Loop Diuretic Efficiency
A Metric of Diuretic Responsiveness With Prognostic Importance in Acute Decompensated Heart Failure

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Background—Rather than the absolute dose of diuretic or urine output, the primary signal of interest when evaluating diuretic responsiveness is the efficiency with which the kidneys can produce urine after a given dose of diuretic. As a result, we hypothesized that a metric of diuretic efficiency (DE) would capture distinct prognostic information beyond that of raw fluid output or diuretic dose.

Methods and Results—We independently analyzed 2 cohorts: (1) consecutive admissions at the University of Pennsylvania (Penn) with a primary discharge diagnosis of heart failure (n=657) and (2) patients in the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) data set (n=390). DE was estimated as the net fluid output produced per 40 mg of furosemide equivalents, then dichotomized into high versus low DE based on the median value. There was only a moderate correlation between DE and both intravenous diuretic dose and net fluid output (r≤0.26 for all comparisons), indicating that DE was describing unique information. With the exception of metrics of renal function and preadmission diuretic therapy, traditional baseline characteristics, including right heart catheterization variables, were not consistently associated with DE. Low DE was associated with worsened survival even after adjusting for in-hospital diuretic dose, fluid output, in addition to baseline characteristics (Penn: hazards ratio [HR], 1.36; 95% confidence interval [CI], 1.04–1.78; P=0.02; ESCAPE: HR, 2.86; 95% CI, 1.53–5.36; P=0.001).

Conclusions—Although in need of validation in less-selected populations, low DE during decongestive therapy portends poorer long-term outcomes above and beyond traditional prognostic factors in patients hospitalized with decompensated heart failure. (Circ Heart Fail. 2014;7:261-270.)

Key Words: cardio-renal syndrome ■ diuresis ■ diuretic ■ heart failure ■ survival

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Acute decompensated heart failure (ADHF) is predominantly a disease of fluid overload. As such, the primary therapeutic objective of most ADHF hospitalizations is fluid removal, with the mainstay of therapy being intravenous loop diuretics. It has been suggested that resistance to loop diuretics is an adverse prognostic indicator, and several authors have described a steep dose–response relationship between the amount of loop diuretic administered and adverse outcomes. However, the dose of loop diuretic prescribed captures much more than simply the amount of diuretic resistance because dose selection is influenced by factors such as perceived disease severity, degree of congestion, and the physician’s individual practices regarding diuretic dosing. In fact, some studies have actually found a lack of survival disadvantage or even a survival benefit associated with higher loop diuretic doses after accounting for these potential confounding factors, illustrating that diuretic dose is not an ideal surrogate for diuretic resistance.

Fundamental to the assessment of diuretic responsiveness is determining how well the diuretic can actually facilitate augmentation of urine production. As such, the amount of urine produced is really only valid in context of the dose of diuretic given. For example, the loop diuretic dose in a patient who has a goal fluid loss of 500 mL will often be significantly less than for a patient who has a goal fluid loss >3 L. However, if both patients required 200 mg of intravenous furosemide to reach their goal, the patient that produced only 500 mL of urine would have much greater diuretic resistance than the patient that produced 3 L despite the identical diuretic dose. A reciprocal analogy

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can be drawn with patients producing similar fluid output with different doses of diuretic. As a result, the primary signal of interest in diuretic responsiveness is really the efficiency with which the diuretic can facilitate urine production, not the absolute dose of diuretic or the absolute production of urine. As such, we hypothesized that a metric of diuretic efficiency (DE), defined as the net fluid lost per milligram of loop diuretic during an ADHF hospitalization, would capture distinct prognostic and potentially mechanistic information from that of raw fluid output or diuretic dose. Accordingly, we sought to investigate the association between DE and clinical variables and outcomes in 2 independent cohorts of ADHF.

**Methods**

Given that decongestion strategies vary substantially across institutions and by the composition of patient population, 2 distinct cohorts of ADHF patients were analyzed separately. The first represents a single-center retrospective cohort of consecutively admitted patients to the Hospital of the University of Pennsylvania (Penn cohort) with which detailed information about diuretic administration was collected. The concept was subsequently validated in a second independent cohort, the prospective multicenter Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial. Details of both cohorts are as follows.

**Penn Cohort**

We reviewed the charts of all patients with a primary discharge diagnosis of congestive HF who had been admitted to noninterventional cardiology and internal medicine services at the Hospital of the University of Pennsylvania between 2004 and 2009. Inclusion required a B-type natriuretic peptide level ≥ 100 pg/mL within 24 hours of admission, receipt of intravenous loop diuretics, and availability of data on fluid intake and output during hospitalization. To focus primarily on the physiology and timing of decongestion, patients with a length of stay ≤ 2 days (who likely underwent limited decongestion) and patients with a length of stay >14 days (who likely had either atypical degrees of congestion or nondiuresis-related problems driving the length of stay) were excluded from the cohort. Patients receiving renal replacement therapy were also excluded. In the event of multiple hospitalizations for a single patient, only the first admission meeting the above inclusion criteria was retained. See Figure IA in the Data Supplement for additional details on patient selection. All-cause mortality was determined via the Social Security Death Index, the Data Supplement for additional details on patient selection. All-cause mortality was determined via the Social Security Death Index, and was ascertained 2.5 years after discharge of the last patient in the data set. The median time from discharge to ascertainment of all-cause mortality was 5.1 years (interquartile range [IQR], 3.7–6.3 years).

**ESCAPE Cohort**

The ESCAPE trial was a National Heart, Lung, and Blood Institute–sponsored, randomized, multicenter trial of therapy guided by pulmonary artery catheter versus clinical assessment in hospitalized patients with ADHF. Methods and results have been published previously. Briefly, 433 patients were enrolled at 26 sites from January 2000 to November 2003. Inclusion criteria included ejection fraction ≤ 30%, systolic blood pressure ≤ 125 mm Hg, hospitalization for HF within the preceding year, treatment during the preceding month with >160 mg of furosemide equivalents daily, and ≥ 1 sign and 1 symptom of congestion. Exclusion criteria included admission creatinine level > 3.5 mg/dL. Patients were randomized to therapy guided by clinical assessment alone versus pulmonary artery catheter and clinical assessment. Treatment goals were resolution of signs and symptoms of congestion, and investigators were encouraged to avoid progressive renal dysfunction or symptomatic systemic hypotension. Patients in the ESCAPE population that did not have data available to calculate net urine output (n=19) and patients that did not have data available on peak loop diuretic dose (n=24) were not included in the current analysis. All-cause mortality was determined 180 days after randomization.

Relative DE in each patient was determined as fluid output per milligram of loop diuretic received (expressed as milliliters of net fluid output per 40 mg of furosemide equivalents). Forty milligrams of furosemide equivalents was chosen as reference because this dose has been reported to produce near-maximal rate of instantaneous natriuresis in a healthy volunteer naive to diuretics. For the Penn cohort, where detailed information on diuretic administration was available, DE was calculated using the cumulative in-hospital net fluid output divided by the cumulative in-hospital amount of intravenous loop diuretic received (cumulative DE). For the ESCAPE cohort, only peak loop diuretic dose received in a 24-hour period was available; thus DE was calculated using the average daily fluid output divided by the peak intravenous loop diuretic (peak DE). Given the desire to compare effect sizes across variables and between cohorts, the median values for DE (Penn cohort: median, 480 [IQR, 195–1024] mL net fluid output per 40 mg furosemide equivalents; ESCAPE cohort: median, 148 [IQR, 61–283] mL net fluid output per 40 mg furosemide equivalents) were primarily used. To allow direct comparison between the cohorts, the primary analyses were repeated using peak DE in the Penn cohort calculated using the median from the ESCAPE cohort. Estimated glomerular filtration rate (eGFR) was calculated using the 4-variable Modified Diet and Renal Disease equation. Worsening renal function was defined as a ≥ 20% decrease in eGFR at any time during hospitalization, unless otherwise specified. Loop diuretic doses were converted to furosemide equivalents with 1 mg bumetanide=20 mg torsemide=80 mg furosemide for oral diuretics, and 1 mg bumetanide=20 mg torsemide=40 mg furosemide for intravenous diuretics. The study was approved or determined to qualify for exemption from institutional review board review by the Hospital of the University of Pennsylvania and Yale University Institutional Review Boards.

**Statistical Analysis**

Values reported are mean±SD, median (quartile 1–quartile 4), and percentile. Independent Student t test or Wilcoxon rank-sum test was used to compare continuous variables between 2 groups of patients. χ² test was used to evaluate associations between categorical variables. Correlation coefficients are Spearman ρ and reported as r² values. The independent association between renal variables associated with DE was determined using logistic regression. Proportional hazards modeling was used to evaluate time-to-event associations with all-cause mortality. Candidate covariates entered in the model were baseline characteristics with <10% missing values and a univariate association with all-cause mortality at P≤ 0.2. In the Penn cohort, these variables consisted of age, race, diabetes mellitus, ischemic HF cause, presence of edema, digoxin use, outpatient loop diuretic dose, thiazide diuretic use, heart rate, systolic blood pressure, B-type natriuretic peptide, serum sodium, hemoglobin, eGFR, and blood urea nitrogen. In the ESCAPE cohort, these variables were age, hypertension, ischemic HF cause, presence of edema, jugular venous distension, baseline β-blocker use, baseline angiotensin-converting enzyme or receptor blocker use, preadmission loop diuretic dose, thiazide diuretic use, systolic blood pressure, serum sodium, eGFR, blood urea nitrogen, and hemoglobin. In-hospital or discharge variables with a theoretical basis for confounding were forced into subsequent models regardless of univariate association with mortality. Models were built using backward elimination (likelihood ratio test) where all covariates with P> 0.05 were retained. Survival curves were plotted for patients with the 4 combinations of DE above or below the median and diuretic dose above or below the median for both cohorts. The x axis was terminated when the number at risk was <10% and statistical significance was determined using the log-rank test. Statistical analysis was performed with IBM SPSS Statistics version 20.0 (IBM Corp, Armonk, NY), and statistical significance was defined as 2-tailed P<0.05 for all analyses except for tests for interaction, where P<0.1 was considered significant.
Table 1. Patient Characteristics of the Penn and ESCAPE Cohorts Grouped by DE

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Penn Cohort</th>
<th></th>
<th>P Value</th>
<th>ESCAPE Cohort</th>
<th></th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low (n=329)</td>
<td>High (n=328)</td>
<td></td>
<td>Low (n=195)</td>
<td>High (n=195)</td>
<td></td>
</tr>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>64.3±15.0</td>
<td>61.3±15.8</td>
<td>0.014*</td>
<td>56.8±14.6</td>
<td>55.2±13.0</td>
<td>0.26</td>
</tr>
<tr>
<td>Black race</td>
<td>65%</td>
<td>64%</td>
<td>0.78</td>
<td>36%</td>
<td>46%</td>
<td>0.040*</td>
</tr>
<tr>
<td>Men</td>
<td>51%</td>
<td>62%</td>
<td>0.008*</td>
<td>77%</td>
<td>73%</td>
<td>0.29</td>
</tr>
<tr>
<td>Medical history</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>75%</td>
<td>71%</td>
<td>0.16</td>
<td>48%</td>
<td>45%</td>
<td>0.54</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>49%</td>
<td>36%</td>
<td>0.002*</td>
<td>34%</td>
<td>34%</td>
<td>0.94</td>
</tr>
<tr>
<td>Ischemic cause</td>
<td>26%</td>
<td>26%</td>
<td>0.91</td>
<td>54%</td>
<td>47%</td>
<td>0.16</td>
</tr>
<tr>
<td>Ejection fraction ≥40%</td>
<td>36%</td>
<td>31%</td>
<td>0.19</td>
<td>0%</td>
<td>0%</td>
<td>N/A</td>
</tr>
<tr>
<td>Admission physical examination</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>88.6±20.6</td>
<td>90.2±19.4</td>
<td>0.31</td>
<td>81.5±14.9</td>
<td>82.4±15.0</td>
<td>0.54</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>135±34</td>
<td>136±33</td>
<td>0.82</td>
<td>104±17</td>
<td>108±16</td>
<td>0.005*</td>
</tr>
<tr>
<td>Jugular venous distention (≥12 cm water)</td>
<td>61%</td>
<td>61%</td>
<td>0.87</td>
<td>53%</td>
<td>53%</td>
<td>0.96</td>
</tr>
<tr>
<td>Edema (≥1)</td>
<td>47%</td>
<td>46%</td>
<td>0.79</td>
<td>38%</td>
<td>34%</td>
<td>0.36</td>
</tr>
<tr>
<td>Hepatouvarc reflux</td>
<td>21%</td>
<td>24%</td>
<td>0.36</td>
<td>78%</td>
<td>82%</td>
<td>0.24</td>
</tr>
<tr>
<td>Cardiac function</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>30 (15–45)</td>
<td>23 (15–42)</td>
<td>0.028*</td>
<td>20 (15–21)</td>
<td>20 (15–25)</td>
<td>0.088</td>
</tr>
<tr>
<td>Laboratory values</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Serum sodium, mEq/L</td>
<td>138±5</td>
<td>139±4</td>
<td>0.028*</td>
<td>136±5</td>
<td>137±4</td>
<td>0.15</td>
</tr>
<tr>
<td>B-type natriuretic peptide, pg/mL</td>
<td>1454 (748–2771)</td>
<td>1285 (692–2312)</td>
<td>0.049*</td>
<td>593 (264–1285)</td>
<td>557 (209–1142)</td>
<td>0.421</td>
</tr>
<tr>
<td>eGFR, ml/min per 1.73 m²</td>
<td>55.4±29.3</td>
<td>61.9±26.2</td>
<td>0.003*</td>
<td>55.6±27.4</td>
<td>59.1±23.4</td>
<td>0.028*</td>
</tr>
<tr>
<td>BUN, mg/dL</td>
<td>33.7±24.2</td>
<td>26.8±20.5</td>
<td>&lt;0.001*</td>
<td>38.6±25.4</td>
<td>31.6±18.9</td>
<td>0.002*</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>11.8±2.1</td>
<td>12.4±2.1</td>
<td>&lt;0.001*</td>
<td>12.9±5.3</td>
<td>12.5±1.8</td>
<td>0.41</td>
</tr>
<tr>
<td>Right heart catheterization variables</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right atrial pressure, mm Hg</td>
<td>13.4±7.8</td>
<td>10.2±5.8</td>
<td>0.010*</td>
<td>14.1±9.0</td>
<td>13.6±10.4</td>
<td>0.69</td>
</tr>
<tr>
<td>Pulmonary capillary wedge pressure, mm Hg</td>
<td>23.8±8.5</td>
<td>23.5±8.3</td>
<td>0.85</td>
<td>26.0±9.4</td>
<td>23.8±8.8</td>
<td>0.19</td>
</tr>
<tr>
<td>Cardiac index, L/min per m²</td>
<td>2.1±0.7</td>
<td>2.1±0.6</td>
<td>0.95</td>
<td>2.0±0.6</td>
<td>2.0±0.6</td>
<td>0.54</td>
</tr>
<tr>
<td>Systemic vascular resistance, dyn-s/cm²</td>
<td>1538±582</td>
<td>1622±618</td>
<td>0.43</td>
<td>1428±753</td>
<td>1474±897</td>
<td>0.71</td>
</tr>
<tr>
<td>Medications (admission)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-Blocker</td>
<td>69%</td>
<td>74%</td>
<td>0.18</td>
<td>63%</td>
<td>60%</td>
<td>0.51</td>
</tr>
<tr>
<td>ACE inhibitor or ARB</td>
<td>60%</td>
<td>68%</td>
<td>0.025*</td>
<td>90%</td>
<td>90%</td>
<td>0.87</td>
</tr>
<tr>
<td>Digoxin</td>
<td>24%</td>
<td>28%</td>
<td>0.25</td>
<td>73%</td>
<td>71%</td>
<td>0.65</td>
</tr>
<tr>
<td>Aldosterone antagonist</td>
<td>17%</td>
<td>18%</td>
<td>0.68</td>
<td>33%</td>
<td>34%</td>
<td>0.91</td>
</tr>
<tr>
<td>Loop diuretic dose, mg</td>
<td>80 (20–160)</td>
<td>40 (0–80)</td>
<td>&lt;0.001*</td>
<td>220 (140–320)</td>
<td>160 (80–320)</td>
<td>0.003*</td>
</tr>
<tr>
<td>Thiazide diuretic</td>
<td>15%</td>
<td>10%</td>
<td>0.046*</td>
<td>13%</td>
<td>13%</td>
<td>0.98</td>
</tr>
<tr>
<td>Medications (discharge)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-Blocker</td>
<td>82%</td>
<td>87%</td>
<td>0.055</td>
<td>52%</td>
<td>60%</td>
<td>0.15</td>
</tr>
<tr>
<td>ACE inhibitor or ARB</td>
<td>70%</td>
<td>87%</td>
<td>&lt;0.001*</td>
<td>83%</td>
<td>88%</td>
<td>0.14</td>
</tr>
<tr>
<td>Digoxin</td>
<td>25%</td>
<td>26%</td>
<td>0.77</td>
<td>72%</td>
<td>80%</td>
<td>0.097</td>
</tr>
<tr>
<td>Aldosterone antagonist</td>
<td>23%</td>
<td>23%</td>
<td>0.90</td>
<td>49%</td>
<td>54%</td>
<td>0.27</td>
</tr>
<tr>
<td>Loop diuretic dose, mg</td>
<td>80 (40–160)</td>
<td>80 (40–100)</td>
<td>&lt;0.001*</td>
<td>120 (60–240)</td>
<td>100 (60–160)</td>
<td>0.035*</td>
</tr>
<tr>
<td>Thiazide diuretic</td>
<td>15%</td>
<td>5%</td>
<td>&lt;0.001*</td>
<td>14%</td>
<td>10%</td>
<td>0.27</td>
</tr>
</tbody>
</table>

DE was calculated as the cumulative net fluid output divided by the cumulative loop diuretic dose (per 40 mg of furosemide equivalent) during hospitalization in the Penn cohort. In the ESCAPE cohort where cumulative diuretic dose was unavailable, DE was estimated using the peak dose of loop diuretic administered in 24 h (per 40 mg furosemide equivalents). DE was then dichotomized about the median to define high vs low DE. ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BUN, blood urea nitrogen; DE, diuretic efficiency; eGFR, estimated glomerular filtration rate; ESCAPE, Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness; N/A, not available; and Penn, University of Pennsylvania.

*Significant P value.
†Data available in n=139 patients in the Penn cohort and n=192 patients in the ESCAPE cohort.
Results

Baseline characteristics of the 2 cohorts are presented in Table 1. There was a broad range of DE represented in the cohorts (Figure 1). There was only a moderate correlation between DE and intravenous diuretic dose (Penn $r^2=0.12$; ESCAPE $r^2=0.21$) or net fluid output (Penn $r^2=0.26$; ESCAPE $r^2=0.21$; Figure II in the Data Supplement). The direct correlation between diuretic dose and net fluid output was also moderate (Penn $r^2=0.27$; ESCAPE $r^2=0.14$). In line with the requirement for baseline high-dose loop diuretic use for enrollment into the ESCAPE trial, loop diuretic doses were generally higher and DE was lower in the ESCAPE population (Table 1).

Baseline and In-Hospital Factors Associated With Low DE

Characteristics of patients with DE above or below the median value (below the median henceforth referred to as low DE) are reported in Table 1. As expected from the nature of dichotomization, the net urine output was significantly less and doses of loop diuretics greater in patients with low DE (Table 2). However, patients with low DE were not universally given high doses of loop diuretics (32.5% had diuretic doses below the median in the Penn cohort and 32.9% in the ESCAPE cohort). Both baseline and discharge loop diuretic doses were greater in patients with low in-hospital DE (Table 1).

Nondiuretic baseline differences between patients with and without low DE, including right heart catheterization variables and physical examination findings, were small and generally not statistically significant across both cohorts (Table 1). The only nondiuretic baseline characteristics associated with DE in both ESCAPE and Penn cohorts were blood urea nitrogen and eGFR (Table 1). Interestingly, the correlation was small between eGFR and diuretic dose (Penn $r^2=0.05$; $P<0.001$; ESCAPE $r^2=0.00; P=0.76$), net fluid output (Penn $r^2=0.00$; $P=0.35$; ESCAPE $r^2=0.03$; $P=0.002$), and DE (Penn $r^2=0.02$; $P<0.001$; ESCAPE $r^2=0.04$; $P<0.001$; Figure 2). In a multivariable model incorporating both eGFR and baseline blood urea nitrogen, only blood urea nitrogen remained significantly associated with low DE (Penn cohort: odds ratio [OR], 1.14 per 10 increase in blood urea nitrogen; $P=0.009$; ESCAPE cohort: OR, 1.19 per 10 increase in blood urea nitrogen; $P=0.005$). In ESCAPE, there was no difference in DE based on randomization to a pulmonary artery catheter–guided treatment strategy ($P=0.72$) or treatment with a pulmonary artery catheter ($P=0.19$). However, among patients randomized to care guided by clinical assessment alone, there was a higher rate of crossover to pulmonary artery catheter use in patients with low DE (OR, 3.5; $P=0.014$). The use of inotropes and length of stay was greater with low DE in the ESCAPE cohort but not the Penn cohort (Table 2). Similar overall findings were noted in the Penn cohort when using the peak DE definition from the ESCAPE cohort (Tables I and II in the Data Supplement).

Diuretic Strategy, Relief of Congestion, and Worsening Renal Function

Overall, the in-hospital treatment approach/outcomes for patients with or without low DE appeared to differ somewhat between cohorts. In both cohorts, low DE resulted in the escalation of diuretic strategies such as higher doses of loop diuretics, greater use of adjuvant thiazide diuretics, and initiation of a loop diuretic infusion (diuretic infusion usage available only in the Penn cohort). In patients with low DE, the maximum 24-hour loop diuretic dose was 4.0 times the baseline dose in the Penn cohort, whereas in the ESCAPE cohort, there was a 2.6-fold increase in maximum furosemide equivalents over the preadmission dose. In ESCAPE, low DE was associated with what appeared to be less complete decongestion. This was evidenced by higher right atrial and pulmonary capillary wedge pressure and discharge physical examination findings consistent with continued volume overload compared with patients with preserved DE (Table 2). Interestingly, despite discharge with persistent congestion, the rate of deterioration in renal function was no different between patients with or without low DE (Table 2). In the Penn cohort, significant differences in the degree of decongestion were not apparent because discharge physical examination findings were not different between groups (Table 2). However, the rate of worsening renal function was substantially greater in the low DE group (Table 2). Overall, the above findings were also noted in the Penn cohort when using the peak DE definition from the ESCAPE cohort (Tables I and II in the Data Supplement).

DE and Prognosis

In the Penn cohort, a total of 346 patients (52.7%) died over a median follow-up of 3.2 (IQR, 1.2–5.2) years, and in the ESCAPE cohort, a total of 75 patients (19.2%) died over a median follow-up of 179 (IQR, 129–180) days. Consistent with previous literature, a loop diuretic dose above the median was associated with significantly reduced survival in both Penn and ESCAPE cohorts (Table 3; Table III in the Data Supplement). However, net fluid output below the median was not associated with survival in either cohort (Table 3). The same lack of association was found for the continuous net fluid output variables, even after accounting for length of stay ($P<0.18$ for both cohorts). Despite the lack of mortality information related to net fluid output, low DE was associated with substantially worsened survival (Table 3). In line with the limited correlation between net fluid output, intravenous loop diuretic...
Table 2. In-Hospital Variables of the Penn and ESCAPE Cohorts Grouped by DE

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Penn Cohort Low (n=329)</th>
<th>High (n=328)</th>
<th>P Value</th>
<th>ESCAPE Cohort Low (n=195)</th>
<th>High (n=195)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuresis-related variables</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cumulative intravenous loop diuretic dose, mg</td>
<td>460 (200–950)</td>
<td>200 (80–340)</td>
<td>&lt;0.001*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average daily intravenous loop dose, mg/d</td>
<td>80 (40–138)</td>
<td>35 (18–63)</td>
<td>&lt;0.001*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak intravenous loop diuretic dose in 24 h, mg</td>
<td>160 (80–260)</td>
<td>80 (40–124)</td>
<td>&lt;0.001*</td>
<td>320 (180–480)</td>
<td>160 (80–280)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Continuous diuretic infusion</td>
<td>8%</td>
<td>2%</td>
<td>0.001*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjuvant thiazide diuretic</td>
<td>22%</td>
<td>9%</td>
<td>&lt;0.001*</td>
<td>34%</td>
<td>25%</td>
<td>0.034*</td>
</tr>
<tr>
<td>Time receiving intravenous diuretic, % of hospitalization</td>
<td>69.6±23.1</td>
<td>61.0±25.7</td>
<td>&lt;0.001*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Net fluid loss, L</td>
<td>2.7 (-0.04–5.9)</td>
<td>5.7 (3.2–9.0)</td>
<td>&lt;0.001*</td>
<td>3.6 (1.0–6.9)</td>
<td>5.6 (3.1–10.4)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Fluid intake, L</td>
<td>7.2 (4.7–11.8)</td>
<td>6.6 (4.2–10.0)</td>
<td>0.090</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluid output, L</td>
<td>10.0 (5.9–16.2)</td>
<td>12.5 (7.8–20.2)</td>
<td>&lt;0.001*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average net daily fluid loss, L</td>
<td>0.5 (−0.1 to 0.9)</td>
<td>1.0 (0.7–1.5)</td>
<td>&lt;0.001*</td>
<td>0.5 (0.2–0.9)</td>
<td>1.4 (0.9–1.9)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>DE (fluid output per 40 mg furosemide equivalents), mL</td>
<td>198 (−8.9 to 347)</td>
<td>1024 (698–1760)</td>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estimated peak dose DE (fluid output per 40 mg furosemide equivalents), mL</td>
<td>92.3 (−3.4 to 174)</td>
<td>456 (296–724)</td>
<td>&lt;0.001*</td>
<td>60 (22–104)</td>
<td>281 (194–552)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>In-hospital inotropes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Milrinone</td>
<td>14%</td>
<td>16%</td>
<td>0.69</td>
<td>20%</td>
<td>14%</td>
<td>0.13</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>2%</td>
<td>1%</td>
<td>0.47</td>
<td>36%</td>
<td>21%</td>
<td>0.001*</td>
</tr>
<tr>
<td>In-hospital maximum change in laboratory variables</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>eGFR, %</td>
<td>−18.8±15.8</td>
<td>−13.0±13.3</td>
<td>&lt;0.001*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Worsening renal function</td>
<td>42%</td>
<td>28%</td>
<td>&lt;0.001*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BUN, %</td>
<td>49.4±55.6</td>
<td>33.5±44.0</td>
<td>&lt;0.001*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bicarbonate, %</td>
<td>20.7±17.2</td>
<td>23.2±51.3</td>
<td>0.86</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Admission to discharge change in laboratory variables</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>eGFR, %</td>
<td>−1.7±26.6</td>
<td>4.9±25.2</td>
<td>&lt;0.001*</td>
<td>0.2±33.2</td>
<td>0.1±25.8</td>
<td>0.97</td>
</tr>
<tr>
<td>Worsening renal function</td>
<td>22%</td>
<td>11%</td>
<td>&lt;0.001*</td>
<td>24%</td>
<td>20%</td>
<td>0.29</td>
</tr>
<tr>
<td>BUN, %</td>
<td>29.9±54.5</td>
<td>15.9±48.1</td>
<td>&lt;0.001*</td>
<td>22.3±61.4</td>
<td>23.0±55.3</td>
<td>0.91</td>
</tr>
<tr>
<td>Bicarbonate, %</td>
<td>11.1±17.7</td>
<td>14.1±52.7</td>
<td>0.95</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium, %</td>
<td>−0.6±3.3</td>
<td>−1.1±4.8</td>
<td>0.43</td>
<td>−1.1±3.2</td>
<td>−1.0±2.8</td>
<td>0.69</td>
</tr>
<tr>
<td>Hospital course</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Length of stay, d</td>
<td>6 (4–9)</td>
<td>5 (4–8)</td>
<td>0.099</td>
<td>9 (6–14)</td>
<td>6 (4–8)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Discharge physical examination</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jugular venous distention (≥8 cm water)</td>
<td>19%</td>
<td>21%</td>
<td>0.563</td>
<td>39%</td>
<td>29%</td>
<td>0.035*</td>
</tr>
<tr>
<td>Edema, ≥1</td>
<td>17%</td>
<td>15%</td>
<td>0.38</td>
<td>7%</td>
<td>2%</td>
<td>0.032*</td>
</tr>
<tr>
<td>Hepatoujugular reflux</td>
<td>4%</td>
<td>4%</td>
<td>0.97</td>
<td>22%</td>
<td>16%</td>
<td>0.11</td>
</tr>
<tr>
<td>Rales</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>14%</td>
<td>4%</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Ascites</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>6%</td>
<td>2%</td>
<td>0.034*</td>
</tr>
<tr>
<td>Right heart catheterization variables at removal†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right atrial pressure, mm Hg</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>11.5±8.5</td>
<td>7.4±4.1</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Pulmonary capillary wedge pressure, mm Hg</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>18.7±7.6</td>
<td>15.5±7.0</td>
<td>0.027*</td>
</tr>
<tr>
<td>Cardiac index, L/min per m²</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>2.3±0.7</td>
<td>2.4±0.6</td>
<td>0.52</td>
</tr>
<tr>
<td>Systemic vascular resistance, dyn·s/cm²</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>1081±489</td>
<td>1135±446</td>
<td>0.48</td>
</tr>
</tbody>
</table>

BUN indicates blood urea nitrogen; DE, diuretic efficiency; eGFR, estimated glomerular filtration rate; ESCAPE, Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness; N/A, not available; and Penn, University of Pennsylvania.

*Significant P value.
†Data available in n=166.
dose, and DE, this mortality disadvantage with low DE seemed to be relatively independent from the absolute dose of diuretic or amount of fluid lost (Table 3). After adjustment for baseline characteristics, only DE remained significantly associated with mortality in both cohorts (Table 3). These findings were also noted in the Penn cohort when using the peak DE definition from the ESCAPE cohort (Table 3). There was a trend toward a stronger association between low DE and mortality in patients with reduced compared with preserved ejection fraction; however, this did not reach statistical significance (Table IV in the Data Supplement). The unadjusted risk for mortality in patients with low DE receiving doses of loop diuretics above or below the median is depicted in Figure 3A and 3B. The risk of death associated with low DE was also present in patients who did not receive high doses of intravenous loop diuretic (dose below the median) in both Penn (adjusted for baseline characteristics; hazards ratio [HR], 1.85; 95% confidence interval [CI], 1.28–2.77; \( P=0.001; \) \( P \) interaction=0.053; Figure 3A) and ESCAPE cohorts (adjusted for baseline characteristics; HR, 4.08; 95% CI, 1.70–9.82; \( P=0.002; \) \( P \) interaction=0.53; Figure 3B). In both cohorts, patients that received low doses of loop diuretic and who had preserved DE had substantially better survival compared with the remainder of the groups (Figure 3). After extensive adjustment for baseline characteristics in addition to in-hospital– and discharge-related variables (length of stay, use of milrinone, dobutamine, adjuvant thiazide use, worsening renal function, hemoconcentration, discharge physical examination findings, and discharge medications), the association between DE and mortality remained in both the Penn (HR, 1.46; 95% CI, 1.15–1.86; \( P=0.002 \)) and ESCAPE cohorts (HR, 3.57; 95% CI, 1.46–8.73; \( P=0.005 \)).

Discussion

In the current analysis, we found that in the setting of ADHF the efficiency with which loop diuretics induce diuresis is strongly and independently associated with survival. Notably, DE was only modestly correlated with diuretic dose and net urine output, but provided distinct prognostic information to either parameter. Furthermore, despite the strong association between DE and mortality, baseline disease severity indicators such as right heart catheterization variables, vital signs, and physical examination findings were remarkably similar between groups. Although the simple metric of DE presented in this analysis is not without shortcomings, it does provide an easily calculated metric that strongly associates with mortality and may have advantage over diuretic dose or fluid output in describing diuretic resistance.

The previously reported association between high doses of loop diuretics and mortality, in conjunction with known direct adverse cardiorenal effects of loop diuretics, raised the possibility that high-dose diuretics were directly causing adverse outcomes. However, a confounding factor is that sicker patients generally receive higher doses of diuretics. Furthermore, after extensive multivariable adjustment or propensity matching, several investigators found no association or even a survival advantage associated with the use of high doses of loop diuretics. Although not formally testing high versus low absolute doses, the Diuretic Optimization Strategies Evaluation (DOSE) trial randomized patients to high versus low intensification of their home diuretics (although the low intensification group still received >120 mg of intravenous furosemide per day) and found no difference in outcomes between groups. Moreover, in the recent Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARRRESS-HF) trial, patients treated with aggressive dosing of diuretics had similar outcomes to those treated primarily with ultrafiltration. In the current analysis,
we found that: (1) diuretic dose did not retain independent prognostic information in fully adjusted multivariable models incorporating both loop diuretic dose and DE; and (2) low DE had an equal, if not worse, prognosis in patients receiving lower doses of loop diuretics. These data add to the growing literature arguing that the bulk of association between in-hospital high-dose loop diuretics and mortality is unlikely to be cause and effect.

Although the long-term mortality associated with DE was consistent across cohorts, the short-term renal and decongestive outcomes were not. In the Penn cohort, there was a strong signal for worsening in renal function in patients

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**Table 3. Risk of Death Associated With Loop Diuretic Dose, Net Fluid Output, and DE in the Penn and ESCAPE Cohorts**

<table>
<thead>
<tr>
<th></th>
<th>Univariable</th>
<th>Multivariable</th>
<th>Multivariable With Adjustment for Baseline Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P Value</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td><strong>Penn cohort</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(cumulative DE)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loop diuretic†</td>
<td>1.56 (1.26–1.93)</td>
<td>&lt;0.001*</td>
<td>1.36 (1.05–1.76)</td>
</tr>
<tr>
<td>Net fluid output†</td>
<td>1.01 (0.82–1.25)</td>
<td>0.93</td>
<td>1.04 (0.80–1.34)</td>
</tr>
<tr>
<td>DE†</td>
<td>1.64 (1.32–2.03)</td>
<td>&lt;0.001*</td>
<td>1.51 (1.17–1.95)</td>
</tr>
<tr>
<td><strong>Penn cohort</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(peak DE)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loop diuretic†</td>
<td>1.56 (1.26–1.93)</td>
<td>&lt;0.001*</td>
<td>1.41 (1.11–1.79)</td>
</tr>
<tr>
<td>Net fluid output†</td>
<td>1.01 (0.82–1.25)</td>
<td>0.93</td>
<td>1.08 (0.84–1.39)</td>
</tr>
<tr>
<td>DE†</td>
<td>1.70 (1.38–2.11)</td>
<td>&lt;0.001*</td>
<td>1.67 (1.31–2.18)</td>
</tr>
<tr>
<td><strong>ESCAPE cohort</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(peak DE)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loop diuretic†</td>
<td>2.46 (1.54–3.94)</td>
<td>&lt;0.001*</td>
<td>1.68 (0.98–2.88)</td>
</tr>
<tr>
<td>Net fluid output†</td>
<td>0.96 (0.61–1.51)</td>
<td>0.86</td>
<td>0.91 (0.54–1.51)</td>
</tr>
<tr>
<td>DE†</td>
<td>3.98 (2.32–6.84)</td>
<td>&lt;0.001*</td>
<td>3.47 (1.97–6.24)</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; DE, diuretic efficiency; ESCAPE, Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness; HR, hazards ratio; and Penn, University of Pennsylvania.

*Significant P value.

†To facilitate comparison of effect sizes, HRs represent the risk for all-cause mortality associated with a value above or below the median with the HR reflecting an exposure of diuretic dose above the median, efficiency below the median, or fluid output below the median. In the Penn cohort, variables entered in the multivariable model consisted of age, race, diabetes mellitus, ischemic heart failure cause, presence of edema, digoxin use, outpatient loop diuretic dose, thiazide diuretic use, heart rate, B-type natriuretic peptide, systolic blood pressure, serum sodium, hemoglobin, eGFR, and blood urea nitrogen. In the ESCAPE cohort, these variables were age, hypertension, ischemic heart failure cause, presence of edema, jugular venous distension, baseline β-blocker use, baseline angiotensin-converting enzyme or receptor blocker use, outpatient loop diuretic dose, thiazide diuretic use, systolic blood pressure, serum sodium, eGFR, blood urea nitrogen, and hemoglobin.
with low DE, but a limited signal for differences in the degree of decongestion achieved as suggested by similar discharge physical examination findings. In ESCAPE, the reciprocal was found with no differences in renal outcomes but substantial persistent volume overload by right heart catheterization variables and multiple physical examination findings. Interestingly, the relative augmentation in diuretic dose over the baseline dose was larger in the Penn cohort (4-fold) than in the ESCAPE cohort (2.6-fold). A common clinical dilemma when diuresing a diuretic-resistant patient is that additional decongestion often comes at the expense of deterioration in renal function. Notably, the ESCAPE trial protocol specifically called for therapy to be adjusted to achieve stable or improving renal function by discharge. Although interesting, the clinical profile of patients enrolled in ESCAPE was substantially different from Penn, and the fidelity of available data is not sufficient to allow speculation that differences in treatment decisions caused discordant renal and decongestive outcomes between cohorts. However, the discordant findings between Penn and ESCAPE cohorts, with respect to the degree of discharge congestion, indicate that low DE may not always translate into an inevitable inability to decongest a patient.

It is widely known that renal function is an important determinant of diuretic responsiveness. Thus, it was somewhat surprising that a strong relationship between eGFR and diuretic dose, net fluid output, or DE was not identified. However, multiple facets of renal physiology contribute to diuretic resistance, only 1 of which is captured by GFR. In the setting of a severely depressed GFR, it has been well described that diuretic responsiveness is impaired.13 However, this relationship is primarily pharmacokinetic and a result of reduced tubular drug delivery rather than true resistance because the relationship between tubular diuretic concentrations and natriuresis is unchanged in chronic kidney disease.31,33 Due to the fact that loop diuretics are avidly bound to albumin, glomerular filtration is actually a minor pathway in which loop diuretics are delivered to their tubular sight of action.13 Rather, active secretion by proximal tubular cells, a process which is dependent on renal blood flow, is primarily responsible for diuretic delivery to the site of action. However, in the setting of HF, the normal relationship between GFR and renal blood flow can be uncoupled by a substantial increase in filtration fraction, weakening the pharmacokinetic relationship between GFR and drug delivery in HF. Perhaps more importantly, it has been thought that the primary source of variability in response to a loop diuretic in patients with HF is actually pharmacodynamic.31 Notably, multiple processes that are distinct from GFR or drug delivery, such as diuretic breaking, distal tubular structural remodeling, and renal neurohormonal activation, can all cause increased tubular sodium reabsorption even in the setting of normal diuretic delivery.13 Although DE seemed to correlate slightly better than diuretic dose or net fluid output, the relationship remained weak. Notably, a very low eGFR did not exclude the possibility of preserved DE, nor did a normal eGFR exclude the possibility of poor DE. Although there are clearly substantial limitations in the assessment of renal function estimated with creatinine-based metrics in the setting of acute HF; these results provide further support that renal function is not the dominant factor driving DE in HF. Rather, it is the complex interplay between cardiac function, renal function, and volume status that ultimately determines diuretic responsiveness.

Limitations
Given the post hoc nature of this study, the limitations of retrospective analyses apply; residual confounding cannot be excluded; and causality is impossible to determine. Although the definition of DE used in the current analyses provides substantially more physiological information compared with the use of diuretic dose or net fluid output alone, it is not a perfect measure of diuretic resistance. The sigmoidal shape of the dose–response relationship of loop diuretics with both threshold and plateau natriuretic portion limits any linear parameter of diuretic resistance unless it is assured that all patients are on the same portion of the dose–response curve. The fact that only 33 patients in the Penn cohort and 17 patients in the ESCAPE cohort received peak loop diuretic doses <40 mg (a dose which produces maximal instantaneous natriuresis in a healthy volunteer) suggests that, in the majority of patients, only through reduced DE was the renal threshold not met. However, patients that received diuretic doses that had put them on the plateau portion of the dose–response curve likely had an underestimation of DE. Additionally, patients that received an adjuvant thiazide diuretic likely had a significant alteration in their loop DE. However, these changes in loop DE induced by nonloop diuretics are not accounted for in these analyses, potentially biasing the results. Furthermore, diuretic resistance is really only relevant in patients with volume overload, and the fidelity with which volume overload can be defined on a population level is limited. As such, it is probable that some patients may have had low DE in response to a dose of diuretic that was in fact appropriate given that they were not volume-overloaded (ie, a patient admitted primarily because of fluid redistribution rather than total body overload). However, the majority of these limitations would be expected to influence associations with loop diuretic dose or raw fluid output as a metric of diuretic resistance more so than DE. The use of creatinine-based metrics for the assessment of renal function in the likely nonsteady state scenario of ADHF is a significant limitation, and thus descriptions of static and dynamic associations with renal function should be considered hypothesis-generating. Although validating the diuretic resistance concept in the multicenter ESCAPE population adds value, the ESCAPE trial was not designed to study DE; the trial required high doses of baseline loop diuretic for inclusion; and cumulative loop diuretic exposure was not collected, requiring the use of 24-hour peak diuretic dose to estimate DE. Furthermore, both the ESCAPE and Penn cohorts used relatively selective inclusion criteria. As a result, the reported observations may not apply to less-selected populations and thus are in need of validation. Additionally, patients with a length of stay of 1 or 2 days were excluded from the Penn cohort. This is potentially an important source of bias because these patients may have responded particularly briskly to diuretics, permitting early discharge. These factors significantly limit the certainty of generalizability of our findings, and as a result, the observations reported in this article should
be interpreted as hypothesis-generating and require validation in unselected cohorts.

Conclusions

Low DE during decongestive therapy portends poorer long-term outcomes above and beyond traditional prognostic factors in patients hospitalized with ADHF. In light of the central role for loop diuretics in the management of volume over-load in HF, additional research is required to validate these findings in less-selected populations, to develop more precise metrics of DE, and to determine whether therapeutic strategies that improve DE can positively impact outcomes.

Acknowledgments

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Disclosures

None.

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16. Testani JM, McCauley BD, Chen J, Shumski M, Shannon RP. Worsening renal function defined as an absolute increase in serum creatinine is a biased metric for the study of cardio-renal interactions. Cardiology. 2010;116:202–212.

**CLINICAL PERSPECTIVE**

When evaluating patients with heart failure (HF) for diuretic resistance, both net urine output and diuretic dose provide incomplete information as isolated parameters. This is because the quantity of urine output after a loop diuretic is only interpretable in the context of the amount of diuretic given. As a result, we hypothesized that a metric of diuretic efficiency (DE; milliliters of net urine output per 40 mg of intravenous furosemide equivalents) would better capture the physiological essence of diuretic resistance and thus would describe distinct prognostic information beyond that of raw fluid output or diuretic dose. In 2 independent cohorts of patients with decompensated HF (n=657 and 390), we found that there was only a moderate correlation between DE and both intravenous diuretic dose and net fluid output ($r^2 \leq 0.26$ for all comparisons), indicating that DE was describing unique information. With the exception of metrics of renal function and preadmission diuretic therapy, traditional baseline characteristics including right heart catheterization variables were not consistently associated with DE. Low DE was associated with worsened survival even after adjusting for in-hospital diuretic dose, fluid output, in addition to baseline characteristics (cohort 1: hazards ratio [HR], 1.36; 95% confidence interval [CI], 1.04–1.78; $P=0.02$; cohort 2: HR, 2.86; 95% CI, 1.53–5.36; $P=0.001$). These findings suggest that DE may be a superior metric than diuretic dose or fluid output to quantify diuretic resistance. Additional research is necessary to further validate these findings.
Loop Diuretic Efficiency: A Metric of Diuretic Responsiveness With Prognostic Importance in Acute Decompensated Heart Failure

Jeffrey M. Testani, Meredith A. Brisco, Jeffrey M. Turner, Erica S. Spatz, Lavanya Bellumkonda, Chirag R. Parikh and W.H. Wilson Tang

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Supplementary Table 1: Patient characteristics of the Penn cohort grouped by Peak diuretic efficiency:

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Diuretic Efficiency</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low (n=329)</td>
<td>High (n=328)</td>
</tr>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (y)</td>
<td>65.8 ± 15.3</td>
<td>61.1 ± 15.3</td>
</tr>
<tr>
<td>Black race</td>
<td>66.5%</td>
<td>63.8%</td>
</tr>
<tr>
<td>Male</td>
<td>47.3%</td>
<td>61.9%</td>
</tr>
<tr>
<td>Medical History</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>74.7%</td>
<td>72.0%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>49.2%</td>
<td>38.2%</td>
</tr>
<tr>
<td>Ischemic etiology</td>
<td>22.9%</td>
<td>27.4%</td>
</tr>
<tr>
<td>Ejection fraction ≥40%</td>
<td>34.0%</td>
<td>32.5%</td>
</tr>
<tr>
<td>Admission Physical Exam</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>90.0 ± 20.3</td>
<td>89.1 ± 19.8</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>135.1 ± 36.1</td>
<td>135.8 ± 31.9</td>
</tr>
<tr>
<td>Jugular venous distention (≥ 12 cm water)</td>
<td>59.7%</td>
<td>61.6%</td>
</tr>
<tr>
<td>Edema &gt; 1+</td>
<td>45.4%</td>
<td>47.2%</td>
</tr>
<tr>
<td>Hepatojugular reflux</td>
<td>22.5%</td>
<td>22.4%</td>
</tr>
<tr>
<td>Cardiac Function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>28 (15, 45)</td>
<td>25 (15, 45)</td>
</tr>
<tr>
<td>Laboratory Values</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum sodium (mEq/L)</td>
<td>137.8 ± 5.2</td>
<td>138.7 ± 4.3</td>
</tr>
<tr>
<td>B-type natriuretic peptide (pg/mL)</td>
<td>1529 (821, 2785)</td>
<td>1291 (659, 2348)</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73m²)</td>
<td>53.3 ± 29.2</td>
<td>61.8 ± 26.7</td>
</tr>
<tr>
<td>BUN (mg/dL)</td>
<td>34.3 ± 24.2</td>
<td>27.9 ± 21.4</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>11.8 ± 2.0</td>
<td>12.3 ± 2.1</td>
</tr>
<tr>
<td>Right atrial pressure (mmHg)</td>
<td>11.9 ± 7.1</td>
<td>11.2 ± 6.7</td>
</tr>
<tr>
<td>Pulmonary capillary wedge pressure (mmHg)</td>
<td>23.1 ± 8.2</td>
<td>23.9 ± 8.4</td>
</tr>
<tr>
<td>Cardiac index (L/min/m²)</td>
<td>2.1 ± 0.8</td>
<td>2.0 ± 0.5</td>
</tr>
<tr>
<td>Systemic vascular resistance (dyn·s/cm⁵)</td>
<td>19.0 ± 7.9</td>
<td>20.4 ± 7.3</td>
</tr>
<tr>
<td>Medications (Admission)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta blocker</td>
<td>67.3%</td>
<td>73.8%</td>
</tr>
<tr>
<td>Medication</td>
<td>ESCAPE Trial</td>
<td>Current Study</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>--------------</td>
<td>---------------</td>
</tr>
<tr>
<td>ACE inhibitor or ARB</td>
<td>55.9%</td>
<td>68.4%</td>
</tr>
<tr>
<td>Digoxin</td>
<td>22.0%</td>
<td>28.0%</td>
</tr>
<tr>
<td>Aldosterone antagonist</td>
<td>12.2%</td>
<td>20.0%</td>
</tr>
<tr>
<td>Loop diuretic dose (mg)</td>
<td>80 (0, 160)</td>
<td>40 (20, 80)</td>
</tr>
<tr>
<td>Thiazide diuretic</td>
<td>16.7%</td>
<td>10.2%</td>
</tr>
<tr>
<td>Medications (Discharge)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta blocker</td>
<td>67.3%</td>
<td>73.8%</td>
</tr>
<tr>
<td>ACE inhibitor or ARB</td>
<td>67.7%</td>
<td>85.0%</td>
</tr>
<tr>
<td>Digoxin</td>
<td>22.5%</td>
<td>26.9%</td>
</tr>
<tr>
<td>Aldosterone antagonist</td>
<td>15.7%</td>
<td>27.4%</td>
</tr>
<tr>
<td>Loop diuretic dose (mg)</td>
<td>80 (40, 160)</td>
<td>80 (40, 160)</td>
</tr>
<tr>
<td>Thiazide diuretic</td>
<td>14.8%</td>
<td>7.1%</td>
</tr>
</tbody>
</table>

eGFR: Estimated glomerular filtration rate, BUN: Blood urea nitrogen, ACE: Angiotensin converting enzyme inhibitor, ARB: Angiotensin receptor blocker. Diuretic efficiency was calculated as the average daily net fluid loss divided by the peak dose of loop diuretic administered in 24 hours (per 40 mg furosemide equivalents). Diuretic efficiency was then dichotomized about the median value in the ESCAPE trial (148 ml/40 mg) to allow direct comparison between cohorts.* Significant p value.
Supplementary Table 2: In hospital parameters of the Penn cohort grouped by Peak diuretic efficiency using the cut point from the ESCAPE trial:

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Low (n=329)</th>
<th>High (n=328)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diuresis Related Parameters</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cumulative IV loop diuretic dose (mg)</td>
<td>380 (160, 830)</td>
<td>240 (120, 495)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Average daily IV loop dose (mg/day)</td>
<td>60 (28, 114)</td>
<td>50 (24, 87)</td>
<td>0.008*</td>
</tr>
<tr>
<td>Peak IV loop diuretic dose in 24 hours (mg)</td>
<td>160 (80, 260)</td>
<td>80 (80, 160)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Continuous diuretic infusion</td>
<td>9.4%</td>
<td>2.4%</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Adjuvant thiazide diuretic</td>
<td>20.1%</td>
<td>12.7%</td>
<td>0.011*</td>
</tr>
<tr>
<td>Time receiving IV diuretic (% of hospitalization)</td>
<td>64.9 ± 24.9</td>
<td>65.3 ± 24.9</td>
<td>0.867</td>
</tr>
<tr>
<td>Net fluid loss (L)</td>
<td>-1.2 (-5.1, 0.5)</td>
<td>-5.5 (-9.4, -3.1)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Fluid intake (L)</td>
<td>7.9 (5.1, 13.2)</td>
<td>6.3 (4.1, 9.9)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Fluid output (L)</td>
<td>9.7 (5.3, 16.0)</td>
<td>12.1 (7.5, 19.6)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Average net daily fluid loss (L)</td>
<td>0.2 (0.1, 0.6)</td>
<td>1.0 (0.7, 1.5)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Diuretic efficiency (mL fluid output/40mg furosemide equivalents)</td>
<td>122.6 (-79.3, 255)</td>
<td>832.8 (483.1, 1497.3)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Estimated peak dose diuretic efficiency (mL fluid output/40 mg furosemide equivalents)</td>
<td>56.4 (-34.6, 110.1)</td>
<td>382.8 (251.1, 638.8)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td><strong>In-hospital inotropes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Milrinone</td>
<td>19.5%</td>
<td>12.3%</td>
<td>0.014*</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>3.0%</td>
<td>0.2%</td>
<td>0.003*</td>
</tr>
<tr>
<td><strong>In-Hospital Maximum Change in Laboratory Parameters</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>eGFR (%)</td>
<td>19.1 ± 16.2</td>
<td>14.0 ± 13.7</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Worsening renal function</td>
<td>41.4%</td>
<td>31.1%</td>
<td>0.007*</td>
</tr>
<tr>
<td>Blood urea nitrogen (%)</td>
<td>-51.8 ± 57.6</td>
<td>-35.3 ± 45.1</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Bicarbonate (%)</td>
<td>-21.0 ± 17.7</td>
<td>-22.6 ± 46.4</td>
<td>0.606</td>
</tr>
<tr>
<td><strong>Admission to Discharge in Laboratory Parameters</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>eGFR (%)</td>
<td>-0.8 ± 29.1</td>
<td>-2.0 ± 24.2</td>
<td>0.560</td>
</tr>
<tr>
<td>Worsening renal function</td>
<td>20.9%</td>
<td>13.9%</td>
<td>0.019*</td>
</tr>
<tr>
<td>Blood urea nitrogen (%)</td>
<td>-30.3 ± 56.7</td>
<td>-18.6 ± 48.3</td>
<td>0.007*</td>
</tr>
<tr>
<td>Bicarbonate (%)</td>
<td>-10.5 ± 18.2</td>
<td>-13.8 ± 47.5</td>
<td>0.299</td>
</tr>
<tr>
<td>Sodium (%)</td>
<td>0.9 ± 5.6</td>
<td>0.8 ± 3.0</td>
<td>0.764</td>
</tr>
<tr>
<td><strong>Hospital Course</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length of stay (days)</td>
<td>7 (4, 11)</td>
<td>5 (4, 8)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td><strong>Discharge Physical Examination</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Condition</td>
<td>Group 1</td>
<td>Group 2</td>
<td>p Value</td>
</tr>
<tr>
<td>------------------------------------</td>
<td>---------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>Jugular venous distention (≥ 8 cm H2O)</td>
<td>19.8%</td>
<td>20.1%</td>
<td>0.942</td>
</tr>
<tr>
<td>Edema &gt; 1+</td>
<td>18.1%</td>
<td>15.1%</td>
<td>0.318</td>
</tr>
<tr>
<td>Hepatojugular reflux</td>
<td>3.8%</td>
<td>3.5%</td>
<td>0.898</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Univariate</th>
<th>Penn Cohort</th>
<th>Final model</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P Value</td>
<td>HR (95% CI)</td>
<td>P Value</td>
</tr>
<tr>
<td>Loop diuretic</td>
<td>1.6 (1.3-1.9)</td>
<td>&lt;0.001</td>
<td>1.2 (0.9-1.6)</td>
<td>0.132</td>
</tr>
<tr>
<td>Net fluid output</td>
<td>1.0 (0.8-1.2)</td>
<td>0.929</td>
<td>1.0 (0.7-1.2)</td>
<td>0.78</td>
</tr>
<tr>
<td>Diuretic efficiency</td>
<td>1.6 (1.3-2.0)</td>
<td>&lt;0.001</td>
<td>1.4 (1.0-1.8)</td>
<td>0.023</td>
</tr>
<tr>
<td>Age (years)</td>
<td>1.03 (1.02-1.04)</td>
<td>&lt;0.001</td>
<td>1.4 (1.2-1.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart rate (per 10 BPM)</td>
<td>0.90 (0.86-0.95)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure (per 10 mmHg)</td>
<td>0.90 (0.87-0.93)</td>
<td>&lt;0.001</td>
<td>0.92 (0.88-0.96)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Loop dose at baseline (per 100 mg)</td>
<td>1.1 (1.05-1.2)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum sodium (per 5 meq/l)</td>
<td>0.79 (0.71-0.88)</td>
<td>&lt;0.001</td>
<td>0.89 (0.79-1.0)</td>
<td>0.071</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>0.89 (0.85-0.94)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Log B-type natriuretic peptide (pg/ml)</td>
<td>1.8 (1.3-2.4)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>eGFR (per 10 ml/min/1.73m²)</td>
<td>0.89 (0.85-0.92)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood urea nitrogen (per 10 mg/dl)</td>
<td>1.2 (1.2-1.2)</td>
<td>&lt;0.001</td>
<td>1.1 (1.1-1.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Black race</td>
<td>0.79 (0.64-0.98)</td>
<td>0.034</td>
<td>1.3 (1.0-1.7)</td>
<td>0.043</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.2 (0.97-1.5)</td>
<td>0.093</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic etiology for HF</td>
<td>1.4 (1.1-1.8)</td>
<td>0.002</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline edema</td>
<td>1.4 (1.1-1.7)</td>
<td>0.004</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline digoxin use</td>
<td>1.4 (1.1-1.7)</td>
<td>0.008</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline thiazide diuretic use</td>
<td>1.5 (1.1-2.0)</td>
<td>0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Univariate</td>
<td>HR (95% CI)</td>
<td>P Value</td>
<td>Final model</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>----------------------------------------------</td>
<td>-------------</td>
<td>---------</td>
<td>---------------------------------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Loop diuretic</td>
<td>2.5 (1.5-3.9)</td>
<td>&lt;0.001</td>
<td>Loop diuretic</td>
<td>1.3 (0.7-2.4)</td>
</tr>
<tr>
<td>Net fluid output</td>
<td>1.0 (0.6-1.5)</td>
<td>0.86</td>
<td>Net fluid output</td>
<td>1.2 (0.7-2.1)</td>
</tr>
<tr>
<td>Diuretic efficiency</td>
<td>4.0 (2.3-6.8)</td>
<td>&lt;0.001</td>
<td>Diuretic efficiency</td>
<td>2.9 (1.5-5.4)</td>
</tr>
<tr>
<td>Age (per 10 years)</td>
<td>1.3 (1.1-1.5)</td>
<td>0.012</td>
<td>Age (per 10 years)</td>
<td>1.2 (0.94-1.5)</td>
</tr>
<tr>
<td>Systolic blood pressure (per 10 mmHg)</td>
<td>0.88 (0.76-1.0)</td>
<td>0.08</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loop dose at baseline (per 100 mg)</td>
<td>1.2 (1.1-1.3)</td>
<td>&lt;0.001</td>
<td>Loop dose at baseline (per 100 mg)</td>
<td>1.2 (1.0-1.3)</td>
</tr>
<tr>
<td>Serum sodium (per 5 meq/l)</td>
<td>0.67 (0.54-0.83)</td>
<td>&lt;0.001</td>
<td>Serum sodium (per 5 meq/l)</td>
<td>0.80 (0.62-1.00)</td>
</tr>
<tr>
<td>Hemoglobin (per 1 g/dl)</td>
<td>1.04 (1.00-1.08)</td>
<td>0.043</td>
<td>Hemoglobin (per 1 g/dl)</td>
<td>1.04 (1.00-1.07)</td>
</tr>
<tr>
<td>eGFR (per 10 ml/min/1.73m³)</td>
<td>0.79 (0.70-0.88)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood urea nitrogen (per 10 mg/dl)</td>
<td>1.3 (1.2-1.4)</td>
<td>&lt;0.001</td>
<td>Blood urea nitrogen (per 10 mg/dl)</td>
<td>1.2 (1.1-1.3)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.70 (0.44-1.1)</td>
<td>0.124</td>
<td>Hypertension</td>
<td>0.58 (0.34-0.98)</td>
</tr>
<tr>
<td>Ischemic etiology for HF</td>
<td>2.1 (1.3-3.4)</td>
<td>0.003</td>
<td>Ischemic etiology for HF</td>
<td>1.54 (0.86-2.7)</td>
</tr>
<tr>
<td>Baseline beta blocker</td>
<td>0.67 (0.42-1.0)</td>
<td>0.079</td>
<td>Baseline beta blocker</td>
<td>0.60 (0.36-0.99)</td>
</tr>
<tr>
<td>Baseline ACE or ARB</td>
<td>0.43 (0.24-0.78)</td>
<td>0.006</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline thiazide diuretic use</td>
<td>1.9 (1.1-3.3)</td>
<td>0.027</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline jugular venous distension</td>
<td>1.5 (0.9-2.4)</td>
<td>0.088</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline edema</td>
<td>1.9 (1.2-3.0)</td>
<td>0.006</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Supplementary Table 4: Association between diuretic efficiency and mortality in patients with and without preserved ejection fraction in the Penn cohort.

<table>
<thead>
<tr>
<th>Patients with:</th>
<th>HR (95% CI)</th>
<th>p Value</th>
<th>p interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ejection Fraction &lt;40%</td>
<td>1.8 (1.4-2.4)</td>
<td>&lt;0.001*</td>
<td></td>
</tr>
<tr>
<td>Ejection Fraction ≥40%</td>
<td>1.4 (1.0-2.0)</td>
<td>0.074</td>
<td>0.245</td>
</tr>
<tr>
<td>Ejection Fraction &lt;50%</td>
<td>1.8 (1.4-2.3)</td>
<td>&lt;0.001*</td>
<td></td>
</tr>
<tr>
<td>Ejection Fraction ≥50%</td>
<td>1.3 (0.9-2.1)</td>
<td>0.209</td>
<td>0.255</td>
</tr>
</tbody>
</table>

HR: Hazard ratio, CI: Confidence interval. Hazard ratios represent cumulative diuretic efficiencies below compared to above the median value.
Supplementary Figure 1: Consort diagram for the Penn Cohort

Admissions screened for eligibility
(1st CHF diagnosis admitted to a non-interventional medical service with an admission B-type natriuretic peptide level available)
N=2077

Eligible admissions
N=1319

Eligible admissions
N=1258

Eligible admissions
N=1207

Eligible admissions
N=1172

Eligible admissions
N=1091

Eligible admissions
N=826

Patients analyzed
N=657

LOS < 3 days, Excluded N=537
LOS > 14 days, Excluded N=221

Chronic hemodialysis
Excluded N=61

BNP < 100 pg/ml
Excluded N=51

Total loop dose unavailable
Excluded N=35

No IV loop administered
Excluded N=81

I/o missing
Excluded N=265

Repeat admission for a single patient
Excluded N=169
Supplementary Figure 2: Scatterplots of diuretic efficiency, loop diuretic dose, and net fluid output in the Penn (Panel A) and ESCAPE cohorts (Panel B)
Supplementary Figure 3: Scatterplots of loop diuretic dose and net fluid output in the Penn (Panel A) and ESCAPE cohorts (Panel B)
Supplementary Figure 4: Kaplan-Meier survival curves grouped by quartiles of diuretic efficiency in the Penn cohort (Panel A) and ESCAPE cohort (Panel B)