

Vasodilators in the management of acute heart failure

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Recent guidelines by the Heart Failure Society of America have recommended consideration for use of nitroprusside, nitroglycerin, or nesiritide in addition to diuretics to achieve hemodynamic and symptomatic improvement. This article reviews the results of

previous studies evaluating the pharmacologic and clinical effects and safety profiles of these drugs in patients with heart failure. (Crit Care Med 2008; 36[Suppl.]:S95–S105)

KEY WORDS: nitroprusside; nitroglycerin; nesiritide; diuretics

Intravenous vasodilators are often used in the treatment of patients hospitalized with heart failure. Recent guidelines by the Heart Failure Society of America have recommended consideration for use of nitroprusside, nitroglycerin, or nesiritide in addition to diuretics in order to achieve hemodynamic and symptomatic improvement (1). The purpose of this article is to discuss in detail available information regarding the pharmacologic and clinical effects of these drugs (Table 1).

NITROPRUSSIDE

Nitroprusside is the sodium (or potassium) salt of a complex molecule made up of ferric cyanide (Fe^{2+} and five cyanide groups) and nitric acid. Its effect appears to be mediated largely by production of nitrosothiol in vasculature, which in turn generates cyclic guanosine monophosphate in vascular smooth muscle and evokes relaxation (2). Nitroprusside has a rapid onset of action, with vasodilating effects detectable within 60–90 secs of initiation of the infusion. Some of the administered nitroprusside decomposes after entering the bloodstream, with the release of cyanide into the circulation (3). Additional cyanide is produced when nitroprusside is metabolized by vascular tissue, which then is further metabolized by the liver to thiocyanate and is slowly cleared by the kidneys

(about a 3- to 4-day half-life). Because of its long half-life, thiocyanate can accumulate during prolonged or high-dose nitroprusside infusions or in the setting of renal dysfunction and can evoke signs and symptoms of thiocyanate toxicity.

Hemodynamic Effects

Nitroprusside reduces the excessively elevated ventricular filling pressures in patients with congestive heart failure (CHF) by multiple mechanisms. The drug diminishes venous tone and thereby increases venous capacitance, with a resultant peripheral shift of central blood volume. By reducing the afterload of both left and right ventricles, nitroprusside decreases ventricular systolic and diastolic volume via greater ventricular systolic emptying and less valvular regurgitation (3–6).

Nitroprusside may also lower ventricular filling pressure by improving ventricular diastolic properties or negating the restraining effect of the pericardium (by lowering intracardiac pressures and volume) (7, 8). Improved renal blood flow may lead to increased diuresis, and this may further contribute to preload reduction mediated by nitroprusside (9).

The use of nitroprusside in patients with decompensated heart failure results in a significant decrease in systemic blood pressure, right atrial pressure, pulmonary arterial pressure, pulmonary artery occlusion pressure (PAOP), and systemic and pulmonary vascular resistance (Fig. 1). These changes are associated with a significant increase in cardiac output and no change in heart rate (4, 5).

In the setting of CHF, nitroprusside generally lowers myocardial oxygen consumption, as it reduces systolic and diastolic wall stress (10, 11). The effect of

nitroprusside on coronary hemodynamics has not been extensively studied in human heart failure. The net effect of nitroprusside on coronary blood flow in patients with significant coronary obstructive disease, however, may be determined by multiple factors, including effect on myocardial oxygen demand, coronary vasodilatory effect, and effect on perfusion pressure as well as diastolic filling time (11–13). In addition, nitroprusside may potentially induce a coronary steal phenomenon by producing vasodilation of nonobstructed coronary beds, thus directing blood flow away from the already maximally vasodilated beds downstream from the coronary artery lesions (14, 15).

In the setting of human CHF, nitroprusside preferentially reduces limb vascular resistance, with an augmentation of limb blood flow comparable in degree to the increase in cardiac output (16). Renal vascular resistance is also reduced in the therapeutic range of nitroprusside; however, the resultant renal blood flow and renal function are heavily dependent on changes in systemic blood pressure and renal perfusion pressure (9, 16). Hepatic-splanchnic vascular resistance and blood flow are not significantly altered during infusion of nitroprusside at therapeutic rates (16).

Neurohormonal Responses

The neurohormonal response to nitroprusside infusion in heart failure varies considerably. Olivari et al. (17) found disparate responses of plasma norepinephrine (NE) in a population of patients with CHF despite similar resting hemodynamics and comparable hemodynamic responses. One group (group I) experienced an increase in plasma NE and the other

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Table 1. Comparison between clinical effects of intravenous vasodilators in the treatment of heart failure

Variables	Nitroprusside	Nitroglycerine	Nesiritide
Clinical studies in heart failure	—	+	+++
Hemodynamic effect	+++	+++	+++
Tolerance	—	++	—
Need for dose titration	+++	+++	—
Effect on coronary blood flow	↓	↑↓	↑
Myocardial ischemia	↑	↓	NA
Effect on urine output	NA	NA	+/-
Effect on neurohormones	↑	↑	↓
Vascular resistance	+	+	+
Evidence of symptomatic improvement	—	—	+

↓, decreased; ↑, increased; NA, not available; +/-, diverse results in different studies.

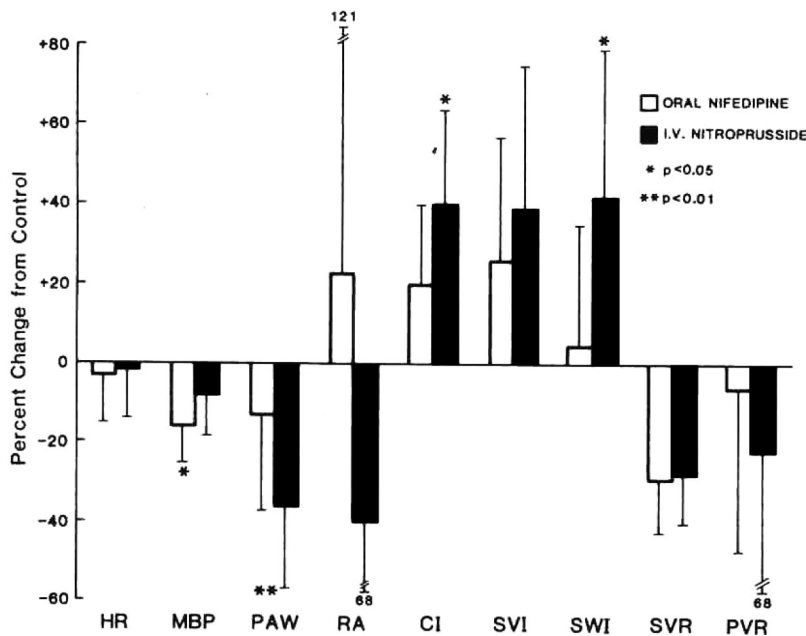


Figure 1. Comparison of percent changes from control after nifedipine and nitroprusside therapy. HR, heart rate; MBP, mean blood pressure; PAW, pulmonary artery occlusion pressure; RA, mean right atrial pressure; CI, cardiac index; SVI, stroke volume index; SWI, left ventricular stroke work index; SVR, systemic vascular resistance; PVR, pulmonary vascular resistance. Reproduced with permission from Elkayam U, Weber L, Torkan B, et al: Comparison of hemodynamic responses to nifedipine and nitroprusside in severe chronic congestive heart failure. *Am J Cardiol* 1984; 53:1321-1325.

group (group II) experienced a decrease during the infusion. Group II patients appeared to be in a more advanced and severe stage of heart failure, with a higher mortality. Differences in baroreceptor and mechanoreceptor sensitivity and responsiveness have been suggested as a cause for disparate responses to NE in the two groups. In a later study, Johnson et al. (18) examined the effect of diuretics and nitroprusside in 34 patients with decompensated heart failure. This therapy resulted in a significant increase in aldosterone levels and plasma renin activity. There was no significant change in NE levels, while endothelin and plasma atrial natriuretic levels showed a significant decrease.

Clinical Application and Administration Indications

Nitroprusside is most commonly employed in the treatment of acute decompensated heart failure (ADHF) (4, 5, 18, 19), complicated acute myocardial infarction (20), and acute valvular insufficiency (21). It is also frequently used in patients who have undergone cardiopulmonary bypass or other cardiac surgery, and it has been shown to be effective for chronic infusion in patients with end-stage CHF awaiting heart transplantation (22).

Nitroprusside is also employed in the evaluation of potential recipients of heart transplantation to determine the reversibility of elevated pulmonary vascular re-

sistance (23). A recent report demonstrated a significant improvement of functional class of patients with end-stage heart failure awaiting heart transplantation with chronic infusion of nitroprusside, which was safer and more effective than dobutamine in relieving symptoms, facilitating unloading therapy, and improving survival (22). Khot et al. (24) examined the effect of nitroprusside in 25 patients with severe aortic stenosis and left ventricular (LV) dysfunction. This therapy, which previously had been considered contraindicated for this patient population, resulted in a significant increase in cardiac output. Based on these results, it was suggested by the authors that nitroprusside may provide a safe and effective bridge to aortic valve replacement in patients with aortic stenosis presenting with severe CHF.

Nitroprusside can effectively augment the hemodynamic effects of other drugs, such as dopamine, dobutamine, and similar agents (25, 26). Combination pharmacologic support is occasionally employed in the intensive care setting to optimize hemodynamic and clinical responses in patients with severely depressed cardiac output and elevated ventricular filling pressures.

Administration

Nitroprusside is administered intravenously with an infusion pump or microdrip regulator system to ensure controlled, precise dosing. Because of its light sensitivity, the infusion set should be shielded. In CHF, the initial dose is 0.10–0.20 $\mu\text{g/kg/min}$; this is gradually advanced as needed to attain the clinical and hemodynamic objectives. The incidence of side effects and toxicity is directly related to the dose and duration of administration. Because of its potent dose-related hemodynamic effect and the difficulties in determining maximal effective dose, nitroprusside is optimally administered with hemodynamic monitoring consisting of pulmonary artery catheterization and a close monitoring of systemic blood pressure.

Potential Adverse Effects and Toxicity

The most commonly encountered adverse effect of nitroprusside administration is systemic hypotension (17, 27). When accompanied by a decrease in coronary perfusion pressure and an increase

in heart rate, nitroprusside-induced hypotension can be detrimental in patients with myocardial ischemia and infarction (14). A worsening renal function has been noted in association with nitroprusside infusions, typically during periods of systemic hypotension or hypoperfusion. Some patients may experience hemodynamic rebound with symptomatic deterioration after the abrupt discontinuation of nitroprusside (28). Gradual discontinuation is therefore recommended to achieve a smoother withdrawal. Nausea, disorientation, confusion, psychosis, weakness, muscle spasm, hyperreflexia, and convulsions are side effects of thiocyanate toxicity, which may occur as plasma thiocyanate concentrations increase to >6 mg (27, 29). The early sign of cyanide toxicity is metabolic (lactic) acidosis. Thiocyanate can be removed with hemodialysis, and cyanide toxicity has been successfully managed with infusions of thiosulfate, sodium nitrate, and hydroxycobalamin.

Conversion of cyanide to prussic acid raises methemoglobin levels and thus lowers the oxygen-carrying capacity of the blood. Thiocyanate and cyanide toxicity are rare during the usual administration of nitroprusside in heart failure ($\leq 3 \mu\text{g/kg/min}$ for ≤ 72 hrs). Nitroprusside can lower systemic arterial oxygen content by causing or exacerbating pulmonary ventilation/perfusion mismatch, probably via dilation of pulmonary arterioles in nonventilated areas (30). However, for most patients receiving nitroprusside, oxygen delivery is still augmented during the infusion because of the increase in cardiac output.

Laboratory data suggest that nitroprusside is capable of diverting blood flow from ischemic or threatened myocardium to normal myocardium by dilating the arterioles in the normal region (14, 15). This potential for so-called coronary steal suggests a preference of nitroglycerin (NTG) over nitroprusside in patients with occlusive coronary artery disease. Other, far less commonly encountered side effects of nitroprusside include reduced platelet number and function, hypothyroidism (thiocyanate impairs iodine transport), and vitamin B12 deficiency (31, 32).

ORGANIC NITRATES

Nitrates have been used for >100 yrs in clinical medicine, predominantly in the treatment of angina pectoris. Although not officially approved by the U.S. Food and Drug Administration for use in ADHF, ni-

trates are frequently used in the treatment of this condition (33), and their use has been recommended in the new guidelines of the Heart Failure Society of America (1).

Mechanism of Effect

Organic nitrates are prodrugs that undergo a complex metabolic biotransformation predominantly in the smooth muscle intracellular space (34). This biotransformation leads to the formation of nitric oxide or a related S-nitrosothiol, which stimulates the enzyme guanylate cyclase and leads to the formation of cyclic guanosine monophosphate in the vascular wall. Cyclic guanosine monophosphate reduces intracellular calcium levels by decreasing its release from the cytoplasmic reticulum and by reducing its influx from the extracellular space. The decrease in intracellular calcium leads to venous and arterial vasodilatation, which is the main cardiovascular effect of these drugs. Endothelial production and release of prostacyclin may also contribute (35). Nitrates are cleared by extraction in the vasculature, hydrolysis in blood, and the action of glutathione-nitrate reductase in the liver (36).

Intravenous Nitroglycerin Dose and Administration

Intravenous NTG is available as 5- and 10-mg/mL solutions that are diluted with normal saline or 5% dextrose solutions to

provide infusions of 100 mg NTG/250 mL (37). Onset of action is immediate, as is offset when the infusion is stopped. Glass bottles and nonpolyvinyl chloride plastic tubing must be used to avoid a loss of the active drug via absorption onto plastics (38). Infusion rates are usually initiated at 10–20 $\mu\text{g/min}$ and titrated upward in a stepwise fashion using 10- to 60- $\mu\text{g/min}$ increments to predetermined end points, such as improvement of symptoms, development of the drug-related side effects, change in a systolic blood pressure or PAOP, or a maximum dose of 200–500 $\mu\text{g/min}$ (39, 40).

Therapeutic Effects of Nitroglycerin in Patients with Heart Failure

Hemodynamic Effects. The potential hemodynamic effects of a therapeutic dose of NTG in patients with CHF include a substantial reduction in right and left ventricular filling pressures, systemic and pulmonary vascular resistance, and systemic blood pressure (Fig. 2). There is little or no change in heart rate, while cardiac output usually increases (39, 40). The mechanisms for increased cardiac output include left ventricular and right ventricular afterload reduction, improvement in myocardial ischemia, and reduction in the degree of mitral regurgitation (37, 41).

Effect on Mitral Regurgitation. Regurgitation of the mitral valve is common in

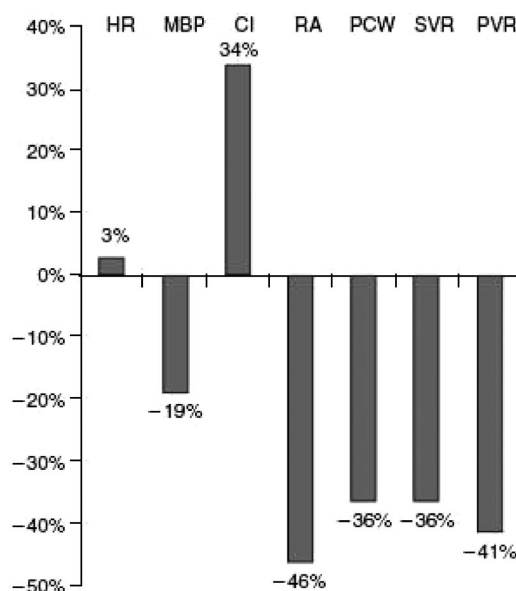


Figure 2. Intravenous nitroglycerin in the treatment of decompensated heart failure. HR, heart rate; MBP, mean blood pressure; CI, cardiac index; RA, mean right atrial pressure; PCW, pulmonary artery occlusion pressure; SVR, systemic vascular resistance; PVR, pulmonary vascular resistance. Reproduced with permission from Elkayam U: Nitrates in the treatment of congestive heart failure. *Am J Cardiol* 1996; 77:41C–51C.

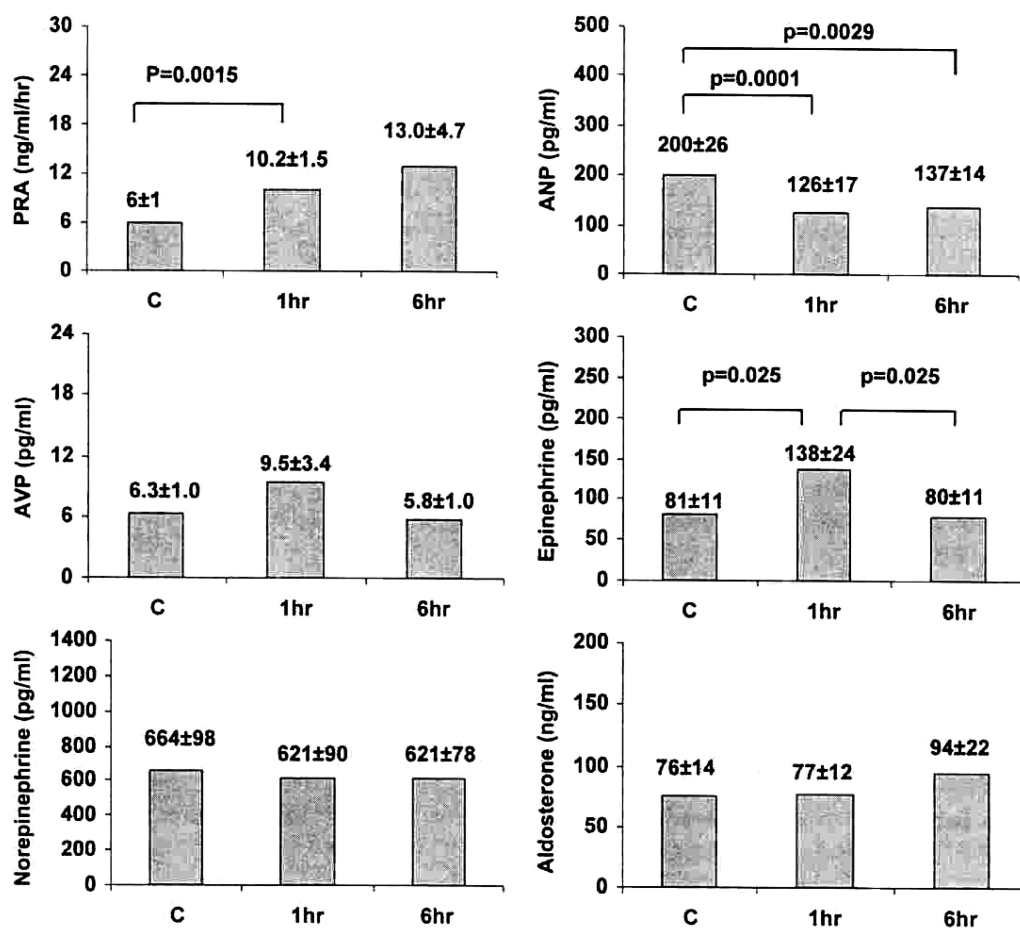


Figure 3. Neurohumoral changes during the first 6 hrs of nitroglycerin infusion. Arterial epinephrine increased after 1 hr of infusion and then returned to the baseline value at 6 hrs. Plasma renin activity (PRA) increased and atrial natriuretic peptide (ANP) decreased throughout the first 6 hrs of the infusion. There was no significant change in arginine vasopressin (AVP), norepinephrine, and aldosterone during nitroglycerin infusion. Reproduced with permission from Dupuis J, Lalonde G, Lemieux R, et al: Tolerance to intravenous NTG in patients with congestive heart failure: Role of increased intravascular volume, neurohumoral activation and lack of prevention with N-acetylcysteine. *J Am Coll Cardiol* 1990; 16:923–931.

patients with CHF, usually due to severe dilation of the left ventricle and the mitral valve annulus. Use of intravenous NTG in a group of patients with chronic, nonischemic mitral regurgitation resulted in a reduction in LV end diastolic volume and mitral valve regurgitant area as well as a marked improvement in the severity of mitral regurgitation and the hemodynamic profile (41, 42).

Neurohormonal Effects. Webster et al. (43) studied the effect of acute and sustained intravenous NTG on hormone secretion in nine patients with CHF. NTG was administered at a dose up-titrated to achieve a 30% to 50% reduction in PAOP (50–245 $\mu\text{g}/\text{min}$) and was associated with a substantial reduction in mean right atrial pressure and PAOP, a mild but significant reduction in systemic blood pressure (85 mm Hg to 78 mm Hg, $p = .04$), and no change in heart rate. These hemodynamic changes were associated with a reduction in plasma atrial natriuretic peptide but also

a significant increase in plasma aldosterone, cortisol, and epinephrine levels with a small and statistically significant increase in plasma NE or plasma renin activity. The effect of intravenous NTG on arginine-vasopressin, plasma renin activity, aldosterone, and atrial natriuretic peptide was also evaluated by Dupuis et al. (40) in 13 men hospitalized with severe CHF (New York Heart Association class IV). The hemodynamic changes induced by NTG were accompanied by an increase in arterial epinephrine and plasma renin activity and a decrease in atrial natriuretic peptide (Fig. 3). In contrast, there was no change in arterial NE, aldosterone, or arginine-vasopressin. By 6 hrs of continuous infusion, arterial epinephrine levels returned to baseline values, possibly due to less pronounced hypotension; however, plasma renin activity remained elevated and atrial natriuretic peptide remained decreased. Dakak et al. (44) also evaluated the hemodynamic and neurohormonal

effects of 12 patients with severe heart failure. NTG dose was $276 \pm 100 \mu\text{g}/\text{min}$, which resulted in considerable hemodynamic effects that were significantly attenuated due to nitrate tolerance after several hours of continuous infusion. NTG infusion was associated with a substantial increase in plasma renin activity and serum aldosterone, while atrial natriuretic peptide showed a marked but transient decrease in keeping with the development of hemodynamic tolerance.

Effect on Coronary Circulation. No information is available on the effect of intravenous NTG on coronary blood flow in patients with heart failure. In an unpublished study performed by our group, intracoronary administration of 200 μg of NTG in a group of 25 patients with heart failure secondary to idiopathic dilated cardiomyopathy resulted in a significant dilation of the epicardial coronary artery diameter by $8\% \pm 4\%$, as well as

an increase in coronary blood flow by $42\% \pm 12\%$ (37). These data suggest a combined effect of NTG on both the epicardial conductance and the resistance of coronary arteries in patients with heart failure due to idiopathic cardiomyopathy.

Effect on Renal Circulation. The effect of intravenous NTG on renal circulation in patients with ADHF has not been studied. Infusion of NTG at a rate calculated to achieve blood concentration of 10^{-7} , 10^{-6} , and 10^{-5} mol/L into the renal artery in patients with heart failure resulted in a significant dilation of the main renal artery with no significant effect on renal blood flow (45). These findings suggest a significant vasodilatory effect of NTG on large-conductance renal arteries but not on small-resistance vessels.

Potential Limitations of Intravenous Nitroglycerin in the Treatment of Acute Decompensated Heart Failure

Side Effects. Table 2 shows the reported side effects of intravenous NTG in 216 patients with ADHF, enrolled in the Vasodilatation in the Management of Acute CHF (VMAC) study (46). The most common adverse effect was headache, which was seen in 20% of the patients, followed by asymptomatic hypotension (8%) and nausea (6%).

Nitrate Resistance

A decreased vasodilatory response and attenuated hemodynamic effect of nitrates have been reported in patients with heart failure. Katz et al. (47) showed a two-fold increase in femoral artery blood flow velocity with intra-arterial infusion of NTG at a concentration of 10^{-7} mol/L in normal subjects. This response, however, was markedly attenuated in patients with heart failure and could be overcome only by increasing the dose to 10^{-5} mol/L. Potential mechanisms for vascular resistance to NTG include an increase in sodium and water within the vascular wall or an increased mechanical compression caused by accumulation of subcutaneous fluid (48), sulfhydryl group deficiency (49), and neurohormonal stimulation leading to activation of vasoconstrictive mechanisms, including catecholamines, angiotensin II, endothelin, and vasopressin, which may attenuate the vasodilatory effect of the drug (50).

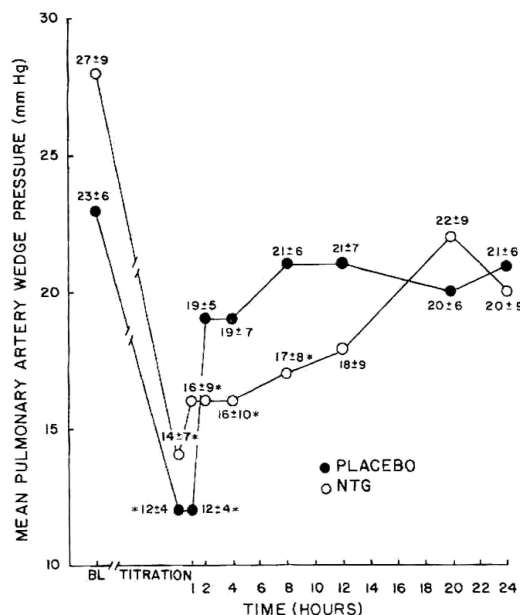


Figure 4. Values of mean pulmonary artery occlusion pressure as measured at baseline (BL), during nitroglycerin (NTG) titration, and during the 24 hrs of the study infusion. After titration of NTG, 16 patients were randomly assigned to receive placebo and 15 patients were assigned to receive NTG. * $p < .05$ vs. BL. Reproduced with permission from Elkayam U, Kulick D, McIntosh N, et al: Incidence of early tolerance to hemodynamic effects of continuous infusion of NTG in patients with coronary artery disease and heart failure. *Circulation* 1987; 76:577-584.

Nitrate Tolerance

Early development of tolerance and marked attenuation of initial hemodynamic effects of intravenous NTG in hospitalized patients with heart failure have been demonstrated by a number of investigators. Elkayam et al. (41), in a randomized, double-blind, placebo-controlled study, documented the early development of tolerance in 31 hospitalized patients with heart failure, which resulted in a significant attenuation of hemodynamic effects (Fig. 4). Analysis of individual data showed the development of early tolerance in approximately half of the patients, which could not be predicted by baseline hemodynamic and neurohormonal values. Similar attenuation of hemodynamic effects of intravenous NTG within several hours of initiation of therapy in hospitalized patients with heart failure has been shown by other investigators (40).

NESIRITIDE

Pharmacokinetics and Elimination

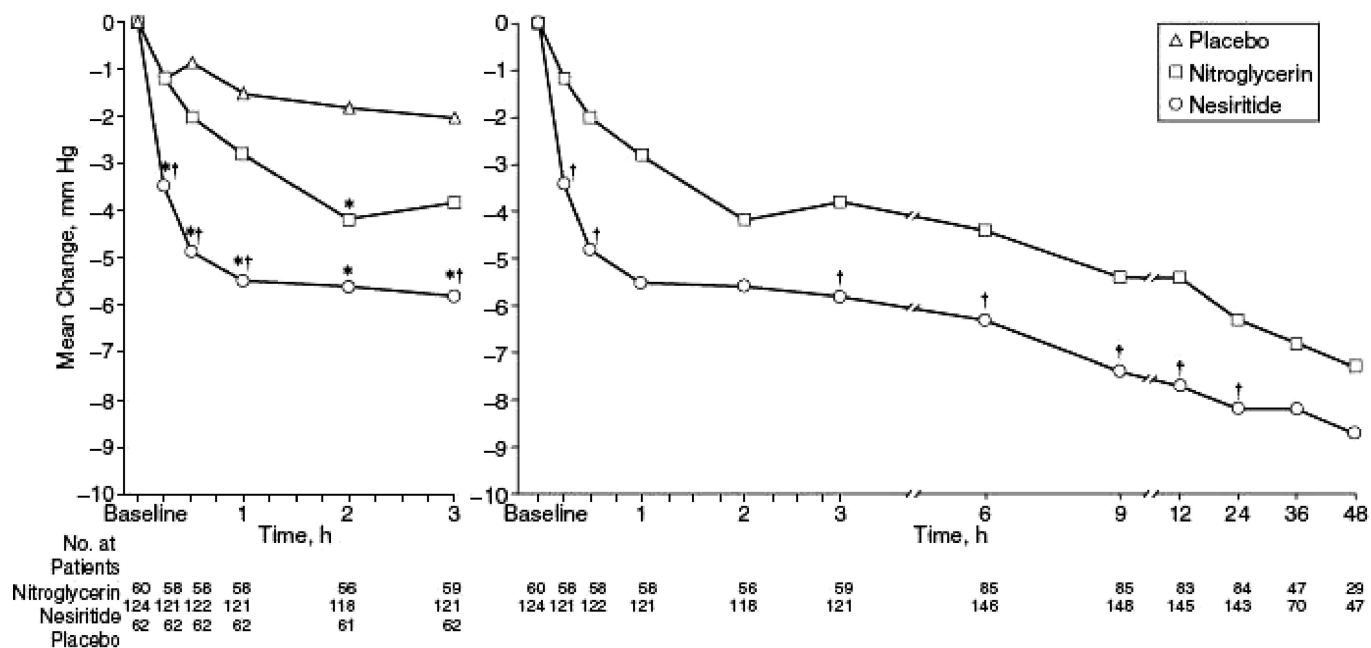
Nesiritide is a sterile, purified preparation of human B-type natriuretic peptide (BNP). It is manufactured from *Escherichia coli* using recombinant DNA

Table 2. Adverse effects of nitroglycerin during first 24 hrs after the start of therapy in 216 patients in VMAC study

Adverse Effect	No. of Patients	%
Cardiovascular		
Hypotension		
Asymptomatic	17	8
Symptomatic	10	5
Nonsustained tidal volume	11	5
Angina pectoris	5	2
Other adverse effects		
General headache	44	20
Pain		
General	11	5
Abdominal	11	5
Catheter	11	5
Nausea	13	6
Any adverse event	146	68

Reproduced with permission from the publication Committee for the VMAC Investigators (Vasodilatation in the Management of Acute CHF): Intravenous nesiritide vs NTG for treatment of decompensated congestive heart failure: A randomized controlled trial. *JAMA* 2002; 287:1531-1540.

technology and has the same 32-amino acid sequence as the endogenous BNP produced by the ventricular myocardium. The mean terminal elimination half-life of nesiritide in patients with heart failure is approximately 18 mins (51). At steady state, plasma BNP levels increase from baseline endogenous levels by ap-



Asterisk indicates $P < .05$ for nesiritide or nitroglycerin compared with placebo; dagger, $P < .05$ for nesiritide compared with nitroglycerin.

Figure 5. Changes from baseline in pulmonary artery occlusion pressure in nitroglycerin, nesiritide, and placebo groups. Reproduced with permission from Publication Committee for the VMAC Investigators [Vasodilatation in the Management of Acute CHF]: Intravenous nesiritide vs. nitroglycerin for treatment of decompensated congestive heart failure: A randomized controlled trial. *JAMA* 2002; 287:1531-1540.

proximately three-fold to six-fold with nesiritide infusion doses ranging from 0.01 to 0.03 $\mu\text{g/kg/min}$. Human BNP elimination from the circulation occurs by three independent mechanisms in the following order of decreasing importance (51): a) binding to cell surface natriuretic peptide clearance receptors (receptor C) with subsequent cellular internalization and isosome proteolysis; b) proteolytic cleavage by neutral endopeptidases present within renal tubular cells and vascular cells; and c) renal filtration clearance of nesiritide. The latter is proportional to body weight and supports weight-adjusted dosing of the drug. Clearance is not influenced significantly by age, gender, race, baseline endogenous BNP concentration, severity of heart failure, or concomitant administration of angiotensin-converting enzyme (ACE) inhibitors. Although nesiritide is eliminated in part through renal clearance, clinical data do not suggest a need for dose adjustment in patients with renal insufficiency.

Clinical Experience

The use of nesiritide in the treatment of ADHF has been investigated more extensively than nitroprusside and nitro-

glycerin. Before its approval for clinical use, nesiritide was studied in ten clinical trials (51) that included almost 1,000 patients, the majority of them with New York Heart Association functional class III or IV heart failure. The mean age of the studied population was 60 yrs, and 56% of all patients were women. Five of the trials were randomized, multicenter, placebo-controlled or active controlled studies in which 772 patients with decompensated heart failure received continuous infusions of nesiritide at doses ranging from 0.01 to 0.03 $\mu\text{g/kg/min}$. Agents used for comparison in the active controlled studies were primarily dobutamine and NTG (46, 52). Most patients (70%) were given nesiritide infusion for ≥ 24 hrs, while 48% received the drug for 24-48 hrs and 22% for > 48 hrs. In controlled trials, nesiritide was used either alone or in combination with diuretics, digoxin, oral ACE inhibitors, anticoagulants, oral nitrates, statins, class III antiarrhythmic agents, β -blockers, dobutamine, calcium-channel blockers, angiotensin II receptor antagonists, and dopamine. Nesiritide has been studied in a broad range of patients, including the elderly, women, African Americans, and patients with history of various cardiovascular conditions, including hypertension, diabetes, postmyocardial infarction, atrial

fibrillation/flutter, nonsustained ventricular tachycardia, LV diastolic dysfunction, and acute coronary syndrome (46). A recent study evaluated the effects of perioperative nesiritide in 272 patients with LV dysfunction undergoing cardiac surgery (the NAPA trial) (53).

Hemodynamic Effects

The VMAC trial (Vasodilatation in the Management of Acute CHF) (46) provided information on hemodynamic effects of currently recommended doses of nesiritide (Fig. 5). This was a multicenter, randomized, double-blind trial designed to compare the clinical effects of nesiritide with those of intravenous NTG when both were added to standard care in patients with decompensated heart failure. In this trial, 489 patients with dyspnea at rest due to decompensated heart failure were treated with either nesiritide (starting with a bolus of 2 $\mu\text{g/kg}$ and followed by continuous infusion of 0.01 $\mu\text{g/kg/min}$) or intravenous NTG at a dose determined by the investigators. The mean systolic blood pressure for the entire group was 121 ± 22 mm Hg and the mean PAOP was 28 ± 6 mm Hg in 246 patients who received invasive hemodynamic monitoring. Nesiritide led to a significant reduction in PAOP, which was observed as

early as 15 mins with a further effect at 1 hr. The effect of nesiritide on PAOP was superior to that of NTG. The administration of nesiritide was also associated with a significant reduction in right atrial pressure and peripheral vascular resistance. Systolic blood pressure was reduced by 4 ± 11 mm Hg (3%) 15 mins after initiation of nesiritide infusion, which was comparable to that of NTG (-3 ± 11 mm Hg) at 15 mins and was less than NTG at 1 hr (3 ± 13 mm Hg vs. 6 ± 14 mm Hg, $p < .05$ for NTG vs. placebo and not significant for nesiritide vs. placebo). Nesiritide also had a significant effect on pulmonary vascular resistance and augmented cardiac output. Through 24 hrs, nesiritide lowered PAOP to a significantly greater extent than did NTG, with no evidence of attenuation of effect (46, 54). At 36 and 48 hrs, PAOP continued to be reduced by a greater magnitude with nesiritide than with NTG (56).

Effect on Coronary Hemodynamics

The use of intravenous nesiritide in a standard dose in ten patients undergoing cardiac catheterization showed a 52% reduction in right atrial pressure, 19% reduction in PAOP, and 11% reduction in mean systemic blood pressure. Coronary blood flow increased 35% ($p = .007$), whereas coronary resistance decreased 23% ($p = .036$) and myocardial oxygen uptake decreased 8% ($p = .045$) (56). The study thus showed that nesiritide exerts coronary vasodilator effects on both the coronary conductance and resistance arteries; despite a decrease in coronary perfusion pressure, coronary artery blood flow was increased, coronary resistance was decreased, and myocardial oxygen uptake was decreased.

Tachyphylaxis

Tachyphylaxis, which results in a rapid and significant attenuation of hemodynamic effects, has been described with the use of continuous infusion of NTG and limits the usefulness of this drug in the treatment of patients with decompensated heart failure (54). In a study by Mills et al. (57), the hemodynamic effects of nesiritide seen at 1 hr after initiation of drug infusion were sustained throughout the 24-hr infusion time. Similarly, the hemodynamic effect of nesiritide was maintained throughout the 24 hrs of the study period in the VMAC study (46).

These findings indicate that unlike NTG, continuous administration of nesiritide is not associated with the development of tolerance to the drug.

Effects on Symptoms

The effects of nesiritide on symptoms of heart failure were evaluated in comparison to placebo and to standard care, which included use of intravenous vasoactive drugs, such as NTG, dobutamine, and milrinone. The double-blind use of nesiritide infused for 6 hrs in 127 class III and IV heart failure patients resulted in a superior hemodynamic improvement compared with placebo, which was also associated with a marked improvement in heart failure symptoms, including dyspnea and fatigue (55). Another study compared the effect of nesiritide with that of standard care in a group of 305 patients admitted to hospitals for decompensated heart failure (55). In this study, 57% of patients randomized to standard care received dobutamine, 19% received milrinone, 18% received NTG, and 6% received dopamine. Nesiritide administration was associated with improvement of heart failure symptoms within the first 6 hrs in the majority of the patients, and the rate of improvement was similar to that seen with standard care.

The VMAC study compared the effect of nesiritide with that of placebo and of intravenous NTG when added to standard heart failure treatment (46). The patients' self-assessed dyspnea score at 3 hrs was significantly improved in the nesiritide group compared with placebo ($p < .034$), while the effect of NTG on change in dyspnea score at 3 hrs was not statistically significant ($p = .191$) compared with placebo.

Neurohumoral Effects

In animals with CHF, release of atrial natriuretic peptide was found to inhibit production of catecholamines, angiotensin II, aldosterone, and endothelin-1, while infusion of antagonists of natriuretic peptide A and B receptors led to a significant increase in the levels of these hormones (51). In the study reported by Colucci et al. (55), the administration of nesiritide at doses of 0.015 and 0.03 $\mu\text{g/kg/min}$ was associated with a significant decrease in plasma aldosterone levels compared with placebo. Evaluation of neurohormonal effects of nesiritide vs. dobutamine was performed in a subset of 82 patients with

decompensated CHF (58). This study showed a significant decrease in endothelin-1 levels during nesiritide infusion compared with a significant increase during dobutamine treatment. There was no significant change in plasma levels of norepinephrine, tumor necrosis factor- α , and interleukin-6.

Effect on Urine Output

Reports on the effect of nesiritide on urine output have resulted in conflicting information. In an efficacy trial (55), patients were blindly randomized to either placebo (42 patients), nesiritide at a dose of 0.015 $\mu\text{g/kg/min}$ (43 patients), or nesiritide at a dose of 0.03 $\mu\text{g/kg/min}$ (42 patients), and intravenous diuretics were withheld for 4 hrs before baseline measurements and for the first 6 hrs of the infusion. The mean urine output over 6 hrs was 560 mL and 659 mL, respectively, in the groups assigned to nesiritide and was 380 mL in the placebo group ($p = .004$). In a comparative trial (55), patients were randomized to standard care (including other vasoactive medications) or to nesiritide given as a bolus of 0.3 or 0.6 $\mu\text{g/kg}$ followed by infusion of 0.015 or 0.03 $\mu\text{g/kg/min}$, and intravenous diuretics could be added at any time. Intravenous diuretics were given to fewer patients in the groups assigned to nesiritide (84% and 74%, respectively) than in the standard therapy group (96%, $p < .001$ for both comparisons). In ten patients after surgery for heart transplant with mean serum creatinine value of 2.82 mg/dL and PAOP >22 mm Hg who were refractory to standard medical therapy, the addition of standard-dose nesiritide resulted in a significant and favorable hemodynamic effect and an increase in average 24-hr urine output from 1625 ± 318 mL to 4641 ± 692 mL ($p < .001$).

Significant enhancement of urine output was also reported in the NAPA trial, where a greater urine output (2926 ± 1179 mL vs. 2350 ± 1060 mL; $p < .001$) was seen during the initial 24 hrs after surgery in patients with symptomatic heart failure due to LV systolic dysfunction undergoing cardiac surgery and receiving nesiritide vs. placebo (53). In contrast, a study by Wang et al. (59) failed to document an effect of nesiritide added to diuretics on urine output in a group of 15 patients with heart failure and worsening serum creatinine. These results probably indicate a variable effect of nesiritide on urine output, which may be related to the

patient population treated and the degree of volume overload.

Effect on Renal Function

A meta-analysis of five randomized clinical trials comparing nesiritide with either placebo or active control suggested an increased risk of worsening renal function in patients with ADHF treated with nesiritide (60). The validity of these findings has been questioned since the studies were not designed to evaluate effect on renal function, information regarding concomitant therapy was not available, and data regarding renal function were incomplete. Further analysis of the same data suggested a dose-related effect of nesiritide on serum creatinine without a significant effect with the standard dose (61) and a strong relationship between nesiritide-associated increase in serum creatinine and the concomitant use of large doses of diuretics (62). In addition, no relationship could be found between a nesiritide-associated increase in serum creatinine (>0.5 mg/dL) and 30-day mortality (63). The recently published NAPA trial demonstrated nesiritide-associated renal protection. Compared with placebo, nesiritide given to patients with symptomatic heart failure due to LV systolic dysfunction undergoing heart surgery was associated with a significantly attenuated peak increase in serum creatinine (0.15 ± 0.29 mg/dL vs. 0.34 ± 0.48 mg/dL; $p < .001$) (53). More information from prospective studies will be needed for further understanding of the effect of nesiritide on renal function in patients with ADHF and its clinical implications.

Safety

The most common side effect associated with the administration of currently recommended doses of nesiritide used in the VMAC study (2- μ g/kg bolus followed by infusion of 0.01 μ g/kg/min in the majority of patients) was headache, which was reported by 8% of the patients (46). However, this adverse effect occurred significantly less often in patients treated with nesiritide than in those treated with NTG (20%, $p < .001$). Symptomatic hypotension was reported in 4% of the patients treated with nesiritide compared with 5% of those receiving NTG. In another study, decreases in blood pressure were found to be dose dependent, and symptomatic hypotension was reported

in 11% of patients with decompensated heart failure during infusion of 0.015 μ g/kg/min and in 17% patients receiving 0.03 μ g/kg/min (55). In the VMAC trial (46), symptomatic hypotension reported during the first 24 hrs of treatment in the nesiritide patients was of longer duration than in patients receiving NTG (2.2 hrs with nesiritide and 0.7 hrs with NTG), most likely due to the longer half-life of nesiritide. None of those episodes resulted in adverse sequelae in either treatment group. Most hypotensive episodes were considered mild to moderate, and only one subject in each treatment group experienced an event that was classified by the investigator as severe. Most events resolved either spontaneously after a dose decrease or discontinuation or with an intravenous volume challenge of ≤ 250 mL. The potential for hypotension may be increased by combining nesiritide with other vasodilators. In the VMAC trial, the frequency of symptomatic hypotension during the first 24 hrs of treatment in nesiritide patients who received an oral ACE inhibitor concomitantly was 6%, compared with 1% in patients not receiving ACE inhibitors (46). This was similar for NTG patients who were on concomitant ACE inhibitors.

Heart Rate and Arrhythmias

The effect of nesiritide on heart rate and ventricular arrhythmias was compared with that of dobutamine in the PRECEDENT study (Prospective, Randomized Evaluation of Cardiac Ectopy with Dobutamine or Nesiritide Therapy) (52). In this study, patients received nesiritide administered at one of two doses (0.015 μ g/kg/min or 0.03 μ g/kg/min) or dobutamine at a minimum dose of 5 μ g/kg/min. The effect of the therapy was assessed by Holter monitoring performed for 24 hrs during drug infusion, which was compared with recordings for a similar period of time before treatment. The study included 246 patients with New York Heart Association class III or IV heart failure; 51% of these patients had ischemic cardiomyopathy.

In contrast to the dobutamine group, which showed a significant increase in heart rate and proarrhythmic effect, the lower nesiritide dose showed no significant effect on heart rate and a significant decrease in the number of couplets, triplets, and episodes of nonsustained ventricular tachycardia; the higher nesiritide dose was associated with no significant

change in heart rate or ventricular ectopic beats. In addition, when using two independent criteria for proarrhythmic effect, dobutamine but not nesiritide was found to be proarrhythmic.

Effect on Short-Term Outcome

From a study comparing blinded nesiritide doses to open-label, nonblinded, physician-selected standard care treatment in hospitalized patients with decompensated heart failure (64), a subgroup analysis of 261 patients who received either dobutamine or nesiritide demonstrated that although there was no difference in length of stay between the two groups, the use of nesiritide was associated with a shorter duration of drug infusion compared with dobutamine (median duration of study drug infusion shorter by 25 hrs at nesiritide 0.015 μ g/kg/min and shorter by 39 hrs at nesiritide 0.030 μ g/kg/min, $p < .001$). Dobutamine was also associated with a higher rate of readmission to the hospital during the first 21 days after discharge (20% vs. 8% [nesiritide 0.015 μ g/kg/min, $p < .05$] compared with dobutamine and 11% [nesiritide 0.030 μ g/kg/min, p not significant]). There was also a trend for a higher readmission rate for heart failure (13% vs. 4% for both groups, $p = .081$). When compared with NTG in the VMAC study, there was no difference in the rate of 30-day readmissions between the nesiritide and the NTG groups (46).

The effect of nesiritide on 6-month mortality was compared with that of dobutamine (64) and NTG (46).

The effect of nesiritide on long-term survival compared with that of dobutamine was evaluated in 261 patients from the open-label subgroup analysis described previously, who were treated with either dobutamine ($n = 58$) or nesiritide in two different doses (0.06 μ g/kg per bolus and 0.030 μ g/kg/min infusion in 100 patients, and 0.03 μ g/kg per bolus followed by 0.015 μ g/kg/min in 103 patients). Despite similar baseline characteristics (except for a higher incidence of ischemic etiology for heart failure and previous myocardial infarctions in the dobutamine-treated patients), the use of dobutamine was associated with higher mortality compared with patients receiving nesiritide (64). The difference in the 6-month mortality rate between patients receiving dobutamine and nesiritide at 0.015 μ g/kg/min was statistically significant.

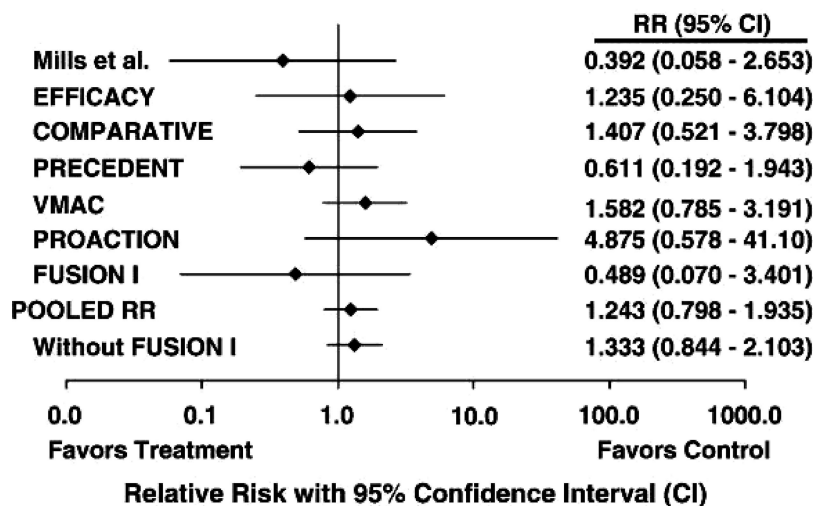


Figure 6. The relative risk (RR) of 30-day mortality with nesiritide therapy is shown for each study, as well as the combined RR across the studies (pooled RR). Compared with control, neither the individual studies nor the pooled RR indicates significantly different risk of mortality with nesiritide use. The large 95% confidence intervals (CI) are due to the very low event rates underlining the uncertainty of RR point estimates. Exclusion of the FUSION I trial from the pooled RR computation (without FUSION I) did not change the result significantly. Reproduced with permission from Arora RR, Venkatesh PK, Molnar J: Short and long-term mortality with nesiritide. *Am Heart J* 2006; 152:1084-1090.

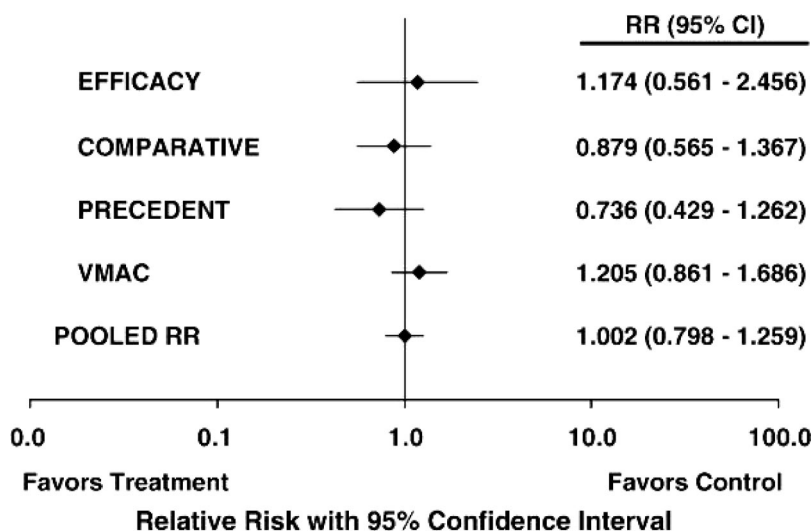


Figure 7. The relative risk (RR) of 180-day mortality after nesiritide therapy is shown for each study, as well as the combined RR across the studies (pooled RR). None of the studies show a significantly increased or decreased RR with nesiritide use. Compared with control, the pooled RR indicates virtually identical risk of 180-day mortality with nesiritide use. CI, confidence interval. Reproduced with permission from Arora RR, Venkatesh PK, Molnar J: Short and long-term mortality with nesiritide. *Am Heart J* 2006; 152:1084-1090.

cant ($p = .04$) in this *post hoc* subgroup analysis.

A recently published meta-analysis of three of the available randomized, blinded, controlled trials evaluating nesiritide compared 30-day mortality in 485 patients randomized to nesiritide and 377 patients receiving other therapies (65). This analysis found a higher mortality ($p = .03$) at 30 days among patients randomized to nesiritide. A later meta-

analysis of seven randomized, controlled nonmortality trials with 30-day mortality data and four with 6-month mortality data, however, failed to demonstrate a significant difference in either 30-day or 6-month mortality between patients with ADHF treated with nesiritide or not (Figs. 6 and 7) (67, 68). A recent analysis of 15,230 patients with ADHF (69) who were included in the ADHERE registry and received vasoactive medications demon-

strated a 41% and 53% lower in-hospital mortality in patients treated with nesiritide compared with milrinone and dobutamine, respectively ($p < .005$) and similar mortality compared with NTG.

The recently published NAPA trial demonstrated a lower 180-day mortality ($p = .046$) in patients with symptomatic heart failure due to LV systolic dysfunction undergoing cardiac surgery treated with nesiritide compared with controls. This study, however, was relatively small, included only 279 patients who received the study drug, and was not designed as a mortality trial (53). More information from adequately powered, prospective studies is needed to evaluate a possible effect of nesiritide on short- and long-term mortality in patients with ADHF.

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