ARTICLE:
- Citation: Peacock, et al “Impact of Intravenous Loop Diuretics on Outcomes of Patients Hospitalized with Acute Decompensated Heart Failure: Insights from the ADHERE Registry” Cardiology 2009;113:12~19
- Country: USA
- Funding Sources: None mentioned

PURPOSE:
- Research Question(s): What is the clinical and renal outcomes associated with lower versus higher IV loop diuretic dose in patients hospitalized with acute decompensated heart failure (ADHF)?
- Hypothesis: There is a clinical difference in outcomes of heart failure patients who receive lower versus higher doses of diuretics.

DESIGN:
- Study Design: Review / Meta analysis. Observation and retrospective data mining of the ADHERE trial
- Outcomes: The patients receiving the lower doses had a lower risk for in-hospital mortality, ICU stay, prolonged hospitalization, or adverse renal effects.

SUBJECTS:
- Subjects:
  - Number of Studies / Subjects: 62,866 patients receiving <160 mg and 19,674 patients >160 mg of furosemide were analyzed. Total: 82,540
  - Inclusion / Exclusion criteria: Patients taking multiple diuretics or diuretics other than furosemide, bumetanide, or torsemide were excluded from analysis. Records for patients on chronic renal dialysis, patients who received intravenous vasoactive therapy, and patients who had missing data regarding gender, race, age, dyspnea at rest, initial heart rate, systolic
or diastolic blood pressure, baseline serum sodium, serum creatinine (SCr), blood urea nitrogen (BUN), or chronic diuretic use were excluded.

- Demographics: 43-49% male, ~75y/o, ~75% white, 20-20% black

METHODS:
- Interventions: High dose >160mg lasix in first 24hrs of hospitalization, Low dose <160mg. (the first 24 h. Bumetanide and torsemide doses were converted to furosemide equivalents as follows: 1 mg bumetanide or 20 mg torsemide considered t0 be equivalent to equal 40 mg furosemide.)

DATA ANALYSIS:
- Statistics Used: Propensity analysis. The propensity score is the conditional probability of assignment to a particular treatment given observed covariates; this score has been shown to reduce the bias inherent in the estimation of the treatment effect in observational studies.
  - The term 'treatment effect' refers to the causal effect of a binary (0–1) variable on an outcome variable of scientific interest
- A regression adjustment for propensity score was utilized, a technique commonly used in observational studies to control for systematic differences between treatment groups. (Variables with more than 10% missing values (BNP, BMI, LVEF, troponin, smoking status, and QRS duration) were not considered in propensity analysis.
- 10 variables (1) age, (2) oral diuretic use prior to hospitalization, (3) history of chronic renal insufficiency, (4) diabetes, (5) heart failure, (6) whether a patient was transferred in from another hospital or admitted to emergency department, (7) peripheral edema, (8) creatinine, and indicator Variables for (9) mid-Atlantic and (10) South regions.
- Multivariable logistic regression was used to adjust group comparisons for treatment propensity, previously identified risk factors (age, BUN, SCr, systolic blood pressure, diastolic blood pressure, dyspnea at rest, initial heart rate, and serum sodium), chronic diuretic use (yes vs. no), gender, and race (% black).

RESULTS:
- Brief answers to research questions:
- Difference in cohorts:
  - Patients who received LDD were older and more likely to be female than patients in the HDD.
  - Patients given HDD were more likely to be black.
  - Patients in the HDD cohort had approximately one third higher rates of diabetes and renal insufficiency.
○ Differences in the prevalence of atrial fibrillation, COPD/asthma, coronary artery disease, hypertension, and peripheral vascular disease among cohorts.
○ There was a consistently higher burden of comorbidity in the HDD group.
○ Patients in the HDD group were more likely to have received non-IV diuretics prior to hospitalization as compared to LDD patients

- Both before and after risk and propensity adjustments, an increase in SCR >0.5 mg/dl occurred less frequently in LDD admissions than in HDD episodes. The prevalence of a 210 ml/min decrease in GFR from baseline to discharge was significantly lower in LDD versus HDD admissions. Significant differences between cohorts were also present after risk and propensity adjustments.
- Initiation of dialysis during hospitalization occurred less often on LDD admissions compared to HDD admissions.
- The prevalence of prolonged total hospital LOS, defined as  days, was significantly lower in LDD episodes than in HDD admissions.
- The LDD group experienced lower mortality than the HDD group. After covariate and propensity adjustments, the in-hospital mortality risk of patients who received LDD was significantly lower compared to those receiving HDD.
- Statistically significant differences existed in almost all categories.

LIMITATIONS
- The ADHERE registry data were collected retrospectively and were observational. Observational data should be regarded as hypothesis generating. This analysis, therefore, does not permit causal inferences regarding the impact of diuretic intensity on clinical outcomes.
- Data collected by medical chart review are dependent upon the accuracy and completeness of documentation and abstraction. For example, the data on LVEF, BNP levels, and troponin levels were missing in >10% of admissions, and were omitted from the propensity analysis.
- The clinical reasons for the initiation of IV diuretics are not collected and therefore could not be considered in this analysis.
- No means of distinguishing between bolus and continuous infusion of diuretic in the dataset.
- Even if you believe propensity score, there may have been baseline differences in the study populations that may have escaped covariate and propensity score adjustments.
- What happens to the patients after the first 24hrs? More / less diuretics?

IMPLICATIONS FOR PRACTICE:
- Applicable to this clinical practice:
Sort of: Yes, because as we are compelled to give diuretics in the ED to all comers with HF, we may begin tipping more into the HDD cohort and possible worse outcomes. No, because we usually do not determine the dosing of diuretics beyond the first in the ED and certainly not for the next 24hrs.

On a broader level it calls into question whether or not diuretics are safely given as a broad sweeping, one-size fits all treatment for a strikingly heterogeneous illness presentation.

- **Feasibility (cost, resources, etc):**
  Does not propose a significant change to current ED practice.

- **Clinically Relevant:**
  Certainly, given the increasing pressure to give diuretics in the ED, an examination of the safety, efficacy, and morbidity associated with diuretic use is welcome. The question is whether we are convinced that the authorized have effectively “removed” all the confounders and examined the pure effect of diuretics on the standard HF patient. Is there even such a thing? Or should we not be looking for a binary algorithm but instead look for a more nuanced approach?
  Instead of asking are high does or low does always better, we should be asking what patient risk factors and characteristics can help define an optimal dose of diuretics, if such a thing exists.

**LEVEL OF EVIDENCE / DECISION FOR USE:**
- **Background**  
  Consider Replication  
  Ready for use

**Level of Evidence:**
- □ Ia  Evidence obtained from meta-analysis of randomized controlled trials
- □ Ib  Evidence obtained from at least one RCT
- □ IIa  Evidence obtained from at least one well-designed controlled study without randomization
- □ IIb  Evidence obtained from at least one other type of well-designed quasi-experimental study
- □ III  Well-designed non-experimental studies
- □ IV  Expert committee reports, opinions of experts