EDITORIAL COMMENT

Natriuretic Peptide-Guided Therapy for Heart Failure

Ready for “Battle” or Too “Scarred” by the Challenges of Trial Design?*

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While natriuretic peptide (NP) testing has gained widespread acceptance for the diagnosis and prognosis of heart failure (HF), as well as risk stratification across the spectrum of cardiovascular disease, a major unanswered question is whether titration of NP levels can be used to “personalize” the treatment of patients with HF. On the surface, this should be a “no-brainer.” After all, on an individual level, NPs are excellent surrogates for wedge pressure in volume-overloaded HF patients; they correlate with New York Heart Association functional class and are better at risk stratification than ejection fraction (1–4). In addition, HF patients who demonstrate low or dropping NP levels over time have better outcomes than those who do not (5). Because HF mortality and readmissions remain unacceptably high, we are clearly still in need of improved monitoring tools. Therefore, it is necessary that we find and refine such tools. Biomarkers are a practical possibility; hence, further trials or NP-guided or other biomarkers are absolutely required.

The BATTLESCARRED (NT-proBNP–Assisted Treatment to Lessen Serial Cardiac Readmissions and Death) trial, as reported by Lainchbury et al. (6) in this issue of the Journal, is the latest and perhaps one of the best trials on NP-guided treatment of HF. In all, 364 outpatients with HF with N-terminal pro-B-type natriuretic peptide (NT-proBNP) >150 pmol/l (roughly 1,300 pg/ml) were randomly assigned to a usual care arm or to 1 of 2 aggressive arms: NP guided or clinically guided. An HF score was utilized to help guide the clinical arm, and NT-proBNP levels were used for the NP-guided arm.

This study demonstrated a number of improved outcomes out to 2 years with the NT-proBNP–guided strategy among patients <75 years of age. These included all-cause mortality, survival or HF readmission, and days alive and not hospitalized with HF. These data have now held true out to 3 years of follow-up.

The recently published TIME-CHF (Trial of Intensified vs. Standard Medical Therapy in Elderly Patients With Congestive Heart Failure) study is the largest trial to date to compare NT-proBNP–guided therapy with symptom-guided therapy in 499 outpatients with HF (7). That study concluded that the NT-proBNP–guided arm did not improve overall clinical outcome. However, like the BATTLESCARRED trial, the study did demonstrate that younger patients (between the ages of 60 and 75 years) had a higher survival free of hospitalization as compared with symptom-guided therapy.

That BNP has shown more effectiveness for patients under the age of 75 years but not for those over that age has been looked upon skeptically, but that can be explained on a number of levels. Aging is associated with a number of changes in the cardiovascular system such as increased vascular stiffness and myocardial stiffness, decreased beta-adrenergic responsiveness, impaired mitochondrial adenosine triphosphatase production, and impaired endothelial function (8–10). The characteristics of elderly HF patients are remarkably different from those of middle-aged HF patients (11). In fact, limited data exist regarding medical treatment of HF in elderly patients, as in most of the landmark randomized controlled trials of HF the mean age of enrolled patients is not representative of real-world HF patients (12,13). Furthermore, across nearly every randomized control study of HF therapies, the benefits of widely accepted drugs for HF treatment were less evident (or absent) in the elderly. Moreover, HF therapies are underutilized for elderly patients (13). Finally, there is no treatment that is proven effective for HF with preserved ejection fraction, which forms a large proportion of older HF patients (14).

Why Do Clinical Trialists Scoff at NP-Guided Studies?

Whenever I listen to the water-cooler discussions about biomarker-guided clinical trials by the so-called “clinical trialists,” skepticism is abundant. A failed primary end point for a biomarker-guided trial should spell the end of that biomarker the same way it does, they believe, for a cardiac drug. Yet, the complexities of biomarker-guided trials are often orders of magnitude tougher than a phase-3 drug study. Consider this: in a phase-3 drug study, the dose is known up front, the inclusion and exclusion criteria are often standard, the patient will receive drug or placebo, and while there is often debate over the primary end point, it

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usually ends up as a variant of mortality. In a biomarker-guided study, however, difficult protocol decisions are undertaken at every turn: what biomarker level you treat to, what medical regimen you use to achieve that goal, how you handle the control group, and finally, what end points are important. A cardiac drug should reduce cardiovascular mortality, but should we hold a biomarker to that same standard? Wouldn’t it be enough to say that this would be a successful study if using a biomarker helped reduce admissions to the hospital, aided in adherence to guideline-based treatment, preserved renal function, and improved quality of life? These are issues that need to be clarified as clinical trialists and biomarker experts morph into one being. Here are some proposed guidelines for running NP-guided trials.

I. Population To Be Tested

1. Age <75 years of age with decreased systolic function.
2. Ischemic or nonischemic left ventricular systolic dysfunction.
3. Pre-randomization levels of 400 for BNP and 5,000 for NT-proBNP or recently destabilized HF.
4. Randomization performed after the diuretic dose is titrated upward.

II. Testing Strategy

1. Acute HF. While dropping NP levels during hospitalization are clearly associated with better short-term outcomes, and in fact many physicians routinely utilize NP levels in the hospital to help obtain euvolemia, it is remarkable that there has never been a randomized inpatient NP-guided treatment study. An acute HF NP-guided intervention trial should take place at the time of hospital admission with decompensated HF and continue to 30 days post-hospitalization. The goal would clearly be to keep the patient decongested with appropriate diuretics and vasodilator titration so as to prevent early readmission.

2. Chronic heart failure. A recent randomized NP-guided HF study from Sweden, presented at European Society of Cardiology–Heart Failure in Nice, was supposed to have both groups aim for the same drug regimen, one trying to lower NP levels by 50%, on levels drawn every 30 days. The NP levels dropped only 10% in both groups, and medication ended up the same across the board. Is it any wonder the study was negative?

The following should be considered when formulating testing strategies:

1. Guideline versus NP guided. If we are ever going to truly personalize outpatient HF treatments, we must be willing to test whether an NP-guided treatment regimen can personalize guideline-recommended treatments. Some patients might go above recommended doses of certain medications, such as spironolactone, or receive a combination of angiotensin-converting enzyme inhibitors with angiotensin receptor blockers or hydralazine and nitrates, whereas others may actually require lower doses of certain medications. For instance, in my practice, a patient on a regimen of carvedilol 12.5 mg twice a day who has a blood pressure of 90 mm Hg and a BNP <200 pg/ml will likely stay on that dose rather than be titrated upward.

2. Consider randomizing NP-guided versus control by center rather than by patient in community settings. As long as the centers are matched with regard to type of patient, treating doctor (cardiologist versus primary care), and medical regimen, you avoid the “learning biases” inherent in single-center randomization. In addition, one could make the case for using nonacademic settings, in which HF specialty groups would mitigate much of the benefit of NP guidance and, furthermore, which do not represent real-world community practice.

3. An NP-guided center should utilize the following:
   a. Bedside or office NP assessment tools.
   b. An algorithm that has pre-defined treatment goals. In other words, in the euvolemic patient, angiotensin-converting enzyme inhibitors, beta-blockers, and aldosterone blockers would be titrated at least to recommended guideline doses. After this, consideration of digoxin and addition of an angiotensin receptor blocker or hydralazine/nitrates could be considered, as well as cardiac resynchronization therapy if indications are met. Along with an “obligatory treatment strategy” would also be the ability to do one’s “best job,” namely, to still be a physician and render rational clinical judgment.
   c. NP sampling at frequent intervals (1 to 2 weeks), with medication adjustments made based on those levels. If the target has not been reached, a medication change must be undertaken as long as blood pressure, renal function, and potassium are under control.
   d. Sampling of NP levels whenever there are symptoms of worsening HF, with follow-up sampling as soon as the condition is improved with treatment.
   e. Some measure of renal function should be taken to help interpret NP levels.
   f. A clinical congestion score, to separate hypovolemic decompensation from progression of disease.
   g. Most importantly, the strategy should include some measure of quality control to ensure that the physician responds to an elevated NP concentration. Simply saying, “I’m OK with the BNP value, because the patient ‘looks OK’” is not acceptable, given what is known about the prognostic value of NPs.

4. Control or usual care group should:
   a. Treat patients according to their usual clinical practice—this would be a mirror of what goes on in clinical practice.
   b. Have a copy of HF guidelines.
c. See patients no more frequently than what is determined the community standard (≈3-month intervals) unless symptoms develop.

5. What should the NP target level be? This is 1 of the more perplexing issues in NP-guided studies. Do we personalize a patient’s target NP value, and if so, how on earth would we do this? A 50% decrease from hospitalization? There are no solid data here, but I would avoid looking at relative changes after hospitalization, as the discharge NP might not reflect the NP 2 weeks later because diuretics still need adjusting. I believe we should aim for the following: a sustained BNP level <200 pg/ml (NT-proBNP 1,000 pg/ml) with the following caveats:
   a. Avoid symptomatic hypotension
   b. Avoid renal insufficiency
      A “time to target” NP study would be interesting, but I think until the target values and treatment algorithms are defined, that will be a difficult undertaking. One of the odd things that has been seen in this area is that some patients take months to achieve their optimal NP concentration, whereas others take only weeks to reach the same value. Are these patients different?

6. What should the end points be? This is the toughest challenge of all, and has been the demise of a number of potentially good therapies. A few statements can be made:
   a. The primary end point will need to be either cardiovascular mortality or total mortality. One year would be the minimal time for such a study.
   b. Sample size needs to be appropriate. A recent sample calculation proposed by Zannad (F. Zannad, personal communication, June 2009) for a cluster randomization of centers for an acute and post-acute HF trial includes:
      • Deaths in the control group equal to 38%;
      • An intraclass correlation of 0.05;
      • It will be necessary to randomize 174 centers;
      • Each including on average 15 patients;
      • With 80% power at a 5% significance level;
      • To detect reduction of mortality of 18%.
      Total = 2,400 patients
   c. An alternative primary end point could be days alive and not in the hospital with congestive heart failure. In the study by Lainchbury et al. (6), NP-guided therapy showed positive results among patients <75 years of age, out to 3 years of follow-up.
   d. Secondary end points will be extremely important and should take into account the following:
      • Number of HF hospitalizations. It is my belief that one of the major beneficial effects of successful NP-guided treatment will be reduced hospitalizations, especially after physicians develop comfort with NP-guided regimens.
      • Number of episodes of destabilized HF not requiring hospitalization. Many centers now manage their patients who have mild destabilization with outpatient therapies rather than admitting them—this is a very relevant sign of impending need for inpatient hospitalization or worse.
      • Surrogate markers:
         i. Renal function—cystatin C, Ngal
         ii. Subendocardial ischemia, necrosis—troponin
      • Percent of patients who have dropped NP levels to pre-selected number.
      • Percent of patients who are below, at, or above guideline-recommended therapy.

Toward the Future

A recent meta-analysis of the TIME-CHF, STARS-BNP (Plasma Brain Natriuretic Peptide-Guided Therapy to Improve Outcome in Heart Failure), and STARBRIGHT (Strategies for Tailoring Advanced Heart Failure Regimens in the Outpatient Setting: Brain Natriuretic Peptide Versus the Clinical Congestion Score) trials, which included 918 patients, found that a strategy using NP levels to guide therapy resulted in a significant reduction in all-cause mortality (15). Thus, it appears that while NP levels are not ready for prime time, thanks to studies like BATTLESCARRED, the waters are certainly calmer. There is still a strong need for more trials, individual peptide targets, more data on patients >75 years of age, an examination of some of the newer biomarkers such as mid region proANP and mid region proADM, and the possibility of using a combination of biomarkers that reflects cardiac wall stress, ischemia, and renal function. Targeting the abnormal biology of HF is crucial to reduce the considerable risk we are seeing with this disease—at the end of the day, we in cardiology must begin to embrace the concept of biologically guided treatment for our patients with HF. Although caveats exist, the BATTLESCARRED study points us in a direction (6). Future studies will need to continue down this path, which is one that we must take.

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