

Original Research

# A retrospective characterization of worsening renal function in patients with acute decompensated heart failure receiving nesiritide

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## ABSTRACT\*

Nesiritide is approved by Food and Drug Administration (FDA) for the treatment of patients with acute decompensated heart failure (ADHF) due its ability to rapidly reduce cardiac filling pressures and improve dyspnea. Numerous studies have shown that renal dysfunction is associated with unfavorable outcomes in patients with heart failure. In addition, there have been reports suggesting that nesiritide may adversely affect renal function and mortality.

**Objective:** The purpose of this retrospective analysis was to assess the effect of dose and duration of nesiritide use and the dose and duration of diuretic therapy on worsening renal function and increased in-hospital mortality in this patient population.

**Methods:** Seventy-five patients who were hospitalized for ADHF and who were treated with nesiritide for at least 12 hours were reviewed retrospectively.

**Results:** The mean increase in SCr was 0.5 mg/dL (range 0 – 4.4 mg/dL). Thirty-six percent of patients (27/75) met the primary endpoint with an increase in SCr > 0.5 mg/dL. Treatment dose and duration of nesiritide did not differ between those patients who had an increase in SCr > 0.5 mg/dL and those who did not ( $p=0.44$  and  $0.61$ ). Concomitant intravenous diuretics were used in 85% of patients with an increase in SCr > 0.5 mg/dL compared to 90% of patients without an increase in SCr > 0.5 mg/dL ( $p=0.57$ ). The in-hospital mortality rate was also higher at 35% in those patients with an increase in creatinine > 0.5 mg/dL compared to 11% in those without ( $p=0.01$ ).

**Conclusion:** Nesiritide was associated with an increase in SCr > 0.5 mg/dL in approximately one-third of patients. The increase occurred independently of dose, duration of nesiritide therapy, blood pressure changes, and concomitant intravenous diuretic use. However, the increase in SCr was associated with an increase in hospital stay and in hospital mortality consistent with previous reports in the literature.

**Keywords:** Natriuretic Peptide, Brain. Heart Failure. Mortality.

## CARACTERIZACIÓN RETROSPECTIVA DEL EMPEORAMIENTO DE LA FUNCIÓN RENAL EN PACIENTES CON FALLO CARDIACO AGUDO DESCOMPENSADO RECIBIENDO NESETIRIDA

### RESUMEN

La nesetirida está aprobada por la Food and Drug Administration (FDA) para el tratamiento de pacientes con fallo cardiaco agudo descompensado (ADHF) debido a su capacidad de reducir rápidamente las presiones de llenado cardiaco y mejorar la dispnea. Numerosos estudios han demostrado que la disfunción renal está asociada con resultados desfavorables en pacientes con fallo cardiaco. Además, ha habido varias comunicaciones de que la nesetirida puede afectar adversamente la función renal y la mortalidad. **Objetivo:** El objetivo de este análisis retrospectivo fue evaluar el efecto de la dosis y la duración del uso de nesetirida y la duración del tratamiento diurético en el empeoramiento de la función renal y el aumento de mortalidad hospitalaria en esta población.

**Métodos:** Se revisaron retrospectivamente 75 pacientes que fueron hospitalizados por ADHF y que fueron tratados con nesetirida por al menos 12 horas.

**Resultados:** El aumento medio de CrS fue de 0,5 mg/dL (rango 0 – 4,4 mg/dL). El 36% de los pacientes (27/75) alcanzó el resultado intermedio con un aumento de CrS > 0,5 mg/dL. La dosis y duración del tratamiento con nesetirida no se diferenció entre los pacientes con un incremento de CrS > 0,5 mg/dL y los que no ( $p=0.44$  and  $0.61$ ). Se usaron diuréticos endovenosos concomitantes en el 85% de los pacientes con aumento de CrS > 0,5 mg/dL, comparados con el 90% de pacientes sin aumento de CrS > 0,5 mg/dL ( $p=0,57$ ). La tasa de mortalidad hospitalaria fue también mayor con un 35% en los pacientes con aumento de creatinina > 0,5 mg/dL comparada con el 11% en los otros ( $p=0,01$ ).

**Conclusión:** La nesetirida se asoció a un aumento de CrS > 0,5 mg/dL en aproximadamente un tercio de los pacientes. El aumento ocurrió independientemente de la dosis, duración de nesetirida, cambios de presión arterial, y uso de diuréticos endovenosos concomitantes. Sin embargo, el aumento de CrS se asoció con aumento de estancia hospitalaria y de mortalidad hospitalaria consistente con comunicaciones previas en la literatura.

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**Palabras clave:** Péptido naturético cerebral. Fallo cardiaco. Mortalidad.

## INTRODUCTION

Heart failure affects approximately 5.2 million Americans each year with a hospital discharge rate of approximately 1 million patients per year.<sup>1</sup> The most common reason for hospitalization is acute, symptomatic decompensation. The predominant symptoms in patients presenting with acute decompensated heart failure (ADHF) are dyspnea and fatigue, both of which are associated with pulmonary venous congestion and low cardiac output.<sup>2</sup> The immediate goal of therapy in this acute decompensated state is to rapidly relieve symptoms and improve the hemodynamic profile.<sup>3</sup> This is commonly accomplished with the use of intravenous diuretics, vasodilators, and sometimes positive inotropic agents which work to decrease cardiac filling pressures and increase cardiac output respectively. Ultimately the primary goal of therapy in this patient population is to decrease the length of hospital stay, prevent re-hospitalization, and decrease mortality.<sup>3</sup>

Patients with ADHF release B-type natriuretic peptide (BNP) in response to increased ventricular volume and stress. Once released, BNP causes vasodilation by binding to type A natriuretic peptide receptors which increase the concentration of cGMP.<sup>4</sup> Nesiritide, a potent vasodilator, is human BNP developed from recombinant *E. coli* DNA. Due to nesiritide's ability to rapidly reduce cardiac filling pressures, it was approved in 2001 for symptomatic relief in patients with dyspnea at rest or with minimal activity.<sup>5-7</sup> Food and Drug Administration (FDA) recommended dosing of nesiritide for vasodilation in ADHF is a 2 mcg/kg bolus followed by an infusion of 0.01 mcg/kg/min. The infusion can be up-titrated by 0.005 mcg/kg/min no more frequently than every 3 hours to a maximum infusion rate of 0.03 mcg/kg/min.

Two controversial meta-analyses were published calling the safety of nesiritide into question.<sup>8,9</sup> Specifically, these analyses concluded that the administration of nesiritide at currently recommended doses significantly increases the risk of renal dysfunction compared with both inotrope and noninotrope based therapies. Further, when nesiritide was compared to noninotrope based therapy it was associated with an increased risk of death within the first 30 days of treatment. In response to these data, the package insert for nesiritide was revised to state the following: nesiritide may affect renal function and may be associated with azotemia in patients whose renal function is dependent on the rennin-angiotensin-aldosterone system. This effect is seen when nesiritide is initiated at doses >0.01 mcg/kg/min. In addition, nesiritide is associated with a trend toward an increase in mortality rate at 30 days; however, the data is insufficient to identify or exclude with

confidence a moderate excess of risk to survival and additional studies need to be conducted.<sup>10,11</sup> It is currently recommended that nesiritide only be used in patients with ADHF presenting to the hospital with shortness of breath at rest or with minimal activity, and it should not be used as a diuretic replacement, to improve renal function, as intermittent outpatient infusions, or for scheduled repetitive use.<sup>12</sup>

Despite this data, documentation of these adverse effects is limited. It has been thought that some of these effects may only occur when nesiritide is prescribed at inappropriately high doses, when the duration of therapy is prolonged, or due to other confounding factors such as concomitant diuretic use. When ADHF patients are over diuresed, significant increases in serum creatine (SCr) can occur.<sup>13</sup> Several studies have indicated that increases in SCr concentrations of 0.3 to 0.5 mg/dL are associated with unfavorable outcomes such as increased length of hospital stay and higher in-hospital mortality rates in patients with heart failure.<sup>14-16</sup> Other confounding factors include age, average systolic blood pressure, angiotensin-converting enzyme inhibitor use or angiotensin receptor blocker use, or cardiac catheterization procedures. Further, ADHF alone carries a poor prognosis and can be clinically challenging to treat.

The objective of our study was to assess the effect of nesiritide on renal function and mortality in patients with ADHF. Specifically, we wanted to assess the effect of dose and duration of nesiritide use and the effect of diuretic use on worsening renal function and increased in-hospital mortality in this patient population.

## METHODS

### Study Design

We performed a retrospective chart review in a tertiary academic teaching institution to evaluate the effect of nesiritide on renal function and mortality in patients with ADHF. The study protocol was approved by the institutional review board at our institution.

### Patients

All patients hospitalized between January 2004 and July 2005 who received treatment with nesiritide were identified through pharmacy records and reviewed for study inclusion. Patients had to be at least 18 years of age and had to have received nesiritide for ADHF for a minimum of 12 hours. Patients were excluded if they received nesiritide for any indication other than ADHF.

### Data Collection and Outcome Measures

Laboratory and demographic data were obtained directly from the patients' electronic medical record. The primary outcome was an increase in SCr >0.5 mg/dL at any time once the patient received nesiritide up to 48 hours post the nesiritide infusion. Secondary outcomes included net urine output, length of hospital stay, in-hospital mortality, and adverse events. Other parameters collected were

nesiritide dose and duration of therapy, diuretic use, age, average systolic blood pressure, angiotensin-converting enzyme inhibitor use or angiotensin receptor blocker use, or cardiac catheterization procedures. Adverse events of interest were number of hypotensive events defined as a systolic blood pressure <80 mmHg and number of patients requiring a medical intervention defined as a reduction in nesiritide dose, discontinuation of nesiritide therapy or hemofiltration due to worsening renal function.

For this study, a clinically significant effect on renal function was defined as an increase in SCr>0.5 mg/dL at any time during the nesiritide infusion and up to 48 hours post the nesiritide use.

### Statistical Analysis

Descriptive statistics were used to summarize the demographic and clinical characteristics of patients. Categorical data were analyzed with the chi-square test. Continuous data were analyzed with the t-test. All p-values were two sided with an a priori significance level of 0.05.

### RESULTS

One-hundred and twenty-five patients were treated with nesiritide during the 18 month study period. Of these patients, 8 were excluded because they were <18 years of age, 12 were excluded because they did not receive nesiritide for at least 12 hours, and 30 were excluded because they did not receive nesiritide for ADHF. The remaining 75 patients were evaluated.

Baseline characteristics of patients the day nesiritide was initiated are presented in Table 1. The mean patient age was slightly higher in those patients who had an increase in SCr > 0.5 mg/dL (63 years versus 55 years, p=0.06). The average blood urea nitrogen (BUN) and SCr recorded the day of nesiritide initiation was 48 mg/dL and 2 mg/dL in patients who had an increase in SCr>0.5 versus 37 mg/dL (p=0.07) and 1.8 mg/dL (p=0.004) in those who did not. There was no difference in ejection fraction (28% versus 29%, p=0.8) or baseline systolic blood pressure (98 mmHg versus 97 mmHg, p=0.9).

Serum Creatinine increase > 0.5 mg/dL	Yes n = 27	No n = 48	p Value
Age, mean (range) yrs	63 (28-84)	55 (25-90)	0.06
Race, No. (%) of patients			
Caucasian	16 (59)	25 (52)	0.56
African American	11 (41)	23 (48)	0.56
Gender, No. (%) of patients			
Male	17 (63)	34 (71)	0.48
Female	10 (37)	14 (29)	0.48
Ejection Fraction, mean (range) %	28 (12.5-55)	29 (15-51)	0.8
SCr, mean (range) mg/dL	2 (1.2-4.2)	1.8 (1-4.3)	0.004
BUN, mean (range) mg/dL	48 (17-98)	37 (111-119)	0.07
SBP, mean (range) mmHg	98 (73-145) 0.74	97 (78-138)	0.9

The mean increase in SCr was 0.5 mg/dL (range 0 – 4.4 mg/dL). Thirty-six percent of patients (27/75) met the primary endpoint of an increase in SCr>0.5 mg/dL. The average SCr during nesiritide administration was 3.34 in the patients who had an increase in SCr > 0.5 versus 1.98 mg/dL (p=0.03) in those who did not. The average discharge SCr was 2.81 in the patients who had an increase in SCr>0.5 versus 1.7 mg/dL (p=0.02) in those who did not. Eleven of the 27 patients who experienced an increase in SCr>0.5 mg/dL required nesiritide to be discontinued. Seven (9%) patients required dialysis.

When comparing the dose and duration of nesiritide used between those patients who had an increase in SCr>0.5 mg/dL with those who did not, there was no significant difference (Table 2). Both groups received an average dose of 0.01 mcg/kg/min (p=0.44), and all patients received a bolus dose of 2 mcg/kg. The average duration of therapy was slightly longer (75 hours, range 16- 216 hours) in the group with an increase in SCr>0.5 mg/dL versus an average of 67 hours (range 14 – 432 hours) in the group who did not (p=0.61). The average time from hospital admission to nesiritide administration did not differ between groups (20 hours versus 19 hours, p=0.6).

Evaluation between patients who had an increase in SCr>0.5 mg/dL with those who did not showed no significant difference between groups with respect to other confounders that may worsen renal function such as diuretic use including both number of days and intravenous use, systolic blood pressure, cardiac catheterization procedures, or nephrotoxic agents with the exception of angiotensin-converting enzyme inhibitor use (Table 2). There were no appreciable differences in the use of intravenous diuretics (85% versus 90%, p=0.57) or length of diuretic therapy (7 days, p=0.87) between the two groups. The average systolic blood pressure before and during nesiritide administration did not differ between groups (98 mmHg, p=0.9 and 93 mmHg, p=0.94), and the number of patients who underwent cardiac catheterization were similar in both groups (37% versus 36 %, p=0.88). Other procedures that may have required intravenous radiocontrast were not recorded. No patients received aminoglycosides, nonsteroidal anti-inflammatory agents, or amphotericin B. There was a difference in angiotensin-converting enzyme inhibitor use (41% versus 67%, p=0.03).

	Yes n = 27	No n = 48	p Value
Serum Creatinine increase > 0.5mg/dL			
Treatment dose mean, median (range) mcg/kg/min	0.011, 0.01 (0.01-0.03)	0.011, 0.01 (0.005-0.03)	0.44
Treatment duration mean, median (range) hours	75, 48 (16-216)	67, 48 (14-432)	0.61
Intravenous diuretics use, No. (%) of pts	23 (85)	43 (90)	0.57
Length of diuretic therapy, mean days	7	7	0.87
ACEI use, No. (%) of pts	11(41)	32 (67)	0.03
Cardiac cath, No. (%) of pts	10(37)	17(36)	0.88
SBP, mean (range) mmHg/duration of nesiritide infusion	93 (65-128)	93 (74-140)	0.94
Number of hypotensive episodes/duration of nesiritide infusion	8	14	0.87
Net UOP, mean (range) mls/24h			
Before nesiritide initiation	-188 (-2928-1287)	453 (-1995-3239)	0.01
During nesiritide infusion	201 (-3526-2045)	1296 (-563-6402)	0.001
Length of hospital stay, mean, median (range) days	18, 13 (2-71)	13, 9 (2-121)	0.18
In-hospital mortality, No. (%) of pts	9 (34)	5 (11)	0.01

Clinical endpoints assessed between both groups are presented in Table 2. There was an increase in hospital stay (18 days versus 13 days,  $p=0.18$ ) and in-hospital mortality (34% versus 11%,  $p=0.01$ ) among those patients who experienced an increase in  $SCr > 0.5$  mg/dL. Net urine output assessed during the nesiritide infusion was significantly increased among those patients who did not experience an increase in  $SCr > 0.5$  mg/dL (1296 mls/24hrs versus 201 mls/24 hrs,  $p=0.001$ ); however, the use of nesiritide appeared to increase net urine output among all study patients (Table 2). Twenty-two patients developed hypotension defined as a systolic blood pressure of  $< 80$  mmHg during nesiritide administration. Of the patients who developed hypotension, 8 (30%) were in the group who experienced an increase in  $SCr > 0.5$  mg/dL and 14 (29%) were in the group who did not with each patient having an average of 1.07 hypotensive episodes ( $p=0.87$ ).

## DISCUSSION

It has been widely reported in the literature that hospitalized patients undergoing treatment for heart failure have dynamic  $SCr$  concentrations.<sup>14</sup> Treatment of ADHF commonly involves the use of diuretics and vasodilators in order to improve symptoms and the hemodynamic profile; however, both of these classes of medications can worsen renal function during the course of treatment. Because of this, health care providers are challenged by the need to provide symptomatic relief without worsening renal function. Further, it has been recognized that there are numerous confounding factors that can contribute to the development of renal dysfunction in patients receiving treatment for ADHF. These include both dose and duration of diuretic and vasodilator use, angiotensin-converting enzyme inhibitor and angiotensin receptor blocker use, hypotension, age, and cardiac catheterization due to intravenous radiocontrast administration.

Nesiritide was widely used in patients with ADHF due to its potent vasodilatory properties and ability to significantly reduce the pulmonary capillary

wedge pressure and improve symptoms in these hospitalized patients. Nesiritide has also been used to enhance diuresis due to its ability to increase urine output by inhibiting the renin angiotensin aldosterone system.<sup>17,18</sup> Despite these proposed beneficial effects, there is some concern that nesiritide may cause renal dysfunction and increase mortality when used to treat patients with ADHF. However, the significance of any of the aforementioned confounding factors has not been adjusted for statistically in the published meta-analyses that suggested nesiritide had a negative effect on renal function and mortality. Further, there has been no direct correlation that worsening renal function seen with nesiritide use is correlated with worse long-term outcomes. The data from the mortality meta-analysis consisting of 3 pooled studies found that nesiritide was associated with a trend toward an increase in mortality at 30 days ( $p=0.59$ ).<sup>7</sup>

Our retrospective analysis showed that 36% of patients treated with nesiritide experienced an increase in  $SCr > 0.5$  mg/dL. Of these patients, 11 required discontinuation of nesiritide therapy and 7 patients required dialysis. Further, of the 36% of patients with an increase in  $SCr > 0.5$  mg/dL, the discharge  $SCr$  remained elevated over baseline with an average  $SCr$  of 2.81 versus an average of 1.7 mg/dL in those who did not. Eleven of the 27 patients who experienced an increase in  $SCr > 0.5$  mg/dL required nesiritide to be discontinued. Seven (9%) patients required dialysis. Given such a large percentage of patients with renal dysfunction, this analysis assessed the effect of several confounding factors that could influence the development of renal dysfunction in patients hospitalized for heart failure. With respect to length of time to nesiritide administration, dose and duration of nesiritide therapy, diuretic use, age, average systolic blood pressure, or cardiac catheterization procedures, it was found that there was no difference between patients who experienced an increase in  $SCr > 0.5$  mg/dL versus those who did not. Baseline characteristics at the time of nesiritide administration were similar between all patients indicating that the 36% of patients who experienced the increase in  $SCr > 0.5$  mg/dL did not have

different baseline severities of heart failure. Both groups had similar baseline serum creatinines and a BUN:SCr ratio >20:1 indicating that there was a reduction in renal perfusion as a result of decreased cardiac output and intravascular volume depletion among all patients. Both groups also had similar systolic blood pressures (98 mmHg versus 97 mmHg). Physical exam findings and the review of systems are not reported due to the individual subjectivity in assessment and the inconsistencies in reporting these findings. There was a difference between groups with respect to net urine output and angiotensin converting enzyme inhibitor use between groups prior to nesiritide infusion. Both net urine output and angiotensin converting enzyme inhibitor use was less in the group of patients who experienced an increase in SCr>0.5 mg/dL indicating that this group of patients may have had a greater level of renal insufficiency at baseline and be less likely to tolerate potent vasodilator therapy.

There is one published retrospective trial that found that worsening renal function associated with nesiritide use in patients with ADHF was seen more often when the duration of therapy was continued for more than 24 hours.<sup>19</sup> Our study does not support that finding. Treatment was continued on average for 8 hours longer in patients who had an increase in SCr>0.5 mg/dL (75 hours versus 67 hours) but the difference was not significant (p=0.61). This study did not look at dose of diuretic used.

Of the patients who experienced an increase in SCr > 0.5 mg/dL, there was a corresponding increase in length of hospital stay and in-hospital mortality. This data supports the current literature that worsening renal function due to any cause in patients hospitalized for heart failure is associated with unfavorable outcomes. Currently, there is no published data from a prospective trial designed to

evaluate nesiritide's effect on renal function and mortality in ADHF.

Our study was limited by its retrospective design and small patient population. Further, because there are numerous confounding variables that can affect renal function in patients with ADHF, the lack of a comparison group to review the incidence of worsening renal function in those patients who did not receive nesiritide makes it difficult to draw any true associations.

## CONCLUSIONS

This retrospective analysis showed that 36% of patients treated with nesiritide for ADHF experienced an increase in SCr concentrations >0.5 mg/dL. This increase was seen irrespective of dose, duration of therapy, age, blood pressure, concomitant intravenous diuretic use and length of diuretic therapy, or cardiac catheterization procedures. Consistent with published data, those patients who experienced an increase in SCr concentrations >0.5 mg/dL also had an increase in hospital stay and in-hospital mortality. Therefore, until data from a randomized, prospectively designed trial is available, nesiritide should be used judiciously, on a case by case basis and only in those patients with ADHF presenting to the hospital with shortness of breath at rest or with minimal activity. Further, we recommend that renal function should be monitored daily because small, transient increases in SCr of 0.3 mg/dL to 0.5 mg/dL have been associated with unfavorable outcomes in patients with ADHF. Therefore we recommend discontinuing nesiritide therapy if the SCr increases by more than 0.2 mg/dl until further safety data are available.

## CONFLICT OF INTEREST

No conflicts of interest.

## References

1. American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart Disease and Stroke Statistics—2007 Update. *Circulation*. 2007;115:e69-e171.
2. DiDomenico RJ, Park HY, Southworth MR, Eyrich HM, Lewis RK, Finley JM. Guidelines for Acute Decompensated Heart Failure Treatment. *Ann Pharmacother*. 2004;38:649-660.
3. The Task Force on Acute Heart Failure of the European Society of Cardiology. Executive summary of the guidelines on the diagnosis and treatment of acute heart failure. *Eur Heart J*. 2005; 26:384-416.
4. Scios Inc. Natreacor (nesiritide) prescribing information. Fremont, CA; 2005.
5. Mills RM, LeJemtel TH, Horton DP, Liang C, Lang R, Silver MA. Sustained hemodynamic effects of an infusion of nesiritide in heart failure. *J Am Coll Cardiol*. 1999;34:155-162.
6. Colucci WS, Elkayam U, Horton DP, Abraham WT, Bourge RC, Johnson AD. Intravenous nesiritide, a natriuretic peptide, in the treatment of decompensated congestive heart failure. *N Engl J Med*. 2000;343:246-253.
7. Young JB, Abraham WT, Warner-Stevenson L, Horton DP, Elkayam U, Bourge RC. Intravenous nesiritide vs nitroglycerin for treatment of decompensated congestive heart failure. *JAMA*. 2002;287:1531-1540.
8. Sackner-Bernstein JD, Skopicki HA, Aaronson KD. Risk of worsening renal function with nesiritide in patients with acutely decompensated heart failure. *Circulation*. 2005;111:1487-1491.
9. Sackner-Bernstein JD, Kowalski M, Fox M, Aaronson K. Short-term risk of death after treatment with nesiritide for decompensated heart failure. *JAMA*. 2005;293:1900-1905.
10. Scios Inc. Natreacor (nesiritide) prescribing information. Fremont, CA;2005.
11. Panel of cardiology experts provides recommendations to Scios regarding Natreacor [press release]. Fremont, CA: Scios Inc.; June 13, 2005. Available from <http://www.sciosinc.com/scios/press/2005> (accessed April 11, 2007).

12. Scios Announces Recommended Use Initiative for Natrecor [press release]. Fremont, CA: Scios Inc.; August 22, 2005. Available from <http://www.sciosinc.com/scios/press/2005> (accessed April 11, 2007).
13. Heywood JT. Combining nesiritide with high-dose diuretics may increase the risk of increased serum creatinine. *Circulation*. 2005;112:451-452.
14. Butler J, Forman DE, Abraham WT, Gottlieb SS, Loh E, Massi BM. Relationship between heart failure treatment and development of worsening renal function among hospitalized patients. *Am J Cardiol*. 2004;147:331-338.
15. Krumholz HM, Chen YT, Vaccarino V, Wang Y, Radford MJ, Bradford WD. Correlates and impact on outcomes of worsening renal function in patients  $\geq 65$  year of age with heart failure. *Am J Cardiol*. 2000;85:1110-1113.
16. McAlister FA, Ezekowitz J, Tonelli M, Armstrong PW. Renal insufficiency and heart failure: prognostic and therapeutic implications from a prospective cohort study. *Circulation*. 2004;109:1004-1009.
17. La Villa G, Fronzaroli C, Lazzeri C, Porciani C, Bandinelli R, Vena S. Cardiovascular and renal effects of low dose brain natriuretic peptide infusion in man. *J Clin Endocrinol*. 1994;78:1166-1171.
18. Koller KJ, Goeddel DV. Molecular biology of the natriuretic peptides and their receptors. *Circulation* 1992;86:1081-1088.
19. Chow SL, Peng JT, Okamoto MP, Heywood JT. Effect of Nesiritide Duration on Renal Function in Acutely Decompensated Heart Failure Patients. *Ann Pharmacother*. 2007;41:556-561.