Evolution of heart failure management: Miles to go

The woods are lovely, dark and deep,
But I have promises to keep,
And miles to go before I sleep,
And miles to go before I sleep.

—Robert Frost, “Stopping by Woods on a Snowy Evening”

Frost’s words are simple yet elegant. They can be interpreted many ways. I see the allegory of life as a journey in this poem. The passage, like the woods, is beautiful, but there is a long, long way to go.

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And so it is with the treatment of heart failure. There is beauty in our understanding of the syndrome’s physiologic complexities and natural history, and of effective treatments uncovered. Still, we’ve a monstrous climb ahead to get to the summit of this clinical challenge in order to start a real descent.

THE PAST, PRESENT, AND FUTURE OF HEART FAILURE THERAPY

Okwuosa et al, in this issue of the Journal, have capably summarized the ABCs of treating heart failure with reduced ejection fraction (also called systolic heart failure), approaching the subject from a perspective on past, present, and future therapies. They summarize heart failure interventions with a guideline-based philosophy, pointing out that these care paths are supposed to be evidence-based. They observe that in the 1960s the standard of care was digitalis, diuretics (furosemide first became available in 1967), and rest. That was about all we had for this problem.

There are now many drugs, devices, and operations that help patients with heart failure. But they never really cure the disease or, more aptly, the syndrome—and therapies are supposed to cure. This limitation of present therapies is important, given the disturbing epidemiology of heart failure, its economic cost, and the suffering of patients. That burden is well detailed.

In addition to curing, the overarching goals of treatment generally are to ameliorate distressing symptoms and to prevent comorbidities. In heart failure with reduced ejection fraction, we want to prevent premature death, stroke, myocardial infarction, congestive states, hospitalization, renal insufficiency, renal failure, cachexia, inanition, feebleness, and respiratory distress, among others.

The ABC mnemonic of Okwuosa et al will help caregivers remember the basics. It is important, however, to put algorithms into proper perspective and to look toward the future.

PROBLEMS WITH EVIDENCE-BASED MEDICINE

Several problems with our current heart failure treatments are rooted in how we perform clinical trials, arguably the premier method of determining truth in clinical practice and the foundation of evidence-based medicine.

Do the trials represent real-world practice? Were the clinical trials that led to regulatory approval and professional society endorsement of the therapies that we prescribe in our offices done in the same sorts of patients as those in our waiting rooms asking for help? Perhaps, for the most part, they have been. And thus, Ok-
wuosa et al have crafted a work relevant to all of us and every patient.

But I believe there are major gaps in the types of participants enrolled in trials, eg, underrepresentation of certain racial and ethnic groups, not to mention the relative paucity of women. The very elderly (a rapidly growing population) have largely been ignored as well, and participants with significant renal insufficiency, anemia, and diabetes mellitus seem far fewer than what we deal with in a busy clinic.

In addition, Okwuosa et al focus only on patients with reduced left ventricular ejection fraction, a group that makes up only about half of the heart failure crowd.

What about quality of life and other important outcomes?
Clinical trials in heart failure with reduced ejection fraction have generally focused on major clinical end points (primarily, but not exclusively, mortality), to the exclusion of quality of life. Though sometimes included in trials, quality-of-life metrics generally get relegated to second-class seats or ‘tween-deck steerage. Perhaps that is because measuring quality of life can be time-consuming and difficult.

Yet, in the words of sociologist William Bruce Cameron, not everything that counts can be counted, and not everything that can be counted counts. That goes for quality of life.

Lies, damned lies, and $P$ values
Quandaries in data management and analysis include what to do about trial dropouts, study power, precision of statistical analysis, intention-to-treat principles, and choice of the $P$ value that defines significance (or not) for any end point observation. Of course, there are myriad sophisticated mathematical and statistical reasons to justify why we don’t simply count on-treatment participants or allow imputation of results when patients or results drop out, forcing us to worship at the altar of $P < .05$.

A review of the $P$ value concept recently appeared with an accompanying editorial by Kyriacou that concluded that “the automatic application of dichotomized hypothesis testing based on prearranged levels of statistical significance should be substituted with a more complex process using effect estimates, confidence intervals, and even $P$ values, thereby permitting scientists, statisticians, and clinicians to use their own inferential capabilities to assign scientific significance.”

How many great treatments have we tossed out because of rigid reliance on old-fashioned approaches to determining therapeutic evidence? Many treatments studied have had great results in a minority of patients in clinical trials but did not have a major positive (or negative) impact on the overall cohort (with lack of primary end point statistical significance). And what to do when the primary end point is a neutral or negative one but secondary end points are positive? Why not focus more attention on those patients benefiting from an intervention despite the overall results of any trial?

Dilemmas of trials
Other issues are that clinical trials cost too much, and that recruitment and follow-up take too long. Intercurrent therapies (and guidelines) can emerge that jeopardize the trial itself or make observations untimely. The dilemma of stacking therapies one on top of another, often making patient compliance impossible, is another problem with clinical trials. Yet this is how we get to the ABCs.

■ A NEW WAY TO DO TRIALS
The information provided by Okwuosa et al is useful and encouraging, but too many gaps exist in our heart failure therapies to permit us to celebrate with exuberance. Too many patients still suffer, too many die too young, and the costs are still too great.

Perhaps the future of therapeutic development should embrace different and better ways to demonstrate real value (relying on the equation of value equals outcomes meaningful to patients, divided by cost) of therapies, including the old, the new, the trashed and the underdeveloped. More creative data analysis to reexamine the current tools on the shelf and the ones tried but discarded is essential.

A position paper from the Cardiovascular Round Table of the European Society of Cardiology concluded that “a coordinated effort involving academia, regulators, industry
and payors will help to foster better and more effective conduct of clinical cardiovascular trials, supporting earlier availability of innovative therapies and better management of cardiovascular diseases.7

Lauer and D’Agostino,8 also in an editorial, argued for innovative methods of doing clinical trials and discovering truth about therapies that are applicable to the future of developing treatments for heart failure with reduced ejection fraction. They noted that “the randomized registry trial represents a disruptive technology” and wondered if it will be “given serious consideration as a way to resolve the recognized limitations of current clinical-trial design.”8

Indeed, conducting megatrials with existing megadatabases using a registry format could help. Registries emerging from early adaptive trial design efforts, particularly when Bayesian analysis theory is applied, might help inform clinical experience faster and more efficiently. Bayesian analysis is a statistical approach that attempts to estimate parameters of an underlying distribution of events in an ongoing fashion based on the observed distribution. A clinical trial of stem cell therapies could, at the end of the trial, be turned into a multicenter registry that would continue to inform us about the more real-world application of newer treatment approaches.

Though the therapeutic cupboard for heart failure is certainly not bare, as Okwuosa et al point out, it is wanting. Let’s look for new therapeutic ABCs differently. We should be attacking the real challenge—curing the disease processes that cause the syndrome. Yes, there are miles to go before we sleep.

REFERENCES