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EDITOR'S PAGE

Why Negative Trials Are Positive for Heart Failure Patients

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This week at the 2016 American College of Cardiology Scientific Sessions, we heard the results from several heart failure trials that were negative or neutral for an intervention that was believed to be a positive advancement for heart failure symptoms and outcomes. As I look back at my 25 years as a clinical trialist in heart failure, over 75% of the trials that I have been in a leadership position for have resulted in a negative or neutral result. I always had the mandate, however, to publish the results in a timely and balanced fashion to advance the field of heart failure.

The reasons for this are very clear.

1. To gain a better understanding of the pathophysiology of heart failure.
2. To prevent publication bias.
3. To highlight any adverse safety events or adverse efficacy outcomes that could be replicated in the therapeutic development by future generations by similar therapeutic agents.

This all began with the FIRST trial published in *American Heart Journal* in 1990 when we investigated the role of intravenous prostacyclin in advanced heart failure, one of the first acute heart failure outcome trials with 6-month follow up (1).

We learned in this trial, which was stopped early by the data safety monitoring board:

1. That the hypothesized drug intervention that looked very positive in phase II studies indeed trended towards harm in a well-powered phase III study.
2. That one of the important insights in this trial was that dobutamine use was associated with a markedly increased risk of morbidity and mortality.
3. That hemodynamic measurements were uncoupled from clinical outcomes.

These findings from this negative trial led to important therapeutic and clinical advances.

1. Prostacyclin, which was widely used with clinical benefits in patients with pulmonary hypertension, is avoided in patients with significant left ventricular dysfunction.
2. Additional outcome studies of inotropes to investigate clinical outcomes were conducted.
3. We hypothesized that the hemodynamic model of acute heart failure should be tested in a randomized controlled clinical trial. The ESCAPE trial (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness) was born from these initial findings (2).

What we learned and published over the subsequent decade was that the inodilator milrinone used and approved in acute heart failure patients was associated with an increased risk of adverse events and clinical outcomes. The routine use of inotropes in acute decompensated heart failure should be reduced.

We conducted the randomized controlled trial of hemodynamic guided therapy versus usual care and found that the use of a pulmonary artery catheter in advanced acute decompensated heart failure was not associated with improved outcomes at 6 months (2). This resulted in a significant reduction of the routine use of pulmonary artery catheters in the management of decompensated heart failure patients.

We tested the hypothesis of a sophisticated vasodilator nesiritide, in a well-powered clinical outcomes trial, the ASCEND trial (A Study Testing the Effectiveness of Nesiritide in Patients With Acute Decompensated Heart Failure) (3). The drug had been approved for the relief of dyspnea, in a clinical trial of <500 patients. The use of this drug had

JACC: HEART FAILURE VOL. 4, NO. 4, 2016
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become mainstream as a secondary agent in the management of acute decompensated failure, rising to an annual use of $700 million a year. The ASCEND trial was brought forth because 2 meta-analyses of small clinical trials suggested a signal of harm on renal function and mortality. In the ASCEND trial, of over 7,000 patients, we found that dyspnea relief was only modest and that there was no significant improvement in rehospitalization or death. However, the drug was safe. The use of nesiritide in the United States precipitously dropped after the ASCEND trial to a baseline rate now of <$50 million of product use per year (4).

In these 3 negative or neutral clinical trials, over 100 abstracts and manuscripts have been published advancing the knowledge of heart failure pathophysiology, and adding insight into the diagnosis, phenotypic characterization, geographic variation, and management of these complicated patients.

In summary, the published negative trials have reduced the use of harmful or ineffective therapies, resulting in hundreds of thousands of lives saved, hospitalizations prevented, and the saving of millions of health care dollars.

It is my strong conviction that negative trials indeed are positive, not in their efficacy signal, but in their contribution to the health of our heart failure patients. This is the reason that heart failure patients consent to be in studies. They consent to advance knowledge with the chance of improving human health, but if not, then to avoid mistakes in the future. Keep publishing your negative trials, including through the JACC HF Dead Letter Office where it's better late than never!

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REFERENCES

1. Califf RM, McKenna WJ, Gheorghiade M, et al. A randomized controlled trial of epoprostenol therapy for severe congestive heart failure: the Flolan International Randomized Survival Trial (FIRST). Am Heart J 1997;134:44–54.

2. Shah MR, O'Connor CM, Sopko G, Hasselblad V, Califf RM, Stevenson LW. Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE): design and rationale. Am Heart J 2001;141:528–35.

3. O'Connor CM, Starling RC, Hernandez AF, et al. Effect of nesiritide in patients with Acute Decompensated Heart Failure (ASCEND-HF). N Engl J Med 2011;365:32–43.

4. Partovian C, Li SX, Xu X, et al. Patterns of change in nesiritide use in patients with heart failure: how hospitals react to new information. J Am Coll Cardiol HF 2013;1:318–24.