The Heart Failure Paradox: An Epidemic of Scientific Success

Presidential Address at the American Heart Association 2013 Scientific Sessions

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Good afternoon, and welcome to the American Heart Association’s (AHA) Scientific Sessions. I am so excited to be here with you in Dallas.

Texas is a huge state and famous throughout the world for so many things: hospitality and graciousness, oil, cowboys, the Alamo, and of course, the television show Dallas. But I always think of Texas as home to the AHA. So I welcome you with the big heart of Texas and thank you for being here. I am truly honored to address you: healthcare professionals, scientists, educators, students, AHA volunteers, and colleagues from around the world.

Today, I’m going to explore the remarkable yet troubling history of heart failure. The state of this common cardiovascular syndrome is remarkable in many ways, particularly because it illustrates our progress in so many areas of science and medicine. Yet it is also troubling, because in just a few short decades, heart failure has developed into a full-blown epidemic, with 23 million people suffering from the disease worldwide.1–3

Heart failure is, very strangely, an epidemic of scientific success. Mortality from cardiovascular disease in general has been decreasing thanks to scientific breakthroughs, so people are living longer. People who have had heart attacks are also benefitting, thanks to science and programs to deliver that care. And all of these older people (and all of us, by the way) live in a world of growing obesity and diabetes rates that fuel the heart failure epidemic.4,5

I could share hundreds of stories about my patients over the past 30 years who exemplify both the tragedy of this disease and the hope that now exists. I will share a few of those stories today. But I’ll also explore some of the larger lessons that can help us deal with this epidemic.

We have come a long way in our understanding and treatment of heart failure. When I started my cardiovascular training at the University of Pennsylvania in 1979, heart failure was considered a terminal illness. The concept of diastolic heart failure was not well recognized, and most treatment was directed toward the patient with a low left ventricular ejection fraction, a dilated cardiomyopathy—or, more simply stated, a poorly squeezing pump. The major drugs then were diuretics and digitalis. Nitroglycerine eased angina or paroxysmal nocturnal dyspnea.6,9

Patients typically died of profound organ failure or sudden cardiac death. Perhaps most distressing were patients with myocardial infarction who had suffered the consequences of abrupt, severe myocardial failure. These patients would rapidly develop acute pulmonary edema and subsequent cardiogenic shock. Often, we could only stand by helplessly, with few ways to save them. However, the fundamental mechanisms of heart failure were already slowly being defined.

In 1967, The New England Journal of Medicine published an important 5-part Medical Progress series,10–14 Drs Braunwald and Sonnenblick, among others, described the impact of an altered load on myocardial contractility, first in isolated cardiac muscles of animals with pressure overload, and then from myocytes obtained from patients with dilated cardiomyopathy and heart failure. Perhaps these observations were most immediately translated to patients with acute cardiogenic shock.

Beginning in 1973, Drs Chatterjee, Franciosa, Cohn, and others described the utility of intravenous vasodilators (nitroprusside or other agents) to reverse the progressive depression of cardiac output in this syndrome.15–18 Using these drugs in a hypotensive patient with pulmonary edema seemed counterintuitive at first, and these clinical pioneers were often met with skepticism.19 But their ideas worked!

And then, these same hemodynamic principles were applied to patients with chronic heart failure and poor left ventricular contractility.20,21 Many early clinical heart failure units were undertaking studies of hemodynamics before and after drugs that altered what was then coined preload or afterload. It was an exciting opportunity for young clinical investigators. But it involved critical contributions and countless hours from patients as measurements were undertaken, often over days, at rest and during exercise.

The effects of many drugs were explored in various labs, including nitroglycerine, prazosin, hydralazine, minoxidil and oral nitrates. These early investigations culminated in the first multicenter trial in chronic systolic heart failure designed to explore how prazosin or hydralazine–isosorbide dinitrate,
compared with placebo, influenced the outcome of survival. V-HeFT (Vasodilator–Heart Failure Trial), published in 1986, produced the first glimmer of hope that mortality could be postponed in patients with chronic heart failure.22

Meanwhile, other important basic investigative paths would lead to the now well-established practice of neurohormonal antagonism, both through the renin-angiotensin-aldosterone axis and via the β-adrenergic system.23,24 In 1987, the CONSENSUS (Cooperative North Scandinavian Enalapril Survival Study) trial was published.25 This trial proved that the angiotensin-converting enzyme inhibitor enalapril could reduce mortality, by 31% at 1 year, in patients with severe heart failure after a myocardial infarction. Carried out by Scandinavian investigators with only 253 patients, CONSENSUS25 was a landmark trial. It ushered in numerous trials with a variety of angiotensin-converting enzyme inhibitors and, subsequently, angiotensin receptor blockers. These drug classes were proven to improve survival and symptoms while reducing recurrent myocardial infarction.26 Equally important was the documentation of the reversal of adverse ventricular remodeling, first demonstrated by the Pfeffers using captopril in an animal model of myocardial infarction in 1985.27

Another fundamental observation was the original description by Waagstein and colleagues in 1975 of the use of β-blockade in patients (Figure 1).28 Previously, physicians were taught that β-blockers were contraindicated in heart failure. But after it was demonstrated that the myocardial β-receptor was desensitized in chronic heart failure with reduced ejection fraction, several daring investigators began clinical trials using metoprolol and then carvedilol in mild to moderate heart failure.29 They were almost uniformly successful.

Nearly 25 years after Dr Waagstein’s original description, the use of β-blockers was tested in patients with severe heart failure. When the COPERNICUS (Ceredivalol Prospective Randomized Cumulative Survival) trial was published in 2001, it demonstrated a 35% reduction in death using carvedilol in these patients.30 β-Blockers became an additional well-established treatment for heart failure with reduced ejection fraction patients.

Most of us think about primary prevention related to lifestyle and medications. Who would have thought we could apply the term to devices? But by 2005, the results of the Sudden Cardiac Death in Heart Failure Trial, known as SCD-HeFT, proved that implanted defibrillators as primary prevention were effective in a wide variety of patients with systolic heart failure.31 Indeed, many have commented on the so-called rise of the machines, because most successful trials during this period included devices.

In the 2002 publication of the MIRACLE (Multicenter InSync Randomized Clinical Evaluation) trial, cardiac resynchronization therapy showed great benefit in a subset of patients with wide QRS.32 A year earlier, in the REMATCH (Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure) trial, a mechanical circulatory support device, now called a ventricular assist device, significantly prolonged lives in end-stage patients.33 Remarkably, over 20 years, the 2-year mortality for a patient with heart failure with reduced ejection fraction went from about 34% in 1986 to about 14% by the 2004 presentation of the SCD-HeFT data.34

What did these astonishing results mean for the chronic heart failure patient? I can’t think of a better example than my patient, William*. We met in 1982. He had been referred to my mentor, Dr Karl Weber. William had an ejection fraction of 25% and had a very limited exercise tolerance despite optimal use of diuretics and digoxin. He had a pronounced tachycardia and an S₃, and we worked hard to exclude other causes for his fast heart rate.

Dr Weber had been intrigued by the Swedish reports regarding β-blockers, and he encouraged me to use a β-blocker in William and another patient. I was terrified! I felt as if I was about to sail off the edge of the flat Earth. Yet as was often the case, Dr Weber’s instincts were correct. We published our results showing how these patients improved in exercise tolerance and had a lower heart rate.35 I continue to follow both patients in my practice more than 30 years later.

William, an engineer by training and inquisitive by nature, was willing to enroll in additional clinical trials. He was randomized to an angiotensin-converting enzyme inhibitor in one study and felt better. His exercise tolerance became almost normal. He was enrolled in SCD-HeFT as well. And in 2007, he had a cardiac resynchronization therapy pace-maker implanted. This normalized his cardiac function, so that his most recent left ventricular ejection fraction was 55%, up from 30% before implantation. William is now 87 years old, vigorous, sharp, and always questioning me about what’s new in heart failure. He is a shining example of a nearly miraculous improvement in survival over the past 3 decades. This would not have been possible without some important components.

The first of these components was the foundation of basic scientific discovery, which so often led to early clinical trials in patients. By the way, we should all remember what unsung heroes these volunteers are. We owe such a debt for their courage and trust in us. With the help of these patients, clinical trialists have worked hard to demonstrate the efficacy of each new therapy, often involving hundreds or thousands of patients.

After publication of the results of the trials, a new weapon emerged: practice guidelines. The AHA and American College of Cardiology first published guidelines for the management of chronic heart failure in 1995.36 The European Society of Cardiology published its guidelines that same year.37 Writing guidelines requires a careful synthesis of trial data: what kinds of patients were enrolled; how old they were; medical problems that might have complicated their course. The strongest guideline recommendations, those rooted in multiple clinical trials, have been translated into performance benchmarks. Programs using these benchmarks also make it possible to calculate the enhanced survival of a population in which all heart failure patients were given evidence-based therapy.38 This is the basis of the AHA’s Get With The Guidelines program for heart failure and other cardiovascular disease states.

Critical observations in the study of this disease have opened whole new avenues of discovery. In 1995,
Dr Ramachandran Vasan and colleagues published data from the Framingham cohort unfolding the epidemiology of diastolic heart failure, patients with the syndrome of heart failure but apparently normal cardiac contractility.39 This was followed by numerous publications about patients with this condition, now called heart failure with preserved ejection fraction (HFpEF).40 Owan and colleagues from the Mayo Clinic found that the prevalence of HFpEF among patients with a discharge diagnosis of heart failure increased significantly from 1987 to 2001 (Figure 2).34 The prevalence of hypertension, atrial fibrillation, obesity, and diabetes increased during the study period as well, while the prevalence of coronary disease remained stable. Most importantly, although survival improved among patients with reduced ejection fraction, it did not improve among patients with HFpEF.

Sadly, we have yet to find a definitive drug or therapy that confers the same improvement on survival for patients with HFpEF as it does for patients with reduced ejection fraction.42–46 One of the major challenges ahead is what the optimal care of the patient with HFpEF should entail. It is a critical issue, considering many real-world patients have been found to fare even worse than patients in clinical trials.47 And when it comes to clinical trials, it’s clear that more diverse subsets are needed.

Heart failure is an equal-opportunity disease, affecting both sexes and all races. However, most systolic heart failure trials have enrolled middle-aged white men, even though heart failure is a disease primarily of the elderly, and at least 50% of heart failure patients are women.48 Until recently, very few women were enrolled in clinical heart failure trials. Some pivotal US trials were carried out primarily in Veterans Affairs clinics, where most patients were men. And women don’t seem to dilate their ventricles in response to injury the same way men do.49,50 Whatever the reasons, more women should be enrolled. In MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy), for example, adequate enrollment enabled the observation that women seemed to benefit more than men from cardiac resynchronization therapy.51

There are compelling data about the importance of racial diversity in clinical trials.52,53 For example, a post hoc analysis of the V-HeFT I trial examining the differential response of blacks and whites found almost all of the benefit was due to improvement in blacks.54 Had sufficient numbers of black patients not been enrolled, it is likely that this trial that sparked a generation of heart failure studies would have been negative.

Figure 1. First patient with heart failure treated with β-blockade. A 59-year-old woman with congestive heart failure caused by dilated cardiomyopathy since 5 years of age was hospitalized with severe heart failure in pulmonary edema with tachycardia. Reproduced from Waagstein et al55 with permission from BMJ Publishing Group Ltd. Copyright © 1975, BMJ Publishing Group Ltd and the British Cardiovascular Society.

Figure 2. Secular trends in the prevalence of heart failure with preserved ejection fraction. A, Increase in percentage of patients with preserved ejection fraction from 1986 to 2002. B, Numbers of admissions to Mayo Clinic hospitals in Rochester, MN, among patients with preserved or reduced ejection fraction, 1986 to 2002. The number with preserved ejection fraction increased during this period, whereas the number of those with reduced ejection fraction did not change. Solid lines represent regression lines for relation between year of admission and percentage of patients with heart failure who had preserved ejection fraction (A) and number of admissions for heart failure with preserved or reduced ejection fraction (B). Dashed lines indicate 95% confidence intervals. From Owan et al.51 Copyright © 2006, Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.
Hospitalization represents a turning point for heart failure patients, with a combined mortality and readmission rate of 30% within 90 days after discharge. There has been a huge focus on reducing hospital readmissions. Hospitals accordingly have employed a variety of techniques and practices to reduce readmissions, as recently compiled by Bradley et al. However, there are no discrete, evidence-based interventions for acute heart failure, whatever the etiology, that have improved postdischarge outcomes. We are in critical need of further research into strategies to keep patients out of the hospital. But we are in even more urgent need of the measurement of more patient-reported health statuses. Actually, we have to truly understand what our patients value most: avoiding hospitalization or living longer. There may be outcomes worse than death for some patients. We must help them find harmony with their disease and learn what that means for each patient.

Where do we go from here? That’s a critical question for all of us. We are standing on the firm foundation of early studies in heart failure with reduced ejection fraction, our past successes. Yet we have so much more to do.

There are too many hospitalizations and an unacceptably high 30-day mortality rate. There are too many patients developing heart failure as a result of obesity and diabetes. There are mechanical circulatory support devices, heart transplantation, and new hybrid operations, such as transcatheter aortic valve replacement, that promise to sustain life even in desperately ill patients. Yet we still don’t know which patients can most benefit; we only know those who are most likely to die. Somehow, we have to connect current and future research more intimately with the well-being of our patients. And we must have renewed efforts into the prevention of heart failure.

If we could control hypertension, as past AHA President Donna Arnett implored us to do last year at this time, we would reduce the incidence of heart failure by approximately 50%. If we could secure more research funding, as then-AHA President Gordon Tomaselli asked for 3 years ago, we could expand basic and clinical research and the analyses of cohort studies.

I’d like to tell you one last story that illustrates how far we have come with heart failure treatment, and how far we need to go. In 1987, a 22-year-old woman named Elizabeth* presented to the hospital in severe heart failure after the birth of her child. We assumed she had postpartum cardiomyopathy. Elizabeth was so desperately ill, and we ultimately performed a heart transplant to save her. She was able to care for her newborn daughter for a few years. But sadly, she succumbed to complications. She was just 29 years old.

Twenty years later, a colleague referred a 19-year-old patient named Martha (Marty) who had a dilated cardiomyopathy. Martha was becoming more symptomatic, but she had hopes of marrying and having children. When I met Marty, she told me her mother developed heart failure as a result of giving birth to her. As I asked more questions, it dawned on me suddenly: Marty was Elizabeth’s daughter! In addition, Marty’s brother died suddenly several years earlier. Elizabeth may have suffered from postpartum cardiomyopathy, but clearly this family had an inherited form of heart disease. I was watching the cycle of familial cardiomyopathy repeat before my eyes. Like her mother, Marty had a significantly dilated left ventricle and early signs of heart failure. There must be an inherited genetic mutation, one we have not yet been able to identify.

Yet thanks to scientific advancement, Marty is thriving. She was recently married, finished nursing school, and is working full time. She exercises vigorously and even finds time to volunteer for the AHA, sharing her incredible story and urging lawmakers to fund more scientific research.

Everyone here knows Marty’s plea is vital for heart failure patients everywhere. Her plea also prompts a question that troubles me deeply: What must we discover that will guarantee Marty a healthy future? We must find new ways to help our patients to live longer and to enjoy the things that really matter.

I now have the extraordinary opportunity to introduce 2 of my patients you heard about earlier. Please meet William, the patient with heart failure, and Marty, the face of our many and valuable past successes. Marty, the face of our future challenges.

References


* Pseudonym.


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