**Abstract**

No study has systematically evaluated the prevalence and dosages of diuretic use for patients after left ventricular assist device (LVAD) implantation. The primary objective was to characterize chronological change in prevalence and doses of loop diuretics after LVAD placement. The secondary objective was to identify correlates of actual doses of loop diuretics.

We retrospectively reviewed medical records of adult patients with LVAD implantation at the University of Kentucky. Prevalence of diuretic use and furosemide equivalent dose were assessed before LVAD implantation and at seven time points thereafter: 1 week, 1 month, 3 months, 6 months, 1 year, 18 months, and 2 years. Correlation analyses and linear mixed modeling were used to identify correlates of diuretic dose before and after LVAD implantation.

Eighty two consecutive eligible patients were reviewed. The prevalence of loop diuretic use was 95% at baseline but significantly lower than that at all subsequent time points (p < 0.048 for all). Nevertheless, more than half of patients on whom we had such follow-up data were on loop diuretics two years after LVAD implantation. Average furosemide equivalent dose was significantly lower at every time point after implantation compared to baseline (p < 0.006 for all). Blood urine nitrogen (BUN) was the most robust predictor of dose after LVAD implant.

The prevalence and average furosemide equivalent dose was significantly reduced after LVAD implantation, but the use of loop diuretic remained more than 50% for up to two years. Consistent association with BUN may indirectly indicate overuse of diuretics post LVAD implant.

**Introduction**

The 2013 International Society for Heart and Lung Transplantation Guidelines for mechanical circulatory support recommend loop diuretics such as furosemide, torsemide and bumetanide as reasonable agents for the management of fluid overload or right ventricular (RV) dysfunction in patients with left ventricular assist device (LVAD). [1] Ideally, most patients with LVAD should not need diuretics, because the heart failure is supposed to be corrected. Yet many patients with LVADs remain on regular loop diuretics.

Patients with LVAD may need diuretics mainly due to suboptimal hemodynamic compensation, right ventricular (RV) failure, or valvular heart disease. [2-4]Up to 38% of patients after LVAD implantation develop aortic insufficiency [5].Because of all these factors, chronic use of loop diuretics for patients after LVAD implantation is not uncommon. Yet, to our knowledge, no study to date has systematicallyevaluated the prevalence of loop diuretic use, their dosages, and correlates of dose for patients after LVAD implantation. Meanwhile, it is important to understand the patterns and determinants of diuretic use after implantation. Patients should be given the minimal necessary diuretic therapy in each clinic visit after implantation, because diuretic therapy has never shown mortality benefits in LVAD patients and overdiuresis could cause adverse effects such as acute kidney injury, metabolic alkalosis, electrolyte imbalances, and hypotension. [6,7]

The primary objective of the present study was to characterize the prevalence and chronological change in dose of loop diuretics after LVAD placement. The secondary objective was to identify correlates of actual loop diuretic dose in multiple follow-up visits.

**Methods**

**Study Design**

With approval from the University of Kentucky Institutional Review Board, we performed a retrospective chart review of patients > 18 years of age who received LVADs between January 2006 and September 2014. Patients were identified using the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS®)database. Patients who died before the initial discharge after LVAD implantation, and patients who had a right ventricle artificial device at any point after LVAD implantation, were excluded from our study. Data were collected from immediately prior to LVAD implantation and from seven time points thereafter: 1 week, 1 month, 3 months, 6 months, 1 year, 18 months, and 2 years. All loop diuretic doses were converted into furosemide equivalents based on oral equivalent dose conversion among bumetanide, torsemide, and furosemide (1:20:40) as per package inserts.

**Analyzing Changes in Prevalence of Diuretic Use**

We fit a generalized linear mixed model with diuretic use (yes or no) as the outcome and time as a categorical predictor. This allowed us to test via linear contrasts whether prevalence at any time point after LVAD implantation: (i) differed significantly from prevalence at the time point immediately preceding; and, (ii) differed significantly from prevalence at baseline. The multiple comparisons in (i) were Bonferroni-adjusted, as were the multiple comparisons in (ii). This data analysis was carried out in Version 9.3 of SAS (SAS Institute Inc., Cary NC), as were those described below except where otherwise noted. A p-value less than 0.05 defined statistical significance.

**Analyzing Changes in Furosemide Equivalent Dose**

Furosemide equivalent doses were summarized at each time point by median and interquartile range. To make comparisons across time points, we employed a square root transformation to reduce non-normality in the distribution of furosemide equivalent doses; we then fit a linear mixed model with square root transformed (SRT) furosemide equivalent dose as the outcome and time as a categorical predictor. This allowed via linear contrasts the same kind of testing as described in the last paragraph, except that mean level of furosemide equivalent dose (on the square root scale) was being compared across time points instead of prevalence.

**Analyzing Correlates of Furosemide Equivalent Dose at Baseline**

We calculated Spearman correlations between furosemide equivalent dose and 49 variables available at baseline.

**Analyzing Correlates of Furosemide Equivalent Dose after Implantation**

Variables significantly associated with furosemide equivalent (or furosemide) dose at baseline, with some exceptions due to hemodynamic alterations accompanying LVAD implantation, were assessed for their relationships with SRT furosemide equivalent dose at four time points after implantation (1 month, 3 months, 6 months, and 1 year). Several additional variables were also assessed, based on expert opinion of their possible importance; some of these had not been measured at baseline, like pump parameters. In total, 38 potential predictors were assessed, 18 from baseline and 20 which were contemporaneous (i.e., measured at one month, three months and so forth). Because we did not routinely perform right heart catheterization after the LVAD, hemodynamic parameters such as cardiac index were analyzed only at baseline. Also, because echocardiographic images after LVAD are not easy to obtain, there were many missing values on variables related to follow-up echoes. Right ventricular systolic function was estimated by two independent echo readers grading from 1 (normal) to 4 (severely impaired).

For each of the potential predictors, a linear mixed model was fit to assess the predictor’s relationship with SRT furosemide equivalent dose after implantation. Time was included as a categorical factor with which the predictor could interact; thus, a predictor might be significantly associated with furosemide equivalent dose at one time point but not another. Because data were missing on some variables even when follow-up did occur, we employed multiple imputation in conjunction with the linear mixed modeling; however, any post-LVAD observation in which the dose was missing was excluded. Results from the multiple imputations were combined into a final set of results using Excel 2013 (Microsoft Corporation, Redmond WA). This includes, for each predictor and each of the four time points, an estimate of how much the mean of SRT furosemide equivalent dose changes with a one-unit increase in the predictor, a 95% confidence interval for the same, and an accompanying p-value.

**Results**

**Acquisition and characteristics of cohort**

Eighty-seven patients were screened and 5 patients were excluded due to right heart mechanical support, yielding 82 patients. Patient characteristics before LVAD implantation are summarized in Table 1. Overall, the mean age was 52.8 (+ 12.7) years and 77% of patients were male. The median (range) of follow-up was 1.3 years (14 days to 5.5 years). Forty eight percent remained on LVAD during the follow-up, 23% was transplanted, 21% died and 7% was explanted. Sixty two percent had ischemic cardiomyopathy and 95 % were on loop diuretics at baseline. The only patients who did not require diuretics prior to LVAD were those in cardiogenic shock on vasopressors and short-term mechanical support. Numbers of patients with diuretic data at various time points following LVAD implantation are documented below Figure 1.

**Prevalence of Loop Diuretics at each follow-up**

The prevalence of loop diuretics significantly decreased already at 1 week follow-up, from 95% to 82% (p=0.048; Figure 1). This number dropped to 67% in 1 month, but 58% and 56% of patients were still on diuretics at 1 and 2 years, respectively. A significant decrease from baseline was maintained from 1 month through 2 year follow-up (p<0.010 versus baseline for each comparison). However, after the initial decline from 95% to 82%, the changes from one follow-up to the next did not achieve significance (p>0.20 for all such comparisons; Figure 1).

**Furosemide Equivalent Dose Chronological Change**

Furosemide equivalent median doses and interquartile ranges are summarized in Table 2. Of note, one patient did not have dosing information and 81 patients were used for the analysis. At baseline and 1 week, the median dose of loop diuretics in furosemide equivalents was 80 mg. The median decreased to 40 mg at 1, 3, and 6 months, and further declined to 20 mg/day at one year and thereafter. The decrease in average SRT furosemide equivalent dose (“SRT” hereafter suppressed) was significant at all time points versus baseline (p<0.006 for such comparisons) and from 1 week to 1 month (p=0.020).

**Correlates of Loop Diuretic Dose before LVAD Implantation**

Table 3 shows Spearman correlations of selected variables with furosemide equivalent dose at baseline. The predictor most strongly associated with furosemide equivalent dose among all variables at baseline was NT-proBNP with Spearman correlation of 0.633 (p=0.001). The predictor having the strongest negative association was cardiac index (CI), for which the Spearman correlation was -0.409 (p<0.001).

**Correlates of Loop Diuretic Dose after LVAD Implantation**

Table 4 shows associations of selected variables with furosemide equivalent dose at four time points after LVAD implantation. Results for other variables appear in the Supplemental Material. BUN was the most consistent predictor of dose after LVAD implantation, with a nearly significant positive relationship at 1 month, a significant positive association at 3 months and 6 months, and a non-significant but positive associations at 1 y ear among all variables examined. None of the LVAD parameters (speed, power, flow, pulsatility) were significantly associated with loop diuretic dose. Information about other data analyses undertaken during the development of this work is available upon request to the corresponding author.

**Discussion**

LVAD dramatically improves hemodynamics in advanced heart failure (HF), increasing left ventricular output.[8] Nevertheless, as many as 20-25% patients may have HF after LVAD, due to either RV failure or incomplete compensation of LV failure.[4,9-11] Persistent fluid retention in pulmonary or systemic circulation, or both, requires diuretics.

To our knowledge, this study is the first to demonstrate chronological change in loop diuretic prevalence and dose after LVAD implantation and to identify the correlates of diuretic dose after LVAD implantation. We found that diuretic use was very prevalent for up to two years after implantation. Before LVAD, 95% of patients were taking diuretics; this number dropped to 82% in 1 week and to 67% in 1 month. One and two years afterward, 58% and 56% of patients, respectively, were still on diuretics. Median furosemide equivalent dose decreased from 80 mg at baseline to 40 mg at 1 month. However, while some patients were on “as needed” diuretic doses, this was not consistently described in medical records and probably resulted in higher estimates of diuretic doses than those actually consumed.

It is plausibly conjectured that diuretic use could be largely eliminated or at least decreased in dose after LVAD implantation, because of LV unloading arising from cardiac output improvement and lower filling pressure.[8]One case series reported that about 20% of patients were taking diuretics after LVAD implantation but before transplant. [12] However, there is no prior study available investigating chronological change in prevalence of diuretic use and diuretic dose. Our cohort study showed that more than 50% of patients were taking loop diuretics as late as 2 years after LVAD implantation, which is considerably higher than the aforementioned 20% though much lower than the initial 95% in our study.

Not unexpectedly, many variables measured at baseline corresponded with furosemide equivalent at baseline. Among those significantly and positively associated with furosemide equivalent dose were measures of right ventricular dysfunction or congestion (right ventricular dysfunction; NT proBNP, and pulmonary artery systolic and diastolic pressures). Cardiac index was significantly and negatively associated with furosemide equivalent dose.

A significant positive association of visually estimated RV dysfunction at baseline with furosemide equivalent dose was not observed after LVAD. However, the right ventricle was often poorly visualized on post-LVAD echoes, and the estimates of RV function were less reliable than at baseline. Patients with the most severe RV failure, namely those requiring RV mechanical support, were excluded from our study as we did not want to mix the effects of LVAD and RVAD. Part of the reason why we did not see more consistent predictors of furosemide equivalent dose after LVAD implant may have been the lack of hemodynamic data – pulmonary arterial pressures and cardiac output – after the implant, as we do not routinely perform right heart catheterization after LVAD. Length of initial hospitalization was significantly associated with furosemide equivalent dose at both 1 month and 3 months post-implantation. Because prolonged hospitalization may relate to complications of LVAD implantation such as RV failure, one can speculate that complications may have been a potential reason for some patients’ high diuretic doses at follow-up.

Persistent association of BUN with the dose of loop diuretics post-LVAD may indicate overdiuresis, when doses are not adjusted frequently or aggressively enough. Because we found few associations of congestion parameters with diuretic doses after LVAD, more attention needs to be given to the dose of the diuretics in each clinic visit after LVAD implant, including in relation to pump parameters.

**Limitations of the Present Research**

This study was retrospective. Thus, when not already documented, physicians’ reasons for loop diuretic prescription – and whether patients were taking diuretics on a regular schedule or as needed – could not readily be retrieved. Another limitation is that far less than 50% of the original cohort of 82 patients was retained through 2 year follow-up. Moreover, patients retained through 2 year follow-up may not necessarily have been representative of the original cohort; although there were no significant differences in average furosemide equivalent or furosemide dose at baseline, when comparing the 16 persons with diuretic use information at 2 years to the 66 persons without, persons with 2 year follow-up data had considerably less variability in furosemide equivalent and furosemide dose at baseline.

Some correlates of dose may have been unrecognized for one of three reasons: (1) they were not incorporated into the medical records; (2) they were not established as significant predictors of baseline dose and were accordingly excluded from subsequent analyses; or, (3) their effects were not strong enough to be perceived with our effective sample sizes and numbers of missing values which were imputed. Further evaluation with a larger sample size and multi-center study, and with strong retention throughout follow-up, may confirm the external validity of some of our findings.

**Conclusions**

The results from this cohort study of LVAD patients indicated that, although significantly decreased from baseline, the use of loop diuretics remained high for up to two years after implantation, with more than half of patients on whom we had such follow-up data taking them at two years. The mean furosemide equivalent dose at all times after LVAD was significantly lower than at baseline. BUN was the most robust predictor of dose after LVAD implantation, with a nearly significant positive relationship at 1 month, a significant positive association at 3 months and 6 months, and a non-significant but positive association at 1 year. However there was no consistent determinant identified otherwise. Nonetheless, our findings may reflect an inconsistent effort to assess patients for ongoing need of diuretics; if that is the case, then more careful serial assessment of diuretic dose is needed, with the possibility of dose adjustment at each clinic visit after LVAD.

**References**

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**Figure Legends**

**Figure 1 Chronological Changes in Prevalence of Loop Diuretic Use and Furosemide Equivalent Dose**

All loop diuretic doses were converted into furosemide doses based on equivalent dose conversion among bumetanide, torsemide and furosemide (1:20:40). The graph displays the median dose at each time point. Effective sample sizes at each time point were: 82, 82, 55, 70, 64, 45, 28, and 16 for the assessment of prevalence; 81, 80, 54, 63, 62, 44, 28, and 14 for the assessment of furosemide equivalent dose; and 61, 73, 43, 52, 49, 34, 23, and 10 for the assessment of furosemide dose.

(\*) Prevalence of loop diuretic use is significantly different versus before LVAD. (#) Average (square root transformed) furosemide equivalent dose is significantly lower versus before LVAD; note that this can (and did) occur without a change in median. Assertions of statistical significance reflect Bonferroni adjustments for multiple comparisons.

Abbreviation: LVAD=Left Ventricular Assist Device