

## Journal Club Eastern Virginia Medical School

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Date: 5/20/11

**CITATION: Felker MG, Diuretic strategies in patients with acute decompensated heart failure. N England J Med 2011; 364: 797-805**

I. WHAT IS BEING STUDIED?	DOSING STRATEGIES OF LASIX IN ACUTE DECOMPENSATED HEART FAILURE
1. Study Objective	Investigate safety and efficacy of optimal dosing and route of administration of lasix in patients with ADHF
2. Study Design	<p><u>Prospective, randomized, double-blind, double-dummy, 2x2 factorial design</u></p> <p>9 sites, in US and Canada</p> <p><u>308 patients randomized to 1 of 4 arms</u> with 2 independent variables each with 2 levels: Low dose (home lasix dose) vs high dose (2.5 X home dose) Continuous vs bolus IV dosing</p> <p>Double dummy- all patients received both IV boluses q12 hours and a continuous infusion, one of which contained furosemide and the other saline placebo</p> <p>All patients evaluated at <u>48 hours</u> (still blinded) and physicians chose: increase dose by 50%, maintain same strategy, or discontinue IV treatment for oral diuretics</p> <p>At 72 hours all treatment open- label/at discretion of treating physician</p> <p>followed/evaluated at 60 days for biomarker levels and recording of</p>

	‘significant events’
3. Inclusion Criteria	<p>Presented within <u>previous 24 hours</u>  <u>ADHF: diagnosed</u> on one symptoms and one sign  Symptom: dyspnea, orthopnea, or edema  Sign: rales, peripheral edema, ascites, or pulmonary vascular congestion on chest xray  ADDITIONALLY:  History of CHF and at least 1 month prior to hospitalization on 80-240mg lasix or an equivalent dose of a different loop diuretic (1mg bumetanide, 20mg torsemide)</p> <p>Thiazides were permitted if had been on long term</p> <p>No specification of EF for inclusion (though compared in group characteristics)</p>
4. Exclusion Criteria	<p>Systolic blood pressure &lt;90mmhg  Serum creatinine level &gt;3.0mg/dl  IV vasodilators  ionotropic agents (excluding digoxin)</p>
5. Interventions Compared	<p>Low dose (home lasix dose) vs high dose (2.5 X home dose)  Continuous vs bolus IV dosing</p>
6. Outcomes Evaluated	<p><u>Efficacy evaluation:</u> subjective “global assessment of symptoms”/GAS, patients asked to mark their general well being on a 10cm vertical line with top labeled “best you have ever felt” and bottom “worst you have ever felt”, this quantified on scale 0 to 100 by measuring the distance in mm from the bottom of the line to their mark.  Groups compared by mean area under the Curve of the GAS visual analogue scale</p> <p><u>Safety evaluation:</u> Creatinine, cystatin C, pro-BNP taken at baseline, 72 hours, and</p>

	<p>60 days  <u>Significance considered pvalue &lt;0.025</u></p> <p><u>PRESPECIFIED Secondary endpoints:</u>  Patient reported dyspnea, changes in body weight/net fluid los, proportion patients free from congestion (JVP&lt;8cm and no orthopnea and trace or no peripheral edema at 72hrs), worsening renal function (creatinine increase&gt;0.3mg/dl), changes in biomarkers at 72hours, day 7 or discharge, and day 60, and clinical end points- composite of death, rehospitalization, or ED visit within 60 days and number of days hospitalized during the 60 days of follow up  <u>Significance considered pvalue &lt;0.05</u></p>
<p><b>II. Are the results of the study valid?</b></p>	
<p>1. Was the assignment of patients randomized?</p>	<p>Yes  Randomly assigned in a <u>1:1:1:1 ratio</u> to low vs high and bolus vs continuous dosing</p> <p>Randomization with <u>permuted blocks</u>, stratified according to clinical site</p> <p><u>Permuted blocks:</u> a random number sequence is generated from a statistical textbook or computer. Each possible permuted block (a grouping of treatment vs control- in this study varying treatment options) is assigned a number. Using each number in the random number sequence in turn selects the next block, determining the next participant allocations. Numbers in the random number sequence greater than the number of permuted block combinations are not used to select blocks.</p>
<p>2. Were all patients who entered the trial properly accounted for and attributed at its conclusions?</p>	<p>No chart or data of those who left the study or were lost to the 60 day follow up</p>
<p>3. Was follow-up complete?</p>	<p>unsure  several supplemental appendixes</p>

	mentioned- but couldn't find these when I got the journal article online either
4. Were patients, health workers and study personnel "blind" to treatment?	Yes
5. Were study groups similar at the start of the trial?	Table 1- baseline characteristics, appear to similar in terms of: age, sex, race, daily lasix, EF's , SBP's/HR, DM, CHF disease modifying drugs, initial creatinine/BNP/sodium, and exacerbation symptomatology
6. Aside from the experimental intervention, were the groups treated equally	Overall care beyond lasix dosing not described- at discretion of caring physicians
<b>III. What were the results?</b>	
1. How large was the treatment effect? (difference between treatment and control group).	<p>No statistical difference found for both the primary safety and efficacy end points or in the secondary end points when comparing continuous versus bolus dosing</p> <p>Less total lasix dosed in continuous group Bolus dosing more likely to require a dose increase at 48 hours, but no difference in switch to oral dosing between bolus and continuous dosing</p> <p>No significant difference in the efficacy end point in low vs high dosing- but note a nonsignificant trend toward greater improvement in the high dosing- this coincides with the secondary end points that were significantly better with high dosing-that of fluid loss, weight loss, and relief from dyspnea.</p> <p>No significant difference in low and high dosing in the primary safety end point (overall difference between groups-change in creatinine) though there was a higher proportion of patients who met the</p>

	<p>prespecified secondary safety end point (rise in creatinine level of more than 0.3mg/dl at any time during the 72 hours of randomization)- no difference in creatinine at 60 days. And noted in adverse events- overall more cases of renal failure with continuous (vs bolus) dosing and in the LOW dose (vs high dose) strategy.</p> <p>Though not powered to find significant events between groups- overall fewer patients with SAE in high vs low dosing. No difference in the <i>median</i> length of hospital stay.</p> <p>No difference in the composite end point (death, rehospitalization, or Ed visit within 60 days) or in total number of days alive out of hospital (to total of 60 days) between any groups.</p>
<p>2. What was the estimated treatment effect at a 95% confidence interval?</p>	<p>There was no real treatment effect, as no significant difference in primary end points between any of the 4 treatment modes. No CI's were given- p values only. CI for the nonsignificant hazard ratio's were listed.</p>
<p>IV. Will the results help me in caring for my patients? (applicable ?)</p>	<p>As the article discusses, their patient population chosen has relatively high lasix requirement already and so the study findings can't be applied to patients with new onset CHF who are lasix naive or taking &lt;80mg lasix daily or its equivalent in an alternative.</p> <p>Did find, in contradiction to prior studies, that continuous dosing was not associated with a lesser degree of renal dysfunction. and that perhaps that increased doses of lasix associated with worse outcomes in patients- was confounded by the disease severity.</p> <p>Study contents applicable for several points. Symptomatic dyspnea is one of the</p>

	<p>focuses of our primary treatment in the Ed. So, in patients requiring BIPAP/ those with severe dyspnea and CHF with fluid overload, more aggressive lasix dosing may decrease their time necessitating BiPap and thus risk of failing and leading to intubation, etc. And it may do this with only a short term bump in creatinine- and this study used doses of lasix I've personally never seen given. I'm not sure I'd give someone 500mg bolus lasix in the Ed because their home dose is 200mg. The study provides a reference to guide dosing in very lasix dependent patients- and that because of loop diuretic "braking phenomenon" this patient population very well may require very high doses of lasix for the same effect as prior low doses.</p> <p>Also have to keep in mind that there was a significant bump in creatinine &gt;0.03mg/dl in the high dose group, and there is no data to determine whether this has a long term effect on outcome.</p>
<p>1. Were all clinically important outcomes considered?</p>	<p>Raw adverse event data poorly presented- blind statement of less hospitalization/SAE's, etc. A study powered to determine significant event rates between groups would be helpful.</p>
<p>2. Are treatment outcomes worth the potential harms?</p>	<p>Again, unsure exact increased risk of harm. Difficult as this disease process itself is a confounder for adverse events. But, if higher dosing can symptomatically relieve dyspnea more quickly and reduce short term risk of intubation and the risks that it poses to this patient population- it's worth a transient bump in creatinine.</p>

Additional Comments:

Hazard ratio: ratio of hazard rates; assumes constant ratio of events in two groups over time. Trial split into distinct time intervals, at each time interval the probability of surviving or not having certain events is calculated and these probabilities are multiplied to give the “probability” of survival/etc up to a given time point.

Unlike RRR, not just a rate in certain time period and so can be taken over time periods-allowing for some leeway with patients lost to follow up.

1=equal treatments

2= at any given time, two times as many patients in active group are having an event compared with the compared group

Kaplan meier curve : The Kaplan-Meier curve displays a statistical estimate of the percent of people receiving a given therapeutic regimen who, at each observation point after entering a trial, continue to do acceptably well on their assigned therapy. Plotting the curves for a trial's different treatment arms on the same chart yields a comparison of the various regimens.

ie Graphical display of the estimates (based on Kaplan-Meier methodology) of the probability of survival, or not experiencing a particular event such as disease progression, at any time over the period of study.

An important advantage of the Kaplan–Meier curve is that the method can take into account some types of censored data, particularly right censoring, which occurs if a patient withdraws from a study, i.e. is lost from the sample before the final outcome is observed. On the plot, small vertical tick-marks indicate losses, where a patient's survival time has been right-censored.

Braking phenomenon: progressively diminishing response to diuretic therapy with ongoing treatment. Due to multiple mechanisms. Ex: chronic loop diuretic therapy leads to structural changes in the kidney itself, including hypertrophy of the epithelial cells in the distal tubules, which enhance distal reabsorption of sodium and limits sodium excretion and diuresis. Heart failure itself shifts dose response curve for loop diuretics down and to the right, requiring higher starting dose to achieve same level of sodium excretion.

(felker et al- Loop Diuretics in ADHF: Necessary? Evil? A Necessary Evil?)