The time-to-treatment concept in acute heart failure: Lessons and implications from REALITY-AHF

Nobuyuki Kagiyama[1,2], *Yuya Matsue*[3,4]

[1]Division of Cardiology, Washington University in St. Louis; St. Louis-MO-*USA*
[2]Department of Cardiology, The Sakakaibara Heart Institute of Okayama; Okayama-*Japan*
[3]Department of Cardiovascular Medicine, Juntendo University School of Medicine; Tokyo-*Japan*
[4]Cardiovascular Respiratory Sleep Medicine, Juntendo University Graduate School of Medicine; Tokyo-*Japan*

Abstract

Acute heart failure (AHF) is a clinical syndrome with devastating prognosis. Despite considerable improvements in the treatment of chronic heart failure, most trials of new drugs for AHF, such as vasodilators, inotropes, and diuretics, have failed to show a prognostic benefit. Therefore, pharmacological treatment of AHF has changed very little, and loop diuretics have remained a cornerstone drug for decades. One of the emerging factors possibly playing an important role in AHF management is the time course of treatment. Several recent retrospective studies have highlighted the importance of early treatment in AHF; however, at the time, support from a prospective study with an adequate number of enrolled patients was lacking. The Registry Focused on Very Early Presentation and Treatment in Emergency Department of Acute Heart Failure (REALITY-AHF) was the first prospective study to specifically focus on the time course of treatment in the very acute phase and its prognostic implication in patients with AHF. Data from the REALITY-AHF revealed that early treatment with intravenous furosemide is significantly associated with lower in-hospital mortality. Although pathophysiological background of this association remains to be investigated, the time course of treatment may be a critical component of AHF treatment, and it will be important to take this factor into account in future clinical studies on AHF. *(Anatol J Cardiol 2018; 20: 125-9)*

Keywords: acute heart failure, prognosis, diuretics, congestion

Introduction

Acute heart failure (AHF) is a life-threatening disease and is a major worldwide public health problem. Annual hospitalization because of AHF is >1 million per year in both the United States and Europe (1). Hospitalization because of AHF signifies a shift into the heart failure trajectory, with a readmission rate of approximately 30% within 30 days after discharge and a 1-year mortality rate of approximately 30% (1, 2). Despite dramatic improvements in the treatment of chronic heart failure over the past decades, most clinical trials regarding the prognostic impact of treatment for AHF has showed neutral results, and the treatment strategy for AHF has not significantly changed. Main pharmacological therapies, such as diuretics and vasodilators as per clinical judgment, remain unchanged from the 1970s (3). In the latest guidelines, diuretics are still the only drug with a class I recommendation for AHF, and "immediate" administration of diuretics is recommended as long as the patient shows congestive symptoms (2, 3). However, there is a paucity of evidence supporting the association between the expeditiousness of treatment and AHF outcomes. In this context, the Registry Focused on Very Early Presentation and Treatment in Emergency Department of Acute Heart Failure (REALITY-AHF), a prospective multicenter registry focusing on the treatment of AHF in the emergency department, was conducted, with the time to the first administration of intravenous diuretics and its short-term prognostic impact as variables of interest (4). In the present review, we further focus on the background necessitating the development of the REALITY-AHF and its implications on future studies and clinical practice.

Time-to-treatment in acute heart failure

As mentioned above, although many clinical trials have investigated the efficacy of novel pharmacological treatments for AHF, most failed to show a prognostic benefit (5, 6). There have been

Address for correspondence: Yuya Matsue, MD, Department of Cardiovascular Medicine, Juntendo University School of Medicine; Cardiovascular Respiratory Sleep Medicine, Juntendo University Graduate School of Medicine, 2-1-1 Hongo, Bunkyo-ku, Tokyo 113-8421-*Japan*
E-mail: yuya8950@gmail.com
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Table 1. Studies focusing on the time-to-treatment in patients with acute heart failure

Author	Year	PubMed ID	Design	Dataset	Patient number	Comparison	Main findings	Reference
Peacock et al.	2007	16741357	Retrospective cohort	ADHERE	4.300 out of 105.388	Patients with nesiritide administration initiated in ED (ED group median 2.8 h) vs. those with nesiritide administration initiated after admission (non-ED group: median 15.5 h)	ED group had higher baseline BP and lower prevalence of baseline renal dysfunction. ED group had a shorter hospital length of stay (5.4 vs. 6.9 days, $P<0.001$) and were more likely to be discharged home (OR 1.154, 95% CI 1.005–1.325).	(13)
Peacock et al.	2009	19925503	Retrospective cohort	ADHERE	35.700 out of 163.457	Patients with early (≤6 h) vasoactive drug (nesiritide, nitroglycerin, nitroprusside, dobutamine, dopamine, or milrinone) administration vs. those with late (6–48 h) administration	In-hospital mortality was significantly lower in the early group (OR 0.87, 95% CI 0.79–0.96) and adjusted odds of mortality increased by 6.8% (95% CI 4.2–9.6%) for every 6 h.	(12)
Wong et al.	2013	23895819	Retrospective cohort	ADHERE-EM	6.971 out of 17.614	The association between the time to first IV HF therapy (loop diuretics, dobutamine, dopamine, milrinone, nesiritide, nitroglycerin, or nitroprusside) and prognosis was analyzed	The median time to first IV HF therapy was 2.3 (IQR 1.1-4.4) h. Time-to-treatment was associated with an increased risk of in-hospital mortality (OR 1.01, 95% CI 1.00-1.02 per h) and a longer length of stay (1.4 h per h).	(21)
Maisel et al.	2008	18687247	Retrospective cohort	ADHERE	58.465 out of 187.575	Time to IV diuretics and time to measure BNP were studied. Their association with in-hospital mortality was also analyzed	In ED setting, delayed measurement of BNP levels and a delay in treatment for AHF were strongly associated. These delays were associated with modestly increased in-hospital mortality (OR 1.021 95% CI 1.010-1.033 per 4 h).	(14)

several explanations for these failures in the development of new drugs capable of improving prognosis in AHF. These include patient heterogeneity, numerous background therapies, sub-optimal matching of drugs, and importantly, timing and duration of interventions. One of the emerging factors that possibly plays an important role in AHF management is the time course of treat-

Table 1. Cont.

Author	Year	PubMed ID	Design	Dataset	Patient number	Comparison	Main findings	Reference
Matsue et al.	2017	28641794	Prospective cohort	REALITY-AHF	1.291 out of 1.682	Patients with early (≤1 h) furosemide administration vs. those with non-early (>1 h) administration.	Patients with early administration had higher BP and more signs of congestion. In-hospital mortality was significantly lower in the early group (2.3% vs. 6.0%, *P*=0.002) vs. the non-early group. Earlier treatment was significantly associated with lower in-hospital mortality (OR 0.39, 84% CI 0.20-0.76).	(4)

BNP - brain natriuretic peptide; BP - blood pressure; CI - confidence interval; ED - emergency department; HF - heart failure; IV - intravenous; OR - odds ratio; IQR - interquartile range

ment (7). It is well-known that even standard treatment improves dyspnea and other symptoms in majority patients with AHF. In the Ularitide Global Evaluation in Acute Decompensated Heart Failure (URGENT) dyspnea study, 77% patients experienced symptom improvement within 6 h of starting standard treatment (8). However, the median time to enrollment in the above-mentioned clinical trials was approximately 15 h from admission (7). Even the TRUE-AHF study, which restricted the enrollment of patients to within 12 h of their initial clinical evaluation (9), showed a time to randomization of 6.1 h (10). It seems quite probable that changes in dyspnea would greatly depend on how early dyspnea was evaluated in the AHF course. For example, given two patients, with baseline dyspnea symptoms evaluated just after emergency department (ED) arrival in one patient and 6 h after ED arrival in the other patient, the latter patient would be expected to be less symptomatic as it is not likely that a symptomatic patient can be in ED for 6 h without receiving any treatment. This difference in "baseline symptoms" could subsequently lead to a difference in the apparent efficacy of a dyspnea intervention given that severe symptoms continuing despite a 6-h treatment is, in a sense, likely to be more refractory than a similar degree of symptoms evaluated just after ED arrival. In other words, patient characteristics are very different between patients who have severe dyspnea just after ED arrival and those who still have severe symptoms at 6 h after ED arrival.

Loop diuretics remain a cornerstone treatment for AHF. However, despite the long history of the drug as a first-line treatment choice in AHF, there are strikingly few data regarding optimization of the use of loop diuretics in patients with AHF, and many questions remain unanswered (11). As yet, the impact of the timing of administration has not been adequately investigated. Several retrospective observational studies recently suggested that early initiation of treatment is associated with a better outcome (Table 1). Using ADHERE registry data, Peacock et al. (12) showed that early initiation of vasoactive drugs was associated with less in-hospital mortality [odds ratio (OR) 0.87 per every 6 h; 95% confidence interval (CI) 0.79-0.96]. Another analysis of ADHERE registry data demonstrated that the initiation of nesiritide in ED was associated with a shorter hospital stay (5.4 vs. 6.9 days, p<0.001) and a reduced likelihood of transfer to the intensive care unit (OR 0.301, 95% CI 0.206–0.440) (13). Using ADHERE registry data, Maisel et al. (14) analyzed the time to intravenous diuretics and found that it was strongly associated with the time to measure B-type natriuretic peptide and significantly associated with in-hospital mortality (OR 1.021 per 4 h, 95% CI 1.010–1.033). Based on these retrospective data and expert opinions, recent HF guidelines recommend immediate management, with pharmacological and non-pharmacological treatment initiated in parallel during the diagnostic workup (2, 3). However, all of these studies were retrospective, post-hoc sub-analyses of datasets acquired with various objectives. There have been no prospective data supporting this recommendation.

REALITY-AHF

To clarify the hypothesis that the time to diuretics is associated with in-hospital mortality in patients with AHF, we conducted REALITY-AHF, a prospective multicenter registry involving 20 hospitals in Japan focused on the treatment of AHF in the very acute phase (4). Consecutive patients with AHF, who were admitted to the participating hospitals via ED, were enrolled in the REALITY-AHF. To investigate the time course of treatment in the very acute phase, vital signs were recorded at the time of ED arrival and at

90 min, 6 h, 24 h, and 48 h after ED arrival. Treatment timings and, specifically, the time from ED arrival to the first administration of intravenous furosemide (door-to-furosemide time; D2F time) were also recorded.

From August 2014 to December 2015, 1,682 patients were enrolled in the registry; among these, 1,291 patients received intravenous furosemide within 24 h from admission and were included in the analysis. The median D2F time was 90 min, and 481 (37.3%) patients received intravenous furosemide within 60 min from admission (early treatment group). Patients in the early treatment group were more likely to present with more obvious HF than those in the non-early treatment group, namely, patients in the early treatment group were more likely to arrive by ambulance, had higher blood pressure and heart rate, had a higher prevalence of New York Heart Association functional class III/IV, and had a higher incidence of physical findings of congestion. In-hospital mortality was significantly lower in the early treatment group than in the non-early treatment group (2.3% vs. 6.0%, p=0.002); this association was maintained after adjustment for potential confounders. Of note, a restricted cubic spline model using D2F time as a continuous variable showed that the predicted in-hospital mortality steeply increased in the first 100 min of the D2F time, leveling off afterwards.

Clinical implications of the REALITY-AHF results and future directions

Using REALITY-AHF data, we showed that the time-to-treatment in the very acute phase of AHF was associated with in-hospital mortality in a prospective manner. This was the first prospective study focusing on the time-to-treatment, and results support a concept of "the earlier, the better" for treating patients with AHF. Our non-linear regression analysis showed that the first 100 min (approximately) might be important in terms of improving outcomes in patients with AHF.

A concept of door-to-balloon time in ST-segment elevation myocardial infarction (STEMI) is widely accepted. In STEMI, a decrease in the coronary flow causes ongoing myocardial ischemia; rapid reperfusion can retrieve the myocardium at risk (15). Results of the REALITY-AHF study suggest that a similar phenomenon exists in AHF. In some patients with AHF, serum troponin and lactate levels are elevated, which is associated with a worse prognosis (16, 17), suggesting that AHF causes myocardial and end-organ damage. An immediate improvement in hemodynamics and relief from ischemia might mitigate further organ damage and subsequently improve outcomes. This hypothesis is supported by previous data from Pre-RELAX-AHF and RELAX-AHF, which showed that treatment with serelaxin significantly attenuated the increase in troponin, creatinine, and hepatic biomarker levels within 2 days and decreased mortality (18, 19). However, the pathophysiological mechanism underlying the association between early treatment and better outcomes remains unclear and must be evaluated in future studies.

In-hospital mortality was linearly elevated with increased D2F time during the first 100 min, but then leveled off. This finding may partially explain the reasons why previous clinical trials of AHF failed. Although most of the drugs tested in the trials were designed to improve hemodynamics of patients with AHF, median times to randomization and initiation of drug administration were after 100 min (6 h at the earliest; by this time, majority patients experienced symptom improvement). These results suggest that there is a right time to prescribe drugs to change the clinical course, which, in most cases, is probably <6 h. In future studies testing clinical and prognostic implications of a course of treatment for AHF, the time course of treatment will be one of the most important factors that need to be considered.

At the same time, results of the REALITY-AHF study should be cautiously interpreted as some potential biases remain, such as a more robust and early confidence in diagnosis in the early treatment group and institutional differences in the quality of care. Diagnostic and therapeutic uncertainty in AHF is associated with less-focused management, resulting in a higher risk of mortality and morbidity (20). Thus, it is possible that difference in diagnostic and therapeutic certainty between early and non-early treatment groups leads to the difference in in-hospital mortality. Unfortunately, as we did not collect data on the time to diagnosis and time to make a therapeutic decision, it is impossible to analyze the interaction between benefit of early treatment and time to diagnosis. Regarding institutional differences in the quality of care, ED and hospital medical systems are potentially different among institutions. It is possible that the D2F time was a proxy of the quality of care, resulting in the apparent association with in-hospital mortality. Although we used generalized estimating equation models to account for the cluster effect of institutional differences and found no significant change in the conclusion, there is a possibility that such institutional differences in the quality of care had an influence on the outcome. However, a randomized control trial in this setting is virtually impossible, and we believe that the design of the REALITY-AHF study was one of the best compromises.

It should be noted that the REALITY-AHF study results are only hypothesis-generating and are not sufficient for urging clinicians to dramatically change their practice. However, the study results reinforce the importance of considering the time-to-treatment concept in patients with AHF, not only from a clinical perspective but also from a scientific perspective. Further studies are warranted to re-confirm and elucidate the mechanistic background of this concept in patients with AHF.

Conclusion

As most of the clinical trials testing prognostic beneficial effects of newly developed AHF drugs have failed, pharmacological treatment of AHF has not changed for decades. The REALITY-AHF study demonstrated an association between the time to furosemide administration and in-hospital mortality in patients

with AHF, with important clinical and scientific implications for the field. The time course of treatment is probably a critical component in AHF treatment and will be increasingly recognized as an important factor to be considered in future studies on AHF. However, elucidation of the pathophysiological background and replication of these findings are needed.

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