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EDITOR'S PAGE

Development of Acute Decompensated Heart Failure Therapies

Is the Journey Over?

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In 1990, as a junior faculty member rounding in the Duke Cardiac Care Unit, Dr. Robert Califf, former Commissioner of the U.S. Food and Drug Administration and professor of medicine at Duke University, and former director of the coronary care unit asked me why we had not made as much progress in the treatment of acute decompensated heart failure (ADHF) as we had made in acute coronary syndrome. At this time, I was differentiating my career from an acute coronary syndrome (ACS) doctor to a heart failure doctor as Dr. Califf's first black sheep fellow who could not follow the ACS tradition of his 15 subsequent fellows. It was clear to me that ADHF was an enormous clinical problem with no definitive therapy. At that time in the coronary care unit, we were treating these patients with furosemide, intravenous (IV) nitroglycerin, and occasionally dobutamine. As we did a publications search to see what evidence was available for treatment of ADHF, there was very little, with very small numbers in randomized trials. This came at a point when Dr. Califf was finishing a 41,000-patient acute myocardial infarction trial. In this capacity, we continued to have conversations and asked the question of whether ADHF was like ACS? The difference was that there was a clear pathophysiologic understanding of conversion of chronic ischemic heart disease to ACS, but there was not a single cause for ADHF.

We simply asked the question: Could it be similar with myocardial injury manifested by biomarker release? We subsequently looked at troponin release in ADHF and were surprised, but pleased, to find that there was a significant release of myocardial injury markers during an episode of hospitalization for heart failure, and that these seemed to be related to an adverse prognosis (1). As the evidence continued, we pushed forward with randomized controlled clinical trials (RCT). The largest RCT to be conducted in the field initially was an investigator-initiated proposal by Dr. Califf with myself and Dr. Michael Cuffe, looking at IV milrinone as standard ADHF treatment. We believed that by using this therapy, we could increase evidence-based therapies before discharge and improve outcomes. In this nearly 1,000-patient study, we found the opposite: that routine IV milrinone was associated with worse outcomes, and there was no substantive benefit. In our subsequent journey of RCTs, the largest RCT to date of heart failure randomized over 7,000 patients revealed no benefit (2). In the most recent programs, phase 2B studies revealed important reductions in troponin release with an associated reduction in mortality (3). There was much encouragement by the relief of dyspnea and reduction of in-hospital worsening heart failure. However, the most recent 2 large clinical trials in acute heart failure showed no difference in outcomes and failed to confirm the findings from the phase 2B study suggesting that we have to take a step back.

Let us concede the following:

1. We do not understand the pathophysiology as thoroughly as we can, unlike ACS and we must do more work in this capacity.
2. We have to understand that 24 to 48 h IV therapy is unlikely to give prolonged benefit in an ADHF population as there are many issues that result in clinical morbidity and mortality following a hospitalization for heart failure.

3. We should focus on transition of care with evidence-based therapy that has demonstrated improvement in heart failure with reduced ejection fraction. To gain benefits, we must focus on implementation with evidence-based therapies at time of discharge.
4. Finally, we need to rally our patients as advocates for more research, greater implementation, and greater participation in clinical trials, so we can answer questions faster and not give up on the journey to develop therapies for ADHF.

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