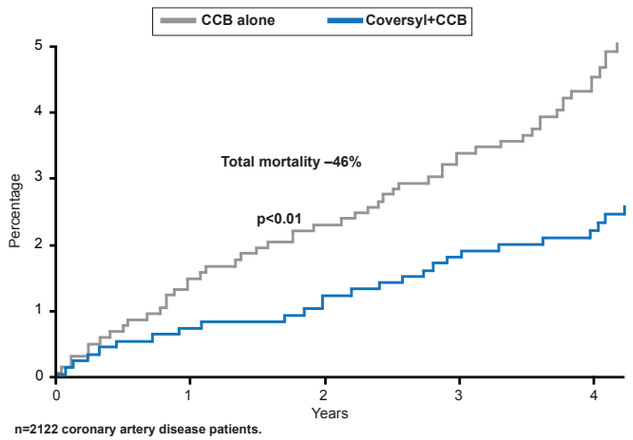
Figure 1 Mortality Benefits of ACE Inhibition in Patients With Coronary Artery Disease



Reproduced from Bertrand ME et al. Clinical synergy of perindopril and calcium-channel blocker in the prevention of cardiac events and mortality in patients with coronary artery disease. Post hoc analysis of the EUROPA study. *Am Heart J* 2010; 159(5):795-802. With permission from Elsevier.

In the Valsartan in Acute Myocardial Infarction study [VALIANT], valsartan was as effective as the ACE inhibitor captopril in reducing all-cause mortality post MI (HR, 1.00; 95% CI, 0.90 to 1.11; p=0.98), but the combination of the two significantly (p<0.05) increased the rate of adverse events (AEs). There was no improvement in survival (HR for combination therapy versus captopril, 0.98; 95% CI, 0.89 to 1.09; p=0.73). AEs that were significantly higher with combination therapy included hypotension (1.9% of subjects vs 0.8% with captopril monotherapy) and renal dysfunction (1.3% vs 0.8%; both p<0.05) [Pfeffer MA et al. *N Engl J Med* 2003]. In ONTARGET, the ARB telmisartan was noninferior to the ACE inhibitor ramipril on the primary composite outcome of death from CV causes, MI, stroke, or hospitalization for heart failure in patients with vascular disease or high-risk diabetes (RR, 1.01; 95% CI, 0.94 to 1.09). The combination was associated with an increased risk of hypotension (4.8% vs 1.7%; p<0.001), syncope (0.3% vs 0.2%; p=0.03), and renal dysfunction (13.5% vs 10.2%; p<0.001) but no increase in benefit (RR, 0.99; 95% CI, 0.92 to 1.07) [ONTARGET Investigators. *N Engl J Med* 2008].

ARBs have also shown benefit in patients with heart failure. In the ELITE II trial the rate of death was similar between losartan and captopril (HR, 1.13; 95% CI, 0.95 to 1.35; p=0.16). Similar frequencies of worsening heart failure (25%) were reported for each group, but losartan was better tolerated, with significantly fewer patients discontinuing treatment because of AEs (p<0.001) [Konstam MA et al. *Am Heart J* 2005]. In the CHARM study, candesartan was generally well tolerated and significantly reduced CV deaths (18% vs 20%; covariate adjusted HR, 0.87; 95% CI, 0.78 to 0.96; p=0.006) and hospital admissions for heart failure (20% vs 24%; p<0.0001).

Ejection fraction or treatment at baseline did not alter these effects [Pfeffer MA et al. *Lancet* 2003]. There are also data from the CHARM study indicating that the use of ARBs may be associated with a decreased incidence of diabetes (HR, 0.78; 95% CI, 0.64 to 0.96; p=0.020) [Yusuf S et al. *Circulation* 2005].

Dr. Elliott noted that ACE inhibition remains the first-line choice for treatment of hypertension, ischemic heart disease, and congestive cardiac failure. Evidence is growing for the efficacy of ARBs but no study to date has shown their superiority over ACE inhibition, which shows definite mortality reduction. Among the ACE inhibitors, only perindopril has solid evidence for mortality reduction.

Surgical Management of Patients With Heart Failure

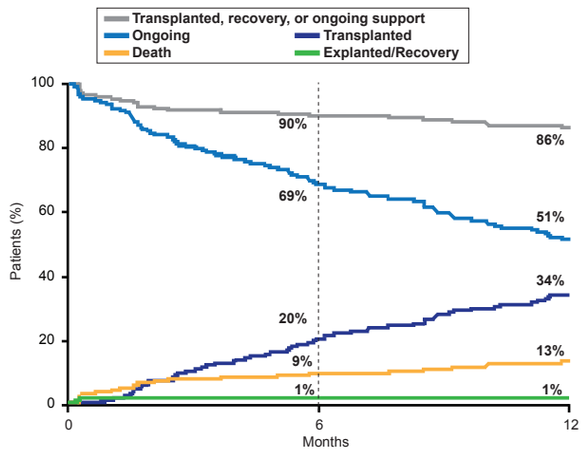
Written by Nicola Parry

Edward B. Savage MD, Cleveland Clinic Florida, Weston, Florida, USA, discussed the use of ventricular assist devices (VADs) and heart transplantation in heart failure patients.

Dr. Savage emphasized that the type of VAD selected may be in part determined by the patient's likelihood of recovery of cardiac function and the anticipated duration of need for VAD therapy. For example, if short-term therapy is anticipated, an intra-aortic balloon pump, the Impella device, the TandemHeart device, or extracorporeal membrane oxygenation could be used; however, these therapies are less suited to long-term outpatient use. The degree of cardiac support needed, the availability and experience of the physician team, and patient characteristics (eg, size of patient, pulmonary function) are also determinants for which device is selected.

For patients who require long-term cardiac support, implantable devices include the Syncardia's Cardiowest total artificial heart; the Heartware ventricular assist system; and Thoratec's HeartMate II (HM II) left VAD (LVAD). As one example, the HM II can be used as an LVAD and is approved as a bridge to heart transplant as well as destination therapy (ie, no heart transplant planned). Data from a postmarket approval study of the first 169 patients enrolled in the Interagency Registry for Mechanically Assisted Circulatory Support [INTERMACS], was consistent with the improved outcomes seen in prior clinical trial data. At 12 months, the survival rate for patients remaining on HM II LVAD support was 86%, compared with only 70% for patients with other types of LVADs (p<0.001; Figure 1) [Starling RC et al. *J Am Coll Cardiol* 2011].

Figure 1. 12-Month Outcomes for HM II LVAD Bridge to Transplant

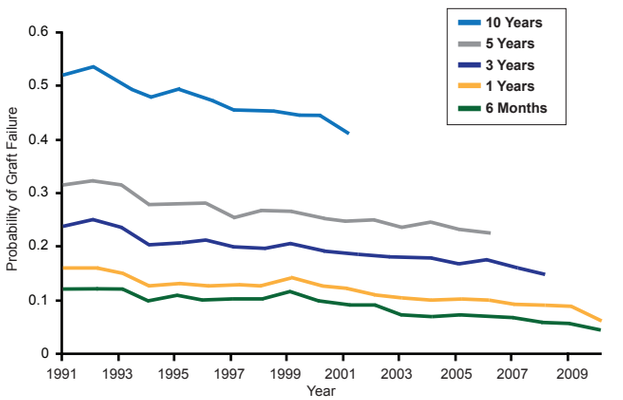


Reproduced from Starling RC et al. Results of the Post-U.S. Food and Drug Administration-Approval Study With a Continuous Flow Left Ventricular Assist Device as a Bridge to Heart Transplantation. *J Am Coll Cardiol* 2011;57(19):1890-1898. With permission from Elsevier.

Dr. Savage reviewed the progress in heart transplantation since 1967. Advancements in immunosuppressive therapy in conjunction with improvements in surgical technique, organ harvesting/preservation, patient selection, and other factors have been the primary reason for continued improvements in patient prognosis. Data on the current characteristics and survival of patients post transplant from the 2011 annual report of the Scientific Registry of Transplant Recipients (SRTR) and Organ Procurement and Transplantation Network (OPTN) were discussed [OPTN and SRTR. OPTN/SRTR 2011 Annual Data Report. Department of Health and Human Services, Health Resources and Services Administration, Healthcare Systems Bureau, Division of Transplantation; 2012. Available at http://srtr.transplant.hrsa.gov/annual_reports/2011/flash/05_heart/index.html]. Dr. Savage mentioned factors associated with reduced waiting times for heart transplant including 1) United Network for Organ Sharing Status 1A or 1B; 2) VAD implantation; and 3) blood type A, B, or AB. Dr. Savage noted that it tends to be more difficult to find a match for patients with type O blood, since they can only receive a heart from a type O donor. The majority of transplanted adults continued to be males and the mean age at transplantation in 2011 was 50.9 years. Coronary artery disease as an etiology of cardiac failure in this population appears to be decreasing while nonischemic cardiomyopathies is increasing.

Dr. Savage concluded by highlighting that although the total annual number of heart transplants performed in the United States remains steady (~1800 to 2000), based on availability of donor hearts, the rate of survival to first graft failure in recipients continues to improve (Figure 2) [OPTN and SRTR. OPTN/SRTR 2011 Annual Data Report. HHS/HRSA/HSB/DOT 2012. Available at http://srtr.transplant.hrsa.gov/annual_reports/2011/flash/05_heart/index.html].

Figure 2. Decreasing Acute and Long-Term Graft Failure



Source: OPTN and SRTR. OPTN/SRTR 2011 Annual Data Report.

New Oral Anticoagulants Can Prevent Stroke Associated With Atrial Fibrillation

Written by Lynne Lederman

Atrial fibrillation (AF), the most common cardiac arrhythmia, is associated with a 5-fold increased risk of stroke. Strokes related to AF are more severe and result in greater morbidity and mortality than strokes from other causes. Alexander Turpie, MD, McMaster University, Hamilton, Ontario, Canada, reviewed the historic role that vitamin K antagonists (VKAs), particularly warfarin, have had in reducing the risk of stroke associated with AF. Problems with older anticoagulants (eg, delayed onset and offset of action, unpredictable dose-response, narrow therapeutic index, and numerous interactions with food and drugs) have led to many patients not receiving needed therapy. In addition, the requirement for regular monitoring and a high risk of intracranial hemorrhage have been especially problematic.

As the population ages, the number of individuals with AF at risk of stroke is increasing. The problems associated with VKAs have resulted in the need for the development of new agents which do not require as close of monitoring. Dr. Turpie reviewed the development of new oral anticoagulant (NOAC) therapies and compared the features of the NOACs with those of warfarin (Table 1).