ashp MIDYEAR 2017
Clinical Meeting & Exhibition

Battling the Resistance: Diuretic Challenges Across the Spectrum of Heart Failure

Snehal H. Bhatt, Pharm.D., BCPS-AQ Cardiology, FASHP
Associate Professor of Pharmacy Practice
MCPHS University School of Pharmacy - Boston
Jessie Dunne, Pharm.D., BCPS
Clinical Pharmacist, Adjunct Professor, University of Kentucky
Karen J. McConnell, Pharm.D., ASH-CHC, BCPS-AQ Cardiology, FCCP
System Director – Clinical Pharmacy Services, Catholic Health Initiatives

ashp 75 CELEBRATING YEARS

Disclosure

All planners, presenters, and reviewers of this session report no financial relationships relevant to this activity.

Objectives

1. Recommend therapies to optimize the diuretic management of a complex patient with decompensated heart failure
2. Evaluate diuretic therapy options in specific patient populations
3. Evaluate pharmacotherapeutic options for dual sequential nephron blockade with various thiazide diuretics
4. Design a pharmacotherapy plan to manage complications of diuretic resistance in acute decompensated heart failure requiring intensive care
5. Develop a transitions of care monitoring plan for heart failure management post hospital discharge

Diuretics in the Guidelines

- In heart failure, the primary mechanism limiting diuretic secretion is usually vasoconstriction of kidney blood vessels due to reduced cardiac output.
- Class I recommendation: Diuretics are recommended in patients with HFrEF who have evidence of fluid retention, unless contraindicated, to improve symptoms. (Level of Evidence: C)
- Loop diuretics are preferred for diuresis; thiazides can be used for hypertension
- Nearly all HF patients will need either chronic or acute treatment with diuretics

J Am Coll Cardiol. 2013;62(16):e147-239.

Joy

Is a 60 year old woman with HF*r*EF (EF 30%) presents to clinic with fluid overload.

- She is 10 lbs. over her dry weight (175 lbs.) and she says this has been progressively worsening over the past week.
- On physical exam, she is a bit dyspneic and has 2+ pitting edema
- She admits to eating more salt “than she should” during Thanksgiving
- She has been taking her furosemide 80 mg twice daily and spironolactone 25 mg/day as directed. She is also adherent with her other HF*r*EF medications.
- She briefly noted that she fell over the weekend and took a few doses of ibuprofen for soreness.
- Labs: K 4.5 mEq/L, Na 140 mEq/L, Mg 2.1 mg/dl, GFR: 45 ml/min
- Blood pressure 128/72 mmHg; HR 68 bpm

- What’s the next best step to manage her hypervolemia?

Diuretic Benefits

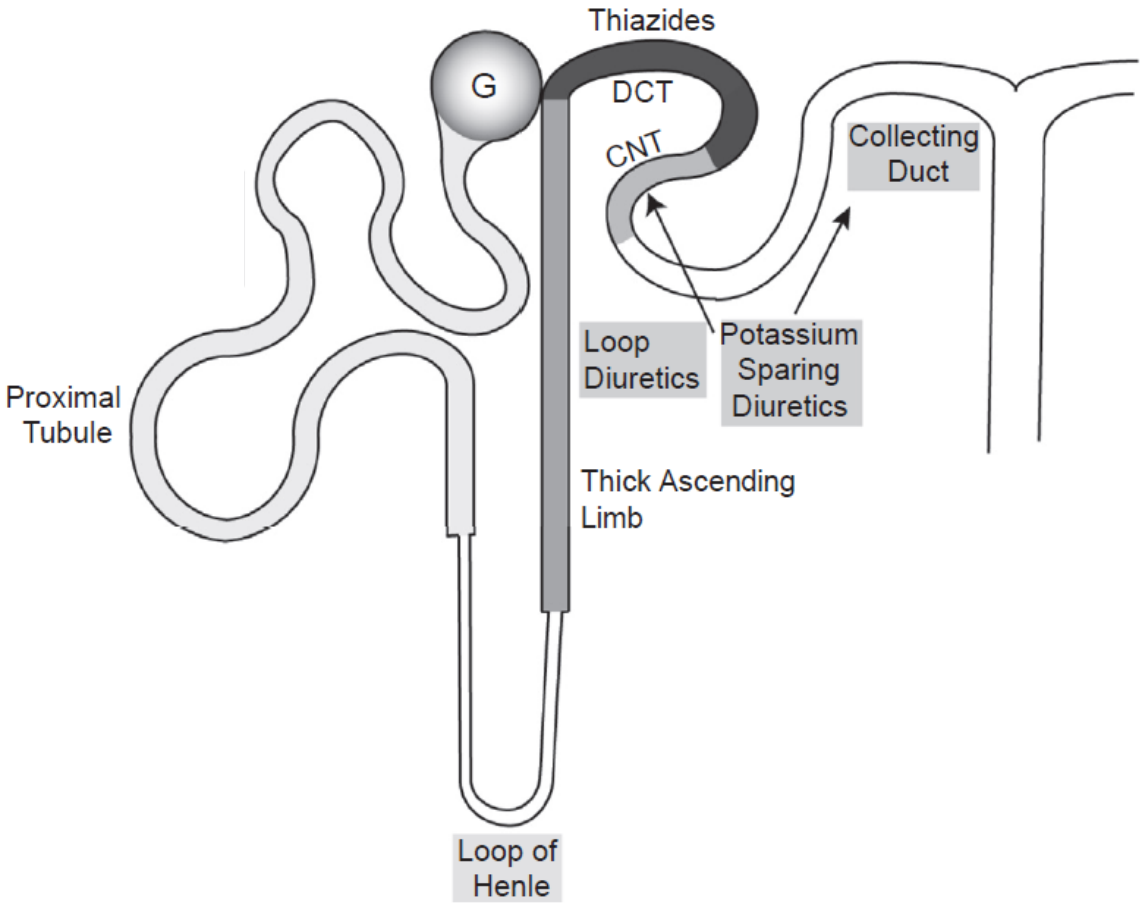
- Goal: Eliminate clinical evidence of fluid retention
  - Short term: Decreased jugular venous distension, pulmonary congestion, peripheral edema
  - Longer term: Improve symptoms of fluid overload and exercise tolerance
- Have not been shown to reduce mortality
- Dosing
  - Too low: Results in fluid retention
  - Too high: Leads to volume contraction, hypotension, renal insufficiency

J Am Coll Cardiol. 2013;62(16):e147-239.

Mechanisms of Action

- Loop diuretics: act on the loop of Henle
- Thiazide diuretics: act on the distal tubule
- K-sparing diuretics: act on the collecting duct
- Aldosterone inhibitors: act on mineralocorticoid receptors

Am J Kidney Dis. 69(1):136-142.



Am J Kidney Dis. 69(1):136-142.

Loop Diuretics

- Most commonly used: furosemide
- Increased oral bioavailability: bumetanide, torsemide
- Ethacrynic acid can be use if loop diuretic allergy
  - $$, not needed for all sulfa allergies
- More effective if combine with moderate dietary Na restriction

J Am Coll Cardiol. 2013;62(16):e147-239.

Restricting Dietary Sodium

- Class IIa: Sodium restriction is reasonable for patients with symptomatic HF to reduce congestive symptoms. (Level of Evidence: C)
- Study limitations make it difficult to give recommendations about daily sodium intake and whether it should vary for
  - Type of HF (HFrEF versus HFpEF)
  - Disease severity
  - HF-related comorbidities (e.g., renal dysfunction)
  - Other characteristics (e.g., age or race)

- Because sodium intake is typically high (>4 g/d) in general, clinicians should consider some degree (e.g., <3 g) of sodium restriction in patients with stage C and D HF for symptom improvement.

J Am Coll Cardiol. 2013;62(16):e147-239.

Loop Diuretic Dosing

- Start with a low initial dose; may then increase (up to double) the dose and titrate according to the patient's weight, diuresis and electrolytes
- Loops retain their efficacy with decreased renal function
- Approximate equivalence:
  - Furosemide 40 mg ~ bumetanide 1 mg ~ torsemide 10-20 mg ~ ethacrynic acid 50 mg

J Am Coll Cardiol. 2013;62(16):e147-239.

Joy

Is a 60 year old woman with HF*r*EF (EF 30%) presents to clinic with fluid overload.

- She is 10 lbs. over her dry weight (175 lbs.) and she says this has been progressively worsening over the past week.
- On physical exam, she is a bit dyspneic and has 2+ pitting edema
- She admits to eating more salt “than she should” during Thanksgiving
- She has been taking her furosemide 80 mg twice daily and spironolactone 25 mg/day as directed. She is also adherent with her other HF*r*EF medications.
- She briefly noted that she fell over the weekend and took a few doses of ibuprofen for soreness.
- Labs: K 4.5 mEq/L, Na 140 mEq/L, Mg 2.1 mg/dl, GFR: 45 ml/min
- Blood pressure 128/72 mmHg; HR 68 bpm

- What’s the next best step to manage her hypervolemia?

Joy

Joy has a few issues

- Edema and dyspnea
- Dietary indiscretion and NSAID use
- Maxing out on her furosemide

What's the next best step to manage her hypervolemia?

- Discontinue her NSAIDs; change to APAP
- Re-emphasize the importance of following her low Na diet
- Changer her furosemide to bumetanide (or torsemide)
  - Furosemide 160 mg/day ~ bumetanide 4 mg/day

Loop Diuretic Dosing

- Once euvolemia achieved, maintenance dosing is continued
  - Often frequent dose adjustments are needed
    - Patients should weigh daily and adjust if weight varies beyond a pre-specified range (higher or lower)
  - Patients may become unresponsive to doses if they
    - Consume large amounts of Na
    - Taking drugs that block drug effects (e.g., NSAIDs)
    - Significant renal impairment

J Am Coll Cardiol. 2013;62(16):e147-239.

Risks of Diuretics

- Adverse effects
  - Fluid depletion
  - Electrolyte depletion
    - K and Mg → causing increased risk of cardiac arrhythmias
  - Hypotension
  - Azotemia
- ADRs are enhanced when 2 diuretics are used concomitantly

J Am Coll Cardiol. 2013;62(16):e147-239.

Joy

Comes back the following week, and she feels better, but she is still 5 lbs. over her dry weight. She has been adherent to her low Na diet, bumetanide 2 mg twice daily, and spironolactone 25 mg/day. She stopped the ibuprofen and no longer needs the acetaminophen since she is feeling better now.

- Labs: K 4.0 mEq/L, Na 138 mEq/L, Mg 2.0 mg/dl, GFR: 40 ml/min
- Blood pressure 124/68 mmHg; HR 68 bpm

What's the next best step to manage her hypervolemia?

- Increase her bumetanide to 3 mg twice daily
- Labs in 1 week
- Call if no improvement over next 3 days

Diuretic Resistance

- Failure to achieve the therapeutically desired reduction in edema despite a full dose of diuretic
- Generally be overcome by
  - IV diuretics (intermittent or continuous infusion)
  - Combination of different diuretic classes (metolazone + a loop)

J Am Coll Cardiol. 2013;62(16):e147-239.

Causes

- Poor adherence to drug therapy or sodium restriction
- Pharmacokinetic issues (e.g., absorption)
- Compensatory increases in sodium reabsorption in nephron sites that are not blocked by the diuretic
- Disease states (e.g., nephrotic syndrome)

Am J Kidney Dis. 69(1):136-142.

Hypervolemia in HF

- The systemic renin-angiotensin system (RAS) is activated in heart failure, causing elevated levels of angiotensin II and aldosterone.
- This causes compensatory upregulation of sodium transporters not blocked by the diuretic, contributing to diuretic resistance
- The dose-response curve for loop diuretics exhibits both a secretory defect and decreased maximal response

Am J Kidney Dis. 69(1):136-142.

Check List

1. Identify target dry weight
2. Start loop diuretic
3. Assess response
    a. If not response, check
        1) Adherence
        2) Use of NSAIDs
4. Check 24 hour Na excretion
    a. If >100 mmol/day, start dietary counselling
5. Increase diuretic dose
6. Add different type of diuretic
7. IV diuretics

Am J Kidney Dis. 69(1):136-142.

ashp 75 CELEBRATING YEARS

Joy

- Is now presenting back at clinic; she called for a same day appointment.
- You can hear rales and she has 3+ pitting edema
- She left her bumetanide at home when she went to visit her family for Christmas, so she took some old furosemide she had in her toiletry bag. She had very little control over what she ate while she was gone.
- She returned last night and she feels terrible.
- Since you are unable to administer IV diuretics in your clinic, you call the admissions department for your local hospital.

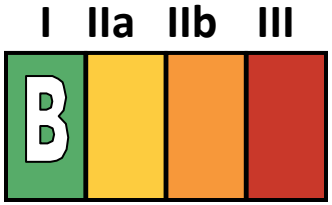
Joy: Inpatient admission

- Joy is directly admitted to the heart failure service for diuresis
- Admission labs:
  - Na: 136 mEq/L
  - K: 4.5 mEq/L
  - Creatinine: 1.8 mg/dL
- Current weight: 95kg (210 pounds)

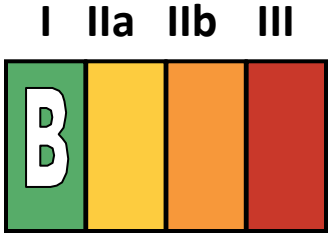
What would you recommend as her initial diuretic dose upon admission?

A. Bumetanide 2 mg IV x 1
B. Bumetanide 4 mg IV x 1
C. Furosemide 80 mg IV x 1
D. Furosemide 200 mg IV x 1

ACC/AHA HF Guidelines: Diuretics for Hospitalized Patients



Patients with HF admitted with evidence of significant fluid overload should be promptly treated with intravenous loop diuretics to reduce morbidity.



If patients are already receiving loop diuretic therapy, the initial intravenous dose should equal or exceed their chronic oral daily dose and should be given as either intermittent boluses or continuous infusion. Urine output and signs and symptoms of congestion should be serially assessed, and the diuretic dose should be adjusted accordingly to relieve symptoms, reduce volume excess, and avoid hypotension.

ashp 75 CELEBRATING YEARS

Diuretic Resistance: Mechanisms

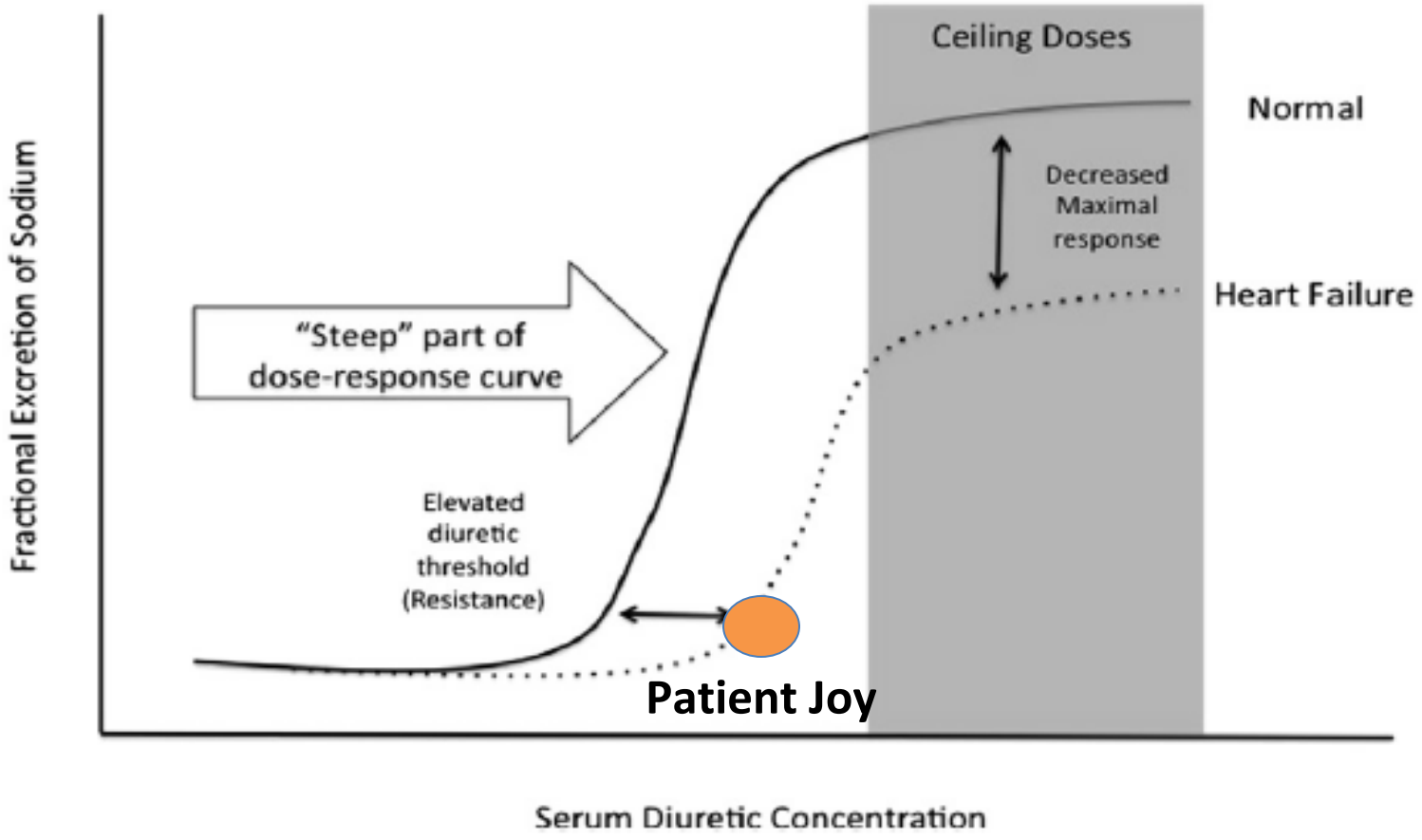
- Reduced bioavailability (gut edema)
- Reduce active OAT secretion into the proximal tubule
- Renal inactivation via glucoronidation (furosemide)
- Dosing that did not reach the diuretic “threshold”
- Increased distal tubular sodium reabsorption
- “Breaking phenomenon”
- “Post-diuretic effect”

Loop Diuretics: Absorption

	Furosemide	Bumetanide	Torsemide
Bioavailability	10 – 100%	80 – 100%	80 – 100%
Affected by food	Yes	Yes	NO

- In 1 study of diuretic absorption during euvolemia and decompensation
  - 47% of oral furosemide patients had a 20% reduction in bioavailability
  - 21% of oral torsemide patients had a 20% reduction

Loop Diuretics: Dose response Curve

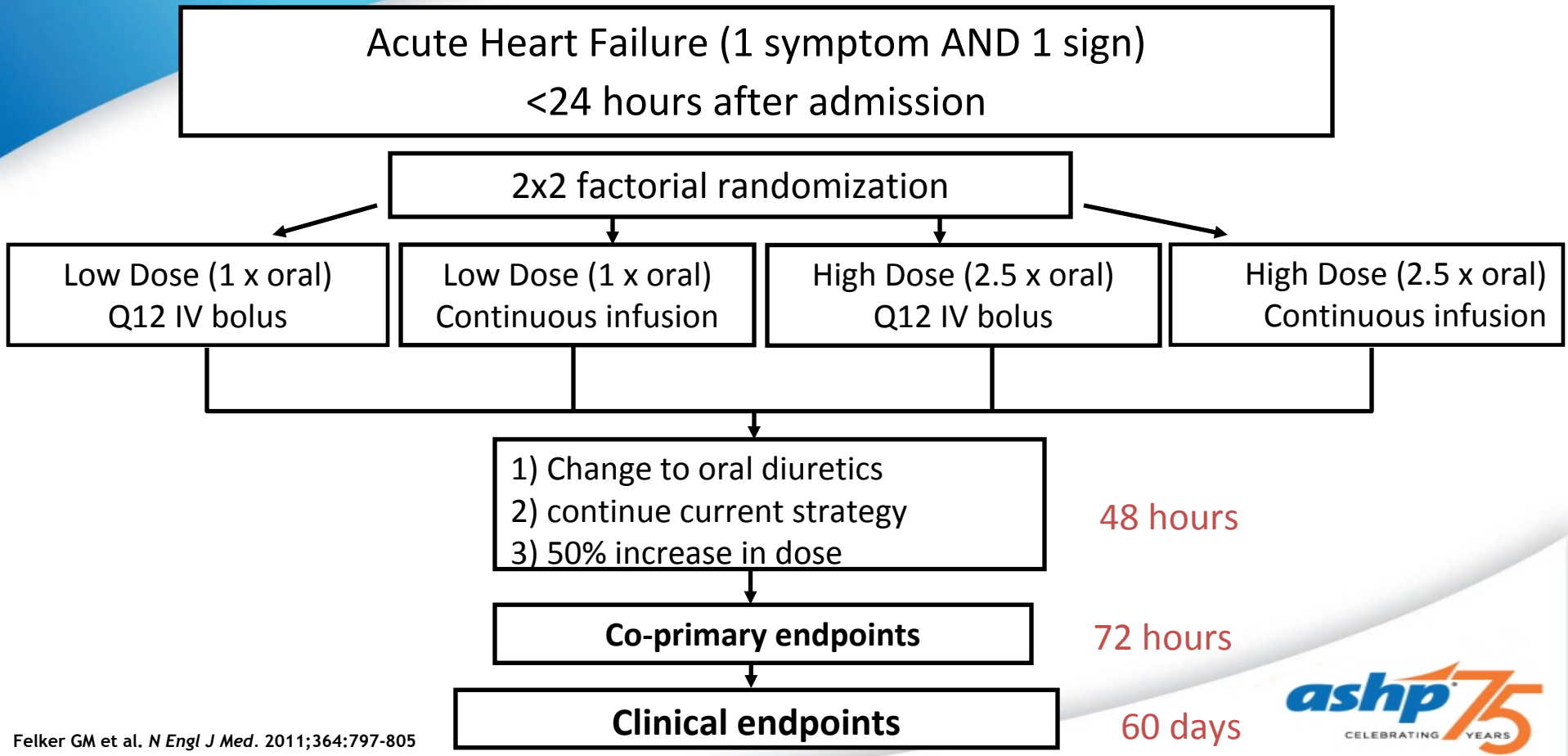


Dose Trial: Objective

- To evaluate the safety and efficacy of various initial strategies of furosemide therapy in patients with acute heart failure
  - Route of administration:
    - Every 12 hours bolus
    - Continuous infusion
  - Dosing
    - Low intensification (1 x oral dose)
    - High intensification (2.5 x oral dose)

Felker GM et al. *N Engl J Med*. 2011;364:797-805

Study Design



Felker GM et al. *N Engl J Med*. 2011;364:797-805

Co-Primary Endpoints

- Efficacy:
  - Patient Global Assessment by visual analog scale (VAS) over 72 hours using area under the curve (AUC)

- Safety:
  - Change in serum creatinine from baseline to 72 hours

Felker GM et al. *N Engl J Med.* 2011;364:797-805

Dose Trial: Results

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

Felker GM et al. *N Engl J Med*. 2011;364:797-805

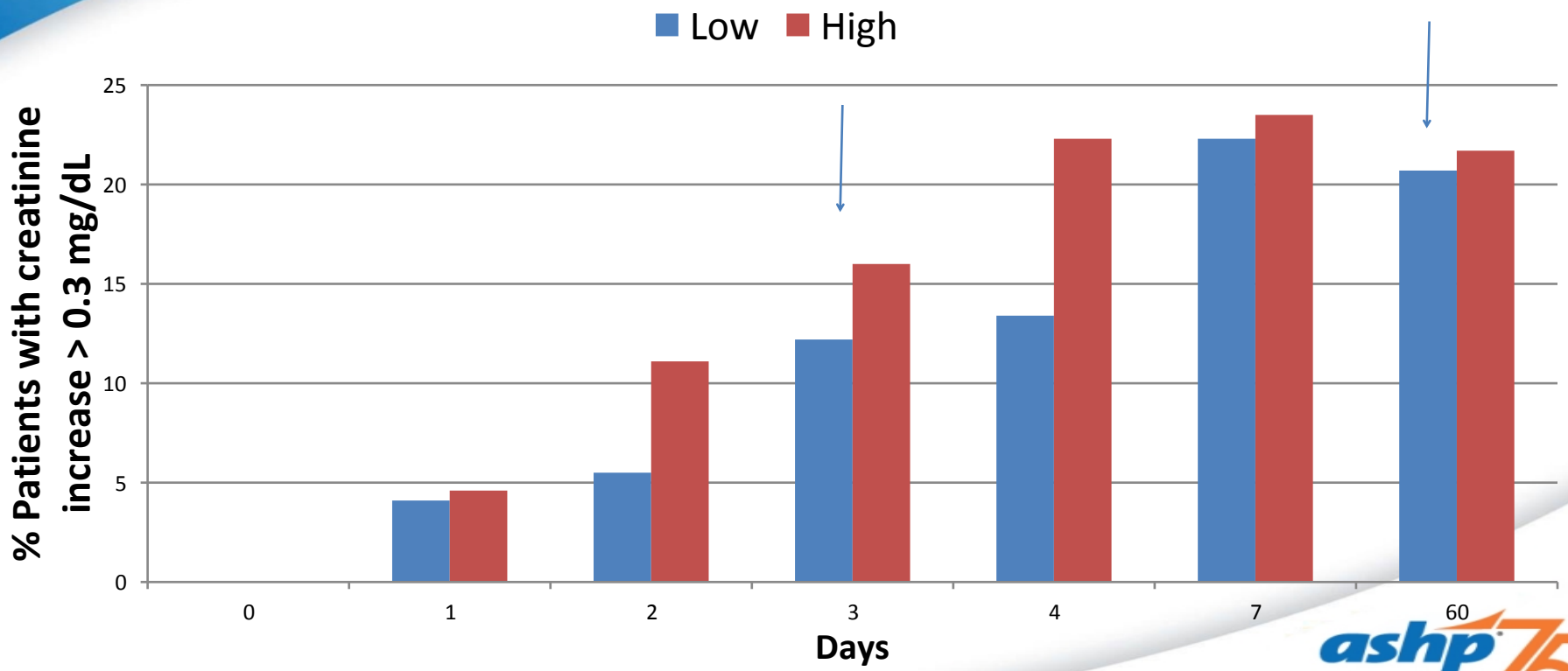
Dose Trial: Secondary Endpoints
Low dose vs. High dose

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

Felker GM et al. *N Engl J Med*. 2011;364:797-805

ashp 75 CELEBRATING YEARS

Proportion of patients with worsening renal function



Felker GM et al. *N Engl J Med*. 2011;364:797-805

Conclusions

- There was no significant difference in global symptom relief or change in renal function at 72 hours for either:
  - Q12 hr. bolus vs. Continuous infusion
    - Global symptom relief: p= 0.47
    - Change in renal function: p= 0.45
  - Low intensification vs. High intensification
    - Global symptom relief: p= 0.06
    - Change in renal function: p= 0.21

Felker GM et al. *N Engl J Med*. 2011;364:797-805

My General Conclusions

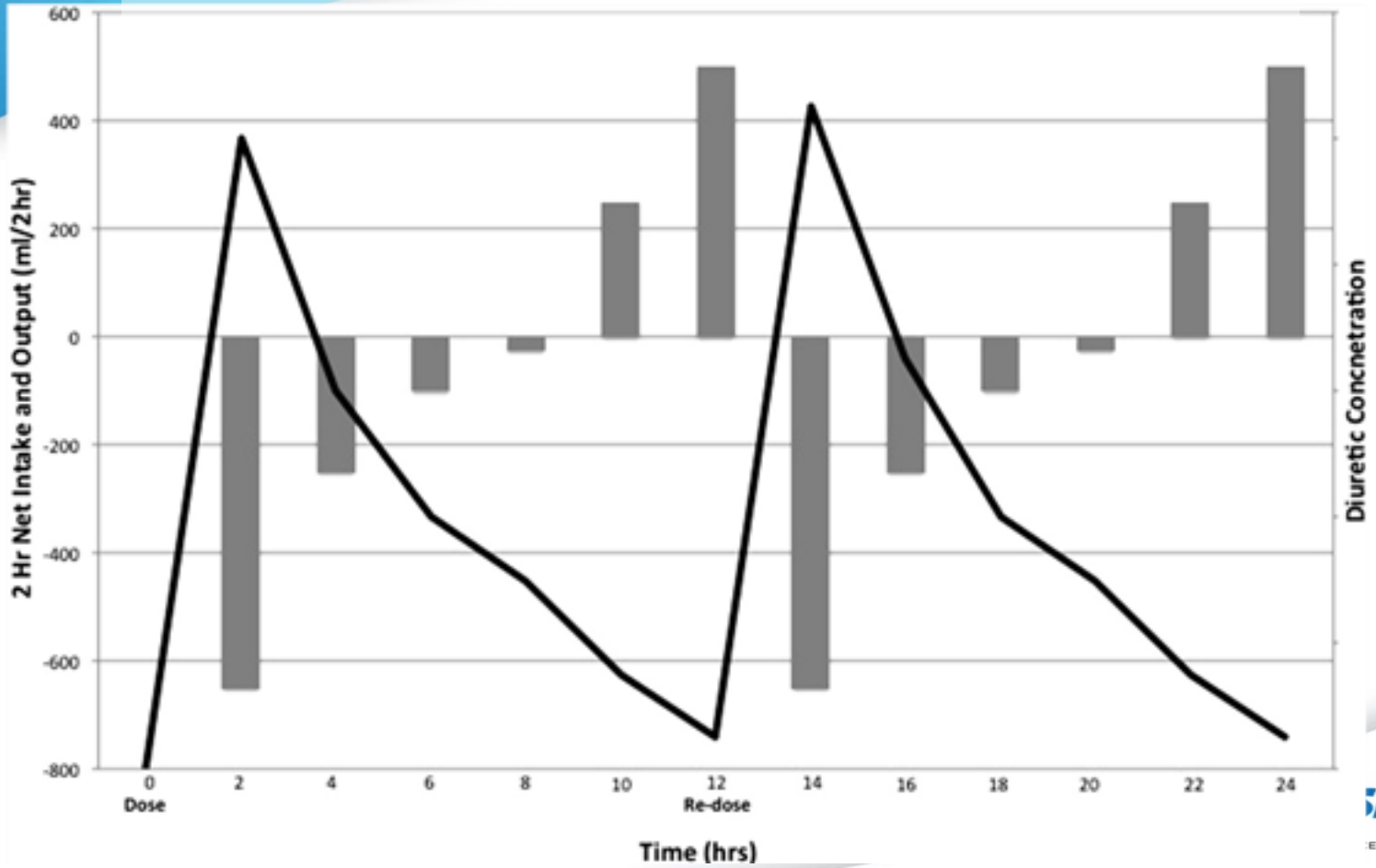
- Give IV loop diuretics:

- Give LOTS OF loop diuretics
  - Don’t be afraid of 2.5 times the outpatient dose
  - Early renal dysfunction did not translate to long term poor outcomes
  - Median doses used in the DOSE trial at 72 hours:
    - Bolus dose group: 592 mg (≈ 200 mg furosemide per day)
    - Continuous group: 480 mg

Hypothetical Scenario

- Over the next 24 hours, Joy fails to reach goals:
- Given Furosemide 100 mg IV x 2 doses (8 am, 4 pm)
  - I: 1850
  - O: 2500

Post-Diuretic Effect



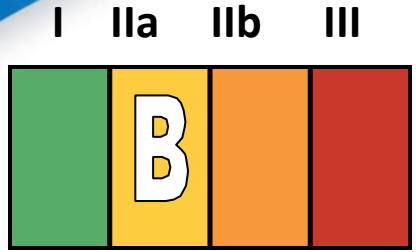
Case Continues

- Over the next 48 hours Joy continues to have suboptimal response to loop diuretics:
  - Furosemide 100 mg IV x 2 doses (8 am and 4 pm)
  - I/O: average, negative 500 mL

What would you do?

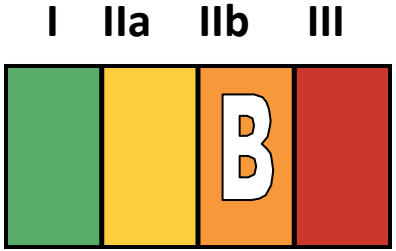
A. Continue furosemide 100 mg bolus dosing
B. Change loop, continue bolus dosing
C. Change to furosemide continuous infusion: 15 mg/hr.
D. Change loop and change to continuous infusion

ACC/AHA HF Guidelines: Diuretics for Hospitalized Patients



<u>When diuresis is inadequate</u> to relieve symptoms, it is reasonable to intensify the diuretic regimen using either:

a. higher doses of intravenous loop diuretics.
b. addition of a second (e.g., thiazide) diuretic.



Low-dose dopamine infusion may be considered in addition to loop diuretic therapy to improve diuresis and better preserve renal function and renal blood flow.

Case Continues

- Despite loop diuretic intensification, Joy still has a suboptimal diuretic response.
  - Weight: down 2 kg from admission (still 14+ kg above dry weight)
  - Creatinine stable
  - I/O: Roughly 750 mL negative

Would you consider adding a second diuretic?

A. Yes – add metolazone PO
B. Yes – add chlorthiazide IV
C. NO – continue to titrate furosemide IV infusion
D. NO – add nesiritide

Dual Sequential Nephron Blockade

- Adding a thiazide/thiazide-type diuretic to loop diuretic
- Addresses reduced loop diuretic effects from distal tubular hypertrophy
  - Allows for “synergy”

Thiazide + Loop: Good news

- 40+ years of published literature in heart failure
- Equal amount of clinical experience!
- We have choices!
  - Metolazone
  - Chlorthiazide
  - Bendroflumethiazide

Thiazide + Loop: Bad news

- Total evidence: 50 papers, but: ONLY 300 HF patients!
  - Heterogeneous patient populations
  - Lack of control groups
  - Wide variety of diuretic regimens studied
  - Small sample sizes
  - Focused on physiology outcomes (urine volume), not clinical outcomes

Which Thiazides have data?

- Metolazone PO
- Chlorthiazide IV
- Hydrochlorothiazide PO
- Bendoflumethiazide
- Quinethazone

Metolazone vs. Chlorthiazide

Study	Patients (n)	Study Type	Urine Output (range)	p Value
Moranville 2015	55 total	Retrospective chart review	Metol: 4828 mL (2800 – 7209 mL) Chlor: 3779 mL (1885 – 6535 mL)	p=0.16
Schulenberger 2016	177	Retrospective cohort	Metol: 1319.6 +/- 1517.4 mL Chlor: 1397.6 +/- 1370.7 mL	p=0.026 non-inferiority

Thiazide combination therapy: Misconceptions

- One thiazide is clearly superior to another
- Thiazide should be administered 30 minutes prior to loop
  - No studies have used thiazides in this manner!
  - Most gave the 2 drugs at the same time

Combination Therapy: Risk/Benefit

Potential Benefits

- Overcome resistance
- Relief of fluid overload/edema
- Weight loss
- Symptom improvement
- Decease in systemic congestion
- Diuresis in CKD
- Prevent Readmission
- Improved ventricular function
- Cost savings

Potential Adverse Effects

- Hypokalemia
- Azotemia/Worsening renal function
- Hyponatremia
- Hypochloremic metabolic acidosis
- Hypotension
- Hypovolemia/Dehydration
- Hypomagnesemia
- Hyperuricemia
- Cardiac Arrhythmias/Ectopy

Combination Therapy: Take Home Points

- Can induce diuresis in patients refractory to high-dose loop diuretics
- Can be effective in patients with CKD (poor renal function)
- Class effect – no evidence that 1 agent is clearly superior
- Close laboratory monitoring:
  - Hypokalemia, Hyponatremia, Hypomagnesemia, etc.
- Safety and effects on morbidity and mortality are still unknown

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

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.

Chen HH. *JAMA.* 2013;310(23):2533-2543

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.

Chen HH. *JAMA.* 2013;310(23):2533-2543

Background: *Low dose dopamine*

- 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.

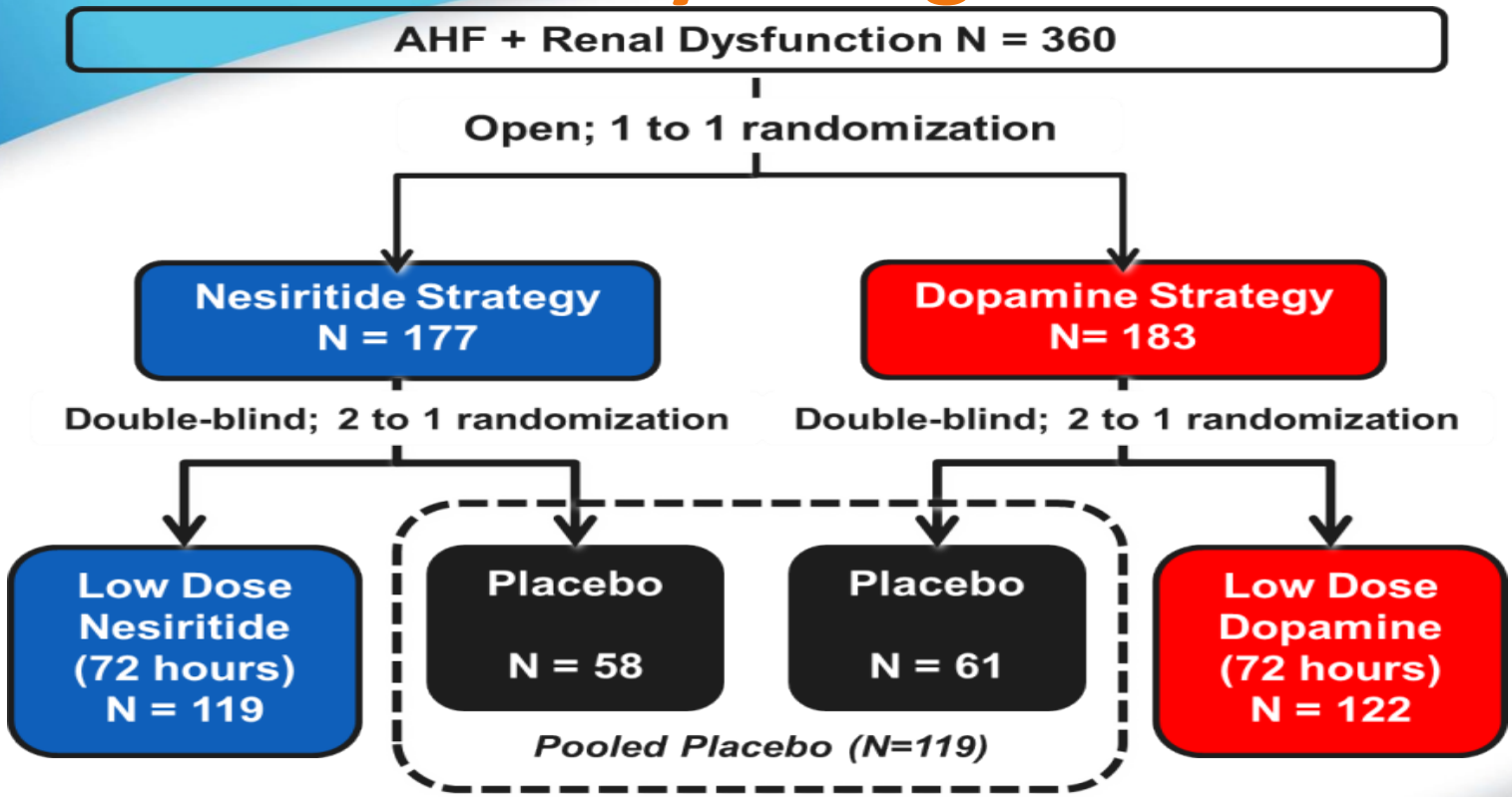
Chen HH. *JAMA.* 2013;310(23):2533-2543

Background: *Low dose nesiritide*

- 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.

Chen HH. *JAMA.* 2013;310(23):2533-2543

Study Design



Standardized Diuretic Dosing For 1st 24 hours

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

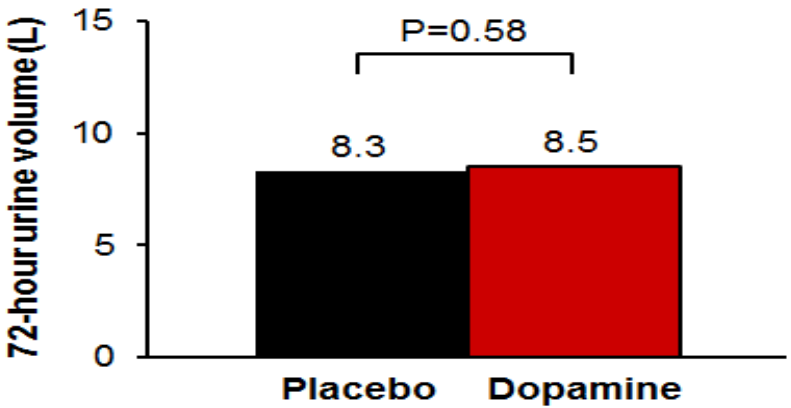
Co-Primary Endpoints

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

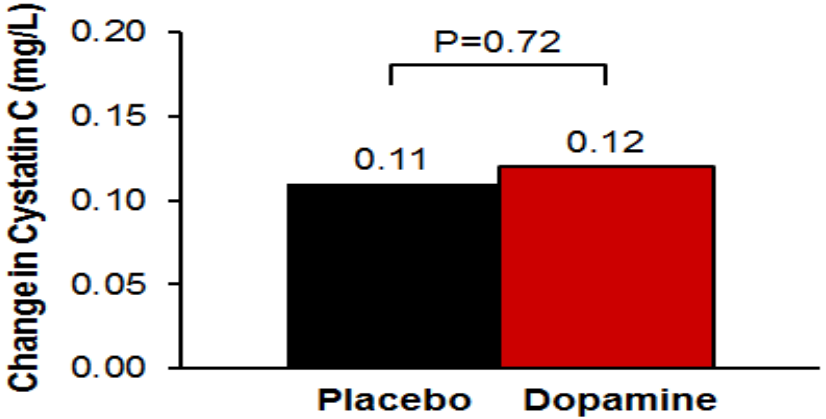
Chen HH. *JAMA.* 2013;310(23):2533-2543

Low Dose Dopamine: *Co-primary End-points*

72 Hour Urine Volume



Change in Cystatin-C



Chen HH. *JAMA.* 2013;310(23):2533-2543

Low Dose Dopamine: *Secondary Endpoints*

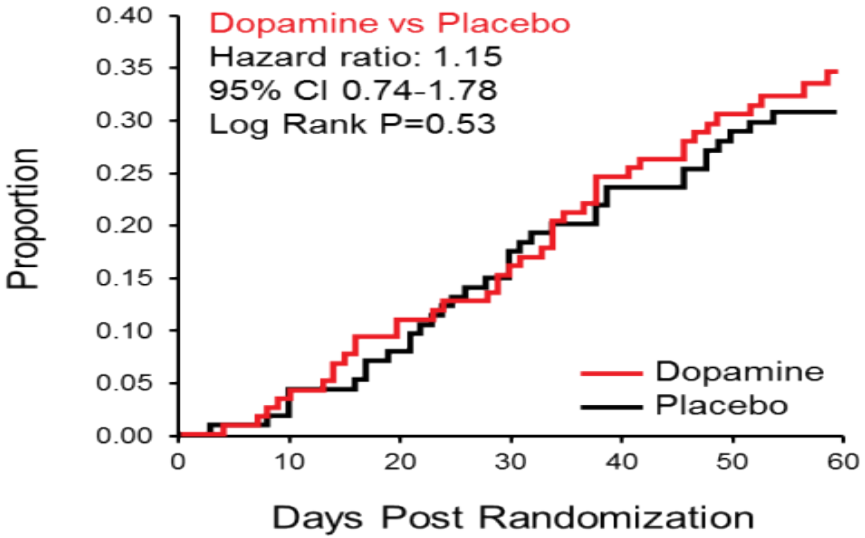
- No significant treatment effect on secondary endpoints reflective of:
  - Decongestion
  - Renal function
  - Symptom relief

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

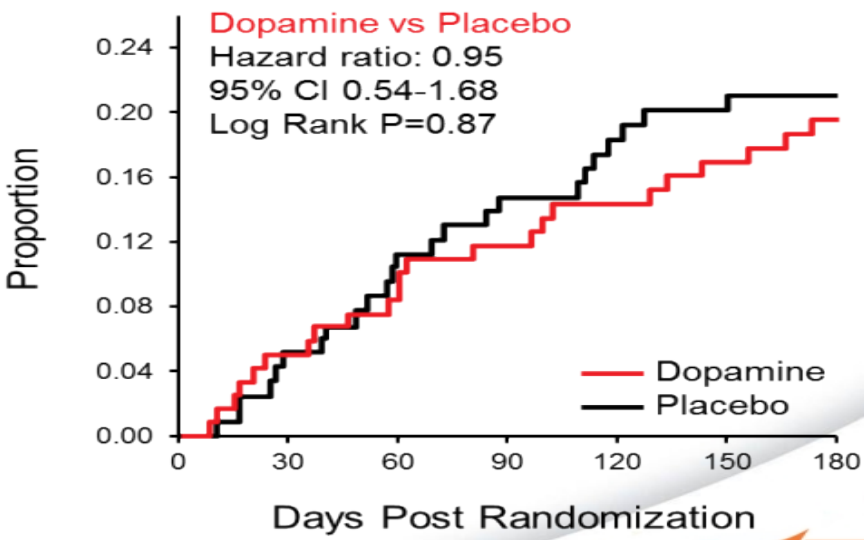
Chen HH. *JAMA.* 2013;310(23):2533-2543

Low Dose Dopamine: *Clinical Outcomes*

60 Day Death/ Unscheduled visit/ HF Readmission



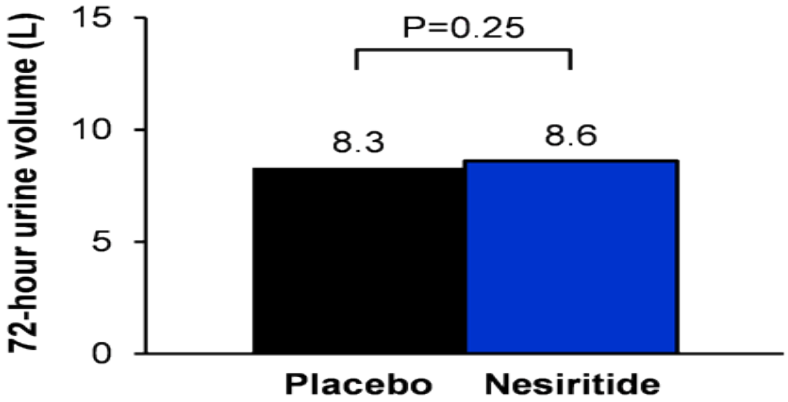
180 Day Mortality



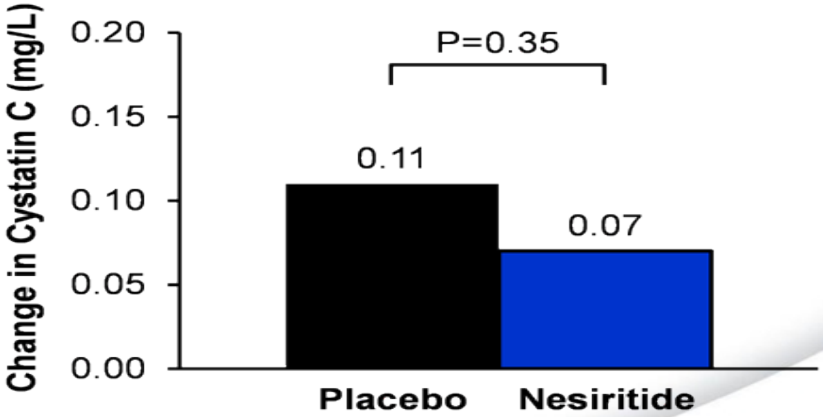
Chen HH. *JAMA.* 2013;310(23):2533-2543

Low Dose Nesiritide: *Co-primary* End-points

72 Hour Urine Volume



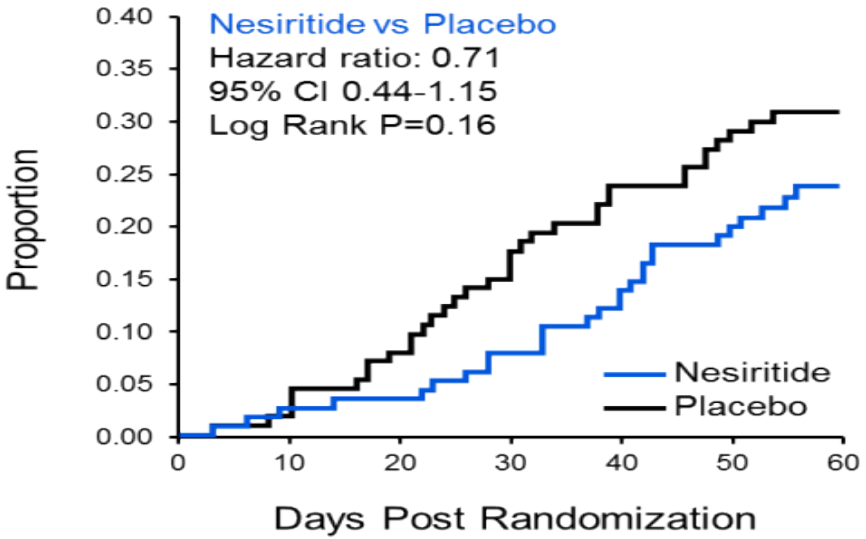
Change in Cystatin-C



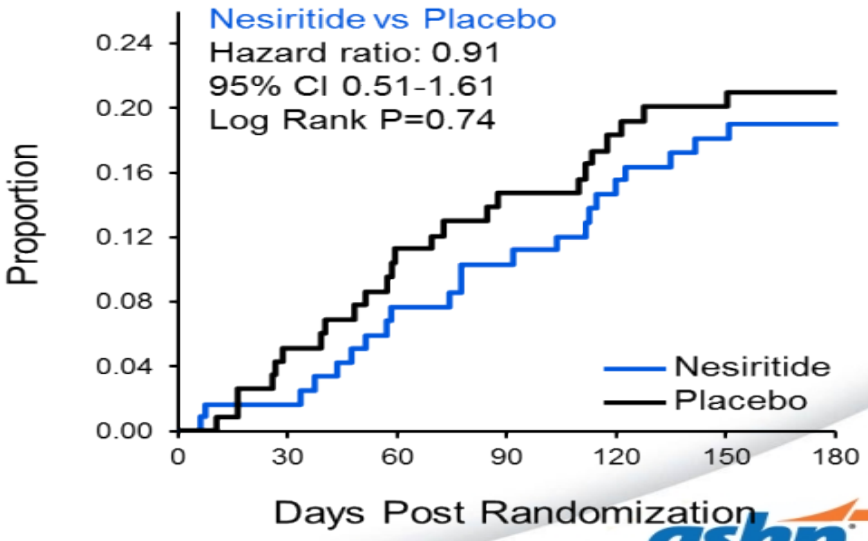
Chen HH. *JAMA.* 2013;310(23):2533-2543

Low Dose Nesiritide: *Clinical Outcomes*

60 Day Death/ Unscheduled visit/ HF Readmission



180 Day Mortality



Chen HH. *JAMA.* 2013;310(23):2533-2543

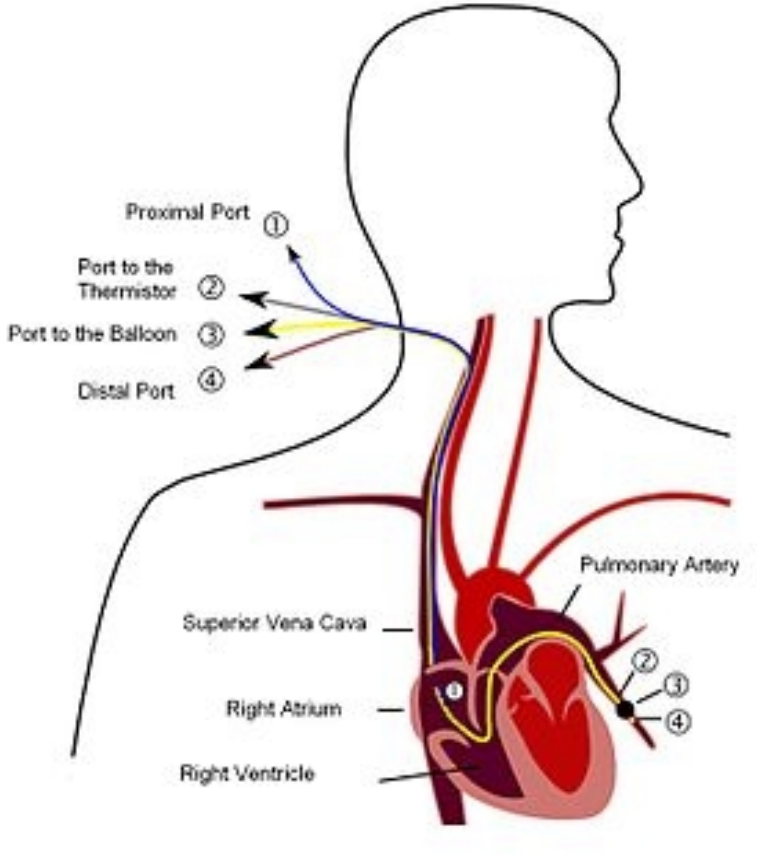
Conclusions

- 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.

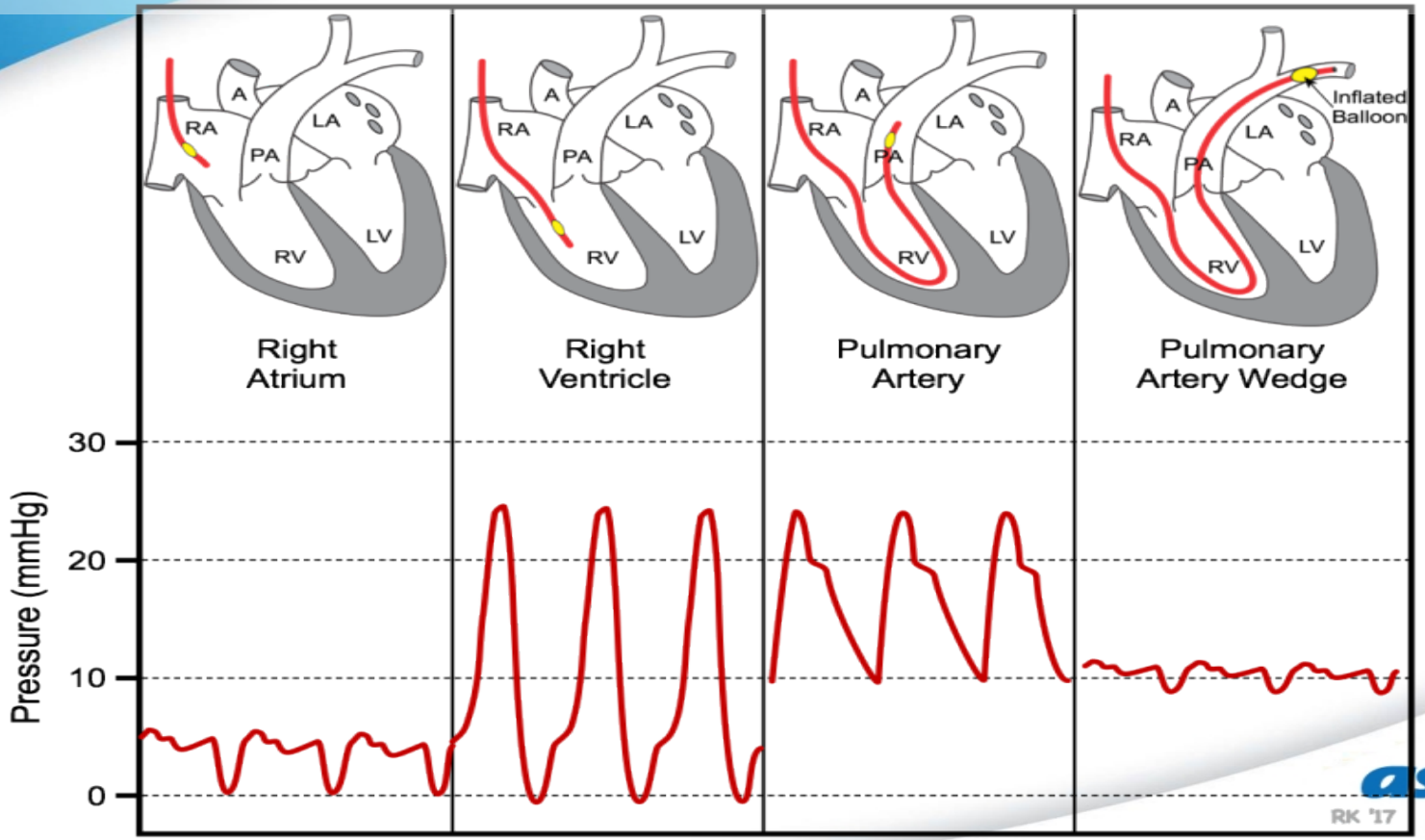
Patient Case: Resistance continues

- Despite our best effort, Joy does not improve
- Remains volume overloaded (weight: 93kg)
  - Occasional hypotension
  - Creatinine: 2.2 mg/dL
  - Sodium: 130 mEqL
  - Potassium: 3.5 mEq/L
- Plan: Right Heart Catheterization

Right Heart Catheterization



Right Heart Catheterization



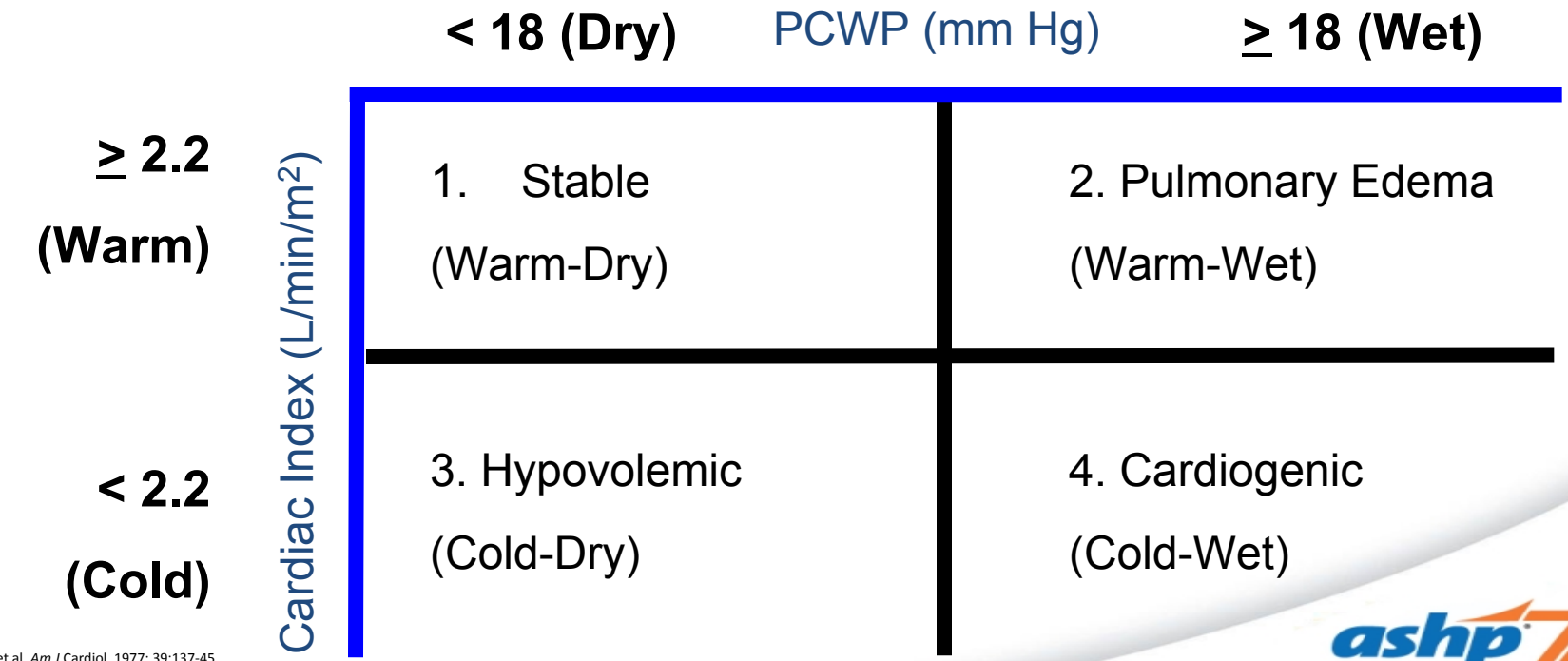
RK '17

ashp 75 CELEBRATING YEARS

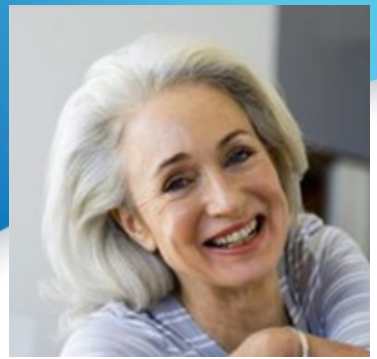
Right Heart Cath: Results

- Right Atrial Pressure: 21 mm Hg
- Pulmonary Artery Pressure: 55/30
- Pulmonary Capillary Wedge Pressure: 28 mm Hg
- Cardiac Index: 1.8

Forrester's Acute Heart Failure Classification



- Forrester JS et al. *Am J* Cardiol. 1977; 39:137-45.
- Hammond DA, et al. *J Intensive Care Med*. 2016; Epub ahead of print Sep 2016: 1-11



Patient Case: Escalating care

- Due to clinical presentation and her right heart catheterization numbers, decision made to transfer patient to a higher level of care.
- Urine output has tapered off despite Joy being maximized on her diuretic regimen of furosemide continuous infusion and metolazone 5 mg daily

Patient case

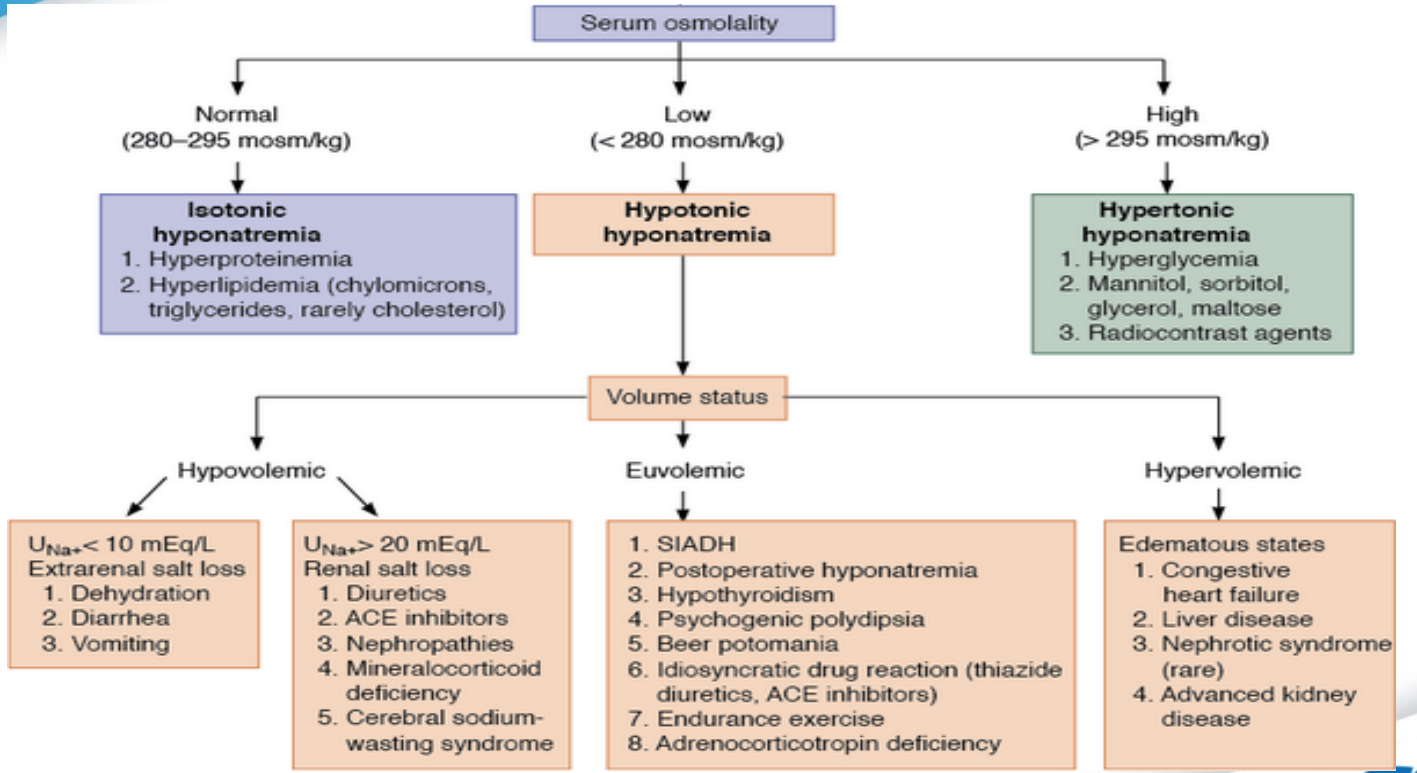
- What other diuretic resistance mechanisms has Joy potentially encountered?

  Hyponatremia

  Cardiorenal syndrome

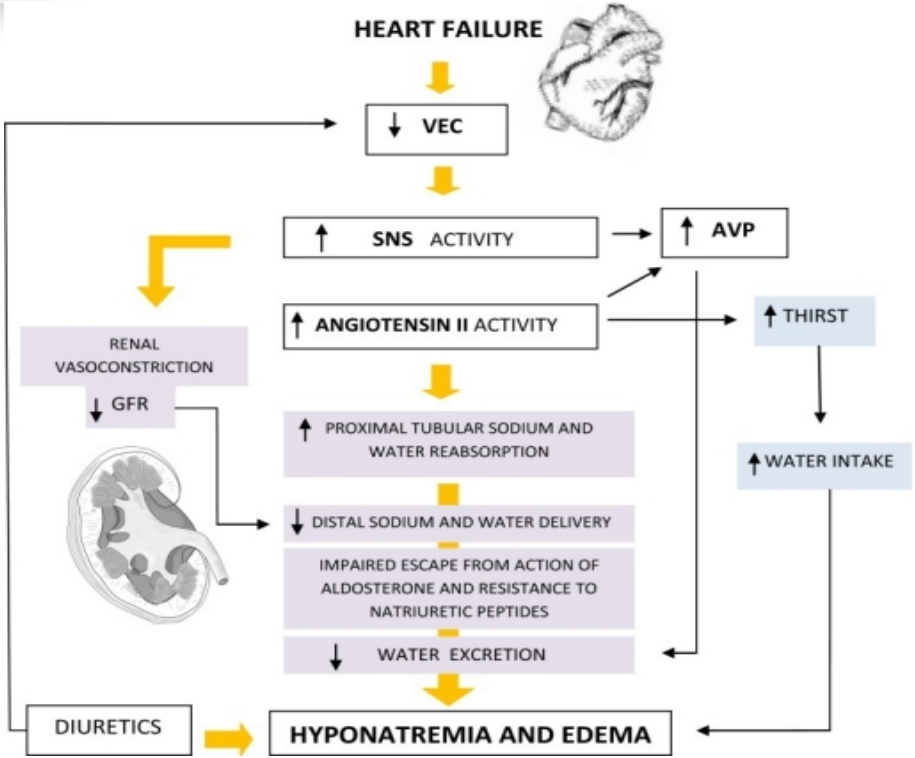
- What are our other options for fluid removal for Joy?

Assessing Hyponatremia



PhD PSGB. Hyponatremia. [Updated 2015 Apr 12]. In: De Groot LJ, Chrousos G, Dungan K, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK279136/

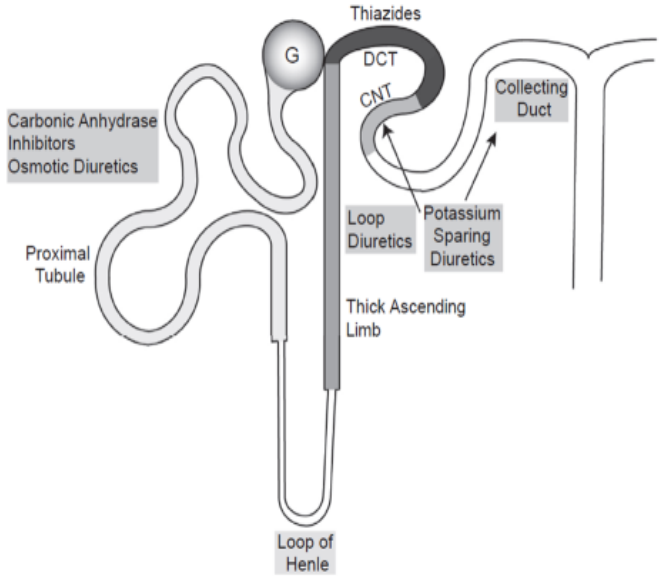
Hyponatremia in Heart Failure



- Potential mechanisms
  - Excess urinary water reabsorption
  - Overexcretion of sodium

Tolvaptan

- Arginine vasopressin (AVP) receptor antagonist with preference for V_2 receptor
  - Increases free water excretion without loss of sodium
- Indicated for use in hypervolemic, hyponatremic states
  - Serum Sodium ≤125 mEq/L



EVEREST Trial

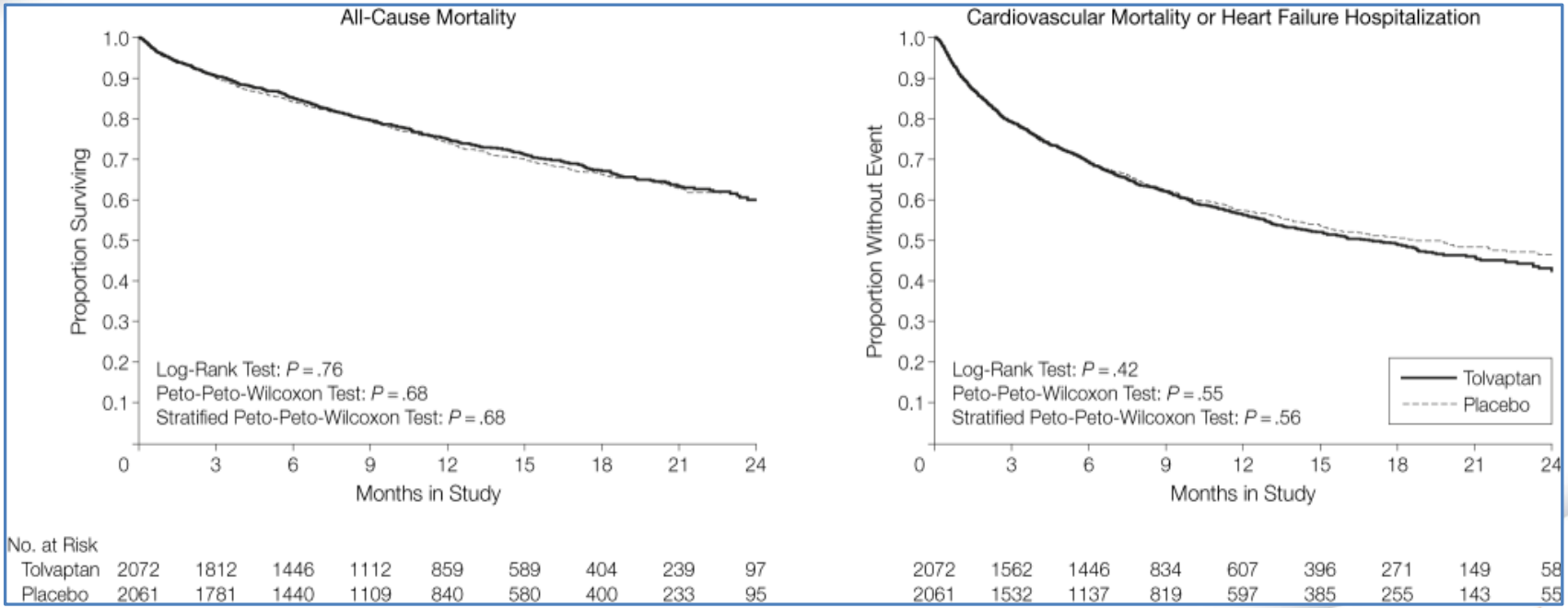
- Purpose: Evaluate the short- and long-term effects of Tolvaptan on heart failure outcomes
  - LVEV ≤40 %
  - NYHA Class III-IV symptoms
  - Admitted for heart failure (HF) exacerbation within the last 48 hours

- Primary outcomes:
  - All-cause mortality
  - Composite of cardiovascular death or HF hospitalization

Konstam MA, et al. JAMA, 2007; 297(12): 1319-1331

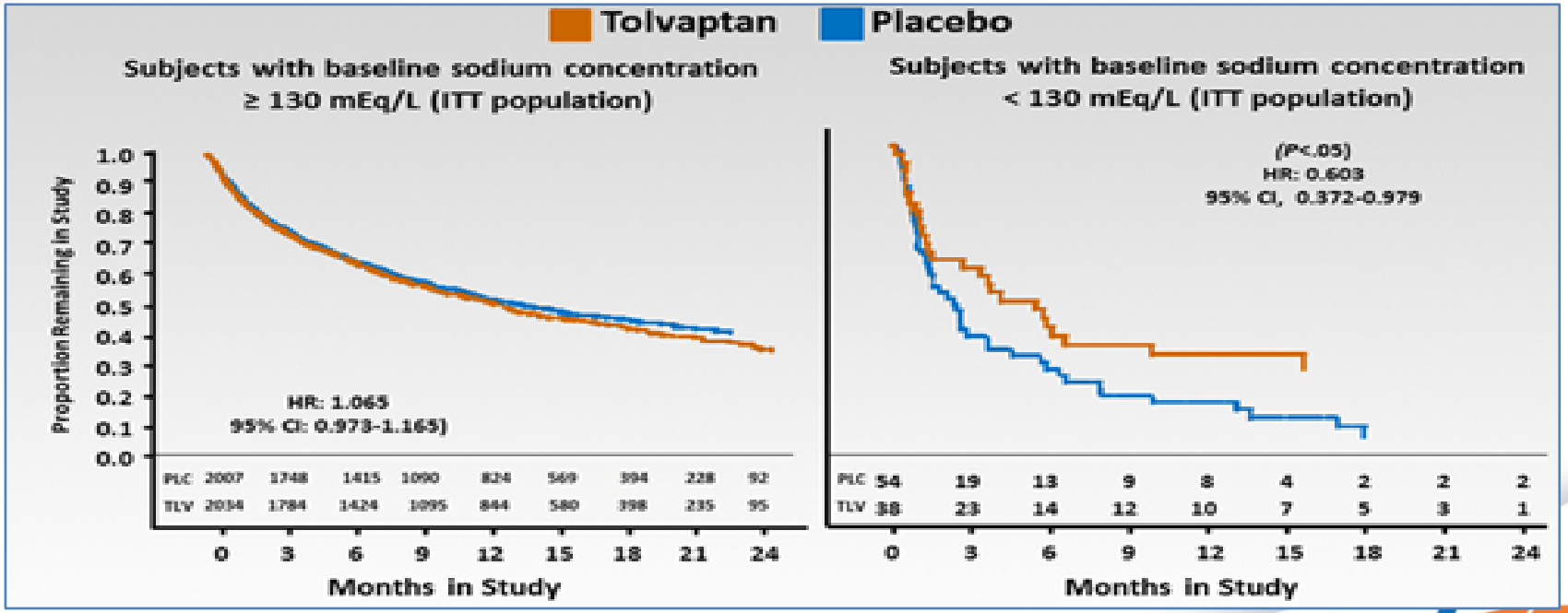
EVEREST Trial

No significant differences for either primary outcome



Konstam MA, et al. JAMA, 2007; 297(12): 1319-1331

EVEREST Trial: Primary Outcome (Baseline Na^+ Subgroup analysis)



Konstam MA. ACC. 2007

EVEREST Trial

- Secondary outcomes
  - Improved dyspnea scores at day one
  - Improved body weight at day 1
  - Increased serum sodium levels at discharge and at 40 weeks
  - Improved pedal edema at discharge and 4 weeks post-discharge

Konstam MA, et al. JAMA, 2007; 297(12): 1319-1331

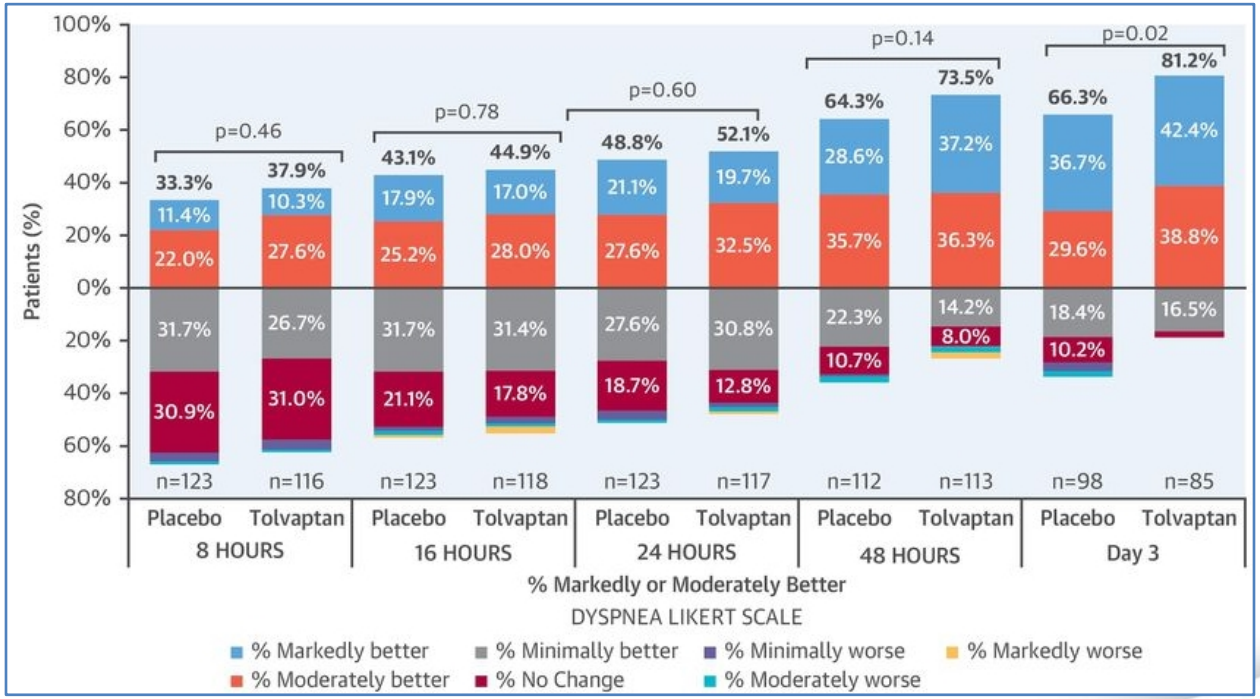
SECRET of CHF

- RCT comparing Tolvaptan to placebo in patients hospitalized with heart failure with dyspnea and at least one other feature
  - eGFR <60 ml/min/1.73 m2
  - Hyponatremia
  - Diuretic resistance

- Primary outcome: change in self-assessed dyspnea score
- Secondary outcomes: change in body weight, daily diuretic dose, change in eGFR, days alive and without hospitalization

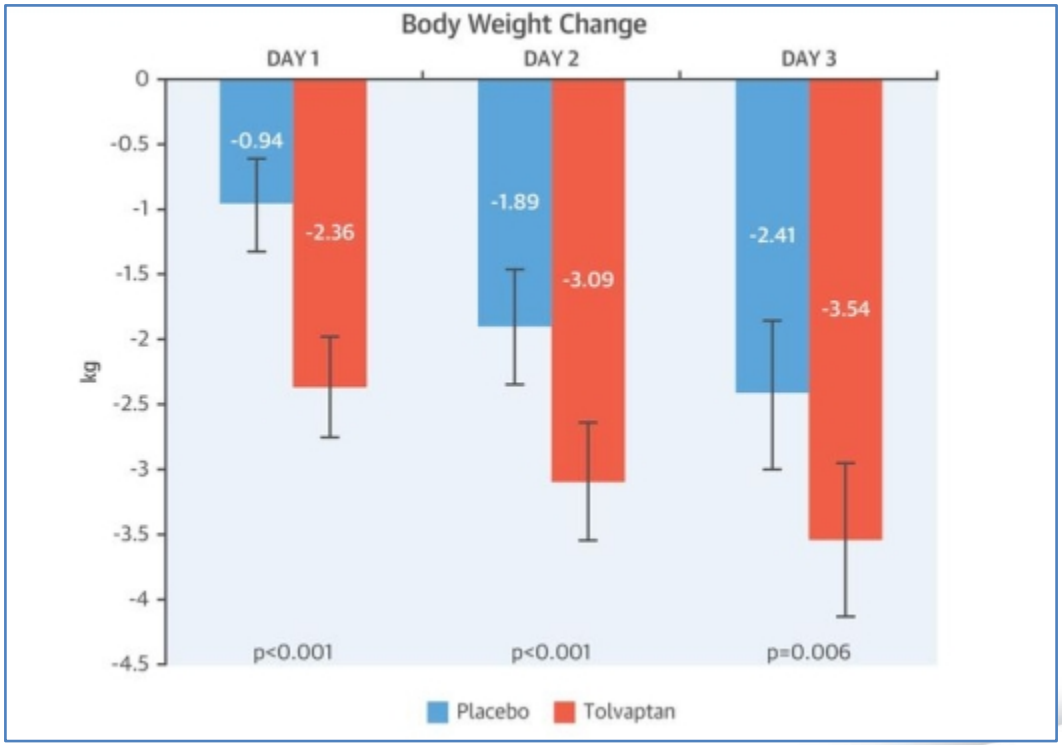
Konstam, et al. J Am Coll cardiol 2017; 69: 1409 - 19

SECRET of CHF: Dyspnea scores



Konstam, et al. J Am Coll cardiol 2017; 69: 1409 - 19

SECRET of CHF: Change in Body Weight



Konstam, et al. J Am Coll cardiol 2017; 69: 1409 - 19

SECRET of CHF

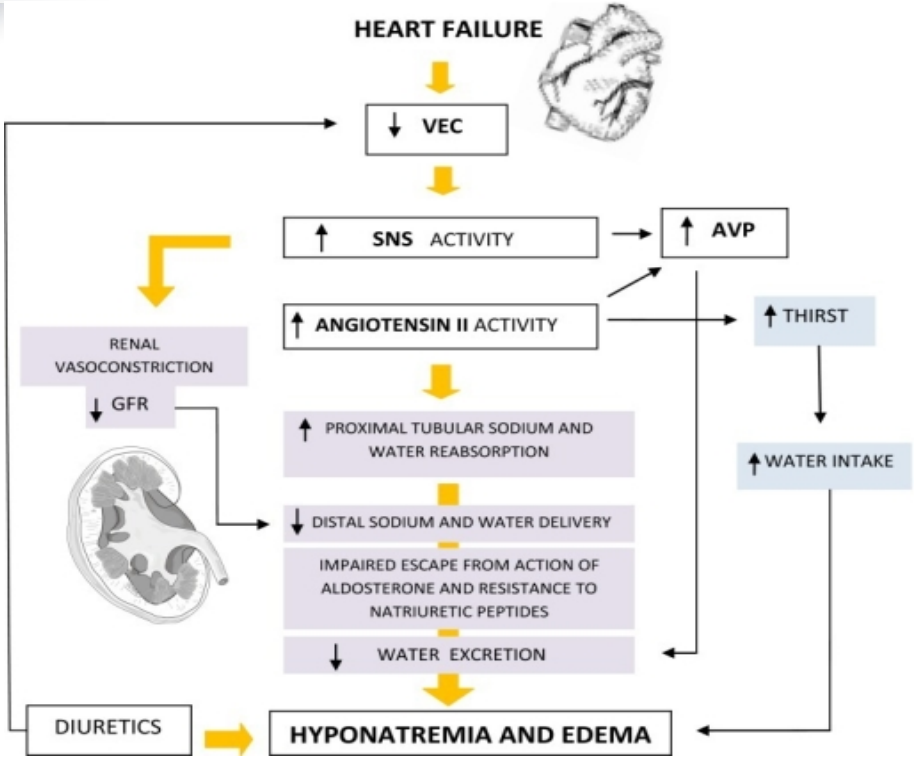
- No difference in change dyspnea scores were seen between the two groups at the 8- and 16-hour time points
  - By day 3, dyspnea scores between groups did reach statistical difference
- Other findings:
  - Significantly greater weight loss in the tolvaptan group
  - Trend to higher diuretic doses needed in the placebo group
  - No significant differences in any other secondary endpoint

Konstam, et al. J Am Coll cardiol 2017; 69: 1409 - 19

Tolvaptan

- In the setting of hyponatremic volume overload, Tolvaptan may be considered in the setting of poor diuresis despite maximized diuretic therapy
  - May improve serum sodium levels and dyspnea scores with several days of use
  - Will not make a significant difference in rate of heart failure hospitalizations or mortality

Hyponatremia in Heart Failure



- Potential mechanisms
  - Excess urinary water reabsorption
  - Overexcretion of sodium

Effects of Sodium Restriction

- High degrees of sodium restriction may lead to:
  - Decreased intravascular volume
  - Decreased responsiveness to administered diuretic therapy
  - Increase in RAAS activation
  - Release of anti-diuretic hormone (vasopressin)

Eur J Heart Fail 2004; 6: 593-9

Hypertonic Saline

- Theorized that in controlled amounts in the acute setting, hypertonic saline solution (HSS) may exert the following effects:
  - Increased osmotic gradient shifts volume from extravascular spaces into the intravascular space
  - Increased circulating blood volume resulting in decreased sympathetic activation
  - Increased renal blood flow
  - Decreased activation of RAAS system

J Surg Res, 1990; 49: 493 - 503

High-Dose Furosemide +/- HSS Infusion

- HSS group:
  - Hypertonic saline 150 ml bolus BID
    - Na <125 mEq/dL: 4.6% HSS
    - Na 126 – 135 mEq/dL: 3.5% HSS
    - Na > 135 mEq/dL: 1.4 – 2.4% HSS
  - Furosemide infusions of 500 – 1000 mg BID
  - Moderate dietary sodium restriction (120 mmol/day)
  - Fluid Restriction (1000 ml/day)
- Standard therapy group
  - Furosemide infusions of 500 – 1000 mg BID
  - Strict dietary sodium restriction (80 mmol/day)
  - Fluid restriction (1000 ml/day)

Am Heart J, 2003; 145: 459 - 66

High-Dose Furosemide +/- HSS Infusion

Primary Endpoints

- During the hospital stay, the HSS group had:
  - Increased urine output
  - Improved natriuresis
  - Increased serum Na levels
  - Greater loss of body weight

Am Heart J, 2003; 145: 459 - 66

High-Dose Furosemide +/- HSS Infusion:

Secondary Endpoints

	HSS	No HSS	P
No of Patients	53	54	
ADE's	---	11	
Readmissions	25	43	<0.05
Mortality	24	47	<0.001
Sudden Death	10	18	
Irreversible HF	10	25	<0.05
Other Causes	4	4	
Survival	55%	13%	

Am Heart J, 2003; 145: 459 - 66

Low-Dose Furosemide +/- HSS Infusion

- HSS group:
  - Hypertonic saline 150 ml bolus BID
    - Na <125 mEq/dL: 4.6% HSS
    - Na 126 – 135 mEq/dL: 3.5% HSS
    - Na > 135 mEq/dL: 1.4 – 2.4% HSS
  - Furosemide 250mg IV BID
  - Moderate dietary sodium restriction (120 mmol/day)
  - Fluid Restriction (1000 ml/day)
- Standard therapy group
  - Furosemide 250 mg IV BID
  - Strict dietary sodium restriction (80 mmol/day)
  - Fluid restriction (1000 ml/day)

Am Heart J, 2003; 145: 459 - 66

Low-Dose Furosemide +/- HSS Infusion:

At Time of Hospital Discharge

	HSS	No HSS	P
Side effects (Tinnitus)	0	71 (7.2%)	<0.0001
NYHA Class II	736 (77.2%)	813 (83.4%)	<0.29
NYHA Class I	217 (22.8%)	161 (16.5%)	<0.006
Hospitalization Time (days)	3.5 ± 1	5.5 ± 1	<0.0001
Ejection Fraction (%)	37.3 ± 5	36.4 ± 6	<0.0001
BNP (pg/mL)	355 ± 105	385 ± 115	<0.0001
Creatinine Clearance (ml/min)	55.4 ± 3.3	48.7 ± 2.1	<0.0001

Am J Med Sci 2011; 342 (1): 27 - 37

Low-Dose Furosemide +/- HSS Infusion

Long-Term Follow-up

- Over a mean follow-up time of 57 ± 15 months, patients who received hypertonic saline and a moderate dietary sodium restriction experienced:
  - Lower hospital readmissions – 18.5% vs 34.2% of patients
  - Lower mortality – 12.9% vs 23.8% of patients
    - Mostly attributed to death due from irreversible heart failure

Am J Med Sci 2011; 342 (1): 27 - 37

Hypertonic Saline

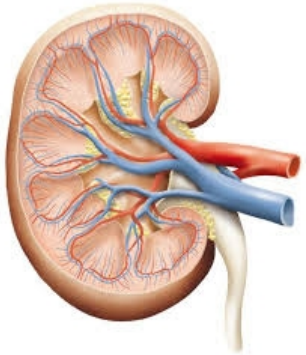
- Hypertonic saline infusions in the inpatient setting may be an effective way to increase diuretic response in patients refractory to standard therapy.
- Short term use may lead to increased UOP and weight loss, shorter length of stay.
- Long-term gentle liberalization of dietary sodium in the setting of refractory heart failure may decrease readmissions and mortality.

Patient case

- The team opted to try Tolvaptan for Joy, but after 3 day of therapy she has only diuresed 1000 ml.
  - Creatinine: 2.6 mg/dL
  - Sodium: 134 mEqL
  - Potassium: 3.5 mEq/L

- Nephrology service is now consulted for assistance with diuresis and continued worsening of renal function.
  - Recommendation made to start ultrafiltration
  - Furosemide and metolazone discontinued at this time

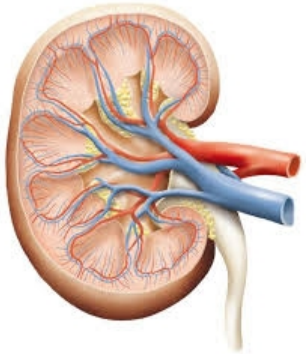
Ultrafiltration



- Type of dialysis modality that is able to pull volume without administration of fluids of any kind
  - Isotonic fluid removal
  - Does not act as full renal replacement therapy

Felker et al. J Am Coll Cardiol 2012; 59: 2145 – 53

Ultrafiltration



- Drawbacks to regular use:
  - Need for large-bore central venous catheters
  - High flow rates with large extracorporeal blood volumes
  - Limited availability
  - Increased resource utilization

Felker et al. J Am Coll Cardiol 2012; 59: 2145 – 53

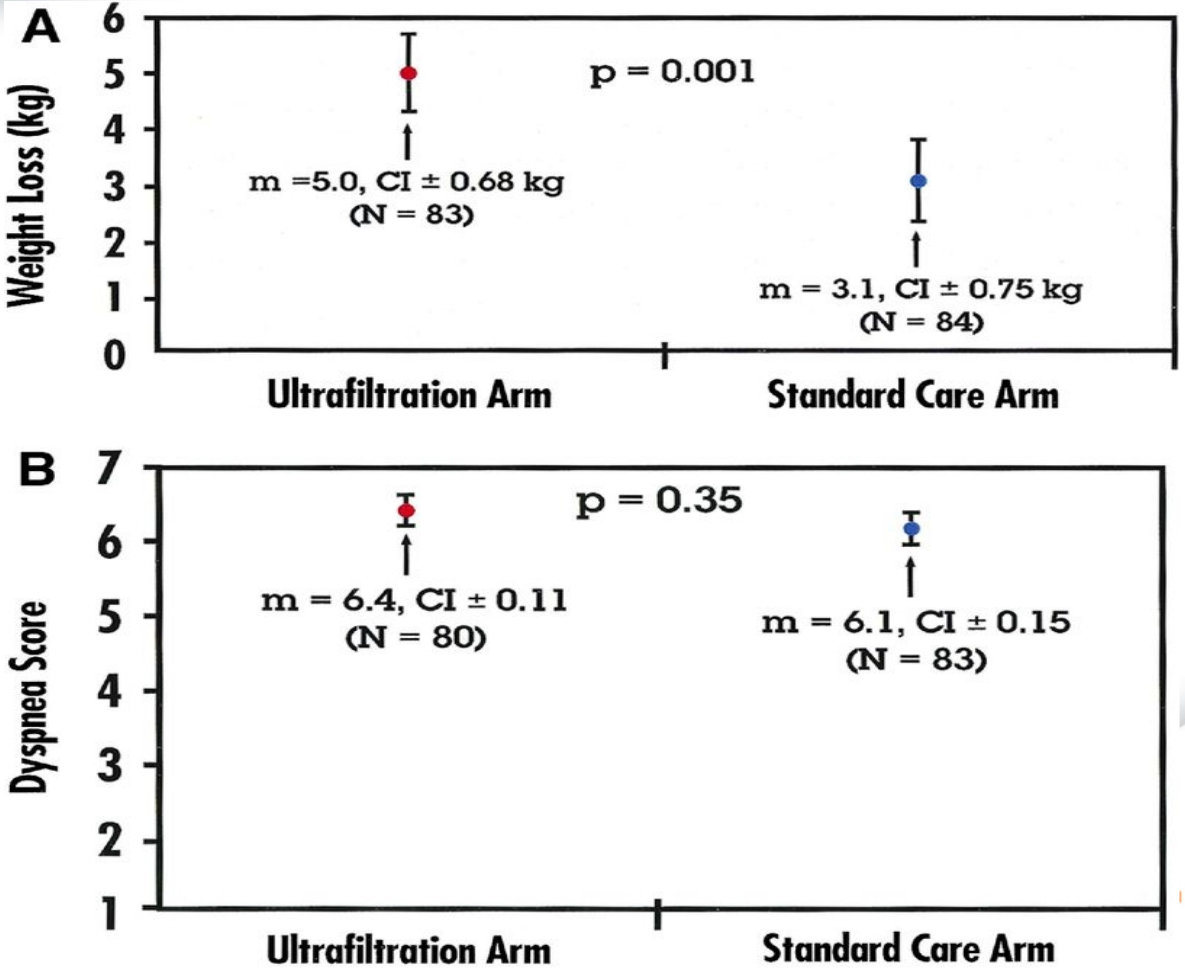
UNLOAD Trial

- Purpose: determine if ultrafiltration is a safe and effective alternative to IV diuretics in the setting of decompensated HF
  - Patients newly hospitalized with decompensated HF and volume overload

- In addition to sodium and fluid restrictions for all, patients were randomized to either ultrafiltration therapy or IV diuretics
  - UF: fluid removal rates up to 500 ml/hr per physician preference
  - Diuretics: doses were at least double home diuretic dose (in furosemide equivalents)

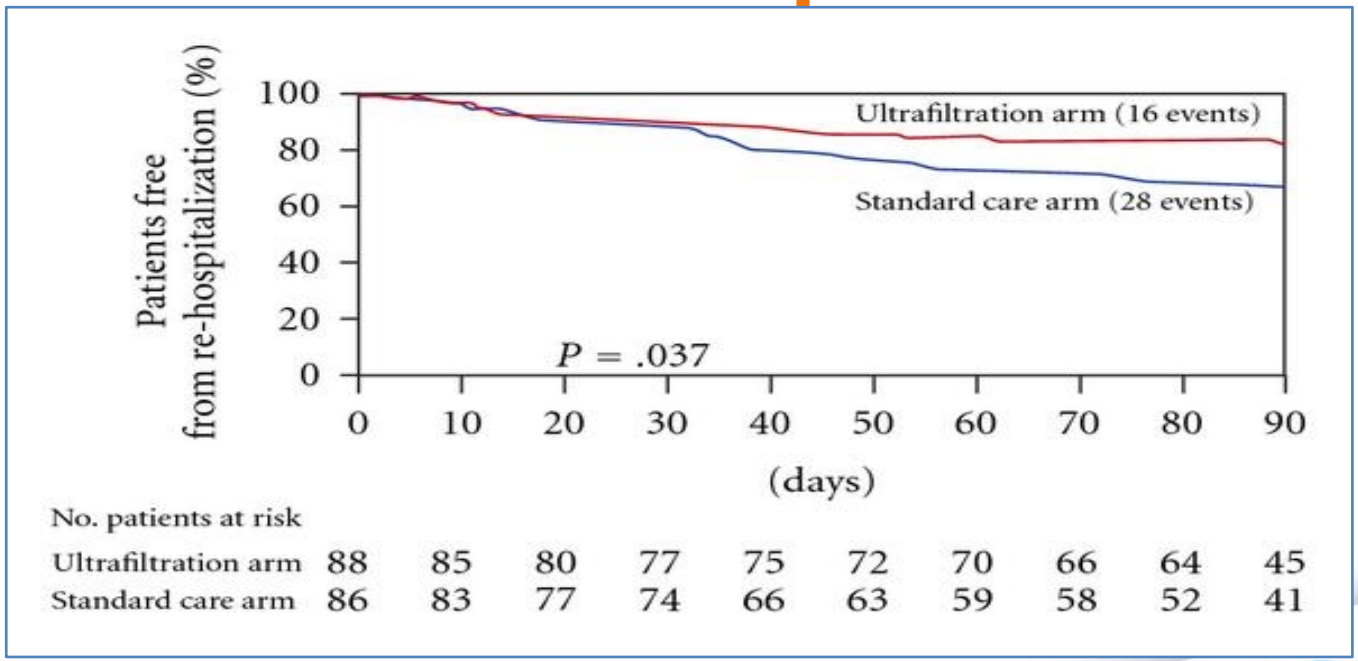
J Am Coll Cardiol 2007; 49: 675 - 83

UNLOAD: Primary Outcomes



J Am Coll Cardiol 2007; 49: 675 - 83

UNLOAD:
Freedom from hospitalizations



J Am Coll Cardiol 2007; 49: 675 - 83

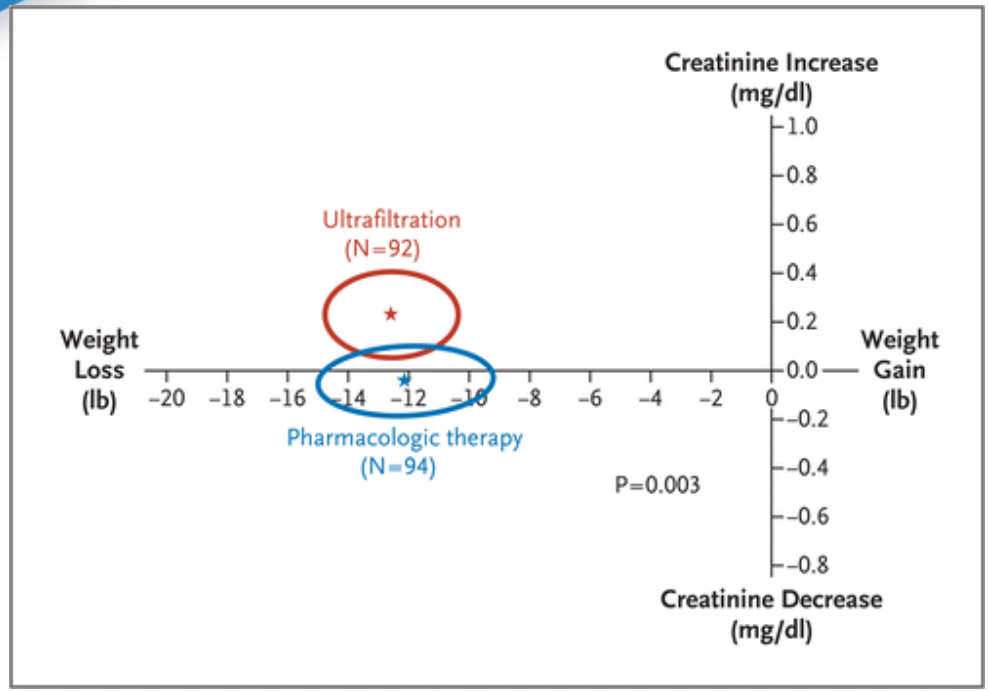
CARRESS-HF Trial

- RCT to compare ultrafiltration to stepped pharmacologic therapy in those admitted with ADHF complicated by cardiorenal syndrome
  - All patients had some degree of acute kidney injury upon admission

- Randomized to one of the following:
  - Ultrafiltration with fluid removal rate of 200 mL/hr
  - IV Diuretics: dose adjusted to maintain urine output of 3-5 L/day

Bart BA, et al. NEJM 2012; 367(24): 2296 - 2304

CARRESS-HF Trial: Primary Outcome



- At 96 hours, patients:
  - NS difference in weight loss
  - Significant increase in SrCr in the UF group

Bart BA, et al. NEJM 2012; 367(24): 2296 - 2304

Ultrafiltration

- May be an necessary option for fluid removal in patients unresponsive to alternative medication options.
  - Requires well trained staff in an ICU setting with invasive lines
  - Provides isotonic fluid removal, which may more completely remove volume from overloaded patients.

Bart BA, et al. NEJM 2012; 367(24): 2296 - 2304

Patient case

- Joy is continued on ultrafiltration for 2 days when it was noticed that her urine output has started to increase and her creatinine has started to decrease.
  - Net negative 4.5 L in this time period
  - Current weight still 3 kg above dry weight
- Ultrafiltration is discontinued and Bumetanide 3 mg IV twice daily and Metolazone 5 mg po daily are initiated

Patient case

- Joy is transferred out of the ICU and is transitioned to an oral diuretic regimen
  - Bumetanide 3 mg twice daily and Metolazone 5 mg on Monday, Wednesday, and Friday
- Edema is improved to 1+ in her lower extremities
- JVD is minimal
- She no longer requires supplemental oxygen, and chest x-ray has shown resolution of pulmonary congestion.

- Joy is ready for discharge from the hospital – HOW DO WE TRANSITION HER TO OUTPATIENT AND AVOID REHOSPITALIZATION?

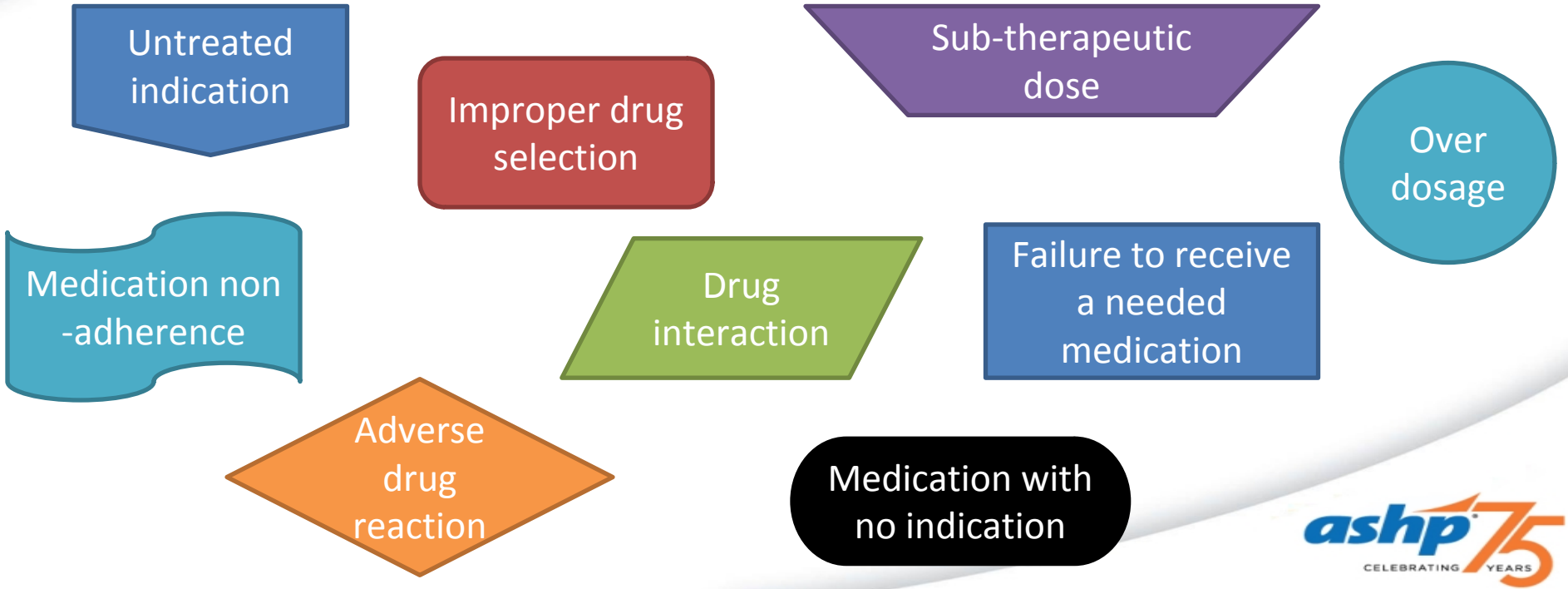
HF Transitions of Care

- Almost ~25% of heart failure patients are readmitted within 30 days
  - Readmission defined as any cause and any hospital
- Many readmissions are considered avoidable
- Medications-related problems (MRP) are the most likely cause of readmission
- 60% of all medication errors occur during transition of are
- 72% of post-discharge adverse events are medication related

Am Geriatric Society 2003; 52:556-557, Improving Care Transitions. Optimizing Medications. March 2012

ashp 75 CELEBRATING YEARS

Medication Related Problems



ashp 75 CELEBRATING YEARS

Pharmacists in TOC Reduce MRP

- Meta-analysis of 13 randomized trials examining 3503 patients
  - Ten studies evaluating the effect of pharmacists intervention during TOC on the incidence of medication errors
    - OR of 0.44 (0.31-0.63)
  - Four studies evaluating showed decrease ED visits
    - OR of 0.42 (0.22-0.78)
    - NNT of 6.2 (3.4-31.4)
- Hospitals should consider implementing this intervention to improve patient safety and quality during transitions-of-care

J Patient Saf. 2017 Jun 30. doi: 10.1097/PTS.0000000000000283

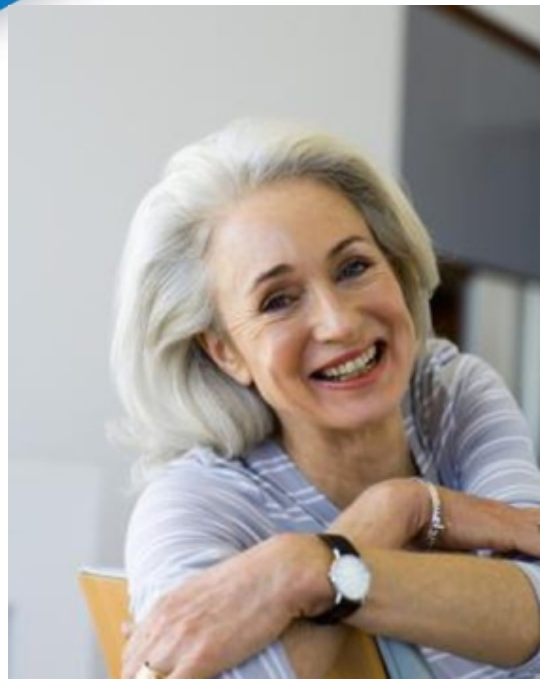
HF Transitions of Care

- Contact primary care physician or am care pharmacist and convey treatment plan
- Determine if patient eligible for home visits or follow-up phone calls
- Appointment for physical exam and vital sign follow-up soon
- Lab Monitoring
  - Electrolytes, renal function
- Ensure the patient understands the importance of regular follow-up and adherence
- Close follow-up on high risk medications

Metolazone

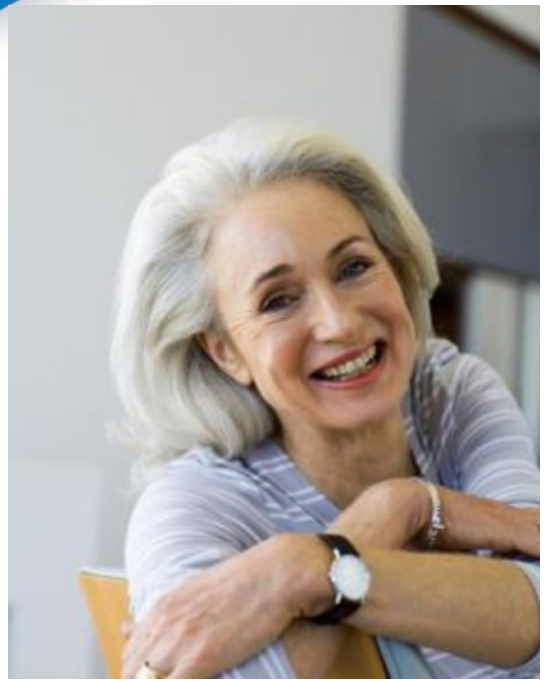
- Combining loop and thiazide diuretics, like metolazone, can cause metabolic disarray if patients are not carefully monitored
- Cardiac arrhythmias can be caused by hypokalemia or hypomagnesemia
- Once patients reach euvolemia, consider tapering down metolazone for a goal to be on one diuretic if possible
- Renal function should also be carefully monitored to ensure patients do not become hypovolemic or suffer acute kidney injury

Joy



- Follows up with you in clinic 1 week after discharge.
  - She is currently taking bumetanide 3 mg twice daily and metolazone 2.5mg on Monday, Wednesday and Friday.
  - Her weight is currently 170 lbs. and she feels fatigued.
  - Labs: K 3.5 mEq/L, Na 133 mEq/L, Mg 1.8 mg/dl, GFR: 28 ml/min
  - Blood pressure 90/58 mmHg; HR 80 bpm
- What's the next best step for Joy?

Joy



- What's the next best step for Joy?
  - Taper her metolazone then discontinue
  - Follow-up with her closely to ensure she maintains her dry weight, electrolyte balance and renal function
    - Set up an appointment within the next 7-10 days
    - Schedule phone follow-up or home visit
  - Educate her on when to call in, how to monitor her weights and take her medications
  - Make sure she understands the importance of adherence to her diet and medications

HF Transitions of Care

Inpatient:
Early education, safe transitions, accurate medication history and reconciliation

Discharge:
Evidence-based medicine, medication schedules, teach-back, meds to beds

Hand Offs:
Provider to provider, pharmacist to pharmacist *communication*

Post Discharge:
Follow-up calls, early appts, home visits

Key Takeaways

- Key Takeaway #1
  - Diuretics are key to the management of HF.
- Key Takeaway #2
  - Dietary and medication adherence issues and drug-drug interactions can contribute to diuretic resistance
- Key Takeaway #3
  - Careful combination of diuretic therapy can help remedy resistance
  - Close monitoring is required for patient safety

Key Takeaways

- Key Takeaway # 4
  - Many mechanisms of diuretic resistance
  - Often, aggressive dosing of loop diuretics is needed to successfully decongest patients
- Key Takeaway # 5
  - Right Heart Cath can guide pharmacotherapy in patients who are not responding to appropriately dosed diuretic regimens
- Key Takeaway # 6
  - Not enough data to support “renal-dose” dopamine, nesiritide, tolvaptan for routine management