Diff’rent Strokes, Different Folks
Advanced Heart Failure’s Changing Outlook

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Since the first heart transplant was performed 45 years ago, the field of advanced heart failure has grown and evolved at a hurried pace. In the United States, ≈2300 heart transplants are now performed every year.1 Mechanical circulatory support device implants are likely to eclipse transplantation in the very near future.2 More important to the broader population of patients living with heart failure and reduced left ventricular ejection fraction (HFREF) is the establishment of multiple neurohormonal antagonist medications and electrophysiological devices to improve survival and quality of life.3

Appropriately, this complex constellation of therapies has encouraged the development of a heart failure subspecialty and centers of expertise. More than 140 centers in the United States currently perform cardiac transplantation,4 and additional centers are now entering this advanced heart failure arena through the provision of destination therapy mechanical circulatory support devices. The Centers for Medicare and Medicaid Services regulates these centers within its jurisdiction.4 In addition, in 2010, the field of Advanced Heart Failure and Transplant Cardiology became an American Board of Internal Medicine–recognized sub-specialty.5

Growing concerns about cost and value in the American healthcare system with regard to this expanding and resource-intensive heart failure care begs the question “How are we doing?” Who are these advanced heart failure centers serving? What therapies are the referral populations getting? And most important, what are the outcomes? Detailed information is available for patients listed for cardiac transplantation1 and those undergoing mechanical circulatory support.2 However, the denominator, those patients who do not go on to transplantation listing or device placement, is relatively unknown. The Medical Arm of Mechanically Assisted Circulatory Support (MedaMACS) prospective registry of medically managed advanced heart failure patients is designed to help fill this gap, but enrollment at the first sites is just now beginning.6

Within this context, Loh et al7 report in this issue of Circulation: Heart Failure on “Temporal Trends in Treatment and Outcomes for Advanced Heart Failure with Reduced Ejection Fraction from 1993–2010: Findings from a University Referral Center.” The experience of the Ahmanson University of California Los Angeles (UCLA) Cardiomyopathy Center is described—one of the largest advanced heart failure programs in the world during the past 2 decades. Through a detailed characterization of clinical characteristics, therapies, and outcomes from 2500 patients in 6-year increments across an 18-year span (era 1: 1993–1998, era 2: 1999–2004, and era 3: 2005–2010), the authors are able to provide a longitudinal view of the breadth of medical and device therapies that have changed advanced heart failure care at their center. A number of these changes are particularly noteworthy and may have implications for the future care of heart failure patients.

First, the UCLA experience documents the change in advanced heart failure treatment profiles as we have moved into the current era of neurohormonal antagonist and electrophysiological device therapies. The use of β-blockers, mineralocorticoid receptor antagonists, cardiac resynchronization therapy, and implantable cardioverter-defibrillators all increased significantly during the 18-year time period. This is not at all surprising given the results of a series of randomized controlled trials released during this period of time. The decreasing use of the older vasodilator therapies of nitrates and hydralazine is also not surprising. Furthermore, it is encouraging, even if expected, to see evidence-based HFREF therapies used at high rates before patient referral for consideration of advanced therapies.

Second, the patient profile at the time of referral for advanced therapies has changed significantly in the past 2 decades. Quite simply, today’s HFREF patients are different folks. The authors describe several echocardiographic indices of ventricular remodeling that improved during the 3 time periods, including a reduction in left ventricular size (left ventricular end-diastolic dimension decreased from 70 mm in the earliest era to 65 mm in the most recent era), a nearly 50% reduction in the number of patients with severe mitral regurgitation, and a concomitant reduction in the percentage of patients with severe tricuspid regurgitation. There was also a statistically significant, although clinically modest, reduction in left ventricular ejection fraction (23.5% in the earliest time period to 22.3% in the most recent period).

Although the advanced HFREF patient profile has clearly changed over time, trends in overall heart failure disease severity at the time of referral are less clear. The UCLA experience partially supports the belief among many clinicians in the field that patients are more ill when they present to an advanced heart failure referral center. This was seen as a

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lower average cardiac output, higher filling pressures, higher natriuretic peptide levels, lower angiotensin-converting enzyme inhibitor/angiotensin receptor blocker usage, and higher risk Seattle Heart Failure Model summary scores in more recent eras. There was also a greater prevalence of comorbid conditions, including atrial fibrillation, diabetes mellitus, anemia, and renal dysfunction.

By contrast, there were other HFREF prognostic markers that seemed to improve during the 3 time periods. Patients in more recent eras had mildly higher systolic and diastolic blood pressures and a decrease in heart rates. It is likely that these changes at least partially reflect the preferential use of β-blockers rather than vasodilators. There were also temporal improvements in other markers of disease severity, specifically lower loop diuretic usage, lower mean loop diuretic dose, and lower New York Heart Association (NYHA) functional class measures.

The NYHA functional class measures are a notable contradiction to trends in other measures. Although it is possible that NYHA measures capture a different domain of heart failure severity, one would generally expect patients with objective evidence of greater congestion and reduced cardiac flows to have more, not less, functional limitation. In the study’s earliest time period, 90% of patients were either NYHA functional class III (32.5%) or class IV (58.4%) at the time they were referred to the UCLA advanced heart failure program.

In the 2 more recent time periods, at the time of referral >25% of patients were NYHA functional class I or II, ≤40% were NYHA class III, and just fewer than 30% were NYHA class IV. The authors note that the assessment of NYHA functional class may have shifted over time as clinician’s experience and expectations changed. This is partially supported by the study’s finding of minimal change in peak oxygen consumption (VO_{peak}), an objective marker of functional capacity, during the 18-year time period. An alternate explanation is that patients were referred earlier in their disease course, perhaps in response to greater awareness of advanced heart therapies. Indeed, the time from heart failure symptoms to referral dropped from 39 months in era 1, to 17 months in era 2, and 28 months in era 3. Whether such referrals patterns are confined to the UCLA program or a nation-wide phenomenon is unknown.

Third, the authors saw a significant drop in all-cause mortality after referral (42% adjusted decrease)—largely attributable to decreases in sudden cardiac death. Not surprisingly, as a trade off for the reduction in sudden death, there were small increases in pump failure–related deaths, transplantation, and mechanical circulatory support. This decrease in sudden cardiac death, in part, reflects the combination of increased use of β-blockers, aldosterone antagonists, cardiac resynchronization therapy, and implantable cardioverter-defibrillators during the study time period. In part, it also reflects referral biases. Therefore, we are unable to conclude to what extent changes in therapy have improved real-world outcomes over time. Within this context, however, progressive improvements in overall survival at UCLA are seen, despite a trend by most measures toward sicker patients over time. Adjustment for a wide range of patient characteristics only increased the association of more recent eras with improved survival. Therefore, the overall message that outcomes are improved is a reasonable and reassuring one.

An unfortunate and sobering finding is that mortality remains very high. Despite major advances in HFREF therapies during the 18-year time period, all-cause mortality among those referred to the UCLA advanced heart failure center only decreased from 36% in era 1 to 31% in era 3. Considering that patients referred to the program were on average only in their early 50s, this further illustrates the devastating nature of HFREF and the need for continued research to improve long-term patient outcomes.

The continued high mortality rates and differing modes of death illustrated by the UCLA experience should prompt us to consider what resources are appropriate for the next generation of integrated advanced heart failure programs. Patients referred to advanced heart failure programs are now more likely to experience death from pump failure or life with ventricular assist devices and cardiac transplantation. From a systems perspective, this may stimulate an even greater demand for increased availability of and improvements in mechanical circulatory support devices, as well as an increase in the number of clinicians who are comfortable managing advanced heart failure therapies. However, it should perhaps also prompt consideration for an increase in palliative care resources. From the patient perspective, people generally want to live longer but also want to avoid prolonged suffering. This dilemma was the introductory theme of a television program from more than 30 years ago but still applies today:

Now the world don’t move to the beat of just one drum, What might be right for you, may not be right for some.

Regardless of how the outlook for advanced heart failure evolves, helping patients referred to advanced heart failure centers understand the trade offs of the therapies we offer is critical to calibrate expectations and promote truly informed decisions that align with their values, goals, and preferences.

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