National PBM Drug Monograph

Nesiritide (Natrecor®)

VHA Pharmacy Benefits Management Strategic Healthcare Group and Medical Advisory Panel

Acute Decompensated Heart Failure-Clinical and Hemodynamic Presentation

Patients with acute decompensated heart failure clinically present with evidence of volume overload. Hemodynamically, these patients will usually have elevated right and left ventricular filling pressures, decreased cardiac output, and increased systemic vascular resistance. No detailed management of acute decompensated heart failure is presented in current guidelines. Despite this, it is well recognized that the primary endpoints are to reduce volume overload and improve hemodynamics by increasing cardiac output, decreasing vascular resistance, and reducing ventricular filling pressures. Diuretics, inotropes and vasodilators are useful in achieving these endpoints.[1] Of all hemodynamic parameters considered, a reduction in left ventricular filling pressure (pulmonary capillary wedge pressure; PCWP) most closely corresponds to improvements in dyspnea at rest.[2] Furthermore, persistently elevated left ventricular filling pressures are associated with a greater risk of progressive heart failure death, sudden death, and overall mortality in patients hospitalized with decompensated heart failure. In a study of 456 patients hospitalized for heart failure due to systolic dysfunction, significantly greater 1 year survival rate (36% vs 18%, $p<0.001$) was shown when left ventricular filling pressure was reduced to near normal values (PCWP <16 mmHg) compared to patients with PCWP >18mmHg.[3] Additionally, in this patient population, hemodynamics such as right atrial pressure, pulmonary atrial pressure, systemic arterial pressure, cardiac index and systemic vascular resistance were not predictive of mortality.

Although depressed cardiac index is usually found in patients with decompensated heart failure, improvements in cardiac index has not been shown to predict clinical outcomes. Use of inotropic agents in decompensated heart failure is usually aimed at improving cardiac index, a hemodynamic parameter not associated with improved clinical outcomes.[4] The Outcomes of Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) was a study in which a 48 hour infusion of milrinone was given to 949 patients hospitalized with decompensated heart failure.[5] In this study, milrinone did not reduce length of hospital stay and was associated with significantly more adverse events (atrial fibrillation and hypotension).

Thus, given the clinical evidence that demonstrates reduction in elevated filling pressures improves clinical outcomes in decompensated heart failure patients, the use of intravenous vasodilators over inotropes seems a more logical approach of pharmacotherapeutic management.

Introduction[6]

Nesiritide (Natrecor®) has been approved for the intravenous treatment of patients with acute decompensated congestive heart failure (CHF) who have dyspnea at rest or with minimal activity. In this patient population, nesiritide reduced pulmonary capillary wedge pressure and improved dyspnea. Nesiritide is a recombinant form of human B-type natriuretic peptide (hBNP) that is manufactured from *E. coli* using recombinant DNA technology. Nesiritide represents the first drug in this novel class of agents.

Pharmacology[6-8]

Three natriuretic peptides have been identified to date: A-type (atrial), B-type (brain), and C-type. ANP and BNP are both synthesized in the cardiomyocytes. Both the atria and the ventricles secrete ANP, but its main site of production is the atria. Atrial and ventricular distention regulate the synthesis and release of ANP. BNP is secreted by the ventricles in direct proportion to ventricular volume expansion and pressure overload. Although plasma ANP and BNP levels increase according to severity of heart failure, BNP levels are usually higher than ANP levels in patients with severe disease. This has been the basis of using plasma BNP levels as a diagnostic marker of heart failure.

Three natriuretic peptide receptors, known as A, B, and C, have been identified. The A and B receptors are found in vascular smooth muscle. When ANP or BNP bind to the A receptor, there is an increased synthesis of guanosine 3'5'-cyclic monophosphate (cGMP), a potent vasorelaxer. Both ANP and BNP are potent systemic vasodilators with relatively balanced vasodilating effects on both arterial and venous vasculature. CNP binds to the B receptor and also demonstrates vasodilating effects. All three natriuretic peptides bind to the C-receptor, which functions mainly as a clearance receptor.

Other effects of natriuretic peptides include natriuresis and diuresis, which are achieved through afferent arteriolar vasodilation and inhibition of sodium reabsorption by the proximal convoluted tubule. Natriuretic peptides also inhibit renin and aldosterone release. All these effects help to improve hemodynamics and symptoms of heart failure.

Value of Endogenous BNP Measurements

The FDA recently approved a rapid BNP immunoassay that measures BNP levels in whole blood or plasma specimens. Preliminary studies have shown that measuring endogenous BNP levels is a valuable diagnostic and prognostic tool in patients with heart failure. In a recent study, of 250 patients presenting to urgent care with the chief complaint of dyspnea, 97 patients diagnosed with CHF had elevated BNP levels (mean 1076 ± 138 pg/ml).[9] Non-CHF patients had a mean BNP concentration of 38 ± 4 pg/ml. The BNP assay was determined to be highly sensitive (92%) and specific (92%) for the diagnosis of CHF. A pilot study of 72 patients hospitalized with decompensated CHF was conducted to determine if BNP levels would predict outcomes of death (during hospitalization or within 30 days of discharge) and readmission for CHF within 30 days of discharge.[10] There were 13 deaths and 9 readmissions for CHF. These patients had increasing BNP levels (mean increase 233 pg/ml) during hospitalization while patients without endpoints had a mean decrease in BNP of 215 pg/ml. Thus, preliminary studies demonstrate the utility of endogenous BNP levels as an important diagnostic and prognostic tool in patients with CHF. BNP levels have been measured to screen for left ventricular dysfunction and directly correlate with wedge pressures.[11]

Pharmacokinetics[6]

Nesiritide shows a biphasic disposition from the plasma.

Terminal half-life ($t_{½}$)	18 minutes
Volume of distribution of central compartment (Vc)	0.043 L/kg
Volume of distribution at steady-state (Vss)	0.19 L/kg
Clearance (CL)	9.2 ml/min/kg

Nesiritide undergoes elimination through 3 different mechanisms in order of decreasing importance:

1) binding to cell surface clearance receptors followed by cellular internalization and then lysosomal proteolysis
2) degradation by endopeptidases located on the vascular lumenal surface
3) renal filtration.

FDA Approved Indication[6]

Nesiritide is indicated for intravenous treatment of patients with acutely decompensated congestive heart failure who have dyspnea at rest or with minimal activity.

Current VA National Formulary Status

Currently, nesiritide is not on the VA national formulary (VANF). Dobutamine, nitroglycerin and milrinone are currently on the VANF.

Dosage and Administration[6]

Nesiritide is available as a 1.5mg single use vial. It can be reconstituted by adding 5 mls of the following preservative free diluents: 5% dextrose, 0.9% sodium chloride, 5% dextrose and 0.45% sodium chloride, or 5% dextrose and 0.2% sodium chloride. Once reconstituted, it is administered in a volume of 250 mls, resulting in a final concentration of 6 µg/ml. This mixture is stable for 24 hours. The recommended dose

of nesiritide is an IV bolus of 2 µg/kg followed by continuous infusion at 0.01 µg/kg/min. There is limited experience in using nesiritide at doses larger than recommended or for greater than 48 hours. Although central hemodynamic monitoring is not required for nesiritide, blood pressure should be monitored closely as the dose-limiting side effect of nesiritide is hypotension. If hypotension occurs during nesiritide administration, the dose should be reduced or discontinued and blood pressure supporting measures should be instituted (i.e., IV fluids, changes in body positions). In the Vasodilation in the Management of Acute Congestive Heart Failure[12] (VMAC) trial, when symptomatic hypotension occurred, nesiritide was temporarily discontinued. Once the patient was stabilized, nesiritide was restarted at a dose reduced by 30% (with no bolus administration). Due to either physical and/or chemical incompatibilities, the following injectable medications should not be co-administered through the same IV catheter as nesiritide: heparin, insulin, ethacrynate sodium, bumetanide, enalaprilat, hydralazine, and furosemide. Sodium metabisulfite, a preservative found in injectable drugs, is incompatible with nesiritide and should not be administered in the same infusion line. The catheter must be flushed between administration of nesiritide and incompatible drugs.

Adverse effects[6]

The most common adverse effect reported in clinical trials was dose-related hypotension. In most cases, hypotension was asymptomatic. Other adverse effects include ventricular tachycardia, headache, nausea, and back pain. In placebo and active-controlled clinical trials, nesiritide was not associated with an increase in ventricular or atrial arrhythmias. Renal function may be affected by nesiritide. When doses higher than that recommended were used, elevations in serum creatinine of greater than 0.5 mg/dl were observed.

Contraindications[6]

Use of nesiritide is contraindicated in patients who are hypersensitive to any of its components. Nesiritide should not be used in patients with cardiogenic shock or in those with SBP <90 mmHg. Nesiritide should be avoided in patients with suspected or known low cardiac filling pressures.

Precautions[6]

Since nesiritide is derived from *E. coli* there is a potential for an allergic reaction. However, no serious allergic or anaphylactic reactions have been reported with nesiritide. Nesiritide is not recommended for patients with significant valvular stenosis, restrictive or obstructive cardiomyopathy, constrictive pericarditis, pericardial tamponade, or other conditions in which cardiac output is dependent upon venous return.

Drug Interactions[6]

No clinical trials have been conducted to specifically investigate potential drug interactions with nesiritide. In clinical trials, nesiritide was used concomitantly with other medications and no drug interactions were reported other than increased frequency of symptomatic hypotension when nesiritide was co-administered with oral ACE-inhibitors. In clinical trials, co-administration of nesiritide with IV vasodilators such as nitroglycerin, nitroprusside, milrinone, or IV ACE-inhibitors was not evaluated.

Citation[13]	Colucci WS, et al. Intravenous nesiritide, a natriuretic peptide, in the treatment of decompensated congestive heart failure
Study goals	To determine the efficacy of nesiritide and to compare nesiritide versus standard therapy in patients with decompensated CHF.
Methods	➢ 432 hospitalized patients with symptomatic CHF, enrolled in one of two studies, an efficacy trial or a comparative trial • **Study Design** –efficacy trial ➢ Randomized, double-blind, placebo-controlled, parallel group trial ➢ Randomization of 127 patients; 42 patients to placebo, 43 patients to nesiritide 0.3 µg IV bolus followed by 0.015 µg/kg/min continuous infusion, 42 patients to nesiritide 0.6 µg IV bolus followed by 0.030 µg/kg/min continuous infusion ➢ Continuous IV infusions of nesiritide and placebo were given for at least 6 hours; during this 6 hour interval, oral vasoactive medications and IV diuretics were held

- Other than study medication, no IV medications during the 6 hour study period was permitted
- Baseline hemodynamic variables were measured 4 hours after oral vasoactive medications and IV diuretics were withheld and these were not restarted until after the 6 hour study period
- Primary outcome measure: change from baseline of PCWP at 6 hours (all patients required Swan-Ganz catheter placement)
- Secondary outcome measures: global clinical status (judged independently by patient and investigator); clinical symptoms of dyspnea and fatigue (rated jointly by patient and investigator); and other hemodynamic measurements (i.e., cardiac index, mean right atrial pressure, pulmonary arterial pressures, systolic blood pressure and heart rate)
- Clinical global status rated by using a 5-category scale (markedly better, better, no change, worse, or markedly worse)
- Clinical symptoms of dyspnea and fatigue rated on a 3-category scale (improved, no change, or worse)

- **Study Design** –comparative trial
  - Randomized, controlled, parallel group trial
  - Randomization of 305 patients:
    - 102 patients given standard therapy, consisting of single IV vasoactive medication (dobutamide, milrinone, nitroglycerin, or nitroprusside) on open label basis
    - Patients given nesiritide doses in a double-blind manner
      - 103 patients given nesiritide 0.3 µg IV bolus followed by an IV infusion of 0.015 µg/kg/minute
      - 100 patients given nesiritide 0.6 µg IV bolus followed by an IV infusion of 0.030 µg /kg/minute
  - At the discretion of the investigator:
    - Dose of standard care medication could be increased and a 2nd IV vasoactive medication could be added to or substituted for the initial medication (including nesiritide)
    - IV diuretics and oral medications could be added at any time
    - Both nesiritide treatment groups could receive nesiritide for up to 7 days
  - Primary endpoints: global clinical status (judged independently by patient and investigator); clinical symptoms of dyspnea and fatigue (rated jointly by investigator and patient) assessed at 6 and 24 hours after treatment initiation and at the end of therapy (lasting up to 7 days)
  - Clinical global status rated by using a 5-category scale (markedly better, better, no change, worse, or markedly worse)
  - Clinical symptoms of dyspnea and fatigue rated on a 3-category scale (improved, no change, or worse)

Criteria

- **Inclusion** (both trials)
  - Symptomatic heart failure that warranted hospitalization for 1 or more IV drugs in addition to diuretics
- **Inclusion** (efficacy trial)
  - pulmonary capillary wedge pressure (PCWP) ≥ 18mmHg
  - cardiac index of ≤ 2.7 L/min/m^2 and
  - SBP ≥ 90 mmHg
- **Exclusion** (both trials)
  - recent MI or unstable angina (within preceding 48 hours)
  - valvular stenosis
  - hypertrophic or restrictive cardiomyopathy
  - constrictive pericarditis
  - primary pulmonary hypertension
  - active myocarditis
- **Exclusion** (comparative trial)
  - Use of IV vasoactive agent (i.e., an intravenous inotrope or vasodilator) for > 4 hours prior to start of the study

Results

Efficacy trial

Mean Change from Baseline at 6 hours

Placebo		**Nesiritide**		**P Value***
		0.015µg/kg/min	**0.030µg/kg/min**	
PCWP	+2.0	-6.0	-9.6	<0.001

*P value for comparison among all 3 groups

- Other hemodynamic changes from baseline caused by nesiritide in a dose dependent fashion:

- Decrease in right atrial pressure
- Decrease in systemic vascular resistance
- Decrease in systolic pulmonary artery pressure
- Decrease in mean pulmonary artery pressure
- Decrease in systolic blood pressure
- Moderate increase in cardiac index
- No substantial change in heart rate

§P value for comparison of both nesiritide groups to placebo

- Compared to the placebo group, both nesiritide groups had significant improvement in dyspnea and fatigue from baseline

Global Clinical Status of Better or Markedly Better from Baseline at 6 hours

	Placebo	Nesiritide 0.015µg/kg/min	Nesiritide 0.030µg/kg/min	P Value§
Judged by:	14%	60%	67%	<0.001
Judged by:	5%	55%	77%	<0.001

§P value for comparison of both nesiritide groups to placebo

- Compared to placebo, nesiritide treated patients experienced significant improvement in global clinical status as judged independently by both patient and physician

Improvement in Symptoms from Baseline at 6 hours

- Symptomatic hypotension caused 1 patient receiving nesiritide 0.030 µg/kg/min to discontinue therapy

Comparative trial

- Duration of therapy was similar among the 3 treatment groups:

Safety

- Dose-related hypotension (usually asymptomatic or mild) was the most common adverse effect in patients receiving nesiritide
- During the 6 hour study period, symptomatic hypotension occurred with the following frequencies:
  - 2% for nesiritide 0.015 µg/kg/min
  - 5% for nesiritide 0.030 µg/kg/min
  - 0% for placebo group

6 hours		0.015µg/kg/min	0.030µg/kg/min	
Dyspnea	61%	63%	65%	Not significant
Fatigue	30%	30%	33%	Not significant
Standard Care 24 hours		**Nesiritide 0.015µg/kg/min**	**0.030µg/kg/min**	**P Value**
Dyspnea	80%	78%	70%	Not significant
Fatigue	55%	55%	51%	Not significant

- Patients in each treatment arm experienced improvements in global clinical status, dyspnea and fatigue at 6 hours, at 24 hours and at the end of therapy
- No significant differences in global clinical status, dyspnea, or fatigue between the groups at any time

- **Safety**
  - Symptomatic hypotension occurred at the following frequencies:
    - 4% for standard therapy group
    - 11% for nesiritide 0.015 µg/kg/min
    - 17% for nesiritide 0.030 µg/kg/min
  - 5 patients receiving nesiritide 0.015 µg/kg/min and 10 patients receiving nesiritide 0.030 µg/kg/min discontinued therapy due to symptomatic hypotension
- Subsequently, researchers published analysis of the incidence of arrhythmogenicity between nesiritide treated patients and dobutamine treated patients in the comparative trial. Arrhythmic events, both life threatening (sustained VT and cardiac arrest) and non-life threatening (nonsustained VT), occurred more frequently in dobutamine treated patients than nesiritide treated patients. However, the study was not powered to look at the incidence of arrhythmias. (Burger AJ et al. Am J Cardiol 2001;88:35-39.)

Conclusions

In the efficacy trial, nesiritide demonstrated improvements in hemodynamic parameters, most notably PCWP, and in symptoms of dyspnea and fatigue. In the comparative trial, nesiritide demonstrated no additional benefit over standard therapy in improving global clinical status, dyspnea, and fatigue. The subgroup analysis (see Silver MA, et al.[14]) of dobutamine versus nesiritide demonstrated shorter duration of drug therapy and less use of IV medications in nesiritide treated patients compared to dobutamine treated patients. In both studies, nesiritide was generally well-tolerated. The most common adverse effect was dose related hypotension that was usually asymptomatic.

Critique

- Strengths (efficacy trial)
  - Randomized, double-blind controlled trial
  - Evaluated both hemodynamic and clinical endpoints
- Limitations (efficacy study)
  - Physicians and patients aware of hemodynamic changes prior to global clinical status or symptoms assessment
  - Clinical symptoms rated jointly by patient and investigator instead of patient alone which has the potential of biasing results
  - Clinical global status, dyspnea and fatigue rated on scales that are not validated (no current gold standard or validated scales exist); however, clinical global status scale has been used previously in long-term efficacy trials for CHF
- Strengths (comparative trial)
  - Nesiritide dose administered in double-blind fashion
- Limitations (comparative trial)
  - Open-label administration of standard therapy
  - Clinical symptoms rated jointly by patient and investigator instead of patient alone which has the potential of biasing results
  - Clinical global status, dyspnea and fatigue rated on scales that are not validated (no current gold standard or validated scales exist); however, clinical global status scale has been used previously in long-term efficacy trials for CHF
  - Nesiritide was not compared against the individual medications that comprised the standard therapy arm, but rather all 4 standard therapy medications
  - No discussion of the dose of standard therapy medications used
  - At the discretion of the investigator, all medication doses could be increased and a second vasoactive medication could replace the initial medication or be added to an existing one, complicating comparability between nesiritide groups and standard therapy group

	➢ No difference in global clinical status, dyspnea, or fatigue at 6 and 24 hours between nesiritide treatment groups and standard therapy, which shows no added benefit of using nesiritide over standard therapy

Citation[12]	Young JB and the Publication Committee for the VMAC Investigators. Intravenous nesiritide vs nitroglycerin for treatment of decompensated congestive heart failure
Study Goals	To compare the safety and efficacy of nesiritide, IV nitroglycerin (NTG), and placebo (PL) when added to standard care medications in patients with acute decompensated CHF.
Methods	• **Study Design** ➢ Multicenter, randomized, double-blind, placebo- and active-controlled trial ➢ 489 patients randomized: 142 patients to PL, 143 patients to NTG, 142 patients to fixed-dose nesiritide, 62 (catheterized) patients to adjustable-dose nesiritide o First 3 hours of study was placebo-controlled with double dummy study drug administration o After 3 hour placebo-controlled period, placebo patients crossed over to active therapy (NTG or fixed-dose nesiritide) ➢ Randomization of patients was stratified by the investigator's decision to use a right heart catheter (n=246), to facilitate hemodynamic monitoring, or not (n=243) ➢ Dose of Study Medications o NTG titrated to hemodynamic or clinical effect based on investigator's discretion o For both nesiritide treatment arms, nesiritide was administered as a 2µg/kg IV bolus, followed by 0.01µg/kg/min infusion for 3 hours o After 3 hours, the adjustable-dose nesiritide group could have their dose increased if SBP ≥100 mmHg and PCWP ≥ 20 mmHg by receiving 1µg/kg IV bolus followed by an increase in the infusion rate by 0.005 µg/kg/min up to a maximum of 0.03 µg/kg/min ➢ All patients received treatment for 24 hours or longer (at the investigator's discretion) ➢ During study drug administration, all patients were already being treated with standard medications, including diuretics, ß-blockers, dobutamine, dopamine, and other chronic oral and transcutaneous cardiac therapies, but IV vasodilators were NOT allowed ➢ Two hours before the start of the study through the end of the 3 hour placebo-controlled period, the following medications were <u>not</u> allowed: IV diuretics, nitroprusside, unblinded IV NTG, IV ACEIs, milrinone and new starts of either dopamine or dobutamine ➢ Primary endpoints: change in PCWP (catheterized patients only) and dyspnea (based on patient self-evaluation) at 3 hours using a 7-point scale with ratings as follows: markedly better, moderately better, minimally better, no change, minimally worse, moderately worse, and markedly worse) ➢ PCWP was measured at baseline, 15 minutes, 30 minutes, 1 hour, 2 hours, and 3 hours after the start of the study medications ➢ PCWP was also obtained at 6, 9, 12, 24, 36, and 48 hours after the start of the study medications, and when the study drug was discontinued (if before 48 hours) ➢ Secondary endpoints: onset of effect on PCWP, effect on PCWP after 24 hours, dyspnea assessment per patient and global clinical status, and overall safety profile.
Criteria	• **Inclusion** ➢ Age ≥ 18 years ➢ Requiring hospitalization and IV therapy for acutely decompensated CHF, with dyspnea at rest, for at least 24 hours ➢ Patients had elevated cardiac filling pressures determined by clinical estimation or direct measure of PCWP ≥ 20 mmHg and presented with at least 2 of the following: o jugular venous distention o paroxysmal nocturnal dyspnea or 2 pillow orthopnea within 72 hours of enrollment o mesenteric congestion causing abdominal discomfort

- evidence of decompensated CHF on chest x-ray
- Patients having the following characteristics were NOT excluded:
  - acute coronary syndrome
  - diastolic dysfunction
  - atrial or ventricular arrhythmias
  - hepatic or renal insufficiency
  - cardiac transplant candidates
  - preserved systolic function (ejection fraction > 40%)

- **Exclusion**
  - SBP consistently < 90 mmHg
  - Volume depletion or cardiogenic shock
  - Requiring mechanical ventilation
  - Receiving IV NTG that could not be withheld
  - Contraindication to IV vasodilator
  - Estimated length of survival less than 30 to 35 days

Results

- Both nesiritide treatment groups (fixed-dose and adjustable-dose) were pooled for study analysis

Primary endpoint: PCWP

	Nitroglycerin (n=60)	**Nesiritide (n=124)**	**Placebo (n=62)**
Baseline	28.0	27.8	27.7
3 hours	24.2	22.0	25.7
Mean change from baseline PCWP	-3.8	-5.8	-2.0
P value, vs placebo	0.09	<0.001	-
P value, nesiritide vs nitroglycerin	-	0.03	-

  - At the 3-hour end-point, nesiritide significantly decreased PCWP compared to either placebo or NTG when added to standard therapy
  - At every time point from 15 minutes to 3 hours, nesiritide significantly decreased PCWP when compared to placebo ($p < 0.05$)
  - At nearly every time point from 15 minutes to 3 hours (except 2 hours), nesiritide significantly decreased PCWP when compared to NTG ($p < 0.05$)
  - Compared to nitroglycerin, PCWP remained significantly lower on nesiritide through 24 hours ($p < 0.05$)
  - Hemodynamic effects of nesiritide were maintained through 48 hours without dose increases, indicating no tachyphylaxis
  - Mean dose of nesiritide during the first 48 hours of the study was 0.01µg/kg/min. The dose was increased in 23 of the 62 patients in the adjustable dose group, with 10 of the 23 receiving up to 0.015 µg/kg/min
  - In catheterized patients, the mean dose of NTG increased from 42µg/kg at 3 hours to 56µg/kg at 24 hours. The mean dose of NTG was 29µg/kg at 3 hours in noncatheterized patients
  - Compared to placebo, at the 3-hour end point, a significant reduction in dyspnea was noted with nesiritide ($p = 0.03$), but not with nitroglycerin. There was not a statistically significant difference between nesiritide and NTG ($p = 0.56$)

- **Safety**
  - During the first 24 hours after start of study drug, a significantly smaller percent of nesiritide treated patients experienced adverse effects compared to NTG treated patients (51% vs 68%, $p \leq 0.001$)
  - Symptomatic hypotension occurred similarly for NTG and nesiritide treatment groups, 5% and 4%, respectively
    - No difference in the severity of the hypotensive episodes or in the need for treatment of hypotension between the nesiritide treated patients and the NTG treated patients
    - Because of its longer half-life, nesiritide treated patients had a longer mean duration of symptomatic hypotension compared to NTG treated patients (2.2 hours vs. 0.7 hours, respectively)
    - Nesiritide had a similar adverse effect profile compared to nitroglycerin except for the more frequent occurrence of headache, 20% vs 8% ($p < 0.001$) and abdominal pain, 5% vs 1% ($p = 0.03$) in NTG treated patients

Conclusion	• In patients with acute decompensated CHF on standard therapy: ➢ Nesiritide demonstrated a statistically significant improvement in PCWP and dyspnea compared to placebo ➢ Nesiritide had a faster onset of action and greater efficacy than IV NTG as demonstrated by significant improvements in PCWP within 15 minutes of drug infusion ➢ Symptoms of dyspnea reported with nesiritide were not significantly different than IV NTG at 3 hours ➢ Nesiritide showed a similar adverse effect profile as NTG, except for the more frequent occurrence of headache and abdominal pain in NTG treated patients
Critique	• Strengths ➢ Randomized, placebo/active controlled trial ➢ Evaluation of both hemodynamic parameters and symptomology ➢ Severely ill patients and those with significant comorbidities participated so that results are representative of "real-world" outcomes • Limitations ➢ When evaluating change in PCWP at 3 hours compared to baseline, nesiritide treatment arm (pooled analysis for both fixed-dose and adjustable-dose) had twice as many patients (n=124) compared to NTG and placebo treatment arms, n=60 and n= 62, respectively ➢ Although statistically significant greater reduction in PCWP in nesiritide group compared to the NTG group, whether or not it may translate to a clinically significant difference depends upon the severity of heart failure ➢ 7 point scale used to evaluate dyspnea is not a validated tool (no current gold standard or validated scales exist) ➢ At baseline, the nesiritide groups had significantly more patients receiving dobutamine or dopamine compared to the NTG group, and significantly more patients in the nesiritide group received an IV vasoactive medication within 24 hours of the study drug. Significantly more patients in the nesiritide group were receiving a diuretic and more were on a class III antiarrhythmic agent at baseline ➢ Patients receiving NTG had dose titrated to either clinical or hemodynamic effect, but no clear definition of what constituted these effects was specified or discussed ➢ For some patients, therapy extended beyond 24 hours, but no mention of criteria used to extend the duration of the therapy, making it unclear who would best benefit from such an extension
Sponsored by	➢ Scios, Inc.

Citation[14]	Silver AM, et al. Effect of nesiritide versus dobutamine on short-term outcomes in the treatment of patients with acutely decompensated heart failure
Study Goals	To determine if therapy with nesiritide affects healthcare costs by comparing hospital length of stay and readmissions, and short-term mortality vs. dobutamine
Methods	• **Study Design** ➢ Subgroup analysis of a multi-center, prospective, open-label (double-blind to nesiritide dose), randomized, active-control trial ➢ 261 patients randomized: 58 to standard care (SC), 103 to nesiritide 0.015µg/kg/min infusion after a 0.3µg/kg IV bolus, 100 to nesiritide 0.030µg/kg/min infusion after a 0.6µg/kg IV bolus ➢ 102 patients in the original trial (see Colucci WS, et al.[13]) were randomized to SC with a single vasoactive agent selected by the investigator (e.g., dobutamine, milrinone, NTG, or nitroprusside). A second vasoactive agent could be added or a different one substituted for the original selection at the

investigator's discretion (nesiritide could not be used as the second agent). This study evaluated the 58 patients who received dobutamine as the first agent selected

- A second IV vasodilator could not be added to nesiritide but another agent could be substituted for nesiritide
- Changes in dose and the total length of therapy was left to the discretion of the investigator
- Prospectively defined endpoints: duration of IV vasoactive therapy, hospital length of stay, all cause hospital readmissions and those due to CHF through day 21, and the need for additional vasoactive agents
- Data collected retrospectively: six month mortality

Criteria

- **Inclusion**
  - Age ≥ 18 years with history of CHF
  - Requiring hospitalization and IV vasoactive therapy for symptomatic, acutely decompensated CHF
- **Exclusion**
  - SBP < 90 mmHg
  - Significant hemodynamic instability warranting inotropic or pressor agents
  - Prior treatment for more than 4 hours with IV vasoactive therapy for current episode of CHF
  - MI within 48 hours prior to study enrollment
  - Valvular stenosis, hypertrophic obstructive cardiomyopathy, constrictive pericarditis, primary pulmonary HTN, acute myocarditis, complex congenital heart disease, shock

Results

Subgroup Analysis of Dobutamine Versus Nesiritide

Characteristics	Dobutamine Subgroup (n=58)	Nesiritide 0.015µg/kg/min (n=103)	Nesiritide 0.030µg/kg/min (n=100)	Overall P Value
Duration of therapy (hours)				
Initial study drug, median (hours)	65	40[a]	26[a]	< 0.001
All IV therapies, median (hours)	65	42[a]	41[a]	0.016
Median length of stay (days)	4.5	5.0	5.0	0.411
Still hospitalized on day 21	7%	2%	4%	0.259
All cause readmission	20%	8%[a]	11%	0.085
CHF readmission	13%	4%	4%	0.081
6 month mortality	31%	18%[a]	24%	0.123

[a] $p < 0.05$, relative to dobutamine

- In comparison to patients (n=58) who received dobutamine as their initial standard care agent, nesiritide treated patients had a shorter duration of drug therapy and a shorter duration of all IV drug therapies
- Fewer hospital readmissions (all cause) and lower mortality were shown in patients treated with nesiritide 0.015 µg/kg/min compared to dobutamine
- There was no difference between nesiritide (both doses) treated patients and dobutamine treated patients with respect to the following:
  - Median length of hospitalization stay
  - Hospitalization still at day 21
  - All cause readmission
  - CHF readmission
  - 6 month mortality

- **Safety**
  - A significantly higher percent of patients experienced asymptomatic hypotension (overall p=0.002) with nesiritide. Symptomatic hypotension occurred more frequently with nesiritide (11% and 17% in the lower and higher dose groups, respectively) compared to the dobutamine group (5%). Nonsustained VT occurred in 10% of patients in the nesiritide 0.015µg/kg/min dose group compared to 5% on dobutamine and 1% who received the higher dose of nesiritide (overall p=0.015)

Conclusion	• In patients with acute decompensated CHF: ➢ Nesiritide was associated with a shorter duration of treatment ➢ Hospital length of stay did not differ between the groups ➢ All-cause hospital readmissions were reduced with nesiritide 0.015µg/kg/min compared to dobutamine ➢ Patients in the nesiritide 0.015µg/kg/min dose group had a significantly lower rate of mortality at 6 months compared to dobutamine
Critique	• Strengths ➢ Double-blinded to nesiritide dose • Limitations ➢ Open-label study design ➢ Selection of SC therapy not randomized ➢ At baseline, significantly more patients in the dobutamine group had ischemia as the primary etiology of CHF and a previous MI compared to the nesiritide groups. The authors suggest that the selection of dobutamine may have resulted in a sicker population in this subgroup ➢ Significantly more patients in the 0.015µg/kg/min nesiritide group were white and had a history of sudden death. Significantly more patients in the 0.030µg/kg/min nesiritide group had a history of sustained VT ➢ Small number of patients in each subgroup and the number of patients in the dobutamine group was smaller than each of the nesiritide groups ➢ Higher than recommended doses of nesiritide used
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Citation[15]	Burger AJ, et al. Evidence of ventricular ectopy at baseline is not predictive of the proarrhythmic effects of dobutamine in the treatment of decompensated CHF: the PRECEDENT study
Study Goals	To compare the effects of nesiritide and dobutamine on heart rate and ventricular arrhythmias during the first 24 hours of treatment for decompensated CHF.
Methods	• **Study Design** ➢ Prospective, randomized controlled, parallel group trial ➢ Randomization of 246 patients, after 24-hour baseline Holter monitoring ➢ Open label use of dobutamine and nesiritide, but blinded with respect to dose of nesiritide o 83 patients given dobutamine at a minimum dose of 5 µg/kg/min o Nesiritide dose: ▪ 84 patients given nesiritide IV infusion at 0.015 µg/kg/minute ▪ 79 patients given nesiritide IV infusion at 0.030 µg/kg/min ➢ Randomization stratified based on patient's known history of sustained or nonsustained ventricular tachycardia ➢ Study medications administered for at least 24 hours during which time: o All patients received Holter monitoring o No other vasoactive medications (i.e., milrinone, nitroprusside, NTG, or dopamine) permitted o Diuretics and all long-term cardiac therapies allowed ➢ Baseline demographics similar between all 3 treatment arms except more dobutamine patients had NYHA class IV CHF than did nesiritide treated patients (36%, 20%, and 23 % in the dobutamine, nesiritide 0.015 µg/kg/min, and nesiritide 0.030 µg/kg/min groups, respectively) o But, no significant difference in Holter monitoring during the 24 hour baseline period ➢ Primary endpoints: o Change from baseline in average heart rate, average hourly premature ventricular beats (PVBs), and hourly repetitive beats during 24 hour study drug infusion period ➢ Secondary endpoints: o Change from baseline in couplets, triplets, ventricular tachycardias (VT) and evaluation of proarrhythmia during 24 hour study drug administration period

- Criteria used to assess proarrhythmia:
  - Velebit Criteria:
    - ≥ 4-fold increase in PVB's
    - ≥10-fold increase in couplets or repetitive forms (couplet or runs of nonsustained VT)
    - Occurrence of a new sustained VT
  - CAPS
    - 10-fold increase in PVBs, if baseline is 10-50 PVBs/hr
    - 5-fold increase in PVBs, if baseline is 51-100 PVBs/hr
    - 4-fold increase in PVBs, if baseline is 100-300 PVBs/hr
    - 3 fold increase in PVBs, if baseline is >300 PVBs/hr
    - 10-fold increase in runs of nonsustained VT also define a proarrhythmic effect, regardless of baseline frequency of episodes

Criteria

- **Inclusion**
  - History of NYHA Class III or IV CHF
  - Patients for whom dobutamine or nesiritide was considered appropriate as a single IV vasoactive agent
  - Patients who were on stable doses of oral antiarrhythmic medications for at least 48 hours prior to study drug infusion or patients not on antiarrhythmic agents
- **Exclusion**
  - Patients with systolic BP consistently < 85mmHg
  - Patients who required IV vasoactive medications during baseline Holter monitoring
  - Patients who required IV antiarrhythmic medication during the 48-hour period prior to study drug administration

Change from Baseline 24 Hour Holter Tape to Treatment 24 Hour Holter Tape

Primary Endpoint	**Dobutamine**	**Nesiritide**	
		0.015 µg/kg/min	**0.030 µg/kg/min**
Mean Average Heart Rate (P values*)	+5 (n/a)	-1 (< 0.001)	+1 (0.002)
Mean Average Hourly PVB's (P values*)	+69 (n/a)	-13 (0.001)	-5 (0.002)
Mean Average Hourly Repetitive Beats (P values*)	+15 (n/a)	-5 (<0.001)	+3 (0.001)

*P values, vs dobutamine

- **Primary Endpoints**
  - During the 24-hour treatment period:
    - Dobutamine group had a significant increase in heart rate from baseline
    - No significant change in heart rate from baseline for both nesiritide groups
    - Significantly more average hourly PVB's for dobutamine group compared to each nesiritide group
    - Significantly more average hourly repetitive beats for dobutamine group compared to each nesiritide group

Secondary Endpoint	**Dobutamine**	**Nesiritide**	
		0.015 µg/kg/min	**0.030 µg/kg/min**
Mean couplets (events/24h) (P values*)	+68 (n/a)	-52 (<0.001)	+3 (0.008)
Mean triplets [events/24h] (P values*)	+22 (n/a)	-5 (< 0.001)	+3 (0.008)
Mean VT [events/24h] (P values*)	+48 (n/a)	-6 (<0.001)	+2 (0.001)

*P values, vs dobutamine

During the 24-hour treatment period:

- Dobutamine was associated with a statistically significant increase in couplets, triplets, and VT compared to each nesiritide groups

	➢ Nesiritide 0.015 µg/kg/min group had a significant decrease in the frequency of VT ➢ Nesiritide 0.030 µg/kg/min group had no significant change from baseline in the frequency of VT ➢ Absence or presence of VT on baseline Holter monitoring was **NOT** predictive of the proarrhythmic effects of dobutamine Proarrhythmic Criteria: ➢ When using the Velebit criteria, 23% of the dobutamine treated patients and 2% of the nesiritide treated patients (p< 0.001) met the criteria ➢ When using the CAPS criteria, 10% of the dobutamine and 0% of the nesiritide treated patients (p=0.001) met the criteria • **Safety** ➢ Both symptomatic and asymptomatic hypotension occurred more frequently in the nesiritide treatment groups than in the dobutamine treatment group o During the first 24 hours of study drug infusion, symptomatic hypotension was reported in 2 (2%), 14 (17%), and 19 (24%) of patients in the dobutamine, nesiritide 0.015 µg/kg/min and nesiritide 0.030 µg/kg/min groups, respectively (p< 0.001) o Nesiritide demonstrated dose related increase in frequency of hypotensive events o Although hypotension occurred more frequently in patients receiving nesiritide, it occurs less commonly for those receiving standard dosing of nesiritide (2µg/kg IV bolus then 0.01µg/kg/min) as demonstrated in the VMAC trial
Conclusion	Dobutamine was associated with significant increases in heart rate and ventricular arrhythmias and its proarrhythmic effect was not dependent on previous arrhythmia history. Nesiritide, at either dose, did not increase heart rate or demonstrate a proarrhythmic effect. Nesiritide dosed at 0.015µg/kg/min actually reduced VT.
Critique	• Strengths ➢ Randomized controlled trial ➢ Double blind administration of nesiritide doses • Limitations ➢ Open-label design with respect to use of dobutamine and nesiritide ➢ Increase in mean average heart rate of 5 beats per minute for dobutamine treated patients is clinically irrelevant ➢ Although researchers reported statistically significant increase in PVBs, hourly repetitive beats, couplets and triplets, there was no discussion of whether patients were symptomatic, required any intervention, or experienced fatality as a result o Dobutamine increases ventricular ectopic activity but these are usually asymptomatic and do not require any intervention[15] ➢ Investigators report that dobutamine's proarrhythmic effect was independent of absence or presence of VT on baseline Holter monitoring, but they did not characterize the type of arrhythmias (i.e., PVBs, hourly repetitive beats, couplets, triplets, or ventricular tachycardias) ➢ Results reported as events per 24-hour so unknown if event was occurring in 1 or several patients ➢ More patients in the dobutamine treatment arm had NYHA class IV CHF compared to each nesiritide group o Patients with heart failure are at greatest risk for proarrhythmic effect of dobutamine[16]
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Cost Analysis

A cost effectiveness analysis was not performed due to the lack of published data on consistent outcome measures such as length of stay, readmission rates, morbidity, mortality and quality of life for comparative agents. PCWP was reported as an outcome measure in the trials; however, the clinical relevance of reduction in PCWP in various grades of heart failure has not been clearly linked to changes in mortality rates. In addition, less than 80% of nesiritide patients in the trials were catheterized to obtain accurate PCWP measures. No change in length of stay, readmission rates, or mortality between dobutamine and both doses of nesiritide was noted in the subanalysis of the trial by Colucci et al. There was a reduction in all-cause readmission and 6 month mortality between the 0.015µg/kg/min dose group and dobutamine. Although not a primary endpoint of the study, all-cause readmissions or those for CHF were not significantly different and neither were death at 7 days or 6 month mortality rates between NTG and nesiritide in the VMAC trial. Published data suggests that nesiritide may be as effective as standard therapy. Comparative safety of nesiritide and standard therapies may only be reliably evaluated when

published data becomes available. A cost minimization analysis was performed below to provide a glimpse of the relative costs of these agents.

Acquisition Costs

- 1.5mg vial of nesiritide = $277.90
- Manufacturer's recommended nesiritide dose:
  - 2 µg/kg IV bolus followed by a continuous infusion at a dose of 0.01 µg/kg/min
- 70 kg patient would require a dose of:
  - 70kg (2 µg/kg) + 0.01 µg/kg/min (70kg x 1440min/day) = 1148 µg/day
  - 48 hours of nesiritide therapy, total drug = 2296 µg
  - Since 1 vial of nesiritide contains 1500 µg and once reconstituted, is stable for only 24 hours, a total of 2 vials would be needed for 48 hours of therapy

Drug	Daily Dose*	Cost/Day/Patient ($)	Cost/48hours/Patient ($)
Nesiritide	**1148 µg**	**277.90**	**555.80**
Dobutamine	5 to 15 µg/kg/min *(10 µg/min)*	31.91-95.73	63.82-191.46
Nitroglycerin	5-20 µg/min *(10 µg/min)*	0.30-1.20	0.60-2.40
Nitroprusside	2-4 µg/kg/min *(3 µg/min))*	15.77-31.53	31.54-63.06
Milrinone	50 µg/kg (bolus) + 0.375 to 0.75 µg/kg/min *(0.5 µg)*	223.91	447.82

*Daily dose based on 70 kg patient

Pharmacoeconomic Data

A pharmacoeconomic analysis used data from two published clinical trials to model a 6 month episode of care for patients treated with either dobutamine or nesiritide during an initial hospital admission for decompensated heart failure.[17] Probability of clinical events such as cardiac arrest, sustained and nonsustained ventricular tachycardia, hypotension, nausea and vomiting, hospital readmission for HF, and death were based on clinical trial data. Two clinicians provided information regarding typical treatment procedures for such events. Using multivariate regression analysis of a national hospital database (HCUP 1997), investigators established length of hospital stay and cost of admission associated with these events. To convert billed charges to actual cost, Medicare cost-to-charge ratios were used. Compared to the dobutamine cohort, investigators found an average episode of care cost for the nesiritide cohort lower by $631 (range $207-$1047). Importantly, the cost of nesiritide or dobutamine was not included because the market price of nesiritide had not been set at the time of the study. Thus, the financial gains realized in this study would probably not exist if the cost of nesiritide was included.

Discussion section

1. Nesiritide as a safe, effective alternative for patients who previously experienced arrhythmias on inotrope therapy or those who are prone to arrhythmia

Unpublished data regarding differences in rates of arrhythmias suggests reduced incidence with nesiritide compared to inotropes. There are multiple confounding factors contributing to arrhythmia rates in CHF patients and peer-reviewed published data is necessary to determine whether there is truly a difference. Some problems identified with the current Scios data on file are: unidentified number of patients actually experiencing arrhythmias, events secondary to arrhythmia requiring intervention are unknown, and differences exist in baseline patient demographics. There is currently no evidence to support improved morbidity/mortality outcomes with use of nesiritide in comparison to inotropes, despite potential differences in arrhythmia rates observed on 24 hour Holter monitoring. Nitroglycerin may be used as an alternative for appropriate patients who cannot tolerate inotropes.

2. ***Nesiritide as a safe, effective alternative in renally compromised patients since it is metabolized mainly by binding to cell surface clearance receptors followed by cellular internalization and then lysosomal proteolysis and minimally through renal excretion***

Standard therapies can be titrated to effect in patients with renal dysfunction. Nesiritide may also affect renal function in susceptible patients. In the 30-day follow-up period of the VMAC trial, 5 patients in the IV nitroglycerin group (2%) and 9 patients in the nesiritide group (3%) required first-time dialysis. Higher doses of nesiritide elevated creatinine.

3. ***Since nesiritide has not been associated with proarrhythmic effects, monitoring requirements may differ in comparison to standard inotrope therapy and be less costly through step-down unit management as compared to ICU level care***

Nesiritide, if not used in conjunction with inotropes, may require less intense monitoring for cardiac effects. It does appear to cause the same incidence of hypotension as nitroglycerin, and would therefore still require aggressive blood pressure monitoring. Typically, patients admitted with acute CHF decompensation require ICU level care and cost savings would not be realized without significant differences in cost of appropriate step-down care. If an ICU bed is not available for inotrope monitoring and critical care nursing is not required, a benefit may be observed in patients for whom nitroglycerin therapy is not tolerated or ineffective.

4. ***Nesiritide as an alternative to short-term nitroglycerin or nitroprusside therapy in the ER for patients to be discharged home the same day***

Nesiritide appears to require the same level of monitoring as nitroglycerin and nitroprusside. For patients who do not appear critical enough for hospital admission but qualify for rescue therapy in the ER, nesiritide may be a reasonable alternative for patients who cannot tolerate standard therapy. Hypotension with nitroglycerin is not an appropriate rationale for substitution with nesiritide, as hypotension rates are similar.

Conclusions

Nesiritide is a novel agent that appears to be effective and well-tolerated in patients with acute decompensated CHF. The most commonly reported side effect of nesiritide was dose-related hypotension, which was usually mild. Although clinical trial data demonstrate improvements in PCWP and dyspnea in patients receiving nesiritide, these trials have limitations that include open-label study design, non-validated scales of symptom assessment, and an unbalanced number of patients in treatment arms. In addition, the majority of trials were sponsored by Scios. In Colucci's comparative trial, no difference in the primary endpoints of global clinical status, dyspnea, or fatigue was noted between the nesiritide treatment groups and standard therapy, demonstrating no added benefit of using nesiritide over standard therapy agents. According to the study conducted by Burger et al., nesiritide seems to lack the proarrhythmic effects of dobutamine. However, most of the endpoints that were evaluated (i.e., PVBs, hourly repetitive beats, couplets, triplets) are usually asymptomatic and often do not require interventions. There is no clear consensus on the management of PVBs, couplets, or triplets in clinical practice. Decisions on whether or not to treat are usually provider specific.

Formulary Recommendation

Nesiritide is the first drug in a novel class of therapeutic agents that can be used to treat acute decompensated heart failure. Because nesiritide has not demonstrated clinical superiority to standard care agents routinely used, its much higher cost cannot justify its use as a first line agent. Additional well-designed comparative trials need to be conducted to help define its exact role in therapy. At this time, nesiritide should remain non-formulary, but made available at all medical centers where acute decompensated CHF is treated. It is recommended that nesiritide be restricted to patients who do not have an adequate response or have a contraindication to standard therapy.

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Contributors: New York VAMC
Nino Marzella, PharmD, Pharmacy Resident
San Diego VAMC
Kavita Sharma, PharmD, Resident
Monica Schaefer, PharmD, Pharmacoeconomics Pharmacist
Melissa Delattre, PharmD, Pharmacoeconomics Resident
Anthony P. Morreale, PharmD, MBA, BCPS, Chief of Pharmacy
Brian Plowman PharmD, MBA, BCPS, Associate Chief of Pharmacy

Reviewed by: Kelley Curtis, RPh, MBA, Drug Information Center, New York VAMC
Elaine Furmaga, PharmD, VA Pharmacy Benefits Management-Strategic Healthcare Group

National PBM Drug Monograph Addendum
Nesiritide (Natrecor®)

VHA Pharmacy Benefits Management Strategic Health Care Group and the Medical Advisory Panel

Also refer to the original nesiritide drug monograph at **http://www.pbm.va.gov/monograph/nesiritidemonograph.pdf**

Introduction[1,2]

Nesiritide (Natrecor® Scios) was approved by the FDA in August 2001 for use in patients with acutely decompensated congestive heart failure (ADHF) who have dyspnea at rest or with minimal activity. The PBM-MAP and VISN Formulary Leaders reviewed nesiritide as a new molecular entity in April 2002 and recommended that the agent remain nonformulary. In a provider memo dated November 18, 2002, the MAP and Cardiology Advisory Group recommended that nesiritide be readily available at all VA medical centers (VAMC) where ADHF is treated (e.g., those with an ICU/CCU). Recommendations in the monograph and memo stated that nesiritide should be reserved for patients who had an inadequate response to or were unable to tolerate standard therapy (e.g., diuretics, vasodilators, ± inotropic agents). As the data were insufficient at the time to determine whether nitroglycerin or nesiritide should be used as second line therapy after high dose diuretics, it was recommended that this issue be discussed at the VISN and/or local levels to determine consensus on protocols and for reviewing utilization.

Recently (May 6, 2005), the manufacturer of nesiritide notified healthcare providers of recent changes to the Effect on Mortality section of the prescribing information for nesiritide, as well as results of two meta-analyses published on the safety of nesiritide compared to control therapy (generally diuretics and nitroglycerin). The results of the meta-analyses and the changes to the prescribing information are summarized in the following sections.

The manufacturer constituted an advisory panel to independently review the data on nesiritide. Due to the potential safety concerns with nesiritide and the inconclusive results based on the small number of events, the panel stated that a large clinical outcome trial should be initiated as soon as possible. The panel recommended that nesiritide should only be used in patients similar to those enrolled in the pivotal clinical trial, who presented to the hospital with ADHF and dyspnea at rest, which is slightly more restrictive than the currently FDA approved indication. The advisory panel also recommended that nesiritide not be used to replace diuretics and that it should <u>not</u> be used in the following situations: for intermittent infusion; for scheduled repetitive use; to improve renal function; to enhance diuresis.

Summary of Meta-Analyses[3,4] (Refer to Tables 1 and 2)

Meta-analyses of data including FDA and drug sponsor documents in addition to clinical trials with nesiritide in patients with ADHF, reported a statistically significant increase in worsening renal function compared to noninotropic controls (RR 1.53; 95% CI 1.16-2.00; P=0.002) and compared to all controls (RR 1.54; 95% CI 1.20-1.99; P=0.001) in pooled data from five trials, and medical intervention due to worsening renal function (11% vs. 4%; RR 2.29; 95% CI 1.07-4.89; P=0.03) from pooled data of two trials compared to noninotropic controls. Another meta-analysis reported a trend toward an increase in 30-day mortality (7.2% vs. 4.0%; HR 1.74; 95% CI 0.97-3.12; P=0.059) from pooled data of three trials compared to noninotropic controls.

Nesiritide Prescribing Information Changes[1] (Refer to Appendices 1 and 2)

The Effect on Mortality section of the Nesiritide Prescribing Information was expanded to include the 30-day mortality data from seven studies (311, 325, 326, 329 [PRECEDENT], 339 [VMAC], 341 [PROACTION], 348 [FUSION]), and 180-day mortality data from four studies (325, 326, PRECEDENT, VMAC) and 16-week data from FUSION. Pooled data from the seven studies (1717 patients) in the product labeling reported a 30-day mortality of 5.3% with nesiritide compared to 4.3% in the control group, a difference that was not statistically significant. Pooled data from the four studies (1167 patients) in the product labeling reported a 180-day mortality of 21.7% with nesiritide compared to 21.5% in the control group, a difference that was not statistically significant.

An additional change to the Nesiritide Prescribing Information is located in the section on Dosing Instructions, and recommends that the IV tubing be primed with 5ml of the solution for infusion (rather than 25ml) before connecting to the patient's vascular access port and before giving the bolus or infusion.

Results of In-Hospital Mortality from the ADHERE Registry[5]

An analysis from the Acute Decompensated Heart Failure National Registry (ADHERE) of 65,180 patient episodes to compare in-hospital mortality of treatment with nesiritide, nitroglycerin, dobutamine, or milrinone has recently become available. The registry is a descriptive evaluation of consecutive patients admitted to participating hospitals that are discharged with a diagnosis of heart failure. The primary objectives of the registry are to document demographics, clinical characteristics, emergency and inpatient management, and medical treatment. The results of in-hospital mortality comparing nesiritide (NES) to nitroglycerin (NTG) as well as nesiritide or nitroglycerin to dobutamine (DOB) are summarized below (refer to the publication for results of additional pair-wise comparisons).

Mortality Odds Ratios	NES (n=4402) vs. NTG (n=5668)	NES (n=4270) vs. DOB (n=3301)	NTG (n=5713) vs. DOB (n=3478)
Unadjusted	1.64 (1.38-1.94)[c]	0.37 (0.32-0.44)[c]	0.24 (0.20-0.28)[c]
Adjusted for Covariates[a]	0.95 (0.78-1.16)[d]	0.47 (0.39-0.56)[c]	0.46 (0.38-0.57)[c]
Adjusted for Covariates and Propensity Score[b]	0.94 (0.77-1.16)[d]	0.47 (0.39-0.56)[c]	0.46 (0.37-0.57)[c]

[a] Adjusted for covariates (age, gender, SBP, DBP, BUN, sCr, sodium, HR, dyspnea)
[b] Adjusted for covariates and propensity score (NES vs. NTG: SBP, BUN, sCr, LVEF, symptom duration, edema, previous HF, QRS > 120 ms; NES vs. DOB: SBP, sodium, BUN, sCr, age, weight, LVEF, edema; NTG vs. DOB: SBP, sodium, BUN, HR, LVEF, symptom duration)
[c] $p < 0.005$
[d] $p = 0.58$

Conclusions and Recommendations[6]

Although long-term outcome trials with nesiritide in patients with ADHF are not available, nesiritide has been associated with an increase in worsening renal function also requiring medical intervention, as well as a trend toward an increase in mortality compared to control (the difference of results reported in the meta-analysis compared to mortality data included in the product labeling may be due to inclusion/exclusion criteria for pooled data). The increase in in-hospital mortality seen with nesiritide compared to nitroglycerin noted in a retrospective evaluation of observational data was no longer statistically significant when adjusted for differences in baseline demographics and clinical characteristics.

It is recommended that nesiritide be reserved for patients with ADHF who have had an inadequate response to or are unable to tolerate standard therapy including high dose diuretics and in most cases vasodilators (specifically, nitroglycerin given intravenously or by other routes, or nitroprusside), and for whom benefits appear to outweigh risk. It is emphasized that nesiritide should be used only in patients with ADHF presenting to the hospital with dyspnea at rest, and should not be used in the outpatient setting at this time.

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Table 1. Meta-analysis	Inclusion and Endpoints	Comparisons and Trial Characteristics	Results	Summary

Sackner-Bernstein et al, Circulation 2005[3]

Seven RCTs identified; five included (due to effects on sCr not available in 2 studies)

Data Sources

FDA documents (Cardiovascular and Renal Drug Advisory Committee meeting documents, Scios NDA); PubMed (nesiritide, clinical trials, humans, English, through 7/2004); manual meeting search (AHA, ACC, HFSA). Data were extracted by two authors

Inclusion Criteria

Randomized, double-blind, parallel group studies of patients with ADHF where effect on sCr were reported

Definition of Worsening Renal Function

Increase in sCr > 0.5 mg/dL recorded at any time during inpatient stay of trial

Worsening Renal Function Intervention

Renal failure requiring dialysis or renal failure requiring medical intervention but not dialysis

Dose Comparisons

A) FDA approved dose (≤ 0.03 mcg/kg/min) vs. noninotropic control therapies
B) ≤ 0.03 mcg/kg/min vs. all control therapies (with or without mandated inotropic control therapies)
C) Low dose (≤ 0.015 mcg/kg/min) vs. noninotropic control therapies
D) Low dose (≤ 0.015 mcg/kg/min) vs. all control therapies
E) All nesiritide doses (up to 0.06 mcg/kg/min) vs. noninotropic control therapies
F) All nesiritide doses (up to 0.06 mcg/kg/min) vs. all control therapies

Trial Characteristics

Study	N	Control
311	103	NI
325	127	NI
326	305	NI
VMAC	498	NTG
PRECEDENT	255	Inotrope

NI=noninotropic agents

Study	Nesiritide Dose (bolus mcg) infusion mcg/kg/min
311	(0.25) 0.015 (0.5) 0.03 (1.0) 0.06 Up to 24 hours
325	(0.3) 0.015 (0.6) 0.03 Up to 5 days
326	(0.3) 0.015 (0.6) 0.03 Up to 12 days
VMAC	(2.0) 0.01 (2.0) up to 0.03 ≥ 24 hours
PRECEDENT	(no bolus) 0.015 (no bolus) 0.03 ≥ 24 hrs-14 days

Frequency of Worsening Renal Function

Study	Nesiritide n/N	Control n/N
311	15/74 (20%)	4/29 (14%)
325	15/85 (18%)	2/42 (5%)
326	36/203 (18%)	9/102 (9%)
VMAC	74/273 (27%)	45/216 (21%)
PRECEDENT	29/162 (18%)	9/83 (11%)
Totals	169/797 (21%)	69/472 (15%)

n=number w/worsening renal function
N=total number of patients

Worsening Renal Function Requiring Intervention

Study	Nesiritide n/N	Control n/N
Medical Intervention		
325	13/85 (15%)	0/42 (0%)
326	19/203 (9%)	6/102 (6%)
Totals	32/288 (11%)	6/144 (4%)
Dialysis		
325	2/85 (2%)	1/42 (2%)
326	3/203 (1%)	2/102 (2%)
VMAC	9/273 (3%)	5/216 (2%)
Totals	14/561 (2%)	8/360 (2%)

n=number w/worsening renal function
N=total number of patients

Development of Worsening Renal Function

Dose	Nesiritide n/N	Control n/N	RR (95% CI)	P
A	134/610 (22%)	60/389 (15%)	1.52 (1.16-2.00)	0.003
B	163/772 (21%)	69/472 (15%)	1.54 (1.19-1.98)	0.001
C	100/442 (23%)	60/389 (15%)	1.46 (1.09-1.95)	0.012
D	99/464 (21%)	69/472 (15%)	1.47 (1.12-1.93)	0.006
E	140/635 (22%)	60/389 (15%)	1.53 (1.16-2.00)	0.002
F	169/797 (21%)	69/472 (15%)	1.54 (1.20-1.99)	0.001

n=number w/worsening renal function
N=total number of patients

Summary of Results

- Treatment with nesiritide statistically significantly increased the incidence of worsening renal function vs. noninotropic controls (RR 1.53; 95% CI 1.16-2.00; P=0.002) (calculated NNH=15 patients for up to 24 hours to up to 12 days treatment with nesiritide for ADHF) and vs. all controls (RR 1.54; 95% CI 1.20-1.99; P=0.001) (calculated NNH=15 patients for up to 24 hours to up to 14 days treatment with nesiritide for ADHF)
- Treatment with nesiritide statistically significantly increased the need for medical intervention (not including dialysis) for worsening renal function vs. controls (RR 2.29; 95% CI 1.07-4.89; P=0.03) (calculated NNH=14 patients for up to 5 days to up to 12 days treatment with nesiritide for ADHF)
- The increase in need for dialysis with nesiritide was not statistically significant vs. controls (RR 1.18; 95% CI 0.05-2.76; P=0.71)

Comments

- Unable to adjust for factors other than treatment group
- Unable to assess long term outcomes

Quality Assessment

- Good (based on internal and external validity)

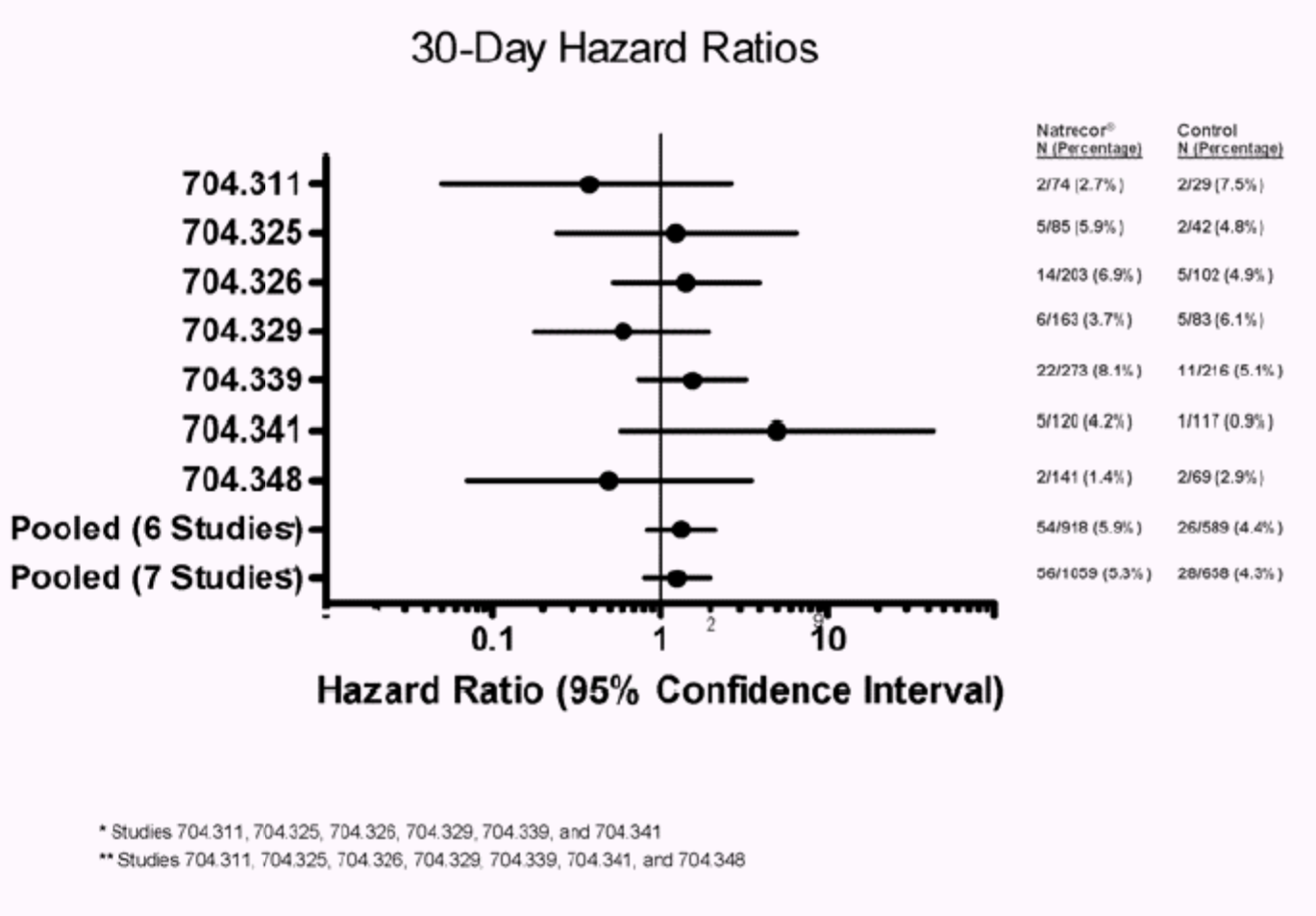
ACC=American College of Cardiology; AHA=American Heart Association; HFSA=Heart Failure Society of America; NDA=new drug application; NNH=number needed to harm; NTG=nitroglycerin; PRECEDENT=Prospective Randomized Evaluation of Cardiac Ectopy with Dobutamine or Natrecor Therapy; RCT=randomized controlled trial; RR=relative risk; VMAC=Vasodilation in the Management of Acute Congestive heart failure

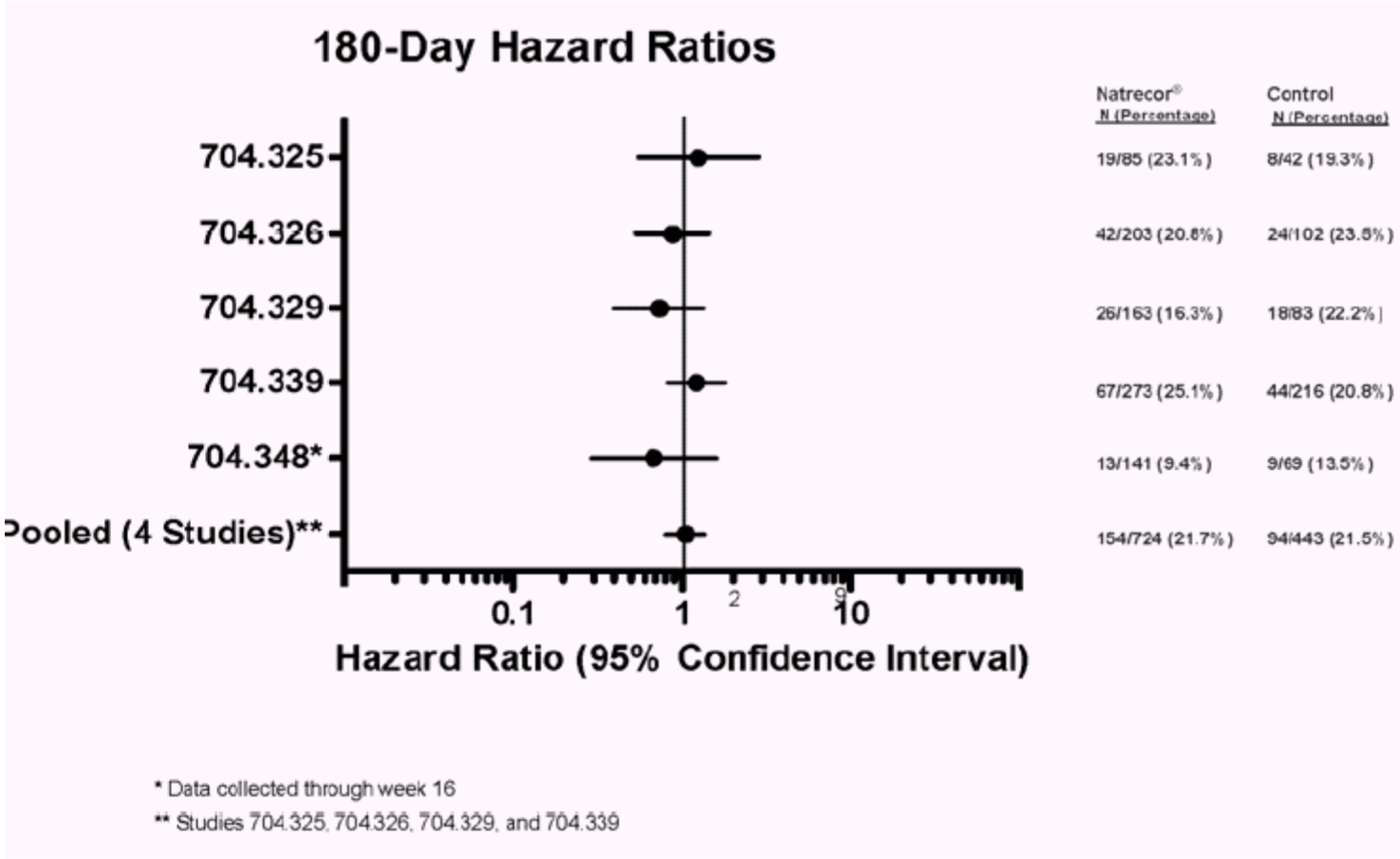
Table 2. Meta-analysis	Inclusion and Endpoints	Comparisons and Trial Characteristics	Results	Summary
Sackner-Bernstein et al, JAMA 2005[4] Twelve RCTs identified; three included that met criteria	**Data Sources** FDA documents (Cardiovascular and Renal Drug Advisory Committee meeting documents, Scios NDA); drug Sponsor (Scios Inc.); PubMed (nesiritide, clinical trials, humans, English); manual meeting search (AHA, ACC, HFSA) through 12/2004. Data abstracted by principal investigator **Inclusion Criteria** Randomized, double-blind, parallel group studies of patients with ADHF; nesiritide single infusion of ≥ 6 hours; control therapy not mandating a positive inotropic agent; mortality during 30 days of follow-up reported **Mortality Outcome Measure** Death within 30 days	**Trial Characteristics** Study / N / Control NSGET / 127 / Placebo [a] VMAC / 498 / NTG or placebo [b] PROACTION / 237 / Placebo [c] [a] No IV vasodilators or inotropes allowed during 6 hour infusion [b] For 3 hours, then randomized again to NTG or nesiritide; catheterized patients randomized to adjustable dose nesiritide or other groups; dobutamine used at discretion of clinician (25.4% nesiritide group vs. 15.1% control; P=0.006) [c] NTG and diuretics (but not inotropes) allowed in each group Study / Nesiritide Dose (bolus mcg) infusion mcg/kg/min NSGET / (0.3) 0.015 (0.6) 0.03 for 6 hours VMAC / (2.0) 0.01 (2.0) up to 0.03 ≥ 24 hours PROACTION / bolus followed by 0.01 infusion minimum 12 hours	**30-Day Mortality** Study / Nesiritide n/N / Control n/N / RR (95% CI) / P NSGET / 6/85 (7.1%) / 2/42 (4.8%) / 1.48 (0.31-7.03) / ND VMAC / 24/280 (8.6%) / 12/218 (5.5%) / 1.56 (0.80-3.04) / ND PROACTION / 5/120 (4.2%) / 1/117 (0.9%) / 4.88 (0.58-41.1) / ND Total / 35/485 (7.2%) / 15/377 (4.0%) / 1.74 (0.97-3.12) / 0.059* n=number of deaths N=total number of patients ND=not determined * Meta-analysis using fixed-effects model (crude 30 day mortality RR 1.91; 95% CI 1.01-3.27; P=0.04, unadjusted Kaplan-Meier 30 day survival HR 1.86; 95% CI 1.02-3.41; P=0.04, and survival adjusted for study HR 1.80; 95% CI 0.98-3.31; P=0.057)	**Summary of Results** ➢ Treatment with nesiritide showed a trend toward increased mortality vs. noninotropic controls (7.2% vs. 4.0%; HR 1.74; 95% CI 0.97-3.12; P=0.059) **Comments** ➢ Able to adjust for baseline differences in treatment groups of VMAC (use of dobutamine) ➢ Included mortality data based on ITT of patients excluded from trial publication (VMAC) ➢ Assumed mortality of patients lost to follow-up (NSGET) or listed as between 15 to 30 days (PROACTION) in favor of nesiritide ➢ Clinical trials not designed to determine difference in mortality ➢ Unable to assess impact of medications or procedures during 30 day follow-up **Quality Assessment** ➢ Good (based on internal and external validity)

ACC=American College of Cardiology; AHA=American Heart Association; HFSA=Heart Failure Society of America; HR=hazard ratio; NDA=new drug application; NSGET=Nesiritide Study Group Efficacy Trial; NTG=nitroglycerin; PROACTION=Prospective Randomized Outcomes Study of Acutely Decompensated Congestive Heart Failure Treated Initially in Outpatients with Natrecor; RCT=randomized controlled trial; RR=relative risk; VMAC=Vasodilation in the Management of Acute Congestive heart failure

Appendix 1.

ADVERSE REACTIONS Effect on Mortality. Natrecor® (nesiritide) prescribing information. Fremont, CA: Scios Inc.; 2005 Apr. http://www.fda.gov/cder/foi/label/2005/020920s008lbl.pdf. Accessed 2005 Jun 2.
Data from Natrecor (Nesiritide) Injection. NDA Application No. 20-920 (Approval date 8/10/2001) at http://www.fda.gov/cder/foi/nda/2001/20-920_Natrecor.htm



Appendix 2.

ADVERSE REACTIONS Effect on Mortality. Natrecor® (nesiritide) prescribing information. Fremont, CA: Scios Inc.; 2005 Apr. http://www.fda.gov/cder/foi/label/2005/020920s008lbl.pdf. Accessed 2005 Jun 2.
Data from Natrecor (Nesiritide) Injection. NDA Application No. 20-920 (Approval date 8/10/2001) at http://www.fda.gov/cder/foi/nda/2001/20-920_Natrecor.htm