

Non intravenous cardiac medications are allowed as needed. The investigator is to be made aware that vasodilators may exacerbate the hemodynamic effect of the blinded treatments. Oral diuretics may be used at any time. If an intravenous diuretic is needed, a bolus dose rather than a constant infusion regimen is preferred.

Contingencies related to dosing:

Symptomatic hypotension: Both drugs (active and dummy) are to be stopped for symptomatic hypotension. Treatment of the hypotensive event is initiated (i.e. normal saline) and the specifics of the hypotensive event are recorded. Once the subject is stabilized, the dose of the study drug can be restarted at a rate 30% less than the infusion at the time of the hypotensive event (no bolus for Natrecor).

Reduction based on clinical response: The infusion rate should be decreased if:

- SBP < 90 mm Hg (unless this BP is appropriate for that subjects)
- PCWP < 12 mm Hg.

Both infusions should be decreased appropriate to the severity of the hemodynamic response. The Natrecor dose should be decreased by 30%, the nitroglycerine dose should be decreased by the investigator's usual practice. The specifics of the event should be recorded. At the discretion of the investigator, the drug can be restarted. For Natrecor, the dose should be decreased by 30% (no bolus) of the dose producing the above hemodynamic response. For nitroglycerine the dose should be restarted per standard practice of the investigator.

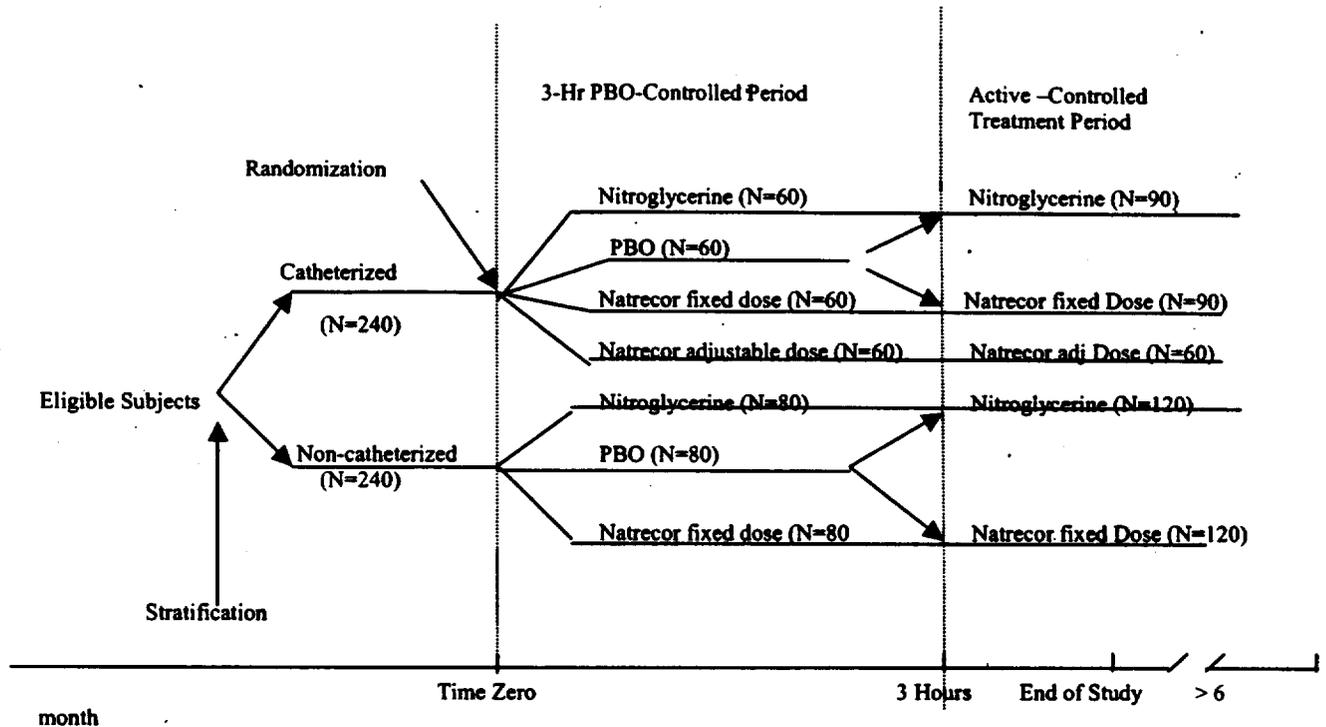
Worsening CHF: The investigator should first optimize the index study treatment. Oral or permitted intravenous drugs should next be added. During the initial three hours of the infusion, the administration of intravenous cardiovascular drugs should be used only if urgently needed. The preferred next medication is dobutamine. During the active controlled period (after hour 3) those subjects recently crossed-over from placebo should have the dose optimized with active drug before adding on other medications.

Long-term continuation of study drug: Some subjects may be continuously treated in a blinded-fashion for > 30 days. After the initial 30 days, subjects at the discretion of the investigator could be treated with open-labeled Natrecor. For these subjects, dosing increases and decreases are predicated on the same regimens as those treated with adjustable dose Natrecor.

A schematic representation of the study is shown as Figure 1. Four of the treatments were employed among those not catheterized (all except the IV Natrecor adjustable dose) and all were employed among catheterized subjects.

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Figure 1. Schematic of study 704.339



Protocol:

Inclusion Criteria:

A total of 480 subjects were to be enrolled equally, distributed between catheterized and non-catheterized subjects.

Eligible subjects were those:

- Greater than 18 years old.
- Have dyspnea at rest, while supine or immediately upon minimal activity such as talking eating or bathing.
 - These subjects must have cardiac disease as the etiology of their symptoms by demonstrating two of the following:
 - JVD;
 - Paroxysmal nocturnal dyspnea or 2-pillow orthopnea within 72 hours of entry;
 - Abdominal discomfort (↓appetite or nausea) due to hepato-splenic congestion;
 - Chest X-ray consistent with heart failure;
- Elevated cardiac filling pressures (estimated among those non-catheterized) and > 20 mm Hg among those who are catheterized;
- Require hospitalization and IV therapy for at least 24 hours for the treatment of acute decompensated heart failure;
- Understand and sign an informed consent;

- Post-MI subjects are not excluded.

Exclusion Criteria:

Subjects will be excluded for:

- SBP < 90 mm Hg;
- Cardiogenic shock, volume depletion, or any other clinical condition that would contraindicate the administration of an IV agent with vasodilatory properties;
- Recent PCWP < 20 mm Hg;
- Clinically unstable and cannot tolerate catheterization or a 3-hour period off medication;
- Subjects who cannot tolerate withholding nitroglycerine (e.g. acute coronary syndrome);
- Received Viagra® (sildenafil) within 24-hours of start of study;
- Known methemoglobinemia;
- Allergic reaction to nitrates, nitroglycerin or Natrecor;
- Requiring mechanical ventilation;
- Potential or actual pregnancy;
- Unlikely to survive 30-35 days;
- Recent treatment with investigational drug;
- Unable or unwilling to comply with the study requirements.

Randomization:

The investigator will decide whether the subject is to have a right-heart catheter in place for the management of their CHF. Once this decision is made, the subject is randomized among the different treatments. The process required the pharmacist to phone an automated telephone randomization system to receive the treatment assignment.

Blinding:

The study was performed as a double-dummy design. Two bottles one containing nitroglycerine or placebo and the second bag containing Natrecor or placebo was attached to a "Y" connector at the infusion site or infused through two different infusion sites. After the first three hours of treatment, the placebo group was to be unblinded and the subjects advanced to the second randomized treatment (i.e. to either nitroglycerine or Natrecor fixed dose) in a blinded manner. In order to protect symptom assessment from contamination by the knowledge of the hemodynamic effect, hemodynamic measurements were to be collected only after the dyspnea measurements and global assessment were performed. The investigator was not to discuss hemodynamic measurements within the hearing range of the subject. A log was kept reflecting the time of unblinding. The treatment of subjects treated either with nitroglycerin or Natrecor was not unblinded but referred to as "on active treatment" and continued after the three-hour time point.

The on-site pharmacist was unblinded as to therapy.

Catheterization Procedures:

A right heart catheter is placed and the appropriate position confirmed by x-ray or fluoroscopy. When stabilized, hemodynamic measurements are to be performed at 5-15 minute intervals until two sets of PCWP measurements are within 15% of each other (not specified is whether the high or low value is to serve as the basis of this 15%). A PCWP \geq 20 mm Hg is the only hemodynamic requirement for enrollment. Catheter placement and eligibility are to be

determined immediately prior to randomization. If ineligible, the subject should not be randomized. The catheter is intended to remain in place for at least 48 hours.

Primary End Point:

The primary objectives of the study are to compare the hemodynamic effect and clinical response of Natrecor to placebo at the 3-hour time point using the all treated, as randomized cohort of those receiving any study drug. Specifically, the two analyses are:

- 1) PCWP (catheterized subjects only).
- 2) Dyspnea evaluation (all subjects).

There are seven possible ratings for the dyspnea rating.

Markedly better = + 3
Moderately better = +2
Minimally better = +1
No Change =0
Minimally worse = -1
Moderately worse = -2
Markedly worse = - 3

The primary endpoints are the change from baseline at 3 hours during the infusion comparing Natrecor to placebo. For the study to be considered a success-both measurements must be significant at a $p < 0.05$. The two Natrecor groups (adjustable and fixed dose) are pooled for wedge pressure measurements. For dyspnea evaluation catheterized (adjustable and fixed Natrecor) and not-catheterized subjects will be pooled for the analyses. Observations are to be made prior to the unblinding of the treatments at the three-hour time point.

Since both analyses had to be statistically significant relative to placebo, no correction was made for the multiplicity of the end points.

For the primary analysis of PCWP, the data is limited to those catheterized. The method of analysis is a one-way ANOVA. A two-sided 95% confidence interval is constructed.

For the analysis of the dyspnea index a two-way ANOVA model with treatment and catheter use as factors. In addition a stratified two-sample Wilcoxon procedure (Van Elteren's test), stratified on right heart catheter use or an ordinal logistic regression using proportional odds model with cumulative logits will be used to assess the robustness of the primary analysis results.

No values were imputed for missing data.

Secondary Objectives:

The secondary objectives are to compare the hemodynamic and clinical effects of Natrecor with IV nitroglycerine and placebo. The hemodynamic parameters that will be assessed are the change from baseline of right atrial pressure (RAP), cardiac output (CO), pulmonary artery pressure (PAP), that fit within the specified time windows. Additional analyses (prespecified) are: the proportion of subjects whose dyspnea is improved at three hours (defined as markedly or moderately improved). A similar assessment will be made for the subject's global assessment.

The following specific measurements are included as secondary study objectives.

- 1) The effect of PCWP and dyspnea 1-hour after the start of study drug.
- 2) The onset of effect treatment on PCWP.
- 3) The effect on PCWP 24 hours after the start of study drug.
- 4) The overall safety profile.

For placebo subjects who are switched to the two active treatments, the baseline is considered the last measurement prior to switching. For the analysis comparing active treatments would be tested in the framework of an ANOVA model

The Cochran-Mantel-Haenszel test for general association with catheter use as the stratification factor or logistic regression, including treatment and catheter use as factors in the model, that will be used to assess dyspnea improvement at 3 hours. Two-way analysis of variance model, with treatment and catheter use as factors and the corresponding non-parametric procedures will be used for the symptom and global assessment evaluations at each follow-up time.

Additional Metrics:

This metric includes a comparison of the need for the addition of IV vasoactive agents and/or diuretics and the effect of adding such medication on the hemodynamic variables during the first three hours of the infusion. Use of a vasoactive drug is defined as either a new administration or an increase in dose of a continued intravenous regimen that includes dobutamine, milrinone, dopamine, nitroprusside, nitroglycerine, amrinone, epinehrine, norepinephrine or neosynephrine. A similar assessment will be made during the first 24-hours of the study.

Also measured are the mean change in body weight from baseline to 24 hours, total urine volume for the first 24 hours, hospital admissions during the first 30 days, deaths during the first 30 days, 90 days, and 6 months post-initiation of treatment.

The method of analysis for each of these additional analyses is the Cochran-Mantel-Haenszel test with catheter use as a stratification factor. For continuous measurements of efficacy, an omnibus F-test followed by pair-wise contrasts for an overall significant result will be applied to the data. The log rank test will be used for the comparison of the 30 day, 90 day and 6 month mortality between treatment groups. Cox proportional-hazard regression model, adjusting potential baseline or time-dependent covariates may be considered as deemed appropriate for the analysis of time to event data.

Other statistical Issues:

No interim analyses were planned for the study.

The power calculation for hemodynamic measurements was based on the unequal randomization of subjects to Natrecor (combine fixed and adjustable doses) versus placebo (2: 1 ratio), with 120 and 60 subjects /group respectively, this sized study has a 88% power to detect a 3 mm Hg drop in PCWP assuming a standard deviation of 6 mm Hg at an $\alpha=0.05$.

For the dyspnea index, there were 200 subjects in the Natrecor group (catheterized subjects both adjustable and fixed infusion =120 subjects + non-catheterized subjects =80 subjects) and placebo catheterized and non-catheterized there were 140 subjects. The study has an 88% power to detect a 0.3 unit difference in the dyspnea scale, assuming a standard deviation of 0.8 at the significance level of 0.05. For the ordinal analysis the sponsor assumed that if the shifts for the treatment group were:

Table 3. Distribution of symptom improvement for power calculation

	+3=much better	+2= moderately better	+1= minimally better	0=No change	-1= minimally worse	-2= moderately Worse	-3= Much worse
Natrecor	5%	20%	25%	40%	5%	5%	0%
Placebo	0%	15%	20%	50%	5%	5%	5%

The Wilcoxon rank test would have a power of 86% to detect a difference between groups at an $\alpha=0.05$.

Protocol-procedure timing:

The timing of specific procedures is shown in Table 4. Hemodynamic measurements were limited to those subjects who were catheterized. The dyspnea evaluation, the other efficacy metric was measured in all subjects and was collected frequently during the initial three hour placebo-controlled period, and also, albeit less frequently during the remainder of the study. Fluid intake and output data was also collected. Weight was measured at baseline and at the end of 24 hours. Mortality was collected monthly during the 6-month post-treatment phase. Hospitalizations were collected only till day 30.

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Table 4. Procedures during study 704.339

	Screening ¹	Baseline	3-Hour Placebo-Controlled Period						Active-Controlled Treatment Period							Post-Treatment Period		
			0	15 min	30 min	1 hr	2 hr	3 hr	6 hr	9 hr	12 hr	24 hr	36 hr	48 hr	Inf end	Day 14-19	Day 30-35	Through 6 months
Informed Consent, Medical History, PE, Ht, Wt, Right Heart Cath.	X																	
Weight	X										X							
Concomitant Medications	X ¹	→	→	→	→	→	→	X ²										
Cardiac Rhythm		X																
BP ¹¹ , HR ¹¹	X	X	X	X	X	X	X	X	X	X	X	→	→	→	X			
Respiratory Rate		X				X	X	X										
PCWP and PAP	X ⁴	X ³	X	X	X	X	X	X	X ¹²	X	X	X ¹²	X ¹²	X ¹²				
CO, RAP		X ⁵				X	X	X			X							
Study Drug Administration ⁴			X	→	→	→	→	X ^{9,10}	→	→	→	→ ¹⁰	→	→	X ¹³			
Troponin, Creatinine Kinase-MB		X ⁶																
Creatinine		X ⁶									X			X ¹⁴	X	X		
Fluid Intake/Output		X ⁷	→	→	→	→	→	→	→	→	X							
Dyspnea Evaluation		X	X	X	X	X	X	X	X		X			X ¹⁵				
Global Clinical Evaluation			X	X	X	X	X	X	X		X			X ¹⁵				
Unblinding								X ⁹										
Adverse Events			X	→	→	→	→	→	→	→	→	→	→	→	X ¹⁶			
Serious Adverse Events			X	→	→	→	→	→	→	→	→	→	→	→	→	X ¹⁷		
Mortality																X ¹⁸	X ¹⁸	X ¹⁹

¹ Obtain within 24 hours before starting Drug.
² Catheterization subjects only.
³ Hold restricted medication from 2 hours before start of study drug through the end of the 3-hour PBO-controlled period.
⁴ Screening PCWP must be ≥ 20 and SBP ≥ 90 mm Hg.
⁵ Obtain within 20 minutes before starting study drug.
⁶ Obtain within 6 hours before starting study drug.
⁷ The subject should try to empty their bladder within one hour before, and as close to the start of study drug as possible. Record all I/O for the 24 hours after the start of study drug.
⁸ Administer study drug as per protocol.
⁹ After all 3-hour assessments have been completed, call ATRS to determine whether subject on PBO or active drug. PBO will be switched.
¹⁰ All subjects should continue study drug for 24 hours.
¹¹ Vitals are to be recorded at the above time point and every three hours. Vitals are also to be recorded upon increase or decrease of dose.
¹² PCWP should be recorded.
¹³ Duration of study beyond 24 ours is left to the discretion of the investigator.
¹⁴ Obtain daily through two days post infusion
¹⁵ Obtain at time of drug discontinuation.
¹⁶ For subjects who receive drug for ≥ 8 days, record 7 days post end of infusion.
¹⁷ Though study day 30.
¹⁸ Obtain on or after day 30.
¹⁹ Obtain mortality status monthly through 6 months after randomization.

Results:

Patient Disposition:

A total of 498 subjects were randomized across 55 sites. Of these subjects nine, were not treated because they did not meet all inclusion/exclusion criteria at the time infusion was to begin. These subjects were excluded from all analyses (including safety and mortality).

The specifics of those who did not received treatment were as follows.

- Subject # 642-501 (randomized to Natrecor, fixed dose) had a blood systolic pressure below 90-mm Hg. This subject died on day 1 for a myocardial infarction.
- Subject # 687-411 (randomized to Natrecor fixed Dose) died of cardiac arrest following randomization and before study drug was started on day 1.
- Subject # 585-501 (randomized to placebo followed by Natrecor fixed dose) withdrew consent when he was informed that he was sustaining a myocardial infarction
- Subject # 369-510 (randomized to placebo followed by Natrecor fixed dose) had improvement in clinical symptoms before the start of infusion.

- Subject # 357-505 (randomized to Natrecor fixed dose) had improvement in clinical symptoms before the start of infusion.
- Subject # 540-406 (randomized to nitroglycerin); • Subject # (554-424 (randomized to nitroglycerin) • # 572-415 (randomized to placebo followed by Natrecor fixed dose) and • Subject #647-401 (randomized to Natrecor adjustable dose) all discontinued before infusion because the baseline PCWP was less than 20 mm Hg.

Among those who entered the study and received infusions two subjects, one subject (catheterized, Natrecor adjustable dose) and one subject (not catheterized subject randomized to placebo followed by Natrecor fixed dose) had no baseline dyspnea information available.

Two subject # 357-502 and #369-518, randomized to Natrecor fixed dose (not catheterized) discontinued due to adverse events during the three hour placebo-controlled period.

There were a total of 487 subjects who completed the three-hour placebo-controlled infusion period. There were four subjects who did not have available hemodynamic (one subject randomized to nitroglycerine and three subjects randomized to Natrecor fixed does). There were, therefore, a total of 246 subjects who were catheterized and had hemodynamic data available at the 3-hour time point. There was one catheterized subject randomized to Natrecor adjustable dose who had no dyspnea data available. There were 486 subjects who had symptom data available at the 3-hour time point.

A total of 487 continued into the 24-hour infusion period. A total of 30 subjects discontinued prior to the completion of 24-hours of infusion. Eighteen of these subjects discontinued due to adverse events, four subjects withdrew consent, four had worsening of their status or had an inadequate clinical response and 4 subjects had improvement of their status obviating the need for longer infusion.

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The number of subjects who had available baseline and 24-hour hemodynamic and dyspnea data were 227 and 481, respectively.

Table 5. Subject accounting

	Catheterized					Not Catheterized				Total
	NAT Adjust. Dose	NTG	NAT Fixed Dose	PBO:NAT Fixed Dose	PBO:NTG	NTG	PBO:NAT Fixed Dose	PBO:NTG	Nat Fixed Dose	
Randomized (Total = 498)	63	62	63	31	32	83	41	41	82	498
Received infusions (Total=489)	62	60	62	30	32	83	39	41	80	489
Missing data at baseline	1	0	0	0	0	0	1	0	0	2
Missing baseline hemodynamics	0	0	0	0	0	N/A	N/A	N/A	N/A	0
Missing dyspnea	1	0	0	0	0	0	1	0	0	2
Missing both	0	0	0	0	0	N/A	N/A	N/A	N/A	0
Did not receive drug (n=9)	1	2	1	1	0	0	2	0	2	9
Died	0	0	1	0	0	0	0	0	1	2
PCWP < 20 mm Hg	1	2	0	1	0	N/A	N/A	N/A	N/A	4
Ongoing MI	0	0	0	0	0	0	1*	0	0	0
Symptoms improved	0	0	1	0	0	0	1	0	1	2
Withdrew consent	0	0	0	0	0	0	1*	0	0	1
Completed 3-hour infusion data available	62	60	62	30	32	83	39	41	78	487
Completed 3-hour infusion missing data	1	1	3	0	0	0	0	0	0	5
Missing hemodynamics	0	1	3	0	0	N/A	N/A	N/A	NA	4
Missing dyspnea	1	0	0	0	0	0	0	0	0	1
Missing both	0	0	0	0	0	0	0	0	0	0
Did not complete 3-hour infusion	0	0	0	0	0	0	0	0	2	2
Died	0	0	0	0	0	0	0	0	0	0
ADR	0	0	0	0	0	0	0	0	2	2
Withdrew consent	0	0	0	0	0	0	0	0	0	0
Worsened or inadequate clinical response	0	0	0	0	0	0	0	0	0	0
Improved	0	0	0	0	0	0	0	0	0	0
Entered 24 hour infusion	62	60	62	30	32	83	39	41	78	487
Completed 24-hour infusion	57	56	58	28	30	79	38	39	72	457
Did not complete 24-hour infusion	5	4	4	2	2	4	1	2	6	30
Died	0	0	0	0	0	0	0	0	0	0
ADR	2	2	2	1	1	3	1	1	5	18
Withdrew Consent	1	1	0	0	0	0	0	1	1	4
Worsened or inadequate clinical response	0	1	2	0	0	1	0	0	0	4
Improved	2	0	0	1	1	0	0	0	0	4

*One subject withdrew consent when he found out that he was undergoing a myocardial infarction.

Since a Swan-Ganz catheter was optional for this study, the reason for catheterization is shown in Table 6. Most subjects were catheterized because hemodynamic values at baseline were uncertain. Catheterization was frequently used to optimize out subject medication. Table 6 below contains both the primary reason and any contributory reason for the insertion of the catheter.

Table 6. Reasons for catheterization (prim= primary reason)

	Nat Adj Dose (n= 62)		NTG (n= 60)		Nat Fixed Dose (n=62)		PBO:Nat Fixed dose (n=30)		PBO: NTG (n=32)	
	Prim	Any	Prim	Any	Prim	Any	Prim	Any	Prim	Any
Low or unstable BP	1 (2%)	7 (11%)	0	4 (7%)	1 (2%)	5 (8%)	0	0	0	3 (9%)
Uncertain hemodynamics	34 (55%)	54 (87%)	32(53%)	46 (77%)	30 (48%)	56 (90%)	13 (43%)	23(77%)	17(53%)	25(78%)
Low cardiac output suspected	10 (16%)	36 (58%)	12 (20%)	29 (48%)	12 (19%)	37 (60%)	7 (23%)	15(50%)	6 (19%)	14(44%)
Potential Transplant Candidate	2 (3%)	7 (11%)	1 (2%)	7 (12%)	6 (10%)	13 (21%)	2 (7%)	10(33%)	1 (3%)	4 (13%)
Significant Renal Dysfunction	1 (2%)	13(21%)	1 (2%)	8 (13%)	0	12 (19%)	1 (3%)	7 (23%)	0	0
Significant Metabolic Abnormality	0	2 (3%)	0	2 (3%)	0	0	0	2 (7%)	0	0
To optimize outsubject Medication	13 (21%)	29 (47%)	11 (18%)	27 (45%)	10 (16%)	26 (42%)	5 (17%)	12 (40%)	7 (22%)	16(50%)
Other	1 (2%)	3 (5%)	3 (5%)	5 (8%)	3 (5%)	6 (10%)	2 (7%)	3 (10%)	1 (3%)	1(3%)

Demographics: The baseline demographics of those enrolled are shown in Table 7

Table 7. Demographics at baseline (Sponsors Tables 3)

	Catheterized			Not-Catheterized		
	NTG (n=60)	Natrecor Fixed ± Adjust (n=124)	PBO (n=62)	NTG (n=83)	Natrecor (n=80)	PBO (n=80)
Age, years mean ± SD	59 ± 15	63 ± 12	59 ± 16	62 ± 14	62 ± 13	65 ± 15
Ethnicity						
Black	17 (28%)	30 (24%)	14 (23%)	18 (22%)	20(25%)	20 (25%)
Caucasian	34 (57%)	76 (61%)	39 (63%)	51 (61%)	42 (53%)	44 (55%)
Other	9 (15%)	18 (15%)	9 (14%)	14 (17%)	18 (22%)	16 (20%)
Gender						
Male	43 (72%)	95 (77%)	47 (76%)	43 (52%)	53 (66%)	56 (70%)
Female	17 (28%)	29 (23%)	15 (24%)	40 (48%)	27 (34%)	24 (30%)
Weight Kg mean ± SD	85 ± 22	81 ± 19	86 ± 23	82 ± 23	85 ± 22	83 ± 24
Etiology of Cardiomyopathy						
Ischemic	27 (48%)	73 (63%)	34 (59%)	34 (42%)	29 (39%)	44 (59%)
Idiopathic, dilated	15 (27%)	24 (21%)	14 (24%)	24 (32%)	21 (28%)	15 (20%)
Hypertensive	7 (13%)	5 (4%)	3 (5%)	8 (11%)	13 (17%)	9 (12%)
Alcohol	1 (2%)	3 (3%)	1 (2%)	0	1 (1%)	1 (1%)
Valvular/Rheumatic	3 (5%)	8 (7%)	4 (7%)	4 (5%)	4 (5%)	2 (3%)
Diabetic	0	0	0	0	2 (3%)	0
Drug	0	0	0	0	1 (1%)	0
Postpartum	0	0	0	1 (1%)	0	0
Viral Myocarditis	2 (4%)	0	1 (2%)	4 (5%)	0	0
Thyrotoxicosis	0	0	0	0	0	0
Other	1 (2%)	1 (1%)	1 (2%)	2 (3%)	0	0
Unknown	0	2 (2%)	0	1(1%)	4 (5%)	3 (4%)
Missing	4 (7%)	8 (6%)	4 (6%)	7 (8%)	5 (6%)	6 (7%)
Hist. Coronary Artery Disease	38 (63%)	91 (73%)	39 (63%)	52 (63%)	43 (54%)	56 (70%)
AICD present	14 (23%)	42 (34%)	18 (29%)	17 (20%)	13 (16%)	18 (23%)
Hist of Cardiac Revascularization	18 (30%)	58 (47%)	25 (40%)	24(29%)	23 (29%)	34 (43%)
Hist Previous MI	28 (47%)	67 (54%)	28 (45%)	31 (37%)	29 (36%)	42 (53%)
MI < 7 days						
Q-wave	0	1 (1%)	2 (3%)	1 (1%)	2 (3%)	2 (3%)
Non-Q-wave	5 (8%)	3 (2%)	1 (2%)	4 (5%)	1 (1%)	4 (5%)
Acute Coronary Syndr < 7 days	6 (10%)	10 (8%)	4 (6%)	14 (17%)	10 (13%)	17 (21%)
<24 hours	1 (2%)	5 (4%)	1 (2%)	8 (10%)	5 (6%)	8 (10%)

The population that was enrolled was reasonably well balanced across treatment groups. Ischemic cardiomyopathy was the most common etiology of heart failure. Coronary artery disease was common and observed in 54-73% of those enrolled. A small fraction of those enrolled had a recent MI (< 7 days, 3-8%). 10-21% had an acute coronary syndrome event within the week prior to the study. There was no overwhelming difference in comparing the catheterized to not-catheterized subjects. Approximately 15-30% of those enrolled had an AICD in place.

The signs and symptoms of CHF are shown in Table 8. Rales and peripheral edema were the most common symptoms and were present in approximately 64-84% of those enrolled. Ejection fraction among those catheterized were somewhat less than that of the not-catheterized subjects. Subjects were largely class III and IV subjects.

Table 8. Symptoms and Severity of CHF at baseline

	Catheterized			Not Catheterized		
	NTG (n=60)	Natrecor Fixed ± Adjust (n=124)	PBO (n=62)	NTG (n=83)	Natrecor (n=80)	PBO (n=80)
Rales present (%)	37 (62%)	92 (74%)	44 (71%)	69 (83%)	55 (69%)	62 (78%)
S3 present (%)	35 (58%)	69 (56%)	40 (63%)	47 (57%)	51 (64%)	48 (60%)
S4 present (%)	15 (25%)	24 (20%)	10 (16%)	22 (27%)	21 (26%)	13 (16%)
Murmurs present (%)	40 (67%)	79 (64%)	37 (61%)	44 (54%)	42 (53%)	49 (61%)
Hepatomegaly present (%)	22 (39%)	52 (44%)	24 (43%)	24 (31%)	26 (34%)	28 (38%)
Pedal Edema present (%)	38 (63%)	78 (63%)	44 (71%)	65 (78%)	65 (81%)	66 (83%)
Ejection Fraction mean ± SD*	24 ± 13	24 ± 12	26 ± 13	27 ± 16	30 ± 14	30 ± 15
EF>40%	6 (11%)	11 (9%)	7 (12%)	13 (18%)	15 (21%)	13 (19%)
Previous NYHA Class (prior to admission)						
I						
II	4 (7%)	10 (8%)	5 (8%)	9 (11%)	7 (9%)	7 (9%)
III	10 (17%)	10 (8%)	2 (3%)	8 (10%)	3 (4%)	5 (6%)
IV	28 (47%)	50 (40%)	24 (39%)	29 (35%)	39 (49%)	35 (44%)
	18 (30%)	54 (44%)	31 (50%)	37 (45%)	31 (39%)	33 (41%)

* Last available measurement, not necessarily associated with this study.

Medications that were taken within six hours of the start of the infusion are shown in Table 9. Inotropic support (PDE III inhibitors, dopamine or dobutamine) were administered to approximately 20% of those enrolled within 6-hours of entry into the study. The exception was the NTG (not catheterized) group in which only 7% received some form of pressor. IV after-load reducers (IV nitroglycerine or nitroprusside) were administered to approximately 5% of those enrolled. IV diuretics were administered to 35% of those enrolled.

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Table 9. Medications taken within 6 hours prior to the start of study drug.

	Catheterized			Not Catheterized		
	NTG (n=60)	Natrecor Fixed ± Adjust (n=124)	PBO (n=62)	NTG (n=83)	Natrecor (n=80)	PBO (n=80)
Diuretics	25(42%)	43 (35 %)	23 (37 %)	50 (60 %)	45 (56 %)	41 (51 %)
IV diuretics	15 (25%)	34 (27 %)	16 (26 %)	34 (41 %)	27 (34 %)	31 (39 %)
Oral diuretics	13 (22%)	18 (15 %)	11 (18 %)	22 (27 %)	24 (30 %)	17 (21 %)
Digoxin	13 (22%)	26 (21 %)	11 (18 %)	24 (29 %)	27 (34 %)	24 (30 %)
IV Digoxin	0	2 (2%)	0	0	0	1(1 %)
Aspirin	12 (20%)	26 (21 %)	11 (18 %)	23 (28 %)	19 (24 %)	27 (34 %)
ACE inhibitors	8 (13%)	26 (21 %)	12 (19 %)	21 (25 %)	25 (31 %)	27 (34 %)
Non-IV Nitrates	7 (12 %)	23 19 %)	10 (16 %)	25 (30 %)	19 (24 %)	18 (23 %)
IV Nitroglycerine	0	3 (2 %)	3 (5 %)	2(2%)	3 (4 %)	1 (1 %)
Beta Blockers	5 (8 %)	16 (13 %)	1 (2 %)	17 (20 %)	12 (15 %)	12 (15 %)
IV Beta blockers	0	1 (1 %)	0	0	0	1 (1 %)
Anticoagulants:						
Warfarin	1 (2 %)	4 (3 %)	1 (2 %)	2 (2 %)	2 (3 %)	3 (4 %)
Heparin	3 (5%)	10 (8%)	7 (11%)	6 (7 %)	9 (11 %)	10(13 %)
Statins	1 (2 %)	3 (2 %)	2 (3 %)	3 (4 %)	1 (1 %)	2 (3 %)
Class III antiarrhythmics	1(2 %)	16 (13 %)	3 (5 %)	4 (5 %)	7 (9 %)	6 (8 %)
Calcium Channel Blockers	2 (3 %)	8 (6%)	2 (3 %)	4 (5 %)	8 (10 %)	9 (11 %)
Angiotensin II Blockers	2 (3 %)	0	1 (2 %)	5 (6 %)	4 (5 %)	1 (1 %)
Hydralazine	3 (5 %)	9 (7 %)	1 (2 %)	3 (4 %)	4 (5 %)	3 (4 %)
Other antihypertensives	0	0	0	1 (1 %)	1 (1 %)	0
Other antiarrhythmics	0	2 (2 %)	0	2 (2 %)	0	0
IIb/IIIa inhibitors	4 (7 %)	2 (2 %)	1 (2 %)	2 (2 %)	2 (3 %)	4 (5 %)
Dobutamine	9 (15 %)	19 (15%)	14 (23 %)	5 (6 %)	16 (20 %)	12 (15 %)
PDE inhibitors	0	2 (2 %)	2 (3 %)	1 (1 %)	0	1(1%)
Dopamine	2 (3 %)	13 (10 %)	1 (2 %)	0	4 (5%)	5 (6 %)
Nitroprusside	0	1 (1 %)	1 (2 %)	1 (1 %)	1 (1 %)	1 (1 %)
Pressors	0	0	0	0	0	0

The medications taken within 24 hours of starting the study drug infusion is shown in Table 10. The pattern of medication use over this longer period prior to entering the study show that 20-25% were treated with intravenous pressors, and approximately 5% with after load reducers. (The NTG not-catheterized group was unusual in the low use of dobutamine =5%). Intravenous diuretics were administered to approximately 45-50% of those enrolled.

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Table 10. Selected medications taken within 24 hours prior to the start of study drug.

	Catheterized			Not Catheterized		
	NTG (n=60)	Natrecor Fixed ± Adjust (n=124)	PBO (n=62)	NTG (n=83)	Natrecor (n=80)	PBO (n=80)
Diuretics	45 (75%)	85 (69%)	47 (76%)	73 (88%)	71 (89%)	73 (91%)
IV diuretics	31 (52%)	64 (52%)	30 (48%)	57 (69%)	51 (64%)	57 (71%)
Oral diuretics	31 (52%)	42 (34%)	25 (40%)	37 (45%)	40 (50%)	31 (39%)
Digoxin	24 (40%)	62 (50%)	29 (47%)	45 (54%)	41 (51%)	38 (48%)
IV Digoxin	0	5 (4%)	1 (2%)	1 (1%)	1 (1%)	2 (3%)
Aspirin	25 (42%)	50 (40%)	20 (32%)	42 (51%)	33 (41%)	35 (44%)
ACE inhibitors	19 (32%)	62 (50%)	29 (47%)	44 (53%)	45 (56%)	42 (53%)
Non-IV Nitrates	18 (30%)	43 (35%)	16 (26%)	37 (45%)	31 (39%)	31 (39%)
IV Nitroglycerine	0	6 (5%)	3 (5%)	6 (7%)	3 (4%)	3 (4%)
Beta Blockers	17 (28%)	30 (24%)	11 (18%)	25 (30%)	20 (25%)	20 (25%)
IV Beta blockers	0	2 (2%)	0	1 (1%)	3 (4%)	3 (4%)
Anticoagulants:						
Warfarin	6 (10%)	11 (9%)	2 (3%)	15 (18%)	13 (16%)	10 (13%)
Heparin	5 (8%)	15 (12%)	7 (11%)	9 (11%)	11 (14%)	13 (16%)
Angiotensin II Blockers	2 (3%)	3 (2%)	5 (8%)	8 (10%)	6 (8%)	4 (5%)
Dobutamine	10 (17%)	21 (17%)	14 (23%)	5 (6%)	18 (23%)	12 (15%)
PDE inhibitors	0	4 (3%)	4 (6%)	1 (1%)	0	1 (1%)
Dopamine	2 (3%)	13 (10%)	1 (2%)	0	5 (6%)	5 (6%)
Nitroglycerine	0	1 (1%)	1 (2%)	1 (1%)	1 (1%)	1 (1%)
Pressors	0	0	0	0	0	0

Taken as a whole, approximately 20-35% of those enrolled was treated with pressors or afterload reducers. Intravenous diuretics were used in approximately 50% of those enrolled. Afterload reducers were administered to a small fraction of those enrolled.

Blinding:

There were several situations where unblinding of treatments occurred during the study but distant in time from the time the subject was infused.

- The investigator of study site # 554 was asked to sign treatment logs. The investigator signed the logs but claims to not have reviewed the treatment assignments. At the time of the unblinding 54 of the 56 subjects whose blinding was compromised were past 14 days and 46/56 subjects were past 30 days follow-up.
- A Scios CRA was unblinded to the list of NTG that was out of specifications. The list included the numbers of eight subjects exposed to the NTG shipment.
- A Scios monitor was inadvertently unblinded to two subject's treatment while on a monitoring visit.
- A Scios monitor was inadvertently unblinded to a PBO/NTG subject during a conversation with a pharmacist.

Dose of study medications:

With respect to the study medication, the sponsor tabulates several subjects whose dosing violated the stipulated protocol. The specifics are tabulated below.

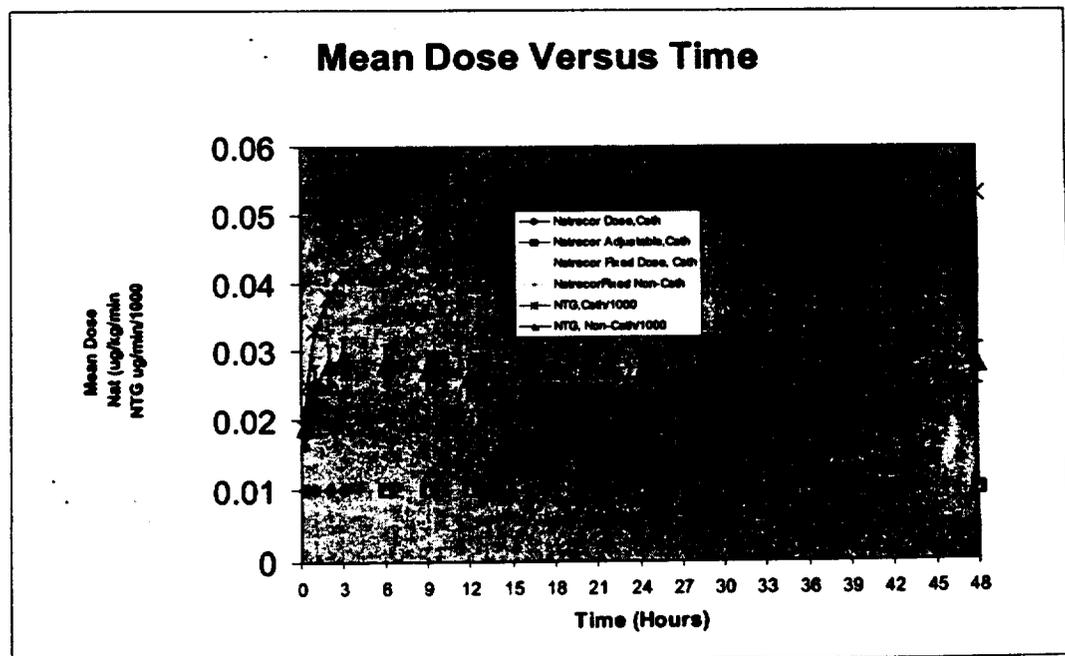
Table 11. Study Drug Dosing Deviations

	NTG	NAT	ALL
Placebo-controlled Period			
Incorrect initial NAT/PBO bolus volume	6	9	15
Incorrect NAT/PBO Infusion flow rate	10	16	26
Active-controlled period			
No crossover NAT/PBO bolus administration	8	7	15
Incorrect crossover NAT/PBO bolus volume > 10%	1	2	3
Incorrect crossover NAT/PBO infusion flow rate >10%	2	4	6
Stop time of infusion > 15 minutes different between two infusions	5	3	8

- # 671-402 this subject had a dose increase to 0.03 ug/kg/min faster than allowed by the protocol.
- # 666-503 received the medication for subject #666-504 who was randomized to the same medication (fixed dose Natrecor).
- # 638-502 (NTG) the infusion line infiltrated at the beginning of the bolus. The remainder of the bolus was administered five hours later. The time of the second bolus was considered as time 0. The subject was not catheterized and the measurements effect only dyspnea and global assessments.
- # 543-405 (PBO/NTG) did not cross over due to PCWP < 12 mm Hg
- # 357-502 and #369518 (both NAT fixed dose) discontinued during the 3-hour phase due to asymptomatic hypotension
- # 636-502 (NAT fixed dose) continued on infusion for 161 days.

The dose of medication in the individual treatment groups is shown in Figure 2. The mean dose of Natrecor, either among those catheterized or not catheterized was the same (0.01 ug/kg/min) during the 3-hour placebo-controlled and 24-hour blinded infusion periods. The dose of NTG increased over time. The increase in dose among those catheterized was faster than among those not catheterized.

Figure 2 Mean dose versus time of Natrecor versus Nitroglycerin



The distribution of subjects who were treated with a specific dose range is shown in Figure 3 for Natrecor- and Figure 4 for the NTG-treated subjects. Among those treated with the fixed dose Natrecor doses (both catheterized and not catheterized), few subjects received doses higher than the 0.01 ug/kg/min dose. Among those treated with the adjustable Natrecor dose, approximately 40% of the subjects at one time received doses centered around 0.015 ug/kg/min. Approximately 20% of those treated with Natrecor had doses reduced (centered around 0.005 ug/kg/min).

The specific reasons for the dosing changes are shown in Table 12. This table includes the placebo crossover subjects into their new treatment regimen. Among those catheterized or not catheterized, many more nitroglycerin subjects had modifications of their dose than did Natrecor subjects. The adjustable dose Natrecor (catheterized) had more dosing changes than fixed dose Natrecor (catheterized) subjects. Subjects could have more than one increase or decrease and the number of increases and decrease in dose are also shown in Table 12. The reasons for the dose reduction are also shown in table 12. Only approximately 10% of those treated either with NTG or Natrecor fixed or adjustable doses had their doses reduced or interrupted due to adverse events. A large proportion of those whose dose was reduced was a consequence of clinical improvement (clinical effect).

Figure 3

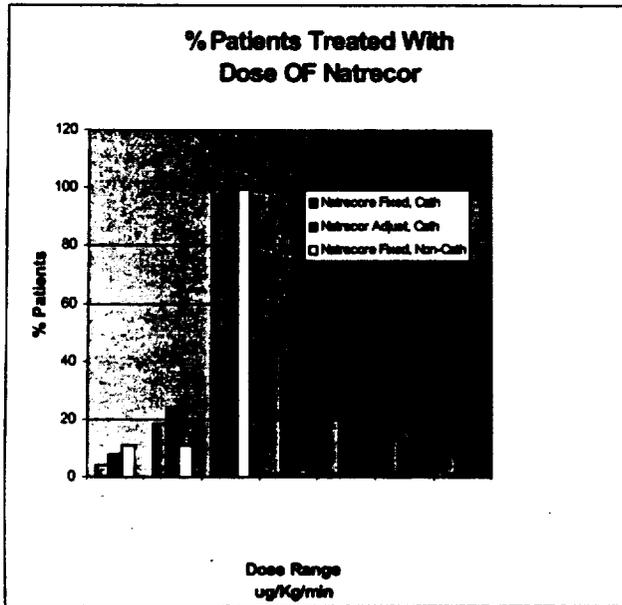
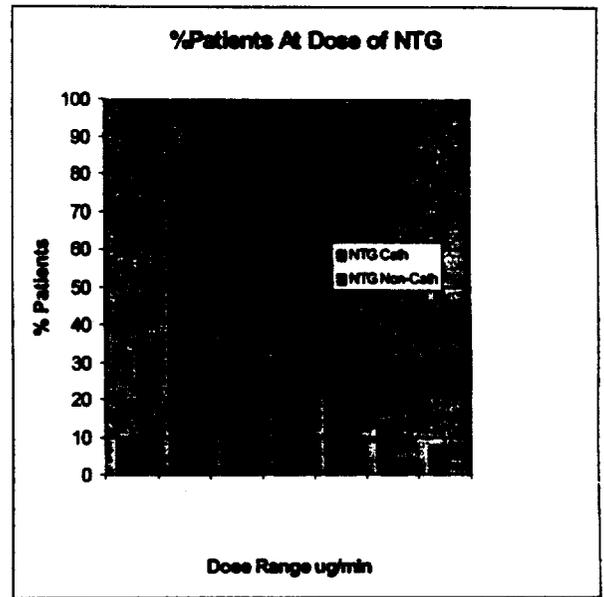


Figure 4



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Table 12 reason for dose change

	Catheterized			Non-Catheterized	
	Natrecor Fixed* (n=92)	Natrecor Adj (N=62)	NTG* (n=92)	Natrecor Fixed (n=119)	NTG* (n=124)
Number remaining on initial dose (% Subjects)	74 (80%)	25 (40%)	29 (32%)	100 (84%)	76 (61%)
Type of dose modification # Pts (%)	18 (20%)	37 (60%)	62 (67%)	19 (16%)	48 (39%)
Dose Increase	4 (4%)	24 (39%)	57 (62%)	2 (2%)	38 (31%)
Dose Reduction	17 (18%)	22 (35%)	30 (33%)	13 (11%)	23 (19%)
Dose Interruption	1(1%)	3 (5%)	4 (4%)	5 (4%)	7 (6%)
Type of dose modification (# events)					
Dose Increase	7	52	291	2	132
Dose Reduction	29	37	50	14	47
Dose Interruption	1	3	4	5	9
Reason for Dose Reduction/Interruptions (# Pts)	18 (22%)	25 (40%)	33 (37%)	18 (15%)	27 (25%)
To clinical effect	7 (8%)	15 (24%)	17 (20%)	2 (2%)	14 (12%)
Adverse event	9 (10%)	6 (11%)	10 (13%)	14 (12%)	9 (9%)
Other/NA	2 (2%)	4 (5%)	6 (8%)	2 (2%)	4 (3%)

* Consists of randomized plus placebo crossovers. Sponsor's table 40.2-40.3

Concomitant medications during the three-hour infusion period are shown in Table 13. During the 3-hour placebo controlled period, approximately 15% (4-23%) of those enrolled were treated with concomitant dobutamine that was ongoing at baseline. Approximately 5% (0-9%) of the subjects enrolled were treated with dopamine at the time of entry and continued while on study drug. One Natrecor fixed dose and one placebo catheterized subjects had dobutamine newly added during this period. One Natrecor (not catheterized subject had dopamine newly added during the infusion.

Table 13 Selected medications taken during 3-hour PBO controlled period

	Catheterized			Not Catheterized		
	NTG (n=60)	Natrecor Fixed ± Adjust (n=124)	PBO (n=62)	NTG (n=83)	Natrecor (n=80)	PBO (n=80)
Diuretics	15 (25%)	26 (21%)	18 (29%)	12 (14%)	17 (21%)	11 (14%)
IV diuretics	9 (15%)	19 (15%)	12 (19%)	10 (12%)	8 (10%)	7 (9%)
Oral diuretics	8 (13%)	9 (7%)	7 (11%)	3 (4%)	6 (8%)	6 (8%)
Digoxin	6 (10%)	9 (7%)	9 (15%)	5 (6%)	6 (8%)	8 (10%)
IV Digoxin	1 (2%)	0	0	1 (1%)	1 (1%)	0
ACE inhibitors	8 (13%)	14(11%)	11 (13%)	11 (13%)	11 (14%)	6 (8%)
Non-IV Nitrates	3 (5%)	10 (8%)	11 (18%)	9 (11%)	9 (11%)	9 (11%)
IV Nitroglycerine	0	0	0	0	0	0
Beta Blockers	4 (7%)	11 (9%)	3 (5%)	3 (4%)	5 (6%)	4 (5%)
IV Beta blockers	1(2%)	0	0	0	0	0
Angiotensin II Blockers	1 (2%)	3 (2%)	1 (2%)	0	1 (1%)	2 (3%)
Dobutamine	8 (13%)	19 (15%)	15 (24%)	3 (4%)	15 (19%)	11 (14%)
Continued at Baseline	8 (13%)	18 (15%)	14 (23%)	3 (4%)	15 (19%)	11 (14%)
New Administration	0	1 (1%)	1 (2%)	0	0	0
PDE inhibitors	0	0	0	0	0	0
Dopamine	2 (3%)	11 (9%)	1 (2%)	0	5 (6%)	4 (5%)
Continued at Baseline	2 (3%)	11 (9%)	1 (2%)	0	4 (5%)	4 (5%)
New Administration	0	0	0	0	1 (1%)	0
nitroprusside	0	0	0	0	0	1 (1%)
Pressors	0	0	0	0	0	0

Primary Efficacy End points

1. **Hemodynamics PCWP at 3 hours:** This parameter was assessed only among those catheterized.

Quality of data: There were 3 subjects who had missing values for PCWP. The three subjects were all in the Natrecor (Fixed dose) regimen. The subjects (# 369417, #540408 and 678404) all completed the three-hour infusion with other hemodynamic data available (notably cardiac output) that showed no deterioration in cardiac function. Censoring of these subjects, therefore, is unlikely to bias the results.

This analysis of interest was the change from baseline at three hours of the infusion. Baseline measurements were to demonstrate stability of the PCWP measurement. Two values of PCWP at baseline were to not differ by more than 15% (of the higher or lower value?) were to be collected within 20 minutes of the start of the infusion and within 5-15 minutes of each other. The last of these values was to serve as baseline.

There were, however, many subjects whose values violated these prespecified criteria for baseline measurement. These deviations included less than two baseline measurements (N=7); at least one of the baseline measurements > 20 minutes before the start of the infusion (N=83); baseline measurements after the start of the infusion (N=9); duplicate measurements outside the 5-15 minute regimen (N=6). These deviations were distributed across all treatments and are not likely to bias the results.

The protocol proposed to maintain a firewall between the assessment of hemodynamics and unblinding of treatment. This unblinding (placebo versus active) was only to take place after the hemodynamics was completed. A log of the time at which the treatment was unblinded was kept. There, however, was no way to guarantee that these values were committed to the CRFs before the unblinding occurred. There were, in addition, several subjects for whom the time of symptom assessment occurred after the time of hemodynamics (the fraction on nitroglycerin: Natrecor: PBO were 1/60: 14/124: 13/62 patients, respectively). Consequently some fraction of patients could have had known hemodynamics at the time symptoms were assessed.

The sponsor's results for wedge pressures are shown below. The FDA's analysis is essentially the same.

Table 14 Pivotal wedge pressure assessment (per sponsor)

	Nitroglycerin (n=60)	Pooled Natrecor (n=124)	Placebo (n=62)
Baseline	28.0 + 5.7	27.7 + 7.0	27.7 + 5.5
3-hour	24.2 + 6.2	21.9 + 7.4	25.7 + 6.6
Mean Change from Baseline Mean + SD	-3.8 + 5.3	-5.8 + 6.5	-2.0 + 4.2
Least Square Mean + SE	-3.8 + 0.7	-5.8 + 0.5	-2.0 + 0.7
p-value versus Placebo	0.087	<0.001	
p-value Natrecor versus Nitroglycerine		0.027	

Three Hour Dyspnea Evaluation:

This metric defines the nature of the dyspnea at baseline as well as the degree of dyspnea at 24-hours. The ordinal descriptive categories consist of:

- At rest while sitting;
- At rest while lying flat or with one pillow;

- With minimal activity (such as talking eating or bathing);
- With walking short distances (such as to the bathroom);
- With walking distances greater than 50 feet;
- With walking up stairs or running;
- The subject did not have difficulty breathing.

At hours ¼, ½, 1, 2, 3, 6 and 24 the subject was asked to rate their change in discomfort from baseline. It is this metric which is part of the primary endpoint of the study.

It is unclear how the metric was finalized prior to unblinding placebo from active treatments.

Quality of the data: There was only one subject with no data (subject # 357-401 treated with adjustable dose Natrecor; catheterized). This subject apparently was confused and could not give cogent symptom responses. Subject # 554-503 (fixed dose, not catheterized) had no descriptive baseline assessment available but had the measurements of change in symptoms collected at the appropriate time. There were 49 subjects who had baseline symptoms assessed at times fairly distant (i.e. > 1 hour) prior to the start of the infusion. The longest pre-infusion assessment of baseline was > 4 hours. Three subjects had their baseline symptoms ascertained at a time point after the start of infusion but generally minutes of the start of infusion.

(Comment: Since the placebo group had a substantial symptomatic benefit, time itself affords some improvement in symptoms. The time from the start of the infusion for which the baseline symptoms were assessed could be important in the assessment of response. I do not have this analysis yet.)

Baseline Measurements: The specific description by the subject of their degree of dyspnea at baseline is shown in Table 15.

Table 15: Description of baseline degree of dyspnea.

	Catheterized					Not Catheterized				Total
	ANAT	FNAT	PLA:NAT	PLA:NTG	NTG	FNAT	PLA:NAT	PLA:NTG	NTG	
	N=62	N=62	N=30	N=32	N=61	N=80	N=40	N=40	N=83	489
At rest while sitting	28 (44%)	31 (50%)	9 (31%)	10 (31%)	29 (48%)	39 (48%)	18 (48%)	19 (48%)	38 (46%)	220(45%)
At rest while lying flat or with one pillow	21 (34%)	14 (23%)	16 (55%)	14 (44%)	20 (33%)	29 (36%)	11 (28%)	16 (40%)	37 (45%)	179(36%)
With minimal activity (such as talking, eating or bathing)	7 (11%)	14 (23%)	2 (7%)	4 (13%)	10 (16%)	7 (6%)	5 (6%)	5 (13%)	5 (6%)	60 (12%)
With walking short distances (such as to the bathroom)	2 (4%)	2 (3%)	2 (4%)	0	2 (6%)	2 (3%)	3 (3%)	0	3 (4%)	15 (3%)
With walking distances greater than 50 feet	3 (5%)	0	0	2 (6%)	0	1 (1%)	2 (3%)	0	0	8 (2%)
With walking up stairs or running	0	1 (2%)	0	2 (6%)	0	1 (1%)	0	0	0	4 (1%)
The subject had no difficulty with breathing	0	0	1 (1%)	0	0	0	0	0	0	1 (<1%)
Not assessed	1 (2%)	0	0	0	0	1(1%)	0	0	0	2 (<1%)

Of those enrolled, 45% had symptoms at rest another 36% had orthopnea. The other subjects enrolled (approximately 19%) had symptoms with mild or more rigorous activities. In reality this fraction of subjects did not adhere to the protocol requirement of dyspnea at rest. Two subjects did not have symptoms assessed at baseline. (Comment: the sponsor notes that symptom assessment was made at times distant to enrollment. At the time they entered the study the sponsor claims the patients all had dyspnea at rest).

The change from baseline is shown below. The p-values reflect the sponsor's analysis. The groups seem well balanced, except that there were fewer subjects who had symptoms at rest those catheterized subjects, who were randomized to placebo followed either by nitroglycerine or Natrecor. Two subjects had missing assessments at baseline. One of these subjects, however, had the symptoms change assessed so that this subject contributed to this analysis. One subject # 357-401 had no measurements taken and was censored from this analysis.

(Comment: Since baseline symptoms may have been different among the different groups, an analysis should be done with baseline symptom as covariate)

Table 16. Change in dyspnea

	NTG (n=143)	Natrecor (N=204)	Placebo (n=142)
3 hour Evaluation			
Markedly better (+3)	14 (12%)	34 (17%)	25 (18%)
Moderately better (+2)	50 (35%)	54 (27%)	24 (17%)
Minimally better (+1)	37 (26%)	64 (32%)	41 (29%)
No Change (0)	33 (23%)	45 (22%)	46 (32%)
Minimally Worse (-1)	5 (3%)	5 (2%)	6 (4%)
Moderately worse (-2)	0 (0%)	1 (<1%)	0 (0%)
Markedly worse (-3)	1 (1%)	0 (0%)	0 (0%)
p-value compared to placebo	0.191	0.034	
p-value Natrecor compared to NTG		0.6	

The sponsor performed an alternate analysis (not the primary end point), assigning a numeric value for each change in symptoms as shown above that is +3 for markedly better, +2 for moderately better etc. The analysis then treated the resultant numbers as a continuous variable. This analysis is shown in Table 17:

Table 17. Analysis treating change in dyspnea as linear outcomes.

	Nitroglycerin (n=143)	Natrecor (N=204)	Placebo (n=142)
3-Hour mean (+ SD)	1.3 + 1.1	1.3 + 1.1	1.1 + 1.2
Least Square Mean + SE	1.2 + 0.1	1.3 + 0.1	1.1 + 0.1
p-Value versus placebo (2-way ANOVA)	0.285	0.050	
p-value Natrecor		0.414	

Other hemodynamic measurements till three hours:

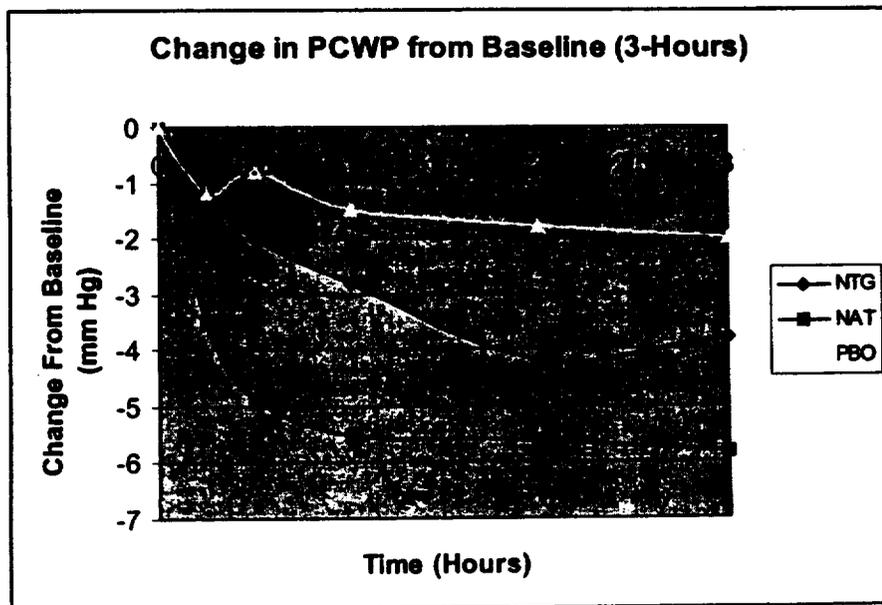
PCWP: The Natrecor adjustable dose and Natrecor fixed dose were pooled as pre-specified for this analysis. Hemodynamic measurements were only available for those with an indwelling catheter. The time course is shown in Table 18 and displayed as figure 5.

The effect on those treated with Natrecor shows a rapid drop in wedge pressure obvious even at 0.25 hours, with a steady effect observed between 1-3 hours the effect of Natrecor is fairly constant. For those treated NTG there is an increase in effect over time. The benefit of NTG did not occur till somewhat later than the effect on wedge pressure observed with NAT.

Table 18. Time course of PCWP

		NTG (n=60)	Natrecor (N=124)	PBO (N=62)
Baseline	N = /Missing ()	60 (0)	124 (0)	62 (0)
	Mean ± SD	28.0 ± 5.7	27.7 ± 7.0	27.7 ± 5.4
0.25 Hr	N= / missing in ()	58 (2)	121 (3)	62 (0)
	Change from Baseline (LS mean ± SE)	-1.2 ± 0.6	-3.5 ± 0.4	-1.2 ± 0.6
	p-value versus NTG		0.002	0.98
	p-value versus NAT			0.001
0.5 Hr	N= / missing in ()	58 (2)	122 (2)	62 (0)
	Change from Baseline (LS mean ± SE)	-2.0 ± 0.6	-4.9 ± 0.4	-0.8 ± 0.6
	p-value versus NTG		0.000	0.18
	p-value versus NAT			0.000
1 Hr	N= / missing in ()	58 (2)	121 (3)	62 (0)
	Change from Baseline (LS mean ± SE)	-2.8 ± 0.7	-5.5 ± 0.5	-1.5 ± 0.7
	p-value versus NTG		0.002	0.2
	p-value versus NAT			0.000
2 Hrs	N= / missing in ()	56 (4)	118 (6)	61 (1)
	Change from Baseline (LS mean ± SE)	-4.2 ± 0.8	-5.6 ± 0.5	-1.8 ± 0.7
	p-value versus NTG		0.139	0.024
	p-value versus NAT			0.000
3 Hrs	N= / missing in ()	59 (1)	121 (3)	62 (0)
	Change from Baseline (LS mean ± SE)	-3.8 ± 0.7	-5.8 ± 0.5	-2.0 ± 0.7
	p-value versus NTG		0.027	0.087
	p-value versus NAT			0.000

Figure 5



Other hemodynamic measurements during first three hours aside from PCWP: Other hemodynamic measurements that were collected during the first three hours are shown in Table 19. With respect to right atrial pressure, there was a statistically (nominal) decrease in the Natrecor group relative to the placebo group as early as one hour into the infusion. At 1 hour, the effect of Natrecor was also superior to NTG in RAP. At 3 hours there was no difference between treatments. The reason for the lack of difference may be a reflection of the escalating NG doses.

With respect to systemic vascular resistance, decrease in resistance by those treated with Natrecor relative to placebo at 1 hour but not at 3 hours.

Table 19: Right atrial pressures and systemic vascular resistance during the three hour placebo-controlled period.

		Right Atrial Pressure			Systemic Vascular Resistance		
		NTG (n=60)	Natrecor (N=124)	PBO (N=62)	NTG (n=60)	Natrecor (N=124)	PBO (N=62)
BL	N = /Missing ()	59 (1)	118 (6)	60 (2)	57 (3)	117 (7)	57 (5)
	Mean + SD	15.9 + 6.8	14.7 + 6.8	14.2 + 7.0	1508.7 + 697	1441 + 589	1384 + 563
1 Hr	N = / missing in ()	58 (2)	120 (4)	60 (2)	57 (3)	118 (6)	59 (3)
	Change from Baseline (LS mean + SE)	-1.0 ± 0.6	-2.6 ± 0.4	-0.2 ± 0.5	-136 ± 63	-236 ± 44	-8 ± 62
	p-value versus NTG		0.014	0.31		0.19	0.149
	p-value versus NAT			0.000			0.003
3 Hr	N = / missing in ()	58 (2)	119 (5)	60 (2)	56 (4)	117 (7)	57 (5)
	Change from Baseline (LS mean + SE)	-2.6 ± 0.6	-3.1 ± 0.4	0.0 ± 0.6	-105 ± 62	-144 ± 43	-44 ± 62
	p-value versus NTG		0.42	0.001		0.598	0.492
	p-value versus NAT			0.000			0.186

The relative effect of the treatments on cardiac index and pulmonary vascular resistance are shown in Table 20. Relative to placebo, Natrecor increases cardiac index (~19 % different) at the 1 hour time point. At the 3-hour time point there was an approximately 5% increase in cardiac index over placebo. At the 3-hour point, there was no difference relative to placebo. At the 1-hour time point, the effect of Natrecor was statistically (nominal) greater than that of NTG, there was no difference at 3 hours.

Natrecor decreased pulmonary vascular resistance, relative to placebo at both the 1 and 3 hour time points. There was no difference between Natrecor and NTG at either of these time points.

Table 20 Baseline and change from baseline for cardiac index and pulmonary vascular resistance.

		Cardiac Index (L/min/M2)			Pulmonary Vascular Resistance		
		NTG (n=60)	Natrecor (N=124)	PBO (N=62)	NTG (n=60)	Natrecor (N=124)	PBO (N=62)
BL	N = /Missing ()	58 (2)	119 (5)	59 (3)	54 (6)	102 (22)	54 (8)
	Mean + SD	2.1 ± 0.8	2.2 ± 0.7	2.2 ± 0.7	271 + 178	250 + 168	236 + 173
1 Hr	N = / missing in ()	57 (3)	120 (4)	60 (2)	51 (9)	106 (18)	57 (3)
	Change from Baseline (LS mean + SE)	0.1 ± 0.07	0.3 ± 0.05	-0.1 ± 0.07	-38 ± 17	-27 ± 12	+28 ± 16
	p-value versus NTG		0.008	0.08		0.6	0.004
	p-value versus NAT			0.000			0.006
3 Hr	N = / missing in ()	56 (4)	120 (4)	58 (4)	51 (9)	103 (21)	55 (7)
	Change from Baseline (LS mean + SE)	0.2 ± 0.07	0.1 ± 0.05	-0.0 ± 0.07	-18 ± 16	-21 ± 12	21 ± 16
	p-value versus NTG		0.79	0.09		0.91	0.082
	p-value versus NAT			0.09			0.037

The effect on mean pulmonary artery pressure is shown in Table 21. There was a decrease in mean pulmonary artery pressure of Natrecor relative to placebo at 1 and 3 hours. There was also a decrease in mean pulmonary artery pressure of Nat relative to placebo at 1 and 3 hours.

Table 21: Baseline and change from baseline for mean pulmonary artery pressures

		Mean Pulmonary Artery Pressure		
		NTG (n=60)	Natrecor (N=124)	PBO (N=62)
BL	N = /Missing ()	60 (0)	122 (2)	62 (0)
	Mean + SD	38.9 + 8.2	38.3 + 8.6	39.2 + 7.7
1 Hr	N= / missing in ()	59 (1)	124 (0)	62 (0)
	Change from Baseline (LS mean + SE)	-2.3 ± 0.8	-4.4 ± 0.5	-0.5 ± 0.8
	p-value versus NTG		0.03	0.09
	p-value versus NAT			0.000
3 Hrs	N= / missing in ()	59 (1)	124 (0)	62 (0)
	Change from Baseline (LS mean + SE)	-2.5 ± 0.8	-5.4 ± 0.6	-1.1 ± 0.8
	p-value versus NTG		0.005	0.22
	p-value versus NAT			0.000

Symptoms up to three hours: The change in subject's symptoms over the initial 3 hours are shown in Table 22. The only significant value occurred at the three-hour time point in comparing the Natrecor treated subjects to placebo. There were no credible differences aside from the placebo-Natrecor comparison at three hours. A graphical representation of dyspnea benefit is shown in Figure 6.

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Table 22: Time course of patient's dyspnea symptoms over the placebo-controlled period.

	0.25 Hours			0.5 Hours			1 Hour			2 Hour			3 Hour		
	NTG N=143	NAT N=204	PBO N=142	NTG N=143	NAT N=214	PBO N=142									
Markedly better	6 (4%)	16 (8%)	9 (6%)	9 (6%)	18 (9%)	11 (8%)	13 (9%)	23 (11%)	13 (9%)	13 (9%)	27 (13%)	18 (13%)	17 (12%)	34 (17%)	25 (18%)
Moderately better	13 (9%)	17 (8%)	19 (13%)	23 (16%)	27 (13%)	19 (13%)	34 (24%)	42 (21%)	30 (21%)	48 (34%)	50 (25%)	26 (18%)	50 (35%)	54 (27%)	24 (17%)
Minimally better	36 (25%)	53 (26%)	27 (19%)	40 (28%)	69 (34%)	48 (34%)	41 (29%)	64 (32%)	49 (35%)	37 (26%)	63 (31%)	49 (35%)	37 (26%)	64 (32%)	41 (29%)
No change	83 (58%)	116 (57%)	86 (61%)	67 (47%)	85 (42%)	63 (44%)	51 (36%)	71 (35%)	47 (33%)	41 (29%)	59 (29%)	44 (31%)	33 (23%)	45 (22%)	46 (32%)
Minimally worse	4 (3%)	0	1 (1%)	4 (3%)	3 (1%)	1 (1%)	3 (2%)	1 (0%)	3 (2%)	1 (1%)	2 (1%)	5 (4%)	5 (3%)	5 (2%)	6 (4%)
Moderately worse	0	0	0	0	0	0	1 (1%)	2 (1%)	0	0	1 (<1%)	0	0	1 (0%)	0
Markedly worse	0	1 (<1%)	0	0	1 (<1%)	0	0	0	0	0	0	0	1 (1%)	0	0
p-value versus NTG		0.4	0.5		0.7	0.5		0.9	0.8		0.8	0.2		0.6	0.2
p-Value versus NAT			0.8			0.96			0.96			0.2			0.03*

Table 23 lists at the p-values for symptom change among those who were catheterized and those not catheterized. The only group that differed were those catheterized. (Comment: This reviewer is concerned that knowledge of wedge pressure effects could have somehow amplified any benefit in symptoms only among catheterized subjects.)

Table 23. P-values for symptom assessment

	0.25 Hours			0.5 Hours			1 Hour			2 Hour			3 Hour		
	NTG N=143	NAT N=204	PBO N=142	NTG N=143	NAT N=214	PBO N=142									
Catheterized															
p-value versus NTG		0.6	0.7		0.7	0.9		0.3	0.96		0.8	0.4		0.4	0.3
p-Value versus NAT			0.9			0.5			0.3			0.2			0.03*
Not Catheterized															
p-value versus NTG		0.5	0.6		0.8	0.3		0.5	0.8		0.4	0.3		0.96	0.4
p-Value versus NAT			0.8			0.5			0.3			0.8			0.4

Table 24 Patient's Global Clinical evaluation

	0.25 Hours			0.5 Hours			1 Hour			2 Hour			3 Hour		
	NTG N=143	NAT N=204	PBO N=142	NTG N=143	NAT N=214	PBO N=142									
Markedly better	7 (5%)	11 (5%)	8 (6%)	8 (6%)	14 (7%)	9 (6%)	8 (6%)	17 (8%)	13 (9%)	14 (10%)	21 (10%)	18 (13%)	16 (11%)	28 (14%)	21 (15%)
Moderately better	11 (8%)	17 (8%)	14 (10%)	18 (13%)	25 (12%)	18 (13%)	31 (22%)	43 (21%)	24 (17%)	38 (27%)	52 (26%)	26 (18%)	48 (34%)	55 (27%)	26 (18%)
Minimally better	37 (26%)	58 (29%)	32 (23%)	46 (32%)	69 (34%)	44 (31%)	45 (31%)	65 (32%)	51 (36%)	41 (29%)	59 (29%)	49 (35%)	30 (21%)	69 (34%)	45 (32%)
No change	85 (60%)	113 (56%)	88 (62%)	64 (45%)	91 (45%)	68 (48%)	53 (37%)	73 (36%)	50 (35%)	41 (29%)	66 (33%)	44 (31%)	41 (29%)	44 (22%)	45 (32%)
Minimally worse	2 (1%)	3 (1%)	0	4 (3%)	4 (2%)	3 (2%)	5 (3%)	5 (2%)	3 (2%)	6 (4%)	4 (2%)	5 (4%)	6 (4%)	7 (3%)	5 (4%)
Moderately worse	0	0	0	0	0	0	1 (1%)	0	0	0	0	0	2 (1%)	0	0
Markedly worse	0	1 (<1%)	0	0	0	0	0	0	0	0	0	0	0	0	0
p-value versus NTG		0.5	0.8		0.6	0.8		0.4	0.6		0.98	0.3		0.3	0.5
p-Value versus NAT			0.7			0.7			0.8			0.3			0.07

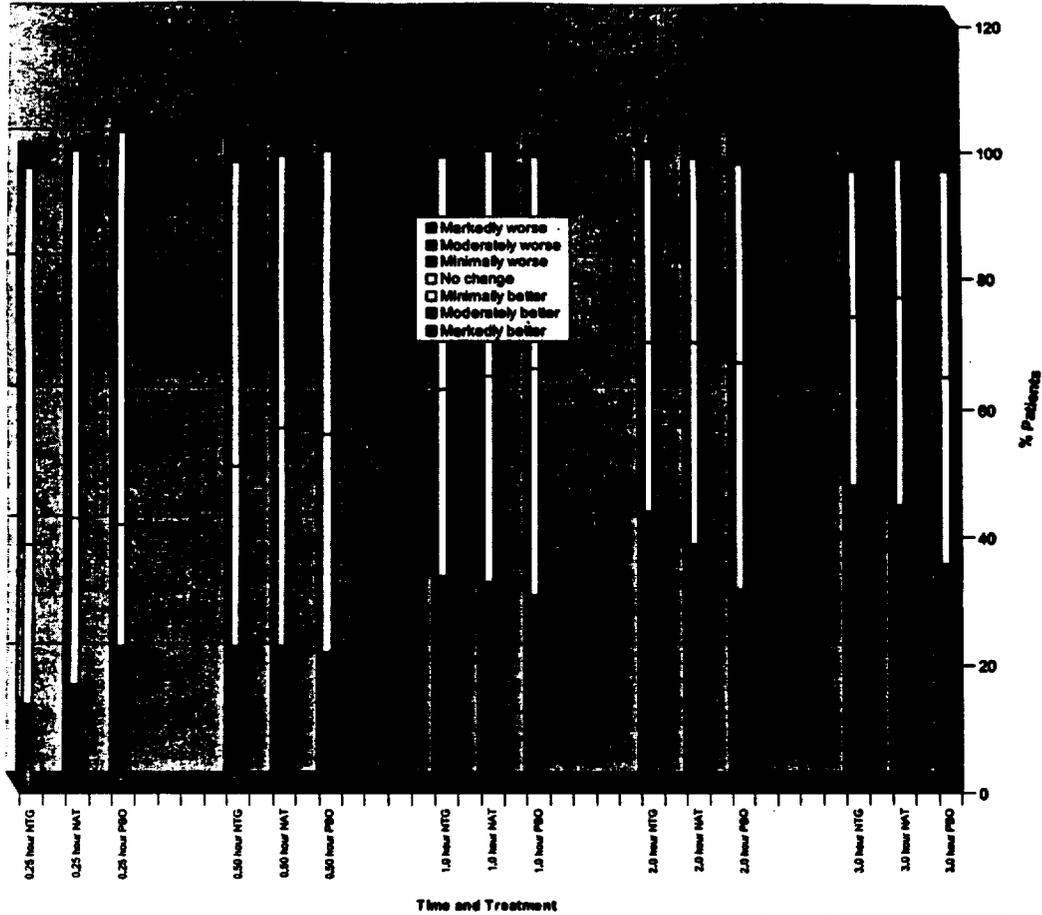
Table 25 lists the global symptom change among those who were catheterized and those not catheterized. The results for global symptoms are fairly similar to that of dyspnea. The data is graphically displayed as Figure 7

Table 25: P-values for global symptom assessment

	0.25 Hours			0.5 Hours			1 Hour			2 Hour			3 Hour		
	NTG N=143	NAT N=204	PBO N=142	NTG N=143	NAT N=214	PBO N=142									
Catheterized															
p-value versus NTG		0.7	0.98		0.6	0.9		0.5	0.8		0.9	0.9		0.3	0.8
p-Value versus NAT			0.7			0.5			0.8			0.7			0.1
Not Catheterized															
p-value versus NTG		0.6	0.8		0.8	0.6		0.6	0.7		0.8	0.2		0.7	0.6
p-Value versus NAT			0.8			0.8			0.94			0.3			0.3

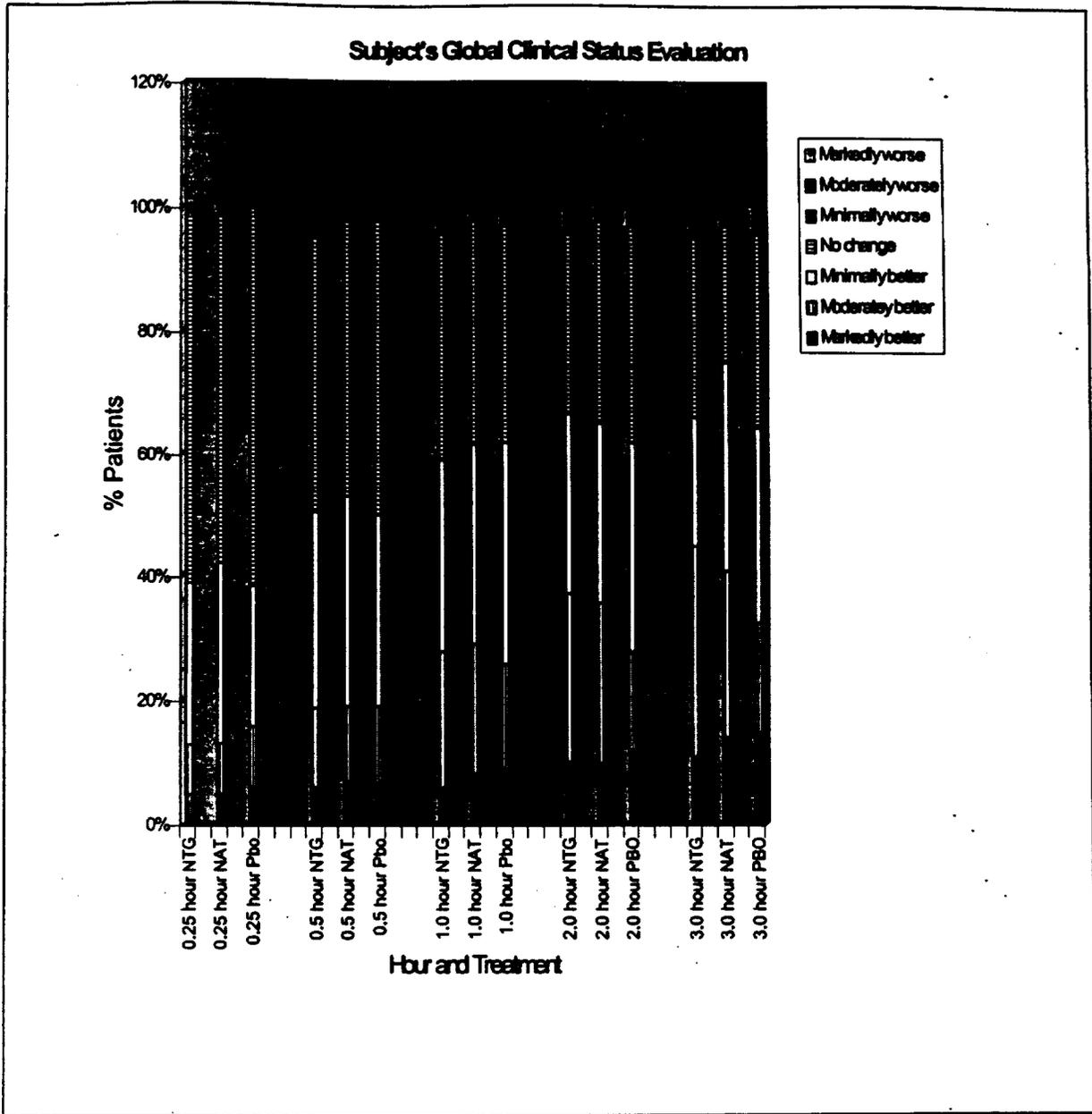
Figure 6

Time Course of Subject's Dyspnea Symptoms



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Figure 7.



With respect to global symptoms, there were no treatment differences during the initial three-hour evaluation when comparing nitroglycerin, Natrecor and placebo. Subject's global evaluation improved over time for all treatments. Few subjects had any deterioration during the initial three hours.

The effect during 24-hours:

Medications: The medications that were concomitantly used during the controlled period are shown in Table 26.

Table 26. Selected medications taken during 24-hour controlled period (PBO subjects have crossed over)

	Catheterized			Not Catheterized	
	NTG (n=92)	Natrecor Fixed (n=92)	Natrecor Adjustable (n=62)	NTG (n=124)	Natrecor Fixed (n=119)
Diuretics	82 (89%)	77 (84 %)	49 (79 %)	116 (94%)	106 (89 %)
IV diuretics	70 (76%)	64 (70 %)	41 (66 %)	93 (75 %)	81 (68 %)
Oral diuretics	43 (47%)	44 (48 %)	20 (32%)	60 (48%)	53 (45 %)
Digoxin	49 (53%)	60 (65 %)	30 (48 %)	76 (61.%)	68 (57%)
IV Digoxin	3 (3%)	2 (2%)	2 (3%)	4 (3%)	3 (3%)
ACE inhibitors	51 (55%)	52 (57 %)	32 (52 %)	71 (57 %)	67 (56 %)
Non-IV Nitrates	34 (37 %)	30 (33 %)	18 (29 %)	41 (33 %)	37 (31 %)
IV Nitroglycerine	1(1%)	0	0	0	0
Beta Blockers	25 (27 %)	24 (26 %)	21 (34%)	37 (30 %)	35 (29 %)
IV Beta blockers	1(1%)	0	0	0	3 (3%)
Angiotensin II Blockers	8 (9 %)	5 (5%)	4 (6%)	11 (9%)	9 (8 %)
Dobutamine	24 (26%)	24 (26%)	21(34%)	9 (7 %)	26 (22 %)
Continued at Baseline	14 (15%)	13 (14%)	13 (21%)	7 (6%)	22 (18%)
New Administration	10 (11%)	11 (12%)	8 (13%)	2 (2%)	4 (3%)
PDE inhibitors	0	0	0	0	0
Dopamine	5 (5 %)	4 (4%)	8 (13 %)	2 (2%)	11 (9%)
Continued at Baseline	3 (3%)	3 (3%)	8 (13%)	0	8 (7%)
New Administration	2 (2%)	1 (1%)	0	2 (2%)	3 (3%)
Nitroprusside	0	1 (1 %)	0	0	0
Pressors	0	0	0	0	0

There were several differences in the nature of concomitant medications used during this portion of the study, this reviewer, however, could not interpret these changes as indicating a relative benefit in any particular treatment. There were more subjects in NTG than Natrecor group who received intravenous diuretics during the 24-hours of the study. Dobutamine was administered to approximately 25% of those who entered this portion of the study. The number of subjects who had new addition of dobutamine was greater among those catheterized than not-catheterized (12% versus 3%), but there did not appear to be a concentration of these subjects in any one treatment group. More Natrecor subjects were treated with dopamine during the 24-hour period; few of these subjects were newly treated. This reviewer cannot ascertain whether there was a difference in the number of subjects that were discontinued from pressors or after load reducers as a consequence of the added intravenous infusion.

Hemodynamics post-3 hours:

After 3 hours, several changes to the infusion occurred. Those who were randomized to placebo were crossed over to either fixed dose Natrecor or NTG. In addition, those subjects in the adjustable dose group could have their doses increased. The intent was to pool those on treatment (even placebo crossover subjects) despite the differences in the duration of exposure to infusion.

PCWP: The effect on wedge pressure is shown in Table 27. The placebo group was crossed over to the individual treatments. The baseline value for those who crossed over was the last measurement (the 3-hour measurement). The effect for the first 24-hours is credible. Results after 24-hours is distorted by the large number of subjects who discontinued at 24-hours, having completed the pre-

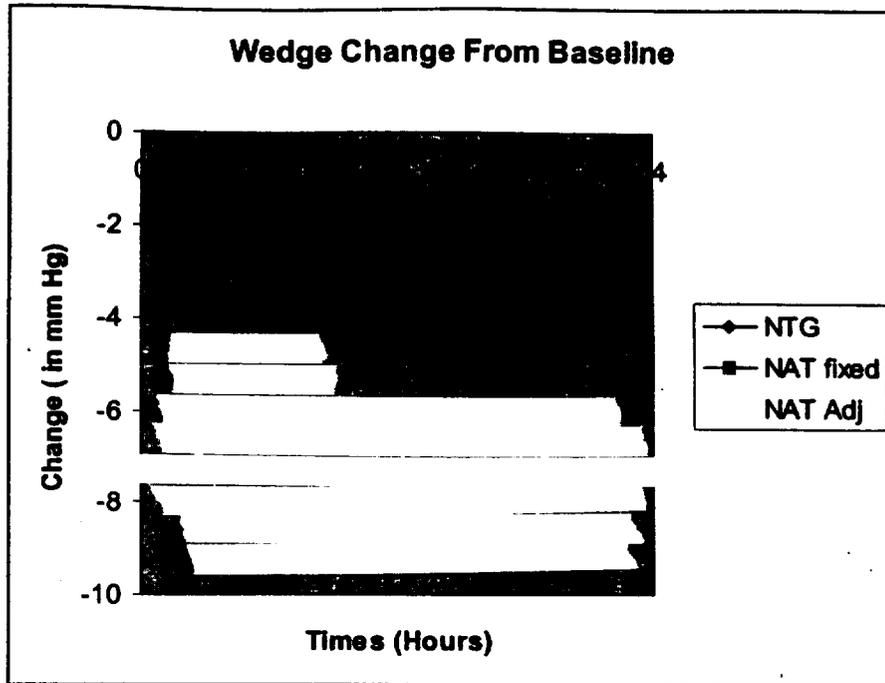
specified time of infusion. There did not appear to be a waning of effect of fixed Natrecor when compared to nitroglycerin during the observation period. Compared to NTG, Natrecor fixed dose was not superior at any time point. Compared to NTG, Natrecor, adjustable dose was superior to NTG at 6, 9, 12 and 24 hours. Values after 24 hours are less reliable due to the large number of subjects no longer treated.

Table 27. PCWP measurements post 3-hours.

		NTG N=92	Natrecor Fixed Dose N=92	Natrecor Adjustable dose N=62
Baseline	N = /missing ()	92 (0)	92 (0)	62 (0)
	Mean + SD	27.2 + 6.8	27.4 + 5.8	27.4 + 7.7
6 Hr	N= / missing in ()	85 (7)	85 (7)	61 (1)
	Change from Baseline (LS mean + SE)	-4.4 + 0.7	-6.0 + 0.7	-6.9 + 0.9
	p-value versus NTG		0.1	0.03
	p-value versus NAT-Fixed			0.4
9 Hr	N= / missing in ()	85 (7)	86 (6)	62 (0)
	Change from Baseline (LS mean + SE)	-5.4 + 0.8	-6.9 + 0.7	-8.1 + 0.9
	p-value versus NTG		0.15	0.02
	p-value versus NAT-Fixed			0.297
12 Hr	N= / missing in ()	83 (9)	84 (8)	61 (1)
	Change from Baseline (LS mean + SE)	-5.9 0.7	-6.6 0.5	-9.2 + 0.9
	p-value versus NTG		0.2	0.001
	p-value versus NAT-Fixed			0.02
24 Hrs	N= / missing in ()	84 (8)	86 (6)	57 (5)
	Change from Baseline (LS mean + SE)	-6.3 + 0.8	-7.5 + 0.8	-9.3 + 1.0
	p-value versus NTG		0.3	0.016
	p-value versus NAT-Fixed			0.1
36 Hrs	N= / missing in ()	47 (45)	36 (56)	34 (28)
	Change from Baseline (LS mean + SE)	-6.8 + 1.2	-8.4 + 1.3	-7.9 + 1.4
	p-value versus NTG		0.3	0.5
	p-value versus NAT-Fixed			0.8
48 Hrs	N= / missing in ()	29 (63)	25 (67)	22 (40)
	Change from Baseline (LS mean + SE)	-7.3 + 1.4	-8.6 + 1.5	-8.9 + 1.6
	p-value versus NTG		0.5	0.4
	p-value versus NAT-Fixed			0.9

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Figure 8



Other Hemodynamic measurements: Other hemodynamic parameters were measured at baseline and 24 hours. The results are shown in Table 28. Compared to NTG, only the RAP at 24-hours for the adjustable dose Natrecor differed from nitroglycerin.

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Table 28. Hemodynamic positive-controlled, double blind period.

		NTG N=92	Natrecor Fixed Dose N=92	Natrecor Adjustable dose N=62
Mean Right Atrial Pressure				
Baseline	N = /Missing ()	90 (2)	90 (2)	57 (5)
	Mean + SD	15.3 + 6.9	14.8 + 6.9	14.5 + 6.1
24 hours	N= / missing in ()	87 (5)	89 (3)	58 (4)
	Change from Baseline (LS mean + SE)	-3.4 + 0.6	-4.3 + 0.6	-5.2 + 0.7
	p-value versus NTG		0.2	0.05
	p-value versus NAT-Fixed			0.3
Systemic vascular Resistance				
Baseline	N = /Missing ()	87 (5)	89 (3)	56 (6)
	Mean + SD	1439 + 641	1441 + 554	1411 + 572
24 hours	N= / missing in ()	83 (9)	86 (6)	56 (6)
	Change from Baseline (LS mean + SE)	-209 + 60	-222 + 058	-175 + 74
	p-value versus NTG		0.9	0.7
	p-value versus NAT-Fixed			0.6
Cardiac Index L/min/m2				
Baseline	N = /Missing ()	88 (4)	91 (1)	57 (5)
	Mean + SD	2.2 + 0.8	2.1 + 0.7	2.3 + 0.8
24 hours	N= / missing in ()	84 (8)	89 (3)	58 (4)
	Change from Baseline (LS mean + SE)	0.2 + 0.08	0.2 + 0.07	0.1 + 0.09
	p-value versus NTG		0.95	0.15
	p-value versus NAT-Fixed			0.1
Pulmonary Vascular Resistance				
Baseline	N = /Missing ()	83 (9)	80 (12)	51 (11)
	Mean + SD	259 + 174	266 + 174	233 + 162
24 hours	N= / missing in ()	74 (18)	81 (11)	49 (13)
	Change from Baseline (LS mean + SE)	-40 + 18	-42 + 17	-40 + 22
	p-value versus NTG		0.9	0.1
	p-value versus NAT-Fixed			0.1
Mean Pulmonary Artery Pressure				
Baseline	N = /Missing ()	92 (0)	91 (1)	61 (1)
	Mean + SD	38.5 + 8.8	38.3 + 7.7	38.1 + 8.8
24 hours	N= / missing in ()	87 (5)	91 (1)	60 (2)
	Change from Baseline (LS mean + SE)	-5.6 + 0.9	-7.5 + 0.9	-7.8 + 1.1
	p-value versus NTG		0.1	0.1
	p-value versus NAT-Fixed			0.8

Dyspnea post-3 hours: Changes in Dyspnea symptoms were measured at 6 and 24 hours. The results are shown in Table 29. There was a clear time-dependent effect, with subjects improving in their dyspnea symptoms over time. There was no obvious benefit when Natrecor is compared to nitroglycerin at either at 6 or 24 hours, in considering the total population or those catheterized. There was, however, an effect, among those not catheterized that suggested a benefit in this subgroup (this is a subgroup of a secondary endpoint). There are no corresponding hemodynamics measurements for those not catheterized.

Table 29 Dyspnea Index post 3-hours.

	All Subjects		Catheterized		
	NTG total	Natrecor Total	NTG Catheterized	NAT Cath Fixed	NAT cath Adjust
6-Hours					
Number enrolled	N=216	N=273	N=92	N=92	N=62
Number with data	N=214	N=265	N=92	N=90	N=57
Markedly better	38 (18%)	57 (22%)	14 (15%)	14 (16%)	15 (26%)
Moderately better	67 (31%)	77 (29%)	28 (30%)	32 (36%)	11 (19%)
Mildly better	54 (25%)	71 (27%)	28 (30%)	22 (24%)	22 (39%)
No change	52 (24%)	56 (21%)	20 (22%)	19 (21%)	9 (16%)
Mildly worse	3 (1%)	2 (1%)	2 (2%)	1 (1%)	0
Moderately worse	0	1 (<1%)	0	1 (1%)	0
Markedly worse	0	1 (<1%)	0	1 (1%)	0
p-value NTG All vs. NAT All	-----	0.4**	-----	-----	-----
p-value Vs NTG Cath	-----	-----	-----	0.7*	0.3*
p-value Vs. NAT Fixed Cath	-----	-----	-----	-----	0.5*
p-value Vs. NAT Cath	-----	-----	0.5*	-----	-----
24-Hours					
Number enrolled	N=216	N=273	N=92	N=92	N=62
Number with data	N=215	N=266	N=92	N=89	N=59
Markedly better	67 (31%)	100 (38%)	33 (36%)	29 (33%)	22 (37%)
Moderately better	76 (35%)	84 (32%)	28 (30%)	29 (33%)	18 (31%)
Mildly better	39 (18%)	53 (20%)	18 (20%)	17 (19%)	13 (22%)
No change	29 (13%)	28 (11%)	11 (12%)	14 (16%)	5 (8%)
Mildly worse	2 (1%)	0	2 (2%)	0	0
Moderately worse	2 (1%)	1 (<1%)	0	0	1 (2%)
Markedly worse	0	0	0	0	0
P-value NTG All Vs. NAT All	-----	0.1**	-----	-----	-----
p-value Vs. NTG Cath	-----	-----	-----	0.7*	0.8*
p-value Vs. NAT Fixed Cath	-----	-----	-----	-----	0.5*
p-value Vs. NAT Cath	-----	-----	0.93*	-----	-----

	Not catheterized	
	NTG total	Natrecor Total
6-Hours		
Number enrolled	N=124	N=119
Number with data	N=122	N=118
Markedly better	24 (20%)	28 (24%)
Moderately better	39 (32%)	34 (29%)
Mildly better	26 (21%)	27 (23%)
No change	32 (26%)	28 (24%)
Mildly worse	1 (1%)	1(1%)
Moderately worse	0	0
Markedly worse	0	0
p-value NTG Vs. NAT not cath	-----	0.8*
24-Hours		
Number enrolled	N=124	N=119
Number with data	N=123	N=118
Markedly better	34 (28%)	49 (42%)
Moderately better	48 (39%)	37 (31%)
Mildly better	21 (15%)	23 (19%)
No change	18 (15%)	9 (8%)
Mildly worse	0	0
Moderately worse	2 (2%)	0
Markedly worse	0	0
P-value NTG Vs. NAT not cath	-----	0.03*

* Wilcoxon ** ANOVA (treatment and catheter placement as covariates)

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Global post 3 hours

Global symptoms of heart failure are shown in Table 30. Assessments were performed both at 6 and 24 hours. Here too, there was a time dependent improvement in symptoms over time. There were no significant differences in comparing those treated with nitroglycerin to those treated with Natrecor, when considering the population as a whole or limiting the analysis to those catheterized. There was, however, an effect, among those not catheterized which suggested a benefit in this subgroup (this is a subgroup of a secondary endpoint).

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Table 30 Global Symptoms (p-value are nominal)

	All subjects		Catheterized subjects		
	NTG total	Natrecor Total	NTG Catheterized	NAT Cath Fixed	NAT cath Adjust
6-Hours					
Number enrolled	N=216	N=273	N=92	N=92	N=62
Number with data	N=215	N=264	N=92	N=89	N=57
Markedly better	35 (16%)	54 (20%)	15 (16%)	13 (15%)	13 (23%)
Moderately better	61 (28%)	84 (32%)	26 (28%)	31 (35%)	16 (28%)
Mildly better	63 (29%)	65 (25%)	30 (33%)	22 (25%)	19 (33%)
No change	51 (24%)	56 (21%)	19 (21%)	20 (22%)	9 (16%)
Mildly worse	4 (2%)	5 (2%)	2 (2%)	3 (3%)	0
Moderately worse	1 (0%)	0	0	0	0
Markedly worse	0	0	0	0	0
p-value NTG total Vs. NAT Total	-----	0.4**	-----	-----	-----
p-value Vs. NTG	-----	-----	-----	0.97*	0.2*
p-value Vs. NAT Fixed	-----	-----	-----	-----	0.3*
p-value Vs. NAT	-----	-----	0.5*	-----	-----
24-Hours					
Number enrolled	N=216	N=273	N=92	N=92	N=62
Number with data	N=214	N=265	N=92	N=89	N=58
Markedly better	60 (28%)	89 (34%)	29 (32%)	24 (27%)	20 (34%)
Moderately better	77 (36%)	91 (34%)	31 (34%)	30 (34%)	19 (33%)
Mildly better	37 (17%)	55 (21%)	15 (16%)	22 (25%)	12 (21%)
No change	34 (16%)	27 (10%)	13 (14%)	12 (13%)	6 (10%)
Mildly worse	3 (1%)	1 (< 1%)	3 (3%)	0	0
Moderately worse	3 (1%)	2 (1%)	1 (1%)	1 (2%)	0
Markedly worse	0	0	0	0	0
p-value NTG total Vs. NAT Total	-----	0.075**	-----	-----	-----
p-value Vs. NTG	-----	-----	-----	0.7*	0.6*
p-value Vs. NAT Fixed	-----	-----	-----	-----	0.3*
p-value Vs. NAT	-----	-----	0.5*	-----	-----

	Not catheterized	
	NTG total	Natrecor Total
6-Hours		
Number enrolled	N=124	N=119
Number with data	N=123	N=118
Markedly better	20 (16%)	28 (24%)
Moderately better	35 (28%)	37 (31%)
Mildly better	33 (27%)	24 (20%)
No change	32 (26%)	27 (23%)
Mildly worse	2 (2%)	2(2%)
Moderately worse	1 (1%)	0
Markedly worse	0	0
p-value NTG Vs. NAT not cath	-----	0.1*
24-Hours		
Number enrolled	N=124	N=119
Number with data	N=123	N=118
Markedly better	31 (25%)	45 (38%)
Moderately better	46 (38%)	42 (36%)
Mildly better	22 (18%)	21 (18%)
No change	21 (17%)	9 (8%)
Mildly worse	0	1 (1%)
Moderately worse	2 (2%)	0
Markedly worse	0	0
p-value NTG Vs. NAT not cath	-----	0.01*

* Wilcoxon ** ANOVA (treatment and catheter placement as covariates)

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Respiratory Rates till 3 hours

Respiratory rates were collected at baseline and 1 and 3 hours during the infusion are shown in Table 31. There were modest decreases in the respiratory rate for all treatments. None of the differences was significant (nominal p-values).

Table 31 Respiratory rates till 3 hours

	All subjects		
	NTG (N=143)	NAT (N=204)	PBO (N=142)
Baseline Mean + SD	23.2 + 4.8	22.4 + 4.8	22.4 + 4.7
1 hour			
N= /missing ()	143 / (0)	201 / (3)	142 / (0)
LS mean + SE	-1.1 + 0.3	-0.9 + 0.3	-0.8 + 0.3
p-Value Vs. NTG			0.6
p-Value Vs. NAT			0.91
3 hours			
N= /missing ()	141 / (2)	198 / (6)	138 / (4)
LS mean + SE	-1.4 + 0.4	-1.3 + 0.3	-0.6 + 0.4
p-Value Vs. NTG			0.91
p-Value Vs. NAT			0.1

In considering only those subjects catheterized, there was no difference in respiratory rates

Among those who were not catheterized, both Natrecor and NTG were marginally but not statistically different when compared to placebo (data not tabulated). At three hours there was a decrease in respiratory rate for NTG and NAT of -1.7 and -1.8 breaths/minute. For placebo the decrease was -0.2 breaths/min. Comparison of active treatments to placebo show a marginally significant decrease in respiratory rate (nominal p-values $0.1 < p < 0.05$).

Net fluid changes: The intake and output for the first 24 hours of infusion are shown in Table 32. There was a net output of more than 1 liter in each treatment group. Neither fluid intake nor fluid output differed among nitroglycerin or Natrecor. Since the fluid changes were measured over the 24-hour period, there was no placebo group for comparison

Table 32 Urine output ml/24 hours.

	NTG (N=216)	NAT Fixed (N=211)	ALL NAT (N=273)	NAT ADJ (N=62)
N= / missing ()	216 / (0)	208 (3)	270 (3)	62 / (0)
Fluid Intake Mean + SD	1674 + 664	1710 + 588	1709 + 626	1705 + 745
Urine Output				
N= / missing ()	214 / (2)	209 / (2)	270 / (3)	61 (1)
Urine Output Mean + SD	-2959 + 1543	-3019 + 1752	-2969 + 1838	-2797 + 2113
Net				
N= / missing ()	214 / (2)	208 / (3)	269 / (4)	61 / (1)
Net Mean + SD	-1279 + 1455	-1308 + 1613	-1257 + 1657	-1082 + 1799

Weight changes: Net weight changes are shown in Table 33. There were no differences in net weight change over the 24-hour period. The weight loss was consistent with the negative fluid balance.

Table 33 Weight Change 24 hours.

	NTG (N=216)	NAT Fixed (N=211)	ALL NAT (N=273)	NAT ADJ (N=62)
N=/ missing ()	216 / (0)	211 (0)	273 (0)	62 / (0)
Baseline Mean + SD	84.8 + 24.1	81.3 + 19.7	81.5 + 20.0	82.3 + 21.2
N=/ missing ()	208 / (8)	210 / (1)	272 / (1)	62 (0)
Net change Mean + SD	-1.1 + 2.3	-1.4 + 3.0	-1.4 + 3.0	-1.3 + 3.2

Sodium Excretion: Sodium excretion data was not collected.

Use of Diuretics: Diuretic use during the 24-hour period is shown in Table 34. The catheterized Natrecor adjustable dose had somewhat lower use of diuretics than the other groups. The mean dose was less among those not catheterized

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Table 34 Use of diuretics.

	Catheterized			Non-Catheterized	
	NTG (n=92)	Natrecor Fixed Dose (n=92)	Natrecor Adjustable dose (n=62)	NTG (n=124)	Natrecor (n=119)
Number taking diuretic	82 (89%)	77 (84%)	49 (79%)	116 (94%)	106 (89%)
Not IV	70 (76%)	64 (70%)	41 (66%)	93 (75%)	81 (68%)
IV	43 (47%)	44 (48%)	20 (32%)	60 (48%)	53 (45%)
Mean dose/subject furosemide	172 ± 137	176 ± 157	173 ± 150.	133 ± 91	136 ± 120

Post-treatment medication: The list of medications used post treatment is shown in Table 35. For most subjects these reflect the treatments after 24-hours of the index infusion. For others who were treated for a longer duration, the medication list reflects post-treatment. There were few outstanding differences. Intravenous diuretics were used in 47-60% of those enrolled. PDE inhibitors were more frequently used in catheterized than in not catheterized subjects. Use of pressors (dobutamine, dopamine) was slightly less frequently used in the Natrecor adjustable group than in the other catheterized groups.

Table 35 Medications taken post treatment

	Catheterized			Not Catheterized	
	NTG (n=92)	Natrecor Fixed (n=92)	Natrecor Adj. (n=62)	NTG (n=124)	Natrecor (n=119)
Diuretics	76 (83%)	77 (84%)	45 (73%)	99 (80%)	96 (81%)
IV diuretics	48 (52%)	55 (60%)	32 (52%)	58 (47%)	63 (53%)
Oral diuretics	58 (63%)	44 (48%)	26 (42%)	66 (53%)	50 (42%)
Digoxin	50 (54%)	51 (55%)	30 (48%)	69 (56%)	53 (45%)
IV Digoxin	1 (1%)	3 (3%)	2 (3%)	4 (3%)	4 (3%)
Aspirin	36 (39%)	36 (39%)	28 (45%)	52 (42%)	52 (44%)
ACE inhibitors	50 (54%)	53 (58%)	35 (56%)	70 (56%)	58 (49%)
Non-IV Nitrates	37 (40%)	29 (32%)	17 (27%)	46 (37%)	40 (34%)
IV Nitroglycerine	6 (7%)	4 (4%)	1 (2%)	1 (1%)	0
Beta Blockers	27 (29%)	19 (21%)	18 (29%)	34 (27%)	33 (28%)
IV Beta blockers	1 (1%)	1 (1%)	0	0	1 (1%)
Anticoagulants:					
Warfarin	10 (11%)	11 (12%)	7 (11%)	22 (18%)	23 (19%)
Heparin	13 (14%)	14 (15%)	9 (15%)	15 (12%)	20 (17%)
Statins	22 (24%)	27 (29%)	13 (21%)	25 (20%)	21 (18%)
Class III antiarrhythmics	9 (10%)	23 (25%)	17 (27%)	12 (20%)	16 (13%)
Calcium Channel Blockers	6 (7%)	7 (8%)	9 (15%)	10 (8%)	23 (19%)
Angiotensin II Blockers	9 (10%)	7 (8%)	5 (8%)	11 (9%)	9 (8%)
Hydralazine	13 (14%)	7 (8%)	12 (19%)	10 (8%)	6 (5%)
Other antihypertensives	2 (2%)	3 (3%)	4 (6%)	2 (2%)	8 (7%)
Other antiarrhythmics	2 (2%)	4 (4%)	2 (3%)	6 (5%)	6 (5%)
IIb/IIIa inhibitors	3 (3%)	3 (3%)	2 (3%)	5 (4%)	3 (3%)
Dobutamine	33 (36%)	31 (34%)	20 (32%)	19 (15%)	28 (24%)
New Administration	20 (22%)	18 (20%)	10 (16%)	13 (10%)	7 (6%)
PDE inhibitors	12 (13%)	8 (9%)	10 (16%)	4 (3%)	6 (5%)
Dopamine	10 (11%)	9 (10%)	9 (15%)	4 (3%)	14 (12%)
New Administration	7 (8%)	8 (9%)	2 (3%)	4 (3%)	7 (6%)
nitroprusside	4 (4%)	2 (2%)	2 (3%)	2 (2%)	0
Pressors	0	2 (2%)	1 (2%)	0	0

Hospitalizations: Hospitalization Days were prolonged by approximately 2 days among the Natrecor-treated subjects when compared to the NTG group. There was a greater fraction of those treated with Natrecor who were still hospitalized at 30 days post-enrollment. Among those discharged, slightly more Nitroglycerin subjects were readmitted during the 30-day post-infusion