Challenges for the Basis of Practice in Heart Failure

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Abstract—Although evidence from clinical trials has significantly informed the management of patients with heart failure, many patients and many clinical situations encountered on a daily basis do not fit neatly into the narrow definitions of trials. In subsequent issues, Circulation: Heart Failure will feature a new series entitled “Challenges for the Basis of Practice,” in which readers may submit challenging cases that call for management considerations and decisions that extend well beyond the evidence. An expert consultant will be invited to comment, and readers can also submit responses to these challenging situations so that numerous viewpoints can be explored. (Circ Heart Fail. 2008;1:81-83.)

Key Words: heart failure ■ trials ■ heart disease

The science of cardiology has helped propel us into the era of evidence-based medicine. For heart failure, the traditional remedy of digoxin was challenged, with subsequent redefinition of benefits and risks. Rational drug development culminated in many clinical trials of new therapies such as neurohormonal antagonists, for which the scope of benefits far exceeds initial anticipation, and inotropic agents, for which the promise has never been fulfilled. Level I and level II recommendations have become the gold and silver currency of the realm. The call to “Get With The Guidelines” resonates with unprecedented union from the American Heart Association, the American College of Cardiology, and the Heart Failure Society of America.1,2 Outcomes with heart failure have dramatically improved as these guidelines have been incorporated into effective heart failure management. The disease concept has stretched to encompass the oxymoronic asymptomatic heart failure, because it is during this time that treatment may be most effective to improve long-term survival, as suggested by 12-year follow-up of the Studies Of Left Ventricular Dysfunction (SOLVD) prevention arm,3 in which mortality benefit was not evident during the formal trial.4 Twenty-five years ago, patients with heart failure were usually referred only for research studies or cardiac transplantation, often dying within 2 years without transplantation. Now, cardiac transplantation is epidemiologically trivial in heart failure management, with which many patients survive beyond 10 years with their own hearts.

Limited Evidence for Practice

The expanded basis of evidence from clinical trials remains limited in application to practice. Although the term practice in relation to medicine has often been invoked as “the repetition of an action in order to become proficient,” this is the last of the definitions of practice.5 The first is “the actual application of a plan or method, as opposed to the theories relating to it,” derived from the Greek praktikos, meaning “concerned with action,” from which also comes the adjective practical. Practical decisions must be made every day in the care of individual patients. What are the gaps between trial-based evidence and practice?

Even for successful trials, the fallacy of the mean renders it unlikely that an individual patient will enjoy the average benefit,6 as has been emphasized by Jay Cohn, the founder of the Heart Failure Society of America. This ambiguity of trial results is amplified when beneficial therapies are stacked. While taking 1 proven drug, the trial population that benefits from a new drug may include patients who would derive benefit from both drugs, but it also may combine responders who benefit from one or the other but not both. There is also no reason to believe that the individual is optimally treated with the target dose in the trial, which demonstrates only that aggregate benefit exceeded aggregate toxicity. These uncertainties apply even for the subjects in the trial. Do trial results encompass the larger populations who would have been excluded for comorbidities, many of which increase with age? The Acute Decompensated Heart Failure National Registry (ADHERE), which with more than 100 000 patients hospitalized with heart failure eclipses all trials together,4 has an average patient age of almost 75 years, even in the group with low ejection fraction heart failure; the mean age of patients in heart failure trials is less than 65 years. Fewer than 25% of hospitalized patients would meet heart failure trial criteria,7 yet hospitalization brings most patients to clinical attention. Even if patients and trial subjects were similar, how would trial participants respond in the usual practice settings outside the reimbursed rigor of research organizations? The community experiences with spironolactone demonstrate how a basis of evidence may be altered in translation to practice.8 The relative priority for implantation of devices may be reexamined in a rural indigent setting where patients were not reimbursed for medications.9 Patients differ from the bases of evidence not only in demographics and practice setting, but also for the changing “natural history” of their disease.

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Daily Practice: What to Do?

Despite the inevitable limitations, the trials have established the key elements from which to design the effective regimen for an individual patient. Armed with the guidelines, the refractory questions most commonly remaining on a daily basis are not which drug to try but when and how to try it. \(^9\)

What is target? What is tolerability? For individual patients, it is often necessary to compare absolute benefits and risks rather than the relative benefits and absolute risks as often advertised. What should be added when first-line therapies are poorly tolerated or ineffective? Will we ever find surrogate end points for heart failure therapies as convenient as blood pressure for hypertension and hemoglobin A1c for diabetes? When does symptomatic relief trump other goals of therapy? Optimal therapy often requires understanding of the nature and timing of activities most important to each individual, and the patient preference for quality versus length of life remaining. \(^11\)

How should the available data be applied to the individual patient? As emphasized during coronary care unit rounds at the University of California Los Angeles by Jan Tillisch, an early proponent of tailored therapy, any fool can make a good decision with good data. If all the relevant data existed, medical care could be relegated to telephone consultants with algorithms. The challenge is to make a good decision with flawed data, which include unbiased trials with limited relevance and relevant experience with unlimited bias. As a keen observer and a clinical trial pioneer, Jay Cohn urges us not to rely exclusively on left brain activity, which converts guidelines to governance and demands new trials to enlighten each uncertainty. Trials can never be performed quickly and cheaply enough to answer even a fraction of the current questions and those raised by each new trial. \(^6,9,12\)

The right brain seeks to extrapolate and integrate pieces of information into whole biological and social organisms. Both the left and right brains need to function in daily practice.

The story of β-blocker use provides examples of translation between trials and practice. Reanalyses of the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF) demonstrated when and why uptitration of β-blockers was halted before target doses and how benefit on outcomes was equivalent when titration was limited by bradycardia. \(^13\)

Crucial to defining realistic expectations outside of trials is the prospective analysis of specific strategies, such as the Cleveland Clinic report demonstrating the 70% success of β-blocker initiation, with only half of those patients reaching recommended target doses when diligently pursued in an unselected heart failure clinical population. \(^13\)

The benefit of β-blockers in patients who did not meet trial criteria was confirmed in a large prospective registry. \(^14\)

Rather than introducing another new therapy, the Cardiac Insufficiency Bisoprolol Study (CIBIS) III helpfully addressed the common clinical dilemma of which neurohor-


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