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Randall C. Starling, MD MPH, James B. Young, MD

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Randall C. Starling, MD MPH; James B. Young MD

Kaufman Center for Heart Failure
Heart and Vascular Institute, Cleveland Clinic, Cleveland Ohio

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Corresponding Author:
Randall C. Starling, MD, MPH
Professor of Medicine
Cleveland Clinic Lerner College of Medicine of the Case Western Reserve University
Kaufman Center for Heart Failure
Robert and Susan Tomisch Department of Cardiovascular Medicine
Heart and Vascular Institute
Cleveland Clinic
Cleveland Ohio 44195
Telephone: 216.444.2268
Fax: 216.636.6974
E-mail: starlir@ccf.org
Felker and colleagues succinctly and accurately describe the results of the TACTICS clinical trial in this issue of the journal. The methods for TACTICS and the SECRET of CHF Trials provide rationale for additional clinical investigation of the V2 arginine vasopression receptor antagonist tolvaptan. It was hypothesized that tolvaptan may allow for less intensification of loop diuretic therapy and a lower incidence of worsening renal function during treatment for congestive heart failure (1). Based on previous observations patients hospitalized with volume overload and symptomatic heart failure were randomized to a fixed dose of diuretic and placebo versus tolvaptan 30 mg given at 0, 24, and 48 hours with the stipulation that therapy was initiated within 24 hours of admission. The primary endpoint was a composite defined as “responders” based upon dyspnea relief and need for rescue therapy at 24 hours. The proportion defined as responders at 24 hours was similar between tolvaptan and placebo. Although this is a trial that did not achieve the primary endpoint (a negative trial) it is an important report and perhaps the final dialogue for the drug tolvaptan and its role in heart failure. There are now over 300 published reports cited in Pub Med when linking “tolvaptan and heart failure.” There are numerous published editorials since 2004 when Francis and Tang initially discussed the aquaretic tolvaptan; they encouraged the need for more data, and acknowledged the awaited results from the EVEREST trials (2,3).

TACTICS, a well-designed and executed clinical trial, attempted to answer an important question that utilized hypothesis generating insights from numerous clinical trials with tolvaptan (4). It is also an expensive drug and value will, therefore, depend on the relationship of outcomes to cost.

Though investigator initiated, the trial was sponsored by industry and currently the drug has a limited FDA approved indication for the treatment of clinically significant hyponatremia. It
was hypothesized that if dyspnea relief is confirmed then tolvaptan may be recognized as a “much needed adjunctive therapy to safely treat congestion in patients with acute heart failure.”

**Was the Hypothesis Valid? Yes**

Tolvaptan is an effective aquaretic drug that results in free water excretion. Tolvaptan has shown trends to reduce dyspnea better than placebo when given in the first 20 hours after hospitalization (5). Patients receiving tolvaptan versus placebo generally have greater weight loss and it was hoped would have lower requirements for loop diuretics and hence less need for “rescue therapy” and improved 30 day outcomes. As loop diuretics are known to result in enhanced neurohormonal activity a reduced need for loop diuretics was expected to improve outcomes. The prespecified primary and secondary endpoints were all well aligned with the established body of knowledge regarding tolvaptan in heart failure. Tolvaptan did result in enhanced fluid and weight loss. Disappointingly the trial yielded negative results.

**What is the Future for Tolvaptan?**

There does not appear to be a justification for additional study of tolvaptan in acute or chronic heart failure. Despite greater weight and fluid loss, the pre-specified endpoints were not met. Perhaps the current baseline for acute heart failure outcomes can be gleaned from the ASCEND HF trial and the hope for the future is that serelaxin will provide incremental improvement (6,7). The authors concluded that the data from TACTICS-HF did not support an expansion beyond the current FDA indication for hyponatremia.

**Future Consideration and Acute Heart Failure**

We agree that effective treatment of acute heart failure represents an unmet need and that current strategies do not effectively reduce dyspnea or important endpoints including mortality and hospitalization compared with “standard of care” background therapy. Mechanical strategies
to remove free water, specifically ultrafiltration have been equally ineffective and the disconnect between weight/fluid loss and dyspnea is well described. It may be time to abandon the dyspnea endpoint in acute heart failure trials based on the difficulty of the measure and the uncertainty of its significance (8,9). Rolofylline reduced early dyspnea but this was dissociated with in-hospital worsening heart failure and outcomes at 60 and 180 days (10). The additional weight loss with tolvaptan did not reduce the tendency for inpatient worsening heart while hospitalized which is felt to represent an important clinical parameter in acute heart failure. The changes in renal function with tolvaptan were small, transient and do not merit further commentary or concern.

In summary the TACTICS-HF provides extremely important data for clinicians and proves clearly that there is no benefit to the use of tolvaptan and its use should be discouraged based upon lack of efficacy and cost. The unmet need to develop better strategies for the treatment of acute heart failure remains a challenge and mandates ongoing investigation.
References


