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EDITORIAL COMMENT

Door-to-Furosemide Therapy in the ED

New Quality Metric or Just a Piece of the Puzzle?*

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"Defer no time, delays have dangerous ends…"
—Henry VI, Part 1, Act 3 (1)

Following definitive data demonstrating importance of rapid reperfusion for improved survival in patients with acute ST-segment elevation myocardial infarction (STEMI), the concept of door-to-balloon time is now a well-accepted quality metric in acute cardiovascular care, and helps stimulate optimal delivery of definitive treatment. It is thus tempting to extend this framework to other cardiovascular emergencies, including the problem of acute heart failure (HF). Patients with acute HF have mortality rates comparable to (and often higher) than those with STEMI, and delays in its treatment are similarly linked to worse outcomes in acute HF. However, although it seems evident that earlier and more direct therapy for acute HF might improve outcomes, prospective data to support this assertion are lacking.

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In this issue of the *Journal*, Matsue et al. (2) attempt to address whether more rapid care of acute HF, as represented by earlier use of intravenous loop diuretics, is associated with better outcomes. In a prospective registry analysis of 1,291 patients presenting with acute HF enrolled in 20 Japanese centers, the investigators studied time to first intravenous diuretic dose relative to in-hospital and 30 day mortality. Among these study participants, approximately one-half had prior HF and the majority had a left ventricular ejection fraction <50%. Study participants were treated via standard of care by managing physicians. In those treated with intravenous loop diuretic, there was a non-normal distribution of door-to-furosemide (D2F) time—the median time to intravenous diuretic was 90 min; however, some patients were not treated for up to 48 h. The investigators then divided the subjects into early (<60 min) and later D2F times; using these categories, 481 patients (37.3%) were classified into the early treatment group and 810 (62.7%) were classified into the nonearly treatment group. Not surprisingly, those patients in the early treatment group were more likely to present with more obvious HF and with more acute symptoms of decompensation. Independent predictors of shorter D2F included arrival by ambulance, more prominent congestion, and higher heart rate. Intriguingly, more patients in the prolonged D2F group had a prior history of HF, more used furosemide prior to presentation, and both groups had similar and substantially elevated concentrations of B-type natriuretic peptide (BNP). So, despite the fact those in the longer D2F group had several well-established predictors of acute HF diagnosis, their treatment was delayed.

In a series of adjusted analyses, the authors examined rates of mortality in those with faster versus longer D2F across quartiles of the Get With the Guidelines risk score; in doing so, those patients treated with intravenous loop diuretic in <1 h had significantly lower mortality across all risk strata. The

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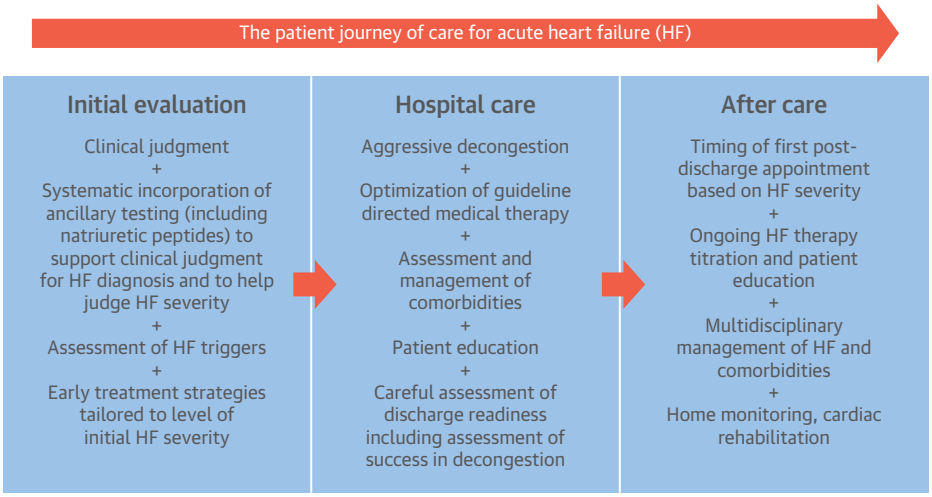
FIGURE 1 **Clinical Care for Acute HF Management**



Optimal care of the patient with acute heart failure requires a multidisciplinary approach with numerous, occasionally complex, steps.
HF = heart failure.

probability of death seemed to peak at a D2F of 100 min or so, after which it fell only to again rise later on. In adjusted models, faster D2F time was predictive of in-hospital survival whether in models adjusted for the Get With the Guidelines risk score (odds ratio: 0.39; 95% confidence interval: 0.20 to 0.76; $p = 0.006$) or in propensity matching (odds ratio: 0.41; 95% confidence interval: 0.18 to 0.89; $p = 0.03$).

The authors are to be congratulated in providing prospective data on an important issue in acute cardiovascular care. Given recent neutral results for emerging therapies in acute HF (3), clinicians are left with use of intravenous loop diuretics as the primary mode of therapy for acute HF patients; in this there are strikingly few data available regarding optimal application of these widely used drugs. Data from prior trials of high versus low dose furosemide in acute HF suggest more aggressive decongestion may be more beneficial (4,5), however these current data suggest that not only more aggressive but also more rapid decongestion therapy may also improve outcomes.

But do we really believe earlier D2F itself leads to reduced mortality, analogous to rapid reperfusion therapy in STEMI?

It is conceivable more rapid reduction in congestion through earlier loop diuresis might help to limit ongoing myocardial and end-organ injury present in those with acute HF and thereby improve outcomes. To support this argument the authors cite data from the RELAX-AHF (Relaxin in Acute Heart Failure) trial of intravenous serelaxin; this analysis showed more substantial improvement in symptoms of congestion along with an improved profile of biomarkers of congestion, cardiac injury, and end-organ damage were associated with better mortality at 6 months (6). However, the authors also point out that early application of ularitide, another intravenous vasodilator, rapidly improved congestion in acute HF, and yet was ineffective at reducing mortality in the TRUE-AHF (Trial of Ularitide's Efficacy and Safety in patients with Acute Heart Failure) trial (3). It is quite certain limiting consequences of congestion (e.g., cardiac and end-organ injury) is a good thing, though results from TRUE-AHF trial as well as recent neutral data from the larger RELAX-AHF-2 study (7) make it harder to argue directly favorable effect of shorter D2F on this basis.

A more likely explanation for the difference in mortality between those with short D2F versus longer D2F in the study by Matsue et al. (2) would be the reason for shorter versus longer D2F: delay in D2F might reflect greater diagnostic or therapeutic uncertainty in patients with longer treatment times. Prior data have unequivocally shown diagnostic ambivalence in acute HF is associated with both delays in loop diuretic use and increase in mortality; diagnostic indecision in patients with acute HF has also been associated with longer hospital lengths of stay and less focused management (8). Additionally, the clinical profile of patients treated earlier—arriving by ambulance, with greater evident congestion,

higher blood pressure, higher heart rate, and shorter duration of symptoms—is consistent with a phenotype of acutely hypertensive HF with pulmonary edema, a presentation that is more obvious and known to be more treatment responsive and also have a more favorable prognosis.

Will D2F become the next quality measure in modern HF care? Though one could understand enthusiasm to do so, it is worthwhile to consider the significant differences in pathophysiology and clinical care between STEMI and acute HF. STEMI generally presents with a sudden onset of signs and symptoms that are tied to a specific underlying pathophysiology (coronary thrombosis). Specific treatments targeting that pathophysiology (e.g., thrombolysis and primary percutaneous coronary intervention) have been shown to improve survival. On the other hand, acute HF patients often present with gradual onset of symptoms (often in a nonspecific fashion) and with a multiplicity of pathophysiologic contributors to the clinical picture. Additionally in contrast to STEMI, no pathophysiological targeted therapies have been successfully developed for the acute HF, and its primary therapy (intravenous diuretics) has not been subject to placebo-controlled trials or shown to improve mortality. Although optimal management of acute HF may begin with the faster prescription of intravenous furosemide, diagnostic and therapeutic follow-up in acute HF is far more complex, and gaps in HF care following admission and initial therapy may be associated with major risk regardless of whether the first dose of furosemide was delivered rapidly.

The failure of more novel therapies for acute HF requires us to make better use of what we already have: optimizing tools for early and accurate diagnosis (e.g., appropriate use of natriuretic peptide testing) linked with early and optimal administration of decongestive therapy and identification of gaps in care (including identifying reversible factors and optimizing GDMT [guideline directed medical therapy]) is crucial for optimal outcomes. Knowing when a patient is ready for discharge and developing individualized approaches to aftercare for each patient are similarly critical. A systemic approach (**Figure 1**) would allow for a more comprehensive assembly of the puzzle that is the optimal management of acute HF. In sum, although it is probably important to rapidly introduce effective decongestion therapy—as "delays have dangerous ends"—optimal acute HF care remains a far more complicated process.

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