Article Appraisal

Article: Time to Furosemide treatment and mortality in patients hospitalized with acute heart failure.

(Matsue et al, J or American college of cardiology, June 2017)

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Background and Study Objective(s):

Acute heart failure is a life-threatening disease that requires rapid diagnosis and treatment. Current Canadian Cardiovascular Society Guidelines recommend diagnosis of acute heart failure in the ED within 2 hours. Previous studies based on retrospective data have hinted at an association between early treatment and reduced mortality. This study set out to prospectively evaluate the association between time to first IV Furosemide (Lasix) dose and all cause in-hospital mortality in acute heart failure presenting to the emergency department.

Study Design:

Japanese-based prospective cohort study of 1291 consecutive patients presenting to 20 participating emergency departments with acute heart failure based on Framingham diagnostic criteria. The study compared those who received their first dose of IV Furosemide within the 60 minutes of arrival to the ED to those who received IV Furosemide between 60 minutes and 24 hours. The primary endpoint was all cause in-hospital mortality. Patients were also followed for 30 days allowing for the additional measurement of 30-day-mortality.

To analyse their results, they first compared characteristics of each group for statistically significant differences, then ran univariable and multivariable logistic regression analyses were performed to evaluate the association between early treatment and in-hospital prognosis. Generalised estimating equation models were used to account for intra institutional correlations. Propensity score matching was performed to control for confounding inter-group differences. They then attempted to graph the relationship between time to Furosemide and all cause mortality with linear regression models combined with restricted cubic spline regression was used to accommodate a nonlinear association between the two variables.

Results:

Of 1291 patients who met inclusion criteria and were treated with IV Furosemide within 24 hours of arrival at the emergency department in acute heart failure, 37.3% were treated within 60 minutes, 62.7% were treated at more than 60 minutes. Patients arriving by ambulance, females, and those demonstrating more significant symptoms of congestion were more likely to receive early treatment. Patients with a previous history of CHF already on loop diuretics/aldosterone blockers were more likely to receive delayed treatment. In hospital all-cause mortality was significantly lower in the early treatment group than in the late treatment group (2.3% vs 6%, p=0.002). Multivariate analysis showed similarly statistically significant results (OR 0.39, 95% CI 0.20 - 0.76, P=0.006). No statistically significant difference in 30 day all-cause-mortality was demonstrated. Finally, the authors also found that the association between door-to-Furosemide time and in-hospital mortality was not linear. Mortality rapidly increased with longer door-to-Furosemide times until approximately the 100 minutes after presentation and then levelled off after this time point.

Validity of Results:

The study effectively accounted for potential confounding variables with multivariate regression analysis, had objective outcomes in terms of mortality, and appropriately confirmed their findings with a propensity score. However, the results may not be clinically valid because: 1) additional heart failure treatment options (such as positive pressure ventilation, etc.) were not measured, so drawing the correlation between Furosemide only and mortality does not capture the scope of therapy, 2) all cause in-hospital mortality was not necessarily related to heart failure and there was no data describing the circumstances of death for each of the patients who died. Without this data we found it hard to correlate their deaths to the heart failure they were admitted with, and subsequently the timing of the Furosemide dose they were given. The study also does not adequately account for the fact that patients with more comorbidities, like chronic kidney disease, frailty and obesity are often harder to diagnose with heart failure, and consequently take longer to initiate therapy for their heart failure. These same comorbidities also increase their chance of all cause mortality while in hospital. Finally, the attempt to graph the time-to-Furosemide vs mortality curve was well intended and statistically well executed, but required complex logarithmic multi-spline linear regression analyses to create a best fit curve of a relationship that is conceptually tenuous to begin with.

Generalizability of Results:

Although the study was well executed and the statistical analysis appropriate for their intentions, the study design did not adequately capture the complexity of acute heart failure diagnosis and management in the emergency department. As such, the results are not generalizable to all patients and situations.

The Bottom Line:

A good reminder that early treatment is likely beneficial in acute heart failure presenting to the emergency department, but the study is hardly robust enough to start institutionalizing time-to-Furosemide targets.