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The Renal Subanalysis of ASCEND-HF: The End of Nesiritide as a Cardio-Renal Therapeutic?

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Over the last three decades there has been a remarkable explosion in our understanding of the natriuretic peptide system. Prior to 1980, only 1 entry can be found in Medline under the search term “natriuretic peptide” while currently there are >22,500. Through this impressive literature, the concept of the natriuretic peptide as an ideal cardio-renal therapeutics emerged with reports of improvement in renal function, neurohormonal activation, fibrosis, and natriuresis amongst other benefits with these agents.¹ As a result, the development of recombinant b-type natriuretic peptide (nesiritide) brought tremendous optimism regarding its potential role in acute decompensated heart failure (ADHF). The drug was approved in 2001 based on a 489 patient trial that did not actually evaluate its cardio-renal effects, but rather demonstrated efficacy via its actions as a vasodilator.² This took the form of a 2 mmHg greater reduction in pulmonary capillary wedge pressure with no additional relief of dyspnea compared to nitroglycerin, but significant superiority over placebo. However, presumably due to 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 cardio-renal effects.^{3, 4} The widespread enthusiasm for nesiritide ended rather abruptly in 2005 after publication of two meta-analyses by Sackner-Bernstein et al demonstrating a 52% increased risk for worsening renal function (WRF, defined as a >0.5 mg/dl increase in creatinine) and an 80% increased risk for death with nesiritide.^{5, 6}

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.⁷ The primary renal endpoint was a 25% worsening in estimated glomerular filtration rate (eGFR), a definition different from that used in the meta-analysis.^{5, 7} Enrolling 7141 patients, the trial was completed in 2010 finding a null effect on the primary efficacy endpoints of the change in dyspnea and death or rehospitalization at 30 days.⁸ Additionally,

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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.⁹ Of the 7007 patients who received the randomized intervention, 4732 (68%) had both admission and discharge creatinine available and 5702 (81%) had at least one in-hospital serum creatinine following the baseline. Notably, evaluation of change in both creatinine and blood urea nitrogen from baseline to 24 hours, end of treatment, and 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 following 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% vs. 27.0%, OR=1.23, $p<0.001$). These discouraging findings follow another recent subanalysis of ASCEND-HF where 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.^{10, 11}

So where does this leave us with nesiritide as a cardio-renal therapeutic? The most straightforward conclusion from the preponderance of the available data is that there is in fact no role for nesiritide at the studied doses in unselected patients with ADHF (i.e., inclusion/exclusion criteria of ASCEND-HF) with the goal of improving renal function. It won't get much clearer than this: in an analysis of >5000 patients randomized to nesiritide where renal function was evaluated 10 different ways, 9 were null and 1 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, "On 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 cardio-renal therapeutic.

However, the story is not nearly as straight forward with respect to whether nesiritide has meaningful value as a cardio-renal therapeutic. The analogy has been drawn to conducting a large study of vitamin B-12 replacement in an unselected population of patients with anemia. If the prevalence of B-12 deficiency were to be low, regardless of the methodologic rigor of the trial, most likely the results of the trial would be null. Much like the conclusion that nesiritide doesn't improve kidney function in the general ADHF population, the conclusion that B-12 is not a useful therapeutic in the general population of patients with anemia is probably also correct. However, we certainly know that B-12 has a potentially lifesaving role in patients with severe B-12 deficiency. The scenario with nesiritide is even more complex since 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 (i.e., 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 don't yet know if a "B-12 deficiency equivalent" patient population exists for the natriuretic peptides, how large this population may be, and more importantly any idea how to actually identify them.

As such, the question remains unanswered if our inability to translate the spectacular pre-clinical findings with natriuretic peptides to the bedside lies within the method with which we are approaching the question or the drug itself. 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 basis upon which expect benefit. Although it could be concluded that the common thread amongst 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 pre-clinical data for nesiritide, could be interpreted as a call to arms to develop strategies to appropriately select patients for this and other promising cardio-renal therapeutics earlier in the development process.

Another important take home point from the current analysis is that we need to be mindful of how we define our renal endpoints since 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 current renal-subanalysis we see that when an absolute change in renal function is 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 utilized an absolute change in creatinine. However, with both the primary ASCEND-HF renal endpoint and in the current analysis, when a relative change was incorporated into the definition the signal was no longer statistically significant. Furthermore, in the current analysis when evaluating continuous changes in creatinine, not even a trend was apparent for worsening renal function with nesiritide.

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 in an ADHF population. Due to this relationship, any absolute increase in creatinine will reflect different degrees of relative change in renal function, depending on baseline creatinine (Figure 1). As a result, 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. Since 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 bias becomes an important consideration (Figure 2). Both the report by Sackner-Bernstein et al and the analysis showing renal harm in the current report used the peak serum creatinine and would thus be subject to possible ascertainment bias.⁵ 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 current report.

Overall, the findings reported by van Deursen et al reinforce the complexities of studying and treating cardio-renal 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 pre-clinical data on natriuretic peptides and the recent encouraging data with neprilysin inhibitors, most likely we have not seen the end of the natriuretic peptide in heart failure. Rather, additional research to better identify the correct patient and attempts to optimize the risk/benefit ratio of our therapeutic approaches will likely be on the horizon.

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Figure 1.

Relationship between serum creatinine and estimated 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 ADHF 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. (Testani et. al., Cardiology 2010)

Figure 2.

Hypothetical scenario by which use of the “peak” serum creatinine could lead to false conclusion that nesiritide causes WRF through ascertainment bias. WRF: Worsening renal function.