

# 79% of Adults Live Within 1 Hour of PCI Hospital

BY BRUCE JANCIN  
Denver Bureau

ATLANTA — Prehospital triage and regionalization of ST-segment elevation MI care is geographically feasible throughout most of the country, Dr. Brahmajee K. Nallamothu said at the annual meeting of the American College of Cardiology.

He presented a national analysis of driving times and distances to hospitals with percutaneous coronary intervention

(PCI) capability. The conclusion: 79% of adults live within 60 minutes of a PCI hospital even after factoring in the time typically required for emergency medical services (EMS) to arrive on the scene and stabilize the patient. The median road distance to the nearest PCI hospital was 7.9 miles, with a median driving time of 11.3 minutes.

However, these averages hide enormous regional variations. Only 48% of adults in rural U.S. Census tracts live within 60

minutes of a PCI hospital, compared with 98% in urban areas. And while, for example, 90% of adults living in the Pacific region are within 60 minutes of a PCI facility, that's true for only 63% in the Dakotas.

Overall, 43 million adults don't live within a 60-minute drive of a PCI hospital. So there can be no one-size-fits-all national template for ST-segment elevation MI (STEMI) regionalization. Novel approaches will be required, especially in rural districts, said Dr. Nallamothu of

the University of Michigan, Ann Arbor.

"This study is a general overview. If STEMI regionalization occurs, it's not going to happen as a national mandate. It'll happen at the local level," he predicted.

The impetus for this study arises from growing interest among health services policy planners in adopting regionalization of STEMI care. The National Heart Attack Alert Program, for example, has called for prehospital triage.

The goal would be to make primary PCI available to a much greater proportion of the 400,000 STEMI patients per year, since there is persuasive evidence that primary PCI is more effective than thrombolytic therapy when it can be performed rapidly by experienced operators.

Dr. Nallamothu's analysis was based on data on nearly 5,000 U.S. hospitals in the 48 contiguous states obtained from the American Hospital Association's annual survey,

## Intravenous B-type natriuretic peptide (BNP) **NATRECOR®** (nesiritide)

### Brief Summary

Natrecor® (nesiritide) for Injection

FOR INTRAVENOUS INFUSION ONLY

R<sub>X</sub> Only

The following is a Brief Summary of the Full Prescribing Information for Natrecor® (nesiritide) for Injection. Please review the Full Prescribing Information prior to prescribing Natrecor.

#### INDICATIONS AND USAGE

Natrecor (nesiritide) is indicated for the intravenous treatment of patients with acutely decompensated congestive heart failure who have dyspnea at rest or with minimal activity. In this population, the use of Natrecor reduced pulmonary capillary wedge pressure and improved dyspnea.

#### CONTRAINDICATIONS

Natrecor is contraindicated in patients who are hypersensitive to any of its components. Natrecor should not be used as primary therapy for patients with cardiogenic shock or in patients with a systolic blood pressure <90 mm Hg.

#### WARNINGS

Administration of Natrecor should be avoided in patients suspected of having, or known to have, low cardiac filling pressures.

#### PRECAUTIONS

**General:** Parenteral administration of protein pharmaceuticals or *E. coli*-derived products should be attended by appropriate precautions in case of an allergic or untoward reaction. No serious allergic or anaphylactic reactions have been reported with Natrecor.

Natrecor is not recommended for patients for whom vasodilating agents are not appropriate, such as 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, or for patients suspected to have low cardiac filling pressures. (See CONTRAINDICATIONS.)

**Renal:** Natrecor may affect renal function in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with Natrecor may be associated with azotemia. When Natrecor was initiated at doses higher than 0.01 mcg/kg/min (0.015 and 0.03 mcg/kg/min), there was an increased rate of elevated serum creatinine over baseline compared with standard therapies, although the rate of acute renal failure and need for dialysis was not increased. In the 30-day follow-up period in the VMAC trial, 5 patients in the nitroglycerin group (2%) and 9 patients in the Natrecor group (3%) required first-time dialysis.

**Cardiovascular:** Natrecor may cause hypotension. In the VMAC trial, in patients given the recommended dose (2 mcg/kg bolus followed by a 0.01 mcg/kg/min infusion) or the adjustable dose, the incidence of symptomatic hypotension in the first 24 hours was similar for Natrecor (4%) and IV nitroglycerin (5%). When hypotension occurred, however, the duration of symptomatic hypotension was longer with Natrecor (mean duration was 2.2 hours) than with nitroglycerin (mean duration was 0.7 hours). In earlier trials, when Natrecor was initiated at doses higher than the 2 mcg/kg bolus followed by a 0.01 mcg/kg/min infusion (i.e., 0.015 and 0.03 mcg/kg/min preceded by a small bolus), there were more hypotensive episodes and these episodes were of greater intensity and duration. They were also more often symptomatic and/or more likely to require medical intervention (see ADVERSE REACTIONS). Natrecor should be administered only in settings where blood pressure can be monitored closely, and the dose of Natrecor should be reduced or the drug discontinued in patients who develop hypotension (see Dosing Instructions). The rate of symptomatic hypotension may be increased in patients with a blood pressure <100 mm Hg at baseline, and Natrecor should be used cautiously in these patients. The potential for hypotension may be increased by combining Natrecor with other drugs that may cause hypotension. For example, in the VMAC trial in patients treated with either Natrecor or nitroglycerin therapy, the frequency of symptomatic hypotension in patients who received an oral ACE inhibitor was 6%, compared to a frequency of symptomatic hypotension of 1% in patients who did not receive an oral ACE inhibitor.

**Drug Interactions:** No trials specifically examining potential drug interactions with Natrecor were conducted, although many concomitant drugs were used in clinical trials. No drug interactions were detected except for an increase in symptomatic hypotension in patients receiving oral ACE inhibitors (see PRECAUTIONS, Cardiovascular).

The co-administration of Natrecor with IV vasodilators such as nitroglycerin, nitroprusside, milrinone, or IV ACE inhibitors has not been evaluated (these drugs were not co-administered with Natrecor in clinical trials).

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** Long-term studies in animals have not been performed to evaluate the carcinogenic potential or the effect on fertility of nesiritide. Nesiritide did not increase the frequency of mutations when used in an in vitro bacterial cell assay (Ames test). No other genotoxicity studies were performed.

**Pregnancy: Category C:** Animal developmental and reproductive toxicity studies have not been conducted with nesiritide. It is also not known whether Natrecor® (nesiritide) can cause fetal harm when administered to pregnant women or can affect reproductive capacity. Natrecor should be used during pregnancy only if the potential benefit justifies any possible risk to the fetus.

**Nursing Mothers:** It is not known whether this drug is excreted in human milk. Therefore, caution should be exercised when Natrecor is administered to a nursing woman.

**Pediatric Use:** The safety and effectiveness of Natrecor in pediatric patients has not been established.

**Geriatric Use:** Of the total number of subjects in clinical trials treated with Natrecor (n = 941), 38% were 65 years or older and 16% were 75 years or older. No overall differences in effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients. Some older individuals may be more sensitive to the effect of Natrecor than younger individuals.

#### ADVERSE REACTIONS

Adverse events that occurred with at least a 3% frequency during the first 24 hours of Natrecor infusion are shown in the following table.

Adverse Events	VMAC Trial		Other Long Infusion Trials		
	Nitroglycerin (n = 216)	Natrecor Recommended Dose (n = 273)	Control* (n = 256)	0.015 (n = 253)	0.03 (n = 246)
<b>Cardiovascular</b>					
Hypotension	25 (12%)	31 (11%)	20 (8%)	56 (22%)	87 (35%)
Symptomatic Hypotension	10 (5%)	12 (4%)	8 (3%)	28 (11%)	42 (17%)
Asymptomatic Hypotension	17 (8%)	23 (8%)	13 (5%)	31 (12%)	49 (20%)
Ventricular Tachycardia (VT)	11 (5%)	9 (3%)	25 (10%)	25 (10%)	10 (4%)
Non-sustained VT	11 (5%)	9 (3%)	23 (9%)	24 (9%)	9 (4%)
Ventricular Extrasystoles	2 (1%)	7 (3%)	15 (6%)	10 (4%)	9 (4%)
Angina Pectoris	5 (2%)	5 (2%)	6 (2%)	14 (6%)	6 (2%)
Bradycardia	1 (<1%)	3 (1%)	1 (<1%)	8 (3%)	13 (5%)
<b>Body as a Whole</b>					
Headache	44 (20%)	21 (8%)	23 (9%)	23 (9%)	17 (7%)
Abdominal Pain	11 (5%)	4 (1%)	10 (4%)	6 (2%)	8 (3%)
Back Pain	7 (3%)	10 (4%)	4 (2%)	5 (2%)	3 (1%)
<b>Nervous</b>					
Insomnia	9 (4%)	6 (2%)	7 (3%)	15 (6%)	15 (6%)
Dizziness	4 (2%)	7 (3%)	7 (3%)	16 (6%)	12 (5%)
Anxiety	6 (3%)	8 (3%)	2 (1%)	8 (3%)	4 (2%)
<b>Digestive</b>					
Nausea	13 (6%)	10 (4%)	12 (5%)	24 (9%)	33 (13%)
Vomiting	4 (2%)	4 (1%)	2 (1%)	6 (2%)	10 (4%)

\* Includes dobutamine, milrinone, nitroglycerin, placebo, dopamine, nitroprusside, or amrinone.

Adverse events that are not listed in the above table that occurred in at least 1% of patients who received any of the above Natrecor doses included: Tachycardia, atrial fibrillation, AV node conduction abnormalities, catheter pain, fever, injection site reaction, confusion, paresthesia, somnolence, tremor, increased cough, hemoptysis, apnea, increased creatinine, sweating, pruritus, rash, leg cramps, amblyopia, anemia. All reported events (at least 1%) are included except those already listed, those too general to be informative, and those not reasonably associated with the use of the drug because they were associated with the condition being treated or are very common in the treated population.

In placebo and active-controlled clinical trials, Natrecor has not been associated with an increase in atrial or ventricular tachyarrhythmias. In placebo-controlled trials, the incidence of VT in both Natrecor and placebo patients was 2%. In the PRECEDENT (Prospective Randomized Evaluation of Cardiac Ectopy with Dobutamine or Natrecor Therapy) trial, the effects of Natrecor (n = 163) and dobutamine (n = 83) on the provocation or aggravation of existing ventricular arrhythmias in patients with decompensated CHF was compared using Holter monitoring. Treatment with Natrecor (0.015 and 0.03 mcg/kg/min without an initial bolus) for 24 hours did not aggravate pre-existing VT or the frequency of premature ventricular beats, compared to a baseline 24-hour Holter tape.

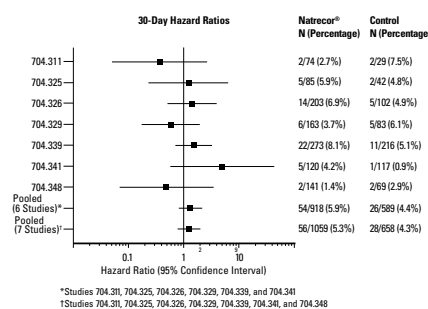
#### Clinical Laboratory

In the PRECEDENT trial, the incidence of elevations in serum creatinine to >0.5 mg/dL above baseline through day 14 was higher in the Natrecor® (nesiritide) 0.015 mcg/kg/min group (17%) and the Natrecor 0.03 mcg/kg/min group (19%) than with standard therapy (11%). In the VMAC trial, through day 30, the incidence of elevations in creatinine to >0.5 mg/dL above baseline was 28% and 21% in the Natrecor (2 mcg/kg bolus followed by 0.01 mcg/kg/min) and nitroglycerin groups, respectively.

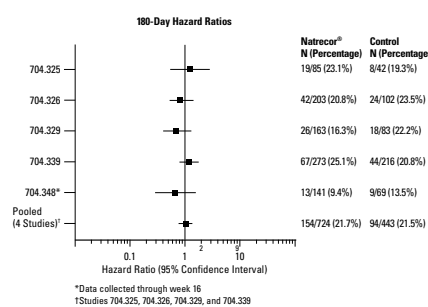
#### Effect on Mortality

Data from all seven studies in which 30-day data were collected are presented in the chart below. The data depict hazard ratios and confidence intervals of mortality data for randomized and treated patients with Natrecor relative to active controls through day 30 for each of the 7 individual studies (Studies 311, 325, 326, 329 [PRECEDENT], 339 [VMAC], 341 [PROACTION], and 348 [FUSION II]).

The figure (on logarithmic scale) also contains a plot for the six studies involving hospitalized or Emergency Department patients combined (n = 1507), and for all 7 studies combined (n = 1717). The percentage is the Kaplan-Meier estimate.



The figure below represents 180-day mortality hazard ratios for randomized and treated patients from all four individual studies where 180-day data were collected, 16 week hazard ratios for Study 348 (180-day data were not collected), and the four studies with 180-day data pooled (n = 1167).



There were few deaths in these studies, so the confidence limits around the hazard ratios for mortality are wide. The studies are also small, so some potentially important baseline imbalances exist among the treatment groups, the effects of which cannot be ascertained.

#### OVERDOSAGE

No data are available with respect to overdosage in humans. The expected reaction would be excessive hypotension, which should be treated with drug discontinuation or reduction (see PRECAUTIONS) and appropriate measures.

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DR. NALLAMOTHU

which he and his coworkers coupled with detailed U.S. Census tract information. They determined that 26% of the nation's hospitals were PCI facilities, and that 42% of U.S. adults had a PCI hospital as their closest hospital.

Among adults with a non-PCI hospital as their closest medical facility, 74% would experience less than 30 minutes of additional delay if their ambulance drove directly to a PCI hospital instead of the nearest hospital. This finding supports the feasibility of prehospital triage, he said.

One audience member noted that only about half of patients with STEMI call EMS; the other half show up in emergency departments as walk-ins, thereby eliminating the possibility of prehospital triage.

Dr. Nallamothu agreed that this is a real obstacle to regionalized STEMI care.

"Community-based strategies to increase the use of EMS have been really unsuccessful to date. That has important implications. For STEMI regionalization to be effective, we're going to need two key components dealing with those two different populations: the patients who use EMS and the ones who don't," he said.

One possibility is more expeditious transfer of non-EMS arrivals at non-PCI hospitals than is now the norm. There is some evidence to suggest that transfer times from non-PCI to PCI hospitals have more to do with institutional relationships than with geographic factors. It may well prove to be the case that aligning financial and other incentives in support of routine swift transfer of non-EMS patients would enable many to arrive within the time window in which primary PCI is advantageous, Dr. Nallamothu said.

The study was funded in part by the National Heart, Lung, and Blood Institute. ■