



National Heart
Lung and Blood Institute

HEART
FAILURE NETWORK



Diuretic Optimization Strategies Evaluation in Acute Heart Failure (DOSE)

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on behalf of the

NHLBI Heart Failure Clinical Research Network

Study Organization

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Background

- IV loop diuretics are the most commonly prescribed therapy for acute decompensated heart failure
- Few prospective studies exist to guide practice, resulting in substantial variation in route of administration and dosing
- Observational data suggest that higher diuretic doses may be associated with risk of worsening renal function, heart failure progression, or death¹
- Cochrane collaboration systematic review suggests continuous infusion may be superior to intermittent bolus dosing²

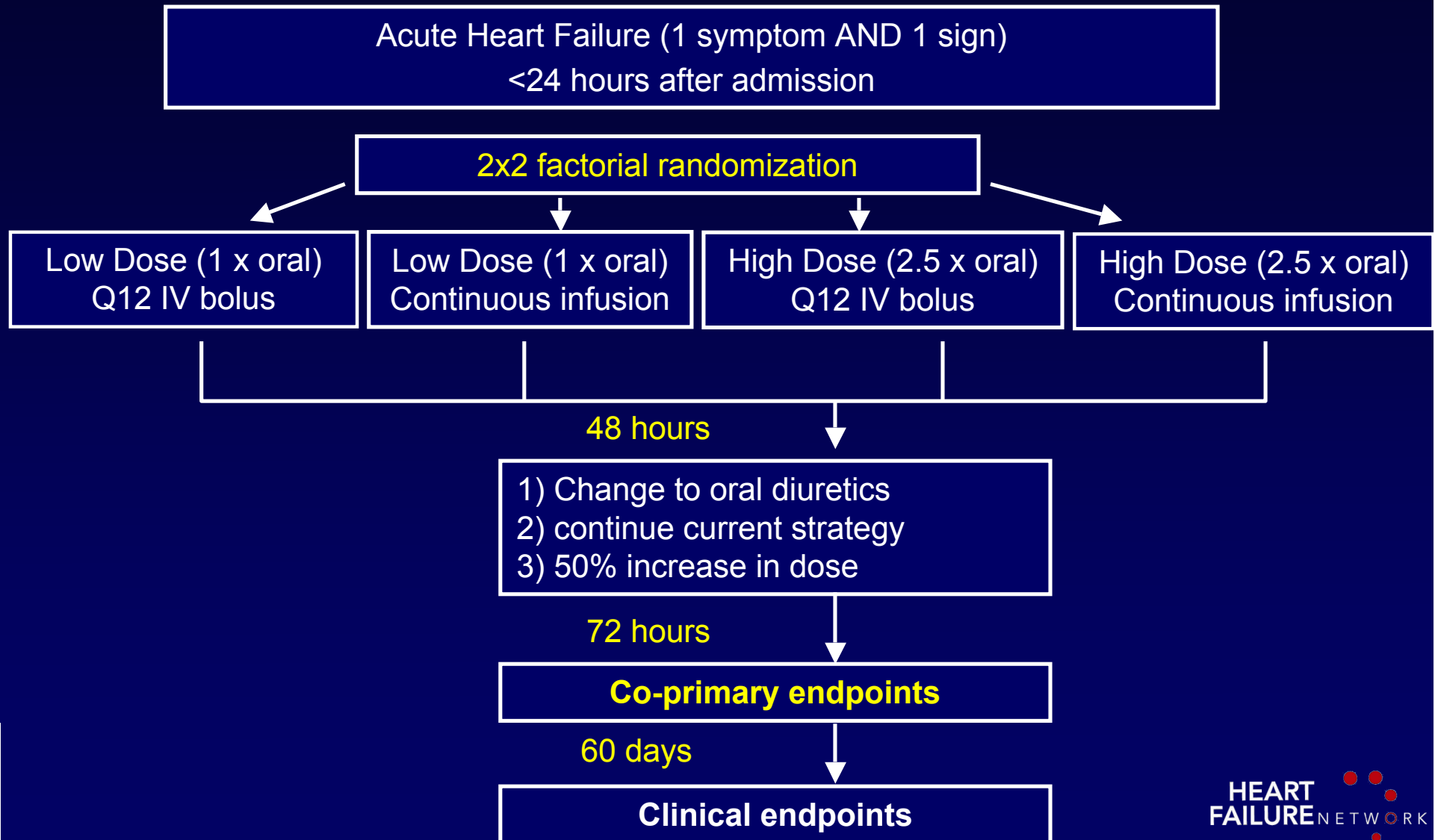
1. Felker, GM et al. Circulation: Heart Failure, 2009

2. Salvator, DR. Cochrane Database, 2005

Aims

- To evaluate the safety and efficacy of various initial strategies of furosemide therapy in patients with ADHF
 - **Route of administration:**
 - Q12 hours bolus
 - Continuous infusion
 - **Dosing**
 - Low intensification (1 x oral dose)
 - High intensification (2.5 x oral dose)

Study Design

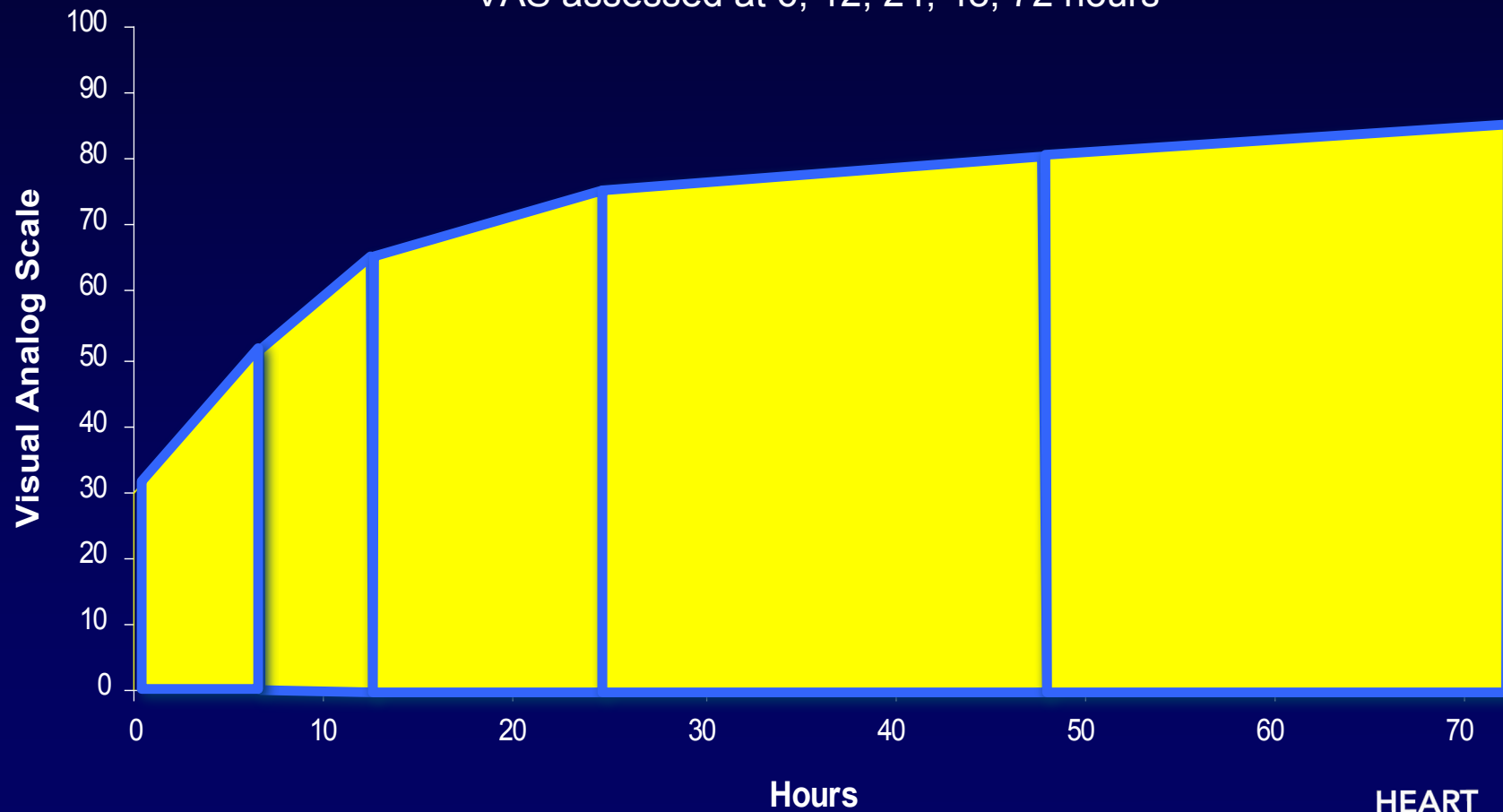


Co-Primary Endpoints

- **Efficacy:**
 - Patient Global Assessment by visual analog scale over 72 hours using area under the curve
- **Safety:**
 - Change in creatinine from baseline to 72 hours

Visual Analog Scale Area Under the Curve

VAS assessed at 6, 12, 24, 48, 72 hours



Secondary Endpoints

- Change in weight over 24, 48, 72, 96 hours
- Freedom from signs and symptoms of congestion at 72 hours
- Bivariate vector of change in creatinine and weight at 72 hours
- Dyspnea VAS AUC over 24, 48 and 72 hours
- Change in serum creatinine at 24, 48, 96 hrs, day 7 (or discharge), and day 60
- Change in cystatin C at 72 hours, day 7 (or discharge) and day 60
- Persistent or worsening heart failure
- Development of worsening renal function (increase in Cr > 0.3 mg/dL at any time during initial 72 hours)
- Treatment failure (persistent heart failure, worsening renal failure, or death)
- Index hospitalization length of stay
- Death, rehospitalization, or ED visit within 60 days

Inclusion-Exclusion Criteria

Inclusion

- ≥ 18 years old
- Prior clinical diagnosis of heart failure with daily home use of oral loop diuretic for at least one month
- Daily oral dose of furosemide ≥ 80 mg and ≤ 240 mg (or equivalent)
- Identified within 24 hours of hospital admission
- Heart failure defined by at least 1 symptom and 1 sign
- Anticipated need for IV loop diuretics for at least 48 hours
- Willingness to provide informed consent

Exclusion

- Received or planned IV vasoactive treatment (inotropes, vasodilators) or ultra-filtration therapy for heart failure
- Systolic BP < 90 mmHg
- Serum creatinine > 3.0 mg/dl at baseline or renal replacement therapy
- BNP < 250 ng/ml or NT-proBNP < 1000 mg/ml (if measured for clinical purposes)
- Acute coronary syndrome within 4 weeks
- Anticipated need for coronary angiography or other procedures requiring IV contrast

Statistical Methods

- Target sample size: 300 patients
 - 88% power for detecting creatinine difference of 0.2 mg/dL
 - 88% power for a 600 point difference in VAS AUC
- 1:1:1:1 permuted block randomization, stratified by clinical site
- Treatment comparisons by “intention to treat”
- Statistical significance: $p \leq 0.025$ for the two primary endpoints, $p \leq 0.05$ for secondary endpoints
- Each treatment factor (route and intensity) compared using general linear model (continuous endpoints), logistic regression (binary endpoints), Cox model and Kaplan-Meier curves (event-time endpoints)

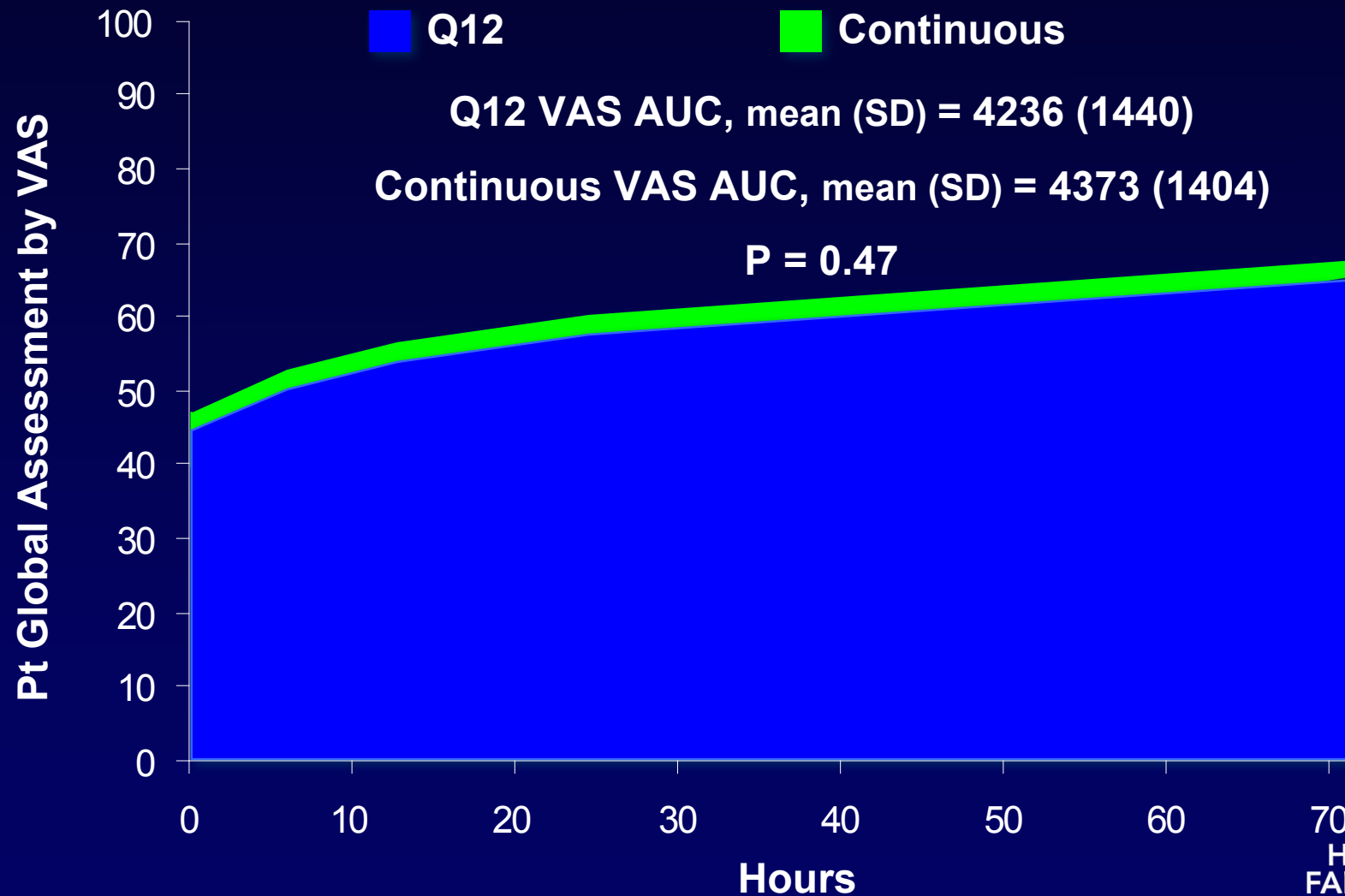
Baseline Characteristics (1)

Characteristic	N = 308
Age, yrs (mean, SD)	66 (14)
Male, % (N)	73% (226)
Race, % white, (N)	72% (222)
Baseline furosemide dose, mg/day, mean (SD)	131 (52)
Ejection fraction, %, mean (SD)	35 (18)
Prior HF hosp in last 12 mos, % (N)	74% (225)
Ischemic etiology, % (N)	57% (176)
Atrial fibrillation or flutter, % (N)	53% (162)
Diabetes mellitus, % (N)	51% (158)

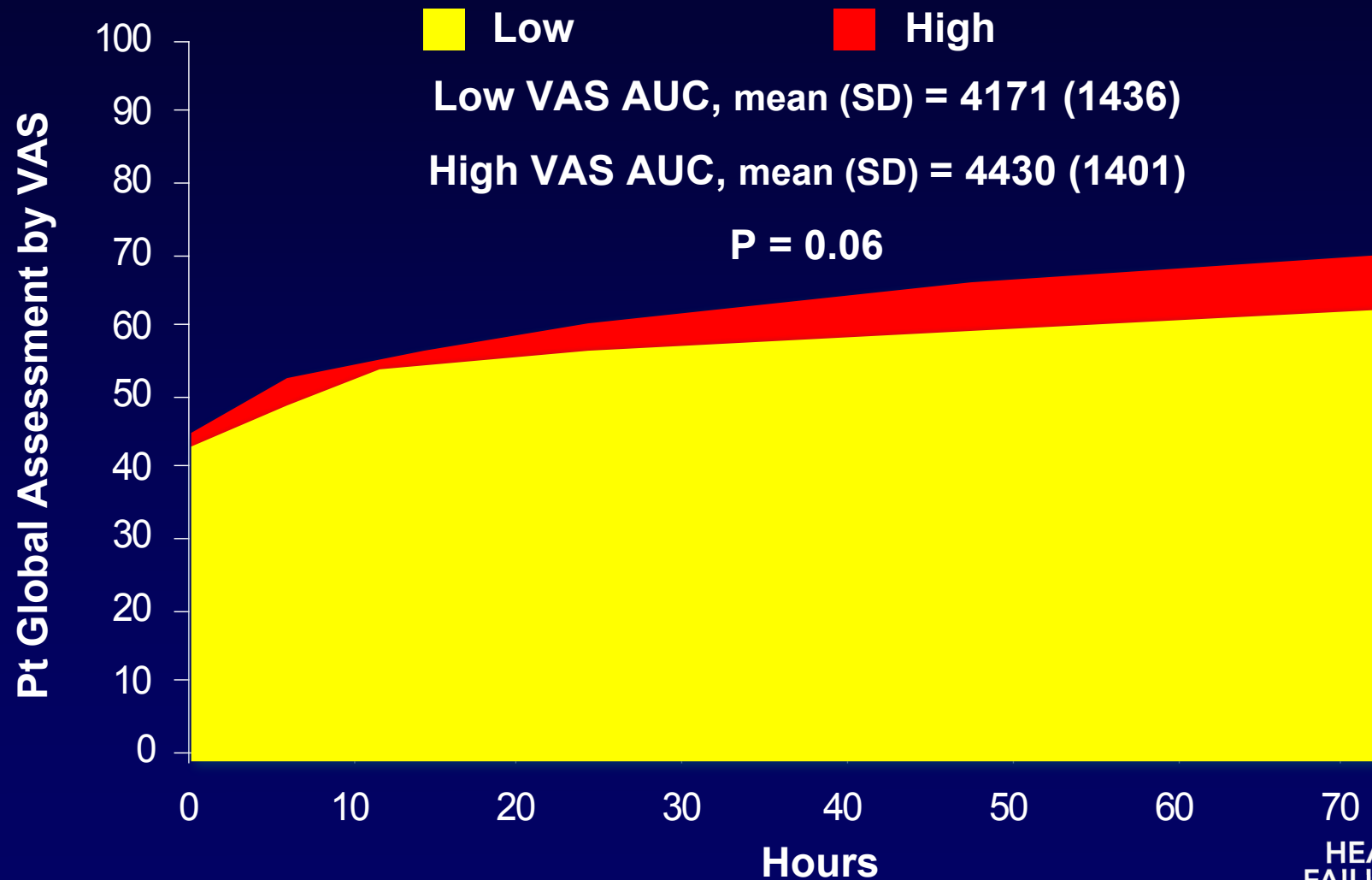
Baseline Characteristics (2)

Characteristic	N = 308
ACE or ARB, %, (N)	64% (197)
Beta blocker, % (N)	83% (256)
Aldosterone antagonist % (N)	28% (86)
Systolic blood pressure, mg, mean (SD)	119 (20)
Heart rate, beats/min, mean (SD)	78 (16)
Jugular venous pulse > 8 cm H ₂ O, % (N)	91% (267)
Rales, % (N)	58% (178)
Sodium, mg/dL, mean (SD)	138 (4)
Creatinine, mg/dL, mean (SD)	1.6 (0.5)
NT-proBNP, pg/mL, mean (SD)	7439 (7319)

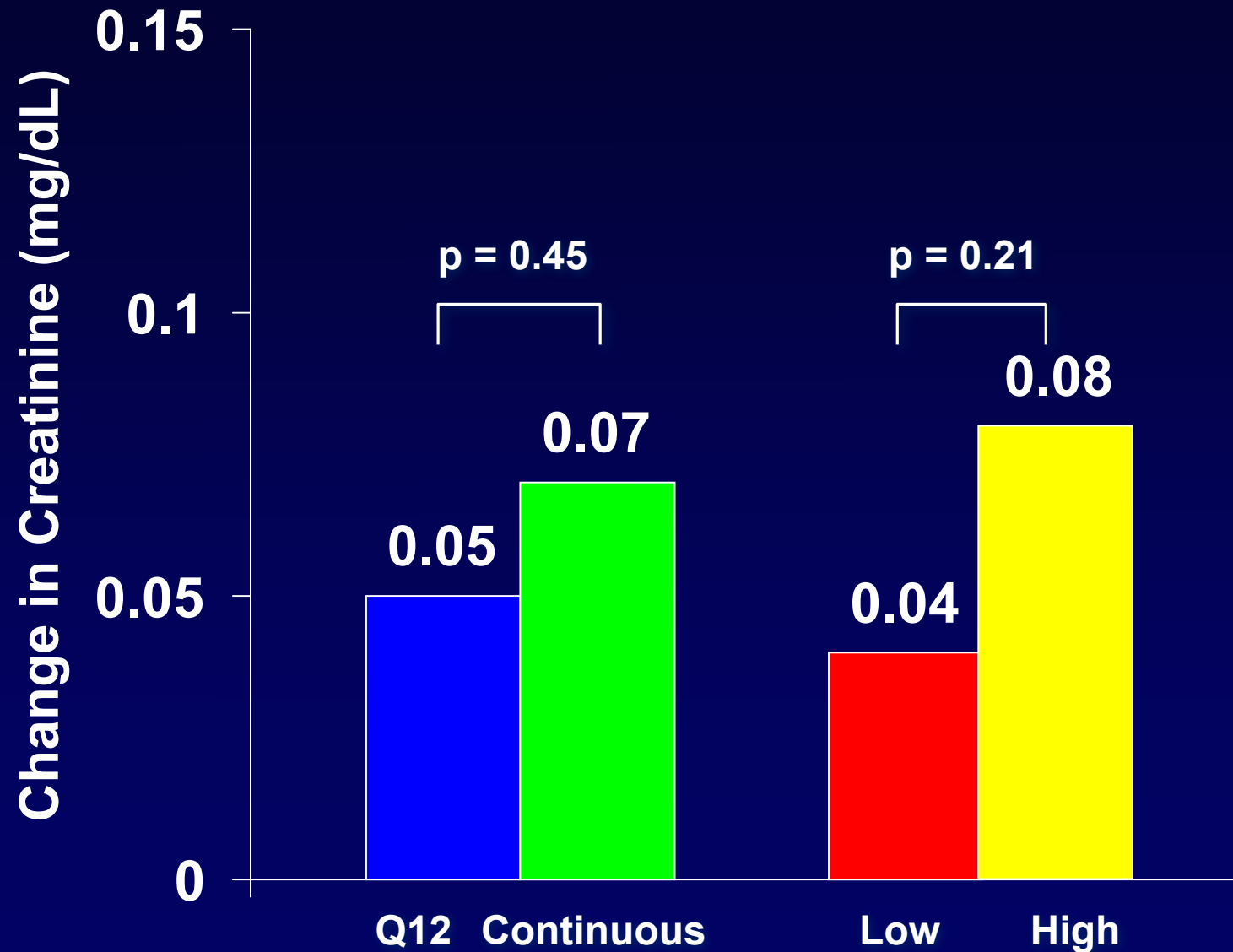
Patient Global Assessment VAS AUC: Q12 vs. Continuous



Patient Global Assessment VAS AUC: Low vs. High Intensification



Change in Creatinine at 72 hours



Secondary Endpoints: Q12 vs. Continuous

	Q12	Continuous	P value
Dyspnea VAS AUC at 72 hrs	4456	4699	0.36
% free from congestion at 72 hrs	14%	15%	0.78
Change in weight at 72 hrs	-6.8 lbs	-8.1 lbs	0.20
Net volume loss at 72 hrs	4237 mL	4249 mL	0.89
Change in NTproBNP at 72 hrs (pg/mL)	-1326	-1773	0.44
% treatment failure	38%	39%	0.88
% with Cr increase > 0.3 mg/dL within 72 hrs	17%	19%	0.64
Length of stay, days (median)	5	5	0.97

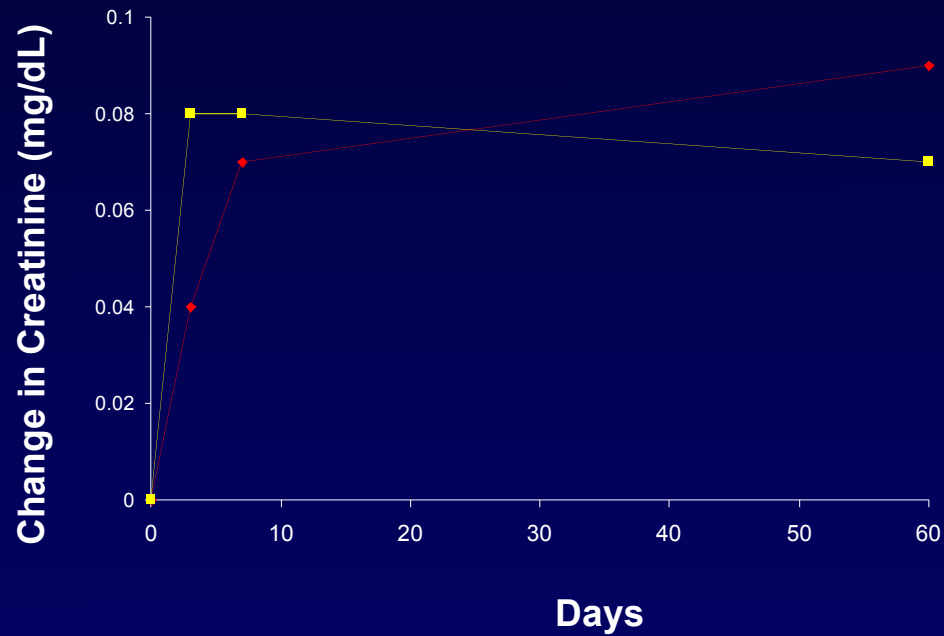
Secondary Endpoints: Low vs. High Intensification

	Low	High	P value
Dyspnea VAS AUC at 72 hours	4478	4668	0.041
% free from congestion at 72 hrs	11%	18%	0.091
Change in weight at 72 hrs	-6.1 lbs	-8.7 lbs	0.011
Net volume loss at 72 hrs	3575 mL	4899 mL	0.001
Change in NTproBNP at 72 hrs (pg/mL)	-1194	-1882	0.06
% Treatment failure	37%	40%	0.56
% with Cr increase > 0.3 mg/dL within 72 hrs	14%	23%	0.041
Length of stay, days (median)	6	5	0.55

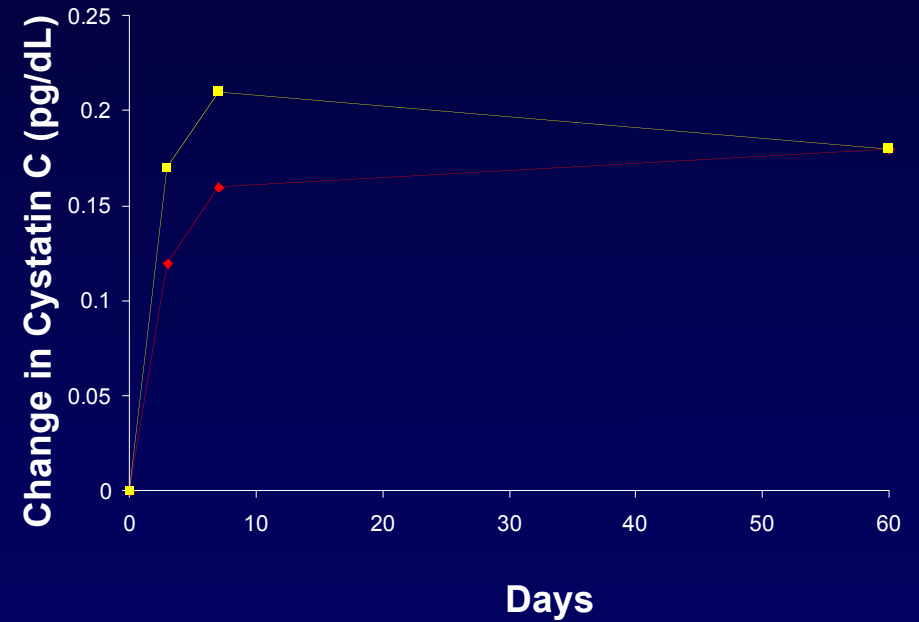
Changes in Renal Function over Time: Low vs. High

— Low — High

Creatinine

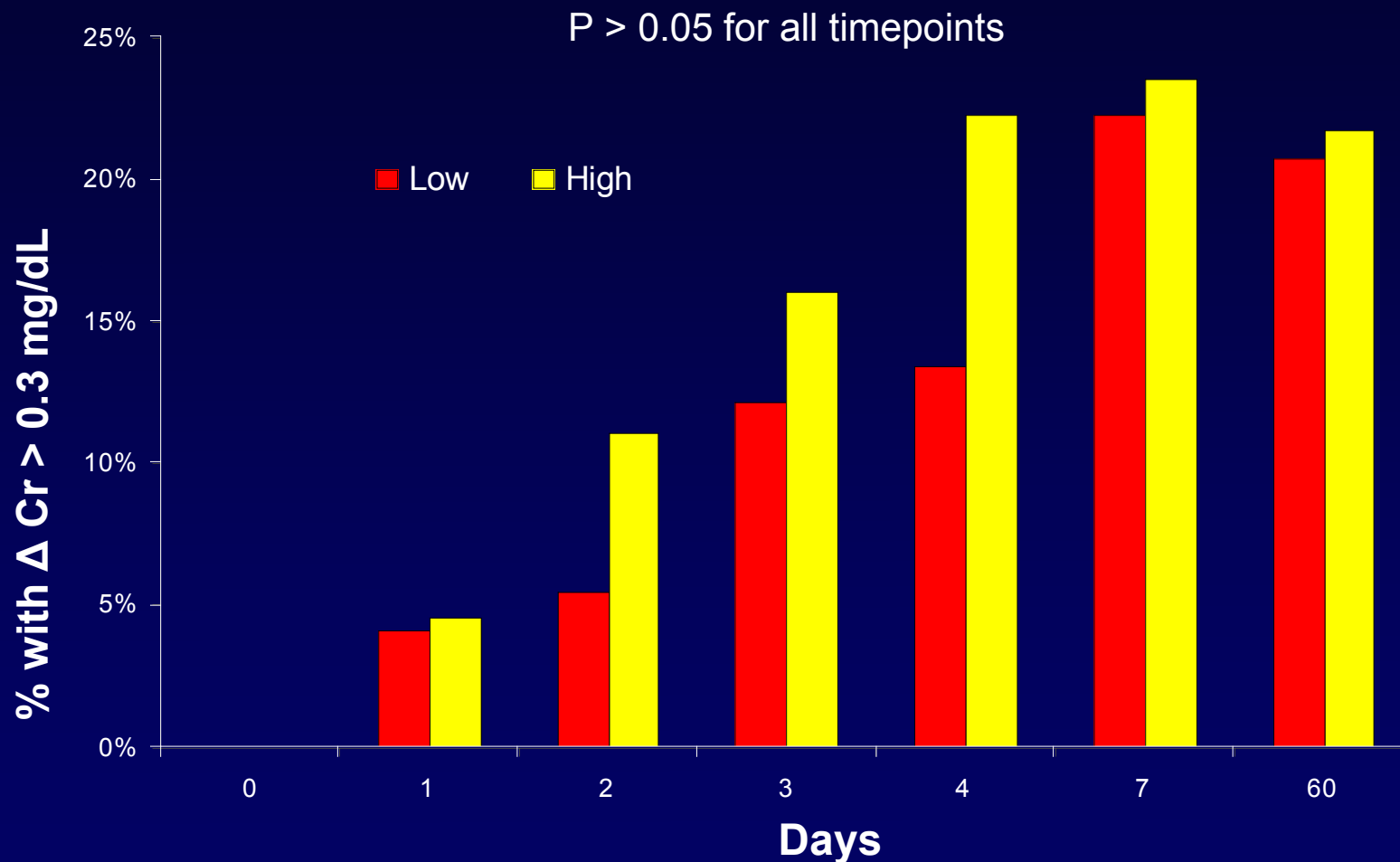


Cystatin C



$P > 0.05$ for all timepoints

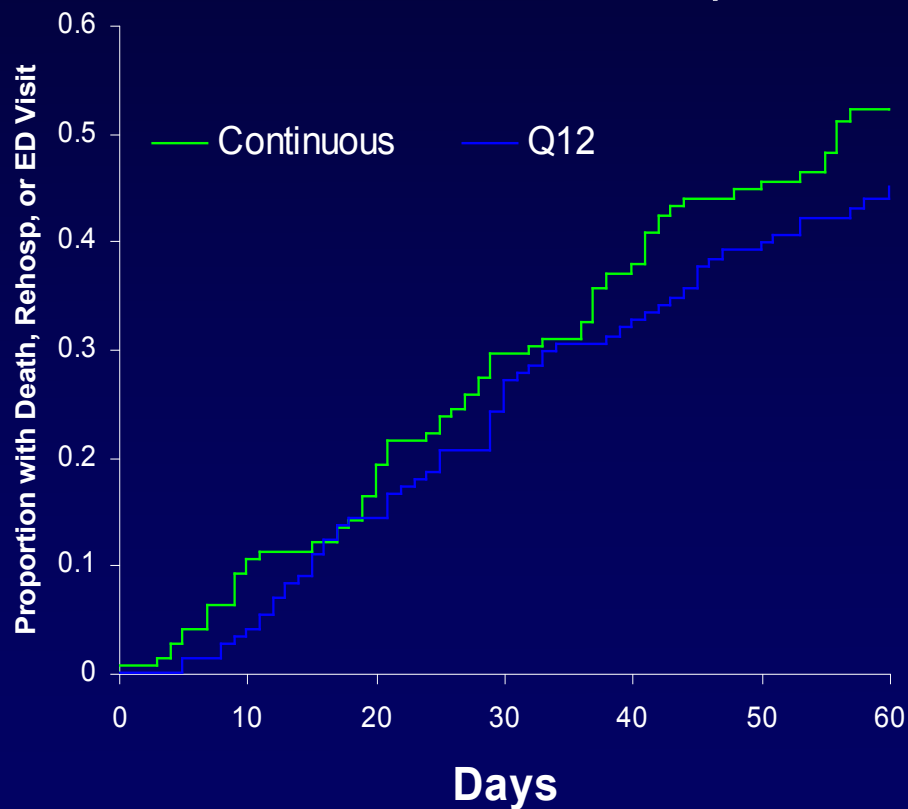
Proportion with Worsening Renal Function*: Low vs. High



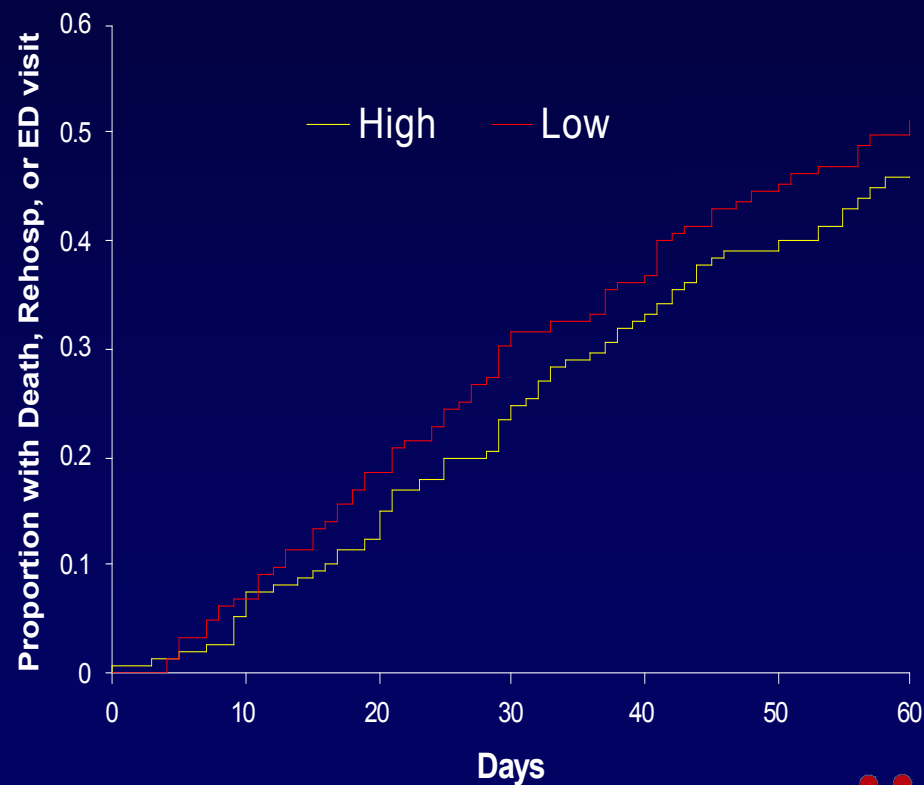
*Based on local lab creatinine values

Death, Rehospitalization, or ED Visit

HR for Continuous vs. Q12 = 1.19
95% CI 0.86, 1.66, $p = 0.30$



HR for High vs. Low = 0.83
95% CI 0.60, 1.16, $p = 0.28$



Limitations

- DOSE evaluated only patients with chronic heart failure and moderate to high diuretic requirements
- DOSE had limited power to detect differences in clinical events
- DOSE protocol allowed changes in therapy at 48 hours based on clinical response, which may have minimized observed differences between groups

Conclusions

- There was no statistically significant difference in global symptom relief or change in renal function at 72 hours for either:
 - Q12 bolus vs. Continuous infusion
 - Low intensification vs. High intensification

Conclusions (2)

- There was no evidence of benefit for continuous infusion compared to Q12 hour bolus on any secondary endpoint
- Despite transient changes in renal function, there was no evidence for higher risk of clinical events at 60 days associated with the high intensification strategy
- High intensification (2.5 x oral dose) was associated with trends towards greater improvement in multiple domains:
 - Symptom relief (global assessment and dyspnea)
 - Weight loss and net volume loss
 - Proportion free from signs of congestion
 - Reduction in NT-proBNP



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- Baylor
- Duke
- Harvard
- Mayo Clinic
- Minnesota
- Montreal
- Morehouse
- Utah
- Vermont

