

# CHANGING THE FACE OF HEART FAILURE TREATMENT: RESULTS FROM THREE PIVOTAL STUDIES

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Several studies importantly affecting the treatment of patients with heart failure were reported at the 2018 American Heart Association Scientific Sessions. In this article, we will review three of them.

## TRED-HF

Among the most important and unique studies was TRED-HF (Withdrawal of pharmacological treatment for heart failure in patients with recovered dilated cardiomyopathy). This small (51 patients) pilot study featured an open-label, randomized, phased withdrawal (ie, standard drug therapy was withdrawn according to a prespecified drug-by-drug schedule, not all at once) of guideline-directed medical therapy in patients who were devoid of heart failure symptoms, were receiving standard multidrug, guideline-based therapy (including loop diuretic,  $\beta$ -blocker, ACE inhibitor, ARB, or MRA, or a combination of these drugs), and who had manifested LVEF  $\leq 40\%$ , abnormal left ventricular end diastolic volume, and an NT-proBNP concentration  $\geq 250$  ng/L (ie, who had had HFREF) an average of 4.9 years from the time that the diagnosis was made and therapy begun and who then improved on therapy to a non-heart failure, noncardiomyopathic state with LVEF that had increased at least 10% to  $>50\%$ , with normal left ventricular end diastolic volume and NT-proBNP concentration  $<250$  ng/L (average=72 ng/L). At the end of 6 months after randomized withdrawal, a comparison was made of the number of patients in each group that remained “recovered.” At that point, therapy was reestablished among those from whom it had been withdrawn and was withdrawn among 25 of the 26 in whom it had been continued and follow-up continued in this cohort.

The results were relatively dramatic. During the initial 6-month follow-up interval, 11 of the 25 patients who were randomized to drug withdrawal (44%) relapsed to their pretherapy state. Medication withdrawal resulted in a mean 9.5% decrease in LVEF versus baseline, a 15 bpm increase in heart rate, a 7 mm Hg rise in diastolic

blood pressure, and a 5.1 point decrease in the Kansas City Cardiomyopathy Questionnaire score, the latter a substantial and clinically meaningful deterioration. Of the 26 patients who continued their prerandomization therapy, none relapsed (between-group difference  $P<0.0001$ ). No patient in either group died, but 3 serious adverse events, none cardiovascular, occurred in the withdrawal group. However, among the 25 patients who underwent withdrawal after completing therapy during the initial 6-month on therapy follow-up, 9 relapsed (a Kaplan-Meier event rate of 36%).

None of the data enabled prediction of those patients who would relapse. Although the study was small, the results were so very consistent that reasonably firm conclusions can be drawn. Specifically, among patients with HFREF, withdrawal of therapy should not usually be attempted, at least until we can predict who will relapse. As the study's presenter, John Halliday, PhD, of Imperial College, London, stated, "Improvement in function represents remission rather than permanent recovery for many patients."

For clinicians, patients, and drug regulatory professionals, the study is highly illuminating. For several distinct cardiovascular indications, multiple drugs now are FDA- and EMA-approved. Once one or several drugs are thus approved, a new drug of another group (so-called "class") for the same indication usually must be tested on a background that includes the already approved drug(s). This is true primarily for ethical reasons, so that all study subjects can be expected to realize the benefits for which the earlier drugs were approved and administered. Therefore, application of the new drug after approval requires simultaneous treatment with the drugs that were used as background drugs during the pivotal clinical trials. To justify stopping one or several of the background drugs, new appropriately designed clinical trials would be needed. Such trials are complex and expensive and generally have not been performed for most indications. Therefore, as new therapies are introduced, the "cocktail" administered for some common conditions, like HFREF, becomes progressively larger, more expensive, and potentially associated with increasing adverse events, implications for pregnancy, or deleterious interactions with drugs given for other indications. TRED-HF is the first trial to assess the risk of discontinuing background drugs for HFREF once clinical and objective indications of reversal of the underlying pathophysiology have been identified.

The results of this pilot study strongly suggest that, at least for HFREF, the current multidrug standard therapy should continue indefinitely. This study can be expected to serve as a template for the study of background removal for other conditions.

**PIONEER-HF**

Another important and potentially practice-changing study was PIONEER-HF (Comparison of Sacubitril–Valsartan versus Enalapril on Effect on NT-proBNP in Patients Stabilized from an Acute Heart Failure Episode). This study compared the effects of the sacubitril-valsartan combination versus enalapril on NT-proBNP change and adverse events among 881 patients with HFREF and acute decompensated heart failure randomized between the two treatments. The data were presented by Eric J. Velazquez, MD of Yale University, US (Yale was one of the institutions participating in this TIMI-organized study).

Study patients were  $\geq 18$  years of age with an LVEF  $\leq 40\%$  and a NT-proBNP concentration  $\geq 1600$  pg/mL or a BNP concentration  $\geq 400$  pg/mL and who had received a primary clinical diagnosis of acute decompensated heart failure, including signs and symptoms of fluid overload. Patients were enrolled  $\geq 24$  hours and  $\leq 10$  days after the initial presentation to the hospital and were still hospitalized when initiated into the study. Prior to randomization, patients needed to be hemodynamically stable (as indicated by systolic blood pressure  $\geq 100$  mm Hg for the preceding 6 hours, no increase in intravenous diuretic dose and no intravenous vasodilators during the preceding 6 hours and no intravenous inotropic drugs for the preceding 24 hours).

Compared with baseline values, NT-proBNP concentration decreased significantly ( $P < 0.001$ ) more (46.7%) at 4 and 8 weeks of randomized therapy in the sacubitril-valsartan group than in the enalapril group (which manifested a 25.3% decrease). Although NT-proBNP is a nonvalidated surrogate for clinical alterations, it does suggest that reduction in fluid overloading was highly unlikely to be less effective on the combination drug than on enalapril. Importantly, the rates of worsening renal function, hyperkalemia, symptomatic hypotension, and angioedema did not differ significantly between the two treatments.

The importance of the results of PIONEER-HF is that the use of the sacubitril-valsartan combination, found to be superior to enalapril in patients with chronic stable HFREF and not to have unacceptable safety problems in that setting in the PARADIGM-HF trial, can also be administered in the setting of acute decompensated heart failure without loss of efficacy and without incurring an adversity penalty. Without these data, therapy-naïve patients with acute decompensated heart failure would need to begin with enalapril or some other ACE inhibitor or ARB and, when stabilized, transition to the combination drug. Thus, PIONEER-HF allows more efficient management of patients with acute decompensated heart failure than had been possible previously, with the likelihood that the mortality benefits of sacubitril-valsartan can be realized earlier than they might be with the current staged-therapy protocol.

## **OPTIMIZE HEART FAILURE CARE: EFFECT OF ADHERENCE TO GUIDELINES VS REHOSPITALIZATION**

Several drugs have been tested for their effects on hospitalization for HFREF. The SHIFT study also assessed the effect of therapy on rehospitalization rates, demonstrating a significant drug-mediated reduction in rehospitalization when that drug was employed on a background of the remainder of guideline-based HFREF therapy. However, the effect of adherence to guideline-recommended therapy has not been systematically assessed from prospectively collected data. In a study mounted by collaborating investigators from institutions within the Russian Federation, data from an international prospective multicenter Optimize Heart Failure Care program that were collected over 12 months from 635 patients hospitalized with worsening heart failure were analyzed to assess the effects of physicians' and patients' adherence to guideline-based therapy on rehospitalization. Physicians' prescribing adherence was classified as good (use of drugs from all guideline-recommended heart failure medication groups), moderate (use of more than half the recommended medication groups), or poor (use of less than or equal to half the guideline-recommended medication groups). Patients' adherence was assessed by patient-reported compliance via a purpose-designed questionnaire. Again, three groups were defined: good (always took all prescribed medications at target doses), moderate (sometimes failed to take all prescribed drugs), or poor (patients failed to take all prescribed medications). As explained by Yuri Lopatin, MD of the Volgograd State Medical University, Volgograd, Russian Federation, who presented the study, after 12 months of follow-up, physicians' adherence did not reveal a clear pattern of hospitalization reduction compared with baseline, but rehospitalization was significantly higher than baseline ( $P<0.0001$ ) when patients' adherence was poor in any physicians' adherence group. The authors concluded that educational initiatives are necessary for both physicians and patients if optimal impact of current drug therapy is to be achieved.

Many other important studies relating to heart failure were presented, but these three have particularly important implications for current care. ■