HF as either HF with reduced EF or HF with preserved EF. Reduced EF is defined as ≤ 40 % and preserved EF as ≥ 50%, as well as borderline EF (41 to 49%) and improved (those with an EF > 40% who previously had reduced EF).[2] The benefits of , disease-modifying therapies have only been demonstrated in heart failure with reduced EF.

Heart failure results in significant morbidity, mortality, and economic burden. It is the primary diagnosis in over one million hospitalizations annually.[2] Additionally, patients hospitalized for HF carry a high risk of rehospitalizations, with a one month readmission rate of 25%.[3] Absolute mortality rates remain high, about 50% within five years of diagnosis.[2] One population cohort study with five year mortality data showed a survival rate of 20% for stage D HF.[4] Total cost of care in the United States is over $30 billion annually, with approximately half spent on hospitalizations. This includes the cost of health care services, medications, and lost productivity.[5] These negative consequences highlight the need for evidence-based guidance on appropriate and effective treatment and management of HF.

Evidence–based guidelines have been jointly published by the ACCF and the AHA since 1995. For the past few years, the 2009 Focused Update highlighted standard care for HF. In 2013, a new set of guidelines were published including new information on the use of natriuretic peptides and aldosterone receptor antagonists. The purpose of this article is to discuss these updates, focusing on the above topics, and reviewing the evidence behind these changes.

Expanded Use of Natriuretic Peptides

Brain natriuretic peptide (BNP) is one of a group of human natriuretic peptides that share a common 17-peptide ring structure.[6] Before activation, BNP is stored as a 108–amino acid polypeptide precursor known as proBNP inside secretory granules in both the ventricles and the atria.[6]

Inside This Issue:

ProBNP is secreted due to volume overload and myocardial stretch. It is then cleaved into the 76-peptide, inert N-terminal fragment NT-proBNP and the 32-peptide, active hormone BNP.[2] The two fragments are secreted into the plasma in equal molar concentrations.[6] High ventricular filling pressure stimulates the release of BNP, which has diuretic, natriuretic, and antihypertensive effects, due to its inhibition of the renin-angiotensin-aldosterone system, as well as effects on systemic and renal sympathetic nervous activity.[2, 6] Natriuretic peptide receptors and plasma endopeptidases clear BNP from the circulation, resulting in a short plasma half-life of about 20 minutes. However, according to available data, no receptor-mediated clearance of NT-proBNP occurs, leading to a longer half-life of 60-120 minutes.[6] Therefore, NT-proBNP plasma concentrations tend to be up to 5 times higher than BNP concentrations.[6]

BNP and NT-proBNP concentrations improve with the treatment of chronic HF, with concentrations lowering over time, which correlates with improved clinical outcomes.[2] Therefore, the current guidelines recommend measuring BNP or NT-proBNP concentrations to assist in establishing prognosis or disease severity in patients with chronic HF.[2] Berger et al studied 452 ambulatory patients with a left ventricular EF < 35% in order to test the value of BNP concentrations for prediction of sudden death.[9] All patients received an ACE inhibitor, beta blocker, diuretic and digitalis, which were up-titrated stepwise to an individual maximum dose. Patients refractory to medical treatment, with documented low output, and an absence of contraindications, were considered for heart transplantation. In case of death, the underlying cause was obtained from the medical chart or from relatives. Deaths were classified as sudden death, pump failure, or resulting from other causes. For prediction of sudden death, only survivors without heart transplantation or a mechanical assist device and patients who died suddenly were analyzed. Over a 5-54 month follow-up period, 298 patients survived without heart transplantation or a mechanical assist device, 89 patients died, and 65 patients underwent transplantation. Cause of death was sudden in 44 patients (49%), pump failure in 31 patients (35%) and other in 14 patients (16%). Univariate risk factors of sudden death were log BNP (P=0.0006), log NT-atrial natriuretic peptide (P=0.003), EF (P=0.005), log NT-proBNP (P=0.006), systolic blood pressure (P=0.01), big endothelin (P=0.03), and NYHA class (P=0.04). Big endothelin, a 38 amino acid peptide, is the precursor of endothelin, a potent vasonconstrictor.[23] In the multivariate model, log BNP level was the only independent predictor of sudden death (P=0.0006). Using a cutoff point of log BNP < 2.11 (130 pg/mL), Kaplan-Meier sudden death–free survival rates were significantly higher in patients below (99%) compared with those patients above (81%) the cutoff value (P=0.0001). The authors concluded that their findings suggest that measurement of plasma BNP allows the identification of patients with a higher risk of sudden death; creating a simple method of identifying patients that would likely benefit from implantable cardioverter-defibrillators (ICD).[9] Despite its publication in 2002, this evidence describing the use of natriuretic peptides as a monitoring parameter in ambulatory patients with chronic HF was first cited in the current guideline.

Not all studies testing the prognostic value of natriuretic peptides result in positive findings. Mckie et al conducted a study with the objective of determining the prognostic value of plasma NT-proBNP for death and cardiovascular (CV) events among patients without risk factors for HF or echocardiographic abnormalities (Table 1). Previous studies[10, 11] had shown that NT-proBNP had prognostic value for CV events in the general population, in the absence of HF. The investigators utilized the clinical and echocardiographic data from the Prevalence of Asymptomatic Ventricular Dysfunction study to identify a healthy normal cohort (n=703) and a stage A/B HF cohort (n=1288). Patients with a history of stage C or D HF were excluded. Age, systolic blood pressure, left atrial volume, and left ventricular mass were significantly lower in the healthy normal subgroup compared with the stage A/B HF subgroup. Female sex and increasing age were both associated with higher than 80th percentile values of NT-proBNP. Patients were followed for death, HF, cerebrovascular accident (CVA), and myocardial infarction (MI) with median follow up of 9.1, 8.7, 8.8 and 8.9 years, respectively. Survival and event

-free rates were estimated using the Kaplan-Meier method. The association of outcomes with clinical and echocardiographic variables and NT-proBNP levels was assessed using Cox proportional hazards regression. In the healthy normal cohort, there were 19 all-cause deaths, 13 HF events, 38 CVA, and 14 MI. No increased risk of any outcome were detected among patients with NT-proBNP levels greater than the age and sex specific 80th percentile. In contrast, there were 170 all-cause deaths, 156 HF events, 236 CVA, and 133 MI in the stage A/B HF cohort. Plasma NT-proBNP values greater than age and sex specific 80th percentiles were associated with an increased risk of all four outcomes ($p<0.001$ for all), even after adjustment for clinical risk factors and structural cardiac abnormalities. The authors concluded that the data does not support the use of NT-proBNP as a cardiovascular biomarker in healthy normal subjects.[12] This has important implications for the use of natriuretic peptides in early detection and primary prevention of CV disease. The investigators conclude that only in the presence of risk factors and/or echocardiographic abnormalities does NT-proBNP hold prognostic value.[12]

New evidence has led the ACCF and AHA to suggest the use of BNP or NT-proBNP guided therapy in order to achieve optimal dosing of guideline directed medical therapy (GDMT) in select euvolemic patients followed by a well-structured HF management program.[2] GDMT is a new term coined by the ACCF/AHA Task Force for denoting optimal medical therapy consisting primarily of Class I recommendations.[2] One of the studies considered in the formulation and classification of this recommendation is the Trial of Intensified vs Standard Medical Therapy in Elderly Patients With Congestive Heart Failure (TIME-CHF). Pfisterer et al conducted a multicenter, blinded, randomized controlled trial (RCT) of 499 patients with the aim of comparing an intensified NT-proBNP guided strategy with the standard symptom guided therapy and to assess whether the NT-proBNP guided therapy was more effective in patients aged $\geq$ 75 years or patients aged 60 – 74 years.[13] Patients were randomized into one of the two treatment strategies; both groups were then stratified per protocol into the two age groups of 60 – 74 years and 75 years or older. The intervention was defined as titrating treatments to reduce symptoms to NYHA class of II or less (symptom guided) or achieving a NT-proBNP concentrations of 2 times or less the upper limit of normal and symptoms to NYHA class of II or less (BNP guided). The primary outcomes were 18 month survival free of all-cause hospitalizations and quality of life. Of note, doses of medications with proven efficacy were titrated to a significantly ($p<0.001$) greater extent in the NT-proBNP guided group in both age groups. Additionally, aldosterone antagonists were given more frequently in the NT-proBNP guided group (72%) versus the symptom guided group (63%; $p=0.05$). Results showed that therapy guided by either modality (NT-proBNP or symptom) resulted in similar rates of survival free of all-cause hospitalizations (41% vs 40%; hazard ratio [HR], 0.91 [95% CI, 0.72-1.14]; $p=0.39$). Quality of life metrics improved similarly in both groups, improving significantly from baseline to month 12 ($p<0.001$) and remaining unchanged from month 12 to month 18. Survival free of hospitalization for HF, a secondary end point, was higher among the NT-proBNP guided group than the symptom guided group (72% vs 62%; HR, 0.68 [95% CI, 0.5-0.92]; $p=0.01$). NT-proBNP guided therapy improved hospitalization-free survival, overall survival, and hospitalization due to heart failure free survival in patients aged 60 to 74 years, but did not in

Table 1 | Clinical Risk Factors for Heart Failure and Echocardiographic Abnormalities[12]

Clinical Risk Factors	Echocardiographic Abnormalities
Coronary artery disease	Left ventricular hypertrophy
Hypertension	Left atrial enlargement
Diabetes mellitus	Regional wall motion abnormalities
Prior MI	Valvular dysfunction
Chronic obstructive pulmonary disease	EF < 50%
History of CV drug use	Diastolic dysfunction
Peripheral vascular disease	
Hyperlipidemia	
Absence of normal sinus rhythm	

those aged 75 years or older who, in addition to a lack of benefit, reported greater adverse effects (10.5% vs 5.5%; p=0.12). The investigators concluded that NT-proBNP guided therapy did not significantly improve overall clinical outcomes or quality of life compared to symptom guided therapy and that the value of BNP levels to guide therapy seems limited despite their importance in diagnosis and prognosis.[13]

A meta-analysis was conducted by Porapakkham et al reviewing the topic of BNP guided HF therapy.[14] Results showed that there was a significantly lower risk of all-cause mortality (relative risk [RR], 0.76; 95% CI, 0.63 – 0.91; p=0.003) in the BNP guided therapy group compared with the standard care group. In patients below the age of 75 years, all-cause mortality was also significantly lower in the BNP guided group (RR, 0.52; 95% CI, 0.33-0.82; p=0.005). However, in patients 75 years or older, there was no reduction in mortality seen with BNP guided treatment (RR, 0.94; 95% CI, 0.71-1.25; p=0.7). Additionally, the risk of all-cause hospitalizations and survival free of any hospitalization was not significantly different between the BNP guided and standard care groups (RR, 0.82; 95% CI, 0.64-1.05; p=0.12 & RR, 1.07; 95% CI, 0.85-1.34; p=0.58). The additional percentage of patients attaining target doses of ACE inhibitors and beta-blockers during the course of the trials averaged 21% and 22% in the BNP guided group and 11.7% and 12.5% in the standard care group. However, aggressive reduction in BNP levels by titration of these medications could potentially result in worsening of outcomes due to hypotension and worsening renal failure, especially in the elderly. The conclusion of the meta-analysis was that BNP guided treatment, compared to standard clinical care, may significantly lower all-cause mortality in patients with chronic HF younger than 75 years, but not in those 75 years and older. A limitation of this meta-analysis is that they were not able to review key clinical endpoints such as hospitalization for HF, as reported by the TIME-CHF study above.[14]

New evidence has emerged that was not included in the development of the current guideline. Savarese et al conducted a meta-analysis resulting in the selection of 12 trials enrolling a total of 2686 patients.[15] Inclusion criteria for a study were as follows: comparison of BNP or NT-proBNP guided therapy compared to a control group in chronic HF patients; randomized protocol; and reporting of clinical end points. Results showed that natriuretic peptide (either BNP or NT-proBNP) guided therapy significantly reduced all-cause mortality (odds ratio [OR] 0.738; 95% CI, 0.596-0.913; p=0.005) and HF related hospitalization (OR 0.554; CI 0.399-0.769; p<0.001), but not all-cause hospitalization (OR 0.803; CI 0.629-1.024; p=0.077). Separate analysis on patients < 75 years or ≥ 75 years was performed, resulting in a significant reduction in all-cause mortality and HF related hospitalization in patients younger than 75 years (OR 0.449; 95% CI 0.207-0.973; p=0.043), but not patients 75 years or older (OR 0.8; 95% CI 0.423-1.513; p=0.493). When assessed individually, NT-proBNP guided therapy significantly reduced all-cause mortality (p=0.007) and HF related hospitalizations (p=0.003), but not all-cause hospitalizations (p=0.438). In contrast, BNP guided therapy did not significantly reduce any of the above clinical outcomes (p=0.371; p=0.142; and p=0.077). However, the separate analysis for BNP- and NT-proBNP-guided therapy needs to be interpreted carefully as no trial was designed to compare BNP versus NT-proBNP guided treatment. Additionally, patients enrolled in the BNP guided therapy studies had lower EF and more aggressive treatment, possibly indicating a sicker population. The authors concluded that natriuretic (particularly NT-proBNP) guided treatment in patients with chronic HF and younger than 75 years is associated with significant reduction of mortality and HF related hospitalization.[15]

While natriuretic peptides are useful to support a diagnosis or exclusion of HF, especially when the etiology of dyspnea is unclear, the use of BNP or NT-proBNP guided management is still controversial due to conflicting evidence. Many of the trials reporting on this topic are small and underpowered, but the existence of comprehensive meta-analyses provides substantial, but not definitive, evidence of the mortality and morbidity benefits of these approaches, especially in patients under 75 years.[2] Select studies on the use of natriuretic peptides in HF are summarized in Table 2.

Table 2 | Selected Studies on the Use of Natriuretic Peptides in the Setting of Heart Failure

Reference & Design	Patients	Study Arms	Objectives & Outcomes	Results
Berger,[9] 2002 Prospective Cohort	N = 452 Ambulatory Age 54 ± 10 years EF 20 ± 7 %	Survivors : n = 293 Patients w/ SD: n = 44 Patients w/ pump failure: n = 31 Mean ± SD observation period: 592 ± 387 days	Use of BNP levels for prediction of SD in ambulatory patients UV & MV predictors of SD	UV risk factors of sudden death ($p < 0.05$): Log BNP Log NT-ANP EF Log BT-proBNP SBP Big endothelin NYHA class MV model: Log BNP Using BNP < 130 pg/ml as cutoff, KM survival rates higher in patients below cutoff (99%) compared to above (81%) ($p=0.0001$)
McKie,[12] 2010 Community-based Cohort	N = 1991 Age, SBP, LA volume, & LV mass significantly lower in healthy group vs stage A/B HF group Data obtained from PAVD study from Olmsted County, MN	Healthy normal: no clinical risk factors for HF or echocardiographic abnormalities Stage A/B HF: 1 or more risk factor or abnormality Mean 8.9 years of mortality follow up	Prognostic value of NT-proBNP for death % CV events among healthy normal patients ACM, HF, MI, CVA Analysis of NT-proBNP	NT-proBNP not shown to be predictive of death or CV events in healthy normal patients NT-proBNP values > age/sex-specific 80th percentiles associated with increased risk of death, HF, CVA, & MI ($p < 0.001$ for all)
Pfisterer,[13] 2009 Multi-Center, Blinded, RCT	N = 499 Age > 60 years EF ≤ 45% NT-proBNP ≥ 2 x upper limit of normal	BNP-guided therapy Symptom guided therapy 18 month follow up	Compare NT-proBNP guided vs symptom guided therapy Primary outcomes: 18 month survival free of ACH & QoL Secondary outcomes: specific causes of death or hospitalization; effects of baseline characteristics on outcome; and tolerability of medication	Survival free of ACH NT-proBNP 41% Symptom 40% HR: 0.91, 95% CI 0.72-1.14 QoL metrics improved similarly amongst both groups Survival free of hospitalization of HF NT-proBNP 72% Symptom 62% HR: 0.68, 95% CI, 0.5-0.92 NT-proBNP guided therapy improved outcomes in patients 60-74 years, but not ≥ 75 years

ACE-I: ACE Inhibitor; ACH: All-Cause Hospitalizations; ACM: All-Cause Mortality; CI: Confidence Interval; CKD: Chronic Kidney Disease; CV: Cardiovascular; CVA: Cerebrovascular Accident; EF: Ejection Fraction; HF: Heart Failure; HR: Hazard Ratio; HTN: Hypertension; KM: Kaplan Meier; LA: Left Atrial; LV: Left Ventricular; LVH: Left Ventricular Hypertrophy; LVSD: Left Ventricular Systolic Dysfunction; MI: Myocardial Infarction; MRI: Magnetic Resonance Imaging; MV: Multivariate; NPGT: Natriuretic Peptide Guided Therapy; NT-ANP: N-terminal Atrial Natriuretic Peptide; NYHA: New York Heart Association; OR: Odds Ratio; PAVD: Prevalence of Asymptomatic Ventricular Dysfunction; P: Prospective; QoL: Quality of Life; RCT: Randomized Controlled Trial; RR: Relative Risk; SBP: Systolic Blood Pressure; SCr: Serum Creatinine; SD: Sudden Death; SHF: Systolic Heart Failure; UV: Univariate

Table 2 Continued | Selected Studies on the Use of Natriuretic Peptides in the Setting of Heart Failure

Reference & Design	Patients	Study Arms	Objectives & Outcomes	Results
Porapakkham,[14] 2010 Meta-Analysis	N = 1726	8 RCTs BNP-guided therapy Usual clinical care Inclusion criteria: > 20 patients & comparing BNP-guided therapy vs usual clinical care in outpatient setting.	Examine overall effect of BNP-guided therapy on CV outcomes in patients w/ HF Outcomes assessed: -ACM -ACH -Survival free of any hospitalization, -Mortality in patients < 75 years and ≥ 75 years -Additional % of patients w/ adjusted HF medications	ACM: RR 0.76, 95% CI 0.63-0.91 ACM in patients < 75 years: RR 0.52, 95% CI 0.33-0.82 ACM in patients ≥ 75 years: RR 0.94, 95% CI 0.71-1.25 Risk of ACH: RR 0.82, 95% CI 0.64-1.05 Survival free of any hospitalization: RR 1.07, 95% CI 0.85-1.34 Additional % of patients achieving target doses of ACE-I and β-blocker: BNP- 21% & 22% Control – 11.7% & 12.5%
Savarese,[15] 2013 Meta-Analysis	N = 2686	12 trials BNP-guided therapy Control group Inclusion criteria: -Comparison of BNP/NT-proBNP guided therapy vs control group -Randomized -Reporting ACM & all-cause or HF hospitalization	Evaluate whether NPGT improves mortality & hospitalization rate compared to standard of care ACM ACH HF-related hospitalization	NPGT reduced ACM (OR 0.738, 95% CI 0.596-0.913) & HF-related hospitalization (OR 0.554, 95% 0.399-0.769) but not ACH (OR 0.803, 95% CI 0.629-1.024) Assessed separately, NT-proBNP guided therapy reduced ACM (OR 0.717, 95% CI 0.563-0.914) & HF-related hospitalizations (OR 0.531, 95% CI 0.347-0.811) but not ACH (OR 0.779, 95% CI 0.414-1.465) BNP guided therapy did not significantly reduce any clinical outcome
Jafri,[16] 2013 Cross Sectional study	N = 190 Age 58 ± 15 years 67.4% males eGFR < 60 ml/min Exclusion criteria: dialysis, obesity (BMI >30 kg/m^2)	w/ SHF: 95 w/out SHF: 95 Conducted over 10 months	Evaluate the effects of impaired renal function on BNP and determine cutoffs predictable of SHF	SHF patients: mean BNP concentrations increased 2.5x from CKD stage 3 to 5; mean NT-proBNP concentrations increased 4x from CKD stage 3 to 5 nonSHF patients: mean BNP concentrations increased 1.5x from CKD stage 3 to 5; mean NT-proBNP concentrations increased 3x from CKD stage 3 – 5 Optimal BNP cutoff of SHF diagnosis for CKD group: 300 pg/ml NT-proBNP cutoff: 4502 pg/ml

Table 2 Continued | Selected Studies on the Use of Natriuretic Peptides in the Setting of Heart Failure

Reference & Design	Patients	Study Arms	Objectives & Outcomes	Results
De Lemos,[17] 2008 Population-based Cohort	N = 2429 Age 44 ± 9 years 56% females 48% black Exclusion criteria: Self-reported history of HF, prior MI, valvular abnormalities, SCr > 2 mg/dl	Men w/ or w/ out LVH or LVSD Women w/ or w/out LVH or LVSD	Evaluation of the screening performance of BNP and NT-proBNP for LVSD or LVH	BNP & NT-proBNP associated with MRI-defined LVH & LVSD among men & women (p<0.0001 for both) In the general population, neither test discriminated well for LVH or LVSD (AUROC <0.7) Among men age ≥ 50 years or with HTN: NT-proBNP AUROC (0.73-0.79) BNP AUROC (0.63-0.69) (P < 0.05) Patients w/ isolated NT-proBNP elevation had worse renal function & more LVH compared to isolated BNP elevation (p<0.05)
Felker,[18] 2009 Meta-Analysis	N = 1627	6 RCTs Inclusion criteria: Prospective, RCT of patients w/ HF, biomarker guided therapy vs control, report ACM	Determine whether NPGT improved mortality in chronic HF ACM	Biomarker-guided therapy reduced ACM compared to control (HR 0.69, 95% CI 0.55-0.86) No evidence of heterogeneity between studies (p=0.42)
Januzzi,[24] 2011 Single-Center, Blinded, RCT	N = 151 Age (mean) 63 years 84.7 % male	NT-proBNP-guided therapy Standard of Care Mean follow up of 10 ± 3 months	Primary endpoint: Total CV events between groups Secondary endpoints: NT-proBNP effect on QoL & cardiac structure Intent to treat used	Total CV events: NT-proBNP: 58 SC: 100 (p=0.009) KM curves time to first event favored NT-proBNP (p=0.03) Elderly patients benefited similarly to younger patients NT-proBNP group: greater improvement in QoL & LV end-systolic & -diastolic volume indexes

Expanded Use of Aldosterone Antagonism

Since the landmark RALES trial showed that the use of spironolactone in patients with chronic HF and left ventricular EF (LVEF) < 35% resulted in a 30% reduction in all-cause mortality as well as a reduced risk of sudden cardiac death and hospitalizations,[19] use of aldosterone antagonists for HF has been a research target. Originally recommended in patients with moderately severe or severe symptoms of HF and reduced LVEF,[7] aldosterone antagonists should now be considered in all patients with NYHA class II-IV and with LVEF ≤ 35%, unless contraindicated.[2] Additionally, following an acute MI, patients with LVEF ≤ 40%, those who develop symptoms of HF, or who have a history of diabetes, should be considered for the initiation of an aldosterone antagonist.[2] Regarding agent selection, the difference is in the selectivity of aldosterone receptor antagonism, not the effectiveness of blocking mineralcorticoid activity.[2] Use of spironolactone, a nonselective antagonist, has been associated with an increased incidence (10%) of gynecomastia or breast pain.[19] In contrast, the incidence of these adverse events with eplerenone is < 1%.[20]

The creatinine (> 2.5 mg/dl in men and > 2.0 mg/dl in women) and potassium (≥ 5.0 mEq/L) cutoffs are still in place, as is the need for careful monitoring.[2] Potassium levels > 5.5 mEq/L should normally trigger discontinuation or, at a minimum, dose reduction of the aldosterone antagonist, unless another cause for the increase is identified.[2] Additionally, worsening renal function should result in a careful evaluation of the patient's medication regimen and consideration for stopping the aldosterone antagonist.[2] In patients where monitoring is not feasible, the risks of hyperkalemia and renal dysfunction may outweigh the benefits of treatment with aldosterone antagonists.[7]

In updating the recommendations for use of aldosterone antagonists in HF, ACCF/AHA cited two studies published since the release of the 2009 Focused Update. The first was a randomized, double-blind, multicenter trial conducted by Zannad et al. The aim was to investigate the effects of eplerenone, added to standard therapy, on clinical outcomes in patients with mild symptoms of HF (NYHA class II). Throughout 278 centers, 2737 patients with NYHA class II and an EF ≤ 35% were randomized to receive eplerenone or placebo. The primary outcome was a composite of death from CV causes or a first hospitalization for HF. The trial was stopped prematurely after a median follow-up period of 21 months. The primary outcome occurred in 18.3% of patients in the eplerenone group compared to 25.9% of patients in the placebo group (HR 0.63, 95% CI 0.54-0.74; p<0.001). In the eplerenone group, 12.5% of patients died compared to 15.5% of those in the placebo group (HR 0.76, 95% CI, 0.62-0.93; p=0.008), with 10.8% and 13.5%, respectively, dying of CV causes (HR 0.76, 95% CI 0.61-0.94; p=0.01). Serum potassium > 5.5 mEq/L occurred in 11.8% of patients in the eplerenone group compared to 7.2% of patients on placebo (p<0.001).[20]

The second study was a randomized, single-blinded trial conducted by Vizzardi et al designed to evaluate the effects of spironolactone administered for six months, in addition to standard therapy, on LV systolic and diastolic functions as well as the functional capacity of patients with NYHA class I to II HF.[21] One hundred sixty-eight patients with LVEF ≤ 40% were randomized to receive either spironolactone or placebo and were assessed by echocardiography, gated single photon emission computed tomography, and various other imaging procedures at baseline and after six months of treatment. Left ventricular EF increased significantly in the spironolactone group (35.2 ± 0.7% to 39.1 ± 3.5% [p=0.01]) compared to no significant difference in the placebo group (35.4 ± 10% to 34.6 ± 10% [p=0.5]). Left ventricular mass, assessed by echocardiography, decreased significantly in the spironolactone group compared to those on placebo (269 ± 74 to 243 ± 67 g vs 250 ± 43 to 247 ± 38 g [p<0.05]). Significant decreases were also seen LV end-systolic and end-diastolic volumes. Serum potassium increased in the spironolactone group from 4.2 ± 0 to 4.6 ± 0.3 mEq/L (p<0.001).[21]

Published after the release of the current 2013 guidelines, Vardeny et al conducted a post-hoc analysis using data from RALES to examine the differences in the incidence of hyperkalemia and efficacy in African Americans (AA) compared with non-AAs. One hundred twenty AAs and 1543 non-

AAs with NYHA class III or IV and left ventricular dysfunction were randomized to spironolactone, titrated to 25-50 mg daily, or placebo. AA patients were significantly younger, more likely to be NYHA class IV, and more likely to have a higher eGFR and heart rate compared with non-AA patients. Serum potassium increased in non-AA patients in the spironolactone group (4.29 ± 0.5 to 4.55 ± 0.49 mEq/L) during the first month of the trial and remained higher throughout. However this did not occur in AA patients (4.32 ± 0.54 to 4.31 ± 0.49 mEq/L) (p=0.03). Non-AA patients were also more likely to demonstrate maximal spironolactone dose (13.9% vs 5.8%, p=0.04) as well as higher rates of hyperkalemia (K^+ > 5.5 mEq/L; 9.7% vs 4.2%; p<0.046) and lower rates of hypokalemia (K^+ < 3.5 mEq/L; 5.6% vs 17.9%; p<0.001). After adjusting for differences in both baseline characteristics and study drug dose, spironolactone reduced the combined end point of death or hospitalization for HF in non-AA patients (HR 0.63; 95% CI 0.55-0.73) but not in AA patients (HR 1.07, 95% CI 0.67-1.71). Although limited by a small number of AA patients and power, these findings suggest that safety and efficacy of aldosterone antagonists may differ by race.[22]

Conclusion

Heart failure can cause significant morbidity and mortality, and carries a considerable economic burden. Patients may present with reduced EF or preserved EF; to date, disease-modifying therapies have only been successful in patients with reduced EF. The ACCF/AHA guidelines highlight standard care, assisting health care practitioners to more effectively manage patients with HF. In 2013, the guidelines were updated to better reflect the available evidence and denote the most current GDMT. A few of the more notable changes were the expanded use of natriuretic peptides in the diagnosis, prognosis, and management of HF, as well as the broadened recommendations regarding the use of aldosterone antagonists. While questions remain regarding special populations, such as the effectiveness of natriuretic-guided therapy in patients > 75 years or the degree to which race affects the clinical benefit of aldosterone antagonists, the updated ACCF/AHA guidelines offer a comprehensive summary of the current literature with the goal of improving the management of HF.

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