Managing Heart Failure in 2013: Changing Paradigms

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ABSTRACT
Heart failure (HF) imposes huge morbidity and mortality on society. In recent times, HF with preserved ejection fraction (EF) has emerged as the predominant form of HF syndromes. Natriuretic peptides (B-type natriuretic peptide [BNP] and N-terminal [NT] pro BNP) have now emerged as preferred biomarkers for diagnosis and guiding further therapy in HF. Ivabradine and Eplerenone are now approved for HF patients who are symptomatic despite optimal therapy. Tolvaptan has been shown to improve hyponatremia as well as dyspnea in patients of HF. Coronary bypass grafting has demonstrated a decrease in cardiovascular death and HF hospitalization in patients with of HF with angina. Cardiac resynchronization therapy has now consistently shown to decrease mortality in Mild HF.

Key words: Cardiac resynchronization therapy, coronary artery bypass grafting, eplerenone, heart failure, ivabradine, natriuretic peptides, preserved ejection fraction, tolvaptan

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Heart Failure (HF) with Preserved Ejection Fraction (EF)

HF with normal EF (EF > 50%) is now being increasingly recognized as the predominant form of HF syndrome over the past decade. Various epidemiological studies have defined the prevalence of HF with normal EF (HFpEF) in the population between 50% and 55%.[1-4] It is more common in elderly and women. Hypertension is the most commonly associated comorbid condition in patients with HFpEF. In a study of participants in the Framingham Heart Study hospitalized for new-onset HF, female sex and atrial fibrillation increased the odds of HFpEF, whereas coronary heart disease, higher heart rate, higher potassium, left bundle branch block (LBBB) and ischemic electro-cardiographic changes increased the odds of HF with reduced EF.[5] Many contemporary studies have now suggested that the prognosis for HFpEF is similar or even worse to that of HF with a reduced EF.[6-8]

Biomarkers-Diagnosis of HF

Natriuretic peptides have become important diagnostic and prognostic tool in management of HF syndromes over past few years. B-type natriuretic peptide (BNP; formerly brain natriuretic peptide), along with its cleavage remnant n-terminal-pro BNP (NT-pro BNP), is synthesized and secreted by the ventricular myocardium in response to increases in volume or pressure in any chamber of the heart. Where the availability of echocardiography is limited, an alternative approach to diagnosis of HF is to measure the blood concentration of natriuretic peptide. A normal natriuretic peptide level in an untreated patient virtually excludes significant cardiac disease, making an echocardiogram unnecessary.

Various studies have tried to decipher the optimal cut off values for natriuretic peptides in acute and chronic setting.[9-15] The recent European Society of Cardiology (ESC) Guidelines on HF; 2012 recommend an exclusion cut-off point of 300 pg/mL for NT-pro BNP and 100 pg/mL for BNP in patients presenting with acute onset or worsening of symptoms. For patients presenting in chronic setting, the optimum exclusion cut-off point is 125 pg/mL for NT-pro BNP and 35 pg/mL for BNP. However, the sensitivity and specificity of BNP and NT-pro BNP for the diagnosis of HF are lower in non-acute patients.[16]
BIOMARKER GUIDED THERAPY FOR HF

Biomarker guided therapy offers the possibility of tailoring therapy according to an objective measure of function - patients with higher BNP/NT-pro BNP levels receive intensive guideline directed medical therapy. Availability of Commercial assays for both peptides with minimal analytical variation, particularly for NT-pro BNP makes them ideal candidates for this purpose.[13] Incremental prognostic value of serial measurements has been shown both in outpatient as well as inpatient settings.[18,19]

As many as 8 randomized trials have tested BNP guided therapy producing mixed results. STARS BNP[20] and BATTLE SCARRED[21] studies found that a BNP guided strategy led to reduction in mortality and hospital stay. On the contrary PRIMA[22] and TIME-CIF[23] did not find any improvement in clinical outcomes. However, both trials did show trend toward favorable outcomes in younger patients (age <75 years). The recently published NORTH STAR monitoring study too failed to demonstrate any benefit of adding serial NT-pro BNP measurement to optimal clinical management.[24] However, multiple meta-analyses of randomized trials of BNP guided therapy have shown consistent reduction in mortality.[15-28] Felker et al. in their metaanalysis of 6 randomized trials of (involving 1627 patients) utilizing serial biomarkers for titrating therapy found a significant mortality advantage for biomarker-guided therapy (hazard ratio (HR) - 0.69, 95% of confidence interval [CI]: 0.55-0.86) compared to control.[24] Notably, these benefits were present despite a generally high use of evidence based therapies at baseline and some degree of on-going intensification of medical therapy in the control group. Most recently published meta-analysis by Savarese et al. demonstrated a significant reduction of mortality (0.738; 95% CI: 0.596 - 0.913; P = 0.005) and HF related hospitalization (OR: 0.554; CI: 0.399-0.769; P = 0.000) in patients with chronic HF with cardiac peptide guided therapy. In particular, NT-pro BNP-guided therapy reduced all-cause mortality and HF-related hospitalization, but not all-cause hospitalization, whereas BNP-guided therapy did not significantly reduce both mortality and morbidity. The status of biomarker guided therapy is still unclear. We will need robust and adequately powered randomized trials to address the issue.

IVABRADINE

Persistently elevated heart rate is related to adverse outcomes.[29-31] Ivabradine is a selective I\textsubscript{1} current inhibitor and slows the heart rate by decreasing the velocity of diastolic depolarization in sinus node cells. The heart rate reduction is independent of effects on myocardial contractility, atrioventricular conduction, ventricular repolarization and blood pressure.[32,33]

The Systolic heart failure treatment with the inhibitor ivabradine trial (SHIFT) analyzed 6588 patients with symptomatic HF and a left-ventricular EF of 35% or lower in sinus rhythm with heart rate 70 beats/min or higher.[34] Patients were also required to have a HF hospitalization in the previous 12 months. Patients were randomized to ivabradine (up-titrated to a maximal dosage of 7.5 mg twice a day) or placebo, added to optimal guideline based therapy. Ivabradine reduced the in the primary composite outcome of cardiovascular death or HF hospitalization by 18% (P < 0.0001), the reduction in cardiovascular death (or all-cause death) was not significant. The absolute risk reduction was 4.2%. This beneficial effect was mainly driven by a favorable effect on HF death/hospital admission.

Ivabradine was associated with a 25% reduction in the total number of hospitalizations (total & recurrent) for HF (902 events vs. 1211 events with placebo; P = 0.0002) during the 22.9- month median follow-up. It also reduced the interval between the first and subsequent hospitalization.[35]

Reduction in heart rate with ivabradine was also associated with improved health related quality-of-life and the magnitude of heart rate reduction is related to the extent of improvement.[36] In the echocardiography sub study of SHIFT, ivabradine was associated with significant reductions in left ventricular end-systolic and end-diastolic volumes and a significant increase in left ventricular ejection fraction (LVEF).[37] The beneficial effects of ivabradine on heart rate were independent of beta blocker dosage and rather linked to baseline heart rate.[38]

Basing on these robust data, the ESC guidelines for HF 2012 recommend Ivabradine to reduce the risk of HF hospitalization in patients in sinus rhythm with an EF <35%, heart rate >70 beats who have persisting symptoms (NYHA Class II-IV) despite optimal medical treatment or who are unable to tolerate a beta-blocker.[38]

EPLERENONE

Mineralocorticoid receptors antagonist (MRA) spironolactone has been shown to improve survival in systolic HF.[39] Eplerenone, a more selective MRA, lacks the progestogenic and antiandrogenic actions of spironolactone. Eplerenone is further distinguished from spironolactone by its shorter half-life and the fact that it does not have any active metabolites.

In the eplerenone post-acute myocardial infarction HF efficacy and survival study (EPHESUS), eplerenone when added to recommended medical therapy significantly decreased all-cause death and death from cardiovascular causes or hospitalization for cardiovascular events among patients with acute myocardial infarction complicated by left ventricular systolic dysfunction and HF.[40] More recently EMPHASIS-HF trial, randomly assigned 2737 patients with New York Heart Association
(NYHA) Class II HF and an EF of <35% to receive eplerenone (up to 50 mg daily) or placebo, in addition to recommended therapy.\[15\] Treatment with eplerenone led to a relative reduction of 37% in cardiovascular death or HF hospitalization. Reductions were also seen in rates of death from any cause (24%), cardiovascular death (24%) hospitalization for any reason (23%) and HF hospitalization (42%).

The new ESC guidelines 2012 recommend an MRA for all patients with persisting symptoms (NYHA Class II-IV) and an EF ≤ 35%, despite treatment with an angiotensin-converting-enzyme inhibitor and beta-blocker, to reduce the risk of HF hospitalization and the risk of premature death.\[16\]

**TOLVAPTAN**

The arginine vasopressin antagonists or “vaptans” block the renal vasopressin - V2 receptor selectively (tolvaptan) or block both the vasopressin V1a/V2 receptors (conivaptan) non-selectively, leading to decreased pulmonary capillary wedge pressure, increase urine volume, weight loss, decrease urine osmolarity and normalization of sodium without adversely affecting renal functions.\[42,43\]

Tolvaptan is a selective V2-receptor antagonist, binding 29 times more avidly to V2-receptors than V1a-receptors. In the acute and chronic therapeutic impact of a vasopressin (ACTIV) in CHF trial, tolvaptan significantly increased mean 24-h urine volume and decreased body weight compared with the placebo in patients with decompensated HF.\[14\] A trend toward greater survival was found in the tolvaptan groups compared with placebo. Importantly, patients with elevated blood urea nitrogen and those with multiple signs of congestion who were treated with tolvaptan experienced lower mortality rates out to 60 days. Such benefits were also demonstrated in out-patient settings too.\[45,46\]

The efficacy of vasopressin antagonism in HF outcome study with tolvaptan (EVEREST) trial evaluated both the short-term and long-term impact of tolvaptan in patients hospitalized with acute decompensated HF and signs and symptoms of volume overload.\[47,48\] The short term clinical status arm of EVEREST trial evaluated the role of tolvaptan, in addition to standard therapy including diuretics, for clinical improvements during the inpatient period. The composite primary end point of patient-assessed global clinical status (assessed as a visual analog score) and body weight reduction, was significantly improved with tolvaptan treatment, driven by reductions in body weight beyond that achieved with standard therapy alone and not by changes in global clinical status.

Patient-assessed dyspnea was positively affected during tolvaptan treatment. Pedal edema (for those patients with edema at baseline) at in-patient day 7 or discharge improved more in the tolvaptan versus the placebo groups.

The long-term follow arm - EVEREST outcome trial assessed dual primary end points of all-cause mortality (for either superiority or non-inferiority) and cardiovascular death or HF hospitalization (for superiority). During a follow-up of 9.9 months, tolvaptan failed to demonstrate any difference in neither of the primary end points (HR- 1.04; 95% CI: 0.95-1.14; P = .55), nor a significant effect on the secondary end points of cardiovascular mortality, cardiovascular death or hospitalization and worsening HF. However, tolvaptan significantly improved secondary end points of day 1 patient-assessed dyspnea, day 1 body weight and day 7 edema with maintenance of renal function. Interestingly in patients with hyponatremia, serum sodium levels significantly increased.

In a post hoc analysis of EVEREST trial,\[49\] tolvaptan modestly improved dyspnea compared with standard therapy alone, regardless if given early or relatively late after hospitalization and also across major pre-specified subgroups, despite on-going background therapy aimed at relieving signs and symptoms.

Tolvaptan’s effects were greatest within 12 h after first dose with an additional, but modest dyspnea improvement benefit irrespective of time after admission.

Two important observations emerge from these randomized controlled trials (RCT’s) of tolvaptan. Tolvaptan has consistently shown improvement is dyspnea and weight gain in acute HF syndromes across all RCTs albeit without significant effect on mortality. Given the prevalence of dyspnea in Acute HF syndromes,\[50\] its relief is of paramount importance both patients and clinicians and its role in regulatory approval has resulted in this symptom being targeted in clinical trials. Apart from tolvaptan, only Phase III randomized controlled trial program to have demonstrated statistically significant improvement in dyspnea is the vasodilation in the management of acute CHF trial for Nesiritide. What we need probably is large and long-term follow-up studies with tolvaptan.

The presence of hyponatremia in setting of HF portends a poor prognosis as shown in various trial and registries.\[51-53\] Each 3-mEq decrease in serum sodium is associated with a 20% of increase in mortality within 60 days. As vasopressin excess contributing to the pathophysiology, the potential use of vasopressin antagonists in this setting is attractive. In the ACTIV in CHF trial, 68 patients (21%) had hyponatremia at randomization. Serum sodium concentrations were observed to rise and often normalize in this cohort. In a subgroup analysis of EVEREST trial, in patients with hyponatremia, serum sodium increased 5.5 mEq/L in the tolvaptan-treated patients compared with an increase of 1.8 mEq/L in the placebo treated patients and the improvement in the tolvaptan-treated patients was maintained throughout the long-term course of therapy. Interestingly changes in serum sodium were dependent on baseline level of sodium with maximal effect in hyponatremic patients.
Currently, tolvaptan is approved by US Food and Drug administration approved for treatment of clinically significant (Na+ <125 mEq/L) hypervolemic and euvolemic hyponatremia resistant to fluid restriction. The new ESC guidelines for HF 2012 recommend say that tolvaptan may be used to treat patients with resistant hyponatraemia in acute HF.

CORONARY REVASCULARIZATION IN HF

At present coronary revascularization is indicated for angina relief in patients of HF. In the surgical treatment for ischemic heart failure trial (STITCH), 1212 patients with an EF <35% and coronary artery disease amenable to coronary artery bypass grafting (CABG) were randomly assigned to medical therapy alone or medical therapy plus CABG.[54] The primary outcome (all-cause death) was not reduced by CABG, but the secondary outcomes of cardiovascular death and death from any cause or cardiovascular hospitalization were significantly reduced.

In the viability sub study of STITCH, presence of a substantial amount of viable myocardium was associated with a greater survival benefit in 601 patients with ischemic left ventricular dysfunction.[58] However, after adjustment for other significant baseline prognostic variables in a multivariable model, the pre-specified viability status was no longer significantly associated with the mortality.

Basing on these data new ESC guidelines recommend CABG in HF patients with angina and two-or three-vessel coronary disease, to reduce the risk of hospitalization for cardiovascular causes and the risk of premature death from cardiovascular causes.[54]

CARDIAC RESYNCHRONIZATION THERAPY (CRT) IN MILD HF

CRT is an established therapy for reducing symptoms and mortality in advanced HF patients (NYHA Class II and IV) with EF <35% in sinus rhythm with QRS >120 ms on electrocardiogram despite optimal medical therapy.[56] Many recent studies have focused on the role of CRT in mild HF.[57]

The REVERSE study tested the hypothesis that CRT in combination with optimal medical treatment can prevent disease progression and reverse LV remodeling in mild systolic HF.[58] Six hundred and ten patients with NYHA functional Class I and II HF with LVEF <40% and QRS duration >120 ms were randomly assigned to active CRT (CRT-on) or control (CRT-off). The primary end point was the HF clinical composite response, which scored patients as improved, unchanged, or worsened. The HF clinical composite response end point, indicated 16% worsened in CRT-on compared with 21% in CRT-off (P = 0.10). In the CRT-on arm, patients experienced a greater improvement in LV end-systolic volume index (−18.4 ± 29.5 ml/m² vs. −1.3 ± 23.4 ml/m², P < 0.0001) and significant delay in time-to-first HF hospitalization (HR: 0.47, P = 0.03).

The MADIT-CRT trial enrolled 1820 patients with ischemic or non-ischemic cardiomyopathy (EF <30%) with QRS duration >130 ms and NYHA Class I or II symptoms.[59] Patients were randomized to receive CRT plus an implantable cardioverter defibrillator (ICD) or an ICD alone. After a follow-up of 2.4 years, CRT reduced the primary end point of death from any cause or a nonfatal heart-failure event, driven primarily by reduction in HF related events (17.2 vs. 25.3%, HR = 0.66; 95% CI: 0.52-0.84; P = 0.001). CRT was associated with a significant reduction in left ventricular volumes and improvement in the ejection fraction. Both ischemic and non-ischemic subsets were benefitted, effects being more evident in the sub group of QRS >150 ms.

The resynchronization/defibrillation for ambulatory heart failure trial (RAFT) trial randomized 1798 patients with NYHA Class II or III HF, a LVEF ≤ 30% and an intrinsic QRS duration of 120 ms or more or a paced QRS duration of 200 ms or more to receive either an ICD alone or an ICD plus CRT.[60] CRT use significantly reduced both the rate of death from any cause (HR 0.75; 95% CI: 0.62-0.91; P = 0.003) and hospitalization for HF (HR = 0.68; 95% CI: 0.56-0.83; P < 0.001). However, more adverse events had occurred in the ICD-CRT group, as compared with 58 in the ICD group (P < 0.001). Sub group analyses found that a significant interaction between treatment and QRS duration (P = 0.003), with ICD-CRT therapy being more effective in patients with an intrinsic QRS duration of 150 ms or more (HR = 0.59; 95% CI, 0.48 to 0.73). QRS morphologic type had a weaker correlation (P = 0.046) such that patients with LBBB appeared to have a greater benefit than patients with non-specific intra-ventricular conduction delay (P = 0.04 for interaction).

Clearly both MADIT-CRT and RAFT showed a significant relation between QRS duration and the treatment effect CRT appeared more effective in patients with a QRS >150 ms and patients with LBBB also seemed to obtain more benefit than non LBBB morphology. The recent ESC guidelines for HF 2012 state that in patients with milder symptoms, CRT is recommended only in those with either a QRS duration >150 ms or >130 ms plus an LBBB pattern.[66]

CONCLUSION

Approach to management of a patient with HF is fast changing. Earlier a reduced EF was sine-qua-non for diagnosing HF, but HF with preserved EF is the now the dominant form of acute HF syndromes. It is of paramount important to recognize this syndrome as it’s prognosis is not very different from systolic HF: Natriuretic peptides are now important adjuncts in diagnosis of HF in the emergency department. Natriuretic Peptide guided
therapy has also now been shown to decrease mortality in multiple meta-analyses.

Ivabradine is a novel and promising addition to the pharmacotherapy of HF. With unequivocal role in decreasing HF hospitalizations, it will help decrease the financial burden imposed by HF. With Eplerenone demonstrating mortality reduction of milder forms HF, we are moving a step forward in the approach preventing progression to end stage HF. Tolvaptan ameliorates hyponatraemia associated with HF. It also confers symptomatic benefit in term of dyspnea and edema relief.

Coronary artery bypass is now established to reduce morbidity for patients of HF with angina. Traditionally viewed as a therapy in advanced HF, CRT has now been consistently shown to reduce left ventricular remodeling and mortality for patients with milder forms of HF too.

In a nutshell, with recent innovations in management, we are moving toward tackling the menace of HF in early stages and attenuating subsequent morbidity.

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