

Paradigm Shifts in Heart-Failure Therapy — A Timeline

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An interactive timeline is available at NEJM.org

With the publication of the PARADIGM-HF trial in the *Journal* (pages 993–1004) we may be entering a new era of treatment for heart failure with reduced ejection fraction. To provide a historical perspective on the beginning of this new epoch, we constructed an interactive timeline (available with the full text of this article at NEJM.org) of 26 randomized, controlled trials in heart-failure treatment that have been published in the *Journal* since 1986. Each of these articles — some demonstrating successes and others documenting disappointments — represents a critical step in the effort to reduce mortality from heart failure with reduced ejection fraction. The timeline includes important milestones, some of which mark paradigm shifts in the treatment of this debilitating disorder.

The timeline makes clear that highly productive research in heart failure has been an international effort. This pattern of international collaboration was continued in PARADIGM-HF, a trial conducted in 47 countries, with principal investigators from Scotland and the United States.

The modern history of therapy for heart failure with reduced ejection fraction began with the introduction of vasodilatation as a treatment for heart failure. The V-HeFT I study (1986; see box for cited *Journal* articles) demonstrated that treatment with hydralazine plus isosorbide dinitrate, as compared with either placebo or prazosin, reduced mortality. Soon thereafter, the CONSENSUS (1987)

and SOLVD-Treatment (1991a) trials established that angiotensin-converting-enzyme (ACE) inhibition with enalapril reduced overall mortality by 16 to 40%. V-HeFT II (1991b) showed that enalapril was superior to the combination of hydralazine and isosorbide dinitrate. The SOLVD-Prevention trial (1992) showed that enalapril's benefit in reducing the rate of hospitalizations for heart failure extended to asymptomatic patients with reduced ejection fraction. These landmark trials ushered in the era of ACE inhibition, which has been the centerpiece of heart-failure therapy for 25 years.

Angiotensin-receptor blockers (ARBs) interfere with the action of angiotensin II at its type 1 receptor, resulting in vasodilatation. These agents interrupt the angiotensin pathway by a different mechanism than ACE inhibitors, which block the conversion of angiotensin I to angiotensin II and also interfere with the breakdown of kinins. The Val-HeFT trial (2001c) introduced the concept of ARB therapy for heart failure, but because treatment with ARBs is not superior to treatment with ACE inhibitors, ARBs have generally been reserved for patients who cannot take ACE inhibitors because of cough or angioedema.

The use of beta-blocker therapy, now a cornerstone of heart-failure treatment, was once considered counterintuitive, because of concern that patients with reduced ejection fraction either would not benefit or would have unacceptable side effects from adrenergic blockade. However, evidence of a mortality benefit

emerged for three beta-blockers, bisoprolol, carvedilol, and sustained-release metoprolol. In the timeline, we include two studies on the alpha- and beta-adrenergic blocker carvedilol (the U.S. Carvedilol Heart Failure Study, 1996, and COPERNICUS, 2001a). Both studies demonstrated that carvedilol led to a substantial reduction in mortality and contributed to our understanding of the role of adrenergic activation in the pathophysiology of heart failure. These studies underscored a novel, transformative approach to therapy.

Another paradigm shift in heart-failure therapy occurred with the RALES trial (1999) of spironolactone, a mineralocorticoid-receptor antagonist (MRA). The investigators reported a 30% reduction in mortality among patients already receiving an ACE inhibitor and a loop diuretic. The EMPHASIS-HF trial (2011a), in which investigators studied the MRA eplerenone in patients with systolic heart failure and mild symptoms, confirmed and extended this finding. Together, these trials added another important drug class to the heart-failure armamentarium.

Not all therapies listed on the timeline proved successful. Drugs with positive inotropic effects, such as the phosphodiesterase inhibitor milrinone, provide a striking example. In a large clinical trial (PROMISE, 1991c), oral milrinone, as compared with placebo, increased mortality among patients with heart failure by 28%. Novel inotropic agents generally proved disappointing.

Heart-Failure Therapy Articles in the *New England Journal of Medicine*

1986. V-HeFT I. Cohn JN, Archibald DG, Ziesche S, et al. Effect of vasodilator therapy on mortality in chronic congestive heart failure. 314:1547-52.
1987. CONSENSUS. The Consensus Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. 316:1429-35.
- 1991a. SOLVD-Treatment. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. 325:293-302.
- 1991b. V-HeFT II. Cohn JN, Johnson G, Ziesche S, et al. A comparison of enalapril with hydralazine–isosorbide dinitrate in the treatment of chronic congestive heart failure. 325:303-10.
- 1991c. PROMISE. Packer M, Carver JR, Rodeheffer RJ, et al. Effect of oral milrinone on mortality in severe chronic heart failure. 325:1468-75.
1992. SOLVD-Prevention. The SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. 327:685-91.
1996. U.S. Carvedilol Heart Failure Study Group. Packer M, Bristow MR, Cohn JN, et al. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. 334:1349-55.
1997. DIG. The Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. 336:525-33.
1999. RALES. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. 341:709-17.
- 2001a. COPERNICUS. Packer M, Coats AJS, Fowler MB, et al. Effect of carvedilol on survival in severe chronic heart failure. 344:1651-8.
- 2001b. REMATCH. Rose EA, Gelijns AC, Moskowitz AJ, et al. Long-term use of a left ventricular assist device for end-stage heart failure. 345:1435-43.
- 2001c. Val-HeFT. Cohn JN, Tognoni G. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. 345:1667-75.
2004. COMPANION. Bristow MR, Saxon LA, Boehmer J, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. 350:2140-50.
- 2005a. SCD-HeFT. Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter–defibrillator for congestive heart failure. 352:225-37.
- 2005b. CARE-HF. Cleland JGF, Daubert J-C, Erdmann E, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. 352:1539-49.
2009. MADIT-CRT. Moss AJ, Hall WJ, Cannom DS, et al. Cardiac-resynchronization therapy for the prevention of heart-failure events. 361:1329-38.
2010. RAFT. Tang ASL, Wells GA, Talajic M, et al. Cardiac-resynchronization therapy for mild-to-moderate heart failure. 363:2385-95.
- 2011a. EMPHASIS-HF. Zannad F, McMurray JJV, Krum H, et al. Eplerenone in patients with systolic heart failure and mild symptoms. 364:11-21.
- 2011b. ASCEND-HF. O'Connor CM, Starling RC, Hernandez AF, et al. Effect of nesiritide in patients with acute decompensated heart failure. 365:32-43.
- 2014a. MADIT-CRT follow-up. Goldenberg I, Kutiyifa V, Klein HU, et al. Survival with cardiac-resynchronization therapy in mild heart failure. 370:1694-701.
- 2014b. PARADIGM-HF. McMurray JJV, Packer M, Desai AS, et al. Angiotensin–neprilysin inhibition versus enalapril in heart failure. DOI: 10.1056/NEJMoa1409077.

An older class of inotropic agents, the cardiac glycosides, also met with disappointment. Since the classic observations of

William Withering, recorded 230 years ago in his extraordinary document, *An Account of the Foxglove, and Some of Its Medical Uses: With Practical*

Remarks on Dropsy, and Other Diseases, digitalis glycosides were a mainstay of therapy for heart failure. However, a trial published in the *Journal* (Digitalis Investigation Group, DIG, 1997) showed unequivocally that digoxin had no beneficial effect on mortality in heart failure, though it did reduce overall hospitalizations and specifically reduced hospitalizations for heart failure by 28%. Despite their long history, cardiac glycosides are no longer first-line therapy for heart failure, though they may be used to mitigate symptoms and prevent hospitalizations for heart failure.

The story of nesiritide, a recombinant B-type natriuretic peptide with vasodilator properties, reinforces the fundamental importance of evidence-based practice. Nesiritide was approved for use in acute heart failure in 2001 to improve dyspnea. Given by infusion, the drug was administered at many outpatient centers established specifically for this purpose. However, the ASCEND-HF trial (2011b) demonstrated no benefit of nesiritide on the coprimary end point of death or rehospitalization for heart failure and no significant improvement in dyspnea. Thus, an interesting and widely used biologic agent proved to be ineffective when subjected to a rigorous clinical trial.

The introduction of cardiac devices represents perhaps the most fundamental paradigm shift exhibited on the timeline. Not appearing on the timeline until 2001, device trials nevertheless appear more frequently than trials of any single class of medical therapy. The timeline includes three types of cardiac devices: the left ventricular assist device (LVAD) in REMATCH (2001b), the implantable cardioverter-defibril-

lator (ICD) in SCD-HeFT (2005a), and cardiac resynchronization therapy (biventricular pacemakers, CRT) in COMPANION (2004), CARE-HF (2005b), MADIT-CRT (2009), and RAFT (2010). All three types of devices have been shown to reduce mortality in heart failure. LVADs may be used as a bridge to cardiac transplantation or, in some patients, as destination therapy. ICDs may be used alone or together with CRT (CRT-D). A recent follow-up study of the MADIT-CRT trial (2014a) demonstrated that as compared with ICD alone, CRT-D reduced mortality among patients with heart failure and mild symptoms, but only when the QRS complex was greater than 130 msec with a left bundle-branch block pattern.

The final entry in the timeline is the PARADIGM-HF trial (2014b), now published in the *Journal*. The study showed that a novel approach to heart-failure therapy,

angiotensin-receptor and neprilysin inhibition with LCZ696, a combination of sacubitril and valsartan, reduced cardiovascular mortality by 20% and overall mortality by 16%, as compared with enalapril. Neprilysin is a neutral endopeptidase involved in the metabolism of a number of vasoactive peptides. The inhibitor blocks the action of neprilysin, resulting in higher levels of peptides such as natriuretic peptides, which have vasodilator properties, facilitate sodium excretion, and most likely have effects on remodeling.

The timeline reveals steady progress, punctuated by paradigm shifts, in the treatment of heart failure over the past 28 years. At the timeline's beginning, two drugs with no mortality benefit — digoxin and diuretics — represented first-line treatment for heart failure. By the timeline's last entry, ACE inhibitors, beta-blockers, aldosterone antagonists,

cardiac devices, and now angiotensin-receptor–neprilysin inhibitors have strong evidence bases demonstrating a reduction in mortality. Still, in the intervention arm of PARADIGM-HF, the mortality rate among patients with heart failure remains about 20% over 2 years, highlighting the reality that this newest entry hardly concludes the compelling story of heart-failure treatment. We anticipate that progress will continue, and we hope that a timeline crafted three decades from now will reveal novel therapies and new paradigms that push our understanding of heart failure to a level unimaginable today.

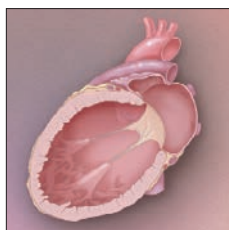
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available at
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Perspective Roundtable: PARADIGM-HF — The Experts' Discussion

Leading cardiologists discuss PARADIGM-HF, a trial of angiotensin–neprilysin inhibition versus enalapril in advanced heart failure.