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Benefit-Risk Assessment of Nesiritide in the Treatment of Acute Decompensated Heart Failure

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Contents

Abstract

Nesiritide is a recombinant form of human B-type natriuretic peptide, a naturally occurring endogenous hormone released by cardiac ventricles in response to an increase in ventricular wall stress. Its use in the treatment of acute decompensated heart failure (ADHF) has been evaluated in a series of randomised controlled clinical trials. It is currently approved in the US for the treatment of ADHF. Nesiritide induces a balanced vasodilation and an indirect increase in cardiac output, but has no actual inotropic effects and exerts a neutral effect on heart rate. In addition, it inhibits adverse neurohormonal activation and, in some individuals, promotes natriuresis and diuresis. In adults with ADHF, nesiritide reduces pulmonary capillary wedge pressure, right atrial pressure and systemic vascular resistance; decreases symptoms of heart failure; and enhances global clinical status. Important questions regarding the risks of nesiritide therapy have recently been raised, and resolution of the safety of nesiritide is a process that remains in evolution. The most frequently reported adverse effect is dose-related hypotension. In addition, nesiritide may cause an acute increase in serum creatinine concentration. This increase seems to be a haemodynamic response to a combination of volume depletion, vasodilation and neurohormonal inhibition.

Nesiritide-induced changes in renal function have not been definitively shown to negatively affect mortality. The effect of nesiritide on all-cause mortality is currently unresolved. Recent meta-analyses of existing databases have raised concerns regarding adverse effects of the drug on 30-day mortality. However, reviews of large, observational, registry databases do not suggest an adverse inpatient mortality effect compared with other vasodilator therapies. Further resolution of the mortality question awaits completion of pending randomised controlled clinical trials.

When used for approved indications and according to recommended dosage and administration regimens, nesiritide represents a reasonable treatment adjunct for ADHF.

Despite the fact that our understanding of the pathophysiology and management of chronic heart failure has improved substantially over the past two decades, the prevalence of heart failure continues to rise. This is evident in the increasing number of hospital admissions for episodes of acute decompensation. In the US, acute decompensated heart failure (ADHF) is currently responsible for approximately 1.1 million hospitalisations annually,[1] with a mean hospital stay of 5.4 days.[2] Similarly, in Europe, there has been a rapid growth in the number of patients living with chronic heart failure and a concomitant increase in the number of hospitalisations for ADHF.[3] ADHF is predominately a disease of the elderly; 74% of ADHF hospitalisations in the US occur in individuals ≥65 years of age, and ADHF is the most common single indication for hospitalisation in this age group.[2] Each year, there are 201.4 ADHF hospitalisations for every 10 000 individuals aged ≥65 years in the US. The risk of hospitalisation for ADHF is slightly greater in women (36.1 per 10 000 individuals) than in men (31.4 per 10 000 individuals).

The current management of ADHF is troublesome, as posthospital morbidity and mortality due to heart failure are problematic. Hospital readmissions are common. In one study, >40% of patients with ADHF were readmitted within 90 days of discharge.[4] Approximately 45% of patients with ADHF will be readmitted at least once and 15% at least twice within 12 months of hospital discharge.[3] Moreover, patients with ADHF have a worse prognosis after hospitalisation.[3] Depending on patient characteristics and clinical status, mortality risks are approximately 4% in-hospital,[5,6] 6–9% at 30–60 days,[5,7,8] 20–40% at 6 months[5,7,9,10] and 30–50% at 1 year.[3,11,12] It is apparent that hospitalisation for ADHF is associated with changes in the natural history of heart failure.

ADHF places a tremendous economic burden on the healthcare system. In 2007, annual estimated direct and indirect cost of heart failure care in the US is $US33.2 billion.[1] Furthermore, approximately 60–75% of these direct expenditures are due to inpatient hospital care.[1,3] In 2001, $US4 billion ($US5912 per hospital discharge) was paid to Medicare beneficiaries for ADHF care, making ADHF the single most expensive hospital admission diagnosis according to the Center for Medicare and Medicaid Administration.[1]

Finally, patients with ADHF frequently have comorbidities such as hypertension, coronary artery disease and renal insufficiency,[3,8,13-15] which can significantly impact on both the treatment of this disorder and its subsequent outcomes. This paper summarises the current treatment options for ADHF, particularly focusing on the benefits and risks associated with nesiritide.

1. Acute Decompensated Heart Failure Treatment Options

In the absence of any pharmacological agents proven to reduce the morbidity and mortality of ADHF, pharmacotherapy for ADHF is aimed at optimising haemodynamic parameters and relieving

symptoms.[3,12,16] Current pharmacological options include intravenous diuretics, vasodilators and inotropic agents.[3,17] Recently published guidelines by the European Society of Cardiology and the Heart Failure Society of America have attempted to outline best strategies for treating this condition.[3,16]

Diuretics are indicated in patients with ADHF who have signs and symptoms of fluid retention.[3] Diuretics are effective at providing symptomatic relief; however, there is little evidence that outcomes are improved.[17] Diuretics have numerous effects that might adversely impact clinical outcomes, including hypotension, electrolyte abnormalities, worsening renal function and neurohormonal activation.[17-23] Use of diuretics, especially in high doses, has been associated with increased morbidity and mortality.[24-28] In an evaluation of >50 000 hospital admissions in the Acute Decompensated Heart Failure National Registry (ADHERE®), use of intravenous diuretics was found to increase the risk of in-hospital mortality (odds ratio [OR] 1.29; 95% CI 1.04, 1.59) after adjustment for baseline covariates and treatment propensity.[28]

Vasodilators are indicated as first-line therapy in the treatment of patients with ADHF who have hypoperfusion but adequate systemic blood pressure.[3] Vasodilators decrease ventricular filling pressures, systemic vascular resistance and myocardial work, and increase stroke volume and cardiac output.[17] Their use in combination with low-dose diuretics has proven to be more efficacious than high-dose diuretics alone.[3] The efficacy of vasodilators, especially nitrates, can be quite dramatic, leading to an improvement in haemodynamics and a reduction in symptoms, but these favourable effects may be limited by the early development of tolerance, requiring frequent dose titrations.[3,17,29] In addition, use of nitrates can result in excessive or inappropriate vasodilation, causing a rapid decline in blood pressure, reflex tachycardia, activation of the sympathetic and renin-angiotensin-aldosterone systems, and fluid retention.[3,29,30] In patients with severe heart failure treated with increasing doses of sodium nitroprusside, profound haemodynamic improvement may occur with substantial increases in cardiac output, consistent with a remarkable unloading effect on the failing ventricle.[30] However, either increasing the dosage of sodium nitroprusside or prolonged exposure to the drug may result in significant increases in plasma epinephrine, renin and aldosterone levels and significant decreases in urine volume and urinary sodium excretion. Thiocyanide toxicity is also an infrequent risk but one which may require urgent intervention.

Inotropic agents are indicated for patients with ADHF who have frank hypotension or hypoperfusion refractory to optimal doses of diuretics and vasodilators.[3] Inotropic agents augment contractility and improve short-term haemodynamics.[3,17] However, they also augment neurohormonal activation, induce adverse events (such as arrhythmias and myocardial ischaemia) and increase mortality.[3,17,31-36] In the ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterisation Effectiveness) trial, use of inotropic agents was associated with an increased risk of death (hazard ratio [HR] 1.75; 95% CI 1.05, 2.92) and death plus rehospitalisation (HR 2.12; 95% CI 1.52, 2.97) after adjustment for blood pressure and renal function.[35]

Levosimendan, an approved agent for the treatment of ADHF in Europe, is currently undergoing clinical investigation to meet US FDA approval.[10] Similar to dobutamine, levosimendan induces adverse neurohormonal activation and tachyarrhythmias,[37-39] but appeared to reduce mortality risk compared with other inotropic agents in small, preliminary evaluations.[10,40] The SURVIVE-W (Survival of Patients with Acute Heart Failure in Need of Intravenous Inotropic Support) trial specifically evaluated this potential mortality benefit.[38,39] This recently completed trial found no significant differences between patients randomised to levosimendan versus dobutamine in the primary endpoint of all-cause mortality at 180 days (HR 0.91; 95% CI 0.74, 1.13) or the secondary endpoints of all-cause mortality at 5 days (HR 0.72; 95% CI 0.44, 1.16) or 31 days (HR 0.85; 95% CI 0.63, 1.15). In the recently completed REVIVE-II (Randomized Evaluations of Levosimendan) trial, the secondary endpoint of 90-

day mortality was *greater*, although not significantly, in patients randomised to levosimendan (15.1%) versus placebo (11.6%).[39] There are no parenteral drugs that have been demonstrated to improve clinically relevant outcomes, including rehospitalisation and mortality.[3,17]

Nesiritide is the most recent addition to the pharmacological armamentarium for ADHF in the US. Its role in the treatment of this disorder has been investigated in randomised controlled clinical trials and the agent is FDA-approved for the treatment of ADHF in the US, but has not received approval for use in Europe.

2. Nesiritide: Pharmacological Profile

2.1 Pharmacodynamic Properties

Nesiritide is a recombinant form of human B-type natriuretic peptide, the endogenous hormone released by cardiac ventricles in response to pressure and volume overload.[9] Synthesised from *Escherichia coli*, it is structurally identical to the endogenous hormone.[41] Its physiological properties are mediated by activation of guanylate cyclase-coupled natriuretic peptide receptor-A on target cells with a subsequent intracellular increase in the second messenger cyclic guanosine monophosphate.[41-44]

Nesiritide has a direct relaxant effect on human vascular tissue.[45] In both healthy volunteers and individuals with heart failure, this effect produces a balanced vasodilation, significantly reducing mean arterial pressure, pulmonary capillary wedge pressure (PCWP) and right atrial pressure.[9,43,46-49] In an evaluation of 19 patients with severe heart failure, nesiritide produced a 48% reduction in mean PCWP and a 56% reduction in mean right atrial pressure (both $p < 0.01$ vs placebo).[43] Similarly, in an evaluation of 16 patients with ADHF, nesiritide produced a 17% reduction in mean arterial pressure ($p < 0.001$), a 41% reduction in PCWP ($p < 0.001$) and a 31% reduction in right atrial pressure ($p < 0.001$) versus placebo.[46] This vasodilation results in an increase in both cardiac index[43,47,48] and coronary blood flow.[50,51] In the previously discussed evaluation of patients with severe heart failure, cardiac index increased by 25% ($p < 0.01$) during nesiritide infusion,[43] and in an evaluation of 10 patients undergoing heart catheterisation, nesiritide increased coronary artery diameter by 15% ($p = 0.007$), peak coronary velocity by 14% ($p = 0.015$) and coronary blood flow by 35% ($p = 0.007$), and reduced coronary resistance by 23% ($p = 0.036$) versus placebo.[50] These changes occurred without potentially detrimental inotropic or chronotropic effects.[47,52,53]

Nesiritide has a potentially beneficial neurohormonal profile.[54,55] It inhibits sympathetic overactivity, decreasing circulating, as well as local cardiac and renal, norepinephrine levels.[46,56] Heart rate variability is an important marker of this sympathetic-parasympathetic imbalance.[54,55] In a randomised, multicentre evaluation, nesiritide 0.015 μg/kg/min significantly improved several indices of heart rate variability (SD of the relative risk [RR] intervals over 24 hours: $p = 0.001$; SD of all 5-minute mean RR intervals: $p = 0.02$; square root of mean squared differences of successive RR intervals: $p = 0.01$) in patients with severely depressed heart rate variability at baseline.[54] Similarly, nesiritide inhibits the renin-angiotensin-aldosterone system, reducing both renin and especially aldosterone levels.[46,47,49,57-62] Given the increased awareness of aldosterone as a contributor to left ventricular remodeling, ventricular irritability and electrolyte imbalance, it is potentially quite intriguing to consider the benefit of compounds that antagonise aldosterone. The RALES (Randomized Aldactone Evaluation Study)[63] and EPHESUS (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study)[64] trials confirmed these benefits and reflect a potential therapeutic role for nesiritide. Finally, nesiritide inhibits the endothelin system.[61,65] Endothelin-1 induces vasoconstriction, sodium retention and mitogenesis.[65] In patients with decompensated heart failure, nesiritide (0.015 μg/kg/min) reduced endothelin-1 levels by 20% ($p < 0.001$);[65] the degree of reduction correlated directly with the degree of baseline elevation.

In healthy volunteers, nesiritide increases the glomerular filtration rate and produces both diuresis and natriuresis in a dose-dependent fashion.[49,58-60,66-68] In the kidney, it inhibits sodium resorption in both the proximal and distal nephron, with its major effect occurring in the distal nephron.[59] Nesiritide also inhibits the tubuloglomerular feedback response that would typically occur in response to increased salt delivery in the distal tubule, thereby preserving this natriuretic effect.[69] However, the renal effects of nesiritide in patients with heart failure are less well established and may be influenced by several factors, including intravascular volume status, concomitant medications and the underlying degree of co-morbid renal insufficiency.[70-72] In such patients, nesiritide has been reported to either decrease[73] or maintain renal blood flow and/or glomerular filtration rate,[43,46,60,72,74,75] and either maintain[46,74] or increase urinary sodium and/or water excretion.[43,47,60] The best assessment of nesiritide and its influence on renal function would be that there are no definitive data to support a true renoprotective effect of nesiritide for patients with heart failure.

2.2 Pharmacokinetic Profile

The pharmacokinetic profile of intravenous nesiritide administration, whether by bolus or continuous infusion, fits a two-compartment model with a distribution half-life of approximately 2 minutes.[76,77] Plasma level is proportional to dose and reaches steady state in <90 minutes.[77] The mean volume of distribution at steady state is approximately 0.19 L/kg.[76]

Nesiritide is eliminated through binding to the clearance receptor natriuretic peptide receptor-C, degradation by neutral endopeptidase-24.11 or glomerular filtration.[42] Its mean terminal elimination half-life is approximately 18 minutes and is associated with approximately 67% of the area under the concentration-time curve.[76] Nesiritide clearance is proportional to bodyweight, with a mean clearance of approximately 9.2 mL/kg/min.[76] Although nesiritide is cleared by the kidney, no dosage adjustment is necessary in patients with renal insufficiency.[76] Nesiritide has been shown to be well tolerated in patients with baseline renal insufficiency,[78,79] and the haemodynamic effects of nesiritide in these patients are similar to those in patients without renal insufficiency.[76]

Pharmacokinetic interactions between nesiritide and most other cardiovascular drugs have not been formally studied.[76] During clinical trials, nesiritide was administered concomitantly with a variety of other medications, including diuretics, digoxin, oral ACE inhibitors, anticoagulants, oral nitrates, HMG-CoA reductase inhibitors (statins), class III antiarrhythmic agents, β-adrenoceptor antagonists, dobutamine, calcium channel antagonists, angiotensin II type 1 receptor antagonists and dopamine without evidence of significant pharmacokinetic interactions.[76] In addition, coadministration of nesiritide and enalapril did not significantly alter the pharmacokinetics of nesiritide.[76] However, administration of nesiritide with high-dose diuretics may increase the risk of acute worsening of renal function as a result of the combined effect of volume depletion, vasodilation and neurohormonal blockade on renal blood flow.[70,80-82]

3. Nesiritide: Therapeutic Experience

The potential therapeutic application of nesiritide as adjunctive parenteral therapy for patients with ADHF has been evaluated in six randomised controlled clinical trials involving >1500 patients (table I).[9,34,47,48,83,84]

Mills et al.[48] performed a double-blind, placebo-controlled, multicentre evaluation of nesiritide therapy in 103 patients with symptomatic heart failure (New York Heart Association [NYHA] class II, III or IV) and left ventricular systolic dysfunction, as evidenced by a left ventricular ejection fraction ≤35% by echocardiography or radionuclide angiography within the preceding 12 months. Subjects were randomised on a 1 : 1 : 1 : 1 basis to 24-hour infusion therapy with nesiritide 0.015 μg/kg/min, 0.03 μg/kg/min or 0.06 μg/kg/min, or placebo, with the study drug infusion initiated at least 2 hours after insertion of a pulmonary artery catheter. The primary efficacy endpoint was central haemodynamics

Table I. Randomised controlled trials of nesiritide in acute decompensated heart failure (Copyright © MedReviews, LLC. Reprinted with permission of MedReviews, LLC. Abraham WT. Nesiritide and mortality risk: individual and pooled analyses of randomized controlled clinical trials. Rev Cardiovasc Med 2005; 6 (2).[83] *Reveiws in Cardiovascular Medicine* is a copyrighted publication of MedReviews, LLC. All rights reserved)

Study	Control	No. of patients		Nesiritide dose (μg/kg/min)	Median (IQR) duration of infusion (h)
		nesiritide	control		
Mills et al.[48]	Placebo	74	29	0.015, 0.03 or 0.06	24.0 (24.0, 24.1)
Efficacy trial[47]	Placebo	85	42	0.015 or 0.03	24.2 (7.8, 47.7)
Comparative trial[47]	Standard care	203	102	0.015 or 0.03	30.4 (23.0, 65.1)
PRECEDENT[34]	Dobutamine	163	83	0.015 or 0.03	24.1 (24.0, 46.5)
VMAC[9]	Nitroglycerin (glyceryl trinitrate)/ standard care	273	216	0.01	24.3 (24.0, 44.2)
PROACTION[84]	Standard care	120	117	0.01	16.9 (12.2, 21.9)

IQR = interquartile range.

during and immediately following study drug infusion. Compared with placebo, nesiritide produced substantial reductions in PCWP (27–39% by 6 hours), mean right atrial pressure and systemic vascular resistance and significant increases in stroke volume index and cardiac output with no effect on heart rate. These haemodynamic effects were evident at 1 hour and were sustained throughout the infusion. Worsening heart failure necessitating termination of study drug occurred in 1% of nesiritide versus 17% of control patients ($p = 0.014$).

The Efficacy trial[47,83] was a double-blind, placebo-controlled, multicentre evaluation of nesiritide therapy in 127 patients with symptomatic heart failure (94% NYHA class III or IV) that warranted admission to the hospital for intravenous therapy in addition to diuretics. All subjects were required to have a systolic blood pressure ≥90mm Hg, a PCWP ≥18mm Hg and a cardiac index ≤2.7 L/min/m^2. Patients were randomised on a 1 : 1 : 1 basis to nesiritide 0.015 μg/kg/min or 0.03 μg/kg/min, or placebo with a minimum infusion duration of 6 hours. Other intravenous vasoactive agents were withheld during this initial 6-hour period. Overall, the median infusion duration was 24.2 hours. The primary outcome parameter was the change from baseline in PCWP at 6 hours. Secondary outcome parameters were global clinical status, clinical symptoms and other haemodynamic measurements. In this trial, nesiritide produced dose-dependent decreases in PCWP, right atrial pressure, systemic vascular resistance and systolic blood pressure, and a moderate increase in cardiac index with no substantial change in heart rate. Global clinical status, as judged by the physician, was better or markedly better compared with baseline in 55%, 77% and 5% of patients in the nesiritide 0.015 μg/kg/min and 0.03 μg/kg/min, and placebo groups, respectively ($p < 0.001$ for both nesiritide vs placebo comparisons). Dyspnoea was improved in 56% (0.015 μg/kg/min) and 50% (0.03 μg/kg/min) of patients receiving nesiritide versus 12% of patients receiving placebo ($p < 0.001$ for both comparisons). Fatigue was reduced in 32% (0.015 μg/kg/min) and 38% (0.03 μg/kg/min) of patients receiving nesiritide ver-

sus 5% of patients receiving placebo ($p < 0.001$ for both comparisons).

The Comparative trial[47,83] was an open-label, multicentre evaluation of nesiritide versus 'standard therapy' in 305 patients with symptomatic heart failure (92% NYHA class III or IV) that warranted hospital admission for intravenous therapy plus diuretics. Patients were randomised on a 1 : 1 : 1 basis to nesiritide 0.015 μg/kg/min or 0.03 μg/kg/min, or standard therapy (consisting of a single intravenous vasoactive agent used for the short-term management of ADHF according to the discretion of the attending physician). Nesiritide administration could be continued for up to 7 days. In all patients, intravenous diuretics and oral medications could be added at any time. The prespecified outcome parameters were global clinical status and clinical symptoms. The median duration of infusion in the nesiritide groups was 30.4 hours. In the standard therapy group, 57% of patients received dobutamine, 19% received milrinone, 18% received nitroglycerin, 6% received dopamine and 1% received amrinone. Global clinical status, dyspnoea and fatigue improved in all three treatment groups, with no significant differences between treatment groups at 6 hours, 24 hours and the end of therapy. Weight loss was similar in the three treatment groups. However, intravenous diuretics were required in fewer nesiritide (84% and 74% for the 0.015 μg/kg/min and 0.03 μg/kg/min groups, respectively) than standard therapy (96%) recipients ($p < 0.001$ for both nesiritide vs standard therapy comparisons).

The PRECEDENT (Prospective Randomized Evaluation of Cardiac Ectopy with Dobutamine or Natrecor Therapy) study[34,83] was an open-label, multicentre, active-controlled evaluation of nesiritide therapy in 246 treated patients hospitalised for ADHF (100% NYHA class III or IV) for which single-agent, intravenous therapy with nesiritide or dobutamine, with or without diuretics, was deemed appropriate. Patients were stratified according to the presence or absence of a known history of ventricular tachycardia and were randomised on a 1 : 1 : 1 basis to nesiritide 0.015 μg/kg/min or 0.03 μg/kg/min, or dobutamine ≥5 μg/kg/min. The minimum infusion duration was 24 hours, during which time no additional intravenous vasoactive medications were permitted. The median infusion duration was 24.1 hours. All patients had 3-channel, 24-hour Holter monitor recordings for the 24 hours immediately before (baseline) and after initiation of study drug. The primary outcome parameters were changes from baseline in mean heart rate, mean hourly premature ventricular beats and mean hourly repetitive beats. Secondary outcome parameters included the frequency of ventricular tachycardia, triplets and couplets. Proarrhythmia was assessed using two previously established criteria, as described by Velebit et al.[85] and in the CAPS (Cardiac Arrhythmia Pilot Study) trial.[86] At baseline, all three treatment groups had similar heart rates and rates of ventricular ectopy. During treatment, heart rate and ventricular ectopy were increased significantly from baseline in patients receiving dobutamine but not in those receiving nesiritide (table II).[34] Velebit proarrhythmia criteria were met by 23% of patients receiving dobutamine versus 2% of patients receiving nesiritide ($p < 0.001$), and CAPS proarrhythmia criteria were met by 10% of patients receiving dobutamine versus 0% of patients receiving nesiritide ($p = 0.001$).

The VMAC (Vasodilation in the Management of Acute Congestive Heart Failure) trial[9,83] was a double-blind, multicentre, placebo- and active-controlled evaluation of nesiritide therapy in 489 patients with dyspnoea at rest or with minimal activity due to decompensated heart failure that was sufficiently serious to require hospitalisation and intravenous therapy. Patients were stratified based on the investigator's decision to use a right heart catheter as part of the management regimen and were randomised within these strata to therapy with nesiritide (0.01 μg/kg/min fixed dose in the non-catheterised strata; fixed- or adjustable-dose nesiritide in the catheterised strata), nitroglycerin (glyceryl trinitrate) [adjustable dose] or placebo for the initial 3 hours, after which patients receiving placebo were randomly crossed over to nesiritide (fixed dose) or nitroglycerin therapy. The minimum infusion duration was 24 hours, and the median duration of infu-

Table II. Effects of study drug on heart rate and ventricular ectopy in the PRECEDENT trial [this table was published in Burger et al. Effect of nesiritide (B-type natriuretic peptide) and dobutamine on ventricular arrhythmias in the treatment of patients with acutely decompensated congestive heart failure: The PRECEDENT Study. Am Heart J 2002; 144 (6): 1102-8,[34] Copyright Elsevier 2002]

Outcome	Mean change from baseline (SD)		
	nesiritide		dobutamine
	0.015 μg/kg/min (n = 84)	0.03 μg/kg/min (n = 79)	(n = 83)
Average heart rate (beats/min)	−0.7 (6)***	1.2 (7)**	5.1 (8)
Time in tachycardia (h)	−0.1 (4.2)*	0.8 (3.5)	1.7 (5.3)
Ventricular tachycardia/24h	−5.6 (17)***	1.5 (60)***	48 (205)
Triplets/24h	−5 (15)***	3 (38)*	22 (86)
Couplets/24h	−51.6 (200)***	38 (317)*	68 (427)
Repetitive beats/24h	−5.1 (19)***	3.3 (34)***	15 (53)
Premature ventricular beats/h	−13 (83)***	−5.2 (96)*	69 (214)

* $p < 0.05$; ** $p = 0.002$; *** $p \leq 0.001$ vs dobutamine.

sion 24.3 hours. Primary outcome parameters were the absolute change in PCWP (catheterised patients) and self-assessment of dyspnoea (all patients) at 3 hours. Secondary outcome parameters included change in PCWP and self-assessment of dyspnoea and global clinical status at 24 hours. At 3 hours, the mean change in PCWP was −2mm Hg in patients randomised to placebo, −3.8mm Hg in patients randomised to nitroglycerin ($p = 0.09$ vs placebo) and −5.8mm Hg in patients randomised to nesiritide ($p < 0.001$ vs placebo; $p = 0.03$ vs nitroglycerin). In addition, at 3 hours, nesiritide produced a significant decrease in dyspnoea compared with placebo ($p = 0.03$) but not nitroglycerin ($p = 0.56$). At 24 hours, patients randomised to nesiritide had a significantly greater reduction in PCWP (−8.2mm Hg) than those randomised to nitroglycerin (−6.3mm Hg; $p = 0.04$), with no significant difference in dyspnoea ($p = 0.13$). Whether global clinical status differed significantly at 24 hours depended on the statistical test employed (2-way ANOVA: $p = 0.04$; Van-Elteren test: $p = 0.08$).

The PROACTION (Prospective Randomized Outcomes Study of Acutely Decompensated Congestive Heart Failure Treated Initially as Outpatients with Nesiritide) trial[83,84,87] was a double-blind, placebo-controlled, multicentre evaluation of nesiritide therapy in 237 emergency department/observation unit patients with dyspnoea at rest or with minimal activity (walking <20 feet) due to decompensated heart failure. Patients were randomised on a 1 : 1 basis to receive standard care plus nesiritide 0.01 μg/kg/min or placebo, with study medication initiated within 3 hours of presentation to the emergency department and continued for a minimum of 12 hours. The median infusion duration was 16.9 hours. Standard care was at the investigator's discretion and could include diuretics, oxygen and ≥1 medication to reduce systemic vascular resistance and improve cardiac contractility. The primary outcome parameters were the safety profile and clinical effects of nesiritide when added to standard care in the emergency department/observation unit setting. Compared with placebo, patients who received nesiritide had small, statistically insignificant reductions in the requirement for inpatient admission (49% vs 55%, respectively; $p = 0.44$) and mean total hospital length of stay if admitted (5.1 days vs 5.5 days, respectively; $p = 0.62$). Of the patients admitted at the index hospitalisation, those who received nesiritide had fewer readmissions than those who received placebo (10% vs 23%, respectively; $p = 0.06$) and a significantly shorter mean total duration of hospitalisation through to study day 30, either including (5.5 days vs 10.2 days, respectively; $p = 0.05$) or excluding (2.5 days vs 6.5 days, respectively; $p = 0.03$) the duration of the index hospitalisation.[84] Eight patients enrolled in the PROACTION trial died from all causes within 30 days after commencement of treatment, seven (5.9%) in the nesiritide group and one (0.9%) in the placebo group (HR 7.03; 95% CI 0.87, 57.15; $p = 0.066$).[88] A narrowing of the difference in all-cause mortality between the nesiritide and placebo treatment groups was

observed at the 180-day time point: 24 (20.6%) patients receiving nesiritide and 20 (17.5%) patients receiving placebo died (HR 1.24; 95% CI 0.68, 2.24; p = 0.479).[88]

3.1 Therapeutic Summary

Nesiritide effectively reduces symptoms and improves haemodynamic parameters in adults with ADHF who are congested at rest and not hypotensive. There are no data to suggest that nesiritide impacts on rehospitalisation or improves mortality. Concerns regarding mortality risk remain and will be more completely addressed in the ASCEND-HF (Acute Study of Clinical Effectiveness of Nesiritide in Subjects with Decompensated Heart Failure) trial, a planned 7000-patient international randomised, double-blind, placebo-controlled trial. Currently, the available data do not suggest a meaningful difference between nesiritide and other available vasodilators with respect to clinical endpoints, other than for a reduction in PCWP. Additional therapeutic uses of nesiritide are currently being studied and include advanced chronic heart failure, postcardiopulmonary bypass during cardiac surgery, in-hospital management for patients awaiting cardiac transplantation, pulmonary hypertension and various forms of cardiac dysfunction in children. However, nesiritide is not indicated for any of these alternative disease states and its use should be limited to patients with ADHF.

4. Nesiritide: Safety Profile

4.1 Overview

Resolution of questions regarding the safety of nesiritide remains an evolutionary process. The greatest concerns have been generated in relation to drug-induced renal insufficiency and 30-day mortality rates after treatment with nesiritide. However, the most frequently reported adverse effects are hypotension and an excessively decreased PCWP; these effects are dose related and consistent with the pharmacological action of the drug.[9,34,47,48] These effects are consistent with those of other vasodilators used in the treatment of ADHF. During the 3-hour placebo-controlled phase of the VMAC trial, significantly fewer overall adverse events occurred in patients randomised to nesiritide than in those randomised to nitroglycerin (p = 0.04).[9] In addition, there were no significant differences in the frequency or severity of ischaemic events, asymptomatic hypotension, symptomatic hypotension or arrhythmias between patients randomised to nesiritide and those randomised to nitroglycerin during the initial 24 hours.

4.2 Haemodynamics

Similar to other vasodilators, nesiritide produces dose-related hypotension. Since early evaluations of nesiritide used a higher dose than the currently approved starting dose (0.01 μg/kg/min), the frequency and potential complications of this hypotension were more pronounced in those evaluations. In the study by Mills et al.,[48] symptomatic hypotension developed in 5%, 4% and 15% of patients receiving 0.015 μg/kg/min, 0.03 μg/kg/min and 0.06 μg/kg/min of nesiritide, respectively, compared with 7% of patients receiving placebo (p = 0.35). In the Efficacy trial,[47] 2% and 5% of patients randomised to nesiritide 0.015 μg/kg/min and 0.03 μg/kg/min, respectively, developed symptomatic hypotension, versus no patients randomised to placebo (p = 0.55). In the Comparative trial, symptomatic hypotension developed in 11% and 17% and required drug discontinuation in 5% and 10% of patients randomised to nesiritide 0.015 μg/kg/min and 0.03 μg/kg/min, respectively, compared with a 4% prevalence and no discontinuations for symptomatic hypotension in patients randomised to 'standard therapy' (p = 0.008 for development of symptomatic hypotension).[47] Finally, in the PRECEDENT study,[34] symptomatic hypotension developed in 17% and 24% of patients randomised to nesiritide 0.015 μg/kg/min and 0.03 μg/kg/min, respectively, compared with 2% of patients randomised to dobutamine (p < 0.001).

The prevalence of symptomatic hypotension in trials using the currently approved starting dose of nesiritide is similar to that seen with other heart failure therapies. In the VMAC trial, symptomatic hypotension developed in 4% of patients randomis-

ed to nesiritide versus 5% of patients randomised to nitroglycerin ($p > 0.99$).[9] However, because of the longer half-life of nesiritide (18 minutes) compared with that of nitroglycerin (≈3 minutes), the mean duration of symptomatic hypotension, when it did occur, was significantly longer in patients randomised to nesiritide (2.2 hours) compared with nitroglycerin (0.7 hours; $p = 0.002$). During the initial 12-hour treatment phase in the PROACTION trial, the frequency of symptomatic hypotension was not significantly different between nesiritide (2%) and standard care (1%) patients ($p > 0.99$).[84,87] All episodes of symptomatic hypotension lasted ≤1 hour and resolved without intervention. In addition, the degree of blood pressure reduction in patients receiving nesiritide was related directly to baseline blood pressure; that is, the greatest reduction in blood pressure occurred in those patients with the greatest degree of baseline hypertension. Overall, the mean reductions in systolic blood pressure with nesiritide were 1.2mm Hg, 12.3mm Hg and 28.7mm Hg in patients with baseline systolic blood pressures <101mm Hg, 101–140mm Hg and >140mm Hg, respectively.[87] It should be noted that even at currently recommended doses, nesiritide may still cause hypotension which may be profound and sustained. While being treated with nesiritide, patients should undergo frequent blood pressure monitoring.

4.3 Arrhythmogenesis

In the Comparative study,[47] the incidence of nonsustained ventricular tachycardia was higher in patients receiving nesiritide (10% in the nesiritide 0.015 μg/kg/min treatment group, 1% in the nesiritide 0.03 μg/kg/min treatment group and 8% in the standard therapy group; $p < 0.02$); however, there was no difference in the incidence of sustained ventricular tachycardia. In the PRECEDENT study,[34] patients receiving the 0.03 μg/kg/min dose of nesiritide experienced more ventricular extrasystoles (6% vs 4%, respectively) and tachycardia (3% vs 1%, respectively) compared with those patients receiving the 0.015 μg/kg/min dose of nesiritide; however, the incidence of nonsustained ventricular tachycardia was not higher (5% vs 6%, respectively). There were no significant differences in the frequency of arrhythmias between nitroglycerin and nesiritide groups in the VMAC trial.[9] Overall, nesiritide is not associated with increased arrhythmogenesis.

4.4 Renal Function

Nesiritide is associated with an increased risk of acute serum creatinine elevation.[73,76] This acute increase in serum creatinine may be a haemodynamic consequence of blood pressure reduction in patients who are volume depleted or exposed to higher-dose diuretic therapy during treatment with nesiritide and/or have underlying kidney dysfunction with loss of renal autoregulatory capability.[70,71,80,89-92] The risk of an acute increase in serum creatinine paralleled the prevalence of symptomatic hypotension in an analysis of pooled data from five nesiritide trials.[71] In an analysis of data from the VMAC trial, the risk of an acute increase in serum creatinine was significantly related to baseline renal insufficiency.[92]

In the VMAC trial, nesiritide was not associated with an increased risk of acute serum creatinine elevation in patients who were receiving low-to-moderate-dose diuretics.[70] In those patients who were receiving high-dose diuretics, defined as a maximum daily dose of furosemide >160mg, bumetanide >4mg, torsemide >80mg, metolazone >10mg, chlorothiazide >1000mg, hydrochlorothiazide >50mg or concurrent treatment with ≥2 of these diuretics regardless of dose, nesiritide was associated with an increased risk of acute serum creatinine elevation.

The risk of acute serum creatinine elevation in patients receiving nesiritide is dose-related; consequently, this effect was seen more often in early trials that used dosages higher than the currently approved starting dose of nesiritide.[71] The risk of acute serum creatinine elevation is less at the currently approved starting dose but does not disappear.[71] In the VMAC trial, the frequency, onset and persistence of acute in-hospital serum creatinine elevations in patients randomised to nesiritide were similar to those in patients randomised to nitroglyc-

Table III. Kaplan-Meier estimates of mortality in randomised controlled trials of nesiritide in heart failure

Study	Control	30-day mortality		180-day mortality	
		nesiritide (%)	control (%)	nesiritide (%)	control (%)
Mills et al.[48]	Placebo	2.7	7.5	NA	NA
Efficacy trial[47]	Placebo	5.9	4.8	23.1	19.3
Comparative trial[47]	Standard care[a]	6.9	4.9	20.8	23.5
PRECEDENT[34]	Dobutamine	3.7	6.1	16.3	22.2
VMAC[9]	Nitroglycerin (glyceryl trinitrate) or placebo	8.1	5.1	25.1	20.8
PROACTION[84]	Standard care[b]	4.2	0.9	NA	NA
FUSION I[61]	Standard care[c]	1.4	2.9	9.4	13.5
Pooled (6 studies)[9,34,47,48,84]		5.9	4.4	NA	NA
Pooled (7 studies)[9,34,47,48,61,84]		5.3	4.3	NA	NA
Pooled (4 studies)[9,34,47]		NA	NA	21.7	21.5

a A single intravenous vasoactive agent used for the short-term management of acute decompensated heart failure according to the discretion of the attending physician.

b Standard care was at the investigator's discretion and could include diuretics, oxygen and ≥1 medication to reduce systemic vascular resistance and improve cardiac contractility.

c Standard care could also include inotropes and antiarrhythmics at the investigator's discretion.

NA = not applicable.

erin.[92,93] Most of these elevations were transient, with approximately 90% resolving within 30 days of institution of either nesiritide or nitroglycerin therapy.[93]

In an analysis of data pooled from 5 randomised nesiritide trials, mortality was assessed at 30 days after nesiritide or control treatment as a function of change in renal indices. In those patients with a serum creatinine increase >0.5 mg/dL who were treated with nesiritide, the HR for 30-day mortality was 1.1 compared with those treated with nesiritide without a serum creatinine increase. In those patients treated with other parenteral therapies who had a serum creatinine increase of >0.5 mg/dL, the HR was 3.4 for 30-day mortality risk compared with those without a serum creatinine increase who were treated with other parenteral therapies.[94] In the VMAC experience, the 30-day mortality rate for patients with a serum creatinine increase >0.5 mg/dL was 8.2% on nesiritide and 11.1% on standard therapy.[9] Risk of dialysis and medical intervention for worsening renal function (serum creatinine increase >0.5 mg/dL) were also compared in this meta-analysis of 5 randomised nesiritide studies that included 1269 patients.[73] This showed that 11.1% (32 of 288) of nesiritide patients compared with 4.2% (6 of 144) of control patients required medical intervention (RR 2.29; 95% CI 1.07, 4.89; p = 0.03); however, there was no difference in the need for dialysis between therapies.

Clearly, more data are required to resolve the significance of observed changes in renal function during nesiritide therapy and their possible relationship to adverse clinical outcomes.

4.5 Mortality

The effect of nesiritide on mortality risk is the most worrisome concern and is currently unresolved and may be difficult to definitively determine from existing databases. The therapeutic trials reviewed above all incorporated a short duration of nesiritide therapy, had numerous confounding factors and low background mortality rates. Importantly, none of the trials was designed or powered to assess mortality.

A pooled analysis of data from three nesiritide trials involving 862 patients reported that nesiritide may be associated with a non-statistically significant increase in 30-day mortality risk compared with other non-inotrope-based control therapies.[95] In this analysis, the 30-day mortality HR for nesiritide therapy after adjustment for study was 1.80 (95% CI 0.98, 3.31; p = 0.06). However, this pooled analysis

has several significant limitations that may have influenced these results. The trials included in this analysis were not designed or powered to assess mortality. There are also substantial differences both between studies and between treatment groups within these studies in mortality risk factors, including heart failure severity, prevalence of acute coronary syndromes and concomitant therapies. These variables are either uncontrolled or inadequately controlled for in this analysis.[92,96] In the VMAC trial, which accounts for >50% of the patients in this pooled analysis, there was significantly greater concomitant use of dobutamine in patients randomised to nesiritide compared with nitroglycerin,[96] and overall in the three trials, inotrope use was greater in patients randomised to nesiritide compared with controls both before and during study drug infusion.[92] In addition, in the VMAC trial, use of class III antiarrhythmic agents was significantly greater in patients randomised to nesiritide compared with those randomised to nitroglycerin, and the patients receiving nesiritide would therefore have been more susceptible to the proarrhythmic and negative inotropic effects of anti-arrhythmic therapy.[96]

In yet another meta-analysis, nesiritide therapy was again associated with a non-statistically significant trend for an increase in 30-day (HR 1.34; 95% CI 0.84, 2.15; p = 0.22) but not 6-month (HR 1.05; 95% CI 0.81, 1.36; p = 0.73) mortality risk.[97] This was a pooled analysis of data from all 1507 patients who have participated in randomised, controlled clinical trials evaluating nesiritide infusion therapy for patients hospitalised with ADHF (table III). However, these data were also not adjusted for baseline differences in mortality risk factors between treatment groups.[97,98] Adjusting for these baseline differences reduces the mortality HRs associated with nesiritide therapy from 1.34 (95% CI 0.84, 2.15) to 1.18 (95% CI 0.74, 1.90; p = 0.49) at 30 days and from 1.05 (95% CI 0.81, 1.36) to 0.98 (95% CI 0.75, 1.26; p = 0.85) at 6 months in this pooled analysis.[97]

Since the original publication of the PROACTION data, two additional deaths have been discovered *post hoc* and both occurred within the 30-day window.[88,99] These events have necessarily changed the calculated risk of death in that trial to an HR of 7.03 (95% CI 0.87, 57.17). A repeat of the original meta-analysis that identified the concerns regarding mortality has been completed with a renewed HR of 1.93 (95% CI 1.06, 3.52).[99]

Several recent retrospective evaluations suggest a neutral effect of nesiritide on mortality. In an analysis of data from the ADHERE® registry involving >15 000 hospitalisations for ADHF requiring intravenous vasoactive therapy with nesiritide (n = 5220), nitroglycerin (n = 6549), dobutamine (n = 4226) or milrinone (n = 2021), vasodilatory therapy with nesiritide or nitroglycerin was associated with significant reductions in risk-adjusted in-hospital mortality compared with inotropic therapy with dobutamine or milrinone, but no significant difference in risk-adjusted mortality between nesiritide and nitroglycerin therapy (table IV).[31] Similarly, nesiritide significantly reduced in-hospital mortality risk compared with milrinone (adjusted OR 0.24; p < 0.001) or dobutamine (adjusted OR 0.29; p < 0.001) in a retrospective cohort analysis of data from 2130 patients with ADHF treated with nesiritide (n = 386), milrinone (n = 433) or dobutamine

Table IV. In-hospital mortality odds ratios for vasoactive therapies in Acute Decompensated Heart Failure National Registry (ADHERE®) [Copyright © MedReviews, LLC. Reprinted with permission of MedReviews, LLC. Abraham WT, et al. In-hospital mortality in patients with acute decompensated heart failure treated with intravenous vasoactive medications: an analysis from the Acute Decompensated Heart Failure National Registry (ADHERE). J Am Coll Cardiol 2005; 46 (1).[31] *Journal of the American College of Cardiology* is a copyrighted publication of MedReviews, LLC. All rights reserved]

Comparison	Odds ratio[a]	95% CI
Nesiritide vs		
Nitroglycerin (glyceryl trinitrate)	0.94	0.77, 1.16
Dobutamine	0.47	0.39, 0.56
Milrinone	0.59	0.48, 0.73
Nitroglycerin vs		
Dobutamine	0.46	0.37, 0.57
Milrinone	0.69	0.53, 0.89
Dobutamine vs		
Milrinone	1.24	1.03, 1.55

a Adjusted for covariates and propensity score.

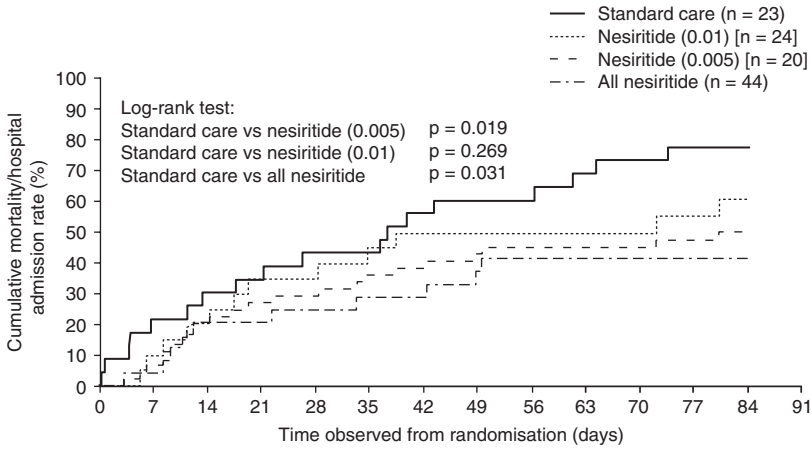

Fig. 1. Combined mortality/hospital admission in high-risk patients enrolled in the FUSION I trial (reproduced from Yancy et al.,[101] figure 6, copyright 2005, with kind permission of Springer Science and Business Media).

(n = 1311) at 32 academic health centres.[32] Nesiritide had a neutral effect on 3-month mortality versus standard care in a retrospective evaluation of 127 patients with ADHF in a community hospital setting.[100]

In the FUSION I (Follow Up Serial Infusions Of Natrecor) trial, serial infusions of nesiritide over a 12-week period had a neutral effect on all-cause mortality compared with usual care in the overall study population (nesiritide 6% vs usual care 10%; p = 0.31) [figure 1],[101] with a trend for mortality risk reduction in the prospectively defined high-risk subgroup (nesiritide 5% vs usual care 17%; p = 0.08).[61] However, 58% of patients given usual care received an intravenous inotropic agent during one or more study visits because of clinical evidence of decompensated heart failure, compared with <2% of nesiritide patients, and this difference in inotrope administration may have significantly influenced these mortality results.

4.6 Safety Summary

Nesiritide produces dose-related hypotension, which at the currently approved starting dose appears to be similar in terms of frequency to that of other intravenous vasodilators. Nesiritide may cause an acute increase in serum creatinine levels. The in-hospital mortality risk of nesiritide may be elevated when compared with non-inotrope treatment regimens but may also be similar to that of other vasodilator therapies used for ADHF. Outcomes with nesiritide in patients with ADHF appear better than those associated with inotropic therapy. Data concerning short-term (≤30-day) mortality risk are conflicting and require further study. Long-term data (3 and 6 months) fail to demonstrate any mortality signal.

These questions are being addressed in the ASCEND-HF trial, which will assess both a short-term in-hospital symptom relief endpoint and 30-day mortality and rehospitalisation outcomes.

Table V. Recommendations on the use of nesiritide made by an expert panel of independent cardiology and heart failure clinicians in June 2005

Use of nesiritide should be strictly limited to patients presenting to the hospital with ADHF who have dyspnoea at rest
Physicians considering use of nesiritide should consider its efficacy in reducing dyspnoea, the possible risks of the drug and the availability of alternate therapies to relieve the symptoms of congestive heart failure
Nesiritide should *not* be used to replace diuretics. Furthermore, because no sufficient evidence is currently available to demonstrate benefit for the applications listed below, nesiritide should *not* be used: for intermittent outpatient infusion; for scheduled repetitive use; to improve renal function; or to enhance diuresis

ADHF = acute decompensated heart failure.

Table VI. Practice guidelines on the evaluation and management of patients with acute decompensated heart failure (ADHF)[16]

General recommendations
Patients admitted with ADHF and evidence of fluid overload should be treated initially with loop diuretics
When congestion fails to improve in response to diuretic therapy, the following options should be considered:
sodium and fluid restriction
increased doses of loop diuretics
continuous infusion of a loop diuretic
addition of a second type of diuretic
ultrafiltration
In the absence of symptomatic hypotension, intravenous nitroglycerin, nitroprusside, or nesiritide may be considered as an addition to diuretic therapy for rapid improvement of congestive symptoms in patients with ADHF
Specific recommendations
In the absence of hypotension, IV nitroglycerin, sodium nitroprusside or nesiritide may be considered as an addition to diuretic therapy for rapid improvement of congestive symptoms in patients admitted with ADHF
Intravenous vasodilators (nitroglycerin or nitroprusside) and diuretics are recommended for rapid relief in patients with acute pulmonary oedema or severe hypertension
Intravenous vasodilators, (nitroprusside, nitroglycerin or nesiritide) may be considered in patients with ADHF and advanced heart failure who have persistent severe heart failure despite aggressive treatment with diuretics and standard oral therapies
Intravenous inotropes (milrinone or dobutamine) may be considered to relieve symptoms and improve end-organ function in patients with advanced heart failure

IV = intravenous.

5. Conclusions

Nesiritide is structurally similar to the endogenous B-type natriuretic peptide released by the myocardium in response to pressure and volume overload. It induces balanced vasodilation, inhibits neurohormonal activation and, in some individuals, promotes natriuresis and diuresis without adverse inotropic or chronotropic effects. In adults with ADHF, nesiritide reduces symptoms and improves haemodynamic parameters. Nesiritide is generally safe and well tolerated when used at appropriate doses and in the absence of hypotension. Its chief adverse event is dose-related hypotension. In addition, nesiritide can cause an acute increase in serum creatinine level that appears to be a haemodynamic response to volume depletion, vasodilator-induced hypotension, concomitant diuretic therapy and neurohormonal inhibition at the level of the kidney. Even though this increase is usually transient and does not seem to adversely affect mortality, its precise impact on mortality remains unresolved. The currently available randomised, controlled clinical trials are inadequate to resolve the effects of nesiritide on mortality. Future and pending trials powered to determine the mortality risk of nesiritide for ADHF are needed. In June 2005, an expert panel of independent cardiology and heart failure clinicians was convened by Scios Inc. to provide guidance and counsel on the ongoing and planned clinical development programme for nesiritide, as well as recommendations for its use (table V).[102] Based on currently available data, nesiritide remains one of several vasodilating treatment options for patients with ADHF. The use of vasodilatory therapy for ADHF should follow current guideline recommendations (table VI).[16] Remaining questions regarding potential risk with nesiritide await the acquisition of more prospective data from adequately powered studies.

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