COLUMBIA UNIVERSITY MEDICAL CENTER

DIVISION OF GENERAL MEDICINE

Senior Medicine Rotation: Evidence-Based Medicine Project

Name: Rachel Easterwood **Date: March 29, 2013**

Case SIGNOUT:

Pt JR is a 54yo man with a PMH of HTN and HLD who presented with increasing SOB for 1 week. Initial exam was significant for O2 sat 90%, bibasilar rales and JVD to mandible. Labs were notable for BNP >4000, Cr 1.3 (bl 1.0), AST/ALT 50/131. CXR indicated pulmonary edema. Of note, the patient has no known history of cardiac disease, with a negative stress test performed just 2 years prior. Additionally, his HTN appears well-controlled. Pt was ruled out for ACS/MI, and diuresis was begun with 20mg IV Lasix bolus BID, with steady improvement of his SOB. TTE was performed and showed EF of 15% with severe BiV dysfxn. Cardiology was involved, and the pt underwent LHC/RHC, which showed no suggestion of ischemic CM. Given that his family history is significant for multiple close relatives with "cardiac arrhythmias and heart failure", etiology thought to be familial CM. Cardiac transplant work-up was initiated.

Clinical Question:
What is the best way to diurese a patient who presents with acute decompensated heart failure?

Background:
Acute decompensated heart failure

- Clinical constellation with development of acute dyspnea with pulmonary edema in setting of elevated left heart filling pressures, usually secondary to LV dysfunction. Of note, dyspnea can occur without pulmonary edema.
    - Other symptoms: tachypnea, wheezing/cardiac asthma, tachycardia, HTN (hypotension can indicate impending cardiogenic shock), JVD, edema
- Most common cause of hospital admissions for patients >65 yo
- Possible etologies include any cause of LV dysfunction (ischemia, HTN, arrhythmia, valvular disease, familial CM, alcoholic CM), severe renal disease, anemia
- Other precipitating events: 'dietary indiscretion', medication non-adherence, iatrogenic volume overload, NSAIDs, recently added negative inotropes (BB, non-dihydro CCB)
- Current management strategies
    - IV loop diuretics are used in ~90% of patients admitted with heart failure
    - Data regarding dosing and administration is lacking → current guidelines are based on consensus opinion
    - Previous smaller studies suggest that high-dose diuresis results in poor outcomes
    - Complications include RAAS activation, renal dysfunction, and electrolyte disturbance

Search Strategy:
Database: Medline "diuresis decompensated heart failure" + randomized controlled trial filter (15 results)

Article chosen:
Felker GM, Lee KL, Bull DA, et al. Diuretic strategies in patients with acute decompensated heart failure. N Engl J Med. 2011;364(9):797-805.

Senior Medicine Rotation: Based Medicine Project (Cont)

Group	Criteria or definition	n
Population screened.	All patients who presented within previous 24 hours with ADHF, diagnosed by presence of at least 1 symptom + 1 sign. Symptoms included dyspnea, othopnea, edema; signs included rales, peripheral edema, ascites, PVC on CXR.	unknown
Inclusion criteria	The above + history of chronic heart failure + oral loop diuretic for at least 1 month prior to admission with a dose equivalent to 80mg-240mg of furosemide PO daily. 20mg of torsemide and 1mg bumetanide were considered equivalent. Thiazides were also permitted if they had been taken long-term. No specifications were made regarding inclusion criteria for ejection fraction on admission.	308
Exclusion criteria	SBP < 90 mmHg or serum Cr >3.0 or requirement of IV vasodilators or inotropes (except digoxin)	unknown
Treatment group 1	Pt randomized to bolus every 12 hours	156
Treatment group 2	Pt randomized to continuous infusion	152
Treatment group 3	Low dose (total IV furosemide dose equal to pt's total daily oral loop diuretic dose in furosemide equivalents)	151
Treatment group 4	High dose (total daily IV furosemide dose 2.5x the total daily oral loops diuretic dose in furosemide equivalents)	157

Primary endpoints:
Two co-primary endpoints
1) Primary efficacy end point: patient global assessment of symptoms
-measured with visual-analogue scale
-patients were asked to evaluate how they felt by marking a 10-cm vertical line
-scored from 0 to 100 by measuring in millimeters
-quantified as the AUC of serial assessments from baseline to 72 hours
2) Primary safety endpoint: change in serum Cr from baseline through 72 hours

Secondary endpoints:
1) patient-reported dyspnea (visual-analogue scale)
2) changes in body weight/net fluid loss
3) proportion of patients "free from congestion" → JVP < 8cm + no orthopnea + no/trace edema @ 72 hrs
4) "worsening renal function" → inc in Cr > 0.3 mg/dL at any time from randomization to 72 hrs
5) worsening or persistent heart failure
6) treatment failure
7) changes in biomarker levels at 72 hours, 7 days, discharge, or 60 days
8) composite of total hospital days or dead during 60 days after randomization

Results:
- Are the Results of the Trial Valid?
  - Randomized?
    - Yes, this trial is prospective, randomized, and double-blinded
    - Patients were randomized 1:1:1:1 to low-dose or high-dose and to either IV bolus q12h or continuous IV infusion furosemide
  - Blinding?
    - Yes, this trial is prospective, randomized, and double-blinded
    - Double-blind double-dummy design was used
    - All pts rec'd both IV bolus q12h AND a continuous infusion, one of which was normal saline and one was furosemide
    - Study treatment was continued for up to 72 hours, co-interventions were allowed and included:

        - At 48 hrs, the physician had the opportunity to adjust strategy based on clinical response → could increase dose by 50%, keep same strategy, or d/c treatment and change to open-label oral diuretics
        - After 72 hours, all treatment was open-label and at discretion of physician
        - Prior treatment remained blinded
    - All patients accounted for at end?
        - Yes, follow-up is complete for all patients to 60 days or to day of death
    - Intention to treat?
        - Yes, all analyses were performed according to intention-to-treat
    - Groups similar at start of trial?
        - Inclusion criteria is quite broad, but ADHF is a clinical diagnosis

Table 1. Baseline Characteristics of the Study Participants, According to Treatment Group.*

Characteristic	Bolus Every 12 Hr (N=156)	Continuous Infusion (N=152)	Low Dose (N=151)	High Dose (N=157)
Age — yr	66.2±13.2	65.8±14.1	65.9±13.3	66.2±13.9
Male sex — no. (%)	115 (74)	111 (73)	110 (73)	116 (74)
White race — no. (%)	114 (73)	108 (71)	106 (70)	116 (74)
Dose of oral furosemide or furosemide equivalent — mg/day	134±53	127±50	131±52	131±51
Ejection fraction (%)	35±18	35±18	33±17	36±18
Hospitalization for heart failure within previous 12 mo — no./total no. (%)	114/155 (74)	111/149 (74)	115/150 (77)	110/154 (71)
Ischemia as cause of heart failure — no. (%)	91 (58)	85 (56)	88 (58)	88 (56)
History of atrial fibrillation or flutter — no. (%)	84 (54)	78 (51)	82 (54)	80 (51)
Diabetes mellitus — no. (%)	81 (52)	77 (51)	77 (51)	81 (52)
Implantable cardioverter–defibrillator — no. (%)	63 (40)	56 (37)	62 (41)	57 (36)
ACE inhibitor or ARB — no. (%)	104 (67)	93 (61)	94 (62)	103 (66)
Beta-blocker — no. (%)	133 (85)	123 (81)	125 (83)	131 (83)
Aldosterone antagonist — no. (%)	42 (27)	44 (29)	43 (28)	43 (27)
Systolic blood pressure — mm Hg	118±19	121±22	120±19	119±21
Heart rate — beats/min	76±14	80±17	78±15	79±17
Oxygen saturation — %	96±3	96±3	96±3	96±3
Jugular venous pressure ≥8 cm of water — no./total no. (%)	137/151 (91)	130/141 (92)	128/141 (91)	139/151 (92)
Orthopnea — no./total no. (%)	134/146 (92)	133/148 (90)	137/147 (93)	130/147 (88)
Sodium — mg/dl	138±4	138±4	138±4	138±4
BUN — mg/dl	37±21	38±24	38±23	37±22
Creatinine — mg/dl	1.5±0.5	1.5±0.5	1.5±0.5	1.5±0.5
NT-proBNP — pg/ml	7308±7097	7570±7557	8125±7624	6758±6961
Cystatin C — mg/liter	1.6±0.5	1.6±0.6	1.6±0.5	1.6±0.6

* Plus–minus values are means ±SD. All P values are greater than 0.05 for the comparisons of baseline characteristics across groups (bolus vs. continuous infusion and low-dose vs. high-dose strategy). To convert the values for blood urea nitrogen (BUN) to millimoles per liter, multiply by 0.357. To convert the values for creatinine to micromoles per liter, multiply by 88.4. ACE denotes angiotensin-converting enzyme, ARB angiotensin-receptor blocker, and NT-proBNP N-terminal pro-brain natriuretic peptide.

    - Equal treatment of groups?
        - Yes, see blinding section above
        - Trial was sponsored solely by the NHLBI

- Are the Results of the Trial important?
    - Size of treatment effect?
        - There was no significant difference between groups regarding both co-primary endpoints (ie, no difference in global assessment of symptoms of patients and change in renal function between low- and high-dose therapy and between continuous infusion and bolus administration) in patients with pre-existing heart failure on outpatient PO diuretic medication
    - Precision of the estimate of the effect?
        - With a sample of 300 patients, this study has an 88% power to detect 600 point difference between groups in both the patient global assessment score and a 0.2 mg/dL change in creatinine; however, the study was not powered to detect statistical significant differences in clinical events

- With the use of two coprimary endpoints, the threshold for significance was p<0.025. For the secondary endpoints, the traditional p<0.05 was used.
- When differences between groups regarding one of the treatment methods were assessed, the statistical model was designed to adjust for the other factor.
- Presence of interaction between the two treatments factors was also tested and controlled for
    - There was no evidence of interaction between mode of administration and the dosing strategy for both co-primary endpoints

Endpoint	Result	Significance
Primary efficacy endpoint	Mean AUC: 4236 w bolus; 4373 with infusion	p=0.47
Primary safety endpoint	Mean Cr change: 0.05±0.3 w bolus; 0.07±0.3 w infusion	p=0.45
Primary efficacy endpoint	Mean AUC: 4430 high-dose; 4171 low-dose	p=0.06
Primary safety endpoint	Mean Cr change: 0.04±0.3 high-dose; 0.08±0.3 low-dose	p=0.21
Morbidity	**Result**	**Significance**
Serious adverse events, total	38% high-dose; 50% low-dose	p=0.03
Serious adverse events, total	44% continuous infusion; 44% bolus	p=0.97
Ventricular tachycardia	4 cases w continuous infusion; 7 cases with bolus	-
Ventricular tachycardia	4 cases w high-dose; 7 cases with low-dose	-
Renal failure	11 cases w continuous infusion; 8 cases with bolus	-
Renal failure	7 cases w high-dose; 11 cases with low-dose	-
Length of stay	5 days across all treatment groups	-
Death/readmission/ED visit	HR 1.15 w continuous infusion	(0.83-1.60)
Death/readmission/ED visit	HR 0.83 w high dose	(0.60-1.16)

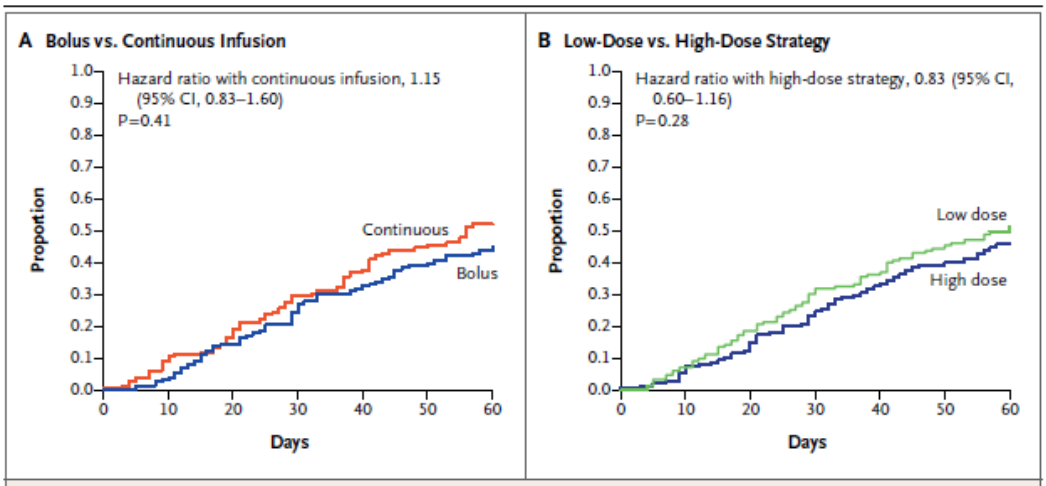

Figure 3. Kaplan–Meier Curves for the Clinical Composite End Point of Death, Rehospitalization, or Emergency Department Visit.

Kaplan–Meier curves are shown for death, rehospitalization, or emergency department visit during the 60-day follow-up period in the group that received boluses every 12 hours as compared with the group that received a continuous infusion (Panel A) and in the group that received a low dose of the diuretic (equivalent to the patients' previous oral dose) as compared with the group that received a high dose (2.5 times the previous oral dose) (Panel B).

- Can I apply these results to my patient?
    - Comparison of my patient to trial patients.
        - My patient had new-onset heart failure, and had not previously been prescribed a diuretic. He would have been excluded from this study; therefore, this study technically cannot be applied to his case. Further studies with different patient populations would be helpful.
    - All clinically important outcomes were considered.
    - Likely benefits outweigh potential harms and cost?
        - Given that this article is showing no significant differences in treatment strategies, patients' diuresis strategies should likely be chosen on a patient-to-patient basis.

Limitations:
-Co-intervention of physicians after 48 hours was not documented in detail, and we don't know how often it occurred. This could have affected the results that were observed after the pre-determined 72-hour period.
-Patient's assessment of their symptoms is incredibly subjective, and the method used is debatable. This was the one statistically significant finding.
-The composite endpoint includes ED visit; this could be for any reason, not necessarily heart failure. There were no specifications for ED diagnosis.
-Again, this study only included patients with pre-existing heart failure already on significant doses of diuretics. Those with new-onset heart failure and/or diuretic-naïve were not included.

References:
Felker GM, Lee KL, Bull DA, et al. Diuretic strategies in patients with acute decompensated heart failure. N Engl J Med. 2011;364(9):797-805.

Hunt SA, Abraham WT, Chin MH, et al. 2009 Focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of HeartFailure in Adults A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines Developed in Collaboration With the International Society for Heart and Lung Transplantation. Circulation. 2009;119(14):e391-479

Salvador DR, Rey NR, Ramos GC, Punzalan FE. Continuous infusion versus bolus injection of loop diuretics in congestive heart failure. Cochrane Database Syst Rev. 2005 Jul 20;(3):CD003178.

Testani JM, Chen J, McCauley BD, et al. Potential effects of affressive decongestion during the treatment of decompensated heart failure on renal function and survival. Circulation 2010;122:265-72.

Dormans TPJ, Vanmetel JJ, Gerlag PG, Tan Y, Russel FG, Smits P. Diuretic efficacy of high-dose furosemide in severe heart failure: bolus injection versus continuous infusion. J Am Coll Cardiol 1996;28:376-82.

Cooper HA, Dries DL, Davis CE, et al. Diuretics and the risk of arrhythmic death in patients with left ventricular dysfunction. Circulation 1999; 100:1311-5.

Uptodate was also referenced. Duane S Pinto, MD, MPH, Stanley Lewis, MD. Evaluation of acute decompensated heart failure.