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EDITOR'S PAGE

N-1 and Sequencing Clinical Heart Failure Trials

Charting the Path for Future Clinical Care

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Recently, we received wonderful news with the results of the DAPA-HF trial, showing a significant reduction in morbidity and mortality with dapagliflozin in heart failure patients with reduced ejection fraction with and without diabetes. We now have a fourth drug class for our armamentarium of therapies to improve survival and reduce hospitalizations in heart failure. As clinicians, how can we implement all these therapies into our clinical practice, and provide for patients, when real-world evidence shows that we are offering triple therapy at rates of only 1% to 10% (1)? We have made little progress in the implementation of novel therapies. On average, it takes us more than a decade or more to get the utilization rates of new drug therapies >80%. Now, we have a fourth drug class that reduces mortality in the setting of 3 drug classes and 2 additional drugs that reduce heart failure hospitalizations.

How can we move forward? What about N-1 clinical trials, so-called knockout trials? What do we know about this clinical science that can help us understand whether adding additional therapies makes sense, or whether we can begin to understand which group of therapies provides the best outcomes? When life was simpler and we only had angiotensin-converting enzyme (ACE) inhibitor therapy, digoxin, and diuretics, we, as a community, conducted N-1 knockout trials, the PROVED trial, and the RADIANCE trial (2). In these trials, the patients were randomized to withdrawal of digoxin in a double-blind fashion. Over a short-term period, rates of worsening heart failure and other intermediate endpoints, such as exercise time, New York Heart Association functional class, and ejection fraction were measured. With high levels of consistency, the group that was allocated to digoxin withdrawal had evidence of worsening heart failure events, sustained reduction in left ventricular ejection fraction, and reduced exercise performance. This suggested that removal of the drug when patients were treated with baseline diuretic agents and ACE inhibitor therapy resulted in a worse outcome in the short term.

In the CIBIS-III study, investigators recruited over 1,000 heart failure patients with reduced ejection fraction with New York Heart Association functional class II or greater symptoms, who were not on an ACE inhibitor or beta-blocker. Patients were randomized to receive bisoprolol or an ACE inhibitor for 6 months followed by the combination for 6 to 24 months (3). The hypothesis was that initiation of the beta-blocker first would be noninferior to the standard of care of initiation of the ACE inhibitor first. The primary endpoint was not met, but in the intention-to-treat analysis the strategies did appear similar, and overall, the totality of evidence suggested that there were similar event rates and adverse effects with the initiation of beta-blocker therapy first versus ACE inhibitor first. This suggests that there were no potential disadvantages with the strategy of initiating a beta-blocker first. However, because the standard of care was initiation of the ACE inhibitor first, this trial really did not demonstrate any significant advantages of the alternative strategy. We applaud the investigators for providing a better understanding of which therapy in sequence should be initiated in the complex world of clinical practice. After 25 years, we are still left with little or no information on whether we should be adding on therapies, or in what sequence.

As a community, what should we do? Let us begin to get comfortable with N-1 trials and begin knockout therapies that will have no effect on mortality but may only affect morbidity. Today, we still see uses of

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digoxin at levels of 20% to 25%. Should we begin to repeat our Digoxin Investigators Group withdrawal trials to see if they still hold an advantage in our armamentarium of therapies? We should design these as intermediate sized trials with worsening heart failure functional status, natriuretic peptide levels, and patient-reported outcomes as endpoints. By doing so, we will set the stage for conducting N-1 trials and begin to understand whether we should keep adding therapies one by one or think more strategically when therapies are developed. In addition, how about sequencing trials that initiate all 4 classes at once initially in small doses versus a staged approach after stabilization or persistent symptoms. This will be a challenging but rewarding time for our patients, in which we have made so many gains in improvement in quality and quantity of life.

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