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EDITORIAL COMMENT

# "Time Is Muscle" in Acute Heart Failure

## Critical Concept or Fake News?*

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Rapid diagnosis and treatment for certain disease states is crucial for improved outcome. The best example of this concept is in the care of ST segment elevation acute myocardial infarction (AMI), where time to treatment is not only linked to better outcomes, but it has also become a central tenet in the care of affected patients (1). Rapid restoration of myocardial perfusion is now a pivotal part of care pathways and quality metrics for AMI care. The extent to which this concept might be extended to the care of other acute cardiovascular diseases has been a topic of active interest and has been explored in stroke, critical limb ischemia, and acute heart failure. In this context, one must ask if it is rational to extend the AMI experience to other disease states. After all, overly hasty decision making might amplify diagnostic and therapeutic mistakes in these high-risk disease states. It is useful to step back from the specifics of individual disease states and ask: what are the required preconditions for time to treatment to be an important determinant of treatment success?

First, a given disease state must have reasonably homogeneous and well-understood pathophysiology, with common treatment targets across the majority of patients presenting with this condition; if heterogeneity exists, noninvasive measures must be able to reliably determine what subgroup is likely to benefit, analogous to ST-segment elevation on electrocardiogram. Second, the unifying pathophysiology must be sufficiently understood so that specific treatments can be developed targeting that process. Third, there must be a window of opportunity whereby timely intervention interrupts or reverses ongoing tissue injury or damage before such damage becomes irreversible. It is readily apparent that AMI meets all these criteria. What about acute heart failure?

Initially, it must be acknowledged that "acute" heart failure is often really "subacute" in that many patients (most typically with chronic signs and symptoms of heart failure) develop acceleration of those signs and symptoms over days to weeks, rather than acutely. Although more genuinely "acute" presentations of heart failure do occur, they are relatively less frequent, and, more commonly, hospitalization is driven by either progression of symptoms that become intolerable to the patient or the need to access the hospital for therapies (such intravenous loop diuretics) cannot be readily provided in the outpatient setting. Second, the underlying pathophysiology of heart failure decompensation is neither homogeneous nor well understood. Indeed, much of the discussion of this topic specifically points out that decompensation is a heterogeneous and incompletely understood process driven to various degrees by myriad underlying pathobiologic mechanisms that differ widely between patients. Finally, there has been substantial interest in the "organ injury hypothesis," which suggests that decompensation is associated with injury to multiple organs (e.g., heart, kidney, liver) and that effective intervention to mitigate or reverse this injury is more likely efficacious in improving outcomes if given as early as possible. Although intellectually attractive, recent large clinical trials focused on this concept have ultimately not been successful (2,3).

We recently discussed results of an analysis focused on time to treatment in acute heart failure (4). Among 1,291 patients enrolled in the REALITY-AHF (Registry Focused on Very Early Presentation

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and Treatment in Emergency Department of Acute Heart Failure) study, the investigators reported early administration of diuretic (<60 min) was associated with better outcome compared with later administration (5). This leads to the compelling concept of shorter "door to diuretic" (D2D) not only as imperative for superior outcome, but also that this metric might be tracked as is "door to balloon" time is for AMI care. We cautioned that the findings from REALITY-AHF might be more complicated than simply suggesting that earlier diuretic treatment reduced mortality, however. Earlier diuretic administration in the nonrandomized REALITY-AHF experience might have been reflective of more secure heart failure diagnosis and delivered in the context of comprehensive heart failure care.

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In scientific publishing, it is unusual to be able to rapidly reassess interesting hypotheses in separate patient populations; however, in this issue of *JACC: Heart Failure*, Park et al. (6) present data on the relationship between D2D and clinical outcomes in patients presenting to the hospital with acute heart failure and enrolled in the KorAHF (Registry [Prospective Cohort] for Heart Failure in Korea) registry. Their key findings are that, in an analysis of 2,761 patients presenting with AHF, patients with early diuretic treatment (defined as D2D time ≤60 min [24% of the study population]) had both similar baseline characteristics and similar in-hospital and post-discharge outcomes as those treated later (D2D >60 min). These results were not substantively changed by risk adjustment (using the Get With the Guidelines Risk Score) or propensity matching to control for unmeasured confounders.

The authors are to be congratulated on an important contribution to the evolving literature on acuity of diagnosis and treatment in AHF. Notable strengths of the current analysis include using a relatively large prospective multicenter registry with standardized long-term follow-up (≥3 years) for clinical outcomes. The investigators have carefully adjusted for both risk profile and have used propensity adjustment to attempt to control for other likely confounders; however, as with every dataset, these data have some important limitations. These include data collection from a single country only, which is a potentially important limitation given that practice patterns of AHF therapy are well known to differ significantly by region globally. For example, it is notable that 55% of patients in their study had de novo heart failure, which is a much higher percentage than that reported from either Europe or the United States.

These data must be considered in the context of other data evaluating the relationship between time to initial AHF therapy and outcomes besides those from REALITY-AHF. Prior data from Maisel et al. (7) have suggested a relationship between early use of natriuretic peptide testing and outcomes in the ADHERE (Acute Decompensated Heart Failure) registry. In contrast, post hoc analyses of other intravenous vasodilator therapies (such as nesiritide) have generally not demonstrated a strong relationship between time to treatment and outcome (8), although such analyses are limited by the lack of an overall treatment effect.

What explains the difference between REALITY-AHF and the data from Park et al. (6) when examining the same question with similar methodology yet with opposing results? Potential differences may include differences in data collection, patient populations, or practice patterns across different countries, although both data sources were single-country, multicenter registries in East Asian countries. Other differences may not be readily apparent from the presented data, or simply be related to the play of chance.

In considering the totality of these findings, we must acknowledge important confounding factors that are unavoidable in the analysis of observational data (e.g., early vs. late diagnosis [and associated therapy] may be significantly associated with the complexity of diagnosis). Patients in whom the diagnosis is more clear (and who therefore are more likely to receive earlier treatment) are more likely to have a more straightforward presentation and potentially, therefore, a better prognosis. For example, patients presenting with more of a "hypertensive heart failure" phenotype often have a more dramatic presentation with acute pulmonary edema and readily identified findings on physical examination and chest radiography. Such patients are thus likely to get earlier therapy and are also known to have a better prognosis than more subacute presentations. This is supported in the current paper by the fact that the early D2D group was more hypertensive, had more New York Heart Association functional class IV symptoms, had more congestion on chest radiograph, and received greater use of mechanical ventilation as an initial therapy. Another important consideration in heart failure is diagnostic complexity: unlike ST-elevation AMI, heart failure remains a clinical and potentially challenging diagnosis in many patients, without a single "gold standard" diagnostic test. Thus it is possible that acute therapy for heart failure may actually be too early (i.e., patients may be treated early for heart failure but may turn out to have

another diagnosis, such as pneumonia or pulmonary embolus).

In summary, the optimal treatment of acute heart failure remains uncertain with regard to both the importance of timing and the specific therapies likely to provide benefit. The totality of available data, including the paper by Park et al. (6), do not provide strong evidence for an important "time to treatment" effect in acute heart failure. Although it certainly stands to reason that prompt diagnosis and initiation of therapy are part of efficient clinical care, the overriding consideration should remain "get it right" rather than "do it fast."

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**KEY WORDS** acute heart failure, heart failure, time to treatment