



**Ultrafiltration versus IV Diuretics for
Patients Hospitalized for Acute
Decompensated Congestive Heart
Failure: A Prospective Randomized
Clinical Trial**

UNLOAD Trial



Investigators & Sites

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- 90% of 1 million HF hospitalizations are due to volume overload
- Hypervolemia contributes to HF progression, mortality and high re-hospitalization rates
- IV diuretics reduce congestion
- IV diuretics may be associated with increased morbidity and mortality
- 20%-30% of HF patients develop diuretic resistance

Study Hypotheses

- Compared to standard IV diuretic therapy for hypervolemic heart failure patients, veno-venous ultrafiltration is:
 - Superior to aggressive IV diuretic therapy in reducing volume overload
 - Associated with sustained clinical benefits
 - Similar to IV diuretics in terms of safety

Primary End Points

■ Efficacy

- Weight loss at 48 hours after randomization
- Dyspnea score at 48 hours after randomization

■ Safety

- Changes in serum blood urea nitrogen, creatinine, and electrolytes at 8, 24, 48 and 72 hours after randomization, discharge, 10, 30 and 90 days
- Episodes of hypotension during the first 48 hours after randomization

Secondary End Points

- BNP levels at 48 hours after randomization, 30 and 90 days
- NYHA class, Minnesota Living with Heart Failure score, Global Assessment score at discharge and follow-up
- Diuretic doses after Ultrafiltration or Standard Care
- Percentage of patients re-hospitalized for HF
- Absolute number of re-hospitalizations for HF
- Days of re-hospitalization for HF
- Unscheduled office and ED visits

Methods

Inclusion Criteria

- ≥ 18 years of age
- Hospitalized with evidence of volume overload by at least two of the following:
 - peripheral edema $\geq 2+$
 - jugular venous distension ≥ 7 cm
 - radiographic pulmonary edema or pleural effusion
 - enlarged liver or ascites
 - pulmonary rales, paroxysmal nocturnal dyspnea or orthopnea
- Randomization within 24 hours of hospitalization

Methods

Exclusion Criteria

- Acute coronary syndrome
- Serum creatinine > 3.0 mg/dl
- Hemodynamic instability requiring inotropic drugs
- Hematocrit $> 45\%$
- Administration of vasoactive drugs prior to randomization
- Contraindications to anticoagulation
- Heart transplant

- Once randomized, all patients:
 - Daily 2 g sodium, 2000 ml fluid intake restriction
 - Oral diuretics discontinued
 - ACE inhibitors, ARBs, β -blockers and digoxin continued

Methods

Study Procedures

■ Ultrafiltration arm:

- Ultrafiltration rate up to 500 cc/hour
- Duration/rate of fluid removal decided by treating physicians
- IV diuretics prohibited during ultrafiltration

■ Standard Care arm:

- IV diuretics as bolus or continuous infusions
- IV doses at least 2 times daily PO dose for the first 48 hours after randomization

Methods

Ultrafiltration Device

- Blood flow adjustable (10-40 ml/minute)
- Total extracorporeal blood volume 33 ml
- Peripheral, midline, or central venous access
- Anticoagulation with heparin recommended

Methods

Statistical Analysis

- Differences between treatment groups:
 - Pearson's chi-square or Fisher's exact test for categorical variables
 - Wilcoxon's rank sum test for continuous variables
- The effects of covariates on weight loss at 48 hours tested using analysis of variance (ANOVA)
- Change over time within treatment groups:
Wilcoxon's matched pairs signed ranks test
- P-values (2-tailed) ≤ 0.05 considered statistically significant

Baseline Demographics and Comorbidities

| Characteristic | Ultrafiltration N=100 | Standard Care N=100 | P Value |
|---------------------------|--------------------------|------------------------|------------|
| Age – years (m ± sd) | 62 ± 15 | 63 ± 14 | 0.823 |
| Male Sex % | 70 | 68 | 0.879 |
| Race | | | |
| Caucasian % | 55 | 52 | 0.489 |
| African American % | 41 | 40 | |
| Other % | 4 | 8 | |
| History of Hypertension % | 74 | 74 | 1.000 |
| Coronary Heart Disease % | 56 | 48 | 0.474 |
| COPD % | 27 | 30 | 0.755 |
| Diabetes % | 50 | 49 | 0.890 |

Baseline Heart Failure Characteristics

| Characteristic | Ultrafiltration N=100 | Standard Care N=100 | P Value |
|--|--------------------------|------------------------|------------|
| Prior Heart Failure % | 95 | 95 | 1.000 |
| Hospitalizations for HF in ≤ 12 Mos. (m ± sd) | 1.6 ± 1.9 | 1.5 ± 1.7 | 0.981 |
| % of patients LVEF ≤ 40 % | 71 | 70 | 0.736 |
| S ₃ % | 44 | 32 | 0.109 |
| JVD > 10 cm % | 68 | 62 | 0.363 |
| Pulmonary Rales % | 60 | 51 | 0.343 |
| Peripheral Edema % | 81 | 79 | 0.860 |

Baseline Functional Capacity and Vital Signs

| Characteristic | Ultrafiltration N=100 | Standard Care N=100 | P Value |
|---------------------------|--------------------------|------------------------|------------|
| NYHA Class | | | |
| m ± sd | 3.4 ± 0.6 | 3.4 ± 0.6 | 0.861 |
| III % | 52 | 48 | |
| IV % | 45 | 45 | |
| MLWHF Score | | | |
| m ± sd | 70 ± 23 | 74 ± 18 | 0.707 |
| Weight (kg) | | | |
| m ± sd | 101 ± 27 | 96 ± 29 | 0.194 |
| Systolic BP (mmHg) | | | |
| m ± sd | 126 ± 26 | 129 ± 24 | 0.233 |
| Heart Rate (bpm) | | | |
| m ± sd | 81 ± 17 | 83 ± 16 | 0.381 |

Baseline Laboratory Values

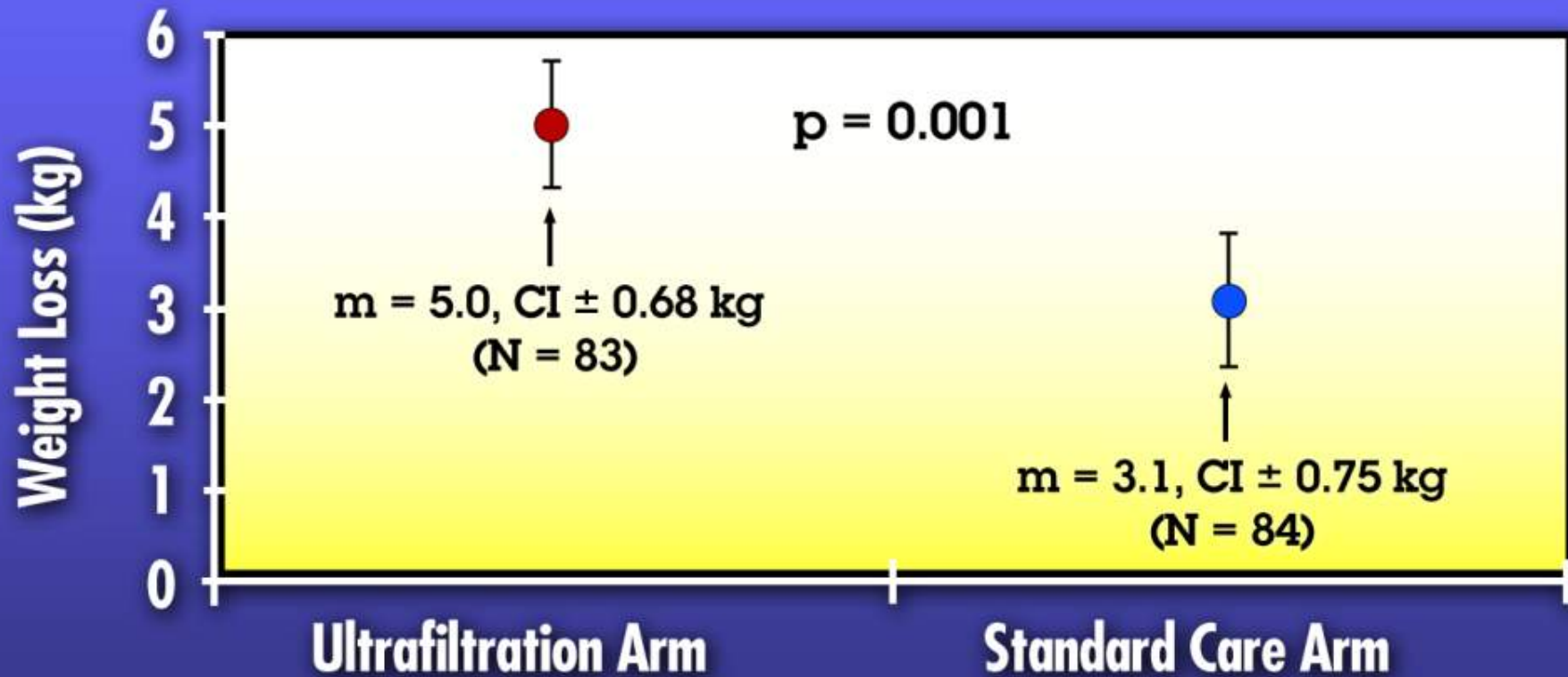
| Characteristic | Ultrafiltration N=100 | Standard Care N=100 | P Value |
|------------------------------------|--------------------------|------------------------|------------|
| BUN (mg/dl) m ± sd | 32 ± 16 | 33 ± 20 | 0.920 |
| Serum Creatinine (mg/dl) m ± sd | 1.5 ± 0.5 | 1.5 ± 0.5 | 0.834 |
| Serum Sodium (mg/dl) m ± sd | 139 ± 4.9 | 139 ± 5.0 | 0.751 |
| Serum Potassium (mg/dl) m ± sd | 4.0 ± 0.6 | 4.2 ± 0.6 | 0.028 |
| Serum BNP (pg/ml) m ± sd | 1256 ± 1203 | 1309 ± 1494 | 0.840 |
| Hematocrit % m ± sd | 36 ± 5 | 36 ± 6 | 0.643 |

Baseline Medications

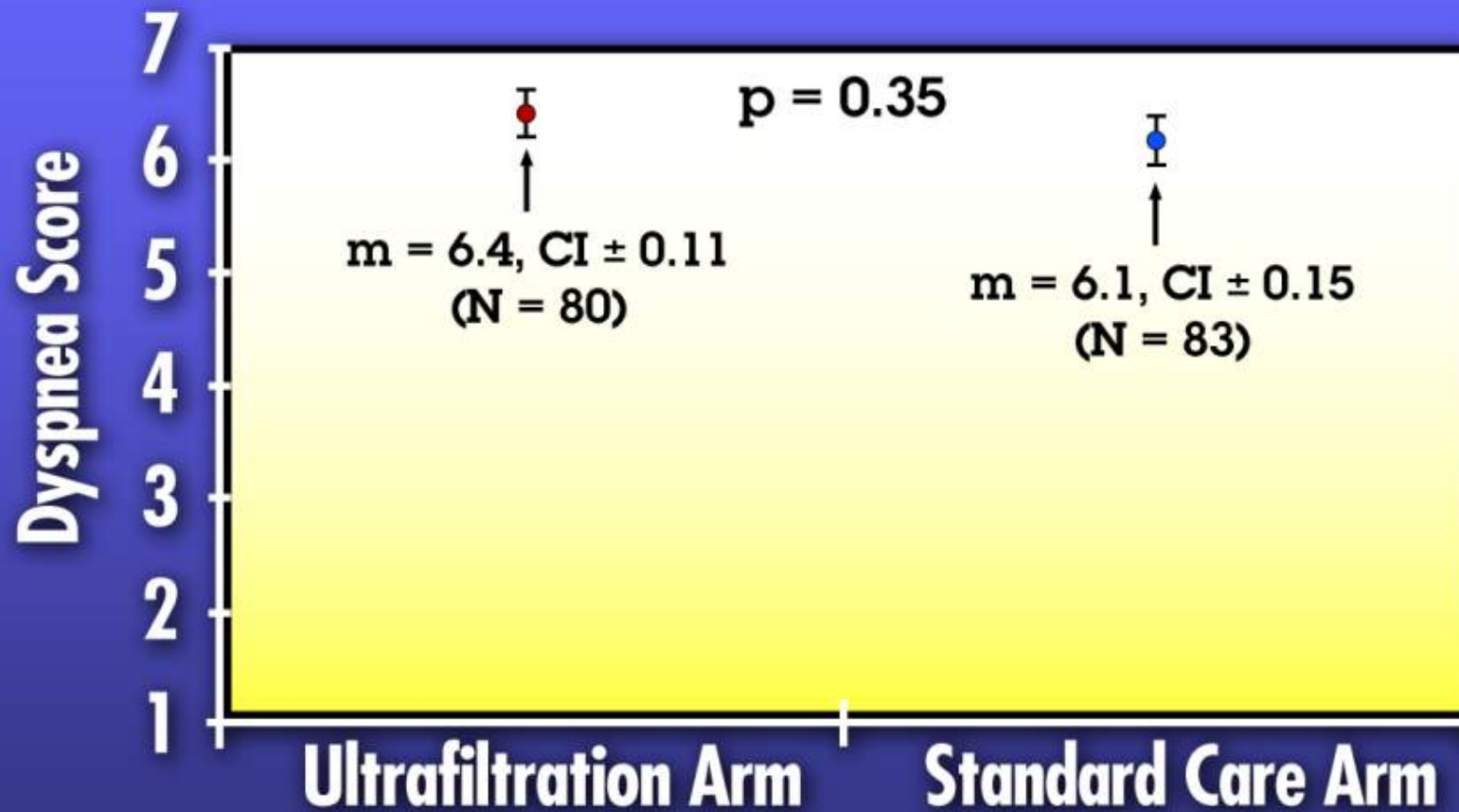
| Characteristic | Ultrafiltration N=100 | Standard Care N=100 | P Value |
|------------------------------------|--------------------------|------------------------|------------|
| ACE Inhibitors % | 49 | 49 | 1.000 |
| ARBs % | 14 | 19 | 0.446 |
| Beta Blockers % | 65 | 66 | 1.000 |
| Calcium Channel Blockers % | 8 | 8 | 1.000 |
| Aldosterone Antagonists % | 21 | 22 | 0.864 |
| Diuretics % | 78 | 80 | 0.860 |
| Loop % | 72 | 77 | 0.517 |
| Thiazide % | 14 | 15 | 1.000 |
| Both % | 10 | 11 | 1.000 |
| Furosemide equivalent mg m ± sd | 129 ± 122 | 119 ± 116 | 0.559 |

RESULTS

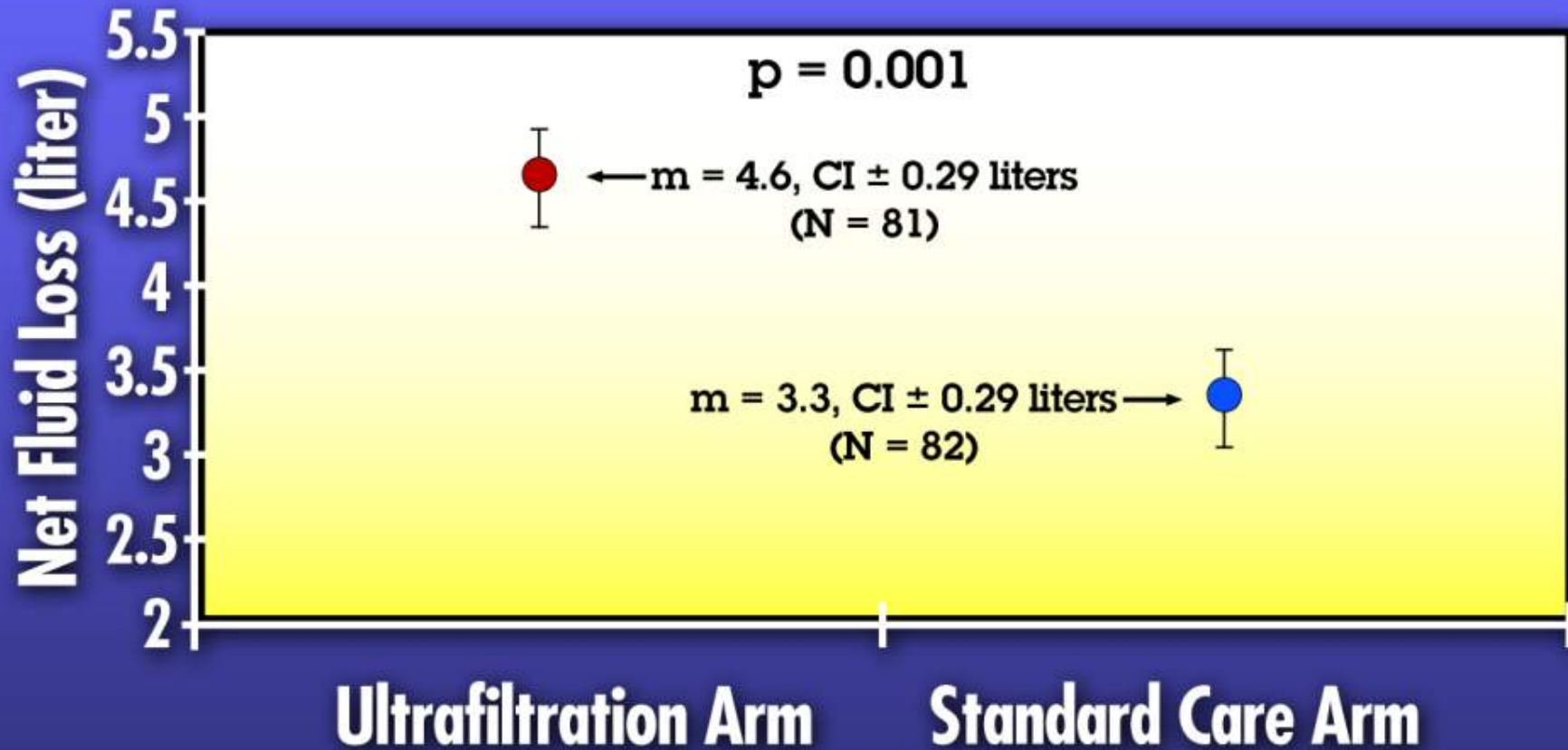
Primary End Point Weight Loss at 48 Hr



Primary End Point Dyspnea Score at 48 Hr



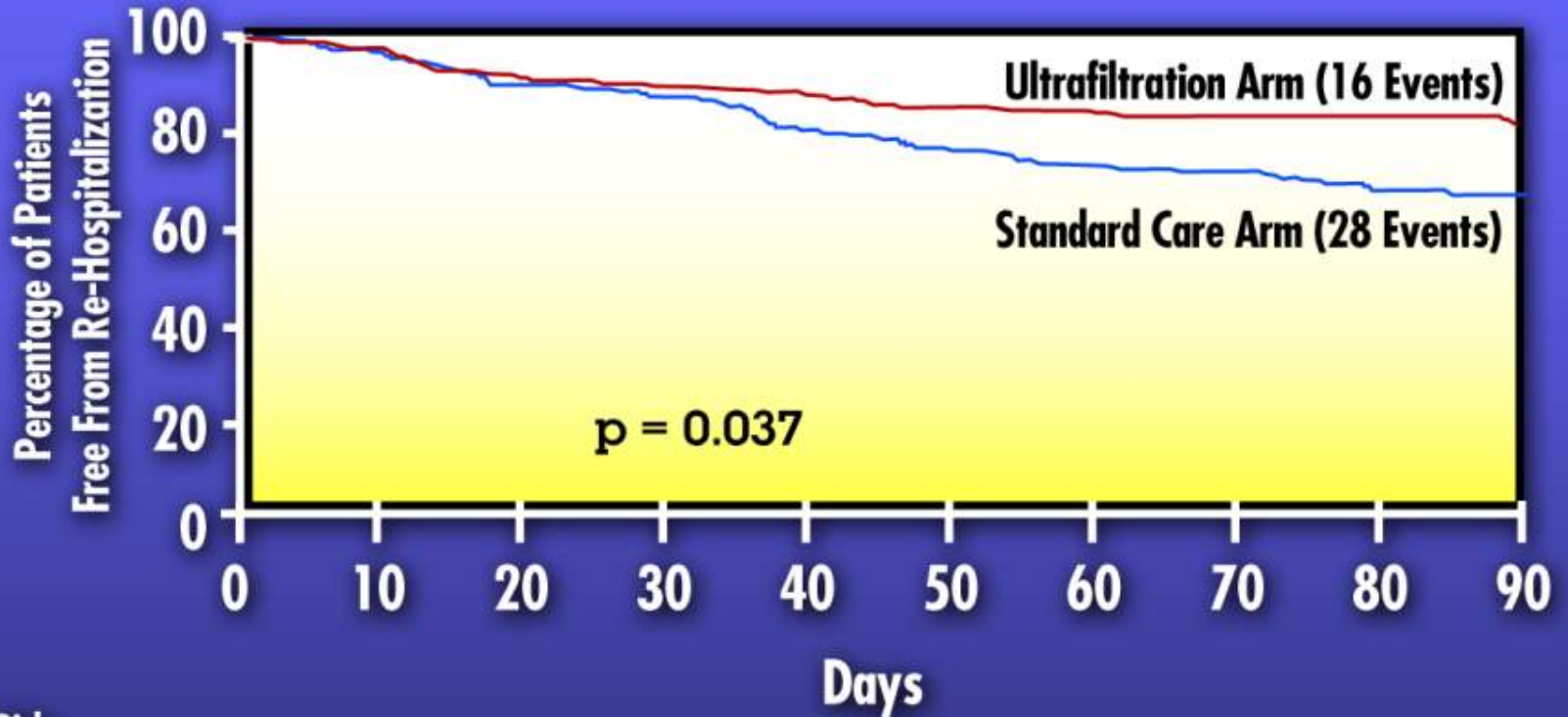
Secondary End Point Net Fluid Loss at 48 Hr



Worsening Heart Failure in 90 days

| | UF | SC | P Value |
|---|-------------|-------------|--------------|
| Patients Re-hospitalized % | 18 | 32 | 0.022 |
| Re-hospitalizations/patient | 0.22 | 0.46 | 0.037 |
| Number of Re-hospitalization days/patient | 1.4 | 3.8 | 0.022 |
| Days Re-hospitalized | 123 | 330 | 0.022 |
| (Unscheduled office + ED visits) % | 21 | 44 | 0.009 |

Freedom From Re-hospitalization for Heart Failure



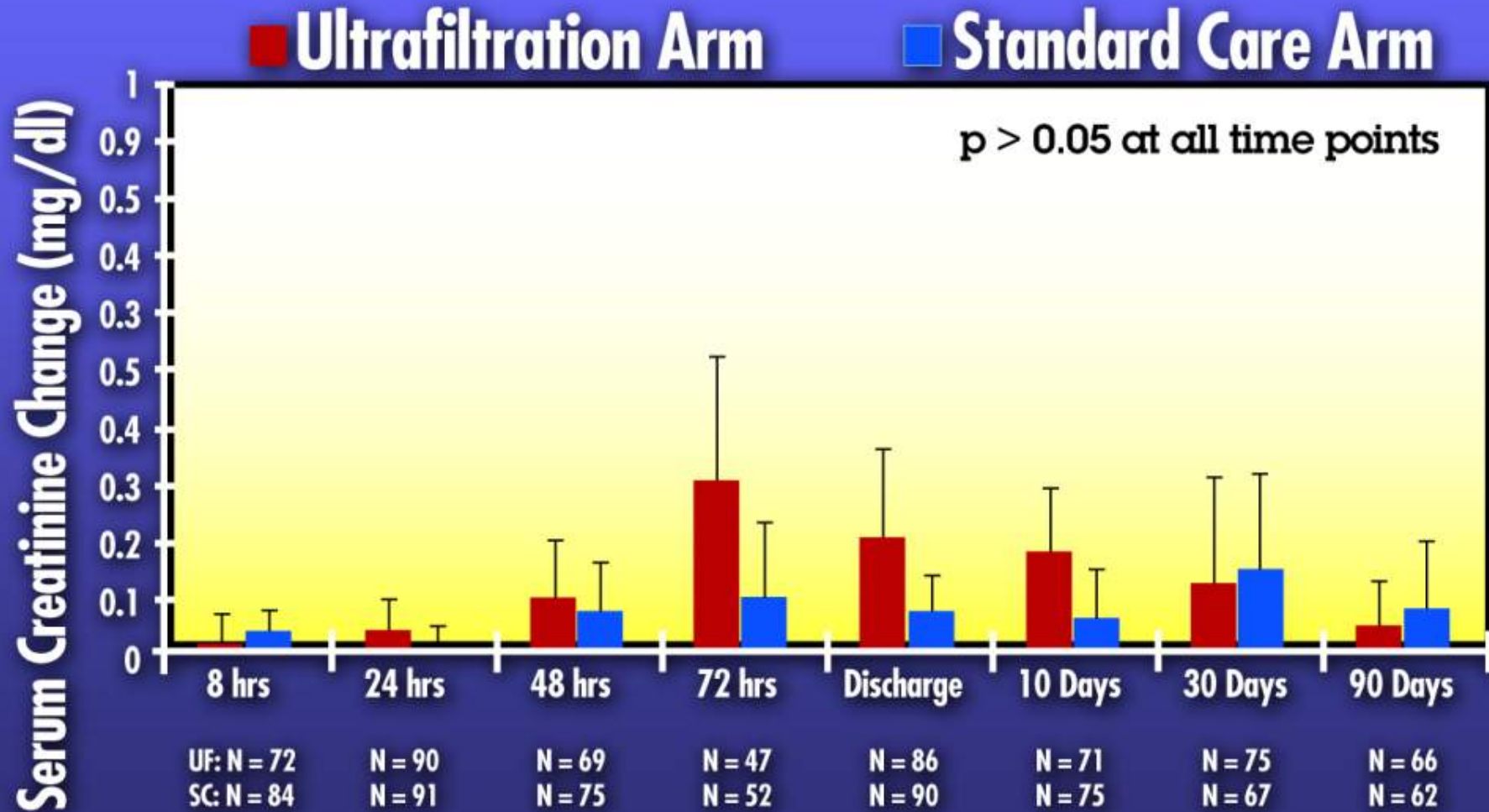
No. Patients at Risk

| | | | | | | | | | | |
|----------------------------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|
| Ultrafiltration Arm | 88 | 85 | 80 | 77 | 75 | 72 | 70 | 66 | 64 | 45 |
| Standard Care Arm | 86 | 83 | 77 | 74 | 66 | 63 | 59 | 58 | 52 | 41 |

Secondary End Points

- Similar improvements occurred in the ultrafiltration and standard care groups in:
 - BNP levels
 - NYHA class
 - MLWHF scores
 - Global Assessment scores
 - 6-Minute Walk Distance

Safety End Points: Change in Serum Creatinine



Adverse events up to 90 days

| | Ultrafiltration | Standard Care | P Value |
|-------------------------|-----------------|---------------|---------|
| Catheter/Needle | 3 | 0 | 0.156 |
| Filter | 5 | NA | 0.154 |
| Infection | | | |
| Catheter related | 1 | 0 | 0.315 |
| Other | 4 | 9 | 0.202 |
| Bleeding | 1 | 7 | 0.032 |
| Hypotension | 22 | 10 | 0.113 |
| Anemia | 3 | 0 | 0.080 |
| Dialysis | 1 | 0 | 0.315 |
| Worsening Heart Failure | 39 | 63 | 0.094 |
| Myocardial Infarction | 3 | 2 | 0.988 |
| Arrhythmias | 10 | 7 | 0.968 |
| Cardiac Arrest | 4 | 6 | 0.987 |
| Neurological | 5 | 15 | 0.070 |

Deaths up to 90 days

■ Ultrafiltration group

9 (9.6%)

- 3 heart failure
- 1 acute renal failure
- 5 unrelated to either heart failure or treatment

■ Standard Care group

11 (11.6%)

- 5 heart failure
- 1 myocardial infarction
- 3 unrelated to either heart failure or treatment
- 2 unknown causes

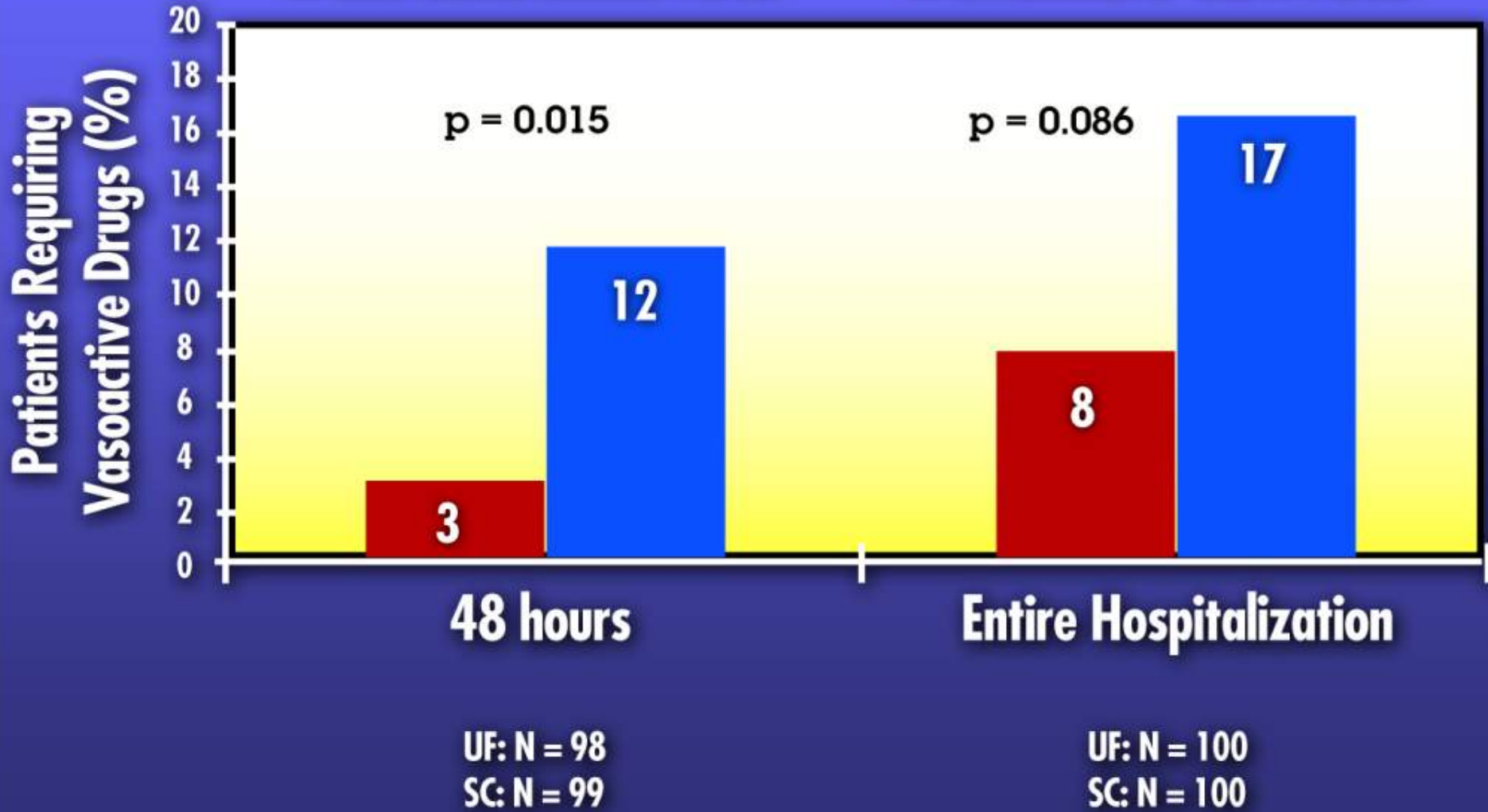
Safety End Points

- No clinically significant differences at each assessment interval in serum BUN, Sodium, Chloride and Bicarbonate levels
- During treatment, a serum potassium level <3.5 mEq/L occurred in 1 (1%) patient in the ultrafiltration group and in 9 (12 %) patients in the standard care group ($p=0.018$)
- Episodes of hypotension during the first 48 hours after randomization were similar in the ultrafiltration 4 (4.4%) and standard care 3 (3%)

Vasoactive Drugs Requirement

■ **Ultrafiltration Arm**

■ **Standard Care Arm**



- Early ultrafiltration produces greater weight and fluid loss than IV diuretics, without adverse impact on renal function

- An early ultrafiltration strategy reduces 90 day:
 - Percentage of patients requiring re-hospitalization for HF
 - Number of HF re-hospitalizations
 - Days of re-hospitalization for HF
 - ED and unscheduled office visits

- UNLOAD is the first trial to demonstrate the superiority of ultrafiltration compared to intravenous diuretics in the treatment of hospitalized volume overloaded heart failure patients.
- These results challenge current medical practice and recommendations.