Original Investigation

Low-Dose Dopamine or Low-Dose Nesiritide in Acute Heart Failure With Renal Dysfunction
The ROSE Acute Heart Failure Randomized Trial

Horng H. Chen, MBBCh; Kevin J. Anstrom, PhD; Michael M. Givertz, MD; Lynne W. Stevenson, MD; Marc J. Semigran, MD; Steven R. Goldsmith, MD; Bradley A. Bart, MD; David A. Bull, MD; Josef Stehlik, MD; Martin M. LeWinter, MD; Marvin A. Konstam, MD; Gordon S. Huggins, MD; Jean L. Rouleau, MD; Eileen O'Meara, MD; W. H. Wilson Tang, MD; Randall C. Starling, MD, MPH; Javed Butler, MD, MPH; Anita Deswal, MD; G. Michael Felker, MD; Christopher M. O'Connor, MD; Raphael E. Bonita, MD, ScM; Kenneth B. Margulies, MD; Thomas P. Cappola, MD, ScM; Elizabeth O. Ofili, MD; Douglas L. Mann, MD; Víctor G. Dávila-Román, MD; Steven E. McNulty, MS; Barry A. Borlaug, MD; Eric J. Velazquez, MD; Kerry L. Lee, PhD; Monica R. Shah, MD, MHS, MSJ; Adrian F. Hernandez, MD, MHS; Eugene Braunwald, MD; Margaret M. Redfield, MD; for the NHLBI Heart Failure Clinical Research Network

IMPORTANCE Small studies suggest that low-dose dopamine or low-dose nesiritide may enhance decongestion and preserve renal function in patients with acute heart failure and renal dysfunction; however, neither strategy has been rigorously tested.

OBJECTIVE To test the 2 independent hypotheses that, compared with placebo, addition of low-dose dopamine (2 μg/kg/min) or low-dose nesiritide (0.005 μg/kg/min without bolus) to diuretic therapy will enhance decongestion and preserve renal function in patients with acute heart failure and renal dysfunction.

DESIGN, SETTING, AND PARTICIPANTS Multicenter, double-blind, placebo-controlled clinical trial (Renal Optimization Strategies Evaluation [ROSE]) of 360 hospitalized patients with acute heart failure and renal dysfunction (estimated glomerular filtration rate of 15-60 mL/min/1.73 m^2), randomized within 24 hours of admission. Enrollment occurred from September 2010 to March 2013 across 26 sites in North America.

INTERVENTIONS Participants were randomized in an open, 1:1 allocation ratio to the dopamine or nesiritide strategy. Within each strategy, participants were randomized in a double-blind, 2:1 ratio to active treatment or placebo. The dopamine (n = 122) and nesiritide (n = 119) groups were independently compared with the pooled placebo group (n = 119).

MAIN OUTCOMES AND MEASURES Coprimary end points included 72-hour cumulative urine volume (decongestion end point) and the change in serum cystatin C from enrollment to 72 hours (renal function end point).

RESULTS Compared with placebo, low-dose dopamine had no significant effect on 72-hour cumulative urine volume (dopamine, 8524 mL; 95% CI, 7917-9131 vs placebo, 8296 mL; 95% CI, 7762-8830 ; difference, 229 mL; 95% CI, −714 to 1171 mL; P = .59) or on the change in cystatin C level (dopamine, 0.12 mg/L; 95% CI, 0.06-0.18 vs placebo, 0.11 mg/L; 95% CI, 0.06-0.16; difference, 0.01; 95% CI, −0.08 to 0.10; P = .72). Similarly, low-dose nesiritide had no significant effect on 72-hour cumulative urine volume (nesiritide, 8574 mL; 95% CI, 8014-9134 vs placebo, 8296mL; 95% CI, 7762-8830; difference, 279 mL; 95% CI, −618 to 1176 mL; P = .49) or on the change in cystatin C level (nesiritide, 0.07 mg/L; 95% CI, 0.01-0.13 vs placebo, 0.11 mg/L; 95% CI, 0.06-0.16; difference, −0.04; 95% CI, −0.13 to 0.05; P = .36). Compared with placebo, there was no effect of low-dose dopamine or nesiritide on secondary end points reflective of decongestion, renal function, or clinical outcomes.

CONCLUSION AND RELEVANCE In participants with acute heart failure and renal dysfunction, neither low-dose dopamine nor low-dose nesiritide enhanced decongestion or improved renal function when added to diuretic therapy.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT01132846

JAMA. 2013;310(23):2533-2543. doi:10.1001/jama.2013.282190
Published online November 18, 2013.

Copyright 2013 American Medical Association. All rights reserved.

Supplemental content at jama.com

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: A complete list of the NHLBI Heart Failure Clinical Research Network appears in eAppendix 1 in the Supplement.

Corresponding Author: Horng H. Chen, MBBCh, Mayo Clinic Cardiovascular Research, Guggenheim 9, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (chen.horng@mayo.edu).

Downloaded From: http://jama.jamanetwork.com/ on 07/30/2016

A primary treatment goal in acute heart failure is to achieve adequate decongestion while avoiding renal dysfunction and other adverse effects.[1,2] Patients with acute heart failure and moderate or severe renal dysfunction are at risk for inadequate decongestion and worsening renal function, both of which are associated with worse outcomes.[3] Renal adjuvant therapies that enhance decongestion and preserve renal function during treatment of acute heart failure are needed.[2,4]

Dopamine is an endogenous catecholamine that, at low doses (≤3 μg/kg/min), may selectively activate dopamine receptors and promote renal vasodilatation.[5,6] Previous studies have suggested that the addition of low-dose dopamine to diuretic therapy enhances decongestion and preserves renal function during diuretic therapy in acute heart failure; however, these studies were small, with variable study designs and dopamine doses.[7-9]

B-type natriuretic peptide is a cardiac peptide with vasodilating, renin- and aldosterone-inhibiting, natriuretic, and diuretic properties.[10] Nesiritide is human recombinant B-type natriuretic peptide and is approved for management of acute heart failure. The recommended dose is a 2-μg/kg bolus followed by infusion at 0.01 μg/kg/min. This dose decreases blood pressure and atrial pressures and produces modest improvement in dyspnea, but does not favorably affect clinical outcomes or renal function, potentially because of its hypotensive effects.[11-13] Small studies using low-dose nesiritide (0.005 μg/kg/min without bolus) in acute heart failure and cardiac surgery patients have demonstrated favorable effects on urine output and renal function.[14,15]

The Renal Optimization Strategies Evaluation (ROSE) trial used a novel study design to test 2 independent hypotheses; namely, as compared with placebo, the addition of low-dose dopamine (2 μg/kg/min; hypothesis 1) or low-dose nesiritide (0.005 μg/kg/min without bolus; hypothesis 2) to diuretic therapy will enhance decongestion and preserve renal function in patients with acute heart failure and renal dysfunction.

Methods

Study Oversight

All study participants provided written informed consent. The National Heart, Lung, and Blood Institute (NHLBI)-sponsored Heart Failure Clinical Research Network investigators conceived, designed, and conducted the ROSE trial. The study protocol and the statistical analysis plan are available in eAppendixes 2 and 3 in the Supplement. The trial protocol was approved by an NHLBI-appointed protocol review committee and data and safety monitoring board and by the institutional review board at each participating site. The Duke Clinical Research Institute served as the data coordinating center.

Study Design

The rationale and design of the ROSE trial have been previously described.[16] Briefly, patients (n = 360) hospitalized for the treatment of acute heart failure who had renal dysfunction (glomerular filtration rate of 15-60 mL/min/1.73 m^2 as estimated by the Modification of Diet in Renal Disease equation) at admission were enrolled within 24 hours of admission. The diagnosis of acute heart failure was based on at least 1 symptom (dyspnea, orthopnea, or edema) and 1 sign of heart failure (rales, edema, ascites, or pulmonary vascular congestion on chest radiography) regardless of ejection fraction. Additional entry criteria are listed in eTable 1 in the Supplement.

To test the 2 independent hypotheses while minimizing the number of patients requiring central line placement for dopamine administration, participants were initially randomized 1:1 in an open fashion to the nesiritide or dopamine strategies (**Figure 1**). Participants in the dopamine strategy were randomized in a double-blind 2:1 ratio to low-dose dopamine (2 μg/kg/min for 72 hours, infused via local guideline-stipulated vascular access) or placebo. Participants randomized to the nesiritide strategy were subsequently randomized in a double-blind 2:1 ratio to low-dose nesiritide (0.005 μg/kg/min for 72 hours, infused via peripheral intravenous access without initial bolus) or placebo. A permuted block randomization scheme stratified by clinical site was performed with an automated web-based system. The placebo patients were pooled across the 2 strategies.

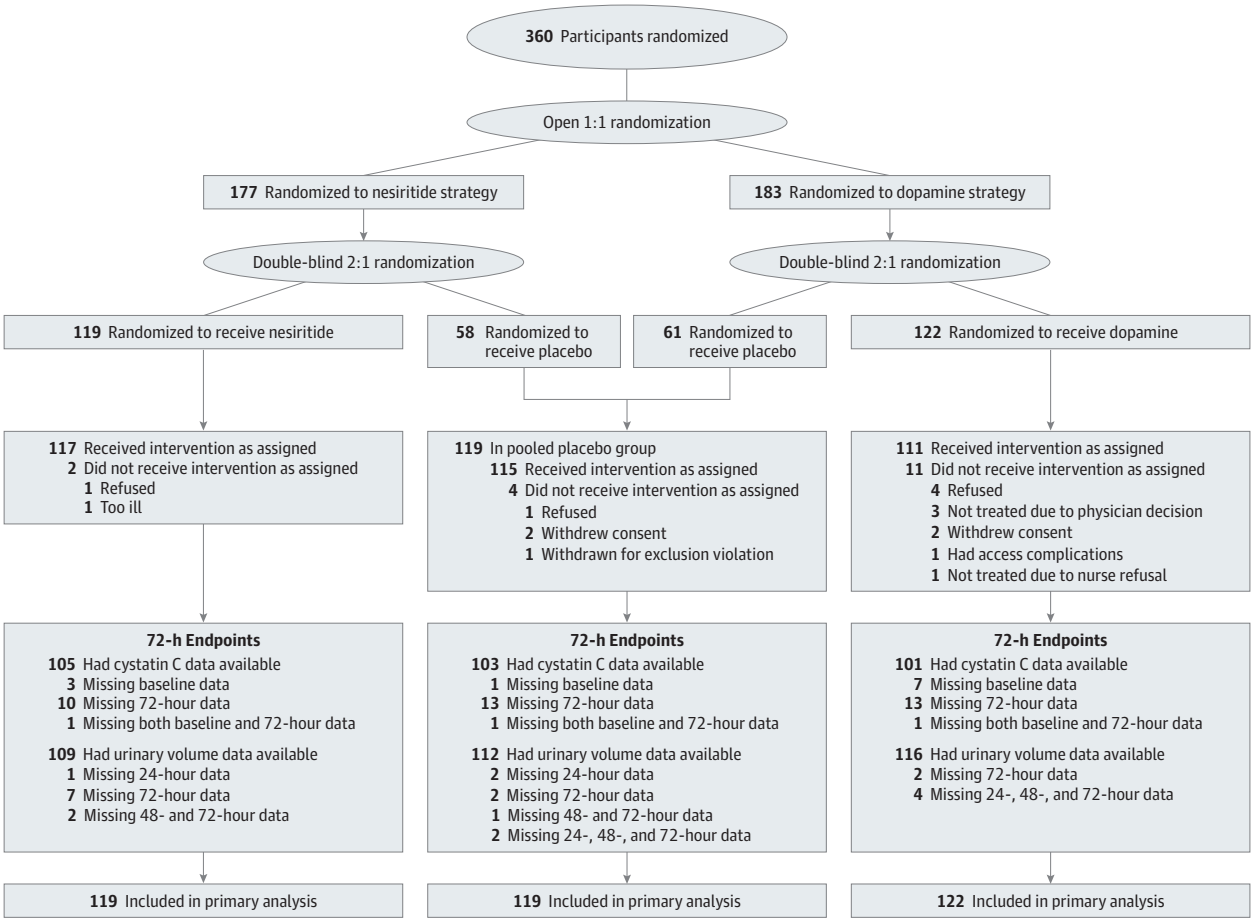
All patients received open-label, intravenous loop diuretic treatment with a recommended total daily dose equal to 2.5 times the total daily oral outpatient furosemide (or equivalent) dose at 7 days before admission, up to a maximum of 600 mg/d. Patients naive to outpatient loop diuretics received intravenous furosemide at 80 mg/d. Half the total daily diuretic dose was administered as a bolus twice daily for at least 24 hours. Use of other medications and diuretic dosing after 24 hours were at the discretion of the clinician. All patients received a 2000-mg sodium diet and 2000-mL fluid restriction in accordance with the Heart Failure Society of America 2010 comprehensive heart failure practice guideline.[1] After the primary end point assessment at 72 hours, study drug was discontinued and subsequent treatment was at the clinician's discretion.

As required in federally funded trials, participant self-identified race and ethnicity was recorded. After consent, participants underwent baseline assessment, which included history and physical examination for signs and symptoms of congestion, recording of cardiovascular medications, measurement of vital signs, phlebotomy for biomarkers (plasma creatinine [traceable to National Institute of Standards and Technology creatinine standard reference material], plasma cystatin C, and plasma N-terminal probrain natriuretic peptide; Heart Failure Clinical Research Network Core Biomarker Laboratory, University of Vermont) and electrolytes (local laboratory), and completion of patient global well-being and dyspnea visual analog scale assessments. Study assessments were repeated at 24, 48, and 72 hours. Daily 24-hour urine collections for volume and urinary sodium excretion were performed for 72 hours. All patients had a telephone assessment of vital status and rehospitalization at 60 and 180 days from randomization.

Copyright 2013 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 07/30/2016

Figure 1. ROSE Patient Flow Diagram



Data on patients screened for eligibility are not available. The primary end points were analyzed with multiple imputation techniques when data were unavailable for the end point.

Trial End Points

The two coprimary end points were the 72-hour cumulative urine volume as an index of decongestion efficacy and the change in cystatin C from randomization to 72 hours as a measure of renal function preservation. A complete list of secondary end points is provided in eTable 2 in the Supplement. Treatment failure was defined as the development of any one of the following during the 72 hours after randomization: type 1 cardiorenal syndrome, as defined by an increase in serum creatinine level of more than 0.3 mg/dL; worsening or persistent heart failure, defined as the need for rescue therapy (additional intravenous vasoactive agent for heart failure treatment, ultrafiltration, or mechanical or respiratory support); significant hypotension requiring discontinuation of study drug; or significant tachycardia requiring discontinuation of study drug.

Statistical Analysis

According to estimates of the variability in the primary outcome measures and missing data rates from previous studies,[17-19] a total sample size of 360 participants would provide 90% power to detect a treatment difference of greater than 1400 mL in cumulative urine volume at 72 hours and 88% power to detect a clinically significant difference (>0.3 mg/L) in the change in cystatin C level between active treatment vs placebo, using a 2-sided .025 level of significance. A difference of 0.3 mg/L in serum cystatin C level is considered to be clinically meaningful because a change in cystatin C level of greater than or equal to 0.3 mg/L at 48 hours in patients hospitalized with acute heart failure was associated with a statistically significant 2-fold increase in 180-day mortality.[20] All treatment comparisons were performed according to the intention-to-treat principle.

General linear models were used to examine the effect of treatment on each coprimary end point, using a type I error rate of .025 for each end point comparison. Treatment comparisons of change in cystatin C level were adjusted for the baseline level. Multiple imputation was used to account for missing data. Sensitivity analyses based on complete data were also performed. For secondary end points, general linear models and logistic regression analysis were used, with significance prespecified at $P < .05$. Time-to-event comparisons were performed with Kaplan-Meier curves, log-rank tests, and Cox proportional hazards mod-

Copyright 2013 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 07/30/2016

Table 1. Baseline Characteristics of the Study Participants According to Treatment Group[a]

Characteristic	Dopamine Strategy		Nesiritide Strategy		Pooled Placebo (n = 119)
	Drug (n = 122)	Placebo (n = 61)	Drug (n = 119)	Placebo (n = 58)	
Age, median (IQR), y	71 (63-80)	72 (63-79)	69 (59-79)	67 (62-77)	70 (62-78)
Male sex, No. (%)	84 (69)	44 (72)	91 (76)	45 (78)	89 (75)
White race, No. (%)	90 (74)	45 (74)	91 (76)	46 (79)	91 (76)
Body mass index, median (IQR)	30.5 (25.4-35.8)	29.9 (26.0-39.4)	31.5 (27.3-37.2)	32.0 (27.6-37.8)	30.9 (26.6-39.1)
Systolic blood pressure, median (IQR), mm Hg	114 (104-127)	117 (106-131)	114 (102-130)	115 (100-125)	116 (103-128)
Edema ≥2+ (scale 0-4+), No./total No. (%)	83/120 (69)	49/61 (80)	79/118 (67)	40/58 (68)	89/119 (75)
Orthopnea, No./total No. (%)	103/116 (89)	56/59 (95)	99/111 (89)	49/57 (86)	105/116 (91)
Jugular venous pressure ≥8 cm water, No./total No. (%)	116/117 (99)	55/59 (93)	106/113 (94)	50/54 (92)	105/113 (93)
Rales, No./total No. (%)	72/120 (60)	31/61 (51)	61/116 (53)	33/57 (58)	64/118 (54)
Ejection fraction, median (IQR), %	35 (23-52)[b]	33 (23-50)	35 (20-55)	25 (20-49)	30 (20-50)
Ejection fraction >50%, No. (%)	30 (25)	13 (21)	38 (32)	13 (22)	26 (22)
Hospitalization for acute HF in previous y, No. (%)	79 (65)	41 (68)	82 (69)	38 (66)	79 (67)
Ischemia as a cause of HF, No. (%)	73 (60)	37 (61)	63 (53)	36 (62)	73 (61)
Diabetes mellitus, No. (%)	71 (58)	41 (67)	62 (52)	26 (45)	67 (56)
History of atrial fibrillation or flutter, No. (%)	78 (64)	38 (62)	65 (55)	34 (59)	72 (61)
Hypertension, No. (%)	97 (80)	50 (82)	100 (84)	51 (88)	101 (85)
Implantable cardioverter-defibrillator, No. (%)	53 (43)	28 (46)	48 (40)	28 (48)	56 (47)
Medications received before hospitalization, No. (%)					
ACE inhibitor or ARB	53 (43)	36 (59)	65 (55)	25 (43)	61 (51)
Hydralazine	26 (21)	11 (18)	19 (16)	12 (21)	23 (19)
Nitrates	33 (27)	18 (30)	27 (23)	12 (21)	30 (25)
β-Blocker	98 (80)	53 (87)	99 (83)	50 (86)	103 (83)
Aldosterone antagonist	34 (28)	20 (33)	39 (33)	16 (28)	36 (30)
Digoxin	26 (21)	18 (30)	30 (25)	15 (26)	33 (28)
Outpatient furosemide-equivalent diuretic, No. (%)	116 (95)	57 (93)	113 (95)	54 (93)	111 (93)
Outpatient furosemide-equivalent dose, median (IQR), mg/d	80 (60-140)	80 (60-130)	80 (60-160)	120 (40-240)	80 (40-160)
Plasma cystatin C, median (IQR), mg/L	1.71 (1.33-2.16)	1.66 (1.35-2.20)	1.66 (1.48-2.13)	1.86 (1.50-2.11)	1.73 (1.43-2.16)
Creatinine, median (IQR), mg/dL	1.59 (1.26-1.97)	1.63 (1.37-1.96)	1.65 (1.34-1.96)	1.70 (1.40-2.06)	1.64 (1.38-2.05)
eGFR, median (IQR), mL/min/1.73 m^2	45.5 (31.2-59.2)	45.1 (32.7-53.1)	43.8 (34.7-55.3)	34.0 (32.6-53.0)	44.5 (32.6-53.0)
Blood urea nitrogen, median (IQR), mg/dL	35 (25-51)	37 (28-50)	38 (28-50)	34 (29-52)	36 (29-52)
NT-proBNP, median (IQR), pg/mL	5760 (2958-11 637)	4349 (1687-9783)	4245 (1847-9100)	6115 (3172-10 851)	5046 (2319-10 091)

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; eGFR, estimated glomerular filtration rate; HF, heart failure; IQR, interquartile range; NT-proBNP, N-terminal probrain natriuretic peptide.

SI conversion factors: To convert blood urea nitrogen to mmol/L, multiply by 0.357; creatinine to μmol/L, multiply by 88.4.

[a] All *P* values are greater than .05 for the comparisons of baseline characteristics across groups.

[b] N = 120 with ejection fraction data.

els. The statistical analysis plan specified several pertinent subgroup analyses, using a conservative framework for subgroup interaction testing (interaction $P < .01$). The current study was designed to compare both study drugs (low-dose dopamine and low-dose nesiritide) with placebo and not with each other, unless both treatments were superior to placebo. All statistical analyses were conducted with SAS version 9 or higher.

Results

Patient Population

A total of 360 participants were enrolled between September 2010 and March 2013 across 26 sites in the United States and Canada (eAppendix 1 in the Supplement). The baseline characteristics of the study groups were similar (**Table 1**). The me-

Copyright 2013 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 07/30/2016

Table 2. Coprimary End Points: Effect of Low-Dose Dopamine vs Placebo or Low-Dose Nesiritide vs Placebo on Cumulative Urine Volume During 72 Hours and Change in Cystatin C Level From Baseline to 72 Hours

	Mean (95% CI)			
	Placebo	Drug	Treatment Difference	*P* Value
Dopamine strategy	Placebo (n = 119)	Dopamine (n = 122)		
Cumulative urine volume from randomization to 72 h, mL	8296 (7762 to 8830)	8524 (7917 to 9131)	229 (−714 to 1171)	.59
Change in cystatin C level from randomization to 72 h, mg/L	0.11 (0.06 to 0.16)	0.12 (0.06 to 0.18)	0.01 (−0.08 to 0.10)	.72
Nesiritide strategy	Placebo (n = 119)	Nesiritide (n = 119)		
Cumulative urine volume from randomization to 72 h, mL	8296 (7762 to 8830)	8574 (8014 to 9134)	279 (−618 to 1176)	.49
Change in cystatin C level from randomization to 72 h, mg/L	0.11 (0.06 to 0.16)	0.07 (0.01 to 0.13)	−0.04 (−0.13 to 0.05)	.36

dian age of the study population was 70 years (interquartile range [IQR], 63.0-70.0 years), 73% were men, and 21% were black. The median ejection fraction was 33% (IQR, 22%-50%), and 94 patients (26%) had an ejection fraction greater than 50%. A majority of patients (67%) had been hospitalized for heart failure within the previous 12 months. By design, patients had moderate to severe renal dysfunction, with a median estimated glomerular filtration rate of 42 mL/min/1.73 m^2 (IQR, 31-54 mL/min/1.73 m^2). The distribution of participants among estimated glomerular filtration rate strata (>60, 60 to >45, 45 to >30, ≤30 mL/min/1.73 m^2) was not statistically different in the dopamine, placebo, and nesiritide groups (dopamine, 20%, 29%, 26%, and 25%; placebo, 18%, 34%, 36%, and 12%; and nesiritide, 17%, 38%, 34%, and 11%, respectively; *P* = .39).

Four placebo, 11 dopamine, and 2 nesiritide patients did not receive study drug (Figure 1). The duration of study drug administration was not significantly different between groups (median duration in hours: dopamine, 72.0 [IQR, 68.9-72.1]; placebo, 71.6 [IQR, 66.0-72.1]; nesiritide, 72.0 [IQR, 48.0-72.1]; *P* = .55). Comparative analysis of the placebo participants from the low-dose dopamine strategy vs low-dose nesiritide strategy did not reveal any significant differences in baseline characteristics (Table 1) or coprimary end points.

Low-Dose Dopamine Strategy

Coprimary End Points

There was no significant difference between low-dose dopamine vs placebo in regard to the 72-hour cumulative urine volume (dopamine, 8524 mL; 95% CI, 7917-9131 vs placebo, 8296 mL; 95% CI, 7762-8830 mL; *P* = .59) or in the change in cystatin C level from baseline to 72 hours (dopamine, 0.12 mg/L; 95% CI, 0.06-0.18 vs placebo, 0.11 mg/L; 95% CI, 0.06-0.16 mg/L; *P* = .72) (**Table 2**).

Secondary End Points

There were no significant between-group differences in other decongestion or renal function end points (**Table 3**), the bivariate end point of change in serum creatinine level and weight at 72 hours after randomization (*P* = .89), or the coprimary end points at 24 or 48 hours (eTable 3 in the Supplement).

There were no deaths and no significant differences between groups in treatment failure at 72 hours. Compared with the placebo group, dopamine-treated patients were less likely to have discontinuation or decreasing of study drug dose because of hypotension and more likely to have discontinuation or decreasing of study drug dose because of tachycardia. However, the overall rate of study drug discontinuation was similar between the 2 groups (Table 3).

At 60 days, there were no significant differences between groups in death, serious adverse events, days alive and free from heart failure hospitalization (Table 3), or the rate of the composite end point of death or rehospitalization or unscheduled visit for heart failure (*P* = .53; eFigure 1A in the Supplement). At 180 days, there were no significant differences between groups in overall mortality (*P* = .87; eFigure 2A in the Supplement).

The total dose of diuretic used during the 72-hour study period was not statistically different in the dopamine treatment group compared with the placebo group (median furosemide equivalent dose, dopamine: 460 mg; IQR, 300-760 vs placebo, 600 mg; IQR, 300-880 mg; *P* = .099). Furthermore, the total fluid intake during the 72-hour study period was not statistically different between the dopamine-treated group and the placebo group (median fluid intake, dopamine: 3923.5 mL; IQR, 3078.5-4687.5 vs placebo 3823.5 mL; IQR, 2982.0-4504.0 mL; *P* = .45).

Subgroup Analysis

The effect of treatment group on the 2 coprimary end points was consistent across prespecified subgroups, with the exception that patients with preserved ejection fraction (>50%) who were receiving dopamine had less urine volume during 72 hours compared with placebo (interaction *P* = .01) (**Figure 2**).

Low-Dose Nesiritide Strategy

Coprimary End Points

There was no significant difference between low-dose nesiritide vs placebo in the 72-hour cumulative urine volume (nesiritide, 8574 mL; 95% CI, 8014-9134 vs placebo, 8296 mL; 95% CI, 7762-8830; *P* = .49) or in the cystatin C level change from baseline to 72 hours (nesiritide, 0.07; 95% CI, 0.01-0.13 vs placebo, 0.11 mg/L; 95% CI, 0.06-0.16; *P* = .36) (Table 2).

Secondary End Points

There were no significant differences between groups in other decongestion or renal function end points (Table 3), the bivariate end point of change in serum creatinine level and weight

Copyright 2013 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 07/30/2016

Table 3. Secondary End Points: Low-Dose Dopamine or Low-Dose Nesiritide vs Placebo[a]

End Points	Placebo	Drug	*P* Value
Dopamine strategy	**Placebo (n = 119)**	**Dopamine (n = 122)**	
Decongestion end points			
Cumulative urinary sodium excretion from randomization to 72 h, mmol	540 (485,595)	527 (473,581)	.75
Change in weight from randomization to 72 h, lb	−7.73 (−9.01 to −6.44)	−7.40 (−8.83 to −5.98)	.82
Change in NT-proBNP level from randomization to 72 h, pg/mL	−2020 (−2724 to −1316)	−2629 (−3470 to −1789)	.43
Renal function end points			
Change in creatinine level from randomization to 72 h, mg/dL	0.02 (−0.4 to 0.08)	0 (−0.7 to 0.08)	.78
Development of type 1 cardiorenal syndrome[b] during 72 h, No. (%)	24 (22)	23 (22)	.88
Symptom relief end points			
Global well-being visual analog scale; AUC from randomization to 72 h	4704 (4442 to 4965)	4553 (4305 to 4801)	.43
Dyspnea visual analog scale; AUC from randomization to 72 h	4998 (4723 to 5272)	4936 (4660 to 5211)	.92
Persistent or worsening HF[c] within 72 h, No. (%)	5 (4)	11 (9)	.14
Clinical outcomes			
Death from any cause within 72 h, No. (%)	0	0	NA
Treatment failure[d] within 72 h, No. (%)	32 (28)	35 (30)	.73
Study drug stopped or dose decreased because of hypotension, No./total No. (%)	12/115 (10.4)	1/111 (0.9)	<.001
Study drug stopped or dose decreased because of tachycardia, No./total No. (%)	1/115 (0.9)	8/111 (7.2)	<.001
Study drug stopped before 72 h for any reason, No./total No. (%)	29/115 (25)	25/111 (23)	.72
Death through day 60, No. (%)	12 (10)	11 (9)	.78
Serious adverse event through day 60, No. (%)	24 (20)	30 (25)	.41
Days alive and free from HF hospitalization at 60 d	46.6 (44.0 to 49.2)	47.3 (45.0 to 49.6)	.68
Mortality at 180 d, %	21.1 (14.7 to 29.9)	19.7 (13.5 to 28.1)	.87
Nesiritide strategy	**Placebo (n = 119)**	**Nesiritide (n = 119)**	
Decongestion end points			
Cumulative urinary sodium excretion from randomization to 72 h, mmol	540 (485 to 595)	515 (468 to 563)	.52
Change in weight from randomization to 72 h, lb	−7.73 (−9.01 to −6.44)	−7.15 (−8.57 to −5.73)	.67
Change in NT-proBNP from randomization to 72 h, pg/mL	−2020 (−2724 to −1316)	−2273 (−3010 to −1536)	.10
Renal function end points			
Change in creatinine level from randomization to 72 h, mg/dL	0.02 (−0.4 to 0.08)	0.02 (−0.06 to 0.09)	.90
Development of type 1 cardiorenal syndrome[b] during 72 h, No. (%)	24 (22)	28 (25)	.55
Symptom relief end points			
Global well-being visual analog scale[c]; AUC from randomization to 72 h	4704 (4442 to 4965)	4498 (4257 to 4740)	.62
Dyspnea visual analog scale; AUC from randomization to 72 h	4998 (4723 to 5272)	4831 (4592 to 5070)	.89
Persistent or worsening HF[d] within 72 h, No. (%)	5 (4)	6 (5)	.77
Clinical outcomes			
Death from any cause within 72 h, No. (%)	0	0	NA
Treatment failure[e] within 72 h, No. (%)	32 (28)	48 (40)	.04
Study drug stopped or dose decreased because of hypotension, No./total No. (%)	12/115 (10.4)	22/117 (18.8)	.07
Study drug stopped or dose decreased because of tachycardia, No./total No. (%)	1/115 (0.9)	0/117	.50
Study drug stopped before 72 h for any reason, No./total No. (%)	29/115 (25)	29/117 (25)	.94
Death through day 60, No. (%)	12 (10)	8 (7)	.35
Serious adverse event through day 60, No. (%)	24 (20)	21 (18)	.62
Days alive and free from HF hospitalization at 60 d	46.6 (44.0 to 49.2)	47.3 (44.9 to 49.7)	.67
Mortality rate at 180 d, %	21.1 (14.7 to 29.9)	19.1 (13.0 to 27.6)	.74

Abbreviations: AUC, area under the curve; HF, heart failure; NA, not applicable; NT-proBNP, N-terminal probrain natriuretic peptide.

[a] Mean (95% CI) unless otherwise specified.

[b] Type 1 cardiorenal syndrome was defined as increase in serum creatinine level of more than 0.3 mg/dL (26.5 μmol/L) during the 72 h after randomization.

[c] Visual analog scale; range 0-100; lower numbers indicate worse score.

[d] Persistent or worsening HF was defined as need for rescue therapy (additional intravenous vasoactive agent for HF treatment, ultrafiltration, and mechanical circulatory or respiratory support) during 72 h after randomization.

[e] Treatment failure was defined as the development of any one of the following during the 72 h after randomization: development of type 1 cardiorenal syndrome as defined above, worsening/persistent HF as defined above, significant hypotension requiring discontinuation of study drug, and significant tachycardia requiring discontinuation of study drug.

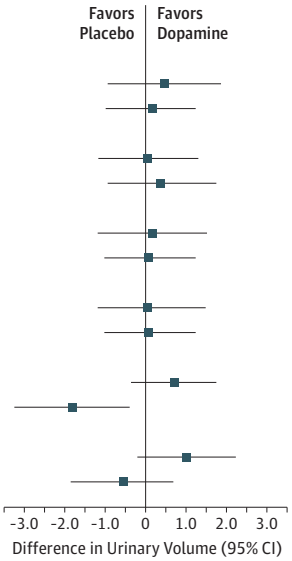
Copyright 2013 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 07/30/2016

Figure 2. Dopamine Strategy Subgroup Analysis

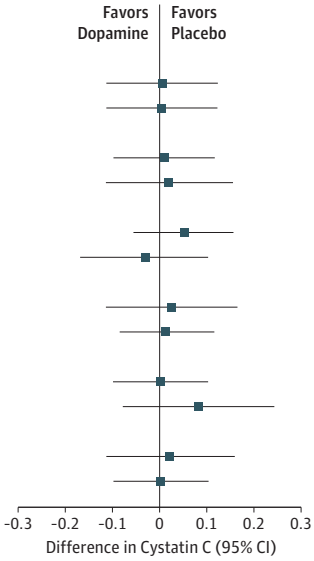
Urinary Volume

Baseline Characteristics	No. of Patients		72-h Urinary Volume, Mean (95% CI)		Treatment Difference, Mean (95% CI)	P Value
	Placebo	Dopamine	Placebo	Dopamine		
Age, y						
≤70	59	55	8.84 (8.07 to 9.62)	9.30 (8.24 to 10.35)	0.45 (-0.86 to 1.77)	.68
>70	53	61	7.76 (7.03 to 8.49)	7.86 (7.18 to 8.55)	0.10 (-0.91 to 1.13)	
Blood urea nitrogen, mg/dL						
≤37	60	61	8.72 (8.00 to 9.44)	8.78 (7.90 to 9.65)	0.06 (-1.09 to 1.20)	.71
>37	51	55	7.91 (7.08 to 8.73)	8.25 (7.37 to 9.19)	0.37 (-0.88 to 1.62)	
Cystatin C, mg/L						
≤1.71	54	55	9.03 (8.20 to 9.87)	9.18 (8.27 to 10.08)	0.14 (-1.10 to 1.39)	.93
>1.71	56	53	7.73 (7.06 to 8.41)	7.80 (7.00 to 8.61)	0.07 (-0.99 to 1.13)	
GFR, mL/min/1.73 m^2						
≤44	58	53	8.14 (7.45 to 8.83)	8.00 (7.03 to 8.98)	-0.14 (-1.33 to 1.06)	.49
>44	54	63	8.54 (7.69 to 9.39)	9.00 (8.20 to 9.79)	0.46 (-0.73 to 1.64)	
Ejection fraction, %						
≤50	89	86	8.13 (7.51 to 8.75)	8.82 (8.08 to 9.56)	0.69 (-0.28 to 1.66)	.01
>50	23	28	9.10 (8.01 to 10.19)	7.26 (6.44 to 8.08)	-1.84 (-3.21 to -0.47)	
Systolic BP, mm Hg						
≤114	57	58	7.87 (7.18 to 8.56)	8.86 (7.97 to 9.76)	1.00 (-0.14 to 2.14)	.06
>114	54	63	8.81 (7.97 to 9.65)	8.22 (7.37 to 9.07)	-0.59 (-1.82 to 0.64)	



Cystatin C

Baseline Characteristics	No. of Patients		72-h Urinary Volume, Mean (95% CI)		Treatment Difference, Mean (95% CI)	P Value
	Placebo	Dopamine	Placebo	Dopamine		
Age, y						
≤70	54	45	0.08 (0.01 to 0.15)	0.09 (0.00 to 0.18)	0.01 (-0.11 to 0.12)	.97
>70	49	56	0.13 (0.05 to 0.21)	0.14 (0.06 to 0.22)	0.01 (-0.11 to 0.12)	
Blood urea nitrogen, mg/dL						
≤37	56	55	0.11 (0.04 to 0.18)	0.12 (0.04 to 0.20)	0.01 (-0.09 to 0.11)	.83
>37	46	46	0.10 (0.02 to 0.18)	0.12 (0.02 to 0.22)	0.02 (-0.11 to 0.15)	
Cystatin C, mg/L						
≤1.71	50	53	0.09 (0.03 to 0.15)	0.14 (0.06 to 0.22)	0.05 (-0.05 to 0.15)	.34
>1.71	53	48	0.12 (0.04 to 0.20)	0.10 (0.00 to 0.20)	-0.03 (-0.16 to 0.10)	
GFR, mL/min/1.73 m^2						
≤44	52	46	0.10 (0.02 to 0.18)	0.13 (0.02 to 0.24)	0.03 (-0.11 to 0.16)	.85
>44	51	55	0.11 (0.04 to 0.18)	0.11 (0.04 to 0.18)	0.01 (-0.08 to 0.11)	
Ejection fraction, %						
≤50	81	78	0.11 (0.05 to 0.17)	0.11 (0.04 to 0.18)	0.00 (-0.09 to 0.10)	.53
>50	22	22	0.10 (0.00 to 0.20)	0.16 (0.03 to 0.29)	0.08 (-0.07 to 0.24)	
Systolic BP, mm Hg						
≤114	52	50	0.07 (-0.01 to 0.15)	0.10 (0.00 to 0.20)	0.02 (-0.11 to 0.15)	.78
>114	51	51	0.14 (0.08 to 0.20)	0.14 (0.07 to 0.21)	0.00 (-0.09 to 0.10)	



Subgroup analysis of treatment effect. A, Cumulative urine volume during 72 hours. B, Change in cystatin C level from baseline to 72 hours with low-dose dopamine vs placebo.

at 72 hours (P = .77), or the coprimary end points at 24 or 48 hours (eTable 3 in the Supplement).

There were zero deaths and no significant differences between groups in symptom relief at 72 hours (Table 2). More nesiritide-treated participants had treatment failure (Table 3), primarily because of a higher rate of study drug discontinuation for hypotension, although the incidence of study drug discontinuation for any cause was similar between treatment groups (Table 3).

At 60 days, there were no significant differences between groups in death, serious adverse events, days alive and free from heart failure hospitalization (Table 3), or the rate of the composite end point of death or rehospitalization or unscheduled visit for heart failure (P = .16) (eFigure 1B in the Supplement). At 180 days, there were no significant differences between groups in overall mortality (P = .74; eFigure 2B in the Supplement).

The total dose of diuretic used during the 72-hour study period was not statistically different in the nesiritide treatment group compared with the placebo group (median furosemide equivalent dose, nesiritide: 481 mg; IQR, 280-760 vs placebo: 600 mg; IQR, 300-880 mg; P = .16). Furthermore, the

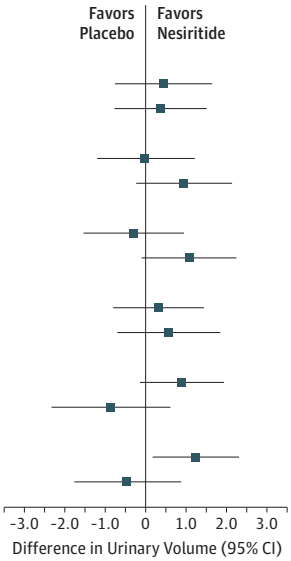
Copyright 2013 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 07/30/2016

Figure 3. Nesiritide Strategy Subgroup Analysis

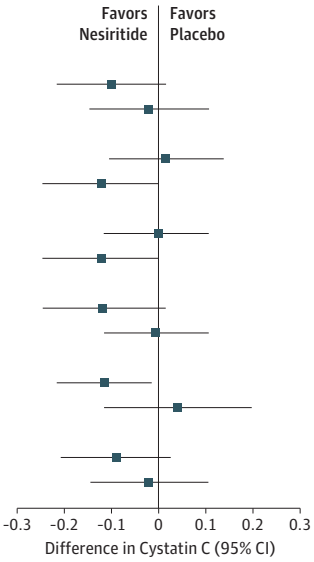
Urinary Volume

Baseline Characteristics	No. of Patients		72-h Urinary Volume, Mean (95% CI)		Treatment Difference, Mean (95% CI)	P Value
	Placebo	Nesiritide	Placebo	Nesiritide		
Age, y						
≤70	59	61	8.84 (8.06 to 9.62)	9.30 (8.50 to 10.10)	0.46 (-0.67 to 1.59)	.92
>70	53	48	7.76 (7.03 to 8.49)	8.14 (7.37 to 8.91)	0.38 (-0.68 to 1.45)	
Blood urea nitrogen, mg/dL						
≤37	60	51	8.72 (8.00 to 9.44)	8.75 (7.85 to 9.65)	0.02 (-1.13 to 1.18)	.24
>37	51	57	7.91 (7.09 to 8.73)	8.88 (8.14 to 9.62)	0.97 (-0.15 to 2.08)	
Cystatin C, mg/L						
≤1.71	54	54	9.03 (8.19 to 9.87)	8.77 (7.97 to 9.57)	-0.27 (-1.44 to 0.90)	.10
>1.71	56	51	7.73 (7.05 to 8.41)	8.83 (7.95 to 9.97)	1.10 (-0.01 to 2.21)	
GFR, mL/min/1.73 m^2						
≤44	58	57	8.14 (7.45 to 8.83)	8.49 (7.71 to 9.27)	0.35 (-0.71 to 1.40)	.76
>44	54	52	8.54 (7.69 to 9.39)	9.13 (8.30 to 9.96)	0.59 (-0.61 to 1.79)	
Ejection fraction, %						
≤50	89	76	8.13 (7.51 to 8.75)	9.03 (8.31 to 9.75)	0.90 (-0.05 to 1.90)	.06
>50	23	33	9.10 (8.01 to 10.19)	8.24 (7.37 to 9.11)	-0.86 (-2.23 to 0.56)	
Systolic BP, mm Hg						
≤114	57	59	7.87 (7.18 to 8.56)	9.14 (8.44 to 9.84)	1.27 (0.28 to 2.26)	.04
>114	55	50	8.81 (7.98 to 9.64)	8.38 (7.45 to 9.31)	-0.43 (-1.68 to 0.83)	



Cystatin C

Baseline Characteristics	No. of Patients		72-h Urinary Volume, Mean (95% CI)		Treatment Difference, Mean (95% CI)	P Value
	Placebo	Nesiritide	Placebo	Nesiritide		
Age, y						
≤70	54	57	0.08 (0.01 to 0.15)	-0.01 (-0.09 to 0.07)	-0.10 (-0.21 to 0.01)	.32
>70	49	48	0.13 (0.05 to 0.21)	0.11 (0.02 to 0.20)	-0.02 (-0.14 to 0.10)	
Blood urea nitrogen, mg/dL						
≤37	56	48	0.11 (0.04 to 0.18)	0.12 (0.03 to 0.21)	0.01 (-1.10 to 0.13)	.12
>37	46	56	0.10 (0.02 to 0.18)	-0.02 (-0.10 to 0.06)	-0.12 (-0.24 to 0.00)	
Cystatin C, mg/L						
≤1.71	50	54	0.09 (0.03 to 0.15)	0.08 (0.00 to 0.16)	0.01 (-0.11 to 0.10)	.16
>1.71	53	51	0.12 (0.04 to 0.20)	0.00 (-0.09 to 0.09)	-0.12 (-0.24 to 0.00)	
GFR, mL/min/1.73 m^2						
≤44	52	55	0.10 (0.02 to 0.18)	-0.01 (-0.10 to 0.08)	-0.12 (-0.24 to 0.01)	.19
>44	51	50	0.11 (0.04 to 0.18)	0.10 (0.02 to 0.18)	-0.01 (-0.11 to 0.10)	
Ejection fraction, %						
≤50	81	72	0.11 (0.05 to 0.17)	-0.01 (-0.08 to 0.06)	-0.11 (-0.21 to -0.02)	.09
>50	22	33	0.10 (0.00 to 0.20)	0.15 (0.05 to 0.25)	0.04 (-0.11 to 0.19)	
Systolic BP, mm Hg						
≤114	52	58	0.07 (-0.01 to 0.15)	-0.02 (-0.09 to 0.05)	-0.09 (-0.20 to 0.02)	.37
>114	51	47	0.14 (0.08 to 0.20)	0.12 (0.02 to 0.22)	-0.02 (-0.14 to 0.10)	



Subgroup analysis of treatment effect. A, Cumulative urine volume during 72 hours. B, Change in cystatin C level from baseline to 72 hours with low-dose nesiritide vs placebo.

total fluid intake during the 72-hour study period was not statistically different between the nesiritide- and placebo-treated groups (median total fluid intake, nesiritide: 3642.5 mL; IQR, 2836.0-4751.0 vs placebo: 3823.5 mL; IQR, 2982.0-4504.0 mL; P = .96).

Subgroup Analysis

The effect of treatment group on the 2 coprimary end points was consistent across prespecified subgroups (**Figure 3**).

Discussion

There is an unmet need for renal-specific therapies that enhance decongestion and preserve renal function in patients with acute heart failure.[2] In the current study, compared with placebo, neither low-dose dopamine nor low-dose nesiritide enhanced decongestion or favorably affected renal function. The event rates of ROSE study participants are similar to those

Copyright 2013 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 07/30/2016

of other acute heart failure trials enrolling patients with renal dysfunction, suggesting that this cohort of patients is representative of contemporary acute heart failure patients with renal dysfunction.[19,21,22] These findings do not support the use of low-dose dopamine or low-dose nesiritide as a renal adjuvant therapy in patients with acute heart failure and renal dysfunction.

The current findings differ from those of previous small studies that suggested the benefits of low-dose dopamine in acute heart failure.[6-9] Most previous studies did not target patients with renal dysfunction,[6,7,9] included only patients with ejection fractions less than 40%,[6-8] used higher dopamine doses,[6,7,9] and used variable durations of dopamine infusion.[6-9] The duration of dopamine used in this study was longer than that of most previous studies to allow sustained effect during 72 hours. In previous studies, different diuretic doses were used in the dopamine and placebo arms, and diuretic doses were not calibrated to the patient's outpatient diuretic requirements.[7-9] The dose of dopamine used here is the most commonly used "renal-specific" dose and is postulated to reduce α- and β-adrenergic–mediated inotropic and proarrhythmic effects.[5] However, the lower rates of hypotension and higher rates of tachycardia observed at this dose suggest incomplete renal specificity.

Guidelines for acute heart failure management state that use of low-dose dopamine to improve diuresis and preserve renal function during diuretic therapy "may be considered" but acknowledge the lack of data supporting efficacy.[2] The current findings do not provide support for this strategy in the most clinically relevant acute heart failure population; namely, patients with renal dysfunction who are at risk for inadequate decongestion and worsening renal function.

To our knowledge, this is the first randomized trial of low-dose nesiritide in patients with acute heart failure. At the recommended dose, nesiritide produces modest improvement in dyspnea but does not favorably affect clinical outcomes, decongestion, or renal function.[12,18,23,24] A case-control study suggested that low-dose nesiritide may provide renal-specific effects because it enhanced decongestion, spared diuretic dose, and improved renal function without hypotension in acute heart failure.[15] However, in the ROSE study, hypotension was still common in nesiritide-treated patients, and low-dose nesiritide did not enhance decongestion or preserve renal function.

Observational studies indicate that dopamine and nesiritide are used in a significant portion of patients with acute heart failure and that their use is associated with longer length of stay, higher costs, and greater mortality.[25] These data suggest that these agents are either harmful or preferentially used in high-risk patients. We tested these 2 agents at doses suggested to have less potential for adverse effects and to provide renal-specific actions in a high-risk acute heart failure population and found no evidence of renal specificity or clinical benefit.

In both the experimental strategies, there was a suggestion of differential treatment effect according to the ejection fraction or blood pressure level. The 72-hour cumulative urine volume was numerically lower with low-dose dopamine compared with placebo in subgroups of patients with higher ejection fraction or higher baseline blood pressure. With low-dose nesiritide, the 72-hour cumulative urine volume was numerically higher compared with placebo in subgroups of patients with lower ejection fraction or lower baseline blood pressure. At low dose, dopamine decreases renal and systemic vascular resistance in patients with heart failure and reduces ejection fraction.[6] Similarly, even at low dose, nesiritide is a systemic vasodilator. Compared with patients with reduced ejection fraction, those with heart failure and preserved ejection fraction experience greater decreases in blood pressure and less increase in stroke volume in response to acute vasodilation because of the unique ventricular vascular properties in this group.[26] The ROSE trial was not powered to assess subgroup differences; therefore, these observations may be due to chance. However, these findings suggest that further investigation of these or other acute heart failure therapies may need to assess the potential for differential responses in heart failure and preserved vs reduced ejection.

Our study had some important limitations. ROSE was not powered to detect differences in clinical events. Furthermore, it allowed the use of diuretics before randomization and adjustments in the diuretic dosing after 24 hours; these factors may have affected the coprimary end points. The estimation of glomerular filtration rate with the Modification of Diet in Renal Disease equation formula assumes that kidney function is stable, an assumption that may not hold in some of these study participants because some may have experienced acute kidney injury in the context of their evolving heart failure exacerbation before admission.

Conclusions

In patients with acute decompensated heart failure and moderate or severe underlying renal dysfunction, neither low-dose dopamine nor low-dose nesiritide enhanced decongestion or improved renal function when added to diuretic therapy.

ARTICLE INFORMATION

Published Online: November 18, 2013. doi:10.1001/jama.2013.282190.

Author Affiliations: Mayo Clinic, Rochester, Minnesota (Chen, Borlaug, Redfield); Duke Clinical Research Institute, Durham, North Carolina (Anstrom, McNulty, Lee, Hernandez); Brigham and Women's Hospital, Boston, Massachusetts (Givertz, Stevenson, Braunwald); Massachusetts General Hospital, Boston (Semigran); Hennepin County Medical Center, Minneapolis, Minnesota (Goldsmith, Bart); University of Utah, Salt Lake City (Bull, Stehlik); University of Vermont, Burlington (LeWinter); Tufts Medical Center, Boston, Massachusetts (Konstam, Huggins); University of Montreal and Montreal Heart Institute, Montreal, Canada (Rouleau, O'Meara); Cleveland Clinic, Cleveland, Ohio (Tang, Starling); Emory University, Atlanta, Georgia (Butler); Michael E. DeBakey VA Medical Center and Baylor College of Medicine, Houston, Texas (Deswal); Duke University Medical Center and Duke Heart Center, Durham, North Carolina (Felker, O'Connor, Velazquez); Thomas Jefferson University, Philadelphia, Pennsylvania (Bonita); University of Pennsylvania, Philadelphia (Margulies, Cappola); Morehouse School of Medicine, Atlanta, Georgia (Ofili); Washington University School of Medicine, St Louis, Missouri (Mann, Dávila-Román); National Heart, Lung, and Blood Institute, Bethesda, Maryland (Shah).

Copyright 2013 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 07/30/2016

Author Contributions: Drs Lee and Anstrom had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Chen, Anstrom, Givertz, Stevenson, Semigran, Goldsmith, Bart, Bull, LeWinter, Rouleau, O'Meara, Felker, O'Connor, Ofili, Dávila-Román, Velazquez, Lee, Shah, Hernandez, Braunwald, Redfield.
Acquisition of data: Chen, Givertz, Stevenson, Semigran, Goldsmith, Bart, Bull, Stehlik, LeWinter, Konstam, Huggins, Rouleau, O'Meara, Tang, Starling, Butler, Deswal, Felker, O'Connor, Bonita, Margulies, Cappola, Ofili, Dávila-Román, Borlaug, Velazquez, Lee, Shah, Hernandez, Redfield.
Analysis and interpretation of data: Chen, Anstrom, Givertz, Stevenson, Semigran, Goldsmith, Bart, Bull, Stehlik, LeWinter, Konstam, O'Meara, Tang, Starling, Butler, Deswal, Felker, Bonita, Margulies, Ofili, Mann, Dávila-Román, McNulty, Borlaug, Velazquez, Lee, Shah, Hernandez, Braunwald, Redfield.
Drafting of the manuscript: Chen, Stevenson, Bart, Bull, O'Meara, Butler, Bonita, Ofili, Mann, Dávila-Román, McNulty, Borlaug, Velazquez, Lee, Shah, Redfield.
Critical revision of the manuscript for important intellectual content: Chen, Anstrom, Givertz, Stevenson, Semigran, Goldsmith, Bart, Bull, Stehlik, LeWinter, Konstam, Huggins, Rouleau, O'Meara, Tang, Starling, Butler, Deswal, Felker, O'Connor, Bonita, Margulies, Cappola, Ofili, Dávila-Román, Borlaug, Velazquez, Lee, Shah, Hernandez, Braunwald, Redfield.
Statistical analysis: Anstrom, Stevenson, Bart, Bull, O'Meara, Ofili, Dávila-Román, McNulty, Velazquez, Lee, Shah.
Obtained funding: Chen, Givertz, Stevenson, Semigran, Bart, Bull, Huggins, O'Meara, Tang, O'Connor, Margulies, Ofili, Dávila-Román, Velazquez, Lee, Shah, Hernandez, Braunwald, Redfield.
Administrative, technical, or material support: Chen, Givertz, Stevenson, Semigran, Bart, Bull, LeWinter, Konstam, Huggins, Rouleau, O'Meara, Butler, Deswal, O'Connor, Ofili, Dávila-Román, Borlaug, Velazquez, Shah, Hernandez, Braunwald, Redfield.
Study supervision: Chen, Givertz, Stevenson, Bart, Bull, LeWinter, O'Meara, Tang, Butler, Deswal, O'Connor, Bonita, Margulies, Cappola, Ofili, Dávila-Román, Borlaug, Velazquez, Shah, Hernandez, Braunwald, Redfield.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Chen reports serving on the board of Zumbro Discovery (as cofounder), receiving grants from Scios Inc, and receiving royalties from Nile Therapeutics, Anexon Inc, and UpToDate and that his institution has licensed patents to Nile Therapeutics and Anexon Inc for designer natriuretic peptides. Dr Anstrom reports serving as a consultant for Pfizer, AstraZeneca, and Bristo-Myers Squibb. Dr Goldsmith reports serving as consultant for Otsuka, Medtronic, Astellas, CHF Solutions, and Bayer; serving on the speakers bureau for Otsuka; and that his institution has received grants from Otsuka, Astellas, and CHF Solutions. Dr LeWinter reports receiving personal fees from Merck outside the submitted work. Dr Konstam reports receiving personal fees from Johnson & Johnson, Novartis, Amgen, and Otsuka, and grants from Merck and Otsuka. Dr O'Meara reports serving on the board for Pfizer, consulting for Servier and Novartis, and serving on the speakers bureau for Pfizer and Servier. Dr Tang reports consulting for Medtronic and St Jude Medical and that his institution received grants from St Jude Medical, Pfizer/Fold Rx, Respicardia Inc, and Abbott. Dr Felker reports consulting for Novartis, Trevena, Otsuka, and Amgen and receiving payment for educational presentations from Novartis, and that his institution has received grants from Novartis, Amgen, and Otsuka. Dr O'Connor reports receiving personal fees from Cardiology Consulting Associates, Novella Clinical Inc, Actelion Pharmaceuticals Ltd, and Faculty Connection; owning stock in Neurotronik/Interventional Autonomics Corporation and Synecore; receiving grants from Roche Diagnostics, GE Healthcare, Johnson & Johnson, Gilead, Critical Diagnostics, BG Medicine, Otsuka, Amgen, and Astellas outside the submitted work; and holding a patent Bisphosphonate Compositions and Methods for Treating Heart Failure, licensed to Biscardia. Dr Cappola reports consulting for TEVA Pharmaceuticals and being a coinventor on pending patents for neuregulin and sFlt-1 as heart failure biomarkers and inventor on a patent for gene expression biomarkers of heart transplant rejection. Dr Mann reports consulting for Nile Therapeutics. Dr Borlaug reports consulting for Medscape, Amgen, and GlaxoSmithKline and that his institution has received grants from Atcor Medical and Gilead. Dr Velazquez reports consulting for Novartis and serving on the speakers bureau for Novartis and Gilead and that his institution has received grants from Abbott Vascular. Dr Hernandez reports consulting for Novartis, Janssen, and Bristol-Myers Squibb and that his institution has received grants from Novartis, Janssen, and Bristo-Myers Squibb. Dr Braunwald reports grants to his institution from AstraZeneca, Johnson & Johnson, Merck, sanofi-aventis, Daiichi Sankyo, GlaxoSmithKline, Bristol-Myers Squibb, Beckman Coulter, Roche Diagnostics, and Pfizer; uncompensated personal fees from Merck; consulting for Genzyme, Amorcyte, Medicines Co, CardioRentis, and sanofi-aventis; uncompensated lectures for Merck & CVRx; and payment for lectures from Eli Lilly, Daiichi Sankyo, Menarini International, Medscape, and Bayer, outside the submitted work. Dr Redfield reports receiving royalties from Anexion and payment for educational presentations from the Heart Failure Society of America and reports unpaid advisory committee membership for Novartis.

Funding/Support: This work was supported by grants from the National Heart, Lung, and Blood Institute (NHLBI) (coordinating center: U10 HL084904; regional clinical centers: U01 HL084861, U10 HL110312, U109 HL110337, U01 HL084889, U01 HL084890, U01 HL084891, U10 HL110342, U10 HL110262, U01 HL084931, U10 HL110297, U10 HL110302, U10 HL110309, U10 HL110336, U10 HL110338). This work is also supported by the National Center for Advancing Translational Sciences (UL1TR000454, UL1TR000135, UL1RR025008, UL1TR000439) and the National Institute on Minority Health and Health Disparities (8 U54 MD007588).

Role of the Sponsor: NHLBI program officers provided advice on the trial design, analysis, and interpretation of the data, as well as the preparation, review, and approval of the manuscript and decision to submit the manuscript for publication. The NHLBI also appointed the protocol review committee and data and safety monitoring board.

Group Information: For a complete listing of the NHLBI Heart Failure Clinical Research Network investigators, see eAppendix 1 in the Supplement.

Disclaimer: The authors are solely responsible for the content of this article, which does not necessarily represent the official views of the NHLBI or the National Institutes of Health.

Additional Contributions: We thank the patients who participated in this study, the Heart Failure Clinical Research Network (HFN) site investigators and coordinators, the members of the HFN data and safety monitoring board and protocol review committee, and the NHLBI representatives.

REFERENCES

1. Lindenfeld J, Albert NM, Boehmer JP, et al; Heart Failure Society of America. HFSA 2010 comprehensive heart failure practice guideline. *J Card Fail*. 2010;16(6):e1-e194.

2. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2013;3. doi:10.1161/CIR.0b013e31829e8776.

3. Ronco C, McCullough P, Anker SD, et al; Acute Dialysis Quality Initiative (ADQI) Consensus Group. Cardio-renal syndromes: report from the consensus conference of the Acute Dialysis Quality Initiative. *Eur Heart J*. 2010;31(6):703-711.

4. Givertz MM, Teerlink JR, Albert NM, et al. Acute decompensated heart failure: update on new and emerging evidence and directions for future research. *J Card Fail*. 2013;19(6):371-389.

5. Maskin CS, Ocken S, Chadwick B, LeJemtel TH. Comparative systemic and renal effects of dopamine and angiotensin-converting enzyme inhibition with enalaprilat in patients with heart failure. *Circulation*. 1985;72(4):846-852.

6. Elkayam U, Ng TM, Hatamizadeh P, Janmohamed M, Mehra A. Renal vasodilatory action of dopamine in patients with heart failure: magnitude of effect and site of action. *Circulation*. 2008;117(2):200-205.

7. Cotter G, Weissgarten J, Metzkor E, et al. Increased toxicity of high-dose furosemide versus low-dose dopamine in the treatment of refractory congestive heart failure. *Clin Pharmacol Ther*. 1997;62(2):187-193.

8. Varriale P, Mossavi A. The benefit of low-dose dopamine during vigorous diuresis for congestive heart failure associated with renal insufficiency: does it protect renal function? *Clin Cardiol*. 1997;20(7):627-630.

9. Giamouzis G, Butler J, Starling RC, et al. Impact of dopamine infusion on renal function in hospitalized heart failure patients: results of the Dopamine in Acute Decompensated Heart Failure (DAD-HF) Trial. *J Card Fail*. 2010;16(12):922-930.

10. Chen HH, Burnett JC Jr. The natriuretic peptides in heart failure: diagnostic and therapeutic potentials. *Proc Assoc Am Physicians*. 1999;111(5):406-416.

11. Publication Committee for the VMAC Investigators (Vasodilatation in the Management of Acute CHF). Intravenous nesiritide vs nitroglycerin

Copyright 2013 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 07/30/2016

for treatment of decompensated congestive heart failure: a randomized controlled trial. *JAMA*. 2002;287(12):1531-1540.

12. O'Connor CM, Starling RC, Hernandez AF, et al. Effect of nesiritide in patients with acute decompensated heart failure. *N Engl J Med*. 2011;365(1):32-43.

13. Chen HH, Cataliotti A, Schirger JA, Martin FL, Harstad LK, Burnett JC Jr. Local renal delivery of a natriuretic peptide: a renal-enhancing strategy for B-type natriuretic peptide in overt experimental heart failure. *J Am Coll Cardiol*. 2009;53(15):1302-1308.

14. Chen HH, Sundt TM, Cook DJ, Heublein DM, Burnett JC Jr. Low dose nesiritide and the preservation of renal function in patients with renal dysfunction undergoing cardiopulmonary-bypass surgery: a double-blind placebo-controlled pilot study. *Circulation*. 2007;116(11)(suppl):I134-I138.

15. Riter HG, Redfield MM, Burnett JC, Chen HH. Nonhypotensive low-dose nesiritide has differential renal effects compared with standard-dose nesiritide in patients with acute decompensated heart failure and renal dysfunction. *J Am Coll Cardiol*. 2006;47(11):2334-2335.

16. Chen HH, Abouezzeddine OF, Anstrom KJ, et al; Heart Failure Clinical Research Network. Targeting the kidney in acute heart failure: can old drugs provide new benefit? Renal Optimization Strategies Evaluation in Acute Heart Failure (ROSE AHF) Trial. *Circ Heart Fail*. 2013;6(5):1087-1094.

17. Felker GM, Lee KL, Bull DA, et al; NHLBI Heart Failure Clinical Research Network. Diuretic strategies in patients with acute decompensated heart failure. *N Engl J Med*. 2011;364(9):797-805.

18. Owan TE, Chen HH, Frantz RP, et al. The effects of nesiritide on renal function and diuretic responsiveness in acutely decompensated heart failure patients with renal dysfunction. *J Card Fail*. 2008;14(4):267-275.

19. Bart BA, Goldsmith SR, Lee KL, et al; Heart Failure Clinical Research Network. Ultrafiltration in decompensated heart failure with cardiorenal syndrome. *N Engl J Med*. 2012;367(24):2296-2304.

20. Metra M, Cotter G, Davison BA, et al; RELAX-AHF Investigators. Effect of serelaxin on cardiac, renal, and hepatic biomarkers in the Relaxin in Acute Heart Failure (RELAX-AHF) development program: correlation with outcomes. *J Am Coll Cardiol*. 2013;61(2):196-206.

21. Teerlink JR, Cotter G, Davison BA, et al; Relaxin in Acute Heart Failure (RELAX-AHF) Investigators. Serelaxin, recombinant human relaxin-2, for treatment of acute heart failure (RELAX-AHF): a randomised, placebo-controlled trial. *Lancet*. 2013;381(9860):29-39.

22. Massie BM, O'Connor CM, Metra M, et al; PROTECT Investigators and Committees. Rolofylline, an adenosine A1-receptor antagonist, in acute heart failure. *N Engl J Med*. 2010;363(15):1419-1428.

23. Gottlieb SS, Stebbins A, Voors AA, et al. Effects of nesiritide and predictors of urine output in acute decompensated heart failure: results from ASCEND-HF (Acute Study of Clinical Effectiveness of Nesiritide and Decompensated Heart Failure). *J Am Coll Cardiol*. 2013;62(13):1177-1183.

24. Wang DJ, Dowling TC, Meadows D, et al. Nesiritide does not improve renal function in patients with chronic heart failure and worsening serum creatinine. *Circulation*. 2004;110(12):1620-1625.

25. Hauptman PJ, Swindle J, Burroughs TE, Schnitzler MA. Resource utilization in patients hospitalized with heart failure: insights from a contemporary national hospital database. *Am Heart J*. 2008;155(6):978-985.e1.

26. Schwartzenberg S, Redfield MM, From AM, Sorajja P, Nishimura RA, Borlaug BA. Effects of vasodilation in heart failure with preserved or reduced ejection fraction: implications of distinct pathophysiologies on response to therapy. *J Am Coll Cardiol*. 2012;59(5):442-451.

Copyright 2013 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 07/30/2016