Renal Subanalysis of the Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF)

The End of Nesiritide as a Cardiorenal Therapeutic?

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Over the last 3 decades, there has been a remarkable explosion in our understanding of the natriuretic peptide system. Among articles published before 1980, only 1 entry can be found in Medline under the search term natriuretic peptide. Currently, however, there are >22,500 publications. In this impressive collection of literature, the concept of the natriuretic peptide as an ideal cardiorenal therapeutic emerged with reports of improvement in renal function, neurohormonal activation, fibrosis, and natriuresis among other benefits with these agents. As a result, the development of recombinant B-type natriuretic peptide (nesiritide) brought tremendous optimism in terms of its potential role in acute decompensated heart failure (ADHF). The drug was approved in 2001 on the basis of a 489-patient trial that did not actually evaluate its cardiorenal effects but rather demonstrated efficacy via its actions as a vasodilator. This took the form of a 2-mmHg greater reduction in pulmonary capillary wedge pressure with no additional relief of dyspnea compared with nitroglycerin but significant superiority over placebo. However, presumably as a result of the great enthusiasm for the mechanism of the drug, sales soared to $390 million by 2004 despite the absence of any large studies showing positive clinical outcomes and even some human data indicating an absence of positive cardiorenal effects. The widespread enthusiasm for nesiritide ended rather abruptly in 2005 after publication of 2 meta-analyses by Sackner-Bernstein et al demonstrating a 52% increased risk for worsening renal function (WRF; defined as >0.5-mg/dL increase in creatinine) and an 80% increased risk for death with nesiritide.

The above chain of events motivated the Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF) trial, which was designed to definitively answer the question of safety and efficacy of nesiritide in a broad spectrum of patients with ADHF. The primary renal end point was a 25% worsening in estimated glomerular filtration rate, a definition different from that used in the meta-analysis. Enrolling 7141 patients, the trial was completed in 2010, finding a null effect on the primary efficacy end points of the change in dyspnea and death or rehospitalization at 30 days. Additionally, there was a 9% relative increase in the odds of the ASCEND-HF definition for WRF, which did not reach statistical significance (P=0.11).

In this issue of Circulation, van Deursen and coauthors present the results of a detailed renal subanalysis of ASCEND-HF, further investigating the effects of nesiritide in this large population. Of the 7007 patients who received the randomized intervention, 4732 (68%) had both admission and discharge creatinine available, and 5702 (81%) had at least 1 in-hospital serum creatinine after the baseline. Notably, the change in both creatinine and blood urea nitrogen from baseline to 24 hours, to the end of treatment, and at discharge was no different between the placebo and nesiritide groups. This lack of superior renal function with nesiritide was also evident in the cumulative distribution curves for serum creatinine and was unaltered after multivariable adjustment. The incidence of WRF defined with a less commonly used definition of an increase in serum creatinine of ≥25% and >0.3 mg/dL was not statistically significant between groups (odds ratio=1.1; P=0.19). However, there was a highly statistically significant increase in the incidence of WRF with nesiritide when defined with the more common definition of an absolute >0.3-mg/dL increase in serum creatinine (31.2% versus 27.0%; odds ratio=1.23; P<0.001). These discouraging findings follow another recent subanalysis of ASCEND-HF in which nesiritide was found to have no influence on fluid output or diuretic requirements, in addition to the recent Renal Optimization Strategies Evaluation (ROSE) trial, which also showed a lack of benefit of nesiritide on renal function and diuresis.

So where does this leave us with nesiritide as a cardiorenal therapeutic? The most straightforward conclusion from the preponderance of available data is that there is in fact no role for nesiritide at the studied doses in unselected patients with ADHF (ie, inclusion/exclusion criteria of ASCEND-HF) with the goal of improving renal function. It will not get much clearer than this: In an analysis of >5000 patients randomized to nesiritide whose renal function was evaluated 10 different ways, 9 analyses showed null results, and 1 analysis showed worse renal outcomes. Nesiritide clearly does not offer renal benefit to the general ADHF population. Importantly, this was the question asked in ASCEND-HF, and the original conclusion of the authors that "[o]n the basis of these results,
nesiritide cannot be recommended for routine use in the broad population of patients with acute heart failure’’ should probably be extended to its use as a cardiorenal therapeutic. However, the story is not nearly as straightforward with respect to whether nesiritide has meaningful value as a cardiorenal therapeutic. The analogy has been drawn to conducting a large study of vitamin B₁₂ replacement in an unselected population of patients with anemia. If the prevalence of vitamin B₁₂ deficiency were to be low, regardless of the methodological rigor of the trial, the results of the trial would most likely be null. Much like the conclusion that nesiritide does not improve kidney function in the general ADHF population, the conclusion that vitamin B₁₂ is not a useful therapeutic in the general population of patients with anemia is probably also correct. However, we certainly know that vitamin B₁₂ has a potentially lifesaving role in patients with severe vitamin B₁₂ deficiency. The scenario with nesiritide is even more complex because the drug is a powerful intravenous vasoactive medication that causes a substantial burden of adverse events such as hypotension. As a result, when nesiritide is administered to patients lacking the potential to derive benefit (ie, median baseline creatinine in ASCEND-HF was 1.2 mg/dL; thus, many patients had normal renal function), only a potential for harm remains. Unfortunately, we do not yet know if a ‘‘vitamin B₁₂ deficiency equivalent’’ patient population exists for the natriuretic peptides, how large this population may be, and, more important, how to identify them.

Therefore, the question of whether our inability to translate the spectacular preclinical findings with natriuretic peptides to the bedside is a result of the method with which we are approaching the question or the drug itself remains unanswered. Notably, agents/strategies such as the adenosine antagonists, vasopressin antagonists, low-dose dopamine, ultrafiltration, and loop diuretic infusions have similarly been the subject of recent negative trials.¹¹⁻¹⁵ Much like nesiritide, the majority of these interventions also had solid preclinical data and theoretical bases on which benefit was to be expected. Although it could be concluded that the common thread among this diverse set of interventions is that none of them work, a more appropriate conclusion may be that the paradigm of the ‘‘one size fits all’’ strategy of ADHF therapy needs critical reappraisal. As a result, the negative renal findings from this ASCEND-HF subanalysis, which are at odds with the remarkably positive preclinical data for nesiritide, could be interpreted as a call to arms to develop strategies to appropriately select patients for this and other promising cardiorenal therapeutics earlier in the development process.

Another important take-home point from the present analysis is that we need to be mindful of how we define our renal end points because seemingly small differences in how and when they are ascertained can produce meaningful differences in the observations. It was easy to dismiss the meta-analytic data of Sackner-Bernstein et al as wrong after the publication of the large, methodologically rigorous primary ASCEND-HF trial results despite the use of a different definition for WRF. However, in the present renal subanalysis, we see that when an absolute change in renal function was used to define WRF, there was in fact a highly statically significant 23% increase in the odds for WRF. Interestingly, this risk falls within the 95% confidence limits of the relative risk published by Sackner-Bernstein et al, which also used an absolute change in creatinine. However, both with the primary ASCEND-HF renal end point and in the present analysis, when a relative change was incorporated into the definition, the signal was no longer statistically significant. Furthermore, in the present analysis, in evaluations of continuous changes in creatinine, not even a trend for WRF with nesiritide was apparent.

It is important to note that the various methods used to evaluate changes in renal function actually query different aspects of biology and are subject to different sources of confounding and bias. Figure 1 depicts the exponential relationship between serum creatinine and estimated glomerular filtration rate (GFR) in an ADHF population. As a result of this relationship, any absolute increase in creatinine will reflect different degrees of relative change in renal function, depending on baseline creatinine (Figure 1). Therefore, in patients with high baseline creatinine levels, very little change in actual renal function needs to occur for these patients to qualify as WRF by a 0.3-mg/dL definition (Figure 1).¹⁶ With respect to bias and confounding, sicker patients commonly have more intense monitoring of electrolytes and serum creatinine. Because patients with the greatest number of creatinine values available will have the greatest number of opportunities to meet the WRF definition, when the “peak” of all available serum creatinine values is used to define WRF, substantial ascertainment

![Figure 1](image-url) Relationship between serum creatinine and estimated glomerular filtration rate (GFR). The solid lines represent an increase in serum creatinine of 0.3 mg/dL from the 10th percentile creatinine value (0.8 mg/dL) to 1.1 mg/dL and the corresponding change in estimated GFR in an acute decompensated heart failure population. The dashed lines represent a 0.3-mg/dL increase in serum creatinine from the 90th percentile value (3.0 mg/dL) to 3.3 mg/dL and the corresponding decrease in estimated GFR. GFR expressed as ml/min/1.73m². Reproduced from Testani et al¹⁶ with permission from the publisher. Copyright © 2010 S. Karger AG, Basel.

![Figure 2](image-url) Hypothetical scenario by which use of the “peak” serum creatinine could lead to the false conclusion that nesiritide causes worsening renal function (WRF) through ascertainment bias.
bias becomes an important consideration (Figure 2). Both the report by Sackner-Bernstein et al and the analysis showing renal harm in the present report used the peak serum creatinine and would thus be subject to possible ascertainment bias. These and many other potential considerations help us to understand the variability in findings with respect to changes in renal function across and even within studies, as observed in the present report.

Overall, the findings reported by van Deursen et al reinforce the complexities of studying and treating cardiorespiratory dysfunction in ADHF, and to a degree, they help us to reconcile the previous renal findings from Sackner-Bernstein et al. However, regardless of whether nesiritide causes a modest increase or no change in creatinine, on average it clearly does not improve renal function or outcomes in unselected patients with ADHF. Given the remarkably strong preclinical data on natriuretic peptides and the recent encouraging data with nephrinylins inhibitors, most likely we have not seen the end of the use of natriuretic peptides in heart failure. Rather, additional research to better identify the correct patient and attempts to optimize the risk-to-benefit ratio of our therapeutic approaches will likely be on the horizon.

Source of Funding
This work was supported by National Institutes of Health grants K23HL114868 and L30HL115790.

Disclosures
Dr Testani reports receiving consulting fees from Novartis Pharmaceuticals.

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Key Words: Editorial為什麼 | cardio-renal syndrome | decompensated heart failure | natriuretic peptides | nesiritide
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_Circulation_. 2014;130:936-938; originally published online July 29, 2014;
doi: 10.1161/CIRCULATIONAHA.114.012076

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2014 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

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http://circ.ahajournals.org/content/130/12/936

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