

Flow Reversal May Improve Embolic Protection

BY TIMOTHY F. KIRN
Sacramento Bureau

SCOTTSDALE, ARIZ. — The flow reversal technique may be a better way to prevent emboli from reaching the brain during a carotid stenting procedure, but not all the evidence is in, Dr. Juan Carlos Parodi said at an international congress on endovascular interventions sponsored by the Arizona Heart Foundation.

In 200 high-risk patients treated so far at

this institution, using the Parodi Anti-Emboli system to create flow reversal, 30-day stroke and mortality has been 1.5%, with no ipsilateral ischemic strokes, said Dr. Parodi, professor of surgery and radiology at Washington University, St. Louis.

Those results are good, but not definitive, because clinical outcome is only one way to measure that a technology is truly intercepting emboli created by the procedure, he said. The other ways are diffusion-weighted MRI and transcranial Doppler, both of

which have shown that when a distal filter is used during the procedure, it appears that some small emboli do escape and reach the brain, where they do block vessels.

The SAPHIRE (Stenting and Angioplasty with Protection in Patients at High-Risk for Endarterectomy) trial is the only randomized, controlled trial of a distal filter, Dr. Parodi said. It reported a 30% reduction in 30-day stroke, death, and myocardial infarction with the filter.

But, diffusion-weighted MR studies sug-

gest that even with a filter somewhere between 9% and 43% will still develop new clinical or subclinical lesions, and transcranial Doppler studies suggest that every procedure releases emboli showers, not all of which is caught by a filter. By comparison, new lesions are seen with the MR technique in 6%-12% of patients who have undergone endarterectomy.

How important these small lesions are remains an open question. Most disappear over time. However, studies have reported that necrotic tissue is sometimes seen around the sites of the lesions, and silent infarctions are associated with a doubling of the risk of dementia, Dr. Parodi said.

Dr. Parodi's flow reversal device, the Parodi Anti-Emboli system, uses a balloon inflated in the common carotid proximal to the lesion being treated, obstructing the flow and creating a negative pressure gradient. A second balloon is inflated in the external carotid artery for internal carotid procedures to prevent backflow, and suction is applied, Dr. Parodi said. The device was recently sold to W. L. Gore and Associates Inc.

Emboli Filters May Not Work, MRI Shows

SCOTTSDALE, ARIZ. — Cerebral protection devices used during carotid stenting procedures do not catch small emboli, and may not prevent stroke and brain damage, according to preliminary results from a study that used diffusion-weighted MRI.

"Cerebral protection devices may not reduce the incidence of new ischemic defects on diffusion-weighted MR," Dr. Michel S. Makaroun said at an international congress on endovascular interventions sponsored by the Arizona Heart Foundation. "Further investigation is definitely warranted."

He presented the results of the first 36 patients treated in a planned larger trial comparing distal-filter protection with no protection; the trial is using MRI of the patients' brains before and after a carotid stenting procedure to visualize lesions that might not be readily clinically apparent.

There was no difference, said Dr. Makaroun, director of the endovascular surgery program at the University of Pittsburgh Medical Center. Of 18 patients who were treated with cerebral protection, 13 had at least one white lesion seen on diffusion-weighted imaging after the procedure that had not been there before. In comparison, 8 of 18 patients treated without protection had any white lesion afterward.

The difference was not statistically significant, given the small number of patients, noted Dr. Makaroun.

The average number of new lesions was the same for both groups, six, and the average size of the lesions was the same as well. Two perioperative strokes occurred, one in each treatment group.

—Timothy F. Kirn

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

Brief Summary Natrecor® (nesiritide) for Injection

FOR INTRAVENOUS INFUSION 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)
Cardiovascular					
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%)
Body as a Whole					
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%)
Nervous					
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%)
Digestive					
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.

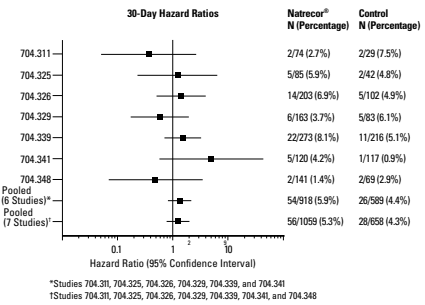
Adverse events that are not listed in the above table that occurred in at least 1% of patients who received any of the above Natrecor doses included: Tachycardia, atrial fibrillation, AV node conduction abnormalities, catheter pain, fever, injection site reaction, confusion, paresthesia, somnolence, 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.

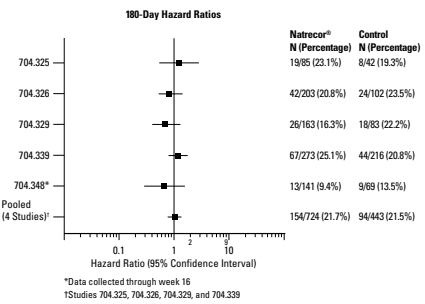
Clinical Laboratory
In the PRECEDENT trial, the incidence of elevations in serum creatinine to >0.5 mg/dL above baseline through day 14 was higher in the Natrecor® (nesiritide) 0.015 mcg/kg/min group (17%) and the Natrecor 0.03 mcg/kg/min group (19%) than with standard therapy (11%). In the VMAC trial, 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]).

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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