Renal Optimization Strategies Evaluation in Acute Heart Failure (ROSE AHF):

A Randomized Clinical Trial

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on behalf of the
NHLBI Heart Failure Clinical Research Network

National Heart, Lung, and Blood Institute

Background
AHF + Renal Dysfunction

- Patients with acute heart failure (AHF) and renal dysfunction are at risk for inadequate decongestion and worsening renal function – factors associated with adverse clinical outcomes.

Background
Low dose dopamine

HEART FAILURE NETWORK

- Low or “renal” dose dopamine may selectively activate dopamine receptors and promote renal vasodilatation.
- Previous small studies suggest that low dose dopamine (2-5 μg/kg/min) may enhance decongestion and preserve renal function during diuretic therapy in AHF.

Background
Low dose nesiritide

HEART FAILURE NETWORK

- Nesiritide at recommended dose (2 μg/kg bolus + 0.01 μg/kg/min infusion) lowers blood pressure and does not favorably impact renal function or clinical outcomes.
- Previous small studies suggest that low dose nesiritide (0.005 μg/kg/min without bolus) may have renal specific actions which enhance decongestion and preserve renal function during diuretic therapy in AHF.

Hypotheses
Novel study design

In patients with AHF and renal dysfunction:

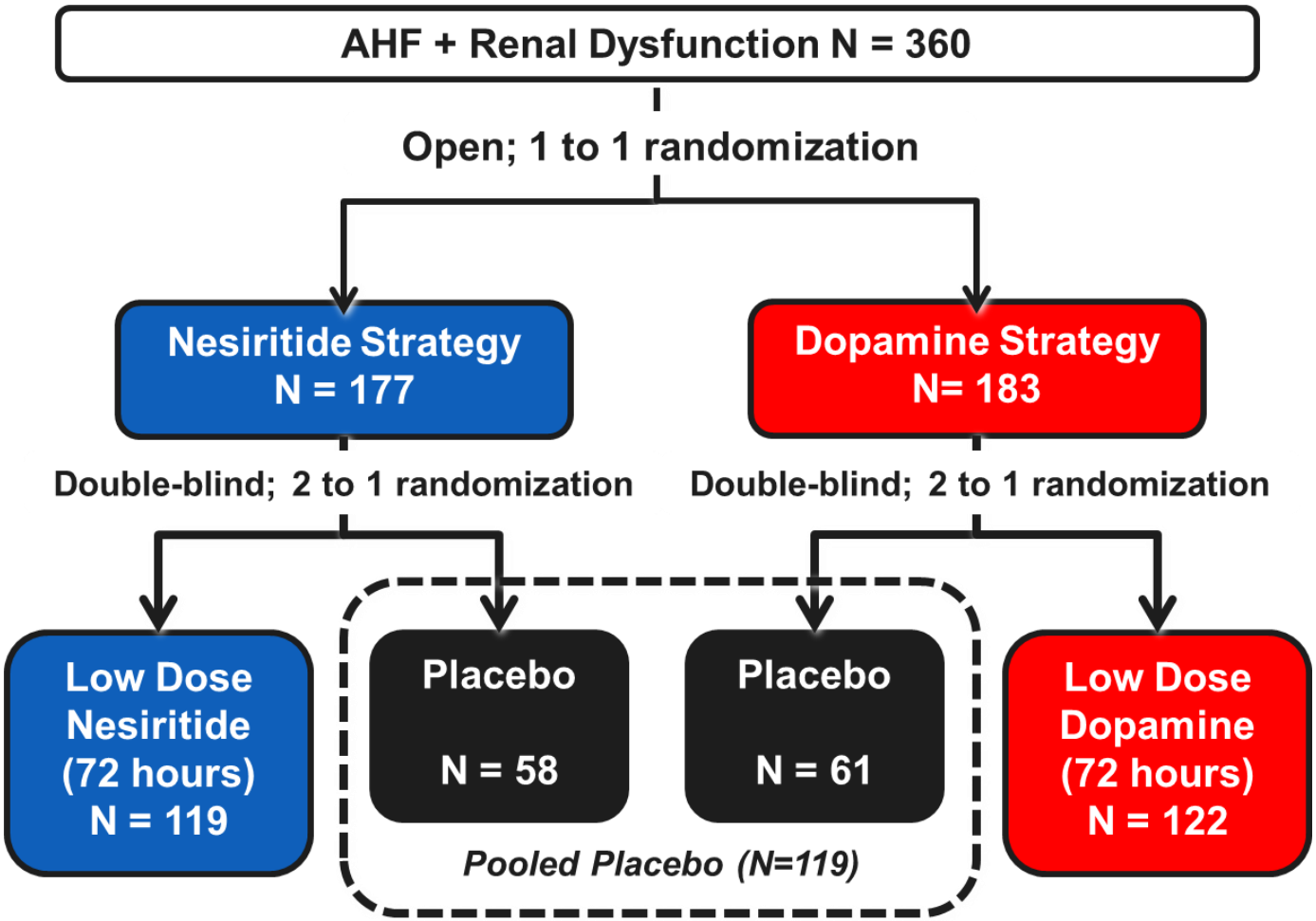
I. As compared to placebo, the addition of low dose dopamine (2 μg/kg/min) to diuretic therapy will enhance decongestion and preserve renal function

II. As compared to placebo, the addition of low dose nesiritide (0.005 μg/kg/min without bolus) to diuretic therapy will enhance decongestion and preserve renal function.

Study Population

- Diagnosis of AHF:
  - ≥1 symptom (dyspnea, orthopnea, edema)
  - ≥ 1 sign (rales, edema, ascites, CXR)
- Enrolled within 24 hours of hospital admission
- Estimated GFR of 15 - 60 mL/min/1.73m^2
  - Modification of diet in renal disease equation

Study Design



Standardized Diuretic Dosing For 1st 24 hours

2.5 x Outpt Furosemide Equivalent in Divided (BID) IV Doses

Co-Primary Endpoints

- **Decongestion Endpoint:** Cumulative urinary volume from randomization through 72 hours
- **Renal Function Endpoint :** Change in serum cystatin-C from randomization to 72 hours

Secondary Endpoints

Decongestion endpoints

- Change in weight: randomization to 72 hrs,
- Change in NT-proBNP: randomization to 72 hrs

Renal function endpoints

- Change in creatinine: randomization to 72 hrs,
- Cardio-renal syndrome (↑Cr > 0.3 mg/dL)

Symptom relief endpoints

- Dyspnea VAS; AUC over 72 hrs

Clinical endpoints

- Drug tolerance
- Adverse events

Statistical Methods

- > 85% power to detect effect (p<0.025) of
  - 72 urine volume of > 1400 ml
  - Change in cystatin C of > 0.3 mg/L
- Treatment comparisons by “intention to treat”
- Multiple imputation for missing data.
- Conservative framework for subgroup interaction testing (interaction p-value <0.01)

Baseline Characteristics

Characteristic	All patients (n=360)
Age (years)	70
Male	73%
AHF hsp in past year	67%
Ischemic etiology	58%
Diabetes	56%
EF > 50%	26%

Median or % shown; No significant between group differences

Baseline Characteristics

Characteristic	All patients (n=360)
Outpt Furosemide Dose (mg)	80
ACE inhibitor or ARB	50%
Beta-blocker	83%
Systolic BP (mmHg)	114
eGFR (ml/min/1.73m^2)	44.5
NT-proBNP (pg/ml)	4972

Median or % shown; No significant between group differences

HEART FAILURE NETWORK

Results
Dopamine Strategy

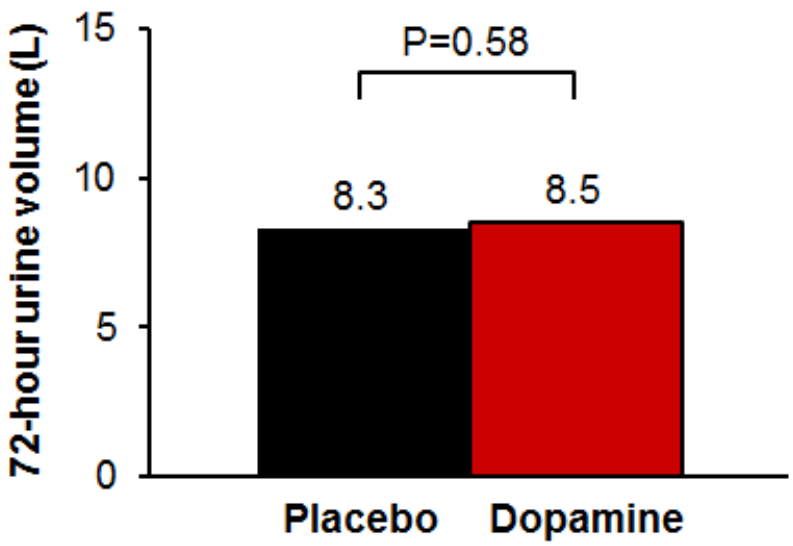
U.S. Department of Health and Human Services
National Institutes of Health

National Heart Lung and Blood Institute
People Science Health

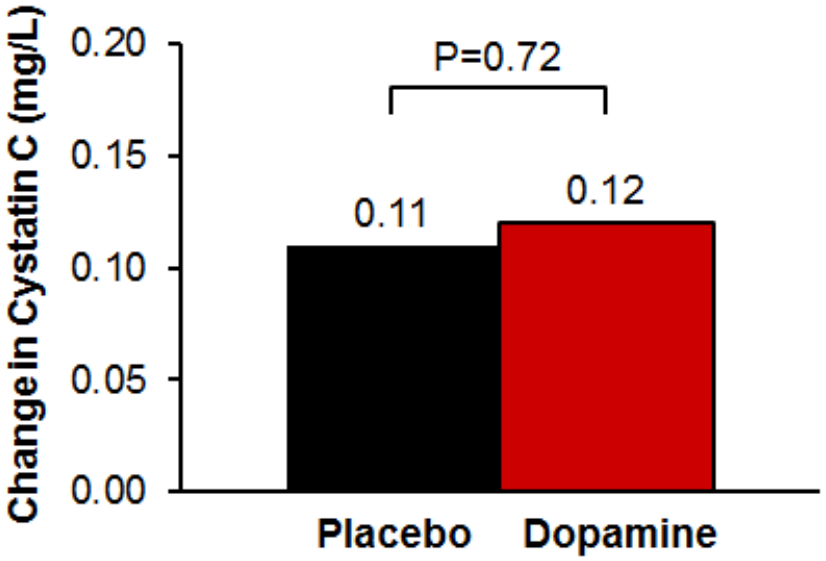
Low Dose Dopamine:
Co-primary End-points

HEART FAILURE NETWORK

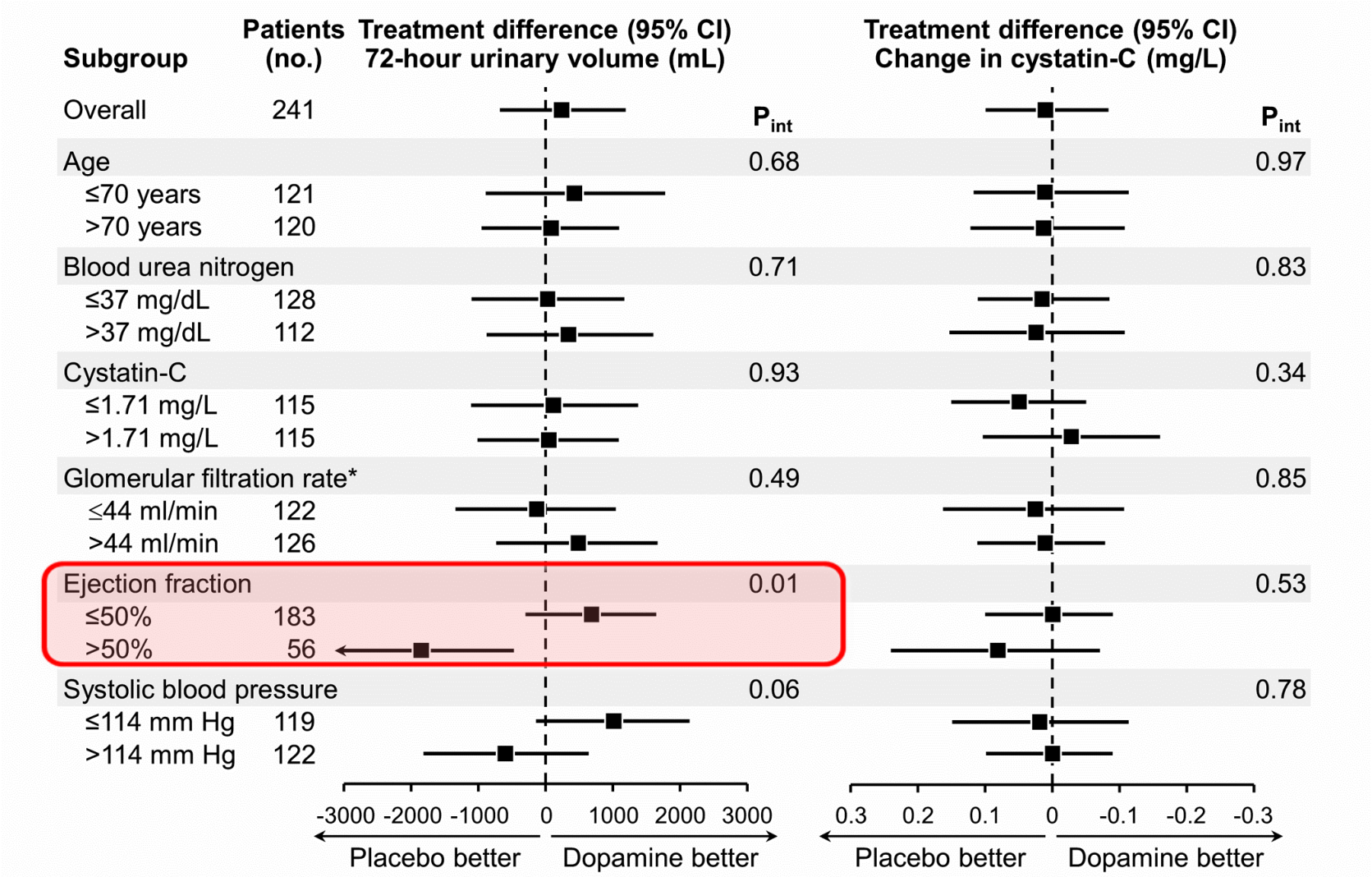
72 Hour Urine Volume



Change in Cystatin-C



Low Dose Dopamine
Sub-group Analysis



Low Dose Dopamine
Secondary Endpoints

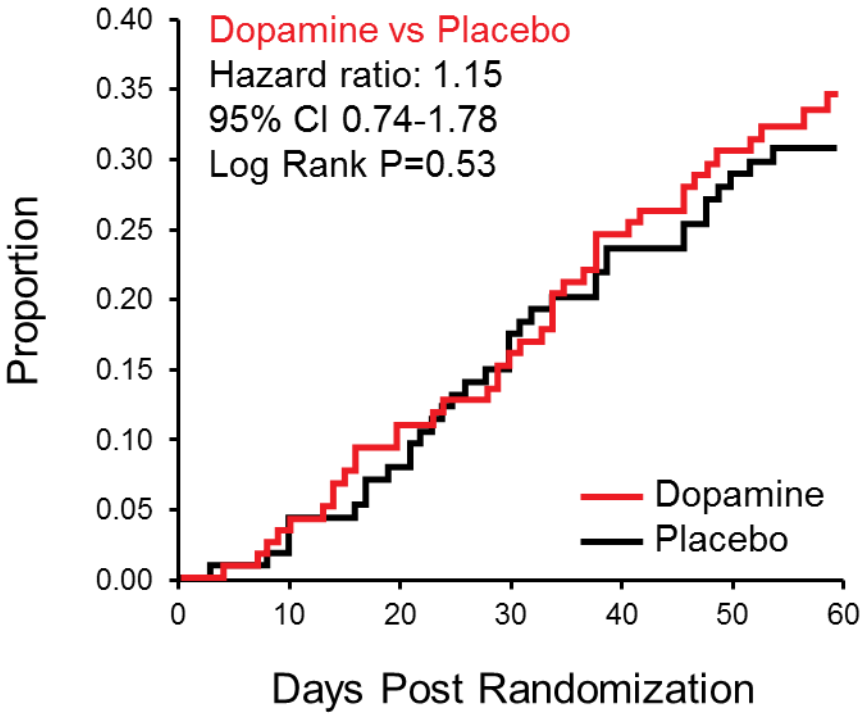
- No significant treatment effect on secondary endpoints reflective of:
  - Decongestion
  - Renal function
  - Symptom relief

Study Drug Tolerance	Dopamine (n=122)	Placebo (N = 119)	P Value
Study drug reduced dose or d/c - Hypotension	0.9%	10.4%	<0.001
Study drug reduced dose or d/c - Tachycardia	7.2%	0.9%	<0.001
Study drug d/c before 72 hrs – Any Cause	23%	25%	0.72

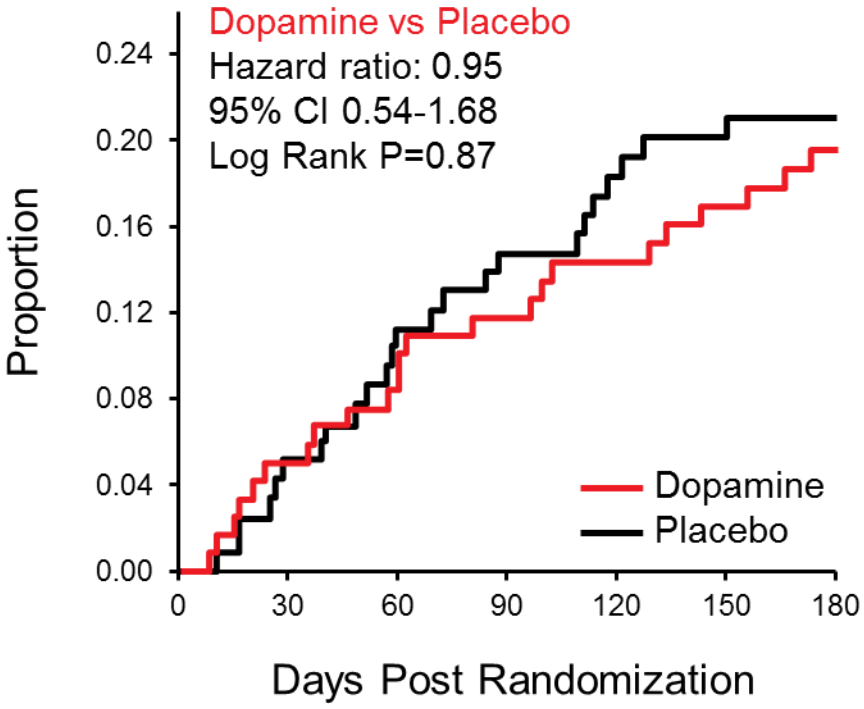
Low Dose Dopamine
Clinical Outcomes

HEART FAILURE NETWORK

60 Day Death/ Unscheduled visit/ HF Readmission



180 Day Mortality



HEART FAILURE NETWORK

Results
Nesiritide Strategy

U.S. Department of Health and Human Services
National Institutes of Health

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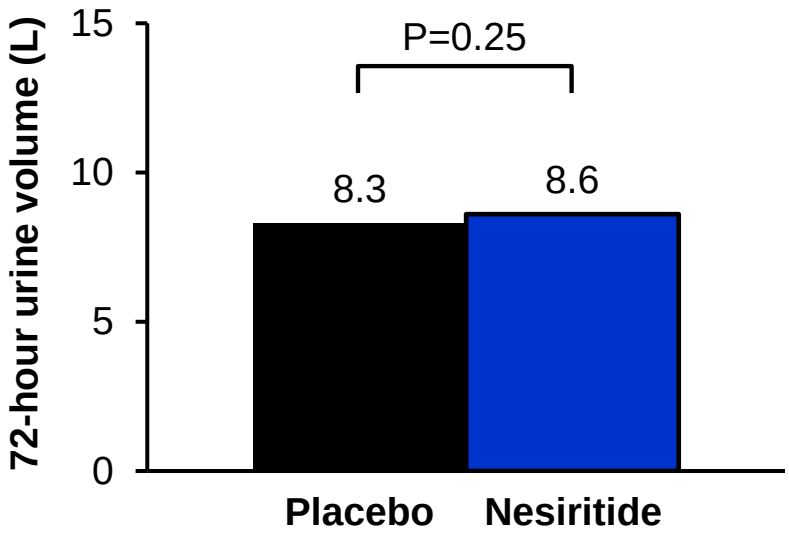
People Science Health

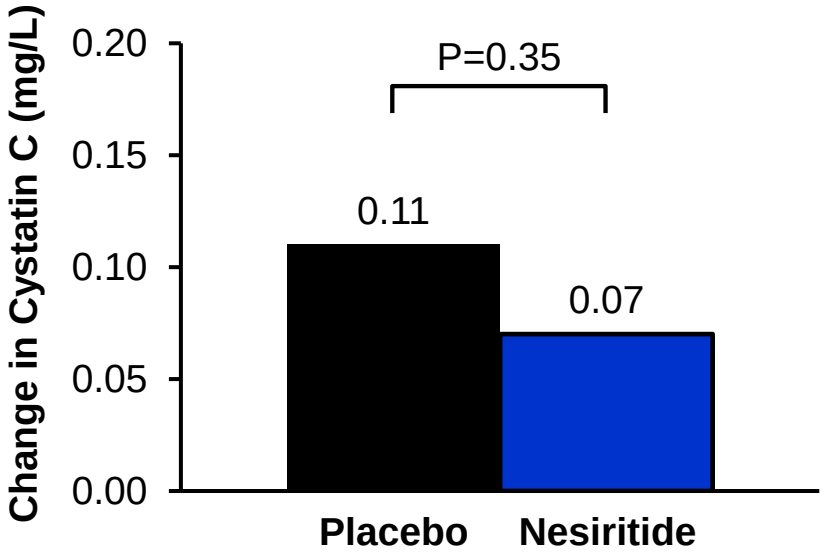
Low Dose Nesiritide
Co-primary End-points

HEART FAILURE NETWORK

72 Hour Urine Volume

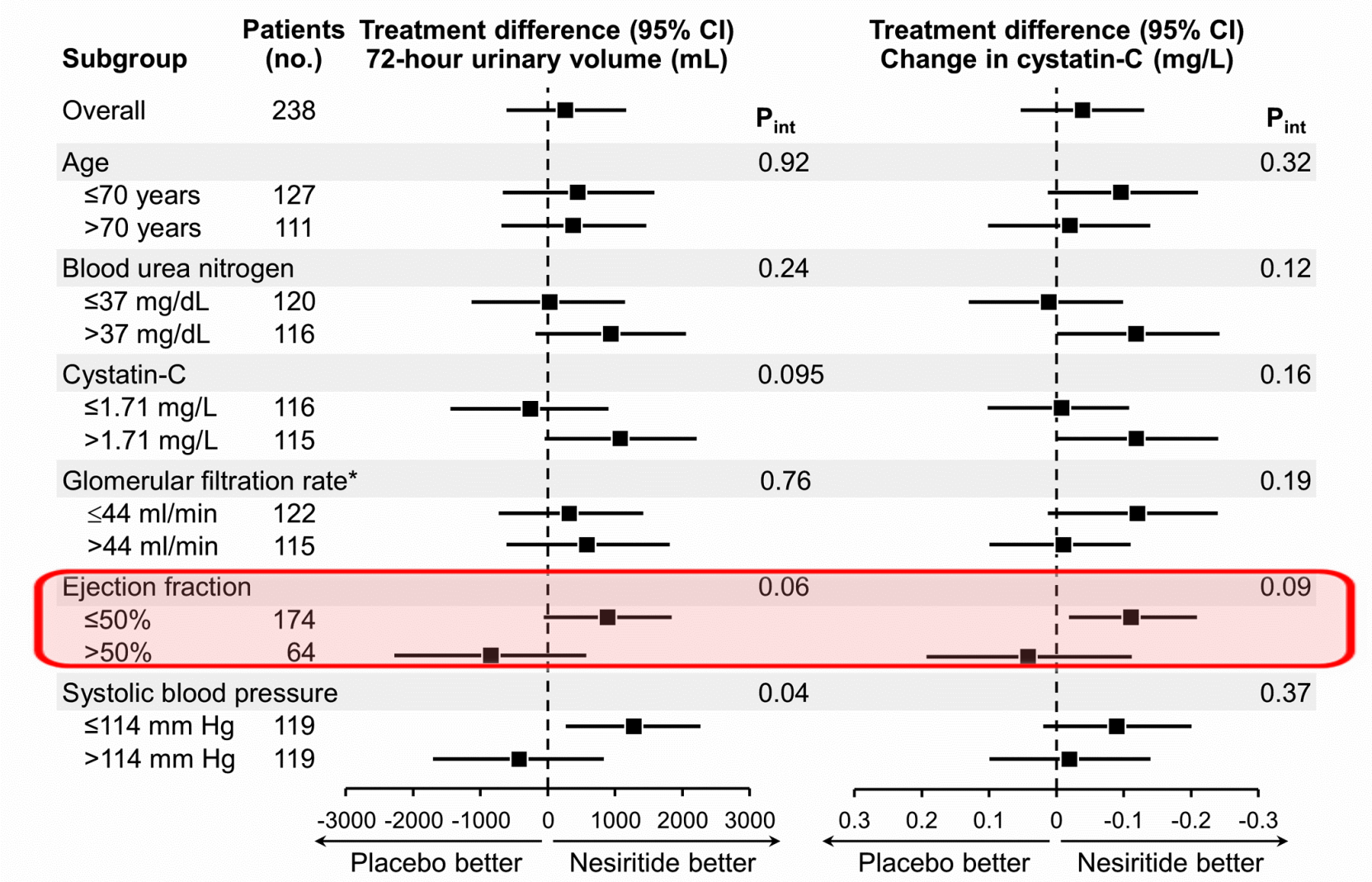


Change in Cystatin-C



Low Dose Nesiritide
Sub-group Analysis

HEART FAILURE NETWORK



Low Dose Nesiritide
Secondary Endpoints

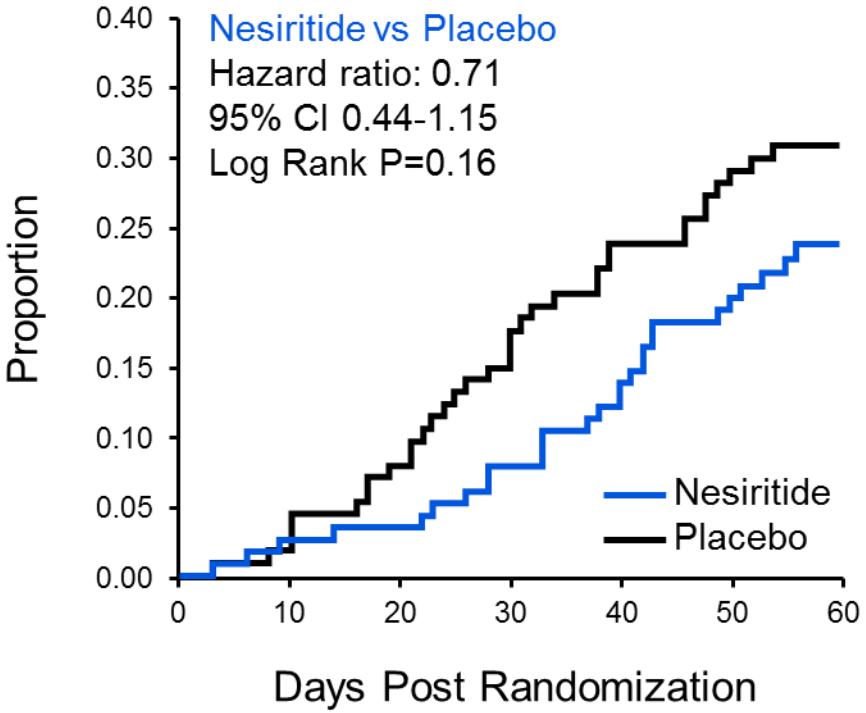
- No significant treatment effect on secondary endpoints reflective of:
  - Decongestion
  - Renal function
  - Symptom relief

Study Drug Tolerance	Nesiritide (n=119)	Placebo (N = 119)	P Value
Study drug dose reduced or d/c - Hypotension	18.8%	10.4%	0.07
Study drug dose reduced or d/c - Tachycardia	0%	0.9%	0.50
Study drug d/c before 72 hrs – Any Cause	25%	25%	0.94

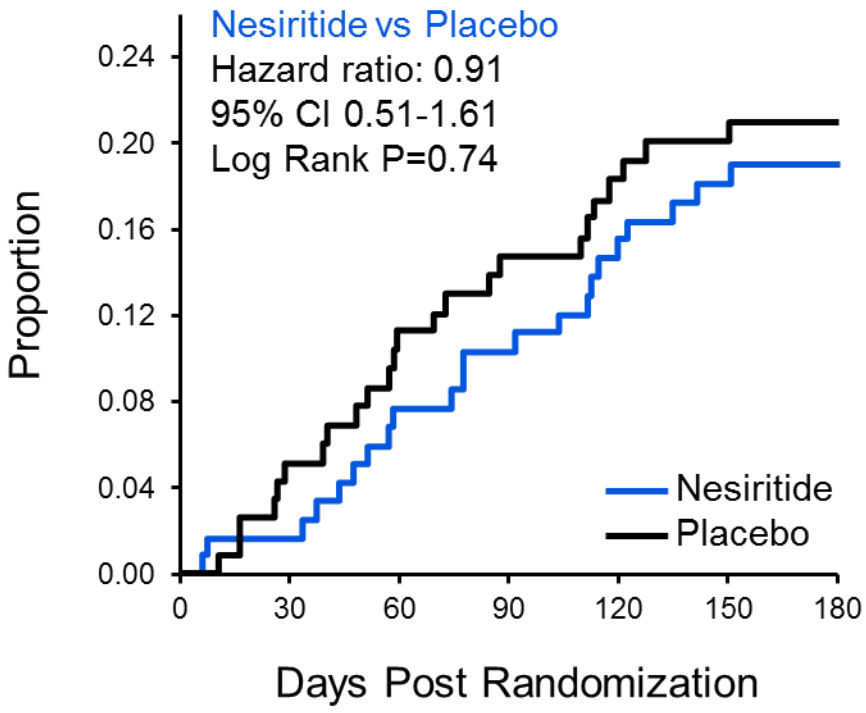
Low Dose Nesiritide
Clinical Outcomes

HEART FAILURE NETWORK

60 Day Death/ Unscheduled visit/ HF Readmission



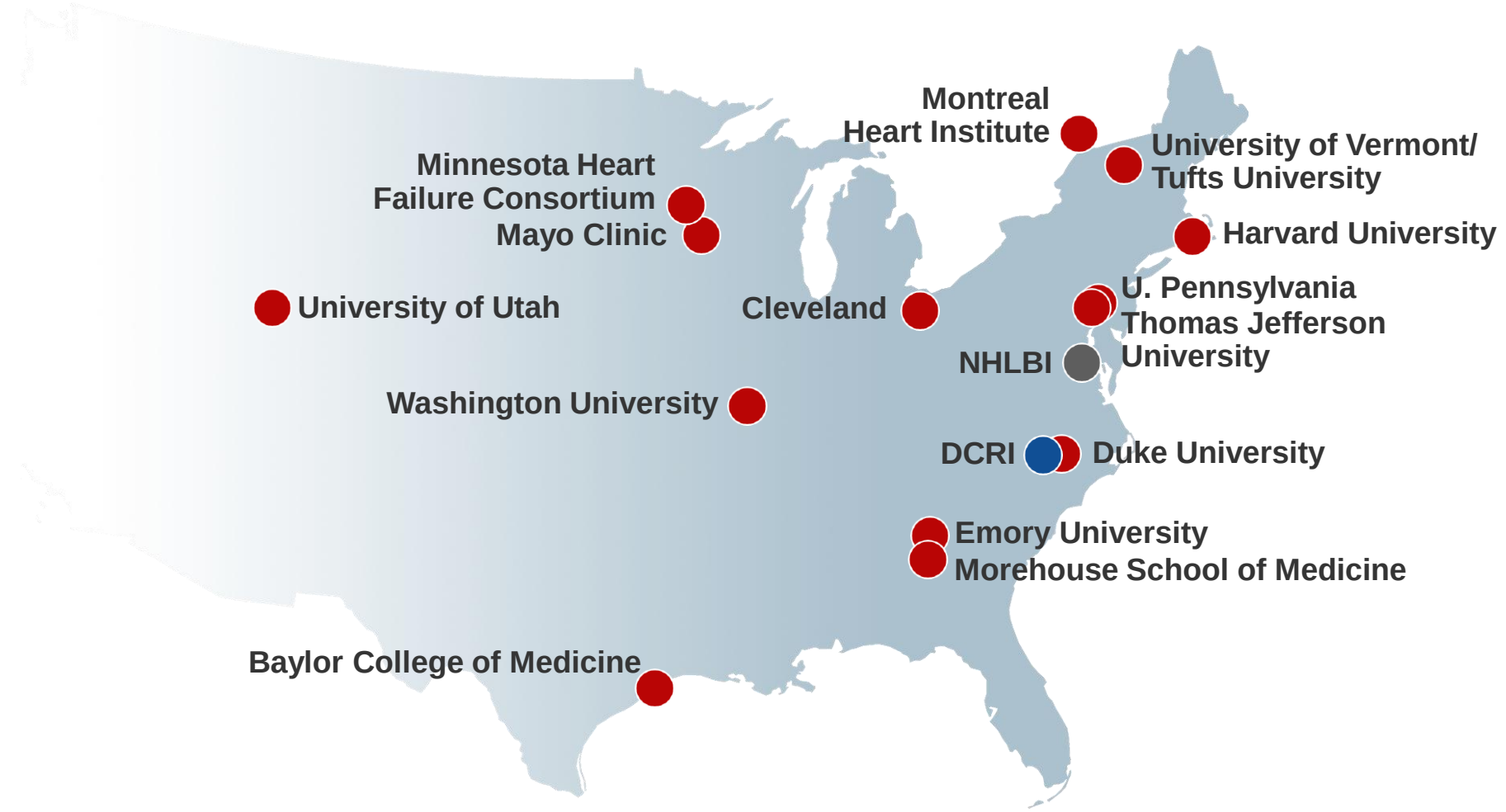
180 Day Mortality

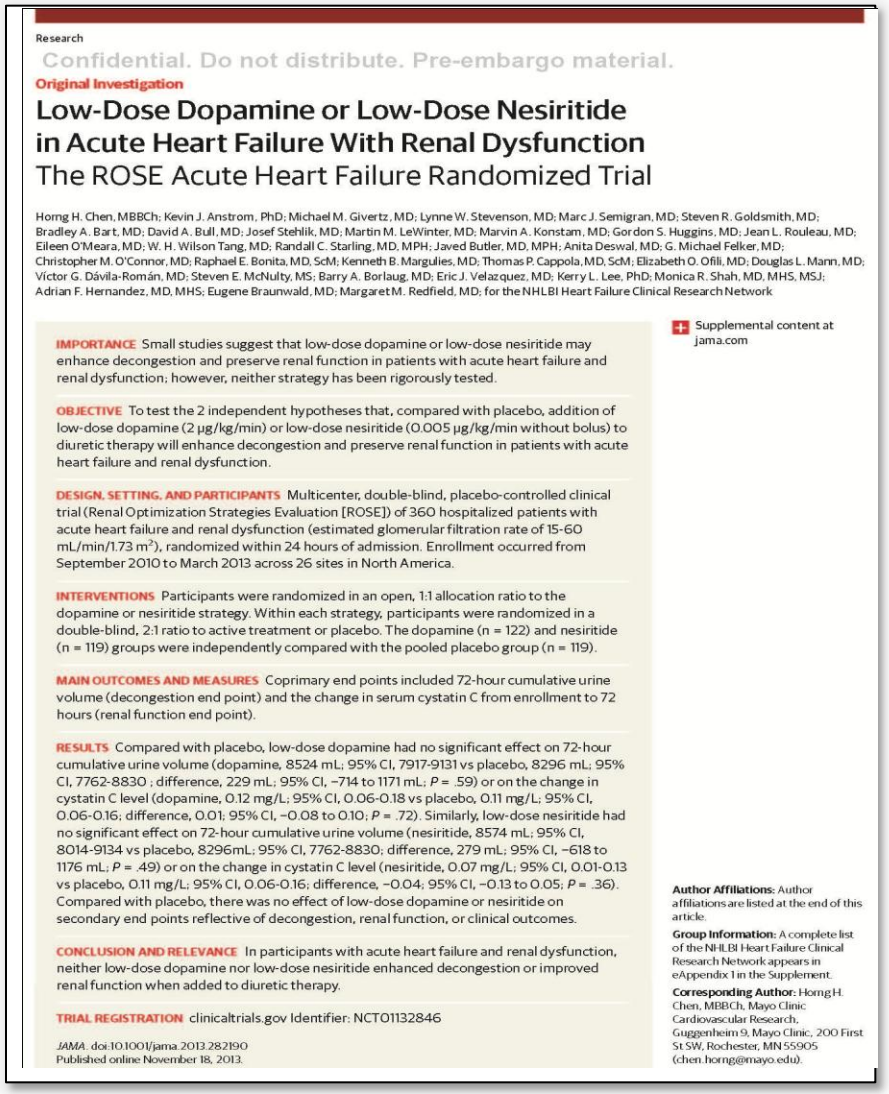


Conclusions

- In patients with AHF and underlying renal dysfunction, when added to standardized diuretic dosing, neither low dose dopamine, nor low dose nesiritide, enhanced decongestion or improved renal function.
- Future investigations of these or other acute heart failure therapies may need to assess the potential for differential responses in heart failure with preserved versus reduced ejection fraction.

HEART FAILURE NETWORK





Research

Original Investigation

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

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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.

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

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