Editorial

Heart Failure: A Major Management Challenge With Encouraging Recent Progress

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Heart failure is a major health problem, affecting an estimated 38 million persons worldwide, accounting for more than a million hospital admissions per year in the United States and Europe, and carrying a prognosis worse than many cancers.[1] Although it has been commonly assumed that most patients with cardiac failure have reduced left ventricular function (referred to as heart failure with reduced ejection fraction [HFrEF]), there is increasing evidence that many patients can have symptoms and signs of cardiac failure with normal left ventricular function (heart failure with preserved ejection fraction [HFpEF]).[2] With increasing understanding of the important role of the adverse effect of neurohumoral factors in heart failure, the focus of pharmacologic attention has moved away from the seemingly logical task of stimulating the heart with inotropic agents[3] to blocking the neurohumoral mediators of the syndrome. Although recent development of innovative approaches to inotropic therapy with inodilation with calcium-sensitizing therapy in with levosimendan[4] and omecantiv mecarbil[5] may yet have the potential to improve systolic performance without increasing the heart's demand for energy, advances in other areas of drug, device, and transplant currently occupy prominence in heart failure management. This Special Issue reviews these exciting recent advances in the treatment of heart failure.

BEYOND ANGIOTENSIN-CONVERTING ENZYME INHIBITORS AND ANGIOTENSIN RECEPTOR BLOCKERS

The role of the renin-angiotensin-aldosterone system (RAAS) inhibitors is also widely accepted, with an extensive evidence base justifying cornerstone status in the treatment of HFrEF.[6] In the most recent meta-analysis of 54,621 patients with heart failure in randomized clinical trials, RAAS inhibition reduced the risks of hospitalization for heart failure by 20%, cardiovascular mortality by 14%, and all-cause mortality by 11%. The effect was less definite in patients whose ejection fractions were not markedly depressed or normal.[7] Whether angiotensin receptor blockers (ARBs) should be favored over angiotensin-converting enzyme inhibitors (ACEis) in the treatment of heart failure because of their better side effects profile remains unclear. The most recent Cochrane review[8] on this topic concluded that ARBs do not reduce total mortality or morbidity compared with ACEis, and recent guidelines recommend that the primary choice of RAAS inhibitor in heart failure remains an ACEi, limiting the use of ARBs to patients who are intolerant of ACEis.[9,10]

Inhibition of aldosterone in heart failure is an increasingly discussed target, not only because it can overcome fluid retention but also because the prospect of inhibiting direct adverse effects of aldosterone on the failing myocardium is alluring. Of the 2 aldosterone antagonists, spironolactone is universally available, and use of eplerenone is restricted in some countries. A concern with hyperkalemia with these drugs is well recognized.[11] However, in recent trials of eplerenone, hyperkalemia was infrequent and not associated with any mortality.[12,13]

Direct renin inhibitors have been used in an attempt to modulate the damaging effects of renin; however, a large trial of aliskrein added to standard therapy in heart failure was disappointing.[14] A new study of aliskrein in combination with enalapril and direct comparison of aliskrein and enalapril is currently under way.[15]

COMBINED ANGIOTENSIN RECEPTOR-NEPRILYISIN INHIBITION

Undoubtedly, the hottest news in the treatment of HFrEF in the past decade has been the September 2014 publication of the PARADIGM (Prospective Comparison of ARNI with ACEi) trial.[16] In this study, a combined angiotensin receptor–neprilysin inhbitor (ARNi) (LCZ696, the first of a new class of drug) was compared with an ACEi (enalapril).

The strongly positive results have generated positive commentary on this trial. The accompanying *New England Journal of Medicine* editorial suggested that the PARADIGM trial "may well represent a new threshold of hope for patients with heart failure."[17] The development of the research leading to this trial has been lucidly described recently[18] and analyzed in detail by Peter MacDonald in this Special Issue.[19] The combination of ARNis used in PARADIGM no doubt presages the development of other ARNis for the treatment of cardiac failure.

NEW DATA ON β-BLOCKERS AND HEART RATE SLOWING

Although the role of β-blockers in the treatment of HFrEF is now well established,[20] the choice of β-blocker in individual patients can be a challenging decision for the clinician. With the extensive evidence base for the use of β-blockers in heart failure,[21] it came as a surprise when an analysis of the treatment of cardiac failure revealed that β-blocker therapy led to a significant reduction in all-cause mortality in patients with sinus rhythm but not in patients with atrial fibrillation.[22] The reasons for apparent lack of benefit of β-blockers in atrial fibrillation is still being analyzed, but the data are discussed in detail by Yura Mareev and John Cleland in this Special Issue of *Clinical Therapeutics*.

DEVICE THERAPY

The role of device therapy in the treatment of cardiac failure is evolving rapidly and becoming an essential part of the mainstream of therapy for cardiac failure. James Marangou and Vince Paul review the evidence for the use of device therapies in heart failure and the challenges in the choice of device for individual patients.[23] They review the strengthening evidence for the value of implantable cardioverter defibrillator therapy in patients with reduced left ventricular function and heart failure and clarify the role of cardiac resynchronization therapy in patients with heart failure and a wide QRS complex. The exciting developments in miniaturization of implantable cardioverter defibrillator and the prospect of remote monitoring of the patient's hemodynamic status indicate an even more important role for devices in the future management of patients with heart failure.

CARDIAC TRANSPLANT

Despite the major advances in drug therapy and devices, cardiac transplant remains an essential resource in the modern management of advanced heart failure. However, there are many limitations to its wide application, including a limited supply of donor organs. Recent advances are reviewed by Andrew Jabbour and Peter MacDonald.[24] The significant advances in donor organ preservation, limitation of ischemia and reperfusion injury, patient selection, and immunosuppression, which they review, are likely to increase the number of heart transplants and improve outcomes for recipients.